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Review

Two decades beyond BRCA1/2: Homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy ☆

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HIGHLIGHTS

- Many homologous recombination genes contribute to hereditary cancer risk.
- Genetic testing for BRCA1/2 is offered within larger gene panels.
- PARP inhibitors are now approved for BRCA-associated ovarian cancer.

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ABSTRACT

Almost exactly 20 years after their discovery, the *BRCA1* and *BRCA2* genes have become the target of the first "personalized" therapy available for patients with ovarian cancer. In December 2014, a poly(ADP-ribose) polymerase (PARP) inhibitor was granted expedited approved by the United States Food and Drug Administration for use in advanced ovarian cancer patients with germline *BRCA1/2* mutations who have received three or more prior lines of chemotherapy. This review article will discuss (1) the *BRCA1* and *BRCA2* genes within the larger context of homologous recombination deficiency; (2) the advances in our understanding of hereditary cancer risk and the dramatic shifts that have occurred in the genetic testing landscape since the landmark 2013 Supreme Court ruling invalidating patents on *BRCA1* and *BRCA2* genetic testing; and (3) the clinical trials leading to the approval of olaparib, the first in human PARP inhibitor.

Contents

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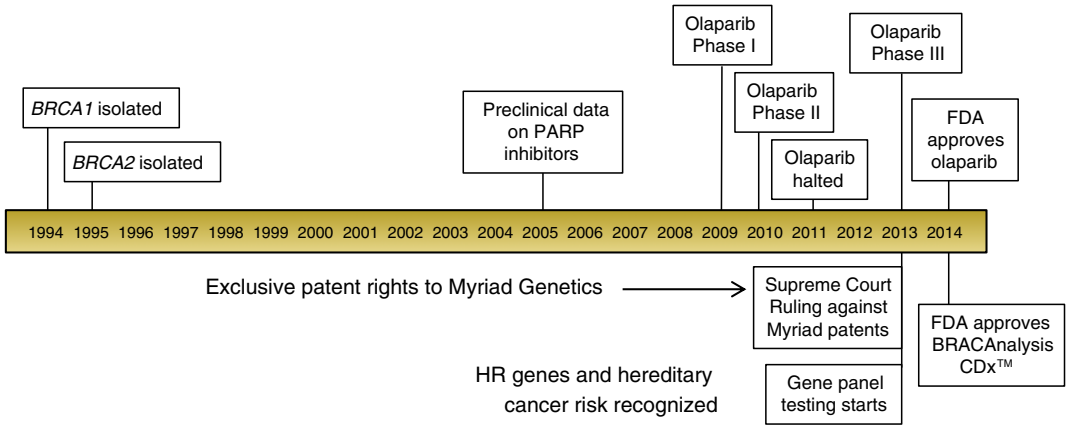


Fig. 1. A timeline of the last two decades: BRCA1/2, homologous recombination, hereditary cancer risk and approval of a targeted therapy for BRCA1/2-associated ovarian cancer.

Introduction—a timeline of the past 20 years

In the two decades since the discovery of the *BRCA1* and *BRCA2* genes in 1994 and 1995 [1,2], the DNA repair pathway within which they work, homologous recombination has become a target for cancer therapy (Fig. 1). In 2005, a decade after the discovery of the BRCA genes, preclinical studies demonstrated that PARP inhibitors selectively target BRCA-deficient cells. Clinical trials of olaparib, the first in human PARP inhibitor, were launched and results for phase 1 and phase 2 studies were reported in 2009 and 2010. Despite promising data, AstraZeneca halted development of olaparib in 2011 but then reversed their decision in 2013 with the launch of phase 3 trials. In December 2014, roughly 20 years after the discovery of *BRCA1*, olaparib was granted accelerated approval by the United States Food and Drug Administration (FDA) as a therapy for ovarian cancer patients with germline *BRCA1/2* mutations who have received three or more prior lines of chemotherapy.

In the past year, the genetic testing landscape for *BRCA1* and *BRCA2* mutations shifted dramatically. In a 2013 landmark ruling, the Supreme Court of the United States invalidated the patents that gave Myriad Genetics the exclusive rights to *BRCA1* and *BRCA2* genetic testing. Many companies now offer *BRCA1* and *BRCA2* genetic testing within larger gene panels that include other genes in the homologous recombination pathway as well as other hereditary cancer genes. Alongside the olaparib approval in December 2014, the FDA also approved the BRACAnalysis CDx™ test by Myriad Genetics as the companion diagnostic test to identify candidates for olaparib treatment.

