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Paediatric update

Inherited cancer in children: practical/ethical problems and challenges

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Abstract

Over recent years significant molecular advances have led to a better understanding of the genetics of both syndromic and non-syndromic paediatric cancers. In addition many hereditary cancer predisposition syndromes are now recognised, some of which have implications for children in affected families. Improvements in gene mutation screening will increase the sensitivity, accuracy and therefore the applicability of genetic testing in these conditions. This review will deal with four main areas pertaining to paediatric cancer genetics (i) genetic aspects of some non-syndromic paediatric cancers (ii) paediatric cancer predisposition syndromes, (iii) the management of children in families with predominantly adult- onset cancer predisposition syndromes and (iv) special ethical, legal, social and psychological considerations in the management of children, with actual or possible genetic cancer predisposition. Current concepts and controversies in the rapidly changing field of paediatric cancer genetics will be examined in detail and the application of existing guidelines and their limitations will be discussed.

1. Introduction

The identification and clinical management of families with an inherited predisposition to cancer ('cancer families') is a good example of how advances in genetics have led to practical applications of direct benefit to individual patients. Over the last two decades, the identified number of cancer-predisposing genes has greatly increased. As a result, new health service demands have been created and 'cancer genetics' has evolved into a medical subspecialty which facilitates the timely transfer of genetic advances from the laboratory to the clinical setting ('translational research'). Until now, cancer genetics services have concentrated on advising adults from families with a genetic predisposition to common adult-onset cancers such as breast and bowel cancer. However, a growing need has now been identified for the planned management of children who may, similarly, have an inherited predisposition to cancer. In this 'Update', we aim to cover some of the relevant issues that arise in paediatric oncology. We deal with four main areas; (i) genetic aspects of some 'non-syndromic' paediatric cancers, (ii) paediatric cancer predisposition syndromes, (iii) the management of children in families with predominantly adult- onset cancer predisposition syndromes and (iv) special ethical, legal, social and psychological considerations in the management of children, with actual or possible genetic cancer predisposition.

2. Non-syndromic paediatric cancers

2.1. Wilms' tumour

Wilms' tumour (WT) of the kidney affects 1 in 10 000 children and accounts for 6–7% of all childhood cancers. The peak age of incidence is in the third and fourth years. It is usually sporadic; less than 1% of cases are familial and 2% occur in specific congenital malformation syndromes (Table 1). Linkage studies located one gene for Familial Wilms' tumour, *FWT1*, to chromosome 17p [1] and other 'familial' loci have also been identified [2]. However, the major gene implicated in WT is *WT1*, which is somatically mutated in 5–10% of sporadic cases (in the tumour cells) although not in the

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Table 1
Genes associated with Wilms' tumour (WT) predisposition

Name	Risk of Wilms' tumour (%)	Clinical features	Gene(s) involved
Syndromic			
Wilms' Tumour-Aniridia-Genito urinary Anomalies-Mental Retardation Syndrome (WAGR) syndrome	30–50	Aniridia, genitourinary abnormalities, mental retardation	Deletion of *WT1* (Wilms' tumours) and *PAX6* (aniridia) from 11p13
Beckwith Wiedemann syndrome	<10	Exomphalos, macroglossia, hyperinsulinism, hemihypertrophy	Possibly more than one gene at 11p15 inactivated by mutations or imprinting abnormalities
Denys Drash syndrome	30–50	Diffuse mesangial sclerosis, ambiguous genitalia	*WT1* missense mutations
Isolated hemihypertrophy	<2	Hemihypertrophy	
Familial WT	15–30	<1 of all WT cases	*FWT1* 17p, *FTW2* 19q13 + others
Non-syndromic			
WT1	5–10 of sporadic WT cases		*WT1*

germ-line. The molecular basis of the associated congenital malformation syndromes is summarised in Table 1.

The currently recommended screening method for children who have syndromes associated with a high risk of WT is 3–4 monthly ultrasound examination until 6–7 years of age [3], although some suggest screening beyond 7 years. The sensitivity of such screening is limited and parents should be informed of this and be vigilant for any abdominal masses; regular parental palpation of the child's abdomen between scans has also been advocated.

2.2. Retinoblastoma

Retinoblastoma (RB), an embryonic tumour of retinal origin, is caused by mutations in the *RB1* gene, which, like *WT1*, is often described as a 'tumour suppressor gene'. It has an incidence of 1 in 15 000, and accounts for 2.5–4% of all childhood cancer with 90% arising in children under 3 years of age [4]. The condition can be hereditary or sporadic and this observation led to Knudson developing the famous 'two-hit' hypothesis of tumour suppressor gene inactivation [5]. In hereditary RB, one mutated allele is inherited in the germline and loss of the second functioning allele is due to somatic inactivation. As a result, there is a 90% chance of developing RB. As there is a high new mutation rate, the family history is often negative. On the other hand, any individual with hereditary RB has a 50% chance of transmitting the mutation to their offspring. Hereditary (genetic) RB includes all multifocal (usually bilateral) RB – around 30% of the total – and also 10–15% of unilateral RB. Mosaicism can occur both in affected and unaffected individuals – in an unaffected individual mosaicism may be somatic or gonadal and will increase offspring risk. Recurrence risks are provided in Table 2. At-risk offspring or known mutation carriers should have regular and thorough ophthalmological examination under anaesthetic from birth to 5 years of age; screening protocols vary a little, but should begin at 2–3 weeks of age, occur every 3 months until the age of 18–24 months, then 4-monthly until 4 years and 6 monthly until 5 years. Genetic analysis detects approximately 90% of germline

Table 2
Risks estimates for siblings and offspring of individuals affected with retinoblastoma

Type of RB	Risk to siblings of affected child	Risk to offspring of affected individual	Molecular testing possible
Bilateral, positive FH	Up to 50% chance of being affected	Up to 50% chance of being affected	Mutation analysis (90% detection rate). Linkage
Bilateral, No FH	5%. This reduces to 1% if mutation is known in affected sib and not present in parents	Up to 50% chance of being affected	Mutation analysis (90% detection rate). Linkage exclusion
Unilateral, positive FH	Up to 50% chance of being affected	Up to 50% chance of being affected	Mutation analysis (90% detection rate). Linkage
Unilateral, No FH	1%	5–10%	Mutation analysis (10% detection rate). Linkage exclusion

RB, retinoblastoma; FH, family history (this should include history of other RB-related tumours such as osteosarcomas).

mutations and predictive testing using mutational analysis or linkage testing should be offered to the parents of at-risk neonates so that screening can be concentrated on mutation carriers.

