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## Integrating biology and access to care in addressing breast cancer disparities: 25 years' research experience in the Carolina Breast Cancer Study

Marc A. Emerson, PhD<sup>1,2</sup>, Katherine E. Reeder-Hayes, MD, MBA<sup>2</sup>, Heather J. Tipaldos, MS<sup>2</sup>, Mary E. Bell, MPH<sup>2</sup>, Marina R. Sweeney, MPH<sup>1</sup>, Lisa A. Carey, MD<sup>2</sup>, H. Shelton Earp, MD<sup>2</sup>, Andrew F. Olshan, PhD<sup>1,2</sup>, Melissa A. Troester, PhD<sup>1,2</sup>

<sup>1</sup>Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, NC, USA

<sup>2</sup>Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

### Abstract

**Purpose of Review**—To review research on breast cancer mortality disparities, emphasizing research conducted in the Carolina Breast Cancer Study, with a focus on challenges and opportunities for integration of tumor biology and access characteristics across the cancer care continuum.

**Recent Findings**—Black women experience higher mortality following breast cancer diagnosis, despite lower incidence compared to white women. Biological factors, such as stage at diagnosis and breast cancer subtypes, play a role in these disparities. Simultaneously, social, behavioral, environmental, and access to care factors are important. However, integrated studies of biology and access are challenging and it is uncommon to have both data types available in the same study population. The central emphasis of Phase 3 of the Carolina Breast Cancer Study, initiated in 2008, was to collect rich data on biology (including germline and tumor genomics and pathology) and health care access in a diverse study population, with the long term goal of defining intervention opportunities to reduce disparities across the cancer care continuum.

**Summary**—Early and ongoing research from CBCS has identified important interactions between biology and access, leading to opportunities to build greater equity. However, sample size, population-specific relationships among variables, and complexities of treatment paths along the care continuum pose important research challenges. Interdisciplinary teams, including experts

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**Corresponding author:** Melissa A. Troester, Phone 919-966-7408, Troester@email.unc.edu.

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#### Conflict of Interest

Marc A. Emerson, Katherine E. Reeder-Hayes, Heather J. Tipaldos, Mary E. Bell, Marina R. Sweeney, Lisa A. Carey, H. Shelton Earp, Andrew F. Olshan and Melissa A. Troester declare no conflicts of interest relevant to this manuscript.

#### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

in novel data integration and causal inference, are needed to address gaps in our understanding of breast cancer disparities

### Keywords

Breast cancer; racial disparities; access to health care; data integration; cancer care continuum

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### Introduction

Black women experience a 42% higher mortality rate compared to white women [1]. Since the 1980s, this mortality gap has increased, partly reflecting disproportionate increases in survival among white women [2]. The disparities are particularly pronounced among younger women, where black women age 45–54 years have a death rate from breast cancer double that of white women of the same age [3]. Younger and black women are more likely to have molecular subtypes of breast cancer that are more aggressive and that lack molecular targets for treatment [4–9]. However, our understanding of biologic factors that account for more aggressive breast cancers in black women remains incomplete, and moreover, is poorly integrated with understanding of how tumor biology interacts with other patient-level factors such as access to care and treatment adherence.

A recent review highlights how both tumor biology and quality of care increase the racial mortality gap [10]. One limitation of previous literature is that often depth of biological data is not found in the same study population as depth of data on treatment and access. For example, the Cancer Genome Atlas project (TCGA) has detailed tumor-level data on RNA, DNA, protein, methylation and other genomic features of breast cancer [11], but patient-level information on things like comorbidities, body mass index, and treatment are lacking. Conversely, SEER and SEER-Medicare or other studies linked to insurance or health care data [1, 12] may offer more detailed understanding of treatment patterns, but are lacking information on tumor subtype. Thus, much research continues to consider tumor biology and access separately, with little integration, and few studies are able to integrate granular and detailed information regarding both biology and access.

