s 22

From: s 47F
Sent: Tuesday, 30 July 2019 8:22 PM
To: s 22
Cc: s 47F ; s 22
Subject: Re: Oncotype Dx [SEC=OFFICIAL]

Thanks – now got my head around it

s 47F

From: s 22
Date: Tuesday, 30 July 2019 at 3:09 pm
To: s 47F
Cc: s 47F s 22

Subject: RE: Oncotype Dx [SEC=OFFICIAL]

Thanks s 47F

All the best for your further labours on this one. Give me a call tonight if you wish to discuss further.
s 47C

s 22
Office of HTA/Technology Assessment and Access Division
Department of Health
s 22
GPO Box 9848, Canberra ACT 2601
s 22

From: s 47F
Sent: Tuesday, 30 July 2019 2:48 PM
To: s 22
Cc: s 47F s 22

Subject: Re: Oncotype Dx [SEC=OFFICIAL]

Thanks s 22 . Will look at this more tonight but in s 47C

Regards

s 47F

From: s 22
Date: Tuesday, 30 July 2019 at 5:08 am
To: s 47F
Cc: s 47F s 22

Subject: RE: Oncotype Dx [SEC=OFFICIAL]

s 47F

Thanks for the email below, the telephone conversation, and the text message.

I will try to respond in progression from the clinical evaluation to the economic evaluation.

CLINICAL EVALUATION

- The randomised comparison in TAILORx (not "Target") was designed to answer a different question than the randomised comparison in MINDACT (for MammaPrint).
- The randomised comparison in TAILORx addressed the question of whether patients receiving hormonal therapy with a low RS from OncotypeDX should also receive chemotherapy or not. The randomised comparison in MINDACT addressed the question of whether patients receiving hormonal therapy with discordant clinical and genomic results should also receive chemotherapy or not. s 47C

- From Figure 1 of the NEJM publication (Sporano et al, 2018), the following differences from the ITT populations were reported:
  - For N=3458 randomised to endocrine therapy alone:
    - 59 (2%) were excluded
    - 185 (5%) also received chemotherapy
    - 116 (3%) withdrew consent
    - 224 (6%) were lost to follow-up
    - Total = 584 (17%)
  - For N=3449 randomised to chemoendocrine therapy:
    - 137 (4%) were excluded
    - 608 (18%) did not receive chemotherapy
    - 148 (4%) withdrew consent
    - 208 (6%) were lost to follow-up
    - Total = 1101 (32%)
- s 47C Pages 14-15 of the supplementary appendix sought to address the impact of incomplete follow-up information. s 47C
- The prespecified noninferiority threshold for TAILORx was set at an HR of 1.322, which was explained in the NEJM publication (Sporano et al, 2018) as corresponding to a "5-year rate of invasive disease-free survival of 90% with chemoendocrine therapy or of 87% or less with endocrine therapy alone" (invasive disease events being a composite of invasive disease recurrence, second primary cancer, or death). This is referenced in the article back to Paik et al 2006 (which is another citation relied on in the resubmission) and an earlier article

by Sporano et al, 2008. In other words, this MCID corresponds to a 3% absolute difference in this outcome at 5 years.

- According to the critique (p76) the noninferiority margin for the secondary outcome of distant recurrence-free interval (DRFI) was set at an HR of 1.61, which reflects a 2.5% difference in this outcome s 47C

- s 47C , MINDACT did not prespecify a noninferiority threshold across the randomised comparison. The EUnetHTA arbitrary threshold was set at an HR of 0.8, s 47C

- Against these TAILORx thresholds, Figures 2 and 3 of the ESC Report provides HRs and their 95% Cis for both the ITT and "as treated" populations for two of the outcomes.
- Hazard ratios (95% Cis) are reported from TAILORx as follows:
    - Invasive disease free survival (freedom from invasive disease recurrence, second primary cancer or death) = 1.08 (0.94, 1.24)
    - Freedom from recurrence of breast cancer at a distant site = 1.10 (0.85, 1.41)
    - Freedom from recurrence of breast cancer at a distant or local-regional site = 1.11 (0.90, 1.37)
    - Overall survival = 0.99 (0.79, 1.22)
- For comparison, MINDACT hazard ratios from the MammaPrint PSD, s 47C
    - Disease-free survival (per protocol): 0.64 (0.43, 0.95) s 47C (per protocol sensitivity): 0.57 (0.37, 0.87) s 47C
    - Distant metastasis free survival (per protocol): 0.65 (0.38, 1.10) s 47C
    - Overall survival (per protocol): 0.63 (0.29, 1.37) s 47C
- Table 3 in the ESC Report reproduces Table 2 of Sporano et al 2018, which reports the 5-year and 9-year survival rates for the various outcomes – all for the ITT population and with standard errors rather than 95% CI. s 47C

- For

ECONOMIC EVALUATION:

- This submission referred to the MINDACT trial to generate clinical decisions in the arm without OncotypeDX and assumed that the RS from OncotypeDX would dictate clinical decisions in the arm with OncotypeDX (see page 111 of the critique). Table 56 summarises the estimated changes in clinical management across the two arms of the model, which shows a shift away from adding chemotherapy when the RS is less than or equal to 25 ("CT sparing"), and a shift towards adding chemotherapy when the RS is greater than or equal to 26 ("CT indicating").
- As with previous submissions, sensitivity analyses relied on ADIS I and ADIS II (each study design described on page 100 of the critique) to estimate changes in clinical practice following the receipt of OncotypeDX results as part of its construction of the economic evaluation (see Table 47 on page 101 of the critique).
- Table 59 of the critique shows that patients with an RS score less than or equal to 25 (the "CT sparing" population) had the same breast cancer transition probabilities irrespective of whether they received hormonal therapy only or hormonal therapy + chemotherapy. This was based on the overall TAILORx conclusions. Thus the model does not account for any concerns about drop-outs or drop-ins via a per protocol analysis. Chemotherapy cost offsets accrued across the arms for this population. The small net QALY gain generated for this population via the "Once-off CT disutility" (see Table 60 of the critique), s 47C

- Table 59 also shows that patients with an RS score greater than or equal to 26 ("CT indicating") get an additional treatment effect from adding chemotherapy, which arises from the Geyer et al re-analysis of the

Paik 2006 retrospective analysis of a prospective trial. This trial has previously been considered by MSAC with concerns expressed. This generates some additional chemotherapy costs, but relatively large net QALY gains, life-year gains and cost of-sets for reduced or delayed recurrence of disease. s 47C

