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Recognition of genetic predisposition in pediatric cancer patients: An easy-to-use selection tool

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Abstract

Genetic predisposition for childhood cancer is under-diagnosed. Identifying these patients may lead to therapy adjustments in case of syndrome-related increased toxicity or resistant disease and syndrome-specific screening programs may lead to early detection of a further independent malignancy. Cancer surveillance might also be warranted for affected relatives and detection of a genetic mutation can allow for reproductive counseling.

Here we present an easy-to-use selection tool, based on a systematic review of pediatric cancer predisposing syndromes, to identify patients who may benefit from referral to a clinical geneticist. The selection tool involves five questions concerning family history, the type of malignancy, multiple primary malignancies, specific features and excessive toxicity, which results in the selection of those patients that may benefit from referral to a clinical geneticist.

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1. Introduction

In literature on this topic, it is often mentioned that 10% of pediatric cancer results from genetic predisposition. This number is derived from a study by Narod and colleagues in 1991 who performed a cancer registry and literature review (Narod et al., 1991). Since 1991, many novel genes predisposing to pediatric cancer have been reported. Examples are germline SMARCB1 mutations in patients with malignant rhabdoid tumors and SUFU mutations predisposing to medulloblastoma (Taylor et al., 2002; Versteege et al., 1998).

Identifying susceptibility for childhood cancer is relevant for the patient and his family. For some patients, this may lead to modified treatment strategies in case of expected increased toxicity or resistant disease as well as surveillance measures for early detection of a further independent malignancy. Family members of patients with an identified cancer predisposition syndrome may benefit from knowledge on increased cancer risks for themselves and also for them a cancer surveillance program might be warranted. Furthermore, detection of a cancer predisposing genetic mutation gives opportunities for reproductive counseling and prenatal diagnosis. Finally, identifying a genetic cause simply answers the question many parents presumably ask themselves: “Why did my child get cancer?”

Although the significance of recognizing tumor susceptibility in children is evident, in daily practice underlying syndromes and positive family histories are easily missed (Knapke et al., 2012; Merks et al., 2005). Recognizing susceptibility for pediatric cancer is further complicated by the fact that mutations in cancer predisposing genes do not necessarily result in a recognizable clinical phenotype. In addition, genetic forms of childhood cancer often lack a clear family history, for instance due to small family size or because the malignancy has arisen due to recessive or de novo germline mutations. Moreover, historically, pediatric cancer is a highly lethal disease and affected children did not grow up to start a family and pass on the predisposing mutation.

An easy-to-use selection tool to identify patients at high risk for...
The combination of pediatric and adult cancer at relatively young age in one family and combinations of different types of cancer should also trigger awareness of cancer susceptibility. Li Fraumeni syndrome, for instance, predisposes for a wide range of malignancies, with particularly high occurrences of soft tissue and bone sarcomas, brain tumors and breast cancer. Cancer in Li Fraumeni syndrome affects children, adolescents and adults.

Autosomal dominant syndromes comprise the majority of conditions that convey an increased risk of cancer at adult age. Several childhood cancer predisposing syndromes, which each individually are rare, show recessive inheritance. Consanguinity increases the birth prevalence of individuals with recessive disorders. Therefore, it is important to ask about family connections among the parents of the affected child.

In the selection tool (Fig. 1), family history-based criteria are mentioned for selection of patients with possible genetic predisposition for childhood cancer. The age of onset cut-off of 45 years for the selection criterion ‘multiple affected relatives’ was chosen to avoid referral of a large number of families affected by common cancers diagnosed after age 50 such as breast cancer.

2. Children with specific malignancies

Several malignancies have such a strong association with genetic predisposition, that diagnosis of these cancers always merits genetic evaluation independent of family history or other factors. Those malignancies are summarized in Table 1 and can be divided in two subgroups: malignancies that are regularly encountered in adult patients, but are extremely rare in children (for instance colorectal cancer due to constitutional mismatch repair deficiency syndrome (Wimmer and Etzler, 2008)) and childhood malignancies highly correlated with one or more specific genetic syndromes (for instance choroid plexus carcinoma and Li Fraumeni syndrome (Krutilkova et al., 2005)). When we composed this list of malignancies, we selected on the strength of the association with a predisposing condition, although exact numbers are often unavailable. In addition, we considered whether the syndrome is recognizable by other features included in our referral test. For instance, many syndromes have been reported in association with Wilms tumor but most of these can be recognized by additional features, like congenital anomalies or overgrowth (Scott et al., 2006). To avoid referral of all children with Wilms tumor, including the children at very low probability of a genetic condition, we did not include this malignancy as a referral criterion.

