Overview of the Clinical Features of Li-Fraumeni Syndrome and the Current European ERN GENTURIS Guideline

Übersicht über die klinischen Merkmale des Li-Fraumeni Syndroms und die aktuelle europäische Leitlinie des ERN GENTURIS

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ABSTRACT

Patients with a tumour-risk syndrome have a significantly increased risk of developing cancer during their lifetime. A positive family history of tumour disease or an unusually early age of onset may be indicative of a tumour risk syndrome. With the diagnosis of a tumour risk syndrome it is possible to recommend a risk-adapted tumour surveillance programme for the patient and (asymptomatic) family members at risk. This facilitates early detection of possible tumours and thus often prevents advanced tumour stages. Li-Fraumeni syndrome is associated with a significantly increased risk of sarcoma and breast cancer in particular, but it is often not diagnosed clinically in those affected. This article reviews the clinical picture, genetic cause and special aspects in the diagnosis and care of patients with Li-Fraumeni syndrome. The initiative resulted from the European reference network GENTURIS, which has set itself the task of improving the identification and care of patients with tumour risk syndromes. A first step is the recent publication of a European guideline for Li-Fraumeni syndrome, which is summarised here and discussed in the context of existing recommendations.

ZUSAMMENFASSUNG

Patienten mit einem Tumor-Risiko-Syndrom haben ein deutlich erhöhtes Risiko, im Laufe des Lebens an Krebs zu erkranken. Hinweise auf ein Tumor-Risiko-Syndrom können eine positive Familienanamnese für Tumorerkrankungen oder ein ungewöhnlich frühes Erkrankungsalter geben. Die Diagnose eines Tumor-Risiko-Syndroms ermöglicht die Empfehlung eines risikoangepassten Tumor-Früherkennungs-Programms für den Patienten und die (asymptomatischen) Risikopersonen in der Familie. Hierdurch können mögliche Tumoren früh erkannt und somit fortgeschrittene Tumorerkrankungen häufig verhindert werden. Das Li-Fraumeni Syndrom geht mit einem deutlich erhöhten Risiko insbesondere für Sarkome und Brustkrebs einher, häufig wird es bei den Betroffenen jedoch klinisch nicht diagnostiziert. Dieser Artikel gibt einen Überblick über das klinische Bild, die genetischen Ursachen

sowie die Besonderheiten in der Diagnostik und Versorgung der Patienten mit einem Li-Fraumeni Syndrom. Die Initiative resultiert aus dem europäischen Referenznetzwerk GENTURIS, das sich die Verbesserung der Erfassung und Versorgung von Patienten mit Tumor-Risiko-Syndromen zur Aufgabe gemacht hat. Ein erster Schritt ist die aktuelle Veröffentlichung einer europäischen Leitlinie für das Li-Fraumeni Syndrom, die hier zusammengefasst und im Kontext bestehender Empfehlungen diskutiert wird.

Introduction

Cancer is still a life-threatening disorder, and this is especially true for cancers in patients with hereditary tumour risk syndromes (TRS). The European Reference Network (ERN) for Genetic Tumour Risk Syndromes – GENTURIS as one of 24 ERNs – was initiated by the European Commission in March 2017. Its mission is to improve the knowledge base and thus identify patients with TRS and to develop uniform treatment concepts across Europe (www.genturis.eu). This includes the development of guidelines at the European level. For TRS patients, cancer screening is crucial, but there are no national guidelines for many of the rare TRSs. One of the first EU guidelines developed by the ERN GENTURIS was prepared for patients with Li-Fraumeni syndrome (LFS) or TP53-associated tumour-risk syndromes. These syndromes, diagnostic and therapeutic aspects as well as the guideline published last year are presented here.

Hereditary TRS is a clinical entity with a significantly increased risk of developing certain tumours, usually due to a pathogenic germline variant in a single gene. As a rule, these are therefore classic monogenic hereditary diseases following the principles of Mendelian inheritance. Patients do not inherit the tumour, but rather the tumour disposition and thus the increased tumour risk.

