Genetic Testing for Cancer Predisposition Syndromes in Adolescents and Young Adults (AYAs).

Authors:

Noelle Cullinan, MB[1],

Michael Capra, MB, MME[1],

Terri P McVeigh, MB BAO BCh, MSc, PhD[2]

Affiliations:

[1]Department of Paediatric Oncology, Children's Health Ireland at Crumlin, Dublin 12, D12 N512, Ireland

[2] Cancer Genetics Unit, Royal Marsden NHS Foundation Trust, London, SW3 6JJ, United Kingdom

Corresponding Author:

Dr Terri McVeigh,

Consultant Clinical Geneticist,

The Royal Marsden NHS Foundation Trust,

Fulham Road,

London, SW3 6JJ,

United Kingdom

Telephone: +44 20 8661 3375

Email: terri.mcveigh@nhs.net

Keywords:

Cancer Predisposition Syndromes; adolescent and young adult; AYA; hereditary cancer

Abbreviations:

AACR: American Association for Cancer Research

ALL: Acute lymphoblastic leukaemia

ASCO: American Society of Clinical Oncology

AYA(s): Adolescent(s) and young adult(s)

CPS: Cancer Predisposition Syndrome(s)

DNA: deoxyribonucleic acid

MIPOGG: McGill Interactive Pediatric OncoGenetic Guidelines

MRI: Magnetic Resonance Imaging

NHS: National Health Service

UK: United Kingdom

VUS: Variant of Uncertain Significance

WAGR: Wilms Tumour, Aniridia, Genitourinary anomalies, Intellectual Disability

WB MRI: Whole Body Magnetic Resonance Imaging

Abstract

Purpose of Review:

Adolescents and young adults (AYAs) represent a unique patient cohort, straddling the realms of paediatric and adult medicine. AYA cancers may include traditionally “paediatric” cancers occurring at older than expected ages, or conversely, adult-onset cancers occurring at unusually young ages. Cancer incidence in AYAs (aged 15-39) is increasing, and disappointingly, survival data are worse than those in paediatric or older adult settings. Early recognition of underlying cancer predisposition syndromes (CPS) in AYAs may facilitate individualised therapies, initiation of tumour surveillance strategies and cascade testing in at-risk relatives. Increasingly, physicians together with the wider AYA multidisciplinary team recognise AYAs as a unique group that merit special considerations, particularly regarding the psychosocial impact of cancer and genetic diagnoses on self-identity, fertility and family planning.

Recent Findings:

AYA referral rates for genetic evaluation are suboptimal, but are improving with expanded access to testing, increasing clinician awareness, and increasing public demand for genomic investigation.

Summary:

Herein, we outline recent developments in CPS testing in the AYA cohort. We highlight clinical tools useful in identifying patients that may warrant genetic counselling and/or genetic testing. We also discuss AYA-specific ethical and psychosocial challenges of genetic testing.

Introduction

Cancer in Adolescents and Young Adults:

Adolescents and young adults (AYAs) with cancer are a unique patient group for a host of reasons, including underlying aetiological factors, tumour biology, survivorship issues, fertility and family planning considerations, psychosocial implications and repercussions for parents, siblings and the wider family. The current definition of "AYA" extends from 15 to 39 years of age(1). This cohort represents the "interface" between paediatric and adult medical care, as the cancers occurring in this patient population may include cancers of older adulthood, occurring at unusually early ages(2) (a characteristic of hereditary cancer predisposition syndromes (CPS)), or cancer diagnoses more typically associated with younger children. Among this cohort, the most common types of cancer identified include cancers of the breast, female genital tract and thyroid, as well as melanoma, haematological malignancies, Central Nervous System (CNS) and germ cell tumours(1).

Table 1: Common Cancers by Age Group(3)

		Age Group			
		0-14 years	**15-39 years(4)**	**40-74 years**	**75+ years**
Males	**Cancer rates per 100,000**	**47**	**253**	**6614**	**12964**
	Common Cancers	Leukaemia	Testis	Prostate	Prostate
		CNS	Lymphoma	Lung	Lung
		Lymphoma	Melanoma	Colorectal	Colorectal
		Sympathetic Nervous System	Sarcoma	Head and Neck	Bladder
		Soft tissue Sarcoma	CNS	Kidney	Kidney
		Other	Colorectal	Other	Other
			Thyroid		
			Leukaemia		
			Kidney		
			Oropharyngeal		
			Lung		
			Bladder		
Females	**Cancer rates per 100,000**	41	414	5779	8263
	Common Cancers	Leukaemia	Breast	Breast	Breast
		Brain	Thyroid	Lung	Lung
		Lymphoma	Melanoma	Endometrial	Colorectal
		Kidney	Lymphoma	Colorectal	Pancreatic
		Soft Tissue	Cervix	Ovarian	Other

	Sarcoma		
	Other	Colorectal	Other
		Endometrial	
		Ovarian	
		CNS	
		Leukaemia	
		Sarcoma	
		Kidney	

Cancer incidence in this cohort is increasing over time(4, 5); and, disease-free and overall survival rates are lower than either the paediatric or older adult populations, reflecting underlying differences in tumour molecular phenotype and disease biology(6).

Germline predisposition to cancer in AYAs

To date, dozens of cancer predisposition syndromes have been identified, most of which are caused by germline pathogenic variants in a tumour suppressor gene. A minority are due to activating germline pathogenic variants in proto-oncogenes. Most CPS are non-syndromic, associated with little/no clinical findings other than an increased cancer risk. Some syndromic cancer predisposition conditions are associated with non-malignant features, many of which manifest earlier in childhood, and may predate the onset of malignant manifestations (e.g. cutaneous manifestations in Type 1 Neurofibromatosis, macrocephaly in PTEN Hamartoma Tumour Syndrome).

