Testing for germline BRCA1/2 mutations has an established predictive role in breast cancer risk assessment. More recently, studies have also identified BRCA1/2 status as clinically relevant in the selection of therapy for patients already diagnosed with breast cancer. Emerging breast and ovarian cancer research indicate that BRCA status predicts responsiveness to platinum-based chemotherapy, as well as to inhibitors of poly(ADP-ribose) polymerase (PARP), owing to the ability of these interventions to inhibit DNA repair pathways. BRCA1/2 mutation testing thus has important and expanding roles in treatment planning for subsets of patients with breast cancer. Recent studies have demonstrated different activity of platinum salts in BRCA1-mutated compared with non-BRCA-mutated breast cancer. Furthermore, phase II/III studies of single-agent PARP inhibitors (PARPi) have shown encouraging progression-free survival results in patients with BRCA1/2-mutated breast cancer, which led to the recent approval of olaparib, the first PARPi to be approved in breast cancer. Determining BRCA1/2 mutation status in this breast cancer subgroup could potentially expand treatment options beyond the current standard of taxane and anthracycline-based chemotherapy. Although attempts have been made to develop scoring systems that measure defects in homologous recombination repair pathways to predict response to platinum or PARPi, none have yet made it into clinical use. In this review, we summarise the recent and ongoing preclinical and clinical studies on the treatment of BRCA-associated breast cancer, and discuss efforts to identify other breast cancer patients who may be responsive to therapies effective in BRCA mutation carriers, including platinum-containing chemotherapy and PARPi.

WHO (AND WHAT) TO TEST FOR BRCA MUTATION

The value of gBRCA1/2m testing for cancer risk reduction in breast and ovarian cancer is well-established. To date, researchers from the Breast Cancer Information Core (https://research.nhgri.nih.gov/bic/) have collated more than 1800 mutations in the BRCA1 gene and 2000 mutations in the BRCA2 (BRCA2) gene, which are present in up to 20% of patients with TNBC, and these represent an opportunity for improved precision treatment. There is also growing evidence that BRCA1/2 mutations (BRCA1/2m) are clinically relevant for identifying subtypes of hormone receptor-positive HER2-negative BC. This review evaluates current research on the treatment of BRCA1-associated BC, and highlights the importance of BRCA1/2m testing to help identify patients with BC who might benefit from platinum-based chemotherapy, as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi). The biological and preclinical evidence supporting the rationale for targeting BRCA1/2m in BC are described, and evidence from recent and ongoing clinical studies with platinum salts and PARPi is highlighted in both advanced and early-stage BC settings. Finally, we briefly explore the biomarkers currently being evaluated for potential future clinical application, including a look beyond BRCA1/2m and the concept of BRCA1ness.

1Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA; 2Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA and 3Dana-Farber Cancer Institute, 450 Brookline Avenue Boston, Boston, MA 02215, USA

Correspondence: Nadine M. Tung (ntung@bidmc.harvard.edu)

Received: 29 September 2017 Revised: 10 April 2018 Accepted: 24 April 2018

Published online: 5 June 2018
OC cluster regions, which are associated with greater OC risk, tended to be located in the central region of each gene; whereas BC cluster mutations were located in the 5′ and 3′ regions.\textsuperscript{7,20} Alterations that appear to confer higher risk include missense mutations in the RING finger, BRCA1 C-terminal (BRCT), and DNA-binding domains, large genomic rearrangements, and founder mutations in both BRCA genes;\textsuperscript{7,20} however, validation is required before these data can be used for clinical risk assessment.

Beyond testing for gBRCA1/2m, a small percentage of BRCA-related cancers contain purely somatic mutations, which can be detected through direct analysis of the tumour tissue or circulating cell-free DNA.\textsuperscript{21,22} The percentage of somatic BRCA1/2m in BC is not well established; however, two studies found that \textasciitilde 3% of unselected primary BCs had a somatic mutation in BRCA1 or BRCA2.\textsuperscript{23,24} By contrast, 19% of 235 unselected OCs were found to harbour a somatic BRCA1/2m.\textsuperscript{25} Among the 28 ovarian tumours with a somatic BRCA1/2m for which a blood sample (germline DNA) was available, 11 (39%) were found not to have a germline BRCA1/2m, suggesting that 7%–8% of OCs harbour only a somatic BRCA1/2m, compared with 3% in BC.\textsuperscript{25} Whereas there is accumulating evidence to support testing for somatic BRCA1/2m to guide therapy, the clinical implications for treatment are not yet clear for BC or OC.\textsuperscript{26} In BC, the rationale for somatic BRCA1/2m testing is less developed than for germline testing, but may soon become reasonable in some settings if specific BRCA1-targeted therapies, such as PARPi, are found to be effective in the presence of BRCA1/2m alone. Of note, although these mutations are uncommon in prostate cancer, data suggest that patients with somatic BRCA1/2m will respond to PARPi.\textsuperscript{27} The efficacy of PARPi for advanced BC with somatic BRCA1/2m is currently being investigated in a study by the Translational Breast Cancer Research Consortium (NCT03344965).

The role of BRCA testing to guide therapy selection in patients already diagnosed with BC is evolving. Box 1 lists the patient characteristics that should trigger testing for BRCA1/2m in those already diagnosed with BC. The presence of BRCA1/2m may offer patients additional or alternative treatment options as discussed in this review, in both early-stage and advanced BC.

### EVIDENCE AND RATIONALE FOR TARGETING BRCA1/2 MUTATIONS

The biologic rationale for targeting BRCA1/2 mutations with PARPi or platinum salts in BC has been supported by preclinical studies investigating these interventions in BC, combined with clinical data assessing carboplatin in OC. Wild-type BRCA1 and BRCA2 are tumour-suppressor genes and their protein products have multiple functions, including serving as key enzymes in the homologous recombination pathway, which is the high-fidelity mechanism for repair of DNA double-strand (DS) breaks.\textsuperscript{28,29} Loss-of-function mutations or silencing of BRCA1/2 disables the homologous recombination pathway, which forces cells to rely on lower fidelity more error-prone pathways for DNA repair, such as non-homologous end-joining, during which mutations and genetic instability may be introduced.\textsuperscript{30–32}

