A Summary of the Inaugural WHO Classification of Pediatric Tumors: Transitioning from the Optical into the Molecular Era

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ABSTRACT Pediatric tumors are uncommon, yet are the leading cause of cancer-related death in childhood. Tumor types, molecular characteristics, and pathogenesis are unique, often originating from a single genetic driver event. The specific diagnostic challenges of childhood tumors led to the development of the first World Health Organization (WHO) Classification of Pediatric Tumors. The classification is rooted in a multilayered approach, incorporating morphology, IHC, and molecular characteristics. The volume is organized according to organ sites and provides a single, state-of-the-art compendium of pediatric tumor types. A special emphasis was placed on "blastomas," which variably recapitulate the morphologic maturation of organs from which they originate.

Significance: In this review, we briefly summarize the main features and updates of each chapter of the inaugural WHO Classification of Pediatric Tumors, including its rapid transition from a mostly microscopic into a molecularly driven classification systematically taking recent discoveries in pediatric tumor genomics into account.

INTRODUCTION

Why Pediatric Tumors Need a Separate Classification

Childhood tumors are fundamentally different in many ways from those occurring in adults. Despite being extremely heterogeneous, they account for only approximately one percent of all tumor diagnoses, but at the same time represent the most common cause of disease-related death in children (1). In contrast to malignancies in adults, which are mostly of epithelial origin and often caused by an extended exposure

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to carcinogens, tumors in childhood are often derived from the mesoderm or neuroectoderm, and, with the exception of hereditary cancer predisposition in approximately 10% of patients, their etiology is largely unknown (2). According to data from the Leukemia and Lymphoma Society, the most common groups of cancer in children, adolescents, and young adults (CAYA; i.e., younger than 20 years) are: leukemia (24.7%), tumors of the nervous system (17.2%), non-Hodgkin lymphoma (7.5%), Hodgkin lymphoma (6.5%), and soft-tissue sarcoma (5.9%). In contrast to cells successively acquiring genetic hits over time in adults, pediatric tumors are typically caused by a maturation block occurring in an immature developing cell type (3). Tumors in children typically carry a much lower burden of genetic aberrations, often driven by a single and thus clonal genetic driver event, such as a translocation leading to an oncogenic fusion (4, 5). Tumors in children predominantly show very limited immune cell infiltration and are thus often considered immunologically "cold" tumors (6–8). All of these unique properties of childhood cancers need to be considered when diagnosing and ultimately treating these children, thus fully justifying a separate World Health Organization (WHO) classification specifically focusing on pediatric tumors. Given the relative rarity of pediatric tumors compared with cancer in adults, cooperation across multiple institutions, national and international consortia, are required to gather enough cases to produce statistically significant data. However, these efforts are complex and face many challenges, including difficulties in communication, sharing biological materials, diverse classification systems applied in different regions of the world, etc. With this in mind, this WHO pediatric tumor classification represents a special effort to use a reproducible and evidence-based taxonomic system, striving for a uniform classification that may result in worldwide improvements.

This new WHO classification of pediatric tumors is intended to support the pathologist responsible for diagnosing the tumor and the multidisciplinary team tailoring treatment intensity to disease risk and matching patients to specific therapies. It should also improve access to molecular genetic testing and, consequently, innovative treatments for children with cancer through increased knowledge of molecularly defined disease subtypes and therapeutic target frequencies resulting from their routine assessment at the time of diagnosis.

Tumor Classification According to WHO Criteria

For the first time, pediatric tumors are covered in a separate volume in the new fifth edition of the WHO classification of tumors. In previous editions, pediatric tumors were covered together with adult tumors in the respective organ systems. As outlined before, it is increasingly clear that many aspects of pediatric tumors differ significantly from those of adults. Even tumors that histologically appear to be of the same type often have distinctive etiology and pathogenesis, which is reflected in their diagnosis and clinical behavior. In the fifth edition series, this has been recognized and the opportunity has been taken to describe these tumors in greater detail.

In keeping with other volumes in the fifth edition series, the WHO Classification of Pediatric Tumors follows a hierarchical classification and lists tumors by site, category, family and type. Each tumor type is described with a common, defined set of characteristics, and where information is not available, this is clearly indicated. The classification is also published on a website, which permits the use of whole-slide images and hyperlinks to evidence cited. Improving the quality of evidence is an important facet of the evolution of the classification of tumors, and hence diagnosis. As a result, we have sought to include new information from methylation studies, and other genomic investigations using HUGO Gene Nomenclature Committee (HGNC) and Human Genome Variation Society (HGVS) notation as appropriate. For those tumors where assessment of proliferation is important for diagnosis or prognosis, we recommend that mitoses are now counted per millimeter squared, thus adhering to standardized international (SI) units, as microscope high-power fields can be of variable size (9). We have also encouraged authors to use medians rather than means when skewed data are being considered. This is particularly important when pediatric age distributions are considered.

Novel Diagnostic Technologies

The diagnostic shift from morphology to molecular analyses is driven by both technology and the need for an even more granular and unbiased classification to optimally serve our patients. Foremost, the introduction of global approaches including next-generation sequencing (NGS), methylome analysis, and proteomics are driving this development. Tumor classification in recent years has been greatly influenced by methylation analysis, being the technology at present best suited for addressing lineage and thereby the cell population of origin of tumors (10, 11). The stability of the diagnostic methylation pattern seen in multiple specimens from the same tumor resection and throughout further progression belies the concept of methylation states representing cellular differentiation rather than neoplastic changes (12). In contrast, NGS focuses on tumor-specific alterations which may be pathognomonic in some instances, especially in the context of genetically "simple" pediatric tumors with gene fusions, focal amplifications, or point mutations. NGS employed in common diagnostic settings addresses differently sized gene panels (13) up to whole-exome (or even whole-genome) sequencing with a tendency to shift toward the latter (14–18). The added value of integrating somatic and germline sequencing data is becoming increasingly evident in this context. One diagnostically valuable NGS technology is RNA sequencing (RNA-seq), which reliably detects pathognomonic gene fusions and provides insight in the activity of gene transcription (19). Diagnostic protein analysis, currently almost exclusively facilitated by IHC, will be supplemented by mass spectrometry–based proteomics allowing simultaneous identification and quantification of several thousand proteins in tumor tissues (20, 21). There is an expectation that this will shed light on the activity of cellular signaling pathways. For example, information about phosphoproteins could lead to recommendations for specific inhibitory therapies. Proteome analyses may turn out to be the most direct approach to tumor characterization, as it combines the readout of cellular responses to epigenetic differentiation settings, tumor-specific structural alterations, and optimization-driven cellular regulation.

In conclusion, future tumor diagnostics are likely to rely on several molecular platforms that contribute orthogonal information to address the questions "where does it come

from?" (methylome analyses), "how far has it gone?" (NGS), and "how to treat the patient?" (NGS, proteomics). That said, morphologic tumor diagnostics is also progressing. Identifying novel tumor types based on their molecular profile is followed by focused histologic and IHC evaluation that frequently detects diagnostic features, which can be assessed with classic technologies. Examples are the primary intracranial sarcoma, *DICER1*-mutant (22, 23), the diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (24, 25), or the recently described neuroepithelial tumor with *PATZ1* fusion (26). Rapid progress is being made with artificial intelligence–based analysis of morphologic images, and this may contribute greatly to tumor evaluation (27, 28). An important task to solve is how to merge the different diagnostic molecular and imaging platforms, including preoperative data, to make a combined evaluation.

Integrated and Layered Diagnoses

A pathologic diagnosis serves the purpose of communicating information relevant for tailored management, including on prognosis and therapeutic options, in the most condensed manner. The diagnosis should be standardized and suitable for local, national, and international communication. Among several approaches, the WHO Classification system emerged as most widely accepted. For a long time, the WHO Classification has provided recommendations on how to reach diagnoses in ways which could be successfully performed in most parts of the world. However, the enormous progress, mainly in molecular diagnosis, which has far-reaching impact on classification, grading, and therapy, is not compatible anymore with such a highly condensed diagnosis or with very different local requirements. When possible, a large body of relevant information needs to be communicated, but the amount of additional information gathered varies from institution to institution and country to country. To overcome this problem, a multilayered diagnosis resulting in an integrated diagnosis has been devised (29, 30). Key to this approach are four of the major characteristics consisting of (i) a compilation of the data from ii–iv to an integrated diagnosis, (ii) a (classic) morphologic evaluation, (iii) a tumor grade, and (iv) a level providing the most salient molecular information. The minimum requirements for reaching the predefined integrated diagnoses are provided by the WHO classification. While many tumors do fit such a matrix, two problems may occur due to either a lack of information or nonmatching information. Where essential molecular tests are not available, the solution is the addition of "not otherwise specified" (NOS) to the morphologic evaluation. In cases where molecular information does not match a WHO tumor type, the addition of "not elsewhere classified" (NEC) to the diagnosis highlights this problem (30, 31). In summary, the integrated diagnosis serves to communicate diagnoses based on different levels of analyses while still maintaining a universal terminology.

ENTITY-SPECIFIC DEVELOPMENTS

Leukemias and Lymphomas

Hematolymphoid neoplasms are the most prevalent group of cancers (38.7%) in CAYA. With increasing knowledge of the genetics of hematolymphoid neoplasms, a molecularly oriented classification has a significant impact on the accuracy of diagnosis, treatment, and prognosis. In recent years, the availability of conjugated or unconjugated mAbs against specific targets (such as CD20, CD19, CD22), small molecules interfering with activated molecular pathways (such as tyrosine kinase inhibitors, γ-secretase inhibitors, FLT3 inhibitors), and genetically engineered chimeric antigen receptor T cells (CAR T) as immunotherapy has broadened the opportunities to target the key genetic aberrations in patients with various leukemias and lymphomas (32–36).

Hematopathology has been at the forefront in the adoption of newly available molecular techniques, and indeed the current WHO classification of hematolymphoid neoplasms has long since evolved from a morphologic classification to a classification that integrates clinical, morphologic, immunophenotypical, and molecular features in the definition of entities (37, 38).

