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Interdisciplinary Management and Genetic Evaluation of Pediatric Cancer Predisposition Syndromes: A Retrospective Cohort Study

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Abstract

Comprehensive knowledge of cancer predisposition syndromes (CPS) is essential for the implementation of surveillance programs with proven clinical benefit. An interdisciplinary expert panel was established at our center to facilitate early identification of children with suspected CPS. This retrospective cohort study assessed the diagnostic yield and clinical impact of this consultation model.

A total of 144 pediatric patients were evaluated. Clinical characteristics, family histories, and molecular diagnostic results were systematically retrieved from medical records. Of the 144 individuals, 99 presented with clinical features suggestive of CPS, of whom 53 had cancer. Clinically unaffected children (45/144) were referred due to positive family history. Prior to consultation, 34 of 99 symptomatic patients had been diagnosed with CPS. Among those symptomatic and undiagnosed undergoing molecular genetic testing, a disease-causing variant was identified in CPS genes in 46% (23/50). Predictive testing in unaffected children revealed the familial pathogenic variant in 43.8% (14/32). Nearly all patients with confirmed CPS (94%) received surveillance recommendations.

The interdisciplinary CPS consultation model substantially contributes to identifying hereditary cancer predisposition in pediatric patients and families. This expert-led approach emphasizes the importance of personalized surveillance strategies for rare CPS entities and provides a scalable foundation for systematic CPS assessment and development of standardized, evidence-based surveillance protocols in pediatric oncology.

Introduction

Genetic predisposition plays a pivotal role in the etiology of pediatric malignancies, with an increasing body of evidence underscoring its substantial contribution to cancer development in children [1–4]. Genomic studies estimate that between 8% and 18% of childhood cancers are associated with underlying germline pathogenic variants [4, 5]. Ideally these pathogenic variants were already known through prior clinical suspicion or family history assessment and targeted genetic testing before a cancer diagnosis is established. However, up to 50% of affected children are diagnosed with a cancer predisposition syndrome (CPS) only after a cancer diagnosis is confirmed and therefore undergoing systematic genomic screening [6], e.g. through established pediatric precision oncology programs such as INFORM, MATCH, ZERO Childhood Cancer Program or iTHER [7, 8]. This underlines the urgent need for improved clinical awareness, optimized screening strategies, and standardized diagnostic protocols to facilitate the early detection of CPS - ideally before the onset of malignant disease - thereby enabling timely surveillance and early intervention.

Identifying germline predisposition variants, even in rare cases of CPS, is of paramount clinical importance. Beyond its implications for early cancer detection - where surveillance and risk reducing measures have demonstrated improved survival outcomes [9–11] - such recognition may also inform treatment stratification and therapeutic decision-making in affected patients [1, 3, 12]. Early detection of

germline variants potentially enables the implementation of personalized therapeutic approaches, optimizes treatment efficacy and ultimately improves the long-term survival and quality of life in pediatric oncology patients [13–20].

At the Hopp Children's Cancer Center Heidelberg (KiTZ) and Heidelberg University Hospital, an interdisciplinary CPS expert panel - comprising pediatric oncologists, human and molecular geneticists, pediatric psychologists, pediatric neurologists, gastroenterologists and endocrinologists, and other relevant specialists - systematically evaluates and analyzes the cause of disease of children with a suspected or confirmed CPS diagnosis. Patients referred for evaluation typically exhibit clinical indicators suggestive of CPS, such as a positive family history, indicator tumors, specific phenotypic features, or nonspecific characteristics, including dysmorphic features. Some are also referred because molecular evidence of CPS was found as part of a precision oncology program. Referrals originate from a broad range of medical specialties, primarily from pediatric oncologists or general pediatricians, but also from other specialists working in pediatric care.

Upon confirmation of a CPS diagnosis, a multidisciplinary approach is adopted to communicate the results and their implications to the patients and their families, enabling informed and shared medical decision-making and facilitating appropriate surveillance or therapeutic adaptations. At the time of data cut-off, 144 patients meeting the predefined selection criteria had been systematically reviewed by our expert panel and included in this retrospective study. Here, we present an analysis of the organizational framework required for optimal patient care, the diagnostic yield of our CPS program, and the clinical challenges encountered in diagnosing and managing pediatric patients with hereditary cancer predisposition syndromes.

Subjects and Methods

In June 2018, an interdisciplinary joint consultation service in pediatric oncology and human genetics was established at Heidelberg University Hospital and the Hopp Children's Cancer Center Heidelberg (KiTZ) to specifically address the needs of pediatric patients with Cancer Predisposition Syndromes (CPS). This specialized consultation is available for children suspected of having CPS based on a specific tumor diagnosis, distinctive physical anomalies, or a family history indicative of an underlying predisposition.

Medical records were retrospectively reviewed for all pediatric and young adult patients (aged 0–21 years) who attended the consultation and were subsequently discussed within the CPS board between 2018 and January 2023 (cut-off). This study was reviewed and approved by the Ethics Committee of Heidelberg University Hospital (Reference: S-800/2022).

The catchment area of the consultation was supra-regional, and patient management followed a standardized protocol without any study-related interventions. Data collection included baseline characteristics, reasons for referral, medical and family history, physical examination findings, results of

prior genetic testing, and clinical recommendations derived from these assessments. Information was obtained from medical records or, where necessary, requested directly from families prior to evaluation.