Survivors of hereditary retinoblastoma (i.e. all bilateral cases and a proportion of unilateral cases) have an increased risk of death from second primary tumours (relative risk (RR) = 60), particularly osteosarcoma, malignant melanoma and brain tumours [52]. This risk appears to be further increased by radiotherapy [6], but applies to the whole body, not just the field of radiation. Effective screening in survivors for such tumours is difficult due to the wide variation in the sites and natural history of the tumours and is not currently advocated, with the exception of visually impaired survivors who should be examined annually for melanomas. All survivors and their medical practioners should be given general advice about potentially serious symptoms and signs to be aware of and those with intact vision should be shown how to self-examine for melanomas.

2.3. Neuroblastoma

Neuroblastoma is a malignant tumour of the primitive sympathetic nervous system and derived from the embryonic crest [7]. Its incidence is similar to Wilms' tumour (1 in 10 000) and it accounts for 5–7% of all tumours under the age of 15 years, 90% of which are diagnosed in the first 5 years of life with a mean age at diagnosis of 2 years. Less than 1% have a family history of neuroblastoma and linkage studies have localised a region on 16p12–13 which may harbour a causative gene [8,9]. As with RB, children with familial (inherited) neuroblastoma often have multiple primary tumours and present at a younger age. Two large studies of screening in newborns for neuroblastomas using urinary catecholamine metabolite measurements have determined that such screening is not effective at the population level [10,11]. Whether screening may be of benefit to the siblings of children with neuroblastoma is unknown.

3. Paediatric cancer predisposition syndromes

3.1. DNA repair disorders

DNA repair disorders are rare conditions mostly inherited in an autosomal recessive manner. Features of the main syndromes are listed in Table 3. These conditions are often associated with congenital abnormalities, small stature, failure to thrive and onset of multiple or unusual malignancies in childhood. Some of the syndromes, such as Fanconi anaemia (FA), can be very heterogeneous and the diagnosis should be considered even if only minor features are present. Sometimes there are clues from ethnic origin (some conditions are more common in certain ethnic groups) or the family history (consanguinity, affected siblings). Many of the syndromes require specific laboratory investigations to aid diagnosis. Because of potential heterogeneity, it is important that siblings of affected index cases are carefully examined and investigated as necessary. In general, these syndromes have a poor prognosis with high concurrent morbidity and often the malignancies are difficult to treat because of increased radiosensitivity and/or chemosensitivity of normal tissues.

FA is characterised by a wide variety of congenital abnormalities, a propensity to develop bone marrow failure and acute myeloid leukaemia (AML), and an increased incidence of solid tumours with young age of onset [12]. FA cells are characterised by chromosomal hypersensitivity to DNA cross-linking agents and the resulting increase in chromosome breakage provides the basis for a diagnostic test. There are at least 11 'complementation groups' and the genes for 8 of these have been cloned [13]. It has recently been shown that one of these genes *FANCD1* is actually *BRCA2* and the rare group of FA patients with biallelic *BRCA2* mutations have an earlier onset of leukaemia and an increased risk of medulloblastomas and Wilms' tumours [14]. The average age of onset of bone marrow failure in the major groups is 7 years and the only curative procedure is haemopoietic stem cell transplantation. Survivors of haematological complications have an increased risk of solid tumours, particular squamous cell carcinomas [15].

Another DNA repair defect syndrome, ataxia telangiectasia (AT) caused by mutations in the *ATM* gene, is characterised at the cellular level by abnormal sensitivity to ionising radiation which induces chromosomal breakage. AT homozygotes commonly develop cerebellar ataxia, telangiectasia and immune defects. There is also a predisposition to malignancies which develop in around 38% of patients and are mostly lymphoid leukaemias of T-cell origin and lymphomas of B-cell origin [16,17].

3.2. Other paediatric cancer predisposition syndromes

3.2.1. Neurofibromatosis Type 1 (NF1)

NF1 is a common autosomal dominant condition that occurs in approximately 1 in 3000 individuals. The most common presenting features are café-au-lait patches and peripheral neurofibromas, but short stature, scoliosis and learning difficulties are also common features. Approximately 50% of cases have no family history and are caused by new mutations. The large size and highly polymorphic nature of the *NF1* gene on chromosome 17q means that genetic testing is currently not routinely undertaken and the diagnosis is made based on clinical criteria. There is an increased risk of tumours affecting 2–5% of individuals which usually