Homologous recombination and hereditary cancer risk

BRCA1 and BRCA2 are critical proteins in the process of homologous recombination repair of double-strand DNA breaks. Germline *BRCA1* and *BRCA2* mutations account for about 5 – 10% of breast cancers and 10 – 18% of ovarian cancers [3]. Many of the other proteins involved in homologous recombination repair are now recognized to also contribute to hereditary cancer risk including ATM, CHEK2, BARD1, BRIP1, Mre11, RAD50, NBS1, RAD51C, RAD51D and PALB2. Table 1 summarizes the studies implicating homologous recombination genes in breast and ovarian cancer susceptibility. Many of these genes were first connected to breast cancer susceptibility [4–11], and more recently, *BRIP1*, *RAD51C* and *RAD51D* were linked to hereditary ovarian cancer risk [9,12,13]. A study utilizing next-generation sequencing on the normal DNA of unselected ovarian cancer patients found deleterious germline mutations in *BARD1*, *BRIP1*, *CHEK*, *MRE11A*, *MSH6*, *NBN*, *PALB2*, *RAD50*, *RAD51C* and *TP53* and estimated these mutations to account for approximately 6% of hereditary ovarian cancer risk [14]. Of note, 30% of patients with a homologous recombination gene mutation in this study had no family history of breast or ovarian cancer. An important caveat to this data is the lack of comparable germline mutation rates in the general unaffected population.

Table 1
Homologous recombination genes linked to hereditary breast and ovarian cancer susceptibility.

Gene	Hereditary breast cancer risk	Hereditary ovarian cancer risk
CHEK2	Am J Hum Genet 2004	Walsh, PNAS 2011
BRIP1	Seal, Nat Genet 2006	Rafnar, Nat Genet 2011
ATM	Renwick, Nat Genet 2006	Walsh, PNAS 2011
NBN	Steffen, Int J Ca 2006	Walsh, PNAS 2011
PALB2	Rahman, Nat Genet 2007	Walsh, PNAS 2011
RAD51C	Meindl, Nat Genet 2007	Meindl, Nat Genet 2010
BARD1	De Brakeleer, Hum Mutat 2010	Walsh, PNAS 2011
MRE11A	Damiola, Breast Ca Res 2014	Walsh, PNAS 2011
RAD50	Damiola, Breast Ca Res 2014	Walsh, PNAS 2011
RAD51D	n/a	Loveday, Nat Genet 2011

These genes implicated in hereditary breast and ovarian cancer susceptibility have important roles in the homologous recombination DNA repair process (Fig. 2). The steps in homologous recombination repair have been reviewed in other articles [15–17] and are schematically described here. In the initial stages of homologous recombination, a double-strand DNA break is recognized by ATM and ATR, kinases which phosphorylate downstream targets including CHEK2, P53, BRCA1 and H2AX. BRCA1, assisted by BARD1 and BRIP1, acts as a scaffold that organizes the remaining proteins to the site of repair. The MRN complex, which consists of MRE11, RAD50 and NBS1, then resects the DNA to form 3′ overhangs that are bound by RPA. BRCA2 is recruited with the assistance of PALB2 and loads RAD51 onto RPA-coated DNA with the assistance of RAD51B, RAD51C and RAD51D. The RAD51 nucleoprotein filament then invades the homologous DNA strand in a process called strand invasion, allowing the remaining DNA repair to occur with the use of the sister chromatid as a template for error-free repair [15–17]. In Fig. 2, BRCA1 and BRCA2 are indicated in red and the other homologous recombination genes/proteins implicated in genetic breast and ovarian cancer susceptibility are indicated in orange.

The BRCA phenotype in serous ovarian cancers

The Cancer Genome Atlas (TCGA) suggests that up to half of high-grade serous ovarian cancers could be deficient in homologous recombination [18]. Deficiency of either BRCA1 or BRCA2 occurs through germline mutation (9% *BRCA1*, 8% *BRCA2*), somatic mutation (3% *BRCA1* or *BRCA2*) or through epigenetic silencing of *BRCA1* (11%). Other genetic changes impacting homologous recombination repair include amplification of *EMSY* (8%), deletion/mutation of *PTEN* (7%), hypermethylation of *RAD51C* (3%), mutation of *ATM* or *ATR* (2%) or mutation of other homologous recombination genes (5%). These tumors

