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ABSTRACT

Germline predisposing pathogenic variants (GPVs) are present in approximately 8–10 % of children with all cancer types. Very rare tumours (VRTs) represent many different diseases, defined with an annual incidence < 2 / 1,000,000, and correspond to 11 % of all cancers in patients aged 0–14 years. Some of these VRTs, including cancer typical for adults, develop in children with a cancer predisposition syndrome (CPS). Classically, three situations lead to consider this association: Some patients develop a VRT for which histology itself strongly suggests a GPV related to a CPS; others are referred for germline genetic testing because of a family or personal history and finally, a systematic molecular genomic tumour analysis, reveals a PV typical to a CPS. Depending on the samples tested and type of analysis performed, information can be directly available about the germline status of such a PV. Depicting the association between CPS and VRT is clinically important as some of these tumour types require adapted therapy, sometimes in the frontline setting, and the proposal of a specific surveillance programme to detect other malignancies. The diagnosis of CPS necessitates a careful familial evaluation and genetic counselling regarding the risks faced by the child or other family members. The aim of this paper is to propose a literature review of solid VRTs occurring in paediatric and young adult patients associated with CPSs.

1. Introduction

Paediatric cancers are rarely determined by environmental exposure to oncogenic factors therefore genetic factors are thought to be more relevant than for adult neoplasms. With systematic molecular sequencing of all paediatric cancers, germline predisposing pathogenic variants (GPV) are identified in approximatively 8–10 % of children [1]. However, recognition of cancer predisposition is difficult when solely selecting based on family history as clinical family history for cancer is not different between individuals with or without GPV. This frequent lack of specific family history was first brought up by Zhang et al. [2]. Paediatric very rare tumours (VRT) encompass a large group of different diseases, primarily defined by their low incidence [3]. They are primarily defined by an annual incidence < 2 / 1,000,000 which, corresponds to 11 % of all cancers in patients aged 0–14 years [4]. Very rare paediatric cancers include both histotypes typically diagnosed at paediatric age (i.e., hepatoblastoma, pleuropulmonary blastoma [PPB], pancreatoblastoma) and tumour types that occur more frequently in adults (e.g., melanoma, carcinomas). VRTs frequently develop in the context of a cancer predisposition syndrome (CPS; Fig. 1). In addition, few are due to environmental exposure. Viral infections may be associated to VRT but rarely, such as papillomavirus and lung carcinoma, Epstein Barr virus and undifferentiated nasopharyngeal carcinoma, hepatitis B and C virus and hepatocarcinoma, or papilloma virus and cervical cancer. Furthermore, some types of translocation-derived carcinomas have been linked to environmental agents, such as exposure to radiation or chemicals. However, most VRTs are of unknown origin such as esthesioneuroblastoma and solid pseudopapillary neoplasm of the pancreas [5,6]. Associations between CPSs and paediatric VRTs have not yet been well-studied. We can distinguish three situations that lead to consider this association: 1- Some VRTs whose histology itself (for instance adrenocortical carcinoma, medullar thyroid carcinoma, pheochromocytoma, colonic carcinoma, PPB, malignant cortical tumour, and pinealoblastoma) are well known to be associated with a CPS, 2- Patients are referred for germline genetic testing due to a familial history suggesting the presence of a CPS 3- A systematic molecular genomic tumour analysis, identifies the presence of a PVsuspicious of being germline in origin which leads to the proposal of a constitutional analysis to confirm the CPS [7–9] (Table 1). In addition, some centres propose a systematic germline screening programme in any child with cancer to identify those with a CPS, considering the overall GPV detection rate of at least 8–10 % in pediatric cancers. Indeed, analysing GPV is usually performed on normal tissue (mostly leukocyte DNA). Even if genetic tumor tissue data can be used as well if available anyway due to other (therapeutic) indications, however, it is less sensitive and thus, not the optimal approach to screen for CPS. Studying tumorigenesis in the context of genetic cancer predisposition provides insights into the biology of tumorigenesis and the control mechanisms of cell growth, cell death, and differentiation. Knowledge of a CPS is crucial for the individual patient, but also for the family. Predictive genetic testing can be offered to all relatives at risk including future children. For the carriers, intensive surveillance programs can be offered to try to avoid cancer or detect them in an early, curable state, while for those relatives in whom the GPV can be excluded, such programs are not required [10]. In most CPS, the variant's penetrance and the clinical phenotype are highly variable within affected families making accurate genetic counselling difficult. Knowledge of a predisposition can also be essential for therapeutic decisions in initial tumour management due to possible excessive toxicity of radiotherapy or specific chemotherapy as well as increased risk of inducing secondary malignancies. Likewise, paediatric oncologists need to be aware of additional features that could be part of the genetic syndrome and may ask for medical intervention or monitoring (Table 2).

The aim of this paper is to describe main solid VRTs occurring in paediatric and young adult patients associated with CPSs in order to guide clinicians in their day-to-day management of these patients.

2. Adrenal cortical tumors and choroid plexus carcinomas

The most frequent CPSs associated to adrenal cortical tumor are heritable *TP53*-related cancer syndromes (Li Fraumeni syndrome, LFS) and Beckwith-Wiedemann syndrome (BWS). Median age at adrenocortical carcinoma (ACC) onset is 1 year (range, 0.5–41).

2.1. ACC in heritable TP53-related cancer syndromes

In the French study, 17 of 77 (22 %) paediatric patients with adrenal cortical tumours, independently of the histology grade, had a germline *TP53* variant, prompting systematic genetic counselling regardless of the histological grade of the adrenal cortical tumor [11]. In Europe, up to 45–50 % of patients with ACC, choroid plexus carcinoma (CPC) or

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hypodiploid acute lymphoblastic leukaemia (HALL) carry a *TP53* germline variant. These numbers are higher in South-America (up to 80 %) due to the Brazilian founder variant. Germline pathogenic variations of *TP53* predispose to LFS, more recently denominated under the term of heritable *TP53*-related cancer syndromes, a cancer predisposition disorder inherited in an autosomal dominant manner. The P53 protein is involved in the control of cell growth and genomic integrity. LFS is characterised by a broad spectrum of early onset cancers, especially in children and young adults, and a risk of developing multiple primary tumours. Classically, diagnosis is identified by updated Chompret criteria, including the familial presentation with history of early onset cancers, presence of multiple primitive tumours (mainly bone or soft tissue sarcomas, breast cancers and CNS tumours), and rare tumours such as ACC, CPC, or rhabdomyosarcoma of anaplastic subtype irrespective of family history [10]. For all tumours related to this CPS, the aim is to adapt genotoxic therapies or tumour imaging surveillance whenever possible, while simultaneously avoiding risks of under-therapy for the first cancer. Notably, most of drugs commonly used in cancer treatment, except microtubule poisons (such as vincristine or taxanes), are highly genotoxic and may also contribute to the development of second malignancies [12,13]. In patients with GPV in *TP53*, radiotherapy should be omitted whenever possible. When indicated, the dose of radiation to the tumour should be standard, but irradiated normal tissue volumes should be reduced by improving spatial tumour targeting and limiting low non-target doses from image guidance and stray radiation, with the use of precision radiotherapy including proton therapy [14]. In line with this, the EXPeRT consensus recommendations for pediatric ACC advice to avoid radiotherapy in pediatric patients with ACC due to its mutagenic effects and limited data on efficacy [15]. Guidelines have been developed to determine which patients should be referred for genetic consultation [10] (TP53-Surveillance-Guideline—ERN-GENTURIS-Version7011.pdf). In carriers of germline *TP53* variants, surveillance protocols, with periodic clinical examination, and with non-ionising imaging such as whole-body magnetic resonance imaging (MRI) without gadolinium, brain MRI and abdominal ultrasound (US), should be recommended early on [16]. These programmes improve patient outcome and are frequently personalised according to the type of GPV, residual activity of *TP53* when information is available, familial history, family opinion, and data from literature (Table 3).

