FAQ for Management Guidelines for *BRCA1* and *BRCA2* Germline Pathogenic Variant Carriers for Healthcare Professionals

**Referral to Clinical Genetics**

- It is recommended that all patients identified as carriers of a germline pathogenic variant (GPV – i.e. class 4 – likely pathogenic variant, or class 5 - pathogenic variant as determined by ACMG/AMP guidelines) in *BRCA1* or *BRCA2* are referred to clinical genetics to receive individualised advice on cancer risks, management of cancer risks, reproductive options and to facilitate cascade testing of at-risk relatives.

**General population cancer risk estimates**

- The estimates presented are from Cancer Research UK ~(personal communication November 2022)~

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Gender</th>
<th>ICD-10 Code</th>
<th>Lifetime risk*</th>
<th>Risk to age 69</th>
<th>Risk to age 79</th>
<th>Method used</th>
<th>Method reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic</td>
<td>Female</td>
<td>C25</td>
<td>1.8%</td>
<td>0.39%</td>
<td>0.89%</td>
<td>CP</td>
<td>Esteve et al. 1994</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Male</td>
<td>C25</td>
<td>1.9%</td>
<td>0.50%</td>
<td>1.06%</td>
<td>CP</td>
<td>Esteve et al. 1994</td>
</tr>
<tr>
<td>Breast</td>
<td>Female</td>
<td>C50</td>
<td>15.3%</td>
<td>7.54%</td>
<td>10.47%</td>
<td>AMP</td>
<td>Sasieni et al. 2011</td>
</tr>
<tr>
<td>Breast</td>
<td>Male</td>
<td>C50</td>
<td>Not calculated</td>
<td>0.03%</td>
<td>0.06%</td>
<td>AMP</td>
<td>Sasieni et al. 2011</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Female</td>
<td>C56 – C57.4</td>
<td>2.0%</td>
<td>0.92%</td>
<td>1.34%</td>
<td>AMP</td>
<td>Sasieni et al. 2011</td>
</tr>
<tr>
<td>Prostate</td>
<td>Male</td>
<td>C61</td>
<td>17.9%</td>
<td>5.74%</td>
<td>12.24%</td>
<td>CP</td>
<td>Esteve et al. 1994</td>
</tr>
</tbody>
</table>

**Method key/Notes:**

- CP - “Current Probability”
- AMP - “Adjusted for Multiple Primaries”
- Age-specific risk was calculated for males and females separately and by five-year age-band, based on the methodology stated. Risk to age X was calculated by summing the age-specific risk up to the relevant age-band.
- These numbers reflect the risk of cancer for people born in 1961.
- For more information on the methodology behind these calculations, please see: https://www.cancerresearchuk.org/health-professional/cancer-statistics/cancer-stats-explained/our-calculations-explained#heading-Eight
Breast, contralateral breast and ovarian cancer cumulative risk estimates

- The estimates presented are from Kuchenbaecker et al., 2017
- This was a prospective cohort study of carriers of PV recruited through 3 consortia. It included 6000 BRCA1 and 3800 BRCA2 GPV carriers. 94% were ascertained through familial cancer clinics and 6% via population-based studies.
- A limitation of this data with respect to ovarian cancer risk is that the study did not include many women of 70 years or older, so the risks artificially appear to plateau at this age.
- Individualised breast, contralateral breast and ovarian cancer risk estimates which incorporate GPV 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) and should be used, particularly for breast cancer risk assessment to advise on starting age of surveillance and risk reducing surgery

Breast cancer screening recommendations

- Are presented from NICE Clinical Guideline CG164 (NICE, 2013) and PHE Protocols for surveillance of women at very high risk of developing breast cancer (Dec 2021)
- https://www.nice.org.uk/guidance/cg164

Oral contraception

Early studies on the effect of oral contraceptive use (OCP) on breast cancer risk among carriers of a pathogenic BRCA1/2 variant have reported conflicting data (Narod et al., 2002; Milne et al., 2005; Haile et al., 2006). Conflicting data may be due to differences in study design, differences in risk based on family history or other factor or OCP formulation. Two meta-analyses and a more recent case-control study have showed that OCP use is not significantly associated with breast cancer risk in carriers of a pathogenic BRCA1/2 variant (Lee et al., 2008; Iodice et al., 2010; Moorman et al., 2013). However, larger prospective trials are likely needed to fully understand the impact of OCP on breast cancer risk in BRCA1/2 carriers.