2.3. Children affected by multiple primary tumors

If a child develops two or more synchronous or metachronous neoplasms, genetic predisposition needs to be taken into account. Important in this respect is that children who seem to have a relapse of their first malignancy, may actually suffer from a second primary malignancy, that is similar to the original disease (Szczepanski et al., 2011).

Another complicating factor in patients with multiple consecutive neoplasms is that consecutive malignancies can have a treatment-related origin rather than being a result of genetic predisposition, or can be caused by a combination of both. This may be encountered more and more frequently, because the treatment of childhood cancer has tremendously improved over the past several decades, resulting in a large and growing population of long-term survivors. In general, the secondary treatment related malignancies are of two main types: acute leukemia and myelodysplastic syndrome after chemotherapy, or solid tumors related to radiotherapy (Bhatia and Sklar, 2002). An example of the latter type is a susceptibility for breast cancer in women treated with chest radiation for pediatric Hodgkin lymphoma (Travis et al., 2005). Other well-established radiation-related solid malignant neoplasms include thyroid cancers, brain tumors and sarcomas (Bhatia and Sklar, 2002). The individual role of chemotherapeutic agents is more difficult to determine, as most children receive multiple agents. An evident association has been found for topoisomerase II inhibitors and alkylating agents and the development of secondary acute myeloid leukemia (Bhatia and Sklar, 2002). The cumulative dose of these agents is an important factor in the actual risk of developing a secondary malignancy.

The timeframe separating the two malignancies can be informative to distinguish between therapy related and genetic predisposition related cancers. The latency between treatment of the primary cancer and the development of a secondary chemotherapy-related leukemia is generally short (~3 years), whereas solid, radiation induced tumors seem to have a latency longer than ten years (Bhatia and Sklar, 2002). As a consequence, genetic cancer predisposition needs to be considered in patients having multiple solid tumors in rapid succession or in patients who develop a second solid tumor without a history of radiotherapy or a second leukemia without a previous chemotherapy treatment.

To conclude: any child with two malignancies should be referred unless the second malignancy is consistent in time and/or tissue type with those expected from their treatment regimen.

2.4. Children with cancer and specific features

To facilitate the recognition of patients that need referral to a clinical geneticist, we here provide an overview in which the currently known childhood cancer predisposing syndromes are primarily categorized based on their phenotypic presentation. Many childhood cancer predisposing syndromes have characteristics in common. These are symptoms unrelated to the malignancy, which are present at birth or develop throughout life and range for instance from benign and subtle skin lesions to life threatening hematological conditions. We have divided these features in seven subgroups (Table 2) that will be explained in this section.
Childhood cancer, indication for referral to a clinical geneticist?

If your patient fulfills one or more of the criteria mentioned below (one or more circles filled), he or she may benefit from referral to a clinical geneticist.

1. Family history of the child with cancer
   - ≥ 2 malignancies at childhood age (≤ 18 years of age)
   - a first degree relative (parent or sibling) with cancer < 45 years of age
   - ≥ 2 second degree relatives with cancer < 45 years of age on the same side of the family
   - the parents of the child with cancer are related, i.e. consanguineous

2. A person with one of these tumors in childhood
   - Adrenocortical carcinoma
   - Atypical teratoid rhabdoid tumor
   - Cerebellar gangliocytoma
   - Choroid plexus carcinoma
   - Endolymphatic sac tumors
   - Hemangioblastoma
   - Hepatoblastoma
   - JMML
   - Low hypodiploid ALL
   - Malignant peripheral nerve sheath tumor
   - Medullary thyroid carcinoma
   - Medulloblastoma
   - Optic glioma
   - Ovarian sertoli-leydig cell tumor
   - Pleuropulmonary blastoma
   - Pituitary blastoma
   - Pineoblastoma
   - Retinoblastoma
   - Schwannoma
   - Subependymal giant cell tumor

   Or
   - A cancer of adult age, i.e. colorectal cancer, ovarian cancer, basal cell carcinoma etc.

3. A child with two malignancies one of those with onset < 18 years of age (unless the 2nd malignancy is consistent in time and/or tissue type with those expected from their treatment regimen).

