Consensus Group Recommendations for Cancer Screening in LFS/*TP53* mutation carriers

Background:

Li-Fraumeni syndrome (LFS) is a rare inherited genetic condition most commonly caused by mutations (pathogenic variants) in the *TP53* gene. Individuals with LFS have a significantly increased lifetime risk of cancer, with risks reported to be 22% by age 5 years, 41% by age 18 and risk approaching 100% by 70 years (Bougeard *et al*. 2015, Mai *et al.* 2016). The most frequent cancers that occur in LFS are sarcoma, breast, brain and adrenocortical cancer, but a wide spectrum of cancer has been reported in families with this condition.

To date, the only nationally agreed screening recommendation for individuals with LFS has been for breast screening (NHSBSP guideline 74). However, over the past five years there has been increasing literature published recommending more comprehensive screening, including whole body MRI (WB-MRI). In view of other countries adopting new screening protocols and published international recommendations on screening for individuals with LFS (Kratz et al. 2017), the UK Cancer Genetics Group (CGG) arranged a consensus meeting on July 6th 2018 to agree a consistent approach to the management of LFS across the country. Further information and resources from the meeting are available here:

http://www.ukcgg.org/news-events/events/ukcgg-tp53-consensus-group-meeting

A pre-meeting survey was sent out to Regional Clinical Genetics centres in the United Kingdom and Ireland. The survey results and the recommendations made by the International TP53 Consensus Group (Kratz et al. 2017), were discussed in depth at the meeting by Clinical Geneticists, Genetic Counsellors, Oncologists, Radiologists and Patient representatives. The recommendations from the meeting are summarised below.

It was recognised that due to the rarity of LFS and pathogenic *TP53* variants, there is, and likely always will be, a limited evidence base to support screening recommendations in terms of early detection and cancer mortality. It is, therefore, recommended that discussion of the screening recommendations with patients includes a thorough discussion of the pros and cons of screening and that future screening recommendations may change as more data become available. It is also recommended that screening data are prospectively collected and audited to inform future practice.

Screening recommendations

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 Discuss importance of making positive lifestyle choices. E.g. Not smoking, eating a healthy diet and keeping physically active and provide appropriate resources.

***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

The above screening programme should be offered to

- 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

The above screening should <u>not</u> be offered to

- 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

We recommend that

- 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)

Recommended core minimum sequence for WB-MRI (adults):

- T1
- T2 fat sat/ STIR OR Diffusion and non fat sat T2
- Images can be acquired in axial or coronal planes or mixture
- Slice thickness (including gap) not greater than 10mm
- Coverage vertex to feet. Note: currently on most scanners arm are not covered adequately and these should evaluated clinically.
- Patient to be recalled for detailed imaging to evaluate uncertain lesions.
- Units wanting to do WBMRI have to opt in (ie self-certify quality for WBMRI) and a minimum number of scans per year in a unit has not been specified.
- Optional sequences at discretion of the unit.

Resources:

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List of attendees:

Name			Specialty	Centre
Dr	Muna	Ahmed	Genetics	GOSH
Dr	Paola	Angelini	Paediatric Oncology	RMH
Dr	Angie	Brady	Genetics	CGG/KGC
Dr	Paul	Brennan	Genetics	Newcastle
Dr	Carole	Brewer	Genetics	Exeter
Dr	Jackie	Cook	Genetics	Sheffield
Dr	Gill	Crawford	Genetics	CGG/Southampton
Dr	Rosemarie	Davidson	Genetics	Glasgow
Dr	Mark	Davis	Oncology/Genetics	CGG/Cardiff
Dr	Bianca	de Souza	Genetics	Guys
Mrs	Verity	Easton	Patient representative	George Pantziarka TP53 Trust
Professor	Ros	Eeles	Oncology/Genetics	RMH
Professor	Gareth	Evans	Genetics	Manchester
Dr	Ian	Frayling	Genetics/Pathology	CGG/Cardiff
Dr	Angela	George	Oncology/Genetics	RMH
Miss	Sarah	Gibson	Genetics	CGG/Exeter
Dr	Andrew	Gogbashian	Adult Radiology	Mount Vernon
Professor	Vicky	Goh	Adult Radiology	Guys
Professor	Andrew	Green	Genetics	Dublin
Dr	Lynn	Greenhalgh	Genetics	Liverpool
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Dr	Dorothy	Halliday	Genetics	Oxford
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Dr	Louise	Izatt	Genetics	CGG/Guys
Dr	Rosalyn	Jewell	Genetics	Leeds
Dr	Robin	Jones	Oncology/Sarcoma	RMH
Dr	Mette	Jorgensen	Paediatric Oncology	GOSH
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Mrs	Michelle	Potter	Patient representative	George Pantziarka TP53 Trust
Miss	Sarah	Pugh	Genetics	Bristol
Dr	Gillian	Rea	Genetics	Belfast
Dr	Aslam	Sohaib	Adult Radiology (SIGNIFY)	RMH
Miss	Beverley	Speight	Genetics	Cambridge
Dr	Stavros	Stivros	Paediatric Neuroradiology	Manchester
Dr	David	Swienton	Adult radiology	Leicester
Prof	Clare	Turnbull	Genetics	Genomics England
Professor	Leslie	Walker	Psychology	Hull
Dr	Rick	Whitehouse	Adult Radiology (SIGNIFY)	Manchester