Li-Fraumeni and heritable *TP53*-related cancer (h*TP53*rc) syndromes CARE PATHWAY
*The Patient Clinical Pathway is "the whole **care pathway** from identification, diagnostics, and multidisciplinary case discussions to surveillance and preventive surgery", so indeed a pathway in time, focusing on **HOW***
Annual Review Recommended
Li–Fraumeni syndrome (LFS) is associated with germline *TP53* variants and carriers have a high lifetime risk of cancer, the most common being sarcoma, breast cancer, brain tumours, and adrenocortical carcinoma. With the wide adoption of next-generation sequencing panels, many individuals with germline *TP53* disease-associated variants lack classic personal or family history of LFS-related cancers. The diversity of clinical presentations associated with germline *TP53* alterations justifies the expansion of the LFS concept to a wider cancer predisposition syndrome designated heritable *TP53*-related cancer (hTP53rc) syndrome. Some *TP53* carriers may have hereditary breast cancer without other LFS manifestations.
At time of diagnosis, or possible diagnosis, ALL patients should be seen in a clinical genetics department or consultation.
All patients' significant complications should be followed up as appropriate, through a nationally recognized h*TP53*rc/LFS reference centre.
Annual review should be undertaken by an oncologist throughout childhood and to adulthood. Surveillance should be lifelong, and comply with the updated ERN GENTURIS guidelines.
Limiting radiation exposure is important in germline *TP53* carriers.
Patients, geneticists, oncologists and GPs should have direct access (telephone or email) to the National h*TP53*rc/LFS Reference Centre for h*TP53*rc/LFS related concerns.

Li-Fraumeni and heritable *TP53*-related cancer (hTP53rc) syndromes Review Checklist

	WHAT TO LOOK FOR	WHEN TO REFER
GENERAL ASSESSMENT	**Birth to age 18 years**: Complete physical examination every 6 months, including blood pressure, anthropometric measurements plotted on a growth curve (with particular attention to rapid acceleration in weight or height), Cushingoid appearance, signs of virilization (pubic hair, axillary moisture, adult body odour, androgenic hair loss, clitoromegaly, or penile growth), and full neurologic assessment. **Adults**: Complete physical examination every 12 months.	Rapidly growing, painful or changing lesions. **REFER** to National h*TP53*rc/LFS Reference Centre or oncology team.
ENDOCRINE	**Birth to age 18 years**: Increased risk of adrenocortical carcinoma (ACC) in children. Complete physical examination every 6 months, including blood pressure, anthropometric, Cushingoid appearance and signs of virilization (pubic hair, axillary moisture, adult body odour, androgenic hair loss, clitoromegaly, or penile growth). Ultrasound of abdomen and pelvis, and ACC-specific blood and urine tests (total testosterone, dehydroepiandrosterone sulphate, androstenedione and cortisol metabolites).	**REFER** to National h*TP53*rc/LFS Reference Centre or endocrinologist, oncologist, if suspicious signs or symptoms.

NEUROLOGICAL	Neurological symptom review, particularly ataxia, headaches, loss of consciousness and visual disturbance.	**REFER** to National h*TP53*rc/LFS Reference Centre or neurologist, if suspicious signs or symptoms.
BREAST	**Adult, females:** In light of the high early-onset breast cancer risk, breast awareness (age 18 years onwards) and clinical breast examination (yearly and starting at age 20 years onwards) is recommended. The option of risk-reducing bilateral mastectomy should be considered and discussed from age 20 years onwards.	**REFER** to National h*TP53*rc/LFS Reference Centre or oncologist, if suspicious signs or symptoms.
PREGNANCY	Pre-natal and pre-implantation testing is available but relies on pre-pregnancy genetic work up.	Both female and male *TP53* carriers, who are planning pregnancy should be **REFERRED** to a clinical genetics consultation.
ANY OTHER NEW SYMPTOMS	Consider other possible complications and remember the increased risk of sarcoma and potentially other malignancies from the h*TP53*rc/LFS spectrum.	**REFER** to appropriate specialist.

UNSURE? Do not hesitate to contact the h*TP53*rc/LFS team if you have any queries (the expertise of our ERN GENTURIS healthcare providers can be found on the website: www.genturis.eu).

Genotype-Phenotype correlations may become increasingly important for personalized risk-adapted surveillance of h*TP53*rc/LFS patients. However, it is currently premature to make adjustments to the surveillance protocol, based solely on genotype due to the lack of precise predictions for individual patients.

Data strongly indicate that surveillance leads to early detection of cancer and significantly improves overall survival. Therefore, surveillance should be offered to the following individuals: (i) those carrying a disease causing *TP53* variant, and; (ii) those fitting the "classic clinical definition" of LFS, without a disease-causing *TP53* variant.

