Li Fraumeni Syndrome

Screening

- No consensus on surveillance until recently
- Must avoid CT as a regular check
- MRI may have a role but no evidence would change prognosis for glioma or sarcoma
- Abdominal USS may have a role in childhood
- No evidence to support regular FBC
- Breast MRI from early 20's best option for women – also NICE approved
- We offer register style approach offer annual MOT

MARIBS Genetic status

Genetic status of women recruited	No.	Cancers detected
Tested BRCA1 carrier	87	14
Tested BRCA2 carrier	42	7
Tested p53 carrier	13	2
Known BRCA1 mutation in the family	74	
Known BRCA2 mutation in the family	51	1
Known p53 mutation in the family	8	
Family history of breast/ovarian cancer	494	15
Family history of Li-Fraumeni syndrome	24	
Unknown	7	
Found to be ineligible	38	
Total	**838**	**39**

Both TP53 detected early aged 29 and 33

MANCHESTER 1824

The University of Manchester

Li Fraumeni Syndrome

Screening

- Whole body MRI highlighted in one report
- Villani A, Tabori U, Schiffman J, Shlien A, Beyene J, Druker H, Novokmet A, Finlay J, **Malkin D**. Biochemical and imaging surveillance in germline **TP53** mutation carriers with Li-Fraumeni syndrome: a prospective observational study. **Lancet Oncol**. 2011;12(6): 559-67
- 3-year overall survival was 100% in the surveillance group and 21% (95% CI 4-48%) in the non-surveillance group (p=0·0155).

Li Fraumeni Syndrome

Screening

- Joint whole body MRI study with Royal Marsden
- SIGNIFY -1cm cuts 40 minute scan
- So far 44 TP53 carriers screened in Manchester –3 malignancies

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The Annabel Evans Memorial Fund

The ROYAL MARSDEN NHS Foundation Trust

NHS National Institute for Health Research

The SIGNIFY Study

Magnetic ReSonance ImaGing screeNing In Li Fraumeni SYndrome: An exploratory whole body MRI study

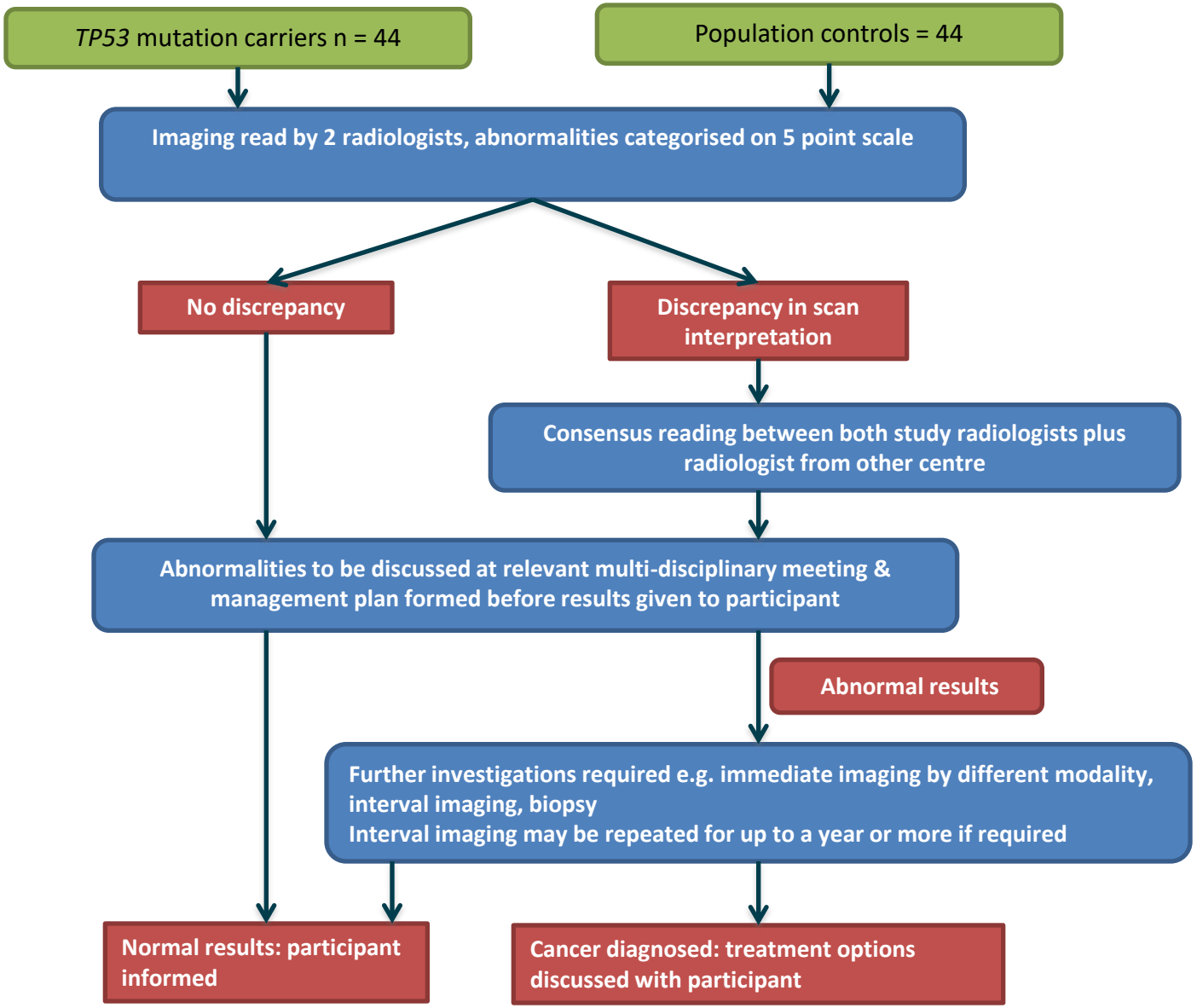
Management of LFS (Pan-Thames Guidelines)

- Open door policy
- Female breast cancer risk:
  - Practice breast awareness and self-examination
  - Annual breast MRI age 20 – 50
  - Annual mammography from age 40
  - Discussion regarding risk-reducing mastectomy
- No other targeted screening recommended or of proven benefit in UK
- Cancer treatment should be optimal: radiotherapy only avoided where another treatment modality is of at least equal benefit
- Predictive testing after appropriate counselling at any age