The classification of hematolymphoid neoplasms in the WHO Classification of Pediatric Tumors focuses on the landscape of these neoplasms in CAYA and is essentially an adaptation of the revised fourth edition of WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (Table 1; refs. 32, 39–41). Consequently, adult-type entities that are rare or practically nonexistent in the CAYA age group, such as chronic neutrophilic leukemia, polycythemia vera, essential thrombocythemia, chronic eosinophilic leukemia, and chronic lymphocytic leukemia (CLL), are not part of the pediatric classification, while they are described in detail in the WHO Classification of Hematopoietic and Lymphoid Tissues. Biological and genetic abnormalities are a defining criterion in some entities, such as chronic myeloid leukemia (CML), acute myeloid leukemia (AML) with recurrent genetic abnormalities, large B-cell lymphoma with *IRF4* rearrangement, and *ALK*-positive anaplastic large cell lymphoma. In other entities, genetic aberrations contribute to the diagnosis, identify prognostic categories, or represent targets potentially amenable to therapy.

Leukemias and Myeloid Neoplasms

Leukemias comprise one fourth to one third of all malignancies in CAYA, with 80% being acute lymphoblastic leukemia (ALL), 15% AML, and 2% CML. Thus, the proportions of the various leukemia types differ markedly from those seen in adults (38% AML, 30% CLL, 15% CML, 11% ALL).

ALL represents the most common type of leukemia in CAYA, with 85% being of B-lineage (B-ALL; B-lymphoblastic leukemia; ref. 42). Most cases show recurrent genetic abnormalities (Table 1 and more detailed in Supplementary Table S1), which have prognostic significance, for example, B-ALL with *ETV6::RUNX1*, *TCF3::PBX1* and high hyperdiploidy is associated with a favorable outcome, whereas B-ALL with hypodiploidy and *KMT2A* rearrangement is associated with a poor prognosis (34). *BCR::ABL*-like (Philadelphia-like) B-ALL is a high-risk B-ALL characterized by heterogeneous genetic alterations, unified by a gene expression profile similar to Ph-positive B-ALL while lacking *BCR::ABL1* gene fusion (43). Genetic alterations are variable and may include *IKZF1* deletion, *CRLF2* rearrangement and overexpression, JAK/IL7R mutations, *ABL1* class fusions, *EPOR* rearrangements, tyrosine kinase pathway activation, and other less common genomic alterations. As a result, for a precise diagnosis it is often

Table 1. Classification of pediatric leukemias and lymphomas

Myeloid neoplasms
- *Myeloproliferative neoplasms*
  - Chronic myeloid leukemia, *BCR::ABL1* positive
- *Myelodysplastic/myeloproliferative neoplasms*
  - Juvenile myelomonocytic leukemia
- *Myelodysplastic syndromes*
  - Refractory cytopenia of childhood
  - Myelodysplastic syndrome with excess blasts
- *Myeloid neoplasms with germline predisposition*
- *Myeloid proliferations associated with Down syndrome*
- *Acute myeloid leukemia and related neoplasms*
  - Acute myeloid leukemia, NOS
  - Acute myeloid leukemia with recurrent genetic abnormalities
    - AML with t(8;21)(q22;q22); *RUNX1::RUNX1T1*
    - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB::MYH11*
    - APL with t(15;17)(q24.1;q21.2); *PML::RARA*
    - AML with *KMT2A*-rearrangement *new*
    - AML with t(6;9)(p23;q34.1); *DEK::NUP214*
    - AML with inv(3)(q21q26)/t(3;3)(q21;q26); *GATA2, RPN1::MECOM*
    - AML with *ETV6*-fusion *new*
    - AML with t(8;16)(p11.2;p13.3); *KAT6A::CREBBP new*
    - AML with t(1;22)(p13.3;q13.1); *RBM15::MKL1*
    - AML with *CBFA2T3::GLIS2* (inv(16)(p13q24)) *new*
    - AML with *NUP98*-fusion *new*
    - AML with t(16;21)(p11;q22); *FUS::ERG new*
    - AML with mutated *NPM1*
    - AML with bZIP mutated *CEBPA*

Mast cell neoplasia
- Mastocytosis

Lymphoid neoplasms

Precursor lymphoid neoplasms
- *B-cell lymphoblastic leukemia/lymphomas*
  - B-LBLL with t(9;22)(q34.1;q11.2); *BCR::ABL1*
  - B-LBLL with t(v;11q23.3); *KMT2A*-rearranged
  - B-LBLL with t(12;21)(p13.2;q22.1); *ETV6::RUNX1*
  - B-LBLL with hyperdiploidy, high
  - B-LBLL with hypodiploidy, near-haploid
  - B-LBLL with hypodiploidy, low
  - B-LBLL with hypodiploidy, high
  - B-LBLL with t(5;14)(q31.1;q32.3); *IGH::IL3*
  - B-LBLL with t(1;19)(q23;p13.3); *TCF3::PBX1*
  - B-LBLL, *BCR::ABL1*-like (Philadelphia-like B-ALL)
  - B-LBLL with iAMP21
- *T-cell and natural killer (NK)–cell lymphoblastic leukemia/lymphoma*
  - T-lymphoblastic leukemia/lymphoma
  - Early T-cell precursor lymphoblastic leukemia
  - NK-lymphoblastic leukemia/lymphoma

Mature B-cell neoplasms
- Primary mediastinal (thymic) large B-cell lymphoma
- Diffuse large B-cell lymphoma, NOS
- EBV-positive diffuse large B-cell lymphoma, NOS
- Large B-cell lymphoma with *IRF4* rearrangement
- Pediatric-type follicular lymphoma
- Pediatric nodal marginal zone lymphoma
- *ALK*-positive large B-cell lymphoma
- Lymphomatoid granulomatosis
- Plasmablastic lymphoma

Table 1. Classification of pediatric leukemias and lymphomas (*Continued*)

Grey-zone lymphoma
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration
Mature T/NK-cell neoplasms
Peripheral T cell lymphoma
Aggressive NK-cell leukemia
Mycosis fungoides
Anaplastic large cell lymphoma, *ALK*-positive
Hepatosplenic T-cell lymphoma
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Systemic EBV$^+$ T-cell lymphoma of childhood
Hydroa vacciniforme lymphoproliferative disorder
Subcutaneous panniculitis-like T-cell lymphoma
Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Histiocytic and dendritic cell neoplasms
Langerhans cell histiocytosis and other histiocytic/dendritic cell neoplasms
Immunodeficiency-associated lymphoproliferative disorders
Primary immunodeficiency associated lymphoproliferative disorders
Post-transplant lymphoproliferative disorders
HIV-associated lymphoproliferative disorders

NOTE: Changes respect to fourth edition of the WHO Classification are highlighted in red (new). Molecularly defined entities are marked in green.

necessary to apply multiple techniques such as gene expression profiling/RNA-seq, FISH, reverse transcription PCR, flow cytometry, and NGS. The treatment of ALL has been a remarkable success story in pediatric oncology, with a meager 5-year overall survival rate of 31% in 1975 that has improved to 90% nowadays due to the adoption of risk-stratified dose-intensive chemotherapy (34). Disease-risk stratification can be improved further by the incorporation of genomic data, which will also aid in tailoring the treatment to minimize long-term side effects (35).

Childhood AML has an overall survival of about 70% despite significant advances in risk classification, chemotherapy intensification, and stem cell transplantation (44, 45). Improved understanding of the tumor biology and molecular pathways of AML provides opportunities to design novel targeted therapies, which will be facilitated by a classification with emphasis on genetic aberrations (45). Subtypes of AML with different recurrent genetic abnormalities are associated with different prognoses (Table 1). Cases of AML that show genetic changes not covered by the defined list can be classified as AML, NOS, appended with the key molecular alterations. The findings of the Children's Oncology Group-National Cancer Institute TARGET AML initiative on the molecular landscape of pediatric AML, based on nearly 1,000 cases, are particularly illuminating, highlighting differences from adult AML (46). Some structural variants, such as new gene fusions and focal deletions of *MBNL1*, *SEB2*, and *ELF1*, are much more prevalent in pediatric compared with adult AML, while some mutations common in adult AML (such as *DNMT3A* and *TP53*) virtually never occur in pediatric AML (46). Some new recurrent mutations (such as *MYC*-ITD, *NRAS*, *KRAS*) have also been discovered (46). It is envisaged that the next edition of the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues will entail more pediatric-specific changes.

Among myeloid neoplasms, juvenile myelomonocytic leukemia (JMML), refractory cytopenia of childhood (RCC), and myeloid proliferations associated with Down syndrome are strictly pediatric diseases.

JMML is characterized by mutations in genes of the RAS signaling pathway (47). *PTPN11*-, *NRAS*- or *KRAS*-mutated JMML shows somatic gain-of-function mutations in nonsyndromic children, while *NF1*- or *CBL*-mutated JMML occurs in type 1 neurofibromatosis and *CBL* mutation–associated syndrome, respectively, characterized by germline mutation and acquired biallelic inactivation of the respective tumor suppressor genes.

RCC is distinct from adult myelodysplastic syndrome, in that the bone marrow is often hypocellular, and somatic alterations commonly seen in the latter, such as mutations in *TET2*, *DNMT3A*, *TP53*, and the spliceosome complex, are usually absent (48–50). In a proportion of cases, monosomy 7 is found (51–54), which was further shown to be associated with germline mutations in *GATA2* or *SAMD9/9L* (55).

Myeloid proliferations associated with Down syndrome encompass transient abnormal myelopoiesis (TAM) and myeloid leukemia of Down syndrome (ML-DS). TAM occurs in newborns, and most cases show spontaneous remission, although ML-DS may supervene in 1 to 3 years in some 25% of cases. The disease is characterized by somatic mutations in *GATA1* ML-DS (56–58) and usually occurs before the age of 5 years. Most cases exhibit features of megakaryoblastic leukemia, and harbor *GATA1* mutations plus additional mutations.

The spectrum of mutations is distinct from other pediatric and adult AML, usually targeting genes encoding cohesin components, signal transducers, and epigenetic regulators (59, 60).

Lymphomas

A subset of pediatric lymphomas is associated with congenital immunodeficiencies or Epstein–Barr virus (EBV) infection, but for the vast majority of children with lymphoma the etiology and predisposing factors are not known (40, 41). Pediatric lymphomas show several features distinct from adult lymphomas. Most are precursor B-cell or T-cell lymphoblastic leukemias/lymphomas, high-grade B-cell lymphomas (particularly Burkitt lymphoma) or, among mature T-cell lymphomas, *ALK*-positive anaplastic large cell lymphomas (41, 61). Low-grade B-cell lymphomas, such as CLL, follicular lymphoma, lymphoplasmacytic lymphoma, and mantle cell lymphomas, rarely occur in the pediatric age group. High-grade lymphomas (such as Burkitt lymphoma and diffuse large B-cell lymphoma) and Hodgkin lymphomas in the pediatric population have an excellent prognosis (often curable in >90%), superior to that observed in adults (62–64). Several lymphoma types occur almost exclusively in the CAYA age group, including pediatric-type follicular lymphoma, pediatric nodal marginal zone lymphoma, large B-cell lymphoma with *IRF4* rearrangement, systemic EBV$^+$ T-cell lymphoma of childhood and hydroa vacciniforme lymphoproliferative disorder.

