Published in final edited form as:

Per Med. 2011 November ; 8(6): 669–679. doi:10.2217/pme.11.67.

Early developments in gene-expression profiling of breast tumors: potential for increasing black–white patient disparities in breast cancer outcomes?

Donna H Odierna[†], Aimee Afable-Munsuz¹, Ogechi Ikediobi², Mary Beattie³, Sara Knight⁴, Michelle Ko⁵, Adrienne Wilson³, and Ninez A Ponce⁵

¹Department of Community Health Sciences, SUNY Downstate School of Public Health, 450 Clarkson Avenue, Box #43, Brooklyn, NY 11203, USA

²Department of Clinical Pharmacy, University of California, San Francisco, 521 Parnassus Ave, Box 0622, San Francisco, CA 94143, USA

³Division of General Internal Medicine, UCSF Cancer Risk Program, University of California, San Francisco, 1635 Divisadero Street, Box 1793, San Francisco, CA 94143-1793, USA

⁴Health Services Research & Development Service, San Francisco Veterans Affairs Medical Center, Departments of Psychiatry & Urology, University of California at San Francisco, Box VAMC – 151R, VAMC Bldg 1, 220-G, University of California, San Francisco, San Francisco, CA 94143, USA

⁵Department of Health Services, UCLA School of Public Health, PO Box 951772, Los Angeles, CA 90095-1772, USA

Abstract

New prognostic tests, such as gene-expression profiling (GEP) of breast tumors, are expected to prolong survival and improve the quality of life for many breast cancer patients. In this article, we argue that GEP has not been adequately validated in minority populations, and that both biological and social factors might affect the broad utility of these tests in diverse populations. We suggest that the widespread use of this technology could potentially lead to suboptimal treatment for black women, resulting in a further increase in black–white patient disparities in treatment response, morbidity and mortality rates. We argue for the need to build a large and diverse evidence base for GEP and other emerging technologies in personalized medicine.

[†]Author for correspondence: Department of Clinical Pharmacy, San Francisco Branch of UC Cochrane Center, University of California, San Francisco, 3333 California St, Box 0613, San Francisco, CA 94118, USA, Tel.: +1 415 502 8227, Fax: +1 415 502 0792, Donna.Odierna@ucsf.edu.

For reprint orders, please contact: reprints@futuremedicine.com

Financial & competing interests disclosure

The study was supported by the UCSF Center for Translational and Policy Research on Personalized Medicine (TRANSPERS P01 CA130818-02A1) National Cancer Institute (NCI) P01 CA 130818 (principal investigator: K Phillips). The study was also supported by the UCSF Clinical and Translational Science Institute, NIH/NCRR UCSF-CTSI Grant Number UL-1 RR024131. Health Services Research and Development, Interdisciplinary Program to Improve Health Care for Veterans with Complex Comorbid Conditions and Health Services Research and Development Investigator Initiated Award (IIR 09-135). Mary Beattie is also funded by the UCSF Breast Specialized Program of Research Excellence (SPORE NCI 2P50 058207) and the Avon Foundation. Adrienne Wilson is funded by the Avon Foundation. Donna H Odierna is funded by the UCSF Center for Clinical and Translational Research and the Flight Attendant Medical Research Foundation. Sara Knight is employed by the Health Services Research and Development Service San Francisco Veterans Affairs Medical Center. This paper is the responsibility of the authors and the perspectives expressed within do not necessarily reflect the views of the Department of Veterans Affairs. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Keywords

African–American women; breast cancer mortality; gene-expression profiling; personalized medicine; racial disparities; social determinants of health

In the USA, breast cancer is the second leading cause of cancer-related deaths for women. Although they are less likely than white women to develop breast cancer, black women are more likely to die from the disease [1]. The high rates of breast cancer morbidity and mortality among black women, relative to white women, have been the subject of many studies and several reviews. These papers found black–white patient differences in biological factors (e.g., more estrogen-receptor negative (ER[−]) and ‘triple negative’ tumors in black women) and social factors (e.g., more race-related social disadvantage and poorer access to healthcare) that might account for some of the black–white patient disparities in breast cancer outcomes [2–7]. Moreover, recent evidence suggests the troubling finding that as cancers become easier to detect and treat, racial/ethnic disparities in cancer mortality increase [8]. While overall breast cancer mortality has declined with improvements in screening and treatment, black–white patient disparities in breast cancer mortality rates have indeed increased. In 1980, breast cancer mortality rates were similar in white and black women (approximately 32/100,000 women per year). Between 1980 and 2007 white women experienced a decrease in breast cancer mortality rates that was not seen in black women. The result, shown in Figure 1, is a substantial black–white patient disparity in breast cancer mortality – the 2007 age-adjusted rate for white women is approximately 23/100,000, compared with approximately 32/100,000 in black women. By contrast, no such widening of black–white patient mortality rates was detected for lung cancer, which has not previously been amenable to early detection and successful treatment, although there have been some recent developments in lung cancer screening using CT scans [9].

Over the past three decades, population health disparities have persisted despite the rapid development and diffusion of new and emerging technologies. We fear that personalized medicine, with its promise of targeted diagnostic and prognostic tests, is more likely to benefit the most privileged populations, potentially increasing present disparities in cancer outcomes. The breast cancer mortality gap could persist or even widen if such tests are not developed for, validated in, and accessed by underserved and minority populations.

Gene-expression profiling (GEP) is a hallmark example of a newly diffusing technology in clinical practice that could further widen black–white patient breast cancer mortality. Studies of breast tumor gene-expression signatures have demonstrated that breast cancer encompasses a group of molecularly distinct neoplastic disorders [10–13]. It is likely that ER[−] and ER positive (ER⁺) breast cancers, which appear in different rates in black and white populations, originate from distinct cell types. These studies led to the creation of GEP tests, which can be used clinically to predict breast cancer prognosis and potentially guide therapy [14,15]. For women with early-stage breast cancer, GEP of tumor tissue provides additional prognostic information beyond traditional clinical predictors [16,17]. This use of personalized medicine can inform individualized treatments, for example, by identifying women for whom the harms of chemotherapy outweigh the benefits [14,18,19]. We argue in this article that GEP may not equally benefit diverse populations. Our perspective is supported by our examination of the validity of three of the GEP assays currently available in the USA, and by contextualizing our findings with the biological and social factors in black–white patient disparities in breast cancer.

