Identifying Patients With Low Relapse Rate Despite High-Risk Estrogen Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Early Breast Cancer: Development and Validation of a Clinicopathologic Assay

François-Clément Bidard, MD, PhD[1]; Grégoire Gessain, MD, PhD[2]; Thomas Bachelot, MD, PhD[3]; Lucie Frechin, MSc[4]; Anne Vincent-Salomon, MD, PhD[1]; Damien Drubay, PhD[2,5]; Jérôme Lemonnier, PhD[6]; Thomas Walter, PhD[1,7,8]; Frédérique Penault-Llorca, MD, PhD[9]; Anne-Laure Martin, PhD[6]; Catherine Gaudin, BSc[6]; Antoine Bichat, PhD[4]; Farah Sassi, MD[2]; Sylvain Berlemont, PhD[4]; Mariana Chavez-MacGregor, MD[10]; Hope S. Rugo, MD[11]; Cécile Badoual, MD, PhD[2,12]; Barbara Pistilli, MD, PhD[2]; Joana Ribeiro, MD[2]; Antonio Di Meglio, MD, PhD[13,14]; Magali Lacroix-Triki, MD, PhD[2]; Ines Vaz Luis, MD, PhD[2,13,14]; Marvin Lerousseau, PhD[4]; and Fabrice André MD, PhD[2,13]

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ABSTRACT

PURPOSE Escalation of adjuvant systemic therapies (eg, with cyclin-dependent kinase 4 and 6 inhibitors) is now indicated for patients with clinically defined high-risk estrogen receptor–positive (ER+)/human epidermal growth factor receptor 2–negative (HER2–) early breast cancer, although it is unclear which will benefit from additional therapies. We developed and validated a prognostic clinicopathologic assay identifying a subpopulation of high-risk patients with good prognosis after standard adjuvant therapies, who may safely forgo treatment escalation.

METHODS We trained a Cox proportional-hazards model that integrates clinicopathologic variables with features derived from digitized hematoxylin-and-eosin–stained resection slides from a retrospective data set. The model assigns each patient to a *low-risk* or *not low-risk* group, reflecting their predicted risk of recurrence. Blind validation was successively performed on high-risk patients from the prospective trials CANTO (ClinicalTrials.gov identifier: NCT01993498) and UNIRAD (ClinicalTrials.gov identifier: NCT01805271).

RESULTS Built on data from 6,164 patients with ER+/HER2– early-stage breast cancer, this assay integrates four clinicopathologic variables, and 10 slide-derived features capturing tumor architecture, microenvironment, and proliferation. In the combined CANTO and UNIRAD trials (n = 633), 95.4% of the *low-risk* patients remained free of distant recurrence and death from breast cancer at 9 years, compared with 76.8% for the *not low-risk* group. Distant recurrence-free interval (subdistribution hazard ratio [HR], 0.21 [95% CI, 0.09 to 0.52]; $P < .001$), invasive disease-free survival (HR, 0.31 [95% CI, 0.16 to 0.60]; $P < .001$), and overall survival (HR, 0.35 [95% CI, 0.13 to 0.97]; $P = .044$) were all statistically significant. Multivariate analyses showed that the assay provided predictive information beyond clinicopathologic variables. Analytical validation showed robustness to data variability.

CONCLUSION The assay demonstrated robust performance in identifying a core group of patients with high-risk ER+/HER2– breast cancer for whom additional adjuvant treatment may be futile.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

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INTRODUCTION

Clinically defined high-risk estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–) early invasive breast cancers (eBC) account for approximately 16% of all eBC cases.[1,2] Until 2022, the standard systemic treatment for these patients consisted of chemotherapy followed by endocrine therapy,[3] as observed in more than 90% of them.[4] With such a regimen, an estimated 60% of patients with high-risk ER+/HER2– eBC remain free of distant metastatic disease at 20 years,[5,6] highlighting that many of these patients may not require additional treatment

CONTEXT

Key Objective

To develop and validate a clinicopathologic assay that identifies patients with high-risk estrogen receptor–positive/human epidermal growth factor 2–negative early invasive breast cancers who have a low risk of distant recurrence after standard therapy.

Knowledge Generated

The assay identified approximately 20% of clinically high-risk patients with over 95% 9-year freedom from distant recurrence across two independent trial cohorts.

Relevance *(K.D. Miller)*

Getting the right treatment to the right patient remains the holy grail of oncology. Adding information from digital pathology to standard clinicopathologic features moves us measurably closer to that goal, sparing approximately 20% of patients from the cost and toxicity associated with further treatment escalation.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

beyond standard chemoendocrine therapy. However, following the results of the monarchE and NATALEE trials,[4,7] the addition of cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) to the chemoendocrine regimen is now recommended by most guidelines for high-risk ER+/HER2− eBC.[8,9]

The current tools available for treatment selection are insufficient for accurately distinguishing high-risk patients with eBC who will relapse after chemoendocrine therapy from those who will not. This includes genomic tools that have been mostly developed and validated to guide the use of adjuvant chemotherapy in low- or intermediate-risk eBC only. The inability to identify a subgroup of patients with high-risk eBC who are actually at low risk of relapse after chemoendocrine therapy represents a critical gap in clinical practice, since these patients are exposed to unnecessary contemporary treatment escalation, which could lead to toxicity and reduced quality of life.

To address this clinical need, we aimed at developing a novel data-driven prognostic assay capable of reclassifying patients initially considered at high risk of relapse but who are at low residual risk after standard adjuvant chemoendocrine therapy, and could safely forgo adjuvant treatment escalation. The secondary objective was to validate the assay in large clinical trial cohorts to assess its ability to accurately identify patients at low risk of relapse who were treated with chemoendocrine therapy alone, without additional treatment.

METHODS

Study Design and Data Sources

The study design comprised four phases (Fig 1): assay development, which focused on constructing an assay integrating clinicopathologic and tumor slide data; assay locking-down, setting the final assay to ensure unbiased application during validation; clinical validation, which assessed the assay's validity in clinical trials data; and analytical validation, which evaluated the assay's robustness under diverse clinical and technical conditions.

The development data set comprised 6,164 patients with ER+/HER2− eBC. This international, multicenter, retrospective cohort comprised 3,877 patients from ScanB,[10] 1,396 from METABRIC,[11] 386 from TCGA-BRCA,[12] and 256 and 249 from two Gustave Roussy cohorts. These patients were selected from each data set according to predefined eligibility criteria: histologically confirmed ER+/HER2− eBC, definitive surgery, and availability of follow-up data. The two Gustave Roussy cohorts additionally excluded patients who had received neoadjuvant chemotherapy. After the development phase (Figs 1B), the assay was locked-down, meaning that no changes were done to any of its components to ensure an unbiased validation.