Table 1
When to consider a cancer predisposition syndrome (CPS) in children with a very rare tumour (VRT)?.

Highly suggestive situations:
1. Children with some CPS may have specific phenotypic features. Examples include Noonan syndrome, neurofibromatosis type 1, Beckwith-Wiedemann syndrome, severe photosensitivity with skin pigmentary changes in xeroderma pigmentosum, etc.
2. Specific cancer types, due to the high percentage of CPS cases among patients with these cancer types, such as adrenocortical carcinoma, choroid plexus carcinoma, hypodiploid ALL, pleuropulmonary blastoma, neuroendocrine tumours, colorectal carcinoma, Sertoli Leydig ovarian tumours, paediatric melanoma, AT/RT, retinoblastoma, etc.
3. Beyond histopathological features, specific tumour genomic signatures, such as chromothripsis in medulloblastoma or hypermutations in high grade gliomas, microsatellite instability in colorectal carcinoma, etc.
4. Presence of secondary, bilateral, multifocal, metachronous neoplasms such as secondary undifferentiated sarcomas within or not a previous irradiation field.
5. Some specific CPS, such as Fanconi anaemia, ataxia telangiectasia, xeroderma pigmentosum or Nijmegen breakage syndrome among others, are associated with severe side effects when affected individuals are exposed to standard doses of chemotherapy; unusual toxicity of the treatments.

Additional situations:
6. Early occurrence of an adult type cancer, such as melanoma, colonic cancer or thyroid carcinoma
7. Identification, by analysis of the tumour, of a genetic variant in a cancer predisposition gene that may be of germline origin
8. Specific family criteria:
   1. Associated benign lesions such as multinodular goitre (DICER1 syndrome) meningiomas (NF2), schwannomatosis (rhabdoid syndrome) and rhabdomyoma (Gorlin).

Abbreviations: CPS, cancer predisposition syndrome; yo, year old; ALL, acute lymphoid leukaemia.

2.2. *ACC in Beckwith-Wiedemann syndrome*

BWS is considered as a CPS with an overall incidence of malignant tumours estimated at 5–10 %. The most common types of embryonal tumours are Wilms tumour (WT, 52 % of all tumours among BWS patients), hepatoblastoma (14 %), neuroblastoma (10 %),

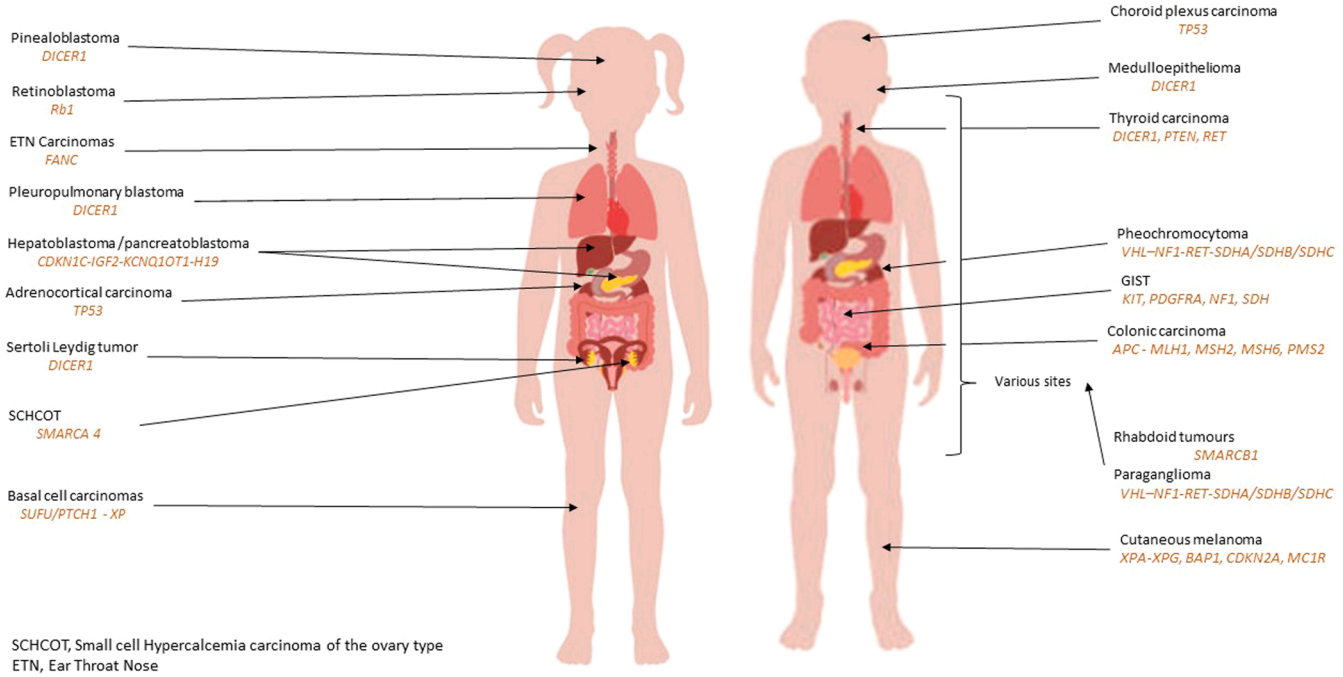

Fig. 1. Distribution of main very rare tumors in children with a cancer predisposition syndrome (Germline predisposing pathogenic variants).

Table 2
Main associated CPSs with very rare tumours occurring during childhood and adolescence.

