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The University of Manchester

Towards a national LFS Service in the NHS

LFS UK, Sept 2018

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Li Fraumeni Syndrome
The TP53 story

Penetrance

- Mutations in DNA core binding domain give typical high penetrance
- 20% childhood cancer
- 50% by 30 years of age
- circa 100% for women and 80% for men by 50
- Difference mainly due to breast cancer

Birch et al 1999; Chompret et al 2003 Bougeard et al 2015

Manchester cohort

- 65 families with TP53 (42 missense)
- 194 mutation carriers
- 120 female
- 48 carriers currently unaffected

Li Fraumeni Syndrome
Screening

- No consensus until recently on surveillance
- Must avoid CT as a regular check
- MRI may have a role but need more 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
- We offer register style approach offer annual MOT

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 30 TP53 carriers screened in Manchester –3 malignancies

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**

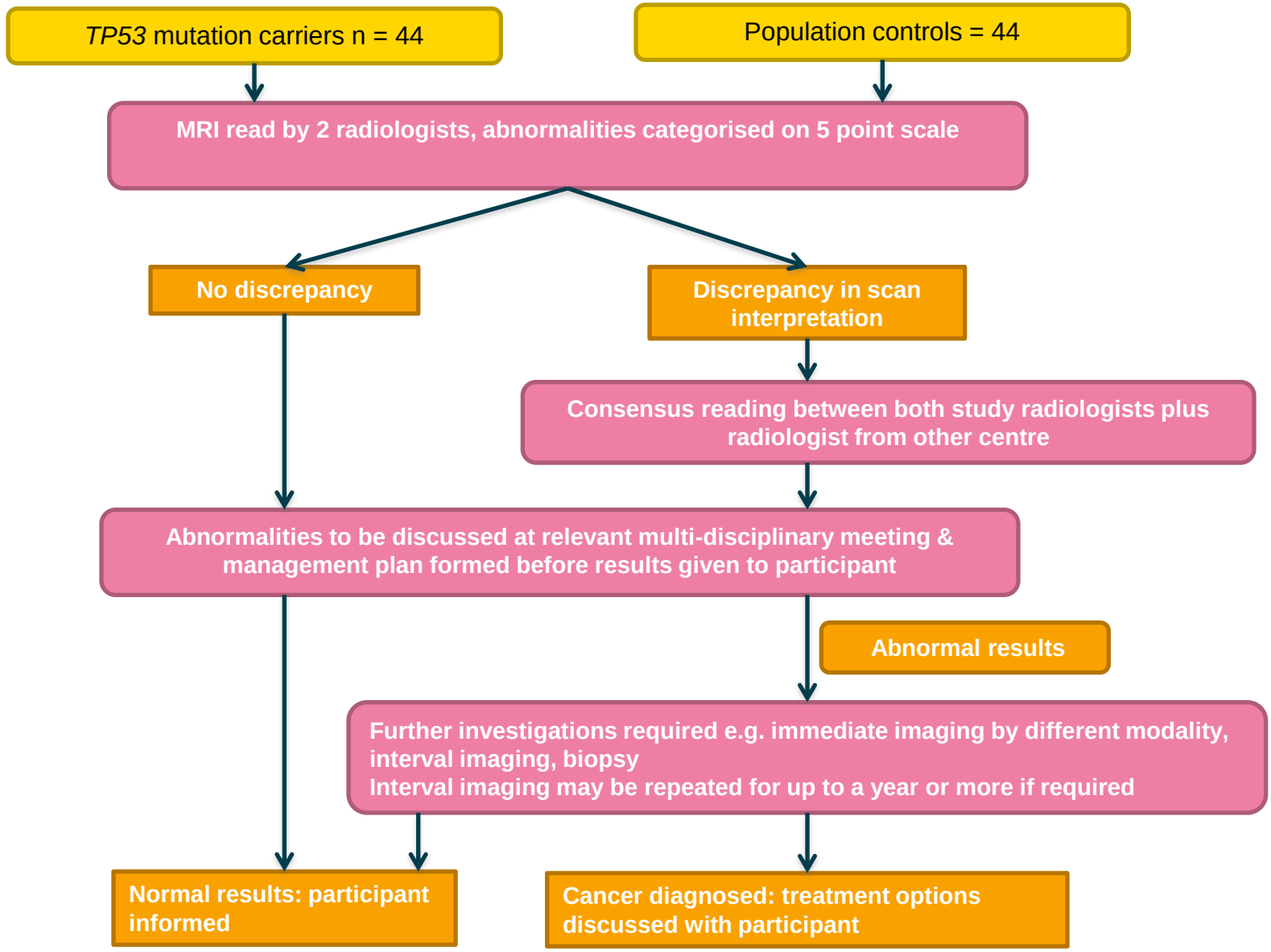
Both TP53 detected early aged 29 and 33

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

Funded by The Annabel Evans Memorial Fund

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

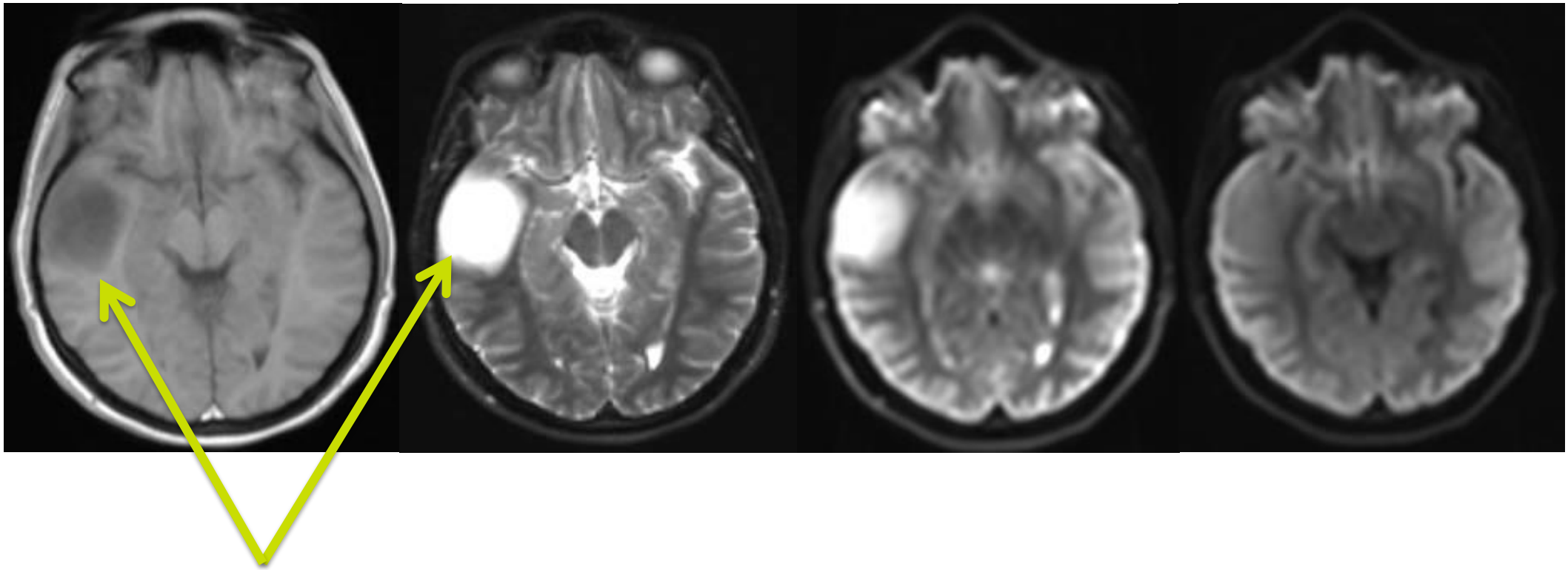
Results

- 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)

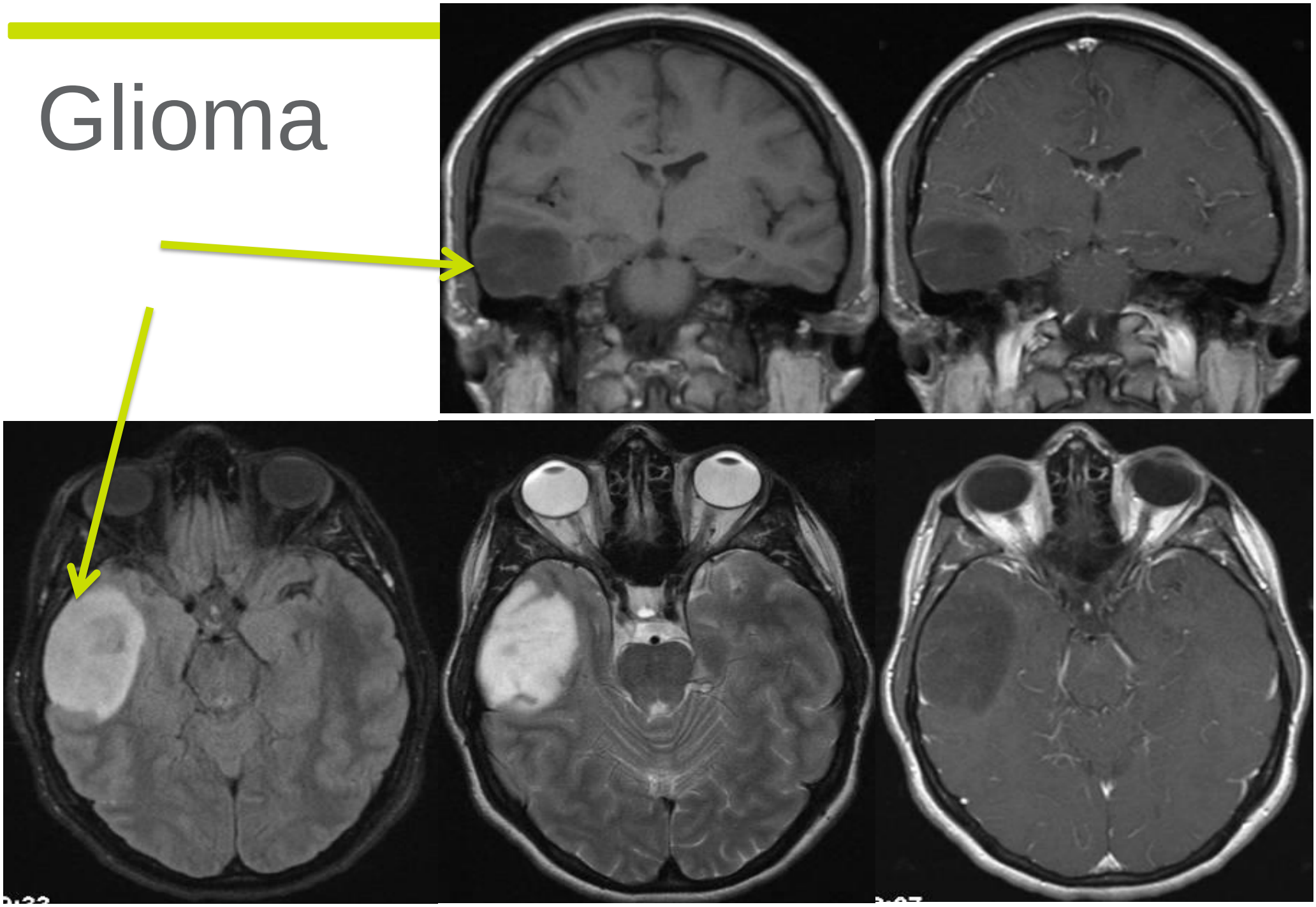
	WB MRI Outcome	Overall	Carriers	Controls
Further investigations triggered by WB MRI	Cancer Detected (true positives)	4	4	0
	Eventual Benign Outcome (false positives)	16	9	7
	Requiring Continued Surveillance/ Treatment (non-malignant)	3	3	0
No further investigations triggered by WB MRI	NAD (true negatives)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

