Running head: Whole body screening, *TP53* mutation carriers, psychosocial morbidity

Psychosocial morbidity in *TP53* mutation carriers – is whole-body cancer screening beneficial?

Kate A. McBride [1,2]; Mandy L. Ballinger [3]; Timothy E. Schlub [2]; Mary-Anne Young [4]; Martin H.N. Tattersall [5], Judy Kirk [6] Ros Eeles [7]; Emma Killick [8] Leslie G Walker [9]; Sue Shanley [4]; David M. Thomas [3]; Gillian Mitchell [4, 10];

[1] School of Science and Health, Western Sydney University, Campbelltown, NSW 2560, Australia; [2] Sydney School of Public Health, Camperdown, NSW 2006, Australia; [3] The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia; [4] Familial Cancer Clinic, Peter MacCallum Cancer Centre, E. Melbourne, VIC 3002, Australia; [5] Department of Cancer Medicine, The Chris O'Brien Lifehouse, Sydney Medical School, Camperdown, NSW 2006, Australia; [6] The Familial Cancer Service, Crown Princess Mary Cancer Centre, Westmead, NSW 2145, Australia; [7] Oncogenetics, The Institute of Cancer Research, London, UK ; [8] Medical Oncology Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK ; [9] University of Hull, Kingston upon Hull, UK; [10] Sir Peter MacCallum Dept. of Oncology, University of Melbourne, Parkville, VIC

Address for correspondence: Kate A McBride

Building 24, School of Science and Health

Western Sydney University

Campbelltown

NSW 2560

k.mcbride@westernsydney.edu.au

00612 4620 3346

Keywords: Li-Fraumeni Syndrome; *TP53*; screening; hereditary cancer; psychosocial; mixed methods

Abstract

Germline *TP53* mutation carriers are at high risk of developing a range of cancers. Effective risk management is an important issue for these individuals. We assessed the psychosocial impact in *TP53* mutation carriers of WB-MRI screening as part of the Surveillance in Multi-Organ Cancer (SMOC+) protocol, measuring the wants and needs, anxiety and depression levels as well as cancer worry in this high cancer risk population. This mixed methods paper reports the preliminary psychosocial findings from 17 participants during their first 12 months on the trial. Psychological questionnaires were completed and in-depth interviews about their experiences undertaken. Overall, we found a significant reduction in participants' mean anxiety from baseline to two weeks post WB-MRI (1.2, 95% CI 0.17 to 2.23 p = 0.025), indicative of some benefit. We did not detect a negative change in short-term depression and cancer worry or change in anxiety/depression/cancer worry/ intrusive thoughts of cancer with time after WB-MRI. Emerging themes show most participants are emotionally supported and contained by screening, despite the current lack of evidence around efficacy of screening. Participants are motivated by their immediate concern of staying alive. For those that do gain emotional reassurance, feelings of abandonment from research are a risk when the study ends. For others, screening is a burden, consistent with the relentless nature of cancer risk associated with Li-Fraumeni syndrome. Families with *TP53* mutations need ongoing support due to the impact on the whole family system. This evaluation may also inform the care of individuals and families with other cancer predisposition syndromes.

Introduction

Individuals with a germline *TP53* gene mutation have the Li-Fraumeni Syndrome (LFS) [1, 2]. They have a high risk of multi-organ cancer, developing often from childhood [3-6]. Soft tissue sarcomas (STS), osteosarcoma, adrenocortical carcinoma (ACC), brain tumours and breast cancer are the most commonly occurring malignancies, with breast cancer predominating in women (~79%) followed by STS for both sexes (~27%) [6]. Approximately 50% of carriers will develop cancer by age 30 [7, 8], with multiple malignancies developing in nearly half of all carriers [2, 6]. Additional primary tumours may be due to the underlying gene mutation or due to the effects of prior therapeutic or diagnostic radiation and/or chemotherapy [3, 9, 10].

Historically, genetic testing rates for mutations in the *TP53* gene have been low due to ethical, social and clinical management concerns [11, 12]. More recently, however, rates of clinical testing for germline *TP53* mutations appear to be increasing due to advances in cancer screening and other clinical management options as well as the availability of germline and tumour panel testing [11]. Once mutation carriers are identified, effective risk management for most of the associated malignancies is an issue. A number of international clinical trials are underway to assess the efficacy of whole body (WB) screening trials with magnetic resonance imaging (MRI) as a core cancer screening modality for this population [13-15]. The psychosocial impact and tolerability of screening in this population is not known.