This study was designed as a single-center retrospective exploratory analysis. Statistical evaluations were performed using SPSS for iOS. Descriptive statistics were applied to summarize the collected data, presenting absolute and relative frequencies, as well as measures of central tendency and dispersion (mean with standard deviation). Data visualization, including bar charts, were generated based on the scale and distribution of the variables with SPSS (Premium V31 for iOS), Excel for Mac and R (version 4.5.1) using R Studio (version 2025.05.1 + 513). Graphical illustrations were generated using BioRender.com and Affinity Designer (version 2.6.3). The primary outcome was the CPS diagnosis rate in previously undiagnosed pediatric patients with suspected CPS, as well as the spectrum of diagnoses made. In addition, the aim was to develop a multidimensional structure and workflow for the causal investigation and medical care of healthy and affected children with suspected CPS.

Results

Interdisciplinary Care Structure for Pediatric Patients with Suspected CPS

To provide comprehensive care for pediatric patients with suspected CPS, an interdisciplinary care framework was first established. Referrals for evaluation originated from a diverse range of sources, including family physicians, hospital-based specialists (such as those from pediatric gastroenterology, neurology, clinical genetics, and oncology), as well as self-help groups or the families themselves. Prior to the consultation, medical assistants contacted the families and collected detailed medical histories, including previous genetic analyses and a preliminary family history to facilitate structured assessment.

Requests were reviewed by the CPS Board, which convened weekly and comprised experts from pediatric oncology, clinical genetics, molecular genetics, and, as needed, specialists from (neuro-)pathology, psychology, neuropediatrics, pediatric gastroenterology and endocrinology. Comprehensive case histories were compiled in advance and shared with board members for pre-consultation review. Patient selection for the consultation by the CPS board was guided by established literature, clinical guidelines, and validated screening questionnaires [21, 22]. The diagnostic strategy and management recommendations were formulated before the consultation, integrating available clinical data and current evidence-based guidelines.

The consultation itself was conducted by specialists in pediatric oncology and human genetics, occasionally joined by a psychologist when psychosocial aspects required consideration. During the session, medical and family histories were reviewed in detail, complemented by a thorough physical examination and standardized photographic documentation. If indicated, genetic testing was initiated during the consultation.

Following the return of molecular results or a definitive clinical diagnosis of CPS, surveillance strategies were implemented in accordance with clinical guidelines. Appointments for ongoing surveillance examinations were scheduled promptly, either at Heidelberg University Hospital or at external institutions with expertise in CPS patient care. Typically, the family physician assumed coordination of surveillance measures, though pediatric oncologists provided support in complex cases, such as in patients with Li-Fraumeni syndrome.

In individuals where a (likely) pathogenic germline variant was identified, genetic testing was extended to family members: minors were evaluated within the CPS consultation, while adults were referred to the clinical genetics department for further assessment. Adults diagnosed with CPS were subsequently referred to the National Center for Tumor Diseases (NCT) or disease-specific specialists within their local healthcare network.

Families with a confirmed clinical or molecular diagnosis of CPS were included in the CPS registry [23] after informed consent and, whenever possible, in prospective scientific studies aimed at advancing understanding of abnormal DNA damage response disorders (ADDRess Research Consortium; http://www.krebs-praedisposition.de/en/cps-research/address/ADDRess ResearchADDRess Research) or improving early cancer detection (http://www.krebs-praedisposition.de/en/cps-research/liquid-biopsy/) (Fig. 1).

Patient Cohort and Related Cancer Diagnoses

A total of 144 children suspected to have a CPS were included in this retrospective study, of whom 75 (52.14%) were female and 69 (47.9%) were male, with a mean age at presentation of 8.3 years (SD 5.5; range 0–21 years). Of these 144, 53 (36.8%) had cancer at the time of or prior to presentation.

Children were referred to the expert panel by in-hospital departments such as the Social-medical Pediatric Aftercare and Pediatric Oncology (n = 96; 66.7%), their own parents (n = 18; 12.5%), other clinics or specialists (n = 16; 11.1%) or their pediatrician (n = 11, 7.6%), with 3 patients path of referral being unknown (2.1%).

Outcome of the study was the CPS diagnosis rate in previously undiagnosed individuals in the preselected cohort. As some of the symptomatic patients (34 out of 99 individuals, 34.3%) and some of the unaffected individuals (10 out of 45, 22.2%) had already been diagnosed with CPS prior to presentation, they had to be considered separately for the determination of the diagnosis rate. The distribution of these subgroups with the respective number of patients is shown in Fig. 2.

Patients were considered symptomatic in this study with a personal history of one or more cancers or with other clinical features suggestive of CPS (Fig. 1). Non-cancer clinical features were for example lateralized overgrowth, macroglossia and omphalocele in Beckwith-Wiedemann syndrome;

macrocephaly and autism in *PTEN* hamartoma tumor syndrome or café au lait macules and axillary freckling in Neurofibromatosis 1.

Unaffected individuals in this study had no personal history of cancer or other clinical manifestations of CPS, but a family history with proven or strongly suspected CPS. They received predictive genetic testing, which is subject to legal regulations in Germany (Fig. 1).

Taking together, 86/144 (60%) individuals of the total cohort were affected by a proven CPS. Ten of the 86 (11.6%) had a clinical diagnosis (e.g. NF1 according to clinical diagnostic criteria) only. Among the 86 individuals with CPS diagnoses, 28 different CPS were diagnosed (Fig. 3).

