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# A multi-dimensional approach to recognize genetic predisposition in children with acute lymphoblastic leukemia

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ABSTRACT

Pediatric acute lymphoblastic leukemia (ALL) is the most common childhood cancer, with significant advances in treatment leading to high cure rates. Recent studies have highlighted the importance of genetic predisposition in ALL. Identifying contributing heritable or *de novo* genetic factors is crucial for potential treatment modifications, early detection of second malignant neoplasms (SMNs) and genetic counseling for surveillance of patients and family members. Multiple syndromes, such as Down syndrome (DS) or Ataxia Telangiectasia (AT), are known to give rise to increased risk for developing ALL. Most of these syndromes can be recognized by the presence of specific clinical features. However, a notable proportion of patients harboring (likely) pathogenic germline variants in cancer predisposition genes (CPGs) can easily be missed due to the absence of these characteristics. Therefore, the diagnosis of cancer predisposition syndromes (CPS) requires multiple approaches that are based on phenotypic characteristics, germline genetic analysis and genomic characterization of the leukemia samples. Despite the recognized benefits, routine screening for germline variants has not yet been implemented in large study groups due to logistical and financial challenges. This review emphasizes the importance of integrating systematic genetic testing into standard care protocols for ALL patients and summarizes current practical considerations for CPS identification in children with ALL.

## 1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer and based on constantly improved diagnostic and therapeutic strategies most children can be cured nowadays [1–3]. However, benefits in survival come with acute and long-term adverse effects, affecting the quality of life during and after treatment [1,3]. Within the last decade it became increasingly evident that genetic predisposition plays an important role in the development of childhood cancers, including pediatric ALL, particularly in the context of cancer predisposition syndromes (CPSs). Identifying pediatric ALL patients at risk is important, as it enables surveillance for early detection of second cancers, genetic counseling and testing of potentially affected relatives. Moreover, the early detection of CPSs allow personalized care and improved long-term outcomes. This includes specific treatment modifications to prevent associated excessive therapy-related toxicities [4,5] and targeted management of related non-cancer health issues (e.g., developmental or immunologic disorders) [6].

In comparison to other pediatric cancers, the prevalence of genetic predisposition in ALL is relatively low. Apart from the well-known ALL-prone genetic constellation of trisomy 21 (Down syndrome, DS), which occurs in 2–5 % of all ALL diagnoses [3,7–10], other ALL predisposition syndromes are rare. Although the relevance of recognizing genetic predisposition in children with ALL is evident, there is no consensus on the optimal diagnostic strategy to identify these CPSs. Some CPSs, such as AT, have distinct clinical characteristics, and are also known as 'overt

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syndromes' [11]; other CPSs have no or only minimal non-cancer features (the covert syndromes) and can easily be missed by clinical selection-based genetic testing. These covert syndromes, which are caused by germline pathogenic variants in *TP53* (Li-Fraumeni syndrome, LFS), *ETV6*, *IKZF1*, *PAX5*, and *RUNX1*, (may) collectively account for ~3–4 % of the ALL diagnoses (Table 1).

The presence of multiple cancers and second malignant neoplasms (SMNs) is another key indicator of pediatric CPSs according to phenotype-based assessment strategies and increased susceptibility is particularly evident in patients with LFS, Ataxia Telangiectasia (AT) and Nijmegen Breakage Syndrome (NBS). Beside relapses, SMNs are among the most concerning long-term effects in pediatric ALL, with varying prognoses depending on the type of the second cancer [12,13]. A retrospective matched case-control study revealed that CPG-related monoallelic likely pathogenic and pathogenic variants (LP/PVs) in ALL patients are associated with subsequent SMN development, and observed in approximately 21 % of such cases [14].

The aim of this review is to summarize practical considerations for CPS identification in children with ALL and to discuss optimal diagnostic strategies.

## 2. Recognition of pediatric ALL CPSs

The identification of germline predisposition in children with ALL has evolved significantly over recent years. Two major strategies are currently applied to determine underlying CPSs, namely phenotype- [15–17] and genotype-guided approaches [18–20]. The expanded somatic genetic characterization of ALL provides an additional layer of information, allowing specific somatic features to serve as key indicators of underlying CPSs. The different aspects that can generally be used for the recognition of ALL-related CPSs are shown in Fig. 1 and highlight a rationale for a multi-dimensional strategy.