Studies assessing the psychosocial effects of carrying a germline *TP53* mutation have focused on genetic testing or the emotional impact of being a mutation carrier [16]. More recently studies have questioned how carriers cope with their *TP53* status in the face of the medical, emotional and social challenges [11]. While the psychosocial impact of *TP53* mutation carriers taking part in screening programs has not yet been investigated in detail, a positive attitude toward screening as a concept has been reported [17]. Data from screening trials in other hereditary cancer populations shows mixed psychosocial effects. Individuals at high risk of pancreatic cancer taking part in a comprehensive screening program (MRI, ultrasound and blood sampling) did not have increased levels of general distress or risk perception [18]. Further, breast MRI and mammogram in women at high risk of breast cancer (mostly from families with a history of breast cancer but also some with a *TP53* mutation) were considered acceptable [19]. In contrast, in a systematic review of screening in hereditary cancer syndromes where carriers are predisposed to multiple malignancies, screening was associated with higher

distress and a reduced quality of life [20]. These conflicting findings highlight the need for a formal evaluation of the psychosocial effects of intensive cancer screening in *TP53* mutation carriers. This may also inform care in other multi-organ cancer predisposition syndromes. In this study, we sought to assess the psychosocial impact on *TP53* mutation carriers of the first 12 months of participation in the Australian SMOC+ trial.

Methods

Participants in the SMOC+ trial were all consented to the psychosocial sub-study. SMOC+ was approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee, East Melbourne, Victoria; approval number HREC/12/PMCC/17. SMOC + originally recruited via the International Sarcoma Kindred Study (ISKS) or through Familial Cancer Clinics (FCC) in New South Wales and Victoria, Australia. ISKS identified *TP53* mutations in a subset of sarcoma patients, whereas the clinic patients were identified because of a personal/family history of *TP53*-related cancers. Participants were eligible if they carried a pathogenic germline *TP53* mutation or were at risk of carrying a mutation due to the presence of a detected *TP53* mutation in a first degree relative, were aged 18-70 years and had an expected lifespan of 3 years or more. All SMOC+ participants were offered annual screening with WB-MRI, annual physical exam, breast MRI (females only) and colonoscopy and/or endoscopy dependent on family history. Participants completed questionnaires and interviews at baseline and at several time points post WB-MRI. We used a mixed methods design [21-23]. Data from the questionnaires were concurrently triangulated with an in-depth analysis of the reported experiences of the participants during their first year on the whole-body screening trial. Equal weight was given to both types of data during the collection and analysis stage. A separate data analysis was conducted for each dataset then triangulated at the interpretation phase of the study. Both qualitative and quantitative data were collected between July 2013 and August 2015.

Qualitative phase

Interview process

Participants were invited to take part in two in-depth semi-structured interviews lasting on average 30 minutes to one hour. All interviews were conducted by K.A.M. and were guided by a schedule, which included open-ended, semi-structured questions covering several broad topics. All interviews were recorded and transcribed. The first interview was conducted prior to the commencement of any cancer screening to evaluate participants' hopes for screening and awareness of cancer risk. The second interview took place 6 months later to allow participants to reflect on their screening experience – the lead

up to the WB-MRI, the screening examination experience itself, feedback of results of screening, awareness of cancer risk and thoughts about future surveillance.

Qualitative data analysis

Transcripts were analysed by thematic (inductive) analysis, informed by grounded theory methodology [24]. Coding team members (K.A.M. & M-A.Y.) read the first six transcripts individually, identified significant content and noted personal reactions and reflections. Findings were recorded individually with supporting quotes. The coding team then met to discuss interpretations and synthesize findings into recurring themes. This iterative process was followed until thematic saturation was reached, after which there were further discussions about additional findings.

Quantitative phase

Procedures

To determine the psychological impact of WB screening, pre-validated scales were completed at baseline and 2, 12, 26 and 52 weeks post WB-MRI (Table 1). The questionnaires for each time point contained pre-validated scales to evaluate various psychosocial outcomes. Permission was sought and given for the use of each of these scales. The scales included the Hospital Anxiety and Depression Scale (HADS) [25] , Impact of Events Scale cancer specific (IoE-C) and MRI specific (IoE-M) [19, 26, 27] and Cancer Worry Scale [28, 29]. Socio-demographic, cancer history and screening history data were collected at baseline.