Inhibition of single-strand (SS) DNA break repair in tumour cells with homologous recombination deficiency\textsuperscript{33} is synthetically lethal, and can cause cell death. Poly(ADP-ribose) polymerase-1 (PARP-1) is an integral enzyme in the repair pathway for SS DNA breaks; PARP-1 detects SS breaks and induces the creation of PAR chains on itself and adjacent nuclear proteins, thus signalling for other DNA repair enzymes to accumulate.\textsuperscript{34} Eventually, PARP-1 ‘PARylates’ itself, allowing it to be released from the DNA and continue its cycle of sensing SS breaks. Therefore, in BRCA-deficient tumours with defective homologous recombination, PARPi prevent the repair of SS DNA breaks, which may lead to the accumulation of DS breaks and stalled DNA replication forks, leading to cell death.\textsuperscript{35} Another way that PARPi may contribute to cell death is through the trapping of PARP proteins on DNA; the trapped PARP-1/DNA complexes can interfere with DNA replication, which also occurs by stalling the DNA replication forks.\textsuperscript{32,35} Preclinical data have demonstrated differences in PARP trapping potency among PARPi (talazoparib exhibited the highest potency, followed by niraparib, olaparib, and rucaparib, with veliparib having the lowest potency). Trapping potencies did not correlate with their respective PARP catalytic inhibition,\textsuperscript{35,36} and it is not clear whether these differences have any significant impact on clinical efficacy or safety.

The wild-type BRCA allele commonly undergoes loss-of-heterozygosity during tumorigenesis in individuals with heterozygous BRCA1/2m, leading to severe deficiency in the homologous recombination pathway.\textsuperscript{20} Therefore, a germline heterozygous BRCA1/2 mutation may be sufficient to identify tumour cells that are more likely to be sensitive to PARPi. In support of this, PARPi strongly reduced the proliferation and survival of cells harbouring defects in homologous recombination due to deficiencies in BRCA1/2 in laboratory and xenograft models.\textsuperscript{37,38} Furthermore, high sensitivity to PARPi was observed in cells with deficiency in homologous recombination repair, including loss-of-BRCA1/2,\textsuperscript{37,39} or loss of another protein essential for repair of DS breaks.\textsuperscript{38} This is not surprising, given that a single-functional BRCA allele is sufficient to maintain homologous recombination.

Notably, preclinical studies investigating platinum salts found that cells lacking functional BRCA1 or BRCA2 were highly sensitive to cisplatin.\textsuperscript{40} This is consistent with platinum-based chemotherapy studies in OC, which reported higher response rates in patients with homologous recombination deficiencies.\textsuperscript{41,42} This sensitivity has been attributed to the formation of covalent crosslinks in the DNA, and an impaired ability of cells to repair this damage in the absence of competent homologous recombination.\textsuperscript{40,42} Improved response rates to platinum-based chemotherapy in patients with BRCA1/2m OC, as well as the high sensitivity of homologous recombination-deficient cells to PARPi and platinum salts, led to clinical studies investigating both of these methods for the identification of responders and prediction of patient outcomes with targeted agents in the treatment of BRCA-related BC, OC, and other tumours. It also stimulated the search for further biomarkers of response.

### BRCA MUTATIONS IN ADVANCED AND METASTATIC BC MANAGEMENT

Evidence regarding the use of BRCA status or homologous recombination competency to guide treatment selection in BC is strongest in the setting of metastatic disease, and several recent
Clinical outcomes in locally advanced and metastatic BC: platinum salts

The largest study testing the ability of gBRCA1/2m status to predict response to platinum salts was the ‘TNT’ Triple-Negative Breast Cancer Trial. Enrolled patients (n = 376) had recurrent, locally advanced or metastatic BC that was confirmed to be triple-negative or occurred in a known BRCA1/2m carrier (regardless of ER, PgR, or HER2 status). Patients were randomised to carboplatin or docetaxel as first-line treatment for recurrent disease, and stratified according to BRCA1/2 status. There was no significant difference in objective response rate (ORR), median progression-free survival (PFS), or overall survival (OS) in the overall population; however, among carriers of a BRCA1/2m (n = 43), the carboplatin group had a significantly higher ORR than the docetaxel group (68% versus 33%; P = 0.03), and the interaction between treatment effect and BRCA status was significant (P = 0.01). Likewise, among mutation carriers, PFS was significantly longer in the carboplatin group versus the docetaxel group (6.8 versus 4.8 months; P = 0.003), and the interaction between treatment effect and BRCA status was significant (P = 0.03). High-response rates to platinum salts in women with BRCA-related metastatic BC have also been reported in other studies, as described in Table 1.

These studies indicate that patients with advanced or metastatic BC associated with gBRCA1/2m have high-clinical response rates to cisplatin and carboplatin, and those response rates are associated with longer PFS. It is not yet clear whether those clinical benefits will translate into longer OS.

Clinical outcomes in locally advanced and metastatic BC: PARPi inhibitors

PARPi have received FDA approval for a variety of indications over the last 4 years. Olaparib has recently (January 2018) received FDA approval for the treatment of patients with gBRCA1/2m HER2-negative metastatic BC who were previously treated with chemotherapy in neoadjuvant, adjuvant, or metastatic settings. This makes olaparib the first PARPi approved for the treatment of BC. Previously, 2014 saw the approval of olaparib for use as monotherapy in patients with deleterious or suspected deleterious gBRCA1/2m advanced OC who were treated with three or more prior lines of chemotherapy, and in August 2017, olaparib received approval for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who experience a complete or partial response to platinum-based chemotherapy. Furthermore, niraparib gained FDA approval in March 2017 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who experience a complete or partial response to platinum-based chemotherapy.

Rucaparib was approved in 2016 for treatment of patients with deleterious BRCA mutation-associated advanced OC who were treated with two or more chemotherapies. Olaparib was the first PARPi to undergo extensive clinical testing in BC. Antitumour responses, measured by ORR, radiologic response, or tumour-marker response, were reported in early studies of women with previously treated and advanced BC or OC. Later, an open-label, single-arm phase II basket study reported results for olaparib monotherapy in 62 women with BRCA1/2m-associated advanced BC. These patients were heavily pretreated, with a mean of 4.6 chemotherapy regimens in the metastatic setting, including 42 (68%) who had received prior platinum therapy (cisplatin or carboplatin). Partial responses were observed in 8 patients (13%) and stable disease ≥8 weeks was observed in 29 patients (47%). Response rates were lower in patients who had received prior platinum therapy (9.5%); 95% confidence interval (CI): 2.7–22.6) compared with those who had not (20%; 95% CI: 5.7–43.7). Although this difference was not statistically significant, it is consistent with the concept that platinum chemotherapy and PARPi may be targeting the same mechanistic pathways (i.e., DNA repair), and therefore may have some degree of cross-resistance. A similar trend related to prior platinum chemotherapy was also observed for pancreatic and prostate cancer. Of note, response to PARPi in OC is strongly associated with responsiveness to platinum chemotherapy; one study demonstrated a 61.5% ORR (by RECIST) to single-agent olaparib in platinum-sensitive OC, but no RECIST responses in platinum-refractory OC. This concept is also supported by a phase II study in which patients with gBRCA1/2m-associated metastatic BC were treated with veliparib alone followed by combination with carboplatin at progression; only 1 of 30 patients responded to combination therapy after progression on veliparib. A phase II study with olaparib is summarised in Table 2.