It is well established that a small but significant proportion of AYAs with cancer will have a CPS. Large population-based studies by several groups have reported an incidence of germline cancer susceptibility syndromes in 7-10% of children/adolescents with a cancer diagnosis(7-10). For the young adult population, data regarding germline susceptibility is more challenging to categorise, with studies primarily focusing on disease-specific findings rather than population-based sequencing studies. Nevertheless, for young adults with early-onset cancers such as invasive breast cancer, the prevalence of moderate-high risk cancer predisposing germline variants ranges from 5.9-23% (11-18), for those with early-onset colorectal cancer 16-35%(19-21), with markedly rising incidence in younger age(22), and for those with certain sarcomas 7%-13%(23, 24).

Aim of review:

This article aims to outline recent developments in CPS testing, clinical tools that will be of use to physicians, and the challenges of genetic testing in the adolescent and young adult population.

Importance of diagnosing Cancer Predisposition Syndromes in AYAs

- ### Addressing the "why":

is significantly influenced by environmental and lifestyle factors as well as by underlying genetic predisposition. As environmental/lifestyle factors require many years of exposure to exert their effects, they are less relevant in the younger patient. An obvious question that arises following a diagnosis of cancer in an AYA is "Why did this happen to me?"(25). Identification of a germline genetic variant can provide clarity and offers patients an explanation for cancer development in each individual case.

- ### Treatment Decisions:

In the setting of a known genetic cancer susceptibility syndrome, physicians may alter therapy strategies in order to avoid adverse effects in genetically predisposed individuals. Clinicians may choose to avoid irradiation (therapeutic or imaging-related) in patients with CPS predisposing to high rates of radiation-induced primary cancers (e.g. Li Fraumeni Syndrome, Nijmegen Breakage Syndrome) or may plan dose adjustments of chemotherapy medications if excessive toxicity is anticipated)(26).

Conversely, clinicians may choose a particular therapy to maximise response rates. Cancers associated with Homologous Recombination Repair Deficiency (HRD) are known to demonstrate increased sensitivity to platinum-based agents(27, 28), and to PARP inhibition(29, 30); while tumours associated with mismatch repair deficiency demonstrate significantly higher response rates to checkpoint inhibitors than mismatch repair-proficient tumours of the same type(31). Furthermore, patients with early stage mismatch repair-deficient colorectal cancer are unlikely to derive any additional benefit from 5-fluorouracil, meaning that this chemotherapeutic agent can be avoided in certain patients with Lynch Syndrome(32).

- **Disease Follow-up, Tumour Surveillance and Prophylaxis:**

Tumour surveillance recommendations concurrent with, or subsequent to, therapy for the primary cancer diagnosis are now in existence for many CPS (33, 34). Surveillance strategies offer the potential to reduce morbidity and mortality through early detection of first and subsequent tumours (35). Consideration of prophylactic surgery for certain cancer types is warranted in certain CPS. Decision-making regarding if and when surgical prophylaxis should be undertaken is complex, and involves a host of factors, including previous cancer history, age-dependent cancer risk, medical consequences of surgery, and psychosocial factors. For example, bilateral salpingo-oophorectomy in a *BRCA1/BRCA2* variant carrier is not recommended before age 35 because of the negative impact of premature menopause on fertility, and bone, heart and brain health, while mastectomy may be considered earlier in adulthood, depending on patient preference. Other surgeries are associated with significant morbidity, but are necessary in light of the high risk of early-onset cancer – for example, early thyroidectomy in patients with Multiple Endocrine Neoplasia (MEN) 2A/2B, pan-proctocolectomy in Familial Adenomatous Polyposis, and gastrectomy in Hereditary Diffuse Gastric Cancer.

- **Cascade testing in the wider family:**

Recognition of an underlying CPS is important, not only for directing therapy strategies in the immediate management of a newly diagnosed malignancy, but also due to the implications for cancer surveillance strategies and cascade testing of family members where appropriate(26). It seems logical that identification of a CPS *prior* to the development of a first malignancy offers the potential for surveillance at regular intervals and counselling of signs and symptoms that families can be aware of, allowing them to seek medical advice early if symptomatology becomes apparent. For some conditions, for which screening is required from the newborn period (e.g. Hereditary Retinoblastoma), pre-symptomatic testing may be performed soon after birth, while for other conditions, testing may be deferred until later childhood/adolescence (e.g. Familial Adenomatous Polyposis, Hereditary Paraganglioma/Phaeochromocytoma), or even early adulthood (Hereditary Breast/Ovarian cancer, Lynch Syndrome).

- **Family Planning**

Discussions regarding fertility and family planning are important for AYAs in the setting of a cancer diagnosis, given that this is the time of life at which family planning is an important consideration, and noting the potential impact of certain surgical interventions or chemotherapeutic agents on fecundity(36). In the AYA with an underlying germline cancer predisposition, this discussion is even more complex. Each child (son or daughter) of an individual with a germline pathogenic variant in a cancer predisposition gene has a 50% chance of inheriting the variant from their parent.

A number of options are available to carriers of pathogenic variants for family planning. For AYAs, this is particularly relevant, given that this is the time of life at which family planning is an important consideration. Options include testing of at-risk progeny during pregnancy (non-invasive prenatal diagnosis, prenatal testing by Chorionic Villus Sampling (CVS) or amniocentesis), or before pregnancy (pre-implantation genetic diagnosis). Some carriers may opt for gamete donation or adoption. Others may choose not to have children(37). Some other carriers may choose to have children naturally, with predictive testing of offspring after birth.

Navigating genetic testing: who and how?

Traditionally, National Health Service (NHS)-funded genetic testing is offered to individuals in whom the *a priori* probability of identifying a causative germline pathogenic variant is at least 10%. Depending on the suspected CPS in question, this probability may be calculated based on histological and/or molecular features of the tumour, family history, age at diagnosis, and associated non-malignant features. Comprehensive discussion of the factors associated with genetic testing for every CPS is beyond the scope of this review. The American Society of Clinical Oncology (ASCO) has, however, issued a comprehensive policy statement in this regard(38).