Table 1 somewhere here

Quantitative data analysis

Descriptive statistics were calculated for demographic and other variables. A paired *t* test was used to determine the short-term effects of the WB-MRI on anxiety and depression (baseline versus 2 weeks post WB-MRI) and cancer worry (baseline versus 12 weeks post MRI). A longitudinal analysis of HADS and CWS scores as well as IoE-C and IoE-M scores was also conducted to assess changes over time, post-MRI. To adjust for correlated responses within each participant, linear mixed modelling was used to describe the longitudinal changes with time in the perception of the lifetime risk of developing cancer, cancer specific worry, anxiety and depression, intrusive thoughts of cancer and intrusive

thoughts relating to the WB-MRI. A random effect for the intercept, and the slope with time were used. Each tool is calibrated permitting the determination of clinical relevance of changes in scores over time for each. SPSS for Windows version 22 was used for all analyses [30].

Results

The SMOC+ trial commenced in July 2013 and continues to recruit participants. Of the 17 participants included in this report, 11 had a past history of malignancy and 6 were unaffected by cancer. Socio-demographic details of the study participants' cancer history and prior MRI screening (n = 17) are presented in Table 2. Mean age at study entry was 43.3 years. The sample consisted of 9 females (53%) and 8 males (47%). At the commencement of the trial 11 participants (65%) had previously been affected by cancer. Nine of the participants had previously had an MRI (either part or whole of body). Malignancy was detected in 3 participants following WB-MRI (2 asymptomatic primary cancers - prostate cancer and a well-differentiated liposarcoma; 1 recurrence of metastatic leiomyosarcoma, and this participant was subsequently withdrawn permanently from the trial due to a limited life expectancy. The participants with new primaries were temporarily suspended from the study until cancer treatment was complete. Sixty-four of 75 (85%) questionnaires were completed, though eight of those not returned are participants suspended from the trial as above. For continuing participants 64/67 (96%) of questionnaires were completed. Fourteen participants took part in the first interview and nine the second (Figure 1). Two participants elected not to take part in the interviews and one not approached due to detection of cancer during screening.

Figure 1 SMOC study flowchart somewhere here

Baseline assessment

At baseline, the mean HADS anxiety and depression scores (n=17) were 5.33 (SE 0.3) and 2.53 (SE 2.1) respectively. Scores of 11 or more suggest clinically significant anxiety or depression while a score of 8-10 suggests borderline anxiety or depression. Three participants had borderline anxiety, a further two had scores suggestive of clinical anxiety and one participant met the clinical cut-off for depression (score >11) (Supplementary Figures 1 and 2). The remaining 11 participants did not display anxiety or depression at clinically concerning levels. The mean CWS score at baseline was 14.0 (SE 0.13). The scale gives a summative score between 8-32; a higher score indicates greater cancer worry. A clinical cut

off of 14 has been shown to indicate severe cancer worry [31] Eight of seventeen (47%) participants scored 14 or more and were considered to have frequent cancer worry (Supplementary Figure 3).

Table 2 Description of participants somewhere here

Quantitative impact of screening

Quantitative results showed a significant 1.2 reduction (95% CI 0.17 to 2.23; p = 0.025, *t* = 2.5, 14 *df*) in short-term anxiety score (HADS) at 2 weeks post WB-MRI from baseline. There was a non-statistically significant reduction in short-term depression (HADS) of 0.67 (95% CI -0.37 to 1.71; p = 0.36, *t* = 0.1.38, 14 *df*) (Table 3). This study had ≥80% power to detect a change of 2 points for HADS anxiety and 2 points for HADS depression. Consequently the non-significant result for depression indicates that any difference in mean score before and after MRI is below what was considered to be a significant change in scores. The longer-term effects on anxiety and depression of the WB-MRI during the first 12 months of the screening trial were assessed for 14 participants. Both anxiety (p = 0.274) (Supplementary Figure 1) and depression scores (p = 0.942) (Supplementary Figure 2) decreased slightly before rising again prior to the second WB-MRI.

The cancer worry scale (CWS) was used to examine how screening impacts the perception of cancer risk burden associated with *TP53*. There was a reduction in the mean CWS after screening (short-term) of 0.21 (95% CI -1.26 to 1.69) although this was not statistically significant (p = 0.758, *t* = 0.35, 14 *df*). Similarly, the longer-term effects of screening on cancer worry during the first 12 months showed a slight decrease over time using linear mixed modelling, though again this was not statistically significant (p = 0.233) (Supplementary Figure 3).

We assessed the longer-term effects of WB-MRI on intrusive thoughts of cancer (as measured by the cancer specific Impact of Events Scale [IoE-C]) and whether they could be contained (that is, kept to a minimum). Reflective of cancer worry scores, there was a trend for IoE-C scores to decrease slightly over time, although this was not statistically significant (*P*=0.091) (Supplementary Figure 4). Lastly, the longer-term effects of the WB-MRI on avoidance and intrusive thoughts about the WB-MRI itself were assessed using the MRI specific Impact of Events Scales (IoE-M). Linear mixed

modelling was not conducted as scores for all participants were consistently minimal. These scores were all well below the clinical cut off for avoidance and intrusive thoughts in relation to the WB-MRI (Supplementary Figure 5).

