Guidelines for the Li-Fraumeni and Heritable TP53-Related Cancer syndromes

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

Recommendation 1

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**) before **46 years**
AND at least one **first- or second degree relative** with a core tumour before **56 years**

or

Multiple primitive tumours

Proband with multiple tumours, **two** of which belong to ***TP53* core tumour** spectrum, the first of which occurred **before 46 years** *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

Breast cancer before **31 years** *irrespective of family history*

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

Recommendation 2

Children and **adolescents** should be tested for germline *TP53* variants if presenting with:
Hypodiploid acute lymphoblastic leukemia (ALL);
or Otherwise **unexplained *sonic hedgehog*-driven medulloblastoma**; or **Jaw osteosarcoma**

Recommendation 3

Patients who develop a **second primary-tumour**, within the **radiotherapy field** of a first core *TP53* tumour which occurred **before 46 years**, should be tested for germline *TP53* variants

Recommendation 4

a. Patients **older than 46 years** presenting with **breast cancer without** personal or familial history fulfilling the "**Chompret Criteria"** should **not be tested** for germline *TP53* variants
b. Any patient presenting with **isolated breast cancer** and **not fulfilling the "Chompret Criteria",** in whom a disease-causing *TP53* variant has been identified, should be referred to an **expert MDT for discussion**

Recommendation 5

Children with any cancer from **southern and south-eastern Brazilian families** should be tested for **the p.R337H Brazilian** founder germline *TP53* variant

II. Pre-symptomatic Testing Recommendations

Recommendation 6

Adult first-degree relatives of individuals with germline disease-causing *TP53* variants should be **systematically offered testing** for the same germline *TP53* variant

Recommendation 7

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**

II. Pre-symptomatic Testing Recommendations

Recommendation 8

The testing in **childhood** of first-degree relatives of individuals with germline disease-causing *TP53* variants **should not** be **systematically offered**, if updated knowledge, based on databases and registries, shows that the variant can be considered as **a low cancer risk *TP53* variant** and does not confer a high cancer risk in childhood:

- The **index case** has **not developed** a childhood cancer; and
- **Childhood cancers** have **not been observed** within the family; and
- This variant has **not already been reported** in other families with **childhood cancers**; and
- This variant **does not correspond** to a **dominant-negative missense variant**

Recommendation 9

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** (before the age of 31 years) 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

III. Surveillance Protocol in carriers of germline disease-causing *TP53* variants

Exam	Periodicity	Age to start	Age to end	Condition	Evidence
Clinical examination*	Every **6 months**	Birth	17 years		Moderate
	Annual	18 years	-		Moderate
Whole-Body MRI without gadolinium	**Annual**	Birth	-	**High cancer risk *TP53* variant** or **previous treatment**	Moderate
		18 years	-		Strong
Breast MRI	**Annual**	20 years	Until 65 years		Strong
Brain MRI**	Annual	Birth	18 years	**High cancer risk *TP53* variant**	Moderate
		18 years	Until 50 years		Moderate
Abdominal ultrasound	Every 6 months	Birth	Until 18 years		Strong
Urine steroids	Every 6 months	Birth	-		Weak
Colonoscopy***	Every 5 years	18 years	-		Weak

With specific attention to signs of virilisation or early puberty, and measurement of arterial hypertension and detection of basal cell carcinoma in radiotherapy fields; **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 * 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*