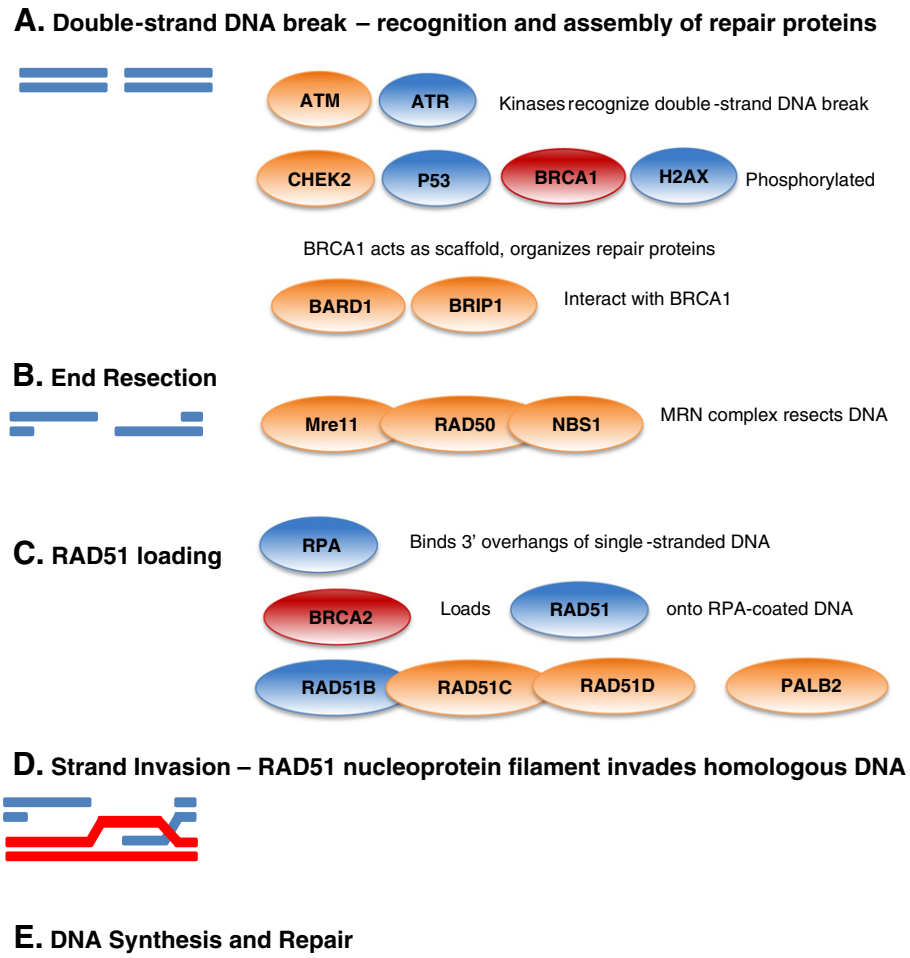


Fig. 2. Proteins implicated in hereditary breast and ovarian cancer risk and their role in homologous recombination repair. The protein products of genes implicated in hereditary breast and ovarian cancer susceptibility are indicated in red (BRCA1 and BRCA2) and orange (other homologous recombination genes more recently linked to cancer risk). A. Double-strand DNA break—recognition and assembly of repair proteins. Homologous recombination repair of double-strand DNA breaks is initiated by recognition by ATM and ATR which phosphorylate downstream targets including CHEK2, P53, BRCA1, and H2AX. BRCA1, assisted by BARD1 and BRIP1, acts as a scaffold to organize the assembly of other repair proteins. B. End resection. The MRN complex, consisting of MRE11, RAD50 and NBS1, resects DNA. C. RAD51 loading. RPA binds the 3′ overhangs of single-stranded DNA. BRCA2 is recruited with the help of PALB2 and loads RAD51 onto the RPA-coated DNA with the assistance of RAD51B, RAD51C, and RAD51D. D. Strand invasion. The RAD51 nucleoprotein filament invades the homologous DNA stand through strand invasion. E. DNA synthesis and repair. The homologous DNA strand provides a template for high-fidelity and error-free DNA synthesis and repair.

are suggested to have the phenotype of "BRCAness" and are predicted to behave like BRCA-deficient tumors despite normal germline *BRCA1* and *BRCA2* genes [19].

The rapidly evolving genetic testing landscape

BRCA1 was identified in 1994 and *BRCA2* was identified in 1995 [1,2]. Since patents were granted in 1997 and 1998, Myriad Genetics has held the exclusive license rights for *BRCA1* and *BRCA2* genetic testing in the United States. These rights were enforced against other clinical diagnostic labs, leading to a monopoly and high testing costs for many years.

In 2009, the *Association for Molecular Pathology v. Myriad Genetics* lawsuit was filed by the American Civil Liberties Union and the Public Patent Foundation on behalf of universities, medical organizations, patient advocacy groups and patients who alleged that genes are a product of nature, making Myriad's patent claims are invalid. On March 29, 2010, the Southern District Court of New York agreed, ruling that all challenged claims were ineligible for patent. Myriad Genetics appealed to the Federal Circuit Appeals Court who overturned the lower court decision on July 29, 2011. This led to an appeal to the United States Supreme Court who unanimously ruled against Myriad Genetics in a landmark ruling delivered on June 13, 2013.

Almost immediately after the Supreme Court decision in June 2013, other clinical diagnostic laboratories started to offer *BRCA1* and *BRCA2* testing, both in isolation as well as part of more comprehensive genetic susceptibility panels. Myriad filed lawsuits against competing companies, including Ambry, Gene by Gene and Pathway Genomics, citing infringement on the remaining patents that were not impacted by the Supreme Court decision. In March 2014, a federal judge denied Myriad's request of injunction, a pre-trial order for competitors to cease *BRCA1/2* testing for the duration of the case. In December 2014, the Court of Appeals for the Federal Circuit ruled that Myriad's patents are invalid. Also in December 2014, the Myriad BRACAnalysis CDx™ test was approved by the United States Food and Drug Administration as the companion diagnostic test to olaparib use in ovarian cancer patients. In January 2015, Myriad dropped its remaining patent disputes and has settled or is in talks with its competitors.