- **Challenges in recognising a CPS:**

Recent strategies by several groups to develop tools that enhance CPS detection have helped to raise awareness of the growing subspecialty of ‘cancer genetics’ within oncology. These tools help flag clinical clues to the existence of an underlying CPS in oncology patients. Despite these developments, there are persistent challenges in providing patients with timely

access to germline genetic testing, particularly in regions with under-resourced clinical genetics services. Furthermore, there are resource implications in terms of provision of appropriate surveillance in children and young adults in whom a CPS is identified. Moreover, genetic testing in any individual is fraught with ethical and psychosocial implications, and careful consideration of these issues is particularly important in the adolescent and young adult cohort.

- **Reliability of family history in CPS detection:**

Family-history based calculations (e.g. Chompret criteria(39), Manchester Score(40)) may not be useful in families with small pedigrees, adoption estrangement, or in the case of misattribution of paternity. Individuals with *de novo* germline variants, or those with autosomal recessive or X-linked cancer predisposition syndromes, may not have a family history of cancer. Furthermore, most germline pathogenic variants in cancer susceptibility genes are associated with incomplete penetrance, meaning that the parents of an affected child may still be carriers of an autosomal dominant condition without manifesting overt clinical signs. It is therefore important to highlight that the absence of a family history of cancer does not preclude a CPS diagnosis.

- **Additional barriers to genetic testing:**

Germline genetic testing in the AYA population has been reported to be under-utilised (41). This may be due to a host of factors, including regional variability in access to clinical genetics services(42). Access to such services is critical, not just for the initial provision of testing to the affected proband, but also to facilitate genetic counselling and predictive testing for at-risk relatives, which may include over 19 relatives depending on the family size and structure, and the inheritance pattern of the disorder in question(43). Another factor influencing use of diagnostic germline testing includes changes in criteria for genetic testing over time, with increasing moves away from family-history based criteria consequent to the reasons outlined here above, and a move towards broader “pan-cancer” panels, panels that are often accessible only through clinical genetics services. Other factors may include lack of knowledge amongst non-genetics health professionals, or failure to recognise a high-risk family history.

Cancer Predisposition Recognition

- ### Cancer Predisposition Recognition Tools:

In an attempt to assist physicians to recognise cancer predisposition syndromes, a number of groups have developed clinical tools that offer guidance for the rationalisation of genetic referrals in children with cancer(44-46).

Jongmans and colleagues, in 2016, focused on characteristics that merit referral for genetic evaluation due to a higher rate of underlying CPS when particular criteria were met(44). These criteria included specific family history criteria (such as a family history of childhood cancers/early-onset adult cancers (<age 45 years) and the presence of consanguinity), the presence of multiple primary cancers, congenital anomalies or patient-specific features suggestive of a hereditary cancer syndrome, excessive toxicity to chemotherapy agents, and the occurrence of specific malignancies that have an associated higher CPS rate. These criteria were subsequently modified to include consideration of genetic evaluation in situations where tumour testing is suggestive of a germline cancer susceptibility syndrome and in settings where clinical features are present that are known to be associated with a CPS in the presence of a malignancy.

Postema and colleagues, in 2017, published details of a clinical instrument designed to facilitate CPS detection, utilizing a childhood cancer syndrome checklist (incorporating patient characteristics, tumour characteristics, family history features and specific physical manifestations) as well as photographic analysis of each patient with interpretation of clinical features by a clinical geneticist(45).

More recently, the MIPOGG (McGill Interactive Pediatric OncoGenetic Guidelines) eHealth tool, developed by Goudie and colleagues, and officially launched at the International Society for Paediatric Oncology Annual Meeting, 2019, has provided health professionals with a downloadable eHealth tool, available for smart devices(46). The tool encompasses >140 tumour specific algorithms for all paediatric cancer types, incorporating clinical characteristics, family history features and tumour characteristics and generates a binary recommendation either for or against genetic referral. It also provides educational modules and links to relevant evidence-based literature.

A “Traffic light” classification system was developed by the Cancer Genetics unit in the Royal Marsden Hospital, NHS Foundation Trust(47), to simplify identification of patients in whom genetic testing should be undertaken (red) or considered (amber), and those in whom testing was unlikely to yield results (green).

Table 2: “Traffic light” classification system developed in the Cancer Genetics Unit in the Royal Marsden Hospital, NHS Foundation Trust (47).

Red	Amber	Green
Refer patient	**Review family history & discuss case with genetics team**	**Unlikely to have a hereditary component**
Breast: <45 years / triple negative at any age / bilateral	Breast	Cervical cancer
Colorectal cancer – MMRd, any age Diagnosed <50	Differentiated thyroid cancer	Vaginal / vulval cancer
Adrenocortical carcinoma	MMRp colorectal cancer	Lung cancer
Parathyroid cancer	Brain tumour	Head and neck cancer
Medullary thyroid cancer	Sarcoma	Low-grade serous/mucinous ovarian cancer
Phaeochromocytoma <40 years / +ve family history	Phaeochromocytoma >40 years	Haematological malignancies
Paraganglioma, any age	MMRp Endometrial	Testicular cancers
Non-mucinous ovarian cancer, any age	Stromal Ovarian / Testicular tumours	Melanoma
Diffuse gastric cancer<40	Malignant peripheral nerve sheath tumour	
Ureteric cancer	Schwannoma	
Retinoblastoma	Any cancer < 40 years	
MMRd tumour, any type	Any cancer with suspicious family history	
	Multiple primary cancers	
	Prostate cancer < 70 years	

The explosion in genomic sequencing technologies and CPS literature led to the publication of several clinical practice guidelines for CPS evaluation. One of the first publications to address this was by Hampel and colleagues on behalf of the American College of Medical Genetics and Genomics and the National Society of Genetic Counsellors(48), followed by recommendations from ASCO(49). Paediatric specific guidelines soon followed, with the publication of recommendations by the Cancer Predisposition Working Group of the Society for Paediatric Oncology and Haematology(50), and the publication of a series of articles published by the American Association for Cancer Research (AACR) outlining cancer predisposition surveillance recommendations for children with cancer and an underlying CPS(34). Systematic approaches for the evaluation of children/adolescents with cancer are now easily accessible and available to physicians(51).