CPS	Gene involved	Types of very rare tumours	Frequently associated tumours	Other pathologic features	Risk of unusual chemotherapy toxicity	Risk of secondary malignancies induced by therapies
Li Fraumeni syndrome	*TP53*	Adrenocortical tumours, carcinoma, choroid plexus carcinoma, lung carcinomas.	Bone sarcomas, breast cancers, high-grade gliomas	-	No	+++
VHL, SDHA/SDHB/ NF1, MEN2, MEN1	*SDHx*, *TMEM127*, *MAX*, *FH*, *RET*, *NF1*, *VHL*, *MEN1*	Neuroendocrine tumours, pheochromocytoma, paraganglioma,	Depending on associated CPS	Depending on associated CPS	No	No
DICER1-related predisposition syndrome	*DICER 1*	PPB, Sertoli Leydig, medulloepithelioma, Differentiated thyroid carcinomas, anaplastic renal sarcoma, pinealoblastoma, cervical RMS.	-	Multinodular thyroid goitre, lung/renal cysts	No	No
Lynch/cMMRD	*MLH1, MSH2, MSH6, PMS2*	Colonic carcinoma	High-grade glioma, haemopathy	-	No	Unknown
Familial adenomatous polyposis	*APC*	Colonic carcinoma, medulloblastoma, hepatoblastoma	-	Desmoid fibromatosis type	No	No
Xeroderma pigmentosum	*XP A-V*	Cutaneous carcinomas, melanoma, internal tumours	-	Skin xerosis, atrophy, wrinkling, telangiectasia, early-onset lentigos and poikiloderma	Yes	++
Beckwith-Wiedemann syndrome	11p 15.5 imprinting dysregulation	Pancreatoblastoma, hepatoblastoma, adrenocortical carcinoma	Nephroblastoma, neuroblastoma	Macrosomia, hemihypertrophy, limb length discrepancy, distinctive facial appearance, abdominal wall defects (omphalocele, umbilical hernia, or diastasis recti), organomegaly (could involve liver, kidneys, spleen, pancreas, thymus, heart, and adrenal glands), nephrological abnormalities (kidney malformations +/- hydronephrosis), cardiac anomalies (persistent ductus arteriosus, persistent foramen ovale, and congenital long QT syndrome), hypotonia. Dysmorphic facies and macroglossia.	No	No
Fanconi anaemia	*FANC* genes	Head and Neck Carcinomas, Oral and gynaecological squamous cell carcinoma	Bone marrow failure, myelodysplasia, and leukaemia.	Short stature, skin pigmentary changes, upper limb malformations, male genitalia abnormalities, microcephaly, ophthalmic and renal abnormalities.	Yes	Unknown
Bannayan-Riley-Ruvalcaba (PTEN), DICER, MEN2	*PTEN*, *DICER1* *RET*	Differentiated Thyroid carcinomas Medullary thyroid carcinoma	Depending on associated CPS	Depending on associated CPS	No	No
Gorlin Goltz	*PTCH1 /SUFU*	Basal cell carcinoma, rhabdomyoma, rhabdomyosarcoma	Medulloblastoma, meningioma	Macrocephalia	No	++
Albinism, Werner syndrome	Various: *CDKN2A,* CDK4	Cutaneous melanoma	Oculo-cutaneous presentation	Albinism: absence of colour in the skin, hair, or eyes, patches of skin that have an absence of colour, strabismus, photophobia, and nystagmus.	No	++
Familial melanoma	*CDKN2A* *CDKN2A-CDKN2B deletion*	Cutaneous melanoma	Pancreatic cancer Sarcoma, Neural System Tumors, Hematological cancers	Neurofibroma	No Unknown	No Unknown
	MC1R		-	-	-	-
BAP1-CPS	*BAP1*	Cutaneous melanoma	Mainly adult mesothelioma, renal carcinoma, uveal melanoma	Pigmented or not pigmented Melanocytic tumors	Unknown	Unknown

(*continued on next page*)

Table 2 (*continued*)

CPS	Gene involved	Types of very rare tumours	Frequently associated tumours	Other pathologic features	Risk of unusual chemotherapy toxicity	Risk of secondary malignancies induced by therapies
Neurofibromatosis Type 1, Carney-Stratakis, KIT, PDGFR germline PV variant, SDH CPS	*KIT, PDGFRA, NF1, SDH A-D*	GIST	Depending on associated CPS	Cutaneous neurofibroma, Café -au-lait spot, plexiform neurofibroma (if NF1)	No	No
SMARCA4	*SMARCA4*	Small cell Hypercalcemia carcinoma of the ovary type, rhabdoid tumor	-	-	No	Unknown
Rhabdoid tumor predisposition syndrome	*SMARCB1*	ATRT, soft part rhabdoid tumour, renal/hepatic RT	-	Schwannomatosis	No	Unknown
Retinoblastoma	*RB*	Retinoblastoma, sarcomas, carcinomas, pinealoblastoma	-	Developmental retardation (if large chromosomal 13 deletion).	No	+++

Abbreviations: AT/ RT, atypical tumour/ rhabdoid tumour; PPB, pleuropulmonary blastoma; RMS, rhabdomyosarcoma; PV, pathogenic variant; CPS cancer predisposition syndrome; GIST, gastrointestinal stromal tumour; RT, rhabdoid tumour.

rhabdomyosarcoma (5 %), and ACC in 3 % of them [17]. Most cancers occur during the first 2 years of life, and the risk of cancer development declines progressively, approaching the risk in the general population after puberty. There is no known increased risk for cancer development in adults with BWS [17,18]. Beckwith-Wiedemann syndrome (BWS), considered as the most common form of lateralized overgrowth syndromes, is a multisystemic genomic imprinting disorder with predisposition to cancer [17,19,20]. The clinical presentation is variable, with some cases lacking some or even all of the characteristic features of the classical BWS, which include among others macroglossia, omphalocele, hemihypertrophy, visceralomegaly, and metabolic abnormalities [17, 19,20]. The prevalence of BWS in population-based studies is estimated at 1/10,300–13,700 although true prevalence rates are thought to be higher due to unrecognized milder phenotypes [17,19]. Most BWS cases are sporadic, inheritance was determined in about 15 % of cases [17]. BWS is associated with abnormal regulation of gene transcription in two imprinted domains on chromosome 11p15.5, which controls the normal regulation of foetal and postnatal growth genes through a process called methylation. Recent advances in the understanding of genotype-phenotype association in BWS show different tumour risk patterns related to molecular subtype. According to the recent international consensus for BWS, for patients with IC1 gain of methylation (IC1 GOM) subtype, the overall risk of malignant tumours is 28 %, compared to lower rates in pUPD11 (16 %), *CDKN1C* (6.9 %) and IC2 LOM (2.6 %) [17]. European guidelines for tumour surveillance are based on the variable risk for malignant embryonal tumours of each molecular subtype and include abdominal US every 3 months until age 7 years for patients with BWS due to IC1 GOM, pUPD11, *CDKN1C* GPV s and other chromosome alternations of the BWS region [18]. A similar approach was suggested by Mass et al. supporting different surveillance approaches depending on the genetic subtype [20]. However, guidelines developed by the American Association for Cancer Research (AACR) Childhood Predisposition Workshop follow an inclusive recommendation regardless of the molecular subtype, abdominal (US every 3 months until the age of 4, and renal US every 3 months from age 4–7 years for all patients with BWS. In addition, patients with *CDKN1C* GPV, who have the highest risk of neuroblastoma among BWS patients, should monitor urine vanillylmandelic acid (VMA), homovanellic acid (HVA) and chest X-ray surveillance every 3 months until the age of 6 years and every 6 months from age 6–10. Children with BWS caused by genome-wide paternal isodisomy (GWpUPD) have been reported to have additional tumours and should be monitored closely [21]. Treatment of tumours associated with BWS follows the usual treatment protocols, with similar survival rates. As in other CPSs, in children with BWS and WT, nephron sparing surgery is recommended, if possible, given the increased risk for bilateral disease [17,18,21].