Symptomatic patients

Among symptomatic patients without a prior diagnosis of a CPS at the time of consultation (n = 65), 50 individuals underwent molecular testing, resulting in the identification of a CPS in 23 cases (23/50, 46%) (Fig. 2). The CPS diagnosis rate among previously undiagnosed clinically affected individuals was thus almost half of the individuals examined in this group. In the remaining 15 cases (15/65, 23.1%), molecular testing was not performed due to different reasons, for example no additional signs of heritable disease in the personal or family history after presentation and: i. Infantile fibrosarcoma with the typical somatic ETV6:NTRK3 fusion; ii. Medulloblastoma with negative tumor sequencing in a research study (MNP2.0); iii. Cafe au lait macules with no additional clinical signs, where the clinical management would not have changed even with a molecular NF1 diagnosis. Notablys 5 of these 15 patients (33.3%) received a clinical CPS diagnosis (NF1; BWS; Enchondromatosis) based solely on their medical history and presenting symptoms.

Among the 53 patients diagnosed with malignancies, 42 individuals (79.2%) had a history of a single tumor, while 11 (20.8%) presented with multiple distinct tumor types. The tumor spectrum, comprising a total of 64 malignancies, is summarized in Fig. 4 (rows 1 and 2) and includes 42 solid tumors (65.6%), 21 central nervous system (CNS) tumors (32.8%), and 1 hematological malignancy (1.6%). Within the subgroup of patients with multiple primary malignancies (n = 11), 10 individuals (90.9%) underwent molecular testing, and a CPS was confirmed in 8 of these cases (80%).

Unaffected individuals

Among 45 unaffected individuals with a known familial predisposition, the following syndromes or associated genes had previously been identified within their families: Li-Fraumeni syndrome in 18 cases (40%), familial adenomatous polyposis in 9 (20%), multiple endocrine neoplasia type I in 6 (13.4%), neurofibromatosis type I in 4 (8.9%), PTEN hamartoma tumor syndrome in 3 (6.7%), hereditary pheochromocytoma/paraganglioma syndrome in 2 (4.4%), WT1-associated syndrome in 1 (2.2%), and 2 individuals (4.4%) had a suggestive family history without a specific suspected diagnosis. In 10 individuals (22.2%), the familial pathogenic variant had already been identified prior to the consultation.

Genetic testing was not performed in 3 individuals (6.7%): in two cases consent was not provided by the family, and in one case because prior testing in an affected family member had yielded a negative result. The remaining 32 individuals underwent predictive genetic testing during the consultation. Of these, 14 (43.8%) were found to carry the familial CPS variant, while 18 (56.2%) tested negative.

Clinical Implications of a CPS-Diagnosis

In the majority of cases, a confirmed CPS diagnosis had clinical relevance for both the affected child and their family members. Of the 76 individuals with a molecularly confirmed CPS, 71 (93.4%) received a surveillance recommendation based on established, published guidelines. The remaining five children did not receive immediate surveillance recommendations for reasons such as: i. adult-onset CPS; ii. comprehensive tumor aftercare also covers surveillance recommendations; iii. Beckwith-Wiedemann syndrome with loss of methylation at IC2 (maternal) and no routine tumor surveillance recommendation. Predictive genetic testing for at-risk relatives including the parents was offered in 41 of the 76 families (53.9%) following the identification of a CPS in the child. In an additional 28 families (36.8%), predictive testing had already been performed prior to the consultation, as the molecular diagnosis was previously known within the family. Predicitve testing was not recommended in 6 families with a molecular confirmed CPS because of molecular evidence of postzygotic mosaicism. A total of 40 individuals (30 symptomatic and 10 unaffected) had received a molecular diagnosis of CPS before the consultation. Consequently, around one third (40/144, 27.8%) of all consultations were focused on determining appropriate clinical management and follow-up measures for previously diagnosed individuals.

Clinical consequences: Illustrative case from a CPS consultation

An 11-year-old boy (Patient 114) was referred to the CPS consultation for guidance on tumor surveillance. His clinical features included macrocephaly (SDS + 4.34), tall stature (SDS + 1.97), learning disability, focal cortical dysplasia, and focal structural epilepsy. Molecular genetic testing had been performed at age 10, prior to the consultation, and revealed a pathogenic *de novo* frameshift variant in *PTEN* (NM_000314.8(*PTEN*):c.464_465dupAT p.(Gly156MetfsTer4)), consistent with a diagnosis of PTEN hamartoma tumor syndrome. The patient was born at 38 weeks' gestation following an uneventful pregnancy, with a birth weight of 4,340 g (+ 2.4 SDS), length of 55 cm (+ 1.7 SDS), and head circumference of 39 cm (+ 2.9 SDS). Clinical examination revealed pinhead-sized indurations on both hands (suspected papillomatous papules), gingival hyperplasia, and a lipoma near the right costal arch. Surveillance was initiated according to published recommendations [24]. Thyroid ultrasound identified a slowly growing focal lesion of the right thyroid lobe at the age of 12 years, which was subsequently resected. Histopathological evaluation confirmed a 1.2 cm follicular thyroid carcinoma (pT1b L0 V1, R0). The patient underwent right and left hemithyroidectomy followed by ablative radioiodine therapy with 3.7 GBq I-131.

