Overcoming Barriers in Ductal Carcinoma In Situ Management: From Overtreatment to Optimal Treatment

Jean L. Wright, MD[1]; Habib Rahbar, MD[2]; Samilia Obeng-Gyasi, MD[3]; Ruth Carlos, MD[4]; Judy Tjoe, MD[5]; and Antonio C. Wolff, MD[1]

Ductal carcinoma in situ (DCIS) is an intraepithelial breast neoplasm accounting for up to 25% of US breast cancers.[1,2] Treatment for this nonlethal diagnosis remains controversial and ranges widely from no surgery to total mastectomy, often with radiation (RT) and/or endocrine therapy (ET). Recent SEER data show that only 2% of US women receive no surgical treatment, whereas 28% undergo mastectomy, often with sentinel node biopsy.[3] Although mastectomy rates for DCIS have decreased over the past 40 years, use of RT after wide local excision (WLE) increased by nearly 20%[3] along with a modest increase in ET use.[4] Consequently, DCIS has become a major driver of breast cancer overdiagnosis and overtreatment.[5] A 2009 National Institutes of Health (NIH) State of Science Conference recommended concerted efforts to decrease indolent DCIS diagnoses, unnecessary surgeries, and excessive adjuvant treatment.[6] Yet, today, despite promising imaging and molecular assays to help optimize DCIS management, these patterns remain largely unchanged or perhaps more prevalent. In this commentary, we describe ongoing controversies in DCIS diagnosis and management that could influence future clinical trial design.

The natural history of DCIS is poorly understood, and the clinical benefit from increased diagnosis and resulting interventions is difficult to quantify. DCIS does not metastasize, but some will become invasive breast cancer (IBC).[7] However, IBC frequency has not decreased proportionately with greater DCIS incidence.[8] Therefore, clinicians and patients will benefit from improved clinical decision tools that account for the impact of observation versus intervention on outcomes other than survival, including local control and quality of life (QOL).

In an effort to decrease unnecessary DCIS detection in lower-risk women, strategies that shift screening from population-based[9] or age-based[10] to risk-based approaches may be beneficial. For example, the Wisdom Trial assigns women to screening regimens on the basis of individual risk (risk prediction model plus polygenic risk score).[11] However, available population-based risk models lack precision for individual clinical decision making, and could put some patients at risk of developing later-stage invasive cancers.[12]

Advanced imaging may help further refine both individual risk estimates and discrimination between higher- and lower-risk DCIS. Mammographic density is associated with breast cancer risk,[13] and greater normal tissue background parenchymal enhancement levels on magnetic resonance imaging (MRI) may improve individual risk assessments over density alone.[14-16] Risk assessment tools on the basis of deep learning mammography[17] and MRI[18] models may outperform established models like Tyrer-Cuzick.

MRI has greater sensitivity for high- versus low-grade DCIS, is nearly 100% sensitive for invasive carcinoma, and is not affected by density. Thus, MRI could decrease overdiagnosis of low-grade DCIS if used to determine which types of calcifications warrant biopsy[19] or for screening women with denser breasts if used alone.[20] But, MRI is not without barriers like cost, false-positives, claustrophobia, and exposure to IV contrast. Still, initial studies evaluating economic feasibility are promising,[21,22] and abbreviated breast MRI sequences[23] could reduce imaging and interpretation times and costs without jeopardizing performance.[24]

There are also questions about the need to immediately surgically excise DCIS. The Comparing an Operation to Monitoring, with or without Endocrine Therapy for low-risk DCIS (COMET),[25] LOw RISk DCIS (LORIS),[26] and Management of LOw-Risk DCIS (LORD)[27] trials compare surgery to active surveillance (±ET) to identify women who could forego or delay upfront surgery. Unfortunately, both LORD and LORIS trials closed prematurely without meeting accrual goals because of recruitment challenges. Also, a recent single-institution study suggested that application of the COMET Trial's eligibility criteria to a retrospective cohort resulted in an IBC underdiagnosis of 12% over 10 years.[28] These challenges highlight a critical need to develop more accurate imaging and tissue-based measures to identify low-risk DCIS if active surveillance is to become a viable approach.