**Table 1**
Prevalence of covert ALL predisposition syndromes in pediatric ALL.

| Gene | Overall prevalence estimation of germline (L)PVs in ALL (%) | Subtype enrichment | Cohort study (cases/ total cohort) | Comment | Reference |
|---|---|---|---|---|---|
| *ETV6* | ~0.8 % | *ETV6::RUNX1*-positive BCP-ALL | 35/ 4405 | Cohort of newly diagnosed ALL patients | [42] |
| *IKZF1* | ~0.9 % | | 45/ 4963 | | [40] |
| *TP53* | ~1 % | Hypodiploid ALL | 13/34 | Sub-cohort of hypodiploid ALL patients | [53] |
| | | | 26/ 3801 | Sub-cohort of non-hypodiploid ALL patients | [43] |
| *RUNX1* | < 0.1 % | T-ALL | 0/4836 | Sub-cohort of BCP-ALL patients | [55] |
| | | | 6/ 1,1354 | Sub-cohort of T-ALL patients | [55] |
| *PAX5* | < 0.1 % | BCP-ALL | 0/250 | Cohort of BCP-ALL patients with somatic *PAX5* deletions | [52] |

Abbreviations: ALL = acute lymphoblastic leukemia, ((L)PVs = (likely) pathogenic variants

### 2.1. Phenotype-guided CPS recognition

The traditional phenotype-guided approach, relying on careful clinical observation, remains a cornerstone for identifying cancer predisposition. This strategy has been systematically refined through the development of various assessment tools. The Jongmans criteria [15] and criteria by Ripperger and colleagues [16] have emerged as a fundamental framework, providing clinicians with specific indicators and thresholds for referral to a clinical geneticist for all children with cancer. These systematic approaches consider not only the immediate clinical presentation with a certain cancer type, but also the presence of non-cancer related characteristics such as congenital abnormalities, skin lesions and neurodevelopmental conditions. Moreover, they recommend assessing the presence of a family history of early-onset cancers or multiple primary cancers in close relatives and familial clustering of non-malignant conditions related to hereditary cancer.

Another initiative to improve the recognition of CPSs is the McGill Interactive Pediatric OncoGenetic Guidelines (MIPOGG) application, developed by a team of clinicians in Montreal, Canada [15–17]. This digital platform transforms traditional clinical assessment methods into an interactive, evidence-based tool that guides clinicians through a comprehensive evaluation of CPSs using simple cancer type-specific dichotomous ("yes" or "no") questionnaires. The major difference between this tool and the previously developed referral criteria is the presence of tumor-specific referral criteria. The platform's regular updates ensure that clinical assessments remain aligned with current genetic discoveries and evolving medical knowledge. MIPOGG has demonstrated a high sensitivity (90.7 %) and negative predictive value (98.6 %) in identifying pediatric-onset CPSs, making it a valuable tool for clinical diagnostic settings. Validation studies showed that MIPOGG correctly identified 99.5 % of patients with a confirmed CPS at the time of primary cancer diagnosis [21,22]. This tool not only standardizes the referral process for CPS evaluation, but also reduces the time to CPS recognition, which is critical for implementing cancer surveillance and cascade testing. The MIPOGG algorithm for ALL patients includes questions regarding characteristics of genetic causes of pediatric ALL including both overt and covert ALL predisposition syndromes.

The effectiveness of structured screening approaches has been demonstrated in clinical research. A study by Schwermer and colleagues implemented a questionnaire-based screening program between 2017 and 2019, comparing results with a control period from 2012 to 2016. The study showed a marked improvement in CPS identification, with 9.4 % of pediatric cancer cases identified during the questionnaire period compared to 5.3 % during the control period. This statistically significant improvement demonstrates the value of structured screening approaches in clinical practice [23]. Similarly, a study involving a cohort of 824 children with neoplasms diagnosed in the Netherlands highlighted that 96 % of CPS cases were identified through a traditional phenotype-guided approach, where clinical observations guided genetic testing decisions [24].

ALL-related CPSs that can be recognized based on their phenotypic features include the autosomal recessive (AR) inherited DNA repair syndromes: AT, NBS, Constitutional Mismatch Repair Deficiency (CMMRD), Fanconi Anemia (FA) and Bloom Syndrome (BS). These syndromes are characterized by distinctive non-cancer features (Fig. 2), which often enable recognition even before the onset of ALL. Nevertheless, due to the rarity of these syndromes, a diagnosis can still be challenging. It is crucial for pediatric oncologists to remain alert to the related phenotypic features of these CPSs.

Another overt ALL-related CPS is neurofibromatosis type 1 (NF1). NF1 can be recognized by skin abnormalities, including café-au-lait spots, freckling in the axillary or inguinal regions and neurofibromas [25]. The appearance of one or two café-au-lait spots is common in the general population, but the presence of more than two is less common. One of the clinical diagnostic criteria for NF1 is the presence of multiple café-au-lait macules (CALMs). Specifically, the criterion is met when an

