Li-Fraumeni syndrome: cancer risk assessment and clinical management

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Abstract | Carriers of germline mutations in the *TP53* gene, encoding the cell-cycle regulator and tumour suppressor p53, have a markedly increased risk of cancer-related morbidity and mortality during both childhood and adulthood, and thus require appropriate and effective cancer risk management. However, the predisposition of such patients to multiorgan tumorigenesis presents a specific challenge for cancer risk management programmes. Herein, we review the clinical implications of germline mutations in *TP53* and the evidence for cancer screening and prevention strategies in individuals carrying such mutations, as well as examining the potential psychosocial implications of lifelong management for a ubiquitous cancer risk. In addition, we propose an evidence-based framework for the clinical management of *TP53* mutation carriers and provide a platform for addressing the management of other cancer predisposition syndromes that can affect multiple organs.

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Introduction

Germline mutations associated with hereditary cancer predisposition syndromes are being identified in a rapidly increasing number of children and adults. This phenomenon is a consequence of increased acceptability of clinical testing for germline mutations as part of cancer risk assessment and management strategies, and the accelerating search for 'druggable targets' through screening of cancer genomes, fuelled by the rapid developments in genomic technologies. Although well-established risk management strategies are in place for common heritable cancers, such as breast, ovarian, colorectal and endometrial cancers,[1,2] managing individuals carrying mutations that are associated with an increased risk of a broad range of cancers over their lifetime is a major clinical problem. Germline mutations in the *TP53* gene, which encodes the tumour suppressor p53, comprise just one of many cancer predisposition syndromes that can affect a range of organs, which collectively pose a considerable challenge to effective cancer risk management in the era of genomic medicine.

Germline *TP53* mutations result in a rare hereditary condition known as Li-Fraumeni syndrome (LFS). LFS is characterized clinically by the development of cancers arising in multiple organ systems, often at a young age.[3–10] In addition, Li-Fraumeni-like (LFL) syndrome is similar to LFS, but defined by less stringent classification criteria (Box 1), and consequently families with LFL syndrome have a lower prevalence of *TP53* mutations; a *TP53* mutation can be identified in 70% of LFS families but only 20–40% of LFL syndrome families.[11] Around 50% of the individuals carrying mutations in *TP53* will develop cancer by the age of 30 years,[12–14] with a lifetime risk of up to 70% in men and almost 100% in women.[15] Owing to this high risk of cancer as well as the substantial associated morbidity and mortality, a compelling need exists for enhanced clinical recognition of these syndromes, with referral of patients identified to appropriate multidisciplinary teams for ongoing management, including genetic counselling, genetic testing, tumour surveillance, cancer risk management and appropriate cancer care. Moreover, unlike other cancer predisposition syndromes, such as familial adenomatous polyposis or hereditary breast and/or ovarian cancer syndrome associated with *BRCA* mutations, effective risk management approaches in carriers of *TP53* mutations remain to be established, particularly in children.[16]

Safe, acceptable and effective risk management strategies are needed to reduce the morbidity and mortality associated with any inherited genetic factor that predisposes to cancer. The first step in developing an effective cancer risk management programme is defining the magnitude of the cancer risk in carriers of specific mutations. Ideally, cancer risk should be ascertained primarily according to genotype, rather than through the family history criteria traditionally used to identify patients with mutations predisposing to cancer. The second step is establishing a robust evidence base in support of the proposed risk management strategies—that is, whether the approaches actually reduce cancer incidence, morbidity and/or mortality.

Germline *TP53* mutations illustrate the difficulties encountered in estimating risk of cancers associated with rare syndromes and in balancing the benefits versus the burdens of the cancer risk management strategies required for a cancer predisposition syndrome with the potential

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Key points

- Inherited cancer predisposition syndromes are increasingly diagnosed due to greater public awareness of germline genetic testing, and also as an incidental finding when somatic mutation testing for 'druggable targets'
- Some inherited cancer syndromes predispose to cancers at multiple sites, such as Li-Fraumeni syndrome (LFS) caused by germline *TP53* mutations, requiring a whole-body approach to cancer risk management
- The 5-year, 10-year and lifetime cancer risk of many the LFS-associated cancers remains unclear and further study is required to provide such data, which can guide cancer risk management
- At present, a limited number of validated screening tests for LFS-associated cancers exist, and no validated screening tests have been studied specifically in people with LFS
- Prospective trials studying the utility and the psychosocial effects of a whole-body approach to screening in LFS are in progress
- A pragmatic schedule for a whole-body approach to screening is proposed while the results of the prospective trials are awaited

Box 1 | LFS diagnosis and genetic testing criteria

Classic LFS criteria[3]

- Proband diagnosed with sarcoma before 45 years of age AND a first-degree relative with a cancer diagnosed at age <45 years, AND a first-degree or second-degree relative with any cancer with onset at age <45 years or a sarcoma at any age

Birch LFL syndrome criteria[4]

- Proband with any childhood cancer, or a sarcoma, brain tumour or ACC with onset at <45 years of age AND a first-degree or second-degree relative with a core LFS cancer (sarcoma, breast cancer, brain tumour, ACC or leukaemia) with onset at any age, AND a first-degree or second-degree relative with any cancer with onset before the age of 60 years

Eeles LFL syndrome criteria[19]

- Two first-degree or second-degree relatives with core LFS malignancies (sarcoma, premenopausal breast cancer, brain tumour, ACC, leukaemia or lung [bronchoalveolar] cancer) at any age

2009 Chompret criteria for *TP53* testing[20,21]

- A proband with a single core LFS tumour (sarcoma, premenopausal breast cancer, brain tumour, ACC, leukaemia or lung [bronchoalveolar] cancer) diagnosed at age <46 years AND at least one first-degree or second-degree relative with a core LFS tumour (except breast cancer if the proband has breast cancer) with onset at age <56 years or with multiple tumours
- OR a proband with multiple tumours (except multiple breast cancers), two of which are LFS core tumours, with the first occurring at age <46 years
- OR a proband diagnosed with an ACC or choroid plexus carcinoma, irrespective of family history

Abbreviations: ACC, adrenocortical carcinoma; LFL, Li-Fraumeni-like; LFS, Li-Fraumeni syndrome.

for broad-ranging organ involvement. Management strategies, falling broadly into cancer prevention and early detection (surveillance) approaches, impose physical, psychosocial and financial burdens on the screened population. Implementing a cancer risk management programme and balancing the effectiveness, costs and harms involved in screening an increasing population of individuals and their families requires cross-disciplinary clinical care and research, bringing together investigators with clinical, genetic and public-health expertise. Multidisciplinary involvement is of particular importance in managing patients with predisposition to cancers in multiple organs. Furthermore, the difference between cancer screening in children and adults should also be considered, as the tumour burden in *TP53* mutation carriers aged <20 years is considerable. Importantly, the emotional burden of surveillance on children might be equal or even greater than that placed on adults exposed to such life-altering intervention. Indeed, at the behest of parents, regular ongoing screening has the potential to make a 'well child' a 'sick child', with disruption associated with risk management having the potential to reduce the child's quality of life and increase their anxiety exponentially. Thus, careful consideration of the emotional, medical and financial burdens of long-term surveillance is required, particularly in children.