3. Pleuropulmonary blastoma, ovarian Sertoli-Leydig cell tumour and thyroid carcinoma in DICER1 Syndrome

DICER1 variants were first discovered in children with PPB, which is considered the main tumour type of DICER1 syndrome [22]. Subsequently, the association with ovarian Sertoli-Leydig cell tumour and gynandroblastoma (mixed tumours with portions of a Sertoli-Leydig cell tumour and a juvenile granulosa cell tumour), ocular medulloepithelioma, cystic nephroma, botryoid rhabdomyosarcoma of the genitourinary tract, pinealoblastoma, and differentiated thyroid carcinoma were described [23,24]. In addition, one of the most frequent neoplastic finding is nodular goiter [25]. The spectrum of DICER1 syndrome is now broadening with the description of other non-malignant VRTs such as nasal mesenchymal hamartomas and pituitary blastomas. An analyse from three large cohorts revealed that by age of 10 years, 5.3 % (95 % CI,

Table 3
Surveillance programme for carriers of germline disease-causing *TP53* variants[9].

Examination	Periodicity	Age to start	Age to end	Condition
Clinical examination*	Every 6 months	Birth	17 years	
	Annual	18 years	-	
Whole body MRI without gadolinium	Annual	Birth	-	High cancer risk *TP53* pathogenic variant or previous therapy
		18 years	-	
Breast MRI	Annual	20 years	65 years	
Brain MRI (1st with gadolinium)		Birth	18 years	High cancer risk *TP53* pathogenic variant
	Annual	18 years	50 years	
Abdominal ultrasound	Every 6 months	Birth	18 years	
Urine steroids	Every 6 months	Birth	18 years	If poor abdominal US quality to follow adrenal glands
Coloscopy	Every 5 years	18 years	-	If previous abdominal radiotherapy or familial history of colonic cancer

* Specific interests: virilization sign, precocious puberty, high blood pressure, and, if previous radiotherapy basal cell carcinomas in radiotherapy fields.

Table 4
Main *DICER1* associated tumours, typical age at manifestation and recommended surveillance, according to Schultz et al.[21].

Organ system / diagnoses	Childhood (1.–10. Y)	Adolescents (11.–19. Y)	Screening
Lungs:			Chest X-ray at birth, then 2 – 3 times per year until 8 years
– Lung cysts	+++	-	
– Pleuropulmonary blastoma*	+++	(+)	
Thyroid gland:			Thyroid ultrasound at 8 years, then every 3 years
– Multinodular goitre	(+)	+++	
– Differentiated Thyroid carcinoma	-	+	
Urogenital tract (girls/women):			Pelvic ultrasound every 6 months from 8th to 40th year of life
– Sertoli-Leydig cell tumour*	(+)	++	
– Cervical rhabdomyosarcoma*	-	+	
Kidney:			Abdominal ultrasound every 6 months from 6th month until 8th year of life, then once a year until 12th year of life
– Cystic nephroma	++	(+)	
– Nephroblastoma	++	(+)	
CNS / eyes			Clinical and ophthalmological assessment every 12 months
– Medulloepithelioma*	+	+	
– Pinealoblastoma*, others	+	+	

Abbreviations: CNS, central nervous system.
* Tumour frequently related to DICER syndrome.

0.6–9.7 %) of non-proband DICER1 carriers had developed a neoplasm (females, 4.0 %; males, 6.6 %) and by age 50 years, 19.3 % (95 % CI, 8.4–29.0 %) [26]. Risk for thyroid carcinoma begins at younger than age 10 years and continues into adulthood. DICER1 is a tumour suppressor gene that encodes an endoribonuclease, which cleaves double-stranded precursor microRNAs, thereby critically interfering with the regulation of expression of numerous genes [27]. GPVs are inherited in an autosomal dominant manner, but de novo variants are observed in about one fifth of cases. Remarkably, the variant's penetrance and the clinical phenotype are highly variable within affected families [28]. The prevalence of *DICER1* variants in the population is estimated to be 1:255–1:10,000. DICER1 syndrome needs to be considered in specific tumours based on minor or major criteria (Table 2).

In case a tumour of the DICER1 spectrum is diagnosed, genetic counselling and testing is indicated for early referral to a surveillance programme. It has been demonstrated that diagnosis of early-stage PPB can result in complete remission and improved survival as some of the more aggressive types evolve from lower stage disease [29]. As with other CPSs, the tumour risk varies depending on the tumour type and age but with a relative low penetrance. Accordingly, the surveillance programme must be adjusted with age and continued into adulthood (Table 4) [30]. Finally, it should be noted that all *DICER1*-associated tumours are classified as VRTs. For these, national and international network and registry structures have been established based on which treatment recommendations have been developed [29].

4. Nevoid basal cell carcinoma

GPV in genes of the Hedgehog signalling pathway (*PTCH1*, *SUFU,* and rarely *PTHC2)* predispose to Gorlin Goltz or nevoid basal cell carcinoma syndrome (NBCCS), an autosomal dominant CPS, associated with developmental abnormalities and a broad spectrum of benign and malignant tumours. Approximately 60 % had the typical phenotypic features with macrocephaly, frontal bossing, coarse facial features, palmar/planta pits, and/or skeletal abnormalities, e.g. of the ribs and vertebrae. Multiple basal cell carcinomas and odontogenic keratocysts contribute to the burden of NBCCS [31]. The median number of nevoid basal cell carcinomas developing during lifetime ranges from 8 to over 1000. The age of onset varies highly among affected individuals, with an average onset by the age of 20, but it was reported as early as the first year of life in *PTCH1* GPV [32]. Medulloblastomas occur in 2–5 % of patients, mostly before the age of 3 years, with a male predominance. In this syndrome, a higher prevalence of medulloblastoma is described in patients with *SUFU* (negative regulator of hedgehog signalling) pathogenic variant with a cumulative risk of medulloblastoma estimated at 13.3 % compared to < 2 % in those with *PTCH1* variant [33]. Meningioma, ovarian and cardiac fibroma, sarcoma, and differentiated thyroid carcinoma have also been reported [34]. Due to the risk of developing multiple NBCCs and meningioma in the radiation field, early identification of variant carriers is important to avoid radiation therapy whenever possible [35]. Follow-up is recommended annually and depends on the genetic background (e.g. no routine brain MRI in carriers of GPV in *PTCH1*) [34].

5. Gastrointestinal stromal tumours

Gastrointestinal stromal tumours (GISTs) are rare tumours mostly manifesting in the stomach and small intestine. Syndromic GISTs are typically multiple, tend to present at a younger age and are associated with distinctive clinical features of the underlying condition [36]. In approximately 5 % of patients, GIST is one of a number of familial predisposing syndromes that harbour germline alterations in *KIT*, *PDGFRA*, *NF1,* and *SDH* subunits [37,38]. These include neurofibromatosis type 1 (NF1) caused by *NF1* GPV, familial GIST syndrome resulting from *KIT* or *PDGFRA* germline alterations, and succinate dehydrogenase (SDH) wild-type GISTs lacking *KIT* and *PDGFRA* variants [37]. NF1 predisposes to other benign and malignant tumours, i.e. cutaneous and plexiform neurofibroma, optic glioma, malignant peripheral nerve sheath tumour, pheochromocytoma, breast cancer, and juvenile myelomonocytic leukemia [39]. Hereditary Paraganglioma-Pheochromocytoma Syndrome" (PGL/PCC) is caused by inactivating germline variants or large deletions in *SDHB*, *SDHC,* or *SDHD* (rarely *SDHA*) genes encoding B/C/D/A SDH subunits and is characterized by gastric GIST and paraganglioma (see chapter 11-c) [40].