- **A One-For-All Physician's Guide to CPS detection:**

Ultimately, all the guidelines outlined above endeavour to assist health professionals to recognise adolescents and young adults with cancer who require genetic evaluation for an underlying CPS. We briefly summarise pointers that might be suggestive of an underlying genetic susceptibility to cancer development.

1. *Histopathological clues*: Tumours of certain histopathological subtypes types are more likely to be associated with an underlying heritable defect than tumours of other types (e.g. Choroid Plexus Carcinoma or Hypodiploid ALL (Li Fraumeni Syndrome), Rhabdoid Tumours (Rhabdoid Tumour Predisposition Syndrome), Sub-ependymal Giant Cell Astrocytoma (Tuberous Sclerosis)). Such tumours warrant referral for genetic evaluation regardless of age of onset, family history or the presence of other features(44, 46, 52).

   Immunohistochemistry is a useful and inexpensive test that can be readily performed on tumours to confirm the presence or absence of certain proteins as a preliminary screen for underlying heritable aetiology. The absence of a particular protein can indicate a corresponding genetic aberration (e.g. Mismatch repair-deficient cancers in patients with Lynch Syndrome(53), SDHB-deficient tumours in Hereditary Paraganglioma-Phaeochromocytoma Syndrome(54, 55)). Certain somatic variants

may reflect an underlying cancer predisposition syndrome caused by DNA repair defects (e.g. *KRAS* c.34G>T in *MUTYH*-associated polyposis(56)). Mutational signatures are becoming increasingly useful in determining the underlying aetiology of a cancer(57).

2. *Congenital anomalies and/or intellectual disability:* The presence of congenital anomalies (e.g. multiple café-au-lait spots and axillary freckling in the setting of Neurofibromatosis Type 1) or intellectual disability (e.g. in the setting of WAGR (11p deletion) syndrome) may raise suspicion for an underlying syndromic CPS and warrants further evaluation (7, 58-60).

3. *Multiple tumours*: The presence of multiple primary cancers at any age is suspicious and warrants careful evaluation.

4. *Family history*: A family history of multiple childhood cancers or cancers affecting close relatives at a young age, and/or the presence of consanguinity raises suspicion for an underlying CPS. Importantly, however, the absence of a family history of cancer does not exclude such a diagnosis. Consequent to the young age of parents in the setting of a childhood/adolescent cancer diagnosis, the prevalence of "*de novo*" mutations, and variable penetrance, family cancer history may be negative, and therefore, does not predict the presence of an underlying CPS in young patients(8). It has previously been established that family history taking by physicians is often incomplete (61), with several strategies and guidelines available to guide clinicians in relation to the minimum family history required for individuals with cancer (62). Family histories change over time, and it is worthwhile revisiting the family history at intervals in follow-up. It is also noteworthy that family history details may not be known to the younger patient, and therefore, should be explored carefully with this in mind.

5. *Unusual age at diagnosis*: The presence of an adult-onset cancer at unexpectedly young ages, or the presence of a more classically childhood-onset tumour in an adult raises suspicion for an underlying germline pathogenic variant.

6. *Unanticipated / excessive toxicity to chemotherapy:* Excessive toxicity to standard chemotherapy dosages may suggest the presence of a DNA repair disorder. (e.g. Fanconi Anaemia)

Challenges of diagnostic genetic testing

There are many challenges and considerations that should be addressed in the decision to offer genetic testing to adolescents and young adults.

- **Assent/Consent in the AYA:**

Consent issues, as aforementioned, may be complicated for medical, ethical and psychosocial reasons. In the first instance, it is paramount that the consenting process is explained in detail so that individual patients can make an informed decision regarding all aspects of testing(62). The discovery of a pathogenic germline variant may have implications for extended family members, with cascade testing in close relatives required in some cases, while there may also be consequences for family planning decisions. Patient should be counselled regarding the potential discovery of variants of uncertain significance (VUS).

Clinical clues may guide genetic testing that involves a limited number of genes, but more often than not, a panel of genes is tested, with many centres internationally now performing whole exome/genome sequencing. This is of particular importance for patients, as, in addition to a CPS diagnosis, there may be additional genetic findings with implications for non-cancer related health issues. The consenting process for genetic testing merits discussion of secondary/incidental findings by experienced health professionals, particularly in younger patients, for whom there may be additional concerns such as implications on health insurance/family planning if all results are disclosed(49). The American College of Medical Genetics have released a policy statement in regard to genomic sequencing, and have published recommendations for reporting of incidental findings(63).

For adolescents, these issues are more difficult to navigate, as the consenting process relies on parents making informed decisions on behalf of their teenage children, many of whom are sufficiently cognitively and psychologically mature to give their assent to testing, but may

not be able to decline testing while they are below the age of consent(64, 65). Age of capacity to consent will, of course, take into account “Gillick Competence”, yet it is important to acknowledge the implications of consenting to extensive genetic sequencing studies, a process that can be difficult to understand even for highly educated adult patients and a process that many health professionals find challenging. Nevertheless, many young adolescents are well informed and can have a good understanding of the issues involved with such decisions. Physicians should aim to engage adolescents in conversations around genetic testing and endeavour to outline the rationale for, potential implications of, and risks/benefits of performing genetic testing. Importantly, the voice of the young person within these discussions must be heard and respected (51, 64). There is also potential to revisit the consenting process at a later date if it is felt that an individual patient requires more time to consider the potential pitfalls of testing, an issue that may be particularly relevant in a vulnerable patient already overwhelmed by their cancer diagnosis(66).

