JAMA Oncology | Original Investigation

Baseline Surveillance in Li-Fraumeni Syndrome Using Whole-Body Magnetic Resonance Imaging
A Meta-analysis

Mandy L. Ballinger, PhD; Ana Best, PhD; Phuong L. Mai, MD; Payal P. Khincha, MD; Jennifer T. Loud, RN; June A. Peters, MS; Maria Isabel Achatz, MD; Rubens Chojniak, MD; Alexandre Balieiro da Costa, MD; Karina Miranda Santiago, MS; Judy Garber, MD, MPH; Allison F. O'Neill, MD; Rosalind A. Eeles, PhD; D. Gareth Evans, MD, FCRP; Eveline Bleiker, PhD; Gabe S. Sonke, MD; Marielle Ruijs, MD; Claudette Loo, MD; Joshua Schiffman, MD; Anne Naumer, MS; Wendy Kohlmann, MS; Louise C. Strong, MD; Jasmina Bojadzieva, MS; David Malkin, MD; Surya P. Rednam, MD; Elena M. Stoffel, MD, MPH; Erika Koeppe, MPH; Jeffrey N. Weitzel, MD; Thomas P. Slavin, MD; Bita Nehoray, MS; Mark Robson, MD; Michael Walsh, MD; Lorenzo Manelli, MD; Anita Villani, MD; David M. Thomas, FRACP; Sharon A. Savage, MD

IMPORTANCE Guidelines for clinical management in Li-Fraumeni syndrome, a multiple-organ cancer predisposition condition, are limited. Whole-body magnetic resonance imaging (WBMRI) may play a role in surveillance of this high-risk population.

OBJECTIVE To assess the clinical utility of WBMRI in germline *TP53* mutation carriers at baseline.

DATA SOURCES Clinical and research surveillance cohorts were identified through the Li-Fraumeni Exploration Research Consortium.

STUDY SELECTION Cohorts that incorporated WBMRI for individuals with germline *TP53* mutations from January 1, 2004, through October 1, 2016, were included.

DATA EXTRACTION AND SYNTHESIS Data were extracted by investigators from each cohort independently and synthesized by 2 investigators. Random-effects meta-analysis methods were used to estimate proportions.

MAIN OUTCOMES AND MEASURES The proportions of participants at baseline in whom a lesion was detected that required follow-up and in whom a new primary malignant neoplasm was detected.

RESULTS A total of 578 participants (376 female [65.1%] and 202 male [34.9%]; mean [SD] age, 33.2 [17.1] years) from 13 cohorts in 6 countries were included in the analysis. Two hundred twenty-five lesions requiring clinical follow-up were detected by WBMRI in 173 participants. Sixty-one lesions were diagnosed in 54 individuals as benign or malignant neoplasms. Overall, 42 cancers were identified in 39 individuals, with 35 new localized cancers treated with curative intent. The overall estimated detection rate for new, localized primary cancers was 7% (95% CI, 5%-9%).

CONCLUSIONS AND RELEVANCE These data suggest clinical utility of baseline WBMRI in *TP53* germline mutation carriers and may form an integral part of baseline clinical risk management in this high-risk population.

Invited Commentary
Related articles
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Sharon A. Savage, MD, Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 9609 Medical Center Dr, Room 6E-456, Rockville, MD 20850 (savagesh@mail.nih.gov).

JAMA Oncol. doi:10.1001/jamaoncol.2017.1968
Published online August 3, 2017.

Li-Fraumeni syndrome (LFS) was first described in 1969 as a highly penetrant cancer-prone syndrome.[1] Formal diagnostic criteria for LFS have subsequently been developed, based on a family or a personal history of a broad spectrum of early-onset cancers, including sarcoma, breast cancer, adrenocortical carcinoma, and brain tumors, often with more than 1 cancer per affected individual.[2-5] Lifetime cancer risks are reported to approach 100% for both sexes in cases identified by family history.[6-8] The exceedingly high cancer risk in LFS often confers a high psychological and medical burden.[9] Pathogenic variants in the tumor suppressor gene, *TP53* (NCBI Entrez Gene 7157), were first identified and subsequently found to cause about 70% of classic LFS in 1990.[10-13] Identification of germline *TP53* mutation carriers has been augmented by increased with increased sequencing of germline and somatic DNA using gene panels and whole-exome and whole-genome testing, owing in part to the influence of precision medicine initiatives.