BRCA1 and *BRCA2* genetic testing is now available through a number of companies including (not a comprehensive list) Ambry Genetics, Counsyl, Gene by Gene, GeneDx, Invitae, Laboratory Corporation of America, Myriad Genetics, Pathway Genomics, Quest Diagnostics and the University of Washington (Table 2). Many companies offer *BRCA1/2* genetic testing within the context of larger gene panels, ranging from 5 to 48 different genes. The panels include various combinations of homologous recombination genes (*BRCA1, BRCA2,*

Table 2
Commercially available BRCA1/2 genetic tests and hereditary cancer risk panels.

Company	BRCA1/2 tests	Panel (number of genes)
Ambry Genetics	BRCA1/2 sequencing and deletion/duplication	BRCAplus (5)
	BRCA1/2 deletion/duplication	GYNplus (9)
	BRCA single site analysis	BreastNext (17)
		CancerNext (28)
		OvaNext (23)
		PancNext (13)
Counsyl	BRCA1 and BRCA2 screen	N/A
Gene by Gene	BRCA1 (only available outside North America)	N/A
	BRCA2 (only available outside North America)	
GeneDx	BRCA1/2 Del/Dup	High/Moderate Risk Panel (20)
	BRCA1/2 sequencing	Breast/Ovarian Cancer Panel (21)
	BRCA1/2 Ashkenazi Founder Mutation Panel	OncoGeneDx Custom Panel (28)
	BRCA1/2 sequencing and Del/Dup analysis	Comprehensive Cancer Panel (29)
Invitae	BRCA1 and BRCA2	Hereditary breast cancer, moderate-risk panel (5)
		Hereditary breast cancer, high-risk panel (7)
		Hereditary breast cancer, extended panel (12)
		Hereditary pancreatic cancer (17)
		Women's hereditary cancers (17)
		Hereditary cancer syndromes (29)
Laboratory Corporation of AmericaLabCorp	BRCAssure—BRCA1/2 comprehensive analysis	N/A
	BRCAssure—BRCA1/2 duplication/deletion analysis	
	BRCA1 targeted analysis	
	BRCA2 targeted analysis	
	BRCA1/2 Ashkenazi Jewish Profile	
Myriad Genetics	BRACAnaylsis CDx	My Risk (25)
Pathway Genomics	BRCATrue	BreastTrue High Risk Panel (7)
	BRCATrue Ashkenazi Jewish (3-site)	
Quest Diagnostics	BRCAvantage, rearrangements	BRCAvantage Plus (7)
	BRCAvantage, comprehensive	
	BRCAvantage, Ashkenazi Jewish Screen	
	BRCAvantage, Ashkenazi Jewish Screen with reflex to comprehensive	
	BRCAvantage, single site	
	BRCAvantage with reflex to BRCAvantage Plus panel	
University of Washington	BRCA1	BROCA (48)
	BRCA2	
	BRCAAJ—Ashkenazi Jewish panel	

ATM, BARD1, BRIP1, CHEK2, MRE11A, NBN, PALB2, RAD50, RD51C, RAD51D, XRCC2) as well as other cancer susceptibility genes (*CDH1, TP53, STK11, PTEN, APC, AXIN2, BMPR1A, CDK4, CDKN2A, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NF1, PMS, SMAD4, VHL*). The BROCA panel offered by the University of Washington also contains genes that are not included in other commercially available panels (*AKT1, ATR, BAP1, CHEK1, CTNNA1, FAM175A, GALNT12, GEN1, GREM1, HOXB13, PIK3CA, POLD1, POLE, PRSS1, RAD51, RET, SDHB, SCHC, SCHD, TP53BP1*). For many of these genes, the magnitude of cancer risk associated with a deleterious mutation has not been clearly defined. Panel testing offers a more comprehensive picture of hereditary cancer risk, but clinical practice guidelines do not always exist to guide decision making.