Although the classification scheme of lymphomas is less molecularly defined compared with the classification of leukemias, most lymphoma types do exhibit distinctive molecular alterations, some of which are defining, such as *ALK*-positive anaplastic large cell lymphoma and large B-cell lymphoma with *IRF4* translocation (as indicated in Table 1).

Soft-Tissue and Bone Tumors

Classifications of soft-tissue and bone tumors have progressively integrated our increasing knowledge regarding recurrent molecular alterations with the traditional diagnostic approach based on morphologic evidence of a lineage differentiation. A token of the limitations of classic morphology for the classification of these tumors was the introduction of a category for "unclassifiable sarcomas" in the 2013 fourth edition of the WHO Classification of Soft Tissue and Bone Tumors. In the current WHO 2020 fifth edition, this has evolved into a growing group of newly characterized tumor types that (at least so far) lack an identifiable lineage of differentiation, but which are now defined by specific recurrent genetic/molecular alterations (ref. 65; Fig. 1A). By and large, the WHO classification of pediatric tumors has been built upon the backbone of the current WHO Classification of Soft Tissue and Bone Tumors. It thoroughly describes entities typical of pediatric age as well as the clinical, pathologic, and molecular features of adult-type tumors frequently occurring in children, including particular pseudotumoral/malformative lesions and hamartomas.

Benign Soft-Tissue Tumors

Benign soft-tissue tumors in children vastly outnumber sarcomas, with benign myofibroblastic and vascular tumors being the most frequently encountered lesions (66). Their accurate characterization requires an expert integration of clinical, histologic, and genetic/molecular findings to define both their potential to progress and their possible role as a sentinel event of more complex syndromes (66, 67). Compared with the 2020 WHO Classification of Soft Tissue and Bone Tumors (65), a special emphasis has been placed on benign vascular lesions, which have been redefined in light of the clinical and pathogenetic orientation of the International Society for the Study of Vascular Anomalies classification (https://www.issva.org/classification). The term "hemangioma" has been dropped and replaced by capillary, venous and arteriovenous malformations, intramuscular vascular anomalies, and lymphatic anomalies, clearly defining their malformative nature and the pathogenetic molecular pathways involved. Furthermore, complex malformations were subdivided into different categories on the basis of molecular alterations and associated syndromes (Table 2).

Soft-Tissue Sarcomas

Soft-tissue sarcomas in children account for 6% to 7% of all childhood malignancies, with rhabdomyosarcomas (RMS) being the most common, while the others are often referred to by pediatric oncologists as "sarcomas other than rhabdomyosarcomas" (67–70).

In line with the WHO Soft Tissue Tumors Classification, four RMS types can be identified: (i) embryonal (ERMS) including the anaplastic variant; (ii) alveolar with *FOXO1* fusions; (iii) spindle/sclerosing RMS including infantile RMS with *VGLL2::NCOA2* rearrangements and RMS with *MYOD1* mutations (while those lacking fusions are morphologic variants of ERMS); and (iv) pleomorphic RMS, which is extremely rare in children and may represent a diagnostic pitfall when dealing with ERMS with diffuse anaplasia (Supplementary Table S2). RMS is highly aggressive, but remarkably responsive to conventional chemotherapy with an overall 5-year survival rate greater than 70% for localized disease (71, 72).

Soft-tissue sarcomas other than RMS account for about 3% to 4% of all pediatric cancers and can be divided into soft-tissue tumors with intermediate prognosis (locally aggressive and/or rarely metastasizing), such as infantile fibrosarcoma or inflammatory myofibroblastic tumor, and high-grade sarcomas, mostly adult-type sarcomas (refs. 73–77; Table 2).

Infantile fibrosarcoma and inflammatory myofibroblastic tumor are both tyrosine kinase–driven neoplasms and share similar pathogenetic mechanisms with the emerging category of "*NTRK*-rearranged spindle cell neoplasm" (65, 78). This latter category, currently classified under "tumors with unknown histogenesis" in the 2020 WHO Classification of Soft Tissue Tumors, has been redefined as "pediatric *NTRK*-rearranged spindle cell neoplasms" and is included in the group of myofibroblastic tumors in the WHO Pediatric Tumor Classification to highlight their clinicopathologic similarities with other pediatric myofibroblastic lesions (e.g., lipofibromatosis, infantile fibrosarcoma, and inflammatory myofibroblastic tumor; ref. 65).

Only the tumor types most frequently occurring in children and adolescents, that is, synovial sarcoma or malignant peripheral nerve sheath tumors, are described in detail. For tumor types only rarely occurring in children, a table with a comprehensive review of reported pediatric cases is provided in the introduction. Adult-type sarcomas in children may

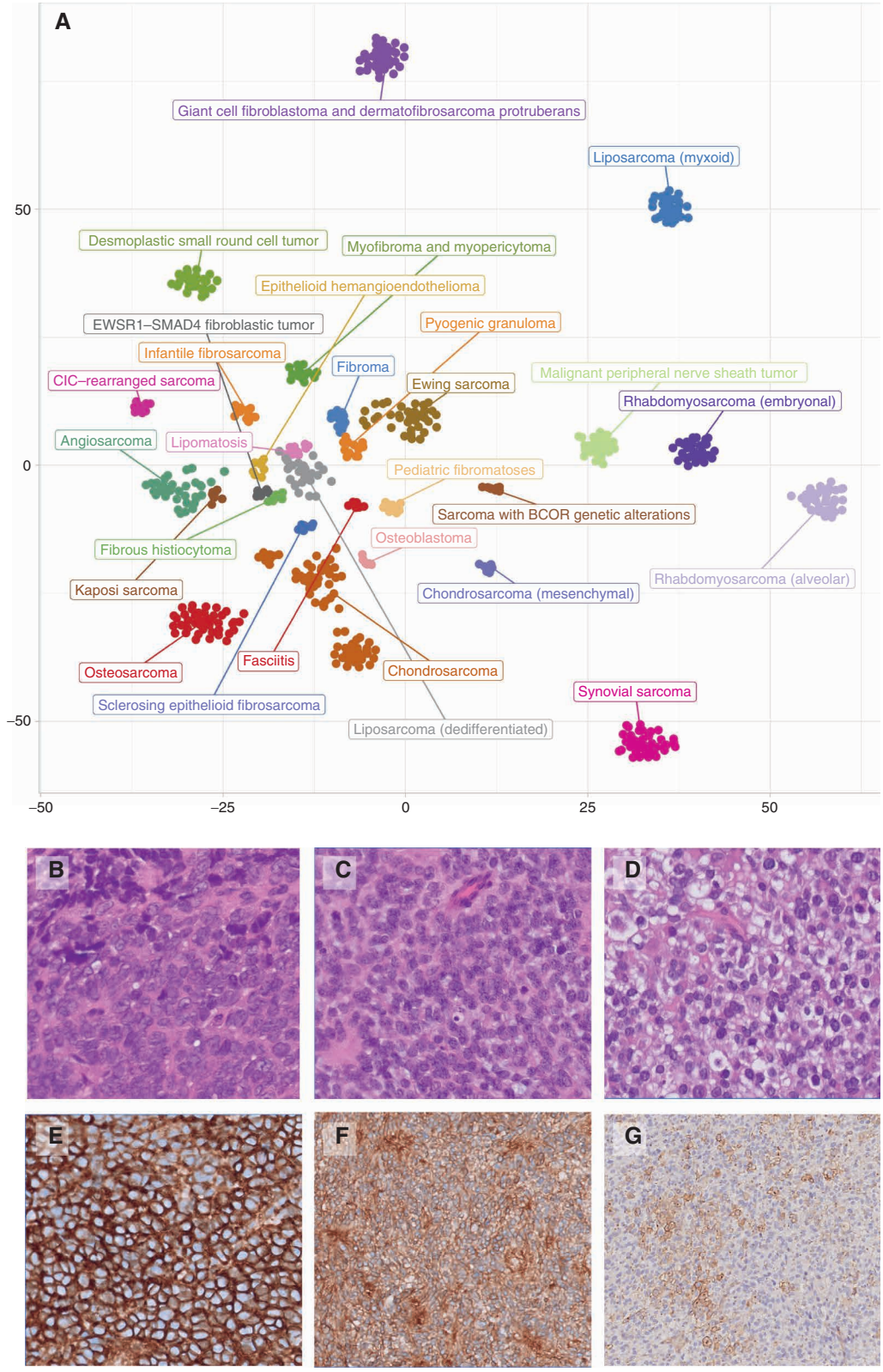

Figure 1. **A,** Intertumoral heterogeneity of soft-tissue and bone tumors as assessed by DNA methylation array. Unsupervised, nonlinear t-distributed stochastic neighbor embedding projection of methylation array profiles of 610 soft-tissue and bone tumor samples. Samples have been selected from a large database of sarcoma datasets to serve as reference profiles for training a supervised classification model based on strict criteria. **B**–**G,** Undifferentiated small round cell sarcomas of bone and soft tissue. **B,** Ewing sarcoma with *EWSR::FLI 1* fusions. **C,** Soft-tissue sarcoma with BCOR alteration (BCOR::MAML3 fusion). **D,** CIC::DUX4 sarcoma. CD99 membranous staining varies from strong and diffuse in ES (**E**) and BCOR::MAML (**F**) to focal in CIC::DUX4 (**G**).