Based on early studies in the Carolina Breast Cancer Study (CBCS) Phase 1 and 2, a population-based case-control study that oversampled black and young women, it was demonstrated that tumor biology, specifically higher incidence of basal-like breast cancer in African American women [5], was an important plausible contributor to mortality disparities. However, as in many other studies of tumor biology, treatment data was lacking as was detailed follow up information. More than twenty-five years of research in the CBCS had generated a large and inter-connected body of research, but many of the more than 160 published studies were oriented toward understanding risk and tumor biology, rather than long term differences in survivorship. In 2008, the study began recruiting phase 3, and has now recruited 3000 women diagnosed with invasive breast cancer to develop a more complete understanding of breast cancer mortality disparities.

In this current report, we will review previous literature on racial mortality disparities in the CBCS, as well as available data for survivorship research. We will consider early attempts to integrate biology and access, and highlight needs and opportunities for future research.

Throughout this review, we refer to *biology*, meaning the molecular, histological, and clinical characteristics of breast tumors and their microenvironments. We refer to *access*, meaning the patterns of health services availability, quality, utilization, and treatment adherence. The central hypothesis underlying our perspective and the driving motivation for the Carolina Breast Cancer Study is that disparities in outcomes are caused by complex interactions of *biology and access*. We will evaluate research across the cancer care continuum, from screening and diagnosis, to staging and treatment, to survivorship, to highlight research gaps and opportunities for data integration.

## Designing Studies to Address Biology and Access to Care Interaction

Beginning in 1993, researchers at University of North Carolina had been studying breast cancer disparities, and the first phase of CBCS (CBCS1, 1993–1996) was designed as a case-control study to study risk factors for breast cancer. Early CBCS findings related to etiology and prevention such as genetic susceptibility, environmental exposures, gene-environment interactions, socio-behavioral and environmental risk factors, with a major emphasis on collecting tumor blocks and incorporating molecular epidemiologic methods into population-based research [13]. CBCS increased its sample size in phase 2 (1996–2001) and added new exposure information (Nonsteroidal anti-inflammatory drugs [NSAID] and anti-depressant use, and dietary practices). This phase also included cases with ductal carcinoma in situ, to begin developing a picture of the early stages of breast cancer etiology [14]. These studies helped elucidate reproductive and behavioral risk factors for breast cancer, including body size and physical activity, environmental exposures, alcohol, smoking and diet factors, and showed that many risk factors identified in white women were also relevant for black women [15–29]. In fact, many of the CBCS findings showed particularly strong effects in black women. For example, positive associations between cigarette smoking and increased Luminal breast cancer risk, but not Basal like, were significant only among black women [30].

These studies also emphasized etiologic heterogeneity according to tumor markers, showing that distinct molecular subtypes may have unique risk factors. Studies showed that 7 or more alcoholic beverages per week was associated with estrogen receptor negative and triple negative breast cancers [31] and highlighted risk associated with body size [32], NSAID use [33], mammographic density [34]. Studies also highlighted greater frequency of aggressive tumor features in young women's breast cancer [35]. Many of these findings were recapitulations of studies in other populations, but the contribution of CBCS1 and CBCS2 data was largely to extend these findings to a more diverse population. Ultimately, data and samples were contributed to large national projects in genetics [36–41] and consortium projects focused on understanding black women's risk such as the African American Breast Cancer Epidemiology and Risk (AMBER) consortium, a National Cancer Institute funded P01 project [42].

More than a decade after the inception of CBCS 1 and 2, data were linked with the National Death Index to evaluate overall and breast cancer specific mortality. These analyses identified patterns of survivorship by exposure, and began to identify some racial differences. For example, analyses were conducted regarding the role of NSAIDs in survival

[33], and the role of pregnancy and obesity in breast cancer mortality [43, 44]. A landmark paper for the study showed that breast cancer specific survival was worse for black women, even when stratifying on clinical markers such as estrogen receptor, progesterone receptor and HER2 [45]. This study was the impetus for a larger survivorship cohort study because of two limitations. The study had elucidated important mortality disparities, but it lacked information on treatment and there was no direct contact with patients to allow detailed resolution of survivorship experiences or intervention opportunities. In addition, treatment guidelines had changed over time, including the advent of HER2-targeted therapies and new guidelines for treating ER positive disease.

