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UNMET NEEDS IN CLINICAL RESEARCH IN BREAST CANCER: Where do we need to go?

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Abstract

This CCR Focus highlights areas in breast cancer research with the greatest potential for clinical and therapeutic application. The six articles in the issue address the state of the science in a broad range of areas with a focus on “hot” though sometimes controversial topics, unanswered questions, and unmet need. From mutational signatures, the cancer genomic revolution, and new inroads in immunotherapy for breast cancer, to unique concerns of vulnerable populations as well as national and global health disparities, these works represent much of the promise of breast cancer research as well as the challenges in the coming years. Each review focuses not only on recent discoveries, but also putting the topic in context including limitations to overcome. This overview is designed to further contextualize the highlighted issues within the broader research landscape. We also present new information from a poll of ALLIANCE for Clinical Trials in Oncology Breast Committee members regarding the most needed and viable potential future NCI-supported clinical trials in breast cancer. The great challenge is to translate the potential benefits of greater scientific knowledge reflected in this Focus series into improvements in outcomes for individuals and populations with breast cancer. A unifying theme across the six articles contained in this CCR Focus is the increasingly recognized value and necessity of collaboration across disciplines from bench to bedside to populations. Only continued and iteratively amplified scientific, clinical and governmental commitment to creating, testing, and implementing new knowledge will reduce the global morbidity and mortality of breast cancer.

INTRODUCTION

Advances in early detection, prevention, risk stratification, and therapeutic strategies as well as supportive care for patients with breast cancer has resulted in important improvements in

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morbidity and mortality. However, there are several areas where advances have not been fully actualized and substantial challenges remain. The challenges range from the need for a deeper understanding of cancer biology, inter- and intra-individual cancer heterogeneity, and inter-individual host biologic heterogeneity, to the challenges of conducting rigorous practice-changing prospective clinical trials tailored to biologically relevant subsets of the disease, and the need for governmental level prioritization and rational implementation of proven screening and therapeutic strategies to populations both in the U.S. and abroad (Figure 1). In this CCR Focus, we highlight select areas in breast cancer research, ranging from base pairs to population health and dissemination of life-saving interventions, that have emerged in recent years as having great promise but also have gaps in necessary knowledge to apply clinically. We also discuss recent efforts of the Breast Committee of the ALLIANCE for Clinical Trials in Oncology of the NCTN to identify highest priority research areas for future practice-changing cooperative group clinical trials.

OVERVIEW OF THIS CCR FOCUS

The genomics revolution has transformed the landscape of clinical research in cancer. Increased understanding of the biology of cancer, driver mutations as potential targets, and the mechanisms of sensitivity and resistance of breast cancer to conventional and newer targeted therapies has led to an explosion of studies seeking to translate laboratory findings to the clinic and address clinical challenges in the lab. In this CCR Focus issue, Nik-Zainal and Morganella begin at the base pair level and review recent work elucidating the potential for mutational scars to reflect a cancer's pathogenesis, and also how this may translate into future therapeutic strategies.(1) They summarize the exciting though controversial area of mutational signatures in breast cancer based on their prior provocative work in this area.(2–5) The focus on the history of the concept, work done to date, potential clinical application, and future promise tells a nice story. It should be noted that although data are intriguing, the extent to which this approach will help make sense of the genomic complexity of breast cancer remains uncertain. Specifically, whether mutational signatures represent the *causative mechanism* influenced by intensity and duration of exposure to specific mutational processes is unknown. And further, whether these will provide an actionable catalogue of mutations at the nucleotide level that portend outcome and targetability is intriguing but unclear.