4. A child with cancer and congenital anomalies or other specific symptoms

<table>
<thead>
<tr>
<th>Sign</th>
<th>Think of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital anomalies</td>
<td>Organs, bones, oral clefting, teeth, eyes, ears, brain, urogenital anomalies, etc.</td>
</tr>
<tr>
<td>Facial dysmorphisms</td>
<td></td>
</tr>
<tr>
<td>Intellectual disability</td>
<td></td>
</tr>
<tr>
<td>Aberrant growth</td>
<td>Length, head circumference, birth weight, asymmetric growth</td>
</tr>
<tr>
<td>Skin anomalies</td>
<td>Aberrant pigmentation i.e. &gt; 2 café-au-lait spots, vascular skin changes, hypersensitivity for sunlight, multiple benign tumors of the skin</td>
</tr>
<tr>
<td>Hematological disorders</td>
<td>Pancytopenia, anemia, thrombocytopenia, neutropenia</td>
</tr>
<tr>
<td>Immune deficiency</td>
<td></td>
</tr>
</tbody>
</table>

5. A child with excessive treatment toxicity
2.4.1. Congenital anomalies

Many molecular defects are known to give rise to congenital anomalies and cancer. Many molecular pathways involved in cancer initiation also play an important role in embryonic development. Numerous studies have demonstrated an increased incidence of congenital anomalies in children with cancer (Narod et al., 1997; Merks et al., 2008). However, in all studies the numbers were too small to determine any significant correlation between tumor types and individual anomalies.

This is illustrated by the relation between oral cleft and cancer development. Several cancer syndromes predispose children to a cleft lip and/or palate. Approximately eight percent of patients with Gorlin syndrome have an oral cleft (Lambrecht and Kreusch, 1997), and also in children with Beckwith Wiedemann syndrome and patients with a CDH1 mutation predisposing to gastric cancer and lobular breast cancer, this is a rarely reported feature (Choufani et al., 2010; Frebourg et al., 2006). Cohort studies however provide no evidence for an increased overall cancer risk for individuals born with oral clefts (Bille et al., 2005; Blot et al., 1980). Apparently, the incidence of oral cleft associated tumor predisposition syndromes, and the co-occurrence of oral cleft and cancer in patients with these syndromes is too low to give a significant correlation within such large population based studies. Nonetheless, if a child develops cancer and has an oral cleft or another congenital malformation, a cancer predisposing syndrome needs to be considered.

2.4.2. Facial dysmorphisms

Facial appearance can be a significant clue in the identification of syndromes. Children with the same syndrome often share characteristic facial features at significantly higher prevalence than a control population. These facial features can be subtle, as for example in Noonan syndrome (Fig. 2).

Pediatric oncologists are not specifically trained in recognizing and describing dysmorphisms by standardized terms. However, cancer predisposing syndromes characterized by dysmorphisms without any other features are extremely rare and therefore most children will still be selected based on other criteria of the tool in case dysmorphisms are not recognized by the oncologist.

2.4.3. Intellectual disability

Studies that address the prevalence rate of intellectual disability (ID) among childhood cancer patients are not available. Such a study would be complicated by the fact that the development of children may be affected directly by a malignancy, for instance in children with a brain tumor, by the patient being chronically ill, as well as by the treatment for cancer. Therefore, while assessing the level of intelligence, one has to inquire for the developmental skills prior to diagnosis of cancer.

Among the causes of cancer predisposing syndromes presenting with ID, two groups of genetic defects can be distinguished. Monogenic aberrations that give rise to both ID and cancer, and chromosomal aberrations, which affect a combination of a cancer predisposing gene and an ID gene. The latter aberrations include pancytopenia. Many of these syndromes predispose to leukemia, primarily acute myeloid leukemia and/or myelodysplastic syndrome. Solid tumors occur in Fanconi anemia, dyserkeratosis congenita and Diamond Blackfan anemia. (Alter, 2007) Table 6 gives an overview of tumor predisposition syndromes affecting

An overgrowth syndrome is defined as a condition with either localized or generalized excessive growth for age and sex. Congenital overgrowth is defined by a neonatal weight above the 97th percentile, while in childhood and adulthood overgrowth is defined by height rather than by weight. Many of the overgrowth disorders present with excessive growth in fetal life and infancy with subsequent decline in growth rate such that adults often have normal growth parameters. The most frequent overgrowth disorder is Beckwith Wiedemann syndrome, characterized by an enlarged tongue, macrosomia, midline abdominal wall defects, ear creases or pits and neonatal hypoglycemia (Choufani et al., 2010).

