Breast Cancers With Magee Equation Score of Less Than 18, or 18-25 and Mitosis Score of 1, Do Not Require Oncotype DX Testing

A Value Study

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ABSTRACT

Objectives: *To investigate use of Magee equations (MEs) to determine which breast cancer cases can be excluded from Oncotype DX testing.*

Methods: *A prospective value study was carried out using data from pathology reports.*

Results: *If all three MEs scores were less than 18 or 31 or higher, the cases were labeled do not send for testing. If any or all scores were 18 to 25, cases were labeled do not send if mitosis score was 1. Of the total 205 cases, 146 (71%) were labeled do not send; of these, the correct call was made in 143 (98%) cases. Two of the three discordant cases had associated nontumor factors, likely resulting in higher scores.*

Conclusions: *Cases with ME scores less than 18, or 18 to 25 and mitosis score 1, do not require Oncotype DX testing, an estimated saving of US$280,000 per 100 clinical requests.*

Breast cancer prognostic and predictive markers can be categorized as clinical (eg, tumor size at presentation and lymph node status), morphologic (eg, tumor grade), immunohistochemical (eg, hormone receptors, Ki-67 labeling index), single gene (*HER2*), or multigene assays (oncotype, mammaprint, breast cancer index, endopredict, prosigna). In the last 15 years, the molecular understanding of breast cancer has improved significantly; however, it is questionable whether the availability of molecular testing has improved our prognostic and predictive ability. Nevertheless, molecular tests are now frequently requested on breast cancer specimens. Although the molecular tests were developed as prognostic tests, they are frequently requested by medical oncologists to make chemotherapy decisions. The complete results of Trial Assigning Individualized Options for Treatment (TAILORx, a prospective clinical trial for oncotype) were only recently published; however, the use of these molecular assays for making chemotherapy decisions had been endorsed much earlier by the national societies.

Of all the available molecular assays for breast cancer prognosis and treatment, the 21-gene recurrence score or Oncotype DX (ODX) is the most widely used assay. A number of studies have shown a correlation of 21-gene recurrence score with routinely reported pathology parameters.[1-5] Our group was the first to show such a correlation.[3] In the 2008 study, we showed a direct correlation between tumor grade and 21-gene recurrence score and an inverse correlation between hormone receptor H-scores and 21-gene recurrence score.[3] Because the original equation was based on less than 50 cases, we built new models using

a much larger database. Three new equations were derived, which were validated on a separate set of 255 cases. These three new equations were published in 2013 and are now commonly referred to as the Magee equations (MEs).[6]

As per internal and external published data, MEs provide a reasonable estimate of actual ODX recurrence score.[6-12] If the estimated recurrence score is low, then the actual recurrence score will be low or intermediate with greater than 95% certainty.[6] If the estimated recurrence score is high, then the actual recurrence score will be high or intermediate with greater than 95% certainty.[6] If the estimated recurrence score is intermediate, then the actual recurrence score will be intermediate or low approximately 85% of the time.[6] These findings have remained constant based on the internal evaluation of a further 1,000 plus cases (since last publication in 2013), indicating the stability of MEs over time.

Recently, one of the MEs, Magee equation 3 (ME3), which utilizes estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 results, has been shown to be chemopredictive and also appears to have prognostic value in the neoadjuvant setting.[13] In this neoadjuvant study of 237 ER positive/HER2 negative tumors, ME3 score of 31 or higher showed a pathologic complete response rate of 36%, compared to only 4% when the score was between 18 and 30, and 0% when the score was less than 18.[13] This shows the strong predictive power of ME3. Additionally, the recurrence rates and death rates were significantly associated with ME3 scores of 31 or higher for patients with residual disease.[13]

Encouraged by these data, we designed this prospective value study, in which we tested the ability of pathologists to triage cases as either send for ODX testing or do not send for testing based on MEs and tumor proliferative activity. All clinical requests were nevertheless sent for ODX testing.

Materials and Methods

The premise of the study was to mainly identify cases that will not require ODX testing, as the benefit of chemotherapy in such patients would be negligible. All clinical requests for ODX testing from later half of 2016 to first quarter of 2018 were included. ME scores were calculated from the data in pathology reports.