Table 3
Features of the main DNA repair disorders

Syndrome	Inheritance, incidence	Primary malignancy	Associated malignancies and clinical features	Chromosome location	Cloned gene	Putative function	Laboratory investigations	Gene tests
Ataxia telangiectasia	AR, 1/40 000–1/100 000	Lymphoma, leukaemia	Telangiectasia, immuno-deficiency, cerebellar ataxia, radiosensitivity. Breast cancer in heterozygotes	11q22	*ATM*	DNA damage response	Raised α-fetoprotein. Hypersensitivity to ionising radiation which induces chromosomal breakage	3
Nijmegen breakage syndrome	AR, unknown. Increased in Eastern Europe	Lymphoma	Microcephaly, developmental delay, immunodeficiency	8q21	*NBS*	DNA damage response	Hypersensitivity to ionising radiation which induces chromosomal breakage	2
Fanconi anaemia	AR, 1/300 000. Increased in Ashkenazi Jews	AML	Squamous cell carcinomas, pancytopenia, short stature. Congenital abnormalities: skeletal, renal	16q24.3 9q22.3 3p25.3 6p21-22 11p15 9p13 2p16	*FANCA* *FANCB* *FANCC* *(FANCD1)* *FANCD2* *FANCE* *FANCF* *FANCG* *FANCI* *FANCJ* *FANCL*	All involved in DNA repair. *FANCD1* has recently been shown to be *BRCA2* and the FA phenotype can be seen in individuals with biallelic *BRCA2* mutations	Hypersensitivity to alkylating agents e.g., Diepoxybutane or Mitomycin C which induce chromosomal breakage	2
Bloom syndrome	AR, several hundred worldwide. Increased incidence in Ashkenazi Jews	Leukaemia, lymphoma	Skin carcinomas, other solid tumours. Short stature, sun-sensitive erythematous lesions	15q26.1	*BLM*	DNA helicase	Increased sister chromatid exchange	2
Werner syndrome	AR, 1/100 000–1/500 000	Sarcoma, melanoma	Cataracts, short stature, premature ageing,	8p11-12	*WRN*	DNA helicase	Increased urine hyaluronic acid	2
Rothmund–Thomson syndrome	AR, unknown	Osteo-sarcoma	Poikiloderma congenita, alopecia, photosensitivity, cataracts, short stature	8q24.3	*RECQL4*	DNA helicase		2
Xeroderma Pigmentosum	AR, 1/1,000 000. Increased in Japanese	Skin cancer	Skin pigmentation actinic keratoses conjunctivitis, keratitis	9q34 2q21 3p25 19q13.2 11 16p13.3 13q32	*XPA* *XPB* *XPC* *XPD* *XPE* *XPF* *XPG*	Nucleotide excision repair	Unscheduled DNA synthesis assay	3

AR, autosomal recessive; AD, autosomal dominant; AML, acute myeloid leukaemia.

Gene tests: 1, genetic testing widely available; 2, genetic testing only available in a few centres with an special interest in the condition; 3, genetic testing only available on a research basis.

N.B. The genetic test status for individual conditions will be subject to change in view of the rapid molecular advances being made and clinicians are recommended to seek advice regarding a current test status with their local clinical genetics service.

arise in the adolescent and adult years and include phaeochromocytoma, neurofibrosarcoma and meningioma. Conversely, optic glioma tends to arise in infancy or early childhood and can be found in 15% of individuals – with around half being symptomatic. These tumours are low grade and non-malignant, but can impinge on the optic nerve or interfere with the hypothalamic-pituitary axis. There is considerable controversy about screening for and the management of these tumours and while regular computerised tomography/magnetic resonance imaging (CT/MRI) surveillance scans are not recommended, children should have an annual ophthalmology assessment (including visual fields) and MRI scanning if a glioma is suspected. If a glioma is asymptomatic, a policy of 'watchful' observation is recommended. Optic gliomas rarely develop after the childhood years.

All individuals with NF1 should be educated about the risks of developing tumours and children should have an annual clinical assessment to try to detect complications at an early stage. Assessment should include information about school performance and general health and the examination should include height and head circumference measurements together with a spine examination (for scoliosis), skin examination and blood pressure measurement. Annual ophthalmological examination of children is recommended until 5 years of age [18].

3.2.2. Beckwith–Wiedemann syndrome

Beckwith–Wiedemann syndrome (BWS) is a complex multigenic disorder caused by alterations in growth regulatory genes on chromosome 11p15. Clinically, it is characterised by macroglossia, macrosomia, hemihypertrophy and abdominal wall defects [19]. The population incidence is around 1 in 10 000, and 85% of these are sporadic with normal karyotypes, although 10–15% have autosomal dominant pedigrees. Around 10–20% of cases are due to paternal uniparental isodisomy of 11p15. A further 2–3% have other chromosome abnormalities involving this region. The overall risk of tumours in BWS is estimated to be 7.5% [20]. The two commonest tumours are Wilms' tumour and hepatoblastoma, but rhabdomyosarcoma, pancreatoblastoma, adrenocortical carcinoma and neuroblastoma have also been described. Most of the increased tumour risk is in the first 5–8 years of life, so it is recommended that children with a diagnosis of BWS have 3-monthly abdominal ultrasounds until 5 years old, then less frequently until the age of 8 years [21]. Screening for neuroblastoma with serial urine catecholamine metabolite measurements and for hepatoblastoma with serial serum α-fetoprotein (AFP) measurements have been suggested, but are not generally performed because of the relatively low risk of these tumours [22]. Children with 'isolated' hemihypertrophy, some of whom may have '*formes frustes*' of BWS, have a significant overlap of tumour types with BWS and a lifetime risk of 5.9%. Therefore, screening protocols similar to those for BWS may also be indicated for these children [23].

3.2.3. Costello syndrome

This very rare condition is also known as facio-cutaneo-skeletal syndrome. The inheritance pattern is unclear, although it is most likely to be 'sporadic' as a result of new dominant mutations. Affected individuals have a facial resemblance to those with Noonan's syndrome and the facial appearance may become coarser with age. Multiple nasal papillomata and excess skin on the hands are characteristic and mental retardation is usually a feature. There have been several case reports of associated tumours, including rhabdomyosarcoma, neuroblastoma and transitional cell carcinoma of the bladder [24]. The overall tumour risk may be as high as 17% [24] and a screening protocol which involves 3–6 monthly ultrasound evaluation of the abdomen until the age of 8–10 years, 6–12 monthly urine catecholamine metabolite measurements until the age of 5 years and annual urinalysis until the age of 10 years has been proposed [24]. However, the evidence base for such a protocol is very limited due to the rarity of the condition and prospective evaluation is required [25].

4. The management of children in families with predominantly adult onset cancer predisposition syndromes

4.1. Colorectal cancer syndromes

The main colorectal predisposition syndromes are detailed in Table 4. Overall, they are likely to account for 2–3% of all colorectal cancers and a higher proportion of young onset (<age 50 years) cancers. Hereditary non-polyposis colon cancer (HNPCC) is the commonest dominantly-inherited colorectal cancer, but as screening in this condition is recommended from age 25 years there are usually no indications for genetic testing during childhood.