More recently, the phase III OlympiAD study (NCT02000622) assessed olaparib monotherapy versus physician’s choice of chemotherapy (capecitabine, vinorelbine, or eribulin) for the treatment of metastatic BC in 302 patients with gBRCA1/2m (Table 2). At the December 2016 data cutoff, PFS by blinded independent central review was significantly longer with olaparib than with physician’s choice chemotherapy (7.0 versus 4.2 months; hazard ratio (HR) 0.58; 95% CI: 0.43–0.80; P < 0.001). An exploratory subgroup analysis of PFS was conducted, and although the study was not powered to detect differences among these subgroups, the HR favoured olaparib versus physician’s choice for patients with TNBC (HR 0.43; 95% CI: 0.29–0.63) and BRCA1/2m carriers of either subtype: BRCA1m (HR 0.54; 95% CI: 0.37–0.79) and BRCA2m (HR 0.68; 95% CI: 0.45–1.07). Another study also reported a doubling of ORR with olaparib versus physician’s choice chemotherapy (59.9% versus 28.8%, respectively) and greater change from baseline in target lesion size with olaparib (~45.1% versus ~14.8%, respectively). A prespecified secondary analysis that examined health-related quality of life found that patients who received olaparib experienced significantly less and significantly delayed deterioration in global health-related quality of life, compared with physician’s choice chemotherapy. In a similarly designed phase III study (EMBRACA, NCT01945775), talazoparib was compared with physician’s choice of therapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in 431 patients with gBRCA1/2m advanced BC (Table 2). Talazoparib significantly prolonged PFS by blinded independent central review (8.6 months, 95% CI: 7.2–9.3 versus 5.6 months, 95% CI: 4.2–6.7; HR 0.54; P < 0.0001), and delayed time to deterioration in global health status/quailty of life (HR 0.38; 95% CI: 0.26–0.55; P < 0.0001), compared with physician’s choice of therapy. Other PARPi that are currently being evaluated in phase II/III clinical studies in advanced cancers related to BRCA1/2m, including BC (rucaparib, veliparib, and niraparib) are described in Table 2.

The results from studies of PARPi in advanced and metastatic BC suggest that these agents are active against BC in women with germline BRCA1/2 loss-of-function mutations, but response rates remain around 60%. Lack of response in BRCA1/2m carriers may be due to several mechanisms of resistance (Fig. 1). Secondary somatic mutations that restore function of BRCA1 or BRCA2 have been reported to predict clinical resistance to PARPi in OC. Furthermore, in mouse models of BRCA1m BC, two mechanisms of PARPi resistance have been reported: loss-of-53BP1, which is associated with partial restoration of homologous recombination, and upregulation of genes that encode drug efflux pumps such as MDR1/P-glycoprotein1. In addition to the monotherapy studies described above, some PARPi are being evaluated in combination with other therapies. While there is promising evidence of improved response in BRCA1/2m carriers, this approach is challenging due to the associated dose-limiting myelosuppression.
| Study | Disease | Phase | Total (n) | \(BRCA_1/2\) (n) | \(TNBC\) (n) | \(BRCA_1/2\) ER\(^+\) (n) | Treatment | Response in overall population | Response in patients with wt\(BRCA_1/2\) | Response in patients with \(gBRCA_1/2\) | Response in patients with \(BRCA_1\) |
|-------|---------|-------|-----------|-----------------|----------------|-----------------|-----------|-------------------------------|----------------------------------|---------------------------------|----------------------------------|
| **Advanced and metastatic breast cancer** | | | | | | | | | | | | |
| TNT\(^{45}\) | Metastatic TNBC or \(BRCA_1/2\) mutation BC | III | 376 | 43 | 363 | 12 | Carboplatin vs docetaxel | ORR: 31% with carboplatin vs 36% with docetaxel | NR | 68% with carboplatin vs 33% with docetaxel | NR |
| TBCRC009\(^{48}\) | Metastatic TNBC | II | 86 | 11 | 86 | 0 | Cisplatin or carboplatin | ORR: 25.6% (22/86) | ORR: 19.7% (13/66) | 54.5% (6/11) | NR |
| NCT01611727\(^{47}\) | Metastatic BC with a \(BRCA_1\) mutation | II | 20 | 20\(^a\) | 14 | 5 | Cisplatin | NR | NR | NR | ORR: 80% CR: 45% |
| Brocade 2 \(\dagger\) NCT01506609\(^{52}\) | Locally recurrent or metastatic BC with a \(gBRCA_1/2\) mutation | II | 99 | 99 | 42 | 56 (ER\(^+\) and/or PgR\(^+\)) | Paclitaxel/carboplatin/placebo (PCP) | 61% | NR | 61% | NR |
| **Early-stage disease** | | | | | | | | | | | | |
| NCT01630226\(^{55}\) | Stage I–II BC with a \(BRCA_1\) mutation | II | 107 \(\dagger\) | 107\(^2\) | 82 | 16 | Cisplatin | NR | NR | NR | pCR: 61% |
| GeparSixto/GBG 66 NCT01426880\(^{67,88}\) | Stage I–II TNBC or HER2 \(+\) BC | II/III | 588 | 50 | 315 | 291 \(BRCA_4\) known | Backbone regimen \pm\) carboplatin | With vs without carboplatin: TNBC pCR: 53% vs 37% 291 \(BRCA_4\) known status: 57% vs 41% | With vs without carboplatin: TNBC pCR: 55% vs 36% | With vs without carboplatin: TNBC pCR: 65% vs 67% | NR |

\(BC\) breast cancer, \(CR\) complete response, \(ER^+\) oestrogen receptor-positive, \(gBRCA_1/2\) germline \(BRCA_1/2\), \(HER2^+\) human epidermal growth factor receptor 2-positive, \(NR\) not reported, \(ORR\) overall response rate, \(pCR\) pathologic complete response, \(PgR^+\) progesterone receptor-positive, \(TNBC\) triple-negative breast cancer, \(wtBRCA_1/2\) wild-type \(BRCA_1/2\)

\(^{\dagger}\)All were HER2-negative, 15 were ER-negative, 17 were PgR-negative, and 14 were TNBC