In response to the need for more detailed follow up and treatment data, CBCS3 was initiated as a case-only cohort study in 2008. Phase 3 continued to leverage the key interdisciplinary strength of the CBCS, and deepened engagement and collaboration with experts in molecular biology, epidemiology, genetics, and clinical expertise. Now, as CBCS3 begins its tenth year of patient contacts and detailed follow-up, the study is poised to integrate biology and access to identify the strongest contributors to differences between black and white women with breast cancer. The central emphasis of the study is deepening rich data on health care access and outcomes to better understand breast cancer mortality disparities across the cancer care continuum.

CBCS3 incorporates technical advances in intrinsic subtype analysis, including detailed RNA expression profiling, DNA sequencing, and immunoprofiling. Early results applied a robust gene expression platform called Nanostring that is optimized for RNA in formalin-fixed paraffin embedded specimens [46, 47], showing that multigene assays can better resolve biological differences between tumors (relative to single marker studies). Published CBCS3 data showed that while immunohistochemical (IHC) assays can identify Basal-like breast cancers from non-Basal-like with reasonable certainty (86% sensitivity), these IHC-based analyses cannot distinguish Luminal A from Luminal B breast cancers (46 of 60 tumors that were Luminal B by PAM50 in CBCS were inappropriately classified as Luminal A by IHC) [48]. IHC assays are also unable to differentiate molecular subtypes such the human epidermal growth factor receptor 2 (HER2)-enriched subtype from Luminal and other subtypes in clinically HER2-positive breast cancers. The study found that with improved PAM50 classification, significantly higher prevalence of poor prognosis tumors are observed in black women compared with white women. In particular there were significantly more Basal-like (35% vs 18%), particularly in younger women, and significantly fewer Luminal A tumors (31% vs 50%) [49].

CBCS3 is continuing to collect RNA-based data on a number of important pathways in breast cancer, and increasingly is integrating this data with other data types, including germline DNA [36] and ongoing efforts to integrate with DNA sequencing-derived mutational signatures. Expression data is also available to complement existing methylation findings [50, 51]. Histopathology data, including results from deep learning are now being integrated with gene expression data [52]. CBCS3 is also collecting recurrence and second primary tumors and to study etiologic heterogeneity by evaluating patterns of recurrence and concordance between first and subsequent tumors [53].

With this resource of tumor biologic data, important data integration steps have been made, but most complex data analyses have involved combining different types of biologic or genomic data. It is much more challenging to combine genomic data with detailed information on survivorship. In the sections that follow, we will detail how CBCS studies are beginning to address integration of biology and access, highlighting challenges and opportunities. To organize this analyses, we will consider the cancer care continuum in its entirety, beginning with screening and diagnosis, progressing to treatment and adherence, and finally considering recurrence and long term survivorship. Following these case studies, we will consider methodologic approaches and conceptual challenges for biology and access integration moving forward.

## Screening and Diagnosis

Patients enter the cancer care continuum at screening and diagnosis, and this is the first opportunity for a more integrated conceptualization of breast cancer. Mammography is a screening tool intended to detect cancers at an earlier stage and thereby increase survivorship. However, access to mammography and mammography facilities are unequally distributed geographic and by racial/ethnic, poverty, work, insurance, education, transportation and cultural factors [54–56]. Access issues and neighborhood segregation create disparities, where black women are more likely to live in areas with higher proportions of inadequate and inappropriate treatment compared to white women [57]. Historically, affluent urban women have experienced greater benefit from screening compared to poorer women of color [58].

However, mammography effectiveness is also influenced by tumor biology. Mammography may have greater sensitivity to detect ER+ or luminal breast cancers [59]. Interval breast cancers are more likely to be triple negative [60–62]. Differences in screening adherence have been hypothesized to contribute to variation in subtype prevalence by race, with highly screened, older white women having the highest prevalence of the most readily detectable, Luminal A breast cancers. However, few studies have evaluated molecular subtype in association with mode of detection (symptomatic vs. screen-detected vs. interval detected) in the modern screening era (i.e. with digital mammography) [63, 64]. These previous papers did not incorporate multigene assays in their assessment of detection differences.