Familial Adenomatous Polyposis (FAP) is characterised by profuse adenomatous colonic polyposis, with affected individuals developing hundreds of polyps by the second decade of life and, unless prophylactic colectomy is performed, over 90% will have developed colorectal cancer by the age of 45 years. In addition to colonic polyps, 80% will have duodenal adenomas and there is an associated 5–10% lifetime risk of small bowel carcinoma. There is also an increased risk of hepatoblastoma, medulloblastoma, papillary carcinoma of the thyroid and desmoid tumours [53]. Desmoid tumours are often found in the small bowel mesentery, usually in female FAP patients. These benign, but treatment-resistant, lesions can grow to a large size, causing

Table 4
Clinical and molecular features of the major colorectal cancer predisposition syndromes

Syndrome	Inheritance, prevalence	Lifetime colorectal cancer risk	Associated malignancies and clinical features	Chromosome Location	Cloned gene	Putative function	Clinical screening	Gene tests
Hereditary non-Polyposis Colorectal cancer (HNPCC)	AD, 1/3000	Males 80% Females 30–50%	Endometrial, ovarian, urinary tract carcinomas	3p21, 2p16, 2p16, 2q32, 7p22,	*MLH1*, *MSH2*, *MSH6*, *PMS1*, *PMS2*	DNA mismatch repair	Biennial total colonic surveillance should start at age 25 years, or five years less than the first cancer case in the family, whichever is the earlier	1
Muir Torre syndrome	AD, rare	Unknown. Likely to be similar to HNPCC	HNPCC variant with sebaceous skin tumours	2p16, 3p21,	*MSH2*, *MLH1*	DNA mismatch repair	As for HNPCC	1
Familial Adenomatous Polyposis (FAP)	AD, 1/14 000	Virtually 100%	Colorectal adenomas, gastric tumours, desmoids, congenital hypertrophy of the retinal pigment epithelium	5q21	*APC*	Regulation of β-catenin	Annual flexible sigmoidoscopy should be offered to at risk family members from age 13–15 years Prophylactic colectomy is recommended between the age of 16 and 20 years Three yearly upper gastrointestinal endoscopy from age 30 years	1
Gardner's syndrome	AD, rare	As for FAP	FAP variant with soft tissue tumours (desmoids), osteomas	5q21	*APC*	Regulation of β-catenin	As for FAP	1
Multiple colorectal adenomas (FAP-like)	AR, unknown	Unknown. Possibly as high as for FAP	Duodenal polyposis congenital hypertrophy of the retinal pigment epithelium	1p34.3-p32.1	*MYH*	Base excision repair	No current guidelines. Screening should probably be similar to FAP	2
Turcot syndrome	AD, rare	As for FAP or HNPCC	FAP variant with CNS tumours e.g., medulloblastoma	5q21	*APC*	Regulation of β-catenin	Depends on gene involved. Either as for HNPCC or as for FAP	1
				3p21 7q22	*MLH1* *PMS2*	DNA mismatch repair DNA mismatch repair		

Peutz–Jeghers syndrome (PJS)	AD, 1/50 000	10–20%	Pancreatic breast ovarian carcinoma	19p13.3	*LKB1*	Serine–threonine kinase	Whole colonic surveillance at three year intervals from age 18 years. Upper gastrointestinal surveillance at three year intervals from age 25 years	2
Familial Juvenile Polyposis (FJP)	AD, 1/50 000	10–40%	Multiple upper GI adenoma carcinoma	18q21.1 10q22 10q23	*SMAD4* *BMPRIA* *PTEN*	TGF-β regulation Phosphatidylinositol phosphatase	Whole colonic surveillance at intervals of one to two years from age 15–18 years or even before if the patient has presented with symptoms. Screening intervals could be extended at age 35 years in at-risk individuals.	2

AR, autosomal recessive; AD, autosomal dominant.
Gene tests: 1, genetic testing widely available; 2, genetic testing only available in a few centres with an special interest in the condition; 3, genetic testing only available on a research basis.
N.B. The genetic test status for individual conditions will be subject to change in view of the rapid molecular advances being made and clinicians are recommended to seek advice regarding a current test status with their local clinical genetics service. Screening recommendations are mainly taken from the guidelines published by Dunlop [51]
CNS, central nervous system; TGF, transforming growth factor.

significant morbidity and mortality, and management is difficult.

FAP is inherited in an autosomal dominant manner, with a disease prevalence of 1 in 8500; approximately a third of cases arise sporadically as new mutations. It is caused by germ-line mutations in the adenomatous polyposis coli (*APC*) gene located on chromosome 5q21. It is a large gene and the clinical phenotype can vary with the location of a mutation; mutations at either end of the gene cause a variant of FAP with few polyps, known as 'attenuated FAP'. Approximately two thirds of individuals with FAP will have flat, oval, pigmented retinal lesions – so-called congenital hypertrophy of the retinal pigment epithelium (CHRPE). CHRPEs do not impair vision, but are present from birth and can be a useful adjunct to diagnosis in at-risk individuals.

At-risk individuals (e.g. children of those affected) are offered at least annual surveillance for the development of colorectal polyps from their early teenage years onward. If the causative mutation is known in the family, predictive genetic testing should be offered. Genetic testing is clearly useful in the prevention of unnecessary screening of unaffected individuals and concentrate resources on those harbouring a mutation [26]. For those individuals who carry the mutation, prophylactic colectomy is the treatment of choice when polyps become established. Where the mutation is not known, entry into a screening programme is advised; during the teenage years sigmoidoscopy suffices, since in classical FAP polyps almost always first occur in the rectum and sigmoid colon. Current guidelines recommend yearly sigmoidoscopy from the ages of 14–19 years. The timing of genetic testing should ideally be planned so a child is old enough to understand the implications, but early enough so that sigmoidoscopy can be avoided in non-mutation carriers.