The cases were labeled as do not send if all three MEs showed scores less than 18 (ie, clearly low risk) or all three equations showed scores 31 or higher (ie, clearly high risk). If any of the equations showed scores in the intermediate range but equal to or less than 25, mitosis score (one of the three components of Nottingham grading) was taken into consideration. If the mitosis score was 1, the case was again labeled as do not send. The MEs scores in decimals were not rounded off for categorization. The remaining cases were labeled as send, that is cases with any MEs score more than 25 to less than 31 and MEs scores from 18 to 25 but mitosis score of 2 or 3. We chose the cutoff of 25, as this is the score at which oncologists may start to feel uneasy and recommend chemotherapy. This is also the cutoff used to exclude cases for randomization in the TAILORx trial and the recently published test results confirm lack of chemotherapy benefit for patients with scores 25 or less.[14] Additionally, a study using a Surveillance, Epidemiology, and End Results database showed the breast cancer-specific mortality to be less than 1% in the ODX recurrence score 18 to 25 subgroup regardless of chemotherapy use.[15] Another study published last year did not show a statistically significant difference in recurrence rate between chemotherapy-treated and chemotherapy-untreated patients with recurrence scores 25 or lower.[16]

Results

A total of 205 cases were included. The age of patients ranged from 35 to 87 years, with the median age of 62 years. Most were early-stage breast cancers. Median tumor size was 1.8 cm. Of the 205 cases, 176 (86%) were lymph node negative, six (3%) showed isolated tumor cells, three (1.5%) showed micrometastasis, 13 (6%) showed one to three positive nodes, and the status was unknown on seven cases (3.5%). The 205 cases included 37 grade 1 (18%), 132 grade 2 (64%), and 36 grade 3 (18%) tumors. A higher number of grade 2 tumors indicates the selection bias for requesting clinical ODX testing. All cases were ER positive. Of the 205 cases, 197 (96%) were HER2 negative and eight (4%) were HER2 equivocal.

Based on data from original pathology reports, 59 (29%) were labeled as send and 146 cases (71%) were labeled as do not send. Of the 146 cases classified as do not send, the correct call was made in 141 cases **Table 1**, that is 98% of the time. For the 141 do not send cases (Table 1) with an actual recurrence score of 25 or less (concordant cases), the

Table 1
Cases Labeled as Do Not Send Based on Magee Equations and Mitotic Activity

Prediction Made Based on Magee Equations and Mitosis Score	Actual Oncotype DX-Recurrence Score ≤25	Actual Oncotype DX-Recurrence Score >25	Total
Do NOT send (expected Oncotype DX recurrence score to be ≤25)	141	3[a]	144
Do NOT send (clearly high risk, expected score to be ≥31)	0	2	2
Total	141	5	146

[a]Considered discordant and summarized in Table 2.

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Table 2
Details on Discordant Cases (ie, Actual Score >25 When Expected to Be ≤25)

Variables	Case 1	Case 2	Case 3
Age, y	59	52	74
Tumor size, cm	5.2	0.7	0.8
Lymph node status	Negative	Negative	Isolated tumor cells
Nottingham score	6	6	6
Histology	Mucinous (intra- and extracellular mucin)	Ductal, no special type	Ductal, micropapillary type
ER H-score	290	280	300
PR H-score	90	25	0
Ki-67 index	2	15	35
Magee score (average)	18	21	23
Actual ODX score	26	30	33
Outcome	Chemotherapy offered, declined by patient	Chemotherapy given, discontinued after 3rd cycle (side effects)	Chemotherapy given and completed
Possible reason for higher ODX score	Low PR	Increased HER2 expression and Ki-67 index in admixed DCIS	Significant Ki-67 labeling of stromal cells

DCIS, ductal carcinoma in-situ; ER, estrogen receptor; ODX, Oncotype DX; PR, progesterone receptor.

average actual recurrence score was 14, with a range from 2 to 25. Only two cases had scores of 25. In fact, 71% of these cases had actual ODX recurrence scores below 18. The two cases predicted to be clearly high risk (Table 1) had ODX recurrence scores of 28 and 57. The three cases that we consider as discordant had actual ODX scores of 26, 30, and 33. These three cases are summarized in **Table 2**. The two discordant cases (cases 2 and 3 in Table 2) with the highest ODX recurrence scores had associated nontumor factors that likely resulted in higher scores.