\(^{\dagger}\)All were HER2-negative (5 HER2 status unknown), 86 were ER-negative (5 ER status unknown), 91 were PgR-negative (6 PgR status unknown), and 82 were TNBC
| Study | Disease | Phase | N  | Treatment | Efficacy in patients with gBRCA1/2m |
|-------|---------|-------|----|-----------|-----------------------------------|
| NCT0049423457 | Recurrent, advanced BC with median 3 prior regimens and BRCA1/2 mutation (BRCA1/2m) | II  | 27 | Olaparib 400 mg BID | ORR: 41% (11/27) |
| OlympiAD NCT0200062261 | Metastatic BC with gBRCA1/2m | III | 302 | Olaparib 300 mg BID vs treatment of physician’s choice (TPC; capcitabine, eribulin, or vinorelbine) | ORR: 60% with olaparib vs 29% with TPC |
|          |        |      |    |           | PFS: 7.0 months with olaparib vs 4.2 months with TPC (hazard ratio 0.58; 95% CI: 0.43–0.80; P < 0.001) |
|          |        |      |    |           | DoR: 64 months with olaparib (IQR, 2.8–9.7) vs 7.1 months with TPC (IQR, 3.2–12.2) |
| EMRACA NCT0194577564 | Advanced BC with gBRCA1/2m | III | 431 | Talazoparib 1 mg/day following platinum-based therapy (cohort 1) vs ≥3 platinum-free cytotoxic-based regimens (cohort 2) | ORR: 21% (95% CI: 10–35) in cohort 1 vs 37% (95% CI: 21–55) in cohort 2 |
|          |        |      |    |           | PFS: 4.0 months in cohort 1 vs 5.6 months in cohort 2 (hazard ratio 0.58; 95% CI: 0.35–0.92) |
|          |        |      |    |           | DoR: 5.8 months (95% CI: 2.8–11.2) in cohort 1 vs 3.8 months (95% CI: 2.8–10.1) in cohort 2 |
|          |        |      |    |           | CBR: 38% (95% CI: 24–53) in cohort 1 vs 66% (95% CI: 48–81) in cohort 2 |
| EMBRACA NCT0194577564 | Advanced BC with gBRCA1/2m (and HER2-negative) | III | 306 | Niraparib vs physician’s choice of chemotherapy | ONGOING |
| Cancer Research UK67 | Previously treated advanced OC or BC with gBRCA1/2m | II  | n = 23 | Rucaparib | 39% of BC patients (9/23) achieved stable disease ≥12 weeks |
| RUBY NCT0250504868 | HER2-negative metastatic BC associated with BRCA1/2m and/or a somatic BRCA1/2m mutation | II  | 41 (est) | Rucaparib | ONGOING |
| Brocade 2 NCT0150660982 | Locally recurrent or metastatic BC with gBRCA1/2m | II  | 284 | Paclitaxel/carboplatin/veliparib (PCV) vs paclitaxel/carboplatin/placebo (PCP) | PFS: 14.1 months with PCV vs 12.3 months with PCP; hazard ratio 0.789 (95% CI: 0.536–1.162); P = 0.227 |
|          |        |      |    |           | ORR: 78% with PCV vs 61% with PCP; P = 0.027 |
| Brocade 3 NCT0216369463 | Locally advanced or metastatic gBRCA1/2m BC (and HER2-negative) | III | 500 | Paclitaxel/carboplatin/veliparib vs paclitaxel/carboplatin/placebo | ONGOING |

BC: breast cancer, BID: twice daily, CBR: clinical benefit rate, CBR24: CBR at 24 weeks, CI: confidence interval, DoR: duration of response, est: estimated, IQR: interquartile range, LOH: loss-of-heterozygosity, gBRCA1/2m: germline BRCA1/2 mutation, OC: ovarian cancer, ORR: objective response rate, PARP: poly(ADP-ribose) polymerase, PCT: physician’s choice chemotherapy, PFS: progression-free survival, TNBC: triple-negative breast cancer, TPC: treatment of physician’s choice. 

Table 2. Selected phase II/III studies with PARP inhibitors in gBRCA1/2m locally advanced and metastatic breast cancer.
BRCA1/2 testing
NM Tung and JE Garber

Potential mechanisms of action and resistance. The left panel illustrates two possible mechanisms of action of PARPi. Upper pathway: Inhibition of PARP enzyme activity or catalytic inhibition interferes with the repair of single-strand breaks, leading to stalled DNA replication forks that requires HR repair. In HR-deficient tumours, such as those with BRCA1/2m, PARPi inhibition results in synthetic lethality. Lower pathway: PARP trapping refers to trapping of PARP proteins on DNA, which also leads to replication fork damage, but because this pathway utilizes additional repair mechanisms, it is not restricted to tumours with HR deficiency. The right panel illustrates three possible mechanisms of resistance to PARPi. These include: (1) secondary mutations in BRCA genes that restore BRCA function and HR; (2) somatic mutation of TP53BP1, causing partial restoration of HR; and (3) increased PARPi efflux mediated by MDR1/P-glycoprotein 1, preventing the drugs from acting at the appropriate sites. The first two mechanisms of resistance restore HR and apply to PARP catalytic inhibition in HR-deficient tumours; whereas, the third mechanism applies to both mechanisms of action of PARPi. BRCA1m BRCA mutation; HR homologous recombination; MDR1 multidrug resistance protein 1; p53BP1 tumour suppressor p53-binding protein 1; PARPi poly(ADP-ribose) polymerase; PARPi PARPi inhibitor

BRCA mutations in early-stage BC management
Although, BRCA status has not strongly influenced outcomes for stage I–III BC, the ability to identify BRCA-related cancers and the development of targeted therapies may lead to improved responses. Several studies have evaluated platinum salts in early-stage BRCA-related BC, mainly in patients with TNBC, and there are ongoing studies evaluating PARPi in this setting.

Clinical outcomes to platinum salts in early-stage BC
Byrski et al. reported pathologic complete response (pCR) to neoadjuvant cisplatin in 65 of 107 women (61%) who had stage I–III TNBC and BRCA1m (Table 1). Although their study helped demonstrate the activity of cisplatin in BRCA1-related early BC, the patient population had extremely favourable characteristics, with 65% of women having node-negative disease and 46% having tumours ≤2 cm. Furthermore, it was a single-arm study and did not compare neoadjuvant cisplatin to standard anthracycline-based chemotherapy; that question is being addressed by the ongoing randomised neoadjuvant INFORM/TBCRC 031 study (NCT01670500).