This Review presents the multitude and magnitude of paediatric and adult cancers associated with germline *TP53* mutations, and evaluates the evidence supporting approaches to the management in this high-risk population in the context of the natural history of the these malignancies. The psychosocial implications of intensive screening and prevention strategies on carriers of inherited *TP53* mutations are also discussed, and a pragmatic cancer risk management strategy for such individuals is proposed.

Germline *TP53* mutations and cancer risk

Ascertainment strategy and cancer risk

The risk of cancer associated with *TP53* mutations can vary substantially depending on the methodology used to identify the studied population. For example, lifetime cancer risk is generally reported to be higher in carriers of *TP53* mutations with a family history of malignancy characteristic of classical LFS or LFL syndrome (Box 1), compared with individuals who are identified using a tumour-based ascertainment strategy agnostic to family history.[17,18] Of note, unlike the earlier LFS–LFL syndrome classification criteria based on clinical patterns,[3,4,19] the Chompret criteria for selection of individuals for *TP53* testing enable identification of individuals at high risk of carrying a germline mutation in *TP53* independent of family history (Box 1).[20,21]

Recognition of the differences in *TP53*-related cancer susceptibility is increasingly important in the current era, owing to the increasing use of genetic screening for druggable targets that can inadvertently uncover germline mutations. At present, most of the published information regarding cancer risk that is used to guide the clinical management of *TP53* mutation carriers is derived from classic LFS or LFL syndrome families; however, nonclassic phenotypes associated with mutations in this gene will probably have variable aetiology, perhaps owing to modifier alleles, mosaicism, *de novo* mutations or less penetrant mutant *TP53* alleles.[18] These differences are likely to be clinically relevant, and therefore risk estimates derived from classic phenotype families cannot simply be extrapolated to populations ascertained through alternative strategies.

Cancer incidence in *TP53* mutation carriers

Germline *TP53* mutations seem to be highly penetrant in the setting of classic LFS; *TP53*-associated cancer eventually develops in 73% of men and almost 100% of women who carry such mutations, with the higher penetrance in the latter predominantly attributable to

Table 1 | Reported spectrum and frequency of tumours associated with germline *TP53* mutations, and screening availability

Tumour type	Number of tumours reported (% of total tumours)						Known benefit of screening	Benefit of early detection	Proven prevention/ prophylaxis
	Birch *et al.** 2001[32]	Olivier *et al.*‡ 2003[17]	Nichol *et al.*§ 2000[31]	Gonzalez *et al.*‖ 2009[33]	Ruijs *et al.*¶ 2010[8]	IARC# 2013[25]			
Breast	38 (25.7)	151 (30.6)	189 (25.6)	44 (32.6)	28 (26.4)	413 (27.8)	Yes[79,81]	Yes[65,109,110]	Mastectomy/SERM/ oophorectomy[16,111]
Soft-tissue sarcoma	19 (12.8)	88 (17.8)	124 (16.8)	38 (28.1)	14 (13.2)	205 (13.8)	ND	Yes[66,67]	ND
Brain	14 (9.5)	69 (14.0)	115 (15.6)	13 (9.6)	13 (12.3)	192 (12.9)	ND	Yes[70–72]	ND
Osteosarcoma	10 (6.8)	66 (13.4)	89 (12.1)	1 (0.7)	9 (9.5)	129 (8.6)	ND	Yes[112,113]	ND
Adrenocortical	7 (4.7)	32 (6.5)	32 (4.3)	14 (10.3)	2 (1.9)	162 (10.7)	ND	Yes[75,114]	ND
Bladder	1 (0.7)	NA**	3 (0.4)	0	1 (0.9)	1 (0.07)	ND	Yes[115]	None
Colorectal‡‡	3 (2.0)	8 (1.6)	19 (2.6)	4 (3.0)	6 (5.6)	43 (2.9)	Yes[85,86]	Yes[116]	Colectomy/polypectomy NSAIDs[117,118]
Gastric§§	7 (4.7)	12 (2.4)	23‖‖ (3.1)	NA**	3 (2.8)	19 (1.3)	Yes[88]	Yes[30,119]	ND
Haematological	10 (6.8)	15 (3.0)	35 (4.7)	6 (4.4)	3 (2.8)	56 (3.8)	ND	ND	ND
Kidney/Wilms	7 (4.7)	0	3 (0.4)	0	3 (2.8)	16 (1.1)	ND	Yes[120,121]	ND
Liver	0	NA**	2 (0.3)	NA**	2 (1.9)	4 (0.3)	ND	Yes[122,123]	ND
Lung	10 (6.8)	17 (3.4)	29 (3.9)	4 (3.0)	6 (5.7)	34 (2.3)	Yes[124]	Yes[125]	ND
Malignant phyllodes	2 (1.4)	NA**	0	2 (1.5)	0	NS#	ND	Yes[126,127]	Mastectomy¶¶
Melanoma	2 (1.4)	6 (1.2)	6 (0.8)	1 (0.7)	1 (0.9)	40 (2.9)	Yes[128,129]	Yes[130,131]	ND
Oesophagus	3 (2.0)	0	3 (0.4)	NA**	0	NS#	ND	ND	ND
Ovary	1 (0.7)	7 (1.4)	16 (2.2)	4 (3.0)	1 (0.9)	26 (1.8)	No[132]	ND	Oophorectomy[111,133]
Pancreas	6 (4.1)	NA**	3 (0.4)	1 (0.7)	4 (3.8)	NS#	Yes[134]	Yes[135]	ND
Prostate	1 (0.7)	NA**	7 (0.9)	1 (0.7)	1 (0.9)	4 (0.3)	Yes[136,137]	ND	ND
Testis	1 (0.7)	0	1 (0.1)	NA**	0	7 (0.5)	ND	ND	ND
Thyroid	0	NA**	5 (0.7)	2 (1.5)	0	NS#	ND	ND	ND
Other	6 (4.1)	23 (4.7)	34 (4.6)	NA**	9 (8.5)	129 (8.7)	NA	NA	NA
Total	148	494	738	135	106	1,485	NA	NA	NA