Discussion

Identifying which patients would benefit from chemotherapy when their tumors are ER positive and HER2 negative has become vital to breast medical oncology. Almost all of the molecular tests that were developed as prognostic assays are now used by medical oncologists for predictive purposes. ODX is the most frequently used molecular assay in the United States for making therapy decisions. The test is reported as a numerical score ranging from 0 to 100 and categorized into low risk of recurrence (scores 0 to less than 18), intermediate risk of recurrence (scores 18-30), and high risk of recurrence (scores 31 or higher).[17] Based on original studies, statistically significant chemotherapy benefit is only seen when the scores fall into the high-risk group (score 31 or higher).[18] In the prospective TAILORx clinical trial, different cutoff points were used and only patients with their tumor ODX scores 11 to 25 were randomly assigned either to endocrine therapy or endocrine plus chemotherapy groups. The results were recently published and showed that endocrine therapy is equal to chemotherapy plus endocrine therapy for patients with ODX recurrence score of 25 or less.[14] Unfortunately, patients with scores 26 to 30 were not randomized and the actual absolute chemotherapy benefit in this group will not be known from this trial.

In the last few years, our group has published multivariable models to estimate the ODX score, first as proof of principle and later as a clinically useful tool to decide if a particular tumor needs ODX testing.[3,6] The models, now commonly known as MEs, have been shown to be strongly chemopredictive in the neoadjuvant setting and also appear to have prognostic value.[13] MEs have also been tested at other institutions and have been found to be clinically useful and cost effective.[7,9-12]

An online calculator for MEs is available for free for anyone to use (http://path.upmc.edu/onlineTools/magee-equations.html). Correlation between ODX and MEs is good but is less than perfect. There are a number of reasons for discordance. ODX measures mRNA levels of 16 genes and MEs use morphologic data and semiquantitative immunohistochemical data for four proteins. We do acknowledge that variability in Nottingham grading and immunohistochemical scoring by different pathologists has the potential to impact MEs scores. However, there are also some problems inherent with mRNA extraction for molecular testing that can alter ODX scores. This issue is less emphasized but a suboptimal macrodissection can significantly impact ODX score.[19] This could be either due to operator-related issues or tumor-related issues. If the operator does not choose to macrodissect or performs inadequate macrodissection, the final ODX score would be impacted by mRNA dilution with nontumorous elements (such as lymphoid cells, benign and proliferative breast tissue). In occasional cases, invasive carcinoma is intimately admixed with other nonmalignant tissues such that a successful macrodissection cannot be performed despite best efforts.

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Nevertheless, based on promising internal and external data, we designed this prospective value study to effectively determine which cases can be safely excluded from ODX testing. It is important to note that MEs scores were calculated using data from pathology reports that were signed out by many different pathologists with variable years of experience and interest in breast pathology. Although slides were reviewed by study pathologists for grading, there were only a handful of cases with a change in Nottingham score/grade. Therefore, data based only on original pathology reports (as would occur in routine practice) were utilized for analysis. The cases were labeled as do not send or send based on MEs scores and tumor mitotic activity prior to sending the case for ODX testing.

In this dataset of clinically requested ODX by medical oncologists, 71% of the cases were labeled as do not send. Our results show that accuracy of labeling the case as do not send was 98%. The 2% discordant cases (three cases), that is cases predicted to have a score of 25 or less, but with an actual score of more than 25, were reviewed to gain further insight.

The three discordant cases had actual ODX recurrence scores of 26, 30, and 33 (Table 2). The first patient had a large tumor with low PR expression (Table 2 and **Image 1**), which is known to result in

