New ERN GENTURIS guideline for Li-Fraumeni and Heritable *TP53*-related cancer syndrome

I. Method:

This guideline has been elaborated by members of the European Reference Network (**ERN**) on the Genetic Tumour Risk Syndromes (**GENTURIS**).
We established a multidisciplinary team of experts representing all relevant disciplines and patients' representatives.
The guideline was based on the best evidence and expert consensus.
337 published articles were assessed

Evidence grading:
strong: consistent evidence and new evidence unlikely to change recommendation and expert consensus
moderate: expert consensus or majority decision but with inconsistent evidence or significant new evidence expected
weak: inconsistent evidence AND expert agreement

II. Cancer patients who should be tested for germline disease-causing *TP53* variants

- **Recommendation 1 (R1):** All patients who meet the modified "Chompret Criteria" should be tested for germline *TP53* variants.
  Familial presentation: Proband with a ***TP53* core tumour** (e.g. **breast cancer**, **soft-tissue sarcoma**, **osteosarcoma, central nervous system tumour**, **adrenocortical carcinoma**) **<46 ys** AND at least one **first- or second degree relative** with a core tumour **<56 ys**
  OR **Multiple primitive tumours**: Proband with multiple tumours, **two** of which belong to ***TP53* core tumour** spectrum, the first of which occurred **<46 ys** *irrespective of family history*
  OR **Rare tumours**: Patient with **adrenocortical carcinoma**, **choroid plexus tumour**, or **rhabdomyosarcoma of embryonal anaplastic subtype** *irrespective of family history*
  OR **Very early-onset breast cancer** <31ys *irrespective of family history*
- **R2:** Children with: Hypodiploid acute lymphoblastic leukemia or unexplained sonic hedgehog-driven medulloblastoma or jaw osteosarcoma
- **R3:** Patients who develop a second primary-tumour, within the radiotherapy field of a first core *TP53* tumour (occurred <46 ys)
- **R4:** Patients >46 ys presenting with breast cancer without personal or familial history fulfilling the "Chompret Criteria" should NOT be tested for germline *TP53* variants
- **R5:** Children with any cancer from southern and south-eastern Brazilian families should be tested for the p.R337H Brazilian founder germline *TP53* variant

III. Pre-symptomatic Testing Recommendations

- **R1:** Adult first-degree relatives of individuals with germline disease-causing *TP53* variants should be systematically offered testing for the same germline *TP53* variant
- **R2:** The testing in childhood, from birth, of first-degree relatives of individuals with germline disease-causing *TP53* variants should be systematically offered, if updated knowledge, based on databases and registries, shows that the variant can be considered as a high cancer risk *TP53* variant conferring a high cancer risk in childhood: The index case has developed a childhood cancer OR childhood cancers have been observed within the family OR this variant has already been detected in other families with childhood cancers OR this variant corresponds to a dominant-negative missense variant
- **R3:** The testing in childhood of first-degree relatives of individuals with germline disease-causing *TP53* variants should be discussed with their parents if cancers have occurred in early adulthood (<31 ys) within the family, or if there is insufficient evidence in the databases or registries to determine the childhood cancer risk. This discussion should address the burden, and uncertain benefits, of surveillance in childhood, before a decision is made whether to test the child for germline disease-causing *TP53* variants.

IV. Surveillance Protocol for Heritable *TP53*-related cancer syndrome (hTP53rc)

Exam	Periodicity	Age to Start	Age to End	Condition	Evidence
Clinical examination with, in children, specific attention to signs of virilisation or early puberty, and measurement of arterial hypertension and, in patients who received radiotherapy, to occurrence of basal cell carcinomas within the radiotherapy field.	Every 6 months	Birth	17 years		Moderate
	Annual	18 years	-		Moderate
Whole-Body MRI	Annual	Birth	-	High cancer risk *TP53* variant* or previous chemo- or radiotherapy	Moderate
		18 years	-		Strong
Breast MRI	Annual	20 years	65 years		Strong
Brain MRI**	Annual	Birth	18 years	High cancer risk *TP53* variant	Moderate
		18 years	50 years		Moderate
Abdominal ultrasound	Every 6 months	Birth	18 years		Strong
Urine steroids***	Every 6 months	Birth	18 years		Weak
Colonoscopy****	Every 5 years	18 years	-		Weak

*A germline disease-causing *TP53* variant should be considered as "high risk" according to the III / R2.
** The first scan should be conducted with i.v. Gadolinium enhancement; in children, brain MRI should alternate with the WBMRI, so that the brain is imaged at least every 6 months
***When abdominal ultrasound does not allow a proper imaging of the adrenal glands.
****Only if the carrier received abdominal radiotherapy for the treatment of a previous cancer, or if there is a familial history of colorectal tumours suggestive of an increased genetic risk.

This guideline does not signify nor intend to be a legal standard of care, it should support clinical decision making, but never replace clinical professionals. No conflict of interest.

Authors: Rita Magenheim[1], Thierry Frebourg[2], Svetlana Bajalica Lagercrantz[3], Carla Oliveira[4], Pan Pantziarka[1] and D. Gareth Evans[5] on behalf of ERN GENTURIS
Affiliation: [1] Community Representative, D, H, UK, BE; [2] Rouen University Hospital and Inserm, F; [3] Karolinska University Hospital, S; [4]Porto Comprehensive Cancer Centre, P; [5]Manchester University Hospital, UK;
https://www.genturis.eu/l=eng/Clinical-practice-guidelines.html *Thierry Frebourg frebourg@chu-rouen.fr*

Co-funded by the EU