The SIGNIFY Study

- Aims to assess:
  - incidence of malignancies diagnosed in asymptomatic *TP53* mutation carriers using whole body MRI technique against general population controls
  - incidence of non-malignant relevant disease
  - incidence of irrelevant findings and the investigations required to determine relevance of MRI findings
  - the psychological impact of whole body MRI screening in *TP53* mutation carriers
- 44 full-body MRI scans for *TP53* mutation carriers
- 44 matched population controls

Imaging Algorithm



Recruitment

- 44 carriers from 37 families and 44 matched controls recruited

	Carriers	Controls
N	44	44
Age, median (range)	38 (19-58)	38 (22-59)
Female, n (%)	27 (61%)	27 (61%)
Male, n (%)	17 (39%)	17 (39%)
Previous diagnosis of cancer, n (%)	18 (41%)	0
Breast	11*	
Sarcoma	6	
Melanoma	2	
Ovarian	1	
Wilms Tumour	1	
Cervical	1	
Adrenocortical carcinoma	1	
Teratoma	1	
History of multiple cancers, n (%)	6 (13.6%)	0

*4 bilateral breast cancer; 2 phylloides tumours

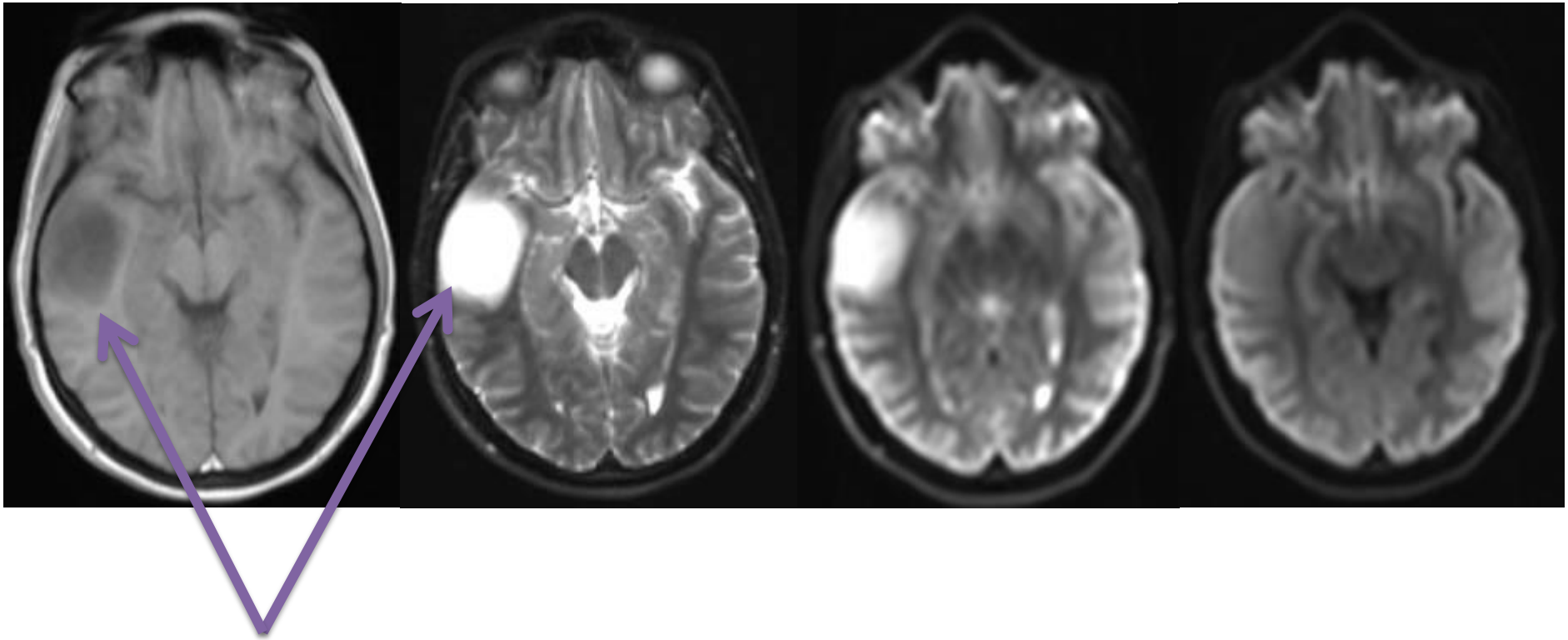
Results

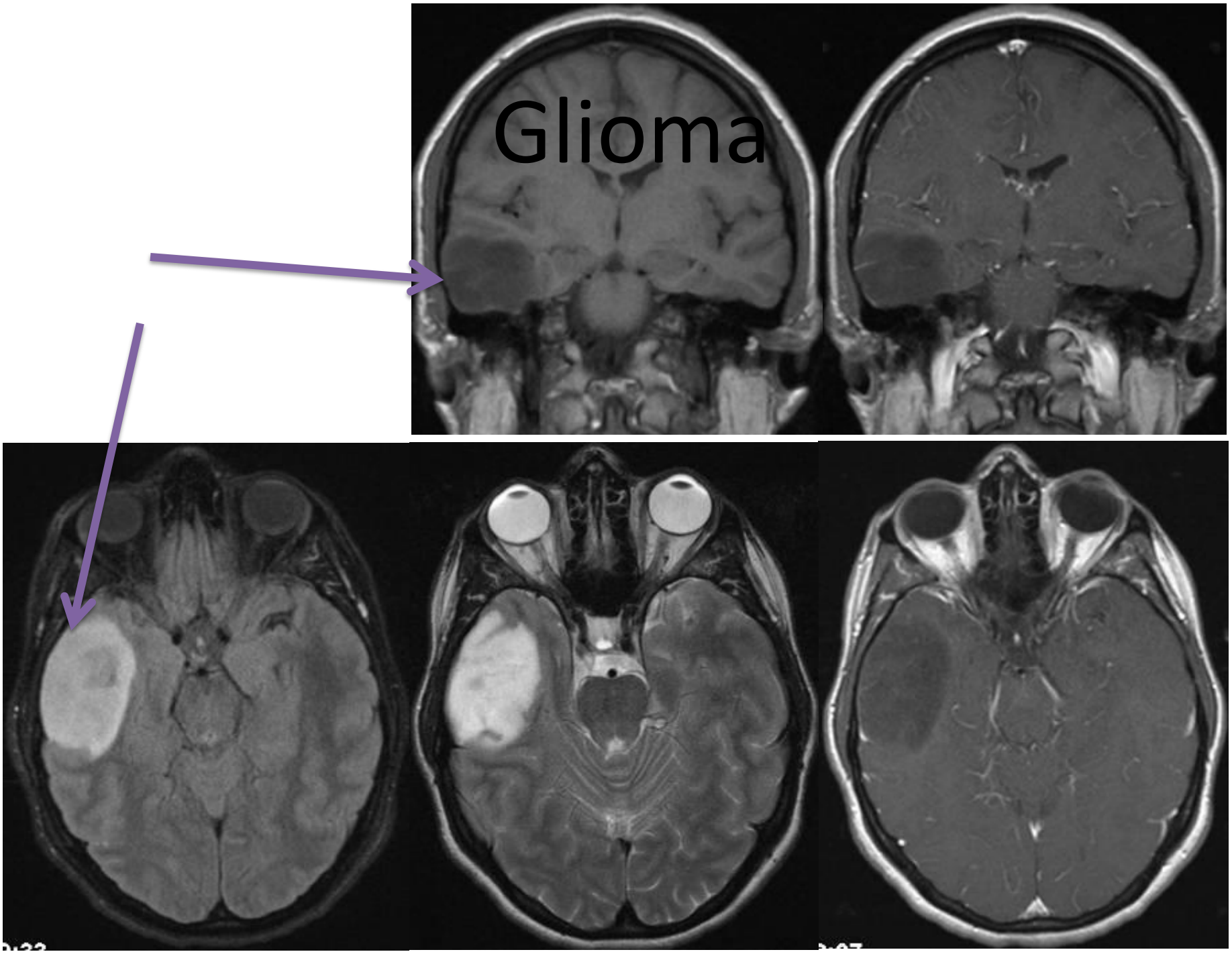
- 6/44 (13.6%) *TP53* mutation carriers diagnosed with cancer during study
- 4/44 (9.1%) cancers diagnosed in *TP53* mutation carriers directly from WB-MRI
  - All asymptomatic
  - 2 participants had two simultaneous primary tumours detected
- 0/44 cancers in controls
  - No statistically significant difference (p = 0.116)
- 2/44 carriers diagnosed with cancer during the study (false negatives)

	WB MRI Outcome	Overall	Carriers	Controls
Further investigations triggered by WB MRI	Cancer Detected (true positives)	4	4	0
	Eventual Benign Outcome (false positives)	16	9	7