We drew upon the Centers of Disease Control and Prevention’s Evaluation of Genomic Applications in Practice and Prevention Program (EGAPPP) Working Group report, ‘Impact

of GEP tests on breast cancer outcomes' [101], augmented by more recent literature. While the EGAPP report highlights the importance of validating these tests in populations with a varying genetic background, the need to validate GEP for diverse racial populations was not prominent in the EGAPP recommendations. There is clear population evidence that there are fundamentally different biological tumor features across racial groups, warranting the discussion of both biological and social factors that contribute to the sources of variation in gene expression. We evaluated the representation of nonwhite women in GEP trials, and identified areas in this literature where the lack of collected or reported data on race hinders measurement of diverse population representation. Specifically, we examined testing and validation in minority populations of three GEP assays that are used in the USA to predict clinical outcomes in patients with breast cancer: Oncotype DX[®] (Genomic Health, CA, USA), the H/I[™] Ratio Signature and Breast Cancer Profiling test (AvariaDX, CA, USA), and MammaPrint[®] (Agendia BV, Amsterdam, The Netherlands).

Oncotype DX is indicated to predict the risk of recurrence in patients with ER⁺, node-negative disease treated with tamoxifen, and to identify patients who may not need adjuvant chemotherapy. Oncotype DX can be used in tissue that is formalin fixed and paraffin embedded, the most common technique for breast tissue preservation in the USA [14].

The H/I ratio test assays a two-gene ratio of *HOXB13* to *IL17R* and molecular grade index. It is indicated to stratify ER⁺ patients into groups with a predicted low risk or high risk of recurrence and a predicted good or poor response to endocrine therapy. The H/I ratio test can also be used in formalin-fixed paraffin-embedded breast tissue [14].

MammaPrint is indicated to aid in prognostic prediction in patients with stage I or II, node-negative disease with a tumor size of up to 5 cm. It requires fresh or frozen breast tissue. MammaPrint is the only GEP test currently available for both ER⁺ and ER⁻ disease [14].

We examined the evidence tables in the EGAPP report [101], and consulted Pubmed experts to conduct a search to identify all Medical Subject Headings and key terms that would encompass GEP for breast cancer. Our search initially yielded 65 more recent articles, in addition to those identified by the EGAPP report. Two authors (Mary Beattie and Adrienne Wilson) reviewed each of these articles for relevance. After reviewing the EGAPP evidence tables and our search results, we excluded laboratory validity studies that compare GEP techniques (e.g., microarray vs RT-PCR), as these studies address assay methods, rather than the relationship of GEP testing to outcomes. We also excluded studies that focused on cost and physician behavior. Table 1 summarizes the final 22 studies used in our examination of GEP and clinical outcomes: 20 from the original EGAPP report and two that were added as a result of our search [20,21].

Approximately half of the studies shown in Table 1 were conducted in western Europe, the other half in the USA. One study was conducted in Japan. In The Netherlands, where the majority of the MammaPrint studies and a third of the H/I ratio test studies were conducted, approximately 14% of the population of the population is non-European [102]. In the USA, women aged 35 and older, nonwhites comprise 28.9% of the female population and African-Americans 11.8% [103]. Of the 22 studies in Table 1, only six, including the Japanese study, reported race/ethnicity in their population characteristics. With the majority of studies not reporting the race/ethnicity of their populations, it is difficult to determine the number of nonwhite patients studied. However, of over 6500 study participants, 471 were coded as nonwhite patients; only 127 (about 2%) were coded as black patients. Under-representation and under-reporting of minority racial/ethnic groups in these studies limits the evidence-base for evaluating the utility of the tests in diverse populations.

Of the six studies that reported race/ethnicity, approximately 23% of the combined patient population was nonwhite; just over 6% was black. Only one study considered the effects of race on outcomes [22]. The small sample size of this study (72 total subjects, 35 of them non-white) precludes meaningful interpretation of interactions between race/ethnicity and GEP on clinical outcomes. None of the six studies appear to have sufficient power for stratified analyses. It is notable that three of the six studies that reported patients' race were located in either Texas (TX, USA) or California (CA, USA), states in which non-Hispanic whites are not majority populations.

In addition to a lack of data on race/ethnicity, there is also little evidence regarding stratified outcomes by ER status. The 12 studies that reported ER status included 918 ER⁻ cases (approximately 14% of all study participants), and typically used ER⁻ status as a control variable or a competing/contributing reference prognostic marker. The two studies that stratified analysis by ER status [23,24] found no association between the marker (H/I ratio test) and clinical outcomes among ER⁻ patients, and all subsequent findings were applied to an ER⁺ population.

Oncotype DX is the most commonly used GEP test in the USA, and it is currently indicated only for early-stage ER⁺, lymph-node-negative breast cancers. Moreover, fewer than 10% of patients in the studies of Oncotype DX shown in Table 1 were ER⁻. Therefore, benefits of this technology are less likely to apply to young women, particularly black women, in whom ER⁻ tumors are more common. Furthermore, only five of the 11 studies reported race/ethnicity, making it difficult to determine the validity of the overall results for different racial/ethnic groups. MammaPrint, which is approved for use in women with ER⁻ tumors, may not be predictive for triple-negative tumors [25] and it has not been tested in nonwhite populations. Questions regarding biological difference and access to effective technologies underscore the importance of understanding how both biomedical and sociomedical factors may contribute individually or in combination to disparate outcomes in diverse populations. These questions may be particularly relevant in discussions regarding the emerging technologies that characterize the practice of personalized medicine.