Among the great success stories in translational 'omics has been the impact of transcriptomic studies on our understanding of breast cancer biology. From the first description of the molecular portraits of breast cancer (6) that identified the now conventional biologic categories of "Luminal A", "Luminal B", "HER2-Enriched", and "Basal-like", to the elucidation that the Basal-like subtype is in fact a different disease entity from other breast cancer subtypes (7), we have an increasingly sophisticated view of the intrinsic subtypes within breast cancer. This has led to the development of multiple commercial and research RNA-based assays for predicting risk of recurrence and need for chemotherapy in hormone receptor-positive, HER2-negative early breast cancer, with two large prospective trials already demonstrating clinical utility of these assays in therapeutic decision-making. (8, 9) Current initiatives include efforts to use gene expression patterns of tumor and immune signatures to prognosticate and tailor treatment in HER2-positive (10–12) and triple negative (13, 14) cancers. The landscape of translational transcriptomics was

recently reviewed in a CCR Anniversary commentary. (15) In this CCR Focus, Yates and Desmedt describe the current state of the science of DNA-based approaches and the challenges of the genomics revolution in how mutational and copy number aberrations relate to personalized medicine and breast cancer treatment. They highlight five major issues hampering our ability to harness the cancer genome to improve patient outcomes and elucidate not only the gaps, but potential steps to move forward.(16) In our view, the greatest obstacles for this work leading to improvements for patients with breast cancer include: a) the limited proportion of breast tumors found to have "actionable" mutations as currently defined, b) the need for integrative DNA- and RNA-based approaches, c) mixed results in terms of patient outcomes of molecularly-targeted approaches to date, d) within-patient tumor heterogeneity and challenges of obtaining optimal tumor testing at any given time, and e) the infrastructure and resource constraints that hamper our ability to implement such testing broadly to reach all patients. (17, 18)

Recent years have seen great successes in the long-studied but previously unyielding field of immunotherapy in cancer. We now know that tumor infiltrating lymphocytes and activated immune signatures in the tumor microenvironment independently affect prognosis and possibly response to therapy in triple negative and HER2-positive disease.(19) With a plethora of research and clinical trials of immune checkpoint and other immunotherapies emerging in breast cancer, we are at the beginning of a potential entirely new paradigm for breast cancer therapy; however at present the optimal means of leveraging the immune system across the biologic diversity of breast cancer remains elusive. Vonderheide and colleagues' comprehensive review of current research and challenges of immunotherapy suggests how this may ultimately play into the treatment of patients with breast cancer.(20) Agents that have already yielded clinical improvements in the treatment of other, previously difficult-to-treat cancers are being tested in patients with breast cancer with hundreds of clinical trials ongoing or in development (www.clinicaltrials.org), and some promising results in early phase studies. (21–24) Tumor infiltrating lymphocytes and immune activation signatures are independently prognostic in triple negative and HER2-positive breast cancer supporting a potential role of immune-based strategies. (25) However, the burden of non-synonomous mutations is lower in breast cancer than in classically immunologically tractable cancers such as melanoma, and breaking immune tolerance appears to be more difficult. It is also likely that different molecular or phenotypic subtypes of breast cancer will derive varying benefit from the addition of immunotherapy to the armamentarium of therapy for patients with breast cancer and antigen unmasking, for example by DNA-damaging chemotherapy or radiation therapy, may have a potential role particularly in the breast tumors with lower mutational burdens (e.g luminal tumors). (26)

Clearly the interplay of tumor genomics and microenvironmental influences, complicates translation from bench to bedside when considering either efficacy in clinical trials or implementation in practice. In the era of the genomics revolution and development of multiple targeted therapies, this has become particularly complex (e.g. understanding and using tumor genomics to guide care) and resource intensive. Insights from social science suggest that these factors are likely to lead to an increase in disparities in access and outcomes in various populations both in the US and worldwide. The articles by Freedman and Partridge and Reeder-Hayes and Anderson focus on micro- and macro- population

issues that present challenges to actualizing and translating progress made beyond the traditional clinical trials setting.(27, 28) Of note, while these articles do not focus on biologic heterogeneity across populations, we do believe that this variable will continue to emerge as an important factor in breast cancer outcomes, and thus have included an arrow from population implementation and dissemination to biologic discovery and translational research in Figure 1. (29)

