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Review

Current insights and future directions of Li-Fraumeni syndrome

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Abstract
Li-Fraumeni syndrome is a rare yet serious hereditary cancer predisposition syndrome, marked by a significant early-life increased risk of developing cancer. Primarily caused by germline mutations in the TP53 tumor suppressor gene, Li-Fraumeni syndrome is associated with a wide range of malignancies. Clinical management of Li-Fraumeni syndrome could be challenging, especially the lifelong surveillance and follow-up of patients which requires a multidisciplinary approach. Emerging insights into the molecular and clinical basis of Li-Fraumeni syndrome, coupled with advances in genomic technologies and targeted therapies, offer promise in optimizing risk assessment, early detection, and treatment strategies tailored to the unique clinical and molecular profiles of affected individuals. This review discusses Li-Fraumeni syndrome in more depth, reviewing molecular, genomic, epidemiological, clinical, and therapeutic aspects of this disease.

Keywords Adolescents and young adults cancer · AYA · Cancer predisposition syndromes · Hereditary cancer · Li-Fraumeni · p53 · TP53

1 Background

Li-Fraumeni syndrome (LFS), also addressed as the "Sarcoma, Breast, Leukemia, and Adrenal Gland" (SBLA) syndrome, is a rare autosomal dominant cancer predisposition syndrome [1]. First described over fifty years ago, the initial suspicion was raised by Frederick P. Li and Joseph F. Fraumeni as an "increased familial susceptibility to cancer" was observed "not only by the large number of members affected but by a seeming excess of multiple primary neoplasms", suggesting a potentially familial origin of the observed malignancies [2, 3]. The diagnosis of LFS is challenging due to its heterogeneous clinical presentation and diagnostic controversies [4, 5]. Moreover, the surveillance of LFS patients poses a further challenge to clinicians, as the individuals commonly face recurrent states of malignancies, either due to genetic predisposition or complications of previous cancer treatments [6, 7]. This review aims to provide comprehensive basic and clinical insight into LSF, discussing this syndrome's genomic, epidemiological, and clinical aspects.

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2 Main text

2.1 Molecular and genomic basis

LFS is primarily associated with germline mutations in the TP53 gene, located on chromosome 17p13 [8, 9]. TP53 encodes the p53 protein, a critical tumor suppressor involved in regulating cell cycle progression, DNA repair, apoptosis, and senescence, with its alterations widely contribute to cancer development [10, 11]. The loss of the tumor suppressor function results in impaired cell cycle regulation, uncontrolled cell proliferation, increased genomic instability, and ultimately, predisposes the affected individuals to cancer development [12–14]. Therefore, TP53 holds fundamental regulatory roles in maintaining cellular responses to stressors, including DNA damage, hypoxia, and oxidative stress, thereby safeguarding genomic integrity [15, 16]. Figure 1 demonstrates the impact of TP53 mutation in terms of genomic and cellular pathways.

The spectrum of TP53 mutations linked to LFS includes various molecular abnormalities, including missense mutations, frameshift mutations, in-frame mutations, splice site mutations, and nonsense mutations [17, 18]. As the most common mutations in this case, missense mutations result in the amino acid sequence alterations in the p53 protein, compromising its structural integrity and functional competence (Fig. 2). Nonsense mutations cause the p53 protein to prematurely truncate, eliminating its tumor suppressor properties and precipitating the onset of an aggressive neoplastic phenotype. Comparably, frameshift mutations disrupt the reading frame of TP53, resulting in aberrant protein translation and functional incapacitation, while splice site mutations interrupt the fidelity of RNA splicing, thereby engendering diverse phenotypic outcomes, depending on the resulting transcript variants [19, 20].

The nucleotide mutation patterns are dominantly C-to-T transitions at CpG dinucleotides, prone to methylation and subsequent deamination, making them hotspots for mutations [21]. Other substitutions, such as G-to-A or A-to-G transitions, occur less frequently and tend to have varying impacts on p53's function [22]. Figures 2 and 3 exhibit the distribution of TP53 mutation variants and mutation effects, highlighting the non-random nature of TP53 mutations, with a marked preference for specific types of transitions and transversions.

Although mutations have been detected in almost every codon, the majority of pathogenic TP53 mutations occur within exons 5 to 8 in the DNA-binding domain (around codons 100 to 300), which is crucial for the protein's ability to mediate tumor suppression [21, 23, 24]. Mutations in the transactivation domain are less common but can disrupt the