2.4.5. Growth failure

Growth retardation, like overgrowth, is an important hallmark of various pediatric cancer predisposing syndromes. These syndromes are mostly caused by mutations in DNA repair genes, mutations in RAS pathway genes or chromosomal aberrations (Table 4). Since cancer treatment can result in growth delay in children, it is important to collect data on the growth of the child before cancer diagnosis. The degree of growth retardation varies between the different syndromes. Some children have growth measures within the normal range for their age and gender, but are shorter compared to their target height. This is frequently observed in children with Noonan syndrome, which is further characterized by mild facial dysmorphisms and congenital heart defects.

2.4.6. Skin lesions

In many tumor predisposition syndromes, cutaneous findings are the presenting symptoms (Karalis et al., 2011). Some skin features manifest in specific periods of life. The mucocutaneous hyperpigmentation in Peutz-Jeghers syndrome for instance, fades after puberty (Reggs et al., 2010) and neurofibromatosis type 1 generally appear not until late childhood or adult age. Therefore, in order to recognize autosomal dominant syndromes, examination of the skin of both parents can be helpful. The observation of palmar pits in a parent of a child with medulloblastoma, is suggestive of Gorlin syndrome (Lo, 2008). Other skin lesions are striking for their appearance early in life. In Xeroderma pigmentosum, marked freckling of the face is present before the age of two years, which is rarely seen in children (Lehmann et al., 2011).

Café-au-lait macules are the most frequent cutaneous manifestation of tumor predisposition. Solitary café-au-lait spots are common birthmarks. The presence of more than one café-au-lait spot is less common. In school-aged children, at least one café-au-lait spot is noted in approximately 25% of children, whereas three or more macules are observed in 1–3% of the children (Shah, 2010). It is unusual for sporadic café-au-lait spots to develop after the age of six years; in syndromes such as Neurofibromatosis type 1, however, new macules may continue to develop throughout childhood and adulthood (Shah, 2010). Specific physical investigation using wood light can be of assistance to improve observation of hyper-as well as hypopigmented skin lesions. The latter can be a hallmark of constitutional mismatch repair deficiency syndrome for instance.

In Table 5 skin lesions associated with childhood cancer predisposing syndromes are summarized.

2.4.7. Hematological abnormalities

In several syndromes, defects in hematopoiesis precede cancer development, including abnormalities of a single cell lineage or pancytopenia. Many of these syndromes predispose to leukemia, primarily acute myeloid leukemia and/or myelodysplastic syndrome. Solid tumors occur in Fanconi anemia, dyskeratosis congenita and Diamond Blackfan anemia. (Alter, 2007) Table 6 gives an overview of tumor predisposition syndromes affecting
A boy with Noonan syndrome caused by a PTPN11 mutation. Note a bilateral downsllant of the palpebral fissures, ptosis, a broad nasal bridge and low set posteriorly rotated ears.

Table 1
Cancer types considered eligible for clinical genetic evaluation.

<table>
<thead>
<tr>
<th>1) Cancers of adult age, which are extremely rare in the pediatric age group</th>
<th>Syndrome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.e. colorectal cancer, ovarian cancer, pheochromocytoma, basal cell carcinoma etc.</td>
<td>Adrenocortical carcinoma</td>
<td>Li Fraumeni syndrome, BWS, MEN1, FAP</td>
</tr>
<tr>
<td></td>
<td>Atyp. teratoid malignant rhabdoid tumor</td>
<td>Rhabdoid Predisposition syndrome</td>
</tr>
<tr>
<td></td>
<td>Cerebellar gangliocytoma</td>
<td>PTEN hamartoma tumor syndrome</td>
</tr>
<tr>
<td></td>
<td>Choroid Plexus Carcinoma</td>
<td>Li Fraumeni syndrome</td>
</tr>
<tr>
<td></td>
<td>Endolymphatic sac tumors</td>
<td>Von Hippel-Lindau syndrome</td>
</tr>
<tr>
<td></td>
<td>Hemangioblastoma</td>
<td>Von Hippel-Lindau syndrome</td>
</tr>
<tr>
<td></td>
<td>Hepatoblastoma</td>
<td>FAP, BWS</td>
</tr>
<tr>
<td></td>
<td>Juvenile myelomonocytic leukemia</td>
<td>Neurofibromatosis type 1, Noonan syndrome, CBL germline syndrome, Constitutional Mosaic Trisomy 8</td>
</tr>
<tr>
<td></td>
<td>Low hypodiploid acute lymphoblastic leukemia</td>
<td>Li Fraumeni syndrome</td>
</tr>
<tr>
<td></td>
<td>Malignant peripheral nerve sheath tumor</td>
<td>Neurofibromatosis type 1</td>
</tr>
<tr>
<td></td>
<td>(Malignant) Schwannoma</td>
<td>Neurofibromatosis type 1 and 2, Schwannomatosis, Carney complex</td>
</tr>
<tr>
<td></td>
<td>Medullary thyroid carcinoma</td>
<td>MEN2</td>
</tr>
<tr>
<td></td>
<td>Medulloblastoma (in particular &lt; 3 years of age)</td>
<td>Neurofibromatosis type 1 and germline mutations in SUFU</td>
</tr>
<tr>
<td></td>
<td>Optic pathway glioma</td>
<td>Neurofibromatosis type 1 and 2, Schwannomatosis, Carney complex</td>
</tr>
<tr>
<td></td>
<td>Ovarian Sertoli-Leydig cell tumor</td>
<td>DICER1 syndrome</td>
</tr>
<tr>
<td></td>
<td>Pleuropulmonary blastoma</td>
<td>DICER1 syndrome</td>
</tr>
<tr>
<td></td>
<td>Pineoblastoma</td>
<td>DICER1 syndrome</td>
</tr>
<tr>
<td></td>
<td>Pituitary blastoma</td>
<td>DICER1 syndrome</td>
</tr>
<tr>
<td></td>
<td>Retinoblastoma</td>
<td>Retinoblastoma predisposition syndrome</td>
</tr>
</tbody>
</table>

