Effect of an Artificial Intelligence Clinical Decision Support System on Treatment Decisions for Complex Breast Cancer

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PURPOSE To examine the impact of a clinical decision support system (CDSS) on breast cancer treatment decisions and adherence to National Comprehensive Cancer Center (NCCN) guidelines.

PATIENTS AND METHODS A cross-sectional observational study was conducted involving 1,977 patients at high risk for recurrent or metastatic breast cancer from the Chinese Society of Clinical Oncology. Ten oncologists provided blinded treatment recommendations for an average of 198 patients before and after viewing therapeutic options offered by the CDSS. Univariable and bivariable analyses of treatment changes were performed, and multivariable logistic regressions were estimated to examine the effects of physician experience (years), patient age, and receptor subtype/TNM stage.

RESULTS Treatment decisions changed in 105 (5%) of 1,977 patients and were concentrated in those with hormone receptor (HR)-positive disease or stage IV disease in the first-line therapy setting (73% and 58%, respectively). Logistic regressions showed that decision changes were more likely in those with HR-positive cancer (odds ratio [OR], 1.58; $P < .05$) and less likely in those with stage IIA (OR, 0.29; $P < .05$) or IIIA cancer (OR, 0.08; $P < .01$). Reasons cited for changes included consideration of the CDSS therapeutic options (63% of patients), patient factors highlighted by the tool (23%), and the decision logic of the tool (13%). Patient age and oncologist experience were not associated with decision changes. Adherence to NCCN treatment guidelines increased slightly after using the CDSS (0.5%; $P = .003$).

CONCLUSION Use of an artificial intelligence-based CDSS had a significant impact on treatment decisions and NCCN guideline adherence in HR-positive breast cancers. Although cases of stage IV disease in the first-line therapy setting were also more likely to be changed, the effect was not statistically significant ($P = .22$). Additional research on decision impact, patient-physician communication, learning, and clinical outcomes is needed to establish the overall value of the technology.

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INTRODUCTION

Computer-based clinical decision support systems (CDSSs) can be valuable aids in the delivery of health care, particularly when decisions require processing rapidly changing or large volumes of information. These decision support tools apply a reasoning engine to a knowledge base and provide clinically relevant insights to appropriate users in the delivery of health care. The technology of these systems ranges from rules, logic, and decision trees to advanced mathematic modeling, natural language processing of unstructured text documents, and machine learning to provide expert interpretations or recommendations. CDSSs have a long history in biomedical informatics and have been developed for many applications, including generating alerts or reminders, delivering preventive services, aiding diagnosis, improving drug prescribing, offering

treatment options, and interpreting tests (eg, ECGs or electroencephalograms).¹⁻³

CDSSs require a strong foundation of evidence for adoption. This evidence should include proof of the quality and validity of the component technologies of the tool, how well the tool performs relative to the standard of care, what impact it has on decision-making processes of clinicians, and how clinical and economic outcomes are affected. We have undertaken a series of evaluations to address several of these questions in a population of patients with complex breast cancer ($N = 1,977$) involving 10 oncologists with varying levels of expertise and an artificial intelligence (AI)-based CDSS. We previously reported the treatment concordance of the CDSS tool and the oncologists in these 1,977 patients with complex breast cancer.⁴ An important and supplementary question is whether use of the CDSS affects

ASSOCIATED CONTENT

Appendix

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

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CONTEXT

Key Objective

To assess the impact of an artificial intelligence (AI)-based clinical decision support system (CDSS) on treatment recommendations for patients with complex breast cancer (N = 1,977) by 10 oncologists uninvolved with the patient cases (fellows, n = 3; attending physicians, n = 4; chief physicians, n = 3).

Knowledge Generated

Use of the AI-based CDSS supported changes in treatment recommendations in 5% (105 of 1,977) of patients at high risk for recurrent or metastatic breast cancer. Changes to initial recommendations were concentrated in those with hormone receptor-positive disease or stage IV disease in the first-line therapy setting, and reasons cited for change were predominantly strength of the evidence provided by the CDSS and, to a lesser extent, patient factors highlighted by the tool and the decision logic of the tool.

Relevance

Treatment of complex breast cancer poses challenges to clinicians as a result of gaps in biologic knowledge and rapid advances in research and information. AI-based CDSSs that can help address the information challenges have the potential to become valuable aids to oncologists.

decisions. This study examines whether oncologists uninvolved with the patient cases would change initial treatment recommendations after using the CDSS. The effects of physician and patient characteristics on decision changes are also estimated.

PATIENTS AND METHODS

Study Design and Patient Population

This study used a cross-sectional design and involved patients previously registered with the Chinese Society of Clinical Oncology to assess whether use of the Watson for Oncology (WfO) CDSS would influence treatment decisions in a group of oncologists. Treatment decisions were recorded from 10 volunteer oncologists with varying years of experience: three oncology fellows (< 3 years), four attending physicians (3-8 years), and three chief physicians (> 8 years). The study oncologists had no involvement in the diagnosis, treatment, or care of the patients at any point before, during, or after the study, and their treatment recommendations were used only to examine the effect of the AI-based CDSS on treatment selection.

The patients originated from five hospitals located in each of China's five regions. Each oncologist reviewed an average of 198 (range, 193-200) different patients with breast cancer independently, and the CDSS evaluated and provided treatment recommendations for all 1,977 patients. The study protocol was reviewed and approved by the institutional review boards of each hospital (ie, Tumor Hospital of Hebei, Jiangsu Province Hospital, Henan Cancer Hospital, 307th Hospital, and Affiliated Hospital of Qingdao University). Each hospital independently determined that the study did not require registration because it was solely an observational study of the effect of a CDSS on treatment recommendations by a group of clinicians

without any connection to the actual patients, treating physicians, care rendered, or clinical outcomes.