Perceptions of participation in screening

Four main thematic areas emerged from the qualitative data: 1) perceived efficacy of screening, 2) burden of screening, 3) burden of a germline *TP53* mutation on their life, 4) containment of the psychological impacts of carrying a germline *TP53* mutation. Exemplary quotations illustrating the themes are presented in Table 4. Here we discuss each theme in turn.

Perceived efficacy of screening

Despite being realistic about the chances of developing cancer, almost universally the participants perceived that the screening would detect cancer if they had it. They also thought that WB screening, specifically the WB-MRI, would detect cancers at an early stage, thus making the cancer more treatable, despite the absence of proof of efficacy of WB-MRI in this population to date. The sense of reassurance is perhaps unsurprising, given these subjects had just been given the all clear following their WB-MRI.

Burden of screening

The lack of a sustained reduction in anxiety and depression measures following the observed short-term reduction may be explained by the qualitative data. Following their initial faith in the WB-MRI being able to detect cancers at an early and treatable stage, longitudinally five participants felt that the screening was burdensome and this increased their worry. The sense of burden was increased when WB-MRI findings needed to be investigated further, or where the MRI coincided with other medical issues and follow up appointments that impacted upon their everyday lives. In other cases, the screening was onerous due to other life circumstances, such as minor illness or where stressors were multiple, both of which exacerbated the effects of taking part in the trial. Ultimately for some, participation in the screening program raised anxiety as a reminder of carrying a *TP53* mutation. One participant said that screening 'brought them (feelings of anxiety) back' and it appeared from the data that for others, those who were well became "sick" because of the ongoing appointments and attendance at various clinical services. Several participants also said the WB-MRI itself made them anxious because of claustrophobia, as well as the discomfort of having to lie in the MRI scanner for so long. Many of the scans took over two

hours. Lastly, a few participants raised the issue of future "abandonment" from the trial – they were aware the trial was limited to three annual WB-MRIs. This appeared to make those participants more anxious in the long-term once the short-term relief had worn off, as they were worried about how they would manage their cancer risk following cessation of the trial.

The burden of a germline TP53 mutation

In addition to the sample size, the qualitative data may shed insight into why cancer worry did not significantly drop over the screened period. For many of those interviewed, the ongoing effect of a germline *TP53* mutation on their lives and their families was apparent, irrespective of the screening. They described the cancer diagnoses and subsequent deaths that had affected their family. The burden of having a *TP53* mutation impacted on the whole family system and meant those interviewed could often not share their burden of cancer worry with their relatives. They also had to face the potential consequences of their children having the gene mutation and the consequent cancer risk. The parents interviewed expressed guilt and worry for possibly passing the mutation on to their children. Parents also worried about becoming ill and the effect of this on children. This was a key motivator for taking part in the trial, despite adding to the overall burden of having a *TP53* mutation in the family.

Containment of the psychological impacts of carrying a germline TP53 mutation

Although of borderline significance, the trend to long-term reduction in cancer worry suggests that intrusive thoughts of cancer may be contained to a certain extent by screening. Consistent with this, most participants reported that both the screening and having a clinical point of contact was emotionally "containing" them. They were aware of their cancer risk but the option of screening and care by a physician provided a way for them to better psychologically cope with their gene mutation. Furthermore, hearing that the MRI was clear provided a positive psychological benefit. Even with a benign incidental finding, the study doctors' confidence in interpreting and explaining the finding reassured and emotionally held the participants. Participants also felt they were "doing" something positive about their gene mutation through screening, and for several participants, the screening negated the need to continually self-symptom seek. This is reflective of having a reduction in intrusive thoughts of cancer which could necessitate the need to self-symptom seek.

Discussion

The psychological effects of genetic testing for *TP53* have previously been assessed quantitatively through a comparison of individuals from *TP53* positive families who did or did not choose to have genetic testing [32] and also in those considering genetic testing for *TP53* [33]. The first study found that 23% of both carriers and non-carriers reported clinically relevant levels of LFS distress: carriers were no more distressed than non-carriers. The second study found that a lower quality of life, higher perceived risk of a *TP53* mutation, an absence of a personal cancer history and number of relatives were indicative of cancer specific distress in the context of genetic testing. These findings are consistent with the results of our baseline assessments in study participants.

