Registry Protocol

Li-Fraumeni-Syndrome-Cancer-Predisposition-Syndrome Registry 01

(LFS-CPS-R01)

Principal Investigators:

Christian P. Kratz, MD
Hannover Medical School
Pediatric Hematolgy and Oncology
Carl-Neuberg-Str. 1, 30625 Hannover
Germany
Phone: +49 511-532 6712
Fax: +49 511-532 9120
Email: kratz.christian@mh-hannover.de

Stefan M. Pfister, MD
Hopp Children's Cancer Center at NCT Heidelberg (KiTZ)
Division of Pediatric Neurooncology
German Cancer Research Center (DKFZ)
Department of Pediatric Hematology and Oncology
Heidelberg University Hospital
Im Neuenheimer Feld 580, 69120 Heidelberg
Germany
Phone: +49 6221 - 42 4617
Fax: +49 6221 - 42 4639
Email: s.pfister@dkfz.de

List of commonly used abbreviations

ACC	Adrenocortical carcinoma
ALL	Acute lymphoblastic leukemia
CPG	Cancer predisposition gene
CPS	Cancer predisiposition syndrome
LFS	Li-Fraumeni syndrome
LFL	Li-Fraumeni like
IARC	International Agence for Research on Cancer

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Synopsis

Title of the registry	Li-Fraumeni-Syndrome-Cancer-Predisposition-Syndrome-Registry 01
Protocol No.	LFS-CPS-R01
Design	Natural History Study
Objectives	• Establish a LFS/CPS registry • Evaluate the feasibility and benefit of cancer surveillance programs • Develop a radiological image database for CPS • Establish a CPS mutation database • Conduct germline-somatic correlations and genotype-phenotype correlations • Optimizing cancer treatment in patients with CPS by close collaboration with GPOH trial groups
Registry Population	500-1000 patients are expected to enroll
Inclusion Criteria	• Written informed consent • Confirmed or suspected diagnosis of LFS/CPS
Methodology	Central review of diagnostic procedures Regular follow-up (annual)
Statistical Methods	The analysis of survival times and other quantitative and qualitative variables will be completed using suitable descriptive methods. Confidence intervals for all estimates will be computed.
Timetable	Start of registry: August 2017
Principal Investigators	Christian Kratz, M.D. Stefan Pfister, M.D.

Flow-chart

	Registry entry	**Annual follow-up**
Medical history	X	X
Physical exam	X	X
Genetic testing results	X	(X)
Surveillance results (radiology, laboratory)	X	X
Electronic version of radiologic images with evidence of malignancies	X	X
5 ml research EDTA blood	X	X
Research tumor specimen*	(X)	(X)

* if not hampering tumor collection through GPOH clinical trial group

- The protocol is funded by the Deutsche Kinderkrebstiftung.
- The investigators have no conflicts of interest.
- The main benefit for enrolled patients is the increased knowledge about their condition. However, these benefits may mainly affect future patients that are not necessarily part of this research. Patients may also benefit from counseling that the registry team offers and from incidental findings that are identified through this research.
- Patients are enrolled after a cancer prone syndrome has been diagnosed.
- After inclusion of a patient, data and specimens that are collected by the treating institution for medical reasons are forwarded to the registry.
- There are no studyspecific procedures.
- Enrolled patients don’t loose extra time through this research.

Registry Team

Registry Coordinator	Christina Dutzmann Medizinische Hochschule Hannover Pädiatrische Hämatologie und Onkologie Carl-Neuberg-Str. 1 30625 Hannover Email: Dutzmann.Christina@mh-hannover.de Tel. +49 511 532 6738
Data Manager	N.N. Medizinische Hochschule Hannover Pädiatrische Hämatologie und Onkologie Carl-Neuberg-Str. 1 30625 Hannover

Collaborators

International

- **Jennifer Perry**, Li-Fraumeni Syndrome Association, P.O. Box 6458, Holliston, MA 01746 USA
- **David Malkin**, MD, Division of Hematology/Oncology, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada
- **Jeffrey Weitzel**, MD, Division of Clinical Cancer Genetics, Department of Medical Oncology, City of Hope, Duarte, CA , USA
- **Sharon Savage**, MD, Clinical Genetics Branch, National Cancer Institute, Bethesda, MD, USA
- **Maria Isabel Achatz**, MD, PhD, Clinical Genetics Branch, National Cancer Institute, Bethesda, MD, USA
- **Thierry Frebourg**, MD, PhD, Department of Genetics, Rouen University Hospital, Rouen, France
- **Louise C. Strong**, MD, FAACR, Department of Genetics, UT MD Anderson Cancer Center, Houston, TX, USA
- **Judy Garber**, MD, MPH, FAACR, Center for Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Boston, MA, USA
- **Sharon Plon**, MD, PhD, and **Surya Rednam**, MD, Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA
- **Joshua D. Schiffman**, MD, High Risk Pediatric Cancer Clinic, University of Utah, Huntsman Cancer Institute, Salt Lake City, UT, USA
- **Kim E. Nichols**, MD, Cancer Predisposition, St. Jude Children's Research Hospital, Memphis, TN, USA
- **Gareth Evans**, MD, MBBS, Department of Genomic Medicine University of Manchester St. Mary's Hospital Manchester, England
- **Rosalind Eeles**, PhD, The Institute of Cancer Research, 15 Cotswold Road, Sutton SM2 5NG, London, UK; Royal Marsden NHS Foundation Trust, London, UK.
- **Marielle W. Ruijs**, MD, PhD, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Family cancer clinic, Amsterdam, The Netherlands
- **Marjolijn Jongmans**, MD, PhD, Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands; Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands; Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands.