Table 2. Classification of pediatric soft-tissue and bone tumors

Soft-Tissue Tumors

Adipocytic tumors
- Lipomatosis
- Lipoblastoma/lipoblastomatosis
- Liposarcoma

Fibroblastic and myofibroblastic tumors
- Fibroblastic and myofibroblastic tumors
- Fasciitis
- Fibrodysplasia ossificans progressiva[a] *new*
- Fibroma of tendon sheath
- Gardner fibroma
- Fibrous hamartoma of Infancy
- Lipofibromatosis
- Inclusion body infantile digital fibromatosis
- Juvenile hyaline fibromatois (Hyaline fibromatosis syndrome)[a] *new*
- Fibromatosis colli
- Calcifying aponeurotic fibroma
- Sinonasal angiofibroma
- Plantar/palmar fibromatoses
- Desmoid fibromatosis
- *EWSR1::SMAD3* positive fibroblastic tumor
- Infantile fibrosarcoma
- Pediatric *NTRK*-rearranged spindle cell neoplasm (provisional entity)[b] *new*
- Dermatofibrosarcoma protuberans/Giant cell fibroblastoma
- Low-grade fibromyxoid sarcoma/Sclerosing epithelioid
- Low-grade myofibroblastic sarcoma
- Inflammatory myofibroblastic tumor

So-called fibrohistiocytic tumors
- Fibrous histiocytoma
- Plexiform fibrohistiocytic tumor
- Tenosynovial giant cell tumor

Vascular tumors
- Capillary malformations
- Venous malformations (Venous hemangioma)[c] *new*
- Arteriovenous malformations (Arteriovenous malformation/hemangioma)[c] *new*
- Intramuscular vascular anomalies (Intramuscular hemangioma)[c] *new*
- Lymphatic anomalies (Lymphangioma and lymphangiomatosis)[c] *new*
- Congenital hemangioma[c] *new*
- Infantile hemangioma[c] *new*
- Hemangioma of placenta *new*
- Pyogenic granuloma
- Epithelioid Hemangioma
- Tufted angioma and kaposiform hemangioendothelioma
- Papillary intralymphatic angioendothelioma (PILA) and retiform hemangioendothelioma
- Pseudomyogenic hemangiendothelioma
- Kaposi sarcoma
- Epithelioid hemangioendothelioma
- Angiosarcoma

Pericytic (perivascular) tumors
- Myofibroma and myopericytoma
- Glomus tumor and glomuvenous malformation

Smooth muscle tumors
- EBV-associated smooth muscle tumor

Skeletal muscle tumors
- Rhabdomyoma
- Rhabdomyosarcoma family
- Ectomesenchymoma

Table 2. Classification of pediatric soft-tissue and bone tumors (*Continued*)

- *Gastrointestinal stromal tumor*
  - Pediatric gastrointestinal stromal tumor (GIST)
- *Peripheral nerve sheath tumors*
  - Schwannoma
  - Neurofibroma
  - Perineurioma
  - Hybrid nerve sheath tumor
  - Granular cell tumor
  - Solitary circumscribed neuroma
  - Ectopic meningioma and meningothelial hamartoma
  - Benign triton tumor/neuromuscular choristoma
  - Malignant peripheral nerve sheath tumor
- *Tumors of uncertain differentiation*
  - Tumors of uncertain differentiation
  - Intramuscular/Juxta-articular myxoma
  - Superficial angiomyxoma
  - Deep angiomyxoma
  - Angiomatoid fibrous histiocytoma
  - Clear cell sarcoma of soft tissue
  - Alveolar soft part sarcoma
  - Extrarenal rhabdoid tumor
  - PEComa
  - Synovial sarcoma
  - Epithelioid sarcoma
  - Myoepithelial tumors of soft tissue
  - Phosphaturic mesenchymal tumor
  - Desmoplastic small round cell tumor
  - Undifferentiated sarcomas (non-small cell round cells)
- *Undifferentiated small round cell sarcomas of bone and soft tissue*
  - Undifferentiated small round cell sarcomas of bone and soft tissue
  - Ewing sarcoma
  - Round cell sarcoma with *EWSR1*–non-*ETS* fusions
  - *CIC*-rearranged sarcomas
  - Sarcoma with *BCOR* genetic alterations

Bone tumors

- *Osteogenic tumors*
  - Subungual exostosis
  - Bizarre parosteal osteochondromatous proliferation
  - Osteoblastoma
  - Osteoid osteoma
  - Chondromesenchymal hamartoma of chest wall
  - Osteosarcoma
- *Chondrogenic tumors*
  - Chondroblastoma
  - Osteochondroma
  - Chondromyxoid fibroma
  - Enchondroma and enchondromatosis
  - Chondrosarcoma
  - Mesenchymal chondrosarcoma
- *Other tumors*
  - Vascular tumors of bone
  - Aneurysmal bone cyst (ABC)
  - Giant cell tumor of bone (GCTB)
  - Non-ossifying fibroma (NOF)
  - Notochordal tumors
  - Simple bone cyst

(*continued*)

Table 2. Classification of pediatric soft-tissue and bone tumors (*Continued*)

Adamantinoma
Osteofibrous dysplasia (OFD)
Fibrous dysplasia

NOTE: Changes with respect to the WHO Classification of Soft Tissue and Bone Tumors 2020 are highlighted in red (new). Molecularly defined entities are marked in green.

[a]Both these entities are typical pediatric nonneoplastic, tumor-forming diseases; fibrodysplasia ossificans progressiva was not included in previous WHO soft-tissue tumors editions; for Juvenile hyaline fibromatosis, the terminology Hyaline fibromatosis syndrome has been added.

[b]This provisional entity corresponds to the emerging group of *NTRK*-rearranged spindle cell neoplasm listed as "tumors of uncertain differentiation" in the WHO Soft Tissue Tumor Classification 2020, the change in the name highlights the morphologic relationship with IMT and infantile fibrosarcoma of these lesions in pediatric patients.

[c]The nomenclature used is in agreement with International Society for the Study of Vascular Anomalies classification (55) and reflects the dichotomy between vascular malformation (with specification of vascular type involved, i.e., venous, arterious or lymphatic or a combination of them) and neoplastic lesions. In parenthesis the corresponding nomenclature in WHO 2020 Soft Tissue Tumor Classification.

differ from their adult counterparts in clinical features, morphology, and/or genetic profile. Examples include (i) myxoid pleomorphic liposarcoma, a liposarcoma type characteristic of the CAYA age group, that can be associated with Li-Fraumeni syndrome, and (ii) synovial sarcoma in children showing minor chromosomal instability (apart from the paradigmatic *SYT::SSX1/SSX2* fusions) compared with its adult counterparts (79). In general, despite the overall aggressive clinical behavior and low responsiveness to chemotherapy of most "adult-type sarcomas," those occurring in children are still associated with a better prognosis (68, 80, 81).

Bone Sarcomas

Bone sarcomas represent 4% to 8% of pediatric malignancies, with Ewing sarcomas accounting for about 40% and osteosarcomas for 50% (69). The new section "undifferentiated small round cell sarcomas" introduced in the 2020 WHO Classification of Soft Tissue and Bone Tumors includes four tumor categories (Fig. 1B–G): Ewing sarcoma, round cell sarcomas with *EWSR1*–non-*ETS* fusions, *CIC*-rearranged sarcoma, and sarcomas with *BCOR* genetic alterations. Sarcomas with *BCOR* alterations are rare, but increasingly recognized by the use of IHC (BCOR and CCNB3) and molecular tests. While BCOR-internal tandem duplication is typical of infantile undifferentiated sarcomas and primitive myxoid mesenchymal tumor of infancy, *BCOR* fusions mostly drive the undifferentiated small round cell sarcomas occurring in adolescents and young adults. By contrast, *CIC*-rearranged sarcomas and *EWSR1*–non *ETS* fusion sarcomas are characteristic of adult age.

The differential diagnosis of undifferentiated small round cell sarcomas requires an integrated approach with different techniques, from the faster and less expensive tests, for example, FISH or RT-PCR, when a preliminary diagnosis is suspected based on morphology, to the more sophisticated and traditionally faster and sometimes even less expensive NGS panels or RNA-seq. Methylation profiling, which is widely used in the diagnostic workup of central nervous system (CNS) tumors, also seems to be a promising diagnostic tool for the classification of soft-tissue sarcomas, especially for the group of undifferentiated small round cell sarcomas (Fig. 1A; refs. 11, 82, 83).

Other Solid Tumors

As previously introduced, the WHO Classification of Pediatric Tumors addresses multiple solid tumors by taking a developmental approach as much as possible, because tumors in children differ from those in adults at several levels: Children are developing organisms, undergoing multiple and marked changes at a speed often inversely proportional to the age of the patient. Congenital and neonatal tumors occur in immature tissues, where the histologic similarities between fetal structures and their neoplastic counterparts may not be immediately obvious (Fig. 2A–F). For example, in peripheral neuroblastic tumors, the most common solid tumor in children, their histologic appearance is almost indistinguishable from the fetal adrenal medulla (84), which is formed by migrating neural crest cell precursors that penetrate (one could say "invade") the fetal adrenal mesoderm–derived cortex. Indeed, congenital adrenal neuroblastoma "*in situ*" is found in between 0.3% and 1% of neonatal autopsies (85). Details on the classification and molecular makeup of neuroblastoma, including its various clinically relevant molecular subtypes and associated genetic alterations, are provided in Supplementary Table S3.

A similar situation occurs with other "blastomas," which variably recapitulate the morphologic maturation of cellular lineages from the organs from which they originate. One of the best examples is nephroblastoma, also known as Wilms tumor, which occurs with a frequency close to that of neuroblastic tumors. This neoplasm reproduces the morphologic steps of renal development to such a high degree that it is challenging to differentiate a nephrogenic rest from small Wilms tumors (86, 87). Approximately 10% of Wilms tumors present histologic changes defined as "anaplasia," if the following specific criteria are met: nucleomegaly (at least three times the size of nonanaplastic nuclei), nuclear hyperchromatism, and abnormal/atypical mitoses.