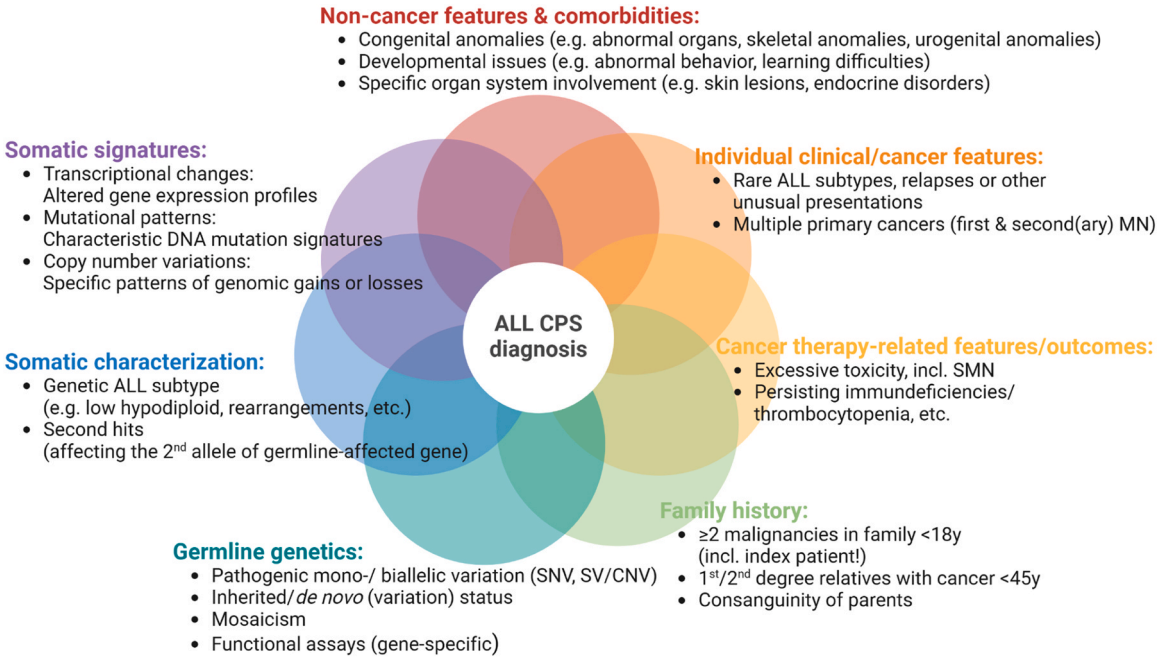


**Fig. 1. Features that can be used for the recognition of ALL-related CPSs,** The identification of germline predisposition in children with ALL is based on clinical evaluation, germline genetic testing, and somatic genetic characterization of ALL. This figure provides an overview of these different features. For the clinical evaluation, it is important to assess the following aspects in a child with ALL: (1) Non-cancer-related features and comorbidities (red), such as congenital anomalies; (2) Cancer-related features (orange), such as ALL relapse or a history of multiple primary cancers; (3) Cancer therapy-related features (yellow), such as excessive toxicity; (4) Family history of cancer (green). The purpose of germline genetic testing (teal) is to identify a pathogenic variant in a cancer predisposition gene. Different types of genetic variants can be distinguished: single nucleotide variants (SNVs), structural variants (SVs), and copy number variants (CNVs). For the benefit of other family members, it is important to distinguish between inherited and de novo variants. Examples of specific aspects of somatic genetic characterization (blue) that can serve as indicators of an underlying CPS include specific leukemia subtypes (e.g., hypodiploid ALL) Somatic signatures (purple) supporting a CPS diagnosis can be e.g. transcriptomic or mutational signatures. Mutational signatures are characteristic patterns of DNA mutations that reflect the biological processes responsible for them. Abbreviations: ALL = acute lymphoblastic leukemia, CNV = copy number variant, CPS = cancer predisposition syndrome, MN = malignant neoplasm, SMN = s malignant neoplasm, SNV = single nucleotide variant, SV = structural variant.

individual has six or more CALMs that are over 5 mm in diameter in prepubertal individuals and over 15 mm in diameter in postpubertal individuals. Café-au-lait spots and freckling in patients with NF1 usually appear in infancy and early childhood. Cutaneous neurofibromas are rare in children, but present in almost all adults with NF1. Therefore, examining the parents' skin should be part of diagnostics, as the autosomal dominant disorder NF1 can be inherited from a parent. A diagnosis of mosaic NF1 should be considered if the child's skin lesions are localized to one side or one segment of the body. In such cases, specific genetic tests on affected tissue may be needed to detect the causal pathogenic variants (PVs) in *NF1* [25,26]. NF1 can overlap with other RASopathies (genetic disorders caused by germline likely pathogenic (LP)/PVs mutations in the RAS/MAPK signaling pathway) such as Noonan syndrome. Noonan syndrome is characterized by short stature, congenital heart defects, developmental delay of variable degrees and facial features [27]. Other findings can include hypotonia, pectus anomalies, cryptorchidism and webbed neck. Nature of these characteristics in children with Noonan syndrome can vary from subtle to severe ones.