- **Implications of genetic testing for insurance:**

Issues related to health insurance relative to a CPS diagnosis are also of concern in the current economic climate (67). The implications of genetic testing for insurance may vary in different regions. In the UK, insurers can request information about diagnostic genetic tests to determine level of cover and cost of a premium. The insurance implications of testing in an AYA may therefore not be apparent for several years.

- **Impact on Patients, Families, Healthcare Resources:**

It is important to acknowledge the impact that adopting CPS surveillance strategies has on patients, their families and on healthcare resources, which in many settings, are already operating at, or near, full capacity.

The psychosocial implications of a CPS diagnosis are not to be underestimated. Nevertheless, literature suggests that, for the most part, families at risk of a CPS are motivated to undergo genetic testing for several reasons including defining cancer risk for themselves and their family members, as well as allowing pre-symptomatic surveillance or enrolment in tumour surveillance protocols following a cancer diagnosis.

The concept of "scanxiety" (anxiety related to surveillance imaging) is a significant issue, with patients and families reporting anxiety in the time leading up to and around surveillance imaging, and in the setting of false positive Magnetic Resonance Imaging (MRI) findings, with several groups acknowledging this aspect of surveillance(33, 68). Despite this, many parents and families feel empowered through enrolment in a surveillance programme, even in the knowledge that tumours may emerge in the intervals between surveillance scans, as established links with medical oncology clinics can allow quicker access if concerning symptomatology emerges between appointments(33, 35, 69).

Surveillance recommendations in the setting of an underlying susceptibility to cancer development typically involves the use of MRI and ultrasound imaging, as well as clinical examination, in an attempt to avoid exposure to ionizing radiation where possible. These modalities are relatively safe. Concerns regarding a potential, but unproven, harm caused by Gadolinium deposition in the brain(70) are offset by the benefit of avoiding the proven risk associated with ionizing radiation exposure(71). MRI is seen as "acceptable" by most patients(68, 72), and importantly gives physicians detailed images of the whole body with high sensitivity and specificity(73, 74), notwithstanding the anxiety related to the enclosed space that poses challenges for some patients(75-77). Issues related to the availability of MRI scanners, the physical time and human resources needed to perform Whole Body (WB) MRI examinations in a comprehensive manner, competing sedation and anaesthesia needs for younger children or complex patients across medical specialties in shared paediatric/adult institutions, the careful interpretation of imaging by radiologists experienced in WB MRI needed for patient care, and follow-up examinations of any areas of concern resultant from WB MRI findings are, however, all important points to consider, not to mention the costs associated with such an undertaking(78, 79).

- **Streamlining access to genomic testing and cancer surveillance for AYAs:**

There is a global shortage of cancer genetics professionals(80), particularly in Ireland, Portugal and England(81). To offset the impact of this shortage on waiting times, "mainstreaming" of certain genetic tests through routine adult oncology and surgical clinics has been successfully implemented in several regions(18, 82, 83). There is a move to greatly expand this approach in the NHS by establishing a National Genomic Medicine Service(84). This has involved a reconfiguration of existing laboratory services, and development of a

National Genomic Test directory to standardise criteria for testing nationally. Non-genetic specialists will be able to order genetic tests relevant to their own specialty, without the need for prior referral to Clinical Genetics services. Initiatives such as the Genomics Education Programme by Health Education England have been established to provide appropriate training to non-genetics professionals working within the NHS. The aim of this strategy is to ensure timely, accurate and equitable access to genomic profiling.

Mainstreaming of genomic profiling in the AYA cohort has significant advantages. Firstly, the rapport between treating clinician, patient and family is already well-established, a relationship that is of critical importance in this vulnerable patient group. Furthermore, rapid access to test results may have direct and immediate influence on decision-making, and waiting times for testing will be essentially eliminated. The potential pitfalls of this approach include a failure to recognise patients in need of testing – a barrier to referral that exists even with the traditional pathway. This can be addressed with ongoing training and education of clinicians, and is likely to be less of an issue as genetic testing becomes more routine in patient care. Appropriate pathways for onward referral of patients with a confirmed CPS are critical to provide post-test genetic counselling and support, and to facilitate cascade testing within the family.

Ensuring access to appropriate surveillance once a CPS is diagnosed is also a major issue, with regional variability in practice. For example, at the present time, although WB MRI has been shown to be effective in, and acceptable to, patients with Li-Fraumeni syndrome(68, 85) this is not yet publicly funded for this patient cohort in the UK Furthermore, there are some CPS for which guidelines regarding surveillance are not yet available for this population (e.g. DICER1 syndrome). Efforts to standardise surveillance recommendations will undoubtedly continue as this subspecialty area evolves from its infancy.

Predictive genetic testing in Adolescents and Young Adults

At the present time, pre-symptomatic genetic testing of unaffected children or adolescents is not recommended unless there is clear medical benefit. For some cancer predisposition syndromes, cancer risks may start early in childhood or adolescence, and therefore testing of individuals at risk of inheriting such conditions should routinely be undertaken before

adulthood, to facilitate early screening and/or risk-reducing surgery. For disorders predisposing only to cancers of adult onset, where surveillance would not start until early adulthood, testing of minors is usually deferred until such a time as the individual at risk is able to provide autonomous, fully informed consent. Furthermore, there are concerns that the test result, be it positive or negative, may cause significant psychological distress(86, 87). However, knowledge of a potential risk may raise certain questions before the age at which testing would ordinarily be undertaken. For example, adolescents at risk of inheriting a familial *BRCA1/BRCA2* variant may have questions regarding the implications of carrier status for decision-making regarding contraception choices. Deferral of testing in at-risk adolescents may lead to feelings of disempowerment(88). Pre-symptomatic testing in AYAs is best undertaken with pre-test counselling by a trained provider, to explore motivations for testing, and provide accurate information in an accessible and age-appropriate manner, as well as with provision of post-test genetic counselling.