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

Accepted on October 25, 2021 and published at ascopubs.org/journal/jco on November 23, 2021: DOI https://doi.org/10.1200/JCO.21.01674

Once intervention is planned, surgery remains the upfront standard. However, re-excisions are needed in 30%-40% of cases, and it is unclear whether MRI can reduce re-excisions without increasing mastectomy rates.[3,29] The high re-excision rates observed with DCIS are because of poor delineation of noncalcified components of DCIS on mammography, lack of palpability, and guidelines from 2016 recommending ≥ 2-mm margins.[30] MRI may better delineate DCIS extent, with numerous studies showing that MRI size more closely matches pathology span than mammography.[31,32] Overall, MRI sensitivity to accurately determine disease extent approaches 90% versus 55% with mammography.[30,33]

Still, the potential for surgical outcome improvements with MRI remains unclear. A meta-analysis[34] and systematic review[35] found limited evidence that MRI reduced reoperation rate, although many of the included studies predated published guidelines to improve quality of imaging acquisition[36] and interpretation.[37] The single-arm ECOG-ACRIN E4112 DCIS trial showed that when MRI is performed in accordance with American College of Radiology accreditation requirements, rate of successful WLE is high (96%) while re-excision (22%) is low.[38] Recent retrospective observational studies showed that MRI decreased number of surgeries[39] and lowered positive margin rate without increasing mastectomies.[40] Finally, a small trial of MRI (IRCIS) showed a lower reoperation rate in the MRI arm in the per-protocol analysis (hazard ratio = 0.59; 95% CI, 0.35 to 1.0), although not in the intention-to-treat analysis (hazard ratio = 0.68; CI, 0.4 to 1.1).[41] Given conflicting data, uncertainty persists about whether MRI can optimize DCIS surgical management. This is likely not going to be resolved without larger definitive trials.[42] Additional technologies are in development to provide real-time assessment of margins using radiofrequency electrical fields[43,44] and advanced localization techniques,[45,46] but these have yet to be rigorously studied to determine impact on surgical outcomes.

Understanding which patients with DCIS require additional therapy after surgery is key to reduce overtreatment. RT is often offered after WLE to reduce risk of in-breast recurrence (IBR),[47,48] which varies substantially with clinicopathologic factors (CPF), including extent, grade, comedonecrosis, margin, age, family history, estrogen receptor status, and use of ET.[49,50] Nonetheless, nearly 75% of women receive RT[3,51,52] with no consensus about who can safely avoid it. The Radiation Therapy Oncology Group (RTOG) trial 9804 randomly assigned women with low-risk DCIS to WLE ± RT, and found IBR rates to be low overall, albeit higher in those who did not receive RT (15.1% *v* 7.1% at 15 years), and modestly continuing to increase with longer follow-up.[53-55] ECOG E5194 omitted RT in clinically low-risk DCIS, and reported a 14.4% 12-year IBR rate in non–high-grade lesions < 2.5 cm and 24.6% in high-grade lesions < 1 cm.[56] Clinical models incorporating CPF to guide DCIS treatment report a wide range of IBR risk depending on CPF, treatment, and length of follow-up.[49,50] In total, it remains challenging to individualize treatment decisions, and consequently, most patients receive RT.

Two tissue-based assays to assess DCIS IBR risk are commercially available in the United States. Oncotype DCIS Score (EXACT Sciences, Madison, WI) is a 12-gene molecular assay that estimates a 10-year IBR risk. The results were initially validated using banked tissue from E5194 (no RT) and found significantly lower 10-year IBR rates in the low-risk group (IBR 10.6%) versus the intermediate-risk (IBR 26.7%) and high-risk (IBR 25.9%) groups.[57] Further prognostic validation of this assay was done in the Ontario Registry[58] including impact of combined CPF and DCIS score,[59,60] and it was also used in the E4112 trial to guide RT use.[38] E4112 showed that use of DCIS score results in lower RT utilization compared with historical data. Half of the study participants had low DCIS scores, and more than 90% of them accepted a recommendation to forego RT.[38]