An autosomal recessive polyposis syndrome similar to FAP, but due to mutations in the *MYH* gene, has recently been identified [27] and this is the only condition listed in Table 4 that is not inherited in an autosomal dominant manner. Because of the autosomal recessive inheritance there is unlikely to be a strong family history in previous generations. The characteristic phenotype of patients with homozygous *MYH* mutations is similar to those in FAP or attenuated FAP, but extracolonic tumours are unusual. *MYH* mutations are thought to account for 23% of *APC* -mutation-negative cases with more than 10 polyps [28] and around 10% of cases with more than 3 polyps [29]. Patients with a phenotype for FAP, but no evidence of vertical transmission should be tested for both *APC* mutations (as nearly a third of cases arise *de novo*) and for *MYH* mutations. Siblings of affected cases will require counselling, screening, and treatment tailored to the type of mutation, as well as to the presence or absence of vertical transmission.

4.2. Breast cancer predisposition syndromes

Around 1% of breast cancers arise in women aged 20–29 years [30] and below this age breast cancer is extremely rare. Approximately 3–5% of all breast cancer is estimated to be due to dominantly inherited genes [31] and two breast cancer genes, *BRCA1* and *BRCA2*, together account for around 85% of familial breast cancer [32]. Women who carry mutations in these genes also have an increased risk of ovarian cancer. In individuals with *BRCA1* and *BRCA2* mutations, breast cancer is nevertheless rare under the age of 25 years. Moreover, mammographic screening for breast cancer in young women is problematic and there are issues regarding both sensitivity and radiation risk in young women [33]. Therefore, predictive testing for *BRCA1* and *BRCA2* in children is not indicated. Girls from families with hereditary breast cancer may have considerable anxiety about their own risks of developing breast cancer, particularly if they have had experience of an affected close relative. This situation needs to be dealt with in a sensitive and tactful manner as does advice about the use of the oral contraceptive pill (OCP). Women taking the OCP have a slightly increased risk of breast cancer [34], but the OCP probably reduces the risk of ovarian cancer in the general population. There is uncertainty about whether *BRCA1/2* carriers have a similar or different or different (and possibly greater) risk of breast and ovarian cancer if they take the OCP [35,36].

Patients with Cowden Syndrome's (CS), a rare disorder due to mutations in *PTEN*, develop clinical features including cobblestone-like papules of the buccal mucosa, multiple facial trichilemmomas and macrocephaly. In females, there is an increased risk of breast and thyroid cancer and, while the earliest recorded age at diagnosis of breast cancer is 14 years [37], most CS breast cancers are diagnosed between 30 and 35 years [38]. Genetic testing in childhood may be indicated as thyroid cysts and multinodular goitre and breast cysts may develop in affected children.

Li-Fraumeni syndrome (LFS) is due to mutations in the *TP53* gene. LFS is strictly defined as: a proband with a sarcoma diagnosed before 45 years of age and a first-degree relative with any cancer under 45 years of age and a first- or second-degree relative with any cancer under 45 years of age or a sarcoma at any age. The overall lifetime risk of cancer is estimated to be 80–90% and has been estimated to be as high as 40% by 16 years [39]. There is an increased incidence of adrenocortical tumour (mean age at diagnosis 4.9 years), bone or soft tissue sarcoma (mean age at diagnosis 15 years), breast cancer, melanoma, leukaemia or myelodysplasia and brain tumours [40,54]. Parents are understandably anxious about their children and there may be considerable pressure for predictive testing. However, as no effective screening exists for these tumours, predictive genetic testing of children is difficult to justify though diagnostic testing of a child with a sarcoma or as adrenocortical tumour should be considered. DNA may be stored for later testing if appropriate.

4.3. Neuroendocrine tumour predisposition syndromes

The main neuroendocrine syndromes, all rare and dominantly inherited, are detailed in Table 5. As they predispose to a varied group of tumours with a wide range of clinical manifestations, screening is intensive and complex and should begin from the age of 5 years for some of the associated tumours (see [41] for guidelines in full on screening in MEN1 and MEN2 (Multiple Endocrine Neoplasia Types 1 and 2)). Gene mutation screening and predictive testing is therefore a useful way of both focusing resources on at-risk individuals and avoiding unnecessary investigations on those who are not at-risk. The mutation detection sensitivity for MEN1 and Von Hippel Lindan (VHL) is in the order of 75–95%, with higher detection rates where there is a positive family history. For MEN2A, the detection rate approaches 98%. Because the lifetime risk of medullary thyroid cancer (MTC) is virtually 100% in MEN2A, prophylactic thyroidectomy is advocated before age 5 years, especially for those mutations associated with a young age at onset [41]. This is one of the very few current examples where predictive genetic testing is advocated in childhood, because it has a direct bearing on the management of at-risk-children.

Phaeochromocytomas are neural crest tumours arising from the adrenal medulla, although they can occur in extra-adrenal sites. They are catecholamine-secreting tumours that can present with hypertension and are benign in around 90% of cases. Genetic factors may be implicated in up to 25% of phaeochromocytoma cases [42]. The most frequent causes of phaeochromocytoma susceptibility are VHL, MEN2, phaeochromocytoma–paraganglioma syndrome (caused by germline mutations in *SDHD* and *SDHB*) and, less commonly, NF1.

4.4. Other

4.4.1. Neurofibromatosis Type 2 (NF2)

NF2 is characterised by vestibular schwannomas, intracranial meningiomas, spinal tumours including schwannomas, cataracts and skin lesions [43]. It is rare with an incidence of approximately 1 in 40 000, but it is associated with considerable morbidity. It is autosomal dominant and mutation testing is possible for the *NF2* gene with a 70% mutation detection rate. Children of affected parents should be considered to be at a 50% risk of NF2 and ophthalmological screening can start at birth as cataracts can affect vision in early life. Formal screening for tumours should start at 10 years and includes two-yearly MRI scans and annual audiology

