Surveillance recommendations for patients with germline *TP53* mutations

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Purpose of review
Li–Fraumeni syndrome is associated with germline *TP53* mutations and carriers have a high lifetime risk of cancer, the most common being sarcoma, breast cancer, brain tumors, adrenocortical carcinoma and leukemia. Germline *TP53* mutation carriers are increasingly being identified as more genomic sequencing is performed in both clinical and research settings. There is a pressing clinical need for effective cancer risk management approaches in this group.

Recent findings
Current clinical surveillance guidelines mainly focus on breast and bowel cancer risk with little consideration for the other cancers common to the syndrome. Imaging technologies are such that the utilization of whole-body MRI imaging for surveillance is viable. Globally, several research groups have included whole-body MRI along with other diagnostic measures in formulating surveillance protocols for *TP53* mutation carriers. Early reports suggest a survival benefit.

Summary
Surveillance protocols for *TP53* mutation carriers have the potential to improve outcomes in individuals and families. Further research is needed to guide the development of an effective and comprehensive surveillance schedule.

Keywords
Li–Fraumeni syndrome, *TP53* gene, whole-body MRI

INTRODUCTION

Li–Fraumeni syndrome (LFS) is a familial cancer predisposition syndrome associated with germline *TP53* mutations. Mutation carriers are at a significantly increased risk of several cancer types, the most common being breast cancer, sarcomas, brain tumors, adrenocortical carcinoma (ACC) and leukemias. Traditionally, LFS families have been ascertained through the presence of strong family cancer histories, but as genomic sequencing capacities improve and become less expensive, *TP53* mutation carriers are increasingly being identified in other settings independent of family history. Unlike more common heritable cancers, such as breast and colorectal cancer in which well established organ-specific cancer prevention and early detection strategies exist, in LFS, the risk of multiorgan tumorigenesis cancer risk management presents a considerable challenge.

In the past, there has generally been a somewhat nihilistic attitude toward clinical management of *TP53* mutation carriers, but there is now an increased call for renewed efforts in this area. This is partly driven by the emergence of new screening methods. MRI first became clinically available in the 1980s and is now widely used for surveillance of individuals at risk of hereditary breast cancer. The availability of whole-body imaging protocols and the absence of ionizing radiation renders MRI potentially suitable for long-term surveillance in the radiosensitive *TP53* mutation carrier population. This article covers the current clinical surveillance guidelines for germline *TP53* mutation carriers, outlines previous surveillance studies and

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KEY POINTS

- Germline *TP53* mutation carriers are increasingly being identified through genomic testing.
- *TP53* mutation carriers have a high lifetime cancer risk and comprehensive cancer risk management is a pressing clinical need.
- Globally, several comprehensive surveillance research protocols utilizing WB-MRI are underway.
- Longer-term evaluation of surveillance schedules for *TP53* mutation carriers is needed.

details the research efforts currently underway. Last, a comprehensive surveillance schedule is endorsed, aimed at achieving an international consensus until the time when sufficient data will inform a standard of care for *TP53* mutation carriers.

LI–FRAUMENI SYNDROME AND *TP53*

Li and Fraumeni [1] initially described four families in which the high frequency of cancer suggested a familial syndrome of neoplastic diseases. In 1988, this was expanded to 24 families in which bone and soft tissue sarcomas, breast cancers, brain tumors, leukemia and ACCs were seen in high incidence [2] and this constellation became known as LFS. These and additional studies revealed the syndrome to be an autosomal dominant hereditary cancer predisposition condition [3,4]. The association between the tumor suppressor gene *TP53* and LFS was made in 1990 when LFS families were found to harbor germline *TP53* mutations [5,6]. To date, over 700 *TP53* mutations have been described in the germline of approximately 760 families [7].

After LFS was originally defined [2], the observation of Li–Fraumeni-like families has led to the formulation of alternate criteria. Approximately 70% of families meeting the classic LFS definition have germline *TP53* mutations [8]. The Chompret criteria have evolved over time and aim to identify the most suitable candidates for *TP53* genetic testing [9–11]. Importantly, the criteria take into account individuals with multiple malignancies (which may be due to de-novo mutations) with 21–35% of those meeting the updated criteria shown to be carriers [10,12,13].