The GeparSixto/GBG 66 study (Table 1) evaluated the addition of carboplatin to standard paclitaxel, doxorubicin, and bevavizumab as neoadjuvant chemotherapy in previously untreated patients with stage II–III TNBC (as well as HER2-positive BC). Patients with TNBC who received additional carboplatin had significantly higher pCR rates and longer disease-free survival; however, a preplanned sub-analysis by BRCA1/2m status noted the unexpected finding that the benefits of adding carboplatin were only significant in patients with wild-type BRCA1/2 (pCR 55.0% with carboplatin versus 36.4% without carboplatin; P = 0.004). No significant pCR benefit was observed in the 50 patients with BRCA1/2m (65.4% with carboplatin versus 66.7% without carboplatin; P = 0.92). Analysis of disease-free survival was similar, with carboplatin only improving disease-free survival in patients with wild-type BRCA1/2. One potential explanation for these results is that anthracycline-based chemotherapy was already effective in patients with BRCA1-related BC, owing to the inability of the tumour cells to repair anthracycline-induced DNA damage. Alternatively, the number of mutation carriers in the study may have been too small to permit detection of a treatment response.
difference. The CALGB 40603 study also reported improved pCR with the addition of carboplatin to neoadjuvant therapy in stage II–III TNBC, although an analysis of response according to BRCA1/2m status has not been reported.18,49 Thus, the role of BRCA testing to guide chemotherapy selection in this setting remains unclear.

Clinical outcomes to PARP inhibitors in early-stage BC
A feasibility study of neoadjuvant talazoparib administered prior to neoadjuvant chemotherapy in patients with gBRCA1/2m and HER2-negative BC reported decreases in tumour volume (median 88%; range 30–98%) in all 13 patients after 2 months of therapy.90 These promising results led to the ongoing phase II study of single-agent talazoparib, with results expected in 2018 (NCT02282345).91 In addition, several PARPi are currently in phase II/III studies for adjuvant or neoadjuvant therapy in women with TNBC or HER2-negative BC and gBRCA1/2m, as described in Table 3.91–93

Local management and the role of prophylactic surgery
The risk of local recurrence after excision and radiotherapy is similar in patients with BRCA1/2m BC and those with sporadic BC.2,4–6,94–96 Due to the ability of ionising radiation to induce DS breaks in DNA, and the involvement of BRCA1 and BRCA2 in repair of DS DNA, it has been suggested that BRCA1/2m-related tumours may be susceptible to the therapeutic and toxic effects of radiotherapy. However, no increased local reaction to radiation therapy has been observed in BRCA1 and BRCA2 mutation carriers with BC. Current guidelines indicate that patients with BRCA1/2m-related BC are not eligible for accelerated partial breast irradiation,19 but that is based on lack of data rather than evidence for increased toxicity or decreased efficacy with accelerated partial breast irradiation; patients with BRCA1/2m-related BC were excluded from accelerated partial breast irradiation studies because they carry a high risk for second primary BC.

In healthy women with BRCA1/2m, preventive salpingo-oophorectomy is recommended to reduce the risk of OC during the fifth decade of life.19,97,98 The effects of salpingo-oophorectomy on preventing BC in healthy premenopausal women with BRCA1m remains controversial,95,100 although the benefits in BRCA1/2m carriers are established. In premenopausal women with a recent diagnosis or history of BC and BRCA1/2m, several large studies have demonstrated that oophorectomy confers strong reductions in risk of subsequent BC, as well as mortality.100–106 Metcalfe et al.105 studied the benefits of oophorectomy soon after a diagnosis of BC in BRCA1/2m carriers (mean age at diagnosis ~42 years). In women with a new primary diagnosis of BC who had bilateral oophorectomy, the adjusted HR for BC-related death was 0.38 (95% CI: 0.19–0.77) for BRCA1m carriers and 0.57 (95% CI: 0.23–1.43) for BRCA2m carriers. Interestingly, the reduction in risk associated with oophorectomy was greater in women with ER-negative BC (HR 0.07; 95% CI: 0.01–0.51) than in women with ER-positive BC (HR 0.76; 95% CI: 0.32–1.78).105 On the basis of these findings, the authors recommend that premenopausal women with newly diagnosed BC be tested for BRCA1/2m and, if mutation-positive, offered salpingo-oophorectomy as part of their treatment plan; however, this approach is controversial and not widely adopted.

HORMONE RECEPTOR STATUS, BRCA MUTATION STATUS, AND RESPONSE TO PARP INHIBITORS
A multinational epidemiologic study characterised the receptor status of breast tumours from women with gBRCA1m (n = 3797) or gBRCA2m (n = 2392)107. Among BRCA1m carriers, 22% of tumours were ER-positive and 21% were PgR-positive, and among BRCA2m

---

**Table 3. Selected ongoing phase II/III studies with PARP inhibitors in gBRCA1/2m early-stage breast cancer**

| Study | Disease | Phase | Status | Treatment |
|-------|---------|-------|--------|-----------|
| NCT0282345 | gBRCA1/2m with either TNBC or ER+ and/or PgR+ and HER2-negative BC | II | ONGOING | Neoadjuvant talazoparib 1 mg (monotherapy) up to 6 months |
| NCT01074970 | TNBC or gBRCA1/2m HER2-negative BC with residual disease | II | ONGOING | Cisplatin IV every 21 days for 4 cycles vs cisplatin (same dose) plus rucaparib on days 1, 2, 3 every 21 days |
| NCT02032823 | gBRCA1/2m with either TNBC or ER+ and/or PgR+ and HER2-negative BC | III | ONGOING | Olaparib tablets vs placebo after surgery and at least 6 cycles of neoadjuvant or adjuvant chemotherapy |
| NCT02282345 | gBRCA1/2m stage I BC ≥ 1 cm, HER2-negative | II | ONGOING | Neoadjuvant talazoparib 1 mg (monotherapy) up to 6 months |
| BRE09-146 | TNBC or gBRCA1/2m early-stage breast cancer, ER+ oestrogen receptor-positive, PgR+ progesterone receptor-positive, NBRCA1/2m | II | ONGOING | Single-agent talazoparib, with results expected in 2018 |
carriers, 77% were ER-positive and 64% were PgR-positive. There is evidence, however, that ER-positive tumours arising in BRCA1/2 carriers have different morphologic features than ER-positive tumours arising in non-carriers, with those in carriers more frequently exhibiting a higher histologic grade, higher oncotype recurrence score, and more often classified as luminal B by gene expression profiling.\textsuperscript{16,107-109} Furthermore, the percentage of ER-positive BC increases with increasing patient age in BRCA1 carriers, but decreases with increasing age in BRCA2 carriers.\textsuperscript{16,107}