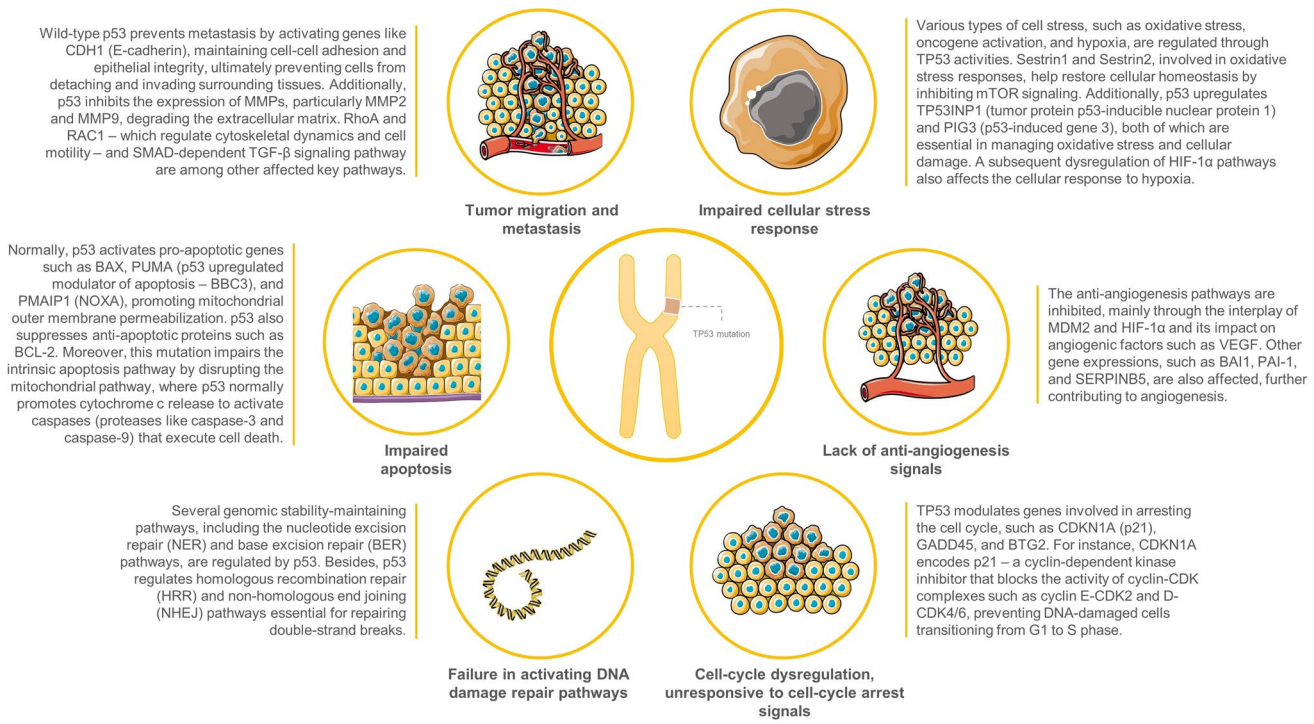

Fig. 1 The impact of TP53 mutation in cellular mechanisms and pathways

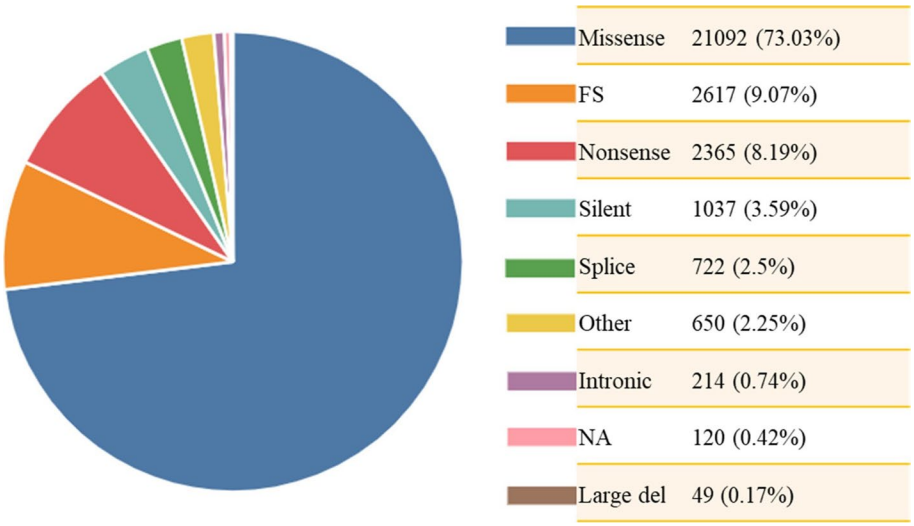

Fig. 2 Distribution of TP53 mutation effect (N = 28,866 – *data from TP53 Database, R20*)

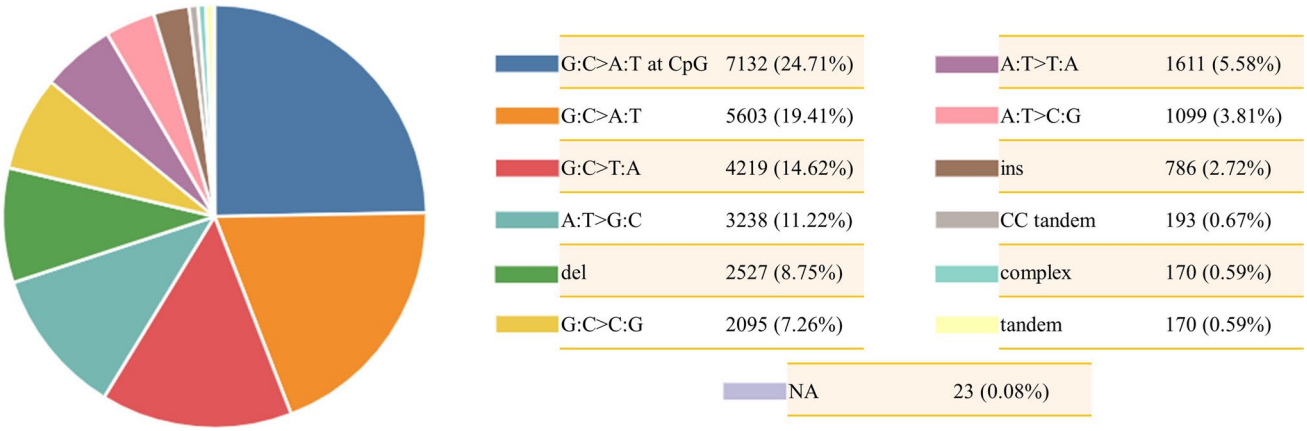

Fig. 3 TP53 mutation variant distribution based on the mutation patterns (N = 28,866 – *data from TP53 Database, R20*)

pro-apoptotic abilities of p53 [25, 26]. Mutations can also occur in the oligomerization domain (exons 9 and 10), often impairing the structural integrity and stability [17, 27]. Codons 175, 245, 248, 273, and 282 are among the most common hotspot mutations [21, 23]. Additionally, specific founder variants of TP53 have also been observed in particular populations, such as R337H and P47S, which are more prevalent among Brazilians and individuals of African descent, respectively, both affecting non-DNA-binding domains [28, 29]. R337H mutation has contributed to a high incidence of adrenocortical carcinoma (ACC), but is notable for its incomplete penetrance [30]. Moreover, Some missense mutations in TP53 have a dominant-negative effect, meaning the mutant p53 protein not only loses its tumor-suppressive function but also interferes with the function of the remaining wild-type p53, exacerbating the cancer risk [31]. Hotspot mutations such as R175H, R248Q, and R273H are examples of dominant-negative mutations [32, 33].

Considering the higher prevalence of hotspot mutations, the profound impact of dominant-negative mutations, and the co-prevalence of founder variations with specific cancer types, recent studies and secondary analyses have focused on potential genotype–phenotype correlations [34, 35]. Although the hotspot variations show a likely shift toward early-onset (before 31) breast cancer and sarcoma, current evidence is inconclusive for any significant correlations [36]. There is still significant variability in how TP53 mutations manifest clinically. Even within families, individuals with the same TP53 mutation can present with different malignancies, different onset ages, and varying treatment responses [37].

2.2 Epidemiology

Studies have shown that LFS is a rare hereditary cancer predisposition syndrome with an estimated prevalence ranging from 1 in 5,000 to 1 in 20,000 individuals in the general population [38]. Geographically, LFS exhibits global distribution

without remarkable ethnic or racial preferences, although certain populations may exhibit founder mutations or higher prevalence rates attributable to genetic drift, population bottlenecks, or consanguinity [39, 40]. Despite its rarity, LFS exhibits considerable variability in penetrance and expressivity, with inter-individual variability in tumor spectrum, age of onset, and disease trajectory, attributable to modifier genes, environmental influences, and stochastic and random events [41–44].

The general viewpoint on LFS suggests a high penetrance of this familial syndrome, with about 80% risk of cancer during the individual's lifespan [45, 46]. Studies estimate that over 350,000 individuals have germline TP53 mutations—substantially more than registered cases—suggesting either a potential underdiagnosis of LFS cases worldwide or variation in its estimated penetrance [47, 48]. Also, there have been several reports of individuals with rare early-onset malignancies and TP53 mutations who have had a negative familial history of cancer, suggesting a potentially higher prevalence of LFS than estimated [49–52].

Tables 1 and 2 present the tumor site distribution of TP53 germline mutations in confirmed carriers and mutations identified in human tumor samples, retrieved from the R20 release of TP53 database [53, 54]. As presented, breasts, soft tissues, brain, adrenal glands, and bones are the most common tumor sites in individuals with TP53 germline mutations.

Around half of the TP53 mutation carriers are expected to develop cancer before the age of 30 [55, 56]. Notably, the prevalence of LFS may be underestimated due to challenges in clinical detection, diagnostic ascertainment, and genetic testing accessibility [57, 58]. The advent of next-generation sequencing (NGS) technologies and expanding indications for genetic testing in oncology practice have facilitated the identification of novel germline TP53 mutations and expanded the clinical spectrum of LFS-associated malignancies beyond the classic triad of sarcomas, breast cancer, and brain tumors [59, 60].

2.3 Clinical features

LFS is characterized by a diverse spectrum of malignancies affecting multiple organ systems. Common tumors associated with LFS include soft tissue sarcomas, breast cancer, brain tumors (such as glioblastoma and medulloblastoma), adrenocortical carcinoma, and leukemia, particularly, acute lymphoblastic leukemia (ALL) [61, 62]. The age of onset for cancer in LFS is typically younger compared to the sporadic cases, with many tumors diagnosed during childhood or early adulthood [20]. Additionally, individuals with LFS are at increased risk of developing multiple primary cancers over their lifetime, further complicating management and surveillance strategies [63].

