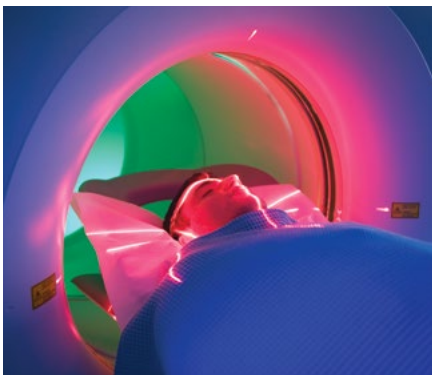
Benefits and burdens of risk management for young people with inherited cancer



A focus on Li-Fraumeni syndrome

CPD

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Background and objective
Discussing population-based cancer risk and screening is common in general practice. Patients with an inherited cancer syndrome, however, may need more nuanced discussions. Li-Fraumeni syndrome (LFS) is a rare, inherited cancer syndrome that affects many organ systems from birth and requires intensive, whole-body cancer risk management. The aim of this study was to explore the risk management experiences of young people (aged 15–39 years) with, or at risk of, LFS.

Methods
Using an interpretive description design, semi-structured interviews were conducted with young people diagnosed with, or at risk of, LFS from across Australia. Interview transcripts were analysed with team-based, codebook thematic analysis.

Results
Thirty young people (mean age 25.5 years) participated. Participants described intensive screening and risk-reducing mastectomy (for women) as their 'best shot' to control their cancer risks with LFS. Engaging in these options as a young person came with a slew of psychosocial implications.

Discussion
General practitioners may help to improve care for young people with inherited cancer syndromes by acknowledging the benefits and complex burdens of their risk management.

INHERITED CANCER SYNDROMES are rare. For example, the population incidence of pathogenic variants for hereditary breast and ovarian cancer (HBOC) is approximately one in 400, and for complex conditions such as Li-Fraumeni syndrome (LFS) it ranges from one in 2000 to one in 20,000.[1–3] While these conditions may be uncommon in the primary care population, their hereditary nature means they cluster in families, and family members may all be cared for by the same general practitioner (GP).[4] GPs' experience with these patients is likely to vary widely, but the need to assess all patients for high-risk cancer features, such as family history of cancer, falls within the remit of primary care.[5] Identifying and referring potentially high-risk patients to a familial cancer centre will, at a minimum, result in a letter summarising the outcomes of cancer risk assessment and recommendations for cancer risk management, mostly screening. For some patients, genetic testing will identify a germline pathogenic variant and a resultant diagnosis of an inherited cancer syndrome, such as HBOC, Lynch syndrome or LFS.

Cancer risk management for inherited cancer broadly consists of either cancer screening – to enable the early detection and treatment of mainly solid tumours – or risk-reducing options, such as prophylactic surgery (eg risk-reducing mastectomy [RRM]) or medication (eg chemoprevention).[6] More common inherited cancer syndromes (eg HBOC and Lynch syndrome) have well established and efficacious risk management guidelines[5] that are mostly associated with good psychological outcomes.[7,8] However, rarer syndromes that may affect multiple organ systems from early ages are challenging to manage, require novel risk management strategies and can be psychosocially more complex.[9]

For example, LFS is caused by pathogenic variants in *TP53* and confers a high risk of breast cancer, soft-tissue and osteosarcoma, brain tumours and adrenocortical carcinoma, among many others, from birth into adulthood.[10] Individuals with LFS have up to a 50% risk of cancer by the age of 31 years, which exceeds 90% by age

the age of 70 years, and a 50% risk of multiple primary cancers.[11] Aside from RRM for women, prevention for LFS is unavailable. Risk management therefore starts in infancy and comprises intensive biochemical and whole-body imaging surveillance.[12] Current evidence suggests that early tumour detection with intensive risk management significantly improves five-year survival (88.8%) when compared with no surveillance (59.6%, $P = 0.0132$).[13] A meta-analysis of 578 individuals with LFS has also shown that whole-body magnetic resonance imaging (MRI) is a key modality; a single baseline scan can detect new, localised cancer at a rate of 7% (95% confidence interval: 5, 9), thus enabling treatment with curative intent at early stages.[14] Intensive risk management with whole-body MRI has since been adopted internationally and, more recently, in Australia (Table 1).[12,15] Being largely experimental, it is only accessible at specialist services in Australia,[16] and its long-term psychosocial implications are still under investigation.[17,18]

Although risk management for LFS is designed to improve cancer outcomes from early in life,[12] the psychosocial impact on young people (aged 15–39 years) is unknown.[19] Young people occupy a formative life stage with complex developmental tasks such as identity exploration, growing independence from family and social role transitions.[20] These tasks are difficult to navigate when living with, or at high risk of, cancer, meaning young people have distinct psychosocial needs that may affect the acceptability of, adherence to and outcomes of screening for LFS. The aim of this study was to explore the everyday experiences of young people with, or at 50% risk of, LFS to better inform their care, specifically focusing on their experiences of risk management.