This case highlights the critical role of the interdisciplinary CPS consultation in translating molecular findings into clinical action. Despite long-standing features such as macrocephaly and learning disability, appropriate tumor surveillance was only initiated following the CPS diagnosis and consultation, enabling timely detection and treatment of a localized thyroid carcinoma.

Diagnoses requiring special consideration

Two special features of genetic diagnosis require particular consideration: Cancer predisposition syndromes as secondary findings, which are particularly susceptible to overestimated penetrances due to selection bias; and postzygotic mosaicism, which could be overlooked, but whose identification is important for the genetic counselling of families.

Secondary findings

In an 8-year-old girl diagnosed with malignant melanoma (patient 88), molecular testing was initiated following presentation in our consultation, but no pathogenic variant was identified in genes classically associated with a melanoma predisposition. However, a pathogenic variant in *LZTR1*, (NM_006767.3(*LZTR1*):c.27del p.(Gln10Argfs*15) associated with a predisposition to develop schwannomas, was detected. The parents had previously consented to the disclosure of additional findings. Based on available literature at the time [25–28], preventive recommendations were initially provided for the child. Subsequently, updated guidance recommended against routine surveillance in individuals with *LZTR1* variants identified solely as incidental findings, due to presumed low penetrance and limited evidence for clinical benefit [29]. As a result, predictive genetic testing was not pursued in the parents, and with the consent of the parents surveillance in the child was discontinued.

In an 17-year-old boy (patient 144), molecular analysis was initiated by the local neuropaediatrics department to investigate a neurodevelopmental disorder. As an incidental finding, a likely pathogenic variant in *SUFU* was identified by sequence analysis at the Institute of Human genetics. Heterozygous disease-causing variants in *SUFU* are associated with nevoid basal cell carcinoma syndrome, which, among other symptoms, leads to a significantly increased risk of medulloblastoma. The family was referred to the CPS consultation to receive counselling regarding the genetic finding and to obtain appropriate surveillance recommendations. In this context, predictive genetic testing was also recommended for the parents.

Mosaicism

In 9 out of 144 children (6.3%), there was evidence suggestive of germline mosaicism for a CPS, e.g. hemihypertrophy or multiple tumors with negative results from germline sequencing of a blood sample. In 6 of these individuals, mosaicism was molecularly confirmed: Patient 3 was diagnosed with CLOVES syndrome due to *PIK3CA* mosaicism presenting with macrocephaly, ventricular asymmetry and hemihypertrophy of the body (NGS panel analyses confirmed a variant in 20% of reads in DNA from

buccal swap, not detectable in DNA from a blood sample). Two unrelated patients (23 and 51) were found to have Maffucci syndrome caused by *IDH1* mosaicism (detected with NGS panel analysis on tumor samples). Maffucci syndrome is characterized by mosaic gain-of-function; no constitutional germline variants in *IDH1* have been reported with this syndrome[30]. In patient 139, a *NF2* mosaicism was detected with NGS in two meningimomas and not in blood in a child with multiple meningiomas, consistent with neurofibromatosis type 2. Patient 171 was diagnosed with hereditary paraganglioma–pheochromocytoma syndrome associated with *HIF2A* mosaicism, presenting with pheochromocytoma, extra-adrenal paraganglioma, and polycythaemia. The disease-causing variant was detectable in both tumors and not detectable in the blood sample with sanger sequencing. Beckwith-Wiedemann syndrome due to mosaic ICR2 hypomethylation in blood was confirmed with MS-MLPA in patient 113 presenting with omphalocele, hypoglycaemia, macrosomia, macroglossia, and nephromegaly.

Discussion

Approximately 10% of all pediatric cancer patients carry a germline CPS, as demonstrated by large cohort studies [3, 31]. The number of recognised CPS-associated genes has expanded in recent years, driven by advances in genomic technologies and clinical diagnostics [1]. Nevertheless, many CPS cases remain undetected, even among children diagnosed with malignancies [6]. Factors contributing to this underdiagnosis include negative family history due to incomplete penetrance of pathogenic variants and the presence of *de novo* germline variants - accounting for roughly 20% of *TP53* mutations in children, postzygotic mosaicism, as well as limited access to or utilisation of genetic testing, and insufficient awareness among healthcare providers. Consequently, CPS diagnoses are often made retrospectively [32], rather than at a stage when risk-adapted surveillance and prevention strategies could be implemented. Although children with CPS can be identified through various pathways - ranging from clinical assessment and predictive testing to incidental germline findings during tumor sequencing - these strategies vary in sensitivity and are not uniformly applied. As a result, a substantial proportion of CPS cases remain undiagnosed, highlighting the need for an integrated diagnostic framework that combines genomic and clinical approaches. Such a model should seamlessly link precision oncology, phenotypic and variant AI-supported evaluation, and predictive testing to enable early and accurate CPS detection - ideally before the onset of malignancy.