The population of patients with breast cancer was the same as that described and reported in an earlier publication on treatment concordance and National Comprehensive Cancer Network (NCCN) guideline adherence between the same group of oncologists and the same WfO CDSS (version 17.6).⁴ Patients age 18 to 65 years with ductal, lobular, metaplastic, or mixed histology tumors were selected from the breast cancer database of the Chinese Society of Clinical Oncology. Patients with adenocystic, tubular, or secretory tumors were excluded because the CDSS had not been trained to evaluate these types of tumors at the time of the study. Data secured included demographic, pathologic, surgical, medical, laboratory, and molecular data. *BRCA* and gene expression profiling data for the patients were unavailable for the study because of the absence of Chinese governmental standards for these tests at the time of this study. Patients with complex breast cancer were selected because of the higher degree of uncertainty regarding their optimal treatment. Patients with complex breast cancer were defined as: those at high risk of recurrence (ie, they met ≥ 1 of the following: age ≤ 35 years, tumor > 2 cm, axillary lymph node positive, human epidermal growth factor receptor 2 [HER2]/neu positive, and triple-negative tumor)⁵ and those with established metastatic disease requiring first- or second-line therapy.

WfO AI-Based CDSS

This CDSS is designed to offer therapeutic options to oncologists making treatment decisions for their patients. It is an AI-based program composed of a reasoning engine, a knowledge base, and data drawn from clinical records. The reasoning engine uses machine learning software technology that scores features of patient attributes that influence breast cancer treatment decisions (eg, organ

function laboratory values, tumor stage, hormone receptor [HR] status, and prior response to therapy), based on Memorial Sloan Kettering Cancer Center (MSKCC) breast cancer training cases. The resulting breast cancer module, approved by MSKCC collaborators, was made available for use in the CDSS. It is updated when new information becomes available that influences approaches to breast cancer management. The knowledge base contained in WfO provides a curated body of knowledge that includes documents from > 300 medical journals and textbooks. It also contains literature that has been hand selected by MSKCC experts as well as NCCN- and MSKCC-specific treatment guidelines. Data abstracted from clinical records comprise the third component of the system and include demographic, medical, surgical, laboratory, pathologic, genomic, and molecular attributes for each patient case. A description of how the CDSS works and how it was evaluated during development is available in the supplement to an earlier report by Somashekhar et al.⁶

Data Collection and Decision Impact Assessment

Patient cases were abstracted from the cancer database and assigned to oncologists in a systematic but nonrandom fashion. Rules for case assignment included: prohibiting assignment of patient cases to an oncologist from his or her hospital system, assigning only cases of stage I to III disease to surgical oncologists because they do not manage the treatment of metastatic breast cancers, allocating patient cases to oncologists upon enrollment, and seeking to provide medical oncologists with equal numbers of early and metastatic breast cancer cases. The CDSS processed each patient case from a standard data form containing the data elements it requires for each case. Clinicians were aware that they would subsequently be provided with recommended treatment options by the CDSS but were blinded to these options until their initial treatment decisions were rendered. After initial treatment decisions were made, clinicians were supplied with the MSKCC preferred therapies from the CDSS, including supporting evidence obtained from the medical literature by WfO and curated by MSKCC breast cancer experts. Clinicians were asked to consider the CDSS recommendations and provide final therapeutic decisions.

The impact of the CDSS on clinician decision making was assessed by: quantifying decision changes overall and by immunohistochemical receptor markers (HRs [estrogen and progesterone receptors] and HER2/neu) and clinico-pathologic variables (TNM stage); assessing whether patient age, oncologist years of experience, or receptor subtype (HR, HER2/neu)/TNM stage affected decision changes; and measuring changes in adherence to NCCN breast cancer treatment guidelines. Clinician reasons for changing treatment decisions were reported and classified as: treatment changed because of superior decision logic from the CDSS, treatment changed because of the strength of the evidence provided by the CDSS, treatment changed

because of patient factors prompted by the CDSS, or treatment offered by the CDSS added as an equivalent option for patient consideration.

Statistical Analysis

Descriptive statistics of the characteristics of patients with breast cancer are presented as numbers and percentages for dichotomous and categorical variables and as means and standard deviations for continuous measures. Included are physician years of experience, patient age, and receptor subtype/TNM stage. A bivariable analysis of these variables by treatment decision change status is also provided. Statistical significance of differences in variable distributions across decision change cohorts was assessed using the Wilcoxon-Mann-Whitney test for continuous measures and Fisher's exact test for dichotomous and categorical variables.⁷⁻⁹ Two multivariable logistic regression models of decision change status (yes v no) were estimated. Although both include prescriber years of experience, patient age, and a vector of indicators for cancer stage, the two models differ in terms of how receptor subtype/TNM stage was entered. Model 1 includes flags for HR-positive HER2/neu-negative, HR-positive HER2/neu-positive, and triple-negative breast cancers (with HR-negative HER2/neu-positive disease as the reference category). Model 2 instead includes indicators for HR-positive (v HR-negative) and HER2-positive (compared with HER2-negative) disease. Because patients were not randomly assigned, physician fixed effects were added to the models to control for unobserved characteristics of the oncologists that might be correlated with other regressors or likelihoods of decision change. Moreover, to account for nonindependence of observations within oncologists, standard errors were clustered at the physician level. All analyses were conducted using Stata MP software (version 16.0; Stata, College Station, TX).