Table 2
Patient characteristics suggestive of hereditary pediatric cancer.

| 1 | Congenital anomalies |
| 2 | Facial dysmorphisms |
| 3 | Intellectual disability |
| 4 | Growth disturbances |
| 5 | Skin lesions |
| 6 | Hematological disorders |
| 7 | Immune deficiency |

2.4.8. Immunodeficiencies

Children with primary immunodeficiencies are at risk for developing cancer, particularly lymphoproliferative disorders. In the majority of these conditions, infections play a pivotal role in the development of lymphomas and carcinomas. In addition, the defect in immune surveillance may affect the ability to identify and eliminate cancer cells (Tran et al., 2008). An example is Wis- kott–Aldrich syndrome, characterized by eczema, thrombocytopenia, immune deficiency, and a high risk (13–22%) of developing lymphomas (Sullivan et al., 1994; Imaj, 2004).

A separate group of immunodeficiency syndromes are the genetic disorders of DNA repair. The development of effective immune responses is dependent on the generation of an enormous number of genetically diverse B and T cells (Oltz, 2001). These unique cells are created by breaking, randomly re-sorting and then joining the DNA sequences coding for antigen receptors. For this process the DNA repair mechanisms normally utilized to maintain genome stability are used (Gennery et al., 2000). As a result, defects in these pathways result both in cancer, mainly tumors of hematopoietic and epithelial origin, and in immunodeficiency. A review of immunodeficiency conditions in children is provided in references (Adriaens et al., 2009) and (Ochs and Hagen, 2014).

2.5. Children with excessive treatment toxicity

Most treatments for cancer give adverse side effects and a proportion of patients will experience significant complications. In some cancer predisposition syndromes, however, the side effects are more severe, which may give a clue for syndrome diagnosis. Examples of excessive treatment toxicity are seen in Ataxia Telangiectasia, Nijmegen Breakage syndrome, and other immunodeficiency and DNA repair disorders. Patients suffering from these syndromes may experience severe complications after standard doses of radiotherapy or chemotherapy, resulting from defective repair of normal tissues following therapy (Biernemann et al., 2011).

In some syndromes, the adverse side effects are not present during the treatment, but become apparent after a time interval.
Patients with Gorlin syndrome are abnormally sensitive to radiation therapy, and may develop a large number of basal cell tumors in the irradiated area several years after exposure (Evans et al., 1991b; Kimonis et al., 1997; Walter et al., 1997). This example illustrates the importance of considering the presence of a syndrome before starting treatment.

3. Discussion

In this article, an overview of symptoms and characteristics is given for the identification of children affected by cancer who are at high risk of carrying a cancer predisposing genetic mutation. Based on these criteria we have developed a selection tool, to be used by the pediatric oncologist for the selection of children who may benefit from referral to a clinical geneticist. To explain how we have chosen the different items on which we have based the selection tool, many examples of cancer prone syndromes and their associated features are given. We would like to state however, that this manuscript does not provide a complete list of all pediatric cancer predisposing conditions and associated symptoms.