Close exchange will occur with Clinical Trial Groups treating patients enrolled in this registry and with members of the German Working Group on Genetic Cancer Predisposition:

Pediatric Oncology: Stefan S. Bielack, Arndt Borkhardt, Ines B. Brecht, Birgit Burkhardt, Gabriele Calaminus, Klaus-Michael Debatin, Hedwig Deubzer, Uta Dirksen, Beate Dörgeloh, Martin Ebinger, Cornelia Eckert, Angelika Eggert, Miriam Erlacher, Jörg Faber, Gudrun Fleischhack, Michael C. Frühwald, Nicolas Gerber, Astrid Gnekow, Norbert Graf, Julia Hauer, Barbara Hero, Simone Hettmer, Katja von Hoff, Martin Horstmann, Björn-Ole Juhnke, Ariana Kamawal, Kornelius Kerl, Thomas Klingebiel, Udo Kontny, Uwe Kordes, Dieter Körholz, Ewa Koscielniak, Christof M. Kramm, Michaela Kuhlen, Andreas E. Kulozik, Andrea Meinhardt, Markus Metzler, Lüder H. Meyer, Olga Moser, Michaela Nathrath, Charlotte M. Niemeyer, Kristian W. Pajtler, Claudia Paret, Alexandra Russo, Stefan Rutkowski, Irene Schmid, Dominik Schneider, Reinhard Schneppenheim, Martin Schrappe, Peter Schütte, Thorsten Simon, Monika Sparber-Sauer, Arend von Stackelberg, Martin Stanulla, Brigitte Strahm, Petra Temming, Andre O. von Bueren, Peter Vorwerk, Olaf Witt, Marcin Wlodarski, Willy Wössmann, Stefanie Zimmermann

Human Genetics: Thomas Illig, Dietmar R. Lohmann, Tim Ripperger, Brigitte Schlegelberger, Olaf Rieß, Christopher Schroeder, Doris Steinemann, Martin Zenker, Gudrun Goehring, Juliane Hoyer, Kathrin Thomay, Susanne Morlot, Lisa Pahl

Gynecology: Rita Schmutzler

Childhood Cancer Registry: Peter Kaatsch, Claudia Spix

Pediatric Surgery: Rainer Nustede, Dietrich von Schweinitz, Roland Kappler, Kristina Becker

Radiology: Frank Wacker

Neuropathology: Ulrich Schüller

1. Introduction

Approximately 2100 cases of childhood cancer are diagnosed annually in Germany. In contrast to adult oncology where environmental factors such as smoking and alcohol contribute in a significant manner to tumorigenesis, these external factors appear to be less contributory in pediatric cancers. The only known quantitatively relevant cause of childhood cancer is genetic cancer predisposition. Over 100 cancer predisposition genes (CPG) that are mutated in patients with cancer predisposition syndromes (CPS) have been identified and recent studies indicate that germline mutations in CPGs occur more frequently than previously thought.[1] **Table 1** shows relevant CPS.

Table 1. CPS groups studied in the proposed LFS-CPS Registry

Li-Fraumeni Syndrome
Wilms' Tumor and Overgrowth Disorders Beckwith-Wiedemann syndrome, Bohring-Opitz syndrome, Mulibrey (muscle, liver, brain, and eye) nanism, Perlman syndrome, Trisomy 18, Simpson-Golabi Behmel syndrome, *WT1*-related syndromes (WAGR, Denys-Drash, Frasier)
Neurofibromatoses 1 and 2, Schwannomatosis
Predisposition to other Neural Tumors Neuroblastoma Predisposition, Retinoblastoma Predisposition, Medulloblastoma Predisposition, Rhabdoid Tumor Predisposition
Gastrointestinal Cancer Syndromes *APC*-related adenomatous polyposis, *MUTYH*-associated polyposis, Peutz-Jeghers Syndrome, Juvenile Polyposis syndrome
Constitutional Mismatch Repair Deficiency
Neuroendocrine Tumors Von Hippel Lindau, Hereditary Pheochromocytoma/Paraganglioma syndromes, Multiple Endocrine Neoplasia 1, Multiple Endocrine Neoplasia 2A and 2B, Multiple Endocrine Neoplasia 4, *CDC73*-Related (Hyperparathyroid-Jaw Tumor) syndrome
Leukemia Predisposition *PAX5, CEBPA, ETV6, RUNX1, GATA2* deficiencies, Robertsonian translocation 15;21, ring chromosome 21, other
DNA Repair and Immunodeficiency Syndromes Ataxia Telangiectasia, Bloom syndrome, Dyskeratosis congenita, Fanconi anemia, Nijmegen breakage syndrome, Xeroderma pigmentosa
Miscellaneous Disorders DICER1 syndrome, PTEN Harmatoma Tumor Syndrome, Hereditary Leiomyomatosis and Renal Cell Cancer, Rasopathies, Sotos syndrome, Weaver syndrome, Rubinstein-Taybi syndrome, Schinzel-Giedion syndrome, NKX2-1 syndrome, Selected metabolic conditions (Ornithine Transcarbamylase Deficiency, L-2-Hydroxyglutaric Aciduria, Tyrosinemia), Other

* CPS that are already being studied by current GPOH efforts will not be re-registered.

2. Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS, OMIM #151623) is a highly penetrant, autosomal-dominant CPS associated with a high risk for soft tissue and bone sarcomas, breast cancer, brain tumors, adrenocortical carcinoma (ACC), choroid plexus tumors, acute leukemia and other neoplasms (Figure 1).[2] Patients with LFS are at increased risk of

developing second and third cancers, particularly if they have survived a childhood cancer.[3] In most cases, LFS is caused by germline mutations of *TP53* coding for the TP53 protein, which functions as a tumor suppressor.[4] Specifically, TP53 is a transcription factor that regulates cell-cycle arrest, cellular apoptosis and DNA-repair. Defective TP53 reduces its transcriptional activity, which decreases cellular growth. Limiting effects of the protein ultimately result in a drastic risk of cancer.[5] It is estimated that >1 in 5,000 persons carry a constitutional *TP53* mutation.[6] If true, there are approximately 16,000 *TP53* germline mutation carriers in Germany. In the *TP53* mutation database of the International Agency for Research on Cancer (IARC), approximately 760 germline mutations are registered from across the world (p53.IARC.fr/). In Brazil the R337H founder mutation affects 0.3% of the population.[7] As we acquire new presentations of the condition, the formal clinical diagnostic criteria for LFS are changing. Therefore, for the purpose of this protocol, we are using a simplified genetic definition of LFS: the presence of a pathogenic germline mutation in *TP53*, which is likely to be more common than implicated by the pure clinical definition.

A recent study described 214 LFS families diagnosed between 1993 and 2013 and included 415 constitutional *TP53* mutation carriers who did not have a cancer diagnosis at the beginning of the study.[5,8] Among *TP53* mutation carriers 322 (78%) developed at least one malignancy during the 20 years study period. A significant number of cancers occurred at a young age, 22% were diagnosed with a cancer by age 5 years and 41% by age 18 years.[5,8] Notably, 4% of participants developed a malignancy during the first year of life.[5,8] In children and adolescents with LFS, osteosarcoma was the most common tumor (30%), followed by ACC (27%), brain tumors (25%) and soft tissue sarcoma (23%).[6,11] Breast cancer was the most frequently encountered malignancy (79% of women) followed by soft tissue sarcoma (27%) in LFS adults. Second neoplasms ocurred in 40% of patients, often within the radiation field suggesting that initial anti-tumor therapy influences the risk of subsequent cancers.