Among some of the innovative approaches in this volume, the developmental angle used to present the group of germ cell tumors (GCT) should be highlighted. This group of heterogeneous neoplasms includes entities that may present in multiple body locations, affect both sexes, and are particularly frequent in pediatric patients. From the advantageous position of their shared developmental origins, this chapter (88) moves along

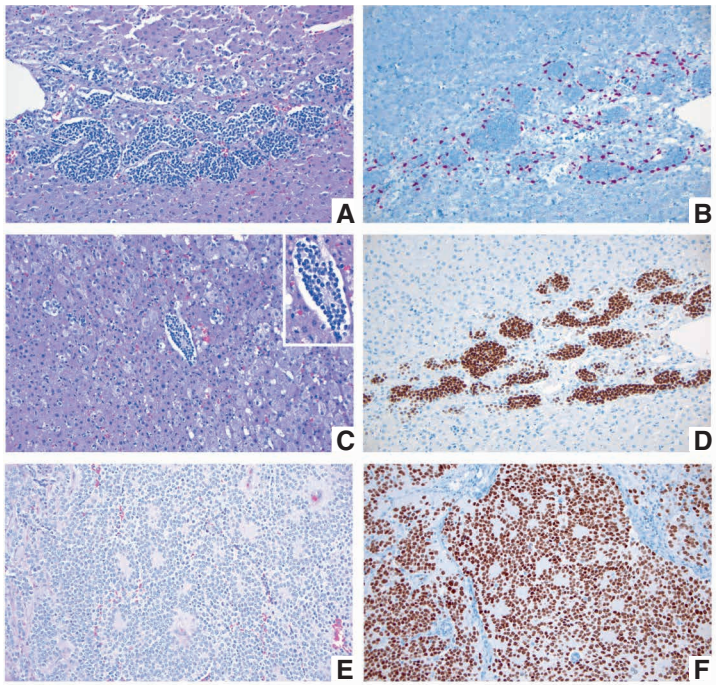

Figure 2. **A–D,** Fetal adrenal gland at 21–22 weeks of gestation. **A,** Migrating neural crest cells penetrate through the mesodermally derived fetal adrenal cortex homing into the future adrenal medulla (H&E; original magnification 200×). **B,** SOX10 IHC stain highlights the nuclei of migrating neural crest cells at the periphery of the migratory clusters, representing future Schwann cell precursors (SOX10 IHC; original magnification 200×). **C,** Migrating neural crest cells forming a Homer Wright rosette, indistinguishable from a similar structure in a poorly differentiated neuroblastoma (see **E** and **F**). The Homer Wright rossete is shown in the center, surrounded by fetal adrenal cortex (H&E; original magnification 200×). Inset shows the nonneoplastic Homer Wright rossete at a higher magnification (400×). Note the fine cytoplasmic prolongations of the future adrenal medullary cells in the center of the rosette. **D,** PHOX2B IHC stain showing strong nuclear reactivity in the migrating neural crest cells of the future fetal adrenal medulla (PHOX2B IHC; original magnification 200×). **E** and **F,** Poorly differentiated neuroblastoma from a 1-year-old patient. **E,** Several Homer Wright rosettes are seen with their characteristic central area of neuropil (H&E; original magnification 200×). **F,** PHOX2B IHC stain highlighting the nuclei of the neoplastic neural crest cells (neuroblasts) in multiple Homer Wright rosettes (PHOX2B IHC; original magnification 200×).

a continuum starting with early embryonic cells to gradually maturing germ cells. The extensive migratory pathways followed by primordial germ cells (PGC) during embryonic phases, mostly along the midline of the body, explain their occurrence in seemingly disconnected places such as the brain, mediastinum, gonads, or sacrococcygeal areas (88). Therefore, the grouping of GCTs adopts a rendition that considers their origins and progressive maturation processes responsible for their wide phenotypical varieties (Table 3). The molecular genetic and epigenetic characteristics responsible for the progressive maturation process are taken into consideration for their corresponding classification. The critical mechanism appears to be the reprogramming of nonneoplastic germ cells allowing migrating PGCs to escape apoptosis, and in later developmental stages, their survival within gonadal and extragonadal niches (i.e., mediastinum and brain), from where they can progress to form GCTs *in situ* and gonadoblastoma-type lesions, early common origins of the germinoma family. Reprogramming of lesions in the germinoma-family line of differentiation may also result in nonseminomatous tumors. Recognizing gonadoblastoma at its incipient stages (89) and discriminating it from its mimics (90) is challenging but important for adequate classification, treatment, and prognostication.

Pediatric tumors of the digestive system are another area in which significant progress has been made (91). In this chapter, several blastomas are presented, including: hepatoblastoma, pancreatoblastoma, and gastroblastoma, which are unusual neoplasms that require a high level of experience for their appropriate classification. Molecular pathology information in this chapter has grown exponentially in the last few years, allowing us to better understand the pathogenesis of these rare tumors. Regarding the pathology of hepatoblastoma (92), taxonomic efforts are based on the International Pediatric Tumor Consensus Classification (93), supported by novel molecular pathology information regarding specific genetic events relevant for this tumor, especially the WNT/β-catenin pathway, which is the most important aberrantly activated signaling pathway in hepatoblastoma (94), although other genetic abnormalities, such as those involving *NFE2L2*, *TERT* promoter, Notch, Sonic Hedgehog, PI3K/AKT, EGFR, and the Hippo/YAP pathway are also becoming known players in the pathogenesis of hepatoblastoma (93–99).

Pancreatoblastoma, which is extremely rare, occurs predominantly in the first decade of life (100, 101) and is also related to genetic aberrations in the WNT/β-catenin pathway (102–104). Other abnormalities include dysregulation of *IGF2* (105, 106). Pancreatoblastoma may be associated with Beckwith–Wiedemann syndrome and familial adenomatous polyposis (107, 108). Gastroblastoma is a recently described tumor (109, 110), arising in the stomach of children and young adults. The tumor shows a recurrent somatic *MALAT1::GLI1* fusion gene (111).

Another chapter included in the pediatric tumor classification covers pediatric skin tumors. To understand pediatric melanocytic lesions, such as giant congenital melanocytic naevi (GCMN) and associated disorders, a developmental approach is again necessary. These are neural crest cell–derived lesions (112) in which mutations lead to clonal expansion resulting in congenital melanocytic nevi (CMN). Although most CMNs harbor *NRAS* mutations (113), up to 8% of them carry *BRAF* mutations (114). Involvement of the CNS (115), association with neurocutaneous melanocytosis, and malignant transformation to melanoma arising in the context of a GCMN, although infrequent, represent ominous situations. A particularly aggressive form of congenital melanoma associated with amplification of mutated *NRAS* has been reported (116). Other pediatric skin tumors include hamartomas, epidermal nevi, and additional mosaicism-related abnormalities, which are frequently difficult to classify morphologically and are thus presented together with relevant molecular genetic features (Table 3).

Table 3. Classification of pediatric solid tumors

Peripheral neuroblastic tumors
- Ganglioneuroma
- Ganglioneuroblastoma, intermixed
- Neuroblastoma
- Ganglioneuroblastoma, nodular (and other composite neuroblastic tumors)

Eye tumors

Conjunctival Neoplasms
- *Hamartomas*
  - Epibulbar choristoma
  - Epibulbar osseous choristoma
  - Phakomatous choristoma
- *Melanocytic Neoplasms*
  - Conjunctival junctional, compound, and subepithelial nevi
  - Inflamed juvenile conjunctival nevus

Uveal Neoplasms
- *Hamartomas*
  - Diffuse choroidal neurofibroma and ganglioneuroma *new*
  - Lisch nodule (iris hamartoma)

Retinal and neuroepithelial tumors
- Retinocytoma
- Retinoblastoma
- Medulloepithelioma

Optic nerve tumors
- Pilocytic astrocytoma and other gliomas of the optic nerve

Germ cell tumors
- *Non-invasive germ cell neoplasia*
  - Intratubular germ cell neoplasia (Male gonadal)
  - Gonadoblastoma
- *Germinoma family*
  - Germinoma/Dysgerminoma/Seminoma (*new* as a unifying entity)
- *Nongerminomatous germ cell tumors*
  - Mature cystic teratoma
  - Extra-gonadal teratoma
  - Monodermal teratomas (Female gonadal)
  - Immature teratoma (Female gonadal)
  - Prepubertal type testicular teratoma
  - Post-pubertal type teratoma
  - Embryonal carcinoma
  - Yolk sac tumor
  - Fetus *in fetu* *new*
  - Choriocarcinoma (nongestational)
  - Malignant mixed germ cell tumors

Renal and male genital tumors

Kidney
- *Nephroblastic and related tumors*
  - Pediatric cystic nephroma
  - Nephroblastoma
- *Molecularly defined renal tumors*
  - Renal cell carcinoma with *MIT* translocations
  - *ALK* driven renal cell carcinoma
  - Eosinophilic, solid and cystic (ESC) renal cell carcinoma (*TSC* related)
  - *SMARCB1*-deficient renal medullary carcinoma
- *Metanephric tumors*
  - Metanephric adenoma
  - Metanephric adenofibroma
  - Metanephric stromal tumor

Table 3. Classification of pediatric solid tumors (*Continued*)

- *Mesenchymal renal tumors*
  - Ossifiying renal tumor of infancy
  - Mesoblastic nephroma
  - Clear cell sarcoma of kidney
  - Malignant rhabdoid tumor of the kidney
  - Anaplastic sarcoma of kidney
  - Renal Ewing sarcoma *new*
- ***Testis***
  - Juvenile granulosa cell tumor of the testis

Female genital tumors

- ***Ovary***
  - *Sex cord-stromal tumors*
    - Ovarian fibroma
    - Sclerosing stromal tumor
    - Juvenile granulosa cell tumor of the ovary
    - Sex cord tumor with annular tubules
    - Papillary cystadenoma
    - Sertoli-Leydig tumor
    - Gynandroblastoma
  - *Other*
    - Small cell carcinoma of ovary, hypercalcemic type
- ***Lower female genital tumors***
  - *Epithelial tumors*
    - Mullerian papilloma
    - Mesonephric remnants and hyperplasia
    - Condyloma acuminatum
- ***Peritoneum***
  - *Mesothelial tumors*
    - Peritoneal inclusion cysts

Breast tumors

- Fibroepithelial tumors
- Juvenile fibroadenoma
- Juvenile papillomatosis

Digestive system tumors

- ***Liver***
  - *Epithelial tumors*
    - Hepatoblastoma
    - Fibrolamellar variant of hepatocellular carcinoma
    - Pediatric hepatocellular carcinoma *new*
  - *Mesenchymal tumors unique to liver*
    - Mesenchymal hamartoma
    - Calcifying nested stromal-epithelial tumor
    - Embryonal sarcoma of the liver
    - Hepatic congenital hemangioma *new*
    - Hepatic infantile hemangioma *new*
    - Hepatic angiosarcoma
- ***Pancreas***
  - *Epithelial tumors*
    - Pancreatoblastoma
    - Pancreatic acinar cell carcinoma
    - Solid pseudopapillary neoplasm
- ***Gastrointestinal tract***
  - *Epithelial tumors*
    - Gastroblastoma
    - Appendiceal NETs