Validation was conducted exclusively on patients with high-risk eBC, defined as histologically confirmed ER+/HER2− eBC with node-positive disease and at least one of the following: four or more positive lymph nodes, grade 3, tumor size ≥50 mm, or Ki-67 ≥20%, consistent with the definition in the monarchE trial.[4] A sensitivity analysis excluding patients with Ki-67 ≥20% as the sole high-risk criterion was also conducted. Validation was successively conducted on two independent external trial cohorts of high-risk ER+/HER2− eBC: one from the CANTO (ClinicalTrials.gov identifier: NCT01993498) clinical trial and the other from the UNIRAD (ClinicalTrials.gov identifier: NCT01805271) clinical trial (Fig 1D). CANTO is a prospective trial conducted across 26 French centers, where patients were treated according to guidelines before the adoption of contemporary escalation

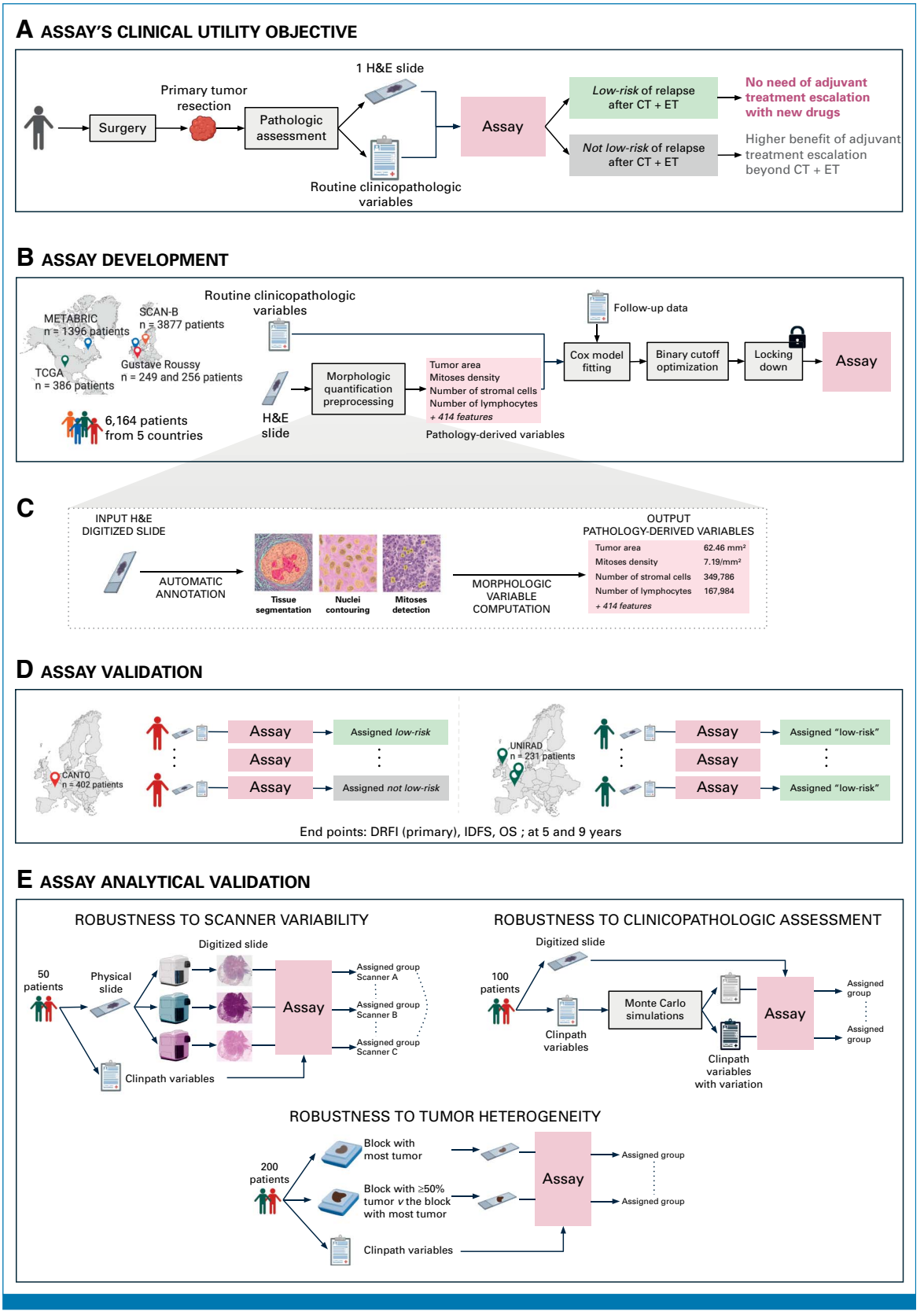

FIG 1. Study design. This figure illustrates the four-phase study design for developing and validating a prognostic assay for ER+/HER2− high-risk early breast cancer. (A) Clinical utility objective: the clinical positioning aimed to develop an assay identifying a subgroup of high-risk patients with minimal residual risk after adjuvant chemoendocrine therapy, who may safely forgo further treatment escalation. (B) Assay development: the prognostic model was trained using a data set of 6,164 patients, integrating clinicopathologic variables with computationally extracted features from (continued on following page)

FIG 1. (Continued). H&E-stained histology digital slides (C). The assay was locked down at the end of the development phase, including after the choice of the cutoff converting continuous risk predictions to group classifications (*low-risk* or *not low-risk*). (D) Clinical validation: the assay was validated in two independent high-risk eBC cohorts, first from the CANTO clinical trial (n = 402) and then from the UNIRAD clinical trial (n = 231), assessing its prognostic performance for DRFI, IDFS, and OS. (E) Analytical validation: robustness was evaluated across tumor heterogeneity, different slide-scanning platforms, and clinicopathologic variability. CT, chemotherapy; DRFI, distant recurrence-free interval; ER+, estrogen receptor–positive; ET, endocrine therapy; H&E, hematoxylin-and-eosin; HER2–, human epidermal growth factor receptor 2–negative; IDFS, invasive disease-free survival; OS, overall survival.

therapies.[13] UNIRAD is a phase III randomized prospective trial conducted across 72 centers in France, Belgium, and the United Kingdom, which evaluated the efficacy of adding everolimus to chemoendocrine treatment in high-risk breast cancer.[14] Only patients from the control arm of the UNIRAD trial, who did not receive everolimus, were included. For this study, Unicancer centrally managed patient selection, and patient and follow-up data collection. From each trial, 500 eligible patients were requested, consecutive from the first enrolled patient while ensuring eligibility compliance. Inclusion criteria were patients with high-risk ER+/HER2– eBC as defined above. Patients treated with neoadjuvant chemotherapy were excluded, as well as patients without available resection tumor blocks. Both cohorts excluded patients treated with CDK4/6 inhibitors, or any other therapy beyond endocrine or chemoendocrine, that is, patients of these cohorts received only hormone therapy with or without chemotherapy as adjuvant treatment, following contemporary guidelines. Locally prepared hematoxylin-and-eosin (H&E)–stained formalin-fixed, paraffin-embedded (FFPE) resection slides were centralized from each inclusion center, and were digitized by Unicancer with a Pannoramic Scan II (3DHISTECH).

Development of the Prognostic Assay

The assay was designed to predict each patient's individual risk of distant relapse using a single H&E-stained digitized slide from FFPE surgical resection tissue of the primary breast tumor, combined with standard clinicopathologic variables assessed at the time of surgery (Fig 1A). Each slide was quantitatively characterized using an automated image-processing pipeline as previously described.[15,16] This pipeline used deep-learning models to annotate tissue structures, nuclei, and mitotic figures, from which 418 morphologic features capturing tumor architecture, microenvironment, and proliferation were derived (Fig 1C; Data Supplement, online only).

A Cox proportional-hazards model with L1 regularization was fitted to the development cohort to identify the optimal subset of predictive features and their relative combinations for accurate prediction of distant relapse (Fig 1B). This model integrated 418 slide-derived features with 21 routine clinicopathologic variables (including tumor size, grade, and receptor status). Post hoc cross-validation within the development cohort was used to determine the optimal threshold for converting continuous risk scores into binary classifications (low-risk *v* not low-risk), maximizing the proportion of patients classified as *low-risk* while ensuring that patients classified as *low-risk* would exhibit a distant recurrence rate below 5% at 8 years. Additional technical details regarding the Cox model development procedure are provided in the Data Supplement.

