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Genetic testing for childhood cancer predisposition syndromes: Controversies and recommendations from the SIOPE Host Genome Working Group meeting 2022

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ABSTRACT

Background: Cancer Predisposition Syndromes (CPSs) have been identified in 7–15 % of children with cancer. The possibilities for germline genetic testing have increased in recent years, presenting new opportunities but also

Abbreviations: ACMG, American College of Medical Genetics and Genomics; CPS, Cancer predisposition syndrome; DICER1, Dicer 1, ribonuclease III; DNA, Deoxyribonucleic acid; MIPOGG, McGill Interactive Pediatric OncoGenetic Guidelines; SIOPE, International Society of Pediatric Oncology Europe; TP53, Tumor protein p53; VUS, Variant of unknown significance; WES, Whole exome sequencing; WGS, Whole genome sequencing.

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challenges. There is currently no consensus on germline genetic testing in children with cancer in diagnostic settings.

Methods: The International Society of Pediatric Oncology Europe (SIOPE) Host Genome Working Group used a consensus development conference method to reach agreement on four key topics: Who do we test? Which genes do we test? What do we disclose? How do we evaluate the benefits of testing?

Results: The Working Group members agreed that: (1) All children with cancer should undergo clinical screening for their risk of harboring a CPS. (2) Targeted genetic testing based on clinical indication is recommended. Comprehensive CPS gene panels with more than 100–150 genes for all children with cancer should preferably be evaluated within research settings. (3) Smaller actionable gene panels can be considered including genes supporting diagnosis or influencing treatment decisions. (4) Clear pre-test information and consenting processes that highlight potential outcomes and implications of germline genetic testing are imperative. (5) Consequences of genetic testing, treatment adaption, and tumor surveillance in children with CPSs, including economic impact and psychosocial factors, should be further explored.

Conclusions: These consensus-based recommendations provide guidance on germline genetic testing in children with cancer. Regular review of these recommendations is essential. Collaboration and the use of data sharing platforms can further improve screening procedures and its impact on care.

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1. Introduction

An increasing number of cancer predisposition syndromes (CPSs) have been associated with childhood cancer in recent decades. Currently, approximately 7—15 % of childhood cancer patients are diagnosed with a CPS [1–6]. Recognition of CPSs is important to identify patients who require treatment adaptations as some CPSs are associated with specific treatment response or increased treatment toxicity when identified in specific neoplasms [7–9]. In addition, CPS identification enables initiation of surveillance for early detection of second primary neoplasms and genetic counseling with cascade testing for at-risk family members [10].

Genetic testing methods have become faster, cheaper, and more widely available. Many pediatric cancer centers have introduced paired tumor-germline sequencing in the diagnostic workup of children with cancer. However, it remains unclear which patients should be offered comprehensive germline genetic testing. In addition, new testing possibilities bring new challenges for genetic counseling, informed consent procedures, and for the interpretation of the test results. Furthermore, there is uncertainty on how to best evaluate the benefit of testing with regard to patients' interests, resource allocation, and economic value.

The European Society for Pediatric Oncology (SIOPE) Host Genome Working Group met on November 14th and 15th 2022 in Paris, France, and held workshops on these topics. The goal was to discuss current diagnostic practices and define consensus-based recommendations for germline genetic testing in children with cancer.

2. Methods

2.1. Study design

We used a consensus development conference method [11] to evaluate four specific topics. Consensus was defined as agreement to a specific statement of at least 80 % of participants during the drafting of recommendations and agreement of all participants on the final manuscript wording.

The SIOPE Host Genome Working Group is an expert group with 114 members from 24 countries as of November 2022. Members are predominantly pediatric hematologists/oncologists but also geneticists, molecular biologists, and other professionals associated with the field of pediatric oncology. All members were invited to participate in a meeting either in-person or online. Prior to the meeting, four topics on genetic workup for childhood cancer patients were selected by the steering committee (FB, MJ, CK, LL, KW, NW) to discuss and find agreement. These topics were: (A) Who do we test? (B) Which genes do we test? (C) What do we disclose? (D) How do we evaluate the benefits of testing?

Participants were divided into four workshops, each addressing one of the topics. The workshops were attended by 45 participants in-person and 28 online, representing 18 countries (***Appendix 1***). Participants were distributed among the workshops according to individual interests.

2.2. Finding consensus

We used a multi-step discussion to reach agreement on a consensus statement. An initial overview of the topic was provided by the workshop leaders. Topics raised in the overviews were addressed point by point with consensus statements from the workshop participants. Additional topics were raised by participants and equally addressed. After the workshops, all consensus statements were reviewed in a plenary session to agree on final statements. Finally, the manuscript was drafted by the working group leaders and shared among all participants for review.