Previously, in our center online selection tools were developed to detect patients with a high familial risk of colorectal cancer and

Table 3

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Malignancies reported</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized overgrowth syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beckwith Wiedemann syndrome</td>
<td>Wilms tumor, hepatoblastoma, adrenocortical carcinoma, neuroblastoma, rhabdomyosarcoma</td>
<td>(Rump et al., 2005)</td>
</tr>
<tr>
<td>Sotos syndrome</td>
<td>Leukemia, lymphoma, Wilms tumor, sacrococcygeal teratoma, neuroblastoma</td>
<td>(Tatton-Brown and Rahman, 2007)</td>
</tr>
<tr>
<td>Simpson Golabi Behmel syndrome</td>
<td>Wilms tumor, hepatoblastoma, neuroblastoma, gonadoblastoma, hepatocellular carcinoma</td>
<td>(Lapunzina et al., 1998)</td>
</tr>
<tr>
<td>Perlmutter syndrome</td>
<td>Wilms tumor</td>
<td>(Alessi et al., 2008)</td>
</tr>
<tr>
<td>Weaver syndrome</td>
<td>Neuroblastoma</td>
<td>(Bassel-Vanagaite, 2010)</td>
</tr>
<tr>
<td>Partial overgrowth syndromes</td>
<td>Wilms tumor, hepatoblastoma, adrenocortical carcinoma</td>
<td>(Bliick et al., 2008; Clericuzio and Martin, 2009)</td>
</tr>
<tr>
<td>Isolated Hemihiperpiglacia</td>
<td>Leukemia, meningioma, retinoblastoma, Wilms tumor</td>
<td>(Lapunzina et al., 2004)</td>
</tr>
<tr>
<td>Macrocephaly-capillary malformation syndrome</td>
<td>Leukemia, meningioma, retinoblastoma, Wilms tumor</td>
<td>(Lapunzina et al., 2004)</td>
</tr>
<tr>
<td>Proteus syndrome</td>
<td>Wilms tumor, meningioma</td>
<td>(Gordon et al., 1995)</td>
</tr>
<tr>
<td>PIK3CA-Related Segmental Overgrowth Syndrome</td>
<td>Wilms tumor, rhabdomyosarcoma</td>
<td>(Mirzaa et al., 2013)</td>
</tr>
<tr>
<td>Ewing sarcoma family of proteins</td>
<td>Cerebellar gangliocytoma, thyroid cancer, breast cancer, endometrial cancer, colon cancer</td>
<td>(Nieuwenhuis et al., 2014)</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>Optic pathway glioma, leukemia, malignant peripheral nerve sheath tumor, Rhabdomyosarcoma, neuroblastoma, bladder cancer</td>
<td>(Walker et al., 2006)</td>
</tr>
<tr>
<td>Costello syndrome</td>
<td>Wilms tumor, medulloblastoma, basal cell carcinoma</td>
<td>(Evans et al., 1991a; Jones et al., 2011)</td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>Medulloblastoma, basal cell carcinoma</td>
<td>(Evans et al., 1991a; Jones et al., 2011)</td>
</tr>
<tr>
<td>Tall stature</td>
<td>Medulloblastoma, basal cell carcinoma</td>
<td>(Evans et al., 1991a; Jones et al., 2011)</td>
</tr>
<tr>
<td>MEN 2B</td>
<td>Medullary thyroid carcinoma, phaeochromocytoma</td>
<td>(Skinner et al., 1996)</td>
</tr>
</tbody>
</table>

* various epigenetic and/or genetic alterations that deregulate imprinted genes on chromosome 11p15.5.