The assay was locked down upon completion of the development phase on November 12, 2024.

Assay Validation

Each patient from the CANTO and UNIRAD trials was processed individually and independently (Fig 1D). The assay was applied to each patient's clinicopathologic and imaging data, assigning them to either the *low-risk* or *not low-risk* group. This assignment process was blinded to outcomes, ensuring no bias in risk group allocation. Once all patient assignments were completed, statistical analysis was conducted.

Statistical Analysis

The primary end point was distant recurrence-free interval (DRFI), measured as the time from surgery to the occurrence of distant metastasis or death from breast cancer, whichever came first. Secondary end points were overall survival (OS), defined as the time from surgery to death, and invasive disease-free survival (IDFS), defined as the time from surgery to the first occurrence of any recurrence, new cancer, or death from any cause. All end points were defined according to Standardized Definitions for Efficacy End Points criteria v2.0.[17]

DRFI was analyzed using cumulative incidence functions, accounting for competing risks, with Gray's test used for comparison between groups. Subdistribution hazard ratios (sHR) were estimated using Fine and Gray models. OS and IDFS were analyzed using Kaplan-Meier methods, with differences between groups evaluated by using the log-rank test. HRs were estimated using Cox proportional-hazards models.

Multivariable regression models adjusted for tumor size, grade, nodal status, and menopausal status tested the assay's independence from standard clinicopathologic factors. To further assess whether standard clinicopathologic variables alone could replicate the assay's risk-group classification (low-risk *v* not low-risk), a logistic

regression model was fitted. This model used only the clinicopathologic variables as predictors, and its performance was evaluated using pseudo-R^2 to quantify the degree to which these variables alone could explain the assay's classifications. Subgroup analyses assessed assay performance across clinically relevant categories, with interaction tests performed by including a product (group × subgroup) in regression models. Exploratory unimodal models (slide-derived features alone or clinical variables alone or extended clinical variables alone) were compared with the final integrated assay to assess incremental predictive value (Data Supplement).

Secondary end points and subgroup analyses were exploratory; thus, no correction for multiple testing was applied. All statistical tests were two-sided with a significance level of $\alpha = .05$, and CIs were set at 95%.

Analytical Validation

The assay's robustness was assessed across the sources of input variability: tumor heterogeneity, slide preparation (cutting, staining), slide scanners, and clinicopathologic variable assessments (Fig 1E). For each experiment, variability was introduced in the assay's input data depending on the source being tested. The assay was then applied to all variations of a patient's data, and classification concordance for *low-risk* versus *not low-risk* assignments was assessed to measure robustness. The overall result for each experiment was calculated as the average percentage concordance across all variations of each patient.

For variability of tumor heterogeneity and pathology laboratory protocols, two H&E slides from two different tumor blocks were prepared in two pathology laboratories for each of 200 cases—one from the block with the most tumor prepared (cut and stained) in Rennes, France, and another from a separate block with at least 50% tumor content compared with the former, if available, prepared in Villejuif, France. For scanner variability, the slide with the most tumor was scanned for 50 patients using three different scanning platforms: SlideView VS200 (Olympus, Tokyo, Japan), NanoZoomer S210 (Hamamatsu, Shizuoka, Japan), and Pannoramic 480 DX (3DHISTECH, Budapest, Hungary). For clinicopathologic variability, a Monte Carlo simulation was applied to the clinicopathologic variables of 100 patients, incorporating parameters derived from real-world discrepancies (Data Supplement).

Ethics Statement

All patients provided informed consent for data use in the CANTO and UNIRAD trials; given the retrospective nature of this work, a waiver of informed consent was granted. Patients in the development data set from Gustave Roussy provided informed consent. The study was approved by the Gustave Roussy Institutional Review Board (IRB2024-458).

RESULTS

Assay Development

Table 1 shows clinicopathologic characteristics of the 6,164 patients of the development cohort (median age was 62 years). Median tumor size was 22.3 mm, and 13.3% of patients had four or more positive lymph nodes. Tumor grade was distributed as follows: grade 1 (15.6%), grade 2 (49.6%), and grade 3 (25.6%).

The assay's development phase resulted in a Cox model that integrates 14 features, including four clinicopathologic variables (number of positive lymph nodes, pathologic tumor size, grade, and percentage of progesterone receptor–positive tumor cells), and 10 slide-derived features (illustrated in the Data Supplement, Fig S12) capturing tumor architecture (tumor area, tumor density at the invasive front, density of invasive tumor nests, and density of in situ tumor nests), tumor microenvironment (area of inflammatory stroma, stromal cell nuclei size, healthy gland size variance, and stromal proportion near in situ tumor), and tumor proliferation (mitotic hotspot count and mitotic density). The assay generates a continuous relapse risk score for each patient, which is then classified into either a *low-risk* or *not low-risk* category using a binary cutoff determined from the development set. The expected performance of the assay, as determined by cross-validation, was 0.26 sHR for DRFI (95% CI, 0.18 to 0.38; $P < .001$).

Clinical Validation

The CANTO validation cohort comprised 402 patients clinically defined at high-risk (Fig 2; Table 1), with a median follow-up of 89 months (IQR, 62-109). Key demographic and clinical characteristics are reported in Table 1. Among 402 patients with clinically high-risk tumors, the assay identified 85 patients (21.1%) in the *low-risk* group. At 9 years, 94.7% of the *low-risk* patients remained free from distant recurrence and death from breast cancer, compared with 77.4% for the *not low-risk* patients (Table 2). DRFI sHR between *low-risk* and *not low-risk* groups was statistically significant (sHR, 0.24 [95% CI, 0.09 to 0.64]; $P = .004$), as was IDFS (HR, 0.33 [95% CI, 0.16 to 0.68]; $P = .003$). OS HR was 0.37, but did not reach statistical significance (95% CI, 0.11 to 1.22; $P = .10$).

The UNIRAD validation cohort comprised 231 patients clinically defined at high-risk (Fig 2; Table 1), with a median follow-up of 84 months (IQR, 62-105). Among 231 patients with clinically high-risk tumors, the assay identified 38 patients (16.5%) in the *low-risk* group. At 9 years, 97.3% of the *low-risk* patients remained free from distant recurrence and death from breast cancer, compared with 74.9% for the *not low-risk* patients (Table 2). DRFI sHR was 0.21, but did not reach statistical significance (95% CI, 0.02 to 1.14; $P = .07$), which we hypothesize is due to the low number of patients,