	Requiring Continued Surveillance/ Treatment (non-malignant)	3	3	0
No further investigations triggered by WB MRI	NAD (true negatives)	63	26	37
	Subsequent Cancer Diagnosis (false negatives)	2	2	0
Total		88	44	44

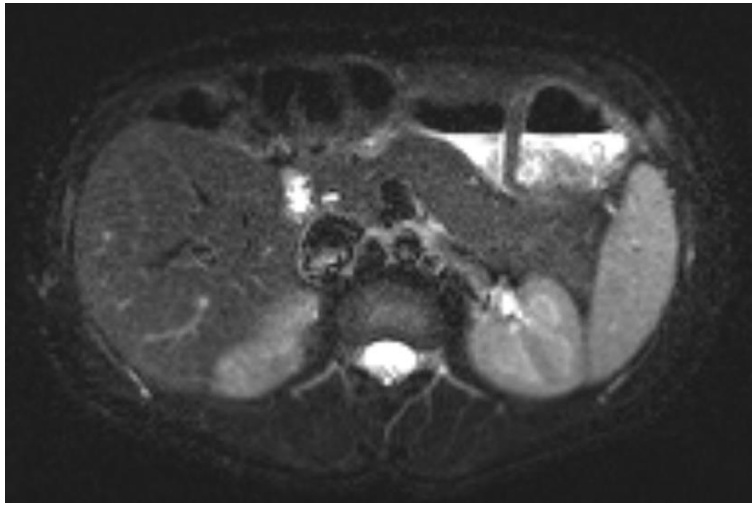
Pt	Sex	Age	Mutation	Abnormality (score) seen on WB MRI	Further Investigations	Cancer	Treatment
1	F	33	c.455C>T p.Pro152Leu	Right temporal lobe cyst (4)	Dedicated brain MRI with contrast	Astrocytoma	Complete resection
2	F	51	c.659A>G p.Tyr220Cys	Left lateral abdominal wall mass - probable sarcoma (4)	US guided biopsy	Myxosarcoma	Complete resection
3	F	45	c.586C>T p.Arg196Ter	Suspicious right renal mass (4) Uterine Fibroid (2)	Abdominal CT, nephrectomy Pelvic MRI, TAH	Chromophobe renal sarcoma Leiomyosarcoma	Complete resection
4	F	24	c.844C>T p.Arg282Trp	Liver lesion, possible focal nodular hyperplasia or hepatic adenoma (3) Right kidney lesion, possible complex renal cyst or solid lesion (3)	1. Dedicated renal and liver MRI with contrast. Suspected sarcomas, nephrectomy and partial hepatectomy 2. Follow-up pelvic MRIs for PEComas detected progressive changes in sacro-iliac joint	1. Renal EAML Liver EAML 1. Sacro-iliac osteosarcoma	1. Complete resection of both tumours 2. MAP chemotherapy completed; surgery advised but patient pursuing proton beam therapy in USA.
5	F	48	c.916C>T p.Arg306Ter	Pericardial cyst (1)	Nil Non study MRI and PET revealed a 12.6cm hilar mass with small left pleural effusion	Mediastinal liposarcoma grade 3	Resection with microscopic positive margins (0/8 lymph nodes involved) and chemotherapy
6	M	27	c.818G>A p.Arg273His	Nil	N/A	Diagnosed with B ALL (not seen on WB MRI)	Chemotherapy