**n* = 501 individuals (age range 0–74 years) from 28 UK families; other cancers include cervix (2), bladder (1) and peripheral nerve system (2), oral cancer (1) and mesothelioma (1). ‡Cancers in 491 carriers of germline *TP53* mutations among LFS and/or LFL syndrome families. §*n* = 185 individuals, comprising combined data from 45 DF–NCI families and 140 additional at-risk kindred identified in a literature search; other cancers include those of the cervix (4), neuroblastoma (2), unknown primary cancers (2), mesothelioma (2) and 21 other neoplasms, including those in gall bladder, ampulla of Vater and urethra. ‖Cancers in 82 patients with *TP53* mutations; not specified (other) cancers include those of the adrenal gland, liver, cervix, oesophagus, stomach, abdomen, heart, testis, thymus and nonmelanoma skin cancer. ¶*n* = 52 individuals, from 24 *TP53*-mutation-positive families in Holland, including carriers and first-degree at-risk relatives; other cancers include those of the cervix (1), bladder (1) and unspecified parts of nervous system (1), unknown primary cancers (6), and mesothelioma (1). #Data compiled in IARC database version R17, November 2013; 'other' tumours were not specified. **Included in 'others' by original study. ‡‡Wong *et al.*[29] found that 12.5% of eight *TP53*-mutation-positive families had CRC age <50 years. §§Masciari *et al.*[30] found gastric cancers in the lineages of 4.9% subjects from 14 *TP53*-mutation-positive families. ‖‖Includes nine Japanese patients. ¶¶No clinical data available but in theory would prevent development of phyllodes. Abbreviations: CRC, colorectal cancer; DF–NCI, Dana-Farber–National Cancer Institute; LFL, Li-Fraumeni-like; LFS, Li-Fraumeni syndrome; NA, not applicable; ND, not determined; NS, not specified; NSAIDs, nonsteroidal anti-inflammatory drugs; SERM, selective oestrogen receptor modulators.

breast cancer.[5,15,22,23] The risk of cancer imparted by *TP53* mutations is evident at an early age, with women in LFS families who carry such mutations having a cumulative 49% risk of developing cancer by the age of 30, whereas men with *TP53* mutations have a 21% cancer risk at the same age.[12]

A wide spectrum of *TP53*-related cancers is observed in the setting of LFS or LFL syndrome (Table 1). Breast cancer and sarcomas (bone and soft-tissue sarcoma), are the most common cancers reported in these conditions, with sarcoma representing around 25% of all *TP53*-related cancers[24] and breast cancer accounting for approximately 27%.[25,26] In addition to the other core cancers associated with germline *TP53* mutations, which include brain tumours, adrenocortical carcinoma (ACC) and leukaemia,[25] the incidence of lymphoma, melanoma, lung, pancreas, prostate and ovarian cancers also seems to be increased in carriers of *TP53* mutations.[6,17,25] In *TP53* mutation carriers, the most common paediatric-onset tumours are choroid plexus carcinoma, gliomas and medulloblastoma.[27,28] Childhood-onset rhabdomyosarcoma is also associated with germline *TP53* mutations.[24] In addition, gastric and colorectal cancers can occur in *TP53* mutation carriers from an early age, although whether tumours in these organs occur more frequently, as well as prematurely, in such individuals compared with in the general population remains unclear (Table 1).[8,17,29–32] Likewise, kidney, testicular, laryngeal, and head and neck cancers might be more frequent in *TP53* mutation carriers than the wider population;[8,25,31–33] however, whether these tumour types arise sporadically in LFS and/or LFL syndrome families or are truly part of the germline *TP53* tumour risk spectrum is not clear at present, largely because, to date, limited segregation of mutations and/or tumour testing has been performed to demonstrate causality.

Table 2 | Tumour-specific cancer risks in relation to germline *TP53* mutations

Tumour type	Observed	Expected	RR (95% CI)	*P* value
Ruijs et al. (2010)[8]*				
Breast	28	4.4	6.4 (4.3–9.3)	0.000
Soft-tissue sarcoma	14	0.23	61 (33–102)	0.000
Brain	13	0.37	35 (19–60)	0.000
Osteosarcoma	9	0.08	107 (49–203)	0.000
Adrenocortical	2	ND‡	ND	ND
Colorectal	6	2.2	2.8 (1–6)	0.049
Liver	2	0.1	18 (2.1–64)	0.017
Pancreas	4	0.54	7.3 (2–19)	0.006
Birch et al. (2001)[32]§				
Breast	38	2.46	ND	0.0126
Soft-tissue sarcoma	19	0.27	ND	<0.0001
Brain	14	0.64	ND	0.009
Osteosarcoma	10	0.05	ND	<0.0001
Adrenocortical	7	0.009	ND	<0.0001
Wilms	4	0.034	ND	0.0005
Malignant phyllodes	2	0.002	ND	0.0003
Garber et al. (1991)[5]‖				
Sarcomas	3	0.22	13.4¶	ND
Breast	15	3.37	4.5¶	ND
CNS	5	0.43	11.5¶	ND
Leukaemia	4	0.67	6.0¶	ND
Adrenocortical	1	0.02	45.5¶	ND
Other tumours	24	19.81	1.2 (0.8–1.8)	ND

*Analysis of 24 *TP53*-mutation-positive families; the expected number of cases was calculated by multiplying person years at risk by the age, gender, calendar period and site-specific cancer incidence rates in the Dutch general population in the Netherlands, and RR was determined using the SIR relative to the risk in the general population. ‡No data available on expected population rate. §Analysis of 28 LFS families; expected number of cancers calculated based on national cancer statistics for England and Wales. ‖Analysis of 24 LFS kindred; RR was calculated using numbers of cancers expected based on gender, age and cancer prevalence rates in the Connecticut Tumor Registry for the specific year analysed. ¶95% CI does not include 1; *P*<0.005. Abbreviations: CI, confidence interval; CNS, central nervous system; LFS, Li-Fraumeni syndrome; ND, not disclosed; RR, relative risk; SIR, standardized incidence ratio.