Endocrine tumors

- ***Thyroid***
  - *Thyroid epithelial tumors*
    - Follicular adenoma of the thyroid

(*continued*)

Table 3. Classification of pediatric solid tumors (*Continued*)

- Papillary thyroid carcinoma
- Medullary thyroid carcinoma
- Spindle epithelial tumor with thymus-like elements

Parathyroid

- Parathyroid endocrine tumors
- Parathyroid adenoma

Adrenal

- Adrenocortical tumors

Tumors of the adrenal medulla and extra-adrenal paraganglia

- Sympathetic paraganglioma
- Parasympathetic paraganglioma (H&N paraganglioma)
- Pheochromocytoma
- Composite pheochromocytoma/paraganglioma

Neuroendocrine neoplasms

Head and neck tumors

Benign

- Squamous cell papilloma of larynx
- White sponge nevus *new*
- Congenital granular cell epulis
- Central giant cell granuloma
- Odontogenic tumors
- Ossifying fibroma
- Sino-nasal tract myxoma
- Nasal dermoid cyst
- Nasopharyngeal dermoidNasal chondromesenchymal hamartoma
- Pleomorphic adenoma

Malignant

- Mucoepidermoid carcinoma
- Acinic cell carcinoma
- Sialoblastoma
- Nasopharyngeal carcinoma
- *NUT* carcinoma
- Melanotic neuroectodermal tumor of infancy

Thoracic tumors

Lung

- Fetal lung interstitial tumor *new*
- Congenital peribronchial myofibroblastic tumor
- Pleuropulmonary blastoma

Heart

- Cardiac rhabdomyoma

Skin tumors

Hamartomas *new*

Epithelial Neoplasms

Squamous

- Angiokeratoma
- Epidermal nevi (nevus sebaceus) *new*
- Pilomatricoma

Melanocytic neoplasms

Nevi

- Congenital neviJunctional, compound, and dermal nevi
- Blue nevus and cellular blue nevus
- Spitz nevus
- Pigmented spindle cell nevus (Reed nevus)

Melanoma

NOTE: Changes respect to the fourth edition of the WHO Classification are highlighted in red (new). Molecularly defined entities are marked in green.

CNS Tumors

The recently published fifth edition of the WHO classification for CNS tumors (summarized in ref. 30) featured a few fundamental paradigm shifts that particularly affected pediatric CNS tumor classification and thus formed the basis for the CNS tumor chapter within the inaugural WHO Classification for Pediatric Tumors. These fundamental changes, among others, included (i) the general concept of integrating histologic patterns with state-of-the art molecular diagnostic readouts to form an integrated diagnosis, (ii) the introduction of designations such as "pediatric-type" and "adult-type" tumor categories for both low- and high-grade gliomas to account for the age-specific biology despite the same histology-related names as well as associated cancer-predisposition syndromes (below), (iii) the inclusion of a multitude of novel tumor entities, many of which are primarily molecularly defined (similar to leukemias and lymphomas and some of the molecularly defined sarcoma types), (iv) the adaptation of tumor grading as a measure for differential aggressiveness of tumors within a tumor type rather than between tumor types, including the suggestion to not report a grade in cases where this could be clinically confusing because the grade would not reflect the expected outcome on current treatment regimens (e.g., WNT-driven medulloblastoma CNS-WHO grade 4), and (v) the widespread introduction of novel molecular diagnostic tools such as DNA methylation analysis for tumor classification, often nominated as an essential diagnostic criterion, particularly for difficult-to-diagnose cases (ref. 30; Fig. 3).

Tumor entities were selected for more detailed discussion in the WHO Classification of Pediatric Tumors if they either mainly occur in children and adolescents, or if a substantial proportion of an "adult-type" CNS tumor class is diagnosed in the pediatric age range (summarized in Table 4). All remaining entities are extensively discussed in the WHO CNS Tumor Classification.

High-Grade Gliomas

Pediatric-type diffuse high-grade gliomas are now clearly separated from adult-type diffuse high-grade gliomas (the latter typically being *IDH*–wild-type glioblastomas with *EGFR* amplification, *TERT* promoter mutation, and/or combination of gain of chromosome 7 and loss of chromosome 10 or, rarely, high-grade, *IDH*-mutant astrocytomas or oligodendrogliomas). In the pediatric setting, four different types are distinguished (Table 4). The designation diffuse midline glioma, H3K27-altered was widened to include subtypes with a different mechanism for the loss of H3K27 trimethylation than H3K27 mutations, for example EZHIP overexpression. Diffuse midline glioma, *EGFR* mutant was newly introduced (Supplementary Table S4).

Infant-type hemispheric glioma was introduced as a new type, which typically occurs in young children and is associated with receptor tyrosine kinase fusions in the *NTRK* family, *ROS1*, *ALK*, or *MET* (117, 118). Diffuse pediatric-type high-grade glioma, H3-wild-type and *IDH*-wild-type represents a mixture of quite different molecular subtypes and certainly needs more granularity, including for instance biologically distinct subtypes that can readily be distinguished by DNA methylation analysis (ref. 119; e.g., the methylation classes pedHGG MYCN, pedHGG RTK1, pedHGG RTK2, and HGG_chr6CTX; Fig. 3). They also include tumors with underlying mismatch repair deficiency (120, 121).

Low-Grade Gliomas

Similar to high-grade pediatric-type gliomas, the designation pediatric-type diffuse low-grade gliomas was introduced to distinguish these latter (mostly MAPK-driven) tumors from their adult-type (typically *IDH*-driven) counterparts. In contrast to pediatric diffuse low-grade gliomas, in adults these tumors generally progress into high-grade gliomas over the disease course. Several new entities, primarily molecularly defined, were introduced in this group, including diffuse astrocytoma, *MYB*- or *MYBL1*-altered (122, 123), polymorphous low-grade neuroepithelial tumor of the young (124), and diffuse low-grade glioma, MAPK pathway–altered (almost as a diagnosis of exclusion), an exemplary family for which a mix-and-match approach can be applied by combining a morphologic diagnosis with a specific genetic alteration, for example diffuse astrocytoma with *FGFR1* mutation (Table 4).

Within the category of circumscribed astrocytic gliomas, high-grade astrocytoma with piloid features was newly introduced (125) and astroblastoma, *MN1*-altered more precisely defined (126, 127). Among glioneuronal and neuronal tumors, diffuse leptomeningeal glioneuronal tumor (128) and diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (24, 25), as a provisional tumor type, were newly added.

Medulloblastomas

For medulloblastomas, the first layer of classification remained consistent with the fourth edition update of the WHO Classification of CNS Tumors in 2016. However, several aspects have changed: (i) histologic subtypes were condensed into one type (medulloblastoma, histologically defined), underscoring that an integrated molecular classification is preferred over a purely histologic classification, (ii) grading was discouraged for clinical low-risk types such as WNT-driven medulloblastoma to prevent confusion with treating physicians and patients as explained above, and (iii) molecular subtypes were introduced for SHH medulloblastomas ($n = 4$) and for non-WNT/non-SHH medulloblastomas ($n = 8$) according to recent publications (129–132). The latter will be of enormous help to prospectively evaluate the predictive and prognostic role of these subtypes in the context of state-of-the-art therapies, for example, allowing for therapy deescalation in the framework of clinical trials for low-risk subtypes other than WNT. Special emphasis was put on the routine assessment of the presence of a cancer predisposition syndrome for all patients with SHH medulloblastoma and *CTNNB1*–wild-type WNT medulloblastoma (133).

Ependymomas

The classification of ependymomas has changed from a mostly morphologic into a primarily molecular classification (Table 4; ref. 12). In the supratentorial compartment, *RELA*-driven ependymoma was changed into *ZFTA*-driven ependymoma because it appeared that this latter fusion partner is the most consistent one found in this entity (134–136). *YAP1* fusion–driven ependymoma was introduced as a new