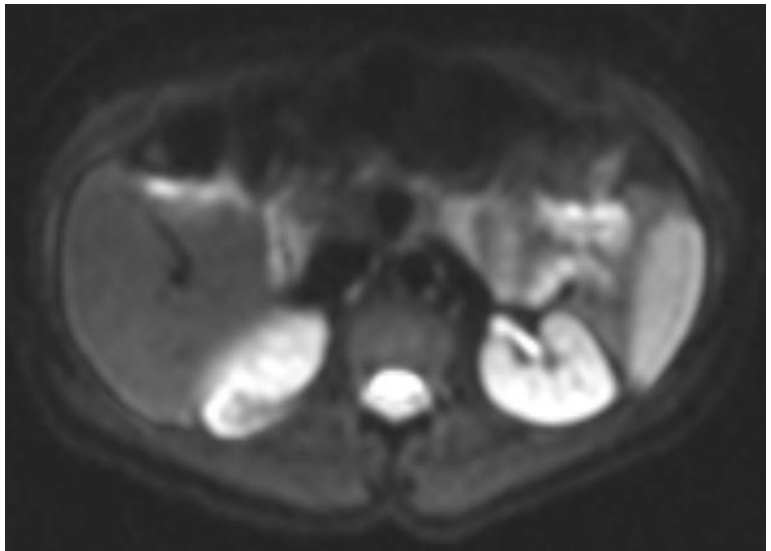
Signify Study - WBMRI

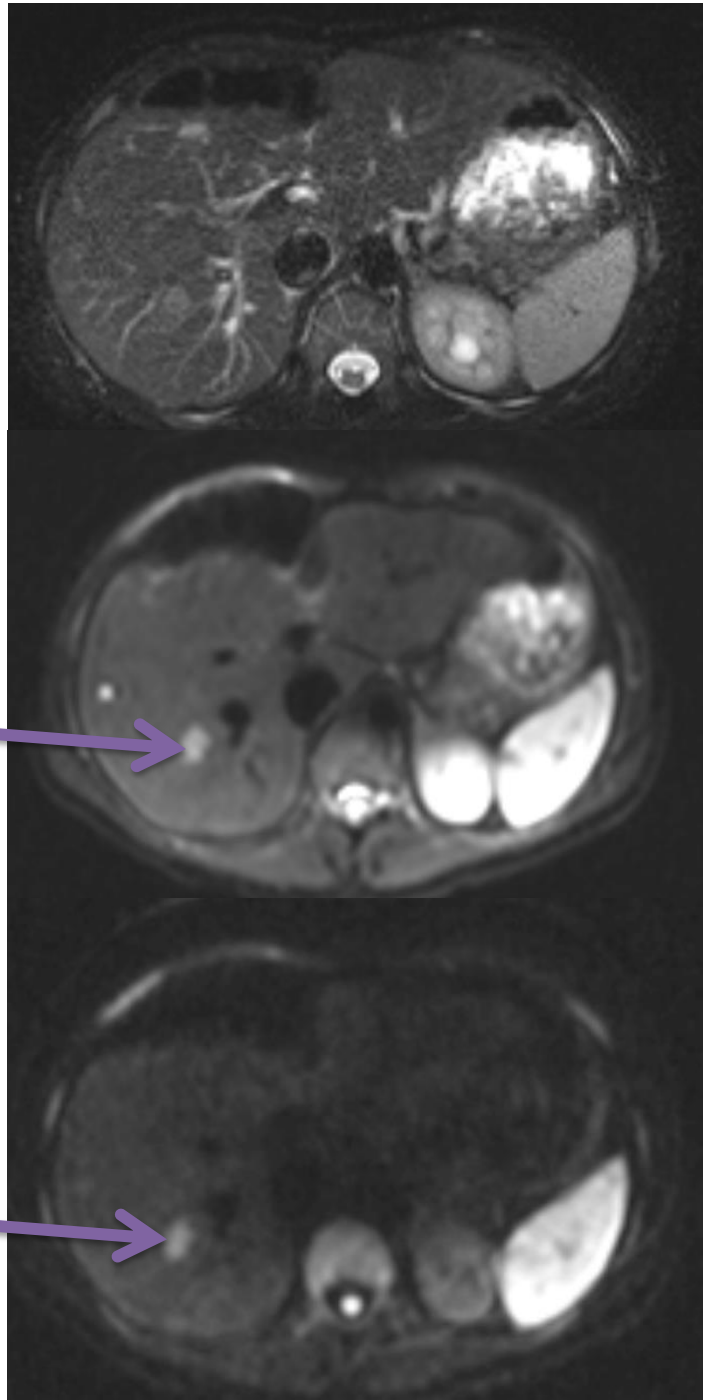



Glioma

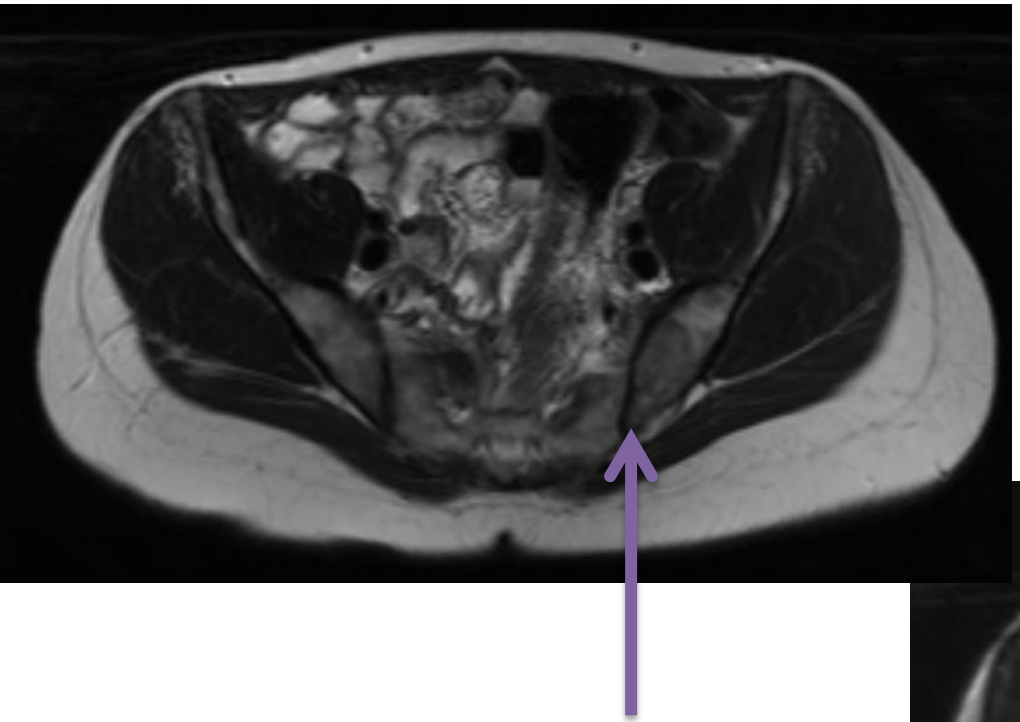
Kidney and Liver Angiomyolipomas

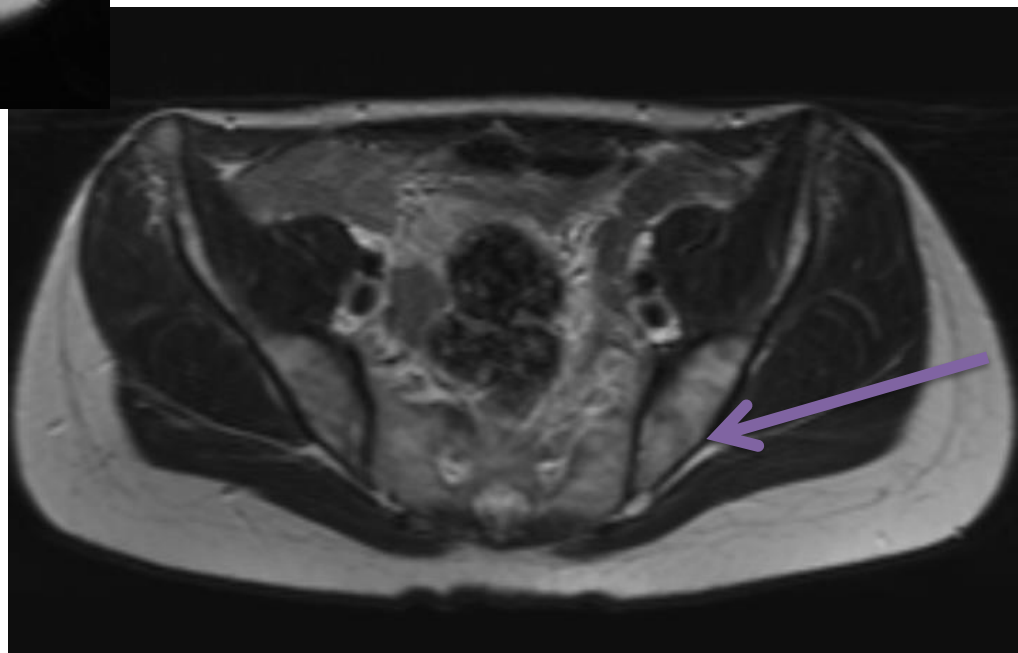




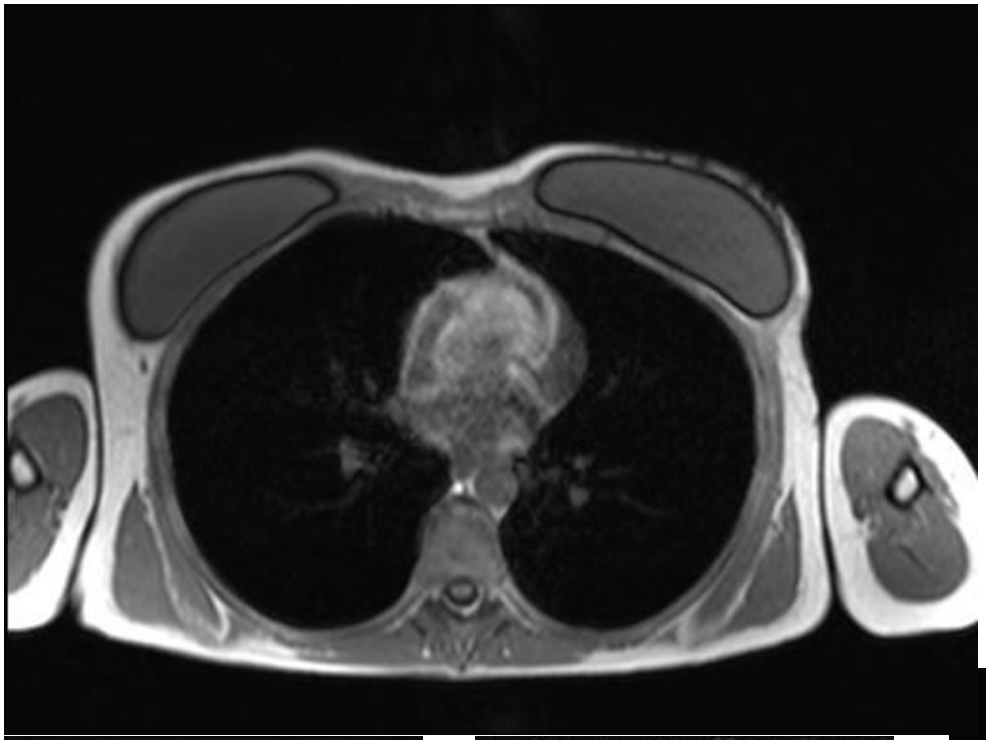


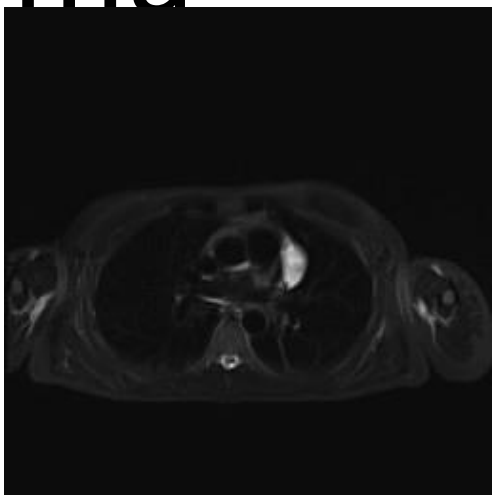
Osteosarcoma

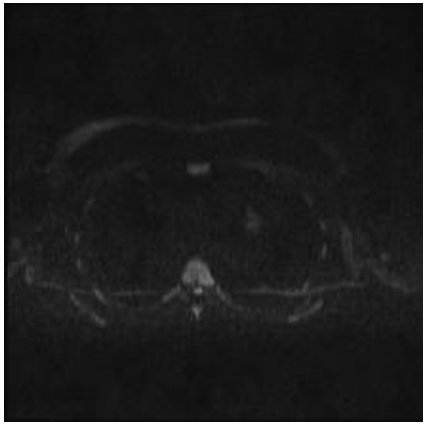


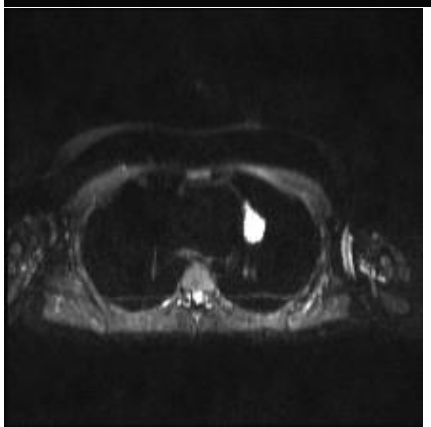


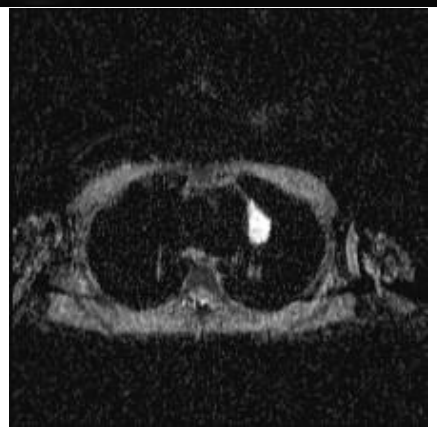
Mediastinal Sarcoma

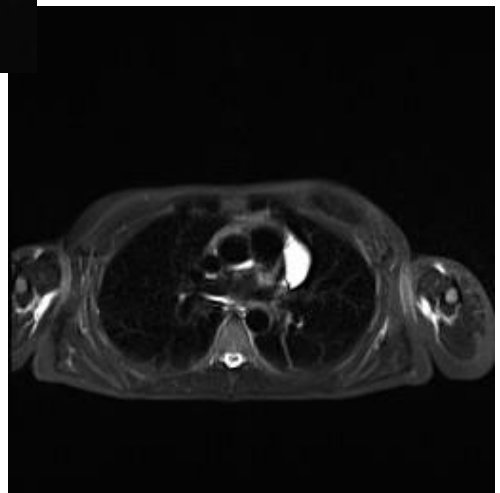




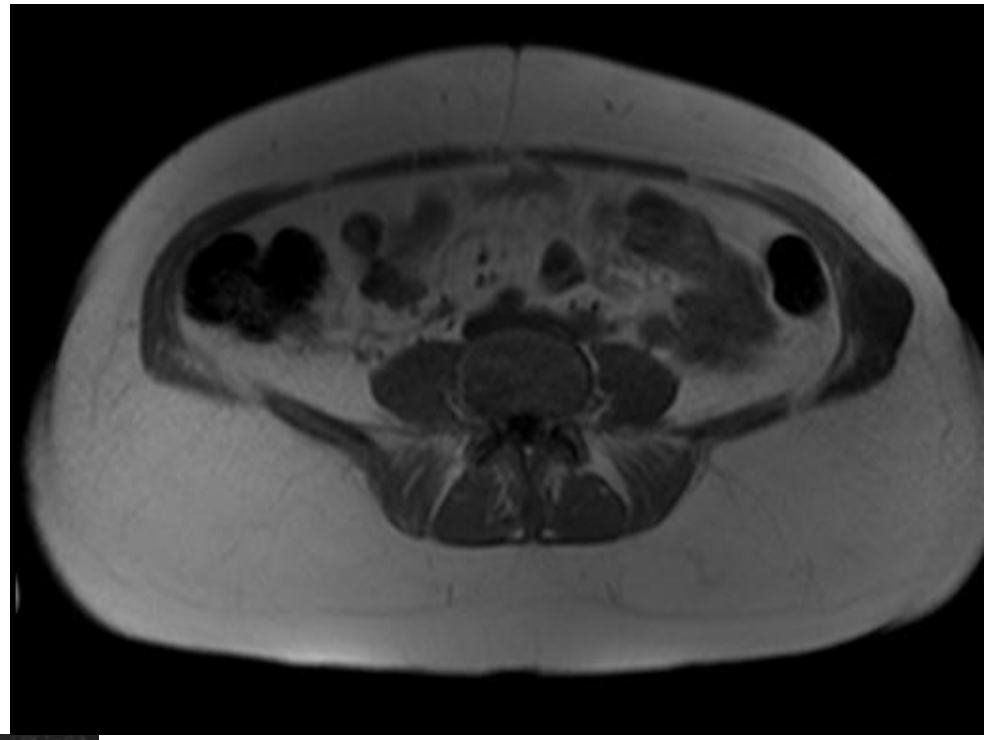


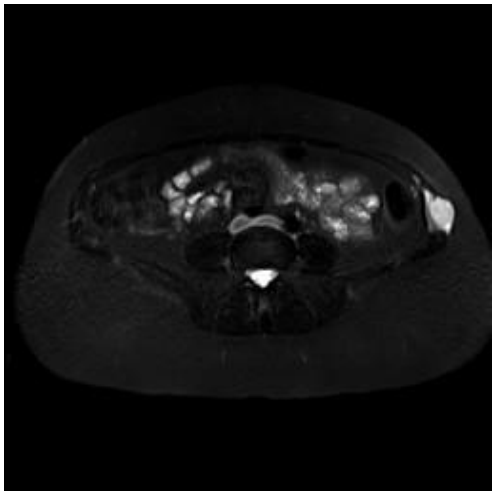


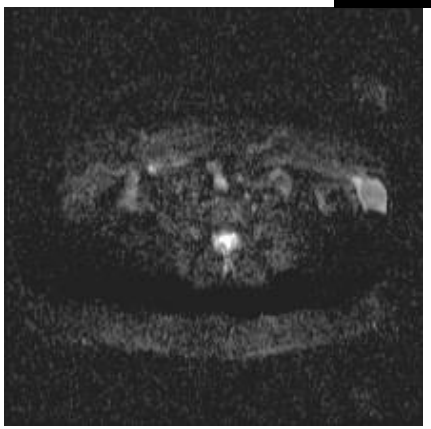


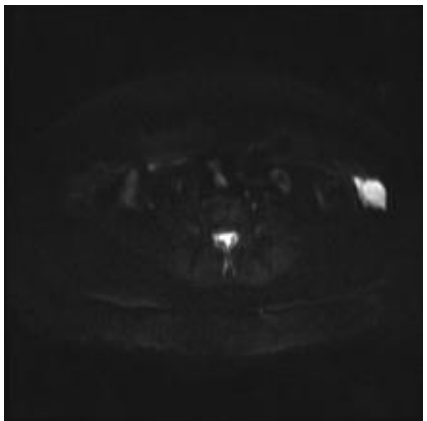


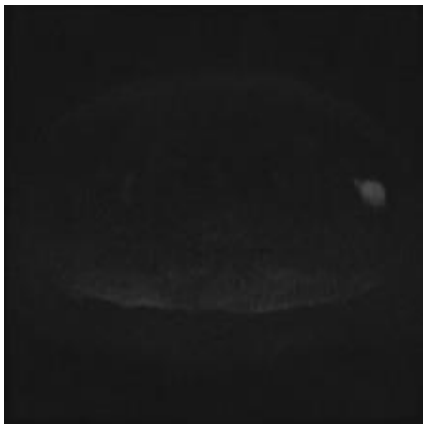
Myxosarcoma











Non-Malignant Findings

- 15 carriers (34.1%) and 7 controls (15.9%) underwent further investigations (p=0.049)
- 6 carriers and 1 control had >1 follow-up investigation; no malignant results