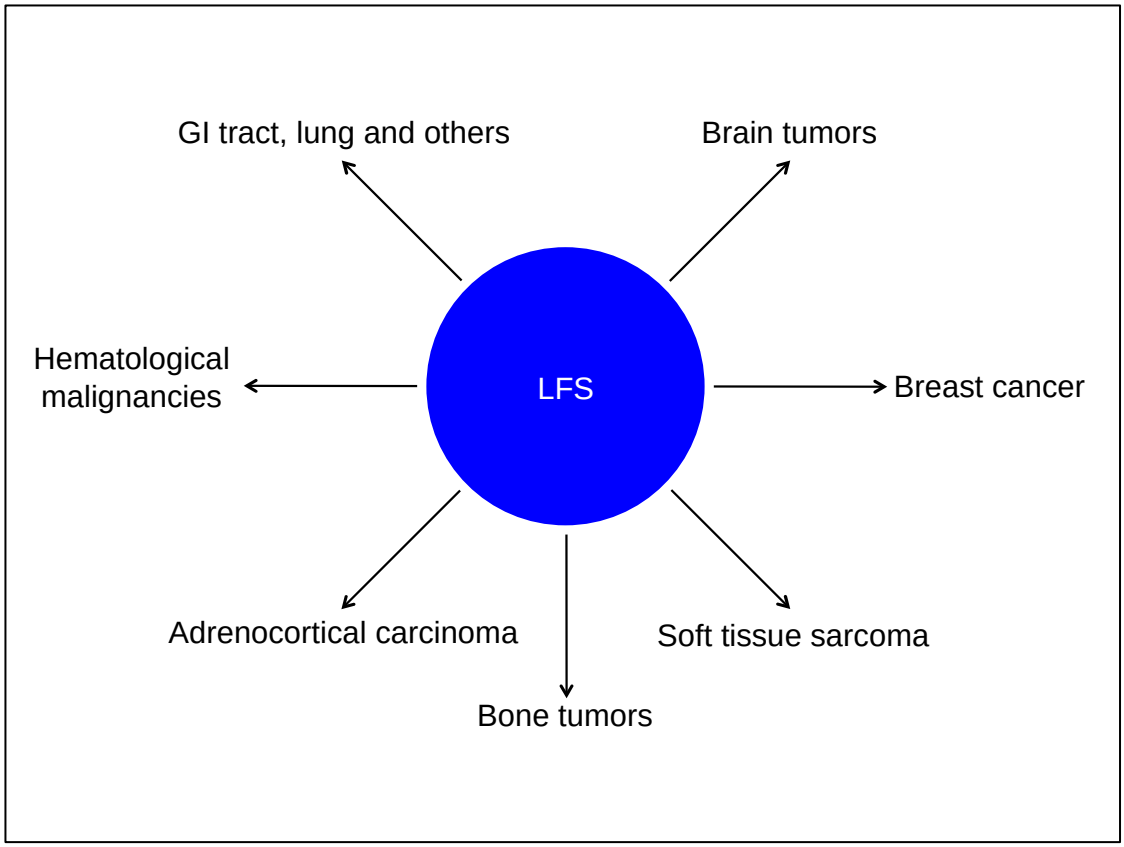

Figure 1. Li-Fraumeni syndrome (LFS) cancer spectrum

3. Li-Fraumeni Syndrome in Pediatric Oncology

Several childhood cancers are strongly associated with LFS. In this age group, 80% of cases of rhabdomyosarcoma of the diffuse anaplasia subtype,[9] 50% of cases of ACC,[10] 50% of cases of secondary (following radiation) glioblastoma, 40% of cases of choroid plexus carcinoma,[8] 40% of cases of low-hypodiploid acute lymphoblastic leukemia (ALL),[11] >10% of children with sonic hedghog subtype medulloblastoma,[12,13] and up to 10% of cases of osteosarcoma[14] are due to a germline *TP53* mutation. Additionally, an increased frequency of *TP53* germline mutations is observed in children with relapsed ALL (2%).[15] Presumably a large proportion of patients with LFS are not diagnosed during childhood or adolescence because many are not tested for constitutional *TP53* mutations. These children and their families with unrecognized *TP53* mutations do not benefit from surveillance strategies (discussed below) or adaptative treatment approaches such as avoidance of radiation therapy whenever possible without jeopardizing cure rates.

4. When is germline *TP53* mutation testing recommended (see also **Table 2)?**

The recommendations for *TP53* germline testing are summarized in the Chompret criteria updated in 2015.[8] **(1) Familial presentation**: Proband with a LFS spectrum tumor (premenopausal breast cancer, soft tissue sarcoma, brain tumor, ACC) prior to age 46 years AND at least one first- or second-degree relative with a LFS tumor (except breast cancer, if the proband has breast cancer) before the age of 56 years or with multiple tumors. **(2) Multiple tumors:** Proband with multiple malignancies (except recurring breast cancer), of which at least two belong to the LFS spectrum before the age of 46 years. **(3) Rare tumors:** Patients with ACC, choroid plexus carcinoma or embryonal anaplastic subtype rhabdomyosarcoma independent of family history. **(4) Breast cancer before age 31 years.**

In recent research projects several additional clinical presentations associated with germline *TP53* mutations have been discovered. Low-hypodiploid ALL in children frequently occurs in the setting of LFS.[11] More than 10% of children with sonic hedghog subtype medulloblastoma have a *TP53* germline mutation.[16,17] Hence in these situations, germline *TP53* testing should be offered. In patients with osteosarcoma, germline *TP53* mutation testing may be considered regardless of family history because constitutional *TP53* defects are present in up to 10% of cases.[1,14] In patients with recurrent ALL and *TP53* mutation identified in the leukemic blasts, a germline *TP53* analysis should be offered.[15] In sequencing projects, *TP53* germline mutations are repeatedly identified in patients who did not fulfill the classical testing criteria. We anticipate that future research projects analyzing the germline of children with cancer will reveal a more complete cancer spectrum of LFS.

Table 2. Clinical features often associated with LFS (*see Section **4.** for details)

Familial presentation*
Multiple tumors*
Rare tumors: ACC, choroid plexus carcinoma, embryonal anaplastic subtype rhabdomyosarcoma
Breast cancer before age 31 years
Childhood cancers with new research showing high percentage of LFS: Low-hypodiploid ALL, sonic hedghog subtype medulloblastoma, osteosarcoma, recurrent ALL and *TP53* mutation identified in the leukemic blasts, glioblastoma following cranial radiation for another cancer
Patients with other ‘adult’ onset cancers occurring at early age such as bronchoalveolar lung cancer, pancreas, early onset colorectal cancer, etc.

5. Phenotype-Genotype Correlation

More than 250 different *TP53* germline alterations are known and the types of mutations resemble those observed in somatic *TP53* defects.[16] Missense mutations