Beyond initial diagnosis, long-term management requires specialized consultation structures and coordinated care planning. CPS encompass a heterogeneous group of rare disorders - most with birth prevalence far below 1 in 3,000. Even relatively common entities such as neurofibromatosis type 1 (NF1) meet criteria for rare diseases. The complexity of CPS management is further compounded by incidental findings, variants of uncertain significance, and evolving tumor spectra over time. For example, malignancy risks associated with *DICER1* and *TP53* variants change with age, necessitating dynamic surveillance strategies, especially during transition from padiatric to adult care. Additionally, hypomorphic variants and reduced penetrance pose challenges for risk prediction. Notably, postzygotic mosaicism likely represents an underrecognized cause of CPS [33–35]. Mosaicism was frequently

suspected in our cohort. Standard tumor-normal sequencing may miss mosaic variants due to skipping of reads with low variant allele frequencies or misclassification as somatic events[33]. However, accurate identification is clinically relevant, as mosaic cases often require the same level of surveillance as individuals with dominantly inherited CPS.

Our findings demonstrate that 28% of consultations involved patients with a pre-established CPS diagnosis, reflecting a substantial demand for ongoing medical management and genetic counselling. The majority of CPS-positive patients in our cohort received surveillance recommendations in line with current guidelines and predictive testing was widely initiated within affected families. While this approach provided additional value for the management of these patients, the long-term clinical benefit of such surveillance in pediatric populations remains to be prospectively validated based on these novel results. Unlike hereditary breast and ovarian cancer (HBOC) or Lynch syndrome - where adult guidelines are underpinned by robust long-term data [36] - surveillance strategies for pediatric CPS are still in development and require prospective validation [37]. Harmonized, evidence-based protocols will be critical for improving outcomes and reducing disparities. Participation in international registries and studies, such as the CPS registry [23], ADDRESS (https://www.krebs-praedisposition.de/en/cps-research/address/), and liquid biopsy-based early detection trials (https://www.krebs-praedisposition.de/en/cps-research/address/), will be essential for this effort.

In parallel, structural barriers such as inadequate health insurance coverage for surveillance, particularly in asymptomatic individuals, must be addressed. Even in countries with comprehensive healthcare systems, such as Germany, cost coverage for preventive measures is not consistently guaranteed. Despite these challenges, the interdisciplinary CPS consultation model described here is effective for integrating diagnostic, therapeutic, and psychosocial expertise. This approach facilitates tailored patient care, enhances diagnostic accuracy, and supports informed clinical decision-making.

Several limitations of this study should be acknowledged. The cohort represents a selected population referred for CPS evaluation, introducing potential referral bias and limiting generalizability. Additionally, the rarity of individual CPS entities and the lack of follow-up data precluded statistically powered subgroup analyses. At the time of data collection, most patients underwent targeted gene panel testing, whereas current approaches increasingly rely on genome or exome sequencing, which may further improve diagnostic yield in the future.

In conclusion, the interdisciplinary CPS consultation model described here offers a comprehensive, patient- and family-centered framework that integrates medical expertise, psychological support, education, and long-term surveillance planning. It serves as a central point of contact across disciplines and plays a key role in refining care pathways for children and families affected by cancer predisposition syndromes. The next step is to implement standardised, prospective, long-term follow-up in registries to collect data that supports the health and health economic impacts of surveillance. Through ongoing collaboration and evidence generation, this model contributes to the advancement of personalised pediatric oncology.

Declarations

Ethical Approval:

This study was reviewed and approved by the Ethics Committee of Heidelberg University Hospital (Reference: S-800/2022). All procedures followed were in accordance with the Declaration of Helsinki.

Declaration of interests:

Author Cornelis van Tilburg reports advisory board relationships with Alexion, Bayer, Novartis and Roche; receiving research grants from BioMed Valley Discoveries and Day One Biopharmaceuticals; speaker honoraria from Ipsen and travel support from Eli Lilly. All other authors report no potential conflicts of interest.

Author Contribution

Statement: Conceptualization: N.D., A.L.N., M.H., T.M., C.P.S., S.M.P., J.K., K.W.P., O.W., K.W., D.T.W.J.; Investigation: S.H., N.D., A.L.N, E.R., L.O., D.C., K.G, P.L., C.S., K.H., H.B., C.M.v.T., M.G., A.F., K.W., T.M., J.K., K.W.P.; Project administration: N.D., A.L.N., K.W.P., Visualization: A.L.N., T.F.; Writing-original draft: N.D., A.L.N., K.W.P.; Writing-review & editing: S.H., E.R., L.O., D.C., K.G., P.L., C.S., K.H., H.B., C.M.v.T., O.W., M.G., A.F., K.W., D.T.W.J., M.H., A.E.K., U.B., T.M., C.P.S., S.M.P., J.K.

Data Availability Statement:

Additional data are available from the corresponding author on reasonable request.