Conclusion:

The unique challenges posed by genetic evaluation of the AYA population merit due diligence by oncologists, clinical geneticists and the wider team of health professionals. Although the issues surrounding genetic evaluation and testing in this population may be complex, the impact of not diagnosing a CPS may be far-reaching with consequences for the individual and the wider family structure. The tumour surveillance protocols and individualized therapies emerging from research initiatives show promise and may reduce morbidity and mortality for this cohort of patients. Recently developed CPS recognition tools offer health professionals, who have not had formal genetic training, an essential resource that will enhance the ability to identify those AYAs who may have a CPS, allowing physicians to rationalise and prioritise referrals to clinical/cancer genetic services in a logical manner. As knowledge advances further, it will be crucial for physicians to remain abreast of developments in the area of cancer predisposition.

••Barr RD, Ries LA, Lewis DR, et al. Incidence and incidence trends of the most frequent cancers in adolescent and young adult Americans, including "nonmalignant/noninvasive" tumors. Cancer. 2016;122(7):1000-8. – ***overview of the epidemiology of cancer in AYAs in USA***

•Pearlman R, Frankel WL, Swanson B, et al. Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer. JAMA Oncol. 2017;3(4):464-71. ***overview of the germline predispostion to Colorectal cancer in AYAs***
•Copson ER, Maishman TC, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018;19(2):169-80. – ***frequency of BRCA variants in patients diagnosed with breast cancer under 40y***

References:

1. Desandes E, Stark DP. Epidemiology of Adolescents and Young Adults with Cancer in Europe. Prog Tumor Res. 2016;43:1-15.
2. Aben KK, van Gaal C, van Gils NA, 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):922-33.
3. CRUK. Cancer Research UK. Cancer Incidence Statistics. Cancer Incidence by age. [Available from: www.cancerresearchuk.org/health-professional/cancer-statistics/incidence.
4. Barr RD, Ries LA, Lewis DR, et al. Incidence and incidence trends of the most frequent cancers in adolescent and young adult Americans, including "nonmalignant/noninvasive" tumors. Cancer. 2016;122(7):1000-8.
5. Fidler MM, Gupta S, Soerjomataram I, et al. Cancer incidence and mortality among young adults aged 20-39 years worldwide in 2012: a population-based study. Lancet Oncol. 2017;18(12):1579-89.
6. Bleyer A, Barr R, Hayes-Lattin B, et al. The distinctive biology of cancer in adolescents and young adults. Nat Rev Cancer. 2008;8(4):288-98.
7. Merks JH, Caron HN, Hennekam RC. High incidence of malformation syndromes in a series of 1,073 children with cancer. Am J Med Genet A. 2005;134A(2):132-43.
8. Zhang J, Walsh MF, Wu G, et al. Germline Mutations in Predisposition Genes in Pediatric Cancer. N Engl J Med. 2015;373(24):2336-46.
9. Grobner SN, Worst BC, Weischenfeldt J, et al. The landscape of genomic alterations across childhood cancers. Nature. 2018;555(7696):321-7.
10. Parsons DW, Roy A, Yang Y, et al. Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. JAMA Oncol. 2016;2(5):616-24.
11. Peto J, Collins N, Barfoot R, et al. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst. 1999;91(11):943-9.
12. Rummel SK, Lovejoy L, Shriver CD, et al. Contribution of germline mutations in cancer predisposition genes to tumor etiology in young women diagnosed with invasive breast cancer. Breast Cancer Res Treat. 2017;164(3):593-601.
13. Bayraktar S, Amendola L, Gutierrez-Barrera AM, et al. Clinicopathologic characteristics of breast cancer in BRCA-carriers and non-carriers in women 35 years of age or less. Breast. 2014;23(6):770-4.
14. Sun J, Meng H, Yao L, et al. Germline Mutations in Cancer Susceptibility Genes in a Large Series of Unselected Breast Cancer Patients. Clin Cancer Res. 2017;23(20):6113-9.

15. Geredeli C, Yasar N, Sakin A. Germline Mutations in BRCA1 and BRCA2 in Breast Cancer Patients with High Genetic Risk in Turkish Population. Int J Breast Cancer. 2019;2019:9645147.
16. Lin PH, Kuo WH, Huang AC, et al. Multiple gene sequencing for risk assessment in patients with early-onset or familial breast cancer. Oncotarget. 2016;7(7):8310-20.
17. Copson ER, Maishman TC, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018;19(2):169-80.
18. Kemp Z, Turnbull A, Yost S, et al. Evaluation of Cancer-Based Criteria for Use in Mainstream BRCA1 and BRCA2 Genetic Testing in Patients With Breast Cancer. JAMA Netw Open. 2019;2(5):e194428.
19. Stoffel EM, Koeppe E, Everett J, et al. Germline Genetic Features of Young Individuals With Colorectal Cancer. Gastroenterology. 2018;154(4):897-905 e1.
20. Pearlman R, Frankel WL, Swanson B, et al. Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer. JAMA Oncol. 2017;3(4):464-71.
21. Mork ME, You YN, Ying J, et al. High Prevalence of Hereditary Cancer Syndromes in Adolescents and Young Adults With Colorectal Cancer. J Clin Oncol. 2015;33(31):3544-9.
22. Levine O, Zbuk K. Colorectal cancer in adolescents and young adults: Defining a growing threat. Pediatr Blood Cancer. 2019;66(11):e27941.
23. Ballinger ML, Goode DL, Ray-Coquard I, et al. Monogenic and polygenic determinants of sarcoma risk: an international genetic study. Lancet Oncol. 2016;17(9):1261-71.
24. Chan SH, Lim WK, Ishak NDB, et al. Germline Mutations in Cancer Predisposition Genes are Frequent in Sporadic Sarcomas. Sci Rep. 2017;7(1):10660.
25. Vetsch J, Wakefield CE, Doolan EL, et al. 'Why us?' Causal attributions of childhood cancer survivors, survivors' parents and community comparisons - a mixed methods analysis. Acta Oncol. 2019;58(2):209-17.
26. Postema FAM, Hopman SMJ, Hennekam RC, et al. Consequences of diagnosing a tumor predisposition syndrome in children with cancer: A literature review. Pediatr Blood Cancer. 2018;65(1).
27. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nature medicine. 2018;24(5):628-37.
28. Telli ML, Timms KM, Reid J, et al. Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer. Clin Cancer Res. 2016;22(15):3764-73.
29. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, et al. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. Cancer discovery. 2015;5(11):1137-54.
30. Pilie PG, Gay CM, Byers LA, et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. Clin Cancer Res. 2019;25(13):3759-71.
31. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science (New York, NY). 2017;357(6349):409-13.
32. Kawakami H, Zaanan A, Sinicrope FA. Microsatellite instability testing and its role in the management of colorectal cancer. Current treatment options in oncology. 2015;16(7):30.