Individuals with a germline *TP53* mutation are also at increased risk of second and subsequent malignancies, and the probability of additional cancers is inversely correlated with younger age at diagnosis of the first malignancy.[34,35] In 525 consecutive patients from a clinical cohort undergoing diagnostic assessments including germline *TP53* testing, half of the identified carriers had two or more primary cancers, compared with 32% in patients without *TP53* mutations.[33] Furthermore, the average age of onset of first malignancy was 21.9 years in the *TP53* mutation carriers, compared with 31.6 years in those without mutations in this gene.[33] Similarly, a prospective cohort of 559 sarcoma probands found that 47% of the carriers of *TP53* mutations had multiple cancers, versus only 15% in the patients without such mutations.[18] This risk of second and subsequent malignancies, in addition to the often early age at onset of malignancies, suggest that increased recognition of *TP53*-related syndromes should result in more-appropriate surveillance and treatment, and therefore more-effective management of the ongoing cancer risk in these patient populations. A practical difficulty faced in attempting to use the currently available data on the cancer risks associated with *TP53* mutations in clinical practice, however, is the form in which these risks are reported. The likelihood of developing cancer is expressed predominantly in terms of lifetime risk, relative risk or 'percentage of people at risk' (Table 2), whereas the annual or 5-year probabilities of cancer development would be more informative in planning approaches to cancer risk management.

Factors influencing cancer risk in LFS

Gene–environment interactions could affect the susceptibility of an individual carrying a *TP53* mutation to the development of cancer. In this regard, the effect of ionizing radiation (diagnostic or therapeutic) in the setting of the fundamental DNA repair defect that can result from mutations in *TP53,* is a major concern. Indeed, a tendency for new primary cancers to occur in regions of the body previously exposed to radiotherapy has been reported.[36–40] Supporting a causative association between exposure to ionizing radiation and development of cancer in individuals with *TP53* mutations, a single 4 Gy dose of radiation is associated with a marked reduction in latency of tumour development in $Tp53^{+/-}$ mice;[41] the median age of tumour development in the irradiated *Tp53* heterozygotes was 40 weeks compared with >70 weeks in the nonirradiated control $Tp53^{+/-}$ mice.[41] However, no reports have clearly defined the extent of cancer risk in patients with *TP53* mutations after radiotherapy. Such data are much needed for optimization of cancer screening and therapeutic decision making, in particular, when considering the balance between the potential benefits and harms of the range of management options available.

Evidence also implicates cigarette smoking in increasing the risk of lung cancer in *TP53* mutation carriers. Indeed, one study found that mutation carriers who smoked had 3.16 times (95% CI 1.48–6.78) the risk of lung cancer compared with the carriers of *TP53* variants who did not smoke.[42] Further efforts are needed to clearly define the factors influencing the risk of cancer in *TP53* mutation carriers, and to enable the development of more-effective screening and prevention strategies.

The clinical relevance of *TP53* variants

Screening for *TP53* mutations is moving away from the familial cancer clinic setting, under the influence of increased accessibility to molecular testing either in the context of research programmes or somatic mutation testing of clinical samples. This approach is likely to raise new challenges, but should also create opportunities to improve our understanding and management of *TP53*-related cancer. For example, the detection rate of *de novo* mutations, as well as unsuspected familial mutations, will increase; correspondingly, a greater burden will be placed on health-care providers due to increased demand for screening, risk management and personalized cancer treatment, in the context of the current lack of knowledge regarding the benefits of these efforts. Familial cancer clinics are naturally enriched in families with classical pedigrees, in which vertical transmission is the norm, whereas *de novo* mutations will, by definition, be present

in individuals without a prior family history of susceptibility to cancer. As noted above, the Chompret criteria for *TP53* mutation testing (Box 1) recognize the important implications of *de novo* mutations by placing increased emphasis on early age of cancer onset and the presence of multiple primary cancers in detecting probands with *TP53* mutations. Moreover, that dichotomisation of individuals into those 'with' or 'without' a *TP53* mutation is clearly artificial is becoming increasingly obvious; mutations can confer a spectrum of consequences on gene function, varying from complete loss of function, through hypomorphism, to neutral and even gain-of-function polymorphisms.[43] Thus, further analysis of the range of *TP53* mutations and their individual associations with disease could improve understanding of the natural history of *TP53*-related cancer and enable better patient stratification, and therefore management of cancer risk.

Indeed, a fundamental boundary lying between biology and the need for clinical 'action' is that the decision to provide a clinical intervention is inherently dichotomous, whereas biology is a continuum. At present, a sufficiently nuanced set of management guidelines that accounts for the continuum of risk associated with genetic variation is not available. The need for quantitative characterization of the consequences of mutations is already recognized by consortia investigating the DNA mismatch repair genes involved in hereditary gastrointestinal tumours (InSiGHT)[44] and tumour suppressor genes related to familial forms of breast cancer (ENIGMA),[45] who are devoting considerable effort to defining the effects of genetic changes in relevant genes and refining guidelines for clinical practice. Clearly, reliance upon pedigree patterns is no longer sufficient to define the likely pathogenicity of genetic variants. On the other hand, progress in identification of genetic variation has surpassed our capacity for functional characterization of these variants, which remains a laborious and time-consuming task.

In fact, studies aimed at assigning pathogenicity to *TP53* variants have several important advantages over those attempting to determine the roles of DNA mismatch repair genes and the tumour suppressor genes *BRCA1* and *BRCA2*. First, a systematic screen of the *TP53* gene has been conducted in a yeast transcriptional assay system, in which every amino acid of the canonical transcript has been substituted with almost all possible residues.[46] This screen has provided an empirical database that can be used to guide clinical decision-making based on probable effects of *TP53* mutations. Second, a large catalogue of somatic cancer-related mutations in *TP53* is available across various databases, such as COSMIC,[47] which provides orthogonal evidence for pathogenicity. Third, somatically acquired mutations in the *BRCA* and mismatch repair genes are less common than mutations in *TP53*,[48,49] thus limiting the available evidence pertaining to the functional implication of each mutation. Finally, relatively simple biological assays applicable to functional studies of *TP53* are available.[50] In the future, efforts using these and other resources should be undertaken to assign clinical pathogenicity to individual variants in *TP53*, similar to the ongoing studies by the ENIGMA and InSiGHT consortia.[44,45]

Genetic modifiers and *TP53*

The variability in age at cancer onset and tumour type associated with germline *TP53* mutations implies that additional genetic factors influence the tumour spectrum and clinical severity. To date, a number of genetic modifiers have been identified as having possible roles in determining the age of onset of cancer as well as the occurrence of multiple malignancies in carriers of germline *TP53* mutations. Further recognition of such genetic modifiers might facilitate individualized evaluations of cancer risk and, as a consequence, could help to define appropriate surveillance and management strategies for use in individuals and families with *TP53* mutations.