A second assay, DCISionRT (PreludeDx, Laguna Hills, CA), used a unique combination of CPF to assess risk of recurrence on a 0-10 scale. Scores ≥ 3 denote high-risk DCIS that corresponds to a 10-year IBR-invasive risk ≥ 10%. DCISionRT was initially studied in archived DCIS and found to distinguish women into a low-risk group (IBR 7%) and a high-risk group (IBR 23%). It also suggested a benefit from RT no > 1% in the low-risk group compared with 12% in the high-risk group[61,62] with similar findings in a separate registry data set, in which nearly half of the RTOG-eligible low-risk DCIS were reclassified as higher-risk.[63] This and other series suggest that the use of a risk score may affect RT recommendations beyond routinely available CPF, yet neither assay has been prospectively tested in randomized trials, which may explain their low penetration in routine care.[64]

The wide range of dose-fractionation and shorter treatment schedules available in DCIS further complicate studies assessing RT. In the setting of whole breast irradiation, moderately hypofractionated schedules of 15-20 treatments are now preferred over more protracted courses.[65] Partial breast irradiation is available to many patients with lower-risk DCIS,[66] and data are emerging on very short-course extreme hypofractionation to the whole breast.[67] As more convenient RT options become available, their perceived burden may be lower. Thus, RT approaches, dose and fractionation, and utilization will evolve over time, and this also requires further study.

ET is also commonly used either instead of or in addition to RT. About half of patients with estrogen receptor–positive DCIS receive ET, which is expected to halve the risk of a new breast cancer event in either breast.[4] Although an aromatase inhibitor may be more effective than tamoxifen,[68] low estrogen–related toxicities may affect adherence and reduce potential benefit. Thus, tamoxifen remains an option and there is interest in exploring lower doses.[69]

In this context of a wide array of adjuvant therapy options and variations, it is important not to lose sight that reductions in IBR are unlikely to impact survival in DCIS.[51] Therefore, patients at a higher risk of IBR could still reasonably forego RT and/or ET, and undergo salvage treatment at the time of recurrence. There is no uniformly acceptable threshold for what constitutes a low risk of IBR, and individual patient preferences will matter.

These observations point to other important gaps in knowledge, including the impact of patient experience and QOL metrics on individual decision making and their relationship to DCIS outcomes. Data on decision making and impact of management choices on QOL among patients with DCIS remain scant and are largely cross-sectional using surveys and retrospective events.[70,71] E4112 showed that patients' level of knowledge about DCIS and treatment options was associated with post-treatment physical and mental well-being,[72] and several studies highlight patients' desire for DCIS knowledge and decision support.[73-76] Therefore, validation and implementation studies evaluating tools to facilitate tailored decision making are another pressing need in DCIS management.

External factors are also important. Racial disparities in breast cancer diagnosis and outcomes are well established[77] and have been exacerbated by the COVID-19 pandemic.[78] Although incidence of DCIS has stabilized in the United States since 2000, rates have increased in Black women,[79] and breast cancer mortality after DCIS is higher among non-Hispanic Black women compared with non-Hispanic Whites.[51] Explanations for racial differences in clinical outcomes are most likely a complex interplay between treatment-related disparities and socioenvironmental exposures.[80,81] Future research should leverage concepts such as allostatic load—a composite measure of physiologic dysregulation secondary to adverse socially patterned exposures (eg, poverty[82])—to understand the implications of race and socioenvironmental factors on epidemiology,[83] treatment receipt, tolerability, and mortality, and identify targets for precision therapy, including biobehavioral intervention.[84]

In future studies, several barriers must also be addressed to allow translational studies to improve DCIS management. First is the need to bank fresh tissue and images across sites in prospective trials to identify novel molecular, pathology, and imaging markers. Follow-up beyond 10 years is needed to capture meaningful outcomes like long-term IBR. Studies must also account for heterogeneity in multimodality care that is driven by factors like region, ethnicity, age, and socioeconomic or insurance status,[85] which also affect clinical trial participation. Fortunately, success in recruitment to recent DCIS trials such as E4112 and RTOG 9804 indicates that funding agencies, investigators, and study participants will be interested in the next generation of trials.