Another important CPS to consider in children with ALL and café-au-lait spots is CMMRD [28]. It has been suggested that the degree of pigmentation and the shape of the hyperpigmented skin macules in patients with CMMRD differ from the café-au-lait spots typically seen in children with NF1, but this distinction can be very challenging, stressing the importance of genetic confirmation [28]. Therefore, a genetic diagnosis is essential.

Although structured screening approaches for phenotypic features of CPS have been proven useful, the major limitation is in children with no or with subtle or atypical features (the covert syndromes).

### 2.2. *Genotype-guided CPS recognition*

A genotype-guided approach overcomes the major limitation of phenotype-guided genetic testing and ensures CPSs recognition, especially nowadays, with significantly decreased costs and increased accessibility of different genetic technologies. This approach leverages molecular genetic testing, such as next-generation sequencing (NGS) panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS), to identify germline pathogenic variants regardless of specific clinical features. While germline NGS sequencing panels have been implemented as standard care in some centers, WES and WGS are further explored in research settings. Patient-parent trio sequencing can be used to differentiate between *de novo* and inherited germline LP/PVs [18,29]

Aiming for a description of the genomic landscape in pediatric ALL, initial genotype-based sequencing studies revealed the presence of up to 12 % of LP/PVs in cancer-related genes and known CPGs, depending on cohort composition and the number of genes assessed [30–34]. Since multiple LP/PVs do not compromise a definitive CPS diagnosis yet, these numbers are not directly comparable to those obtained using phenotype-driven genetic testing. Yet, these cohort-based broad sequencing studies alongside with targeted approaches, genomic analysis of familial ALL and genome-wide association testing did contribute to delineation of the spectrum of genetic variation related to pediatric ALL [35–43]. The genotype-guided approach has proved particularly valuable in identifying LP/PVs in genes associated with covert ALL predisposing syndromes. For example, LFS patients without a family-history of cancer who developed non-hypodiploid ALL, were missed by phenotype-driven approaches alone [19].

A major challenge in genotype-guided approaches is the high rate of variants of uncertain significance (VUSs), identified in CPS gene panel