Table 5
Clinical and molecular features of the main neuroendocrine syndromes

Syndrome	Inheritance/ Incidence	Primary malignancy	Associated malignancies and clinical features	Chromosome location	Cloned gene	Putative function	Clinical screening	Gene tests
Multiple endocrine neoplasia Type 1	AD 1/60 000	Parathyroid adenoma	Entero-pancreatic tumours e.g. gastrinoma, insulinoma. Carcinoid tumours, anterior pituitary tumours, adrenal cortex tumours	11q13	*Menin*	Transcription regulator	Annual serum calcium, parathyroid hormone (PTH), fasting glucose, insulin, gastrin, secretin-stimulated gastrin, glucagons, proinsulin. 3-yearly pituitary MRI scans, octreotide scans, abdominal CT scans. See also [31]	2
Multiple endocrine neoplasia Type 2	AD 1 per million	Medullary thyroid carcinoma	Type 2A: pheochromocytoma, parathyroid hyperplasia Type 2B: pheochromocytoma, mucosal ganglioneuromatosis, Marfanoid habitus	10q11.2	*RET*	Transmembrane receptor tyrosine kinases	Management should be based on DNA testing [31]. Prophylactic thyroidectomy is the treatment of choice. Serum calcitonin pre- and post-op, annual urine VMA and catecholamines	2
Von Hippel-Lindau	AD 1 in 36 000	Renal clear cell carcinoma	Pheochromocytoma, retinal and cerebellar haemangioblastoma	3p25	*VHL*	Regulator of transcriptional elongation by RNA polymerase II	Annual urine microscopy, VMA and catecholamine measurements, ophthalomogy assessment, renal USS or MRI. 3-yearly brain MRI or CT	2

AR, autosomal recessive; AD, autosomal dominant.

Gene tests: 1, genetic testing widely available; 2, genetic testing only available in a few centres with an special interest in the condition; 3, genetic testing only available on a research basis.

N.B. The genetic test status for individual conditions will be subject to change in view of the rapid molecular advances being made and clinicians are recommended to seek advice regarding a current test status with their local clinical genetics service. CT, computerised tomography; MRI, magnetic resonance imaging; PTH, parathyroid hormone; VMA, vanillylmandelic acid; USS, ultrasound scan.

tests, including auditory brainstem response [43]. As these investigations are non-invasive, the issue of presymptomatic genetic testing is problematic in children and there are arguments both for testing in childhood and for deferring until a child is old enough to make an informed decision about testing.

4.4.2. Nevoid basal cell carcinoma syndrome (Gorlin's syndrome)

This autosomal dominant condition with an incidence of around 1 in 56 000 is due to mutations in the *PTCH gene* and is characterised by macrocephaly with a characteristic facial appearance, jaw cysts and a propensity to develop basal cell carcinomas (BCCs). These are influenced by sun exposure, but may occur below the age of 10 years [44,45]. Affected individuals should avoid excess sun exposure and be advised to wear ultra violet (UV) protective sunglasses and high factor sunscreens as the skin surrounding the eyes (and also on the nose and ears) is particularly vulnerable to BCCs. Radiotherapy should be avoided whenever possible and children should be reviewed at regular intervals (3–6 monthly) by a dermatologist. The jaw cysts can be treated by surgical removal.

There is also an increased risk of other tumours including medulloblastoma and neurological examination at six monthly intervals until the age of 3 years and yearly until the age of 7 years has been advocated. Beyond this age, medulloblastoma would be very unlikely to develop. *PTCH* gene mutations are found in around half of all cases of Gorlin's syndrome [46,47] and this can be used to identify at-risk individuals who would benefit from screening. If the family mutation is not known the diagnosis can sometimes be made in infants at-risk by radiographic means (calcification of falx, rib anomalies, calcification of ovarian fibromas).

5. Ethical considerations in the genetic testing of children

It is important to distinguish diagnostic from presymptomatic genetic testing in children. An example of a diagnostic genetic test would be *APC* gene mutation screening in a child with multiple colorectal polyps, where the purpose is to confirm the suspected clinical diagnosis of FAP. The issues surrounding such diagnostic testing are similar to other diagnostic tests in childhood.

An example of presymptomatic genetic testing (also called predictive genetic testing) would be testing a *healthy* child with no features of FAP for an *APC* gene mutation known to be in their family. Such testing is justifiable only when the test result will change medical care in childhood [48]. In reality, this currently applies to only a small number of genetic cancer predisposition syndromes [49] (Table 6), but this list is likely to expand in the future. Presymptomatic genetic testing raises complex psychosocial, ethical and legal considerations [50].

When a child is not competent to give consent, the main consideration in genetic testing should be the welfare of that child. Parents and health professionals need to carefully weigh information about the possible benefits and harm that may result from the test. The cornerstone of this process is 'informed consent' or, at least, assent. One of the main concerns about presymptomatic testing in childhood is the potential loss of autonomy for the child. When the child who has been tested reaches maturity, the right of that child to decline testing or the possibility of withholding genetic test results has effectively been lost. Other important issues relate to maintaining privacy and confidentiality of genetic test results in children, to minimise the potential risk of stigmatisation and discrimination in later life.

Genetic testing can have important psychological consequences for the child [50]. Presymptomatic testing of children can disrupt family dynamics with parents taking a different attitude to a child who has inherited a cancer predisposition gene which may in turn affect relationships between siblings. Often the family has experienced the trauma of a several members developing cancer at a young age and this increased morbidity and mortality can lead to dysfunctional family relationships and economic hardship. The parent may feel guilt that

Table 6
Cancer predisposition syndromes where the genetic test result will alter clinical management in children

Syndrome	Gene	Gene tests	Surgical management (prophylactic surgery)	Medical management (screening)
Familial adenomatous polyposis	*APC*	1	N	Y
Multiple endocrine neoplasia Type 1	*MEN1*	2	N	Y
Multiple endocrine neoplasia Type 2	*RET*	2	Y	Y
Von Hippel-Lindau	*VHL*	2	N	Y
Retinoblastoma	*RB1*	2	N	Y
Neurofibromatosis Type 2	*NF2*	2	N	Y

Gene tests: 1, genetic testing widely available; 2, genetic testing only available in a few centres with an special interest in the condition; 3, genetic testing only available on a research basis.