At least 3–5% of all (solid) cancers – depending on the type of tumour and age of the patient, possibly considerably more – originate from a TRS. With almost 500 000 cases of cancer [1] annually in Germany, this amounts to at least 15 000–25 000 cases per year. Typical general criteria for suspected presence of TRS include:

- unusually early tumour onset
- multiple primary tumours in the patient's medical history
- Familial clustering of tumours
- Typical range of tumours in the patient's/family medical history
- rare tumours
- specific molecular tumour findings

TRS is suspected when taking the medical history of the patient and family. It has preventive and possibly therapeutic significance for the patient as well as for family members and is therefore highly relevant clinically. Once the genetic cause of a TRS has been established, information on the tumour risks, the appropriate preventive measures and possibly existing individual therapeutic measures are available for the specific TRS.

LFS Definition and Clinical Presentation

LFS is an autosomal dominant TRS with a prevalence of approximately 1 : 5000, caused by pathogenic germline variants in the *TP53* tumour suppressor gene on chromosome 17p13. The primary neoplasms resulting from the inactivation of the p53 protein occur throughout life, i.e. from early childhood to late adulthood. Tumour-free survival to 30, 45 and 60 years of age is estimated at 55%, 15% and 5% respectively for women and 65%, 50% and 12% respectively for men [2, 3]. The range of tumour diseases is broad overall and differs between children and adults. Depending on the patient's age, the following tumours are most common:

- Childhood: Adrenocortical carcinoma, choroid plexus tumour, rhabdomyosarcoma, medulloblastoma
- Adolescence and early adulthood: Osteosarcoma, breast cancer, leukaemia, glioma, soft tissue sarcoma (malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma)
- Late adulthood: Pancreatic cancer, prostate cancer

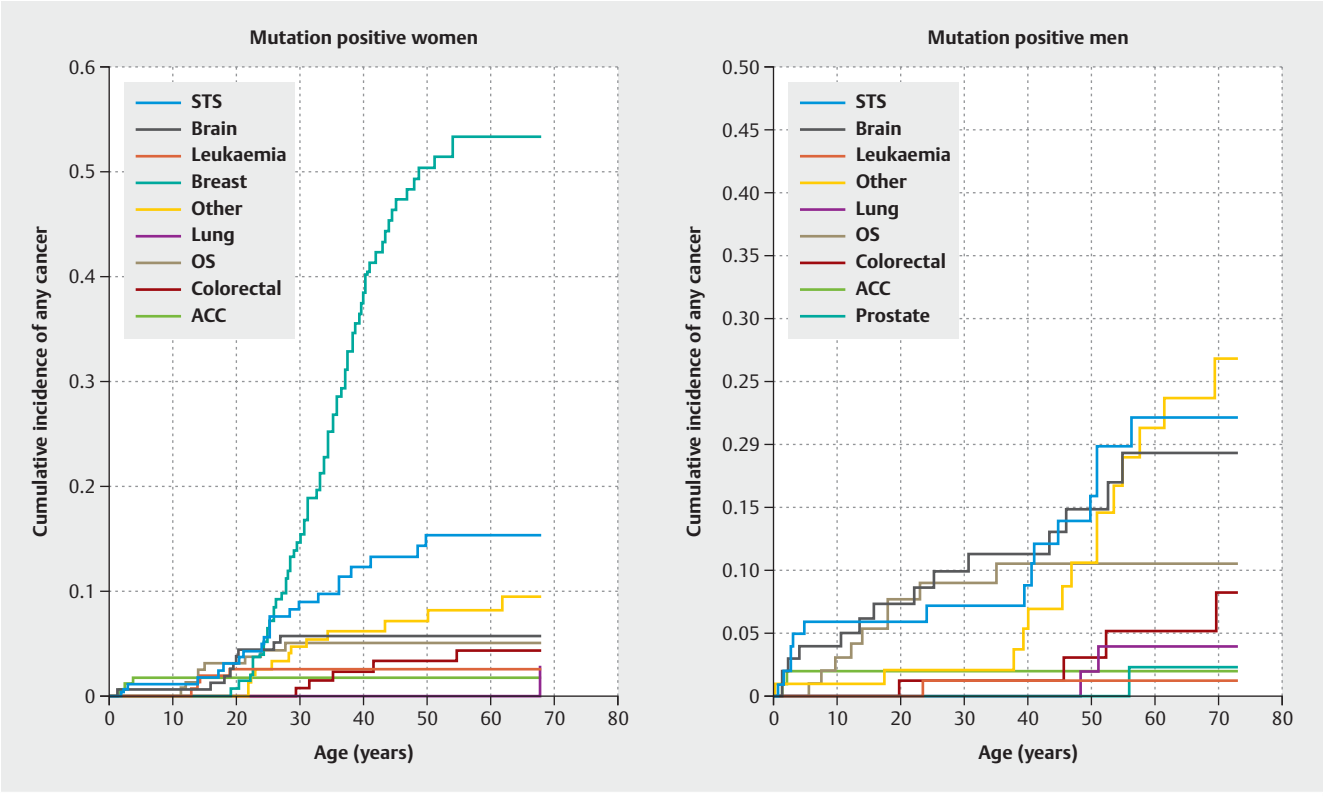
Synchronous and metachronous tumour disorders are possible. ▶ **Fig. 1** shows the incidence by age. A typical family tree and clinical course are illustrated in ▶ **Fig. 2a** and **b**. The clinical variability of the LFS is determined partly by the varying residual activity of the p53 protein, since not all pathogenic variants in *TP53* result in a complete loss of function. On the other hand, only some of the modifying genetic factors are known to date, and the same applies to lifestyle and environmental factors.