Penetrance of *SDH* GPV is quite low suggesting that genetic counselling should be propose to all patients with *KIT/PDGFRA*-wild type GISTs, regardless of their history of syndromic features [41]. Periodic computed-tomography-scan or 18F-FDG PET computed tomography have been suggested for surveillance, associated to Neck and abdominal MRI with plasmatic/urinary tests [36]. Specific therapeutic management must be proposed for these syndromic GISTs, in particular because of their intrinsic resistance to the TKIs classically proposed in adults as first line.

6. Rhabdoid tumours

Rhabdoid tumours (RTs) are rare and aggressive cancers of infancy that affect the central nervous system (CNS) in 2/3 of cases, but also extra-cranial locations such as kidney, liver, and soft tissues [42]. In

more than 90 % of cases, they are due to a biallelic somatic PV in *SMARCB1*, a constant member of the SWI/SNF chromatin remodeler. In the few remaining cases, *SMARCA4* is inactivated instead of *SMARCB1* [43]. Multifocal synchronous or asynchronous RTs, along with rare familial cases, have highlighted the existence of a genetic predisposition syndrome. The current estimation of germline pathogenic variants among patients with RTs is approximately 20 %. Most cases are due to *de novo* GPV s, with a high penetrance of early onset (before 2 years of age in general) of tumours. Rarely, GPV are inherited. Most RT predisposition syndromes (RTPS) due to GPVs in *SMARCB1* (*RTPS1*) result from truncating variants, while missense GPVs in *SMARCB1* rather expose to schwannomatosis. Despite a relatively strong phenotype to genotype correlation, some patients or families may have overlapping phenotypes. The exact tumor spectrum of *RTPS1* may not be fully recognized since patients die early; adults may be exposed to rare sarcomas or brain tumours. Finally, GPVs in *SMARCA4* account for the rare patients with RT and no *SMARCB1* GPV (RTPS2); families with RTPS2 are mainly affected by ovarian small cell carcinoma, hypercalcaemic type (SCHCOT), which share some features with RTs [44]. However, it appears that the penetrance of RTPS2 is much lower, with so far only one family reported to show both RTS and SCCOHT; conversely, RTPS1 does not expose to SCCOHT, suggesting a "preferential" tumour risk for each RTPS.

7. Skin carcinoma and melanoma

Cutaneous melanoma is a malignant tumor of the skin resulting from the transformation of melanocytes, cells derived from the neural crest, specialized in the production of photoprotective pigments. Pediatric cases of this cancer are very rare in European countries, with a stable pre-pubertal incidence rate involving < 1 in 100,000 persons per year, in contrast to adolescent melanoma, whose incidence has been increasing for more than 20 years, in connection with unprotected sun exposure [45]. Pediatric melanoma also represents a very heterogeneous group of malignancies with clinical, histologic, and genetic features different from adult melanoma; moreover, prognosis is variable among subtypes [46,47]. In some cases, paediatric melanoma is capable of invading regional lymph nodes, but when the metastasis is surgically removed, the child is cured of the disease. In other cases, melanoma unfortunately sometimes progresses dramatically, causing the death of the child.

To date, the risk factors for childhood melanoma include: giant congenital melanocytic nevi (GCN), transplacental metastasis from a mother with melanoma, inherited diseases such as xeroderma pigmentosum, immunodeficiency and albinism [48]. In congenital nevi (CN), *de novo* mutations occurring post-zygotically affecting a single oncogene have been identified. These are either $NRAS^{Q61R}$ mutations [49] or *BRAF* chromosomal translocations [50], as well as rare translocations. The risk of transformation of a CN into melanoma is estimated at 1–2 %, this risk can reach 10–15 % for GCN [51].

Melanomas can occur in children in the context of Xeroderma Pigmentosum (XP), an autosomal recessive disease but sometimes in an apparently sporadic manner. Patients with XP develop numerous precancerous actinic keratosis lesions early in life with later development, if not excised, of skin cancers with, in order of frequency, squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. In patients with XP, the mean age for the first non-melanoma and melanoma tumour are 9 and 22 years versus 67 and 55 years in patients without XP. XP is a rare autosomal recessive DNA repair-deficiency disorder that predisposes to cancer, especially skin cancer, but also leukaemia and multiple other tumours such as cerebral and spinal gliomas and various solid tumours of the internal organs. Height nucleotide excision repair (NER) proteins and their genes have been shown to cause XP (*XPA, XPB, XPC, XPD; XPE, XPF, XPG* and *XPV*). *XPA* to *XPG* are involved in different steps of NER in the presence of DNA damage, whereas *XPV* is involved in the post replication repair of damaged DNA [52]. Diagnosis is usually easy when XP is already diagnosed in the family, but more difficult in case of an unremarkable family history. Children are born with a normal skin appearance, but then show extreme sensitivity to sun exposure with severe or exaggerated tanning, burning or blistering. Over time, the skin undergoes premature ageing, with progressive xerosis, atrophy, wrinkling, telangiectasia, early-onset lentigines which increase in size, number and colour, and poikiloderma. The anterior part of the eye is particularly susceptible to the damaging effects of ultraviolet radiation (UVR), and 90 % of XP patients present an ocular involvement leading to severe visual impairment. The cutaneous features of XP, their progression and patients' propensity to early-onset cancer result from an accumulation of UVR-induced photoproducts and unrepaired DNA damage [52]. Oxidative stress and the cumulative DNA damage in neurons are responsible for neurodegeneration. Multiple skin tumours are common on sun-exposed areas and the prevention of these lesions relies on an aggressive attitude of non-sun exposure. Regular (at least every 3 months) paediatric, dermatological, ophthalmological, and neurological follow-up is essential. Early excision of every skin lesion with pathological finding is necessary to avoid progression of precancerous lesions and to diagnose skin cancers at an early stage [53]. Treatment of skin cancer relies primarily on early excision of each suspicious lesion. Targeted therapy, such as BRAF and MEK inhibitors, check point inhibitors, and CTLA-4 inhibitor, seems to be effective and well-tolerated for melanomas or huge skin cancers in XP [54,55]. Chemotherapy and radiotherapy should be used with caution as in other DNA repair deficiencies due to the high risk of severe toxicity. XP patients are also predisposed to internal cancers with CNS tumours, haematological malignancies, thyroid and gynaecological tumours. XP-C patients appear to be at highest risk for internal tumours [56]. Specific information and follow-up for early diagnosis of internal tumours is mandatory for these patients.