Biomedical & sociomedical factors in black–white patient disparities in breast cancer

Black female patients are more frequently diagnosed with late-stage breast cancer than white patients [4,26], even though they generally have similar rates of mammographic screening [27]. When differences have been found in mammographic screening rates, they do not satisfactorily explain later-stage diagnosis among black women [28,29]. It is unclear whether late stage diagnosis is explained by later detection of disease or due in part to more aggressive forms of disease being more common among black women. While stage at diagnosis is a crucial factor in survival, it does not fully account for the black–white patient differences in mortality rates [30]. The literature documents a spectrum of biological and social determinants that may contribute to black–white patient disparities in breast cancer outcomes.

Breast cancer biology & GEP

The utility of GEP may vary in biologically diverse forms of breast cancer. Population-based evidence suggests that tumor characteristics associated with poorer prognosis are more prevalent among black women. Specifically, triple negative breast tumors (ER⁻, progesterone-receptor negative, and HER2 negative) are more common in women in their 20s and 30s, and in black women of all ages [29,31–36]. Triple negative breast cancers are

known to be aggressive, display shorter survival times and a high mortality rate [37,38], and they exhibit high rates of recurrence within 5 years of diagnosis [39].

Regardless of ER status, black women are still more likely to die of breast cancer than white women, pointing to differences in access to care and in biological responses to breast cancer treatments [40]. A recent study found that black women who are ER⁺ were less likely than white women to receive a 21-gene recurrence score, suggesting differential genomic testing by race [41]. Another study suggested differential treatment; among commercially insured women, black women with newly diagnosed ER⁺ tumors were less likely than white women to receive estrogen blocking therapies and were twice as likely to die of their disease [42]. While reasons for black–white patient care disparities are not often documented, biological factors such as comorbidity and social justice factors such as poverty and medical mistrust can affect physicians' care recommendations and patients' decisions and reaction to treatment [5].

Social disadvantage is associated with poor health outcomes & more aggressive cancers

Social health determinants are important factors in the distribution of illness, the progression of disease, and access to and success of treatment. In the USA, racial segregation, poverty and other social disadvantages are responsible for as many deaths as health behaviors and pathophysiological causes [43]. There is growing evidence that more aggressive forms of breast cancer are associated with social disadvantage [2,3], and that socioeconomic status and race act together to increase disparities in breast cancer mortality rates [44,45]. Causal pathways linking social deprivation directly to more aggressive forms of cancer remain poorly understood, but may involve such diverse factors as exposure to environmental toxins, physical and social environments that predispose individuals to obesity, chronic stress and generalized vulnerability to disease. Obesity in particular has been linked to a higher likelihood of ER⁺ tumors and increased tumor growth and metastasis [46,47]. The emerging field of epigenetics provides evidence that both social deprivation and changes in gene expression affect resistance to disease and risk of cancer [48,49].

Failure to validate GEP in diverse groups could result in inappropriate treatment & poor health outcomes for underserved populations

Our examination of the evidence base shows that few of the studies assessing GEP and clinical outcomes reported race/ethnicity data or stratified analyses by ER status. It is unknown if recurrence scores and classifications would vary across diverse populations of women who are ER⁺ (for whom most tests were designed), and, more generally, equally predict recurrence in diverse populations of women who are heterogeneous with regard to tumor biology. GEP focuses on tumor genetics; it is unclear if or how host characteristics, including race, affect tumor profiles or the prognostic value of GEP in diverse populations. Moreover, in addition to biological and social factors that may affect the utility of GEP, systems-level factors may also be relevant. For example, because of hospital protocols for processing breast tissue, options for many patients in the USA are limited to Oncotype DX and other tests that use paraffin-embedded tissue only. Although GEP-based tests inform treatment decisions, we are not suggesting differential treatment by race. Rather we are endorsing equal access to personalized medicine diagnostics and the information this provides.

We must also consider access to care in the larger sense. As society makes technological advances, it is important to ensure that all segments of the population enjoy equal access to health-improving technologies. Although by some accounts the overall quality of care in the

USA is generally improving, healthcare disparities have not on the whole improved; racial and ethnic minorities still receive markedly poorer-quality care and less access to care than whites, and low-income groups fare even worse when compared with those with high incomes [104]. Area-level characteristics such as sociodemographics and access to cancer specialists may also contribute to black–white patient disparities in treatment utilization and cancer-related mortality [50].

Socially and economically disadvantaged patients may lack the resources that would allow them to take advantage of health-promoting social and technological advances that can improve overall population health while leaving them behind [51]. Patients also need meaningful access to optimal treatment, which can minimize morbidity and promote recovery [104]. Prognostic tests that have been tested in one segment of the population but that are used to make treatment decisions for all could lead to over- or under-treatment for some patients. For example, because of the limited options for treating ER[−] cancer, under-treatment by chemotherapy could have more serious consequences for black women, who are more likely than other women to have that form of the disease.

Beyond targeting genomics in personalized medicine

Although personalized medicine is meant in part to provide individualized, genetically informed treatment to each patient regardless of phenotype or racial identity, lived experience affects both gene expression [48] and overall health outcomes [52]. GEP takes into account tumor genetics, but other ‘race-based’ factors – including racism, discrimination, social disadvantage and the stress that these engender – may be just as important in determining disease risk factors, prognosis and response to treatment. We encourage the personalized medicine community to recognize that social health determinants can shape both gene-expression patterns and risk factors. We agree with others whose work suggests that to increase our understanding of patterns of disease and develop appropriate interventions, we must study genetic, social and environmental health determinants [2,3,30,47,53–55].

Conclusion & future perspective

We fear that the growing racial disparities in breast cancer outcomes that began in the 1980s could continue or accelerate if new technologies fail to provide equal benefit across racial and ethnic groups. Although two large ongoing trials of GEP (Trial Assigning Individualized Options for Treatment Rx [TAILORx] [105] and Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid Chemotherapy [MINDACT] [106]) include women with ER⁺ disease, the proportion of nonwhite women in these trials is currently unknown. We question whether the use of GEP in breast cancer diagnostics and treatment has the potential to increase breast cancer health disparities by improving outcomes for the population as a whole while leaving static or worsening breast cancer morbidity and mortality rates for black women and other groups that may differ from the ‘average patient’.