Although the clinical characteristics and molecular basis for LFS have been known for decades, no universally accepted approach exists for risk management. Current guidelines focus on the risk for breast cancer, primarily because organ-specific surveillance measures,[14-16] such as magnetic resonance imaging (MRI) of the breast, are already widely used for screening in cognate high-risk syndromes. However, because breast cancer constitutes only a proportion of the surgically resectable cancers to which *TP53* mutation carriers are prone, novel, effective methods for cancer surveillance are needed across a broad range of body or corporeal sites. Within the past 5 years, emerging studies have suggested improved clinical outcomes for *TP53* mutation carriers with intensive screening.[17-20] The Toronto protocol, which incorporates whole-body MRI (WBMRI) among other modalities, was associated with improved survival.[17] Neonatal screening for the Brazilian *TP53* founder mutation resulted in adrenocortical tumors being detected at an early, more curable stage.[18] Of note, a recent UK study detected malignant neoplasms in 14% of *TP53* mutation carriers at baseline WBMRI.[19] Psychological benefit has also been reported from participation in an LFS surveillance program.[20] However, in part because of the rarity of LFS, definitive evidence of the benefits of screening are lacking.

To generate evidence for the efficacy of WBMRI as a surveillance tool for carriers of pathogenic germline *TP53* mutations, we report herein the findings of a meta-analysis of 13 prospective cohorts conducted in 6 countries. We assessed the detection rates of asymptomatic cancers using WBMRI as part of baseline assessment of *TP53* mutation carriers, measured by the rate of identification of investigable lesions and new primary cancers that can be treated with curative intent.

Key Points

Question Does baseline whole-body magnetic resonance imaging detect asymptomatic cancers at a curable stage in germline *TP53* mutation carriers?

Findings In a meta-analysis of 13 cohorts that included 578 participants, the estimated overall detection rate for previously unrecognized new, localized malignant neoplasms by a single baseline scan in *TP53* mutation carriers was 7%, and the false-positive rate was 42.5%. All screen-detected new cancers were treated with curative intent.

Meaning Baseline evaluation with whole-body magnetic resonance imaging offers important clinical utility in the management of cancer risk in *TP53* mutation carriers.

Methods

Study Selection

Clinical and research surveillance cohorts were identified through the Li-Fraumeni Exploration Research Consortium.[21] Cohorts that were formed from January 1, 2004, through October 1, 2016, that performed WBMRI in individuals at any age were considered (eTable 1 in the Supplement). All research cohorts had ethical approval from their ethics boards, and written informed consent was obtained from participants or guardians as appropriate.

Participants were not required to be newly diagnosed for any of the studies included in this meta-analysis. All cohorts included the brain in the WBMRI scan except the Huntsman Cancer Institute cohort. All participants were asymptomatic at the time of the baseline scan. The details of imaging protocols for contributing cohorts, including the use of contrast and organ-specific sequences, are given in eTables 2 to 14 in the Supplement. All participants were known carriers of pathogenic *TP53* mutations or were obligate carriers by pedigree.

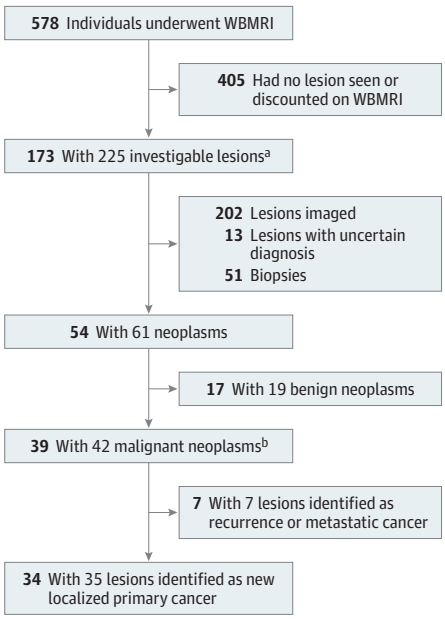
Data Extraction and Classification

Data were extracted by investigators from each cohort and synthesized by 2 of us (M.L.B. and D.M.T.). Lesions were considered to be investigable if further clinical follow-up was required in the opinion of the study investigator, including additional imaging or biopsy. The true-positive rate for WBMRI was defined as the rate of detection of localized, primary cancers that were treated with curative intent. False-positive lesions were defined as those considered initially to be neoplastic (all neoplasms in the **Figure**) but that subsequently were determined on further investigation to be benign tumors, recurrences of previous cancers, or incurable metastatic cancers. Low-grade gliomas were classified as malignant. The treatment intent (curative or palliative) after diagnosis was recorded in each case.