Table 1 Tumor site distribution of TP53 germline mutations in confirmed carriers (Tumor distribution N = 2591—*data from TP53 Database, R20: July 2019*)

Tumor site	Count (%) n = 2591
Breast	815 (31.46%)
Soft tissues	315 (12.16%)
Brain	289 (11.15%)
Adrenal gland	247 (9.53%)
Bones	241 (9.3%)
Hematological	108 (4.17%)
Colorectum	73 (2.82%)
Lung	72 (2.78%)
Skin	60 (2.32%)
Ovary	49 (1.89%)
Stomach	30 (1.16%)
Kidney	23 (0.89%)
Prostate	12 (0.46%)
Testis	10 (0.39%)
Liver	8 (0.31%)
Head and neck	8 (0.31%)
Esophagus	3 (0.12%)
Larynx	3 (0.12%)
Bladder	2 (0.08%)
Others	223 (8.61%)

Table 2 Tumor site distribution of TP53 mutations identified in human tumor samples of primary tissues, body fluids, and cell-lines, based on mutated samples per samples analyzed (Tumor distribution N = 28,866 – *data from TP53 Database, R20: July 2019*)

Tumor site	Count (%) n = 28,866
Colorectum	3673 (12.72%)
Respiratory system	3528 (12.22%)
Breast	2928 (10.14%)
Female genital organs	2887 (10%)
Head and neck	2874 (9.96%)
Esophagus	1891 (6.55%)
Brain	1871 (6.48%)
Hematological	1707 (5.91%)
Bladder	1522 (5.27%)
Liver	1210 (4.19%)
Skin	1063 (3.68%)
Stomach	985 (3.41%)
Pancreas	492 (1.7%)
Male genital organs	434 (1.5%)
Soft tissues	432 (1.5%)
Bones	294 (1.02%)
Kidney	149 (0.52%)
Other	926 (3.21%)

2.3.1 Sarcoma

Sarcomas are a hallmark presentation of LFS, constituting a significant proportion of malignancies encountered in affected individuals. Sarcomas contribute to one-fourth of all tumors in LFS patients, with the majority of cases exhibiting before 50 years old [64].

The mesenchymal tumors arise from connective tissues, including but not limited to bones, cartilage, muscle, adipose tissue, and blood vessels, in different locations such as extremities, retroperitoneum, and head and neck regions, resulting in malignancies such as osteosarcoma [65], Ewing sarcoma [66], chondrosarcoma [67], rhabdomyosarcoma [68], leiomyosarcoma [69], liposarcoma [70], angiosarcoma [71], malignant peripheral nerve sheath tumors (MPNSTs) [72], and gastrointestinal stromal tumors (GISTs) [73]. Sarcomas generally vary in histologic subtypes, and could be accompanied by diverse clinical presentations and therapeutic responses.

LFS-related sarcomas usually develop in childhood or early adulthood, often preceding the diagnosis of other LFS-associated malignancies. The clinical presentations of sarcomas in LFS are characterized by their heterogeneity and tendency for metastasis and dissemination through the body [74]; therefore, any clinical suspicion is typically followed by comprehensive imaging studies and histopathological evaluations [75]. Rhabdomyosarcoma and osteosarcoma are among the most common sarcoma subtypes encountered in LFS [8].

2.3.2 Breast *cancer*

In addition to sarcomas, LFS patients are at a significantly greater risk of breast cancer. In fact, breast cancer is the most prevalent cancer in female patients with LFS [76]. Previous studies have indicated that women with LFS experience breast cancer almost three decades earlier than the general population, usually with a mean onset age of around 32–38 [76–79]. Studies have suggested the potential impact of reproductive factors since significant protective effects of breastfeeding for over seven months have been observed in respective populations [80].

Breast cancer in the context of LFS often exhibits aggressive histopathological features, including high histologic grade and overexpression of HER2/neu oncogene, tending towards an inferior overall survival compared to sporadic cases [77, 81]. Many LFS cases of breast cancer are estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2)-positive, suggesting the potential association of early-onset HER2-positive breast cancer with the presence of TP53 mutations [82].

Clinical presentations of breast cancer are diverse and could be the earliest presenting signs and symptoms of LFS. Notably, breast cancers in LFS frequently emerge at a younger age compared to sporadic cases, making early breast cancer an alarming sign for clinicians to initiate an in-depth workup for LFS [56, 76, 83].

2.3.3 Brain tumors

Central nervous system (CNS) tumors could range from high-grade gliomas, namely glioblastoma multiforme, to embryonal tumors, such as medulloblastoma, with variable histologic subtypes and clinical behaviors [84, 85]. These CNS tumors may present with neurological symptoms, including headaches, seizures, focal deficits, and merely cognitive impairments, prompting diagnostic evaluation with further neuroimaging modalities [86].

Glioma, including astrocytoma, oligodendroglioma, and glioblastoma, along with medulloblastoma and choroid plexus carcinoma, are the most common subtypes of brain cancer associated with LFS [85, 87–89]. Glioma exhibits infiltrative growth patterns and aggressive histologic features, commonly with therapeutic resistance [90, 91]. Medulloblastoma is another LFS-associated brain tumor arising from the cerebellum, characterized by the propensity for metastatic dissemination via cerebrospinal fluid (CSF) [92].

2.3.4 Adrenocortical carcinoma

On the other hand, ACC could present with nonspecific or constitutional symptoms such as abdominal pain. Although ACC cases are generally sporadic, further evaluation for genetic predispositions such as LFS or multiple endocrine neoplasia (MEN) syndrome is recommended upon diagnosis [93].

Arising from the adrenal cortex, ACC usually presents with an aggressive clinical course, propensity for metastatic spread, and poor prognosis [94]. The clinical presentations of ACC in LFS are variable and nonspecific, often mimicking symptoms of other adrenal disorders, including Cushing's syndrome, or constitutional symptoms such as fatigue, weight loss, and abdominal fullness [95]. Notably, ACC may also be accidentally detected in imaging studies performed for unrelated indications, or during treatment for other diagnoses [96].

2.3.5 Hematologic malignancies

Hematologic malignancies might not be the initial denoting manifestation of LFS, but, in the case, they could present with unspecific or constitutional symptoms, along with splenomegaly, lymphadenopathy, or blood count abnormalities in further clinical evaluation and workup [97]. Although LFS accounts for less than 1% of ALL cases—the most frequently reported LFS-linked leukemia—in children, it comes with a significant predisposition to adverse treatment outcomes and second cancers [97, 98]. Furthermore, studies have reported an estimated six times higher risk of developing leukemia in the LFS population [99]. Acute myeloid leukemia (AML), myelodysplastic syndromes, and lymphomas are also linked to LFS, but present with lower incidence [100]. TP53 mutation and LFS are linked to 10–15% and 5% of AML cases, respectively [101].

As a consequence of dysregulated proliferation and differentiation of hematopoietic precursors, culminating in the emergence of abnormal hematopoietic clones with malignant potential, hematologic malignancies often display aggressive clinical behaviors in LFS patients, with resistance to conventional therapies, relapse, and propensity for recurrence [102–105].

2.3.6 Other presentations

Not all cases of LFS typically present with the discussed presentations, as many LFS cases have been reported with other malignancies. For instance, some studies have indicated melanoma as a potentially LFS-related malignancy; however, the association between LFS and melanoma is currently indefinite [106–108].

Figure 4 displays the most common tumor sites and clinical presentations of LFS**.**