Molecular Genetic *TP53* Diagnostics

The criteria for indicated molecular genetic analysis of *TP53* are shown in ▶ **Table 1**. Molecular genetics confirms the presence of LFS through the identification of a disease-causing germline variant in *TP53*. Contrary to an initial hypothesis, LFS is not associated with variants in *CHEK2*.

Since *TP53* has a more complex structure than was initially known, previous analyses did not always cover all regions of the gene. For example, *TP53* encodes at least 8 different mRNA isoforms formed by alternative splicing or different promoter activity [4, 5], resulting in up to 12 different protein isoforms. Recent data also reveal that intron 9 encodes two alternative exons (9β and 9γ) [6]; likewise, intron 1 has been shown to be a hot spot for genomic rearrangements. Previous analyses of *TP53* carried out some time ago with unremarkable results should therefore be repeated where necessary.

As *TP53* is currently mostly investigated by NGS (next-generation sequencing) multigene analyses, *TP53* variants are inevitably also found in cancer patients who do not meet established clinical criteria for *TP53* testing (▶ **Table 1**). Although this may complicate the interpretation of *TP53* variants, it can also identify LFS patients with a new ("de novo") pathogenic variant who are not identified by clinical criteria because of their unremarkable family history. The proportion of de novo *TP53* variants is estimated at up to



▶ **Fig. 1** Tumour incidence in LFS for women and men, adapted from Mai et al. [2].

30% [7], which is quite common compared to the de novo variant percentage in other tumour suppressor genes such as *BRCA1* and *BRCA2* (estimated at less than 5% [8]). On the other hand, the known phenotypic spectrum of LFS is extended to milder courses.

TP53 Mosaic Variants

A disease-causing genetic variant inherited from one parent is usually heterozygous in all body cells as well as in the germ cells (oocytes, spermatozoa) of a patient. This results in a 50% risk of recurrence in offspring. However, *TP53* variants often emerge as genetic mosaics, a juxtaposition of cells with and without the causative genetic variant [9]. There are basically two constellations to be differentiated here:

