# Quadruple-Negative Breast Cancer: An Uneven Playing Field

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## INTRODUCTION

Triple-negative breast cancer (TNBC) is clinically defined as the absence of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). The approximately 15%-20% of breast cancers (BCs) that are triple negative represent an aggressive subtype that is more likely to have a poor prognosis.[1] Highly heterogeneous, the TNBC collective comprises multiple independent molecular subtypes, underpinned by unique biologic pathways. The chief TNBC subtyping systems are briefly outlined in Figure 1.[2-4] Among these, the widely accepted Lehmann molecular classification categorizes TNBC into: basal-like (BL1 and BL2), immunomodulatory, luminal androgen receptor (LAR), mesenchymal, and mesenchymal stem-like.[3] The subtypes also respond differently to available therapies. For example, the LAR tumors have a low proliferation rate and are less sensitive to standard chemotherapy, whereas the basal type is characterized by high proliferation and greater sensitivity to chemotherapy.[5] Lumped with TNBC is the highly recalcitrant quadruple-negative breast cancer (QNBC), simplistically designated as a TNBC subset that lacks androgen receptor (AR) expression. In fact, 70%-80% of TNBCs are veritably QNBCs (ie, are AR negative).[6,7]

African ancestry is one of the risk factors associated with TNBC. Among different populations, the incidence of TNBC is far greater in West African women (53.2%) and African American (AA) women (29.8%) compared with their European American (EA) counterparts (15.5%).[8] This strongly suggests a genetic predisposition to the disease.[9,10] AR-positive TNBCs are predominantly of a luminal subtype, whereas QNBCs tend to be the aggressive basal-like.[2,11] A comprehensive AR assessment study by Davis et al[12] reported that in all BC subtypes, AA women showed a propensity toward absence of AR expression, with the greatest frequency of loss observed in TNBCs. In addition, AA women with AR-negative TNBC experienced worse overall survival than EA women. The most cogent result from the study demonstrated that, relative to EAs, QNBCs in AA women express distinct enriched basal and immune (BL1, BL2, and immune modulatory) signatures.[12] For example, PD-1, programmed death-ligand 1 (PD-L1), and CTLA-4 (immune checkpoint inhibitors), along with CD4 expression on T cells, were found to be significantly increased in both QNBC overall and in AA-QNBC as opposed to EA-QNBC. Thus, a lack of AR results in a difference in tumor-linked immune response, which depends on genetic ancestry.[12] Although it is widely accepted that AR plays a role in BC progression,[13] its function as a prognostic biomarker in TNBC remains ambiguous.[14-19] A recent study found that AR-positive status displayed population-specific patterns, conferring a better prognosis in US and Nigerian cohorts and a poor prognosis in India, Ireland, and Norway cohorts and was of no prognostic value in a UK cohort.[20] It has also been proposed that the ER status determines the prognostic role of AR; AR denotes good prognosis in ER-positive BC, but its role in ER-negative BC is indeterminate.[21] In part, the equivocality surrounding the results can be attributed to differences in the anti-AR antibodies used, as well as the staining and scoring methods across studies, compounded by variable thresholds used to define AR positivity. In addition, small sample sizes and differences in the ethnic makeup of cohorts impair congruity in results.

The glaring racial disparity is not just confined to the prevalence and molecular portraiture of this intractable disease but spills over to treatment options as well, for the AA demographic. Regarding TNBC, the field of precision medicine is hamstrung, owing to its highly heterogeneous nature as well as a dearth of actionable targets. Typically, early-stage TNBC is treated with a combination of local (surgery and radiotherapy) and systemic therapy (chemotherapy), given the absence of targets responsive to endocrine or HER2 blockade. Chemoresistance is, however, fairly common in TNBC. A minority of patients with metastatic TNBC will have germline BRCA mutations and evidence of PD-L1 expression, enabling targeted treatment with poly ADP-ribose polymerase (PARP) inhibitors and immunotherapy, respectively.[22,23]

Drugs targeting the AR are a recent and promising line of investigation.[22] Despite conflicting reports on its merits as a prognostic marker, AR antagonists such as bicalutamide and enzalutamide have exhibited encouraging results, principally in the subset of patients with TNBC who belong to the LAR molecular subtype (that is partly dependent on AR signaling).[24-30] However, because only 20%-25% of TNBCs express AR, it leaves a vast majority of patients with TNBC who are in