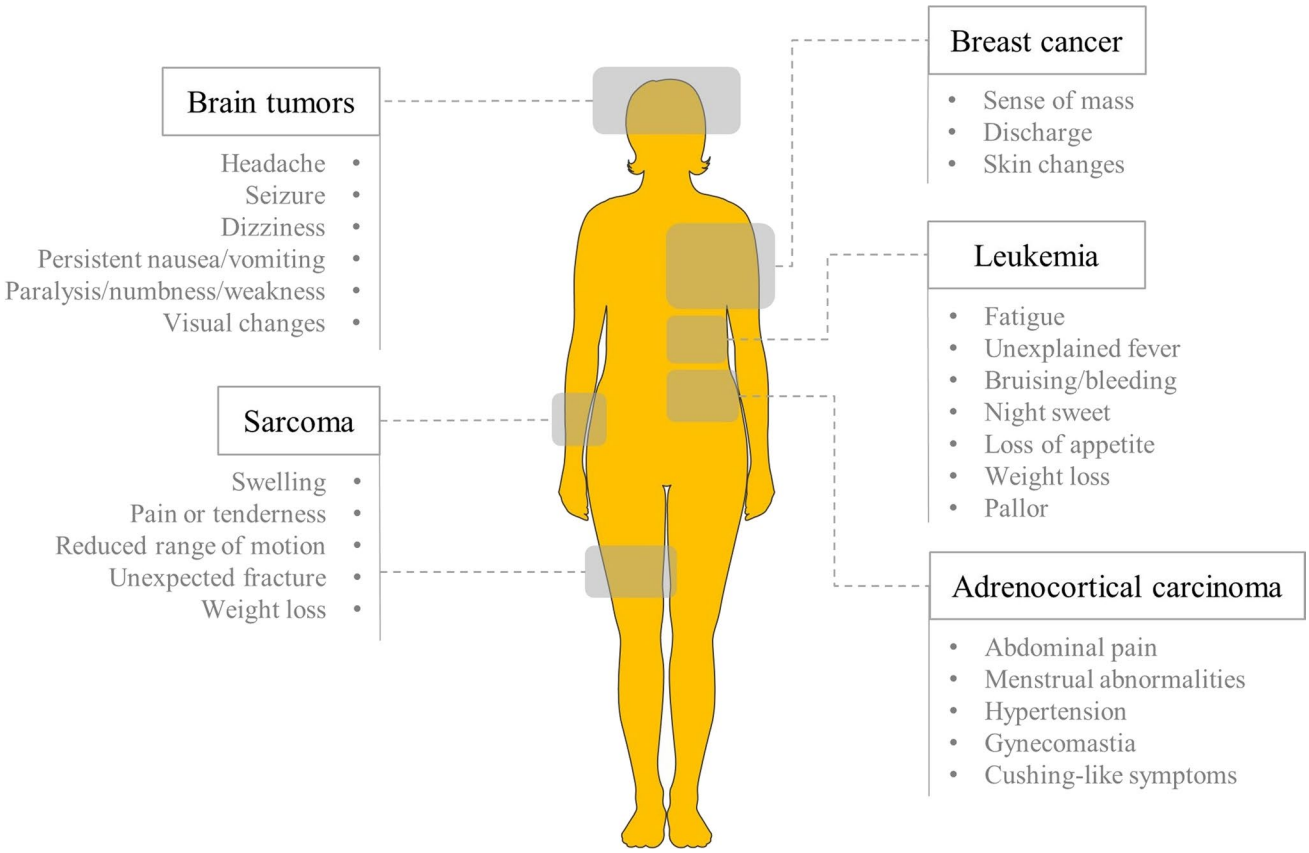

Fig. 4 The most common malignancies of Li-Fraumeni syndrome, along with their most common clinical presentations

2.4 Diagnosis

The diagnosis of LFS should be based on a combined clinical and genetic approach. Nonetheless, the definite diagnosis of LFS relies on TP53 mutation. However, several diagnostic criteria have been introduced to help clinicians effectively diagnose LFS and Li-Fraumeni-like syndrome (LFLS) cases, including the classic criteria, Chompret and its updated criteria, the Birch criteria, and the Eeles criteria [110–113]. Table 3 summarizes the proposed criteria for both LFS and LFLS.

The classic criteria for LFS include:

1. Diagnosis of sarcoma before age 45 in an individual
2. A relative (first-degree) with any cancer before age 45
3. Another relative (first-/second-degree) with any cancer before age 45, or a sarcoma at any age

Individuals meeting the clinical criteria are referred to genetic testing for TP53 mutations. In addition to genetic testing, comprehensive familial pedigree analysis plays a vital role in clarifying the hereditary basis of cancer predisposition syndromes, including LFS. Patients with other combinations for personal or familial history of malignancies could still be considered clinically high-risk for LFS and managed accordingly. Importantly, in cases of high clinical suspicion, a negative result for the detectable pathogenic variants does not exclude the LFS diagnosis [114].

The National Comprehensive Cancer Network (NCCN) recommends testing for individuals complying with CRIT-7 (testing criteria for LFS), including individuals fulfilling classic LFS or Chompret criteria, individuals with personal/familial history of pediatric hypodiploid ALL, and people with cancer with a pathogenic/likely pathogenic (P/LP) TP53 variant identified on tumor-only genomic testing, with germline evaluation considered in patients with an age of cancer diagnosis before 30 years old, or per clinician discretion [115]. However, in case the criteria are unmet, testing for other hereditary syndromes should be considered.

Table 3 Diagnostic criteria for Li-Fraumeni syndrome, requiring further screening for germline TP53 mutation

Disease	Diagnostic criteria	Description
Li-Fraumeni syndrome	Classic criteria	Presence of all the following: - Sarcoma diagnosed at age < 45 years; - First-degree relative < 45 with any cancer; - First/second-degree relative with sarcoma at any age or any cancer < 45 years
	Chompret criteria (updated)	The presence of one of the following: - Tumor from the Li-Fraumeni spectrum (sarcoma, breast cancer, central nervous system tumor, adrenocortical carcinoma, leukemia, or lung cancer) < 46, and at least one first/second-degree relative with Li-Fraumeni tumor (except breast cancer if the proband has breast cancer) < 56 or with multiple tumors; - Multiple tumors (except multiple breast tumors), two of which belong to the Li-Fraumeni spectrum, with the first one occurring < 46; - Diagnosis of adrenocortical carcinoma, choroid plexus tumor, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of age and family history - Breast cancer < 31
Li-Fraumeni-like syndrome	Birch criteria	Presence of all the following: - Any childhood cancer, or sarcoma, brain tumor, or adrenocortical carcinoma diagnosed < 45; - First/second-degree relative with a Li-Fraumeni spectrum cancer (sarcoma, breast cancer, brain tumor, adrenocortical carcinoma, or leukemia) at any age; - First/second-degree relative with any cancer < 60
	Eeles criteria	Two first/second-degree relatives with Li-Fraumeni spectrum tumor at any age

2.5 Management, surveillance, and screening

Considering the high risk of developing cancer at a young age, individuals with LFS require lifelong surveillance and screening to detect tumors at an early, potentially curable stage. The preferred screening modalities and intervals should be based on the treating physicians' discretion. Although there are controversies among current surveillance protocols, some routine screenings are recommended in most guidelines, including [109, 114, 116, 117]:

- Triannual (until 18) or biannual/annual (after 18) clinical examination
- Annual whole-body magnetic resonance imaging (MRI)
- Bi/triannual abdominopelvic ultrasound
- Annual breast MRI and mammography for women starting at age 20
- Routine blood and urinary workup, including a complete blood count with differentials, along with blood inflammatory markers and available cancer biomarkers–a peripheral blood smear could also be helpful
- Annual brain MRI
- Colonoscopy every 2–5 years, beginning from age 18–25

Table 4 compares LFS surveillance protocols from the latest guidelines and consensuses in more detail [109, 114–118]. Recent studies have also proposed novel cell-free DNA (cfDNA) approaches toward early cancer detection in LFS patients [119].

Routine clinical examination is necessary for LFS patients [120]. Starting from basic vital signs, clinicians should look after any indicating symptoms and signs, including pallor, unexplained weight loss, Cushing's-like facial features, night sweet, persistent or progressive pain, sense of lump, bulge, or swelling, headache, seizure, visual disturbance in any form, hemoptysis, chest pain, shortness of breath, or any skin changes. The management of LFS requires a multidisciplinary approach, involving genetic counseling, cancer surveillance, risk reduction strategies, and personalized treatment interventions. Lifestyle modifications should be made to reduce cancer risk, including smoking cessation and maintaining a healthy weight [121].