RESULTS

Characteristics of patients with breast cancer by TNM stage/receptor subtype are listed in Table 1. Overall, patients had a mean age of 47 years, and oncologists had a mean of 10 years of experience. As a proportion of total patients, 14% had stage I, 32% had stage II, 15% had stage III, and 39% had stage IV disease. The distribution of patients by HR status showed that 46% had HR-positive HER2/neu-negative, 19% had HR-positive HER2/neu-positive, 16% had HR-negative HER2/neu-positive, and 19% had triple-negative tumors.

Study oncologists changed their treatment recommendations in 5% (105 of 1,977) of all patient cases after reviewing the CDSS recommended treatment options and supporting evidence (Table 2). Decision changes were concentrated among those with HR-positive disease (77 of 105; $P = .06$) and those with stage IV disease in the first- (61 of 105; $P < .001$) or second-line therapy setting (10 of 105; $P < .01$). In general, patient cases of stage II or III

TABLE 1. Sample Variable Statistics Overall and by Receptor Subtype

Variable	Overall		HR Positive HER2/neu Negative (n = 904)		HR Positive HER2/neu Positive (n = 375)		HR Negative HER2/neu Positive (n = 324)		TNBC (n = 374)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Oncologist experience, years										
Mean	10									
SD	9									
Patient age, years										
Mean	47									
SD	9									
Patients	1,977	100	904	46	375	19	324	16	374	19
Stage										
IA (T1N0M0)	278	14	85	9	75	20	46	14	72	19
IIA (T0N1M0, T1N1M0, T2N0M0)	429	22	201	22	73	19	64	20	91	24
IIB (T2N1M0, T3N0M0)	194	10	84	9	42	11	34	10	34	9
IIIA (T3N1M0, T0N2M0, T1N2M0, T2N2M0, T3N2M0)	192	10	98	11	33	9	34	10	27	7
IIIB (T4N0M0, T4N1M0, T4N2M0)	5	< 1	2	< 1	3	1	0	0	0	0
IIIC (any T, N3M0)	94	5	57	6	23	6	10	3	4	1
IV, first line (any T, any N, M1)	396	20	180	20	75	20	78	24	63	17
IV, second line (any T, any N, M1)	389	20	197	22	51	14	58	18	83	22

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; SD, standard deviation; TNBC, triple-negative breast cancer.

disease had lower rates of decision change. Patient-level data for all patient cases with decision changes are listed in Appendix [Table A1](#).

Logistic regression modeling results are summarized in [Table 3](#). The models simultaneously adjusted for patient age, years of physician oncology experience, HR subtype/TNM tumor stage, and control for physician-specific effects. Model 1 incorporates HR and HER2/neu subtypes as distinct variables, and model 2 combines HR and HER2/neu subtypes into two variables to examine overall receptor effects. In both models, years of clinician oncology experience and patient age were not associated with treatment decision changes. In model 2, cases of HR-positive tumors were significantly more likely to have a decision change (odds ratio [OR], 1.58; $P < .05$). Results from both models indicate that cases of stage IIA or IIIA disease were less likely to be changed (OR, 0.29; $P < .05$ and OR, 0.08; $P < .01$, respectively). The positive relationship between stage IV disease in the first-line therapy setting and decision change did not reach statistical significance. It is worth noting that oncologist 4 was significantly less likely to reconsider treatment decisions (OR, 0.12; $P < .01$).

Types of treatment changes and reasons for changes are summarized in [Table 4](#). In 69% (72 of 105) of the patient cases with decision changes, initial treatments were replaced by CDSS recommendations. In the remaining 31% of patient cases, the recommended treatment was added as equivalent option for the patient to consider.

Study clinicians indicated that the strength and currency of the evidence provided by the CDSS accounted for 64% (67 of 105) of their changes, patient factors disclosed by the CDSS accounted for 23%, and stronger decision logic provided by the CDSS accounted for 13% of changes. Examples of decision changes by receptor status for early and metastatic breast cancers are listed in [Table 5](#), and patient case vignettes of decision changes are summarized in Appendix [Table A2](#).

As listed in Appendix [Table A3](#), adherence to NCCN treatment guidelines increased slightly but significantly after exposure to the CDSS therapeutic options (0.5%; $P < .01$). Nearly all were HR-positive cancers (eight of nine).

DISCUSSION

Clinical decision support tools face many challenges for clinical adoption, including technical quality (eg, validity and reproducibility), knowledge base currency and completeness, reasoning engine quality and transparency, operational efficiency (eg, usability and workflow integration), and performance (eg, concordance, decision changes, and clinical, economic, and health services outcomes).¹⁰ The authors are engaged in studies examining some of the challenges related to performance. Using the same 10 oncologists and patients with complex breast cancer (N = 1,977), cross-sectional observational studies were conducted to evaluate treatment concordance between oncologists and an AI-based CDSS and changes in

TABLE 2. Sample Variable Statistics by Decision Change Status

Variable	Changed Decision ^a (n = 105)		Did Not Change Decision (n = 1,872)		P ^b
	No.	%	No.	%	
Oncologist experience, years					.39
Mean	11		10		
SD	10		9		
Patient age, years					.18
Mean	46		47		
SD	9		9		
Receptor subtype					
HR positive HER2/neu negative	54	51	850	45	.23
HR positive HER2/neu positive	23	22	352	19	.44
HR negative HER2/neu positive	11	10	313	17	.10
TNBC	17	16	357	19	.52
HR positive (v HR negative)	77	73	1202	64	.06
HER2/neu positive (v HER2/neu negative)	23	22	352	19	.44
Stage					
IA	18	17	260	14	.39
IIA	8	8	421	22	< .001
IIB	7	7	187	10	.31
IIIA	1	1	191	10	< .001
IIIB	0	0	5	0	1.000
IIIC	0	0	94	5	.01
IV (first line)	61	58	335	18	< .001
IV (second line)	10	10	379	20	.01

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; SD, standard deviation; TNBC, triple-negative breast cancer.