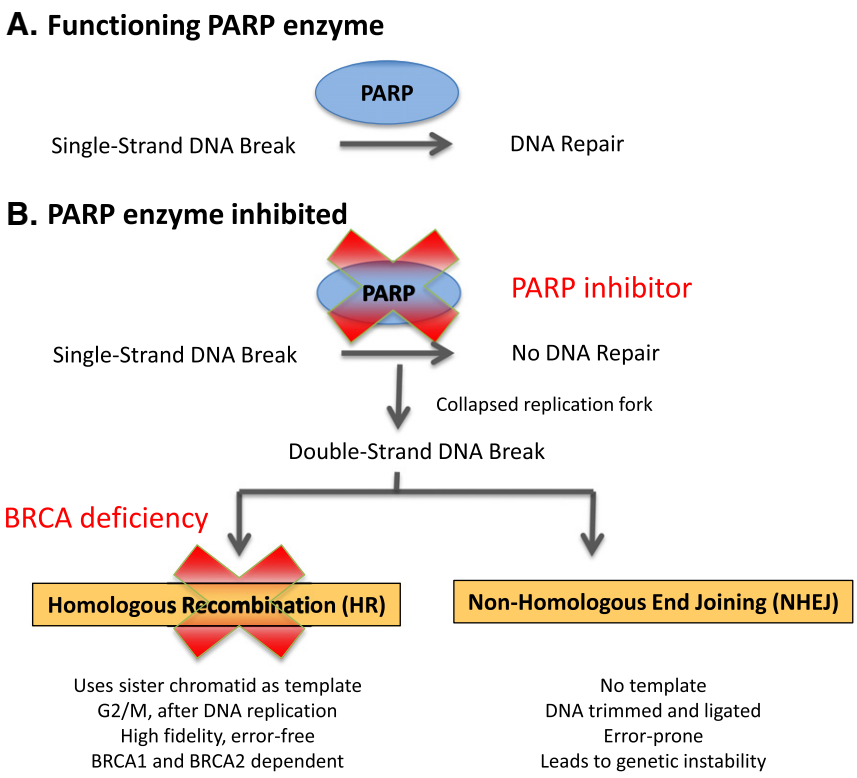
Targeting homologous recombination

The phenotype of BRCA-deficient ovarian cancers is of enhanced survival [20–23], largely attributed to a better response to platinum chemotherapy. This phenotype of enhanced survival appears to also extend to ovarian cancers with deficiencies in other homologous recombination genes [24]. Reversion mutations in the *BRCA1/2* genes can restore the coding frame and allow for the expression of functional BRCA protein, reversing the survival benefit by conferring resistance to platinum [25,26]. BRCA1/2-deficient breast and ovarian cancers also appear to have an enhanced response to doxorubicin and pegylated liposomal doxorubicin [27,28].

BRCA1/2-deficient cancers are now recognized as the target for a class of drugs known as PARP (poly(ADP-ribose) polymerase) inhibitors. PARP inhibitors are thought to work through direct blocking of PARP enzymatic activity as well as through PARP accumulation on DNA in a process called PARP trapping [29,30]. PARP inhibitors induce synthetic lethality in BRCA-deficient tissues. Deficiency of PARP or BRCA alone has no impact, but a deficiency in both leads to a lethal effect (Fig. 3).

PARP represents a family of enzymes involved in base excision repair, a key pathway in the repair of single-strand DNA breaks (Fig. 3A). When PARP is inhibited, single strand DNA breaks are converted into double-strand DNA breaks through collapse of the replication fork (Fig. 3B). A double-strand DNA break can be repaired by one of two different pathways: homologous recombination or non-homologous end joining (NHEJ). Homologous recombination occurs in the G2 or M phase of the cell cycle when a sister chromatid is available to use as a template for repair. Because a template is available, homologous recombination is a high fidelity, error-free form of DNA repair. In contrast, NHEJ does not utilize a template. The DNA is simply trimmed and ligated and this error-prone mechanism of repair can lead to genetic instability [15]. In BRCA-deficient tumors, homologous recombination is not functional, and the cell is directed towards error-prone repair and cell death.

The absence of either a functioning homologous recombination (HR) or base excision repair (BER) pathway has no detrimental impact on cell viability, but the deficiency of both together leads to synthetically lethal death (Fig. 3C). Normal cells (HR+, BER+), untreated BRCA-deficient cancer cells (HR−, BER+), and normal non-cancer cells treated with a PARP inhibitor (HR+, BER−) are all viable conditions. However, BRCA-deficient cancer cells treated with a PARP inhibitor (HR−, BER−) are selectively targeted for a synthetically lethal cell death.



C. Deficiency in HR and BER together lead to synthetic lethality

Condition	HR	BER	Outcome
Normal cells	+	+	Viable
BRCA deficient	-	+	Viable
Normal cells, PARP inhibitor	+	-	Viable
BRCA deficient, PARP inhibitor	-	-	Cell Death

Fig. 3. PARP inhibitors induce synthetic lethality in BRCA deficient cells. A. In the presence of functioning PARP enzyme, single-strand DNA breaks are repaired. B. When the PARP enzyme is inhibited, single-strand DNA breaks are converted into a double-strand DNA break through collapse of the replication fork. In BRCA-deficient tumor cells, homologous recombination repair of double-strand DNA breaks is impaired and cells are directed towards the error-prone repair process of non-homologous end joining which leads to genetic instability and cell death. C. Cells deficient in either homologous recombination (HR) or base excision repair (BER) maintain viability, while cells deficient in both through BRCA deficiency and PARP inhibition undergo synthetically lethal cell death.