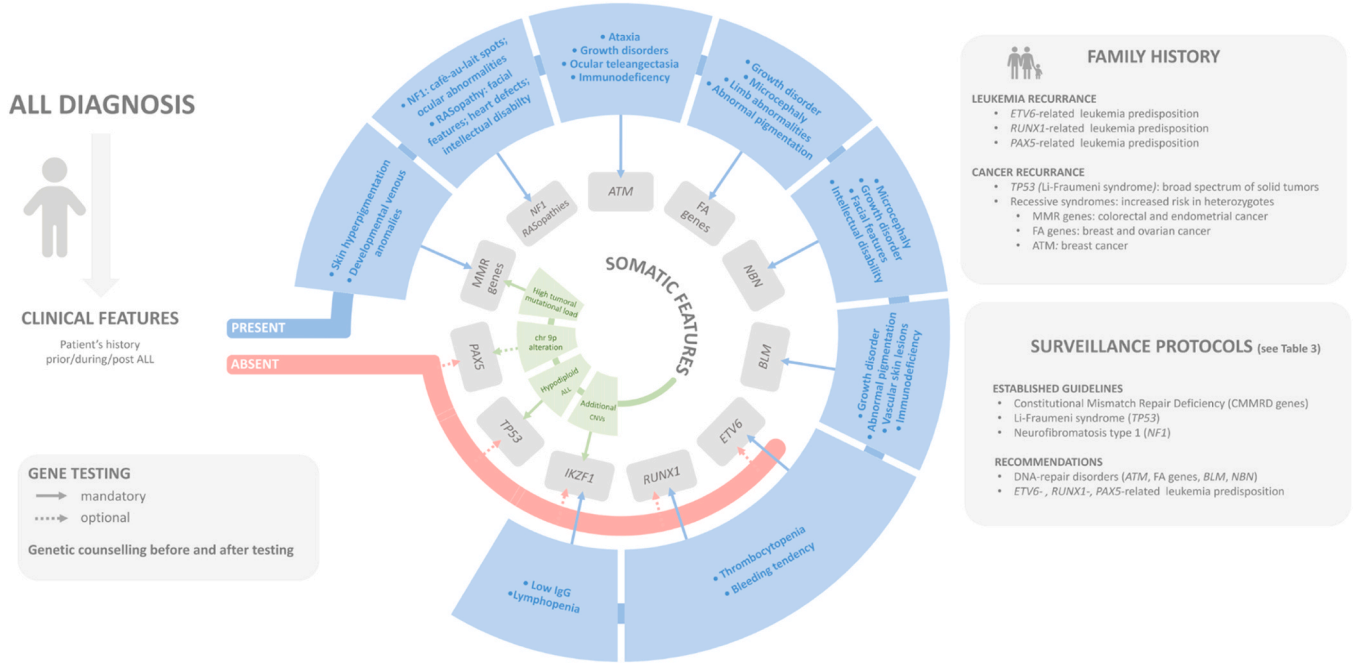


**Fig. 2. Diagnostic workflow for CPS detection in ALL patients.** Targeted genetic testing for specific CPSs in children with ALL can be guided by clinical features (light blue) and somatic genetic characterization of ALL (green). Continuous arrows represent features with a clear indication for germline genetic testing for a specific CPS. Dashed arrows represent features where germline genetic testing for a specific CPS can be considered. In the absence of any suspicious features of an underlying CPS, germline genetic testing for a covert CPS can be considered. In addition to the patient's history and somatic features of ALL, family history can help guide targeted genetic testing for specific CPSs. Some CPSs are characterized solely by leukemia recurrence, while others are associated with a broader range of cancer types. Examples are described in the textbox '*Family History*'. The textbox '*Surveillance Protocols*' provides an overview of CPSs for which established surveillance guidelines and expert-based recommendations exist. Abbreviations: ALL = acute lymphoblastic leukemia, CMMRD = constitutional mismatch repair deficiency, CPS = cancer predisposition syndrome, FA = Fanconi anemia, MMR = mismatch repair.

sequencing [19,20,33,44]. Distinguishing LP/PVs from VUSs in pediatric cancers can be challenging, particularly in covert syndromes, where supportive evidence based on pronounced clinical characteristics is often lacking. Furthermore, variant spectra in genes associated with childhood-onset diseases differ from those in adults, possibly reflecting historical evolutionary pressures [45]. According to this concept, phenotypes of highly constrained genes are unfavorable, preventing inheritance of loss-of-function variants to the next generation. Due to this evolutionary pressure, certain variants in publicly available data remains scarce, making it difficult to classify a potentially deleterious variant as LP/PVs according to standard diagnostic guidelines, i.e. the criteria provided by the American College of Medical Genetics and Genomics (ACMG) plus gene-specific refinements (e.g. from Clinical Genome Resource, ClinGen) [46]. The development of functional assays to determine and compare pathogenicity of germline variants in ALL predisposition genes can provide important information about the pathogenicity of VUSs. Although these assays are still performed in a research setting, they have significantly contributed to the understanding of variants in genes associated with covert ALL predisposition, like *TP53*, *ETV6*, *IKZF1*, and *RUNX1* [40,47–49].

### 2.3. Leukemia-based features of ALL predisposition

In addition to phenotypic and genotypic germline analyses, specific somatic features in leukemic blasts itself can also serve as important indicators of an underlying CPS. For example, the presence of a fully heterozygous pathogenic CPS variant in a sample with lower blast percentage may indirectly indicate that the detected variant is also present in normal cells. Furthermore, according to Knudson's two-hit hypothesis [50], classical tumor suppressor genes (TSGs) follow a characteristic biallelic inactivation pattern and identification of only a 'single hit' in a CPS gene may be indicative for the presence of a germline variant. Finally, specific cancer subtypes or mutational patterns may be indicative for an underlying CPS.

#### 2.3.1. The Knudson's two-hit hypothesis in pediatric ALL

Several ALL predisposition genes follow the two-hit principle. For example, in cases with germline pathogenic missense variants in *PAX5*, the development of B-ALL typically depends on the somatic acquisition of additional somatic *PAX5* deletion or variants [39,51], although this may be different for germline deletions of *PAX5* [52]. Also in LFS, a second hit is frequently observed by aneuploidy or homozygosity of the *TP53* locus on chromosome 17 [53]. However, two hits are not always identified in ALL-predisposing conditions, as exemplified by *ETV6* germline variants where biallelic inactivation of *ETV6* is observed in only 30 % of cases [54] or *RUNX1* germline variants in T-ALL, where the *RUNX1* wild-type allele is preserved [55]. These observations lead to important diagnostic considerations. First, specific chromosomal aneuploidies or regions of copy neutral loss of heterozygosity of the *PAX5* or *TP53* loci in the absence of somatic mutations in these genes may be indicative for an underlying germline variant. Second, the absence of a second hit in an ALL predisposition gene should not automatically exclude the pathogenicity of a germline variant, particularly in genes like *ETV6*, *IKZF1* and *RUNX1*, where alternative leukemogenic mechanisms may operate. Third, the identification of a potential second hit in the leukemic cells can provide crucial evidence for properly classifying a germline VUS.

#### 2.3.2. Leukemia subtypes related to CPSs

Specific leukemia subtypes can serve as molecular indicators of underlying hereditary cancer syndromes, warranting germline genetic testing even in the absence of canonical clinical criteria. A clear example involves low-hypodiploid ALL, which is a strong indicator of LFS. *TP53* mutations occur in more than 90 % of the low-hypodiploid cases and up

to 40 % of these children harbor germline *TP53* pathogenic variants, even in cases without typical LFS features or family history [43,53,56,57]. This observation has led to revised genetic testing guidelines, recommending *TP53* germline testing for all patients with low-hypodiploid ALL regardless of age or family history [58,59].