Freedman and Partridge discuss the recent advances in our understanding of issues facing special populations with breast cancer including age-related disparities, i.e. very young and very old patients; and concerns and management strategies when treating patients who are overweight or obese. Similarly, challenges exist for the minority of breast cancer patients who are men and have historically been treated extrapolating from datasets and clinical studies comprised predominantly of women.(27) Each of these special populations face challenges which this article highlights along with the exciting ongoing work in these vulnerable groups of patients to elucidate and overcome them to optimize care and outcomes. Notably, the review does not cover all vulnerable subpopulations with long-standing or emerging recognition of unique medical and/or psychosocial concerns such as patients with substantial comorbidities, and LBGT individuals.

Reeder-Hayes and Anderson bring together two distinct areas of disparities: breast cancer disparities in the U.S., and global breast cancer disparities.(28) Their combined analysis conveys the importance of understanding the root causes of health outcomes disparities; understanding those root causes is key to overcoming them. In 1995, Link and Phelan published on the theory of fundamental causes to explain why the association between socioeconomic status (SES) and mortality persists despite radical improvement in our understanding of disease and explanatory risk factors. (30) Their proposal - that the enduring association is because SES embodies an array of resources such as money, knowledge, prestige, power, and beneficial social connections that affect health outcomes - appears to hold regardless of country as well. Thus, when considering disparities in outcomes across populations, while the issues within the U.S. are different from those elsewhere on the globe, especially from a legal, governmental, and cultural standpoint, the universal theme of resources and how they are utilized and prioritized in any system, emerges as of paramount importance regardless of setting.

The challenges and opportunities of the six topics covered in this Focus series highlight the importance of collaboration and stakeholder involvement in the design of effective and successful clinical research addressing gaps in knowledge. Clinical trials include novel therapeutic trials focused on improving efficacy, trials focused on comparative effectiveness of specific strategies, and risk stratification trials for tailored approaches. While all are worthy, some are suitable for large-scale practice-changing trials performed in the national cooperative group setting, and some may address research and knowledge gap questions raised in this Focus series.

In our roles as co-chairs of the ALLIANCE for Clinical Trials in Oncology Breast Committee of the National Cancer Institute’s National Clinical Trials Network (NCTN), we are mindful of the role of national cooperative groups in addressing clinically relevant