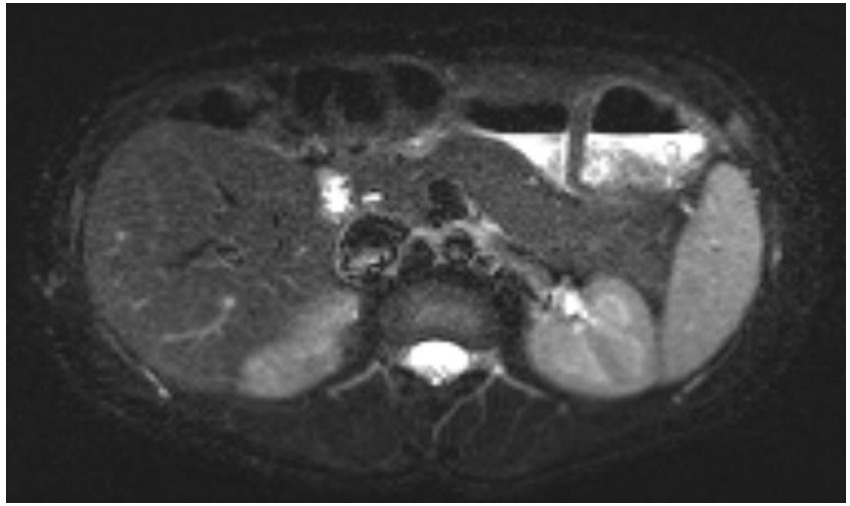
Signify Study - WBMRI

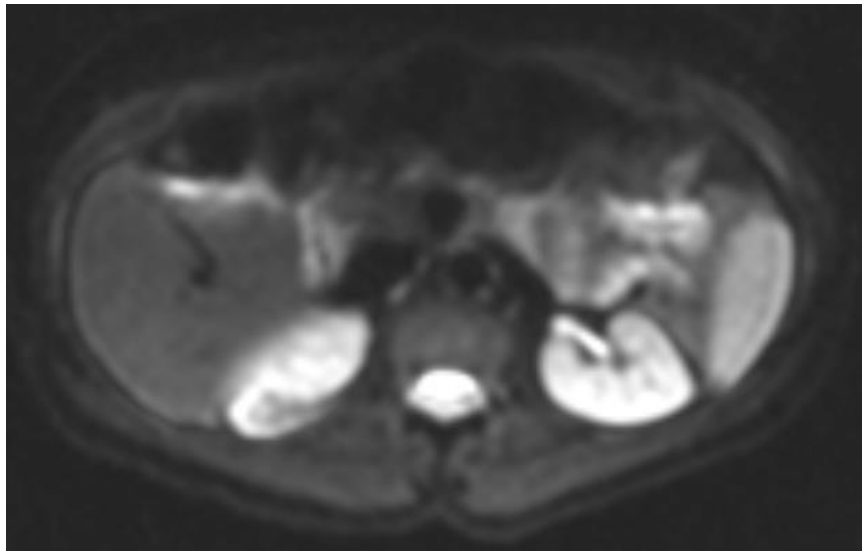


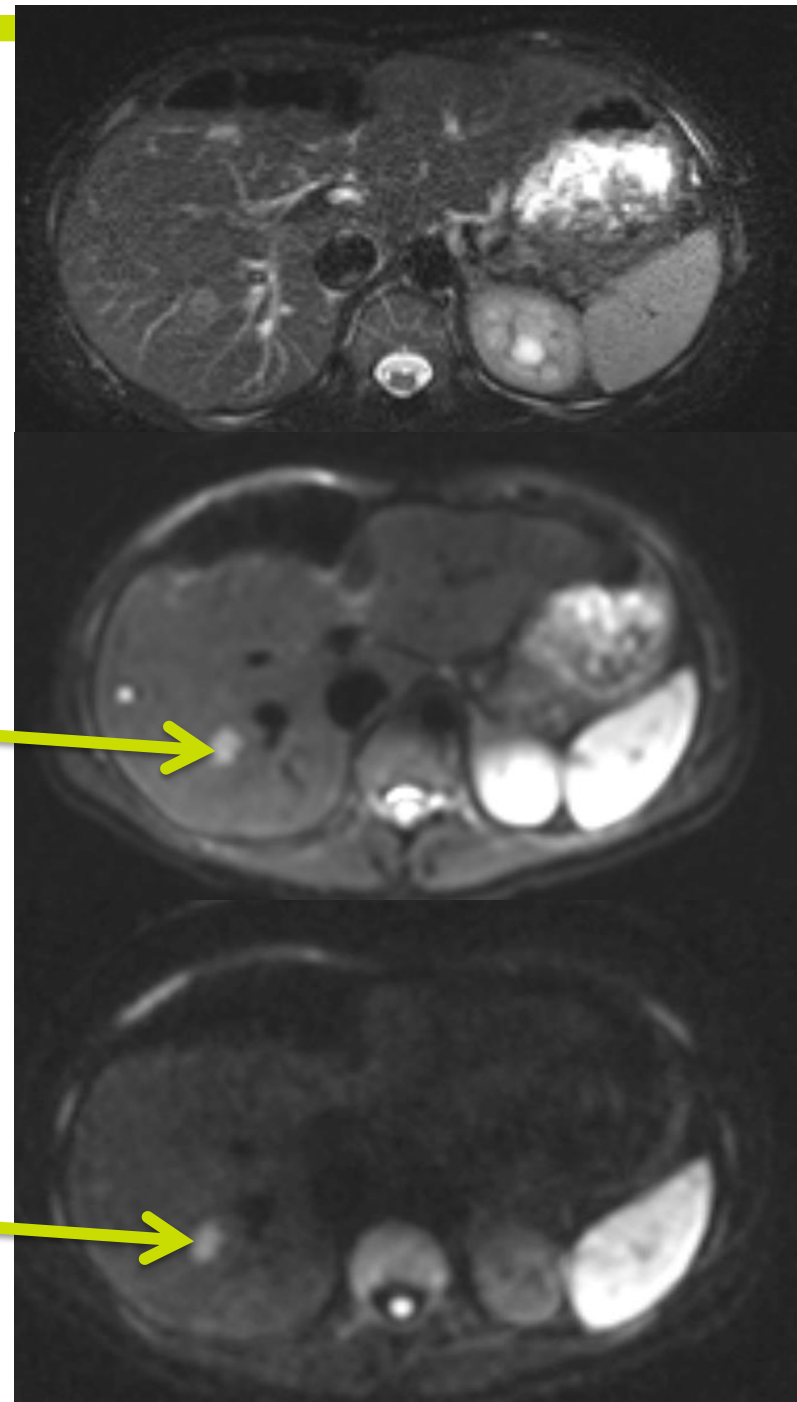
Glioma



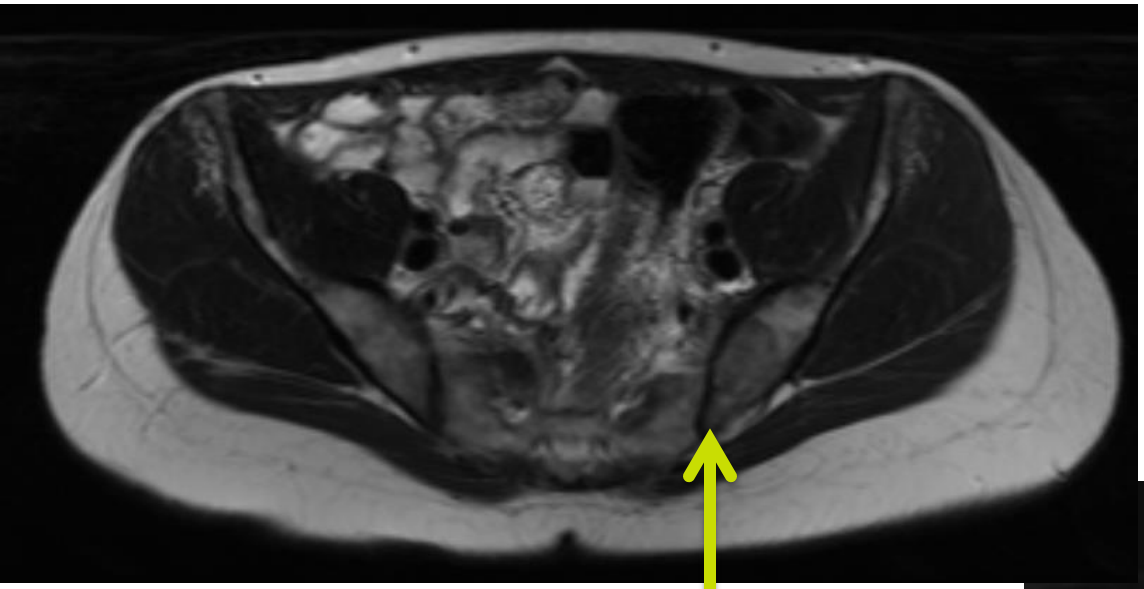
Kidney and Liver Angiomyolipomas

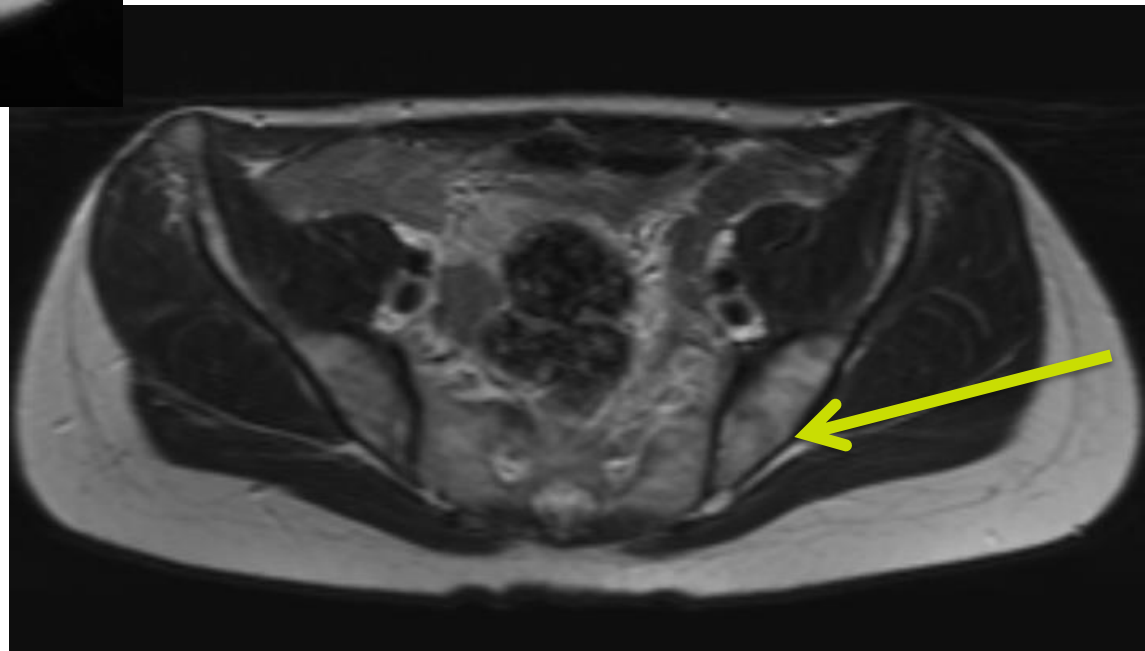




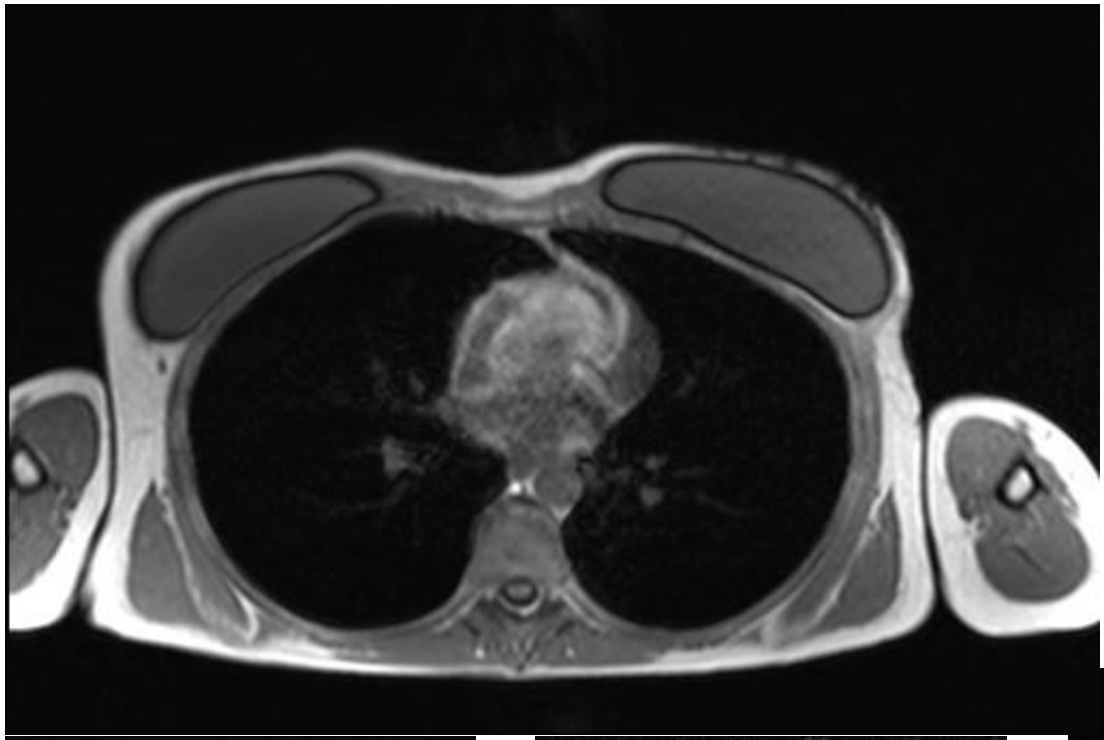


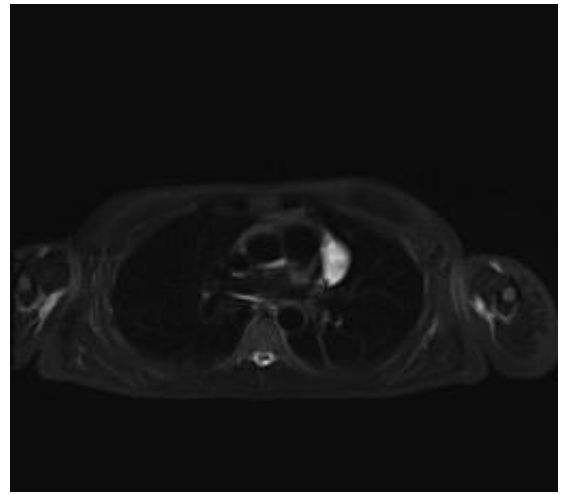
Osteosarcoma

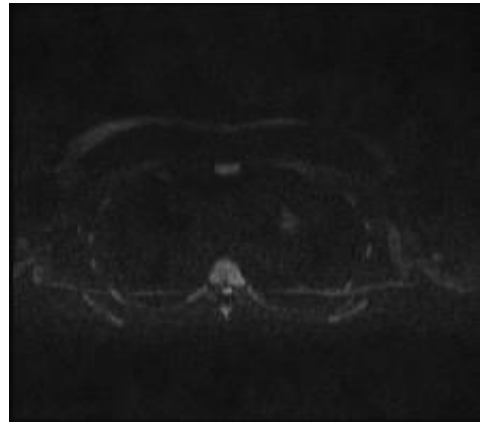


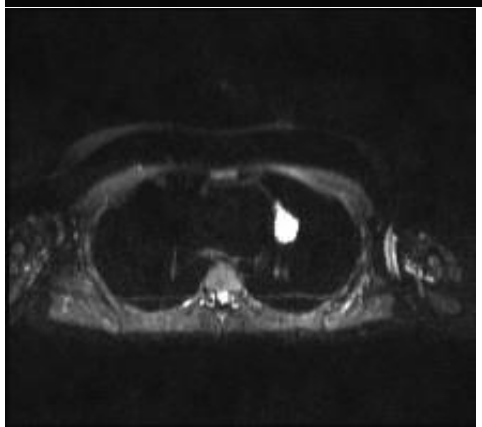


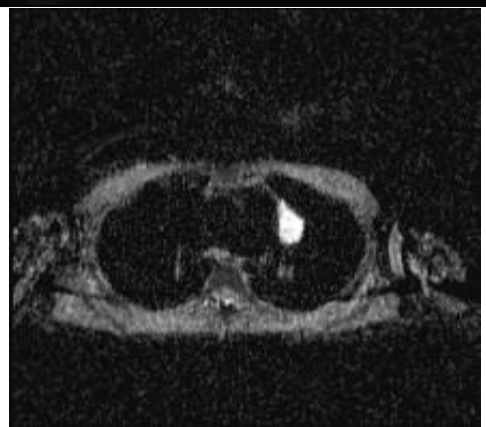
Mediastinal Sarcoma

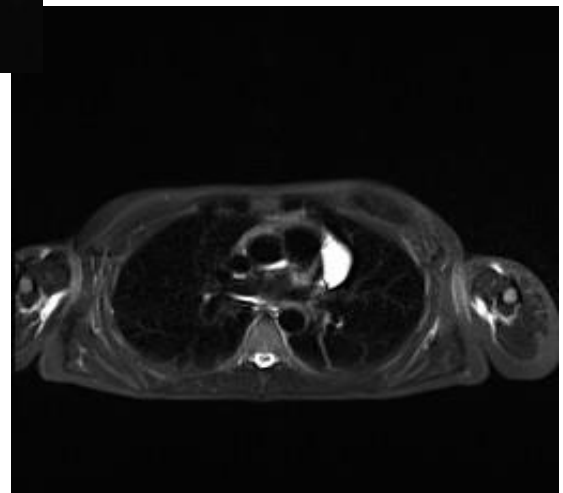




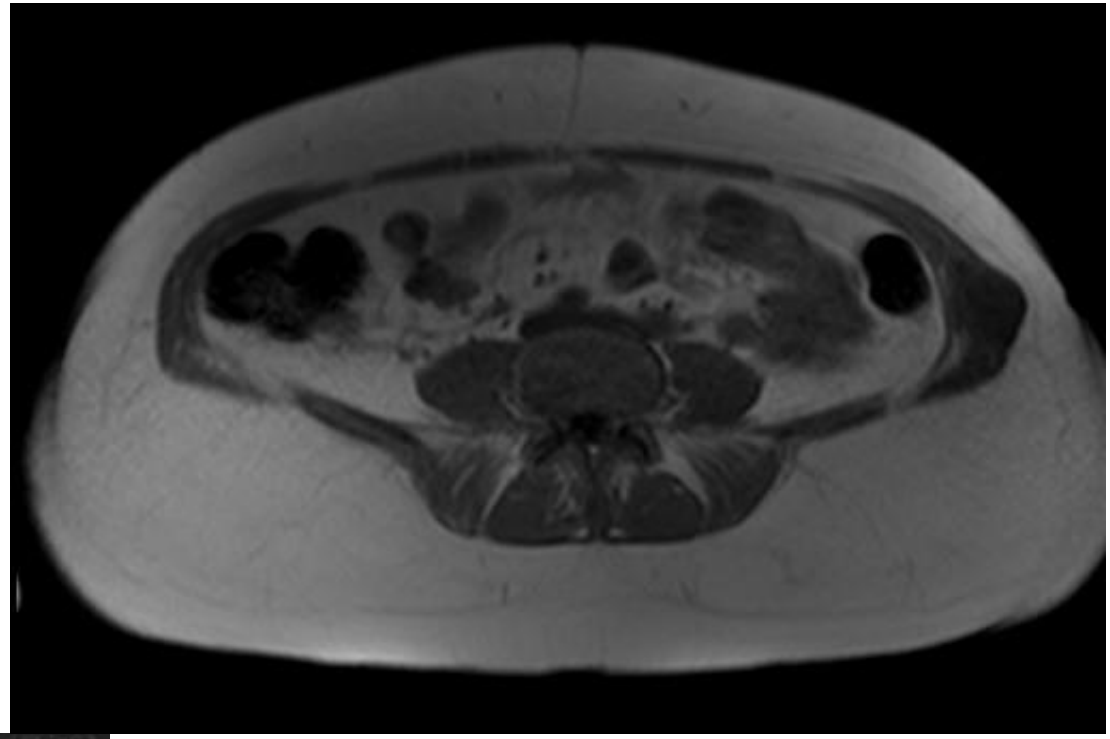


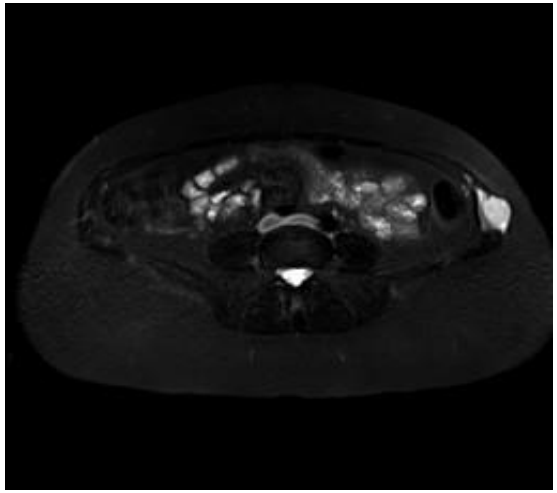


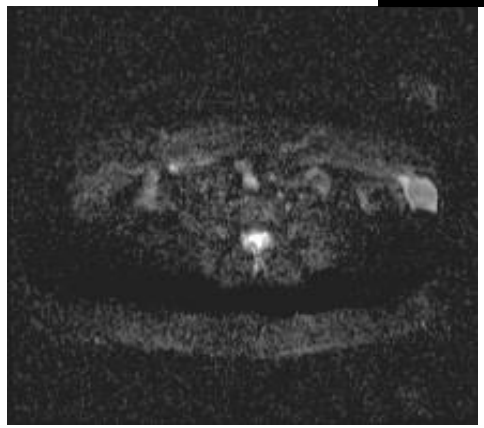


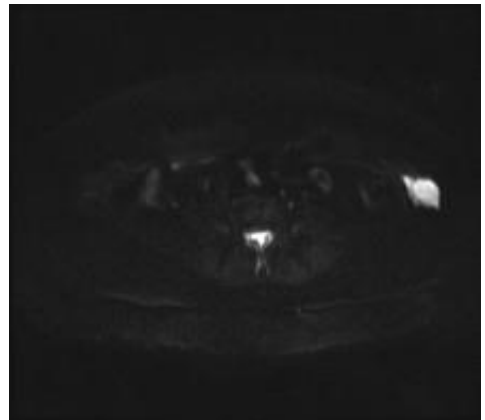


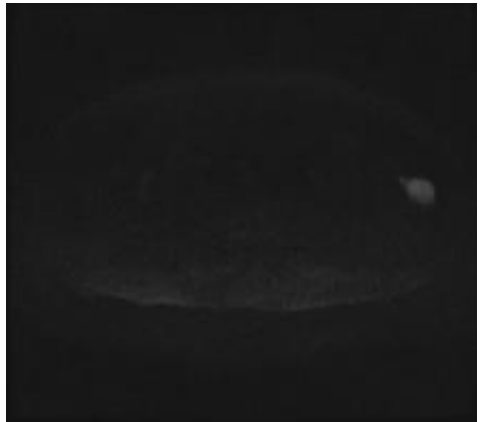
Myxosarcoma











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