33. Malkin D, Nichols KE, Schiffman JD, et al. The Future of Surveillance in the Context of Cancer Predisposition: Through the Murky Looking Glass. Clin Cancer Res. 2017;23(21):e133-e7.
34. Brodeur GM, Nichols KE, Plon SE, et al. Pediatric Cancer Predisposition and Surveillance: An Overview, and a Tribute to Alfred G. Knudson Jr. Clin Cancer Res. 2017;23(11):e1-e5.
35. Villani A, Shore A, Wasserman JD, 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. 2016;17(9):1295-305.
36. Murphy D, Klosky JL, Reed DR, et al. The importance of assessing priorities of reproductive health concerns among adolescent and young adult patients with cancer. Cancer. 2015;121(15):2529-36.
37. Friedman LC, Kramer RM. Reproductive issues for women with BRCA mutations. Journal of the National Cancer Institute Monographs. 2005(34):83-6.
38. American Society of Clinical O. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol. 2003;21(12):2397-406.
39. Tinat J, Bougeard G, Baert-Desurmont S, et al. 2009 version of the Chompret criteria for Li Fraumeni syndrome. J Clin Oncol. 2009;27(26):e108-9; author reply e10.
40. Evans DG, Harkness EF, Plaskocinska I, et al. Pathology update to the Manchester Scoring System based on testing in over 4000 families. J Med Genet. 2017;54(10):674-81.
41. McVeigh TP, Sundar R, Diamantis N, et al. The role of genomic profiling in adolescents and young adults (AYAs) with advanced cancer participating in phase I clinical trials. Eur J Cancer. 2018;95:20-9.
42. Delikurt T, Williamson GR, Anastasiadou V, et al. A systematic review of factors that act as barriers to patient referral to genetic services. Eur J Hum Genet. 2015;23(6):739-45.
43. McVeigh TP, Donnelly D, Al Shehhi M, et al. Towards establishing consistency in triage in a tertiary specialty. Eur J Hum Genet. 2019;27(4):547-55.
44. Jongmans MC, Loeffen JL, Waanders E, et al. Recognition of genetic predisposition in pediatric cancer patients: An easy-to-use selection tool. Eur J Med Genet. 2016;59(3):116-25.
45. Postema FA, Hopman SM, de Borgie CA, et al. Validation of a clinical screening instrument for tumour predisposition syndromes in patients with childhood cancer (TuPS): protocol for a prospective, observational, multicentre study. BMJ Open. 2017;7(1):e013237.
46. Goudie C, Coltin H, Witkowski L, et al. The McGill Interactive Pediatric OncoGenetic Guidelines: An approach to identifying pediatric oncology patients most likely to benefit from a genetic evaluation. Pediatr Blood Cancer. 2017;64(8).
47. Moss CA, Cojocaru E, Hanwell J, et al. Multidisciplinary interventions in a specialist Drug Development Unit to improve family history documentation and onward referral of patients with advanced cancer to cancer genetics services. Eur J Cancer. 2019;114:97-106.
48. Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015;17(1):70-87.

49. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. J Clin Oncol. 2015;33(31):3660-7.
50. Ripperger T, Bielack SS, Borkhardt A, et al. Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. Am J Med Genet A. 2017;173(4):1017-37.
51. Kuhlen M, Wieczorek D, Siebert R, et al. How I approach hereditary cancer predisposition in a child with cancer. Pediatr Blood Cancer. 2019;66(11):e27916.
52. Postema FAM, Hopman SMJ, Aalfs CM, et al. Childhood tumours with a high probability of being part of a tumour predisposition syndrome; reason for referral for genetic consultation. Eur J Cancer. 2017;80:48-54.
53. Lynch HT, Lynch PM, Lanspa SJ, et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet. 2009;76(1):1-18.
54. Gaal J, Stratakis CA, Carney JA, et al. SDHB immunohistochemistry: a useful tool in the diagnosis of Carney-Stratakis and Carney triad gastrointestinal stromal tumors. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2011;24(1):147-51.
55. Gill AJ. Use of SDHB immunohistochemistry to identify germline mutations of SDH genes. Hered Cancer Clin Pract. 2012;10(Suppl 2):A7-A.
56. Aimé A, Coulet F, Lefevre JH, et al. Somatic c.34G>T KRAS mutation: a new prescreening test for MUTYH-associated polyposis? Cancer Genetics. 2015;208(7):390-5.
57. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415-21.
58. Merks JH, Ozgen HM, Koster J, et al. Prevalence and patterns of morphological abnormalities in patients with childhood cancer. JAMA. 2008;299(1):61-9.
59. Narod SA, Hawkins MM, Robertson CM, et al. Congenital anomalies and childhood cancer in Great Britain. Am J Hum Genet. 1997;60(3):474-85.
60. Miller RW. Childhood cancer and congenital defects. A study of U.S. death certificates during the period 1960-1966. Pediatr Res. 1969;3(5):389-97.
61. Wood ME, Kadlubek P, Pham TH, et al. Quality of cancer family history and referral for genetic counseling and testing among oncology practices: a pilot test of quality measures as part of the American Society of Clinical Oncology Quality Oncology Practice Initiative. J Clin Oncol. 2014;32(8):824-9.
62. Lu KH, Wood ME, Daniels M, et al. American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. J Clin Oncol. 2014;32(8):833-40.
63. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(2):249-55.
64. Bush LW, Bartoshesky LE, David KL, et al. Pediatric clinical exome/genome sequencing and the engagement process: encouraging active conversation with the older child and adolescent: points to consider-a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018;20(7):692-4.
65. Brierley J, Larcher V. Adolescent autonomy revisited: clinicians need clearer guidance. J Med Ethics. 2016;42(8):482-5.