Table 4

<table>
<thead>
<tr>
<th>Growth retardation syndromes</th>
<th>Low birth-weight</th>
<th>Short stature</th>
<th>Microcephaly</th>
<th>Malignancies reported</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA repair syndromes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosaic Variegated Aneuploidy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Wilms tumor, rhabdomyosarcoma</td>
<td>(Jacquemont et al., 2002)</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>−5%</td>
<td>+</td>
<td>−20%</td>
<td>MDS, AML, ALL, squamous cell carcinomas of the head, neck and anogenital region</td>
<td>(Alter, 2003)</td>
</tr>
<tr>
<td>Rothmund Thomson syndrome</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Osteosarcoma, skin cancer</td>
<td>(Wang et al., 2001)</td>
</tr>
<tr>
<td>Cartilage Hair Hypoplasia</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Lymphoma, basal cell carcinoma</td>
<td>(Taskinen et al., 2008)</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>AML, lymphoma, epithelial cancers</td>
<td>(German, 1997)</td>
</tr>
<tr>
<td>Nijmegen Breakage syndrome</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Lymphoma, medulloblastoma, glioma, rhabdomyosarcoma</td>
<td>(Wegner et al., 1999)</td>
</tr>
<tr>
<td>Ras related disorders</td>
<td></td>
<td></td>
<td></td>
<td>leukemia, lymphoma</td>
<td>(Kratz et al., 2011; Kratz et al., 2015)</td>
</tr>
<tr>
<td>Cardio Facio Cutaneous syndrome</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
<td>leukemia, lymphoma</td>
<td>(Kratz et al., 2011; Kratz et al., 2015)</td>
</tr>
<tr>
<td>Costello syndrome</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>Rhabdomyosarcoma, neuroblastoma, bladder cancer</td>
<td>(Kratz et al., 2011; Kratz et al., 2015)</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>Leukemia, neuroblastoma, rhabdomyosarcoma</td>
<td>(Kratz et al., 2011; Kratz et al., 2015)</td>
</tr>
<tr>
<td>Noonan syndrome with multiple lentigines</td>
<td>−</td>
<td>&lt;50%</td>
<td>−</td>
<td>Leukemia, neuroblastoma</td>
<td>(Kratz et al., 2011)</td>
</tr>
<tr>
<td>Chromosomal aberrations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>Leukemia</td>
<td>(Muller and Rubinstein, 1995)</td>
</tr>
<tr>
<td>(Mosaic) Trisomy 18</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Hepatoblastoma</td>
<td>(Maruyama et al., 2001)</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Gonadoblastoma</td>
<td>(Bianco et al., 2009)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubinstein Taybi syndrome</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>Various</td>
<td>(Kratz et al., 2011; Kratz et al., 2015)</td>
</tr>
<tr>
<td>Mulibrey Nanism</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Wilms tumor</td>
<td>(Kratz et al., 2011)</td>
</tr>
</tbody>
</table>
breast cancer. These tests guide clinicians and patients through appropriate family history collection and provide an instant conclusion regarding the presence or absence of an increased hereditary cancer risk (https://www.radboudumc.nl/pages/hereditarycancer.aspx). Evaluation of the colorectal cancer referral test revealed a high sensitivity in detecting individuals with

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Cutaneous features of childhood cancer predisposition syndromes.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin lesions</strong></td>
<td><strong>Syndrome</strong></td>
</tr>
<tr>
<td>Abnormal pigmentation</td>
<td>Cafe-au-lait spots</td>
</tr>
<tr>
<td>Hypopigmented macules</td>
<td></td>
</tr>
<tr>
<td>Auxiliary freckling</td>
<td>Pigmented macules on mucosal surfaces, face, fingers and peri-anal.</td>
</tr>
<tr>
<td>Lentigines</td>
<td>Marked freckling of sun-exposed areas</td>
</tr>
<tr>
<td>Reticular pigmentation</td>
<td></td>
</tr>
<tr>
<td>Epidermal naevi</td>
<td></td>
</tr>
<tr>
<td>Vascular changes</td>
<td>Cutaneous hemangiomas</td>
</tr>
<tr>
<td>Angiofibromas</td>
<td></td>
</tr>
<tr>
<td>Telangiectasias</td>
<td></td>
</tr>
<tr>
<td>Capillary malformations</td>
<td></td>
</tr>
<tr>
<td>Facial naevoid flammans</td>
<td></td>
</tr>
<tr>
<td>Photo sensitivity</td>
<td>Sun-sensitive butterfly facial rash</td>
</tr>
<tr>
<td>Poikiloderma</td>
<td>Severe sun-sensitivity</td>
</tr>
<tr>
<td>Skin tumors</td>
<td>Mucosal neuromas</td>
</tr>
<tr>
<td>Cutaneous neuromas</td>
<td>Lipomas</td>
</tr>
<tr>
<td>Neurofibromas</td>
<td>Schwannomas</td>
</tr>
<tr>
<td>Neurofibromatosis papules</td>
<td>Cutaneous myxomas</td>
</tr>
<tr>
<td>Cutaneous myxomas</td>
<td>Acral keratosis</td>
</tr>
<tr>
<td>Facial sebaceous epidermal naevi</td>
<td>Trichoepitheliomas</td>
</tr>
<tr>
<td>Other</td>
<td>Facial milia</td>
</tr>
<tr>
<td>Scleroderma-like skin changes</td>
<td>Seborrheic dermatitis</td>
</tr>
<tr>
<td>Premalignant actinic keratoses</td>
<td>Sebaceous and dermoid cysts</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>Shagreen patch</td>
</tr>
<tr>
<td>Scleroderma-like skin changes</td>
<td>Palmar or plantar pits</td>
</tr>
<tr>
<td>Plantar hyperkeratosis</td>
<td>Plantar hyperkeratosis</td>
</tr>
<tr>
<td>Acral keratosis</td>
<td></td>
</tr>
<tr>
<td>Trichoepitheliomas</td>
<td>Eczema</td>
</tr>
<tr>
<td>Pilomatricomas</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Facial milia</td>
</tr>
<tr>
<td>Scleroderma-like skin changes</td>
<td></td>
</tr>
</tbody>
</table>