Similarly, recurrent structural abnormalities involving chromosome 9 have been recently linked to *PAX5* germline variants. *PAX5*, a critical B-cell lineage transcription factor, functions as a tumor suppressor in B-ALL [55,60]. Somatic *PAX5* mutations, found in approximately one-third of B-ALL cases, can include chromosomal rearrangements, copy number aberrations and SNV, with mutations frequently clustering in the DNA-binding paired domain [61]. The identification of germline *PAX5* variants has revealed a novel CPS specifically associated with B-ALL development [39,51,52,62–65]. The characterization of the germline pathogenic missense variants demonstrate key features of *PAX5*-associated predisposition: incomplete penetrance, requirement for loss of the wildype allele in leukemic cells and hypomorphic protein function; while germline missense variants retain partial functionality, leukemic transformation requires somatic inactivation of the second allele, typically through chromosomal mechanisms including 9p deletion, isochromosome 9q [i(9)(q10)], or dicentric chromosome 9. Thus, while the true prevalence of *PAX5* germline variants remains undefined due to limited systematic screening, the presence of somatic 9p alterations may serve as a valuable molecular indicator for underlying germline predisposition.

#### 2.3.3. *Mutational signatures*

Beyond chromosomal changes, specific mutational signatures can also indicate underlying CPS, particularly in case of DNA repair syndromes. In the context of ALL, this is particularly applicable for the mismatch repair (MMR) deficiency syndromes, which result in a high tumor mutational burden (number of mutations/Mb), widespread microsatellite instability (MSI) and recognizable mutational signatures [66]. The identification of these MMR deficiency signatures in ALL, especially in childhood cases, should prompt consideration of CMMRD or Lynch syndrome [67–70].

## 3. An integrated multidimensional approach

Each of the above described approaches has its advantages and disadvantages. However, combining these features in an integrated multidimensional approach could reveal an accurate diagnosis in the majority of cases (Fig. 2).

The value of integrating both phenotype-guided and genotype-guided approaches in a complementary way is increasingly recognized, and may be helpful in overcoming the challenges of a genotype-guided approach. The experience with such a combined strategy in ALL is limited. Four prospective pediatric pan-cancer studies have been performed in which an ALL-specific evaluation can be made (Table 1) [19,20,33,44]. All four studies performed CPS gene panel based sequencing and also reported whether the CPS patients fulfilled clinical criteria indicating an underlying CPS, thus enabling a comparison between the phenotype-guided and genotype-guided approaches. In these studies, CPS prevalence in ALL patients varied from 4 % to 9 %. Trisomy 21 (an overt CPS) was the most common reported CPS among ALL patients, followed by LFS (a covert CPS). These studies also revealed that the two approaches are complementary, with several CPSs being detected only by a single method. Therefore, combining these two strategies will likely be more effective, particularly in ALL where it facilitates the identification of both overt and covert ALL predisposition syndromes.

Importantly, the detection of a germline LP/PV in a CPG through a genotype-driven approach does not necessarily indicate a causal link with ALL. An important subgroup of the LP/PVs with uncertain relevance for ALL development are those in classical adult-onset CPGs such as hereditary breast cancer genes (e.g., *ATM, CHEK2, BRCA1, BRCA2* and *PALB2*) and Lynch syndrome related genes (*MSH2*, *MSH6*, *MLH1* and *PMS2)*. Some genotype-guided studies in children with cancer have claimed that heterozygous LP/PVs in these adult-onset CPGs are significantly associated with pediatric cancers and show cancer type specificity [71,72]. However, to date, such an enrichment has not been described specifically for pediatric ALL. For ALL cases where a germline pathogenic variant in an adult-onset CPG has been identified, the inclusion of sequencing of the leukemia itself can be informative. For example, analysis of tumor mutational load and mutational signatures may provide evidence for a role in leukemia development [70] and may have subsequent implications for treatment [71]. Although most of these adult-onset CPSs are included in CPS gene panels because of the association with recessive syndromes with high risk of cancer (CMMRD, AT, FA), testing for these genes in ALL should be performed with caution and, in case of a CPS diagnosis, somatic analysis is recommended.

Applying a multidimensional approach can also be effective in cases where a VUS has been identified using (panel-based) sequencing. Since covert ALL predisposition syndromes may present with clinical features (Fig. 2), physical re-examination may reveal subtle syndrome-specific phenotypic features like skin aberrations, persistent immunodeficiencies or other congenital features that were initially overlooked but may support causality of an identified VUS. Along the sample line, specific characteristics of the leukemia, such as LOH, second hit mutations or specific mutational signatures, may further assess the causality of the identified germline VUS.