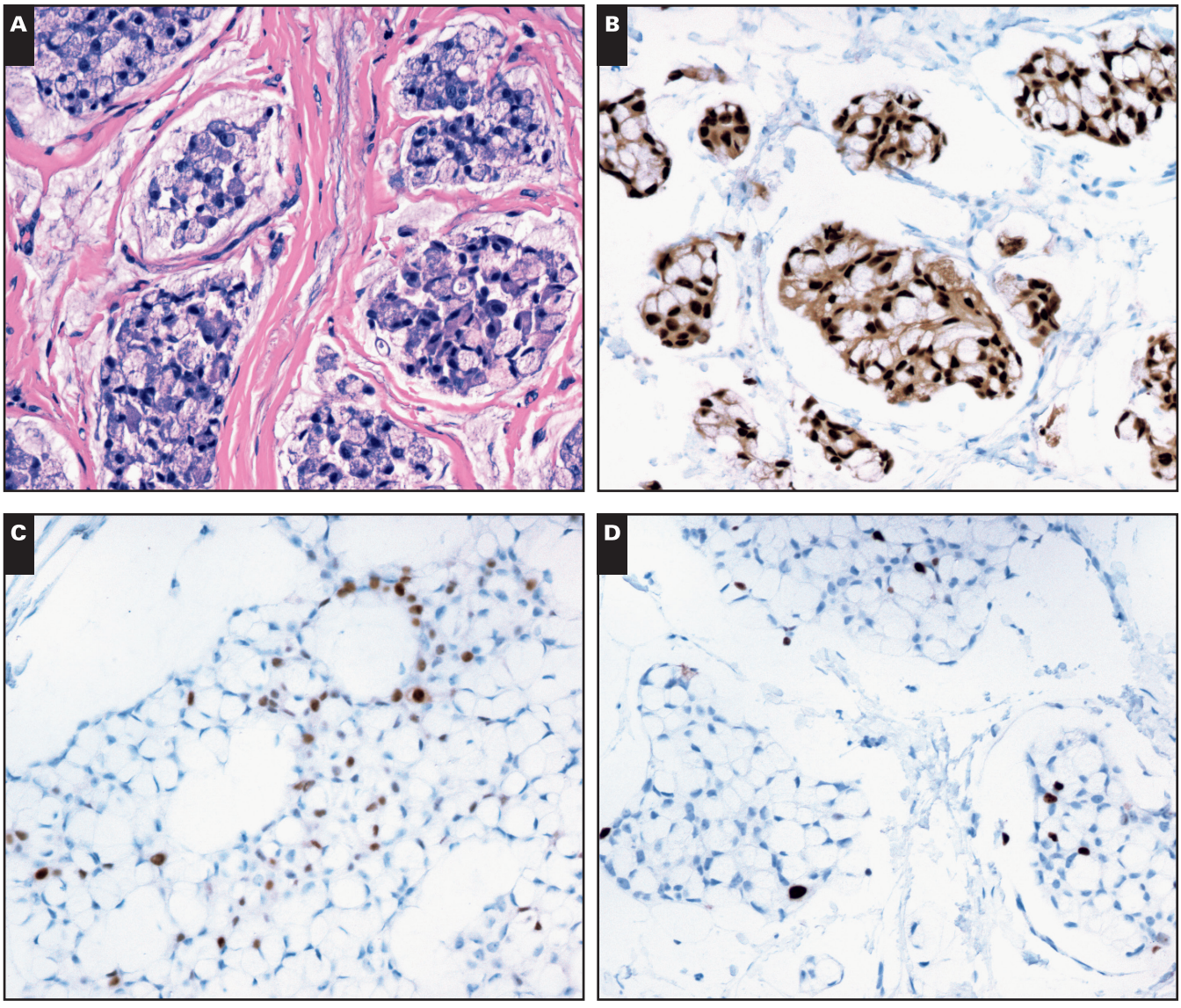

Image 1 One of five discordant cases (case 1 in Table 2) with average Magee equations score of 18 and actual Oncotype DX recurrence score of 26. This was a mucinous carcinoma with both intracellular and extracellular mucin (**A**, H&E, x200). The tumor showed diffuse strong reactivity for estrogen receptor (**B**, x200) and scattered weak reactivity for progesterone receptor (**C**, x200). The Ki-67 labeling index was very low (**D**, x200).