- Combining these two populations generates a base case that is more favourable that either subpopulation, which are regarded as mutually exclusive on either side of the RS score of 25. This base case therefore has a net cost offset for chemotherapy, full cost offsets for reduced recurrent disease and overall slightly larger net QALY gain

s 47C

I trust that this provides all the information you were looking for. Apologies for any typos in this email. Happy to drill further for you if needed.

s 22
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s 22

From: s 47F
Sent: Sunday, 28 July 2019 9:13 PM
To: s 22
Cc: s 47F
Subject: Oncotype Dx [SEC=No Protective Marking]

Dear s 22

s 47C

Might be good to talk through perhaps

Regards

s 47F

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s 22

From: s 47F
Sent: Tuesday, 30 July 2019 8:28 AM
To: s 22 . s 47F
Cc: s 47F s 22
Subject: RE: Oncotype Dx [SEC=OFFICIAL]
Attachments: NEJMoa1904819 Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer.pdf

Talking about MINDACT-type alignment… and more in the attached though only published in June or in Chinese if you prefer https://nejmqianyan.cn/article/YXQYoa1904819?sg=AbW1NGsHw3NxPd6F, pls also see comments on this:
https://www.ascopost.com/issues/july-10-2019/clinical-risk-enhances-utility-of-tailorx-findings-in-young-women-with-breast-cancer/

The NEW ENGLAND JOURNAL of MEDICINE

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Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer

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ABSTRACT

BACKGROUND

The use of adjuvant chemotherapy in patients with breast cancer may be guided by clinicopathological factors and a score based on a 21-gene assay to determine the risk of recurrence. Whether the level of clinical risk of breast cancer recurrence adds prognostic information to the recurrence score is not known.

METHODS

We performed a prospective trial involving 9427 women with hormone-receptor–positive, human epidermal growth factor receptor 2–negative, axillary node–negative breast cancer, in whom an assay of 21 genes had been performed, and we classified the clinical risk of recurrence of breast cancer as low or high on the basis of the tumor size and histologic grade. The effect of clinical risk was evaluated by calculating hazard ratios for distant recurrence with the use of Cox proportional-hazards models. The initial endocrine therapy was tamoxifen alone in the majority of the premenopausal women who were 50 years of age or younger.

RESULTS

The level of clinical risk was prognostic of distant recurrence in women with an intermediate 21-gene recurrence score of 11 to 25 (on a scale of 0 to 100, with higher scores indicating a worse prognosis or a greater potential benefit from chemotherapy) who were randomly assigned to endocrine therapy (hazard ratio for the comparison of high vs. low clinical risk, 2.73; 95% confidence interval [CI], 1.93 to 3.87) or to chemotherapy plus endocrine (chemoendocrine) therapy (hazard ratio, 2.41; 95% CI, 1.66 to 3.48) and in women with a high recurrence score (a score of 26 to 100), all of whom were assigned to chemoendocrine therapy (hazard ratio, 3.17; 95% CI, 1.94 to 5.19). Among women who were 50 years of age or younger who had received endocrine therapy alone, the estimated (±SE) rate of distant recurrence at 9 years was less than 5% (≤1.8±0.9%) with a low recurrence score (a score of 0 to 10), irrespective of clinical risk, and 4.7±1.0% with an intermediate recurrence score and low clinical risk. In this age group, the estimated distant recurrence at 9 years exceeded 10% among women with a high clinical risk and an intermediate recurrence score who received endocrine therapy alone (12.3±2.4%) and among those with a high recurrence score who received chemoendocrine therapy (15.2±3.3%).

CONCLUSIONS

Clinical-risk stratification provided prognostic information that, when added to the 21-gene recurrence score, could be used to identify premenopausal women who could benefit from more effective therapy. (Funded by the National Cancer Institute and others; ClinicalTrials.gov number, NCT00310180.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sparano at Montefiore Medical Center, 1695 Eastchester Rd., Bronx, NY 10461, or at jsparano@montefiore.org.

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Clinicopathological features, including tumor size, histologic grade, and the presence of axillary lymph-node metastases, provide prognostic information about disease recurrence in women who have localized breast cancer after surgery, but these features have not been shown to be predictive of benefit from adjuvant chemotherapy.[1] In women with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative early breast cancer, the 21-gene recurrence-score assay provides prognostic information that is independent of clinicopathological features,[2] and a high score (on a scale of 0 to 100) indicates a higher rate of distant recurrence and is predictive of chemotherapy benefit. A high score has been defined as 31 or higher on the basis of the prospective validation National Surgical Adjuvant Breast and Bowel Project (NSABP) B20 and Southwest Oncology Group S8814 trial cohorts[3,4] or 26 or higher on the basis of the NSABP B20 trial cohort.[5,6]

The prospective Trial Assigning Individualized Options for Treatment (TAILORx) showed that endocrine therapy alone was noninferior to adjuvant chemotherapy plus endocrine (chemoendocrine) therapy in women with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer and a 21-gene recurrence score of 11 to 25. An exploratory analysis indicated some benefit of chemotherapy in women 50 years of age or younger who had a recurrence score of 16 to 25. The trial also showed a low percentage of women with distant recurrence (3%) at 9 years with endocrine therapy alone if the recurrence score was 0 to 15, irrespective of age.[7,8]

Here, we report the results of secondary analyses of the TAILORx trial that were designed to determine whether clinical risk, as assessed with the use of an algorithm that integrates tumor size and histologic grade, adds prognostic information to the 21-gene recurrence score and predictive information regarding the benefit of chemotherapy. We further examined the relationship between age and the absolute chemotherapy benefit in women who were 50 years of age or younger and had a recurrence score of 16 to 25.

METHODS

TRIAL DESIGN AND PATIENTS

TAILORx, a prospective clinical trial, was sponsored by the National Cancer Institute and was coordinated by the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN) Cancer Research Group, as previously described.[7] Women who participated in the trial provided written informed consent, including a statement of willingness to have treatment assigned or randomly assigned on the basis of the 21-gene Oncotype DX recurrence-score assay performed in a central laboratory (Genomic Health).[2]

OBJECTIVE AND DEFINITION OF CLINICAL RISK

The standardized definitions for efficacy end points (STEEP) criteria were used for end-point definitions.[9] One end point was the distant recurrence–free interval, referred to here as distant recurrence (defined as the time from registration to the date of distant recurrence of breast cancer, or of death with distant recurrence, if death was the first manifestation of distant recurrence). Another end point was invasive disease–free survival, defined as the time from registration to the first event of recurrence (distant or locoregional), second primary cancer (excluding nonmelanoma skin cancers), or death without evidence of recurrence.