Attitudes towards cancer screening in this population have also been assessed [17]. Prior to any structured screening trials, that study examined what screening advice was given to germline *TP53* carriers living in the Netherlands, to what degree mutation carriers adhered to the advice and what, if any, were the psychological consequences of screening. They found 78% of its participants received a tailored screening program with most of the respondents (90%) believing screening would detect tumours at an earlier stage and that screening gave them a sense of control (84%). This optimistic perception of the benefits of screening is consistent with our findings. In contrast, the psychosocial effects of WB-MRI screening in germline *TP53* mutation carriers has not been previously reported. Our data suggest that participation in the SMOC+ WB-MRI cancer-screening program does not have a negative psychosocial impact. Similar to the Netherlands study, for many of the Australian participants, the WB-MRI screening seems to aid coping in the face of a proven or suspected germline *TP53* mutation due to a perceived benefit of screening, at least in the short term [17]. Anxiety scores were highest at baseline, but were significantly reduced two weeks post WB-MRI, indicating this initial high anxiety was temporary and perhaps related to anticipation of the WB-MRI. This is reflected in the Impact of Events MRI (IoE-M) data, where no participants had intrusive thoughts post WB-MRI. These data are consistent with previous research showing high-risk women attending for breast screening had high levels of baseline psychosocial morbidity that reduced following screening. It appears that individuals are often at their most vulnerable at recruitment and just prior to having their screening [19].

These quantitative data are reflected in the qualitative data, as the presence of stress and anxiety around the screening itself were reported. In addition to anxiety about the possibility of a cancer diagnosis, some participants reported claustrophobia due to the nature of the WB-MRI itself. Once the WB-MRI was over and a clear result given, however, participants felt reassured. Practically, anxiety around the WB-MRI itself could be reduced by providing appropriate support and information [34]. Comprehensive information about what to expect during the scan, length of the scan, relaxation techniques and sedation for particularly nervous participants are approaches that could be discussed in even more detail at recruitment [35, 36]. Minimising time from recruitment to scanning may also reduce pre WB-MRI anxiety. In this trial, once patients were recruited, they waited on average three weeks for the WB-MRI (range 1 to 8 weeks), due to the challenging logistics of securing access to an MRI scanner for the required length of time.

Some participants also reported the screening process to be a burden as they progressed through their first year. Other stressors, such as worry about their children having *TP53* testing, relationship difficulties or multiple medical appointments because of their mutation, added to the perceived burden of screening. Consistent with previous findings, it was also clear that having a *TP53* mutation is often an unrelenting burden in the lives of participants, due to the strain it places on the family system and relationships. An example is the responsibility of having to manage distress in children because their parent was ill. In some cases the screening appeared to exacerbate this burden because of the time involved and follow up appointments. The screening also appears to serve as a reminder of their mutation status: it "brings them back" and was described as making them "sick" even though they are well. These participants may need ongoing support, particularly as many felt they could not share their cancer worry with those closest to them. Nonetheless, participants still acknowledged that they wanted to have screening because of their belief in the effectiveness of the screening and being motivated by being well for their family and children. Several voiced concern about how they would access WB-MRI once the clinical trial had ceased. This highlights that the SMOC+ clinical trial is the only means by which most germline *TP53* mutation carriers in Australia can currently access WB-MRI screening. The cost of WB-MRI was cited by several participants as being another key motivator for taking part in this clinical trial. Healthcare is being accessed via the research "back door" [37]. This raises the potential for a perception of "abandonment" by the research team when the study concludes, as many of the research team are also part of the clinical team responsible for these patients. This could be a concern for the participant's ongoing relationship with the clinical team.

The psychological benefit for study participants is likely due to their perception that the WB-MRI can detect cancers at an earlier, more treatable stage, thus conferring a possible survival benefit. This is yet to be proven, but the results of SMOC+ and at least two other studies will soon be released, addressing this critical question. Regardless of its evidence base, screening gave participants a sense of control, reduced self-symptom seeking, and made them "freer in life", perhaps because they had a clinical point of contact. This was reflected in the slight (though non statistically significant) reduction of intrusive and worrying thoughts about cancer. As poignantly described by one young participant, having a clear WB-MRI made him "feel like the rest of the world". These findings suggest that, for some, the WB-MRI trial provides a mechanism to help to emotionally contain the distress associated with the often over-whelming burden of Li-Fraumeni syndrome. However, in others there were unmet support needs, although it is not clear to what extent these are exacerbated by screening. Despite being informed of WB-MRI results by the study doctor and having a clinical point of contact, several participants indicated a greater ongoing need to have someone they could email or telephone to ask questions or if they were worried about symptoms. Many questions concerned associated cancer risks, more detail on scan results and updates on *TP53* research. Several participants were directed back to the FCC for additional psychosocial support. This suggests that for individuals with a germline *TP53* mutation, there are long-term ongoing clinical contact needs. This may explain why anxiety and depression initially dropped post WB-MRI but started to climb again part way through the year as contact with the research team diminished.