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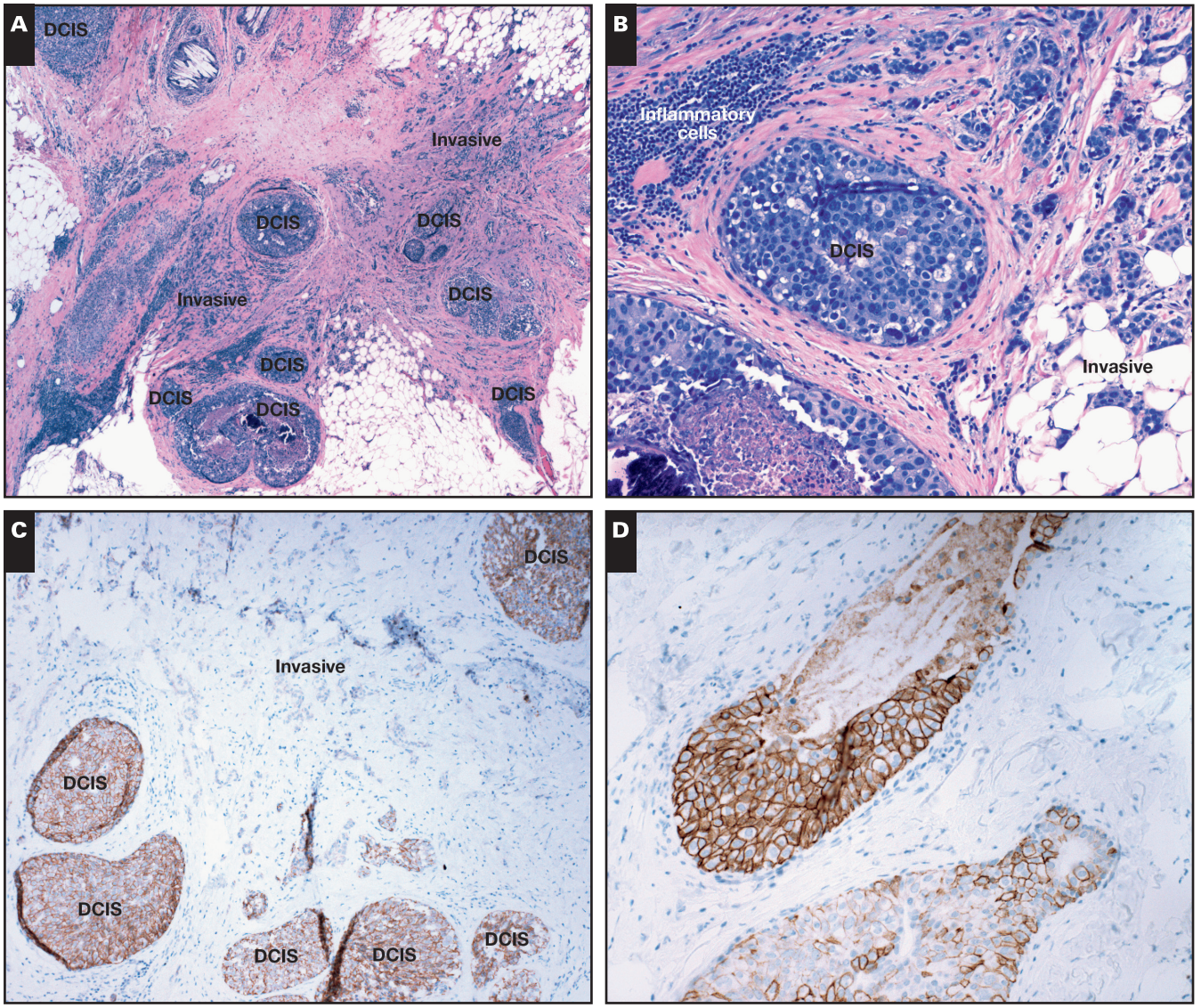

Image 2 Discordant case 2 (in Table 2) with average Magee equations score of 21 and actual Oncotype DX recurrence score of 30. The tissue block sent for testing showed abundant admixed ductal carcinoma in situ (DCIS) along with invasive ductal carcinoma (**A**, H&E, x20 and **B**, H&E, x200). The DCIS showed increased HER2 expression in comparison to invasive carcinoma (**C**, x40). Additional DCIS was present in the immediate vicinity in the same block and heterogeneously showed increased HER2 expression (**D**, x200).

higher ODX recurrence score.[20-22] However, the tumor was of mucinous subtype with very low Ki-67 labeling index (2%). Given the tumor morphology and proliferation index (Image 1), it is questionable whether recurrence score of 26 in this case warranted chemotherapy. Nevertheless, the patient was offered chemotherapy but declined all systemic therapies (endocrine and chemotherapy).