research. In November 2016, we surveyed the ALLIANCE Breast Committee membership, comprised of academic and community oncologists engaged in large scale clinical trials, regarding what they perceived to be key clinical questions as well as the feasibility of recruiting to trials addressing those questions. Fifty-seven responding committee members chose from among 11 broad research areas identified by ALLIANCE leadership. The findings of this survey have been analyzed descriptively and refined in order to identify the top ranking concepts (See Table 1). The gaps in knowledge identified by this survey by practicing clinicians illustrates the changing culture of breast cancer research, in which the multidisciplinary team including scientists, clinical and public health researchers, patient advocates, and clinicians are anxious to formally test biologic and health services advances. For example, the top-ranked priority was identifying patients at risk of late relapse using genomics, and testing novel endocrine therapy to prevent such late relapse in hormone receptor-positive early breast cancer. Transcriptomic assays show promise in this realm (31, 32), which may be further aided by identifying relevant driver mutations in the primary as described in Focus article #2(16), although it should be noted that mature datasets with a high proportion of banked primary tissue that are large enough to address late relapse are rare, complicating design of trials to address this question. Next in priority was immunotherapy, the subject of Focus #3.(20) Most participating sites in the ALLIANCE have competing studies of these drugs, whose role is of high clinical and pharmaceutical interest. The NCTN is developing its first trial in this sphere, a large adjuvant immune checkpoint inhibitor trial in high-risk triple negative residual disease. Optimizing and developing intermediate biomarkers for outcome using pre-operative therapy for ER-positive breast cancer was also considered high priority. A currently accruing ALLIANCE study, ALTERNATE (NCT01953588), will test the clinical utility of an immunohistochemistry-based prognostic score, the PEPI score (33). At this time, testing for clinical utility of mutational analyses of the type described in Focus articles #1 and #2 (1, 16) is premature, even though several other highly rated “unmet needs” involved genomic applications that may be informed by these sorts of mutational analyses, including optimizing treatment choices for hormone receptor-positive breast cancer, decision-making regarding need for radiation therapy, and identifying targetable aberrations in triple negative disease. As noted, RNA-based assays have begun to be studied in several of these realms, including guiding metastatic treatment in hormone receptor-positive disease (34), determining need for dual HER2-targeting and less aggressive regimens (10, 11), and tailoring radiation therapy to those at higher risk of locoregional failure. (35) Integrating and targeting DNA aberrations into such clinical problem-solving requires additional study but is clearly an opportunity. Several of the highest priority research gaps centered on improving delivery of care, including interventional studies to improve adherence to medication. This ranked highly in part because it is common, negatively impacts outcome, and in particular affects vulnerable breast cancer patients such as African-American (36–38) and women at both ends of the age spectrum. (36, 39–42). Comparative effectiveness, namely the comparison of existing approaches to determine greatest benefits and harms, was also felt to be an understudied topic, and one ripe for the cooperative group setting since these are difficult to fund studies outside of the federal sphere, and often have substantial public policy implications. Specific issues related to causes of nonadherence and the need for rigorous determination of best

therapies within and across populations are topics discussed in the FOCUS articles by Freedman and Reeder-Hayes.(27, 28)

Several unifying themes emerge from both the challenging topics of the Focus articles and the survey of research gaps in the clinic. First, advances in breast cancer outcomes cannot be achieved without attention to the heterogeneity of the disease. The molecular vernacular derived from RNA-based assays identifying Luminal A, Luminal B, basal-like and HER2-Enriched have informed how we perceive breast cancer, and, increasingly, how we treat breast cancer.(6) Integrating the transcriptome, the genome (potentially including mutational signatures) and the tumor microenvironment with relevant clinical variables will be crucial to improving treatment options. Second, that comparative effectiveness research should be incorporated broadly into clinical research. It is as important to understand how well our treatment strategies work across populations and in various settings as it is to develop the strategy in the first place. Finally, the fundamental cause theory of disparities suggests that as we develop more effective treatment approaches and strategies, under-resourced individual patients with breast cancer, and diverse groups both in the US and abroad will be increasingly left behind. Unless we are proactive in identifying barriers to access and care, disparities will increase as progress is made.

SUMMARY

There is much work to be done and many challenges exist in our mission to end the suffering that breast cancer brings. Nevertheless, optimism prevails given the exciting work that has stemmed from global research collaborations and communications, recognition of the need for international clinical and translational trials, as well as an increasing attention to reducing disparities within and across populations. Knowledge gaps in each of these is narrowing, but great opportunities are highlighted in the topics covered by this CCR Focus series.

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References

1. Nik-Zainal S, Morganella S. Mutational Signatures in Breast Cancer: The Problem at the DNA Level. Clin Can Res. 23 xx–xx.
2. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature. 2013; 500(7463):415–21. [PubMed: 23945592]
3. Alexandrov LB, Jones PH, Wedge DC, Sale JE, Campbell PJ, Nik-Zainal S, et al. Clock-like mutational processes in human somatic cells. Nature genetics. 2015; 47(12):1402–7. [PubMed: 26551669]