Although a substantial percentage of patients with BRCA1/2 BC are also hormone receptor-positive, the influence of hormone receptor-positive disease on DNA-targeted therapy efficacy is still being evaluated. One clue may come from observations concerning loss-of-heterozygosity of the wild-type allele in BRCA1 carriers, which is observed at a similar rate in ER-positive and ER-negative tumours, thereby suggesting a similar degree of impairment to the homologous recombination pathway.\textsuperscript{15,16} Clinical data to address this question are limited, but three olaparib studies reported outcomes in patients with ER-positive BC. In the ICEBERG 1 study (NCT00494234), 12 patients in the 400 mg olaparib arm had ER-positive disease and treatment responses were observed.\textsuperscript{57}

In another study (Study 42), responses to olaparib as late-line therapy were observed in 4 of 32 patients (12.5%) with ER-positive disease and 4 of 30 (13.3%) with ER-negative disease.\textsuperscript{58} The phase III OlympiAD study enrolled patients with either hormone receptor-positive or TNBC. Recently, exploratory sub-group analyses for PFS demonstrated that the hazard ratio favouring olaparib versus chemotherapy for BRCA carriers of either subtype.\textsuperscript{61} In addition, the ABRAZO study showed similar response rates to talazoparib for BRCA1/2 carriers with metastatic ER-positive and TNBC: 29% and 26%, respectively.\textsuperscript{65} Although larger studies are needed, these results indicate that ER-positive BC in BRCA1/2 carriers are responsive to PARPi.

BEYOND BRCA MUTATIONS: BRCA1NESS AND SCORING SYSTEMS

Another evolving aspect of testing to predict responsiveness to agents that interfere with DNA repair is the use of assays or scoring schemes that indicate the activity level of the homologous recombination pathway.\textsuperscript{106} Tumours that exhibit clinical and biological features of gBRCA1/2m disease, despite not having a gBRCA1/2m, are thought of as having BRCA1ness.\textsuperscript{111} BRCA1/2 proteins are essential components of the homologous recombination pathway for repair of DS breaks in DNA; loss-of-homologous recombination in the absence of a gBRCA1/2m represents one form of BRCA1ness. For example, BRCA1ness may arise as a result of somatic loss or epigenetic silencing of tumour BRCA in the absence of gBRCA1/2m.\textsuperscript{43} In addition, numerous other proteins participate in the homologous recombination pathway, and mutations in their corresponding genes may also confer BRCA1ness and subsequently, response to platinum agents or PARPi.

Current data support the hypothesis that tumours deficient in homologous recombination are susceptible to PARP inhibition.\textsuperscript{29} For example, olaparib demonstrated activity in a phase II study in patients with metastatic, castration-resistant prostate cancer and germline or somatic mutations in DNA repair genes.\textsuperscript{27} Among 49 evaluable patients, 16 (33%) had a response and 12 remained on therapy for >6 months. Post hoc analysis in prospectively collected biopsy samples demonstrated a response to single-agent olaparib in 14 of 16 patients who were biomarker-positive, defined as having a homozygous deletion or biallelic deleterious mutation of a DNA repair gene (e.g., BRCA2, ATM, CHEK2). Among biomarker-negative patients, only 2 of 33 (6%) had a response to olaparib.\textsuperscript{27}

Rather than sorting the tangle of how each genetic variation might influence responsiveness to treatment, research has focused on the development of scoring systems intended to quantify the competency of the homologous recombination pathway. Currently there are three prominent scoring systems: homologous recombination defect large-scale transition (HRD-LST), HRD-loss-of-heterozygosity (HRD-LOH), and HRD-telomeric allelic imbalance (HRD-TAI).\textsuperscript{112-114} In the TBCRC 009 study, the sum of the HRD-LOH and HRD-LST scores was associated with response to platinum therapy in patients with metastatic TNBC (HRD-LOH/HRD-LST score of 12.68 for responders versus 5.11 for non-responders; \( P = 0.032 \)).\textsuperscript{48} This scoring approach is also being explored in the neoadjuvant setting. The HRD-TAI score\textsuperscript{114} and an unweighted combination of all three HRD scores\textsuperscript{15} predicted responsiveness to neoadjuvant platinum therapies in women with TNBC. By contrast, the HRD score failed to identify which TNBC patients with metastatic disease had a better response to platinum versus docetaxel during the TNT study (discussed earlier),\textsuperscript{45} although analysis was performed on primary rather than metastatic BC samples.

Using a high-depth whole-genome sequencing approach rather than a targeted sequencing approach, another tool called HRDetect was developed as a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures. A lasso logistic regression model identified six distinguishing mutational signatures and HRDetect identified BRCA1/2-deficient tumours with 98.7% sensitivity. In addition, in a cohort of 560 individuals with BC, HRDetect identified 22 tumours with somatic loss-of-BRCA1 or BRCA2 and 47 tumours with functional BRCA1/2 deficiency, none of which had mutations detected with standard analysis. Thus, integrating a method such as HRDetect or other deep sequencing approaches into the clinical assessment process could potentially identify a larger proportion of patients who may have selective therapeutic sensitivity to PARPi.\textsuperscript{116} Recently, an elevated HRDetect score was associated with response to platinum chemotherapy in an observational study of patients with advanced BC;\textsuperscript{117} however, HRDetect has not yet been correlated with therapeutic responses to PARPi. Another recent study evaluated a novel gene expression signature-generating algorithm to predict therapeutic response to PARPi.\textsuperscript{110} The authors demonstrated that the gene expression signatures may be used to identify PARPi-sensitive cancer cell lines, primary patient-derived tumour cells, and patient-derived xenografts. In addition, these gene expression profiles were found to outperform currently accepted clinical biomarkers of response, including BRCA1/2m status.

At this time, scoring systems are still investigational and require further validation before they can be considered for routine clinical use. These scoring systems, or similar methods, may hold the promise of a relatively simple way to incorporate the status of BRCA mutations, BRCA silencing, and non-BRCA mutations into a single score that indicates the competency of homologous recombination and predicts response to platinum-based therapies. Further studies are also needed to determine whether any of these systems predict response to PARPi.