A prespecified secondary trial objective was to determine whether clinical risk, as assessed with the use of the Adjuvant! algorithm, added information regarding prognosis for recurrence and prediction of chemotherapy benefit to that projected by the Oncotype DX test.[7] Classic pathologic information and outcome results were also used to refine models based on classic information and genomic tests. Adjuvant! is a tool that uses clinicopathological characteristics to provide estimates of breast cancer outcomes at 10 years on the basis of the Surveillance, Epidemiology, and End Results registry data and treatment effects associated with adjuvant chemotherapy and endocrine therapy derived by the Early Breast Cancer Trialists' Collaborative Group meta-analysis that has been validated in several data sets.[10,11]

Since Adjuvant! is no longer available for clinical use, we assessed the prognostic information provided by a binary clinical-risk categorization based on the Adjuvant! algorithm as used in the MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy) trial.[12] A low clinical risk was defined as the probability of breast cancer–specific survival at 10 years without systemic therapy among more than 92% of women

with estrogen receptor–positive tumors who received endocrine therapy alone, as projected by Adjuvant! (version 8.0).[11] Clinical risk was defined as low if the tumor was 3 cm in diameter or smaller and had a low histologic grade, 2 cm or smaller and had an intermediate grade, or 1 cm or smaller and had a high grade; the clinical risk was defined as high if the low-risk criteria were not met.

OVERSIGHT

This trial was coordinated by the ECOG-ACRIN Cancer Research Group, with other federally funded groups participating, including the Southwest Oncology Group, the Alliance for Clinical Trials in Oncology, NRG Oncology, and the Canadian Cancer Clinical Trials Network.

The statistical analysis was performed by the second author, the manuscript was written by the first author, and a final version of the manuscript, incorporating changes recommended by the coauthors, was reviewed and approved by all the authors, who vouch for the accuracy and completeness of the data and the adherence of the trial to the protocol (available with the full text of this article at NEJM.org). No one who is not an author contributed to the manuscript. No commercial support was provided in the planning or execution of the trial, but commercial support was provided by Genomic Health, the makers of the 21-gene risk score tool, for collection of follow-up information from the treatment sites.

STATISTICAL ANALYSIS

This analysis involved the same intention-to-treat population previously described.[7] Event-free rates were estimated with the use of the Kaplan–Meier method, with confidence intervals computed with log–log transformation and Greenwood's variance. Hazard ratios were estimated with the use of partial likelihood analysis of the Cox proportional-hazards model, with confidence intervals symmetric on the log-ratio scale. No corrections for multiple comparisons were made.

RESULTS

CLINICAL-RISK CATEGORY, 21-GENE RECURRENCE SCORE, AND AGE

The trial was conducted from April 2006 to October 2010. Of the 9719 women in the trial who were included in the primary intention-to-treat population and who had data that could be evaluated, information regarding clinical risk, including both tumor size and histologic grade, was available for 9427 (97.0%), of whom 6615 (70.2%) had low clinical risk and 2812 (29.8%) had high clinical risk, with a similar distribution according to age (≤50 years vs. >50 years). The recurrence score was high (a score of 26 to 100) in 589 patients (8.9%) with low clinical risk and in 770 patients (27.4%) with high clinical risk; these distributions were also similar according to age. Endocrine therapy administered to women who were reported to be premenopausal at registration and to have a recurrence score of 11 or higher included tamoxifen in 78% of the women (including 35% who crossed over to an aromatase inhibitor) and ovarian function suppression alone or in combination with an aromatase inhibitor in 13%; 7% of the women were reported to receive an aromatase inhibitor, which could indicate either incorrect reporting of menopausal status at registration or chemotherapy-induced menopause.

CLINICAL-RISK CATEGORY AND PROGNOSIS

Prognostic information provided by the clinical-risk category is shown in Figure 1. Estimated hazard ratios reflect the comparison of the high clinical-risk group with the low clinical-risk group; a hazard ratio greater than 1 indicated that a high clinical risk was prognostic for a higher event rate. The clinical-risk category added prognostic information regarding distant recurrence in patients who received endocrine therapy alone and who had an intermediate recurrence score of 11 to 25 (hazard ratio, 2.73; 95% confidence interval [CI], 1.93 to 3.87) and in patients treated with chemoendocrine therapy who had an intermediate recurrence score (hazard ratio, 2.41; 95% CI, 1.66 to 3.48) or a high recurrence score of 26 to 100 (hazard ratio, 3.17; 95% CI, 1.94 to 5.19).

In a model of distant recurrence incorporating clinical risk and the recurrence score for the group of patients with an intermediate recurrence score (6496 patients and 240 distant recurrences), significant prognostic information was provided by both the clinical-risk level (hazard ratio for high vs. low risk, 2.42; P<0.001) and the continuous recurrence score (hazard ratio for an increase of 1 point in the recurrence score, 1.08;