occur in approximately 70% of cases and is the most common aberration type, most often altering residues within the DNA-binding domain.[10,16] In addition, other alterations and defects exist (splicing, intragene deletions, frameshift, nonsense, inframe insertion/deletion, intronic).[10] One-fifth (20%) of LFS families have one of six hotspot mutations (R175H, G245S, R248Q, R248W, R273H, R282W)[10] and 25% of patients have a *de novo* mutation.[17] The *TP53* germline mutation type and its effect on TP53 function influence the penetrance in carriers as well as the cancer site and the risk of secondary malignancies. The highest cancer risk is associated with dominant negative *TP53* mutations within the DNA-binding domain. Such mutations are detected commonly in LFS patients with brain tumor (62%), osteosarcoma (40%), and rhabdomyosarcoma (36%). Non-dominant negative *TP53* mutations occur more frequently in patients with ACC (76%).[5,8] Phenotype-genotype correlations may become increasingly important for risk-adapted surveillance for LFS patients. Therefore, a *TP53* catalogue such as that found in the IARC registry and the LiFE Consortium are valuable resources. Such databases also allow estimation of pathogenicity of a given variant, but data is currently not bening systematically collected in Germany. This German LFS-CPS Registry has the potential to contribute substantially to existing international activities in order to provide an even broader picture of the *TP53* and other CPG germline mutation spectrum. Not only specific mutations, but also genetic modifiers influence the LFS phenotype. These modifiers include the *MDM2* polymorphism rs2279744,[18] *TP53* polymorphisms, such as a duplication within intron 3 (PIN3),[19,20] telomere length[21] and the accumulation of CNVs (Copy number variations).[22] In order to study these modifiers and other factors, a biobank of blood samples from LFS/CPS patients is being established within the German LFS-CPS Registry.

6. Early Detection and Prevention

In recent years, with the aim of early tumor detection and positive effects on treatment-related morbidity, suggestions for clinical surveillance of *TP53* mutation carriers have been proposed from Australia, the United States (National Comprehensive Cancer Network Guidelines) and Canada. Over an 11-year period, investigators in Toronto, Salt Lake City and Los Angeles (subsequently Columbus) prospectively followed and reported on the feasibility and outcomes of children and adults enrolled in a multi-modality protocol that has been named the ‘Toronto

protocol'.[23,24] In patients who decided to undergo surveillance, compliance with key components of the protocol was >90%. An improved overall survival (OS) was observed in individuals undergoing surveillance: 5y OS 88.8% vs. 59.6% (Surveillance vs. Non-Surveillance).[24] We will employ a modified version of the Toronto protocol that has been developed recently by a group of international LFS experts participating in a CPS workshop organized by the American Association for Cancer Research (Table 3).[25]

Table 3 Recommended LFS Screening Protocol (based on the Toronto Protocol[23,24] with minor modifications).[25]

Children (birth to age 18 years)
General assessment • Complete physical examination every 3–4 months, including blood pressure, anthropometric measurements plotted on a growth curve (with particular attention to rapid acceleration in weight or height), Cushingoid appearance, signs of virilisation (pubic hair, axillary moisture, adult body odour, androgenic hair loss, clitoromegaly, or penile growth), and full neurological assessment • Prompt assessment with primary care physician for any medical concerns
Adrenocortical carcinoma: • Ultrasound of abdomen and pelvis every 3–4 months • In case of unsatisfactory ultrasound, blood tests*# may be performed every 3–4 months: total testosterone, dehydroepiandrosterone sulfate, and androstenedione
Brain tumor • Annual brain MRI *(first MRI with contrast; thereafter without contrast if previous MRI normal, and no new abnormality)*
Soft tissue and bone sarcoma • Annual WBMRI
Adults
General assessment • Complete physical examination every 6 months • Prompt assessment with primary care physician for any medical concerns
Breast cancer • Breast awareness (age 18 years onwards) • Clinical breast examination twice a year (age 20 years onwards) • Annual breast MRI screening‡ (age 20–75) • Consider risk-reducing bilateral mastectomy
Brain tumor (age 18 years onwards) • Annual brain MRI *(first MRI with contrast; thereafter without contrast if previous MRI normal)*
Soft tissue and bone sarcoma (age 18 years onwards)
• Annual WBMRI‡
• Ultrasound of abdomen and pelvis every 12 months
Gastrointestinal cancer (age 25 years onwards) • Upper endoscopy and colonoscopy every 2-5 years
Melanoma (age 18 years onwards) • Annual dermatological examination

*Serial specimens obtained at the same time of day and processed in the same laboratory
#The efficacy of biochemical surveillance for detection of adrenocortical carcinoma has not been shown
‡ Breast MRI/ultrasound of abdomen and pelvis to alternate with annual WBMRI (at least one scan every 6 months)
MRI: magnetic resonance imaging. WBMRI: whole body MRI, head-to-toe including entire upper and lower extremities.

7. Psychological Aspects

Families affected by multiple cancers within one member or within the whole of the family often have questions about the cause of the tumors and desire to be educated about prevention. For a family, the knowledge of the presence of constitutional *TP53* mutation and the potential benefits of this knowledge must be juxtaposed to the potiential harm such as anxiety, insecurity, guilt, dysfunctional family interactions, loss of private medical information and discrimination. A thorough discussion of these risks is obligatory prior to consent for *TP53* germline mutation analysis. It is also important to provide psychosocial support for families dealing with this information as well as the loss of siblings, parents or other family members. Although not stated as an immediate aim, a long-term goal is to address the serious psychosocial concerns of LFS patients and their relatives. We are keenly aware of the importance of this issue based on previous experience and intereaction with LFS families and recommend counseling and psychological support for families affected by LFS.