The aetiology of other melanomas, out of the XP syndrome, in children is not fully understood, though several risk factors have been identified and the aetiology is multifactorial [57]. One of the most important risk factors for melanoma is exposure to ultraviolet (UV) radiation [58]. Children who spend a lot of time outdoors without adequate protection are at a higher risk of developing melanoma. Furthermore, children with specific phenotypic characteristics such as fair skin, light hair, light-coloured eyes, freckling, dysplastic nevi, or numerous melanocytic nevi, may have a higher risk of melanoma. Other risk factors for melanoma in children include genetic susceptibility. Familial melanoma is defined by the presence of at least two cases in first-degree relatives. Up to 10 melanoma susceptibility genes with high penetrance have been described; among them, *CDKN2A* is the gene most frequently implicated in familial forms of adult skin melanoma [59]. However, various studies in young people who developed melanoma before the age of 18 years, have shown that germline mutations in genes predisposing to adult melanoma, including *CDKN2A*, are very rare [60,61]. Few cutaneous melanoma cases between 9 and 14 years were reported in either *CDKN2A/P16* + or *CDKN2A/P16*- families [62]. However, current guidelines do not recommend adult melanoma predisposing genes testing in minors as sun protection for prevention must be independent of child-carrier status, to avoid phenocopies in adulthood [62,63]. A particular very rare syndrome involving *CDKN2A* has also been described, OMIM 155755 (https://omim.org/entry/155755) named melanoma-astrocytoma syndrome, associated with large germline deletion at 9p21 locus. These genomic deletions encompass the *CDKN2A* (encoding $p16^{INK4A}$ and $p14^{ARF}$ proteins) and *CDKN2B* (encoding $p15^{INK4B}$ protein) tumor suppressor genes as well as *CDKN2BAS,* an antisense noncoding RNA also designated as ANRIL [64]. Adult and children cancers observed were mainly cutaneous melanomas, various neural system tumours including benign neurofibromas various haematological cancers [65]. Interestingly, a large *de novo* 9p21 deletion identified in monozygotic twins caused an astrocytoma at 10 years in one twin and was followed by the occurrence of several IR-induced scalp melanomas [66].

BAP1 tumor suppressor gene has been originally identified as a binding partner of *BRCA1*. It encodes a desubiquitinase, regulating many important cellular functions, such as DNA repair and replication, transcriptional regulation of development/ differentiation, cell cycle, metabolism, apoptosis/cell survival, ferroptosis [67]. Pediatric melanocytic lesions with loss of BAP1 protein expression related to two *BAP1* somatic inactivating events constitute a separate entity [68]. However, underlying germline mutations are rare (12 %) and mainly identified in children with a family history of adult cancers suggestive of the *BAP1* syndrome (mesothelioma, uveal melanoma, melanocytic tumors and cutaneous melanoma, clear –cell renal cancers) [69]. Current *BAP1* carriers guidelines includes dermatological exam starting at 18–20 years [70]; however, two 8 years old melanoma-affected children have been reported in Australia (unpublished observations, in [70]). Other genetic syndromes that increase the risk of melanoma include XP (see above) along with LFS [70].

The observation of a greater frequency of CN in red-haired children in England served as a hypothesis to search for a possible role of the *MC1R* gene on the occurrence of CN and pediatric melanoma. This gene encodes a protein which is a receptor located in the outer membrane of melanocytes. Its role is to activate signalling pathways allowing the proliferation of melanocytes and the synthesis of photoprotective pigments, in response to exposure to ultraviolet (UV) rays. In mammals, the pigmentation of the skin, hair and hair results from the ratio between pheomelanin, yellow/red and eumelanin, dark. Pheomelanin is the base pigment; its synthesis induces a depletion of glutathione, a trap for free radicals, hence an increase in these independently of exposure to UV [71]. Activation of the *MC1R* receptor allows the synthesis of eumelanin which, on the contrary, absorbs free radicals. During human evolution, mutations have occurred in the *MC1R* gene allowing lightening of the skin for the synthesis of Vitamin D, in adaptation to a life in regions less sunny than Africa, the cradle of humanity. Some genetic variants of *MC1R* produce a less efficient receptor, leading to less or no synthesis of eumelanin; the so-called RHC (Red Hair Color) genetic variants produce a completely deficient MC1R receptor; the individual then only synthesizes pheomelanin. In some individuals, *MC1R* gene variants may be masked by a dark phototype but are still associated with an increased risk of melanoma in adults (PMID: 29795986); these variants are more common in children with CN or pediatric/adolescent. The role of other constitutional factors and environmental influences is currently being further investigated in an EU/founded international project (MELCAYA / https://www.melcaya.eu/).

8. Retinoblastoma

Retinoblastoma is the most frequent paediatric neoplasm arising in the developing retina with a worldwide incidence of between 1/15,000 and 1/20,000 live births. In high-income countries, patients with unilateral disease are diagnosed around two years of age, while bilateral disease is detected at a median age of one year. The *RB1* gene was identified early on as a tumour suppressor gene and used to validate Knudson's two-hit hypothesis: cells bearing a double hit on both *RB1* alleles almost irremediably transform to retinoblastoma cells. Penetrance is approximately 90 %, though this figure varies according to the variant and parental allele [72]. Heterozygous GPV s of *RB1* define a heritable predisposition that gives rise to retinoblastoma when a secondary somatic event occurs in the retina. In the heritable form of the disease, the first hit on the *RB1* gene is present in the germline, thus defining a predisposition state. Alternatively, non-heritable retinoblastomas most often appear when two somatic events inactivate *RB1*. Such a genetic model of tumorigenesis is sufficient for adequate genetic counselling, but genetic analysis of the *RB1* gene cannot solve every case with suspected hereditary retinoblastoma [72]. All children with retinoblastoma must be tested for germline predisposition, without consideration of age of onset or laterality. The importance of identifying a germline hit lies in the oncological risk for the patient (risk of relapse, risk of bi/-trilateral disease, risk of second tumours) and for the patient's relatives. Radiotherapy during first line of treatment likely contributed to the significantly increased risks observed for cancers of the brain, nasal cavities, and orbit in retinoblastoma survivors. Recent protocols without any radiotherapy may lead to an important reduction in secondary malignancies. The increased risk of melanoma is probably due to factors independent of radiation, because risks were elevated in both irradiated and non-irradiated patients [73].

9. Head-and-neck and gynaecologic squamous cell carcinomas

Fanconi Anemia (FA) is associated with an increased number of solid tumours, mostly in older patients, life-time risk is reported to be 20 % by the age of 48 [74]. The most frequently diagnosed solid tumours include early onset head and neck squamous cell carcinoma (HNSCC) with oral and gynaecological squamous cell carcinoma (SCC). Other less frequent solid tumours include brain malignancies, WT, neuroblastoma, hepatoblastoma and renal cell sarcoma. Solid tumours occur more frequently in patients with FA who underwent haematopoietic stem cell transplantation (HSCT), due to DNA damaging chemotherapy and graft versus host disease (GVHD) of epithelial surfaces [74,75]. FA is caused by GPVs in one of the at least 23 *FANC* genes resulting in defective DNA repair. FA is an inherited in an autosomal recessive manner leading to chromosomal instability. It is characterized by congenital malformations, progressive bone marrow failure (BMF), and susceptibility to malignancy. Although rare, FA is the most common congenital BMF syndrome with an estimated prevalence of 1:130,000. FA is found in every ethnic group, but higher rates were reported in specific populations, mainly due to founder effects or consanguinity [75,76]. FA is a multi-system disease with highly variable clinical presentation. The most frequent abnormalities include short stature, skin pigmentary changes, upper limb malformations, male genitalia abnormalities, microcephaly, and ophthalmic and renal abnormalities. However, approximately one third of FA patients do not present with apparent malformations. There is a well-established genotype-phenotype correlation in many clinical manifestations of FA. Similarly, cancer risk depends on the genetic subtype, with rare solid tumours more prevalent among patients with biallelic GPV s in *FANCD1/BRCA2* [74,75]. The diagnosis of FA relies on chromosomal breakage studies as well as molecular studies using either dedicated gene panels or whole exome sequencing. The most common FA-associated malignancies include acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS).