The use of PARP inhibitors in BRCA-deficient tumors was born out of the observation that loss of PARP1 function induces the formation of nuclear RAD51 foci, a marker of active double-strand DNA break repair [31]. This led to the hypothesis that inhibition of PARP in BRCA-deficient cells would cause accumulation of DNA lesions that would not be adequately repaired. In 2005, compelling pre-clinical data demonstrated that BRCA-deficient cells are 1000-times more sensitive to PARP inhibitors than wild type cells [32,33].

Clinical development of PARP inhibitors

Olaparib—phase 1

Following the compelling preclinical data demonstrating selective targeting of BRCA-deficient cells by PARP inhibitors, a phase 1 clinical trial was rapidly initiated to test olaparib, the first in human PARP inhibitor. The trial recruited patients with refractory solid tumors and was enriched for *BRCA1* and *BRCA2* germline mutation-carriers (22 of the 60 patients) [34]. A supplemental secondary cohort of 50 additional *BRCA1/2* mutation carriers was subsequently recruited [35]. A maximum tolerated dose of oral olaparib 400 mg twice daily was identified through dose escalation. The drug was well tolerated causing mainly mild fatigue and gastrointestinal toxicities and toxicities did not differ based on germline *BRCA1/2* mutation status of the patients. Pharmacokinetic studies demonstrated PARP inhibition to be occurring in peripheral tissues [34].

Responses appeared to be limited to germline *BRCA1/2* mutation carriers in this phase 1 trial. Clinical benefit, defined as complete response + partial response + stable disease, was seen in 63% (12 of 19) *BRCA1/2* mutation carriers. Among the 9 patients with partial responses, 8 had ovarian cancer. When looking at the overall patient population of 60 patients, 16 (27%) had a response. There were no responses in any sporadic ovarian cancers [34].

In the secondary cohort of *BRCA1/2* mutation carriers, PARP response correlated with platinum sensitivity with 69% of platinum sensitive patients responding to PARP inhibitors compared to 45% of platinum resistant and 23% of platinum refractory patients [35]. The major

conclusions of this trial were that responses appeared to be limited to the *BRCA1/2* mutation carriers and the clinical benefit rate correlated with platinum sensitivity [34,35].

Olaparib—phase 2

The phase 1 findings led to a series of phase 2 proof-of-concept trials published in 2010 confirming the efficacy and tolerability of olaparib in patients with *BRCA1/2*-associated advanced ovarian and breast cancer [36,37]. Both trials demonstrated higher response rates at the higher dose of oral olaparib 400 mg twice daily than at the lower dose of 100 mg twice daily. At the higher dose, 33% of ovarian cancer patients [36] and 41% of breast cancer patients [37] responded to treatment.

Another phase 2 trial published in 2011 was the first to demonstrate activity of olaparib in sporadic ovarian cancers [38]. In addition to recruiting patients with germline *BRCA1/2* associated ovarian and breast cancer, the trial also included patients with sporadic high grade serous ovarian cancer and sporadic triple negative breast cancer. All patients were treated with the higher dose of olaparib 400 mg twice daily. This trial confirmed a 41% response rate in *BRCA1/2* mutation carriers with ovarian cancer, but in contrast to the phase 1 trial findings, 24% of patients with sporadic ovarian cancer also responded to PARP inhibitor treatment. Platinum sensitivity correlated with response to PARP inhibition in both subsets of patients. Among patients with platinum sensitive ovarian cancers, 60% of germline *BRCA1/2* mutation carriers and 50% of patients with sporadic tumors responded. Among platinum-resistant patients, 33% of germline *BRCA1/2* and 4% of sporadic patients responded. There were no responses in any patients with triple-negative breast cancer. The demonstration of activity in sporadic ovarian cancer suggests a possible expansion of the patient population that might benefit from these drugs. The trial also suggested that platinum sensitivity is a surrogate marker for homologous recombination deficiency [38].

Another phase 2 trial published in 2012 tested the hypothesis that olaparib would be more effective than standard of care, defined as pegylated liposomal doxorubicin, in platinum-resistant *BRCA1/2*-mutated ovarian cancer with a progression-free interval of less than 12 months [39]. The trial demonstrated no difference in response rates between patients treated with olaparib 200 mg twice daily (25% response), olaparib 400 mg twice daily (31% response) or pegylated liposomal doxorubicin (PLD) 50 mg/m^2 (18% response). Patients treated at the lower and higher doses of olaparib had progression-free survival (PFS) times of 6.5 months and 8.8 months respectively, which was no different than the PFS of 7.1 months among patients treated with PLD. However, the 7.1 month PFS in the chemotherapy arm was greater than expected compared to historical controls of about 4 months, leading the authors to suggest that this patient population with germline *BRCA1/2* mutations may indeed be more sensitive to this type of drug. The authors also commented that there were twice as many grade 3 toxicities in the patients receiving PLD and that PARP inhibitors might be a reasonable alternative with a better toxicity profile in this patient population [39].