Through a data linkage between CBCS and the Carolina Mammography Registry, we observed that black women had similar rates of screening adherence to white women, but were more likely to develop interval breast cancers (cancers detected between regular screenings) [65]. Interval cancer was also associated with triple-negative clinical subtype and non-Luminal A molecular subtype (by more rapid progression and tumor features that are hard to detect by mammography), whereas screen-detected cancers tended to be more indolent, smaller and more frequently low genomic risk. These strong associations between interval cancers and poor-prognosis genomic features (non-Luminal A subtype and high risk of recurrence score) suggest that aggressive tumor biology is an important contributor to detection disparities by race. Moreover, these findings suggest that screening access or adherence differences interact with tumor subtype.

While screening mammography leads to early detection of some TNBCs and does benefit black women [66], it is important to develop improved understanding of where some of the failures may occur. Ongoing CBCS research is evaluating whether specific subtypes are more likely to present as masses (rather than as readily detectable calcifications). Notably, compared to white women, black women are less likely to present with calcifications and more likely to present with masses (mostly associated with aggressive subtypes) [67]. Better understanding tumor biology can also improve breast cancer screening methods. Other research has shown that mammographic features (e.g., calcification type and mass shape/margins) are associated with breast cancer subtypes [68].

## Treatment/ Adherence

After diagnosis, there may be differences in types of treatment and also timeliness of treatment initiation or completion. Previous literature shows that timeliness of care improves survival, yet this relationship is a complex interaction of clinical factors, tumor biology, and SES factors [69]. Previous studies have shown that black women experience greater delays in care than white women at multiple points along the treatment pathway including diagnostic delay (time from detection to medical consultation/diagnosis) [70, 71] and treatment delay (time from diagnosis to the initiation of treatment) [70, 72–75]. Black women experience delay in radiation therapy, and these delays are partly explained by differences in geographic access to radiation facilities [76] [77]. In addition, black patients experience delays in initiating and completing chemotherapy [78–81] and experience longer delays in initiating appropriate endocrine therapy [82]. Although differential insurance coverage may explain some of these differences in time to treatment, black women are still more likely to experience delays [70, 74, 73, 76] and to fare worse [73, 83, 78, 79] after controlling for insurance type. These delays have been demonstrated to be particularly impactful on clinical outcomes of triple negative breast cancer [78, 83].

Similar to previous work, early papers in CBCS3 showed differences in access without incorporating biologic insights. For example, women of lower income and residents of rural areas were less likely to receive breast conserving surgery [84]. We also found that a larger proportion of black women (43%) had delays in first treatment (more than 30 days), compared to white women (38%) [75]. For younger women (under age 50), the racial disparity in treatment delay was even greater. Additionally, the disparity by race was present when stratified by treatment type (e.g. surgery, radiation, chemotherapy, etc.). It is likely that these treatment delays relate to a range of socioeconomic factors aside from race (e.g. marital status, insurance status, etc.). However, these analyses focused primarily on understanding differences in access, with less attention to biology.

A first attempt to integrate biology and access in understanding treatment decisions utilized genomic data to understand black-white differences [49]. Multigene precision medicine tools, such as Oncotype DX and Prosigna/PAM50, are important for optimizing treatment. The most frequently used genomic prognostic assay in ER+/HER2- patients is the Oncotype Dx. Through medical record abstraction, CBCS3 data showed that the uptake rates for Oncotype DX were similar in black and white node-negative patients of CBCS overall, but also found that among higher-risk women with node-positive disease, use of the test was



higher in white women [85]. Application of Oncotype DX in higher risk women, is not guideline concordant. However, even guideline discordant utilization of genomic testing may influence treatment decisions. Our data showed that there were no racial differences in adjuvant chemotherapy initiation among women with similar Oncotype DX risk scores [85, 86]. This raises at least a couple of possibilities: (1) women who receive genomic testing differ systematically from those that do not, and (2) genomic tools could also function to create more equity in prescribing patterns by providing a clear decision aid.