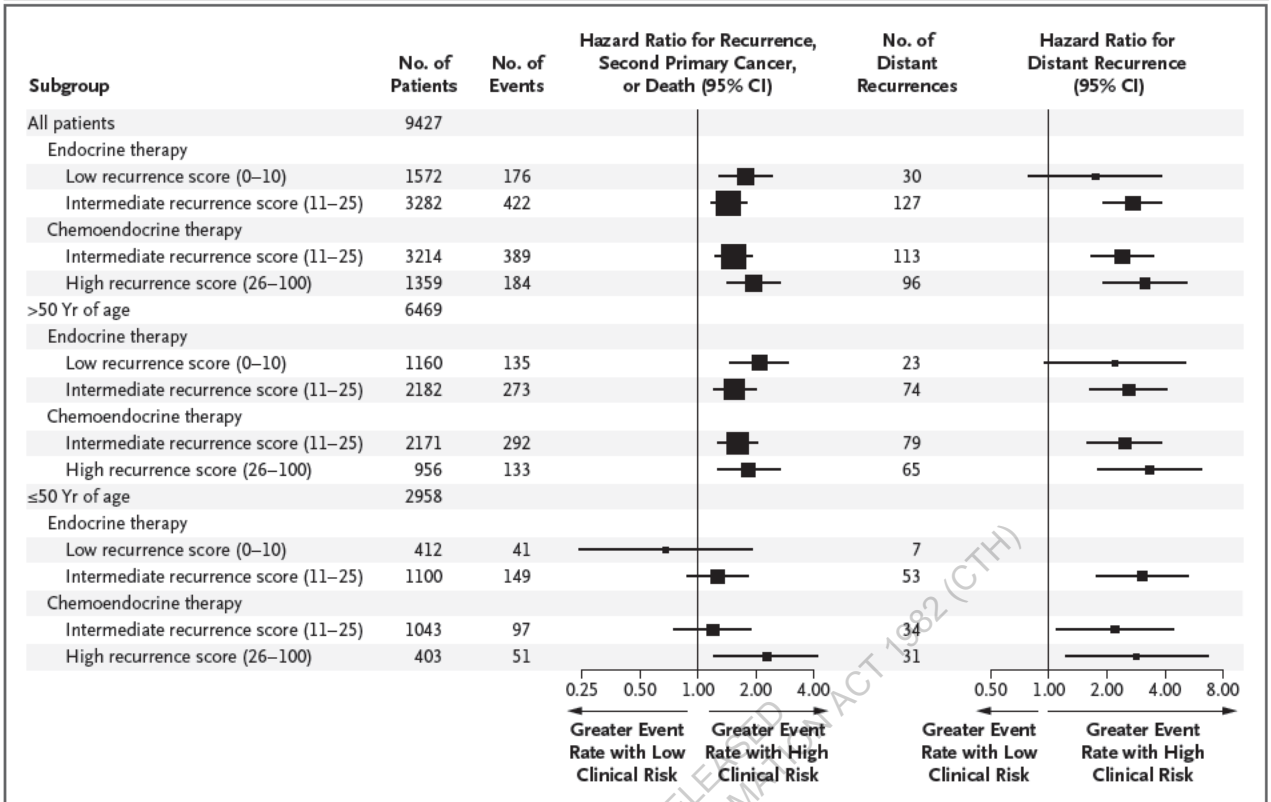

Figure 1. Effect of Clinical Risk on Prognosis in the Entire Population and Stratified According to Age.

Hazard ratios and 95% confidence intervals (CIs) for a high versus low clinical risk of invasive disease recurrence, second primary cancer, or death and for distant recurrence (a hazard ratio of >1 indicates a higher event rate with high clinical risk) are shown. There were no distant recurrences among 64 patients in the subgroup who had a high clinical risk and a low recurrence score. CIs have not been adjusted for multiple comparisons, and inferences drawn from the intervals may not be reproducible. The size of each square corresponds to the size of the subgroup; the horizontal lines represent the 95% CI.

P<0.001). Similar findings were noted for rates of invasive disease–free survival events (defined as freedom from invasive disease recurrence, second primary cancer, or death).

An evaluation of the effect of clinical risk on prognosis with respect to distant recurrence and invasive disease–free survival, stratified according to age, showed similar prognostic effects in women older than 50 years of age and in women 50 years of age or younger. Weaker associations between clinical risk and distant recurrence were observed in older women who had a low recurrence score (a score of 0 to 10) than among those who had a higher recurrence score, and no association was observed in younger women with a low recurrence score, which may be explained at least partly by the lower event rate among younger women and the smaller sample size.

CLINICAL-RISK CATEGORY AND CHEMOTHERAPY BENEFIT

Estimated treatment hazard ratios for 6496 women with an intermediate recurrence score who were randomly assigned to endocrine or chemoendocrine therapy are shown in Figure 2. An estimated hazard ratio of greater than 1 indicates a higher recurrence rate with endocrine therapy alone than with chemoendocrine therapy. The level of clinical risk was not predictive of chemotherapy benefit in women who had an intermediate recurrence score in the entire population, nor in the 4353 women who were older than 50 years of age or the 2143 women who were 50 years of age or younger (Fig. 2A). Trends suggested a chemotherapy benefit in 476 women who were younger than 50 years of age and had a recurrence score of 21 to 25, but these trends did not vary according to clinical risk (Fig. 2B).

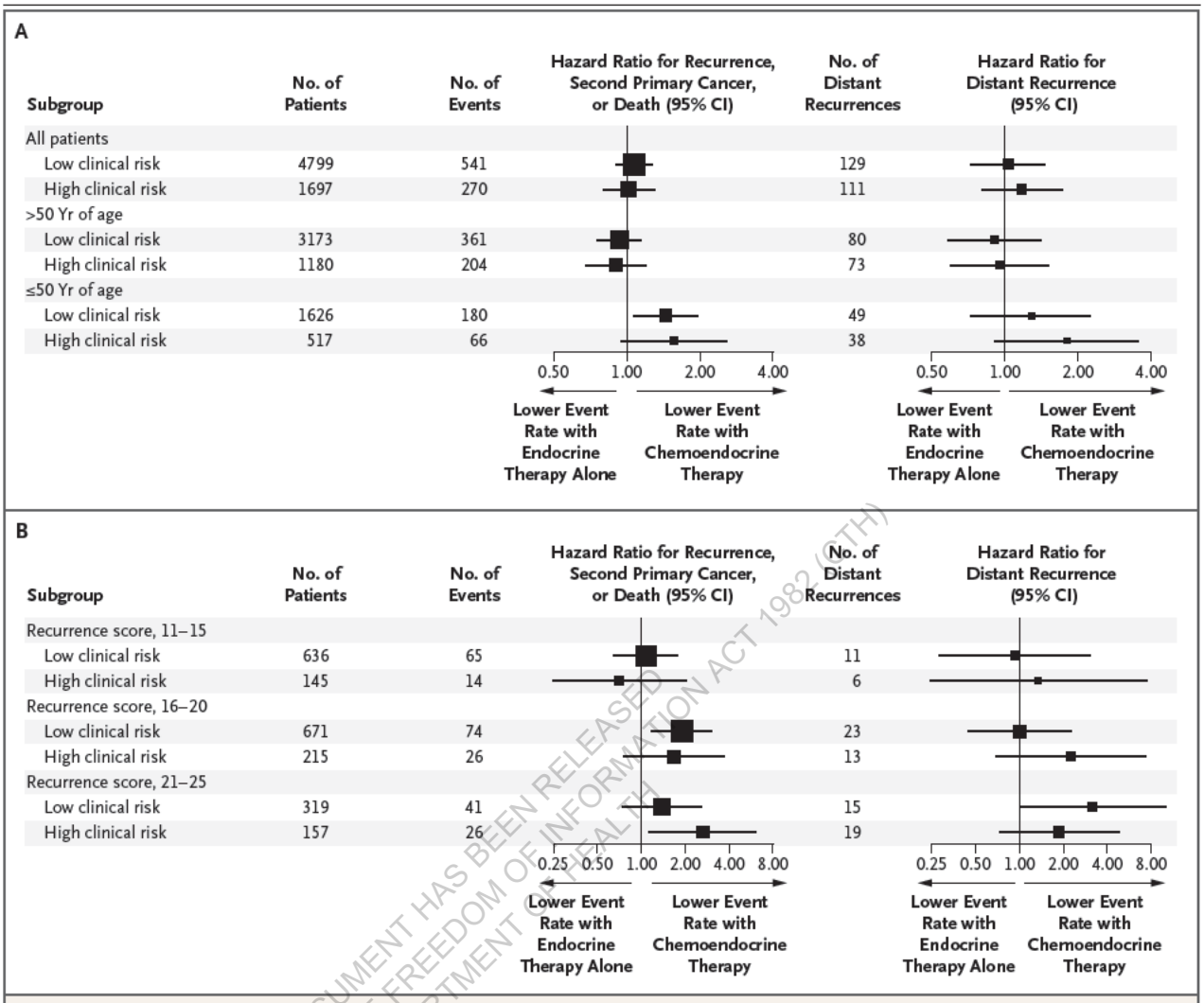

Figure 2. Effect of Clinical Risk on Prediction of Chemotherapy Benefit.