Olaparib—maintenance therapy

To test the impact of olaparib as maintenance therapy in an ovarian cancer patient population in remission, a randomized, double-blind, placebo-controlled, phase 2 trial was conducted [40]. This trial enrolled patients with high-grade serous ovarian cancer with or without a germline *BRCA1* or *BRCA2* mutation who had previously received at least 2 prior lines of platinum-based chemotherapy and had a partial or complete response to their most recent platinum-based chemotherapy regimen. Patients receiving oral olaparib 400 mg twice daily had a longer PFS of 8.4 months compared to 4.8 months in patients taking placebo. These data were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2011 and subsequently published in 2012 [40]. In late 2011, however, AstraZeneca announced that they would not continue development of olaparib for serous ovarian cancer because the benefit in PFS was not projected to translate into an improvement in overall survival (OS).

Fortunately, AstraZeneca reversed this decision in 2013 after a retrospective analysis of the phase 2 data was presented at the 2013 ACSO Annual Meeting (subsequently published in 2014) [41]. A preplanned analysis of the data was presented based on *BRCA1/2* mutation status. Among 131 patients receiving olaparib and 123 patients receiving placebo, 56% and 50% of patients had a deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2*. The subanalysis demonstrated the greatest benefit to germline *BRCA1*/2 mutation carriers with a difference in PFS of 11.2 months compared to 4.3 months in patients receiving olaparib versus placebo (hazard ratio 0.18, 95% confidence interval 0.10, 0.31, $p < 0.0001$). Patients with sporadic ovarian cancer had a more modest improvement in PFS of 7.4 months versus 5.5 months (hazard ratio 0.54, 95% confidence interval 0.34, 0.85, $p = 0.0075$). There was no difference in OS in either subgroup [41].

The SOLO1 and SOLO2 phase 3 trials were initiated in June 2013 to investigate the use of olaparib in treatment and maintenance for patients with advanced ovarian cancer after new diagnosis (SOLO1) and after platinum-sensitive recurrence (SOLO2) (Table 3). Both trials were designed with PFS as the primary endpoint with the hopes that a large PFS benefit would be sufficient for regulatory approval.

Table 3
Ongoing phase 3 PARP inhibitor trials in ovarian cancer.

Trial	Patients	Eligibility	Treatment arms
NCT01844986 SOLO 1 AstraZeneca	344 ovary All BRCA1/2+	Maintenance after new diagnosis, advanced stage high grade serous or endometrioid, after platinum treatment	1. Olaparib 2. Placebo
NCT01874353 SOLO 2 AstraZeneca	264 ovary All BRCA1/2+	Maintenance after recurrence, platinum-sensitive	1. Olaparib 2. Placebo
NCT02282020 SOLO 3 AstraZeneca	411 ovary All BRCA1/2+	Platinum sensitive relapsed ovarian cancer, ≥2 prior lines chemotherapy, olaparib vs. physicians choice of weekly paclitaxel, topotecan, PLD or gemcitabine	1. Olaparib 2. Physician's choice chemotherapy
NCT01968213 ARIEL 3 Clovis Oncology	540 ovary BRCA1/2+ and sporadic	Maintenance after recurrence, platinum-sensitive	1. Rucaparib 2. Placebo
NCT01847274 NOVA Tesaro	360 ovary BRCA1/2+ and sporadic	Maintenance after recurrence, platinum-sensitive	1. Niraparib 2. Placebo

FDA advisory committee votes against accelerated approval of olaparib for maintenance therapy

Shortly thereafter, there was considerable enthusiasm that olaparib could be granted accelerated approval by the FDA. However, in June 2014, the Oncologic Drugs Advisory Committee (ODAC) reviewed the data on use of olaparib as monotherapy for maintenance treatment in patients with *BRCA1/2*-associated platinum-sensitive relapsed ovarian cancer. Citing safety concerns with the risks of myelosuppression, fatigue, nausea, abdominal pain and the small but concerning risk for myelodysplatic syndrome and acute myelogenous leukemia, ODAC voted 11 to 2 against accelerated approval for this indication and recommended waiting for the confirmatory results of the SOLO2 trial [42].

Olaparib monotherapy in germline BRCA1/2-associated advanced cancers

In a study presented at ASCO in 2013 and published in November 2014, the efficacy and safety of single agent oral olaparib were evaluated in a spectrum of germline *BRCA1/2*-associated cancers, including platinum-resistant ovarian cancer, heavily pretreated breast cancer, pancreatic cancer previously treated with gemcitabine and prostate cancer with progression on hormonal or systemic therapy. Therapeutic responses were seen in a broad range of tumors [43]. Among 193 patients with platinum-resistant ovarian cancer, 31.1% responded, 40% had stable disease greater than 8 weeks, 21% progressed and the median PFS and OS were 7 months and 16.6 months. Among 62 patients with heavily pretreated breast cancer, 12.9% responded, 47% had stable disease, 37% progressed and the median PFS and OS were 3.7 months and 11 months. Among 23 patients with pancreatic cancer, 21.7% responded, 35% had stable disease, 39% progressed and the median PFS and OS were 4.6 months and 9.8 months. Among 8 patients with prostate cancer, 50% responded, 25% had stable disease, 25% progressed and the median PFS and OS were 7.2 months and 18.4 months. These data suggest activity of single-agent olaparib in a broad range of *BRCA1/2*-associated cancers, irrespective of anatomic origin [43].