Surveillance schedule for germline *TP53* carriers

CANCER	PERIOD	METHOD	FREQUENCY
ACC	Birth – 18 years	Abdominal ultrasonography and cortisol metabolites in urine.	Every 3–4 months
BREAST	From 18 years	Breast awareness	Monthly
	From 20 years	Clinical breast examination	Annually
	From 20 years	Breast MRI*	Annually
	From 20 years	Optional, Breast ultrasound	Annually
	Consider risk-reducing bilateral mastectomy		
BRAIN	From 18 years (potentially earlier, if indicated by family history or the *TP53* variant is associated with childhood onset)	Brain MRI (first MRI with contrast; thereafter without contrast if previous MRI normal and no new abnormality)*	Annually
SARCOMA	From 18 years (potentially earlier if indicated by family history or the *TP53* variant is associated with childhood onset)	WB-MRI*	Annually
OTHER	Adjusted surveillance *(i.e.* colonoscopy) could be considered, if indicated by family history or previous abdominal radiotherapy		

ACC, adrenocortical carcinoma; WB-MRI, whole-body MRI.
(*) Breast MRI/US of abdomen and pelvis to alternate with annual WBMRI (at least one scan every 6 months).

It is important to have a high level of clinical suspicion of malignancy concerning the *a-priori* cancer risk that these patients possess.

Li-Fraumeni and heritable *TP53*-related cancer(h*TP53*rc) syndromes care pathway

European Reference Network for rare or low prevalence complex diseases
Network Genetic Tumour Risk Syndromes (ERN GENTURIS)

Faculty: .....

Family name:

Given name(s)

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

Annual Review Recommended

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With the wide adoption of next-generation sequencing panels, many individuals with germline *TP53* disease-associated variants lack classic personal or family history of LFS-related cancers. The diversity of clinical presentations associated with germline *TP53* alterations justifies the expansion of the LFS concept to a wider cancer predisposition syndrome designated heritable *TP53*-related cancer (h*TP53*rc) syndrome. Some *TP53* carriers may have hereditary breast cancer without other LFS manifestations.

WHEN	WHOM	REVIEWS CARRIED OUT BY
At time of (possible) diagnosis	All patients	clinical genetics department or consultation
	Those with significant complications	the nationally recognized h*TP53*rc/LFS reference centre. Annual review should be undertaken by an oncologist throughout childhood and to adulthood. Surveillance should be lifelong, and comply with the updated ERN GENTURIS guidelines.
Limiting radiation exposure is important in germline *TP53* carriers.		
Patients, geneticists, oncologists and GPs should have direct access (telephone or email) to the National hTP53rc/LFS Reference Centre for hTP53rc/LFS related concerns.		

Li-Fraumeni and heritable *TP53*-related cancer (h*TP53*rc) syndromes Review Checklist

Clinical Presentation:
..... ☐
Other symptoms:
.....
Genetic counselling completed ☐
Date Completed: .....

Clinical diagnosis
.....
Genetic Test '+'ve ☐
Diagnosis Date: .....

General Health Check:
Please record the follow as soon as possible and then annually:
Height
.....
Weight
.....
Blood Pressure
.....

Surveillance schedule for germline *TP53* carriers

CANCER	PERIOD	METHOD	FREQUENCY
ACC	Birth – 18 years	Abdominal US and cortisol metabolites in urine.	Every 3–4 months
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	From 20 years	Clinical breast examination	Annually
	From 20 years	Breast MRI*	Annually
	From 20 years	Optional, Breast ultrasound	Annually
	Consider risk-reducing bilateral mastectomy		
BRAIN	From 18 years^	Brain MRI~	Annually
SARCOMA	From 18 years^	WB-MRI*	Annually
OTHER	Adjusted surveillance *(i.e.* colonoscopy) could be considered, if indicated by family history or previous abdominal radiotherapy		

ACC,adrenocortical carcinoma; US,ultrasonography; WB-MRI,whole-body MRI
* Breast MRI/US of abdomen and pelvis to alternate with annual WBMRI (at least one scan every 6 months).
^potentially earlier, if indicated by family history or the *TP53* variant is associated with childhood onset.
~ first MRI with contrast; thereafter without contrast if previous MRI normal and no new abnormality.

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NEUROLOGICAL: Neurological symptom review, particularly ataxia, headaches, loss of consciousness and visual disturbance.	**REFER** to National hTP53rc/LFS Reference Centre or neurologist, if suspicious signs or symptoms. ☐ **Date Referred**: .....
BREAST: **Adult, females:** In light of the high early-onset breast cancer risk, breast awareness (age 18 years onwards) and clinical breast examination (yearly and starting at age 20 years onwards) is recommended. The option of risk-reducing bilateral mastectomy should be considered and discussed from age 20 years onwards.	REFER to National hTP53rc/LFS Reference Centre or oncologist, if suspicious signs or symptoms. ☐ **Date Referred**: .....
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ANY OTHER NEW SYMPTOMS: Consider other possible complications and remember the increased risk of sarcoma and potentially other malignancies from the h*TP53*rc/LFS spectrum.	**REFER** to appropriate specialist ☐ **Date Referred**: .....
UNSURE? Do not hesitate to contact the PHTS team if you have any queries	

Doctor: .....
Review date: .....
Faculty: .....
www.genturis.eu

Notes:
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