^aDecision changes involved either replacement of the original recommendation in its entirety or addition of other therapeutic options to the original recommendation.

^bP values from tests of differences in variable distributions across decision change using Wilcoxon-Mann-Whitney test for prescriber experience and age and Fisher's exact test for all other variables.

treatment decisions after use of the tool. The first study showed that concordance on treatment occurred in 55% (1,096 of 1,977) of patient cases, was lowest for HR-positive tumors (52%), and was highest for triple-negative breast cancer (71%).⁴ It also showed that disagreement on recommended treatment (nonconcordance) occurred in 45% (881 of 1,977) of patient cases. Nonconcordance resulted from differences in clinical judgement between the tool and oncologists in 21% of patient cases, greater NCCN guideline adherence by the oncologists in 15%, and unavailability of treatments in China in 5% or in the CDSS in 4%.

This study used a blinded pre- versus postexposure design to evaluate the influence of the CDSS on treatment decisions. The study showed that oncologists at academic cancer centers in China altered initial treatment decisions in 105 patient cases (5% of total) when including the tool as part of their overall decision-making process, increasing concordance from 0.56 before use of the tool to 0.61 after

use of the tool. Changes in treatment decisions occurred most often for those with HR-positive breast cancer or those with stage IV disease in the first-line therapy setting. This finding reflects the complexity of treating these breast cancer subtypes. For HR-positive invasive breast cancer, decisions regarding the use of adjuvant chemotherapy are challenging, particularly when gene expression profiling is not available to guide decisions.¹¹ In addition, these decisions involve choices regarding ovarian function suppression and treatment duration with antiestrogens or aromatase inhibitors. The occurrence of more frequent treatment changes for stage IV disease in the first-line therapy setting may be a result of the greater uncertainty of pathophysiologic and biomolecular mechanisms in metastatic breast cancer compared with early breast cancer and the availability of more therapeutic options for stage IV disease in the first-line therapy setting compared with stage IV disease in the second-line setting.^{12,13}

TABLE 3. ORs From Logistic Regression of Oncologists' Decision Change, Before and After CDSS Use (N = 1,502)

Variable	OR (95% CI)	
	Model 1	Model 2
Oncologist experience, years	1.04 (1.00 to 1.09)	1.04 (1.00 to 1.09)
Patient age, years	1 (0.98 to 1.03)	1 (0.98 to 1.03)
HR positive HER2/neu negative	2.04 (0.90 to 4.65)	
HR positive HER2/neu positive	2.3 (0.71 to 7.41)	
HR negative HER2/neu positive (reference)	1 (1.00 to 1.00)	
TNBC	1.6 (0.56 to 4.55)	
HR negative (reference)		1 (1.00 to 1.00)
HR positive		1.58 (1.11 to 2.24)*
HER2/neu negative (reference)		1 (1.00 to 1.00)
HER2/neu positive		1.12 (0.66 to 1.92)
Stage IA (reference)	1 (1.00 to 1.00)	1 (1.00 to 1.00)
Stage IIA	0.29 (0.09 to 0.89)*	0.29 (0.09 to 0.88)*
Stage IIB	0.58 (0.19 to 1.78)	0.57 (0.18 to 1.76)
Stage IIIA	0.08 (0.01 to 0.47)**	0.08 (0.01 to 0.47)**
Stage IIIB ^a		
Stage IIIC ^a		
Stage IV (first line)	2.03 (0.65 to 6.31)	2 (0.67 to 5.99)
Stage IV (second line)	1 (0.37 to 2.74)	1.01 (0.37 to 2.81)
Oncologist 1 (reference)	1 (1.00 to 1.00)	1 (1.00 to 1.00)
Oncologist 2	0.68 (0.30 to 1.52)	0.7 (0.30 to 1.61)
Oncologist 3 ^a		
Oncologist 4	0.12 (0.07 to 0.19)**	0.12 (0.08 to 0.19)**
Oncologist 5	0.51 (0.25 to 1.03)	0.52 (0.25 to 1.07)
Oncologist 6	0.86 (0.41 to 1.79)	0.89 (0.41 to 1.89)
Oncologist 7	0.97 (0.39 to 2.43)	0.99 (0.40 to 2.44)
Oncologist 8	2.09 (0.75 to 5.82)	2.1 (0.75 to 5.88)
Oncologist 9	1 (1.00 to 1.00)	1 (1.00 to 1.00)
Oncologist 10 ^a		
Constant	0.03 (0.01 to 0.12)**	0.04 (0.01 to 0.13)**

NOTE. Standard errors were clustered by oncologist.

Abbreviations: CDSS, clinical decision support system; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OR, odds ratio; TNBC, triple-negative breast cancer.

^aBecause the following regressors were perfectly correlated with decision change, 475 fewer observations were included in the models: stage IIIB (n = 5), stage IIIC (n = 94), oncologist 3 (n = 185), and oncologist 10 (n = 191).

* $P < .05$.