Other ongoing work on treatment is addressing differences in endocrine adherence [87–89]. Oral adjuvant endocrine therapy (ET) dramatically reduces the risk of cancer-specific mortality and recurrence, but between 30% and 50% of women with HR+ disease never initiate ET, which can differ by race [90–92]. Using CBCS data, compared to white women, black women reported greater ET underuse and nonadherence. Major predictors of nonadherence by race included differential risk perception, lack of shared treatment decision making, and worse side effect burden [88].

A recent interesting finding that suggests potential for integration of tumor biology, chemotherapy, and endocrine adherence data. ER+ black women in SEER have higher rates of chemotherapy and lower rates of endocrine therapy initiation [93, 94]. It is unclear why apparently similar clinical indications are leading to different treatment patterns by race, but it would be helpful to understand whether chemotherapy treatment affects adherence rates. A recent study also showed that chemotherapy prevalence differed by race only among women who did not receive genomic testing [95]. These data suggest that treatment decisions vary by tumor biology in ways that are as yet not fully understood. Future research should evaluate not just chemotherapy initiation, but details on chemotherapy discontinuation, endocrine adherence, and genomic testing to gain a more complete picture of interactions among these variables.

## Early Recurrence, Survival, and Quality of Life

For over 20 years we have known that African American (AA) women have a higher burden of breast cancer mortality. These differences are also attributable to black women being at greater risk of hormone receptor- and HER2 receptor-negative cancers [5, 96–98] more advanced stage [99] and higher grade at diagnosis [100], and other adverse tumor biology among black women [100, 101, 49]. Research conducted in the CBCS has demonstrated that black and young women have higher rates of the aggressive, treatment refractory basal-like subtype and lower rates of estrogen receptor positive Luminal A breast cancer than white women [5]. However, our research has also shown that the prevalence of the basal-like subtype does not fully explain mortality disparities [45]. Substantial disparities exist within subtype, such that even among a homogeneously defined group of Luminal A breast cancers, survival is substantially reduced for black women. Some of these differences may reflect inherent breast cancer biology, which may derive from ancestral genotype. Black women have significantly greater haplotype diversity, and GWAS studies from the CBCS have identified several new haplotypes/loci relevant in black and younger women [102]. In a recent transcript-wide association study published in CBCS, it was demonstrated that germline variation predicted gene expression in tumors, but that models derived in white

women had poor predictive ability in black women, and *vice versa* [103]. However, race-stratified models were able to identify several alleles that had significant ability to predict survival. These findings underscore the need for larger studies and consortia where sufficient numbers of black and white patients can be included.

CBCS3 is not fully mature for understanding long term survival outcomes, having only followed patients for a median of seven years. However, some early endpoints are showing important results. Physical activity after breast cancer diagnosis has been associated with improved survival, and in CBCS3, black women were less likely to meet national physical activity guidelines after diagnosis [104]. Using health-related quality of life (HRQOL) instruments, Whites reported physical and functional scores 2–2.5 points higher than blacks and these racial differences persisted more than two years after diagnosis [105]. Both modifiable patient-level factors, like smoking and obesity, and non-modifiable factors, including younger age, black race and comorbid conditions, were associated with poorer HRQOL [106].

Financial toxicity has been shown to adversely affect survival and overall quality of life. CBCS investigators found that treatment-related adverse financial impacts were reported by more than one-half of black women and more than one third of white women [107]. A majority of this adverse financial impact was due to lost income after breast cancer diagnosis. Black women with breast cancer experienced a significantly higher risk for all measured adverse financial impact (including decrease in income, financial barrier to care, transportation barrier to care, job loss and insurance loss). Higher cancer-related financial burden can affect treatment choice, treatment compliance, and cancer outcomes [107]. Thus, policies that help limit the effect of cancer-related financial strain are needed.