8. Cancer Treatment in Individuals with Li-Fraumeni Syndrome

Currently there are no detailed recommendations for the treatment of cancer in individuals with LFS. In general, because patients with LFS have a high risk for therapy related cancers, while maintaining a curative intent, radiotherapy[26] should be avoided and likewise, when feasible, alkylating chemotherapy agents should be omitted.[26] The present effort will undoubtedly identify more LFS cases. A cancer treatment evaluation will be undertaken in this study to generate an overview of therapy related toxicities and late effects of cancer treatment in individuals with LFS. This data will serve as a basis for adaptive treatment recommendations. It is also desirable to identify drugs or classes of drugs, which circumvent the TP53 defect[27] and thus are particularly usefully for the treatment of LFS associated cancers. For example, a pilot study in the USA is evaluating the use of metformin, an oral diabetes medicine with putative anti-cancer activity to prevent cancers in LFS patients (https://clinicaltrials.gov/ct2/show/NCT01981525).

9. Registry design

This is a prospective and retrospective natural history registry. We anticipate enrollment of around 100 new LFS/CPS patients per year. In addition, we will also enroll patients already diagnosed with LFS/CPS (**Table 1**). Patients who are identified as being eligible according to the inclusion criteria will enter the registry. We intend to exchange LFS/CPS data with childhood cancer trial groups. This is important to allow for treatment adjustments, toxicity and outcome analyses.

10. Participating centers

The pediatric hematology and oncology of Hannover Medical School, Hannover, Germany is the Coordinating Center for the LFS-CPS-R01 study. Centers from all nations may participate.

11. Registry population

Written informed consent is required for participation. Patients ≥18 years of age will give consent, and for patients ≤17 years of age, their parent(s) or legal guardian(s) must give consent, the patients if adequate.

12. Inclusion criteria

Patients with LFS/LFL or other CPS enrolled in this registry are to meet the following inclusion criteria:

- Adult patients: Written informed consent by the patient
- Children and adolescents: Written informed consent by the caretakers and whenever possible assent by the patient
- As soon as enrolled children become 18 years old, they will be contacted in oder to confim their willingness to participate in the registry
- Confirmed diagnosis of LFS/CPS (no age restriction)
- Suspected diagnosis of LFS/CPS (no age restriction), (**Table 4**) unless a CPS is ruled out by appropriate testing

Table 4 Clinical situations in which a CPS should be considered[28]

Childhood cancer: Indication for genetic counseling?*

*updated Jongmans criteria [Jongmans et al., 2016]

if at least one criterion is fulfilled, your patient may benefit from genetic counseling

1. Family history (3 generation pedigree)

O ≥2 malignancies occurred in family members before age 18 years, including index patient
O Parent or sibling with current or history of cancer before age 45 years
O ≥2 first or second degree relatives in the same parental lineage with cancer before age 45 years
O The parents of the child with cancer are consanguineous

2. One of the following Neoplasms was diagnosed:

O Adrenocortical carcinoma / adenoma
O ALL (low hypodiploid)
O ALL (ring chromosome 21)
O ALL (Robertsonian translocation 15;21)
O ALL relapse (*TP53* mutated)
O AML (Monosomy 7)
O Basal cell carcinoma
O Botryoid rhabdomyosarcoma of the urogenital tract (fusion-negative)
O Chondromesenchymal harmatoma
O Choroid plexus carcinoma / tumor
O Colorectal carcinoma
O Cystic nephroma
O Endolymphatic sack tumor
O Fetal rhabdomyoma
O Gastrointestinal stromal tumor
O Glioma of the optic pathway (with signs of NF1)
O Gonadoblastoma
O Hemangioblastoma
O Hepatoblastoma (*CTNNB1* wildtype)
O Hepatocellular carcinoma
O Infantile myofibromatosis
O Juvenile myelomonocytic leukemia
O Keratocystic odontogenic tumor
O Large cell calcifying Sertoli-cell-tumor
O Malignant peripheral nerve sheath tumor
O Medullary thyroid carcinoma
O Medulloblastoma (SHH activated)
O Medulloblastoma (WNT activated, *CTNNB1* wildtype)
O Medullary renal cell carcinoma
O Medulloepithelioma
O Melanoma
O Meningioma
O Myelodysplastic syndrome
O Myeloproliferative neoplasms (except CML)
O Myxoma
O Neuroendocrine tumor
O Paraganglioma / pheochromocytoma
O Parathyroid carcinoma / adenoma
O Pineoblastoma
O Pituitary adenoma / tumor
O Pituitary blastoma
O Pleuropulmonary blastoma
O Renal cell carcinoma
O Retinoblastoma
O Rhabdoid tumor
O Rhabdomyosarcoma with diffuse anaplasia
O Schwannoma
O Schwannomatosis
O Sertoli-Leydig cell tumor
O Sex cord stromal tumor with annular tubules
O Small cell carcin. of the ovary hypercalcemic type
O Squamous cell carcinoma
O Subependymal giant cell astrocytoma
O Thyroid carcinoma (non-medullary)
O Transient myeloproliferative disease
O Other rare cancers or cancers that typically occur in adults, unusually early manifestation age