Clinicians should consider that patients with TP53 mutations with a history of previous malignancy are prone to the development of a second cancer [122]. Radiation-induced malignancies are one of the more prevalent malignancies

Table 4 Surveillance protocols based on the latest guidelines and recommendations

Surveillance Component	Toronto Protocol (2016) [116]		NCCN (2024) [115]		AACR (2017) [117]		GENTURIS (2020) [109]		SEOM & AEGH (2020) [118]		Japanese LFS Expert Group (2021) [114]	
Adrenocortical carcinoma	From birth to 40y	- Abdominopelvic US, q 3-4 m - Blood tests[a], q 3-4 m - 24 h urine cortisol (if feasible)	Beginning in infancy	- US, q 3-4 m	From birth (to 18y)	- Abdominopelvic US, q 3-4 m - Blood tests[b] (if US unsatisfactory), q3–4 m	From birth to 18y	- Abdominal US, q 6 m - Urine steroids (if US not useful), q 6 m	From birth to 18y	- Abdominopelvic US, q 3-6 m - Blood tests[b] (if US unsatisfactory), q 3-6 m	From birth to 17y	- Abdominopelvic US, q 3-4 m - Blood tests (if US impossible), q3-4m[c]
Brain tumor	From birth	- Brain MRI, q 1y	Beginning in infancy	- Brain MRI, q 1y	From birth	- Brain MRI, q 1y[d]	From birth to 18y	- Brain MRI in high-risk TP53 variants[e], q 1y	From birth	- Brain MRI[d], q 1y	From birth	- Brain MRI, q 1y[f]
							From 18 to 50y	- Brain MRI, q 1y				
Breast cancer	From 18y onwards	- Breast self-examination, q 1 m	From 18y onwards	- Breast awareness	From 18y onwards	- Breast awareness	From 18 to 65y	- Breast MRI, q1y	From 18y onwards	- Clinical breast exam, q 6 m	From 18y onwards	- Breast (self-) examination
	From 20-25y[g] onwards	- Clinical breast examination, q 6 m	From 20y[h] onwards	- Clinical breast examination, q 6-12 m - Breast screening: • 20-29y[h]: Breast MRI[i], q 1y[j] • 30-75y: Breast MRI[i] + mammography, q 1y • > 75y: Per case decision • TP53 P/LP variants treated for breast cancer, and who have not had a bilateral mastectomy: Breast MRI + mammogram, q 1y	From 20y onwards	- Clinical breast examination, q 6 m			From 20 to 75y	- Breast MRI, q 1y	From 20y onwards	- (Clinical) breast examination, q 6 m
	From 20y[g] to 75y	- Mammography and breast MRI, q 1y			From 20 to 75y	- Breast MRI, q 1y[k]					From 20 to 75y	- Breast MRI, q 1y[k]
	- Consider risk-reducing bilateral mastectomy		- Discuss risk-reducing mastectomy, addressing psychosocial and quality-of-life aspects - For patients diagnosed with breast cancer, mastectomy is preferred over lumpectomy/radiation to reduce radiation-induced sarcoma risk		- Consider risk-reducing bilateral mastectomy				- Consider risk-reducing bilateral mastectomy		- Consider risk-reducing mastectomy	

Table 4 (continued)

Surveillance Component	Toronto Protocol (2016) [116]		NCCN (2024) [115]		AACR (2017) [117]		GENTURIS (2020) [109]		SEOM & AEGH (2020) [118]		Japanese LFS Expert Group (2021) [114]	
Gastrointestinal cancer	From 25y[l] onwards	- Colonoscopy, q 2y	From 25y[m] onwards	- Colonoscopy and upper endoscopy, q 2-5y - Patients with prior whole body/ abdominal RT: colonoscopy is recommended 5y after treatment	From 25y onwards	- Upper endoscopy and colonoscopy, q 2-5y	From 18y onwards	- Colonoscopy (only in case of previous abdominal cancer RT or familial history of colorectal cancer), q 5y	From 18y onwards	- Colonoscopy (in cases of previous abdominal RT or family history of colorectal cancer), q 5y	From 25y onwards	- Upper and lower GI endoscopy, q 2-5y
Soft tissue and bone sarcoma	From birth to 18y	- Whole-body MRI, q 1y	Beginning in infancy	- Whole-body MRI q, 1y	From birth to 18y	- Whole-body MRI q, 1y	From birth to 18y	- Whole-body MRI (without gadolinium enhancement) for high-risk TP53 variants[e] or patients with prior chemotherapy/RT, q 1y	From birth	- Whole-body MRI without gadolinium enhancement, q 1y	From birth to 17y	- Whole-body MRI q 1y[n]
	From 18y onwards	- Whole-body MRI, q 1y - Abdominopelvic US, q 3-4 m			From 18y onwards	- Whole-body MRI q, 1y[k] - Abdominopelvic US, q 1y	From 18y onwards	- Whole-body MRI, q 1y			From 18y onwards	- Whole-body MRI, q 1y[k,n] - Abdominopelvic US, q 1y
Melanoma	From 18y onwards	- Dermatological examination, q1y	From 18y onwards	- Dermatological examination, q1y	From 18y onwards	- Dermatological examination, q1y	–	–	–	–	From 18y onwards	- Dermatological examination, q1y
Leukemia/ lymphoma	From birth	Blood tests[o], q 3-4 m	–	–	–	–	–	–	From birth	- Complete blood count (prior leukemogenic drugs), q 1y	–	–
Prostate cancer	–	–	From 40y onwards	- PSA, q 1y	–	–	–	–	–	–	–	–
General assessment	From birth to 18y	- Complete physical examination, q 3-4 m - Prompt assessment by PCP for any medical concern	Beginning in infancy	- Comprehensive physical examination, including neurologic examination with high index of suspicion for rare cancers and second malignancies in cancer survivors every 6-12 m	From birth to 18y	- Complete physical examination, q 3-4 m - Prompt assessment by PCP for any medical concern	From birth to 17y	- Clinical examination with specific attention to signs of virilization or early puberty and measurement of blood pressure, q 6 m	From birth to 18y	- Whole physical examination, q 4-6 m	From birth to 17y	- Complete examination, q 3-4 m - Cooperation with attending physician

Table 4 (continued)

Surveillance Component	Toronto Protocol (2016) [116]		NCCN (2024) [115]		AACR (2017) [117]		GENTURIS (2020) [109]		SEOM & AEGH (2020) [118]		Japanese LFS Expert Group (2021) [114]	
	From 18y onwards	- Complete physical examination, q 3-4 m - Prompt assessment by PCP for any medical concern	Adulthood	- Comprehensive physical exam including neurologic examination with high index of suspicion for rare cancers and second malignancies in cancer survivors, q 6-12 m - Screening recommendations should take into account personal and family history of cancer (5-10y before earliest diagnosis)	From 18y onwards	- Complete physical examination, q 6 m - Prompt assessment by PCP for any medical concern	From 18y onwards	- Clinical examination with specific attention to the occurrence of basal cell carcinomas within the radiotherapy field in patients who received RT, q 1y	From 18y onwards	- Whole physical examination, q 6 m	From 18y onwards	- Complete physical examination, q 6 m - Prompt assessment by attending physician for any medical phenomenon

[a]Blood tests include 17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, and androstenedione

[b]Blood tests include total testosterone, dehydroepiandrosterone sulfate, and androstenedione

[c]Blood tests include total testosterone, dehydroepiandrosterone, androstenedione

[d]First MRI with contrast, thereafter without contrast if previous MRI normal and no new abnormality

[e]High-risk TP53 variants: Childhood cancer in individual/family members, variant that has already been associated with childhood cancers, and variants corresponding to a dominant-negative missense variant

[f]First MRI with contrast, thereafter contrast is not necessary as long as the previous MRI is normal and no new abnormalities are confirmed

[g]Or five to ten years before the earliest breast cancer detection in the family (whichever comes first)

[h]Or at the age of the earliest diagnosed breast cancer in the family, if < 20y

[i]With and without contrast

[j]Or mammogram, if MRI is unavailable (Breast MRI is preferred due to concerns regarding the risk of radiation exposure in P/LP variant carriers)

[k]Breast MRI and abdominopelvic US to alternate with annual whole-body MRI (at least one scan q 6 m)

[l]Or ten years before the earliest colon cancer detection in the family (whichever comes first)

[m]Or five years before the earliest known colorectal or gastric cancer in the family

[n]Whole-body MRI is performed from head to toe, including all limbs

[o]Blood tests include complete blood count, erythrocyte sedimentation rate, and lactate dehydrogenase

h Hour, *m* Month(s), *MRI* Magnetic resonance imaging, *P/LP* Pathogenic/likely pathogenic, *PCP* Primary care physician, *PSA* Prostate-specific antigen, *q* Every, *RT* Radiation therapy, *US* Ultrasound, *y* Year(s), *LFS* Li-Fraumeni syndrome, *NCCN* National Comprehensive Cancer Network, *AACR* American Association for Cancer Research, *ERN-GENTURIS* European Reference Network on the Genetic Tumor Risk Syndromes, *SEOM* Sociedad Española de Oncología Médica, *AEGH* Asociación Española de Genética Humana

among LFS patients with a history of previous malignancy [6, 123]. Given the significance of breast cancer in female patients with LFS, a total bilateral prophylactic mastectomy has also been recommended; however, this decision should be made according to each individual's status of health and personal history of cancer, familial history, principles, and wishes [124].