## Long-term Survivorship

Long term survivorship is a large and growing area for further research. It is estimated that there are roughly 3.8 million women living as breast cancer survivors in the US [108]. Issues related to long term survivorship include side effects of treatment, adjuvant hormone therapy adherence, social support, body image, quality of life and acculturation. Figure 1 shows that CBCS is positioned to study several key domains, including the 5 major domains included in the American Society for Clinical Oncology (ASCO) survivorship guidelines [109]. The ASCO guidelines address issues in the transition from treatment to survivorship and include surveillance for breast cancer recurrence, screening for second primary cancers, management of long-term and late effects, health promotion, care coordination and practice implications. Continuing to ten years after diagnosis, CBCS has collected information that represents all of the ASCO domains.

By conducting this research in a prospective cohort, we can assess evolution of patient concerns over time. For example, a common reason for choosing mastectomy over breast conservation therapy is the desire to avoid recurrence. Similarly, a major reason for choosing contralateral prophylactic mastectomy is for peace of mind about not having cancer recurrence in the future. Whether more extensive treatment such as mastectomy is actually associated with lower fear of recurrence is not known. Little is known about racial



differences in fear of recurrence, although white women are more likely to choose more extensive surgery. An association between fear of recurrence and overutilization of services could have important implications for initial treatment, psychosocial management during survivorship, and policy. The 7-year and 10-year CBCS3 surveys include a 5-item instrument for assessing fear of recurrence, measuring the level of worry about diagnostic tests, other types of cancer, recurrence, death, and children's health [110]. The study is also following patients' unmet needs (using a measure called Cancer Survivors' Unmet Needs [CaSUN] [111]) and levels of health activation, using a patient activation measure [112]. These long-term survival questions lean toward questions about access and health services, but continuing to incorporate our knowledge about the original tumor biology and the risk of recurrence these women are likely to experience will provide key context for understanding these data.

## Data Integration Approaches

Combining biological data, such as „omics data, with other classical epidemiologic data is not without challenges. Analytic approaches and machine learning tools are increasingly available to address some challenges, but there are several conceptual hurdles that remain. As outlined in Lopez de Maturana et al. [113], factors such as high correlation/collinearity between biological and access variables, the different nature of information, hierarchical dependence of data, heterogeneity of definitions, population substructure, disease heterogeneity, and dynamic nature of health processes are only a few of the possible hurdles. These problems are further compounded when working across multiple datasets.

One approach for coping with complex datasets that we have applied in the CBCS3 is latent class analysis (LCA). Our work with LCA illustrates some of the potential and challenges of data integration. LCA is a person-centered, dimensionality reduction analytical methods to more comprehensively characterize and understand this complex “social-contextual and biological mixture,” that can vary between people. Dimensionality reduction allow us to evaluate overall patterns that vary between people. A person-oriented approach can be contrasted with a variable-oriented approach like factor analysis, where the emphasis is on identifying relations between variables and it is assumed that these relations apply across all people.

In CBCS3, we used LCA to study barriers to care, tumor characteristics patterns, and individual level SES. We examined differences in more than 20 variables, and summarized these variables in only three sets of variables: SES, barriers to care, and tumor biological features [114]. We found that frequency distributions of all three classes varied by race and age, with lower SES, more barriers to care, and more aggressive aggregated tumor biological factors for younger and black women. The approach was data driven and can be contrasted with studies that use composite scores (e.g., area-level education or income and/or individual insurance) to capture SES [115–117]. While composite scores may be straightforward to calculate, they cannot be readily exported across datasets because SES manifests in different way in distinct populations [118]. Other studies have highlighted this challenge. For example, Palumbo et al. found lack of concordance when comparing the latent class variables with a continuous neighborhood SES index, concluding that SES characteristics

were better represented by multiple latent classes than by a single index. Comparison of results from Palumbo et al. to our findings in CBCS3 show that the latent classes can be interpreted across studies. Despite formulating their latent classes differently, their work had findings similar to those from CBCS, showing that latent-class defined SES (i.e., higher proportions of neighborhoods with people single with dependents, below poverty line, low vehicle access, black race) was associated with more aggressive tumor characteristics (i.e., lower proportions of early stage, smaller size and lower grade) [119]. This work shows that data dimensionality reduction can be effective in defining some health determinants and can help elucidate relationships between factors.

