The inaugural WHO classification of childhood tumors provides a unified, updated resource for diagnostics

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The first classification of pediatric cancers soon to be published by the International Agency for Research on Cancer (IARC) as part of the new

World Health Organization (WHO) Classification of Tumors series was summarized in a review article published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Pediatric tumors differ radically from adult tumors in terms of tumor types, etiology, biology, and therapeutic approaches," said the article's first and co-corresponding author Stefan M. Pfister, MD, director of the Hopp Children's Cancer Center Heidelberg (KiTZ) and head of the Division of Pediatric Neurooncology at the German Cancer Research Center (DKFZ). "Therefore, a pediatric age-focused classification is an instrumental step in allowing practitioners to identify the best treatment option on the basis of the most precise and accurate diagnosis."

Tumor classification helps stratify each disease entity in a hierarchical system based on predefined criteria. Since 1956, the WHO has promoted the publication of the Classification of Tumors, more commonly known as the WHO "blue books." Each book provides a state-of-the-art classification of tumors for each organ. Previously, pediatric tumors were incorporated together with adult tumors in organ-specific tumor classifications.

The inaugural WHO Classification of Pediatric Tumors, which will be published as part of the fifth edition of the Classification of Tumors series, presents a single, updated compendium of all the tumor entities that may occur in childhood or adolescence, divided by organ sites. The authors incorporated traditional morphology, immunohistochemistry, and molecular characteristics to provide essential criteria for the definition of tumor types.

"A holistic perspective should consider a childhood tumor not only as an organ-site disease, but as an organ-site disease in the context of a developing organism," said co-corresponding author Rita Alaggio, MD, head of the Pathology Unit, Department of Laboratories, at Bambino

Gesù Children's Hospital in Rome.

The pediatric blue book also reflects the general transition from traditional diagnostic approaches based on histological/microscopic findings and immunohistochemistry to the new technologies for molecular diagnosis based on tumor genomics, which have brought a major revolution in the tumor classification criteria.

Mesenchymal (soft tissue) tumors are still mostly classified by morphologic criteria, with genetic analysis complementing the traditional approach, while central nervous system tumors and leukemias are mostly classified on the basis of recurrent molecular or epigenetic alterations. This may soon be complemented by additional emerging technologies, such as more standardized proteomics and single-cell or liquid biopsy analyses, the authors note.

In some parts of the world, access to modern pathology and methodology is still a rate-limiting step. However, according to the authors, shifting to unbiased and reproducible (molecular) diagnostic criteria, which form the basis for the current classification, may eventually help middle- and low-income countries that typically suffer from a significant shortage in subspecialized pathologists and pathology training to increase diagnostic precision. This will additionally require the development of affordable tests and supporting networks for middle- and low-income countries, complemented by artificial intelligence approaches to potentially predict molecular classes from histology samples in the future.

While sporadic (non-hereditary) genetic alterations play a key role in the development of the majority of pediatric tumors, approximately 10 percent of the cases are associated with hereditary cancer predisposition syndromes. The pediatric blue book contains a classification of the cancer predisposition syndromes and identifies the challenges associated with diagnosis and treatment.

According to the authors, the inaugural edition of the WHO Classification of Pediatric Tumors has been an ambitious project involving a large number of contributors from all over the world. This joint effort was aimed at collecting state-of-the-art knowledge on all pediatric tumors from different perspectives involving multiple disciplines, emphasizing the specific needs and challenges of the pediatric and adolescent age groups.

"Spending 2 to 3 percent of the cost of a modern cancer therapy to establish a precise, unbiased, and unambiguous diagnosis that harmonizes molecular tumor typing, prognostic and predictive biomarkers, and potential cancer predisposition is an extremely good investment to improve patient outcomes and spare treatment side effects," said Pfister.

One limitation of this effort is that tumor classification and molecular characterization are moving targets, so any classification can only provide an up-to-date snapshot reflecting the current knowledge. "For this reason, the WHO has implemented mechanisms to update specific aspects of the classifications between editions," commented Alaggio. "Additionally, the WHO will have all tumor classifications in an online format where they can also be updated in real time."

More information: Stefan M. Pfister et al, A Summary of the Inaugural WHO Classification of Pediatric Tumors: Transitioning from the Optical into the Molecular Era, *Cancer Discovery* (2021). DOI: 10.1158/2159-8290.CD-21-1094

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