Methods

This analysis is nested in a larger qualitative interview study exploring young people's experiences of LFS in Australia.[21] This project was informed by interpretive description, a methodology aimed at developing knowledge for clinical practice.[22] All procedures were

Table 1. Australian risk management recommendations for individuals with a pathogenic *TP53* variant

Cancer type associated with LFS	Recommended risk management in Australia from eviQ[15]
Sarcomas and other solid organ tumours	Children (<18 years) and adults (≥18 years) • Annual whole-body MRI
Adrenocortical carcinoma	Children • Four-monthly abdominal ultrasonography from birth to 10 years of age • If concerning features identified from ultrasonography or clinical examination, perform blood tests including: 17 OH-progesterone, total testosterone, dehydroepiandrosterone sulphate, androstenedione
Brain tumours	Children and adults • Annual brain MRI
Breast cancer	Adults • Surgical – Offer risk-reducing bilateral mastectomy for women aged <50 years with self-surveillance of breast area afterwards • Surveillance – Breast awareness from age of breast development – Annual breast MRI from age 20 years (mammogram and ultrasonography only to be considered if MRI unavailable) – if pregnant/lactating, consider ultrasonography • Risk-reducing medication – Consider tamoxifen in consultation with a medical oncologist
Colorectal cancer	Adults • Colonoscopy every 2–5 years from the age of 20 years or younger depending on family history
Gastric cancer	Adults • Endoscopy every 2–5 years from the age of 25 years or younger if there is a family history of gastric cancer or a high ethnic risk (eg East Asian background)
Haematological cancers	• No evidence of benefit for screening of asymptomatic individuals
General assessment	• Biannual (for children) and annual (for adults) clinical review with complete physical including: blood pressure, height, weight, examination for signs of virilisation (children) and neurological exam from time of genetic diagnosis • Awareness and prompt reporting of any new symptoms • Awareness of increased risk for rare malignancies and the increased risk of a second malignancy after a first diagnosis • Avoidance of unnecessary radiation exposure for screening or therapeutic purposes

LFS, Li-Fraumeni syndrome; MRI, magnetic resonance imaging

approved by the Human Research Ethics Committees of the Peter MacCallum Cancer Centre, Melbourne (HREC/16/PMCC/196).

Population, sampling and recruitment

The researchers purposively sampled participants using clinical databases from four genetic services in Victoria, Western Australia and Queensland.[23] Individuals aged 15–39 years and diagnosed with, or at 50% risk of having, a pathogenic germline variant in *TP53* were invited to participate. The researchers aimed to recruit 15–30 participants for this study to achieve adequate information power.[24] Participants were invited by mail, at upcoming clinical appointments by their treating clinician, and by family members who had contact with a genetic service. Written consent was obtained for all participants; those under the age of 18 years provided written assent with written consent from a parent/guardian.

Data collection and analysis

RFS conducted all interviews by telephone or in person between May 2017 and January 2019. Participants aged <18 years could elect to have a parent/guardian present. Interviews were guided by a semi-structured schedule developed by a multidisciplinary team using previous research.[19] Interviews were audio-recorded, transcribed verbatim and de-identified prior to analysis. The researchers used codebook thematic analysis to generate findings with inductive coding.[25] The codebook was updated, and analytical decisions were discussed at regular team meetings to generate themes. Recruitment ceased after the target of 30 participants was reached. QSR NVivo 12.6.0 supported data analysis and management.

Results

A total of 51 individuals were approached for this study; 11 did not respond or were uncontactable, and 10 declined. The final sample consisted of 30 participants (mean age 25.5 years, range 17–38 years): 26 had a pathogenic variant in *TP53*, while four had not undergone genetic testing

Table 2. Participant characteristics (n = 30)