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 10, 2019 and published at ascopubs.org/journal/go on February 19, 2020: DOI https://doi.org/10.1200/JGO.19.00366

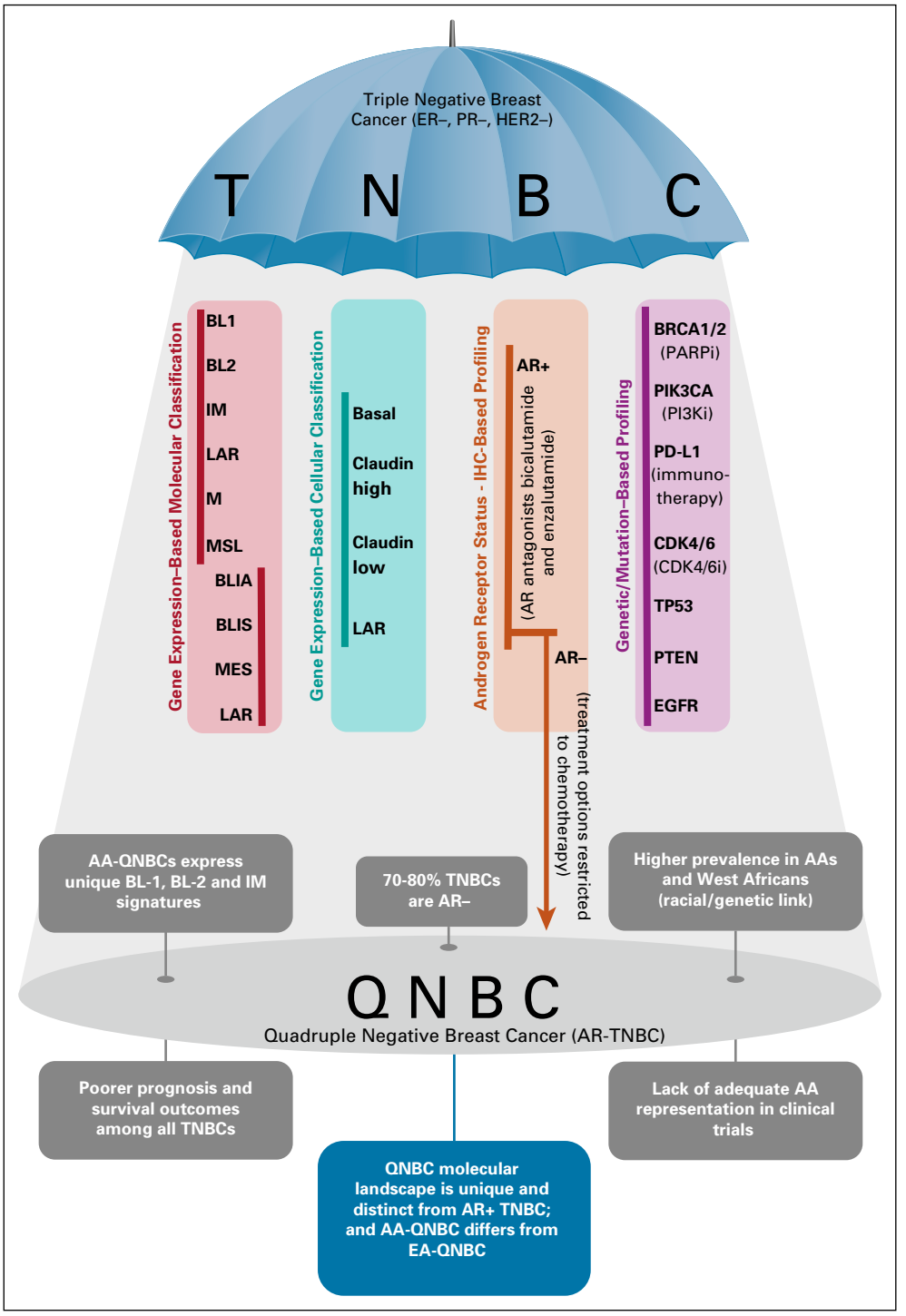


**FIG 1.** Triple-negative breast cancers (TNBCs) make up a highly heterogeneous group that can be classified variously, as outlined in the long columns (data adapted[2-4]). Quadruple-negative breast cancer (QNBC) is clinically defined as an androgen receptor (AR)–negative TNBC and is briefly characterized in the lower half of the schematic. There is a pressing need to extricate QNBC from the shadows of TNBC and classify it as a unique, clinically relevant BC subtype. AA, African American; BL, basal-like; BLIA, basal-like immune associated; BLIS, basal-like immune suppressed; CDK4/6i, CDK4/6 inhibitors; IHC, immunohistochemistry; IM, immunomodulatory; LAR, luminal androgen receptor; M, mesenchymal; ML, mesenchymal stem-like; PARPi, PARP inhibitor; PI3Ki, PI3K inhibitor.

