TP53 Germline Pathogenic Variant Carriers: Management Guidelines for Healthcare Professionals

General information:

- Germline pathogenic variants (GPVs) in *TP53* are associated with Li-Fraumeni syndrome (LFS) or the more recently described heritable *TP53*-related cancer syndrome (h*TP53*rc).
- *TP53* heterozygotes are at substantially increased risk of a wide spectrum of cancers, therefore an intense surveillance protocol including whole-body MRI (WB-MRI) based on the Toronto Protocol is now recommended in the UK due to demonstration of a survival benefit using international data, although the numbers in the studies have been small[1].
- Due to the rarity of h*TP53*rc, we are continually building evidence for surveillance recommendations and advice may therefore change as more data becomes available. A thorough discussion of the pros and cons of surveillance should always be carried out.
- Some missense variants have a dominant-negative effect. These tend to be highly penetrant and are detected in families with childhood cancers. Conversely, null variants may have a lower penetrance and are identified in families with mostly adult cancers.[2] Until further genotype phenotype correlation is possible, in the UK management recommends for all TP53 GPV follow the same recommendations detailed below.

Associated risks:

- The most commonly associated cancers with h*TP53*rc are **bone and soft tissue sarcoma, very early onset breast cancer** (in females only), **central nervous system malignancies and adrenocortical cancers.**
- As h*TP53*rc is rare, it is difficult to give precise estimates for cancer risk.[3]
- Breast cancer is by far the most common malignancy in females with h*TP53*rc with the risk increasing significantly >20yrs and greatest risk 20-39 years. The cumulative risk is estimated as being ~85% by 60ys.[4]
- Overall cancer risks were initially reported to be as high as 22% by 5yrs, 41% by 18rys and 100% by 70yrs.[3] However, with expansion of genetic testing (outside the context of a strong family history) there is recognition that the phenotypic spectrum is likely to be broader and for some families associated with a lower cancer risk than originally described.

Management recommendations:

Surveillance	**WB-MRI** annually from birth. General anaesthetic is acceptable if required. This should be undertaken in centres with sufficient radiology expertise to report the imaging, consider referral outside local department if necessary. **Brain MRI** annually from birth. The use of gadolinium is advised for the first scan but not subsequent ones. **Abdominal USS** 3-4monthly from birth to 18yrs. Biochemistry (17 OH-progesterone, testosterone etc) should only be undertaken when USS unsatisfactory. **Breast MRI** annually 20-70yrs for females via the very high risk screening programme (VHRS). **Gastric** Helicobacter pylori (HP) one-off test. **Skin review** annually from 18yrs by GP with low threshold for referral to dermatology. **Colonoscopy** only indicated if family history of colorectal cancer/polyposis as per BSG hereditary colorectal cancer guidelines.[5] Microcytic anaemia should prompt investigation for GI malignancy (routine FBC *not* advised). Full surveillance protocol recommended for patients with GPVs in *TP53* (including lower-penetrance variants), germline mosaicism (verified in two tissues) and also for patients with a clinical diagnosis of classic LFS[2] without a confirmed GPV. Those at 50% risk of a GPV should *not* be offered full surveillance but women in this category can still be offered breast MRI (20-50yrs) via VHRS and children should be offered an open access return to clinic. All children should be managed via specialist paediatric oncology clinics.
Surgery	Risk reducing mastectomy can be considered from 20yrs. Informed consent and shared decision making with the patient is paramount.
Other	When treating cancer in patients with h*TP53*rc, priority should be given to surgical or ablative treatments avoiding radiotherapy where possible due to radiosensitivity and high cancer risk.[3]
Lifestyle advice	-Patients should receive detailed discussion of 'red flag' symptoms in both children (see George Pantziarka website) and adults. -Advise on using high SPF sunscreen and covering up in the sun. -Provide information on the benefits of smoking cessation, minimising alcohol intake, maintaining a healthy weight and being physically active to lower the chance of developing cancer.
Family matters	-Refer to clinical genetics to facilitate genetic testing in at-risk family members, can be considered in childhood. -Refer to clinical genetics for discussions on reproductive options.

References

(1) Hanson H, Brady A et al; 'UKCGG Consensus Group guidelines for the management of patients with constitutional *TP53* pathogenic variants'; *J Med Genet;* 2021;58:135–139. doi:10.1136/jmedgenet-2020-106876
(2) Frebourg T, Lagercrantz SB et al 'Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes'; EJHG (2020) 28:1379-1386
(3) Bougeard G, Renau-Petel M et al; 'Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. *J Clin Oncol* 2015;33:2345–52.
(4) National Comprehensive Cancer Network (NCCN). Genetic/familial high-risk assessment: breast and ovarian. Version 2. 2015
(5) Monahan KJ, Bradshow N et al; Guideliens for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/UKCGG; *Gut;* 2020;69;411-44

Patient resources

- The George Pantziarka TP53 Trust http://www.tp53.co.uk/
- Coppafeel https://coppafeel.org/
- breastcancernow.org "Someone like me" https://breastcancernow.org/information-support/support-you/someone-me-telephone-support

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