

## CCR 20<sup>th</sup> Anniversary Commentary: Triple-Negative Breast Cancer in 2015—Still in the Ballpark

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The research article by Dent and colleagues, which was published in the August 1, 2007, issue of *Clinical Cancer Research*, provided a clinical description of metastatic progression of triple-negative breast cancers. Finding successful treatment strategies

for women with triple-negative breast cancer remains a challenge. *Clin Cancer Res*; 21(17); 3813–4. ©2015 AACR.

See related article by Dent et al., *Clin Cancer Res* 2007;13(15) August 1, 2007;4429–34

There are three kinds of fruits—apples, oranges, and others. Does this classical adage (attributed by some to Aristotle) apply to breast cancer as well? We can infer a lot about how to treat a breast cancer by knowing its estrogen receptor (ER) and its HER2 status, but for those cancers that are negative for these two markers, is there much to be gained by dividing them into smaller subclasses? It would be helpful if we could subdivide cancers into groups with varying propensities to metastasize, but it would be even better if we could divide them into various groups that would benefit from different treatments. This remains an elusive goal.

The best way to divide breast cancers remains an unsettled question. One of the first molecular-based attempts to do this was the intrinsic subtype classification of Perou and colleagues (1). Gene-expression profiles were used to create five different subgroups of breast cancer. One type, called "basal breast cancer," lacked expression of both ER and progesterone receptor (PR), and did not overexpress HER2—i.e., these cancers were "triple negative." "Triple negative" has become a common term, as opposed to "basal," because of its simple definition and because it can be identified by a pathologist as part of a normal diagnostic workup of a breast tumor. Triple-negative breast cancers and basal breast cancers are not identical, and nonbasal triple-negative breast cancers have unique properties (2). In 2015, we do not endorse routine staining for CK or EGFR in pathology laboratories, because of the lack of standardization and proven clinical utility, but expression profiling has become a viable commercial test in the form of the PAM50, MammaPrint, and Oncotype Dx. These tests are designed to provide the oncologist with advice regarding whether or not to give tamoxifen or chemotherapy (of the non-

tailored sort). Other classifiers can be based on genomic signatures, such as copy-number variants and mutations. Other subdivisions of triple-negative breast cancer (3) reveal ever-increasing complexity and subtypes, including an immunomodulatory subtype: treatment of cell lines with this phenotype (3) and immunohistochemical studies (4) suggest that specific immunologic therapies might be effective for this subtype (5). Clinical trial results are awaited.

Collins and Varmus (6) speak of a new era of precision oncology, in which each cancer is dissected and classified, such that treatment is guided by identifying the particular pathway that is impaired. Unlike Aristotle's parsimonious classification, in the extreme view, each cancer has a different genomic signature and can be considered a subgroup in its own right. Moreover, a single cancer is genetically heterogeneous, and there is no guarantee that a single treatment will be effective against all the malignant clones that compose the tumor mass. Using single-cell sequencing techniques, Wang and colleagues (7) studied the extent of clonal genetic diversity in ER-positive and triple-negative cancers. They found that triple-negative cancer cells had a very high intrinsic mutation rate and this generated extensive genomic diversity.

The challenge to find a targeted treatment for triple-negative breast cancer is still with us. In terms of treatment for subgroups, effective treatments can be identified in two ways. One way is to design a new treatment to complement a deficiency in a gene or in the abundance of a protein within the cancer itself, such as the use of a PARP inhibitor, olaparib, to treat breast cancer with deficient DNA repair (8). Olaparib has been used with some success in triple-negative breast cancers but is not approved for this use and may ultimately have activity only in *BRCA*-related triple-negative breast cancer. An adjuvant trial of bevacizumab in triple-negative cancers brought negative results (9). Androgen receptor is overexpressed in approximately 30% of triple-negative cancers, and antiandrogen therapies are under investigation (3). A second approach is to give an established drug to a subset of patients who might benefit. For example, platinum agents have seen a rebirth in the treatment of triple-negative cancers with some success, but further stratification of patients suggests that they may be effective only in cases with germline *BRCA1* mutations (10). In a recent study by Byrski and colleagues (11) from Poland, 61% of 107 triple-negative *BRCA1*-positive patients achieved a

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pathologic complete response to neoadjuvant cisplatin. Surprisingly, the response rate was similar for women with ER-positive cancers (56%) and for those with ER-negative cancers (61%). Thus, the role of platinum agents in the treatment of triple-negative cancers with normal *BRCA1* function or with somatic loss of *BRCA1* has not yet been resolved. Further, the choice between cisplatin and the less-toxic carboplatin has not been compared.

Several studies done in the past 5 years correlate germline *BRCA1* mutation status with triple-negative status (12), and now in many jurisdictions, genetic testing is routinely offered to women diagnosed with triple-negative breast cancer who are under age 60. It has been known for some time that triple-negative cancers are overrepresented among black women, and this seems to extend to Mexican women as well. Among Mexican women, about 25% with triple-negative cancers carry a *BRCA1* mutation (13). It is not yet known if this is also the case for women of Mexican origin who live in the United States. In the future, trials of triple-negative breast cancer patients will need to incorporate *BRCA1* status as well. *BRCA1* carriers with triple-negative cancer often respond to oophorectomy, but it is not clear why cancers

expressing ER receptors should benefit from an antihormonal approach.

In summary, since our publication in 2007 (14), much new information has been gathered over the molecular makeup, biology, natural history, and complexity of triple-negative breast cancer. Although currently available adjuvant chemotherapy is a very effective treatment for most women with triple-negative breast cancer, this new information is leading to new clinical treatment strategies, and early clinical results are encouraging.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** S.A. Narod, R.A. Dent, W.D. Foulkes

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