Panel A shows the effect of clinical risk on prediction of chemotherapy benefit in 6496 women with a recurrence score of 11 to 25 (on a scale of 0 to 100, with higher scores indicating a worse prognosis or a greater potential benefit from chemotherapy) who were randomly assigned to endocrine therapy or chemotherapy plus endocrine (chemoendocrine) therapy, and stratified according to age. A total of 4353 women were older than 50 years of age, and 2143 women were 50 years of age or younger. Panel B shows the effect of clinical risk on prediction of chemotherapy benefit in 2143 women who were 50 years of age or younger and had a recurrence score of 11 to 25. Estimated hazard ratios are shown for treatment (endocrine vs. chemoendocrine therapy) and 95% CIs for invasive disease–free survival and distant recurrence (a hazard ratio >1 indicates that chemoendocrine therapy is better). CIs have not been adjusted for multiple comparisons, and inferences drawn from the intervals may not be reproducible. The size of each square corresponds to the size of the subgroup; the horizontal lines represent the 95% CI.

AGE AND CHEMOTHERAPY BENEFIT

We further evaluated chemotherapy benefit as a function of age and menopausal status in 4338 women with a recurrence score of 16 to 25 (Fig. 3). We found that a chemotherapy benefit was most evident at 45 years of age in premenopausal women and waned at younger and older ages and with menopause, consistent with an effect due to chemotherapy-induced premature menopause. Similar results were found when age (without menopausal status) was evaluated as a continuous variable with the use of a natural spline (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

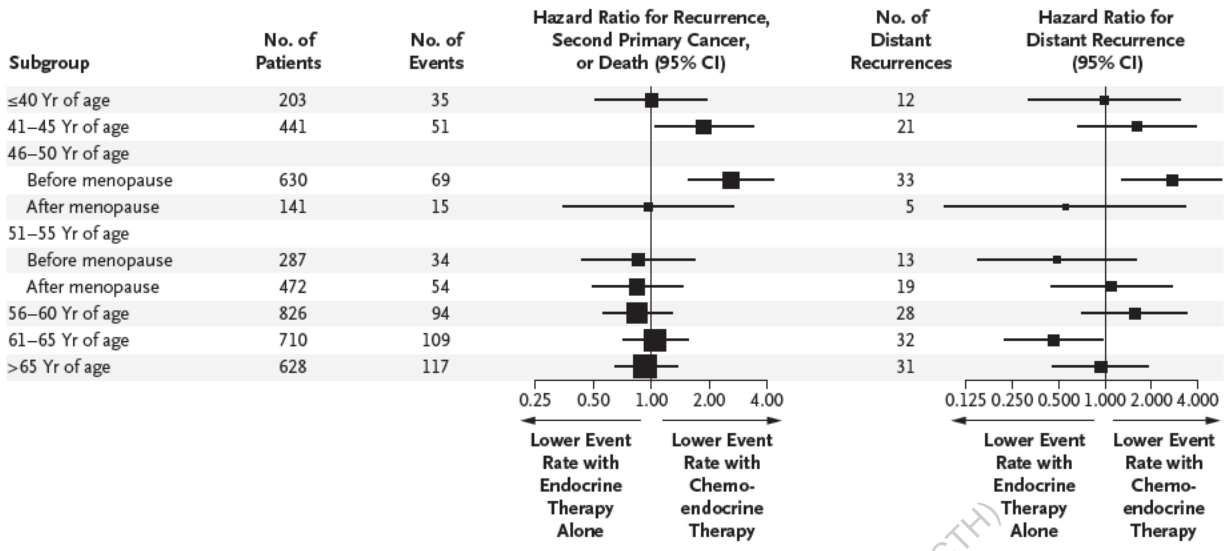

Figure 3. Effect of Age and Menopausal Status on Chemotherapy Benefit.

Shown is the effect of age and menopausal status on chemotherapy benefit in 4338 women who had a recurrence score of 16 to 25 and were randomly assigned to endocrine therapy or chemoendocrine therapy. Estimated treatment hazard ratios (endocrine vs. chemoendocrine therapy) and 95% CIs for rates of distant recurrence at 9 years are shown (a hazard ratio >1 indicates that chemoendocrine therapy is better). Menopause was defined as an age of 60 years or older; an age of 45 to 59 years with spontaneous cessation of menses for at least 12 months before registration; an age of 45 to 59 years with cessation of menses for less than 12 months before registration and a follicle-stimulating hormone (FSH) level in the postmenopausal range (or >34.4 IU per liter if the institutional range was not available); prior bilateral oophorectomy; or age younger than 60 years with prior hysterectomy without bilateral oophorectomy and an FSH level in the postmenopausal range (or >34.4 IU per liter if the institutional range was not available). CIs have not been adjusted for multiple comparisons, and inferences drawn from the intervals may not be reproducible. The size of each square corresponds to the size of the subgroup; the horizontal lines represent the 95% CI.

EVENT RATES AT 9 YEARS, STRATIFIED ACCORDING TO AGE

Kaplan–Meier estimates of event rates at 9 years, stratified according to age, are shown in Table 1. In 6469 women who were older than 50 years of age (two thirds of the trial population), the mean (±SE) distant recurrence rate at 9 years was similar, irrespective of use or nonuse of chemotherapy, in the cohort with an intermediate recurrence score, regardless of whether the clinical risk was low (4.0±0.7% vs. 3.5±0.6%) or high (8.3±1.5% vs. 9.3±1.9%). Similar findings were noted with respect to invasive disease–free survival.