The influence of *MDM2* polymorphisms

In the past decade, the presence of the T>G variant of single nucleotide polymorphism (SNP) 309 in the *MDM2* gene, particularly together with the *TP53* polymorphisms that result in the production of Arg72Pro variant of p53, has been associated with a younger age at cancer diagnosis among carriers of germline *TP53* mutations.[51–55] For example, in a study of 61 French *TP53* mutation carriers, the mean age of cancer onset in individuals carrying the *MDM2* SNP309 G allele was significantly lower than in the carriers homozygous for the T allele (19.6 years versus 29.9 years; $P<0.05$).[53] Similar findings were reported in a cohort of 213 carriers of germline mutations in *TP53*, with the effects of the *MDM2* SNP309 G allele found to be more pronounced in women.[54] Individuals expressing an arginine allele of the p53 codon 72 polymorphism (*TP53* PEX4; rs1042522) also developed tumours earlier compared with carriers homozygous for the allele encoding proline at this position.[53,56] Furthermore, a cumulative effect of both polymorphisms was observed, with the carriers of both a *MDM2* SNP309 G allele and a p53 Arg72 encoding allele having a mean age at cancer onset of 16.9 years compared with 43 years in those homozygous for both the *MDM2* SNP309 T allele and the Pro72 p53 variant.[53,56] This finding is suggestive of an interaction between the *MDM2* SNP309 G allele and the *TP53* allele encoding p53 Arg72. Whether the accelerated tumour formation due to the SNP309 G allele is specific to *TP53* mutation carriers remains unclear.[57]

Modifier effects of *TP53* polymorphisms

Other polymorphisms within *TP53* can modify the penetrance of germline mutations in *TP53,* including a 16bp duplication in intron 3 (PIN3; rs17878362) and a SNP at codon 72 (PEX4). The *TP53* PIN3 variant has been shown to be particularly important in determining the cancer risk in Brazilian carriers of the Arg337His (R337H) *TP53* mutation, with cancer onset observed on average 19 years earlier in individuals homozygous for the nonduplicated A1 allele compared with those with the A1A2 PIN3 genotype, who were heterozygous for the A2 allele containing the 16bp duplication (aged 28 years versus 47 years).[56] Although *TP53* PEX4 was associated with an earlier age of cancer onset in the previously described French cohort comprising carriers of germline *TP53* mutations (12.6 years),[53] the study of Brazilian patients with LFS only

reported a small, statistically insignificant modifier effect of *TP53* PEX4 on age at cancer onset; the difference in the mean age at onset of only 8.3 years in the Brazilian population studied (30.5 years in those expressing Arg72 p53 versus 38.8 years in individuals homozygous for the Pro72-encoding allele).[56] Thus, studies aimed at confirming the effects of these alleles on the risk of cancer will be important.

The potential role of telomere shortening

A trend towards earlier age at cancer onset in subsequent generations of families harbouring a germline *TP53* mutation suggests that 'genetic anticipation' might also influence cancer susceptibility in this population.[58] Anticipation is an observed phenomenon in which a genetic disorder presents at a progressively earlier age in each subsequent generation. Whether anticipation is a real phenomenon in LFS or whether this observation is a spurious consequence of the methods used to ascertain LFS families remains unclear. Progressive telomere shortening has been implicated as a mechanism underlying this putative phenomenon in LFS families.[59,60] For instance, Tabori *et al.*[60] found that telomere lengths were shorter in *TP53* mutation carriers with cancer than in mutation carriers without cancer and individuals with wild-type *TP53*. Furthermore, telomere attrition was more extensive in carriers with childhood-onset cancer than carriers with adult-onset disease.[60] These findings are consistent with those of another study,[59] which reported telomere length in carriers of *TP53* mutations with cancer was considerably shorter that those observed in healthy noncarriers, with a tendency for shorter telomere lengths in *TP53* mutation carriers affected during childhood compared with those in patients with adult-onset cancer.

TP53 copy number variation

Copy number variation has also been suggested as an underlying mechanism influencing the phenotype of carriers of germline *TP53* mutations. In one study,[61] 75% of the general population had four or fewer copy number variations per genome (mean of 2.93), whereas *TP53* mutation carriers demonstrated a marked increase in copy number variation, with a mean of 12.19 copy number variations per genome. Furthermore, the children of *TP53* mutation carriers were considerably more likely to have more copy number variations than those observed in their parent with mutant *TP53*.[61] A dose–response relationship between the frequency of copy number variation and the severity of the LFS phenotype was also suggested, as individuals affected by cancer were found to have a greater number of copy number variations than those without cancer, though this failed to reach statistical significance.[61]

TP53 mutations and chromothripsis

Chromothripsis, characterized by large chromosome rearrangements that seem to be the result of a catastrophic event during cancer development, might also be a phenomenon linked to mutations in *TP53*.[62,63] Genome sequencing of paediatric medulloblastoma specimens linked chromothripsis with *TP53* mutations in tumours associated with mutations in the Hedgehog pathway.[63] These findings imply that *TP53* can interact with the Hedgehog pathway to determine the patterns of genomic rearrangement in this rare cancer type. However, further studies are required to investigate the relationships between *TP53* mutations, Hedgehog signalling, chromothripsis and cancer.

Screening in *TP53* mutation carriers

A number of *TP53*-associated cancers have a natural history that includes an early presymptomatic phase that is potentially amenable to early detection, which could improve the outcome of therapy, including disease-specific survival. In particular, validated screening tests are known to reduce mortality associated with breast and colorectal cancer,[64,65] although the performance of these screening strategies has not been examined specifically in the populations of *TP53* mutation carriers. Improved outcomes with earlier presentation have also been shown for other cancers commonly observed in patients with LFS (Table 1). For example, the prognosis of many sarcoma subtypes is improved when surgical margins are clear,[66,67] with tumour size also identified as a predictor of local recurrence,[62,64] which has led to the, as yet untested, hypothesis that early detection of sarcoma would improve overall outcome. By contrast, no proven benefit of early detection of leukaemia has been reported, probably reflecting the rapid onset of symptoms after the results of blood film analyses become diagnostic. In addition, the clinical implications of detecting asymptomatic primary brain tumours is not clear,[65] although achieving gross total resection, which is presumably more likely in the earlier stages of disease but remains unproven, does confer a survival benefit in glioma,[66,67] medulloblastoma[68] and choroid plexus carcinoma.[69,70]