However, a major limitation of data dimensionality reduction is that it often does not clearly elucidate underlying mechanisms or actionable public health strategies. It is very difficult to change SES or all the components that comprise barriers to care. Evaluation of single modifiable factors may seem more tractable for interventions. For example, if financial or transportation barriers exist, it may seem feasible to address these individually. However, previous research also suggests that seemingly simple solutions may not always have expected results [120–122]. Patients who report transportation and financial barriers may exhibit numerous other barriers to health care access, such that a simple intervention such as providing transportation services does not address the underlying barrier. Examining one barrier at a time may not adequately define the most effective interventions. Thus, balancing mechanistic understanding and appropriate modeling of complexity may sometimes be at odds. Or alternatively, they may be complementary approaches that should be used in concert.

Some recent novel approaches have developed data integration mechanisms that are pathway-focused or mechanistic by nature. These data integration approaches are particularly appealing because they hypothesize a mechanism that allows for targeted interventions. For example, Cheng and Levy considered disparities in treatment burden broadly, formulating a quantitative, multivariable measure of the workload that patients put into their care [123]. When patients are given more health care tasks than they can manage or afford, they are at risk for becoming overburdened, which can lead to decreased adherence. Workload varies by tumor aggressiveness, underscoring the inherent link between access and biology. Creative approaches that are inherently mechanistic, such as workload, are an important way to leverage epidemiologic data in concert with complex biological data.

## Advancing Research in Biology and Access Disparities

In summary, this review retrospectively assessed research arising from the Carolina Breast Cancer Study, emphasizing the evolution of the field of breast cancer disparities and the current challenges faced by the field. There are many emerging research opportunities and resources, including analyses of rich electronic health care and insurance claims records, linkage of SEER data with detailed biological analyses, and efforts to improve representation of racial minorities in clinical research. As these efforts progress, our analysis of results from CBCS suggest that creating equity in health care access will require an

interdisciplinary approach with creative approaches for dealing with data complexity and an emphasis on integrating biology and access.

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•• Of major importance

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ASCO Domain	Data collection time point*							
	Baseline	Yr-1	Yr-2	Yr-4	Yr-6	Yr-7	Yr-9	Yr-10
<b>Surveillance for recurrence</b>								
History/physical								
Screening (1)								
Laboratory tests								
Signs of recurrence								
Risk evaluation (2)								
Endocrine tx impacts (3)								
<b>Screening for second primary</b>								
Cancer screenings (4)								
<b>Assessment of effects (5)</b>								
Body image concerns								
Lymphedema								
Cardiotoxicity								
Cognitive impairment								
Depression/anxiety (6)								
Fatigue								
Bone health								
Musculoskeletal health								
Pain and neuropathy								
Infertility								
Sexual health								
Premature menopause (7)								
<b>Health promotion</b>								
Information								
Obesity								
Physical activity								
Smoking cessation								
<b>Care coordination (8)</b>								
Survivorship care plan								
Communication (9)								
Inclusion of family								
Abbreviation: ASCO = American Society for Clinical Oncology (1) Screening for local recurrence or new primary breast cancer; (2) Risk evaluation and genetic counseling; (3) Endocrine treatment impacts, symptom management; (4) Cancer screenings for average risk patient; (5) Assessment/management of physical/psychosocial long-term/late effects of breast cancer/treatment; (6) Distress, depression, and anxiety; (7) Premature menopause/hot flashes; (8) Care coordination and practical implications; (9) Communication with oncology team *Baseline includes a mail-in questionnaire; Yr-2 includes a telephone survey and Appendix A; Yr-6 includes a telephone survey and Appendix B; Yr-10 includes a telephone survey, Cancer Survivors' Unmet Needs measure (CaSUN), Patient Activation Measure 13 (PAM-13), and Appendix C; all other years include a telephone survey								

**Figure 1.** American Society of Clinical Oncology Survivorship Domains and Corresponding Data Collection Activities in CBCS3.