** $P < .01$.

Oncologists in this study reported that their decisions to change treatment recommendations predominantly resulted from the strength and currency of the evidence provided by the CDSS. This likely reflects the ability of AI technologies to gather and process large and rapidly changing knowledge bases for breast cancer treatment.^{14,15} Practicing clinicians are limited in their ability to replicate this information processing capacity because of time constraints from patient care and administrative duties, as well as human cognitive limits.^{16,17}

Patient factors and the decision logic of the CDSS were also cited as reasons for altering decisions. For example, patient factors highlighted by the tool included potential treatment interactions with comorbidities such as cardiovascular disease or drug-drug interactions. Decision logic-related changes resulted from a comparison by clinicians of the logic of the tool with their own clinical reasoning and subsequent decisions to use the former for determining their final treatment recommendations. Information processing capacity, complete and accurate

TABLE 4. Reasons for Treatment Decision Changes Overall and by Receptor Subtype

Type of Treatment Change	Reason for Change	Overall (N = 105)		HR Positive HER2/neu Negative (n = 54)		HR Positive HER2/neu Positive (n = 23)		HR Negative HER2/neu Positive (n = 11)		TNBC (n = 17)	
		No.	%	No.	%	No.	%	No.	%	No.	%
Replaced initial treatment	Decision logic	14	13	9	17	3	13	0	0	2	12
Replaced initial treatment	Strength evidence	34	32	21	39	4	17	3	27	6	35
Replaced initial treatment	Patient factors ^a	24	23	11	20	8	35	4	36	1	6
Added as option to initial treatment	Strength evidence	33	31	13	24	8	35	4	36	8	47

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer.

^aPatient factors disclosed by artificial intelligence decision support tool (eg, age-related toxicity risk, comorbidity risks, drug-drug interactions).

information, and individual heuristics are well-established contributors to medical logic and clinical decision making.¹⁸

Available studies show a wide range of rates for changes to breast cancer treatment decisions in response to expert reviews. Numerous methodologic and population sampling factors help explain these differences, including statistical power, HR/TNM profiles, access to therapies, clinician expertise, and patient preferences. Examples of some published data include: a study of 200 patients with breast cancer reporting a major change in management for 13% of patients after expert panel imaging reviews,¹⁹ a study of expert panel imaging reviews resulting in treatment plan changes for 11.7% of 158 patients undergoing breast surgery,²⁰ and a study of 75 patients with breast cancer reviewed by a multidisciplinary tumor board resulting in different treatment recommendations for 43% of patients.²¹ These studies did not report which aspects of the interaction between the tool or expert panel

and the clinician may have led to decision changes, which is a key contribution of our study.

The high incidence of breast cancer globally suggests that an AI-based CDSS-enabled single-digit rate of change in treatment decisions could potentially affect large numbers of high-risk patients with breast cancer.²² Much additional research is warranted to replicate these findings and uncover which aspects of the clinician-patient tool interaction are of greatest value to clinicians and patients. Given the potential scale for deployment of validated cancer treatment decision support tools, it is equally imperative to undertake rigorous prospective and controlled clinical studies on patient and health system outcomes from use of these tools.¹⁰ The number and design of these studies will need to account for many factors known to affect these outcomes, such as the absence of any gold standard or single correct answer for treatment of complex breast cancer, local practice patterns, quality of care management, availability and affordability of therapies, patient preferences, and social support systems.

TABLE 5. Examples of Decision Changes by Receptor Subtype for Patient Cases of Early or Metastatic Breast Cancer

TNM Stage	Initial Decision	Revised Decision	Reason for Change
HR positive HER2/neu negative			
EBC	AC-T	ddAC-T	Strength of evidence greater
MBC	AC	OFS + fulvestrant	Decision logic better
HR positive HER2/neu positive			
EBC	TC + H	ddAC-TH	Strength of evidence greater
MBC	OFS + NSAI + L	LX	Patient factors
HR negative HER2/neu positive			
EBC	TH	ddAC-TH	Strength of evidence greater
MBC	XH	TH, NH	Strength of evidence equivalent
TNBC			
EBC	TC	AC-T	Strength of evidence greater
MBC	NX	GP	Strength of evidence greater

Abbreviations: A, anthracycline; C, cyclophosphamide; ddAC-T, dose-dense adriamycin, cyclophosphamide, and taxane; ddAC-TH, dose-dense doxorubicin, cyclophosphamide, taxane, and trastuzumab; EBC, early breast cancer; GP, gemcitabine and platinum; H, trastuzumab; L, lapatinib; MBC, metastatic breast cancer; N, vinorelbine; NSAI, nonsteroidal aromatase inhibitor; OFS, ovarian function suppression; T, taxane; X, capecitabine.

This study has several strengths and limitations. Study strengths include a large number of patient cases of breast cancer, a focus on patient cases posing challenging treatment decisions for oncologists, and insight into reasons for altering treatment decisions. In addition, clinicians were blinded to the therapeutic options offered by the CDSS when their initial treatment decisions were rendered. Limitations of the study include the relatively small number of clinicians involved in the study, the academic nature of the cancer treatment settings, and the use of a version of the CDSS that has undergone periodic updates since this study was conducted. It is also unknown if the initial decisions of the study oncologists were affected by the knowledge that they would subsequently be shown recommendations from a CDSS.

In conclusion, this report provides evidence that an AI-based CDSS helped to revise initial treatment decisions by oncologists for subsets of high-risk patients with breast cancer (HR-positive disease and stage IV disease in the first-line therapy setting). Further research is needed to gain a fuller understanding of decision impact for all patients with breast cancer in different treatment settings. Decision impact studies from use of a CDSS should also examine differences between treatments recommended by oncologists and treatments chosen by patients, as well as whether the tool improves patient and physician learning, communication and trust, and patient agency. Most importantly, research is needed to assess whether decisions affected by the use of these tools improve clinical, quality-of-life, and health system outcomes.