In summary, the management of DCIS will evolve from overtreatment for the average patient to optimization for an individual once several issues have been addressed: Will fewer cases of DCIS diagnosis compromise benefits from earlier detection of IBC? Could some patients with DCIS avoid surgery? Will advances in imaging help optimize surgery and allow patients to undergo one single procedure, be it breast conservation or mastectomy? Will tumor profiling optimally identify patients who could avoid radiation? Will improved shared decision-making strategies result in greater care satisfaction? Finally, can we identify biologic changes induced by adverse social environments as targets to reduce health disparities in care on long-term DCIS treatment outcomes? Extensive work performed since the 2009 NIH State of Science Conference directive has provided the groundwork of knowledge and technology necessary to guide a new generation of studies to address these key questions and generate evidence that will meaningfully affect clinical outcomes for an individual patient.[86,87] The time to resolve these issues for a more informed future is now.

AFFILIATIONS

[1]Johns Hopkins University, Baltimore, MD
[2]University of Washington, Seattle, WA
[3]The Ohio State University, Columbus, OH
[4]University of Michigan, Ann Arbor, MI
[5]Novant Health, Greensboro, NC

CORRESPONDING AUTHOR

Jean L. Wright, MD, Johns Hopkins University, 401 N Broadway St, Baltimore, MD 21287-0019; e-mail: jeanwright@jhmi.edu.