4. Nik-Zainal S, Davies H, Staaf J, Ramakrishna M, Glodzik D, Zou X, et al. Landscape of somatic mutations in 560 breast cancer whole-genome sequences. Nature. 2016; 534(7605):47–54. [PubMed: 27135926]
5. Glodzik D, Morganella S, Davies H, Simpson PT, Li Y, Zou X, et al. A somatic-mutational process recurrently duplicates germline susceptibility loci and tissue-specific super-enhancers in breast cancers. Nature genetics. 2017; 49(3):341–8. [PubMed: 28112740]
6. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000; 406(6797):747–52. [PubMed: 10963602]
7. Hoadley KA, Yau C, Wolf DM, Cherniack AD, Tamborero D, Ng S, et al. Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. Cell. 2014; 158(4):929–44. [PubMed: 25109877]
8. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. The New England journal of medicine. 2015; 373(21):2005–14. [PubMed: 26412349]
9. Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. The New England journal of medicine. 2016; 375(8):717–29. [PubMed: 27557300]
10. Carey LA, Berry DA, Cirrincione CT, Barry WT, Pitcher BN, Harris LN, et al. Molecular Heterogeneity and Response to Neoadjuvant Human Epidermal Growth Factor Receptor 2 Targeting in CALGB 40601, a Randomized Phase III Trial of Paclitaxel Plus Trastuzumab With or Without Lapatinib. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2016; 34(6):542–9. [PubMed: 26527775]
11. Fumagalli D, Venet D, Ignatiadis M, Azim HA Jr, Maetens M, Rothe F, et al. RNA Sequencing to Predict Response to Neoadjuvant Anti-HER2 Therapy: A Secondary Analysis of the NeoALTTO Randomized Clinical Trial. JAMA oncology. 2016
12. Llombart-Cussac A, Cortes J, Pare L, Galvan P, Bermejo B, Martinez N, et al. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. The Lancet Oncology. 2017; 18(4):545–54. [PubMed: 28238593]
13. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. The Journal of clinical investigation. 2011; 121(7):2750–67. [PubMed: 21633166]
14. Burstein MD, Tsimelzon A, Poage GM, Covington KR, Contreras A, Fuqua SA, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. Clinical cancer research: an official journal of the American Association for Cancer Research. 2015; 21(7):1688–98. [PubMed: 25208879]
15. Gingras I, Desmedt C, Ignatiadis M, Sotiriou C. CCR 20th Anniversary Commentary: Gene-Expression Signature in Breast Cancer--Where Did It Start and Where Are We Now? Clinical cancer research: an official journal of the American Association for Cancer Research. 2015; 21(21):4743–6. [PubMed: 26527804]
16. Yates LR, Desmedt C. Translational Genomics: Practical Applications of the Genomic Revolution in Breast Cancer. Clin Can Res. 2017; 23 xx–xx.
17. Massard C, Michiels S, Ferte C, Le Deley MC, Lacroix L, Hollebecque A, et al. High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial. Cancer discovery. 2017
18. Le Tourneau C, Delord JP, Goncalves A, Gavoille C, Dubot C, Isambert N, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. The Lancet Oncology. 2015; 16(13):1324–34. [PubMed: 26342236]
19. Savas P, Salgado R, Denkert C, Sotiriou C, Darcy PK, Smyth MJ, et al. Clinical relevance of host immunity in breast cancer: from TILs to the clinic. Nature reviews Clinical oncology. 2016; 13(4): 228–41.