These results add to a previous study describing the support systems used by LFS subjects attending a clinic for cancer screening [11]. That study showed that many of their participants had few psychosocial symptoms and appeared well connected and resilient, even though some had already been affected by cancer. Many of the American participants in the study also seemed to have adapted to their "illness" and appeared to easily negotiate medical systems, though it was difficult to ascertain time since mutation detection in these individuals. It is possible the difference in ease of negotiating medical systems among the participants in this study may reflect cultural differences between Australia and the USA. Notably, participants in that study who appeared to cope had a good support network. The few participants in our study who reported psychosocial symptoms had only recently undergone testing for *TP53* and may not have had sufficient time to build up a strong support network. Consistent with research in other family cancer syndromes, the mutation carriers in this study appear to have continuing psychosocial support needs and require access to someone with syndrome-specific knowledge to discuss their concerns/symptoms [29, 38]. The FCCs could consider extending their care beyond the genetic

counselling and testing process to the cancer screening process or local specialists could be identified as the point of contact depending on local circumstances.

Germline *TP53* mutation carriers may benefit from more streamlined cancer screening that provides them with clinical and psychosocial support. Currently risk management clinics (RMCs) provide multidisciplinary care for women at high risk of breast and ovarian cancer across many locations in Australia [39]. Clinical nurse consultants, expert in the management and psychosocial support of high-risk women, are part of these clinics. The nurses coordinate screening, follow up appointments and provide practical as well as emotional support. A very high proportion of women have reported that their needs were being met by the RMC [39]. To leverage off this screening infrastructure already in place, the function of the RMC could be expanded beyond breast/ovarian cancer to include *TP53* mutation carriers, with a clinical nurse consultant or a genetic counsellor knowledgeable in *TP53* who can be accessed as and when needed by carriers. Non-blood relatives, such as partners, could also be offered ongoing psychosocial support, given the reinforcement by this study's data as well as other studies that *TP53* can impact the whole family system [11]. Several additional innovative strategies for germline *TP53* mutation carriers might include a telephone-based peer support scheme [40], an online resource of digital videos designed to provide reliable and easily accessible information for patients with genetic conditions [41] and educational support groups [42]. An evaluation of such strategies is needed.

From a psychosocial perspective, it seems that WB-MRI is an acceptable cancer screening modality for this population, at least within the context of a clinical trial. There was some positive psychosocial benefit of screening, despite baseline anxiety around the WB-MRI itself, although it is clear that having a proven or suspected *TP53* mutation has a major impact on a patient's life and that the impact of screening is only part of the burden or relief of some of the overall burden of being a mutation carrier. Ongoing evaluation and an economic analysis of the benefit of earlier cancer detection in highly cancer prone populations like *TP53* mutation carriers is needed. In the absence of this, ongoing clinical support and a long-term framework to provide psychosocial care to germline *TP53* mutation carriers is an alternative strategy that should be evaluated.

Limitations

The screening trial, and thus this preliminary data, has a small sample size, although this is offset to some extent by the excellent questionnaire response rate and the use of qualitative methods. The trial is ongoing. All participants in this psychosocial assessment had agreed to take part in the WB-MRI screening trial. While our early results showed some benefits of participation in the screening trial, we did not investigate the psychosocial status of *TP53* mutation carriers who chose not to participate in the trial.