EQUAL CONTRIBUTION

J.L.W. and H.R. are cofirst authors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.01674.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Cowell CF, Weigelt B, Sakr RA, et al: Progression from ductal carcinoma in situ to invasive breast cancer: Revisited. Mol Oncol 7:859-869, 2013
2. Chootipongchaivat S, van Ravesteyn NT, Li X, et al: Modeling the natural history of ductal carcinoma in situ based on population data. Breast Cancer Res 22:53, 2020
3. Worni M, Akushevich I, Greenup R, et al: Trends in treatment patterns and outcomes for ductal carcinoma in situ. J Natl Cancer Inst 107:djv263, 2015
4. Flanagan MR, Rendi MH, Gadi VK, et al: Adjuvant endocrine therapy in patients with ductal carcinoma in situ: A population-based retrospective analysis from 2005 to 2012 in the National Cancer Data Base. Ann Surg Oncol 22:3264-3272, 2015
5. Alvarado M, Ozanne E, Esserman L: Overdiagnosis and overtreatment of breast cancer. Am Soc Clin Oncol Ed Book 32:e40-e45, 2012
6. Allegra CJ, Aberle DR, Ganschow P, et al: NIH state-of-the-science conference statement: Diagnosis and management of ductal carcinoma in situ (DCIS). NIH Consens State Sci Statements 26:1-27, 2009
7. Schnitt SJ: Diagnosis of ductal carcinoma in situ in an era of de-escalation of therapy. Mod Pathol 34:1-7, 2021
8. Virnig BA, Tuttle TM, Shamliyan T, et al: Ductal carcinoma in situ of the breast: A systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst 102:170-178, 2010
9. Helvie MA, Bevers TB: Screening mammography for average-risk women: The controversy and NCCN's position. J Natl Compr Canc Netw 16:1398-1404, 2018
10. Oeffinger KC, Fontham ET, Etzioni R, et al: Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. JAMA 314:1599-1614, 2015
11. Esserman LJ, Study W, Athena I: The WISDOM study: Breaking the deadlock in the breast cancer screening debate. NPJ Breast Cancer 3:34, 2017
12. Kopans DB: The wisdom trial is based on faulty reasoning and has major design and execution problems. Breast Cancer Res Treat 185:549-556, 2021
13. Duffy SW, Morrish OWE, Allgood PC, et al: Mammographic density and breast cancer risk in breast screening assessment cases and women with a family history of breast cancer. Eur J Cancer 88:48-56, 2018
14. Liao GJ, Henze Bancroft LC, Strigel RM, et al: Background parenchymal enhancement on breast MRI: A comprehensive review. J Magn Reson Imaging 51: 43-61, 2020
15. Thompson CM, Mallawaarachchi I, Dwivedi DK, et al: The association of background parenchymal enhancement at breast MRI with breast cancer: A systematic review and meta-analysis. Radiology 292:552-561, 2019
16. Watt GP, Sung J, Morris EA, et al: Association of breast cancer with MRI background parenchymal enhancement: The IMAGINE case-control study. Breast Cancer Res 22:138, 2020
17. Yala A, Lehman C, Schuster T, et al: A deep learning mammography-based model for improved breast cancer risk prediction. Radiology 292:60-66, 2019
18. Portnoi T, Yala A, Schuster T, et al: Deep learning model to assess cancer risk on the basis of a breast MR image alone. AJR Am J Roentgenol 213:227-233, 2019
19. Baltzer PAT, Bennani-Baiti B, Stottinger A, et al: Is breast MRI a helpful additional diagnostic test in suspicious mammographic microcalcifications? Magn Reson Imaging 46:70-74, 2018
20. Comstock CE, Gatsonis C, Newstead GM, et al: Comparison of abbreviated breast MRI vs digital breast tomosynthesis for breast cancer detection among women with dense breasts undergoing screening. JAMA 323:746-756, 2020