  - carriers had average 2.33 (95% CI: 1.17 to 3.50) additional investigations
  - controls 1.14 (95% CI: 0.79 to 1.49)
  - not significant: p=0.101

	Total Number Additional Investigations	1 investigation (n)	2 investigations (n)	3 investigations (n)	4+ investigations (n)
Carriers (n=15)*	35	9*	1*	1	4
Controls (n=7)	8	6	1	0	0

igations

- 1 carrier had a non-malignant incidental finding that needed intervention (rheumatology referral)
- 3 (6.8%) lesions in 2 *TP53* carriers require continued surveillance

Investigations

	Overall (n=22)	Carriers (n=15)*	Controls (n=7)
Total investigations	44	35	8
Radiation positive imaging	8	8	0
Other imaging	29**	21*	8
Biopsy/removal before definitive diagnosis	2	2*	0
Other investigations	4	4*	0

* Including investigations for non-malignant findings in 3 *TP53* carriers with eventual cancer diagnoses
**3 scans pending (2 carriers, one control)

Summary

- Malignancy prevalence in *TP53* carriers cohort of 13.6%
  - Detection rate of WB-MRI 9.1%
  - 2 cases of simultaneous primary cancers
- No cancers identified in controls
- The peak annual incidence rate for malignancy in *TP53* carriers is ~3%, therefore suggests significant lead time for screening to be effective
- Of the 2 false-negatives:
  - sarcoma likely to be detected at annual screening if implemented
  - leukaemia would not have been detected; additional screening as per Toronto protocol could be considered

- Significantly higher incidental finding rate in carriers vs controls, warranting additional investigations (some radiological)
  - unknown psychological impact - data pending

- Detection rate suggests a baseline WB-MRI scanning without contrast should be adopted into national guidelines for management of adult *TP*53 mutation carriers (in addition to existing breast MRI imaging).

Study Sites

- Study sites:
- Royal Marsden Hospital
- Foundation Trust
  - Central Manchester Hospitals Foundation Trust
  - Mater Private Hospital, Dublin (recruits will undergo MRI at RMH)