Most factors in breast cancer disparities are almost certainly biological and social. However, some aspects of the disparities problem could be addressed through operational changes. For example, increasing the ability of pathologists to collect and analyze fresh-frozen tissue samples, as required by MammaPrint, could potentially allow for GEP analysis of more ER[−] tumors. Although this measure alone may not impact disparities, it would allow more options for women with ER[−] tumors and the clinicians who care for them. Other factors may call for completely different and as yet undiscovered scientific approaches. Still others may require major shifts in social and health system policies that ensure that all populations

benefit from the scientific advances that can improve overall health, disease prevention and screening, and access to effective and appropriate treatment.

However, without development and validation studies that recruit and analyze underserved and minority populations, we do not have the information needed to avoid GEP-related increases in black–white patient disparities in breast cancer outcomes. We suggest that further studies on breast cancer and GEP-based tests should aim to enroll diverse populations, including African–American women and other groups of particular interest by conducting studies in locations where these groups represent a substantial percentage of the population, and by developing creative and culturally sensitive recruitment protocols; apply oversampling and other study designs that can provide sufficient data for drawing statistically sound conclusions about the use of GEP and outcomes in diverse populations; include multidimensional study measures such as self-reported race, genetic factors, social disadvantage and hormone receptor status subtypes (i.e., HER positive, HER2 positive and triple negative); and illuminate the relative contribution of each of these factors.

The focus of this article has been on GEP in breast cancer but the issues we raise are relevant throughout the field of personalized medicine. For example, the difficulties of developing tests to predict cancer, as well as the general importance of validating new technologies on appropriate samples were well described by Buchen in a feature article in *Nature* [56]. The author praised the research design that led to the development of Oncotype DX, but stressed that the test's clinical utility is still under study, with results expected only in 2014. An editorial in *JAMA* expressed concerns that the findings of much biomarker research are not widely applicable, in part because researchers do not select appropriate study groups [57]. In the same issue, Ioannidis and Panagiotou [58] found that the findings of highly-cited but small initial studies often overstated the predictive ability of many biomarkers, potentially leading to widespread use of ineffective technology while increasing the perceived value and actual costs of the tests. The authors cautioned that this could waste precious healthcare resources by sharply raising costs without providing commensurate benefit, and suggested that interpretation of the literature be accompanied by a healthy dose of skepticism. A recent piece in this journal encouraged payers and healthcare decision-makers to examine the utility of a wide range of molecular tests and their ability to improve health outcomes in diverse clinical populations [59]. If as in other industries [60], small studies funded by the sponsors of emerging technologies produce findings favorable to the sponsor's products, policy-makers should routinely provide public funding for larger studies that can produce or validate results that can then be used with confidence by payers and other healthcare decision-makers. Moreover, given the complexity of genomic research, both private- and public-sector scientists could increase confidence in their findings by providing others with access to their data and enabling them to replicate their work. While support for data sharing of publicly-funded research is common, the Cochrane Collaboration recently issued a statement calling for governments to require that investigators share their data and protocols from clinical trials regardless of funding source, or to establish a central, accessible repository for such data [107].

Before we invest scarce healthcare resources in broad applications of new technologies we need strong evidence of their utility in the general population and in population subgroups, particularly those that experience health disparities. Health research, ideally, informs policy and practice. Minorities, women, older adults, low-income and other marginalized populations have historically been under-represented in health research, raising questions regarding the effectiveness of interventions for these groups. Evidence-based medicine has the potential for greatly improving population health. To fulfil this promise and extend the benefits to the largest number of people we need to have a representative and well-validated evidence base. By adequately enrolling and retaining patients from populations that

experience health disparities, collecting relevant measures such as race/ethnicity, and analyzing subgroup outcomes in studies of GEP and other emerging personalized medicine technologies we can leverage the value of innovations and potentially reduce the cancer burden across diverse populations. We should not squander that opportunity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Kathryn Phillips and Lisa Bero for their substantial intellectual contributions and for commenting on the early drafts of our article; Lisa Hirsch for editing and proofreading; and Cathy Samayoa for research assistance. The authors convey additional thanks to the TRANSPERS Measurement in Diverse Populations Core research team for motivating this study and to the TRANSPERS Training Core for catalyzing the completion of the manuscript through its works in progress meetings.

Bibliography

Papers of special note have been highlighted as:

▪ of interest

▪▪ of considerable interest

1. Smigal C, Jemal A, Ward E, et al. Trends in breast cancer by race and ethnicity: update 2006. *CA Cancer J Clin.* 2006; 56(3):168–183. [PubMed: 16737949]
2. Dunn BK, Agurs-Collins T, Browne D, Lubet R, Johnson KA. Health disparities in breast cancer: biology meets socioeconomic status. *Breast Cancer Res Treat.* 2010; 121(2):281–292. [PubMed: 20437200]
3. Vona-Davis L, Rose DP. The influence of socioeconomic disparities on breast cancer tumor biology and prognosis: a review. *J Womens Health (Larchmt).* 2009; 18(6):883–893. [PubMed: 19514831]
4. Dignam JJ. The ongoing search for the sources of the breast cancer survival disparity. *J Clin Oncol.* 2006; 24(9):1326–1328. [PubMed: 16549827]
- 5▪. Gerend MA, Pai M. Social determinants of Black–white disparities in breast cancer mortality: a review. *Cancer Epidemiol Biomarkers Prev.* 2008; 17(11):2913–2923. Guided by the social determinants of health disparities model and identified barriers, particularly those that are modifiable, that could be the focus of future efforts to reduce disparities in breast cancer mortality. [PubMed: 18990731]
6. Newman LA, Griffith KA, Jatoi I, Simon MS, Crowe JP, Colditz GA. Meta-analysis of survival in African American and white American patients with breast cancer: ethnicity compared with socioeconomic status. *J Clin Oncol.* 2006; 24(9):1342–1349. [PubMed: 16549828]
7. Dignam JJ. Differences in breast cancer prognosis among African–American and Caucasian women. *CA Cancer J Clin.* 2000; 50(1):50–64. [PubMed: 10735015]
- 8▪. Tehranifar P, Neugut AI, Phelan JC, et al. Medical advances and racial/ethnic disparities in cancer survival. *Cancer Epidemiol Biomarkers Prev.* 2009; 18(10):2701–2708. Compared racial/ethnic survival differences in cancers that were categorized by their overall 5-year survival rates into levels of amenability to medical intervention. As amenability increased, black–white patient mortality differences widened. Similar results were found for most, but not all minority populations. [PubMed: 19789367]
9. National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011; 365(5):395–409. [PubMed: 21714641]
10. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA.* 2001; 98(19):10869–10874. [PubMed: 11553815]

11. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci USA*. 2003; 100(14):8418–8423. [PubMed: 12829800]
12. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000; 406(6797):747–752. [PubMed: 10963602]
13. Sotiriou C, Neo SY, McShane LM, et al. Breast cancer classification and prognosis based on gene expression profiles from a population-based study. *Proc Natl Acad Sci USA*. 2003; 100(18): 10393–10398. Describes the background, biology and development of gene-expression signatures in breast cancer. Discusses the clinical utility of gene-expression profiling tests and ongoing validation trials of this technology. [PubMed: 12917485]
14. Marchionni L, Wilson RF, Wolff AC, et al. Systematic review: gene expression profiling assays in early-stage breast cancer. *Ann Intern Med*. 2008; 148(5):358–369. [PubMed: 18252678]
15. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. *N Engl J Med*. 2009; 360(8): 790–800. [PubMed: 19228622]
16. Wang Y, Klijn JG, Zhang Y, et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. *Lancet*. 2005; 365(9460):671–679. [PubMed: 15721472]
17. Liu R, Wang X, Chen GY, et al. The prognostic role of a gene signature from tumorigenic breast-cancer cells. *N Engl J Med*. 2007; 356(3):217–226. Examined a 186-gene ‘invasiveness’ signature, and found that it was associated with survival in breast cancer as well as in medulloblastoma, lung cancer and prostate cancer. [PubMed: 17229949]
18. Carlson R, Brown E, Burstein H, et al. NCCN Task Force Report: adjuvant therapy for breast cancer. *J Natl Compr Canc Netw*. 2006; 4(Suppl 1):S1–S26.
19. Harbeck N, Jakesz R, St Gallen. Breast Cancer Treatment Consensus Report. *Breast Care*. 2007; 2(3):130–134.
20. Asad J, Jacobson AF, Estabrook A, et al. Does oncotype DX recurrence score affect the management of patients with early-stage breast cancer? *Am J Surg*. 2008; 196(4):527–529. [PubMed: 18809056]
21. Toi M, Iwata H, Yamanaka T, et al. Clinical significance of the 21-gene signature (Oncotype DX) in hormone receptor-positive early stage primary breast cancer in the Japanese population. *Cancer*. 2010; 116(13):3112–3118. [PubMed: 20564629]
22. Chang JC, Makris A, Gutierrez MC, et al. Gene expression patterns in formalin-fixed, paraffin embedded core biopsies predict docetaxel chemosensitivity in breast cancer patients. *Breast Cancer Res Treat*. 2007; 108(2):233–240. [PubMed: 17468949]
23. Jerevall PL, Brommesson S, Strand C, et al. Exploring the two-gene ratio in breast cancer – independent roles for HOXB13 and IL17BR in prediction of clinical outcome. *Breast Cancer Res Treat*. 2007; 107(2):225–234. [PubMed: 17453342]
24. Ma X-J, Wang Z, Ryan PD, et al. A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. *Cancer Cell*. 2004; 5(6):607–616. [PubMed: 15193263]
25. Desmedt C, Haibe-Kains B, Wirapati P, et al. Biological processes associated with breast cancer clinical outcome depend on the molecular subtypes. *Clin Cancer Res*. 2008; 14(16):5158–5165. [PubMed: 18698033]
26. Summers C, Saltzstein SL, Blair SL, Tsukamoto TT, Sadler GR. Racial/ethnic differences in early detection of breast cancer: a study of 250,985 cases from the California Cancer Registry. *J Women’s Health*. 2010; 19(2):203–207.
27. Swan J, Breen N, Graubard BI, et al. Data and trends in cancer screening in the United States: results from the 2005 National Health Interview Survey. *Cancer*. 2010; 116(20):4872–4881. [PubMed: 20597133]
28. Jones BA, Kasl SV, Curnen MG, Owens PH, Dubrow R. Can mammography screening explain the race difference in stage at diagnosis of breast cancer? *Cancer*. 1995; 75(8):2103–2113. [PubMed: 7697601]
29. Hunter CP, Redmond CK, Chen VW, et al. Breast cancer: factors associated with stage at diagnosis in black and white women. Black/White Cancer Survival Study Group. *J Natl Cancer Inst*. 1993; 85(14):1129–1137. [PubMed: 8320742]

