BRCA1, a Potential Predictive Biomarker in the Treatment of Breast Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. List the biomarkers that are currently used and those that may be of potential use in the management of breast cancer.
2. Explain how BRCA1 is involved in the development of both inherited and sporadic breast cancer.
3. Discuss the potential role of BRCA1 as a determinant of response to different types of chemotherapy agents.
4. Describe the relationship between BRCA1 and basal-like breast cancer.

ABSTRACT

To date, estrogen receptor, progestogen receptor, and HER2/neu represent molecular biomarkers currently used in routine clinical practice to aid treatment decisions. Over the last few years, a large body of preclinical and retrospective clinical data has accumulated that suggests that BRCA1 mutation functions as a novel predictive marker of response to chemotherapy. This article reviews the role of BRCA1 as a predictive marker of chemotherapy response in breast cancer and examines the link between BRCA1 deficiency and the basal-like phenotype.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women, accounting for 23% of cases [1]. It is estimated that approximately 1 in 11 women will suffer from the disease at some point in their lifetime. There were over 200,000 cases diagnosed in the U.S. alone in 2005, and the incidence of new cases continues to rise worldwide such that there will be an estimated 1.45 million new cases globally in 2010. Improvements in the treatment of breast cancer over the last few decades mean that overall mortality from the disease is...
falling [2]. However, despite these improvements, 30%–40% of women will still either be diagnosed with metastatic cancer or develop metastases and eventually die from their disease [1].

Although surgery is the mainstay of treatment of early breast cancer, the main focus after surgical resection is to determine which women will gain benefit from adjuvant therapies such as chemotherapy, radiotherapy, and hormonal therapies. Presently, treatment decisions are made based on histopathological tumor characteristics. Metastatic breast cancer is incurable; however, this is a heterogeneous disease in which some women will survive only a few weeks whereas others will survive many years. There are many different treatment options available for women with metastatic disease, including chemotherapy, radiotherapy, and hormonal therapy, and it is essential to give treatments that provide maximal benefit. Molecular markers currently used to predict treatment response in both early and metastatic breast cancer include estrogen receptor (ER)-α, progesterone receptor (PgR), and HER2/neu (Fig. 1). In addition, some centers use a 21-gene expression profile (Oncotype DX) to estimate the chance of recurrence or response to chemotherapy [3]. Many other molecular markers have been examined, and their roles as prognostic and predictive factors have been evaluated. None of these have proven reproducible enough to be used in routine clinical practice; therefore, the search to find biomarkers that will predict response to treatments continues.

In this article, we examine (a) molecular markers currently in routine use to determine treatment decisions in breast cancer, (b) the role of BRCA1 as a determinant of differential chemosensitivity in both the preclinical and clinical settings, (c) the relationship between BRCA1 and the basal-like phenotype, and (d) the concept that BRCA1 may be a potential novel predictive biomarker.

**MOLECULAR MARKERS USED TO PREDICT TREATMENT RESPONSE**

Currently, ER, PgR, and HER2/neu status are molecular markers used in the routine treatment of breast cancer (Fig. 1). The presence or absence of ER and PgR are valuable prognostic factors providing predictive value as to the potential benefits from hormonal therapy (Fig. 1). Approximately 70% of metastatic breast tumors are ER and/or PgR positive, and these patients tend to have a greater chance of effective tumor response and longer overall survival than patients with ER/PgR-negative tumors since they can be targeted with treatments such as tamoxifen, a selective ER modulator [4–6]. Furthermore, patients with ER/PgR-positive early breast cancer have a reduced risk of recurrence and death following adjuvant hormonal therapy, whereas patients with ER/PgR-negative disease derive minimal benefit from these treatments [7]. The value of ER status as a predictive marker extends to potential benefit from chemotherapy with those patients with ER-negative tumors appearing to gain greater benefit from chemotherapy in both the metastatic and adjuvant settings. However, treatment decisions on the basis of ER have not yet been evaluated prospectively [8].