OCP use may reduce the risk of ovarian cancer. Two meta-analyses have demonstrated that OCP use significantly reduced the risk for ovarian cancer for both BRCA1 and BRCA2 carriers (Iodice et al., 2010; Moorman et al., 2013).

We advise that women discuss contraception with their GP to assess the range of available options. OCP use can be considered, providing patients are informed about the need for further data to fully understand impact on breast cancer risk and alternative contraceptive methods have been discussed.
Pancreatic, male breast and other cancer risk estimates

The estimates presented are from personal communication with Prof. Gareth Evans and Dr Emma Woodward utilising information available from registry information at the Manchester Genetics service.

BRCA1 pancreatic cancer risks

Risk to age 80-years for male BRCA1 carriers was calculated to be 3.4% and for female BRCA1 carriers 0.54%, based on 8 and 4 pancreatic cancers respectively in 1111 males and 2732 female presumed or tested BRCA1 carriers.

BRCA2 pancreatic cancer risks

Risk to age 80-years for males BRCA2 carrier was calculated to be 4.8% and for female BRCA2 carriers, 2.2%, based on 15 and 18 pancreatic cancers respectively in 1138 males and 2762 female presumed or tested carriers. All index cases tested before diagnosis who did not have breast or ovarian cancer were excluded.

Pancreatic cancer risks are also detailed in Li et al., 2022 who suggest that the cumulative lifetime risks are similar for BRCA1 and BRCA2 (Male BRCA1: 3% (2-5%) by age 80; Female BRCA1: 2% (2-4%) by age 80; Male BRCA2: 3% (2-5%) by age 80; Female BRCA2: 2% (1-4%) by age 80; but that relative risks are slightly higher for BRCA2 (BRCA1; RR 2-3 lifetime risk - 1-4%, BRCA2; RR 3-6 lifetime risk-3-5%. RR was also higher for BRCA2 carriers under 65 years. This paper only considered first primary pancreatic cancer diagnosis (i.e not taking into consideration cases who had been affected with a previous breast/ovarian cancer)

It is important to consider relevant family history and other risk factors e.g. smoking when discussing pancreatic cancer risks.

Li et al., also reported a possible association between BRCA1 and BRCA2 GPV and stomach cancer. They reported BRCA1 absolute risks for stomach cancer to age 80 of 1.6% (male) and 0.7% (female); and BRCA2 3.5% (male and female). However, the association between BRCA GPV and stomach cancer remains under considerable debate.

Prostate cancer risk estimates

- The estimates presented are from Nyberg et al., 2020 and Li et al., 2022. rounded to nearest whole %.

- Nyberg (2020) was a prospective cohort study (EMBRACE) of GPV carriers recruited via familial cancer clinics. It included 376 BRCA1 and 447 BRCA2 mutation carriers.

- Li (2022) was a retrospective cohort study of GPV carriers recruited through 26 consortia globally. It included 7281 families ascertained through familial cancer clinics and 337 families via population-based studies (i.e. unselected for family history).

- The Nyberg data when unadjusted for PSA screening effects reported much higher cumulative risks; 29% (17 to 45) by age 85 for BRCA1 and 60% (43 to 78) by age 85 for BRCA2 which are much higher than those presented in Li (2022) and likely explained by the detection of indolent prostate cancers undetectable in the absence of screening. The Nyberg data presented in the table is adjusted for screening effect.
Other factors may influence prostate cancer risks. Risks for BRCA2 GPV carriers increase with the number of relatives affected by prostate cancer. Prostate cancer risks are also affected by the location of the BRCA2 GPV within the gene. BRCA2 GPV both within and outside the ovarian cancer cluster region (OCCR) are associated with elevated prostate cancer risk compared to the general population. However, carriers of variants within the OCCR may be at comparatively lower risk than carriers of variants outside the OCCR. At present this does not alter surveillance recommendations and the same recommendations are made for all BRCA2 carriers.

**Prostate cancer screening recommendations**

- BRCA2 recommendations are based on European Association of Urology guidelines (Mottet et al., 2021), and interim results from the IMPACT study (Page et al., 2019).

**References:**