30. Polite B, Olopade OI. Breast cancer and race: a rising tide does not lift all boats equally. *Persp Biol Med*. 2005; 48(1):166–175.
31. Huo D, Ikpat F, Khramtsov A, et al. Population differences in breast cancer: survey in indigenous African women reveals over-representation of triple-negative breast cancer. *J Clin Oncol*. 2009; 27(27):4515–4521. [PubMed: 19704069]
32. Lund MJ, Butler EN, Bumpers HL, et al. High prevalence of triple-negative tumors in an urban cancer center. *Cancer*. 2008; 113(3):608–615. [PubMed: 18484596]
33. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. 2006; 295(21):2492–2502. [PubMed: 16757721]
34. Morris GJ, Naidu S, Topham AK, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database. *Cancer*. 2007; 110(4):876–884. [PubMed: 17620276]
35. Bowen RL, Duffy SW, Ryan DA, Hart IR, Jones JL. Early onset of breast cancer in a group of British black women. *Br J Cancer*. 2008; 98(2):277–281. [PubMed: 18182985]
36. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA*. 2009; 302(15):1685–1692. [PubMed: 19843904]
37. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype. 2007; 109:1721–1728.
38. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res*. 2007; 13(15):4429–4434. [PubMed: 17671126]
39. Dawson SJ, Provenzano E, Caldas C. Triple negative breast cancers: clinical and prognostic implications. *Eur J Cancer*. 2009; 45(Suppl 1):27–40. [PubMed: 19775602]
40. Menashe I, Anderson WF, Jatoi I, Rosenberg PS. Underlying causes of the black-white racial disparity in breast cancer mortality: a population-based analysis. *J Natl Cancer Inst*. 2009; 101(14):993–1000. Used data from the NCI's Surveillance, Epidemiology and End Results program to follow over 244,000 US women diagnosed with breast cancer. The authors concluded that black women had a higher risk of death of breast cancer, particularly in the first few years after diagnosis.
41. Lund MJ, Mosunjac M, Davis KM, et al. 21-gene recurrence scores: Racial differences in testing, scores, treatment, and outcome. *Cancer*. 2011 (Epub ahead of print). 10.1002/cncr.26180
42. Short LJ, Fisher MD, Wahl PM, et al. Disparities in medical care among commercially insured patients with newly diagnosed breast cancer. *Cancer*. 2010; 116(1):193–202. [PubMed: 19877115]
43. Galea S, Tracy M, Hoggatt KJ, Dimaggio C, Karpati A. Estimated deaths attributable to social factors in the United States. *Am J Public Health*. 2011; 101(8):1456–1465. [PubMed: 21680937]
44. Yu X. Socioeconomic disparities in breast cancer survival: relation to stage at diagnosis, treatment and race. *BMC Cancer*. 2009; 9(1):364. [PubMed: 19828016]
45. Niu X, Pawlish K, Roche L. Cancer survival disparities by race/ethnicity and socioeconomic status in New Jersey. *J Health Care Poor Underserved*. 2010; 21:144–160. [PubMed: 20173261]
46. Rose DP, Vona-Davis L. Influence of obesity on breast cancer receptor status and prognosis. *Expert Rev Anticancer Ther*. 2009; 9(8):1091–1101. [PubMed: 19671029]
47. Kwan ML, Kushi LH, Weltzien E, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res*. 2009; 11(3):R31. [PubMed: 19463150]
48. Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci USA*. 2004; 101(49):17312–17315. [PubMed: 15574496]
49. Ma H, Zhou Z, Wei S, et al. Shortened telomere length is associated with increased risk of cancer: a meta-analysis. *PLoS ONE*. 2011; 6(6):e20466. [PubMed: 21695195]
50. Haas JS, Brawarsky P, Iyer A, Fitzmaurice GM, Neville BA, Earle C. Association of area sociodemographic characteristics and capacity for treatment with disparities in colorectal cancer care and mortality. *Cancer*. 2011; 117(18):4267–4276. [PubMed: 21413000]
51. Link BG, Northridge ME, Phelan JC, Ganz ML. Social epidemiology and the fundamental cause concept: on the structuring of effective cancer screens by socioeconomic status. *Milbank Q*.

1998; 76(3):375–402. Seminal work linking social disadvantages that function as the ‘fundamental cause’ of health disparities to lowered ability to adopt nonroutine health-protective technology. The authors examined social distribution of cancer screenings, and found evidential support that ‘innovations beneficial to health are carried out within the context of inequalities that shape the distribution of the health benefit, thereby affecting patterns of mortality’. [PubMed: 9738168]

52. Fackenthal JD, Olopade OI. Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. *Nat Rev Cancer*. 2007; 7(12):937–948. [PubMed: 18034184]
53. Via M, Gignoux CR, Roth LA, et al. History shaped the geographic distribution of genomic admixture on the island of Puerto Rico. *PLoS ONE*. 2011; 6(1):e16513. [PubMed: 21304981]
54. Ziv E, Shepherd J, Smith-Bindman R, Kerlikowske K. Mammographic breast density and family history of breast cancer. *J Natl Cancer Instit*. 2003; 95(7):556–558.
55. Olopade OI, Grushko TA, Nanda R, Huo D. Advances in breast cancer: pathways to personalized medicine. *Clin Cancer Res*. 2008; 14(24):7988–7999. [PubMed: 19088015]
56. Buchen L. Missing the mark: why is it so hard to find a test to predict cancer? *Nature*. 2011; 471:428–432. [PubMed: 21430749]
57. Bossuyt PM. The thin line between hope and hype in biomarker research. *JAMA*. 2011; 305(21):2229–2230. [PubMed: 21632488]
58. Ioannidis JP, Panagiotou OA. Comparison of effect sizes associated with biomarkers reported in highly cited individual articles and in subsequent meta-analyses. *JAMA*. 2011; 305(21):2200–2210. [PubMed: 21632484]
59. Quinn B. Personalized diagnostics: the struggle for position. *Per Med*. 2010; 7(3):263–273.
60. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ*. 2003; 326(7400):1167–1170. [PubMed: 12775614]
61. Habel LA, Shak S, Jacobs MK, et al. A population based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. *Breast Cancer Res*. 2006; 8(3):R25. [PubMed: 16737553]
62. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006; 24(23):3726–3734. [PubMed: 16720680]
63. Mina L, Soule SE, Badve S, et al. Predicting response to primary chemotherapy. Gene expression profiling of paraffin-embedded core biopsy tissue. *Breast Cancer Res Treat*. 2006; 103(2):197–208. [PubMed: 17039265]
64. Esteva FJ, Sahin AA, Cristofanilli M, et al. Prognostic role of a multigene reverse transcriptase PCR assay in patients with node-negative breast cancer not receiving adjuvant systemic therapy. *Clin Cancer Res*. 2005; 11(9):3315–3319. [PubMed: 15867229]
65. Cobleigh MA, Tabesh B, Bitterman P, et al. Tumor gene expression and prognosis in breast cancer patients with 10 or more positive lymph nodes. *Clin Cancer Res*. 2005; 11(24 Pt 1):8623–8631. [PubMed: 16361546]
66. Gianni L, Zambetti M, Clark K, et al. Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer. *J Clin Oncol*. 2005; 23(29):7265–7277. [PubMed: 16145055]
67. Cronin M, Pho M, Dutta D, et al. Measurement of gene expression in archival paraffin-embedded tissues. Development and performance of a 92-gene reverse transcriptase-polymerase chain reaction assay. *Am J Pathol*. 2004; 164(1):35–42. [PubMed: 14695316]
68. Paik, S.; Shak, S.; Tang, G. Risk classification of breast cancer patients by the recurrence score assay. Comparison to guidelines based on patient age, tumor size, and tumor grade; Presented at Annual San Antonio Breast Cancer Symposium; San Antonio, TX, USA. 8–11 December 2004; (Abstract 104)
69. Jansen MP, Sieuwerts AM, Look MP, et al. HOXB13-to-IL17BR expression ratio is related with tumor aggressiveness and response to tamoxifen of recurrent breast cancer. a retrospective study. *J Clin Oncol*. 2007; 25(6):662–668. [PubMed: 17308270]