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APPENDIX

TABLE A1. Deidentified Patient-Level Data for Decision Changes (n = 105)

Patient	Age (years)	Stage	Receptor Subtype	Original Decision		Revised Decision	Type of Change
A010023	48	IA	HR positive HER2/neu positive	TC + H	ddAC-TH		2
A010027	39	IA	HR positive HER2/neu positive	AC-TH	PH, TC + H		3
A010058	49	IIA	HR negative HER2/neu positive	TH	ddAC-TH		2
A010271-1	46	IV, first line	HR negative HER2/neu positive	TH	TH, AI + H		4
A010288-1	34	IV, first line	HR negative HER2/neu positive	LX	LX, NH		4
A010312-1	58	IV, first line	TNBC	GP	GP, G, X		4
A010317-1	42	IV, first line	HR positive HER2/neu negative	OFS + NSAI, OFS + NSAI + CDK4/6i	OFS + NSAI + CDK4/6i		2
A010333-1	35	IV, first line	HR positive HER2/neu negative	OFS + fulvestrant, OFS + NSAI + CDK4/6i, T	OFS + fulvestrant, OFS + NSAI + CDK4/6i		3
A010412	54	IA	HR positive HER2/neu positive	TCH	TH		2
A010421	51	IA	HR positive HER2/neu positive	TCH	TH		2
A010424	36	IA	HR negative HER2/neu positive	ddAC-TH	TH		2
A010431-1	54	IV, first line	HR negative HER2/neu positive	TH	TH, NH		4
A010455	46	IIB	HR positive HER2/neu negative	Did not recommend adjuvant radiotherapy	Recommended adjuvant radiotherapy		2
A010464-1	52	IV, first line	HR positive HER2/neu positive	OFS + NSAI + H, OFS + fulvestrant + H	OFS + NSAI + L		1
A010472-1	47	IV, first line	TNBC	X	X, N		4
A010501-1	59	IV, first line	HR positive HER2/neu negative	Exemestane + everolimus	X		3
A010613-1	28	IV, first line	HR positive HER2/neu positive	OFS + NSAI + L	LX		3
A010615-1	48	IV, first line	TNBC	X	T		2
A010617-1	49	IV, first line	HR negative HER2/neu positive	TH	NH		3
A010668-1	44	IV, first line	HR positive HER2/neu negative	TX	TX, liposomal doxorubicin		4
A010672-1	53	IV, first line	HR positive HER2/neu positive	OFS + NSAI + CDK4/6i	OFS + NSAI + CDK4/6i, OFS + fulvestrant + CDK4/6i		4
A010709-1	45	IV, first line	HR positive HER2/neu positive	NHP	NHP, OFS + SAI + H		1
A010735-1	60	IV, first line	HR positive HER2/neu negative	Fulvestrant + CDK4/6i	Fulvestrant + CDK4/6i, NSAI + CDK4/6i		4
A010745-1	41	IV, first line	HR positive HER2/neu positive	TH	TH, NH		4
A010752	54	IIB	HR positive HER2/neu negative	TC	AC-T		2
A012001	55	IV, first line	TNBC	GP	GP, X		4
A012003	26	IV, first line	HR positive HER2/neu negative	OFS + NSAI	OFS + NSAI, OFS + fulvestrant + CDK4/6i		2
A012005	44	IV, first line	HR positive HER2/neu positive	TH	TH, NH		4
A012006	34	IV, first line	HR negative HER2/neu positive	TH	TH, NH		4
A012009	53	IV, first line	TNBC	TX	TX, NX		4
A012010	50	IV, first line	HR positive HER2/neu negative	NSAI	NSAI, fulvestrant + CDK4/6i		2
A012017	36	IV, first line	TNBC	TX	TX, X		4
A012034	64	IV, first line	HR positive HER2/neu positive	TH	TH, NSAI + H		4

(Continued on following page)

TABLE A1. Deidentified Patient-Level Data for Decision Changes (n = 105) (Continued)