In 2958 women who were 50 years of age or younger (one third of the trial population), use or nonuse of chemotherapy in the group with an intermediate recurrence score was associated with similar distant recurrence rates at 9 years if the clinical risk was low (3.9±1.0% and 4.7±1.0%, respectively), but distant recurrence rates were lower with the use of chemotherapy in the group with high clinical risk (6.1±1.8% and 12.3±2.4%, respectively). Rates of distant recurrence at 9 years were very low among patients who were 50 years of age or younger who had a low recurrence score, irrespective of clinical-risk category (≤1.8±0.9%). Owing to fewer second primary cancers and deaths, rates of invasive disease–free survival events were lower among younger women across all recurrence-score groups than among women who were older than 50 years of age.

The level of clinical risk also added prognostic information with regard to distant recurrence in the 1359 women (both younger and older women) with a high recurrence score who received chemoendocrine therapy. Distant recurrence rates were also low among 589 women with a high recurrence score and low clinical risk who received chemotherapy (7.0±2.4% among older women and

Table 1. Distant or Locoregional Disease Recurrence, Second Primary Cancer, or Death, and Distant Recurrence at 9 Years, According to Use or Nonuse of Adjuvant Chemotherapy, Stratified According to Age, Recurrence Score, and Clinical Risk (Intention-to-Treat Population).*

Variable	Clinical Risk	No. of Patients	Estimated Probability of Recurrence, Second Primary Cancer, or Death	Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI)†	Estimated Probability of Distant Recurrence	Hazard Ratio for Distant Recurrence (95% CI)†
			percent		*percent*	
Patients >50 yr		6469				
Low recurrence score (0–10)						
No chemotherapy	High	281	27.2±4.5	2.09 (1.47–2.96)	7.4±3.4	2.20 (0.95–5.08)
No chemotherapy	Low	879	13.3±1.5		2.6±0.8	
Intermediate recurrence score (11–25)						
No chemotherapy	High	577	23.2±2.6	1.56 (1.21–2.00)	9.3±1.9	2.61 (1.65–4.11)
No chemotherapy	Low	1605	13.6±1.1		3.5±0.6	
Chemotherapy	High	603	22.6±2.3	1.61 (1.27–2.04)	8.3±1.5	2.49 (1.60–3.87)
Chemotherapy	Low	1568	15.7±1.3		4.0±0.7	
High recurrence score (26–100)						
Chemotherapy	High	542	32.1±4.4	1.85 (1.28–2.66)	19.8±3.9	3.35 (1.82–6.14)
Chemotherapy	Low	414	19.3±3.8		7.0±2.4	
Patients ≤50 yr		2958				
Low recurrence score (0–10)						
No chemotherapy	High	64	9.3±4.5	0.68 (0.24–1.92)	0	0
No chemotherapy	Low	348	13.3±2.3		1.8±0.9	
Intermediate recurrence score (11–25)						
No chemotherapy	High	265	19.8±3.0	1.27 (0.89–1.83)	12.3±2.4	3.06 (1.78–5.25)
No chemotherapy	Low	835	17.4±1.8		4.7±1.0	
Chemotherapy	High	252	13.5±3.0	1.19 (0.76–1.88)	6.1±1.8	2.20 (1.10–4.40)
Chemotherapy	Low	791	11.3±1.4		3.9±1.0	
High recurrence score (26–100)						
Chemotherapy	High	228	24.0±4.2	2.27 (1.22–4.19)	15.2±3.3	2.87 (1.23–6.65)
Chemotherapy	Low	175	14.8±4.2		6.2±2.5	

* Plus–minus values are Kaplan–Meier estimates ±SE.
† A hazard ratio greater than 1 indicates that high clinical risk was prognostic for a higher event rate. Confidence intervals have not been adjusted, and inferences drawn from the intervals may not be reproducible.

6.2±2.5% among younger women) and were similar to those among older women with a low recurrence score and high clinical risk (7.4±3.4%) who received endocrine therapy alone. In contrast, among 770 women with a high recurrence score and high clinical risk, distant recurrence rates were high among both older and younger women despite the use of chemotherapy (19.8±3.9% and 15.2±3.3%, respectively).

ESTIMATION OF CHEMOTHERAPY BENEFIT IN REDUCING DISTANT RECURRENCE AT 9 YEARS

We previously reported that the estimated absolute reduction in the mean (±SE) rate of distant recurrence at 9 years associated with adjuvant chemotherapy among women 50 years of age or younger was 1.6±1.9 percentage points in those with a recurrence score of 16 to 20 and 6.4± 4.9 percentage points in those with a recurrence

score of 21 to 25.[7] Here, we provide estimates of the absolute benefit of chemotherapy, further stratified according to clinical risk (Table 2). In 476 women with a recurrence score of 21 to 25, the absolute chemotherapy benefit in the subgroup with low clinical risk (6.4±4.9 percentage points) was similar to that in the subgroup with high clinical risk (8.7±6.2 percentage points). In the 886 women with a recurrence score of 16 to 20, there was an estimated chemotherapy benefit with high clinical risk (6.5±4.9%) but not with low clinical risk (−0.2±2.1%). The sample size was small in some of the subgroups examined; this contributed to higher standard errors than estimates for the entire cohort with a recurrence score of 11 to 25.

PROGNOSIS IN WOMEN 50 YEARS OF AGE OR YOUNGER

Among women who were 50 years of age or younger, most of whom were premenopausal and treated with tamoxifen alone or followed sequentially with an aromatase inhibitor, the distant recurrence rate at 9 years was less than 5% (≤1.8±0.9%) among those with a low recurrence score, irrespective of clinical risk, and an intermediate recurrence score with low clinical risk (4.7±1.0%) (Table 1). In contrast, the rate of distant recurrence at 9 years exceeded 10% among women with high clinical risk and an intermediate recurrence score who received endocrine therapy alone (12.3±2.4%) and in those with a high recurrence score who received chemoendocrine therapy (15.2±3.3%).

DISCUSSION

The recurrence score based on the 21-gene breast cancer assay provides robust prognostic information regarding distant recurrence[2] and predicts chemotherapy benefit or lack thereof[3,4,7]; clinicopathological features provide prognostic information that is complementary to that of this assay.[13-15] The integration of genomic and clinical information may provide a more accurate estimation of prognosis for individual patients than could be provided by either the genomic or clinical information alone.[16] Our analysis confirmed that clinical-risk stratification based on tumor size and histologic grade, when added to the 21-gene recurrence score, provided prognostic information about recurrence but not predictive information regarding chemotherapy benefit.