Statistical Analysis

Random-effects meta-analysis methods[22] for proportions were used to aggregate the data from the 13 participating cohorts. Meta-analyses were performed to estimate the proportion of participants found to have 1 or more investigable lesions, the proportion of participants found to have 1 or more new primary cancers, and the proportion of investigable lesions determined to be new primary cancers, with approximate 95% CIs.[23] The between-cohort heterogeneity τ^2, along with the associated *P* value, was estimated using the DerSimonian-Laird method. A logit transformation was used to calculate the overall proportions. Cohort participants were additionally subdivided by sex and by age group (0-17, 18-40, or >40 years of age) to identify age-dependent trends in cancer detection rates and

Figure. Flowchart of Disposition of Participants Undergoing Whole-Body Magnetic Resonance Imaging (WBMRI)



Many lesions underwent biopsies and imaging. Some participants had benign and malignant lesions.

[a] Defined as those who required any intervention (eg, additional imaging or biopsy).

[b] Identified after biopsy in all but 4 cases of glioma or astrocytoma, in which the diagnosis was established with imaging alone. The total number of individuals in whom a benign or malignant neoplasm was identified includes 2 individuals in whom 2 cancers each were diagnosed, including one with 1 localized primary cancer and 1 recurrent cancer and the other with 2 new primary cancers.

to be consistent with prior management recommendations.[17] Tests of subgroup differences were conducted using the Cochran Q test. All analyses were performed with R software, version 3.3.1,[24] using version 4.6-0 of the meta package.[25]

Results

Research Surveillance Study Characteristics

This meta-analysis included 578 participants (376 female [65.1%] and 202 male [34.9%]; mean [SD] age, 33.2 [17.1] years) with deleterious germline *TP53* mutations from 13 cohorts who underwent baseline WBMRI from January 1, 2004, through October 1, 2016 (eTable 1 in the Supplement). Of these, 134 (77 female and 57 male) were aged 0 to 17 years, 246 (164 female and 82 male) were aged 18 to 40 years, and 198 (135 female and 64 male) were older than 40 years. Germline *TP53* variant data available for participants showed 183 unique events, including 91 missense, 26 nonsense, 8 frameshift, and 20 intronic variants and 38 insertions or deletions. Almost half of the participants (280 of 578 [48.4%], of whom 211 were female) had been diagnosed with at least 1 prior malignant neoplasm. Of the 264 female participants older than 17 years for whom information was available, 17 (6.4%) had a single mastectomy and 110 (41.7%) had a double mastectomy.

A flowchart outlining the disposition of participants included in the meta-analysis is given in the Figure. Of the 578 participants, 225 lesions requiring further investigation were observed in 173 participants. Forty-two malignant lesions were diagnosed in 39 individuals, with most of the diagnoses based on biopsy findings. Four of the 42 malignant lesions were brain tumors diagnosed based on imaging alone. Of the new malignant neoplasms, 35 localized primary cancers were diagnosed in 34 individuals, all of whom were treated with curative intent. The false-positive rate, defined here as the proportion of suspected neoplasms that were benign, recurrences of preexisting cancers, or newly diagnosed metastatic cancers, was 42.5% (26 of 61).