- 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.

UK LFS guidelines

- Meeting of Cancer Genetics Group July 6th 2018
- Experts in oncology, genetics, radiology as well as representation from LFS community
- Unlikely guidelines will be funded until June 2019 earliest

Tumour	Screening recommendation
ACC	Abdominal USS 3-4 monthly birth-18 years Biochemistry (17 OH-progesterone, total testosterone, DHEAS, androstenedione) should only be performed where there is an unsatisfactory USS
Breast Cancer	Annual dedicated MRI from age 20-70 (As per NHSBSP 74) Consider risk reducing mastectomy from age 20
Brain tumour	Annual dedicated brain MRI from birth (first MRI with contrast)*
Sarcoma	Annual WB-MRI from birth*
Haematological	Not indicated due to lack of evidence
Colon	Colonoscopy only indicated when family history of colorectal cancer or polyposis. Consider other, possibly co-inherited, causes as appropriate.
Gastric	Recommend Helicobacter pylori testing and eradication if required Endoscopy not indicated due to lack of evidence
Skin	Annual dermatology review from 18yrs (GP or Dermatology)
Physical examination	Full physical examination 3-4 monthly in children (including blood pressure, anthropometric measurements, signs of virilisation and neurological exam) Routine physical examination not recommended in adults – advise detailed discussion of “red flag” symptoms and low threshold for fast track referral of persistent or unusual symptoms
Other	Recommend detailed discussion of “red flag” symptoms in both children and adults and provide information on relevant resources

Screening recommendations