CONCLUSION

BRCA1/2 mutations occur in women with all BC subtypes, but more commonly in those with early onset or a suggestive family history. Recent studies have found evidence that BRCA1/2m carriers with BC have high rates of response to platinum salts in the metastatic and neoadjuvant settings; currently, most of the data were derived from BRCA1/2m carriers with TNBC. For BRCA1/2m carriers with metastatic TNBC, platinum chemotherapy has been shown to be superior to docetaxel in the first-line setting. For BRCA1/2m carriers in the early setting, it is not yet clear whether platinum agents are superior to, or provide additional benefit to conventional anthracycline-based or taxane-based chemotherapy. However, for BRCA1/2m carriers with newly diagnosed TNBC for whom an anthracycline is contraindicated, a platinum-based
regimen is reasonable. For BRCA1/2m carriers with hormone receptor-positive BC, standard chemotherapy should likely be used until more data regarding the efficacy of platinum chemotherapy are available.

Evidence also supports BRCA1/2m status as a predictor of responsiveness to PARPi in patients with metastatic BC. For BRCA1/2m carriers with metastatic disease and fewer than two chemotherapy regimens in the metastatic setting, use of the PARPi olaparib results in a significantly longer PFS and better quality of life than standard chemotherapy. Now that the first PARPi has been approved in BC, olaparib can be recommended for BRCA1/2m carriers with HER2-negative metastatic BC. Ongoing studies will address whether PARPi may also provide benefit for BRCA1/2m carriers in the early setting, and future studies should seek to determine the relative efficacy of platinum agents compared with PARPi in the metastatic setting, as well as the efficacy of platinum chemotherapy after progression with PARPi.

Studies assessing the benefit of combining PARPi with chemotherapy will need to be compared to treatment with PARPi monotherapy; given the myelosuppression observed when combining PARPi with chemotherapy. These will need to compare continuous treatment with PARPi monotherapy to combinations of chemotherapy with either a reduced dose or intermittent PARPi schedule. Current research is focused on identifying larger subsets of patients with similar responsiveness to these therapies, such as those with de novo somatic BRCA mutations, mutations in other genes associated with the homologous recombination pathway for DNA repair, or those exhibiting BRCA-associated mutational signatures or other evidence of homologous recombination deficiency.

BRCA testing was previously used in BC patients solely to predict the risk of future cancers and guide surgical therapies. As mutation status increasingly informs optimal management of BC, including choice of systemic therapy, efforts to identify all BC patients with germline or somatic BRCA mutations will become even more essential. Given the availability of comprehensive and affordable gBRCA1/2m testing and the utility of the information for treatment options, it may be reasonable to consider genetic testing more widely than past criteria have allowed. The recent test-to-treat criteria (Box 1) acknowledges the importance of not overlooking patients with metastatic BC who may have gBRCA1/2m, and may benefit from PARPi treatment. The recent oncologist-led mainstream approaches to genetic testing may allow greater access to testing and more complete data for these analyses in the near future.18

ACKNOWLEDGEMENTS

The authors extend thanks to Java Solis, PhD, Ken Scholz, PhD, Greg Tardie, PhD, and Joan Hudson of the Lockwood Group (Stamford, Connecticut, USA) for providing medical writing and editorial support, which was in accordance with Good Publication Practice (GPP3) guidelines. Medical writing and editorial support for this manuscript was funded by the AstraZeneca LP, Wilmington, DE, and Merck & Co., Inc., Kenilworth, NJ. This manuscript was funded by AstraZeneca LP and Merck & Co., Inc. The sponsor participated in manuscript review and the decision to submit the paper for publication.

AUTHOR CONTRIBUTIONS

AstraZeneca conforms to the guidelines set forth by GPP3, the International Committee of Medical Journal Editors for Authorship (ICMJE), and the International Society of Medical Publication Professionals (ISMPP). The authors meet all criteria for authorship as set forth by these guidelines.

ADDITIONAL INFORMATION

Competing interests: N.M.T. reports research funding from Ambry Genetics (no salary support). J.E.G. reports consulting for Biogen, Helix, Novartis (spouse), GTx (spouse), and research support from Ambry Genetics, Novartis (spouse).