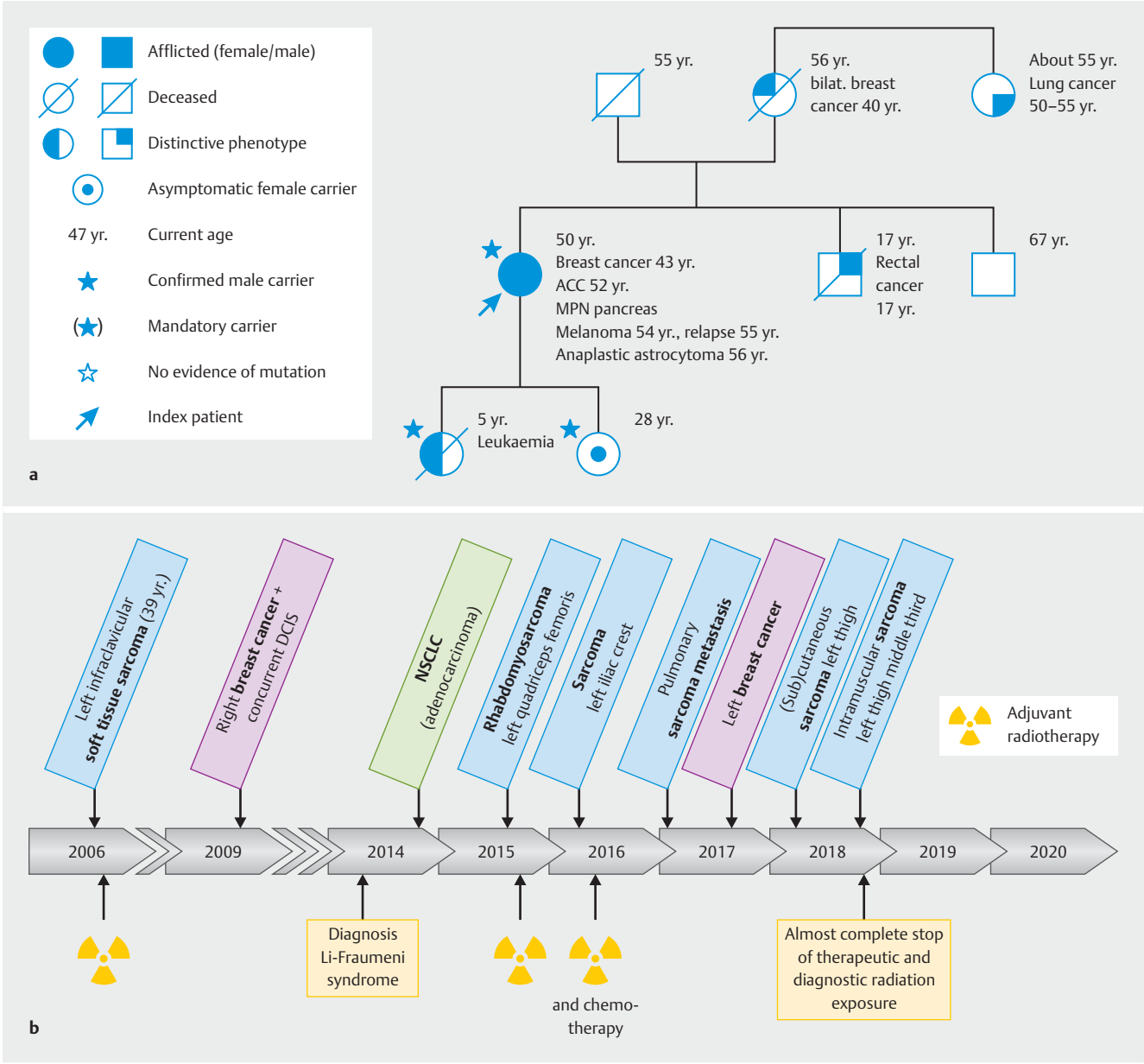
1. A variant may be present in isolation only in the germ cells of an individual. While such persons themselves are clinically healthy, they may have offspring with LFS. If several germ cells are affected, this is known as a germ cell mosaic, i.e. a juxtaposition of germ cells with and without a variant.
2. Variants can arise in early embryonic development and are then present in several, but not all, body tissues, which can impact on the clinical phenotype. This is called a somatic or postzygotic mosaicism. Depending on when this de novo variant occurred during embryonic development, more or fewer tissue parts or tissues are affected. The presence of *TP53* alterations as somatic or postzygotic mosaic should be considered in patients with apparently sporadic tumour disease strongly suggestive of a disease-causing *TP53* variant (e.g. early adrenocortical carcinoma, choroid plexus carcinoma and breast cancer before 31 years of age, multiple typical primary tumours) [10]. Molecular genetic analyses of a blood sample with such mosaics may be unremarkable. There is no increase in risk for siblings, as the parents do not carry this variant in their germ cells.

Variants only present in tumour tissue (somatic mutations) must be distinguished from the previously described mosaic constellations. *TP53* variants in tumours are among the most common genetic alterations in malignancies and do not imply the presence of LFS; they are mostly sporadic tumours.

Detection of a *TP53* variant in a blood analysis therefore does not confirm the clinical diagnosis of LFS, since a high percentage of circulating tumour DNA in the presence of tumour disease with a somatic *TP53* variant can mimic the presence of a germline variant.

Similarly, the phenomenon of clonal haematopoiesis can simulate the presence of LFS [11, 12]. These are somatic *TP53* variants in a clonal population of haematopoietic stem cells. Such alterations are detected with increasing frequency from around the age of 30, especially in smokers and following chemotherapy or radiotherapy [13, 14].