Although TAILORx showed that endocrine therapy was noninferior to chemoendocrine therapy in women with an intermediate recurrence score (a score of 11 to 25),[7] we performed an exploratory analysis in accordance with recommended guidelines in order to determine whether any subgroup might derive some benefit from adjuvant chemotherapy.[17] There was a significant interaction between chemotherapy treatment, age (≤50 vs. >50 years) or menopausal status, and recurrence score, suggesting a modest but clinically meaningful reduction in the rate of distant recurrence with chemotherapy among younger or premenopausal women who had a recurrence score of 16 to 25.[7] Similar findings were noted in a population-based study indicating a chemotherapy benefit emerging at a recurrence score above 15 in women who were 50 years of age or younger and above 25 in women who were older than 50 years.[18]

Adjuvant chemotherapy is associated with nearly twice the reduction in the rate of death from breast cancer among women younger than 50 years of age as compared with older women[1]; this has been attributed to a dual effect, which includes a direct cytotoxic effect in eradicating micrometastatic disease and an antiestrogenic effect from chemotherapy-induced ovarian failure and premature menopause.[19,20] The interaction among age, recurrence score, and chemotherapy benefit observed in TAILORx is therefore consistent with the greater treatment effect of adjuvant chemotherapy in younger women.

Although the potential pitfalls of a subgroup analysis to identify more effective therapies in trials with a superiority design have been well described[17] and the exploratory analyses presented here were not adjusted for multiple comparisons, caution is warranted when withdrawing potentially lifesaving therapy on the basis of a noninferiority trial such as TAILORx, especially when the findings are biologically plausible and supported by population-level data, as described here. Given the incremental benefits observed with ovarian suppression plus tamoxifen or an aromatase inhibitor as compared with tamoxifen alone in premenopausal women[21,22] and the low percentage of premenopausal women who received ovarian suppression in TAILORx, it is possible that similar incremental benefits

observed in younger women who received chemotherapy and had a recurrence score of 16 to 25 could be achieved with ovarian suppression and an aromatase inhibitor, as observed in other trials.[21,22] This potential is supported by data indicating that a low-to-midrange recurrence score and high estrogen receptor 1 gene (*ESR1*) RNA expression are predictive of benefit from tamoxifen.[23,24] For patients who are approaching menopause, a strategy of an initial 2-to-5-year course of tamoxifen followed by a switch to an aromatase inhibitor at the time of natural menopause is another reasonable approach.[25] This may be especially true for women with a high *ESR1* RNA score obtained as part of the 21-gene assay, which is prognostic for late recurrence 5 or more years after diagnosis and thus may identify women who are more likely to benefit from continued antiestrogen therapy beyond 5 years.[26]

Recurrence rates reflect the underlying recurrence risk, the benefit from adjuvant endocrine therapy, and the benefit from adjuvant chemotherapy, the latter of which has little effect on nonrecurrence events such as contralateral breast cancer or second primary cancers.[27-29] Estimation of an absolute chemotherapy benefit requires tools to estimate the underlying risk of recurrence and the treatment effect of chemotherapy, which may vary in magnitude according to tumor biologic features.

When the recurrence score was further stratified according to clinical risk among TAILORx patients as described here, there was no evidence of chemotherapy benefit at 9 years in the subgroup with a low clinical risk and a recurrence score of 16 to 20, whereas the addition of chemotherapy was associated with lower rates of distant recurrence ranging from approximately 6 to 8 percentage points among women with a recurrence score of 21 to 25, irrespective of clinical risk, and a recurrence score of 16 to 20 with high clinical risk. This absolute chemotherapy benefit is similar to the benefit seen in unselected patients with node-negative, hormone-receptor–positive breast cancer,[30] but it is substantially less than the absolute benefit of 25 percentage points observed in patients with a high recurrence score of 26 to 100.[6] The treatment effect associated with chemotherapy in this subgroup is similar to that observed with ovarian suppression plus an aromatase inhibitor as compared with tamoxifen.[21,22] The level of clini-

Table 2. Recurrence, Second Primary Cancer, or Death, and Distant Recurrence at 9 Years, According to Use or Nonuse of Adjuvant Chemotherapy in Women Younger than 50 Years of Age, Stratified According to Recurrence Score and Clinical Risk (Intention-to-Treat Population).*

Variable	Clinical Risk	No. of Patients	Estimated Probability of Recurrence, Second Primary Cancer, or Death	Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI)†	Estimated Probability of Distant Recurrence	Estimated Absolute Chemotherapy Benefit	Hazard Ratio for Distant Recurrence (95% CI)†
			percent		*percent*	*percentage points*	
Recurrence score of 16–20							
No chemotherapy	Low	328	19.6±3.1	1.89 (1.18–3.04)	4.6±1.5	−0.2±2.1	1.00 (0.44–2.28)
Chemotherapy	Low	343	9.5±1.8		4.8±1.5		
No chemotherapy	High	107	19.0±4.5	1.68 (0.76–3.72)	11.9±3.9	6.5±4.9	2.26 (0.70–7.34)
Chemotherapy	High	108	16.3±5.8		5.5±3.0		
Recurrence score of 21–25							
No chemotherapy	Low	158	19.7±4.5	1.38 (0.74–2.57)	11.4±3.9	6.4±4.9	3.16 (1.01–9.94)
Chemotherapy	Low	161	15.8±4.0		5.0±3.0		
No chemotherapy	High	75	26.4±5.4	2.63 (1.14–6.05)	18.8±5.0	8.7±6.2	1.86 (0.73–4.74)
Chemotherapy	High	82	11.4±3.8		10.1±3.7		

* Plus–minus values are Kaplan–Meier estimates ±SE.
† An estimated hazard ratio of greater than 1 indicates a higher recurrence rate with endocrine therapy alone than with chemoendocrine therapy. Confidence intervals have not been adjusted, and inferences drawn from the intervals may not be reproducible.

cal risk also added prognostic information for women with a high recurrence score who were receiving chemoendocrine therapy, irrespective of age, and thus could be used to identify patients with very high risk for whom testing of new therapeutic approaches in clinical trials is warranted.

In conclusion, binary clinical-risk stratification based on tumor size and histologic grade added prognostic information to the 21-gene recurrence score, but not prediction of a large chemotherapy benefit. The addition of this information enabled more precise identification of subgroups of younger women who may derive some benefit from more effective antiestrogen therapy than a course of tamoxifen.

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APPENDIX

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REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.
2. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-26.
3. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24:3726-34.
4. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene Recurrence Score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol 2010; 11:55-65.
5. Sparano JA, Paik S. Development of the 21-gene assay and its application in clinical practice and clinical trials. J Clin Oncol 2008;26:721-8.
6. Geyer CE Jr, Tang G, Mamounas EP, et al. 21-Gene assay as predictor of chemotherapy benefit in HER2-negative breast cancer. NPJ Breast Cancer 2018;4:37.
7. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018;379:111-21.
8. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 2015;373:2005-14.
9. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol 2007;25:2127-32.
10. Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model Adjuvant! for early breast cancer. J Clin Oncol 2005;23:2716-25.