- Participant Identification Centres
  - St George's (London)
  - Birmingham Women's Hospital
  - Southampton University Hospital Trust
  - North Cumbria University Hospitals
  - Guy's Hospital
  - Southern General Hospital Glasgow
  - Great Ormond Street
  - Sheffield Children's NHS Foundation Trust
  - Institute of Genetic Medicine, Newcastle
  - Churchill Hospital, Oxford
  - Royal Liverpool Women's NHS Foundation Trust
  - University Hospitals Bristol NHS Foundation Trust
  - Ninewells Hospital and Medical School, Dundee

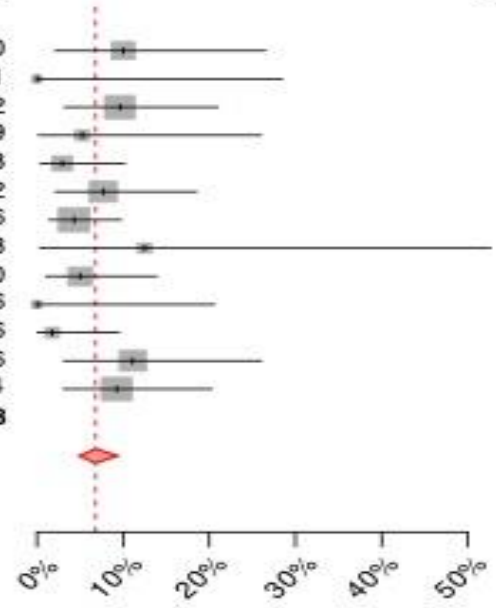
Meta analysis of WB MRI in press JAMA oncology 2017

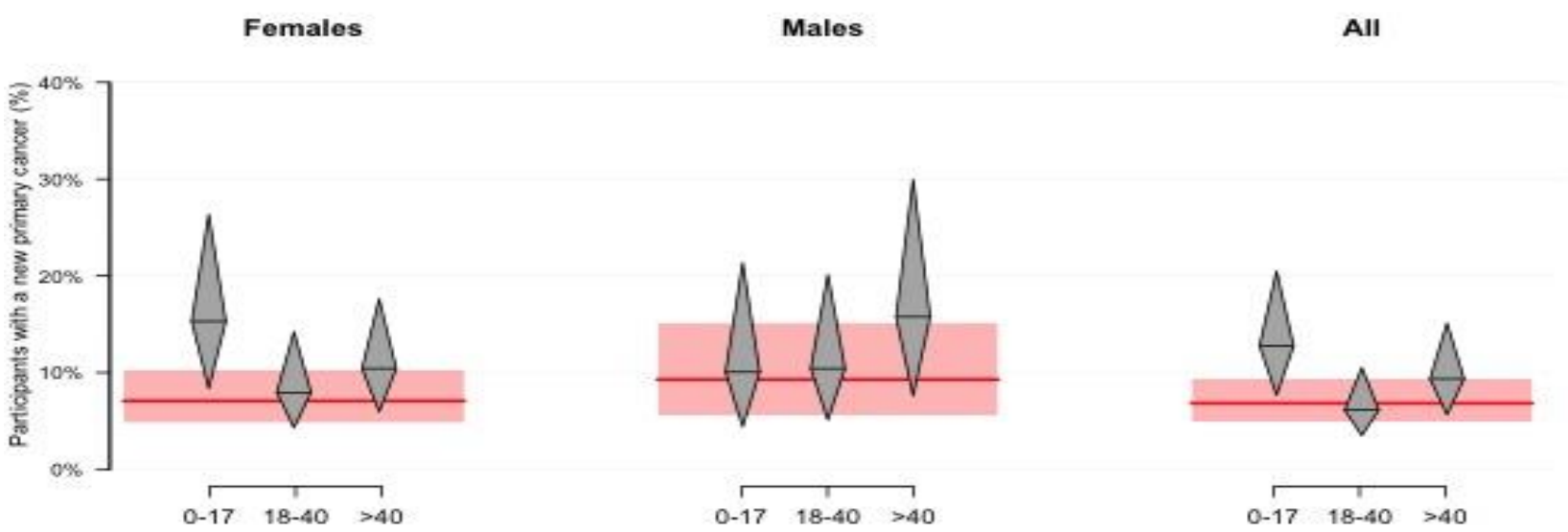
- Baseline scans from 13 studies
- 578 participants, the overall detection rate for previously unrecognized new localized malignancies by a single baseline WBMRI in *TP53* mutation carriers was 7% (95% confidence intervals 5-9%). The false positive rate was 43%. All screen-detected new cancers were treated with curative intent.