The epidermal growth factor receptor HER2/neu is overexpressed or amplified in approximately 30% of breast cancers, and its presence is associated with a worse prognosis [9, 10]. The human monoclonal antibody trastuzumab was developed to bind the HER2/neu receptor and block its activity [11]. Treatment with single-agent trastuzumab results in a 20%–30% response rate in HER2/neu-positive metastatic breast cancer with an added survival benefit [12, 13] (Fig. 1). The addition of cytotoxic chemotherapy to trastuzumab has been shown to further enhance patient response, and the use of trastuzumab as an adjuvant treatment has initially been reported to result in improved disease-free survival in patients with HER2/neu-positive disease [14, 15].

**BRCA1 AND INHERITED BREAST CANCER**

It is estimated that 5%–10% of all breast and ovarian cancer cases are inherited, and the breast cancer susceptibility genes BRCA1 and BRCA2 have been identified as being responsible for 21%–40% of these cases [16–18]. Women who carry a germline mutation in BRCA1 have a cumulative
lifetime risk of 50%–85% of developing breast cancer and 12%–60% of developing ovarian cancer [17]. BRCA1-mutated breast tumors are characteristic in that they occur at an early age of onset and are generally ER, PgR, and HER2/ neu negative and poorly differentiated with a poor prognosis. Somatic BRCA1 mutations are rarely observed in sporadic breast cancer; however, both BRCA1 mRNA and protein expression are downregulated in approximately 30% of sporadic breast cancers and 70% of ovarian cancer cases [19]. It is believed that this may be due to nonmutational mechanisms such as (a) acquired methylation of the BRCA1 promoter or (b) malfunctions in the upstream pathways that regulate BRCA1 expression.

The BRCA1 tumor suppressor gene was identified by positional cloning on chromosome 17q21 in 1994 and encodes a 1,863-amino acid, 220-kDa nuclear phosphoprotein with three important structural motifs, including a highly conserved amino-terminal RING (Really Interesting New Gene) finger motif, a nuclear localization motif, and tandem BRCT (BRCA1 C-Terminal) motifs at its C terminus [20–23]. BRCA1 is a multifunctional protein that has been implicated in many normal cellular functions such as DNA repair, transcriptional regulation, cell-cycle checkpoint control, and ubiquitination [24]. Consequently, the presence or absence of functional BRCA1 has a significant effect on cellular response to chemotherapy. The following sections outline our current understanding of the role of BRCA1 in modulating chemotherapy responses in both preclinical and clinical studies.

**BRCA1 AND THE PRECLINICAL RESPONSE TO CHEMOTHERAPY**

**BRCA1 and DNA-Damaging Chemotherapy**

BRCA1 plays an important role in the repair of DNA damage through associations with proteins involved in the repair of DNA double-strand breaks (DSBs) by homologous recombination and nonhomologous end-joining, respectively [25, 26]. In addition, BRCA1 is associated with a large protein complex termed the BRCA1-associated surveillance complex that contains proteins involved in nucleotide excision repair (NER) [27]. DNA-damaging drugs cause DNA DSBs either directly or indirectly, and it is widely accepted that the absence of BRCA1 expression leads to hypersensitivity of cells to DNA damage-based chemotherapy. It was initially reported that overexpression of BRCA1 in human breast cancer cell lines resulted in increased resistance to cisplatin. Furthermore, antisense inhibition of endogenous BRCA1 expression promoted increased sensitivity to cisplatin that was associated with decreased DNA repair by NER and increased apoptosis [28]. In addition, abrogation of BRCA1 protein expression using mRNA-specific ribozymes in HBL100 breast cancer cells resulted in increased sensitivity to both cisplatin and etoposide [29].

Similarly, BRCA1-deficient mouse embryonic stem cells displayed defective DNA repair and a 100-fold increased sensitivity to the alkylating agent mitomycin C [30]. This sensitivity was reversed upon correction of BRCA1 mutation in one allele. Several other mouse studies have confirmed that the loss of BRCA1 function increased sensitivity to a range of DNA-damaging chemotherapeutic agents [31–34].