The review of the other two discordant cases (cases 2 and 3 in Table 2) suggests the presence of nontumor-related factors responsible for higher ODX recurrence score. Case 2 with ODX recurrence score of 30 had admixed ductal carcinoma in situ that heterogeneously showed significantly increased Ki-67 labeling index and HER2 expression compared to the invasive carcinoma **Image 2**. Case 3 with ODX recurrence score of 33 showed extensive biopsy site associated fibrosis and significant Ki-67 staining within stromal cells **Image 3**. Acs et al[23] have previously shown the impact of proliferating stromal cells in the biopsy cavity on ODX recurrence score. In these two cases, the reliability of high ODX recurrence score and chemotherapy benefit is questionable.

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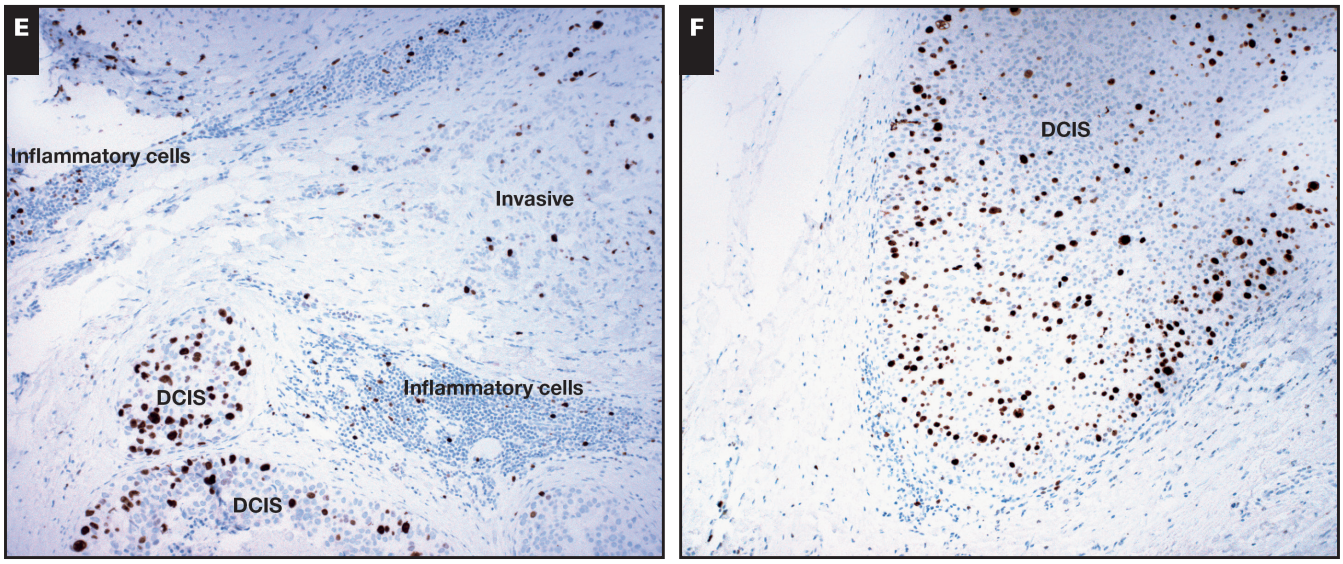

Image 2 (cont) The DCIS also heterogeneously showed increased Ki-67 labeling index in comparison to invasive carcinoma (**E**, x100). DCIS in the immediate vicinity in the same block with increased Ki-67 labeling index (**F**, x200).