CANCER RISK

There is a wide spectrum of *TP53*-associated malignancies observed in LFS families. The most common are premenopausal breast cancer and sarcomas (bone and soft tissue) accounting for approximately 27 [14] and 25% [15] of cancers, respectively. Other characteristic LFS cancers are brain tumors and leukemias [7]. In childhood, the most common cancers are ACC, choroid plexus carcinoma, gliomas and medulloblastoma [16]. An increased incidence of melanoma, lymphoma, pancreatic, lung, prostate and ovarian cancers [7,17] has been recorded with gastric [18] and colorectal cancers [19] and malignant phyllodes breast tumors [20] also possibly associated. Recently, anaplastic rhabdomyosarcoma [15,21] and sonic hedgehog-subtype medulloblastoma [22] have been associated with germline *TP53* mutations.

Cancer risk estimates in *TP53* mutation carriers have largely been based on families ascertained using classic or Chompret criteria that, by definition, require significant family cancer histories. In such settings, 49% of women and 21% of men will develop cancer by the age of 30 years [23], increasing to almost 100% of women and 73% of men over a lifetime [24,25]. There is also an increased risk of second and subsequent cancers [12,26,27]. Sarcoma-affected *TP53* mutation carriers are more likely to have multiple primary cancers than noncarriers [27]. Given the current cure rates in many cancers, there is clearly a need for adequate secondary surveillance in this population.

Genotype–phenotype correlations have been observed in *TP53* mutation carriers. Early age at diagnosis is associated with nonsense, frameshift and splice mutations [17]. Missense mutations in the DNA-binding domain are often in families with breast cancer and brain tumors. The R337H variant that occurs in exon 10 is prevalent among *TP53* mutation carriers in Southern Brazil and is strongly associated with ACC [28]. Choroid plexus carcinomas, leukemia and breast cancers also occur at increased incidence in these families [20,29].

A number of genetic modifiers have been identified in *TP53* mutation carriers that may play a role in cancer susceptibility. These include MDM2 SNP309 [30–32] and *TP53* polymorphisms PIN2, PIN3 and PEX4 [33]. Telomere shortening has been associated with an increasingly earlier age of cancer onset in successive generations of *TP53* mutation carriers [34,35], and DNA copy number variation may play a role in determining phenotype [36].

Individuals and families ascertained via approaches blinded to family history may have a reduced lifetime cancer risk compared with those ascertained on family history [17,27]. Indeed, as more *TP53* mutation carriers are identified, the range of associated phenotypes will continue to expand and contribute to further understanding

the differences in *TP53*-related cancer susceptibility. Cancer risk estimates in *TP53* mutation carriers will be revised over time, and these may need to be calculated and presented in an ascertainment-specific manner.

CURRENT SURVEILLANCE RECOMMENDATIONS

Current clinical guidelines for cancer surveillance in mutant *TP53* carriers focus predominantly on breast and bowel cancer for which surveillance regimes are recognized to be beneficial, albeit evaluated in other settings such as familial breast and familial bowel cancer (Table 1). For *TP53* mutation carriers, the National Comprehensive Cancer Network recommends a surveillance schedule that includes clinical breast examination, breast MRI and mammogram in various age brackets from 20 years of age [37]. An annual comprehensive physical examination, colonoscopy every 2–5 years and additional surveillance based on individual family histories is also recommended [37]. The UK National Institute for Health and Care Excellence recommends annual breast MRI [38]. In Australia, annual physical examination and breast MRI is recommended along with colonoscopy 2–5 yearly dependent on family history [39]. These surveillance recommendations do not take into account other common *TP53*-associated malignancies such as sarcomas and brain tumors, which both depend on effective surgery to achieve the best outcomes.

PREVIOUS SURVEILLANCE STUDIES

There have been few studies investigating a whole-body approach to surveillance in the *TP53* population. Given the rarity of the condition, there are a relatively small number of eligible individuals for such studies and as such randomized, controlled, trial designs are not feasible. An early report utilized F18-fluorodeoxyglucose (FDG)-PET/computed tomography in a whole-body approach to surveillance [40]. Baseline scans detected malignancies in 3/15 (20%) *TP53* mutation carriers. Although the levels of radiation exposure using F18-fluorodeoxyglucose-PET/computed tomography were acknowledged as not ideal in this population, the study nevertheless demonstrated the potential value in a whole-body approach to surveillance [40]. In 2011, Villani *et al.* [41▪] described a comprehensive surveillance study employing whole-body MRI (WB-MRI) in 33 individuals from eight mutant *TP53* families. Of 33 adult and pediatric *TP53* mutation carriers, 18 individuals self-selected for the comprehensive surveillance group with another 16 opting for standard care (one individual was in both the groups at different time points). Over a 3-year interval, 12 high-grade malignancies were observed in the nonsurveillance group compared with 10 tumors (five cancers, three low-grade gliomas, one myelodysplastic syndrome and one thyroid adenoma) in seven individuals in the surveillance group. Overall survival (3 years) was 100% in the surveillance group compared with 21% in the nonsurveillance group [41▪]. Despite some limitations including a small sample