Improved survival in patients with ACC was reported after early detection of the disease, with the extent of resection and tumour size reported to have prognostic value in several studies.[75–77] Of particular interest, a Brazilian study has assessed the efficacy of an ACC surveillance strategy among children found to have a *TP53* mutation through a programme of genetic screening in newborns.[78] This study, published in 2013,[78] found that ACCs detected via the surveillance programme, which comprised periodic clinical, laboratory and ultrasonography assessment, had lower weights ($P = 0.003$) and volumes ($P = 0.007$) compared with those detected among the nonsurveillance group. Furthermore, overall tumour stage was lower and the children displayed less virilization (that is, development of male characteristics due to excessive hormone production) in the screening cohort compared with the nonsurveillance group, although these differences were not statistically significant, a result that might be confounded by the small numbers of cases reported. In addition, patients in the surveillance group were generally disease free 31–48 months after diagnosis, despite the used of less-intensive therapy reported in these individuals, compared with poorer outcomes in the nonsurveillance group that included relapse (two of eight patients relapsed 5–70 months post diagnosis compared with none in the

screened group) and death (one of eight individuals died compared with none in the screened group).[78] Of note, this study[78] included a high proportion of individuals with the unique Arg337His (R337H) founder mutation, which is present at increased rates and, furthermore, is associated with paediatric ACC in the Brazilian population.[78] Indeed, the study did not address the need for continued surveillance for other tumours that can occur in *TP53* mutation carriers. Moreover, data from one-off screening studies, such as this Brazilian study,[78] should be extrapolated to other populations with caution, given that surveillance should be both long-term and cover all tumours that occur in carriers of germline *TP53* mutations.

Methodological approaches to screening

At present, the effectiveness of cancer screening tests specifically in *TP53* mutation carriers is unclear. Furthermore, owing to the low prevalence of such mutations, performing randomized controlled trials of cancer screening in this population will be difficult, if not practically and ethically impossible, particularly among children. Data on the probable utility of screening programmes are, therefore, extrapolated from the findings of cancer screening studies relevant to the malignancies associated with LFS and LFL syndrome in carriers of other types of germline mutations or the general population.

With this in mind, MRI-based breast screening in women with germline *BRCA* mutations has resulted in the detection of more tumours in this organ, and generally at earlier stages, than mammography alone;[79–83] however, no survival benefit has been associated with screening protocols using breast MRI, presumably due to the relatively short follow-up periods reported in these studies compared with the extended natural history of breast cancer. Given the additional concern regarding the increased sensitivity of carriers of mutations in *TP53* to ionizing radiation, breast MRI represents a valuable alternative screening strategy, where available, although mammography is still a reasonable alternative for those women without access to MRI. The total ionizing radiation dose that women are exposed to during the recording of two-view digital mammograms using modern instrumentation is low at 3.7 mGy,[84] and any increase in cancer risk resulting from this radiation dose is likely to be outweighed by the benefit of early detection of breast cancers, given the high risk of this disease in women with *TP53* mutations.

Faecal occult blood testing (FOBT)[85] and colonoscopy[86,87] both have proven efficacy in reducing mortality associated with colorectal cancers, even in the general population and populations at moderate risk of this disease; thus, screening using these methods is a reasonable strategy for surveillance in *TP53* mutation carriers, who can be considered at moderate risk of colorectal cancer. For gastric cancer, most studies have focused on the efficacy of endoscopic screening in populations with a high annualized risk of this disease (for example, East Asian men have an age-standardized incidence of gastric cancer of 42 cases per 1,000 compared with nine cases per 1,000 in men in Western Europe and North America),[88] but the results of these investigations do suggest a possible role for endoscopic screening at regular intervals in carriers of *TP53* mutations.[30,89] For most 'core' malignancies related to germline mutations in *TP53*, such as sarcoma, brain tumour and ACC, well-established screening tests do not exist, although evidence from the Brazilian study[78] suggests that clinical, laboratory and ultrasonography surveillance for ACCs is effective in earlier detection of this tumour type and is associated with improved outcomes, as outlined earlier.

The lack of established screening tests for the remaining majority of *TP53*-associated cancers and the range of anatomical locations at risk makes a whole-body approach to screening attractive. In this regard, fluorodeoxyglucose PET combined with CT has been explored as a possible strategy. Using these combined modalities, three of 15 asymptomatic *TP53* mutation carriers had malignant tumours identified (one stage II and one stage III papillary thyroid tumour, and a stage IIA 3 cm oesophageal adenocarcinoma).[90] Lesions were detected in five other participants in this study, but these proved benign after further investigation.[90] Although potentially curable lesions were identified using this approach, the major theoretical drawback is the exposure of a radiosensitive population to additional ionizing radiation;[34,91,92] thus, the overall value of this screening modality remains a subject for further research.

Whole-body MRI (WB-MRI) is an attractive alternative modality that avoids exposure to ionizing radiation.[92] Indeed, early studies investigating WB-MRI as a cancer surveillance strategy in *TP53* mutation carriers have now been performed,[93] and organ-specific MRI for pancreatic cancer[94] and lung cancer[95] have been examined in other selected at-risk populations. However, the sensitivity and specificity of WB-MRI across the range of tumours observed in LFS, as well as the adverse event profile, acceptability, costs and clinical utility of this approach remain unknown. Given the rarity of *TP53* mutations, pooling of data from collaborative international research efforts is required to give studies in the population carrying such mutations sufficient statistical power to draw meaningful conclusions. In this respect, several WB-MRI screening trials in *TP53* mutation carriers and/or patients with LFS are underway internationally (Box 2). For example, in the UK, the SIGNIFY trial[96] is currently comparing the incidence of malignancy in asymptomatic *TP53* mutation carriers versus unrelated population controls using WB-MRI and brain MRI. The LIFSCREEN project,[97] currently recruiting asymptomatic *TP53* mutation carriers in France, is a randomized intervention trial evaluating WB-MRI as an addition to brain and breast MRI, ultrasonography of the abdomen and physical examination as early detection methods for malignancies, compared with the standard follow-up care. In Australia, the SMOC (Surveillance of Multi-Organ Cancer prone syndromes) trial[98] of WB-MRI plus clinical examination, FOBT and colonoscopy, breast MRI, and blood counts in *TP53* mutation carriers is currently recruiting participants, and the data obtained will be pooled with data from the SIGNIFY study.[96] These screening trials have clear value, and their