TABLE 1. Baseline Characteristics in the Development and Validation Cohorts

Characteristic	Development Cohort (N = 6,164)	CANTO (n = 402)	UNIRAD (n = 231)	Combined CANTO and UNIRAD (n = 633)
Age, median, years (IQR)	62.5 (52.5-71.8)	55.2 (45.2-65.2)	52.0 (46.5-62.0)	54.0 (46.0-64.0)
Age, years, No. (%)				
<55	1,827 (29.6)	200 (49.2)	129 (55.8)	329 (52.0)
≥55	4,337 (70.4)	202 (50.2)	102 (44.2)	304 (48.0)
Menopausal status,[a] No. (%)				
Premenopausal	595 (9.7)	174 (43.3)	85 (36.8)	259 (40.9)
Postmenopausal	4,911 (79.7)	220 (54.7)	145 (62.8)	365 (57.7)
Missing	658 (10.7)	8 (2.0)	1 (0.4)	9 (1.4)
Primary tumor size, cm, No. (%)				
≤2	3,497 (56.7)	131 (32.6)	64 (27.7)	195 (30.8)
2-5	2,318 (37.6)	213 (53.0)	109 (47.2)	322 (50.9)
>5	284 (4.6)	58 (14.4)	54 (23.4)	112 (17.7)
Missing	65 (1.0)	0	4 (1.7)	4 (0.6)
Positive lymph nodes, No. (%)				
0	3,335 (54.1)	0	0	0
1-3	1,966 (31.9)	221 (55.0)	107 (46.3)	328 (51.8)
4-9	658 (10.7)	136 (33.8)	84 (36.4)	220 (34.8)
≥10	161 (2.6)	45 (11.2)	40 (17.3)	85 (13.4)
Missing	44 (0.7)	0	0	0
Tumor stage, No. (%)				
I	2,373 (38.5)	0	0	0
IIA	1,896 (30.8)	85 (21.1)	41 (17.7)	126 (19.9)
IIB	964 (15.6)	108 (26.9)	46 (19.9)	154 (24.3)
IIIA	748 (12.1)	164 (40.8)	100 (43.3)	264 (41.7)
IIIB	26 (0.4)	0	0	0
IIIC	157 (2.5)	45 (11.2)	40 (17.3)	85 (13.4)
Missing	0	0	4 (1.7)	4 (0.6)
Histologic grade, No. (%)				
Grade 1	959 (15.6)	41 (10.2)	12 (5.2)	53 (8.4)
Grade 2	3,055 (49.6)	192 (47.8)	121 (52.4)	313 (49.4)
Grade 3	1,576 (25.6)	168 (41.8)	98 (42.4)	266 (42.0)
Missing	574 (9.3)	1 (0.2)	0	1 (0.2)
Chemotherapy, No. (%)				
Adjuvant chemotherapy	525 (8.5)	393 (97.8)	229 (99.1)	622 (98.3)
No chemotherapy	4,881 (79.2)	9 (2.2)	2 (0.9)	11 (1.7)
Missing	758 (12.3)	0	0	0
Endocrine therapy, No. (%)				
Neoadjuvant endocrine therapy	8 (0.1)	4 (1.0)	0	4 (0.6)
Adjuvant endocrine therapy	3,982 (64.6)	392 (99.0)	231 (100)	623 (98.4)
Endocrine therapy, missing timing	997 (16.2)	1 (0.2)	0	1 (0.2)
No endocrine therapy	419 (6.8)	5 (1.2)	0	5 (0.8)
Missing	758 (12.3)	1 (0.2)	0	1 (0.2)
Ki-67 status, No. (%)				
<20%	2,433 (36.9)	69 (17.2)	47 (20.3)	116 (18.3)
≥20%	1,809 (29.3)	177 (44.0)	105 (45.5)	282 (44.5)
Missing	1,922 (31.2)	156 (38.9)	79 (34.2)	235 (37.1)

(continued on following page)

TABLE 1. Baseline Characteristics in the Development and Validation Cohorts (continued)

Characteristic	Development Cohort (N = 6,164)	CANTO (n = 402)	UNIRAD (n = 231)	Combined CANTO and UNIRAD (n = 633)
Patients meeting high-risk criteria, No.				
Excluding patients with Ki-67 ≥20% as the sole high-risk criterion	1,536	320	199	519
Including all patients with at least one high-risk criterion (including Ki-67 ≥ 20%)	1,881	402	231	633

NOTE. Values may not add to 100% because of rounding error, or because data are unavailable, or could not be assessed.
[a]Menopausal status is at the time of diagnosis, with all male patients categorized as premenopausal. Pathologic tumor size, number of positive lymph nodes, and tumor stage are derived after primary surgery.

as was the case for OS (HR, 0.27 [95% CI, 0.04 to 2.05]; $P = .21$). IDFS HR was 0.24 and was statistically significant (95% CI, 0.06 to 0.99]; $P = .049$).

On the combined CANTO and UNIRAD validation cohorts, the assay identified 123/633 patients (19.4%) in the *low-risk* group. At 9 years, 95.4% of the *low-risk* assigned patients remained free of distant recurrence and death from breast cancer, compared with 76.8% for the *not low-risk* patients. Statistical significance was reached for both DRFI (0.21 [95% CI, 0.09 to 0.52]; $P < .001$; Fig 3A), IDFS (0.31 [95% CI, 0.16 to 0.60]; $P < .001$; Fig 3B), and OS (0.35 [95% CI, 0.13 to 0.97]; $P = .044$; Fig 3C).

Absolute performance results are synthesized in Table 2 and relative performance in the Data Supplement (Table S1).

To address concerns about the use of Ki-67 ≥20% as a high-risk criterion, we performed a sensitivity analysis excluding patients who were included solely on that basis (n = 114). In this reduced validation cohort (n = 519), the assay maintained strong performance for DRFI (sHR, 0.17 [95% CI, 0.04 to 0.72]; $P = .008$), IDFS (HR, 0.19 [95% CI, 0.06 to 0.60]; $P = .001$), and OS (HR, 0.48 [95% CI, 0.15 to 1.56]; $P = .22$) (Data Supplement, Table S2). Absolute 9-year event-free rates in the *low-risk* group remained high: 96.5% for DRFI, 94.0% for IDFS, and 93.3% for OS. Rates for the

