Hereditary Breast and Ovarian Cancer syndrome: *CHEK2*
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***

Periodic Review Recommended

A woman with a heterozygous *CHEK2* pathogenic variant* has on average a moderately increased lifetime risk of breast cancer. Breast cancer risk also depends on other factors, mainly family history of breast cancer in first- and second-degree relatives, breast density, type of variant, heterozygous or homozygous state and polygenic factors:

- Carriers of a truncating variant face an average increased risk of about 2-3 fold in the absence of family history, and it might be much higher if they report a family history of breast cancer in first and/or second-degree relatives.
- Female carriers of truncating variants who have had breast cancer, have an increased risk for second primary breast cancer (about 2-fold).

An estimation of an individual's future risk of developing breast cancer using family history, genetic and other risk factors can be assessed using CanRisk (www.canrisk.org).

There is likely a moderate risk association for prostate cancer predisposition for men with truncating variants. There is some weak association with other type of tumours, but they do not reach the threshold for clinical utility.

Polygenic risk scores, once in routine clinical practice, could help with more precise risk stratification, especially when included in a multifactorial risk tool.

**Available data pertains primarily to truncating variants. Missense variants tend to be associated with reduced risk and penetrance with some exceptions (such as p.(Arg117Gly); risk associated with CHEK2 missense variants p.(Ile157Thr) and p.(Ser428Phe) does not reach currently accepted levels of clinical actionability (RR>2) and should not be reported.*

All individuals identified as carriers of a pathogenic variant in *CHEK2* should be offered genetic counselling early in their patient journey.

Periodic review for individuals with a pathogenic variant in *CHEK2* should be undertaken by a specialist in *CHEK2* (clinical geneticist, oncologist, surgeon, gynaecologist). Surveillance should be continued if the person is in good health. Surveillance may depend on the level of the risk, which depends on the specific pathogenic variant, and other genetic and non-genetic risk factors. Guidelines can differ in different EU countries, as robust evidence for risk-stratified surveillance is still evolving. (Marmolejo et al, European Journal of Medical Genetics 2021, PMID 34606975)

For individuals who are not carriers of the familial *CHEK2* variant, residual risk estimation for breast cancer should be provided as there might still be a higher risk for breast cancer as there may be other risk factors in the family. Based on the residual risk estimation results, surveillance guidance should be provided to guide future surveillance. An estimation of an individual's future risks of developing breast cancer using family history, genetic and other risk factors can be assessed using CanRisk (www.canrisk.org).

HBOC-*CHEK2* heterozygote (with truncating variants) Review Checklist—Adults (30+)		
	WHAT TO LOOK FOR	**WHEN REFERRAL and WHERE TO**
BREASTS	Promote breast awareness: women should be familiar with their breasts and promptly report changes to their health care provider. Follow country-specific recommendations starting between age 30 and 40 years of age (or starting 5-10 years earlier than the youngest breast cancer in the family). The type of image-based screening (mammography, ultrasound or MRI) will depend on multifactorial breast cancer risk assessment. Personalised risk assessment using CanRisk (www.canrisk.org) is advised to generate a personalised risk estimation, that can be used alongside country-specific guidelines. Screening modalities should be regularly re-evaluated (every 5-10y) according to updated risk evaluation, and personal/familial risk factors. Risk-reducing bilateral mastectomy for women without a prior diagnosis of breast cancer, and contralateral risk-reducing mastectomy for women with breast cancer are not routinely offered but may be considered based on personalized risk assessment and shared medical decision making. If needed, discussion at a multidisciplinary team consisting of at least a representative from clinical genetics, oncology, breast surgery, plastic surgery, radiology and gynaecology is advised.	In case of an abnormal mammography or MRI of the breasts and if signs or symptoms associated with breast cancer, refer to breast centre for investigation.
PROSTATE	Discuss annual PSA in shared decision-making process, particularly in case of family history of prostate cancer.	
PSYCHOLOGICAL BURDEN	Despite a short-term increase in anxiety scores when a pathogenic variant is identified, most studies show a good emotional response at mid and long term. Offer a referral to counselling service, if needed.	
PREGNANCY	Prenatal diagnosis is not recommended.	Carriers (both male and female) who are planning pregnancy may receive reproductive counselling if requested.
Other	If other cancers are present in the family, adapt surveillance based on family history and according to the country-specific recommendations. Provide education on modifiable risk factors for cancer.	

Hereditary Breast and Ovarian Cancer (HBOC)
CHEK2 heterozygote
Clinical 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

Periodic Review Recommended

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• Female carriers of truncating variants who have had breast cancer, have an increased risk for second primary breast cancer (about 2x).
An estimation of an individual's future risks of developing breast cancer using family history, genetic and other risk factors can be assessed using CanRisk (www.canrisk.org).
There is a likely moderate risk association for prostate cancer predisposition for truncating variants. There is some weak association with other type of tumours, but they do not reach the threshold for clinical utility.
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HBOC *CHEK2* heterozygote Review Checklist — Adults 30+

Clinical Presentation:

..... ☐
..... ☐
..... ☐

Other symptoms:

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Genetic counselling completed ☐

Date Completed:
.....

Clinical diagnosis

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Genetic Test '+'ve ☐

Diagnosis Date:
.....

General Health Check: Please record the follow as soon as possible and then annually:

Height

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Weight

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Notes:

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WHAT TO LOOK FOR	WHEN TO REFER
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OTHER: If other cancers are present in the family, adapt surveillance based on family history and according to the country-specific recommendations. Provide education on modifiable risk factors for cancer.	

Doctor: ..... Review date: ..... Faculty: .....