References

1. Malkin D (2011) Li-fraumeni syndrome. Genes & cancer 2(4):
2. Kamihara J, Rana HQ, Garber JE (2014) Germline *TP53* Mutations and the Changing Landscape of Li-Fraumeni Syndrome. Human Mutation 35(6): 654-62 DOI 10.1002/humu.22559
3. McBride KA, Ballinger ML, Killick E, et al. (2014) Li-Fraumeni syndrome: cancer risk assessment and clinical management. Nature Reviews Clinical Oncology 11(5): 260-71 DOI 10.1038/nrclinonc.2014.41
4. Li FP, Fraumeni JF, Mulvihill JJ, et al. (1988) A cancer family syndrome in 24 kindreds. Cancer Research 48(18):
5. Ruijs MWG, Verhoef S, Rookus MA, et al. (2010) *TP53* germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. Journal of Medical Genetics 47(6): 421-8 DOI 10.1136/jmg.2009.073429
6. Bougeard G, Renaux-Petel M, Flama J-M, et al. (2015) Revisiting Li-Fraumeni Syndrome from *TP53* mutation carriers. Journal of Clinical Oncology Published ahead of print: DOI DOI: 10.1200/JCO.2014.59.5728
7. Hwang SJ, Lozano G, Amos CI, Strong LC (2003) Germline p53 mutations in a cohort with childhood sarcoma: Sex differences in cancer risk. American Journal of Human Genetics 72(4): 975-83
8. Lustbader ED, Williams WR, Bondy ML, Strom S, Strong LC (1992) Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. American Journal of Human Genetics 51(2): 344-56
9. Limacher JM, Frebourg T, Natarajan-Ame S, Bergerat JP (2001) Two metachronous tumors in the radiotherapy fields of a patient with Li-Fraumeni syndrome. International Journal of Cancer 96(4): 238-42 DOI 10.1002/ijc.1021
10. Chadaz T, Hobbs SK, Son H (2013) Chest Wall Sarcoma F-18-FDG PET/CT in a Patient With Li-Fraumeni Syndrome. Clinical Nuclear Medicine 38(10): 818-20

11. Peters J, Kene R, Bremer R, Givens S, Savage S, Mai P (2015) Easing the Burden: Describing the Role of Social, Emotional and Spiritual Support in Research Families with Li-Fraumeni Syndrome. Journal of Genetic Counseling:

12. Evans DG, Lunt P, Clancy T, Eeles R (2010) Childhood predictive genetic testing for Li-Fraumeni syndrome. Familial Cancer 9(1): 65-9 DOI 10.1007/s10689-009-9245-9

13. Australia New Zealand Clinical Trials Registry (2013 September 4) A pilot surveillance study investigating whole body magnetic resonance imaging and other diagnostic procedures in people at high risk of cancer (SMOC) ACTRN12613000987763. http://www.ANZCTR.org.au/ACTRN12613000987763.aspx. Sydney (NSW), NHMRC Clinical Trials Centre, University of Sydney (Australia),

14. ClinicalTrials.gov (2011 October 31) LIFSCREEN : Evaluation of Whole Body MRI for Early Detection of Cancers in Subjects With P53 Mutation (Li-Fraumeni Syndrome) NCT01464086. Bethsheda (MD), National Library of Medicine (US),

15. Clinicaltrials.gov (2012 27 November) Magnetic Resonance Imaging Screening in Li Fraumeni Syndrome (SIGNIFY)NCT01737255. In (US) NLoM (ed). vol. 28 January. Bethsheda (MD),

16. Patenaude AF, Schneider KA, Kieffer SA, et al. (1996) Acceptance of invitations for p53 and BRCA1 predisposition testing: Factors influencing potential utilization of cancer genetic testing. Psycho-Oncology 5(3): 241-50 DOI 10.1002/(sici)1099-1611(199609)5:3<241::aid-pon235>3.3.co;2-y

17. Lammens CRM, Bleiker EMA, Aaronson NK, et al. (2010) Regular surveillance for Li-fraumeni syndrome: advice, adherence and perceived benefits. Familial Cancer 9(4): 647-54 DOI 10.1007/s10689-010-9368-z

18. Maheu C, Vodermaier A, Rothenmund H, et al. (2010) Pancreatic cancer risk counselling and screening: impact on perceived risk and psychological functioning. Familial Cancer 9(4): 617-24 DOI 10.1007/s10689-010-9354-5

19. Hutton J, Walker LG, Gilbert FJ, et al. (2011) Psychological impact and acceptability of magnetic resonance imaging and X-ray mammography: the MARIBS Study. British Journal of Cancer 104(4): 578-86 DOI 10.1038/bjc.2011.1

20. Gopie JP, Vasen HFA, Tibben A (2012) Surveillance for hereditary cancer: Does the benefit outweigh the psychological burden?-A systematic review. Critical Reviews in Oncology Hematology 83(3): DOI 10.1016/j.critrevonc.2012.01.004

21. Teddlie C, Tashakkori A (2009) The foundations of mixed methods research: Integrating quantitative and qualitative techniques in the social and behavioural sciences. Thousand Oaks, CA, Sage

22. Tashakkori A, Teddlie C (2010) Sage Handbook of Mixed Methods in Social & Behavioral Research. 2nd ed. Thousand Oaks, California, Sage