REFERENCES

1. Bordeleau, L., Panchal, S. & Goodwin, P. Prognosis of BRCA-associated breast cancer: a summary of evidence. Breast Cancer Res. Treat. 119, 13–24 (2010).
2. Brekelmans, C. T., Tilanus-Linthorst, M., Stuijts, C. V., van Oudwaaal, A., Menke-Pluymers, M. B. & Bartels, C. C. et al. Tumour characteristics, survival and prognostic factors of hereditary breast cancer from BRCA2, BRCA1- and non-BRCA1/2 families as compared to sporadic breast cancer cases. Eur. J. Cancer 43, 867–876 (2007).
3. Chen, S. & Parmigiani, G. Analysis of BRCA1 and BRCA2 penetrance. J. Clin. Oncol. 25, 1329–1333 (2007).
4. Goodwin, P. J., Phillips, K. A., West, D. W., Ennis, M., Hopper, J. L. & John, E. M. et al. Breast cancer prognosis in BRCA1 and BRCA2 mutation carriers: an international prospective breast cancer family registry population-based cohort study. J. Clin. Oncol. 29, 21–29 (2011).
5. Kuchenbaecker, K. B., Hopper, J. L., Barnes, D. R., Phillips, K. A., Mooij, T. M. & Roos-Blom, M. J. et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 317, 2402–2416 (2017).
6. Pierce, L. J., Levine, A. M., Rebbeck, T. R., Ben-David, M. A., Friedman, E. & Solin, L. J. et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J. Clin. Oncol. 24, 2437–2443 (2006).
7. Rebbeck, T. R., Mitra, N., Wan, F., Sinilnikova, O. M., Healey, S. & McGuffog, L. et al. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. JAMA 313, 1347–1361 (2015).
8. Rennert, G., Biallard-Naggan, S., Barnett-Greiner, O., Bar-Joseph, N., Zhang, S. & Rennert, H. S. et al. Clinical outcomes of breast cancer in carriers of BRCA1 and BRCA2 mutations. N. Engl. J. Med 357, 115–123 (2007).
9. Howlader, N., Altekruse, S. F., Li, C. L., Chen, V. W., Clarke, C. A. & Ries, L. A. et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J. Natl Cancer Inst. 106, 1–8, https://doi.org/10.1093/jnci/dju1055 (2014).
10. Lehmann, B. D., Bauer, J. A., Chen, X., Sanders, M. E., Chakravarty, A. B. & Shyr, Y. et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J. Clin. Invest 121, 2750–2767 (2011).
11. Mayer, I. A., Abramson, V. G., Lehmann, B. D. & Pietenpol, J. A. New strategies for triple-negative breast cancer—deciphering the heterogeneity. Clin. Cancer Res. 20, 792–790 (2014).
12. Miquel-Cases, A., Steuten, L. M., Retel, V. P. & van Harten, W. H. Early stage cost-effectiveness analysis of a BRCA1-like test to detect triple negative breast cancers responsive to high dose alkylating chemotherapy. Breast 24, 397–405 (2015).
13. Telli, M. Evolving treatment strategies for triple-negative breast cancer. J. Natl Compr. Cancer Netw. 13(5 Suppl), 652–654 (2015).
14. Emborgo, T., Mose, K. I., Bednar, E., Oakley, H. D., Litton, J. K., Lu, K. H., et al. Universal BRCA testing and family outreach for women with triple negative breast cancer. Cancer Res. 76, Suppl 4 (2016) AbstraP2-09-08.
15. Lips, E. H., Debipersad, R., Scheereman, C. E., Mulder, L., Sonke, G. S. & van der Kolk, L. E. et al. BRCA1-mutated estrogen receptor positive breast cancer shows BRCAAness, suggesting sensitivity to drugs targeting homologous recombination deficiency. Clin. Cancer Res. 23, 1236–1241 (2017).
16. Tung, N., Wang, Y., Collins, L. C., Kaplan, J., Li, H. & Gelman, R. et al. Estrogen receptor positive breast cancers in BRCA1 mutation carriers: clinical risk factors and pathologic features. Breast Cancer Res. 12, R12 (2010).
17. Balmana, J., Diez, O., Rubio, I. T. & Cardoso, F., ESMO Guidelines Working Group. BRCA in breast cancer: ESMO Clinical Practice Guidelines. Ann. Oncol. 28(Suppl 6), v31–v34 (2017).
18. Moyer, V. A., U. S. Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann. Intern Med. 160, 271–281 (2014).
19. National Comprehensive Cancer Network. NCCN: Clinical Practice Guidelines in Oncology: Breast Cancer, version 1.2018. Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.aspx.
20. Couch, F. J., Nathanson, K. L. & Offit, K. Two decades after BRCA: setting paradigms in personalized cancer care and prevention. Science 343, 1466–1470 (2014).
21. Weigelt, B., Comino-Mendez, I., de Bruijn, I., Tian, L., Meisel, J. L. & Garcia-Muirillas, I. et al. Diverse BRCA1 and BRCA2 reversion mutations in circulating cell-free DNA of therapy-resistant breast or ovarian cancer. Clin. Cancer Res. 23, 6708–6720 (2017).
22. Christie, E. L., Fereday, S., Doig, K., Pattnaik, S., Dawson, S. J. & Bovtewll, D. D. L. Reversion of BRCA1/2 germline mutations detected in circulating tumor DNA from patients with high-grade serous ovarian cancer. J. Clin. Oncol. 35, 1274–1280 (2017).
103. Finch, A. P., Lubinski, J., Moller, P., Singer, C. F., Karlan, B. & Senter, L. et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. *J. Clin. Oncol.* **32**, 1547–1553 (2014).

104. Huzarski, T., Byrski, T., Gronwald, J., Gorski, B., Domagala, P. & Cybulski, C. et al. Ten-year survival in patients with BRCA1-negative and BRCA1-positive breast cancer. *J. Clin. Oncol.* **31**, 3191–3196 (2013).

105. Metcalfe, K., Lynch, H. T., Foulkes, W. D., Tung, N., Kim-Sing, C. & Olopade, O. I. et al. Effect of oophorectomy on survival after breast cancer in BRCA1 and BRCA2 mutation carriers. *JAMA Oncol.* **1**, 306–313 (2015).

106. Mavaddat, N., Peock, S., Frost, D., Ellis, S., Platte, R. & Fineberg, E. et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J. Natl. Cancer Inst.* **105**, 812–822 (2013).

107. Mavaddat, N., Barrowdale, D., Andrulis, I. L., Domchek, S. M., Eccles, D. & Nevanlinna, H. et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol. Biomark. Prev.* **21**, 134–147 (2012).

108. Larsen, M. J., Kruse, T. A., Tan, Q., Laenholm, A. V., Bak, M. & Lykkesfeldt, A. et al. Classifications within molecular subtypes enables identification of BRCA1/BRCA2 mutation carriers by RNA tumor profiling. *PLoS ONE* **8**, e64268 (2013).

109. Shah, P. D., Patil, S., Dickler, M. N., Offit, K., Hudis, C. A. & Robson, M. E. Twenty-one-gene recurrence score assay in BRCA-associated versus sporadic breast cancers: Differences based on germline mutation status. *Cancer* **122**, 1178–1184 (2016).

110. McGraal, D. J., Lin, C. C.-J., Garnett, J., Liu, Q., Mo, W. & Dai, H. et al. Improved prediction of PARP inhibitor response and identification of synergizing agents through use of a novel gene expression signature generation algorithm. *NPJ. Syst. Biol. Appl.* **3**, 1–12 (2017).

111. Lim, D. & Ngeow, J. Evaluation of the methods to identify patients who may benefit from PARP inhibitor use. *Endocr. Relat. Cancer* **23**, R267–R285 (2016).

112. Popova, T., Manie, E., Rieunier, G., Caux-Moncoutier, V., Tirapu, C. & Dubois, T. et al. Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation. *Cancer Res.* **72**, 5454–5462 (2012).

113. Abkevich, V., Timms, K. M., Hennessy, B. T., Potter, J., Carey, M. S. & Meyer, L. A. et al. Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. *Br. J. Cancer* **107**, 1776–1782 (2012).

114. Birkbak, N. J., Wang, Z. C., Kim, J. Y., Eklund, A. C., Li, Q. & Tian, R. et al. Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents. *Cancer Discov.* **2**, 366–375 (2012).

115. Telli, M. L., Timms, K. M., Reid, J., Hennessy, B., Mills, G. B. & Jensen, K. C. et al. Homologous recombination deficiency (HRD) score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer. *Clin. Cancer Res.* **22**, 3764–3773 (2016).

116. Davies, H., Glodzik, D., Morganella, S., Yates, L. R., Staaf, J. & Zou, X. et al. HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures. *Nat. Med.* **23**, 517–525 (2017).

117. Zhao, E. Y., Shen, Y., Pleasance, E., Kasaian, K., Leelakumari, S. & Jones, M. et al. Homologous recombination deficiency and platinum-based therapy outcomes in advanced breast cancer. *Clin. Cancer Res.* **23**, 7521–7530 (2017).

118. George, A., Riddell, D., Seal, S., Talukdar, S., Mahamdallie, S. & Ruark, E. et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. *Sci. Rep.* **6**, 1–8, (2016).