N.B. The genetic test status for individual conditions will be subject to change in view of the rapid molecular advances being made and clinicians are recommended to seek advice regarding a current test status with their local clinical genetics service. N, no; Y, yes.

they are responsible for the potential risk to their offspring and may wish to remove the uncertainty by testing them. Children who are tested and found not to carry the cancer predisposing gene may experience survivor guilt and worry about their relationship with affected siblings. Conversely, children that carry the gene may experience heightened anxiety related to fears about future health. Feelings of guilt, insecurity and altered perception of self may also occur. Further emotional complications may arise from the "medicalisation" of the child who may require invasive screening procedures (e.g. flexible sigmoidoscopies in FAP gene carriers) as a result of a positive gene test. However, there can be psychological benefits from gene testing, such as the removal of uncertainty and the opportunity to openly discuss the cancer predisposition which may have hitherto been suppressed in the family.

These issues underlie the importance that discussions on genetic testing are done in a sensitive, comprehensive and inclusive manner by fully trained specialist health professionals, such as genetic counsellors and clinical geneticists, in a relaxed and comfortable environment. Multiple sessions should be encouraged so that the child and their family have time to fully think through the consequences of genetic testing. It is also very important that cultural beliefs and family values about privacy, truth-telling and disclosure are respected.

6. Summary

A large number of known inherited cancer predisposition syndromes have been identified and this is set to increase as our knowledge of cancer genetics expands. Improvements in mutation screening opportunities and techniques will increase the sensitivity and accuracy and, therefore, the applicability of genetic testing. Presymptomatic 'predictive' genetic testing in children is only indicated where the test result will change medical care during childhood. At present, this circumstance applies to only a few conditions. When testing is indicated it should be undertaken by experienced health professionals who are able to deal with the resultant psychological, emotional, ethical and legal complexities in a sensitive, informative and respectful manner.

References

1. Rahman N, Arbour L, Tonin P, Renshaw J, Pelletier J, Baruchel S, *et al*. Evidence for a familial Wilms' tumour gene (FWT1) on chromosome 17q12-q21. *Nat Genet* 1996, **13**(4), 461–463.
2. Rapley EA, Barfoot R, Bonaiti-Pellie C, Chompret A, Foulkes W, Perusinghe N, *et al*. Evidence for susceptibility genes to familial Wilms tumour in addition to WT1, FWT1 and FWT2. *Br J Cancer* 2000, **83**(2), 177–183.
3. Pritchard-Jones K. Controversies and advances in the management of Wilms' tumour. *Arch Dis Child* 2002, **87**(3), 241–244.
4. Newsham IF, Hadjistilianou T, Cavenee WK. Retinoblastoma. In Vogelstein B, Kinzler KW, eds. *The genetic basis of human cancer*. New York, McGraw-Hill, 2001, pp 357–386.
5. Knudson Jr AG. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA* 1971, **68**(4), 820–823.
6. Eng C, Li FP, Abramson DH, Ellsworth RM, Wong FL, Goldman MB, *et al*. Mortality from second tumors among long-term survivors of retinoblastoma. *J Natl Cancer Inst* 1993, **85**(14), 1121–1128.
7. Schwab M, Westermann F, Hero B, Berthold F. Neuroblastoma: biology and molecular and chromosomal pathology. *Lancet Oncol* 2003, **4**(8), 472–480.
8. Weiss MJ, Guo C, Shusterman S, Hii G, Mirensky TL, White PS, *et al*. Localization of a hereditary neuroblastoma predisposition gene to16p12-p13. *Med Pediatr Oncol* 2000, **35**(6), 526–530.
9. Maris JM, Weiss MJ, Mosse Y, Hii G, Guo C, White PS, *et al*. Evidence for a hereditary neuroblastoma predisposition locus at chromosome16p12-13. *Cancer Res* 2002, **62**(22), 6651–6658.
10. Woods WG, Gao R-N, Shuster JJ, Robison LL, Bernstein M, Weitzman S, *et al*. Screening of infants and mortality due to neuroblastoma. *N Engl J Med* 2002, **346**(14), 1041–1046.
11. Schilling FH, Spix C, Berthold F, Erttmann R, Fehse N, Hero B, *et al*. Neuroblastoma screening at one year of age. *N Engl J Med* 2002, **346**(14), 1047–1053.
12. Tischkowitz MD, Hodgson SV. Fanconi anaemia. *J Med Genet* 2003, **40**(1), 1–10.
13. Levitus M, Rooimans MA, Steltenpool J, Cool NF, Oostra AB, Mathew CG, *et al*. Heterogeneity in Fanconi anemia: evidence for two new genetic subtypes. *Blood* 2003, **20**, 20.
14. Wagner JE, Tolar J, Levran O, Scholl T, Deffenbaugh A, Satagopan J, *et al*. Germline mutations in BRCA2: shared genetic susceptibility to breast cancer, early onset leukemia and fanconi anemia. *Blood* 2004, **8**, 8.
15. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi's anemia. *Blood* 2003, **101**, 822–825.
16. Morrell D, Cromartie E, Swift M. Mortality and cancer incidence in 263 patients with ataxia telangiectasia. *J Natl Cancer Inst* 1986, **77**(1), 89–92.
17. Taylor AM, Metcalfe JA, Thick J, Mak YF. Leukemia and lymphoma in ataxia telangiectasia. *Blood* 1996, **87**(2), 423–438.
18. Health supervision for children with neurofibromatosis. American academy of pediatrics committee on genetics. *Pediatrics* 1995;**96**(2 Pt 1):368–72.
19. Weksburg R, Shuman C. Beckwith–Wiedeman syndrome. In Cassidy SB, Allanson JE, eds. *Management of genetic syndromes*. 1st edn. New York, Wiley-Liss, 2001, pp 49–69.
20. Wiedemann H-R. Tumours and hemihypertrophy associated with Wiedemann–Beckwith syndrome. *Eur J Pediatr* 1983, **141**, 129.
21. Beckwith JB. Nephrogenic rests and the pathogenesis of Wilms tumor: developmental and clinical considerations. *Am J Med Genet* 1998, **79**(4), 268–273.
22. Everman DB, Shuman C, Dzolganovski B, O'Riordan MA, Weksberg R, Robin NH. Serum alpha-fetoprotein levels in Beckwith–Wiedemann syndrome. *J Pediatr* 2000, **137**(1), 123–127.
23. Hoyme HE, Seaver LH, Jones KL, Procopio F, Crooks W, Feingold M. Isolated hemihyperplasia (hemihypertrophy): report of a prospective multicenter study of the incidence of neoplasia and review. *Am J Med Genet* 1998, **79**(4), 274–278.
24. Gripp KW, Scott CI, Jr L, Nicholson DM, McDonald-McGinn JD, Ozeran MC, *et al*. Five additional Costello syndrome patients with rhabdomyosarcoma: proposal for a tumor screening protocol. *Am J Med Genet* 2002, **108**(1), 80–87.
25. DeBaun MR. Screening for cancer in children with Costello syndrome. *Am J Med Genet* 2002, **108**(1), 88–90.