Due to defective DNA repair, treatment of malignant tumours in FA patients with DNA damaging drugs and/or radiation therapy is challenging, requiring experienced multidisciplinary efforts by surgeons, radiotherapists, medical oncologists and other FA specialists to provide the best comprehensive care. Affected patients are at high risk of excessive toxicity and second malignancies. Surveillance recommendations for non-HNSCC and non-gynaecological SCC were recently published, supporting the use of MRI and US imaging rather than X-ray and CT studies to avoid radiation-induced DNA damage. FA patients should undergo periodic ear-nose-throat, gastroenterology, oral, dermatological and gynaecological evaluation to detect early epithelial lesions.

10. Colorectal cancers

Colorectal cancer (CRC) is one of the most common cancer types in adults worldwide. Most CRC cases are sporadic (70–80 %), with 20–30 % showing evidence for familial disease, and 5–10 % related to a known genetic syndrome [77]. Hereditary CRC is associated with other extracolonic cancer risks and is traditionally divided into non-polyposis and polyposis syndromes. Hereditary nonpolyposis colorectal cancer (Lynch syndrome) is the most common of the hereditary colon cancers. However, as colon cancers associated with Lynch syndrome almost always presents at adulthood, this review will focus on the CPS that could present at childhood.

10.1. Peutz-Jeghers syndrome (PJS)

PJS is an autosomal dominant polyposis syndrome, with multisystem involvements that include distinctive mucocutaneus freckling involving the mouth, nose, perianal area, hands and feet among others. Diagnosis of PJS is based on the presence of any one of the following: 1) At least 2 histology confirmed PJ polyps, 2) Any PJ polyp in an individual with known PJS in the family, 3) Characteristic mucocutaneous pigmentation in an individual with known family history of PJS, and 4) any number of PJ polyp in an individual with a characteristic pigmentation [78]. The prevalence estimates of PJS vary from 1/25,000 to 1/200,000. Over 90 % of individuals with PJS have *STK11* GPV. Children with PJS have early onset development of gastrointestinal hamartomatous polyps that can be found at any part of the gastrointestinal tract but are most common in the small bowel and colon. Intussusception is common, occurring in 15 % of children with PJS by age 10, and in 50 % of PJS patients by age 20 [79]. Children with PJS have increased incidence of cancer, although most cancers associated with PJS occur in adulthood including colon cancer, sex cord stromal tumors, breast, pancreatic and lung cancers among others. The overall risk of cancer in PJS is estimated at up to 50 % at 60 years, but the risk for malignancy in childhood is very low with only 2.8 % of patients diagnosed with a PJS related tumor before age 20 years [80]). Guidelines on surveillance of patients with PJS recommend upper endoscopy, colonoscopy and small-bowel capsule endoscopy beginning at age of 8 years, and to continue surveillance every 1–3 years if the initial evaluation revealed characteristic polyps. In patients with no evidence for early polyposis, further evaluations can start at age 18 years. Some authors recommend to begin surveillance at age of 18, reflecting the low identifying large polyps that can cause obstructions and intussusception, most recent guidelines support earlier rather than late initial evaluation. A yearly evaluation of testicular masses is recommended from birth. Screening for gynaecological tumors, pancreatic tumors and breast cancers begin at adulthood [81].

10.2. Constitutional mismatch repair deficiency (CMMRD)

Lynch syndrome (LS) is a CPS caused by heterozygous germline alterations in the DNA mismatch repair (*MMR*) genes and it is the most common hereditary CPS, with an estimated prevalence of 1:300 with an autosomal dominant pattern. *MMR* PGV (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) results in increased risk for early onset CRC as well as endometrial cancer, ovarian, non-colonic gastrointestinal cancers, and uro-biliary tract tumours, which typically presents from the third decade of life. CRC is only rarely observed at childhood or adolescence, but presentations at young age usually carry the acquired somatic second hit and associated high burden of mutations. Biallelic *MMR* alterations result in an aggressive form of CPS (CMMRD), presenting with early onset of various cancer types that differ from those seen in LS. Over 60 % of CMMRD patients have *PMS2* PGV. Patients with CMMRD can present with brain tumors (50 %), and haematological malignancies including lymphomas and leukemias (30 %) at childhood, and with gastrointestinal malignancies (50 %) in early adulthood. Other tumors include Wilms tumor, neuroblastoma, osteosarcoma and other rare tumors. Up to 40 % of patients will have metachronous second malignancies [82]. Patients with CMMRD typically present with café au-lait spots and other signs of neurofibromatosis like disease, agenesis of the corpus callosum, and immunoglobulin deficiencies. A scoring system that can assist in identifying patients eligible for genetic testing of CMMRD was developed by the European Consortium Care for CMMRD [83]. Surveillance for patients with CMMRD include brain MRI starting at 2 years of age, and gastrointestinal screening beginning in childhood. Colonoscopy evaluations are recommended from age of 8 years, and upper endoscopy is recommended from age of 10. There are no clear recommendations on best practice surveillance for hematologic malignancies, and careful clinical evaluation should be performed on a regular basis [82].

10.3. Juvenile polyposis syndrome (JPS)

JPS is a rare autosomal dominant familial polyposis syndrome, associated with an increased risk for gastric, small intestinal and colorectal cancer in young adulthood with occasional cases of childhood gastrointestinal malignancies. Incidence is estimated at 1/100,000. JPS presents with multiple, usually 50–100 polyps typically in the colon, but can also involve the upper gastrointestinal tract [84]. Any child with multiple juvenile polyps involving the upper and lower gastrointestinal tract, five or more juvenile polyps in the colon or any number of juvenile polyps with a family history of cancer, should be tested for JPS. Presentation in childhood usually involves episodes of severe anemia and gastrointestinal obstruction. JPS is associated with two known genes, *SMAD4* and *BMPR1A*, both encoding members of the TGF-β/BMP pathway. Furthermore, also Cowden syndrome (caused by GPVs in *PTEN*) and Gorlin syndrome (*PTCH1*) present with juvenile polyps. Nevertheless, many cases of JPS have no known genetic cause. There is 10–50 % overall risk for colon cancer in patients with JPS and a median age of 35 years [85]. Surveillance begins at age 12–15 years, unless clinically indicated earlier, and should be considered for all first-degree relatives, even if no genetic cause was identified. Patients with *SMAD4* PGV should be also evaluated for Hereditary Hemorrhagic Telangiectasia (HHT) [86].