Therefore, especially in case of a low allele frequency of a *TP53* variant, the diagnosis can only be confirmed by analysing different tissues.



▶ **Fig. 2** **a** Family tree of an LFS family. **b** Timeline of diagnoses and treatment of a patient with LFS.

Interpretation of *TP53* Variants

Assessment of loss-of-function variants (frameshift or nonsense variants, splice variants, deletions of single or multiple exons) is often clear-cut. Interpretation of the more common missense variants, on the other hand, is much more challenging. Here, a distinction must be made between loss-of-function and dominant-negative variants, which result in inactivation of the normal protein through tetramer formation with p53 wild-type proteins [15]. The dominant-negative *TP53* variants have a higher penetrance, especially in childhood, than loss-of-function variants.

Sequence variants are classified according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) [16]. These so-called ACMG-AMP Guidelines are based on 28 different criteria from various categories. The classification also includes phenotype and family history data (▶ **Table 1**). Other aspects include the frequency of the variant in population databases (e.g. gnomAD), bioinformatics predictions of the effects of the variant on splicing and physicochemical alterations, and functional analyses. To address this complexity, a *TP53*-specific Variant Curation Expert Panel (VCEP) was established under the umbrella of the ClinGen Consortium (https://www.clinicalgenome.org) to refine *TP53*-specific ACMG AMP criteria. Since only variants of the ACMG-AMP classes 5 (pathogenic) and 4 (probably pathogenic) have clinical consequences, the current ERN guideline only designates variants of these two classes as “disease-causing” 17]. For this reason, differentiating class 1–3 variants (benign, probably benign and variant

of uncertain significance) from class 4 and 5 variants has a high clinical relevancy and should only be carried out by experts with appropriate qualifications.

Screening and Prevention According to the Current ERN Guideline on Cancer Screening in LFS

The ERN guidelines should be understood as complementary to the national guidelines already present in some European countries. They represent the minimum care necessary for patients with LFS from the perspective of the European experts; this can be supplemented by the provisions from the respective national guidelines. Notwithstanding the guidelines, clinical patient care in special individual cases may be guided by expert opinion.

The ERN GENTURIS guidelines on LFS are based on a trial demonstrating that an intensified cancer surveillance programme increased the overall survival of LFS patients by over 20% 5 years after diagnosis [18].

The ERN GENTURIS guideline recommends the closely-monitored cancer surveillance programme listed in ▶ **Table 2** [17]. The table contrasts the ERN recommendations with those of an international expert group [19]. Notable differences include that in childhood, the physical examination and ultrasound study of the abdomen and pelvis (as well as blood testing, if needed) are undertaken every 3–4 months instead of every six months. In addition, an upper GI endoscopy and colonoscopy are recommended regardless of patient and family history. An annual dermatological examination is also recommended, as well as a clinical breast examination for women aged 20 and over every six months. Since the risk of cancer is not solely defined by the variant, the international recommendations always recommend to start screening at birth or at the time of diagnosis, regardless of whether it is a (probably) pathogenic variant in the *TP53* gene with a high risk of cancer in childhood. Moreover, with the exception of breast MRI (20–75 years), there is no "upward" age limit (applies in particular to cranial MRI). Apart from these non-invasive procedures, the option of a prophylactic bilateral mastectomy should be discussed in view of the high risk of breast cancer.

In addition, general signs of possible neoplasms should be assessed immediately; these include weight loss, fever, night sweats, fatigue and initially painless swelling in the muscles or connective tissue as a common symptom of sarcoma. Exogenous factors such as smoking, radioactive radiation, excessive UV radiation should be avoided as much as possible.

Tumour Biology

P53 fulfils numerous functions, including cell cycle regulation in the context of DNA repair, cellular ageing, cell death, autophagy, and metabolism. The physiological p53 tetramer binds to DNA in a sequence- or structure-specific manner; interactions take place between the 12 p53 isoforms already described as well as the proteins p63 and p73. Alterations in the *TP53* gene result in the tumour suppressor function of p53 not being sufficiently effective and that, for example, the function of an activated oncogene can also be taken over. The same variant can induce different functional effects under different conditions, in healthy tissue and in the tumour. In many cases the second allele is inactivated in the tumour by deletion, missense mutation or uniparental disomy [20].

▶ **Table 1** Clinical criteria [21] for *TP53* testing and Chompret criteria [22–24].