Meta-analysis Results

eFigure 1 in the Supplement presents the meta-analysis for the proportion of participants found to have 1 or more investigable lesions by WBMRI. Overall, 31% (95% CI, 26%-35%) of participants were estimated to have 1 or more investigable lesions. No sex differences were detected (estimated proportion of 31% in both sexes; $P = .90$, Cochran Q). The proportion of investigable lesions identified tended to increase with age from 29% among participants younger than 18 years to 30% among those aged 18 to 40 years and 34% among those older than 40 years, but this increase was not statistically significant ($P = .60$ overall, Cochran Q).

eFigure 2 in the Supplement presents the meta-analysis of the proportion of individuals in whom 1 or more new cancers was diagnosed. Overall, an estimated 7% (95% CI, 5%-9%) of participants were determined to have 1 or more new primary malignant neoplasm. We found no significant difference between male and female participants (9% and 7%, respectively; $P = .40$, Cochran Q). The proportion of cancers identified increased with age in male participants from 10% among those younger than 18 years and those aged 18 to 40 years to 15% among those older than 40 years; female participants experienced a midlife reduction in malignant neoplasms detected by WBMRI (from 15% among those aged <18 years to 8% among those aged 18-40 years and 10% among those aged >40 years), but neither difference was statistically significant ($P = .30$ for female and $P = .60$ for male participants, Cochran Q). A meta-analysis of the proportion of investigable lesions subsequently identified as a new primary cancer is given in eFigure 3 in the Supplement. Overall, an estimated 18% (95% CI, 12%-27%) of investigable lesions identified by WBMRI were determined to be new primary cancers, with no sex difference (18% for female and 22% for male participants; $P = .50$, Cochran Q). The proportion of cancers identified was highest in those younger than 18 years (31%) compared with those aged 18 to 40 years (16%) and those older than 40 years (18%), but this difference was not statistically significant ($P = .15$ overall, Cochran Q).

Clinical Spectrum of New Primary Cancers Detected by WBMRI

The 35 new primary cancers identified by baseline WBMRI occurred in 34 participants (1 woman older than 40 years had a synchronous localized chromophobe renal cell carcinoma and a localized uterine leiomyosarcoma). No new primary cancers were clinically metastatic at diagnosis. The patterns of

Table. New Localized Primary Malignant Neoplasms Detected by WBMRI

Age Group by Participant Sex	Morphologic and Topographic Findings	Age at Diagnosis, y
0-17 y		
Male	Adrenocortical carcinoma	2
	Osteosarcoma of the leg	9
	Low-grade glioma[a]	15
	Osteosarcoma of the fibula	12
Female	Choroid plexus carcinoma	4
	Low-grade glioma[a]	6
	Low-grade glioma[a]	13
	Osteosarcoma of the chest	13
	Astrocytoma	13
	Papillary thyroid cancer	17
	Renal carcinoma	17
	Spinal chordoma	17
18-40 y		
Male	Osteosarcoma of the rib	29
	Colorectal cancer	21
	Osteosarcoma of the rib	29
Female	Renal and liver epithelioid angiomyolipomas	24
	Chondrosarcoma of the sacroiliac joint	29
	Undifferentiated pleomorphic sarcoma of the shoulder	30
	Astrocytoma	33
	Chordoma of the clivus	40
	Thyroid carcinoma	40
>40 y		
Male	Prostate adenocarcinoma	41
	Prostate adenocarcinoma	46
	Lung adenocarcinoma	54
	Leiomyosarcoma of the bowel	63
Female	Low-grade spindle cell sarcoma of the chest	41
	Lung adenocarcinoma	54
	Chromophobe renal cell carcinoma and uterine leiomyosarcoma	45
	Ductal carcinoma in situ of the breast	49
	Abdominal myxosarcoma	51
	Well-differentiated liposarcoma of the lumbar region	52
	Lung adenocarcinoma	64
	Invasive ductal carcinoma of the breast	66
	Lung adenocarcinoma	43

Abbreviation: WBMRI, whole-body magnetic resonance imaging.

[a] Currently under surveillance with short-interval MRI, with the intent to resect at a later stage.

cancers observed vary by age and sex (**Table**). All 7 bone sarcomas were observed in participants younger than 40 years, with no sex difference, whereas 5 of 7 soft-tissue sarcomas arose in participants older than 40 years. A single adrenocortical tumor was found in a child, as was a choroid plexus carcinoma. The diversity of cancers to which *TP53* mutation carriers are prone was evident. Other cancers identified included carcinomas of the lung (4 participants, all aged >40 years), kidney (1 female participant in each age group), thyroid (1 female participant aged <18 years and 1 aged 18-40 years), prostate (2 male participants aged >40 years), and bowel (1 male participant aged 18-40 years). We only observed 2 breast cancers (a ductal carcinoma in situ and an invasive ductal carcinoma, each in 1 woman aged >40 years). These findings may reflect the high rate of mastectomies and/or prior breast cancer diagnoses in the female population undergoing screening, as well as the use of dedicated breast MRI sequences outside WBMRI.