2.6 Treatment

There is no approved and definite treatment for LFS, and most LFS patients undergo the conventional treatment strategies available for each cancer [114]. The management of LFS almost entirely depends on a combination of surveillance protocols, risk reduction strategies, and therapeutic interventions tailored to the specific tumor types and clinical characteristics of affected individuals. The standard treatment regimens for LFS-related cancers have traditionally involved DNA-damaging systemic cytotoxic chemoradiation, which can lead to subsequent tumors [125]. Meanwhile, recent studies have explored alternative therapeutic strategies that may offer more targeted and less genotoxic options for LFS patients. Table 5 presents recent and ongoing clinical trials focusing on LFS patients. The most common proposed therapeutic candidates are:

2.6.1 Immune checkpoint inhibitors

Immune checkpoint inhibitors, chiefly the programmed cell death protein-1 and its ligand (PD-1/PD-L1)- and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4)-targeting antibodies, have shown promising clinical activity in various solid tumors and hematologic malignancies associated with LFS [126, 127]. By blocking inhibitory signaling pathways in the tumor microenvironment, these agents could enhance the antitumor immune response, potentially leading to tumor regression and prolonged patient survival [128]. Studies evaluating immune checkpoint inhibitors as monotherapy or in combination with other therapeutic modalities are underway to assess their efficacy and safety in individuals with LFS-associated cancers, including the United States Food and Drug Administration (FDA)-approved Nivolumab and Pembrolizumab, and FDA-approval pending Sintilimab – which has been recently approved and included in the National Reimbursement Drug List (NRDL) of China (Table 5) [129–135].

2.6.2 Adoptive cell therapy

Adoptive cell therapy, including chimeric antigen receptor (CAR) T-cell therapy and tumor-infiltrating lymphocyte (TIL) therapy, is another proposed approach for the treatment of LFS-associated malignancies [136, 137]. CAR T-cell therapy involves engineering the patients' T cells to express chimeric antigen receptors targeting specific tumor antigens, while TIL therapy involves isolating and expanding tumor-infiltrating lymphocytes with antitumor activity ex vivo before reinfusion into patients [138]. The CAR T-cell-based combination strategies have demonstrated improved overall survival in previous studies [139, 140].

2.6.3 Cytokine-based therapies

Cytokine-based therapies, such as interleukin-2 (IL-2) and interferon-alpha (IFN-α), modulate the immune response and enhance the antitumor activity of immune effector cells, including T cells and natural killer (NK) cells [141, 142]. Cytokine-based therapies have been investigated as either monotherapy or in combination with other immunotherapeutic agents for LFS-associated malignancies [143–145].

2.6.4 TP53 reactivators

Small molecule drugs designed to reactivate mutant TP53 proteins represent a promising therapeutic strategy for individuals with LFS-associated tumors [146, 147]. Eprenetapopt (PRIMA-1^{Met}, APR-246) and RITA (Reactivating p53 and Inducing Tumor Apoptosis) have shown preclinical efficacy in restoring the transcriptional activity, inducing cell cycle arrest, and promoting apoptosis in cancer cells with dysfunctional TP53 [133, 148–150].

Table 5 Recent and ongoing registered trials for documented Li-Fraumeni syndrome and TP53 mutation

Trial group	Clinicaltrials.gov ID	Study status	Country	Study type	Study population	Intervention(s)	Measured primary outcomes
Monotherapy	NCT01981525	Completed	USA	Phase I trial	Adults (> 18) with documented positive germline TP53 mutation	Metformin	Tolerability of metformin, up to 2 years (toxicity assessment by CTCAE v4.0), plus the effect of metformin administration on circulating IGF-1, insulin, and IGFBP3 (time frame: two years)
	NCT03789175	Completed	USA	Phase I/II trial	Adults (> 18) with Li-Fraumeni syndrome and confirmed TP53 mutation	Nicotinamide riboside	Change in phosphocreatine recovery time constant, measurement from baseline to 12 weeks of supplementation, using the 31P-MRS skeletal muscle submaximal exercise
	NCT05512377	Active, recruiting	International multicenter	Phase II trial	Adult (> 18) patients with locally advanced/metastatic, MDM2 amplified, TP53 wild-type biliary tract/pancreatic ductal adenocarcinoma, and other solid tumors	Brigimadlin (BI 907828)	ORR in patients, up to 30 months
Combination therapy	NCT06088030	Active, recruiting	China	Phase II trial	Under-18 children and young adults with pathological diagnosis basis of malignant tumor and germline or somatic P53 mutations*	Arsenic trioxide combined with chemotherapy	ORR four weeks after the combination therapy
	NCT03377725	Withdrawn	China	Phase III trial	Adult patients (> 18) with MDS	Arsenic trioxide and Decitabine	RFS in patients, up to 6–8 months after complete release
	NCT03381781	Unknown status	China	Phase II trial	Adults (> 18) AML patients with p53 mutations	Arsenic trioxide, Decitabine, and Cytarabine	RFS in patients, up to 6–8 months after complete release
	NCT06088030	Active, recruiting	China	Phase II trial	Child and young adult (< 18) p53-mutated patients with pathological diagnosis of malignant tumor*	Arsenic trioxide in combination with chemotherapy	ORR four weeks after the combination therapy
	NCT03855371	Active, recruiting	China	Phase I trial	Newly diagnosed adult (> 18) AML/MDS patients with p53 mutants*	Arsenic trioxide and Decitabine	Side effects during the trial and ORR after four cycles
	NCT04778397	Terminated	International multicenter	Phase III trial	Treatment-naïve adult patients (> 18) with TP53 mutant AML	Combination of Magrolimab or Venetoclax with Azacitidine	OS in patients, up to death or end of study (up to 27 months)

Table 5 (continued)

Trial group	Clinicaltrials.gov ID	Study status	Country	Study type	Study population	Intervention(s)	Measured primary outcomes
	NCT04277442	Active, not recruiting	USA	Phase I trial	Adult (> 18) patients with newly diagnosed TP53-mutated AML	Nivolumab in combination with Decitabine and Venetoclax	Incidence of adverse events and response rate, up to 3 cycles
	NCT05280626	Not started	Undefined	Phase II trial	Adult (> 18) DLBCL patients with P53 mutation with PD-L1 expression	Combination of Sintilimab and R-CHOP	Complete response rate, up to one year
	NCT04023916	Unknown status	China	Phase II trial	Adult (> 18) TP53-mutant and PD-L1-positive DLBCL patients	Combination of Sintilimab and R-CHOP	Complete remission rate, every three months until thirty months after the last patient's enrollment
	NCT06366347	Not started	USA	Phase II trial	Adults (> 18) patients with advanced/recurrent ER + , MMRP, TP53 wild-type endometrial cancer	Letrozole/Abemaciclib vs Pembrolizumab	Median PFS in patients, up to 2 years
	NCT04159155	Active, recruiting	Canada	Phase II/III trial	Adult (> 18) patients with pure serous endometrial carcinoma or other histotypes (endometrioid and clear cell) with abnormal/mutant-type p53	Radiation therapy (EBR), high-dose-rate vaginal brachytherapy, and Niraparib	Three-year DFS in patients
	NCT05197192	Active, recruiting	Germany	Phase III trial	Adult (> 18) patients with documented CLL/SLL requiring treatment according to at least one of the following: 17p-deletion, TP53-mutation, or complex karyotype (3 or more chromosomal aberrations in 2 or more metaphases)	Acalabrutinib, Obinutuzumab and Venetoclax	PFS 50 months after FPI
	NCT02909972	Active, recruiting	USA	Phase I trial	Adult (> 18) patients with relapsed/refractory AML or Advanced MDS with wild-type TP53	Sulanemadlin (ALRN-6924) as monotherapy or combination therapy with Cytarabine	Safety and tolerability of mono-/combination therapy of Sulanemadlin with Cytarabine until 30 days after the last treatment cycle