Box 2 | International screening recommendations in *TP53* mutation carriers

USA[138]
- Annual clinical breast examination and mammogram (with or without breast MRI starting at age 20–25 years)
- Breast self-examination starting 18 years and discussion of RRM
- Annual physician examination
- Colonoscopies every 2–5 years
- Other targeted tumour surveillance based on family history of cancer

Australia[69]
- Annual breast MRI at age 20–50; consider mammogram with or without ultrasonography if unable to access MRI
- Consider breast ultrasonography in pregnant and/or lactating women
- Consider bilateral RRM followed by self-surveillance of breast area
- Consideration of risk-reducing medication (selective oestrogen receptor modulators)
- Colonoscopies every 5 years if no family history; if family history of CRC is known, screening can be increased to every 2–5 years from 25 years or from an age 10 years before the youngest onset of CRC observed in the family
- Any other screening modality should only be offered in the context of a clinical trial
- Avoidance of radiation exposure for screening or therapeutic purposes, if practicable

France[139]
- Annual physical examination
- Annual breast MRI from 20 years of age
- Avoidance of radiation therapy
- Discussion of prenatal diagnosis recommended

Abbreviations: CRC, colorectal cancer; RRM, risk-reducing mastectomy

Box 3 | WHO screening principles[99]
- The condition should be an important health problem
- A treatment for the condition should exist
- Facilities for diagnosis and treatment of the disease should be available
- The disease should have a latent stage
- A test or examination for the condition should exist
- The diagnostic or screening test should be acceptable for use in the general population
- An adequate understanding of the natural history of the disease is necessary
- Policy on whom to treat must be agreed upon
- The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole

results are eagerly anticipated. Nevertheless, to assess the value of ongoing surveillance, long-term prospective surveillance studies are needed, potentially spanning the lifetime of *TP53* mutation carriers enrolled, rather than incidence studies with limited follow-up periods. Furthermore, the current absence of firm evidence on which to base predictions of disease phenotypes in individual patients (that is, age at cancer onset, cancer type or both) necessitates evaluation of screening modalities for their ability to detect lesions at a curative stage.

Current screening programmes in LFS

The WHO has reported principles to justify and guide development of screening programmes (Box 3),[99] which have been expanded and updated by Sir Muir Gray for the UK screening committee.[100] Arguably, most of the principles outlined by these organizations[99,100] are met with regard to screening for a number of the malignancies associated with *TP53* mutations. One issue complicating the development of screening programmes, however, is that the natural history is well known for only some of the cancers associated with LFS. Furthermore, this knowledge might only be applicable to cancers in patients with particular *TP53* mutant alleles; other *TP53* alleles or genetic modifiers, about which less is known, might be associated with different qualitative and quantitative effects on tumour development. As a general rule, cancers with mutations in *TP53* are recognized as biologically aggressive,[101] which reinforces the need of cancer screening in patients with germline mutations in *TP53*. Nevertheless, current cancer screening advice for individual *TP53* mutation carriers is largely extrapolated from studies in the general population or patients with non-LFS hereditary syndromes, or represents clinician judgement individualized primarily based on the history of cancer within each family. Indeed, international consensus on the components of a cancer screening programmes for *TP53* mutation carriers is lacking,[10] and therefore the personalized guidance for *TP53* mutation carriers varies across institutions, regions and countries.

Of note, intriguing results supporting the development and prospective evaluation of a comprehensive screening strategy specifically in the LFS population were published in 2011.[93] This study included 33 adult and paediatric individuals from eight families with confirmed *TP53* mutations, who were offered access to a comprehensive cancer screening protocol (Box 4).[93] Importantly, this study was not randomized, as 18 participants elected to undergo cancer surveillance and 16 did not—one participant was in both groups after switching to the surveillance cohort after being diagnosed with cancer.[93] During the 3-year follow-up interval, 12 high-grade, high-stage cancers were observed in the nonsurveillance group.[93] By contrast, 10 asymptomatic tumours were detected in seven individuals in the surveillance group, five malignant and five low grade and/or premalignant, with one of the latter classified as myelodysplastic syndrome (MDS) and one as thyroid adenoma.[93] The benefits of early detection of thyroid adenoma are debatable, however, the potential benefit of the early detection of MDS is known, afforded by early intervention before malignant transformation. Furthermore, early identification of MDS could be important in determining the importance of therapy-associated leukaemogenesis, and thus might increase our understanding of how therapy affects long-term outcomes in carriers of mutations in *TP53*.[102] Promisingly, all patients in the surveillance group were alive at the end of the study (median follow-up period of 24 months), compared with only two individuals in the nonsurveillance group ($P = 0.0155$).[93] The authors acknowledged the limitations of this study,[93] including the small sample size, lack of randomization and the inclusion of retrospective data from some of the families included in the analysis. Nonetheless, this study has paved the way for the ongoing surveillance studies discussed earlier, as well as the adoption of cancer surveillance protocols in *TP53* mutation carriers by a number of institutions worldwide, as highlighted at a LFS consortium meeting in 2012.[10]

Box 4 | The Villani *et al.*[93] surveillance strategy

All patients
- Annual brain and whole-body MRI
- Complete blood count, with assessment of erythrocyte sedimentation rate and serum lactate dehydrogenase levels, every 4 months

Children only
- Ultrasonography of the abdomen and/or pelvis every 3–4 months
- Complete urinalysis and hormonal blood tests every 3–4 months

Adults women only
- Twice-yearly clinical breast examination from 20–25 years of age or at an age 5–10 years before the earliest age at onset of breast cancer in the family
- Annual mammography and breast MRI from age 20–25 years

All adults
- Annual dermatological examination
- 2-yearly colonoscopies from age 40 years or at an age 10 years before the earliest age of colorectal-cancer-onset recorded in family
- Pelvic and abdominal ultrasonography every 6 months

Box 5 | Proposed tumour surveillance schedule in patients with *TP53* mutations

ACC
- Abdominal ultrasonography every 3–4 months from birth to age 10 years*

Breast cancer
- Training and education in breast self-examination starting from 18 years of age
- Clinical breast examination every 6–12 months starting at 20–25 years old
- Annual breast MRI starting at age 20–25 years until age 50 years‡
- Discussion of risk-reducing bilateral mastectomy

Brain cancer
- Brain MRI to be included in annual whole-body MRI analyses
- Annual neurological examination
- Advise prompt reporting of new neurological symptoms

Sarcoma
- Annual whole-body MRI*
- Annual comprehensive physical examination
- Encourage awareness of any new symptoms

Haematopoietic cancer
- Annual full blood count from the age of 18 years

CRC
- 5-yearly colonoscopies,§ increasing to 2–5-yearly from age 25 years or, in cases with a known family history of this disease, from an age 10 years before the earliest onset of CRC in the family
- A full explanation of the risks associated with colonoscopy should be given

Gastric cancer
- 5-yearly endoscopy with a full explanation of the risks of endoscopy, increasing to 2–5-yearly from age 25 years or, in cases with a known family history of this disease, from an age 10 years before that at which the youngest onset of gastric cancer was observed in the family

*The optimal scheduling and selection of all tests in children remains a subject for discussion and research. ‡If breast MRI is not possible, consider annual mammography, with or without breast ultrasonography, plus discussion of risk-reducing bilateral mastectomy on a case-by-case basis; however, concern about cumulative ionizing radiation remains. §On the basis of the National Comprehensive Cancer Network (NCCN) guidelines for individuals with one first-degree relative with CRC with onset ≥50 years of age.[140] Abbreviations: ACC, adrenocortical carcinoma; CRC, colorectal cancer.