10.4. Familial adenomatous polyposis (FAP)

FAP is an autosomal dominant disease caused by GPV s in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21, encoding a protein that acts in the WNT pathway to regulate cell cycle, apoptosis and cell adhesion. Approximately 25 % of FAP cases in children are caused by *de novo* GPVs, thus lacking the usual familial presentation [86]. Patients with FAP GPVs display early development of multiple adenomatous colorectal polyps with thousands of polyps evident in adult FAP patients. Non-colonic manifestations of FAP include osteoma of the mandible and skull, disruption of tooth development and number, retinal pigmented epithelial (REP) hamartomas, desmoid tumours, skin fibromas, epidermoid cysts and other rare features [86]. The prevalence of FAP is estimated at 1:8000. The risk of colorectal cancer increases with age, reaching almost 100 % of patients by age 40–50 years. There is evidence that different variants in the *APC* gene are related to various degrees of disease severity. The most severe presentation is usually related to variants between codon 1250–1464, in particular codon 1309 variants, and variants near the c-terminal domain usually correlate with a milder disease form and therefore surveillance in these patients usually starts later than those with GPVs associated with high-risk disease [86]. Guidelines for cancer surveillance recommend annual flexible sigmoidoscopy beginning at age 10–12 years, with transition to yearly colonoscopy once polyps are detected. Prophylactic colectomy in adolescence or early adulthood is standard, given the high rates of CRC in this population. Upper endoscopy every 1–4 years is recommended beginning at age 25–30 [87]. There is some evidence supporting the prophylactic use of non-anti-inflammatory drugs and selective COX-2 inhibitors to reduce the number and size of rectal adenomas, but the efficacy of prophylactic treatment as cancer prevention remains to be proven [87]. Patients with FAP have increased risk for development of desmoid tumours, especially following abdominal surgery. Patients with a family history of desmoid tumours should undergo an abdominal MRI every 3–5 years following abdominal surgery. Surveillance guidelines support surveillance for papillary thyroid cancer, especially in female patients beginning at age 15–18 years. There are no clear indications for imaging studies for other FAP-related tumours such as medulloblastoma and hepatoblastoma, although parents and physicians should be alert and proceed with appropriate evaluation in suspected cases [87].

11. Endocrine tumours

The diagnosis of an endocrine tumour in children and adolescents is highly suspicious of an underlying CPS including multiple endocrine neoplasia (MEN1, MEN2), hereditary paraganglioma-pheochromocytoma syndrome (HPGL), von Hippel-Lindau disease (VHL), and PTEN hamartoma tumour syndrome (PHTS, Cowden disease). Other CPS such as Neurofibromatosis type 1, LFS and LS, which are characterized by other tumour entities, are likewise associated with an increased risk for rare endocrine tumours [88]. Diagnosis of a neuroendocrine tumour (NET), ACC, or medullary thyroid carcinoma (MTC) should prompt genetic counselling and testing. Due to the predominance of pathogenic germline variants in so called pseudohypoxic genes (*VHL*, *SDH*) in children and adolescents with pheochromocytoma/paraganglioma, there is a high risk for multifocal, recurrent, and metastatic disease. Surveillance recommendations consider the age of highest risk and earliest tumour onset as well as the genetic background.

11.1. Multiple endocrine neoplasia type 1 (MEN1)

MEN1 is a rare genetic syndrome caused by GPV in *MEN1*. It predisposes to tumours of the parathyroid glands with primary hyperparathyroidism (PHPT), pancreatic islet cells, and adenohypophysis (anterior pituitary neuroendocrine tumours, PitNET). Approximately 10 % of MEN1 patients develop adrenal tumours, of which 14 % are ACCs [89]. The MEN1 tumour spectrum includes more than 20 endocrine and non-endocrine tumours occurring in various combinations. The penetrance of any neoplasia is over 50 % at age 20 years and over 95 % at age 40 years. Tumour surveillance should start at 5 years of age.

11.2. Multiple endocrine neoplasia type 2 (MEN2)

Multiple endocrine neoplasia type 2 (MEN2) comprises MEN2A and MEN2B syndrome and is caused by GPV s in the *RET* protooncogene. Patients with MEN2 mainly develop MTC (MEN2A and B), primary hyperparathyroidism (pHPT) (MEN2A), and mucosal and gastrointestinal (ganglio-)neuromas (MEN2B). Approximately 50 % of patients with MEN2 develop pheochromocytoma (PHEO) [90]. In certain GPVs in MEN2A, there is an association with cutaneous lichen amyloidosis and Hirschsprung's disease. Characteristic of MEN2B is the early onset of aggressive MTC in approximately 95 % of patients [91]. Prophylactic thyroidectomy is recommended before the age of one year and later on in MEN2A. In most cases, MTC occurs before the age of 35 and in 70 % of cases it has already metastasized to the cervical lymph nodes at the time of diagnosis. Cure in patients with MTC can only be achieved by complete surgical resection including metastases.

11.3. Hereditary paraganglioma-pheochromocytoma syndrome (HPGL)

Hereditary pheochromocytoma/paraganglioma syndromes are caused by heterozygous GPVs in *SDH*, *MAX*, *TMEM127, FH, MDH2* [92]. The clinical presentation is characterized by numerous signs and symptoms of catecholamine excess leading to arterial hypertension including hypertensive crisis among others and often have a paroxysmal nature. By definition, pheochromocytomas are located within the adrenal gland whereas paragangliomas can occur from the base of the skull, neck, upper and lower mediastinum abdomen, and to the pelvis. The secretory type including non-secreting tumours depends on the germline variant and can be used for diagnostics. In addition, HPGL is associated with GISTs, renal cell tumours, and papillary thyroid adenomas.

11.4. Von Hippel-Lindau syndrome (VHL)

Von Hippel-Lindau syndrome (VHL) is inherited in an autosomal dominant manner. VHL is caused by variants in *VHL*, encoding the VHL tumour suppressor. VHL is characterised by a wide spectrum of different tumours including early onset pheochromcytoma/paraganglioma, hemangioblastomas (HB) of the brain, spinal cord, and retina, and a predisposition to clear cell renal cell carcinoma (RCC) and renal cysts, PHEO, pancreatic cysts, and neuroendocrine tumours (NET), endolymphatic sac tumours (ELST), and cysts of the epididymis and adnexa. The penetrance of different tumours is impacted by the *VHL* variant, the latter tailoring surveillance.

11.5. PTEN hamartoma tumour syndrome (PHTS, Cowden disease)

The PTEN hamartoma tumour syndrome (PHTS) encompasses several conditions caused by variants in *PTEN*: Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-associated proteus syndrome (PS) and proteus-like syndrome. Clinically, PHTS is characterized by macrocephaly, gastrointestinal polyposis, lipomas, vascular malformations, and mental retardation/autism spectrum disorder. In addition, there is a predisposition to numerous adult onset malignancies including breast and endometrial carcinoma, colorectal carcinoma, renal cell carcinoma, melanoma, but also differentiated thyroid carcinoma. Because the expression of symptoms varies and the phenotypic characteristics are also present in the general population, PHTS diagnosis is often overlooked [93].

12. Conclusions

Treatment of children and young adolescents with VRTs is always a challenge, given the scarce data and limited experience of most paediatric oncologists. Additionally, many of them occur in the context of exceptional CPSs (Table 2). Familial predisposition to cancers adds a psychological burden on both families and physicians, with numerous surveillance measures and repeated evaluations always reminding of the possibility that their child might develop a life-threatening disease. Advances in genetic studies provide an insight into the biology of tumorigenesis and the control mechanisms of growth, cell death, and cell differentiation. At the same time, knowledge of cancer predisposition is crucial for the affected patient and the family. Early identification of a CPS and the implementation of surveillance strategies were able to identify early-stage lesions, reduce exposure to radiation in chromosomal breakage syndromes and improve overall survival. However, despite the great strides made in the care of VRTs in the context of CPS, further progress will happen if physicians are aware of the key symptoms of CPS and molecular findings and consequently initiate germline testing and / or refer patients with pediatric cancers to genetic centres for further work-up applying existing knowledge and guidelines. In addition, international collaboration of both physicians and scientists working together with families and caregivers to ensure continued improvement in survival and overall well-being are important.

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Consent statement

Not applicable.

Declaration of Competing Interest

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