20. Vonderheide RH, Domchek SM, Clark AS. Immunotherapy for breast cancer: what are we missing? Clin Can Res. 2017; 23 xx–xx.
21. Cancer discovery. 2017. Atezolizumab Extends Survival for Breast Cancer.
22. Dirix, LY., Takacs, I., Nikolinakos, P., Jerusalem, G., Arkenau, H-T., Hamilton, EP., et al. AACR-SABCS. San Antonio, TX: AACR; 2015. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A phase Ib JAVELIN solid tumor trial.
23. Gentzler R, Hall R, Kunk PR, Gaughan E, Dillon P, Slingluff CL Jr, et al. Beyond melanoma: inhibiting the PD-1/PD-L1 pathway in solid tumors. Immunotherapy. 2016; 8(5):583–600. [PubMed: 27140411]
24. Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R, et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2016; 34(21):2460–7. [PubMed: 27138582]
25. Luen SJ, Savas P, Fox SB, Salgado R, Loi S. Tumour-infiltrating lymphocytes and the emerging role of immunotherapy in breast cancer. Pathology. 2017; 49(2):141–55. [PubMed: 28049579]
26. Criscitiello C, Curigliano G. Immunotherapy of Breast Cancer. Progress in tumor research. 2015; 42:30–43. [PubMed: 26377084]
27. Freedman RA, Partridge AH. Emerging Data and Current Challenges for Young, Old, Obese, or Male Patients with Breast Cancer. Clin Can Res. 2017; 23 xx–xx.
28. Reeder-Hayes KE, Anderson BO. Breast Cancer Disparities at home and abroad: A Review of the Challenges and Opportunities for System-Level Change. Clin Can Res. 2017; 23 xx–xx.
29. Daly B, Olopade OI. A perfect storm: How tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change. CA: a cancer journal for clinicians. 2015; 65(3):221–38. [PubMed: 25960198]
30. Phelan JC, Link BG. Controlling Disease and Creating Disparities: A Fundamental Cause Perspective. The journals of gerontology Series B, Psychological sciences and social sciences. 2005; 60(Special_Issue_2):S27–S33.
31. Sestak I, Cuzick J, Dowsett M, Lopez-Knowles E, Filipits M, Dubsky P, et al. Prediction of late distant recurrence after 5 years of endocrine treatment: a combined analysis of patients from the Austrian breast and colorectal cancer study group 8 and arimidex, tamoxifen alone or in combination randomized trials using the PAM50 risk of recurrence score. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2015; 33(8):916–22. [PubMed: 25332252]
32. Buus R, Sestak I, Kronenwett R, Denkert C, Dubsky P, Krappmann K, et al. Comparison of EndoPredict and EPclin With Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence After Endocrine Therapy. Journal of the National Cancer Institute. 2016; 108(11)
33. Ellis MJ, Tao Y, Luo J, A'Hern R, Evans DB, Bhatnagar AS, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. Journal of the National Cancer Institute. 2008; 100(19):1380–8. [PubMed: 18812550]
34. King TA, Lyman JP, Gonen M, Voci A, De Brot M, Boafo C, et al. Prognostic Impact of 21-Gene Recurrence Score in Patients With Stage IV Breast Cancer: TBCRC 013. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2016; 34(20):2359–65. [PubMed: 27001590]
35. Solin LJ, Gray R, Baehner FL, Butler SM, Hughes LL, Yoshizawa C, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. Journal of the National Cancer Institute. 2013; 105(10):701–10. [PubMed: 23641039]
36. Daly B, Olopade OI, Hou N, Yao K, Winchester DJ, Huo D. Evaluation of the Quality of Adjuvant Endocrine Therapy Delivery for Breast Cancer Care in the United States. JAMA oncology. 2017
37. Roberts MC, Wheeler SB, Reeder-Hayes K. Racial/Ethnic and socioeconomic disparities in endocrine therapy adherence in breast cancer: a systematic review. American journal of public health. 2015; 105(Suppl 3):e4–e15.
38. Reeder-Hayes KE, Meyer AM, Dusetzina SB, Liu H, Wheeler SB. Racial disparities in initiation of adjuvant endocrine therapy of early breast cancer. Breast cancer research and treatment. 2014; 145(3):743–51. [PubMed: 24789443]

39. Hershman DL, Kushi LH, Shao T, Buono D, Kershenbaum A, Tsai WY, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2010; 28(27):4120–8. [PubMed: 20585090]

40. Llarena NC, Estevez SL, Tucker SL, Jeruss JS. Impact of Fertility Concerns on Tamoxifen Initiation and Persistence. Journal of the National Cancer Institute. 2015; 107(10)