11. Mook S, Schmidt MK, Rutgers EJ, et al. Calibration and discriminatory accuracy of prognosis calculation for breast cancer with the online Adjuvant! program: a hospital-based retrospective cohort study. Lancet Oncol 2009;10:1070-6.
12. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 2016;375:717-29.
13. Goldstein LJ, Gray R, Badve S, et al. Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features. J Clin Oncol 2008;26:4063-71.
14. Tang G, Shak S, Paik S, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. Breast Cancer Res Treat 2011;127:133-42.
15. Tang G, Cuzick J, Costantino JP, et al. Risk of recurrence and chemotherapy benefit for patients with node-negative, estrogen receptor-positive breast cancer: recurrence score alone and integrated with pathologic and clinical factors. J Clin Oncol 2011;29:4365-72.
16. Dowsett M, Turner N. Estimating risk of recurrence for early breast cancer: integrating clinical and genomic risk. J Clin Oncol 2019;37:689-92.
17. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine — reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-94.
18. Hortobagyi GN, Shak S, Sledge GW Jr, et al. Breast cancer-specific mortality (BCSM) in patients (pts) with node-negative (N0) and node-positive (N+) breast cancer (BC) guided by the 21-gene assay: a SEER-genomic population-based study. Cancer Res 2019;799:4 Suppl:P3-11-02. abstract.
19. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol 2006;24:5769-79.
20. Swain SM, Jeong J-H, Geyer CE Jr, et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. N Engl J Med 2010;362:2053-65.
21. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 2015;372:436-46.
22. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med 2018;379:122-37.
23. Paik S, Tang G, Kim C, et al. Expression of the 21 genes in the Recurrence Score assay and tamoxifen clinical benefit in the NSABP study B-14 of node negative, estrogen receptor positive breast cancer. J Clin Oncol 2005;16:Suppl:510. abstract.
24. Kim C, Tang G, Pogue-Geile KL, et al. Estrogen receptor (ESR1) mRNA expression and benefit from tamoxifen in the treatment and prevention of estrogen receptor-positive breast cancer. J Clin Oncol 2011;29:4160-7.
25. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793-802.
26. Wolmark N, Mamounas EP, Baehner FL, et al. Prognostic impact of the combination of Recurrence Score and quantitative estrogen receptor expression (ESR1) on predicting late distant recurrence risk in estrogen receptor-positive breast cancer after 5 years of tamoxifen: results from NRG Oncology/National Surgical Adjuvant Breast and Bowel Project B-28 and B-14. J Clin Oncol 2016;34:2350-8.
27. Early Breast Cancer Trialists' Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379:432-44.
28. Mamounas EP, Tang G, Liu Q. The importance of systemic therapy in minimizing local recurrence after breast-conserving surgery: the NSABP experience. J Surg Oncol 2014;110:45-50.
29. Bertelsen L, Bernstein L, Olsen JH, et al. Effect of systemic adjuvant treatment on risk for contralateral breast cancer in the Women's Environment, Cancer and Radiation Epidemiology Study. J Natl Cancer Inst 2008;100:32-40.
30. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. J Natl Cancer Inst 1997;89:1673-82.

s 47C

Table 6 Summary of disaggregated incremental cost and effectiveness in CT sparing only[a]

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	s 47C	$0.00	s 47C
Chemotherapy	$1,253.65	$3,116.03	-$1,862.38
Hormone therapy	$3,160.85	$3,160.85	$0.00
Recurrent disease	$5,791.22	$5,791.22	$0.00
Total	s 47C	**$12,068.10**	s 47C
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.6530**	**13.6530**	**0**
Disease-free	*13.4577*	*13.4577*	*0*
Post recurrence	*0.1953*	*0.1953*	*0*
QALY	**13.4621**	**13.4575**	**0.0045**
Disease-free	*13.3066*	*13.3021*	*0.0045*
Post recurrence	*0.1554*	*0.1554*	*0*
		$ per life year gained	**$NA**
		$ per QALY gained	s 47C

Text in italics indicate values calculated during the critique Source: 72 p155 of the SBA, ODX_EconModel.xlsm

[a] That is, moving any patients with RS ≤25 treated with HT + CT in the usual care arm to HT only in the Oncotype DX arm

Table 7 Summary of disaggregated incremental cost and effectiveness in CT indicating only[a]

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	s 47C	$0.00	s 47C
Chemotherapy	$3,672.22	$3,116.03	$556.19
Hormone therapy	$3,175.34	$3,160.85	$14.50
Recurrent disease	$4,750.80	$5,791.22	-$1,040.43
Total	s 47C	**$12,068.10**	s 47C
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.7665**	**13.6530**	**0.1135**
Disease-free	*13.6063*	*13.4577*	*0.1486*
Post recurrence	*0.1602*	*0.1953*	*-0.0351*
QALY	**13.5752**	**13.4575**	**0.1177**
Disease-free	*13.4477*	*13.3021*	*0.1456*
Post recurrence	*0.1275*	*0.1554*	*-0.0279*
		$ per life year gained	s 47C
		$ per QALY gained	

Text in italics indicate values calculated during the critique Source: 72 p155 of the SBA, ODX_EconModel.xlsm

Typographical error corrected in blue.

[a] That is, moving any patients with RS ≥26 treated with HT only in the usual care arm to HT + CT in the Oncotype DX arm

1

Table 8 Summary of disaggregated incremental cost and effectiveness from base case

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	s 47C	$0.00	s 47C
Chemotherapy	$1,809.84	$3,116.03	-$1,306.19
Hormone therapy	$3,175.34	$3,160.85	$14.50
Recurrent disease	$4,750.80	$5,791.22	-$1,040.43
Total	s 47C	**$12,068.10**	s 47C
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.7665**	**13.6530**	**0.1135**
Disease-free	*13.6063*	*13.4577*	*0.1486*
Post recurrence	*0.1602*	*0.1953*	*-0.0351*
QALY	**13.5798**	**13.4575**	**0.1222**
Disease-free	*13.4522*	*13.3021*	*0.1501*
Post recurrence	*0.1275*	*0.1554*	*-0.0279*
		$ per life year gained	s 47C
		$ per QALY gained	

Text in italics indicate values calculated during critique
Source: Table 69, p153, Table 70 and 71 p154 of the SBA, ODX_EconModel.xlsm

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