Table 5 (continued)

Trial group	Clinicaltrials.gov ID	Study status	Country	Study type	Study population	Intervention(s)	Measured primary outcomes
	NCT03931291	Completed	USA	Phase II trial	Adults (> 18) with TP53 mutated AML or MDS following ASCT	Combination therapy of Eprenetapopt (APR-246) with Azacitidine	RFS in patients with TP53 mutated AML or MDS after HSCT
	NCT02448329	Completed	South Korea	Phase II trial	Children and young adults (< 20) with advanced TP53-mutation harboring gastric adenocarcinoma, resistant to first-line 5-FU/platinum-based chemotherapy	Combination therapy of Adavosertib (AZD1775) with Paclitaxel	ORR in patients after eight weeks
	NCT06130579	Active, recruiting	China	Phase II trial	Child, adult, and young adults (> 12) with TP53 + AML/MDS post-Allo-HSCT with no history of severe/uncontrolled GVHD	Interferon-α	Incidence of relapse (blasts ≥ 5% post-HSCT), up to one year
Diagnostic trial	NCT03176836	Active, recruiting	Canada	Single-group diagnostic pilot study	Pediatric (< 18) Li-Fraumeni syndrome kindreds carrying a known TP53 mutation or obligate mutation carriers	Diagnostic tests of whole body STIR MRI, DW-MRI, and PET-MRI	Imaging traits on suspected tumors: Signal heterogeneity, mass effect, and neurovascular bundle involvement (STIR MRI); necrosis, and signal/necrosis ratio STIR and DW MRI): FDG metabolic activity and uptake (PET-MRI), or other additional imaging findings
	NCT02950987	Active, not recruiting	USA	Single-group diagnostic study	Adults and children meeting the defined Li Fraumeni syndrome (Germline p53 mutation carriers, members of families meeting classic LFS criteria, and obligate carriers by pedigree)	Whole body MRI	Return of pediatric and adult patients with Li Fraumeni syndrome year after year for four annual scans
	NCT01464086	Completed	France	Phase III trial study	5–71 year old patients with P53 mutation	Whole body MRI	Incidence of cancer during the first three years

*with previously shown partial/complete response

AML Acute myeloid leukemia, *BR* Bendamustine and Rituximab, *CLL* Chronic lymphocytic leukemia, *CTCAE* Common Terminology Criteria for Adverse Events, *DLBCL* Diffuse large B-cell lymphoma, *DFS* Disease-free survival, *DW-MRI* Diffusion-weighted magnetic resonance imaging, *EBR* External Beam Radiation, *ER* Estrogen receptor, *FCR* Fludarabine, Cyclophosphamide, and Rituximab, *GVHD* Graft-versus-host disease, *HSCT* Hematopoietic stem cell transplant, *IGF-1* Insulin-like growth factor 1, *IGFBP3* Insulin-like growth factor binding protein 3, *MDM2* Mouse double minute 2 homolog, *MDS* Myelodysplastic syndrome, *MMRP* Mismatch repair proficient, *MRI* Magnetic resonance imaging, *ORR* Objective response rate, *OS* Overall survival, *PET* Positron emission tomography, *PFS* Progression-free survival, *R-CHOP* Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, *RFS* Relapse-free survival, *STIR* Short Tau inversion recovery

2.6.5 DNA damage response inhibitors

DNA damage response (DDR) pathway-targeting agents, such as poly(ADP-ribose) polymerase (PARP) inhibitors and ataxia telangiectasia and Rad3-related (ATR) inhibitors, have shown efficacy in preclinical models of LFS-associated malignancies, particularly in tumors with homologous recombination deficiency (HRD) [151–154].

2.6.6 Bruton's tyrosine kinase inhibitor

Bruton's tyrosine kinase (BTK) inhibitors are a class of targeted therapeutic agents that are generally considered in the treatment of B-cell malignancies, including B-cell chronic lymphocytic leukemia (B-CLL) and mantle cell lymphoma (MCL) [23, 155, 156]. BTKi is vital in B-cell receptor signaling, lymphocyte activation, and proliferation [157]. Small molecule BTK inhibitors irreversibly bind to the active site of BTK, thereby inhibiting its kinase activity and downstream signaling cascades, thus disrupting B-cell receptor signaling and promoting apoptosis of malignant B cells [158]. Ongoing research efforts try to evaluate the safety and effectiveness of BTK inhibitors, such as Acalabrutinib, in combination with other targeted therapies for LFS patients [156].

2.6.7 MDM2/X inhibitors

MDM2/X inhibitors disrupt the interaction between murine double minute 2 (MDM2) or its homolog murine double minute X (MDMX) and the tumor suppressor protein p53. This interaction basically leads to apoptosis evade. By inhibiting MDM2/X, these small molecule inhibitors restore p53 function, leading to cell cycle arrest, apoptosis, and tumor growth inhibition [159]. From several experimental agents of this class, Milademetan (DS-3032b), Sulanemadlin (ALRN-6924), and Brigimadlin (BI 907828) are extensively studied, showing promising results in the very early trials [146, 160–163].

2.6.8 Monoclonal antibodies

Monoclonal antibodies (mAbs) specifically target the antigens expressed on the surface of cancer cells or immune cells in the tumor microenvironment. Initiating various mechanisms of action, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and blockade of tumor growth signaling pathways, several mAbs, such as Rituximab (anti-CD20), Obinutuzumab (anti-CD20), and Magrolimab (anti-CD47), are under investigation for LFS patients [164–167].

2.6.9 Arsenic trioxide

Arsenic trioxide is a cytotoxic agent primarily used in treatment-resistant leukemia [168]. Preclinical studies have provided strong evidence for the potential positive impact of arsenic on the survival of LFS patients [169]. Widely considered in early-phase trials of LFS treatment nowadays, arsenic trioxide is generally well-tolerated, but it could result in serious adverse effects, including QT interval prolongation, cardiac arrhythmias, hepatotoxicity, and neurotoxicity [170–172]. Close monitoring of cardiac function, electrolyte levels, and hepatic function is recommended during treatment with arsenic trioxide to minimize the risk of adverse events.

2.6.10 Other agents

Some existing medications and agents have also been explored as adjuvant LFS treatments. Metformin, a widely used oral antidiabetic agent, has attracted attention for its potential anticancer properties beyond its glucose-lowering effects [173, 174]. Metformin acts primarily by activating AMP-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis, leading to inhibition of mTOR signaling, suppression of hepatic gluconeogenesis, and modulation of cellular metabolism [175, 176]. Although Metformin might not be the primary choice of treatment in LFS patients, given its efficacy in modulating the metabolic profile, the low cost, and accessibility, it could be considered as a preventive agent, especially in individuals with metabolic disorders or obesity-associated cancers [177, 178]. Likewise, nicotinamide riboside, the precursor of nicotinamide adenine dinucleotide (NAD^+), could lead to increased NAD^+ levels,

thereby activating sirtuins and other NAD^+-dependent enzymes involved in DNA repair, chromatin remodeling, and mitochondrial function [179–181]. Previous studies have suggested that nicotinamide riboside enhances cellular stress resistance, inhibiting tumorigenesis and promoting cancer cell apoptosis [182, 183].