Age group (yr)	Gender	Morphology and Topography (age at diagnosis, yrs)
0-17	Male	Adrenocortical carcinoma (2)
		Osteosarcoma, leg (9)
		Low grade glioma* (15)
		Osteosarcoma, fibula (12)
	Female	Choroid plexus carcinoma (4)
		Low grade glioma* (6)
		Low grade glioma* (13)
		Osteosarcoma, chest (13)
		Astrocytoma (13)
		Papillary thyroid cancer (17)
		Renal carcinoma (17)
		Spinal chordoma (17)
18-40	Male	Osteosarcoma, rib (29)
		Colorectal cancer (21)
		Osteosarcoma, rib (29)
	Female	Renal and liver epithelioid angiomyolipomas (24)
		Chondrosarcoma, sacroiliac joint (29)
		Undifferentiated pleomorphic sarcoma, shoulder (30)
		Astrocytoma (33)
		Chordoma, clivus (40)
		Thyroid carcinoma (40)
>40	Male	Prostate adenocarcinoma (41)
		Prostate adenocarcinoma (46)
		Lung adenocarcinoma (54)
		Leiomyosarcoma, bowel (63)
	Female	Low grade spindle cell sarcoma, chest (41)
		Lung adenocarcinoma (54)
		Chromophobe renal cell carcinoma & uterine leiomyosarcoma (45)
		Ductal carcinoma in situ, breast (49)
		Abdominal myxosarcoma (51)
		Well differentiated liposarcoma, lumbar region (52)
		Lung adenocarcinoma (64)
		Invasive ductal carcinoma, breast (66)
		Lung adenocarcinoma (43)

Study	Individuals with cancer	Particip.	Percent	95% CI	Weight
SMOC	3	30	10%	(2%, 27%)	8.3%
COHR	0	11	0%	(0%, 28%)	1.5%
MDACC	5	52	10%	(3%, 21%)	14.0%
TXCH	1	19	5%	(0%, 26%)	2.9%
ACCCC	2	68	3%	(0%, 10%)	6.0%
SIGNIFY	4	52	8%	(2%, 19%)	11.4%
NCI LFS	5	116	4%	(1%, 10%)	14.8%
MSKCC	1	8	12%	(0%, 53%)	2.7%
DFCI	3	60	5%	(1%, 14%)	8.8%
U–MHS	0	16	0%	(0%, 21%)	1.5%
Life-Guard	1	56	2%	(0%, 10%)	3.0%
TP-HSC&CHLA	4	36	11%	(3%, 26%)	11.0%
TP-HCI	5	54	9%	(3%, 20%)	14.0%
		578			
Random effects Meta-Analysis			**7%**	**(5%, 9%)**	

Heterogeneity: τ^2=0, p=0.74





	Females			Males			All		
# Studies	11	12	12	7	11	10	11	12	12
# Particip.	77	164	135	57	82	63	134	246	198

Brain tumours using dedicated brain MRI

Age group (yr)	Gender	Morphology, age at detection (yrs)	Treated with curative intent	Detected on WBMRI also?
0-17	Male	Low grade glioma, 11	Yes	No
		Low grade glioma, 15	Yes*	Yes
		Astrocytoma, 10	Yes	Not performed
	Female	CPC, 1	Yes	Not performed
		CPC, 4	Yes	Yes
		Low grade glioma, 4	Yes	No
		Low grade glioma, 6	Yes*	Yes
		Low grade glioma, 9	Yes	No
		Low grade glioma, 13	Yes*	Yes
		Astrocytoma, 13	Yes	Yes
		Astrocytoma, 11	Yes	Not performed
18-40	Female	Low grade glioma, 24	No	No
		Astrocytoma, 29	Yes	No

New AACR guidelines published June 2017

Children (birth to age 18 years)
General assessment
• Complete physical examination every 3–4 months, including blood pressure, anthropometric measurements plotted on a growth curve (with particular attention to rapid acceleration in weight or height), Cushingoid appearance, signs of virilization (pubic hair, axillary moisture, adult body odor, androgenic hair loss, clitoromegaly, or penile growth), and full neurologic assessment
• Prompt assessment with primary care physician for any medical concerns
ACC
• US of abdomen and pelvis every 3–4 months
• In case of unsatisfactory US, blood tests[a], [b] may be performed every 3–4 months: total testosterone, dehydroepiandrosterone sulfate, and androstenedione
Brain tumor
• Annual brain MRI (first MRI with contrast; thereafter without contrast if previous MRI normal and no new abnormality)
Soft tissue and bone sarcoma
• Annual WBMRI

New AACR guidelines published June 2017

Adults
General assessment
• Complete physical examination every 6 months
• Prompt assessment with primary care physician for any medical concerns
Breast cancer
• Breast awareness (age 18 years onward)
• Clinical breast examination twice a year (age 20 years onward)
• Annual breast MRI screening[c] (ages 20–75)
• Consider risk-reducing bilateral mastectomy
Brain tumor (age 18 years onward)
• Annual brain MRI (first MRI with contrast; thereafter without contrast if previous MRI normal)
Soft tissue and bone sarcoma (age 18 years onward)
• Annual WBMRI[c]
• US of abdomen and pelvis every 12 months
Gastrointestinal cancer (age 25 years onward)
• Upper endoscopy and colonoscopy every 2–5 years
Melanoma (age 18 years onward)
• Annual dermatologic examination

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