Psychosocial effects of screening

Currently, the psychological effects of an intensive cancer screening programme on *TP53* mutation carriers are not clear, but encouragingly a positive psychological benefit has been reported for cancer screening in LFS families.[103] Indeed, 90% of 45 respondents said that they believed earlier detection of cancer would be beneficial and 84% stated that screening gave them a sense of control.[103] However, data from screening studies in other populations at high risk of cancer have reported mixed results. Both breast MRI and mammographic screening in women at high risk of breast cancer (predominantly individuals from families with a history of breast cancer and a few known *TP53* mutation carriers) were considered acceptable by those undergoing these procedures.[104] Furthermore, a study comprising 198 individuals at high risk of pancreatic cancer undergoing a comprehensive screening programme (including MRI, transcutaneous ultrasonography and blood sampling), found that screening did not lead to substantially increased levels of general distress or risk perception.[105] By contrast, a systematic review of the psychological burden of screening in hereditary cancer syndromes found that surveillance of individuals at high risk of developing multiple malignancies was associated with higher distress and a reduced quality of life.[106] These contrasting findings highlight the need for formal study of the acceptability and psychosocial outcomes in any evaluation of cancer-screening programmes in *TP53* mutation carriers, particularly among children who potentially face lifelong screening, starting at a young age.

Proposed evidence-based screening

We propose that a systematic approach to ongoing cancer screening in adults and children with *TP53* mutations and/or LFS should be taken, with the aim of developing an international consensus cancer screening programme in this high-risk population. The available evidence lends support to an intensive approach, as undertaken by a number of clinics;[96–98] however, clarification of the level of benefit that such an intensive screening programme can provide in this population is clearly required before this approach is adopted internationally as the standard of care. Ideally, a formal prospective evaluation, with parallel psychosocial evaluation to assess the subjective effects of regular, extensive and ongoing cancer screening, should be undertaken. Arguably, a prospectively evaluated schedule of screening should commence early in life, with a baseline clinical review together with annual interventions that include a comprehensive physical and neurological examination, WB-MRI, additional breast MRI and clinical breast examination in women only from age 20 years, brain MRI, FOBT and a full blood count in adults, and abdominal ultrasonography, with or without assessment of blood hormone levels (in children aged <10 years only; Box 5). Additional investigations that should be performed at varying time points, as indicated by family history and deemed clinically appropriate, include colonoscopy and endoscopy of the upper gastrointestinal tract. Importantly, this whole-body cancer screening protocol should not replace any tumour-specific surveillance required for a previous cancer diagnosis, which would need to be incorporated into the screening programme.

Some families display patterns of tumour incidence characteristic of LFS and/or LFL syndrome despite having no detectable mutations in *TP53*. In such families, we would recommend the same systematic approach to ongoing screening, and also suggest that they should be invited to participate in research programmes, as appropriate. In a

research context, such families would be well suited to whole-exome analyses to identify the putative contributory genes underlying their apparent cancer predisposition.

The exact setting and the health-care professionals involved in the proposed screening programme will depend on circumstances of the individual patient and the local health-care environment. Nonetheless, a multidisciplinary setting is critical to the success of such a screening programme, with a responsible professional nominated to coordinate patient care upon entry of the individual to the programme. For example, with regard to individuals without current or prior cancer, this role could be performed by staff members at a Familial Cancer Service, who have expertise in this area through their existing mutation-carrier follow-up programmes. By contrast, the specialist(s) involved in the treatment of individuals with symptomatic disease or a prior cancer diagnosis might elect to coordinate the whole programme, either alone or in conjunction with the Familial Cancer Service.

The cancer screening schedule we propose (Box 5) does not obviate the importance of nongenetic risk factor modification. In individuals with germline mutations in *TP53*, encouragement and support in leading a healthy lifestyle, and discussion of the potential role of therapies that reduce the risk of breast cancer, such as tamoxifen and risk-reducing mastectomy,[107,108] will also play an important part in the cancer-risk management programme.

Conclusions

The literature on cancer screening in families with known *TP53* mutations or LFS is limited and the data that do exist are restricted to the outcomes of uncontrolled screening in small patient cohorts,[90,93] which provide limited or no information on the psychosocial consequences or financial costs of screening. Hence, decisions on performing cancer screening in these individuals are typically extrapolated from the outcomes of screening programmes conducted in the general population or in distinct groups at high risk of cancer. Large randomized controlled trials of cancer screening strategies in carriers of germline mutations in *TP53* will be challenging given the low prevalence of such polymorphisms. Accordingly, the outcomes of currently active screening programmes should be collected systematically, so that the data obtained can be combined. Ultimately, a formal clinical trial of cancer screening will be required to enable the development of evidence-based, cost-effective, safe and acceptable cancer screening guidelines for all individuals who are at increased cancer risk in our community, exemplified by carriers of mutations in *TP53*.

Review criteria

We searched PubMed for English-language full-text manuscripts and abstracts published between 1988 and 2013. The search terms used, alone and in various combinations, were "Li-Fraumeni syndrome", "TP53", "germline", "p53", "surveillance", "early detection", "surgical management", "brain tumours", "CNS", "sarcoma", "soft tissue sarcoma", "osteosarcoma", "gastric cancer", "colorectal cancer", "adrenal cortical carcinoma", "breast cancer" and "leukaemia". The reference lists of the articles identified were also searched for additional relevant publications.

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Author contributions

D.M.T. and G.M. contributed equally to this Review. K.A.M. researched the data for the article. All authors contributed substantially to discussion of content, the writing of the article review and/or editing of the manuscript before submission.