Malignant neoplasms of the brain represent an important feature of LFS. Twelve of 13 cohorts included the brain as a routine part of the WBMRI protocol. In this meta-analysis, brain tumors appeared to be more common in children and young adults. Of 6 brain tumors identified by WBMRI, 5 were observed in children and 1 in a woman in the group aged 18 to 40 years (Table). We attempted to determine the ability of the dedicated brain component of WBMRI in identifying brain tumors. We compared the outcomes of WBMRI with the dedicated brain MRI when such comparisons were available (eTable 15 in the Supplement). Of 10 brain tumors identified in individuals undergoing WBMRI and a dedicated brain MRI, only 5 were identified by the WBMRI, whereas the remainder were identified by dedicated brain MRI but not by WBMRI. For the 5 brain tumors that were missed on WBMRI, none of the scans used contrast.

Discussion

This meta-analysis provides, to our knowledge, the first statistically robust estimate of the potential clinical utility of WBMRI in screening *TP53* mutation carriers. Overall, 1 in 14 participants undergoing their first WBMRI was found to have a primary malignant neoplasm, which was then treated with curative intent. The rate of detection of localized malignant neoplasms was remarkably consistent between individual cohorts, studies of which were conducted across 6 countries and 13 institutions. The rate at which cancers were identified appeared to be highest among children and lowest among young adults and increased again among older adults. The spectrum of cancers shifts with age, with a greater number of brain tumors and bone sarcomas in children and a range of epithelial malignant neoplasms in older adults. All screen-detected cancers were treated with curative intent, although the follow-up of those participants in whom cancers were identified and treated curatively was too short to assess long-term outcomes. Whole-body MRI does not reliably identify brain tumors in *TP53* mutation carriers. Another important outcome of WBMRI is the detection of benign but clinically significant lesions that are medically actionable, for example, by causing organ damage through local growth or undergoing malignant transformation in this high-risk population.

The absence of breast cancers in this screened population was notable. Breast cancer is the most common diagnosis among women with *TP53* mutations who are younger than 40 years,[8] but only 2 women with breast cancer were identified in this meta-analysis (both aged >40 years). This finding may reflect the high percentage of women who had undergone unilateral or bilateral mastectomy before study entry (127 of 264 [48.1%]), the inability of WBMRI to detect small breast lesions, or the routine use of dedicated breast MRI in women at high risk for breast cancer.

To put the results of this meta-analysis of WBMRI in *TP53* mutation carriers into the context of current clinical genetics practice, we compared these results with those achieved through screening using dedicated breast MRI in women at high risk for breast cancer owing to germline *BRCA1/2* mutations. Breast MRI is widely approved, recommended, and reimbursed for early detection of cancer in women at high risk for breast cancer.[14-16] The Ontario Breast Screening Program[26] screened 2207 women at high risk for breast cancer by using mammography or breast MRI. The detection rate of breast MRI was 1% in that series, consistent with rates of previous large-scale studies.[27,28] The rate of screen-detected cancers in other series was similar.[29] However, specific incidence rates for *TP53* mutation carriers can be as high as 4.4%,[30] and the results are often premalignant comedo with histologic findings for ductal carcinoma in situ. [30]

An important aspect of population screening is the false-positive rate because the investigation of lesions that are subsequently clinically insignificant is a source of potential psychological distress, medical morbidity, and cost. Almost 1 in 3 participants in this WBMRI meta-analysis were found to have an investigable lesion, and nearly 1 in 5 lesions (18%) were malignant and appropriately treated with curative intent. Comparison with breast MRI is useful. The false-positive rate for the combination of breast MRI with mammography has been variably reported to range from 4% to 30%,[27-29] rates lower than that observed in our series (42.5%). A recent report on the acceptability of WBMRI in the population with LFS observed that screening reduces anxiety for participants and may provide psychological benefit.[20]

