

Tables/figure legends

Figure 1. Methods for detecting homologous recombination repair deficiency (HRD). HR = homologous recombination. Individual assays (HRDetect, LOH, NtAi, LST and GIS) are described in the text. The two commercially available assays that combine *BRCA* mutation and genomic instability scores are described in the green box.

Figure 2. Rationale for using homologous recombination deficiency (HRD) tests to establish PARPi benefit in ovarian cancer. A) Tumours with evidence of HRD, determined using currently available tests, are more likely to respond to platinum salt chemotherapy and PARPis but factors such as resistance mechanisms mean overlap is incomplete. B) Schema for assessing clinical validity and clinical utility of HRD biomarkers.

Figure 3. Trends for incremental benefit from PARPi across HRD defined subgroups. A forest plot displays the hazard ratios and 95% confidence intervals for PARPi benefit as reported the key phase II/III clinical trials of HGOC, detailed in the same order as Table 2. The box size indicates the number of patients (n). Solid and dashed error bars indicate primary and exploratory analyses respectively. Similar trends are seen across trials with incremental PARPi benefit across homologous recombination deficient (HRD) and homologous recombination proficient (HRP) subgroups. The greatest benefit is observed in the *BRCA* mutant cohort (s, t and g prefix = somatic, tumour and germline) (red), followed by those with high genomic instability scores (GIS) or loss of heterozygosity (LOH) scores or a *BRCA* mutation (dark orange) (these are equivalent to the Myriad Genetics and Foundation medicine commercial assay 'HRD positive' subgroups), the *BRCA*wt group with GIS/LOH-high (light orange) and finally in the HRP *BRCA*wt (light blue) and the *BRCA*wt/GIS/LOH-low score (dark blue) subgroups. Caution is advised in comparing absolute results between trials due to important differences in trial design (some of which are described in Table 2). Results are included where they were presented in the original publications.

Table 1. Summary of critical evidence review of HRD tests

For each HRD test, where relevant, LOE as per Simon criteria [18] (**Supplementary Table 3**) and EGAPP ranking [19] is provided. For EGAPP ranking, clinical validity is defined as “accuracy of prediction of PARP inhibitor sensitivity” and clinical utility describes the “accuracy of prediction of PARP inhibitor benefit” in the first-line and platinum-sensitive relapsed maintenance settings. Clinical utility is reported as Good, Fair, or Marginal, where marginal reflects the fact that the studies may not have been poor in general but may not have been designed to address the specific question. LOE and EGAPP ranking is designed to evaluate genomic (not functional) tests and is only provided for HRD tests for which there is sufficient clinical evidence to evaluate. Tumour *BRCA* incorporates both germline (inherited) *BRCA* and somatic (acquired) *BRCA* mutations. GIS = genomic instability score, LOH is loss of heterozygosity score.

Table 2. Pivotal randomised controlled trials of PARPi maintenance therapy in HGSOE (relates to Figure 3). Benefit from PARPi versus placebo is displayed as progression free survival (PFS) and hazard ratios (HR) with 95% confidence intervals (CI). These HRs are presented in the same order in the forest plot in Figure 3. Primary endpoint analyses are denoted by purple highlighting. Heterogeneity between trials includes but is not limited to eligibility criteria and stratification criteria, some of which are presented. Additional exploratory analyses of HRD (homologous recombination deficiency) and homologous recombination proficiency (HRP) subgroups that were predefined (dark grey) or performed post-hoc (white) are presented. CR = complete response, PR = partial response, HRR = homologous recombination deficiency. Mutation in *BRCA1* or *BRCA2* gene = *BRCA* mutant (nature of mutation denoted by prefix “s” = somatic, “t” = tumour and “g” = germline) and *BRCA1/2* wild-type = *BRCAwt*. Genomic scar tests include the genomic instability score (GIS) and loss of heterozygosity score (LOH).

Table 3. Regulatory approvals of PARP inhibitor use in gynaecological malignancy. FDA = US Food and Drug Administration. EMA = European Medicines Agency. OC = ovarian cancer, FTC= fallopian tube cancer, PPC = primary peritoneal cancer. *See <https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools> for details of FDA approved companion diagnostics

Supplementary Tables

Supplementary Table 1. Systematic review strategy

Supplementary Table 2. Shortlisted studies selected for critical evidence review

Supplementary Table 3. LOE criteria (Simon Criteria)

Supplementary Table 4. Germline *BRCA1/2* mutations studies for critical evidence review and LOE/EGAPP summary

Supplementary Table 5. Somatic *BRCA1/2* mutations studies for critical evidence review and LOE/EGAPP summary

Supplementary Table 6. HRR gene mutations beyond *BRCA1/2* studies for critical evidence review and LOE/EGAPP summary

Supplementary Table 7. *BRCA1* promoter methylation studies for critical evidence review

Supplementary Table 8. Genomic scar assays studies for critical evidence review and LOE/EGAPP summary

Supplementary Table 9. Genomic signatures studies for critical evidence review

Supplementary Table 10. Functional assays studies for critical evidence review