The HCC1937 cell line has, until recently, represented the only human breast cancer cell line derived from a patient with a BRCA1 mutation. It was observed that these cells were significantly more sensitive to cisplatin compared with BRCA1 wild-type human breast cancer cell lines [35]. Furthermore, it was demonstrated that HCC1937 cells were also more sensitive to the DNA-damaging agents etoposide and bleomycin and that this effect was abrogated following reconstitution of wild-type BRCA1 [36].

A recent preclinical study has emphasized the potential of using BRCA1 (and BRCA2) dysfunction to predict response to therapy. It was demonstrated that inhibition of poly(ADP-ribose) polymerase enzymatic activity could selectively target BRCA-mutant cells, sensitizing them to persistent DNA double-strand breaks and ultimately apoptosis [37].

**BRCA1 and Microtubule-Interfering Agents**

The two major types of microtubule-interfering agents are the vinca alkaloids and the taxanes. The vinca alkaloids, including vincristine and vinorelbine, act to destabilize microtubules, whereas the taxanes paclitaxel and docetaxel promote microtubule polymerization and stabilization, ultimately leading to the disruption of mitosis and subsequent apoptosis [38, 39]. Paclitaxel also induces apoptosis through other mechanisms such as phosphorylation of the antiapoptotic gene Bcl-2, upregulation of the proapoptotic gene Bak, and activation of the c-Jun NH2-terminal kinase (JNK)/stress-activated protein kinase apoptotic pathway (SAPK) [39].

The first preclinical evidence that BRCA1 could mediate response to antimicrotubules was derived from the report that inducible expression of exogenous BRCA1 resulted in a synergistic increase in sensitivity when these cells were treated with paclitaxel and vincristine [40]. Increased resistance to paclitaxel and vincristine was subsequently reported upon mRNA-specific ribozymal inhibition of BRCA1 [29]. These effects were correlated with a decrease
in the G2/M cell-cycle checkpoint and an increase in apoptosis associated with the JNK/SAPK pathway.

Furthermore, the BRCA1-deficient HCC1937 breast cancer cells were reported to be resistant to paclitaxel [35]. However, reconstitution of wild-type BRCA1 in these cells resulted in a 1,000-fold increase in sensitivity, and these effects were associated with mitotic checkpoint activation and increased apoptosis. An explanation for this may be derived from the observation that BRCA1 mediates the activation of MEKK3 kinase, an upstream regulator of JNK [41].

In summary, it is evident that BRCA1 can regulate differential sensitivity to different classes of chemotherapy agents in vitro. The absence of BRCA1 results in increased sensitivity to DNA damage-based chemotherapy, whereas the presence of BRCA1 promotes an increase in sensitivity to antimicrotubule agents. These observations could have a significant impact on the clinical management of breast cancer because these different types of chemotherapy agents are used in various treatment regimens in both early and metastatic breast cancer (Fig. 2).

**BRCA1 AND CLINICAL RESPONSE TO CHEMOTHERAPY**

To date, all clinical studies examining the prognostic and predictive value of BRCA1 in breast cancers have been difficult to interpret because they have been retrospective and included both BRCA1 and BRCA2 patients. Although they share some similarities, the molecular profiles of BRCA1 and BRCA2 tumors are distinct, as shown by microarray analysis [42].

Initial indications that the predictive value of BRCA1 and response to different chemotherapy agents in preclinical models could be transferred into a clinically useful prognostic and predictive tool were derived from a small study in Ashkenazi Jews that evaluated 38 patients with locally advanced breast cancer [43]. Seven of these patients had germline mutations in BRCA1 and a further four had BRCA2 mutations. All patients received anthracycline-based neoadjuvant chemotherapy, and it was shown that 10 of 11 patients with BRCA mutations had a clinical complete response compared with only 8 of 27 noncarrier patients with sporadic breast tumors. Following surgery, four of nine breast cancer patients had a complete pathological response compared with only one noncarrier. From this study, it was inferred that tumors with BRCA1 mutation were highly sensitive to anthracycline-based chemotherapy regimens.