21. Froelich MF, Kaiser CG: Cost-effectiveness of MR-mammography as a solitary imaging technique in women with dense breasts: An economic evaluation of the prospective TK-study. Eur Radiol 31:967-974, 2021
22. Mango VL, Goel A, Mema E, et al: Breast MRI screening for average-risk women: A Monte Carlo simulation cost-benefit analysis. J Magn Reson Imaging 49: e216-e221, 2019
23. Rahbar H, Lee JM, Lee CI: Optimal screening in breast cancer survivors with dense breasts on mammography. J Clin Oncol 38:3833-3840, 2020
24. Harvey SC, Di Carlo PA, Lee B, et al: An abbreviated protocol for high-risk screening breast MRI saves time and resources. J Am Coll Radiol 13:374-380, 2016
25. Hwang ES, Hyslop T, Lynch T, et al: The COMET (Comparison of Operative versus Monitoring and Endocrine Therapy) trial: A phase III randomised controlled clinical trial for low-risk ductal carcinoma in situ (DCIS). BMJ Open 9:e026797, 2019
26. Cancer Research UK: A trial comparing surgery with active monitoring for low risk DCIS (LORIS). https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-comparing-surgery-with-active-monitoring-for-low-risk-dcis-loris
27. The Netherlands Cancer Institute: Management of low-risk (grade I and II) DCIS (LORD). https://clinicaltrials.gov/ct2/show/NCT02492607
28. Oseni TO, Smith BL, Lehman CD, et al: Do eligibility criteria for ductal carcinoma in situ (DCIS) active surveillance trials identify patients at low risk for upgrade to invasive carcinoma? Ann Surg Oncol 27:4459-4465, 2020
29. Langhans L, Jensen MB, Talman MM, et al: Reoperation rates in ductal carcinoma in situ vs invasive breast cancer after wire-guided breast-conserving surgery. JAMA Surg 152:378-384, 2017
30. Menell JH, Morris EA, Dershaw DD, et al: Determination of the presence and extent of pure ductal carcinoma in situ by mammography and magnetic resonance imaging. Breast J 11:382-390, 2005
31. Bartram A, Gilbert F, Thompson A, et al: Breast MRI in DCIS size estimation, breast-conserving surgery and oncoplastic breast surgery. Cancer Treat Rev 94: 102158, 2021
32. Marcotte-Bloch C, Balu-Maestro C, Chamorey E, et al: MRI for the size assessment of pure ductal carcinoma in situ (DCIS): A prospective study of 33 patients. Eur J Radiol 77:462-467, 2011
33. Jansen SA, Newstead GM, Abe H, et al: Pure ductal carcinoma in situ: Kinetic and morphologic MR characteristics compared with mammographic appearance and nuclear grade. Radiology 245:684-691, 2007
34. Fancellu A, Turner RM, Dixon JM, et al: Meta-analysis of the effect of preoperative breast MRI on the surgical management of ductal carcinoma in situ. Br J Surg 102:883-893, 2015
35. Canelo-Aybar C, Taype-Rondan A, Zafra-Tanaka JH, et al: Preoperative breast magnetic resonance imaging in patients with ductal carcinoma in situ: A systematic review for the European Commission Initiative on Breast Cancer (ECIBC). Eur Radiol 31:5880-5893, 2021
36. Rahbar H, Partridge SC, DeMartini WB, et al: Clinical and technical considerations for high quality breast MRI at 3 Tesla. J Magn Reson Imaging 37:778-790, 2013
37. Mann RM, Cho N, Moy L: Breast MRI: State of the art. Radiology 292:520-536, 2019
38. Lehman CD, Gatsonis C, Romanoff J, et al: Association of magnetic resonance imaging and a 12-gene expression assay with breast ductal carcinoma in situ treatment. JAMA Oncol 5:1036-1042, 2019
39. Lam DL, Smith J, Partridge SC, et al: The impact of preoperative breast MRI on surgical management of women with newly diagnosed ductal carcinoma in situ. Acad Radiol 27:478-486, 2020