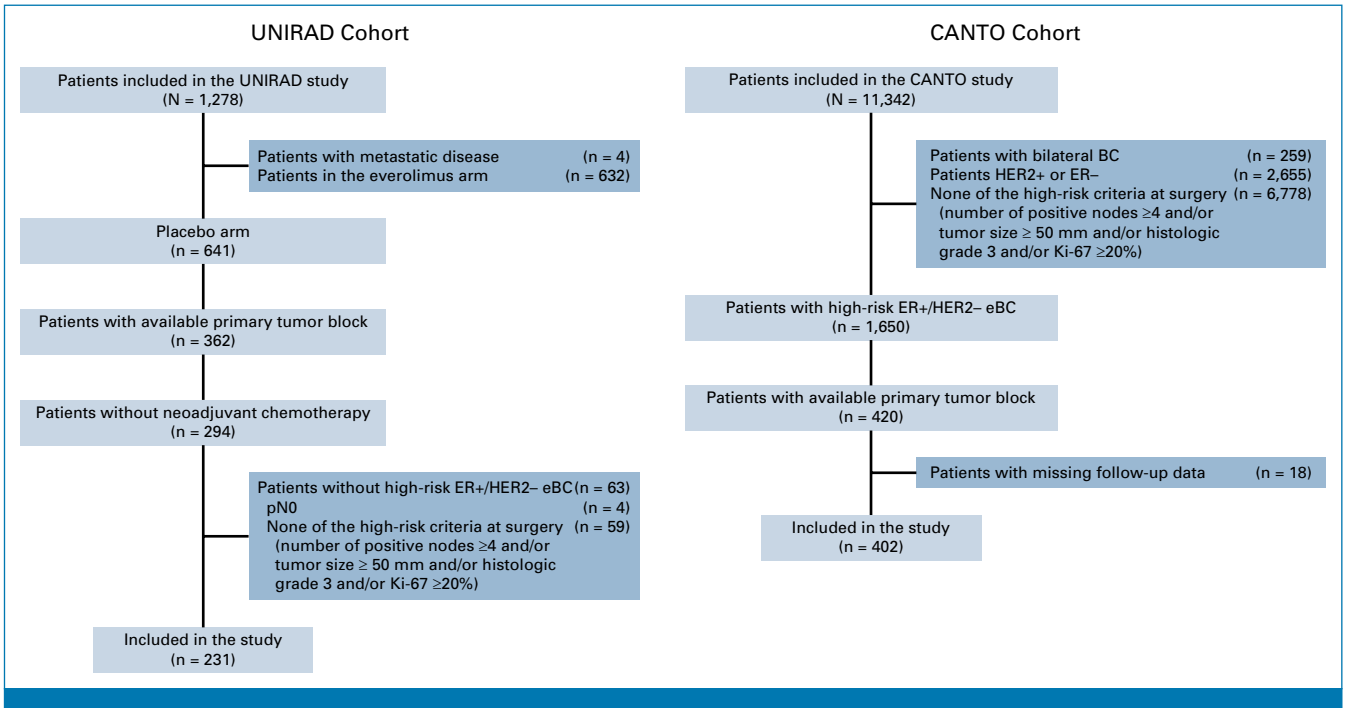

FIG 2. Flowchart of UNIRAD and CANTO. The flowchart illustrates the selection process for patients from the UNIRAD and CANTO cohorts included in the analysis. Patients were initially screened on the basis of the availability of primary tumor blocks, with exclusions made for those without samples. Patients who received neoadjuvant chemotherapy were excluded, as were those who did not meet the high-risk criteria, which included having node-positive tumor with at least one of the following: four or more positive lymph nodes, tumor size ≥50 mm, histologic grade 3, or Ki-67 ≥20%. In the UNIRAD cohort, 231 patients with high-risk ER+/HER2− eBC were included, while 402 patients were included from the CANTO cohort after excluding individuals with missing follow-up or event data. BC, breast cancer; eBC, early invasive breast cancer; ER+, estrogen receptor–positive; ER−, estrogen receptor–negative; HER2+, human epidermal growth factor receptor 2–positive; HER2−, human epidermal growth factor receptor 2–negative.

TABLE 2. Prospective-Retrospective Absolute Performance Metrics of the Assay

End Point and Cohort	Patients Assigned "Low-Risk"		Patients Assigned "Not Low-Risk"	
	Rate at 5 Years	Rate at 9 Years	Rate at 5 Years	Rate at 9 Years
Freedom from distant recurrence and death from breast cancer				
CANTO	**98.7 ± 2.5**	**94.7 ± 3.8**	86.4 ± 2.1	77.4 ± 2.9
UNIRAD	**97.3 ± 4.4**	**97.3 ± 4.4**	92.9 ± 2.0	74.9 ± 4.4
Combined	**98.2 ± 1.6**	**95.4 ± 2.8**	89.0 ± 1.5	76.8 ± 2.4
IDFS				
CANTO	96.1 ± 2.9	89.2 ± 4.2	80.9 ± 2.3	68.9 ± 3.1
UNIRAD	97.3 ± 4.4	93.2 ± 6.0	90.9 ± 2.2	70.7 ± 4.5
Combined	96.5 ± 2.0	90.3 ± 3.3	84.8 ± 1.7	69.9 ± 2.6
OS				
CANTO	100.0 ± 0.0	93.2 ± 5.0	95.3 ± 1.3	87.1 ± 2.4
UNIRAD	97.3 ± 4.4	97.3 ± 4.4	96.8 ± 1.4	88.8 ± 3.7
Combined	99.2 ± 1.4	94.5 ± 3.4	95.9 ± 1.0	87.8 ± 1.9

NOTE. Bold highlights the primary end point (DRFI) for the *low-risk* group. Event-free survival rates at 5 years and 9 years for patients stratified into *low-risk* and *not low-risk* groups on the basis of the assay classification. For freedom from distant recurrence and death from breast cancer, event rates were estimated using the CIF, accounting for competing risks. For OS and IDFS, event rates were estimated using the KM method. Values are expressed as point estimates ± SE. SEs were derived from Greenwood's formula for KM estimates and the Aalen-Johansen estimator for CIF estimates.

Abbreviations: CIF, cumulative incidence function; DRFI, distant recurrence-free interval; IDFS, invasive disease-free survival; KM, Kaplan-Meier; OS, overall survival.

not low-risk group were 77.9%, 71.0%, and 86.8%, respectively (Data Supplement, Table S3 and Fig S13). These findings confirm the assay's robustness, independent of Ki-67–based inclusion.

Subgroup Analyses

The *low-risk* group's DRFI remained consistent across subgroups (Fig 4A), with sHR ranging from 0.17 to 0.44. All *P* values for subgroup interactions were nonsignificant. HR for IDFS ranged from 0.23 to 0.71 (Figs 4B), with no significant interaction *P* values. In particular, the sHR for DRFI was consistent across premenopausal patients (sHR, 0.19 [95% CI, 0.05 to 0.76]; $P = .02$) and postmenopausal patients (sHR, 0.24 [95% CI, 0.07 to 0.76]; $P = .01$), as was the case for IDFS (premenopausal HR, 0.31 [95% CI, 0.11 to 0.87]; $P = .03$, and postmenopausal HR, 0.33 [95% CI, 0.14 to 0.76]; $P = .01$). 35 of the 266 patients with grade 3 were assigned to the *low-risk* group. Among grade 3 patients, 0/35 assigned *low-risk* had an IDFS event, while 52/231 (22.51%) assigned *not low-risk* had an IDFS event. No patient with more than 10 lymph nodes were assigned to the *low-risk* group, and one patient out of 112 with a tumor size larger than 5 cm was assigned to the *low-risk* group. Excluding pN3 and pT3 patients, the assay identified 26.1% (122/467) of the patients as *low-risk* (Data Supplement, Table S4).

Independence Testing

The DRFI sHR of the assigned groups, adjusted for menopausal status, tumor size, nodal status, and grade, was statistically significant (sHR, 0.37 [95% CI, 0.14 to 0.96]; $P = .04$). The adjusted HR for IDFS was also statistically significant (HR, 0.43 [95% CI, 0.21 to 0.87]; $P = .02$). Logistic regression confirmed that clinicopathologic variables alone could not fully account for the assay's binary predictions (pseudo $R^2 = 0.35$). Exploratory unimodal models (routine clinicopathologic variables or slide-derived variables) obtained worse results than the current bimodal assay, with sHR ranging from 1.74 to 2.64 compared with the latter (Data Supplement, Tables S4 and S5, and Fig S14). These findings suggest that the assay captures additional, independent information beyond what is provided by clinicopathologic data.

Robustness of the Assay

For robustness to tumor heterogeneity and pathology laboratory protocols, among the 200 sampled patients, 127 tumors had an additional tumor block containing at least 50% tumor content compared with the block with most tumor. The assay's assigned groups between interblock slides were concordant in 96.9% of cases (123/127). For scanning platforms robustness, the assay obtained a reproducibility of 100% (150/150) across each pair of digitized slides scanned on three scanners (450 pairs of slides; Data Supplement, Figs S15-S18). For the assessment of clinicopathologic variables, 97.8% of the assigned groups were concordant across all 1,000 Monte Carlo simulations for each of the 100 patients.