Characteristics	Mean (range)
Age (years)	
Age at interview	25.5 (17–38)
Age at genetic testing	22.4 (5–35)
Time since genetic testing at study (years)*	3.2 (0.3–16)
	n (%)
Age distribution	
Aged 15–17 years	3 (10)
Aged 18–29 years	20 (67)
Aged 30–39 years	7 (23)
Sex	
Female	20 (67)
Male	10 (33)
***TP53* variant status†**	
Inherited *TP53* positive	24 (80)
De novo *TP53* positive	2 (7)
50% risk and untested	4 (13)
Ethnicity	
Caucasian	26 (87)
Asian	4 (13)
Current residence	
Victoria	20 (67)
Western Australia	6 (20)
Queensland	2 (7)
New South Wales	1 (3)
New Zealand	1 (3)
Cancer history	
Diagnosed with cancer once	7 (23)
Diagnosed with cancer multiple times	4 (13)
Risk management	
Whole-body screening with WBMRI	20 (67)
Whole-body screening not including WBMRI	2 (7)
BC and CRC screening, skin and physical examination	3 (10)
BC screening only	2 (7)
None‡	3 (10)
Risk-reducing surgery	
Risk-reducing mastectomy	6 (20)
Hysterectomy + bilateral salpingo-oophorectomy§	2 (7)

**Refers to n = 26 who underwent genetic testing*
†Variant status refers to participants' genetic test results, either inherited from a parent or de novo variants that arise in embryonic development and are not inherited from a parent
‡Participants not enrolled in risk management were untested and at 50% risk
§Refers to the surgical removal of both ovaries and fallopian tubes
BC, breast cancer; CRC, colorectal cancer; WBMRI, whole-body magnetic resonance imaging

and were at 50% risk of having a variant (Table 2). All except three were engaged in risk management; most (20/30) were enrolled in intensive risk management with whole-body MRI in Victoria (Table 1), although seven only had organ-specific screening available at services in other states. The researchers identified a core tension in the accounts of participants about the utility and burdens of risk management for LFS. This tension is described in this article using illustrative quotes. Pseudonyms are used throughout, and participant age in years, variant status (+ve, de novo or 50% risk) and cancer status (no cancer or cancer[s]) are provided to contextualise their responses.

The benefits and burdens of screening for LFS

> *[Risk management] makes me feel like I'm doing the right thing for my body. It does also make me very aware of how fragile I am …* (Tasha, 24, +ve, no cancer)

Participants perceived both organ-specific and whole-body cancer screening as a fundamental means to gain control over LFS. Being able to detect cancers early for a potentially better prognosis provided participants 'peace of mind' (Ben, 23, +ve, no cancer) or 'breathing room' (Jamie, 25, de novo, multiple cancers) from the incessant threat of new or recurrent cancer and was perceived as the 'right thing' to do for their body (Tasha, 24, +ve, no cancer). Although screening was participants' 'best shot' (Carolyn, 34, +ve, no cancer) at controlling their health with LFS, it was in tension with several perceived burdens. First, with limited alternative options to increase their longevity other than lifelong intensive screening, some described a loss of control over their future and themselves:

> *I hate [screening], I really hate it. It makes me feel like I've lost control over myself in a way that doesn't sit well with me. But I also understand that this is my best shot right now. I'm used to having options [though], and this is the first-time where it's like, 'you do this or you're [expletive]'.* (Carolyn, 34, +ve, no cancer)

Second, participants also understood that screening was limited to diagnosing cancers at early stages and did not reduce their cancer risk. The limitations of screening were evident when participants spoke of rarer cancers associated with LFS (eg brain tumours), where early detection was no guarantee of a better prognosis:

> *I know that breast cancers can be difficult to cure, but I'm much more afraid of getting glioblastoma or sarcoma because even if they find them [early], my odds of survival probably still aren't that good.* (Catherine, 24, +ve, no cancer)

Committing to intensive screening for LFS to detect possibly untreatable cancers therefore required considerable emotional investment as the benefits were unclear.

Third, the lead-up to and process of whole-body MRI scans was distressing for some participants. Ruminating on the possible outcomes of their scans and the implications of a finding made them feel vulnerable. Attending appointments and wondering 'is today going to be the day?' was a common experience and principal burden among those who attended screening (Tasha, 24, +ve, no cancer).

> *I'm in the MRI machine for three hours and it's just going through my head, like: 'What are you going to do if they find something? What are going to be your immediate actions and how are you going to deal with this? What are you going to do with your study … what if you get really sick, like, what happens?' It's a downward spiral of those thoughts.* (Melissa, 20, +ve, no cancer)

Participants also described screening for LFS as a lifelong commitment, which was a daunting prospect because of the regularity of screening and worry associated with its outcomes, especially for participants diagnosed with LFS at young ages.