Patient	Age (years)	Stage	Receptor Subtype	Original Decision	Revised Decision	Type of Change
A012038	38	IV, first line	HR positive HER2/neu positive	NH	NH, OFS + NSAI + H	4
A012044	43	IV, first line	HR positive HER2/neu negative	TX	OFS + NSAI	3
A012048	53	IV, first line	HR positive HER2/neu negative	NSAI	Fulvestrant	2
A012056	38	IV, first line	HR positive HER2/neu negative	AC	OFS + fulvestrant	1
A012059	59	IV, first line	HR positive HER2/neu positive	TXH	TH	3
A012071	34	IV, first line	HR negative HER2/neu positive	TH	TXH	3
A012077	42	IV, first line	TNBC	GP	GP, X	4
A012079	37	IV, first line	HR positive HER2/neu negative	OFS + NSAI	OFS + NSAI, OFS + fulvestrant + CDK4/6i	1
A012080	38	IV, first line	HR positive HER2/neu negative	NX	NX, X	4
A012084	48	IV, first line	HR positive HER2/neu negative	NSAI	NSAI, X	4
A012085	38	IV, first line	HR positive HER2/neu negative	TX, GT	GT, TX, liposomal doxorubicin	4
A012087	48	IV, first line	HR positive HER2/neu positive	Exemestane + everolimus + H	Exemestane + everolimus + H, L + H	4
A012090	46	IV, first line	TNBC	NP	NP, X	4
A012095	40	IV, first line	TNBC	GP	GP, X	4
A012101	30	IV, first line	HR positive HER2/neu negative	OFS + NSAI	OFS + NSAI, X	4
A012105	58	IV, first line	HR positive HER2/neu positive	XH	Fulvestrant + H	3
A012117	39	IV, first line	HR positive HER2/neu negative	OFS + fulvestrant	OFS + NSAI	2
A012120	44	IV, first line	HR positive HER2/neu negative	Fulvestrant	NSAI	2
A012122	51	IV, first line	HR positive HER2/neu positive	XH	NSAI + H	3
A012123	45	IV, first line	TNBC	NX	GP	2
A012127	47	IV, first line	HR negative HER2/neu positive	XH	NH	2
A012132	33	IV, first line	HR positive HER2/neu negative	Fulvestrant	NSAI	2
A012134	35	IV, first line	HR positive HER2/neu negative	OFS + fulvestrant	OFS + NSAI	2
A012135	30	IV, first line	HR positive HER2/neu negative	OFS + fulvestrant	OFS + NSAI	2
A012137	43	IV, first line	HR positive HER2/neu negative	OFS + fulvestrant	OFS + NSAI	2
A012139	47	IV, first line	HR positive HER2/neu negative	OFS + fulvestrant	OFS + NSAI	2
A012140	53	IV, first line	HR positive HER2/neu negative	Fulvestrant	NSAI	2
A012166	60	IV, first line	TNBC	GP	X	3
A012167	65	IV, first line	TNBC	TX	G, X	1
A012438	26	IV, first line	TNBC	TX	TP	2
A012449	29	IV, first line	HR positive HER2/neu negative	TX	OFS + NSAI	3
A012462	38	IV, first line	HR positive HER2/neu positive	OFS + NSAI + H	TH	3
A012464	32	IV, first line	HR positive HER2/neu negative	TX	TX, N	4

(Continued on following page)

TABLE A1. Deidentified Patient-Level Data for Decision Changes (n = 105) (Continued)

Patient	Age (years)	Stage	Receptor Subtype	Original Decision	Revised Decision	Type of Change
A012465	43	IV, first line	HR positive HER2/neu positive	OFS + NSAI + H	TH	3
A012466	51	IV, first line	HR positive HER2/neu negative	NSAI	NSAI, X	4
A012470	40	IV, first line	HR positive HER2/neu negative	TX	OFS + NSAI	3
A012530-2	50	IV, second line	HR positive HER2/neu negative	NSAI	NSAI, X	4
A012531-2	37	IV, second line	HR positive HER2/neu negative	X	OFS + NSAI	3
A012532-2	59	IV, second line	HR positive HER2/neu negative	NSAI	NSAI, X	4
A012533-2	33	IV, second line	TNBC	TH, NH	TH	1
A012538-2	46	IV, second line	HR positive HER2/neu negative	OFS + NSAI	OFS + NSAI, X	4
A012543-2	53	IV, second line	HR positive HER2/neu negative	NSAI	NSAI, X	4
A012545-2	27	IV, second line	HR positive HER2/neu positive	TH	TH, OFS + NSAI + H	4
A012553-2	37	IV, second line	HR positive HER2/neu positive	OFS + NSAI + H	NH	3
A012618-2	39	IV, second line	HR positive HER2/neu negative	X, OFS + NSAI	OFS + NSAI	1
A012643-2	45	IV, second line	HR positive HER2/neu negative	X	X, NSAI	4
A0210016	46	IIA	TNBC	AC-T	ddAC-T	2
A0210020	50	IA	HR positive HER2/neu negative	ddAC-T	AC, TC	3
A0210029	41	IA	HR positive HER2/neu negative	Did not recommend adjuvant chemotherapy	TC, AC	1
A0210202	40	IIB	HR positive HER2/neu negative	AC, TC	ddAC-T	2
A0210214	60	IIA	HR positive HER2/neu negative	Did not recommend adjuvant chemotherapy	AC, TC	1
A0210215	50	IIA	HR positive HER2/neu negative	AC, TC	ddAC-T	2
A0210363	51	IIA	HR positive HER2/neu positive	Did not recommend adjuvant radiotherapy	Recommended adjuvant radiotherapy	1
A0210366	56	IIB	HR positive HER2/neu negative	Did not recommend adjuvant radiotherapy	Recommended adjuvant radiotherapy	2
A0210377	54	IIB	HR positive HER2/neu negative	Did not recommend adjuvant radiotherapy	Recommended adjuvant radiotherapy	2
A0210388	42	IIA	HR positive HER2/neu negative	AC-T	ddAC-T	2
A0210631	44	IA	HR positive HER2/neu negative	AC-T	TC	3
A0210774	43	IA	HR positive HER2/neu negative	Did not recommend adjuvant chemotherapy	TC	3
A0210786	60	IIIA	HR positive HER2/neu negative	Did not recommend adjuvant radiotherapy	Recommended adjuvant radiotherapy	1
A0210791	48	IA	HR negative HER2/neu positive	TH	AC-TH	3
A0210810	53	IA	HR negative HER2/neu positive	TH	AC-TH	3
A0210811	61	IA	HR positive HER2/neu negative	Did not recommend adjuvant chemotherapy	TC	3
A0210855	58	IA	HR positive HER2/neu negative	Did not recommend adjuvant chemotherapy	TC	1
A0210858	41	IIB	TNBC	Did not recommend adjuvant radiotherapy	Recommended adjuvant radiotherapy	2
A0210860	37	IIA	HR positive HER2/neu negative	TC	AC-T	2
A0210862	59	IIB	HR positive HER2/neu negative	Did not recommend adjuvant radiotherapy	Recommended adjuvant radiotherapy	2