3. Results

There are different approaches to identify patients with a CPS: (i) a phenotype-driven approach, where genetic testing is offered only to a selected group of patients at increased risk for a CPS based on clinical evaluation; (ii) a phenotype-agnostic approach where all patients are comprehensively genetically tested for all genes known to be associated with CPSs (using approaches with more than 100–150 genes at a time); and (iii) a combined approach where all patients are genetically tested for a restricted number of genes and clinically evaluated for the risk of an underlying CPS to specifically perform additional phenotype-driven genetic testing. To assist with the phenotype-driven approach, various clinical screening tools have been developed to identify children at increased risk for a CPS [12–14]. The phenotype-agnostic genetic testing strategy circumvents the need to identify patients for specific CPS evaluation. Next generation sequencing techniques utilizing comprehensive gene panels, whole exome (WES) or whole genome sequencing (WGS) approaches can be used to test all genes that are known to be associated with CPSs or all disease-associated genes.

All testing strategies for identification of CPSs have advantages and shortcomings. Clinical assessment can identify clinical signs of syndromes, of which the underlying genetic aberration might be missed by standard sequencing (e.g. CPSs caused by epigenetic mutations and low-level mosaic mutations) [15]. However, patients with a CPS characterized by a less recognizable clinical phenotype and lacking a suggestive family history can be missed by clinical assessment but identified through broad genetic testing (e.g. Li-Fraumeni syndrome) [16]. Using a comprehensive gene panel upfront as part of the diagnostic work-up of the tumor may be beneficial in identifying CPSs earlier and can aid in tumor classification and selection of the optimal therapy. However, when testing a large number of genes, there is a higher probability of detecting findings that may not necessarily benefit the tested individual and may lead to dilemmas. Examples include the identification of variants of unknown significance (VUSs) and pathogenic variants in genes with an unproven role in the etiology of the patient's cancer type.

The choice of the diagnostic approach in a center greatly depends on local resources, financial and technical conditions, the availability of clinical geneticists/CPS experts, and local regulations. Taking these differences into consideration, we present the following recommendations:

4. Who and what to test

4.1. Recommendation 1: all children with cancer should undergo clinical screening to assess their risk of harboring a CPS

Given that a significant proportion of children with cancer have a

Table 1
Components of informed consent for germline genetic testing in children with cancer.

- Reasons for doing a test and what it assesses
- Explanation that genetic testing always has limitations and can only identify information based on current knowledge which might change in the future
- Difference between tumor (somatic) genetic testing and germline (constitutional) genetic testing
- Information on results that will be returned, to whom the results will be reported, and options for choice (such as secondary findings)
- Potential impact of a positive test result on health (increased cancer risk or other health conditions)
- Potential surveillance options and/ or treatment adaptations
- Potential psychosocial burden of a positive test result, and timing of genetic testing
- Potential impact of a diagnosis for other members of the family or future offspring
- Further long-term implications such as insurance implications (influenced by local legislation or policy)

Table 2
Possible results of germline genetic testing, their explanation and recommendations for disclosure.

Result category	Subcategory	Explanation	Reporting to patients/ families
(Likely) pathogenic variants	Causative	(Likely) pathogenic variants in cancer predisposition syndrome (CPS) genes with established causality towards the patient's cancer type	Yes
	Uncertain causality	(Likely) pathogenic variants in established CPS genes but without established causality towards the patient's cancer type	Consider reporting if actionable, according to local practice
	Unsolicited finding/ incidental finding	(Likely) pathogenic variants in genes not explaining the phenotype of the patient and not matching the indication for testing	Consider reporting if actionable, according to local practice
Variants of unknown significance (VUS)		Variants with unclear clinical significance or unclear potential to cause disease: unclear if these variants are disease-causing (pathogenic) or benign	No, unless additional data to upgrade to (likely) pathogenic status
Carrier status for recessive disease		Heterozygous (likely) pathogenic variants in genes associated with a well characterized recessive disorder	Discouraged, unless families explicitly wish to receive this information after appropriate counselling, can be adapted according to local practice

CPS and considering the profound clinical implications for patients and their families, we strongly recommend that clinical screening of all children and adolescents with cancer should be performed for their risk of harboring a CPS. As clinical assessment depends on the expertise of the healthcare provider, we recommend the use of tools designed to assist clinicians in identifying patients at an increased risk of CPSs [12,13,15,17], which should be regularly updated to the latest knowledge. Roughly one third of patients are stratified as being at increased risk of a CPS through these tools [2,18]. Patients identified should be referred for genetic assessment, ideally by a clinical geneticist or other physician with expertise in pediatric CPSs to choose an appropriate genetic testing strategy. With this strategy, more than 90 % of those with a (likely) causal CPS are identified [2,14,19].