26. Terdiman JP, Conrad PG, Sleisenger MH. Genetic testing in hereditary colorectal cancer: indications and procedures. *Am J Gastroent* 1999, **94**(9), 2344–2356.
27. Al-Tassan N, Chmiel NH, Maynard J, Fleming N, Livingston AL, Williams GT, *et al*. Inherited variants of MYH associated with somatic G:C–>T:A mutations in colorectal tumors. *Nat Genet* 2002, **30**(2), 227–232.
28. Sampson JR, Dolwani S, Jones S, Eccles D, Ellis A, Evans DG, *et al*. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MYH. *Lancet* 2003, **362**(9377), 39–41.
29. Sieber OM, Lipton L, Crabtree M, Heinimann K, Fidalgo P, Phillips RK, *et al*. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. *N Engl J Med* 2003, **348**(9), 791–799.
30. Swanson GM, Lin CS. Survival patterns among younger women with breast cancer: the effects of age, race, stage, and treatment. *J Natl Cancer Inst Monogr* 1994;(16), 69–77.
31. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer* 1994, **73**(3), 643–651.
32. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, *et al*. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The breast cancer linkage consortium. *Am J Hum Genet* 1998, **62**(3), 676–689.
33. Johnstone PA, Moore EM, Carrillo R, Goepfert CJ. Yield of mammography in selected patients age < or = 30 years. *Cancer* 2001, **91**(6), 1075–1078.
34. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative group on hormonal factors in Breast Cancer. *Lancet* 1996;**347**(9017):1713–27.
35. Modan B, Hartge P, Hirsh-Yechezkel G, Chetrit A, Lubin F, Beller U, *et al*. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001, **345**(4), 235–240.
36. Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H, *et al*. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary ovarian cancer clinical study group. *N Engl J Med* 1998, **339**(7), 424–428.
37. Starink TM, van der Veen JP, Arwert F, de Waal LP, de Lange GG, Gille JJ, *et al*. The Cowden syndrome: a clinical and genetic study in 21 patients. *Clin Genet* 1986, **29**(3), 222–233.
38. Longy M, Lacombe D. Cowden disease. Report of a family and review. *Ann Genet* 1996, **39**(1), 35–42.
39. Le Bihan C, Moutou C, Brugieres L, Feunteun J, Bonaiti-Pellie C. ARCAD: a method for estimating age-dependent disease risk associated with mutation carrier status from family data. *Genet Epidemiol* 1995, **12**(1), 13–25.
40. Kleihues P, Schauble B, zur Hausen A, Esteve J, Ohgaki H. Tumors associated with p53 germline mutations: a synopsis of 91 families. *Am J Pathol* 1997, **150**(1), 1–13.
41. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, *et al*. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001, **86**(12), 5658–5671.
42. Maher ER, Eng C. The pressure rises: update on the genetics of phaeochromocytoma. *Hum Mol Genet* 2002, **11**(20), 2347–2354.
43. Evans DG, Sainio M, Baser ME. Neurofibromatosis type 2. *J Med Genet* 2000, **37**(12), 897–904.
44. Evans DG, Ladusans EJ, Rimmer S, Burnell LD, Thakker N, Farndon PA. Complications of the naevoid basal cell carcinoma syndrome: results of a population based study. *J Med Genet* 1993, **30**(6), 460–464.
45. Shanley S, Ratcliffe J, Hockey A, Haan E, Oley C, Ravine D, *et al*. Nevoid basal cell carcinoma syndrome: review of 118 affected individuals. *Am J Med Genet* 1994, **50**(3), 282–290.
46. Aszterbaum M, Rothman A, Johnson RL, Fisher M, Xie J, Bonifas JM, *et al*. Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. *J Invest Dermatol* 1998, **110**(6), 885–888.
47. Boutet N, Bignon YJ, Drouin-Garraud V, Sarda P, Longy M, Lacombe D, *et al*. Spectrum of PTCH1 mutations in French patients with Gorlin syndrome. *J Invest Dermatol* 2003, **121**(3), 478–481.
48. Clarke AJ. The Genetic Testing of Children. In Harper PS, Clarke AJ, eds. *Genetics society and clinical practice*. Oxford, Bios, 1997, pp 15–29.
49. American society of clinical oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 2003;**21**(12):2397–2406.
50. MacDonald DJ, Lessick M. Hereditary cancers in children and ethical and psychosocial implications. *J Pediatr Nurs* 2000, **15**(4), 217–225.
51. Dunlop MG. Guidance on gastrointestinal surveillance for hereditary non-polyposis colorectal cancer, familial adenomatous polypolis, juvenile polyposis, and Peutz-Jeghers syndrome. *Gut* 2002, **51**(Suppl. 5), V21–V27.
52. Meadows AT. Second tumours. *Eur J Cancer* 2001, **37**(15), 2074–2081.
53. Thomas D, Pritchard J, Davidson R, Mckiernan P, Grundy RG, De Villede Goyet J. Familial hepatoblastoma and *APC* gene mutations: renewed call for molecular research. *Eur J Cancer* 2003, **39**(15), 2200–2204.
54. Ribeiro RC, Figueiredo B. Childhood adrenocortical tumours. *Eur J Cancer* 2004, **40**(8), 1117–1126.