However, multidimensional diagnostic strategy rely heavily on local resources, financial conditions and the expertise of multidisciplinary teams, including hemato-oncologists, genetic counselors, molecular geneticists and bioinformaticians.

Until now, prospective systematic CPS screening approaches have only been performed in research settings in individual centers and, despite several reports underscoring the benefit, routine screening of germline variants has thus far not been incorporated in the standard ALL protocols of the large study groups. Potential hurdles include the logical and financial challenges that implementation in a large study framework would entail. Nevertheless, we recommend routine CPS screening in pediatric ALL patients by combining systematic clinical evaluation with germline genetic analysis and, if feasible, molecular characterization of the leukemia.

One of the reasons why identifying genetic predisposition in children with cancer is important is the ability to initiate surveillance aiming to early detection of second cancers. Table 3 provides an overview of the available, established guidelines and recommendations for surveillance of ALL-related CPSs [59,67,73–76].

## 4. Novel genes in ALL predisposition

In addition to the thus far ~45 genes that are associated with ALL predisposition [11], several novel childhood ALL predisposing genes have emerged. For most of these novel genes, the number of studies are still limited and much of the knowledge on prevalence, cancer risk, comorbidities and genotype-phenotype correlations is lacking. Nevertheless, these studies indicate that the landscape of ALL predisposition is not yet fully explored and more (rare) genetic factors may await discovery.

Novel ALL predisposing genes have often been discovered in ALL cases that were highly suspected for an underlying genetic cause, but in which the involvement of known ALL predisposition genes could be excluded. Such a high suspicion could be based on suspected syndromic features, including intellectual disability, bone marrow failure or immune disorders. For example, germline homozygous mutations in the Src homology 2B adaptor protein 3 gene *SH2B3*, a regulator of lymphoid cell proliferation, were identified in a consanguineous family with autoimmunity and ALL [77]. Whereas somatic inactivation of *SH2B3* was found to be enriched in, particularly, iAMP21 ALL [78–80], evidence accumulates that individuals with bi-allelic *SH2B3* alterations

**Table 2**
Overview of studies in which CPS gene panel sequencing was performed in unselected, newly diagnosed children with ALL.

| Study (i) | N (Total cohort) | Age | N (ALL patients) | Seq. technique | CPS prevalence ALL patients | CPS specification (ii) | Comments CPS patients |
|---|---|---|---|---|---|---|---|
| Byrjalsen et al. (Denmark) [19] | 198 | 0–17 | 57 | WGS, panel 314 genes | 8.8 % (5/57) | BRCA2 (n = 1), CHEK2 (n = 1), MUTYH (n = 1), Trisomy 21 (n = 1), TP53 (n = 1) | 1 pt diagnosed before ALL diagnosis (trisomy 21)<br>0/4 newly diagnosed pts (after ALL diagnosis) had suspicious clinical features for an underlying CPS (based on MIPOGG criteria) of whom 1 pt had an established causal association between CPS and ALL |
| Wagener et al. (Germany) [33] | 160 | 0–18 | 48 | WES, panel 295 genes | 6.3 % (3/48) | ATM homozygous (n = 1), PTPN11 (n = 1), TP53 (n = 1) | 1 pt diagnosed before ALL diagnosis (biallelic pathogenic variant *ATM*)<br>2/2 newly diagnosed pts had suspicious clinical features for an underlying CPS (based on Ripperger criteria); both pts had an established causal association between CPS and ALL |
| Friedrich et al. (Germany) [44] | 139 | 0–18 | 27 | WES, panel 433 genes | 3.7 % (1/27) | BRCA2 (n = 1) | 0/1 newly diagnosed had suspicious clinical features for an underlying CPS (based on Ripperger criteria); no established causal association between CPS and ALL |
| Bakhuizen et al. (The Netherlands) [20] | 1052 | 0–18 | 213 (iii) | WES, panel 143 genes | 7.5 % (16/213) | ATM (n = 1), BRCA2 (n = 1), CDKN2A (n = 1), ETV6 (n = 1), PMS2 (n = 1), SDHA (n = 1), TP53 (n = 1), Trisomy 21 (n = 9) | 10 pts diagnosed before ALL diagnosis (ETV6, trisomy 21)<br>1/6 newly diagnosed had suspicious clinical features for an underlying CPS (based on MIPOGG criteria); this was the only pt with an established causal association between CPS and ALL |

(i) Details about the search strategy to identify these studies are included in the Supplementary Data
(ii) All CPSs include heterozygous (likely) pathogenic variants unless stated otherwise.
(iii) 133/213 patients diagnosed with ALL completed CPS gene panel sequencing.
Abbreviations: CPS = cancer predisposition syndrome, pt(s) patient(s), WES whole exome sequencing, WGS whole genome sequencing