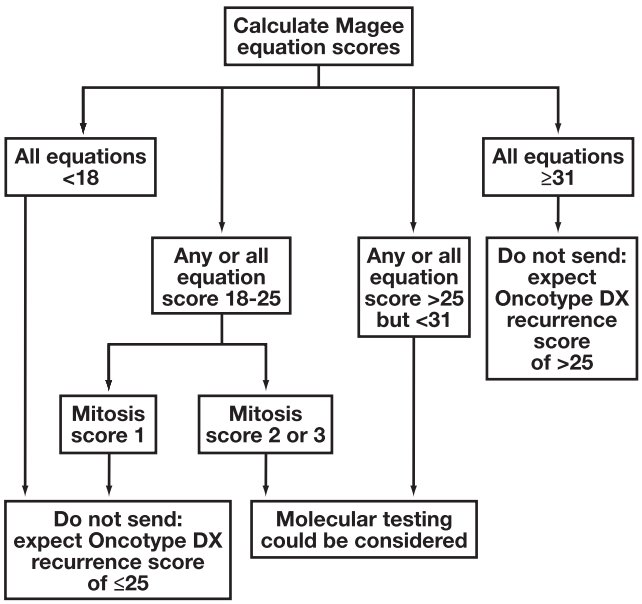

Figure 1 An algorithmic approach to safely withhold Oncotype DX testing in routine practice.

Apart from MEs, there are other published models that show routinely reported histopathologic and immunohistochemical data can predict ODX recurrence score in clinically meaningful ways.[1,2,4,24-29] Our current study further supports the use of pathology data to estimate the ODX recurrence score. Additionally, the current study defines an algorithmic approach to safely omit ODX testing Figure 1.

Based on our study results, we conclude that cases with MEs scores of less than 18, or 18 to 25 with mitotic activity score of 1, almost always have actual ODX recurrence score of 25 or less. ODX testing on such cases lacks clinical value. Over 70% of clinical requests fall into such category. Use of pathology-based models such as MEs in routine practice has the potential to save at least US$280,000 per 100 clinical ODX requests. We encourage pathologists and oncologists to use MEs in their own practice for further validation to potentially save and direct funds for more appropriate clinical use.

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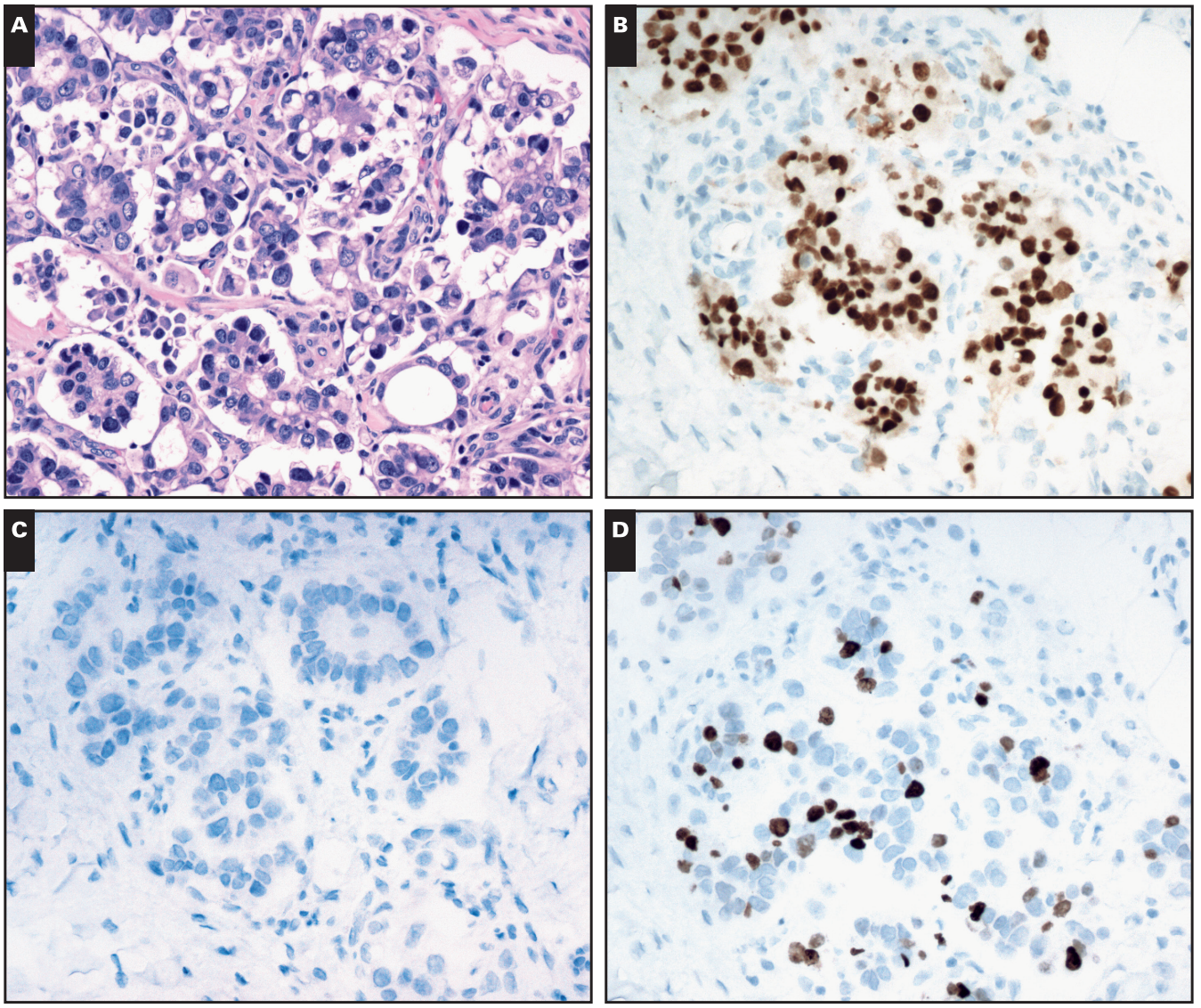

