## CHEK2 Germline Pathogenic Variant Carriers
### Management Guidelines for Healthcare Professionals

### General information

- Germline pathogenic variants (GPV - including class 4 likely pathogenic and class 5 pathogenic variants) in CHEK2 are associated with an increased risk of female breast cancer (FBC). There is an association with ER positive breast cancers.
- In general, risks for truncating variants are greater than for missense variants. For most missense variants, relative risk for FBC is < 2 and should not influence clinical management in isolation. The missense variant c.349A>G.p.(Arg117Gly) is reported to have a similar risk to truncating variants.
- c.470T>C.p.(Ile157Thr) and c.1283C>T.p.(Ser428Phe) are lower risk alleles (OR <1.5) and in isolation should not influence clinical management.
- Biallelic CHEK2 heterozygotes have been shown to have a higher risk for invasive BC, are more likely to be diagnosed at or before age 50, and are more likely to have multiple primary BCs. However, lifetime risk estimates are difficult to quantify due to small study sizes.
- CHEK2 GPV are associated with an increased risk of breast cancer with many other cancers including but not limited to renal, thyroid, gastric, pancreatic cancer and haematological malignancies, however studies are conflicting and more data are required to confirm these associations.
- Whilst an early case series suggested that CHEK2 may predispose to Li-Fraumeni syndrome (LFS), subsequent studies have conclusively shown that variants in CHEK2 are not associated with LFS.

### Risks associated with CHEK2 germline pathogenic variants (95% confidence intervals)

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Odds ratio (OR)</th>
<th>Cancer risk to age 80</th>
<th>Population cancer risk to age 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (female)</td>
<td>2.66 (95% CI 2.27-3.11)</td>
<td>c.1100del (p.Thr367fs)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2.13 (95% CI 1.60-2.85)</td>
<td>other truncating variants</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2.69 (95% CI 1.46-4.94)</td>
<td>c.349A&gt;G.p.(Arg117Gly)</td>
<td>5</td>
</tr>
<tr>
<td>Breast (male)</td>
<td>3.13 (95% CI 1.94-5.07)</td>
<td></td>
<td>6</td>
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<tr>
<td>Prostate</td>
<td>OR 3.29 (95% CI 1.85-5.85)</td>
<td>c.1100del (p.Thr367fs)</td>
<td>7</td>
</tr>
<tr>
<td>Colorectal</td>
<td>OR 1.8 (95% CI 1.2-2.7)</td>
<td>c.1100del (p.Thr367fs)</td>
<td>8</td>
</tr>
</tbody>
</table>

### Clinical management recommendations: It is important to manage patients in the context of their family history of cancer

#### Screening
- **Breast**: Should be based on individualised risk assessment using tools such as CanRisk (for those with truncating variants), and in accordance with NICE guidelines on familial breast cancer (CG164).
  - *Moderate risk surveillance* (lifetime risk of 17-29%): annual mammograms 40-49 years then NHSBSP
  - *High risk surveillance* (lifetime risk of ≥30% but <40%): annual mammograms 40-59 years then NHSBSP
  - *Very high-risk screening* (lifetime risk of ≥40% and 10-year risk of 8% 25-29 yrs, 30-39 years or 12% 40-49 yrs): refer to VHR
  - Biallelic CHEK2 carriers (truncating variants): recommend VHR

- **Prostate**: Men can discuss pros and cons of PSA screening with their GP. Consider family history.

- **Colorectal**: CanRisk assay results can be used to determine surveillance in those at very high risk. CHEK2 carriers, but can be considered in context of family history of breast cancer.

#### Risk-reducing surgery
- **Breast**: Consider discussion of risk-reducing mastectomy if lifetime risk ≥30%, in conjunction with an individualised risk assessment using tools such as CanRisk and appropriate counselling.

#### Chemoprevention
- No specific studies of CHEK2 carriers, but can be considered in context of family history of breast cancer.

#### Cancer management
- At present CHEK2 GPV carrier status does not influence therapeutic options.

#### Lifestyle information
- Provide information about regular self-breast examination.
- Provide information on the benefits of smoking cessation, minimising alcohol intake and maintaining a healthy weight to lower the chance of getting cancer.
- Contraception: use of oral contraceptive pill (OCP) is not contraindicated, but requires informed discussion and consideration of alternative forms of contraception.

#### Family matters
- Refer to clinical genetics to facilitate genetic testing in at-risk family members.
- Refer to clinical genetics for discussions on reproductive options.

#### Psychological
- Consider referral for clinical psychology support if appropriate.

### References

ACMG Clinical Practice Resource for CHEK2: Hanson et al., 2023 PMID: 37490054

1) Population cancer risk figures to age 80 based on CRUK data (personal communication) and reflect the risk of cancer for people born in 1961
2) Individualised breast, contralateral breast and ovarian cancer risk estimates which incorporate germline PV carrier status, personal risk factors and where relevant breast cancer receptor status, polygenic risk score and breast density, are available at https://canrisk.org/ (Lee et al., 2021)

### Patient resources

- breastcancernow.org “Someone like me” https://breastcancernow.org/information-support/support-you/someone-me-telephone-support
- Coppafeel https://coppafeel.org/