 

fact quadruple negative bereft of this class of drugs. In several BCs, tumor cell proliferation is marked by an overactive cyclinD-CDK4/6 holoenzyme, and, as such, inhibitors of CDK4/6 have proved successful in reining in cancer progression among patients with metastatic disease with hormone-positive BC.[31] Among the TNBC subgroups, LAR has shown sensitivity to CDK4/6 inhibition; however, the basal-like subtype is resistant to it.[32] PI3K inhibitors are another group of promising therapeutics that can be applied to PIK3CA-mutant TNBCs. Because the PIK3CA kinase mutations are more frequently found in AR-positive TNBCs (40%) as compared with AR-negative (4%),[33] the QNBC group is deprived of this line of intervention as well. Most of the TNBC-combating therapeutics target AR-positive TNBCs, which ends up deepening the inequalities in treatment options. Currently, no targeted drugs are available or under development for patients with QNBC, and their treatment options are restricted to chemotherapy. Yet another consideration is a switch in hormone receptor status that often follows cancer recurrence, especially so in TNBC, which exhibits elevated metastatic potential. Angajala et al[34] observed an increase in QNBC subtype at second profile status of TNBC that had progressed to a recurrent/metastatic stage. So although AR-positive TNBC exhibited a heterogeneous profile with a greater frequency of being diagnosed as AR negative at an advanced stage, QNBC displayed a more stable phenotype.[34] In view of the complex role of AR in BC and the distinctive characterization its presence and absence effects in the TNBC landscape, it is imperative to include AR analysis in routine clinical practice (together with the assessment of ER, PR, and HER2 expression). Because there is little consensus on AR positivity cut-off as determined by immunohistochemistry, a more reliable means of assessment, such as an androgen-driven gene signature, should be depended on instead.

As exemplified by the study by Davis et al,[12] the QNBC landscape diverges from that of TNBC, and the absence of AR manifests distinctively in AA versus EA women. The mechanistic action of AR is not yet clearly delineated in TNBC. Thus, identifying key AR-dependent proteins that may differ with race, BC subtypes, disease progression, and prior treatment would prove pivotal in mapping the TNBC landscape. This in turn will help discriminate QNBC from TNBC and the molecular nature of AA-QNBC compared with EA-QNBC, with the final goal of identifying potential druggable targets. However, this blueprint of TNBC/QNBC research, though robust, is bound to fail in the face of unequal racial composition that marks most study cohorts. Clinical trials suffer from an underrepresentation of racial minorities,[35] and an adequate inclusion of AA women and women of African descent in these studies is indispensable to advance QNBC research.

To recapitulate, the major fraction of TNBCs are AR negative (ie, QNBC phenotype), which overwhelmingly afflicts AA women and expresses a unique racial fingerprint. Prevalence of the disease and poorer survival outcomes in AA and West African women strongly indicates a genetic predisposition. However, we cannot discount the role of socioeconomic factors, such as poverty and barriers to health care access,[36] in contributing to mortality differences and exacerbating the disparities. Moreover, the treatment research focus on AR-positive TNBC (such as AR antagonists) inadvertently fuels these imparities. Relegating QNBC to a TNBC-subtype position is taking a parochial view of a complex disease, one that warrants an independent classification as a singular, clinically relevant BC subtype. Extricating it from the shadows of TNBC and extensively annotating its molecular features will aid in paring down the disparity gap that currently ails QNBC research (Fig 1).


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## SUPPORT

Supported by National Cancer Institute Grant No. R01CA239120 (R.A.).


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**Keerthi Gogineni**
**Honoraria:** Pfizer, Eli Lilly
**Research Funding:** Pfizer (Inst), Calithera Biosciences (Inst), Merck (Inst)
**Travel, Accommodations, Expenses:** Eli Lilly

No other potential conflicts of interest were reported.

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