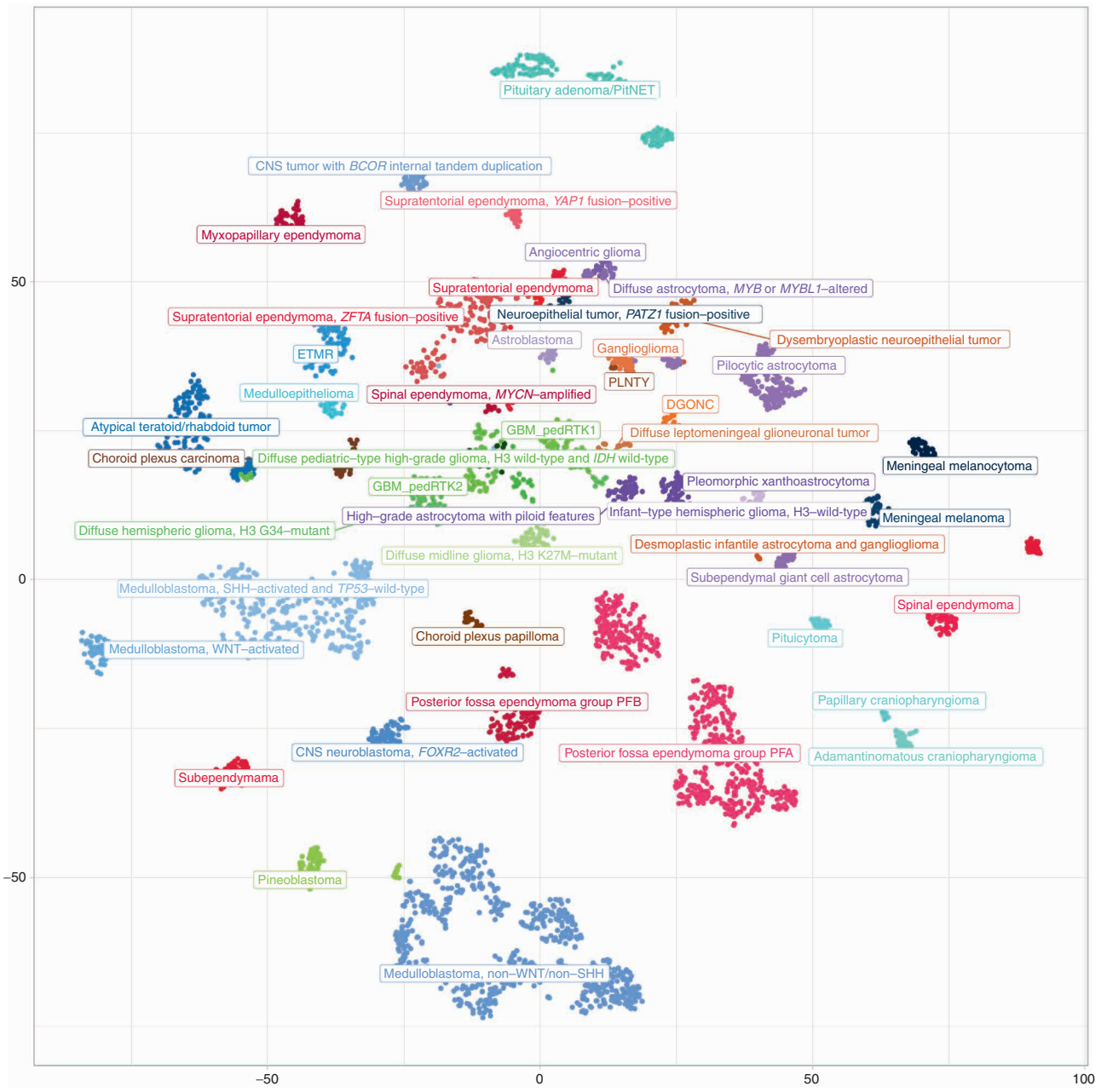

Figure 3. Molecular groups of pediatric CNS tumors (at the level of superfamilies). Unsupervised, nonlinear t-distributed stochastic neighbor embedding (t-SNE) projection of methylation array profiles from 4,427 tumors. Samples were selected from a large database of >90,000 CNS tumor datasets to serve as reference profiles for training a supervised classification model based on strict criteria: all these samples showed a high calibrated classification score (>0.9) when applying the brain tumor classifier available at https://www.molecularneuropathology.org.

type (12). In the infratentorial region, molecularly defined posterior fossa group A and B (PFA and PFB) ependymomas were introduced, the first category based on a loss of H3K27 trimethylation in the tumor and/or a methylation profile indicative of PFA ependymoma (137). In the spinal region, the recently described type of *MYCN*-amplified ependymoma was introduced, a diagnosis associated with particularly unfavorable outcome (138, 139). The difficulty of standardized grading of ependymoma (especially between grade 2 and grade 3) was flagged with a caveat, and assigning a CNS WHO grade is no longer required as part of the diagnosis of ependymomas in children (140).

Other CNS Tumors, Provisional Entities, and Emerging Entities

Within the category "other embryonal tumors" (Table 4), molecularly defined CNS neuroblastoma, *FOXR2*-activated, and CNS tumor with *BCOR* internal tandem duplication were newly introduced. Cribriform neuroepithelial tumor (CRINET), typically associated with *SMARCB1* mutations yet

Table 4. Classification of pediatric CNS tumors

Gliomas, glioneuronal, and neuronal tumors
- *Pediatric-type diffuse low-grade gliomas*
  - Diffuse astrocytoma, *MYB* or *MYBL1*-altered new
  - Angiocentric glioma
  - Polymorphous low-grade neuroepithelial tumor of the young new
  - Diffuse low-grade glioma, MAPK pathway-altered new
- *Pediatric-type diffuse high-grade gliomas defined by H3 status*
  - Diffuse midline glioma, H3 K27-altered
  - Diffuse hemispheric glioma, H3 G34-mutant new
  - Diffuse pediatric-type high-grade glioma, H3-wild-type and IDH-wild-type new
  - Infant-type hemispheric glioma new
- *Circumscribed astrocytic gliomas*
  - Pilocytic astrocytoma
  - High-grade astrocytoma with piloid features new
  - Pleomorphic xanthoastrocytoma
  - Subependymal giant cell astrocytoma
  - Astroblastoma, *MN1*-altered
- *Glioneuronal and neuronal tumors*
  - Gangliglioma
  - Desmoplastic infantile ganglioglioma/Desmoplastic infantile astrocytoma
  - Dysembryoplastic neuroepithelial tumor
  - Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC)[a] new
  - Diffuse leptomeningeal glioneuronal tumor
  - Multinodular and vacuolating neuronal tumor new
- *Ependymal tumors*
  - Supratentorial ependymoma
  - Supratentorial ependymoma, *ZFTA* fusion-positive
  - Supratentorial ependymoma, *YAP1* fusion-positive new
  - Posterior fossa ependymoma
  - Posterior fossa ependymoma, Group PFA new
  - Posterior fossa ependymoma, Group PFB new
  - Spinal ependymoma, *MYCN*-amplified new
  - Myxopapillary ependymoma

Choroid plexus tumors
- Choroid plexus papilloma
- Atypical choroid plexus papilloma
- Choroid plexus carcinoma

CNS embryonal tumors
- *Medulloblastomas, molecularly defined*
  - Medulloblastoma, WNT-activated
  - Medulloblastoma, SHH-activated & *TP53*-wild-type
  - Medulloblastoma, SHH-activated & *TP53*-mutant
  - Medulloblastoma, non-WNT/non-SHH
- *Medulloblastoma, histologically defined*
  - Medulloblastoma, histologically defined
- *Other CNS embryonal tumors*
  - Atypical teratoid/rhabdoid tumor
  - Cribriform neuroepithelial tumor[a] new
  - Embryonal tumor with multilayered rosettes
  - CNS neuroblastoma, *FOXR2*-activated new
  - CNS tumor with *BCOR* internal tandem duplication new
  - CNS embryonal tumor NEC/NOS

Pineal region tumors
- Pineoblastoma

(*continued*)

Table 4. Classification of pediatric CNS tumors (*Continued*)

Melanocytic tumors
Meningeal melanocytosis and melanomatosis
Tumors of the sellar region
Pituitary endocrine tumors
Pituitary adenoma/PitNET
Pituitary blastoma new
Craniopharyngiomas
Adamantinomatous craniopharyngioma

NOTE: This table lists CNS tumor types that mainly occur in children and adolescents as well as "adult-type" CNS tumors of which a substantial proportion is diagnosed in the pediatric age range (*, provisional tumor type for which additional published studies are needed for full acceptance). Importantly, other "adult-type" CNS tumors (e.g., spinal ependymoma, meningioma, astrocytoma IDH-mutant) may occur in children as well, those tumors are extensively discussed in the WHO CNS Tumor Classification. According to WHO terminology, Table 4 distinguishes between categories, families, and types of tumors. For example, the family "Pediatric-type diffuse low-grade gliomas" represents one of the five families in the overarching category "Gliomas, glioneuronal tumors and neuronal tumors," with in this family four tumor types as listed in the table. Of these, diffuse low-grade glioma, MAPK pathway–altered represents a group of tumors for which a mix-and-match approach can be applied by combining a morphologic diagnosis with a specific genetic alteration. Also, diffuse pediatric-type high-grade gliomas, H3-wild-type and *IDH*-wild-type in fact represent a mixture of quite different molecular subtypes from which in the future particular members can be expected to emerge as a clinically relevant, more narrowly defined tumor type (included in current WHO chapter pedHGG MYCN, pedHGG RTK1, pedHGG RTK2; other molecular subtypes such as HGG_chr6CTX not yet included).

Changes with respect to WHO Classification of CNS Tumors 2016 are highlighted in red (new). Molecularly defined entities are marked in green.

[a]Provisional entities.

biologically distinct from atypical teratoid/rhabdoid tumor (AT/RT), was introduced as a provisional entity (141). The emerging entity *PATZ1* fusion–positive tumor, which was not included in the CNS tumor classification yet, was, however, mentioned in the introduction to the CNS tumor chapter of the classification already (142–145). The largest series of these tumors published to date was published only after the editorial meeting of the WHO (26). In addition, embryonal tumor with multilayered rosettes (ETMR) was divided into two subtypes: (i) ETMR with C19MC amplification and (ii) ETMR with *DICER1* mutations (often germline; ref. 146). For both pineoblastoma and AT/RT, the molecular consensus subtypes were introduced as recently published (147, 148).

In summary, the CNS tumor chapter of the WHO classification for Pediatric Tumors was mostly adopted from the new CNS tumor classification, which was written at the same time. This classification will certainly be of enormous value not only for diagnosticians, but also for treating physicians, researchers, and patients across the world.

Cancer Predisposition

Genetic predisposition is the major known cause of childhood cancer. Research in this area, including integrated germline and cancer genomic profiling, is highly relevant, as it provides important biological insights into the causes of childhood cancer and represents a unique opportunity to translate this knowledge into improving individualized childhood cancer prevention, surveillance, and treatment in the future.

Definition of the Term Cancer Predisposition Syndrome

Cancer predisposition syndromes (CPS) are distinct genetic or epigenetic conditions associated with an increased cancer risk compared with the general population. Causes vary and may include, but are not limited to, constitutional chromosomal anomalies, pathogenic—mainly inactivating but also activating—variants in single cancer predisposition genes, copy number changes, and epigenetic mechanisms (149–152). Several CPSs are characterized by germline mosaicism (151). Patients with CPS need to be distinguished from individuals harboring cancer risk alleles that are not associated with a defined syndrome identified through genome-wide association studies (153, 154). Such low-penetrant cancer risk alleles are likely to contribute to all childhood cancers. It is estimated that at least 10% of children with cancer have an underlying CPS, with the proportion of children with a CPS being substantially higher for selected cancer types (150). Estimates in some more recent studies (15, 16, 155) are even higher; however, this higher incidence might be based on certain selection biases (e.g., enrichment for relapse patients) and the stringency of filtering in terms of causality of the underlying germline mutation. New syndromes continue to be identified (156, 157). The percentage of underlying germline genetic variants in cancer predisposition genes varies between populations and may be characterized by founder mutations, among other factors (158).