23. Creswell JW (1994) Research design: Qualitative and quantitative approaches. Thousand Oaks, CA

24. Patton MQ (2002) Qualitative Research and evaluation methods. Thousand Oaks, California, Sage

25. Zigmond AS, Snaith RP (1983) The Hospital Anxiety and depression scale. Acta Psychiatrica Scandinavica 67(6): 361-70 DOI 10.1111/j.1600-0447.1983.tb09716.x

26. Horowitz M, Wilner N, Alvarez W (1979) Impact of event scale - measure of subjective stress. Psychosomatic Medicine 41(3): 209-18

27. Lerman C, Narod S, Schulman K, et al. (1996) BRCA1 testing in families with hereditary breast-ovarian cancer - A prospective study of patient decision making and outcomes. Jama-Journal of the American Medical Association 275(24): 1885-92 DOI 10.1001/jama.275.24.1885

28. Lerman C, Trock B, Rimer BK, Jepson C, Brody D, Boyce A (1991) Psychological side-effects of breast cancer screening. Health Psychology 10(4): 259-67 DOI 10.1037/0278-6133.10.4.259

29. Douma KFL, Aaronson NK, Vasen HFA, et al. (2010) Psychological distress and use of psychosocial support in familial adenomatous polyposis. Psycho-Oncology 19(3): 289-98 DOI 10.1002/pon.1570

30. IBM Corp (2012) IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, IBM Corp.,

31. Custers JAE, van den Berg SW, van Laarhoven HWM, Bleiker EMA, Gielissen MFM, Prins JB (2014) The Cancer Worry Scale Detecting Fear of Recurrence in Breast Cancer Survivors. Cancer Nursing 37(1): E44-E50 DOI 10.1097/NCC.0b013e3182813a17

32. Lammens CRM, Aaronson NK, Wagner A, et al. (2010) Genetic Testing in Li-Fraumeni Syndrome: Uptake and Psychosocial Consequences. Journal of Clinical Oncology 28(18): 3008-14 DOI 10.1200/jco.2009.27.2112

33. Peterson SK, Pentz RD, Marani SK, et al. (2008) Psychological functioning in persons considering genetic counseling and testing for Li-Fraumeni syndrome. Psycho-Oncology 17(8): 783-9 DOI 10.1002/pon.1352

34. Dewey M, Schink T, Dewey CF (2007) Claustrophobia during magnetic resonance imaging: Cohort study in over 55,000 patients. Journal of Magnetic Resonance Imaging 26(5): 1322-7 DOI 10.1002/jmri.21147

35. Tazegul G, Etcioglu E, Yildiz F, Yildiz R, Tuney D (2015) Can MRI related patient anxiety be prevented? Magnetic Resonance Imaging 33(1): 180-3 DOI 10.1016/j.mri.2014.08.024

36. Caruso A, Bongiorno L, Vallini I, Russo P, Tomao F, Grandinetti ML (2006) Breast cancer and distress resulting from magnetic resonance imaging (MRI): The impact of a psychological intervention of emotional and informative support. Journal of Experimental & Clinical Cancer Research 25(4): 499-505

37. Townsend A, Cox SM (2013) Accessing health services through the back door: a qualitative interview study investigating reasons why people participate in health research in Canada. Bmc Medical Ethics 14: DOI 10.1186/1472-6939-14-40

38. Power TE, Robinson JW, Bridge P, Bernier FP, Gilchrist DM (2011) Distress and Psychosocial Needs of a Heterogeneous High Risk Familial Cancer Population. Journal of Genetic Counseling 20(3): 249-69 DOI 10.1007/s10897-010-9344-7

39. Brennan ME, Robinson K, Brand A, Kirk J (2008) A multidisciplinary risk management clinic for women at high genetic risk of breast and ovarian cancer - Experience and evaluation. Breast 17(2): 206-7 DOI 10.1016/j.breast.2007.11.021

40. White VM, Young M-A, Farrelly A, et al. (2014) Randomized Controlled Trial of a Telephone-Based Peer-Support Program for Women Carrying a BRCA1 or BRCA2 Mutation: Impact on Psychological Distress. Journal of Clinical Oncology 32(36): 4073-U285 DOI 10.1200/jco.2013.54.1607

41. Iredale R, Mundy L, Hilgart J (2011) An Online Resource of Digital Stories About Cancer Genetics: Qualitative Study of Patient Preferences and Information Needs. Journal of Medical Internet Research 13(3): DOI 10.2196/jmir.1735

42. Landsbergen KM, Brunner HG, Manders P, Hoogerbrugge N, Prins JB (2010) Educational-support groups for BRCA mutation carriers satisfy the need for information but do not affect emotional distress. Genetic Counseling 21(4): 423-37