In a further retrospective study of 278 women, it was demonstrated that patients with BRCA1 mutation fared worse if they did not receive chemotherapy when compared with similar noncarrier patients who also did not receive adjuvant chemotherapy (relative ratio of 3.3). Therefore, it seems that patients with BRCA1 mutation gained more benefit from chemotherapy [44].

A more recent study confirmed that tumors arising in BRCA1-mutation carriers are more chemosensitive [45]. This study investigated response to neoadjuvant anthracycline-based chemotherapy in 15 BRCA1, 5 BRCA2, and 57 sporadic breast tumors. A clinical response was observed in 100% of BRCA1 tumors compared with 80% and 63% of BRCA2 and control tumors, respectively. Following surgery, a pathological complete response was observed in 53% of BRCA1 patients, whereas no BRCA2 patients and only 14% of sporadic controls had a similar response (p = .01). This study suggests that tumors with BRCA1 mutations are more chemosensitive than both BRCA2-mutated and sporadic breast tumors.

Further evidence that BRCA1-mutation carriers have an enhanced response to DNA-damaging agents comes from a recent study of 131 familial cases of breast cancer, 19 of which had BRCA1 and 8 of which had BRCA2 mutation, and their 261 matched controls [46]. These patients all had small tumors and were treated with breast-conserving surgery followed by radiotherapy to the breast. In this study, median time to ipsilateral breast cancer recurrence was 80 months in breast cancer patients compared with 39 months in noncarriers and 46 months in controls. Conversely, it was noted that time-to-recurrence in the nonirradiated, contralateral breast was shorter in breast cancer patients. Although only a small number of events occurred, this study suggests that patients with BRCA1 mutation gain more benefit from treatments that exert their effect by causing DNA damage, including local treatments such as radiotherapy. However, caution must be observed when correlating...
**BRCA1** mutational status with endpoints such as survival or disease-free survival since the potential predictive power of **BRCA1** may be affected by its impact on overall prognosis. Conversely, studies that have attempted to evaluate the prognostic impact of **BRCA1** have been confounded by its impact on chemotherapy response.

The effect of **BRCA1** does not seem to be limited to breast cancer. A study of 71 patients with epithelial ovarian cancer, including 22 **BRCA1** and 12 **BRCA2** patients, demonstrated that breast cancer patients had a higher response rate following platinum-based chemotherapy [47]. In addition, it was observed that these breast cancer patients had longer overall survival (91 months vs. 54 months, \( p = .046 \)) and a longer disease-free survival (49 months vs. 19 months, \( p = .16 \)). A further study in ovarian cancer found that upon multivariate analysis **BRCA1** mutation was an independent predictor of reduced risk of relapse and death, with hazard ratios of 0.52 and 0.38, respectively [48]. Although the study was not conclusive, it did suggest that this reduced risk may be influenced by more intensive treatment and better response to cisplatin chemotherapy.

Mutations of **BRCA1** are rarely observed in sporadic breast tumors; however, up to 30% of cases have reduced expression of **BRCA1** mRNA and protein [49, 50]. To date, studies examining reduced **BRCA1** mRNA levels in sporadic breast cancer and its role in chemotherapy response have shown results that contradict preclinical data. In one specific study, a quantitative real-time polymerase chain reaction (PCR) approach was used to assess **BRCA1** mRNA levels from tumor biopsies of 51 patients with locally advanced or recurrent breast cancer. These patients received epirubicin and cyclophosphamide and were categorized into either high or low levels of **BRCA1**. However, only 32% of tumors with low **BRCA1** mRNA levels were found to respond to DNA damage-based chemotherapy compared with a 65% response rate in tumors with high levels of **BRCA1** mRNA [51]. However, a recent investigation in non-small cell lung cancer has indicated that tumors with low levels of **BRCA1** did respond better to neoadjuvant chemotherapy, including gemcitabine and cisplatin [52]. These patients had improved median survival and decreased risk of death compared with patients with high levels of **BRCA1**. There have been few studies examining **BRCA1** in response to taxane-based chemotherapy in breast cancer. One study has reported that low levels of **BRCA1** tended toward increased sensitivity to neoadjuvant docetaxel, but this did not reach statistical significance [53]. Studies focused on the analysis of **BRCA1** as a predictive biomarker in inherited forms of breast and ovarian cancer have been aided by the standardized techniques for mutation detection such as sequencing-based approaches. The question as to whether sporadic tumors with reduced expression behave in the same way as **BRCA1**-mutant tumors remains somewhat unresolved, and these studies are limited by the lack of standardized techniques for quantifying **BRCA1** through either immunohistochemistry or PCR. It is essential, therefore, that a standardized approach such as that provided by quantitative real-time PCR be developed to facilitate further meaningful studies in the sporadic form of the disease.