***** Children under 20 kg need sedation, examination without anaesthetic may be possible from age 5 with help of dedicated play specialist. Feed and wrap approach may also be possible in first year Radiology should be informed of any current clinical symptoms to inform interpretation of scan

Eligible individuals

- Patients with a pathogenic TP53 variant (class 4 or 5 according to ACMG guidelines)
- Patients with low penetrance pathogenic variants, until further data on cancer risk available
- Patients with constitutional (germline) mosaicism for a pathogenic variant (verified by confirmation in two tissues)
- Patients affected with cancer fulfilling Classic LFS criteria without a pathogenic TP53 variant (confirmation of cancer diagnoses required).

Classic LFS criteria = **proband** with a sarcoma diagnosed before age 45 years
AND a **first-degree relative** with any cancer before age 45 years
AND a **first- or second-degree relative** with any cancer before age 45 years or a sarcoma at any age

Ineligible people

- Patients at 50% risk of familial variant
  - Patients at 50% risk should have appropriate counselling and support, but should be encouraged to consider testing in order to access cancer screening
  - Paediatric patients at 50% risk should continue to be offered support and review in a Specialist clinic, but screening is not appropriate unless confirmed to have inherited familial variant
  - Adult patients at 50% risk can be offered annual breast MRI
- Patients with a Li-Fraumeni-like family history. Screening should be offered on the basis of cancer in the family according to other recommended guidelines e.g. breast cancer

Other Recommendations

- Co-ordination of screening in children should be co-ordinated and managed through Specialist Paediatric Oncology clinics
- Co-ordination of screening in adults should be co-ordinated and managed through Clinical Genetics.
- WB-MRI should be only undertaken where there is relevant expertise. Local Clinical Genetics Centres may wish to consider referral for this to another centre/MDT, working to the radiology working group standards (protocol in development)

Conclusions

- New guidelines for screening in LFS and TP53
- Whole body MRI a mainstay

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Acknowledgments

- Genetic register
  - Prof Gareth Evans
  - Dr Tara Clancy
  - Dr Fiona Lalloo
  - Emma Woodward
- Cancer Genetics Group
  - Helen Hanson
- Childrens tumour register
  - Jill Birch
- SIGNIFY
- Ros Eeles
- Liz Bancroft
- Sibel Saya