CMMR-D – Constitutional mismatch repair-deficiency syndrome; NF-1 – Neurofibromatosis type I; NF-2 – Neurofibromatosis type II; MEN – multiple endocrine neoplasia.

breast cancer. These tests guide clinicians and patients through appropriate family history collection and provide an instant conclusion regarding the presence or absence of an increased hereditary cancer risk (https://www.radboudumc.nl/pages/hereditarycancer.aspx). Evaluation of the colorectal cancer referral test revealed a high sensitivity in detecting individuals with

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Cancer predisposition syndromes associated with preceding hematological abnormalities.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td><strong>Cell lineage</strong></td>
</tr>
<tr>
<td>Congenital amegakaryocytic thrombocytopenia</td>
<td>All lineages</td>
</tr>
<tr>
<td>Schwachmann Diamond syndrome</td>
<td>All lineages</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>All lineages</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>All lineages</td>
</tr>
<tr>
<td>Familial mosaic monosomy 7 syndrome</td>
<td>All lineages</td>
</tr>
<tr>
<td>Diamond Blackfan anemia</td>
<td>Anemia</td>
</tr>
<tr>
<td>Cartilage hair hypoplasia</td>
<td>Anemia, lymphopenia, neutropenia</td>
</tr>
<tr>
<td>Familial platelet disorder with predis. for AML</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>Thrombocytopenia, neutropenia</td>
</tr>
<tr>
<td>Severe congenital neutropenia</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>ETV6 related familial leukemia</td>
<td>Thrombocytopenia and red cell macrocytosis</td>
</tr>
<tr>
<td>GATA2 deficiency</td>
<td>Neutropenia, deletion of dendritic cells, neutrophils, B and NK cells</td>
</tr>
<tr>
<td>ANKR2D6-related thrombocytopenia</td>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>
increased risk of Lynch syndrome, even if used by nonmedical staff members (Dekker et al., 2014). The success of this selection tool enthused us to develop something similar for children with pedi-atric cancer, which of course is a much more heterogeneous group of conditions.

The selection tool presented here has several limitations. The input in the test is based on the physical examination, the medical history and the pedigree evaluation performed by the pediatric oncologist. Many studies have demonstrated poor family history data in medical records (Wood et al., 2014). The test in itself may already improve this part of clinical care for children with cancer because it reminds physicians of collecting a family history. However, along with implementing this test in routine clinical care it is essential to educate users of the test in the essentials of collecting a thorough family history and what questions can be asked specifically. The same is true for the physical examination by which congenital anomalies, skin lesions and dysmorphisms are detected. Educational sessions using pictures of recognizable features, or a period of training alongside a clinical geneticist in daily practice may improve the skills of the pediatric oncologist and thereby the sensitivity of the test.

Another limitation of the test is a lack of evidence based studies to support decisions about which criteria to include. Regarding topics for which scientific literature was lacking, choices were made based on experience and expertise of the authors. Validation of the test at larger scale will reveal whether adjustments need to be made.

We would like to make it abundantly clear that the guidelines described are meant for genetic referral of a child already diagnosed with cancer and the test should not be used for consideration of a cancer susceptibility syndrome in a child without a cancer diagnosis. Although there are a number of cancer predisposing disorders with for instance growth failure or intellectual disability there are many more genetic conditions associated with these features that do not have a substantial cancer risk. In addition, it is important to realize that molecular genetic testing will not be indicated in all children picked-out by the selection tool. The tool helps to select children who may benefit from referral to a clinical geneticist and the geneticist will apply a further selection and will decide in which patients molecular testing is indicated.

In conclusion, we have developed an easy-to-use selection tool, based on a systematic review of pediatric cancer predisposing syndromes, to select patients who may benefit from genetic counseling. We believe that structural application of the selection tool for each newly diagnosed child with cancer will augment the detection of children with a genetic predisposition for cancer. Future studies are needed to reveal the sensitivity and specificity of this tool.

Conflicts of interest

There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmg.2016.01.008.

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