> *I got diagnosed [with LFS] at 15, and you're like, 'I have 70 years to think about this.' … I have scans every three months and you just get worried every three months, and to know that could go on for 70 years is just really scary.* (Anna, 17, +ve, cancer)

Indeed, screening could only provide temporary proof that one's body was healthy before the cycle would have to begin again, in some cases quite soon. Continually dredging one's body for 'secrets' (Carolyn, 34, +ve, no cancer) was an exhausting proposition and underscores the cyclical nature of emotional burden associated with screening for LFS. Moreover, beginning whole-body surveillance with MRI heralded a new relationship with one's body.

> *I'm a little nervous, not just about the [MRI] procedures and things, more like the realisation that my body is not going to have any secrets from me anymore …* (Carolyn, 34, +ve, no cancer)

Carolyn (34, +ve, no cancer) described discomfort at being subjected to a powerful form of technological knowing with MRI that superseded her own knowing of her body. Instead, her material body potentially harboured 'secrets' (ie cancer) that had to be managed by constant surveillance and was separate to her sense of self (ie disembodied). Despite intensive screening enabling the early detection of some cancers, participants were keenly aware that it was a significant undertaking, both physically and emotionally.

Taking preventive action: The benefits and burdens of risk-reducing surgery in the context of LFS

> *I mean with a [breast cancer] risk that high, I'd rather be alive with fake boobs than have cancer but still have real ones.* (Sarah, 20, +ve, no cancer)

Young women were all acutely aware of their 'obscenely' high breast cancer risk with LFS (Catherine, age 24 years,+ve, no cancer), and while they had varied views on RRM, more than half (12/20) planned to or had completed the procedure from as early as 22 years of age. RRM enabled women to evade the anticipated future they perceived as being written in their

genes: that of a breast cancer patient. Although RRM offered control over breast cancer risk, women were aware of its physical and emotional toll, as well as its implications for family formation and breast feeding. Michelle (27, +ve, no cancer) had completed an RRM and recounted:

> *I was really bummed out about [the RRM] because I didn't want to do the surgery. There weren't many cons it was just me, like, my emotional side, like not having breasts and if I want to have a baby I can't breastfeed and all that. But the pros outweigh the cons because I could be putting myself in danger by getting [breast] cancer and then I might not even be able to have a kid ...*

Women recognised that they could not reduce cancer risk for other body parts in the same way as breast cancer. Referring to RRM, Carolyn (34, +ve, no cancer) described, 'I feel like cutting something off means that it's gone. Whereas I'm not sure what else I could cut off for the other cancers'. For some women, however, the removal of body parts to reduce cancer risk was routine: 'I get anything cut off that I don't need' (Kirsty, 37, +ve, multiple cancers). Indeed, two women had completed hysterectomies and removed their ovaries prophylactically, despite uterine and ovarian cancer risk not being associated with LFS.

> *I have my left side mastectomy for the cancer and all of my nodes in my armpit are all gone. And then I chose to have the right side [removed] and then I also chose to have a hysterectomy with all my ovaries and tubes and everything out. Because I can reduce [the risk of] four cancers right there. If I still had them ... you never know. I've reduced four [cancer risks]; I'll take that chance.* (Ashley, 34, +ve, cancer)

Completing these procedures underscores how the severe health threat of LFS can affect patient decision making, where the removal of body parts, even when not at risk, is perceived as a viable approach to maintain health. It also suggests that health professionals operated outside of risk management guidelines for LFS by facilitating these surgeries that are not indicated in the cancer risk management guidelines.

By contrast, young men in the sample had no preventive options and resisted relating to or considering a future self that was defined by having cancer.

> *I'm not 'the cancer guy', [cancer] doesn't define my life or anything so there is no point, in my eyes, worrying about the future where I get cancer and get sick and have trouble with that. I might as well look forward to a normal, healthy life and then if I do get sick, I can deal with that.* (Ben, 23, +ve, no cancer)

Without an alternative to increase their longevity, young men described a level of acceptance with screening being the norm in their life and something they 'have' to do.

> *[Screening] is just something that I have to do ... it's like paying the bills or something, you just have to do it. It's just another part of life for me having this gene [variant].* (Felix, 20, +ve, no cancer)

Discussion

This study reports on the risk management experiences of young people with, or at risk of, LFS. The present findings contribute to the small body of evidence to date that can help young people make informed decisions about risk management in the context of rare inherited cancer.[9] Similar to previous research with adults with LFS, in the face of high cancer risk, young people in this sample viewed early detection from risk management as a critical means of control over LFS.[18,26]