DISCUSSION

Our assay identifies a subgroup of patients with ER+/HER2– eBC who, despite meeting contemporary criteria for adjuvant

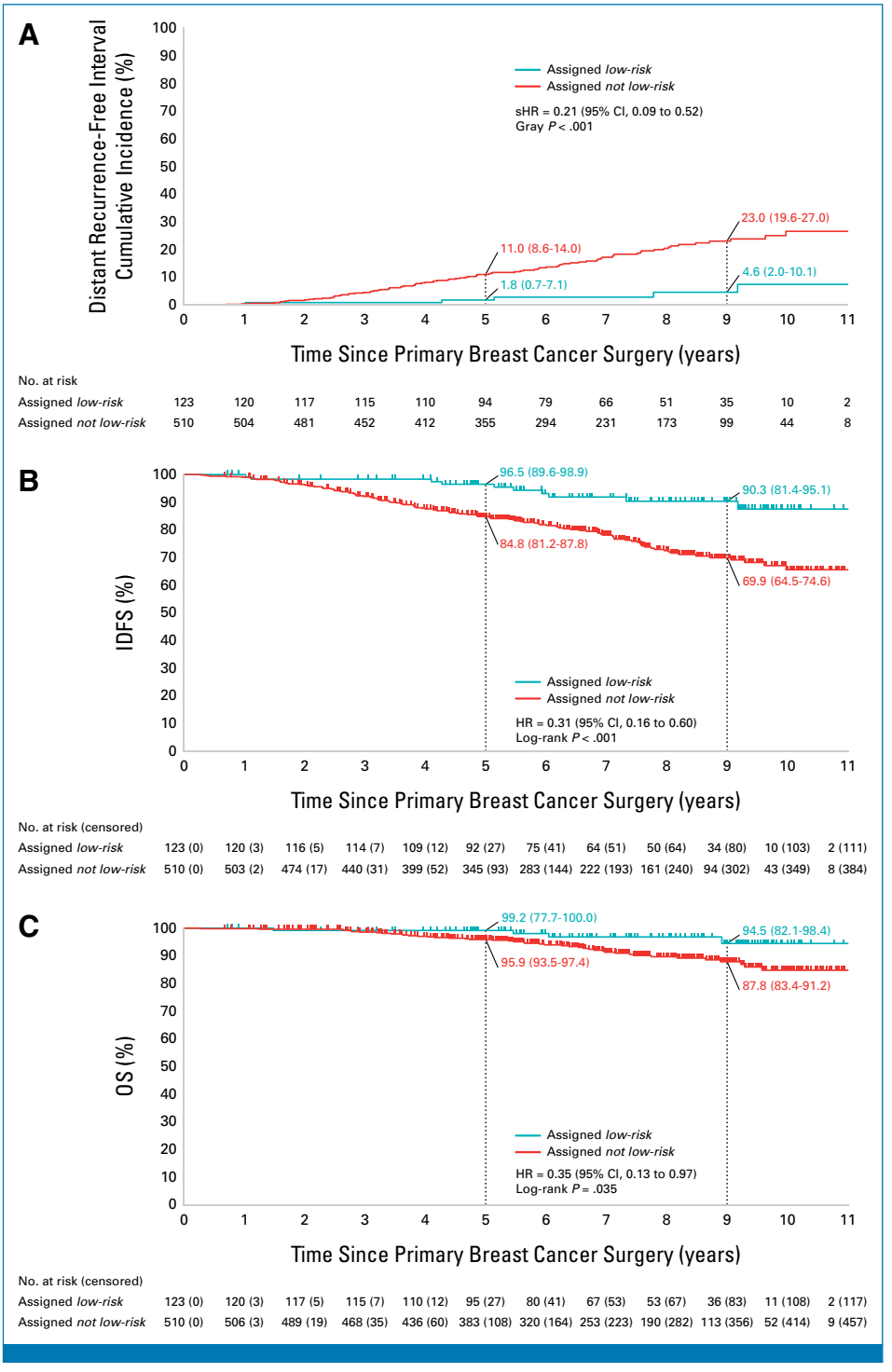

FIG 3. Survival analyses by risk group (low-risk *v* not low-risk) assigned by the assay. Survival outcomes for DRFI, IDFS, and OS on the combined CANTO and UNIRAD cohorts, stratified by the risk group classification (low-risk *v* not low-risk) assigned by the assay. (A) DRFI estimated using the CIF to account for competing risks such as deaths unrelated to breast cancer. sHR and 95% CI were calculated using the Fine and Gray model, with *P* values obtained from Gray's test. (B) IDFS estimated using Kaplan-Meier survival analysis. HR and 95% CI were derived from Cox proportional-hazards models, with statistical significance assessed using the log-rank test. (C) OS also estimated using Kaplan-Meier survival analysis, with HR and 95% CI calculated using Cox proportional-hazards models and *P* values obtained from the log-rank test. In each figure, survival curves for the *low-risk* group (teal) and *not low-risk* group (red) are shown. Numbers at risk are displayed below the *x*-axis. Summary estimates of sHR (for DRFI) or HR (for IDFS and OS), with (continued on following page)

FIG 3. (Continued). their corresponding *P* values, are reported within the plots. CIF, cumulative incidence function; DRFI, distant recurrence-free interval; IDFS, invasive disease-free survival; HR, hazard ratio; OS, overall survival; sHR, subdistribution hazard ratios.