Limitations

Important limitations and unanswered questions arise from this study. The surveillance protocols used in each cohort were heterogeneous. Subgroup meta-analyses such as these can be challenging to interpret because the meta-analysis estimates are calculated by incorporating estimated weights for each cohort rather than by pooling data across studies. Weighting is a valuable part of meta-analyses because it reduces the influence of cohorts with small amounts of data while these data can still be included in the aggregated analysis. Incorporation of study weights calculated independently in each subgroup or combined analysis may lead to observations such as ours that cancer diagnosis rates in the aggregate of participants aged 18 to 40 years is lower among male and female participants combined than among either group alone.

Other important questions involve the optimal use of WBMRI in relation to participant age and sex because the nature and incidence of cancers vary substantially in *TP53* mutation carriers. The excess of female to male participants in our study may be attributable to the greater engagement of women in health care.[31] In addition, when WBMRI or other components of a surveillance program should be introduced as part of follow-up for patients with an existing cancer diagnosis is unclear. Most cohorts contributing to this meta-analysis did not use contrast; however, the question of the importance of contrast as an effective component of a WBMRI protocol remains open. Careful follow-up will be required to fully document any safety issues associated with WBMRI screening. Opportunity exists for optimization of WBMRI protocols with faster acquisition sequences and improved imaging technologies. In this meta-analysis, individual cohorts varied widely in eligibility criteria regarding time since curative treatment for a previous cancer, although only 7 malignant neoplasms detected by WBMRI were recurrences of previous malignant neoplasms.

Finally, we cannot estimate the false-negative rate for WBMRI from our data because this meta-analysis describes the results of a single baseline scan. Only follow-up will determine whether occult cancers were missed by WBMRI. Longitudinal follow-up of *TP53* mutation carriers is very limited, with only 1 study reported to date.[17] Longer-term follow-up of these patients will be essential to reveal the rate of cancer development in these cohorts, identify the optimal scheduling of WBMRI, and determine whether early detection of cancers in *TP53* mutation carriers will translate into decreased morbidity and better survival. Estimates of the cost-effectiveness of WBMRI also lie beyond the scope of the present study but will be important to implementation in clinical practice.

Conclusions

Cancer screening in germline *TP53* mutation carriers is especially challenging because of the wide spectrum of associated malignant neoplasms. Baseline WBMRI identified a new and treatable malignant neoplasm in as many as 7% of *TP53* mutation carriers, confirming that this modality enables clinically useful early detection of cancer in this highly cancer-prone population across a broad range of health systems. The meta-analysis presented herein suggests that WBMRI adds significantly to the armamentarium available to clinicians seeking to improve the likelihood of early tumor detection and subsequent improved outcomes. Although further research is required, our findings suggest that WBMRI may be a useful component of the routine baseline assessment of *TP53* mutation carriers in children and adults.

ARTICLE INFORMATION

Accepted for Publication: May 15, 2017.

Published Online: August 3, 2017. doi:10.1001/jamaoncol.2017.1968

Author Affiliations: Cancer Division, Garvan Institute of Medical Research, Sydney, Australia (Ballinger, Thomas); Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland (Best, Savage); Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland (Mai, Khincha, Loud, Peters, Achatz); Department of Imaging, A. C. Camargo Cancer Center, São Paulo, Brazil (Achatz, Chojniak); Department of Medical Oncology, A. C. Camargo Cancer Center, São Paulo, Brazil (Balieiro da Costa); National Institute for Oncogenomics, A. C. Camargo Cancer Center, São Paulo, Brazil (Santiago); Center for Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Boston, Massachusetts (Garber); Department of Pediatric Hematology/Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts (O'Neill); Division of Genetics and Epidemiology, The Institute of Cancer Research and Royal Marsden National Health Service Foundation Trust, London, England (Eeles); Department of Genetic Medicine, St Mary's Hospital, Manchester, England (Evans); Division of Psychosocial Research and Epidemiology, the Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam (Bleiker); Department of Medical Oncology, the Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam (Sonke); Family Cancer Clinic,

the Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam (Ruijs); Department of Radiology, the Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam (Loo); Department of Pediatric Hematology/Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City (Schiffman, Naumer, Kohlmann); Department of Genetics, The University of Texas MD Anderson Cancer Center, Houston (Strong, Bojadzieva); Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada (Malkin, Villani); Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada (Malkin); Department of Pediatrics, Section of Hematology-Oncology, Texas Children's Cancer Center, Baylor College of Medicine, Houston (Rednam); Department of Internal Medicine, University of Michigan, Ann Arbor (Stoffel, Koeppe); Division of Clinical Cancer Genetics, City of Hope, Duarte, California (Weitzel, Slavin, Nehoray); Clinical Genetics Service, Memorial Sloan Kettering Cancer Center, New York, New York (Robson); Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, New York (Walsh); Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, New York (Manelli).

Author Contributions: Drs Ballinger and Best served as equal first authors. Drs Thomas and Savage served as equal senior authors. Drs Ballinger and Savage had full access to all data and take responsibility for data integrity and analysis.
Study concept and design: Thomas, Savage.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ballinger, Best, Thomas, Savage.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Best.
Obtained funding: Achatz, Ballinger, Garber, Eeles, Bleiker, Schiffman, Strong, Stoffel, Weitzel, Thomas, Savage.
Administrative, technical, or material support: Mai, Khincha, Santiago, O'Neill, Ruijs, Naumer, Kohlmann, Bojadzieva, Koeppe, Nehoray, Walsh, Villani.
Study supervision: Thomas, Savage.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported in part by the intramural research program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute (Dr Savage); the Australasian Sarcoma Study Group (Drs Ballinger and Thomas); the Johanna Sewell Research Foundation (Dr Ballinger); grants APP1067094 and APP1130419 from Cancer Australia's Priority-Driven Collaborative Cancer Research Scheme (Drs Ballinger and Thomas); Canadian Institutes for Health Research; Canadian Cancer Society (Drs Malkin and Villani); Terry Fox Research Institute (Drs Malkin and Villani); SickKids Foundation (Drs Malkin and Villani); Soccer for Hope Foundation (Drs Malkin and Villani); STOP CANCER (Dr Slavin); Oxnard Foundation (Drs Slavin and Weitzel); American Cancer Society (Dr Weitzel); grant 02-2013-044 from the Avon Foundation (Dr Weitzel); the Annabel Evans Research Fund and support from the National Institute for Health Research to the Biomedical Research Centre at the Institute of Cancer Research, Royal Marsden National Health Service Foundation Trust, and Cancer Research UK support to the Cancer Imaging Centre at The Institute of Cancer Research and Royal Marsden National Health Service Foundation Trust (Dr Eeles); grant RC4CA153828 (Dr Weitzel); the LFS Association (Dr Garber); the Dana-Farber Cancer Institute Pediatric Solid Tumor Program (Dr Garber); Adult Cancer Genetics and Prevention Program (Dr Garber); and Sue and Radcliffe Killan Endowed Chair (Dr Strong).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank all study participants and referring clinicians for their valuable contributions.

REFERENCES

1. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms: a familial syndrome? *Ann Intern Med*. 1969;71(4):747-752.

2. Chompret A, Abel A, Stoppa-Lyonnet D, et al. Sensitivity and predictive value of criteria for *p53* germline mutation screening. *J Med Genet*. 2001;38(1):43-47.

3. Bougeard G, Sesboüé R, Baert-Desurmont S, et al; French LFS Working Group. Molecular basis of the Li-Fraumeni syndrome: an update from the French LFS families. *J Med Genet*. 2008;45(8):535-538.

4. Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from *TP53* mutation carriers. *J Clin Oncol*. 2015;33(21):2345-2352.

5. Tinat J, Bougeard G, Baert-Desurmont S, et al. 2009 Version of the Chompret criteria for Li Fraumeni syndrome. *J Clin Oncol*. 2009;27(26):e108-e109; author reply e110.

6. Chompret A, Brugières L, Ronsin M, et al. *P53* germline mutations in childhood cancers and cancer risk for carrier individuals. *Br J Cancer*. 2000;82(12):1932-1937.

7. Wu CC, Shete S, Amos CI, Strong LC. Joint effects of germ-line *p53* mutation and sex on cancer risk in Li-Fraumeni syndrome. *Cancer Res*. 2006;66(16):8287-8292.

8. Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among *TP53* mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer*. 2016;122(23):3673-3681.

9. Peters JA, Kenen R, Bremer R, Givens S, Savage SA, Mai PL. Easing the burden: describing the role of social, emotional and spiritual support in research families with Li-Fraumeni syndrome. *J Genet Couns*. 2016;25(3):529-542.

10. Malkin D, Li FP, Strong LC, et al. Germ line *p53* mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science*. 1990;250(4985):1233-1238.

11. Srivastava S, Zou ZQ, Pirollo K, Blattner W, Chang EH. Germ-line transmission of a mutated *p53* gene in a cancer-prone family with Li-Fraumeni syndrome. *Nature*. 1990;348(6303):747-749.

12. Olivier M, Eeles R, Hollstein M, Khan MA, Harris CC, Hainaut P. The IARC *TP53* database: new online mutation analysis and recommendations to users. *Hum Mutat*. 2002;19(6):607-614.

13. Varley JM. Germline *TP53* mutations and Li-Fraumeni syndrome. *Hum Mutat*. 2003;21(3):313-320.

14. Daly MB, Pilarski R, Berry M, et al. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Breast and Ovarian, Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. December 7, 2016. Accessed March 2, 2017.

15. The National Institute for Health and Care Excellence (NICE). Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. NICE clinical guideline 164. https://www.nice.org.uk/guidance/CG164. June 2013. Updated March 2017. Accessed March 2, 2017.

16. Cancer Institute NSW. eviQ Cancer treatments online: risk management for adults with a *TP53* mutation. https://www.eviq.org.au/Protocol/tabid/66/categoryid/66/id/749/Risk+Management+for+adults+with+a+TP53+Mutation+.aspx. Updated June 7, 2017. Accessed March 2, 2017.

17. Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol*. 2016;17(9):1295-1305.

18. Custódio G, Parise GA, Kiesel Filho N, et al. Impact of neonatal screening and surveillance for the *TP53* R337H mutation on early detection of childhood adrenocortical tumors. *J Clin Oncol*. 2013;31(20):2619-2626.

19. Saya S, Killick E, Thomas S, et al; SIGNIFY Study Steering Committee. Baseline results from the UK SIGNIFY study: a whole-body MRI screening study in *TP53* mutation carriers and matched controls. *Fam Cancer*. 2017;16(3):433-440. doi:10.1007/s10689-017-9965-1

20. McBride KA, Ballinger ML, Schlub TE, et al. Psychosocial morbidity in TP53 mutation carriers: is whole-body cancer screening beneficial? *Fam Cancer*. 2017;16(3):423-432.

21. Mai PL, Malkin D, Garber JE, et al. Li-Fraumeni syndrome: report of a clinical research workshop and creation of a research consortium. *Cancer Genet*. 2012;205(10):479-487.

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.

23. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. *Am Stat*. 1998;52(2):119-126.

24. R Team. *A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statisical Computing; 2016.

25. Schwarzer G. meta: An R package for meta-analysis. *R News*. 2007:40-45.

26. Chiarelli AM, Prummel MV, Muradali D, et al. Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the Ontario High Risk Breast Screening Program. *J Clin Oncol*. 2014;32(21):2224-2230.

27. Kuhl CK, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol*. 2005;23(33):8469-8476.

28. Leach MO, Boggis CR, Dixon AK, et al; MARIBS Study Group. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet*. 2005; 365(9473):1769-1778.

29. Kriege M, Brekelmans CT, Obdeijn IM, et al. Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer. *Breast Cancer Res Treat*. 2006;100(1):109-119.

30. Evans DG, Lennard F, Pointon LJ, et al; UK Study of MRI Screening for Breast Cancer in Women at High Risk (MARIBS). Eligibility for magnetic resonance imaging screening in the United Kingdom: effect of strict selection criteria and anonymous DNA testing on breast cancer incidence in the MARIBS Study. *Cancer Epidemiol Biomarkers Prev*. 2009;18(7):2123-2131.

31. Dryden R, Williams B, McCowan C, Themessl-Huber M. What do we know about who does and does not attend general health checks? findings from a narrative scoping review. *BMC Public Health*. 2012;12:723.