It is important to regularly re-evaluate survivors for any newly emerging signs of a CPS in their personal or family history. All pediatric cancer survivors have an increased risk of developing second primary neoplasms, which is partly due to treatment exposures, but can be further increased by a CPS [10]. While there are no specific tools for this purpose, the tools developed for newly diagnosed patients can also be used for survivors [20]. Additionally, survivors may require evaluation of cancer risk for their future children and counseling related to reproductive options.

4.2. Recommendation 2: the implications of comprehensive CPS gene panel testing in all children with cancer should be preferably evaluated within a research setting

Testing of all children with cancer for a comprehensive range of cancer predisposition genes can enhance our understanding of cancer etiology. However, this approach cannot replace the clinical evaluation employed in the phenotype-driven approach since CPSs will be missed. In most centers, the phenotype-driven approach currently strikes the best balance in terms of resource management, reduces the risk of unrelated or ambiguous findings, and minimizes distress to families [21,22]. Therefore, the application of comprehensive genetic testing of CPS genes in all children with cancer can be included in a clinical setting but is preferably evaluated in a research context with analysis of benefits and impacts of such an approach.

When opting for a CPS gene panel approach, curated childhood CPS lists previously published can be utilized, such as those available at www.pediatric-cancer-predisposition-genepanel.nl [23] or https://panelapp.genomicsengland.co.uk/panels/243/. It is essential to ensure that these lists are regularly updated to incorporate the latest knowledge. These gene panels typically also include adult-onset CPS genes, such as the mismatch repair genes and breast cancer predisposing genes, since these genes are involved in childhood-onset CPSs when both alleles are affected. There is increasing evidence that heterozygous pathogenic variants in specific adult-onset CPS genes can influence the occurrence of selected childhood cancers [24,25] and increase the second neoplasm risk [26–28]. Identifying these children can impact treatment decisions (e.g. patients with mismatch-repair deficiency may show disease response to immune checkpoint inhibitors [29]), risk assessment for specific treatments (e.g. radiation, organ-sparing surgery), surveillance for subsequent neoplasms, and family counselling. These newly observed associations are an example of knowledge derived from genetic sequencing in large cohorts and we recommend collecting data for further scientific evaluation.

4.3. Recommendation 3: Employing a focused actionable germline gene panel at the time of diagnosis for pediatric cancer patients can be considered

There can be advantages in promptly diagnosing certain syndromes in clinical routine workup of childhood neoplasms. It may be prudent to routinely assess a concise panel of genes at the time of diagnosis, that can be important for establishing the correct tumor diagnosis, informing treatment choices, and determining eligibility for clinical trials. Examples of such genes include *DICER1* (for correct tumor diagnosis since this syndrome is associated with many rare cancers), *TP53* and the Fanconi anemia genes (for the reduction of genotoxic therapy, if possible) [30,31]. To limit incidental findings and VUSs, tumor-group-specific gene panels can be applied, such as a brain tumor CPS panel or even cancer-specific gene panels such as a medulloblastoma panel. This requires more efforts to keep all panels up to date.

5. What to disclose

5.1. Recommendation 4: patients and their family should be informed in advance about the potential outcomes and implications of germline genetic testing

With the emergence of paired tumor-germline sequencing in the diagnostic workup of children with cancer, new challenges arise for the informed consent procedure for germline diagnostics. The information is usually provided shortly after the cancer diagnosis and is often delivered by non-geneticists. It is important to distinguish between tumor and germline testing and to highlight potential implications for the patient and their family in the case of identification of a CPS. Patients and caregivers should be informed in advance about which results they will receive and the choices they have of receiving results. It may be helpful to develop information sheets for clinicians to guide them through the informed consent procedure (Table 1). When disclosing results, information provided should include the consequences for the patients (increased cancer risk or other health conditions), screening

recommendations, and testing of family members.

While aiming to uncover disease-causing variants that explain cancer development in a patient, there is a risk of uncovering variants of unknown significance (VUS) and pathogenic variants that do not explain the phenotype of the patient. In Table 2 we have summarized the different types of findings that may be encountered. We recommend following the guidelines for diagnostic Next Generation Sequencing that have been published by EuroGentest and the European Society of Human Genetics [32,33] and using the classification system by the American College of Medical Genetics and Genomics (ACMG) with, where available, ClinGen Variant Curation Expert Panel (VCEP) specifications [34,35]. In accordance with these guidelines, all (likely) pathogenic variants that are associated with CPSs should be reported in the genetic test report.