**Table 3**
Overview of surveillance guidelines for ALL-related cancer predisposition syndromes.

| Gene (symbol) | Established surveillance guidelines | Recommendations for surveillance |
|---|---|---|
| *CMMRD genes (MSH2, MSH6, PMS2, MLH1)* | ERN Genturis Guideline CMMRD [67] | |
| *TP53* | ERN Genturis Guideline TP53 [59] | |
| *NF1* | ERN Genturis Guideline NF1 [73] | Recommendations AACR CPS workshop RASopathies [74] |
| DNA-repair disorders *(ATM, FA genes, BLM, NBN)* | | Recommendations AACR CPS workshop genomic instability disorders [75] |
| *ETV6, RUNX1, IKZF1 and PAX5* | | Recommendations AACR CPS workshop hematopoetic malignancy [76] |

Abbreviations: AACR = American Association for Cancer Research ALL = acute lymphoblastic leukemia, CMMRD = constitutional mismatch repair deficiency, CPS = cancer predisposition syndrome, ERN = European Reference Networks, FA = Fanconi anemia

more typically present with JMML and myeloproliferative neoplasia [81–83]. Another example involves the gene *USP9X*, an X-linked gene associated with a complex syndromic neurodevelopmental disorder in females, which was recently identified as a female-restricted leukemia predisposition disorder. Additionaly, the gene was shown to be a somatic driver for ALL development [84].

Another relevant indicator for an underlying genetic condition is the presence of recurrent primary diagnosis of ALL, i.e. recurrent diagnosis of ALL where a relapse is excluded based on discordance in immunoglobulin or T cell receptor rearrangement and patterns of somatic mutations. Genetic studies in such cases have revealed a constitutional germline deletion involving the *RAG1/RAG2* locus on 11p12 in a patient with second T-ALL [85], and germline activating variants in the JAK kinase family member gene *TYK2* in two patients with recurrent primary T-ALL and BCP-ALL, respectively [86]. Of note, these causes may be very rare, as no other cases have been reported since.

Occasionally, the incidence of leukemia diagnosis in a child with a syndrome without a clear link to cancer predisposition can lead to novel germline findings. An example is the diagnosis of BCP-ALL in a patient with Cornelia-de-Lange syndrome (CdLS) harboring a germline frameshift mutation in the cohesin complex gene *NIPBL* [87]. This finding triggered a follow-up study revealing three ALL patients with a recurrent variant in another cohesin gene *RAD21* [88]. Although CdLS does not seem to be associated with an increased risk of cancer, low pathogenic variants in cohesin family genes, which are not causative of CdLS, might increase the risk of cancer, including ALL [89].

Finally, novel associations have been identified by screening large cohorts for genes that are considered as reasonable candidates. Examples include the B-cell transcription factor gene *TCF3*, which has an evident role as a driver in non-hereditary BCP-ALL and the DNA damage repair gene *NBN*, for which biallelic pathogenic germline variants cause the ALL predisposition syndrome NBS [90–92]. Heterozygous pathogenic variants in these genes were found to be enriched in BCP-ALL compared to controls, but were shown to have similar outcomes compared to non-carriers [90–92]. These findings contribute to our understanding of the etiology of BCP-ALL, but the penetrance of such variants is likely too low to be of relevance in a clinical setting.

Despite these new discoveries, unexplained cases with high suspicion for an underlying genetic cause still remain, even after extensive genetic analyses. Strikingly, this includes rare cases with a positive family history of childhood ALL, even after comprehensive genetic studies. Although these cases are rare, they suggest that alternative insufficiently explored mechanisms may exist, involving e.g. complex structural variants or epigenetic aberrations. A strategy to further investigate those cases might be to systematically analyse and compare the spectrum of

somatic aberrations between affected family members to identify commonalities that hint towards a leukemia-initiating mechanism or pathway.

## 5. Conclusion/perspective

A comprehensive approach, integrating germline genetic analysis, systematic clinical evaluation and genotyping of the leukemia, offers the greatest potential for accurate recognition of ALL-related CPSs. This review has outlined the rationale for a multi-dimensional strategy in identifying CPSs in children with ALL by advocating the integration of phenotype-guided, genotype-guided and leukemia-based assessments into standard care. While challenges remain, the benefits of early detection, risk-adjusted treatment, and informed genetic counseling make the implementation of routine CPS screening a critical step forward in pediatric ALL management.

## CRediT authorship contribution statement

**Junk Stefanie V:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Daugs Katherina:** Conceptualization, Methodology, Writing – review & editing. **Bettini Laura R:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Jongmans Marjolijn CJ:** Supervision. **Melina Mescher:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Arndt Borkhardt:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Kuiper Roland P:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Giovanni Cazzaniga:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Bakhuizen Jette:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2025.100320.

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