Table 1. Current clinical surveillance recommendations for *TP53* mutation carriers

Organization	Country	
National Comprehensive Cancer Network (NCCN)	USA	Annual complete physical examination (including skin and neurologic examination)
		Breast
		Clinical examination every 6–12 months (age 20–25 years)
		Annual MRI (preferred) or MMG (age 20–29 years)
		Annual MRI and MMG (age 30–75 years)
		Colorectal
		Colonoscopy every 2–5 years (starting age 25 years)
National Institute for Health and Care Excellence (NICE)	United Kingdom	*Breast*
		Annual MRI (age above 20 years)
eviQ	Australia	Annual complete physical examination
		Breast
		Annual MRI (age 20–50 years)
		Colorectal
		Colonoscopy every 2–5 years dependent on family history (age above 25 years)

MMG, mammogram.

size, the inclusion of some retrospective patient data and participant self-selection into the comparator groups introducing a potential source of bias, the study demonstrated the feasibility of a comprehensive surveillance protocol in the *TP53* population. A recent study in Southern Brazil offered neonatal screening for the *TP53* R337H mutation and subsequent surveillance for adrenocortical tumors (ACTs) in mutation carriers [42▪▪]. Of 699 mutation carriers, 347 (49.6%) self-selected for surveillance. The seven ACTs detected in the surveillance group were lesser in weight ($P = 0.003$), lower in volume ($P = 0.007$) and the children undergoing surveillance displayed less virilization compared with the nonsurveillance group (eight ACTs). All surveillance participants ($n = 7$) diagnosed with ACTs remained disease free 31–48 months after diagnosis compared with two out of eight patients that relapsed in the nonsurveillance group and one of these who succumbed to the disease [42▪▪]. Although this study is large, population based and occurred across multiple centers, it applies to the *TP53* R337H mutation only and focuses on ACTs that occur at increased frequency in this population. Extrapolation of the findings to other *TP53* mutation carrying populations is potentially fraught.

CONSIDERATIONS IN SURVEILLANCE OF *TP53* MUTATION CARRIERS

Assessing cancer susceptibility in *TP53* mutation carriers presents challenges. Although *TP53* mutations appear highly penetrant in LFS, as more mutation carriers are identified by family history-independent mechanisms, the *TP53*-associated phenotypes are becoming more varied. This may be due to de-novo mutations, mosaicism, genetic modifiers or variations in *TP53* allele penetrance, and long-term clinical information will be important in determining the effect of these. Limiting radiation exposure also appears important in *TP53* mutation carriers [43], so extended surveillance schedules should exclude radiation exposure as far as practicable. Working toward understanding the factors contributing to *TP53*-associated cancer risk is highly relevant as clinical management strategies aim to become increasingly personalized. At present, there are insufficient data on which to construct a set of clinical guidelines that accounts for a spectrum of *TP53*-associated risk, so any surveillance recommendations are necessarily targeted at the *TP53* core cancers and tailored according to family history.

Children that harbor *TP53* mutations are at significantly increased risk of cancer [24]. This susceptibility at an early age presents many psychological and ethical issues for families and healthcare professionals in terms of genetic testing and surveillance [44,45]. Consideration of all the implications and the provision of cross-disciplinary care are required to achieve effective management.

The psychological impact of participating in a comprehensive surveillance program on *TP53* mutation carriers is unknown. Psychological benefit was reported in LFS individuals that had undergone a range of regular surveillance [46]. In other high cancer risk populations, both positive and negative impacts have been reported [47–49]. It is imperative that the acceptability and psychological impact of surveillance in *TP53* mutation carriers be investigated and understood.