70. Goetz MP, Suman VJ, Ingle JN, et al. A two-gene expression ratio of homeobox 13 and interleukin-17B receptor for prediction of recurrence and survival in women receiving adjuvant tamoxifen. *Clin Cancer Res*. 2006; 12(7 Pt 1):2080–2087. [PubMed: 16609019]
71. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med*. 2006; 355(6):560–569. [PubMed: 16899776]
72. Reid JF, Lusa L, De Cecco L, et al. Limits of predictive models using microarray data for breast cancer clinical treatment outcome. *J Natl Cancer Inst*. 2005; 97(12):927–930. [PubMed: 15956654]
73. Buyse M, Loi S, van't Veer L, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst*. 2006; 98(17):1183–1192. [PubMed: 16954471]
74. Glas AM, Floore A, Delahaye LJ, et al. Converting a breast cancer microarray signature into a highthroughput diagnostic test. *BMC Genomics*. 2006; 7:278. [PubMed: 17074082]
75. Espinosa E, Vara JA, Redondo A, et al. Breast cancer prognosis determined by gene expression profiling. A quantitative reverse transcriptase polymerase chain reaction study. *J Clin Oncol*. 2005; 23(29):7278–7285. [PubMed: 16129846]
76. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med*. 2002; 347(25):1999–2009. [PubMed: 12490681]
77. van't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature*. 2002; 415(6871):530–536. [PubMed: 11823860]

Websites

101. Agency for Healthcare Research and Quality, US Department of Health and Human Services. Impact of gene expression profiling tests on breast cancer outcomes. www.ahrq.gov/downloads/pub/evidence/pdf/brcancergene/brcangene.pdf Full evidence report sponsored by the US Center for Disease Control as a technology assessment. Provides a thorough and detailed assessment of three gene-expression profiling tests and concludes that Oncotype® DX is furthest along the validation pathway, followed by MammaPrint®, and that the H/I ratio test requires further validation. The report also concluded that, for all three tests, the relationship of predicted to observed risk in different populations still needs further study
102. Central Intelligence Agency. The World Factbook. Ethnic Groups; www.cia.gov/library/publications/the-world-factbook/fields/2075.html
103. US Census Bureau. Black Alone Population. www.census.gov/population/www/socdemo/race/ppl-ba10.html
104. Highlights from the National Healthcare Quality and Disparities Reports. www.ahrq.gov/qual/nhdr10/Key.htm Measures trends in effectiveness of care, patient safety, timeliness of care, patient centeredness and efficiency of care, and presents the latest available findings on quality of and access to healthcare
105. TAILORx. www.cancer.gov/clinicaltrials/search/view?cdrid=472066&version=healthprofessional
106. MINDACT. www.eortc.be/services/unit/mindact/MINDACT_websiteii.asp
107. Cochrane Collaboration. The Cochrane Collaboration supports free access to all data from all clinical trials. www.cochrane.org/about-us/our-policies/support-free-access-to-all-data-from-all-clinical-trials
108. National Cancer Institute. The SEER Cancer Statistics Review. 1975–2007. http://seer.cancer.gov/csr/1975_2007/browse_csr.php?section=4&page=sect_04_zfig.09.html

Executive summary

Black–white patient disparities in breast cancer

- Although they are less likely to be diagnosed with breast cancer, black women are more likely to die of breast cancer. This disparity relates to differences in tumor biology as well as differences in sociomedical variables.

Gene-expression profiling of breast tumors

- Gene-expression profiling (GEP) technology is rapidly growing in its uptake and clinical utility, particularly for breast cancer.
- In the USA, a recent report compared three different GEP tests for breast tumors: Oncotype DX[®], MammaPrint[®] and the H/I ratio test.
- Two of the three tests studied in this report (Oncotype DX and the H/I ratio test) are only indicated for estrogen-receptor positive tumors.

Will black women be excluded from GEP technology?

- Black women are less likely than white women to meet the indications for Oncotype DX than white women because they have higher rates of estrogen-receptor negative disease than white women. Oncotype DX is the most commonly used GEP technology in the USA.
- Black women in the USA are often more economically and socially disadvantaged and have worse access to healthcare than white women. They may be excluded from GEP technology as a result.
- Existing research provides an inadequate basis for evaluating the utility of the tests for black women. Our review indicates that the evidence base for GEP technology and clinical outcomes for black women includes only 127 cases (2% of the available evidence) from peer-reviewed and published literature.

Will women with estrogen-receptor negative breast cancer be excluded from GEP technology?