However, engaging in experimental and intensive whole-body screening (eg whole-body MRI) meant continually dredging one's body for 'secrets' and physical manifestations of cancer risk with uncertain outcomes. Partaking in the cyclical process of cancer screening was distressing for many in the sample and supports reports of 'scanxiety' among adults with LFS and cancer survivors attending post-treatment survivorship care.[17,18,27] For some participants, the prospect of having to cope with scanxiety and the medicalisation of their body for their entire life was daunting. While recent work suggests that using whole-body MRI for baseline screening and follow-up investigations does not increase cancer worry or depression,[17] the present sample showed that repeatedly anticipating whole-body scan outcomes introduced a psychosocial complexity to screening, with implications for screening fatigue and drop out that could lead to poor cancer outcomes from late detection. The study was unable to assess the long-term psychosocial effects of intensive risk management, and it remains a critical topic for future research.[17]

As the range of clinical severity between different *TP53* variants becomes clearer, risk-adapted screening for LFS based on mutation type may indicate intensive screening is only necessary in certain cases. Though genotype–phenotype evidence is still emerging, risk-adapted screening could mean fewer individuals need to unnecessarily navigate the psychosocial complexity of intensive protocols.[12] In the meantime, psychosocial interventions for those engaged in intensive screening could prove helpful to mitigate and manage potential distress. Further research is required in this area, although clear care plans with built-in psychosocial check-ups and referral to psychological services for specific therapy (eg cognitive behavioural therapy) could be useful. GPs could play a key part in the coordination of this support by facilitating Mental Health Treatment Plans, especially for individuals in regional areas with limited access to specialist genetic counselling support.

A unique finding was that, for one participant, the diagnostic power of whole-body MRI introduced a new relationship with her material body, creating a fragmented sense of body and self. Although this fragmented sense of the body has been linked with the imaging of certain body parts (eg the breast),[28] the novel use of whole-body imaging technology for cancer screening heralds new and underexplored implications for bodily perceptions of disease and identity that merits further investigation.[29,30]

Experiences of RRM in the context of LFS mirror those of young women with *BRCA1/2* variants,[31] albeit at younger ages. For most women in the present study, the benefits of RRM in almost eliminating their high breast cancer risk outweighed the physical toll of drastic surgery and the psychosocial burdens of adapting to a new body image and being unable to breastfeed. However, beyond breast cancer there are no other risk-reducing options for the wide range of LFS-related cancers. Nonetheless, two women in the sample had organs not associated with LFS removed prophylactically, underscoring the severe health threat LFS poses. It is important that GPs are aware of the potential for cancer worry among young people with LFS and how it can affect decision making about risk management options. The health professionals who supported these procedures may have been misinformed about appropriate risk management for LFS, or they may have acted on medical and/or psychosocial information not apparent in the interview. Having an awareness of available evidence-based options may help GPs guide patient decision making and help to identify those in need of additional decisional support. Risk-reducing options were not available for men, and their experiences of coping with high cancer risk with no prevention require additional research.

The role of general practice

It is important that GPs are aware that although risk management for inherited cancer syndromes improves cancer outcomes, it comes with psychosocial implications. The benefits of intensive and experimental protocols especially (eg for LFS) can have a complex relationship with the physical, emotional and psychsocial burdens experienced by patients. GPs can play a key part in supporting patients with inherited cancer syndromes by coordinating support services and organising Mental Health Treatment Plans.

It is recommended that GPs be mindful of access barriers to experimental risk management protocols for some inherited cancer syndromes. Referring high-risk patients to interstate services or having links with local oncologists who specialise or have an interest in familial cancer may help establish shared-cared arrangements with GPs based on available risk management guidelines.

GPs have a key role in enquiring about their patients' family history of cancer and referring those with high-risk features (eg strong family history, cancer diagnoses at young ages or family members diagnosed with an inherited cancer syndrome) to clinical genetics services for cancer risk assessment, genetic counseling and risk management.

Conclusion

Though rare, individuals with early onset inherited cancer conditions can present in primary care. Taking seriously the concerns of potentially high-risk individuals and referring them to a genetics service could be life saving. Risk management is available for individuals with high cancer risk and should be discussed as an option, addressing both benefits and burdens across the lifespan.

Implications for general practice

- GPs play a key role in managing familial cancer by accurately and promptly referring high-risk individuals to familial cancer centres for genetic counselling and risk management.
- Risk management for inherited cancer is a critical part of care provided to high-risk individuals, but little is known about risk-management experiences outside of common inherited cancers (eg breast and colorectal cancer).
- Keeping individuals engaged in cancer risk management can be challenging, especially for complex, intensive, multimodal protocols that have a growing evidence base (eg risk management for LFS).
- Young people experience cancer risk management in ways that are different to adults because of their transitional life stages, which may affect the acceptability of, adherence to and outcomes of screening.
- GPs should be aware of inherited cancer syndromes and how young people may experience the burdens and utility of cancer risk management.

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