The chemopreventive approaches, using medications such as Tamoxifen and Raloxifene, have also been proven effective [184], but are still controversial due to their adverse effects and low patient compliance.

2.7 Challenges

LFS, and the broader context of TP53 mutation research, face various challenges affecting both patients and healthcare providers, including:

2.7.1 Development of targeted therapies

Although TP53 is one of the most frequently mutated genes in cancer, developing therapies that effectively target mutant TP53 has proven difficult.

2.7.2 Variants of uncertain significance

Variants of uncertain significance (VUS), the mutations that their impact – whether pathogenic or benign – on the molecular function and cancer risk is not fully understood, impose clinical challenges in genetic counseling, risk assessment, potential surveillance protocols, and decision-making for both patients and healthcare providers [185]. Guidelines lack clear recommendations for this population, as the cancer risk associated with VUS is uncertain and lacks sufficient data. Although in silico models deliver useful predictions, these models are generally not sufficient to guide clinical decision-making [186]. Meanwhile, the Clinical Genome Resource (ClinGen) TP53 variant curation expert panel has introduced a set of guidelines launched to classify TP53 variants, provide consistent and reliable interpretations of their clinical significance, and help distinguish pathogenic mutations from benign variants and VUS [187, 188].

2.7.3 Germline vs somatic TP53 mutations

Differentiating between germline and somatic mutations is one of the major challenges with TP53 mutations identified through NGS. While the inherited germline mutations lead to LFS, somatic mutations are not heritable. When a TP53 mutation is detected via an NGS panel, it is not immediately clear whether it is germline or somatic–possibly originating from clonal hematopoiesis of indeterminate potential (CHIP) [115]. Misinterpretation of somatic TP53 mutations as germline can lead to unnecessary cancer surveillance in individuals who do not have LFS. Moreover, the detection of low variant allele frequencies (VAF) in TP53 mutations adds complexity to the interpretation. VAF represents the proportion of sequencing reads containing a variant, and low VAFs suggest somatic mutations arising from clonal hematopoiesis rather than true germline mutations [189].

NGS panels often include TP53 to identify mutations for tumor profiling or assessing hereditary cancer risk. In older adults, however, or those with CHIP, TP53 mutations detected in blood or bone marrow samples may be false positives for germline testing, leading to misdiagnosis [190]. Consequently, patients with a CHIP-related TP53 mutation might be unnecessarily subjected to LFS cancer surveillance for solid tumors due to the miscalculated cancer risk [115]. Moreover, TP53 mutations with low VAF may lead to clinical dilemmas for testing family members, as the mutation may be somatic rather than germline.

2.7.4 Overlapping syndromes and genetic mimics

LFS overlaps with some other cancer-predisposing syndromes, complicating the diagnosis and risk assessment. CHEK2 (checkpoint kinase two) and BRCA1/2 (breast cancer genes 1 and 2) are among the most famous LFS-mimicking mutations. For instance, mutations in CHEK2—also a tumor suppressor gene—referred to as the 'CHEK2-associated Li–Fraumeni syndrome' or 'Li-Fraumeni syndrome 2', are occasionally misclassified as a subtype of LFS [191]. CHEK2 encodes a serine/threonine kinase regulating the cellular response to DNA damage, and its mutations result in a tumor predisposition syndrome, associated with a moderately increased risk for later-onset development of less broad cancers, including breast, prostate, and gastrointestinal tumors [191–193]. Moreover, CHEK2 is considered a low-penetrance gene compared

to TP53, suggesting that not all individuals with CHEK2 mutations will develop cancer [194]. Studies have highlighted the clear and significant distinctions in the clinical presentations of TP53 and CHEK2 pathogenic variant carriers and the lack of association between CHEK2 and TP53-related LFS [195]. While both TP53 and CHEK2 are involved in DNA repair and tumor suppression, CHEK2 mutations do not confer the same features as LFS, and since it could lead to inappropriate management and suboptimal surveillance, their classification as an LFS subtype is generally discouraged.

2.7.5 Limited long-term data

As only a small proportion of LFS patients show long-term adherence to the surveillance protocols, the long-term follow-up data on LFS patients, particularly in relation to the effectiveness of surveillance programs and therapeutic interventions, is limited, negatively affecting the development of clinical evidence-based prevention and treatment guidelines [196]. The impact of intensive screening on patient survival and quality of life over long periods is not fully understood so far, and data on the long-term risks and complications, including the risks of radiation exposure from frequent imaging, are rare.

2.7.6 Cancer surveillance and overdiagnosis

Lifelong cancer surveillance is essential for patients with confirmed pathogenic TP53 mutations. However, striking the right balance between early cancer detection and overdiagnosis still remains a significant challenge [197]. Extensive screening protocols, often including annual whole-body MRIs, can lead to false-positive results or detection of indolent cancers that may never progress to a clinically significant disease. Meanwhile, some patients may not follow the full range of recommended screenings due to a lack of resources or understanding of the significance of TP53 mutations, potentially leading to missed early detection opportunities.

2.7.7 Access to care

Access to genetic testing and specialized cancer care for individuals at risk of or diagnosed with LFS varies widely by region and healthcare system [198]. In some areas, the availability of genetic testing, surveillance, and specialized treatments may be limited, creating disparities in patient outcomes. The cost of genetic testing, preventive surgeries, or frequent cancer screenings can be prohibitive for some families, potentially leaving patients with suboptimal care or late-stage cancer diagnoses. Moreover, not all clinicians are fully aware of LFS or the need for comprehensive genetic testing in patients with a family history of cancers, leading to inadequate care in some cases.

2.7.8 The complexity of multidisciplinary care

The management of LFS requires a multidisciplinary approach, involving geneticists, oncologists, surgeons, radiologists, psychologists, and other specialists. Coordinating care across these domains can be difficult, particularly in healthcare settings without established protocols for hereditary cancer syndromes.

2.7.9 Psychosocial burden

The psychosocial challenges faced by individuals with LFS are significant, as it often affects multiple generations within a family, leading to fear of developing cancer and anxiety about passing the mutation on to offspring [199]. The ongoing stress of living with an increased risk of cancer, along with the emotional toll of frequent surveillance, can be overwhelming for patients and their families.

3 Future directions

Advancements in genomic technologies have facilitated the identification of novel therapeutic agents and the development of targeted therapies for LFS-associated malignancies. Novel cancer therapies, including various cancer immunotherapy modalities, checkpoint inhibitors, adoptive cell therapies, and various agents and methods of targeted therapy, hold promise in improving treatment outcomes and reducing cancer burden in individuals with LFS (Table 5).

Additionally, ongoing research efforts aim to elucidate the molecular mechanisms underlying LFS pathogenesis and identify potential biomarkers for early detection and risk stratification. Longitudinal cohort studies and population-based registries are essential in clarifying the natural history, risk factors of recurrence, and outcomes associated with LFS. Furthermore, molecular epidemiological studies leveraging genomic technologies and bioinformatics analyses offer insights into the genetic determinants, mutational signatures, and clonal evolution patterns underlying LFS-associated tumorigenesis, guiding precision medicine approaches and targeted interventions tailored to the unique molecular profiles of individual tumors.

4 Conclusions

Li-Fraumeni Syndrome poses significant challenges in clinical management due to its diverse spectrum of associated malignancies and the need for lifelong surveillance and interventions. A comprehensive understanding of the molecular basis, clinical manifestations, diagnostic criteria, screening strategies, and management options for LFS is crucial for optimizing patient care and outcomes. Continued research efforts aimed at clarifying the underlying mechanisms, optimum and effective surveillance strategies, and developing targeted therapeutic approaches are essential for improving the prognosis of individuals affected.

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