- Women with estrogen-receptor negative breast cancer currently only qualify for MammaPrint GEP testing. MammaPrint requires fresh frozen tissue samples, and many US hospitals do not routinely sample and store tissue with this technique.
- In our study, the evidence base for GEP technology and clinical outcomes in women with estrogen receptor negative tumors includes 918 cases (14% of available evidence) from peer-reviewed and published literature. Most research findings on GEP apply to estrogen-receptor positive patients.

Future perspective

- Without a representative and well-validated evidence base, GEP technology could potentially exacerbate growing black–white patient disparities in breast cancer outcomes.
- Researchers should adequately enroll clinically relevant populations in studies of GEP-based tests and include study measures such as self-reported race, genetic factors, social disadvantage and hormone receptor status subtypes.
- Policy-makers should explore options for social and health system policies that ensure that all populations have meaningful access to scientific advances that

can improve disease prevention, screening, treatment and increase overall health.

Figure 1. Evidence of increasing black–white patient disparity in breast cancer mortality, from the Surveillance, Epidemiology and End Results Program, USA NIH
 Rates are age-adjusted to the US standard population (19 age groups – census pages 25–1103). Regression lines are calculated using the Joinpoint Regression Program Version 3.4.3, April 2010, NCI.
 Data taken from [108].

Table 1
Gene-expression profiling validity studies on breast cancer outcomes and racial/ethnic diversity.

First author (year)	Geographic location	Sample size	ER negative, n (%)	Race reported (yes/no)	Racial/ethnic composition, n (%)	Ref.
<i>Oncotype® DX</i>						
Toi <i>et al.</i> (2010) [‡]	Japan	200	0	Yes	Asian 200 (100)	[21]
Asad <i>et al.</i> (2008) [‡]	USA	85	0	No	n/a	[20]
Chang <i>et al.</i> (2007)	USA, UK	72	21 (29.2)	Yes	White 37 (51.4) [‡] Hispanic 11 (15.3) Black 19 (26.4) Asian 4 (5.6) Unknown 1 (1.4)	[22]
Habel <i>et al.</i> (2006)	USA	790	108 (13.7)	Yes	White 629 (79.6) [‡] Hispanic 20 (2.5) Black 67 (8.5) Asian 74 (9.4)	[61]
Paik <i>et al.</i> (2006)	USA, Canada	651	0	No	n/a	[62]
Mina <i>et al.</i> (2006)	USA	45	16 (35.6)	No	n/a	[63]
Esteve <i>et al.</i> (2005)	USA	149	46 (30.9)	Yes	White 126 (84.6) [‡] Hispanic 8 (5.4) Black 10 (6.7) Asian 5 (3.4)	[64]
Cobleigh <i>et al.</i> (2005)	USA	78	Unknown	No	n/a	[65]
Gianni <i>et al.</i> (2005)	Italy USA	89 82	31 (34.8) 48 (58.5)	No No	n/a n/a	[66]
Cronin <i>et al.</i> (2004)	USA	62	Unknown	No	n/a	[67]
Paik <i>et al.</i> (2004)	USA, Canada	668	0	Yes	White 615 (92.1) [‡] Black 31 (4.6) Other 22 (3.3)	[68]
Oncotype DX totals		2971	270(9.5)		White 1407 (74.9) [‡] Hispanic 39 (2.1) Black 127 (6.8)	

First author (year)	Geographic location	Sample size	ER negative, n (%)	Race reported (yes/no)	Racial/ethnic composition, n (%)	Ref.
<i>HITM Ratio Signature & Breast Cancer Profiling test</i>						
Jansen <i>et al.</i> (2007)	The Netherlands	1252	0	No	n/a	[69]
Jerevall <i>et al.</i> (2007)	Sweden	357	99 (27.7)	No	n/a	[23]
Goetz <i>et al.</i> (2006)	USA	206	0	Yes	White 190 (92.2) [‡]	[70]
Ma <i>et al.</i> (2006)	USA	852	214 (25.1)	No	n/a	[24]
Fan <i>et al.</i> (2006)	The Netherlands	295 [§]	69 (23.4)	No	n/a	[71]
Reid <i>et al.</i> (2005)	Italy	58	0	No	n/a	[72]
H/I ratio test totals		3,020	382 (12.7)		White 190 (92.2) [‡]	
<i>MammaPrint[®]</i>						
Buyse <i>et al.</i> (2006)	France, England, Sweden	307	90 (29.3)	No	n/a	[73]
Fan <i>et al.</i> (2006) [¶]	The Netherlands	295 [§]	69 (23.4)	No	n/a	[71]
Glas <i>et al.</i> (2006)	The Netherlands	145 [#]	Unknown	No	n/a	[74]
Espinosa <i>et al.</i> (2005)	Spain	96	Unknown	No	n/a	[75]
van de Vijver <i>et al.</i> (2002)	The Netherlands	295	69 (23.4)	No	n/a	[76]
van't Veer <i>et al.</i> (2002)	The Netherlands	98	38 (38.8)	No	n/a	[77]
MammaPrint totals		796	266 (38.0)			
Grand totals		6787	918 (13.5)		White 1597 (77.2) [‡] Hispanic 39 (1.9) Black 127 (6.1) As 283 (13.7) Unknown 1 (<0.0) Other 22 (1.1)	

Data for all studies except Toi et al. (2010) [21] and Asad et al. (2008) [20] abstracted from the 2008 Evaluation of Genomic Applications in Practice and Prevention Program (EGAPP) Working Group report, 'Impact of gene-expression profiling tests on Breast Cancer Outcomes' [101].

[†] Studies not included in the original EGAPP report.

[‡] Non-Hispanic white patient.

[§] Same sample used in van de Vijver (2002) [76] (not contributing to the total n).

[#] Combined two subsamples from van de Vijver (2002) [76] and van't Veer (2002) [77] (not contributing to the total n).

[¶] Fan et al. (2006) [71], which appears twice, is counted as one study.