(Continued on following page)

TABLE A1. Deidentified Patient-Level Data for Decision Changes (n = 105) (Continued)

Patient	Age (years)	Stage	Receptor Subtype		Original Decision		Revised Decision	Type of Change
A0210866	63	IA	HR	positive	HER2/neu negative	Did not recommend adjuvant chemotherapy	TC	1
A0210887	49	IA	HR	positive	HER2/neu negative	Did not recommend adjuvant chemotherapy	TC	3
A0211030	45	IIA	HR	positive	HER2/neu negative	Did not recommend adjuvant chemotherapy	TC	1
A0211180	45	IA	TNBC			TC	AC-T	2
A0211217	39	IA	HR	positive	HER2/neu positive	TC + H	TH	2
A030109	61	IA	HR	positive	HER2/neu positive	AC-TH	AC-TH, TH, CMF + H	4

Abbreviations: A, anthracycline; AI, aromatase inhibitor; C, cyclophosphamide; CDK4/6i, cyclin-dependent kinase 4 or 6 inhibitor; dd, dose dense; F, fluorouracil; G, gemcitabine; H, trastuzumab; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; L, lapatinib; N, vinorelbine; NSAI, nonsteroidal aromatase inhibitor; OFS, ovarian function suppression; P, platinum; SAI, steroidal aromatase inhibitor; TNBC, triple-negative breast cancer; X, capecitabine.

TABLE A2. Decision Change Case Examples

Revised Patient Case	Reason for Decision Change
A 54-year-old patient with stage T2N1M0 and HR-positive HER2/neu-negative breast cancer. Clinician's initial decision was TC for adjuvant chemotherapy. The decision was changed to ddAC-T after reviewing the NCCN breast cancer treatment guidelines available in the AI-based CDSS. Although both TC and ddAC-T are NCCN-preferred treatments, the clinician's review of the studies for both was interpreted as ddAC-T study protocols tending to include more patients at higher risk than the TC studies (eg, lymph node-positive breast cancers, as in this case).	Strength of evidence (Citron ML, et al: J Clin Oncol 21:1431-1439, 2003)
A 38-year-old patient with HR-positive HER2/neu-negative breast cancer metastatic to bone. Clinician's initial decision was AC chemotherapy. The decision was changed to OFS + fulvestrant because the CDSS decision logic caused the clinician to reconsider treatment selection, as a part of his greater decision-making process. The logic included the consideration that the patient had metastasis only to bone, low tumor burden, and slow progression, making the OFS + fulvestrant less toxic and more suitable therapy. This study showed fulvestrant improved progression-free survival (16.6 v 13.8 months; hazard ratio, 0.797; $P = .0486$) compared with anastrozole.	Better decision logic (Robertson JFR, et al: Lancet 388:2997-3005, 2016)
A 60-year-old patient with stage IV TNBC. Clinician's initial decision was GP chemotherapy. The decision was changed to capecitabine because the CDSS offered therapeutic options that were less aggressive and potentially less toxic because of the age of the patient. The safety and efficacy of the alternative treatment derived from a study of capecitabine in older women with advanced breast cancer.	Patient factors (Bajetta E, et al: J Clin Oncol 23:2155-2161, 2005)
A 41-year-old patient with TNBC, T2N1M0. Clinician's initial decision was AC-T. The decision was changed to ddAC-T based on the strength of the evidence provided by the 2018 NCCN guidelines presented by the CDSS NCCN breast cancer treatment guidelines available in 2018, which categorized ddAC-T as a preferred therapy with stronger supporting evidence than AC-T. AC-T was categorized as other recommended intervention, which has less supporting evidence of efficacy, safety, or toxicity.	Strength of evidence

Abbreviations: AC, adriamycin plus cyclophosphamide; AC-T, adriamycin, cyclophosphamide, and paclitaxel; AI, artificial intelligence; CDSS, clinical decision support system; ddAC-T, dose-dense adriamycin, cyclophosphamide, and paclitaxel; GP, gemcitabine plus platinum (carboplatin or cisplatin); NCCN, National Comprehensive Cancer Network; OFS, ovarian function suppression; TC, paclitaxel plus cyclophosphamide; TNBC, triple-negative breast cancer.

TABLE A3. Adherence to NCCN Guidelines Before and After WfO Disclosure (N = 1,977)

Variable	NCCN Guideline Adherence						P ^a
	WfO Disclosure						
	Before		After		Change		
	No.	%	No.	%	No.	%	
Overall	1,896	95.90	1,905	96.36	9	0.46	.003 ^b
Receptor subtype							
HR positive HER2/neu negative	866	95.80	873	96.57	7	0.77	.01
HR positive HER2/neu positive	348	92.55	349	92.82	1	0.27	.32
HR negative HER2/neu positive	311	96.28	311	96.28	0	0.00	1.00
TNBC	371	99.20	372	99.47	1	0.27	.32
Stage							
I	267	96.04	270	97.12	3	1.08	.08
II	591	94.86	594	95.35	3	0.48	.08
III	277	95.19	278	95.53	1	0.34	.32
IV (first line)	384	96.97	386	97.47	2	0.51	.16
IV (second line)	377	96.92	377	96.92	0	0.00	1.00

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; TNBC, triple-negative breast cancer; WfO, Watson for Oncology.

^aP values for differences in adherence between pre- and post-WfO disclosure by Fisher's exact test (unless otherwise noted).

^bWilcoxon-Mann-Whitney test.