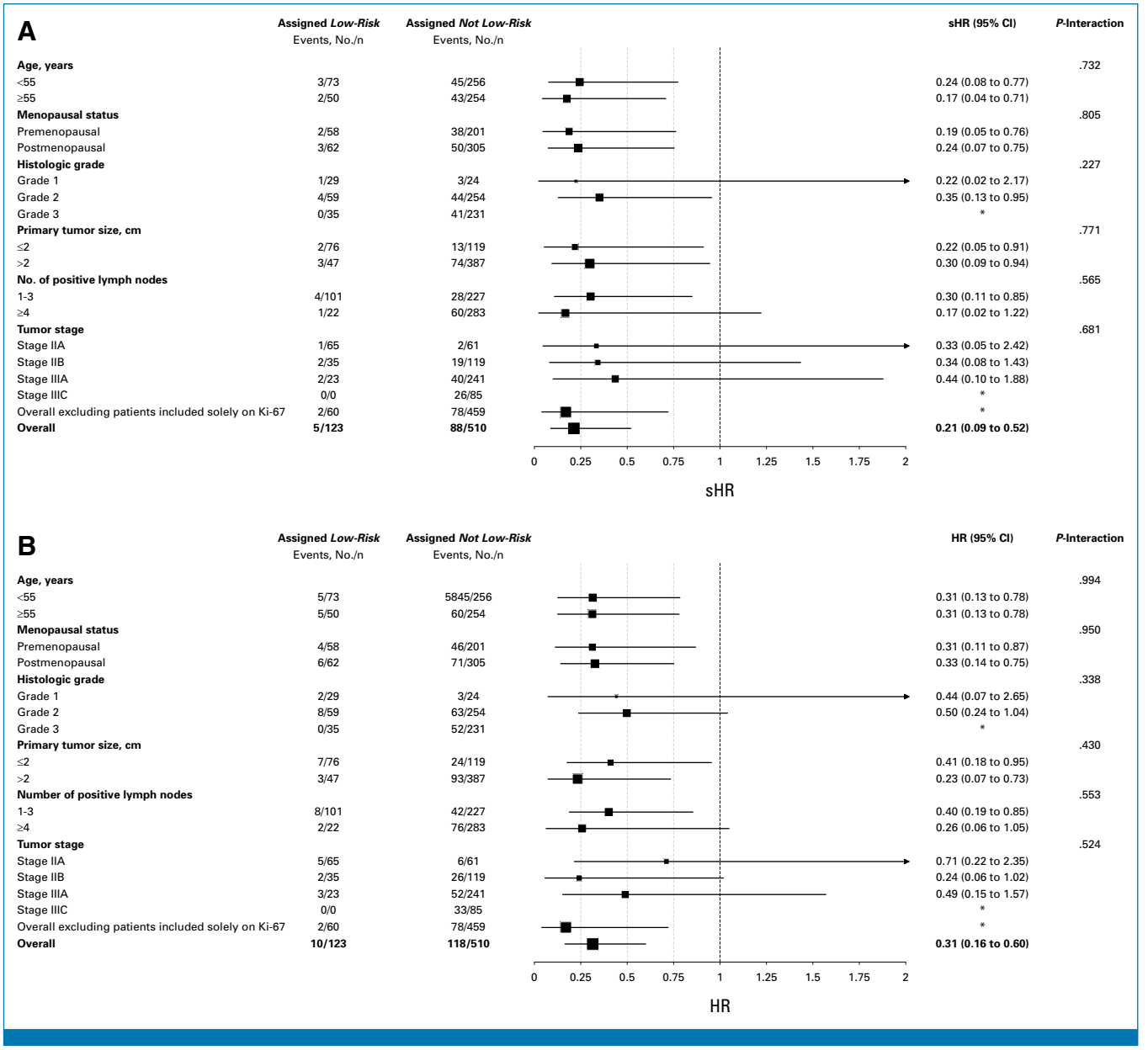

FIG 4. Subgroup analyses of DRFI and IDFS. Forest plots showing subgroup analyses of survival outcomes for (A) DRFI and (B) IDFS on the combined CANTO and UNIRAD cohorts. The *x*-axis represents sHR for (A) or HR for (B), with the vertical dashed line at 1.0 indicating no difference between the assigned *low-risk* and *not low-risk* groups. Squares represent the point estimates, with their size proportional to the number of patients in each subgroup. Horizontal lines denote 95% CI. In both plots, the overall hazard ratio and confidence interval are summarized in the row labeled *Overall*. Rows marked with * indicate subgroups where no events occurred in the *low-risk* group, making it impossible to compute HR or sHR values for those categories. (A; DRFI): sHR were estimated using Fine and Gray models to account for competing risks (deaths unrelated to breast cancer). Gray's test was used to compute *P* values for differences across subgroups, and p-interaction values evaluate heterogeneity between subgroups. (B; IDFS): HRs were calculated using Cox proportional-hazards models. The log-rank test was used to compute *P* values for differences across subgroups, and p-interaction values assess heterogeneity between subgroups. DRFI, distant recurrence-free interval; HR, hazard ratio; IDFS, invasive disease-free survival; sHR, subdistribution hazard ratio.

therapy escalation, demonstrate excellent long-term outcomes after chemoendocrine therapy alone. Under current guidelines, these patients would typically be considered for additional targeted treatments such as CDK4/6 inhibitors and inclusion in trials.[8,9,18] However, our validation demonstrates that the assay-defined *low-risk* group has minimal residual relapse risk without these intensified therapies. Thus, this selective de-escalation approach could reduce unnecessary treatment exposure, associated toxicity, and health care costs while preserving excellent patient outcomes.

This assay-driven de-escalation paradigm mirrors the evolution of chemotherapy de-escalation over the past two decades, with landmark trials such as TAILORx, MINDACT, and RxPONDER.[19–21] Notably, the *low-risk* group identified by our assay demonstrates relapse rates comparable with node-negative intermediate-risk patients reported in the TAILORx trial (5.5% at 9 years for pN0 intermediate-risk *v* 4.6% at 9 years for our assay, with 87 and 84 months of median follow-up, respectively).[19] Given that the patients in the Oncotype DX intermediate-risk subgroup have been deemed ineligible for adjuvant escalation,[8,22] our assay's similar residual risk suggests that the newly identified *low-risk* patients could similarly avoid additional adjuvant interventions without compromising survival. Hence, the logic guiding chemotherapy de-escalation could be extended to targeted therapy escalation, reinforcing the principle of optimization of individualized treatment.

The prospective-retrospective design of this study offers a significant strength, replicating the conditions of a prospective trial.[23] Importantly, the assay was locked-down after development, without any changes afterward, and the validation was blinded to outcomes and to cohort distributions. Clinical utility beyond treatment selection intervention was further demonstrated with the independence to the traditional clinicopathologic variables used for treatment selection.

Our study has several limitations. First, the validation cohorts did not include, by design, patients treated with neoadjuvant chemotherapy. Its performance on patients thus treated is therefore unknown. Additionally, the assay's ability to predict relapse risk from presurgical biopsies remains uncertain. Both these aspects could be addressed in future studies. Moreover, the assay identified almost no patients with N3 disease (≥10 positive lymph nodes) or T3 tumors (>5 cm) as *low-risk*, which limits its applicability in these very high-risk subgroups. However, since the majority of patients currently eligible for adjuvant contemporary treatment escalation do not have N3 or T3 tumors,[1,2] the assay retains substantial clinical utility for identifying patients who may safely avoid treatment escalation.

Our findings illustrate how detailed characterization of tumor biology using contemporary computational methods can reveal novel prognostic insights with the potential to refine clinical decision making in breast cancer. Given its simplicity, robustness, and reliance on routinely collected clinicopathologic variables and standard H&E slides, our assay is particularly well suited for eventual integration into routine clinical practice, offering a pragmatic approach toward more personalized patient care.

AFFILIATIONS

[1]Institut Curie, Paris, France
[2]Gustave Roussy, Villejuif, France
[3]Centre Léon Bérard, Lyon, France
[4]Spotlight Medical, Paris, France
[5]U1018, Inserm, Paris, France
[6]Unicancer, Paris, France
[7]Mines Paris—PSL, Paris, France
[8]U1331, Inserm, Paris, France
[9]Centre Jean Perrin, Université Clermont Auvergne, Inserm, U1240, Clermont-Ferrand, France
[10]University of Texas MD Anderson Cancer Center, Houston, TX
[11]City of Hope Comprehensive Cancer Center, Duarte, CA
[12]Inserm U970, Paris, France
[13]U981, Inserm, Paris, France
[14]PRISM, Inserm, Gustave Roussy, Villejuif, France

CORRESPONDING AUTHOR

Marvin Lerousseau, PhD; e-mail: marvin.lerousseau@spotlightmedical.com.

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AUTHOR CONTRIBUTIONS

Conception and design: François-Clément Bidard, Grégoire Gessain, Lucie Frechin, Anne Vincent-Salomon, Damien Drubay, Antoine Bichat, Hope S. Rugo, Joana Ribeiro, Magali Lacroix-Triki, Marvin Lerousseau
Provision of study materials or patients: Thomas Bachelot, Anne Vincent-Salomon, Jérôme Lemonnier, Frédérique Penault-Llorca, Catherine Gaudin, Barbara Pistilli
Collection and assembly of data: Grégoire Gessain, Thomas Bachelot, Anne Vincent-Salomon, Jérôme Lemonnier, Anne-Laure Martin, Catherine Gaudin, Farah Sassi, Sylvain Berlemont, Barbara Pistilli, Magali Lacroix-Triki
Data analysis and interpretation: François-Clément Bidard, Grégoire Gessain, Thomas Bachelot, Lucie Frechin, Anne Vincent-Salomon, Thomas Walter, Frédérique Penault-Llorca, Antoine Bichat, Mariana Chavez-MacGregor, Cécile Badoual, Barbara Pistilli, Joana Ribeiro, Antonio Di Meglio, Ines Vaz Luis, Marvin Lerousseau, Fabrice André
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Identifying Patients With Low Relapse Rate Despite High-Risk Estrogen Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Early Breast Cancer: Development and Validation of a Clinicopathologic Assay