3. O **Genetic tumor analysis reveals defect suggesting a germline predisposition**

4. O **A patient with ≥2 malignancies (**e.g. secondary, bilateral, multifocal, metachronous**)**

5. O **A child with cancer and congenital or other anomalies**

Sign	***Think of***
O Congenital anomalies	Abnormal organs, skeletal anomalies, oral clefting, abnormal teeth, urogenital anomalies, abnormal hearing or vision, etc.
O Facial dysmorphism	
O Mental impairment, developmental delay	Abnormal behavior, learning difficulties
O Abnormal growth	Height, head circumference, birth weight, hemihyperplasia, growth chart
O Skin anomalies	Abnormal pigmentation such as ≥2 café-au-lait spots, vascular lesions, hypersensitivity to sun, benign tumors, etc.
O Hematological abnormalities (not explained by current cancer)	Pancytopenia, anemia, thrombocytopenia, neutropenia, leukopenia, macrocytic erythrocytes
O Immune deficiency	Frequency of infections, lymphopenia
O Endocrine anomalies	Primary hyperparathyroidism, precocious puberty, gigantism/acromegaly, Cushing syndrome

6. O **The patient suffers from excessive toxicity of cancer therapy**

13. Enrollment and patient registration

Enrollment is to start August 1, 2017. Follow-up of the patients is planned for at least 10 years.

14. Objectives

- Establish a LFS/CPS registry
- Evaluate the feasibility and benefit of cancer surveillance programs
- Develop a radiological image database for CPS
- Establish a CPS mutation database
- Conduct germline-somatic correlations and genotype-phenotype correlations
- Optimizing cancer treatment in patients with CPS by close collaboration with GPOH trial groups

15. Endpoints

- Development of cancer
- Development of non-malignant complications
- Physical anomalies
- Death

16. Documentation of the diagnostic procedures

Prior to registration of a patient, the diagnosis of an LFS/LFL/CPS needs to be confirmed by genetic testing (mutation analysis and/or other confirmatory tests) and/or meeting clinical criteria confirming or suggesting an underlying CPS based on history and family history or non-malignant anomalies (**Table 4**).

16.1 Initial procedures in patients with confirmed LFS/LFL/CPS:

- Reasons for CPS testing and date of LFS/LFL/CPS diagnosis
- Results of genetic testing
- Medical history of CPS patient
- Family medical history
- Physical exam
- Results of images (e.g. for tumor surveillance)*
- Results of laboratory tests (e.g. for tumor surveillance)*
- Electronic copy of images (images showing evidence of malignancy only)

- 5 ml EDTA blood
- To prevent duplication of efforts, tumor specimens will be collected from patients only if this not impeding with respective GPOH clinical trial groups.

*The following cancer surveillance guidelines can be accessed openly online and have been developed internationally and/or reviewed and through international CPS experts participating in a CPS workshop organitzed by the American Association for Cancer Research.[29] All recommendations can also be accessed here: http://clincancerres.aacrjournals.org/pediatricseries

1. Pediatric cancer predisposition imaging: focus on whole-body MRI.[30]
2. Recommendations for surveillance for children with leukemia-predisposing conditions.[31]
3. Recommendations for childhood cancer screening and surveillance in DNA repair disorders.[32]
4. Clinical management and tumor surveillance recommendations of inherited mismatch repair deficiency in childhood.[33]
5. Cancer screening recommendations for individuals with Li-Fraumeni syndrome.[25]
6. Cancer and central nervous system tumor surveillance in pediatric neurofibromatosis 1.[34]
7. Cancer and central nervous system tumor surveillance in pediatric neurofibromatosis 2 and related disorders.[35]
8. Cancer surveillance in gorlin syndrome and rhabdoid tumor predisposition syndrome.[36]
9. Von Hippel–Lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetics, and surveillance recommendations in childhood.[37]
10. PTEN, DICER1, FH, and their associated tumor susceptibility syndromes: clinical features, genetics, and surveillance recommendations in childhood.[38]
11. Recommendations for cancer surveillance in individuals with rasopathies and other rare genetic conditions with increased cancer risk.[39]
12. Genetic counselor recommendations for cancer predisposition evaluation and surveillance in the pediatric oncology patient.[40]
13. Retinoblastoma and neuroblastoma predisposition and surveillance.[41]
14. Cancer screening recommendations and clinical management of inherited gastrointestinal cancer syndromes in childhood.[42]
15. Surveillance recommendations for children with overgrowth syndromes and predisposition to wilms tumors and hepatoblastoma.[43]
16. Multiple endocrine neoplasia and hyperparathyroid-jaw tumor syndromes: clinical features, genetics, and surveillance recommendations in childhood.[44]

16.2 Documentation of the regular (annual) follow-up

- Results of genetic testing
- History
- Family history
- Physical exam
- Images performed for cancer surveillance (electronic copies of pathologic images only)

- Laboratory tests performed for cancer suveillance
- 5 ml EDTA blood if not done previously
- To prevent duplication of efforts, tumor specimens will be collected from patients only if this not impeding with respective GPOH clinical trial groups.

17. Data handling and reporting

Data will be entered by participating institutions employing a remote data entry data base. Alternatively, for clinics with low recruitment rate or who do not participate in other studies/registries of the GPOH, paper forms are to be filled which are then entered by the registry center. Also, the registry collects medical records that are evaluated centrally.

17.1. Reporting and recording of data

Follow-up information is required on a 12 monthly basis.