CURRENT SURVEILLANCE RESEARCH PROTOCOLS

Globally, many groups are currently implementing comprehensive surveillance protocols for *TP53* mutation carriers in the clinical research setting. The 'Toronto Protocol' [41▪] as detailed earlier continues to recruit children and adults in Canada and several sites in the United States. In France, the LIFSCREEN project (eligibility 5–70 years of age) is randomizing asymptomatic *TP53* mutation carriers to two arms: current recommended clinical surveillance or current recommended clinical surveillance with the addition of WB-MRI over 2 years, with evaluation of cancer incidence over 3 years being the primary objective [50]. The Magnetic Resonance imaging Screening in Li Fraumeni Syndrome (SIGNIFY) study in the United Kingdom is utilizing WB-MRI to compare cancer incidence in adult *TP53* mutation carriers compared with control patients [51]. In Australia, the Surveillance Study in Multi-Organ Cancer Prone Syndromes (SMOC) study in adult *TP53* mutation carriers has a surveillance schedule including annual WB-MRI, physical examination, fecal occult blood test, colonoscopy, breast MRI and full blood evaluation [52]. A comprehensive project investigating many aspects of LFS including development of a cancer surveillance program is being led by the National Institutes of Health Clinical Center in the United States [53]. A Li–Fraumeni WB-MRI study for children and adults is running out of the Dana-Farber Cancer Institute [54] and a Brazilian study based on the Toronto Protocol is also underway. A number of these studies are investigating the psychological impacts of undergoing comprehensive surveillance.

PROPOSED COMPREHENSIVE SURVEILLANCE SCHEDULE

There is currently no level 1 evidence [55,56] on surveillance methods and their efficacy in *TP53* mutation carriers. Principles to inform the

Table 2. Proposed surveillance schedule for *TP53* mutation carriers

Cancer	Starting age	Surveillance method	Frequency
ACC	Birth – 10 years	Abdominal ultrasonography	3–4 monthly
Breast	18 years	Breast self-examination	
	20–25 years	Clinical breast examination	6–12 monthly
	20–25 years until 50 years	Breast MRI	Annually
Brain	Potentially childhood	WB-MRI	Annually
Sarcoma	Potentially childhood	WB-MRI	Annually
Leukemia	18 years	Full blood evaluation	Annually
Colorectal	25 years (earlier if indicated by family history)	Colonoscopy	2–5 yearly
		Fecal occult blood test	Intervening years
Gastric	25 years (earlier if indicated by family history)	Endoscopy	2–5 yearly

ACC, adrenocortical carcinoma; WB-MRI, whole-body MRI.

development of surveillance schedules are well established [57,58] and appear consistent with surveillance for most *TP53*-associated malignancies. An evidence-based surveillance schedule has been proposed previously that aims at providing a template for international consensus whereas research efforts into the many facets of participating in a comprehensive surveillance protocol for *TP53* mutation carriers are ongoing [59▪]. The proposed schedule (Table 2) includes annual physical examination, WB-MRI including brain, additional breast MRI and clinical breast examination for females, fecal occult blood test, full blood evaluation, abdominal ultrasound, blood hormone levels (optional) and additional investigations deemed clinically appropriate that may include colonoscopy and upper gastrointestinal endoscopy.

The use of WB-MRI as part of a comprehensive surveillance strategy for *TP53* mutation carriers is attractive for a number of reasons including the lack of ionizing radiation, the ability to scan the entire body and the sensitivity of the technique to many of the LFS cancers, especially sarcomas. However, the need for further investigations in this group that has a concerning a-priori cancer risk, and therefore arouses a high level of clinical suspicion, is something that must be managed cautiously, particularly if invasive further investigations are being contemplated. These issues are being addressed specifically in the SIGNIFY and SMOC research protocols detailed previously.

CONCLUSION

Comprehensive surveillance in *TP53* mutation carriers may improve clinical outcomes. Research into some aspects of surveillance is underway but further work is needed to evaluate surveillance schedules in this cancer-prone population more fully. Owing to the small number of mutant *TP53* carriers, unified efforts across multiple centers will most likely be necessary to investigate all aspects of surveillance satisfactorily. In the meantime, a consistent approach to surveillance in *TP53* mutation carriers may provide further insights while more detailed studies are underway.

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Conflicts of interest

There are no conflicts of interest.

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The nature of the research and the rarity of the condition mean that studies run over a number of years.

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