**BRCA1** and the Basal Phenotype

There is now mounting evidence that there is a strong link between **BRCA1** deficiency and the basal-like phenotype (Table 1). It has been known for many years that the normal breast epithelial tissue is made up of two distinct cell types, namely an inner luminal layer of cells and an outer basal/myoepithelial layer of cells. Standard histopathological practice does not differentiate between tumors arising from these different cell types. However, immunohistochemical studies clearly demonstrate that approximately 20% of breast tumors express cytokeratin (CK) 5/6, 14, and 17 consistent with a basal-like pattern [54]. Furthermore, molecular profiling using DNA microarray analysis has demonstrated that breast tumors can be classified according to their genetic profile [55–57]. Tumors can be subdivided into ER-positive/luminal tumors, HER2-positive tumors, and ER-negative/basal-like tumors. The latter two subtypes are associated with a poorer prognosis. The use of microarray analysis is expensive, but it has been shown that a panel of four immunohistochemical markers (ER, HER1, HER2, and CK5/6) can accurately predict which breast tumors fall into the basal category [58]. Categorizing tumors in this way may give additional prognostic information over traditional markers currently in use, leading to improved treatment decisions.

Tumors that arise in patients with a germline mutation in **BRCA1** tend to be associated with a particular phenotype. Following suggestions that breast tumors related to **BRCA1** mutation may be of higher grade, a study by the Breast Cancer Linkage Consortium showed that in a cohort of 440 patients, including 118 carriers of **BRCA1** mutation, there was a higher proportion of high-grade tumors in the **BRCA1** patients [59]. These findings were confirmed by a second study that examined 182 tumors, of which 119 were **BRCA1**-mutated. Results showed that **BRCA1** tumors were less likely to express ER (10% **BRCA1** vs. 65% of sporadic controls), PgR (21% vs. 59%), and HER2/neu (3% vs. 15%) [60]. In this study, **BRCA1** tumors were more likely to express p53. Taken together, these results suggest that **BRCA1** tumors tend to be ER, PgR, and HER2 negative (triple-negative) and therefore share similarities with tumors that are classified as basal-like in origin. To investigate this fur-
ther, a study of 292 tumors identified 76 that were both ER- and HER2/neu-negative. Following immunohistochemistry for CK5/6, it was found that 40 of the 76 tumors expressed these markers and that they were statistically significantly associated with BRCA1 mutation [61]. A second study examined CK5 and 14 in a set of 42 hereditary breast cancers and found that 78% of BRCA1-related tumors were positive for these markers [62]. The expression of basal cytokeratins was not only strongly associated with BRCA1 mutation and other features of BRCA1 tumors such as ER, PR, and HER2 negativity, but was also associated with a worse outcome [63]. A further marker of the basal epithelium, p-cadherin, was also found to be associated with BRCA1 tumors; p-cadherin is common in breast tumors that exhibit a basal phenotype, namely, ER- and HER2-negative tumors, and was also found to be associated with a worse prognosis [64, 65].