66. Lake PW, Kasting ML, Dean M, et al. Exploring patient and provider perspectives on the intersection between fertility, genetics, and family building. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2020.
67. Snyder C. Evolution of cancer risk assessment and counseling related to psychological, financial and legal implications. Fam Cancer. 2016;15(3):493-6.
68. Bancroft EK, Saya S, Brown E, et al. Psychosocial effects of whole-body MRI screening in adult high-risk pathogenic TP53 mutation carriers: a case-controlled study (SIGNIFY). J Med Genet. 2019.
69. Lammens CR, Bleiker EM, Aaronson NK, et al. Regular surveillance for Li-Fraumeni Syndrome: advice, adherence and perceived benefits. Fam Cancer. 2010;9(4):647-54.
70. Gulani V, Calamante F, Shellock FG, et al. Gadolinium deposition in the brain: summary of evidence and recommendations. The Lancet Neurology. 2017;16(7):564-70.
71. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet (London, England). 2012;380(9840):499-505.
72. Oliveri S, Pricolo P, Pizzoli S, et al. Investigating cancer patient acceptance of Whole Body MRI. Clin Imaging. 2018;52:246-51.
73. Anupindi SA, Bedoya MA, Lindell RB, et al. Diagnostic Performance of Whole-Body MRI as a Tool for Cancer Screening in Children With Genetic Cancer-Predisposing Conditions. AJR Am J Roentgenol. 2015;205(2):400-8.
74. Jasperson KW, Kohlmann W, Gammon A, et al. Role of rapid sequence whole-body MRI screening in SDH-associated hereditary paraganglioma families. Fam Cancer. 2014;13(2):257-65.
75. Eshed I, Althoff CE, Hamm B, et al. Claustrophobia and premature termination of magnetic resonance imaging examinations. J Magn Reson Imaging. 2007;26(2):401-4.
76. Dewey M, Schink T, Dewey CF. Claustrophobia during magnetic resonance imaging: cohort study in over 55,000 patients. J Magn Reson Imaging. 2007;26(5):1322-7.
77. Thorpe S, Salkovskis PM, Dittner A. Claustrophobia in MRI: the role of cognitions. Magn Reson Imaging. 2008;26(8):1081-8.
78. Saade-Lemus S, Degnan AJ, Acord MR, et al. Whole-body magnetic resonance imaging of pediatric cancer predisposition syndromes: special considerations, challenges and perspective. Pediatr Radiol. 2019;49(11):1506-15.
79. Greer MC. Imaging of cancer predisposition syndromes. Pediatr Radiol. 2018;48(9):1364-75.
80. Stoll K, Kubendran S, Cohen SA. The past, present and future of service delivery in genetic counseling: Keeping up in the era of precision medicine. Am J Med Genet C Semin Med Genet. 2018;178(1):24-37.
81. Lynch SA, Borg I. Wide disparity of clinical genetics services and EU rare disease research funding across Europe. J Community Genet. 2016;7(2):119-26.
82. McCuaig JM, Armel SR, Care M, et al. Next-Generation Service Delivery: A Scoping Review of Patient Outcomes Associated with Alternative Models of Genetic Counseling and Genetic Testing for Hereditary Cancer. Cancers (Basel). 2018;10(11).
83. Stearnes G, Nichols CB, Schofield L, et al. Uptake of testing for germline BRCA mutations in patients with non-mucinous epithelial ovarian cancers in Western

Australia: a comparison of different genetic counseling methods. Int J Gynecol Cancer. 2019;29(6):1038-42.
84. NHS Genomic Medicine Service [Available from: https://www.england.nhs.uk/genomics/nhs-genomic-med-service/.
85. Saya S, Killick E, Thomas S, et al. Baseline results from the UK SIGNIFY study: a whole-body MRI screening study in TP53 mutation carriers and matched controls. Fam Cancer. 2017;16(3):433-40.
86. Duncan RE, Gillam L, Savulescu J, et al. "You're one of us now": Young people describe their experiences of predictive genetic testing for Huntington disease (HD) and familial adenomatous polyposis (FAP). American Journal of Medical Genetics Part C: Seminars in Medical Genetics. 2008;148C(1):47-55.
87. Vetsch J, Wakefield CE, Warby M, et al. Cancer-Related Genetic Testing and Personalized Medicine for Adolescents: A Narrative Review of Impact and Understanding. Journal of adolescent and young adult oncology. 2018;7(3):259-62.
88. Mand C, Gillam L, Duncan RE, et al. "It was the missing piece": adolescent experiences of predictive genetic testing for adult-onset conditions. Genetics in Medicine. 2013;15(8):643-9.