40. Yoon GY, Choi WJ, Kim HH, et al: Surgical outcomes for ductal carcinoma in situ: Impact of preoperative MRI. Radiology 295:296-303, 2020
41. Balleyguier C, Dunant A, Ceugnart L, et al: Preoperative breast magnetic resonance imaging in women with local ductal carcinoma in situ to optimize surgical outcomes: Results from the randomized phase III trial IRCIS. J Clin Oncol 37:885-892, 2019
42. Rahbar H, Tjoe JA: Breast MRI in the setting of DCIS: Quality trials are still needed to determine its value. Eur Radiol 31:5877-5879, 2021
43. Thill M, Dittmer C, Baumann K, et al: MarginProbe®—Final results of the German post-market study in breast conserving surgery of ductal carcinoma in situ. Breast 23:94-96, 2014
44. Thill M, Roder K, Diedrich K, et al: Intraoperative assessment of surgical margins during breast conserving surgery of ductal carcinoma in situ by use of radiofrequency spectroscopy. Breast 20:579-580, 2011
45. Janssen NNY, van la Parra RFD, Loo CE, et al: Breast conserving surgery for extensive DCIS using multiple radioactive seeds. Eur J Surg Oncol 44:67-73, 2018
46. Kapoor MM, Patel MM, Scoggins ME: The wire and beyond: Recent advances in breast imaging preoperative needle localization. Radiographics 39:1886-1906, 2019
47. Fisher B, Costantino J, Redmond C, et al: Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. N Engl J Med 328:1581-1586, 1993
48. Early Breast Cancer Trialists' Collaborative Group, Correa C, McGale P, et al: Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010:162-177, 2010
49. Rudloff U, Jacks LM, Goldberg JI, et al: Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. J Clin Oncol 28:3762-3769, 2010
50. Silverstein MJ: The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. Am J Surg 186:337-343, 2003
51. Narod SA, Iqbal J, Giannakeas V, et al: Breast cancer mortality after a diagnosis of ductal carcinoma in situ. JAMA Oncol 1:888-896, 2015
52. Sagara Y, Freedman RA, Wong SM, et al: Trends in adjuvant therapies after breast-conserving surgery for hormone receptor-positive ductal carcinoma in situ: Findings from the National Cancer Database, 2004-2013. Breast Cancer Res Treat 166:583-592, 2017
53. McCormick B, Winter K, Hudis C, et al: RTOG 9804: A prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J Clin Oncol 33:709-715, 2015
54. McCormick B. Randomized trial evaluating radiation following surgical excision for "good risk" DCIS: 12-year report from NRG/RTOG 9804. Presented at 2018 ASTRO Annual Meeting. , October 21, 2018 (abstr LBA1)
55. McCormick B, Winter KA, Woodward W, et al: Randomized phase III trial evaluating radiation following surgical excision for good-risk ductal carcinoma in situ: Long-term report from NRG Oncology/RTOG 9804. J Clin Oncol 39:3574-3582, 2021
56. Solin LJ, Gray R, Hughes LL, et al: Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. J Clin Oncol 33:3938-3944, 2015
57. Solin LJ, Gray R, Baehner FL, et al: A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst 105:701-710, 2013
58. Rakovitch E, Nofech-Mozes S, Hanna W, et al: A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. Breast Cancer Res Treat 152:389-398, 2015
59. Paszat L, Sutradhar R, Zhou L, et al: Including the ductal carcinoma-in-situ (DCIS) score in the development of a multivariable prediction model for recurrence after excision of DCIS. Clin Breast Cancer 19:35-46, 2019
60. Rakovitch E, Gray R, Baehner FL, et al: Refined estimates of local recurrence risks by DCIS score adjusting for clinicopathological features: A combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. Breast Cancer Res Treat 169:359-369, 2018
61. Bremer T, Whitworth PW, Patel R, et al: A biological signature for breast ductal carcinoma in situ to predict radiotherapy benefit and assess recurrence risk. Clin Cancer Res 24:5895-5901, 2018
62. Wärnberg F, Garmo H, Folkvaljon Y, et al: A validation of DCIS biological risk profile in a randomised study for radiation therapy with 20 year follow-up (SweDCIS). Cancer Res 78, 2018 (4 suppl; abstr GS5-08)
63. Weinmann S, Leo MC, Francisco M, et al: Validation of a ductal carcinoma in situ biomarker profile for risk of recurrence after breast-conserving surgery with and without radiotherapy. Clin Cancer Res 26:4054-4063, 2020
64. Piltin MA, Hoskin TL, Day CN, et al: Use of the twelve-gene recurrence score for ductal carcinoma in situ and its influence on receipt of adjuvant radiation and hormonal therapy. Ann Surg Oncol 28:4294-4303, 2021
65. Smith BD, Bellon JR, Blitzblau R, et al: Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol 8:145-152, 2018
66. Correa C, Harris EE, Leonardi MC, et al: Accelerated partial breast irradiation: Executive summary for the update of an ASTRO evidence-based consensus statement. Pract Radiat Oncol 7:73-79, 2017
67. Murray Brunt A, Haviland JS, Wheatley DA, et al: Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 395:1613-1626, 2020
68. Margolese RG, Cecchini RS, Julian TB, et al: Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): A randomised, double-blind, phase 3 clinical trial. Lancet 387:849-856, 2016
69. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al: Randomized placebo controlled trial of low-dose tamoxifen to prevent local and contralateral recurrence in breast intraepithelial neoplasia. J Clin Oncol 37:1629-1637, 2019
70. Bloom JR, Stewart SL, Napoles AM, et al: Quality of life of Latina and Euro-American women with ductal carcinoma in situ. Psychooncology 22:1008-1016, 2013
71. Janz NK, Mujahid MS, Hawley ST, et al: Racial/ethnic differences in quality of life after diagnosis of breast cancer. J Cancer Surviv 3:212-222, 2009
72. Carlos RC, Snyder BS, Lehman CD, et al: Decision quality and quality of life after treatment for DCIS: A trial of the ECOG-ACRIN cancer research group (E4112). High Impact Clinical Trials. RSNA, 2017. http://rsna2017.rsna.org/program/index.cfm
73. Shumway DA, McLeod CM, Morrow M, et al: Patient experiences and clinician views on the role of radiation therapy for ductal carcinoma in situ. Int J Radiat Oncol Biol Phys 100:1237-1245, 2018
74. Ozanne EM, Schneider KH, Soeteman D, et al: onlineDeCISion.org: a web-based decision aid for DCIS treatment. Breast Cancer Res Treat 154:181-190, 2015
75. Nyhof BB, Wright FC, Look Hong NJ, et al: Recommendations to improve patient-centred care for ductal carcinoma in situ: Qualitative focus groups with women. Health Expect 23:106-114, 2020
76. Mercieca-Bebber R, King MT, Boxer MM, et al: What quality-of-life issues do women with ductal carcinoma in situ (DCIS) consider important when making treatment decisions? Breast Cancer 24:720-729, 2017