Olaparib receives FDA approval for treatment of BRCA-mutated advanced ovarian cancer

After the ODAC vote against accelerated approval for olaparib as a maintenance therapy in ovarian cancer, AstraZeneca submitted additional information to the FDA to support the use of olaparib in treatment of patients with *BRCA1/2*-associated advanced ovarian cancer who have received three or more prior lines of chemotherapy. Among 137 such heavily pretreated patients receiving oral olaparib 400 mg twice daily, 34% had objective responses that lasted an average of 7.9 months. Based on this data, on December 19, 2014, the FDA granted accelerated approval for olaparib to be used for this indication. The approval is contingent upon results of the ongoing SOLO3 clinical trial (Table 3). In this trial, ovarian cancer patients with BRCA1/2-associated relapsed platinum-sensitive ovarian cancer who have received two or more prior lines of chemotherapy will be randomized to olaparib versus physician's choice of single-agent chemotherapy (weekly paclitaxel, topotecan, pegylated liposomal doxorubicin or gemcitabine). The primary outcome measure is progression free survival.

Ongoing clinical trials evaluating PARP inhibitors in ovarian cancer

In addition to the SOLO trials studying olaparib, two additional PARP inhibitors, rucaparib (Clovis Oncology) and niraparib (Tesaro) are currently being evaluated in Phase 3 trials of maintenance treatment after platinum-sensitive recurrent ovarian cancer (Table 3). In contrast to the SOLO trials which are exclusively recruiting patients with germline BRCA1/2 mutations, the ARIEL 3 (studying rucaparib) and NOVA (studying niraparib) trials are recruiting both sporadic and BRCA1/2 ovarian cancer patients. Veliparib (AbbVie) has been evaluated as a single-agent treatment in BRCA1/2+ persistent or recurrent ovarian cancer in the GOG 280 phase 2 trial presented at the 2014 annual Society of Gynecologic Oncology meeting [44]. The overall response rate of 26% was thought to support investigation of veliparib in a phase 3 trial. Iniparib (BiPar, Sanofi-Aventis) is no longer considered a PARP inhibitor [45]. BMN-673 (BioMarin) is not specifically being tested in ovarian cancer at this time.

Conclusions

Since the discovery of the *BRCA1* and *BRCA2* genes two decades ago, significant advances have been made that make the homologous recombination DNA repair pathway a predictive and therapeutic target in oncology. BRCA1 and BRCA2 are critical members of homologous recombination DNA repair, which utilizes the sister chromatid (homologous chromosome) as a repair template to promote high-fidelity, error-free repair of double-stranded DNA breaks. Individuals with a germline mutation in *BRCA1* or *BRCA2* have a heightened risk of developing breast, ovarian and other cancers. In these individuals, cancer cells have lost normal BRCA1 or BRCA2 activity and have impaired function, whereas non-tumor cells maintain a functional copy of the *BRCA1* or *BRCA2* gene. This differential absence/presence of homologous recombination activity in cancer and non-cancer cells has led to the ability to selectively target BRCA-deficient cancer cells with an emerging class of compounds called PARP inhibitors. PARP is involved in base excision repair, the key pathway to repair single-strand DNA breaks. With PARP inhibition, single-strand DNA breaks are converted into double-strand DNA breaks which cannot be repaired in BRCA-deficient cancer cells. Thus, PARP inhibitors work though the concept of synthetic lethality, where deficiency of either PARP or BRCA alone has no impact on cell viability, but the loss of both results in a lethal effect. PARP inhibitors have been in clinical development since 2005, when compelling pre-clinical data demonstrated BRCA-deficient cells to be orders of magnitude more sensitive to PARP inhibitors than wild type cells. In December 2014, two decades after the discovery of the *BRCA1/2* genes, olaparib, the first in human PARP inhibitor was approved for treatment of patients with germline BRCA1/2-associated advanced ovarian cancer who have received three or more prior lines of chemotherapy. This approval represents the first “personalized” therapy for ovarian cancer. Alongside the approval of olaparib was the approval of the Myriad Genetics BRACAnalysis CDx™ test as the companion diagnostic to identify patients eligible for olaparib treatment.

Other genes in the homologous recombination pathway are now recognized to contribute to hereditary cancer risk, and although the exact magnitudes of elevated risk are not yet defined, these genes are included on multi-gene panel testing that include *BRCA1* and *BRCA2*. Since the 2013 ruling by the United States Supreme Court invalidating patent rights to *BRCA1* and *BRCA2* genetic testing, there are numerous companies offering testing as part of larger gene panels.

Conflict of interest statement

No conflicts of interest.

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