It is clear from the above studies that tumors arising in patients with BRCA1 mutations tend to exhibit a very similar histological phenotype to basal-like tumors. This similarity extends to gene expression profiles. By reanalyzing previously published datasets, which included tumors from patients with BRCA1 mutations, and using hierarchical clustering of genes associated with the basal-like phenotype, it was shown that BRCA1 tumors tend to fall into the basal-like category [57]. As previously mentioned, sporadic breast cancers with decreased expression of BRCA1 tend to exhibit a similar triple-negative phenotype to both BRCA1-mutant tumors, and therefore, these tumors may also fall into the basal-like category [66]. The cell type of origin from which basal-like tumors develop remains a matter of speculation. It has been proposed that breast tumors may develop from a common mammary gland stem cell, and BRCA1 has been reported to function in normal differentiation pathways in breast tissue [67–69]. It is possible, therefore, that the loss of BRCA1 in a breast cancer stem cell may result in deregulated differentiation, leading specifically to the development of tumors with basal-like characteristics.

It has recently been reported that tumors that exhibit a basal-like genetic profile may have a better response to neoadjuvant chemotherapy than those that exhibit a luminal genetic profile [70]. In a study of 82 breast cancers that were treated with neoadjuvant chemotherapy that included DNA-damaging agents and paclitaxel, 45% of tumors classified as basal-like through molecular profiling demonstrated a pathological complete response, whereas only 6% of luminal tumors responded in a similar way. This finding is particularly intriguing because it suggests that the genotypic similarity observed between BRCA1-deficient and basal-like tumors may extend to a phenotypic similarity in terms of response to chemotherapy.

### Table 1. Key tumor characteristics of breast tumors arising in patients with BRCA1 germline mutations compared with sporadic breast tumors classified as either basal or luminal in origin

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BRCA1</th>
<th>Basal</th>
<th>Luminal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>ER</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CK5/6</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>CK14</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CK17</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>p-cadherin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Chemosensitivity</td>
<td>Sensitive</td>
<td>Sensitive</td>
<td>Less sensitive</td>
</tr>
</tbody>
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Abbreviations: CK, cytokeratin; ER, estrogen receptor.

### CONCLUSION

ER, PgR, and HER2/neu have proven to be very successful biomarkers that accurately predict benefit to treatment with tamoxifen and trastuzumab, respectively. However, it has proven more difficult to identify further biomarkers that could help predict response to specific chemotherapy drugs to tailor current chemotherapy regimens in an effort to gain maximum benefit with minimal exposure to unnecessary drugs. Despite this, we feel that there is overwhelming preclinical evidence to suggest that BRCA1 could be useful as a predictive marker of response to different types of chemotherapy agents. Clinical evidence to date has suggested an increased benefit from DNA damage-based chemotherapy for patients with BRCA1 germline mutations. In sporadic breast cancer cases, there is conflicting evidence as to whether tumors with epigenetic inactivation of BRCA1 will
derive a similar benefit to DNA damage-based chemotherapy. There is currently insufficient evidence to suggest that BRCA1 status should be considered when assigning adjuvant treatment particularly in node-negative patients; however, we feel that the use of BRCA1 as a potential biomarker should be examined more fully in prospective clinical trials, not only in breast cancer but also in other cancers where BRCA1 seems to play a role in the development of the tumors such as ovarian, prostate, and non-small cell lung cancer.

The advent of high-throughput technologies has led to startling discoveries regarding the global genetic heterogeneity of breast tumors. There is now mounting evidence that tumors arising in patients with germline mutations of BRCA1 are strongly associated with tumors of the basal-like phenotype. This raises interesting questions regarding the biology of these tumors and the exact role that BRCA1 plays in their tumorigenesis. We feel that studies need to be designed to further address the relationship between BRCA1 inactivation (both genetic and epigenetic) and the basal-like phenotype. Furthermore, can tumors that exhibit the basal-like phenotype be used as a predictor of BRCA1 mutation or at least identify an enriched population that can be screened? Finally, it has already been suggested that basal-like tumors, similar to BRCA1-mutated tumors, are more sensitive to neoadjuvant chemotherapy; therefore, further clinical investigations are now required to determine whether the basal-like phenotype can be used to predict treatment outcomes.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
The authors indicate no potential conflicts of interest.

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**ADDITIONAL READING**