77. Sparano JA, Brawley OW: Deconstructing racial and ethnic disparities in breast cancer. JAMA Oncol 7:355-356, 2021
78. Wang Q, Berger NA, Xu R: Analyses of risk, racial disparity, and outcomes among US patients with cancer and COVID-19 infection. JAMA Oncol 7:220-227, 2021
79. Ryser MD, Hendrix LH, Worni M, et al: Incidence of ductal carcinoma in situ in the United States, 2000-2014. Cancer Epidemiol Biomarkers Prev 28: 1316-1323, 2019
80. Zhang S, Liu Y, Yun S, et al: Impacts of neighborhood characteristics on treatment and outcomes in women with ductal carcinoma in situ of the breast. Cancer Epidemiol Biomarkers Prev 27:1298-1306, 2018
81. Bailes AA, Kuerer HM, Lari SA, et al: Impact of race and ethnicity on features and outcome of ductal carcinoma in situ of the breast. Cancer 119:150-157, 2013
82. McEwen BS: Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci 840:33-44, 1998
83. Xing CY, Doose M, Qin B, et al: Prediagnostic allostatic load as a predictor of poorly differentiated and larger sized breast cancers among Black women in the Women's circle of health follow-up study. Cancer Epidemiol Biomarkers Prev 29:216-224, 2020
84. Adams-Campbell LL, Taylor T, Hicks J, et al: The effect of a 6-month exercise intervention trial on allostatic load in Black women at increased risk for breast cancer: The FIERCE study. J Racial Ethn Health Disparities 10.1007/s40615-021-01145-x [epub ahead of print on September 27, 2021]
85. Ward EM, DeSantis CE, Lin CC, et al: Cancer statistics: Breast cancer in situ. CA Cancer J Clin 65:481-495, 2015
86. Ades F, Tryfonidis K, Zardavas D: The past and future of breast cancer treatment-from the papyrus to individualised treatment approaches. Ecancermedicalscience 11:746, 2017
87. Lukong KE: Understanding breast cancer—The long and winding road. BBA Clin 7:64-77, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Overcoming Barriers in Ductal Carcinoma In Situ Management: From Overtreatment to Optimal Treatment

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Jean L. Wright
Honoraria: American Society for Radiation Oncology
Research Funding: Oncospace
Patents, Royalties, Other Intellectual Property: Spouse receives royalties from UpToDate (I)
Expert Testimony: Marshall Dennehy

Habib Rahbar
Research Funding: GE Healthcare (Inst)
Other Relationship: Philips Healthcare (Inst)

Ruth Carlos
Travel, Accommodations, Expenses: GE Healthcare
Other Relationship: Journal of the American College of Radiology (Inst)
Uncompensated Relationships: GE Healthcare

Antonio C. Wolff
This author is an Associate Editor for *Journal of Clinical Oncology*. Journal policy recused the author from having any role in the peer review of this manuscript.
Consulting or Advisory Role: Ionis Pharmaceuticals
Patents, Royalties, Other Intellectual Property: A.W. has been named as inventor on one or more issued patents or pending patent applications relating to methylation in breast cancer, and has assigned his rights to JHU, and participates in a royalty sharing agreement with JHU
Open Payments Link: https://openpaymentsdata.cms.gov/physician/357301/summary

No other potential conflicts of interest were reported.