Clinical criteria of classic LFS
A patient with ▪ sarcoma diagnosed before the age of 45, AND ▪ a first-degree relative with cancer before the age of 45, AND ▪ a first or second-degree relative with cancer diagnosed before the age of 45 or a sarcoma regardless of age.
Chompret criteria
A patient with ▪ a tumour on the LFS spectrum (soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumour, adrenocortical carcinoma, leukaemia, or bronchoalveolar lung cancer) before the age of 45 years AND ▪ at least one first- or second-degree relative with a tumour of the LFS spectrum (except breast cancer, if the patient has breast cancer) before the age of 56 or with multiple tumours. OR ▪ A patient with multiple tumours (except multiple breast tumours), two of which belong to the LFS spectrum and the first of which occurred before the age of 46. OR ▪ A patient with adrenocortical carcinoma or choroid plexus tumour, or anaplastic rhabdomyosarcoma, regardless of family history. OR Breast cancer before the age of 31

Chemotherapy and Radiotherapy

It should be noted that the loss of p53 function can lead to the use of genotoxic chemotherapeutic agents and/or radiotherapy resulting in the emergence of additional neoplasms due to iatrogenic cell damage [19]. About 30% of the LFS patients who have undergone therapeutic radiotherapy develop a second neoplasia in the region irradiated.

Potentially risky therapeutic and diagnostic measures should therefore be administered with great caution. They can be employed if there are no less genotoxic alternatives and the diagnostic work-up and treatment are required in the current situation.

Databases

There are various unresolved issues with LFS:

1. How high are the tumour risks depending on the *TP53* variant present?
2. What are risk-modifying genetic and non-genetic factors?
3. How can we improve prevention and screening?
4. How can we address the psychosocial aspects?
5. How can we improve cancer treatment in patients with LFS?

▶ **Table 2** Recommendations for cancer screening: Comparison of the ERN GENTURIS guideline [17] with an international guideline [19].

ERN-GENTURIS guideline		**International guideline**	
Type of examination	**Time**	**Type of examination**	**Time (starting at birth or at time of diagnosis, unless otherwise stated)**
Complete physical examination (in children, look in particular for virilisation or premature puberty and measure blood pressure; after radiotherapy, look for the presence of basal cell carcinoma in the area irradiated).	Every six months starting at birth, annually starting at 18 years of age	**Complete physical examination** (including blood pressure, growth curves, pseudo-Cushing appearance, signs of virilisation, and complete neurological assessment).	Every 3–4 months in childhood, every six months in adulthood
Whole-body MRI (depending on the findings without gadolinium)	Annually, starting at birth in the presence of a (probably) pathogenic germline variant in the *TP53* gene that is assessed to be associated with a high risk of cancer* or after previous chemotherapy or radiotherapy; otherwise starting at the age of 18 years	**Whole-body MRI**	Annually (every six months alternating with breast MRI and ultrasound of the abdomen and pelvis)
In women: Breast MRI	Annually, between 20 and 65 years of age	**In women: Breast MRI**	Annually, between 20 and 75 years of age (every six months alternating with whole-body MRI)
–	–	**In women:** Clinical breast examination	Every six months, starting at 20 years of age
Cranial MRI (with gadolinium at the initial examination, then without contrast medium depending on the findings)	Annually, starting at birth in the presence of a (probably) pathogenic germline variant in the *TP53* gene, which is estimated to be associated with a high risk of cancer*; otherwise starting at the age of 18 years up to 50 years of age, especially in childhood every six months, alternating with whole-body MRI	**Cranial MRI** (with contrast medium at initial scan, then without contrast medium if previous MRI normal and no new pathologies).	Annually
Abdominal ultrasonography	Every six months starting from birth until the age of 18 years	**Abdominal and pelvic ultrasonography**	Every 3–4 months in childhood, annually in adulthood (every six months alternating with whole-body MRI)
Urine steroid profile, if the abdominal ultrasonography does not allow adequate visualisation of the adrenal glands.	Every six months starting from birth until the age of 18 years	If ultrasound quality is inadequate, **blood profile** (total testosterone, dehydroepiandrosterone sulphate and androstenedione).	Every 3–4 months in childhood
Colonoscopy	Every 5 years starting at the age of 18, if there is a family history of colorectal cancer or radiotherapy of the abdomen due to a previous cancer.	**Upper GI endoscopy and colonoscopy**	Every 2–5 years starting at 25 years of age
–	–	**Dermatological examination**	Annually, starting at 18 years of age

* If there is a family history of childhood cancer, or if it is a variant that has already been described in the literature or in databases, or if it is a so-called "dominant negative" missense variant.

