ERN GENTURIS Plain Language Summary: *Guidelines for the identification of individuals who should be tested for germline disease-causing TP53 variants and for their subsequent clinical management*

INTRODUCTION

The *TP53* gene is susceptible to genetic spelling changes, often called mutations or genetic variants. If these variants are present in all body cells, they are called "germline variants". This is different from somatic variants which are only present in tumour tissues. Some germline variants in the *TP53* gene can mean people who have them have a high chance of developing certain cancers, especially early in life. Historically the clustering of these cancers was known as Li-Fraumeni syndrome (LFS), but because there are lots of other ways these changes to *TP53* can cause cancers, in the guideline they are called "heritable *TP53*-related cancers (h*TP53*rc) syndrome". Not all changes to *TP53* are harmful, in the guideline the changes to the *TP53* gene that are known to increase a person's cancer risk are called "germline disease-causing *TP53* variants". The guideline builds on the internationally recognised approach to testing for *TP53* changes, known as the "Chompret criteria".

Diagnosis of h*TP53*rc syndrome is mainly performed by cancer geneticists, adult or paediatric oncologists. Diagnosis of h*TP53*rc syndrome is difficult, due to the wide range of clinical presentations (i.e. clinical symptoms) and great variability in age of tumour-onset between families or within the same family. Germline disease-causing *TP53* variants can be detected in cancer patients either with or without familial history of cancers.

Individuals carrying germline *TP53* disease-causing variants have a high risk of developing multiple primary cancers in their lifetime. Once individuals develop their first tumour, treatment with radiotherapy and certain chemotherapies may increase their risk of developing other cancers. Therefore, testing for disease-causing *TP53* variants should take place before starting treatment. And if a disease-causing *TP53* variant is found, priority should be given to surgical or ablative treatments, avoiding radiotherapy when possible and using only non-genotoxic chemotherapies.

GUIDELINE AIMS

The h*TP53*rc syndrome guideline has been created to assist healthcare professionals provide the most up-to-date approaches to diagnosis and surveillance of cancer-free individuals and cancer patients

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who carry disease-causing *TP53* variants. The guideline was based on the best evidence and the consensus of experts in caring for people with h*TP53*rc. It presents recommendations to support care, but a clinician, in discussion with an affected individual, may tailor the exact care to the person's preferences and needs.

SCOPE & PURPOSE OF THE GUIDELINE

The scope of this guideline is for the identification of individuals who should be tested for germline disease-causing *TP53* variants, testing of their first degree-relatives and for surveillance (screening for cancer) of individuals with a germline disease-causing *TP53* variant.

GUIDELINE SUMMARY: SURVEILLANCE PROTOCOL IN CARRIERS OF GERMLINE DISEASE-CAUSING *TP53* VARIANTS

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 blood pressure 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 without gadolinium enhancement	Annual	Birth	-	High cancer risk *TP53* variant** or patient previously treated by chemotherapy 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

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Urine steroids	Every 6 months	Birth	18 years	When abdominal ultrasound does not allow a proper imaging of the adrenal glands	Weak
Colonoscopy***	Every 5 years	18 years	-	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	Weak

*This grading is based on published articles and expert consensus.

**A germline disease-causing *TP53* variant should be considered as "high risk" if 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.

***The first scan should be conducted with I.V. Gadolinium enhancement; in children, brain MRI should alternate with the Whole-Body MRI, so that the brain is imaged at least every 6 months.

KEY RECOMMENDATIONS

Recommendations for cancer patients

All patients who meet the modified "Chompret Criteria" should be tested for *TP53* disease-causing variants

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

Patients who develop a second primary core *TP53* tumour, within the radiotherapy field, should be tested for germline *TP53* variants

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

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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 multi-disciplinary team for discussion

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

Pre-symptomatic Testing Recommendations for people without cancer

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

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

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

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.

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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.

PSYCHOLOGICAL NEEDS

Germline disease-causing *TP53* variants cause an increased risk in children and young adults of cancer, screening and prevention programs means a high burden both for the individual and their family. Diagnosis, in a family, of an inherited cancer predisposition comes with a long-term awareness of cancer, experiences of illness, and anticipation of reduced life expectancy. Those families have often witnessed the death of loved ones, and seen several family members suffer from cancer simultaneously, which can result in a severe emotional burden. Services that deliver these diagnoses, and the surveillance that follows, are encouraged to support the formation and continuation of support groups, whether face-to-face or online, for affected people to support each other.

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