18. Statistical analysis

Overall survival (OS) is defined as the time from birth until last follow-up or event (death from any cause). Event-free survival (EFS) is defined as the time from birth to last follow-up or first event (cancer, death of any cause). Survival times will be calculated according to the Kaplan-Meier method and comparisons between different patient groups will be performed using the log-rank test. For multivariate analyses, the Cox proportional hazard regression model will be used. The analysis of the distribution of qualitative and quantitative variables will be done using suitable descriptive univariate and multivariate methods. Two-sided 95% confidence intervals will be calculated for all estimates.

Statistical analyses will employ the statistical software SPSS (Statistical Package for Social Sciences) and SAS (Statistical Analysis System). All analyses will be documented and saved. The transfer of the data from the study database will be performed after checking the data for plausibility.

19. Changes in protocol

Any change or addition to this protocol requires a written protocol amendment. If an amendment significantly affects the safety of the patients, the scope of the

investigation or the scientific quality of the registry, it should be formally approved by the Ethics Committee, and communicated to the regulatory authority, as required by law. After approval, an amendment becomes an integral part of the protocol. The Principal Investigators are authorized to decide the discontinuation of the registry due to relevant medical or administrative reasons.

The above-mentioned requirements do not preclude any immediate action taken by the investigators in the interests of the patients' safety. In the case where such an immediate change to the protocol is implemented and the principal investigators should be notified immediately.

20. Ethical and legal considerations

The study will be conducted in accordance with the Declaration of Helsinki (Appendix 2), the current revision of ICH Topic E6 (Appendix 3), Guideline for GCP: "Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), and the legal requirements of each participating country in its valid version. It is mandatory that all considerations regarding the protection of the patients be carried out in accordance with the Declaration of Helsinki. The data protection will be granted according to the local law.
To ensure compliance the investigators agree, by written consent to this protocol, to fully cooperate with compliance checks by allowing access to all documentation by authorized individuals.
This natural history study aims at impoving the knowledge about cancer prone syndromes, the major known cause of childhood cancer. Therefore, we intentionally enroll children into the study. Without studies of this kind, the prognosis of affected children cannot be improved. We respect if assent is not given by children, even if parents provide informed consent.

21. Patient information and informed consent

"Patient" refers to adult patients and parent(s)/legal guardian(s) of patients who are minors. All patients must sign and personally date an approved informed consent form after receiving detailed written and verbal information about the reason, the nature, and the methods of the registry. The informed consent complies with regulatory requirements. The written informed consent must be obtained before the entry of the patient into the registry.

Furthermore, the patient must be notified that participation is voluntary and that he/she may withdraw from the registry at any time and that withdrawal of consent will not affect his/her right to the most appropriate medical treatment or affect the doctor/patient relationship. A written patient information leaflet will be handed to the patient, whose contents have to be discussed with the patient by the investigator. The investigator will provide the patient ample time and opportunity to inquire about details of the registry and to decide whether or not to participate in the registry. All questions about the registry will be answered to the satisfaction of the patient. The patient should be given sufficient time to read and understand the statement him/herself before signing his/her consent and dating the document. Neither the investigator nor the registry staff will coerce or unduly influence a patient to participate or to continue to participate in the registry. Personal information will be treated as strictly confidential and will not be publicly available. The patient will receive a copy of the written informed consent once signed, and the original version of the informed consent has to be kept in the investigator file.

22. Patient withdrawal

A patient may withdraw from the registry at any time, at his or her own request, for any reason, specified or unspecified, and without penalty or loss of benefits to which the patient is otherwise entitled.

23. Disclosure and confidentiality

Throughout this registry, all data will be treated confidentially. For data recording and analysis, patients will be identified only by a patient identification number and never by their full name, and/or initials. The legal provisions by the respective Laws will be heeded. The rules of the Bundes-/Landesdatenschutzgesetzes (BDSG/LDSG BW) will be followed.

The investigators are responsible for keeping sufficient information for every patient (name, date of birth, internal clinic number, patient identification number, gender, informed consent), in order to identify the patient. According to the ICH-GCP-guidelines these documents (Patient Identification List) have to be archived for at least 15 years.

By conducting this registry, the investigators agree that they and their staff will maintain all information in strict confidence. The investigators are requested to insist on similar confidentiality for this information from other bodies such as the Hospital Scientific Committees and Ethic Committees/Institutional Review Boards that have been consulted by the investigator. Registry documents will be stored appropriately to further ensure their confidentiality. It is understood that the confidential information provided to the investigators will not be disclosed to others without direct written authorization from the patient and/or his/her family. Such information will not be communicated by telephone to potential or enrolled patients or to any other individual.

24. Independent Ethics Committee / Institutional Review Board

Prior to implementation of this registry, the protocol, patient information forms and the proposed informed consent must be reviewed and approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). Signed and dated approval by the IEC/IRB must be obtained by prior to registry initiation and patient enrollment. The investigators are committed in accordance with local requirements to inform the IEC/IRB of any emergent problem and/or protocol amendments.

25. Insurance

The aim of this registry is the collection of epidemiological data based on a standardized diagnostic approach and not the investigation of clinical or pharmacological properties of drugs. The registry is therefore exempt from clinical trials insurance coverage according to law. Patients are covered by the public liability insurance of their hospitals.

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