Classification of CPSs

For the purpose of this review, CPSs are classified into the following eight different groups (Fig. 4): (i) Li-Fraumeni syndrome (LFS); (ii) constitutional mismatch repair deficiency (CMMRD); (iii) predisposition to neural tumors, including neuroblastoma, glioma, medulloblastoma, retinoblastoma, and rhabdoid tumors; (iv) Wilms tumor predisposition—these are often overgrowth syndromes (159); (v) endocrine tumor predisposition; (vi) predisposition to gastrointestinal tumors; (vii) predisposition to hematologic malignancies including leukemia, lymphoma, and myelodysplastic syndrome (e.g.,

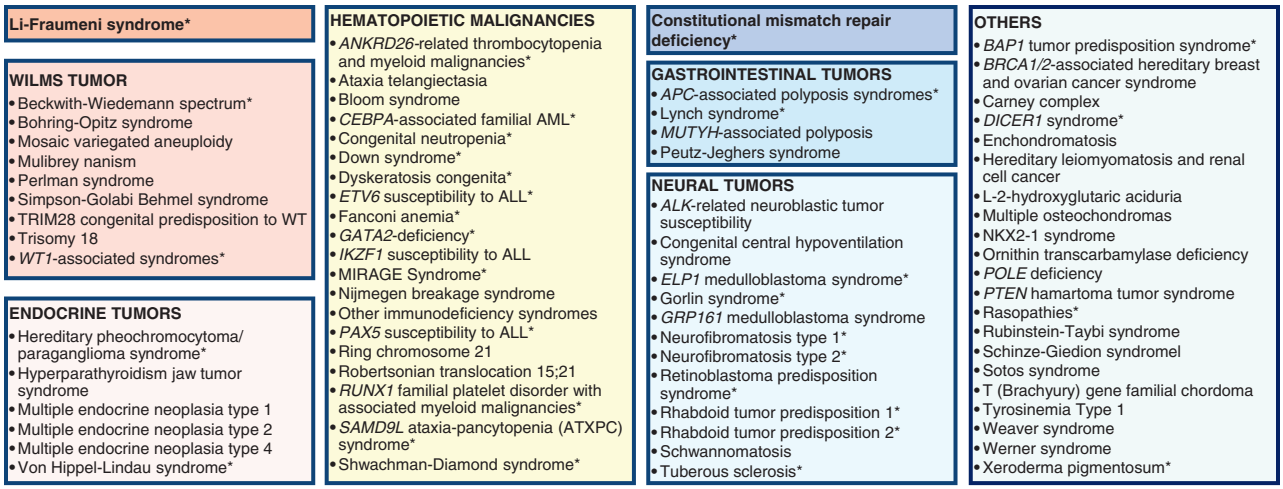

Figure 4. Overview on CPSs. For the purpose of this review, syndromes were grouped into eight categories: (1) Li-Fraumeni syndrome; (2) syndromes predisposing to Wilms tumor; (3) syndromes predisposing to endocrine tumors; (4) syndromes predisposing to hematopoietic malignancies; (5) constitutional mismatch repair deficiency; (6) other syndromes predisposing to gastrointestinal tumors; (7) syndromes predisposing to neural tumors; and (8) other cancer-prone syndromes. Cancer predisposition syndromes listed in the WHO Classification of Pediatric Tumors and displayed in Suppementary Table S5 are marked with an asterisk.

Fanconi anemia, among others); and (viii) other CPS (e.g., *DICER1* syndrome) not classified within one of the other groups. Many of the syndromes listed within one main category predispose to a broader cancer spectrum in and outside the specific CPS category, while others are associated with neoplasms in restricted organ systems. The tumor risks vary substantially between syndromes and genetic subtypes (e.g., Fanconi anemia; ref. 160). LFS and CMMRD are singled out because of the particularly high cancer risk and broad cancer spectrum (161, 162). LFS is also the most commonly diagnosed CPS among children with cancer (4, 150, 163). The list of selected CPSs as listed in the WHO Classification of Pediatric Tumors is provided in Supplementary Table S5.

Adult-Type CPSs

Diagnostic criteria and distinct associated phenotypic characteristics (164) have been established for the most common CPS; however, with the increasing use of high-throughput genetic and genomic profiling technologies in the clinical laboratory, the number of new abnormalities and phenotypic spectra are evolving including previously unrecognized associations, and patients not meeting diagnostic criteria are being identified (163). This is particularly true for adult-type CPS. The increasing use of agnostic germline sequencing has shown that children with cancer not uncommonly harbor pathogenic/likely pathogenic variants in genes mutated in adult-type CPS. Examples include heterozygous pathogenic variants in mismatch repair genes *MSH2*, *MSH6*, *MLH1*, and *PMS2* that typically cause Lynch syndrome and heterozygous pathogenic variants in *BRCA1/2* associated with hereditary breast and ovarian cancers. While recessive conditions associated with these genes cause CMMRD and Fanconi anemia, respectively, and are well established high-risk CPSs in children, it is currently unclear to what extent heterozygous variants in such genes that also occur at low frequencies in healthy individuals contribute to cancer risk in children and adolescents. Statistically significant associations have been shown for medulloblastoma (*BRCA2*, *PALB2*; ref. 133) and non-Hodgkin lymphoma (*BRCA2*; ref. 165). It has also been shown that childhood cancer survivors who carry variants in DNA repair genes such as *BRCA2* have an increased risk of subsequent neoplasms (166). Studies analyzing both germline and tumor genomes (to search for loss of heterozygosity and other characteristic CPS-specific somatic signatures) are crucial to further clarify these associations as well as their predictivity for the potential therapeutic use of PARP inhibitors (16, 18).

Diagnosis of a CPS

Patients with CPS may have clinical features prompting physicians to suspect and evaluate the diagnosis. These clinical features include individual and family cancer history, tumor type, presentation (e.g., multifocal, bilateral) as well as somatic molecular characteristics, and physical features (167, 168). Clinical tools have been developed to identify these signs systematically (169, 170). However, a significant proportion of CPS is not captured by these tools (171). In addition, agnostic gene panel or exome-based germline analyses are increasingly being employed, leading to the identification of patients with a CPS who lack obvious clinical signs or symptoms, as well as to the discovery of previously unknown CPS associations (156, 157, 163, 166).The diagnosis of a CPS may be challenging due to the notion that variants identified in a CPS gene may be of uncertain significance, and variant interpretation challenges should be taken into consideration. Functional tests such as chromosomal breakage analysis in patients with Fanconi anemia (172) can help to establish the diagnosis. Clinical tumor sequencing of pediatric cancers is also becoming increasingly used, and as a result underlying cancer predisposition germline variants are often identified while sequencing the tumor (173, 174). Pathologists and geneticists have an important role in recognizing specific tumor types associated with cancer syndromes and should

actively participate in the multidisciplinary teams evaluating these patients (175).

Clinical Implications

While it is essential for children with specific cancer types to be diagnosed or to rule out a specific CPS in order to make appropriate clinical decisions, ethical aspects need to be considered and easy access to genetic counseling should be a requirement for specialized centers diagnosing and treating children with cancer. The diagnosis of a CPS may have broad clinical implications including identification of other affected family members through trio or cascade testing, cancer prevention, cancer surveillance, adjusted cancer therapy to account for resistance to conventional therapy and/or increased toxicity, and need for psychosocial support (150). For some patients carrying a pathogenic or likely pathogenic variant in a CPS gene, direct clinical implications for the affected child may be less obvious. For example, a heterozygous variant in *BRCA1/2* may have no immediate clinical implications for the affected child with cancer, but it may be relevant for the patient later in life, and for affected family members identified through cascade testing. This is because the cancer risks associated with these variants increase in adults, warranting specific medical recommendations (e.g., breast cancer screening and prophylactic mastectomy).

Summary and Outlook

It is increasingly recognized that childhood cancer has a strong genetic component. While germline genetic factors are likely to play a role in all children with cancer, distinct CPSs (Fig. 4) are currently identified in at least 10% of patients. Genomic testing, including family-based trio sequencing, may reveal a new landscape of childhood cancer predisposition. International collaborative studies are needed to improve treatment strategies, prevention, and surveillance programs for children with CPS.

The following areas, among others, will need to be further addressed in the future: (i) discovery of additional germline (epi)genetic mechanisms contributing to childhood cancer and corresponding somatic signatures; (ii) cancer epidemiologic studies to better define cancer risks and environmental as well as (epi)genetic risk modifiers; (iii) improved cancer surveillance through better imaging and biomarker monitoring; (iv) cancer prevention trials with a focus on high-risk CPS; (v) interventional treatment studies for patients with cancer with various CPSs; and (vi) role of digenic, multigenic mutations as well as the emerging utility of polygenic risk scores (171, 176, 177).

CONCLUSION

Pediatric tumors represent a particular challenge due to their rarity, heterogeneity, different pathogenetic mechanisms compared with adult tumors, strong impact of hereditary cancer predisposition, and need for therapeutic strategies that optimize for survival chances while minimizing risks for long-term sequelae.

Since the 1970s, international clinical trials have spearheaded a multidisciplinary approach that helped change the natural history of pediatric leukemias as well as solid and brain tumors, resulting in a dramatic increase in overall survival and a better quality of life for the majority of patients. Uniformity in diagnosis is critical to these efforts. Unfortunately, mortality rates remain high for advanced diseases and for specific entities, for which survival rates have plateaued for more than two decades. The integration of classic histologic diagnoses with advanced molecular techniques such as methylation profiling, RNA-seq, whole-genome sequencing, or whole-exome sequencing (including tumor and control tissue) represent a step change in the categorization of pediatric cancers and definition of prognostic and/or predictive subgroups or biomarkers to be included in the standard diagnostic process, paving the way toward more personalized therapeutic strategies.

The inaugural edition of the WHO Classification of Pediatric Tumors provides a basis for a multilayered diagnostic process that reflects two important aspects:

1. Meeting the needs of regions with varying level of access to state-of-the art molecular technologies.
2. Acknowledging the current transition from a traditional system of classification focused on "cell type" to an integrated approach, also comprising many newly recognized "molecular entities."

In line with this, the section "essential and desirable diagnostic criteria" included in the fifth WHO edition represents the first basic morphologic diagnostic level, enriched by a modern, more focused histologic and IHC as well as broader molecular evaluation (including DNA methylation and NGS), often derived from the experience in the correlation between molecular patterns and histology (including the use of artificial intelligence–based approaches). In the future, this may be further complemented with novel technologies that add additional information to the tissue analysis, such as single-cell approaches and proteomics. Noninvasive, NGS-based liquid biopsies to detect circulating tumor DNA seem a promising tool to plan therapeutic strategies and monitor tumor evolution, although technical variability is currently a limiting factor to implementation in routine clinical practice. The integration with information on tumor microenvironment from circulating extracellular vesicles (exosomes) might, in the future, provide additional important diagnostic/prognostic data (178).

It is difficult to predict whether molecular platform analyses or even liquid biopsies will fully replace histologic diagnosis on tumor tissue biopsies in the future. However, it is increasingly clear that molecular techniques are providing a new, powerful lens to current histologic evaluation, while it will remain of key importance to actually investigate representative tumor material.

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