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François-Clément Bidard
Consulting or Advisory Role: Pfizer, AstraZeneca, Lilly, Novartis, Roche, SAGA Diagnostics, Daiichi-Sankyo, Foresight Diagnostics, Inatherys, Menarini Silicon Biosystems
Speakers' Bureau: Novartis, AstraZeneca, Lilly, Daiichi-Sankyo, Roche
Research Funding: Novartis (Inst), Pfizer (Inst), Menarini Silicon Biosystems (Inst), Prolynx (Inst), Merck KGaA (Inst), GE Healthcare (Inst), SAGA Diagnostics (Inst), MSD (Inst), Personalis (Inst), Tempus (Inst), Roche (Inst)
Patents, Royalties, Other Intellectual Property: *ESR1* & MSI detection techniques (patents) (Inst), Prognosis assessment by a digital pathology assay in early breast cancer (Inst)
Travel, Accommodations, Expenses: Roche, Pfizer, AstraZeneca, Novartis, Daiichi-Sankyo

Grégoire Gessain
Employment: Spotlight Medical
Leadership: Spotlight Medical
Stock and Other Ownership Interests: Spotlight Medical

Thomas Bachelot
Consulting or Advisory Role: Novartis, Pfizer, Seagen, Daiichi Sankyo/Astra Zeneca, Lilly
Research Funding: Novartis (Inst), AstraZeneca (Inst), Seagen (Inst), Pfizer (Inst), Daiichi Sankyo/Astra Zeneca (Inst)
Travel, Accommodations, Expenses: Roche, Pfizer, AstraZeneca, Novartis

Lucie Frechin
Employment: Spotlight Medical
Stock and Other Ownership Interests: Spotlight Medical

Anne Vincent-Salomon
Stock and Other Ownership Interests: Primaa, IBEX Medical Analytics
Honoraria: Roche, AstraZeneca, MSD Oncology, Daiichi Sankyo/AstraZeneca, Leica Biosystems, IBEX Medical Analytics
Consulting or Advisory Role: IBEX Medical Analytics, Primaa
Research Funding: NanoString Technologies (Inst), AstraZeneca (Inst), IBEX Medical Analytics (Inst), MSD Avenir (Inst)
Travel, Accommodations, Expenses: NanoString Technologies, Roche/Genentech, IBEX Medical Analytics
Other Relationship: IBEX Medical Analytics

Thomas Walter
Honoraria: Incyte, IPSEN, Bristol Myers Squibb Foundation, Pierre Fabre, SERVIER, AstraZeneca, Advanced Accelerator Applications, MSD Oncology, ITM Oncologics, Terumo
Consulting or Advisory Role: Advanced Accelerator Applications, Orano Med, Terumo, Sirtex Medical, ITM Isotope Technologies Munich
Research Funding: Biodena, Advanced Accelerator Applications, Ipsen, Roche/Genentech
Travel, Accommodations, Expenses: MSD Oncology

Frédérique Penault-Llorca
Consulting or Advisory Role: AstraZeneca, AstraZeneca/Daiichi Sankyo, BMS, AstraZeneca (Inst), Lilly, Lilly (Inst), Novartis, Pfizer, Bayer, Roche, Roche (Inst), MSD/AstraZeneca, MSD, GlaxoSmithKline, Illumina, Exact Sciences, NanoString Technologies, Gilead Sciences, Eisai Europe, Janssen, Astellas Pharma, Amgen, SERVIER, Myriad Genetics, BeiGene
Research Funding: Bayer (Inst), MSD (Inst), Myriad Pharmaceuticals (Inst)
Travel, Accommodations, Expenses: Roche (Inst), MSD (Inst), Bayer (Inst), Pfizer, Novartis, Lilly, Daiichi Sankyo/AstraZeneca, GlaxoSmithKline

Antoine Bichat
Employment: Spotlight Medical
Stock and Other Ownership Interests: Spotlight Medical

Sylvain Berlemont
Employment: Spotlight Medical
Leadership: Spotlight Medical
Stock and Other Ownership Interests: Spotlight Medical

Mariana Chavez-MacGregor
Employment: MD Anderson Physician's Network
Consulting or Advisory Role: Exact Sciences, Lilly, AstraZeneca/Daiichi Sankyo, Roche/Genentech, Adium Pharma, Merck, AstraZeneca, Novartis, Gilead Sciences
Research Funding: Novartis (Inst), Genentech/Roche (Inst), Pfizer (Inst), Lilly, AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca, Exact Sciences, Zodiac Pharma, Novartis, Gilead Sciences
Uncompensated Relationships: Legacy Healthcare Services, The Hope Foundation

Hope S. Rugo
Honoraria: Mylan/Viatris, Chugai Pharma
Consulting or Advisory Role: Napo Pharmaceuticals, Sanofi, Bristol Meyer
Research Funding: OBI Pharma (Inst), Pfizer (Inst), Novartis (Inst), Lilly (Inst), Merck (Inst), Daiichi Sankyo (Inst), AstraZeneca (Inst), Gilead

Sciences (Inst), Hoffmann-La Roche AG/Genentech, Inc (Inst), Stemline Therapeutics (Inst), Ambryx (Inst)
Open Payments Link: https://openpaymentsdata.cms.gov

Cécile Badoual
Research Funding: Sanofi (Inst)

Barbara Pistilli
Consulting or Advisory Role: Puma Biotechnology, Pierre Fabre, Novartis, Myriad Genetics, AstraZeneca, Daiichi Sankyo/UCB Japan, Olema Oncology (Inst)
Research Funding: Pfizer (Inst), Puma Biotechnology (Inst), Merus (Inst), Daiichi-Sankyo (Inst), Gilead Sciences (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: Pfizer, AstraZeneca, MSD Oncology, Novartis, Pierre Fabre, Daiichi Sankyo Europe GmbH

Joana Ribeiro
Honoraria: Novartis
Consulting or Advisory Role: Pfizer
Speakers' Bureau: MSD Oncology
Research Funding: Roche/Genentech
Travel, Accommodations, Expenses: Novartis, Roche, Lilly

Magali Lacroix-Triki
Honoraria: Myriad Genetics, AstraZeneca, Daiichi Sankyo/AstraZeneca, MSD Oncology, Roche Diagnostics Solutions, Exact Sciences
Consulting or Advisory Role: Roche
Travel, Accommodations, Expenses: Exact Sciences

Ines Vaz Luis
Honoraria: AstraZeneca (Inst), Novartis (Inst), Sandoz, Servier Monde (Inst), Chugai Pharma (Inst), Institut de Recherches Internationales Servier (Inst)
Research Funding: Resilience Care (Inst)
Travel, Accommodations, Expenses: Novartis

Marvin Lerousseau
Employment: Spotlight Medical
Leadership: Spotlight Medical
Stock and Other Ownership Interests: Spotlight Medical

Fabrice André
Consulting or Advisory Role: Guardant Health (Inst), AstraZeneca (Inst), Lilly, Daiichi Sankyo (Inst), Roche (Inst), Lilly (Inst), Pfizer (Inst), Owkin (Inst), Novartis (Inst), N-Power Medicine (Inst), SERVIER (Inst), Gilead Sciences (Inst), Boston Pharmaceuticals (Inst), Relay Therapeutics (Inst), Relay Therapeutics
Research Funding: AstraZeneca (Inst), Novartis (Inst), Pfizer (Inst), Lilly (Inst), Roche (Inst), Daiichi (Inst), Owkin (Inst), Guardant Health (Inst)
Travel, Accommodations, Expenses: Novartis, Roche, GlaxoSmithKline, AstraZeneca

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