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Figures

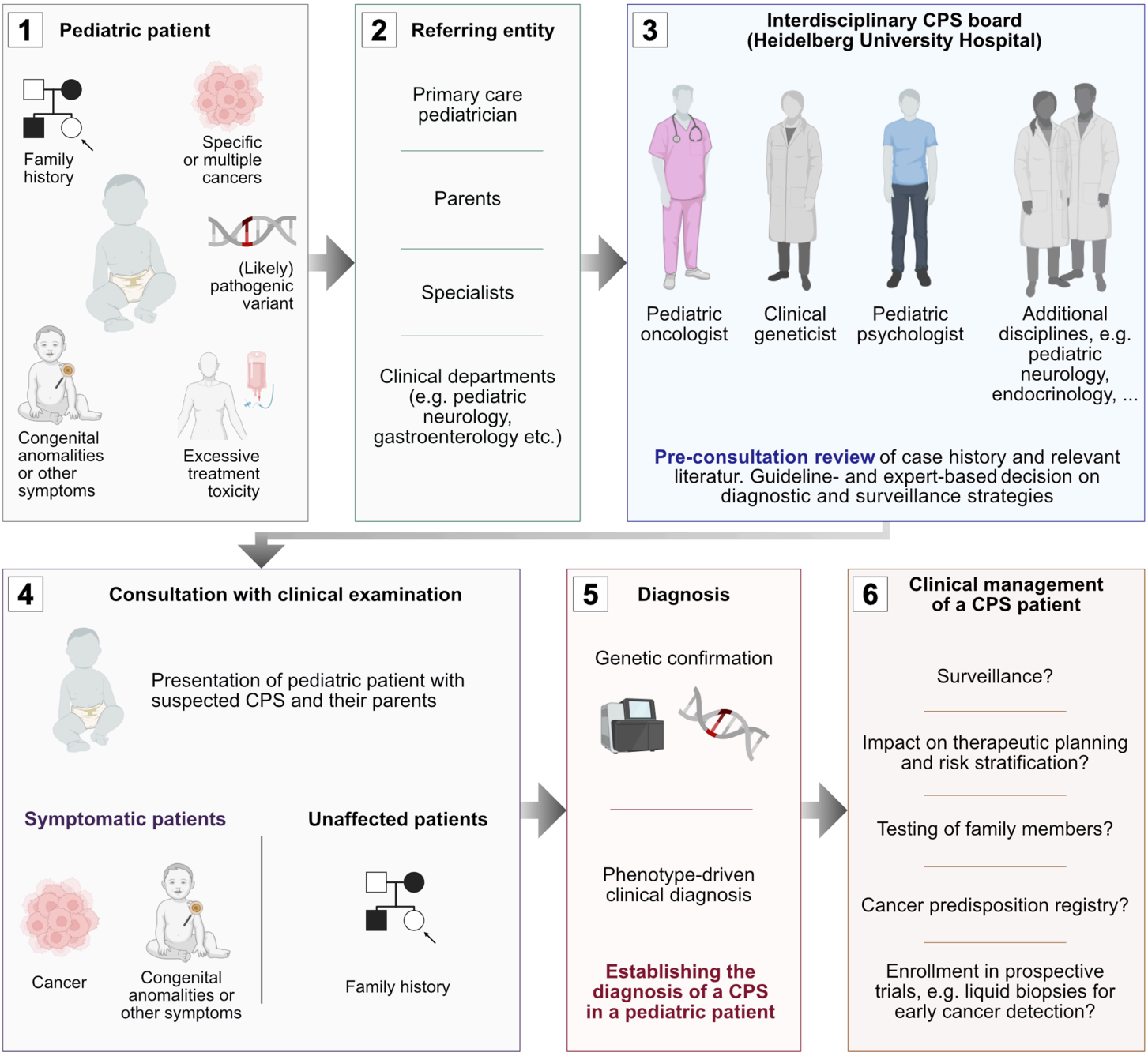


Figure 1

Schematic representation of the patients (1) and their referral pathways (2), the interdisciplinary CPS Board including discussed unaffected and symptomatic patient groups (3;4), and potential clinical consequences (6) following CPS confirmation (5).