These issues can only be resolved by collecting relevant data from LFS patients and their families. LFS is included in the following databases:

- In Germany, an LFS registry was established in 2017 to collect blood and tumor specimens as well as clinical and genetic data from LFS patients. Registration is possible for patients themselves or through their doctors. The registry cooperates internationally with the Li-Fraumeni Exploration (LiFE) Research Consortium, with the so-called LiFT-UP trial, and with the international LFS patient organisation, which also has a German branch (https://lfsa-deutschland.de).

- The "Research4Rare" research networks funded by the German Federal Ministry of Education and Research (BMBF) aim to improve the diagnosis of rare diseases. The LFS register described above is part of one of these joint BMBF projects, within the framework of which a clinical whole-body MRI trial is being carried out.
- Other registries of the German Consortium on Familial Breast and Ovarian Cancer and the German Consortium for Familial Colorectal Cancer are administered centrally for all participating sites.
- The German Society of Human Genetics (Deutsche Gesellschaft für Humangenetik e. V.) organises expert working groups with the participation of patient representatives, including the working group "Hereditary Tumour Diseases", with more than 30 active sites to establish and operate databases and registries, including TRS with LFS.

These and other pertinent registries, actors and activities are listed as examples in ▶ **Table 3**.

These numerous activities should be available for use throughout Germany by all specialties to improve the identification and care of all patients and families with hereditary tumour disposition, including LFS.

Outlook

In conclusion, the identification and correct classification of monogenic hereditary TRS is important, as patients and asymptomatic carriers require specialised long-term medical care. On the one hand, there is a high lifetime risk for a specific and often broad range of tumours, as well as a high risk of recurrence in first-degree relatives. On the other hand, efficient risk reduction is possible through TRS-specific intensified screening programmes and surgical measures. For some TRS, there are now also specific approaches to drug treatment. Nevertheless, it can be assumed that a large number of families still remain unidentified and thus do not receive adequate care.

TRS thus stand paradigmatically for an extremely successful concept of preventive oncology and individualised (personalised) medicine. Virtually every doctor will encounter them in every age group, and they sometimes show marked clinical variation, even within the same family. Professional care of patients and their relatives particularly requires multispecialty cooperation between human genetics, pathology and various clinical specialties. Diagnostics, coordination of screening and treatment should involve specialised centres.

Key Messages

LFS is one of the hereditary TRSs of childhood and adulthood, and is often not diagnosed.

An EU guideline complementing existing national and international recommendations has just been established for the LFS.

Clinical consequences should only be considered for (probably) pathogenic *TP53* germline variants, but not for variants of undetermined relevance.

▶ **Table 3** Registry and database examples of LFS patients.

No.	Registry/Database	Authority
1.	Li-Fraumeni syndrome cancer predisposition syndrome registry 01 www.krebs-praedisposition.de	Working Group on Genetic Cancer Predisposition of the Society of Paediatric Oncology and Haematology (GPOH)
2.	HerediCaRe database www.konsortium-familiaerer-brustkrebs.de	German Consortium on Familial Breast and Ovarian Cancer
3.	Hereditary colorectal cancer www.hnpcc.de	German Consortium on Familial Colorectal Cancer
4.	Registry and database on tumour disposition syndromes www.gfhev.de	German Society of Human Genetics
5.	Registry ERN GENTURIS www.genturis.eu	European Reference Network on Genetic Tumour Risk Syndromes (ERN-GENTURIS)
6.	Research4Rare www.research4rare.de/register-biobanken	Research networks on rare diseases, Centres for Rare Diseases in Germany
7.	German Genome Phenomenon Archive (GHGA) www.ghga.de	German Genome Phenomenon Archive
8.	Infrastructure platform for biobanks and registries www.tmf-ev.de	Technology and Methods Platform for Networked Medical Research (TMF)
9.	Comprehensive analysis of registries and databases www.medizininformatik-initiative.de	Medical informatics initiative

Special considerations must be taken into account in the diagnosis and tumour treatment of LFS patients, in particular the strict indication of measures involving radiation exposure.

Patients should be cared for in a multispecialty team at specialised centres.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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