In many centers, heterozygous (likely) pathogenic variants for recessive conditions (carrier status) are not reported to the patient, unless the index patient is clinically suspected to have the recessive condition. This underscores the importance of the clinical assessment of the patient. Knowledge of these variants is important for clinicians in order to consider additional genetic testing for identification of the second pathogenic variant (e.g. intronic splice site mutations, gross genomic alterations). Carrier status may be reported to affected individuals if the parents of the index patient are consanguineous and after appropriate counselling of the implications of such results with explicit consent of patients and caregivers.

Preferably, VUSs are only reported if further analyses (e.g. segregation analyses, RNA-sequencing) are considered useful for reclassification of the variant. Reporting of VUSs might depend on local practice. In the report, VUSs should be clearly labeled and their classification explained. VUSs are prone to causing misunderstandings, particularly if interpreted by non-geneticists. To simplify and improve variant interpretation, we encourage adding detailed clinical information to the genetic test request form. Additionally, tumor (sequencing) data can aid in the interpretation of the variant. For example, loss of heterozygosity or tumor mutational signature and tumor mutational burden can be helpful.

Another important finding is the identification of a pathogenic variant that does not explain the phenotype of the patient. The terms "secondary" or "unsolicited" findings are commonly used for pathogenic variants in genes not implicated in the etiology of cancer or variants in CPS genes for which there is no proven causal association with the patient's cancer type. With increasing use of germline testing, it has become clear that the phenotypic spectrum of distinct CPSs is broader than previously thought [16], highlighting the importance of collecting these data in a research context.

6. How to evaluate the benefits of testing

6.1. Recommendation 5: more research is needed to evaluate the consequences of CPS identification, its impact on treatment, patient care, and tumor surveillance

A major challenge is the evaluation of the benefits of genetic testing and subsequent tumor surveillance. The threshold for tumor surveillance has been previously defined as cumulative childhood cancer incidence of 5 % or greater by age 20 years. At 1—5 % cancer incidence, the benefits and risks can be discussed with the patient and family to tailor possible surveillance to the needs of the affected family [21]. For many genes, penetrance is still not elucidated, which requires further research in large cohorts. Survival benefits of genetic testing with corresponding cancer surveillance have not been assessed for many CPSs. The impact on life years gained and quality of life needs to be better understood. Other relevant outcomes include treatment adaptation, improvement of extent of tumor resection, and preservation of organ function [36]. There is a need to better evaluate the psychosocial burden for patients and family members who have had testing for, were informed about their own or a family member's CPS diagnosis, are living with a CPS, and are undergoing surveillance [37–40].

The societal and economic impact of genetic evaluation strategies needs to be better calculated to allow clinicians to justify interventions. The costs of surveillance need to be estimated and weighed against additional treatment costs for patients who did not undergo regular surveillance in addition to the "costs" of not being able to go to school or work (for a while) [41]. Pre-symptomatic surveillance was shown to be effective for patients with *TP53*-related CPS in different settings [42,43], however, for many other CPSs this has not been shown. Overall, the impact not only on the index patient, but also on the family and community should be better understood.

While national registries have reported data on outcome after childhood cancers [44], data on predisposition and associated surveillance is largely lacking. Possible tools that could support these evaluations are data sharing platforms for surveillance programs and international CPS registries [45]. Collecting comparable variables could allow better comparison of different approaches. Compliance with recommendations and feasibility need to be assessed and future recommendations evaluated.

7. Conclusions

This report presents the first consensus-based recommendations on germline genetic testing in children with cancer in Europe by the SIOPE Host Genome Working Group.

All children with cancer should undergo clinical screening for their risk of harboring a CPS. The application of comprehensive phenotype-agnostic CPS gene panels in all children with cancer is preferably evaluated in a research context to assess its impact and to broaden knowledge on the phenotypic spectra of distinct CPSs. Informed consent procedures with clear pre-test communication about the potential outcomes and implications of germline genetic testing and then clear disclosure of genetic test results to patients and families are imperative. The evaluation of the benefits of CPS testing with treatment adaption and tumor surveillance remains a major challenge. The survival benefits, impact on quality of life, treatment intensity, and economic implications of genetic evaluation strategies need to be better understood.

Overall, these consensus-based recommendations aim to guide clinical practice and improve the management of children with CPSs. Regular review of these recommendations is essential. Collaboration will further enhance the evaluation of outcomes.

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Conceptualization. **Nicolas Waespe:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jette J. Bakhuizen:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

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Appendix A. Supporting information

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