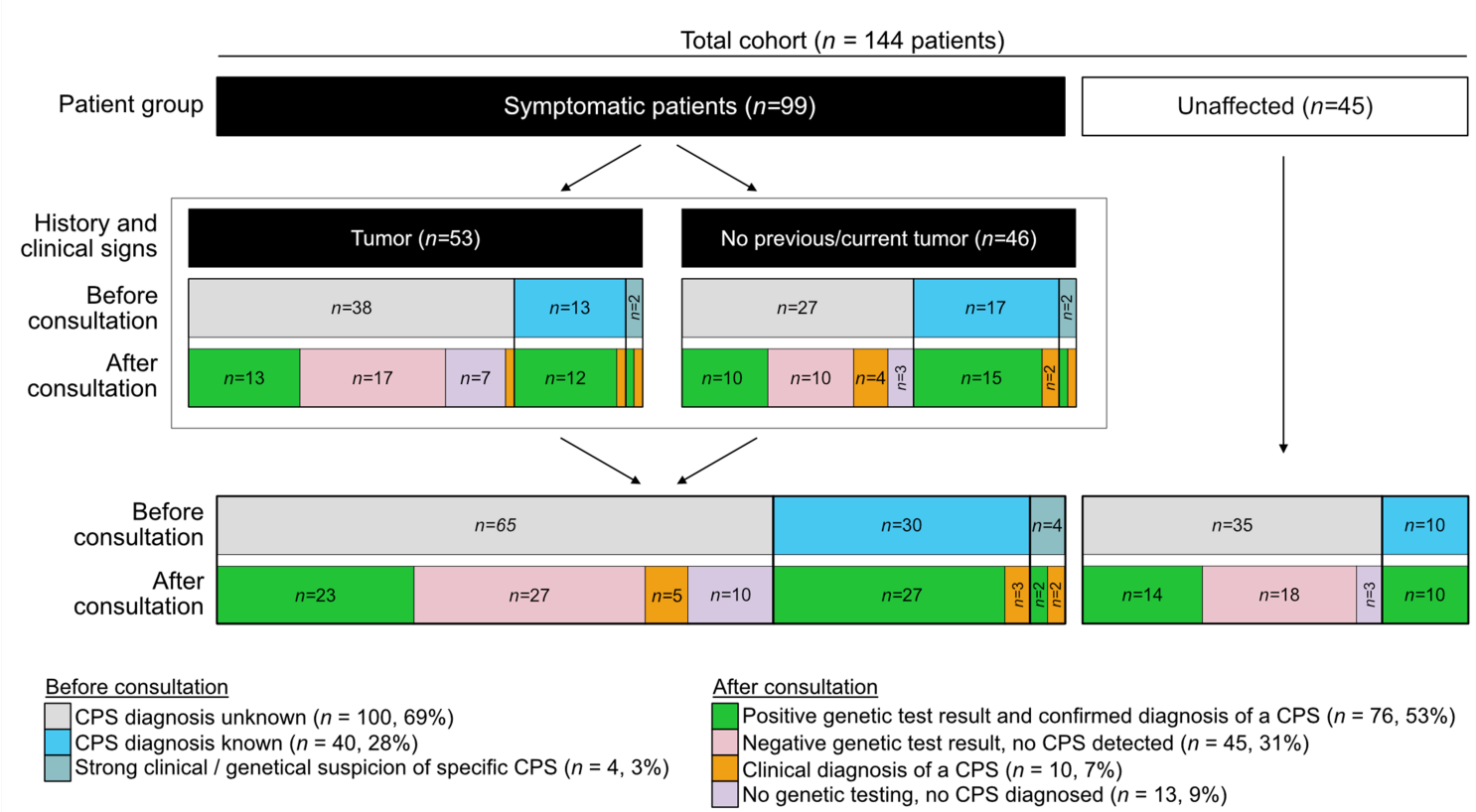


Figure 2

Diagnostic rates in symptomatic patients and in clinically unaffected individuals before and after consultation. CPS: cancer predisposition syndromes; uD = CPS diagnosis unknown before consultation; pD = positive CPS diagnosis known before consultation; cD = strong clinical suspicion of specific CPS before consultation; PC = positive genetic test result and confirmed CPS diagnosis; NC = no CPS detected; NT = no testing, no clinical diagnosis; CD = clinical CPS diagnosis after consultations