41. Neugut AI, Zhong X, Wright JD, Accordino M, Yang J, Hershman DL. Nonadherence to Medications for Chronic Conditions and Nonadherence to Adjuvant Hormonal Therapy in Women With Breast Cancer. JAMA oncology. 2016; 2(10):1326–32. [PubMed: 27281650]

42. Partridge AH, Wang PS, Winer EP, Avorn J. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2003; 21(4):602–6. [PubMed: 12586795]

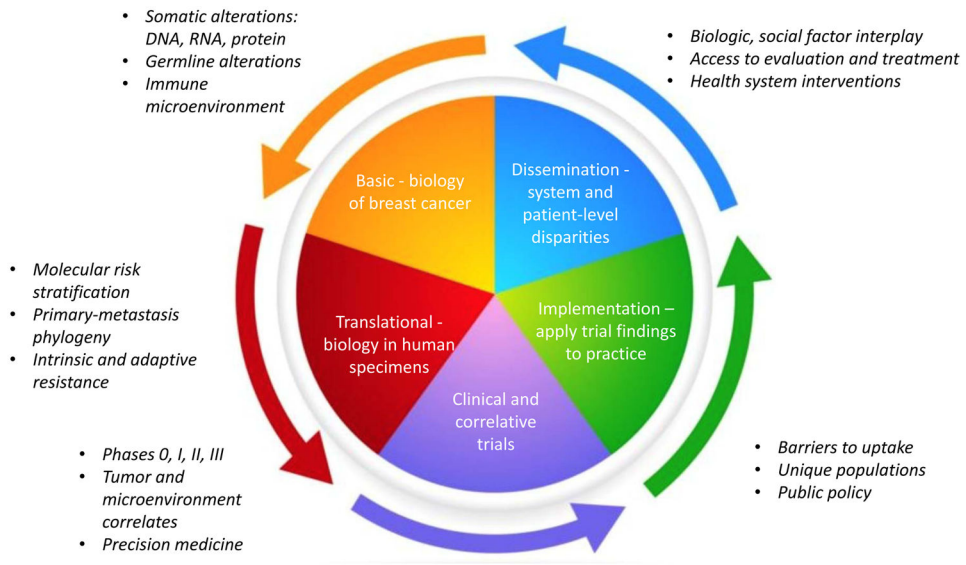

Figure 1.
Model of Bench to Bedside to Population

Table 1

ALLIANCE Breast Committee member ranking of concepts considering priority and ability to accrue

Rank	Concept	Goal	Status
1	Genomics of late relapse in HR+ disease	Tailor endocrine therapy	Poorly understood, difficult to study prospectively
2	Immunotherapy in triple negative disease	Improved outcomes	Multiple ongoing trials
3	Neoadjuvant therapy in ER+ disease	Testing novel approaches, reducing chemotherapy use	Ongoing trials
4	Genomics to optimize treatment for metastatic HR+HER2−	Clarify optimal use of chemotherapy vs endocrine therapy	Poorly understood, difficult to study prospectively
5	Genomics to guide management of locoregional disease	Tailor surgical and radiation therapy	Ongoing trials
6	Tailoring therapy in HER2+ by clinical and molecular assays	Fewer drugs in lower risk disease; Omitting chemotherapy	Difficult trial design, some modest successes
7	Adherence intervention studies in HR+ disease	Improve outcomes through adherence to existing drugs	Multifactorial root causes complicate design
8	Incorporating comparative effectiveness research into clinical trials	Broader-based understanding not only of what works but in whom	Prospective studies and correlative work ongoing
9	Molecularly tailored therapy in triple negative disease	Tailoring cytotoxics, Incorporating novel therapy	Multiple novel therapy and diagnostics trials ongoing
10	Immunooncology correlates into clinical trials	Impact of mutation load, neoantigen unmasking on TILS/immune cells?	Multiple efforts to clarify/validate immune correlates