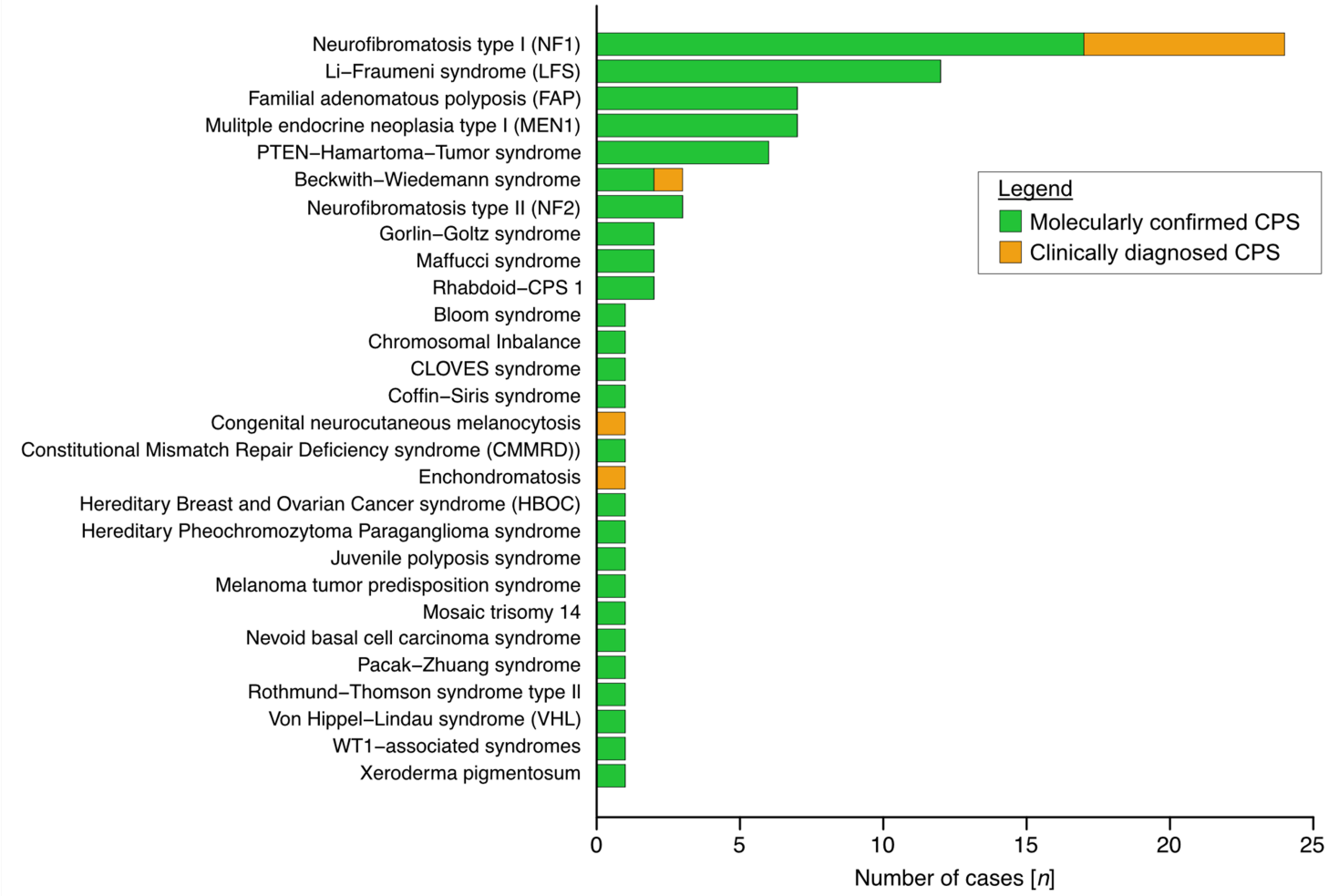


Figure 3

Number of individuals with CPS diagnoses in the cohort and performed genetic analyses to identify the diagnosis: 28 different CPS in 85/144 (59%) individuals with and without cancer (80/144 (55,6%) molecular diagnoses and 5/144 (3,5%) clinical diagnosis only).

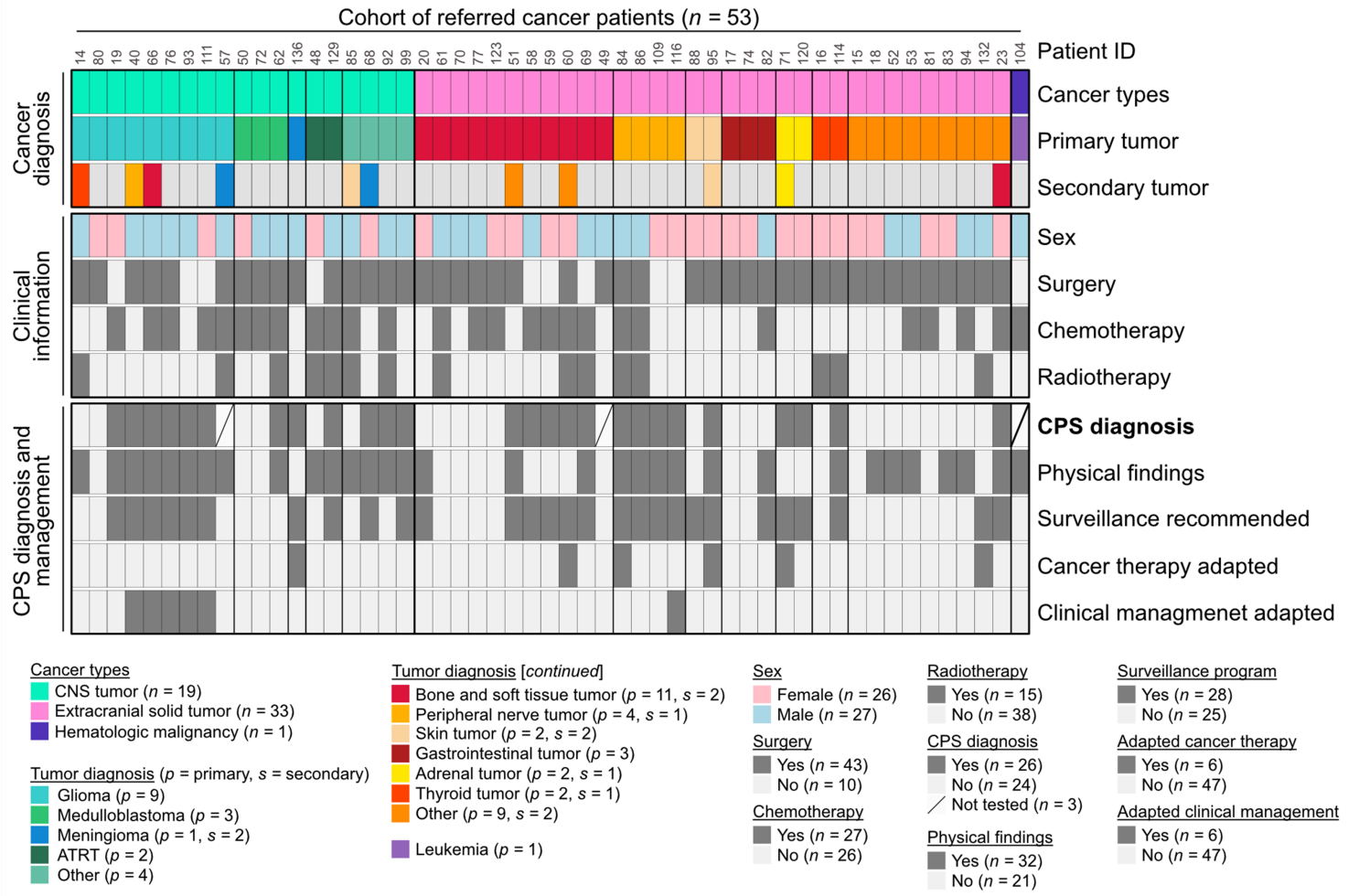


Figure 4

Tumor blot illustrating the distribution of 64 tumors across 53 patients. The first line (‘Cancer Types‘) categorizes tumors as CNS, extracranial solid, or hematologic malignancy. The second and third line (‘Primary and Secondary Tumor’) specifies tumor entities according to the color legend below. Additional markers indicate a confirmed CPS diagnosis, inclusion in surveillance programs, therapy regimen for the diagnosed tumor, gender and physical findings in the patient.