Image 3 Discordant case 3 (in Table 2) with average Magee equations score of 23 and actual Oncotype DX recurrence score of 33. The tumor was a micropapillary type carcinoma (**A**, H&E, x200) with strong reactivity for estrogen receptor (**B**, x200). The tumor was negative for progesterone receptor (**C**, x200), with relatively high Ki-67 labeling index (**D**, x200).

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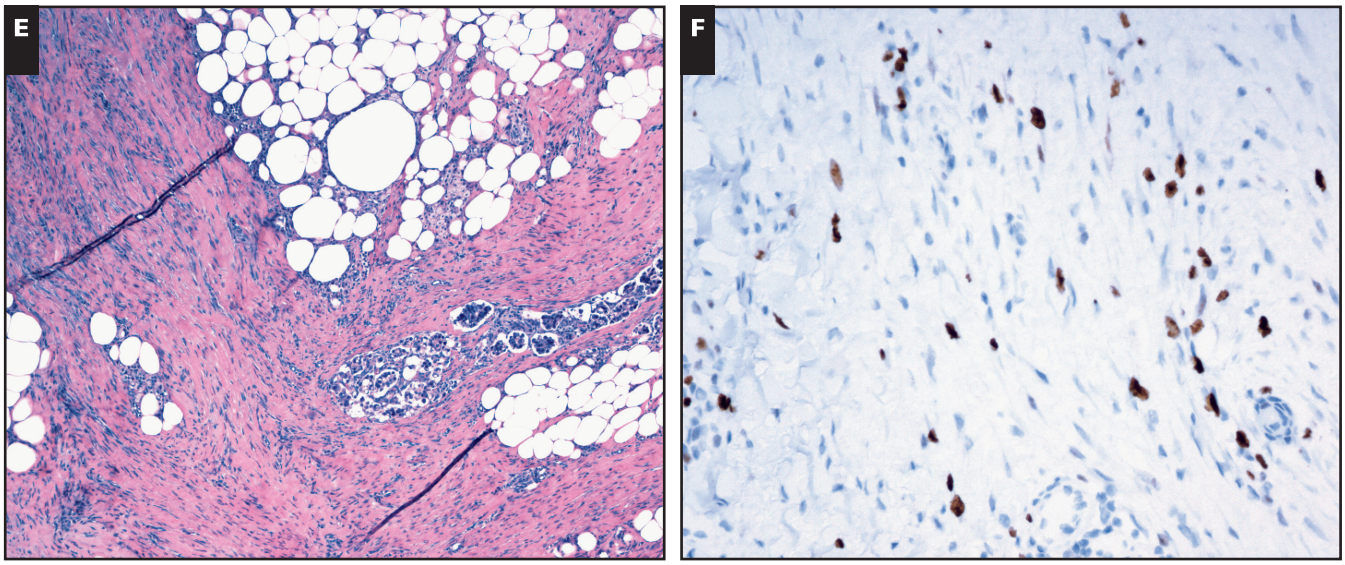

Image 3 (cont) However, the invasive tumor component constituted only a small part of the overall tissue in the block (sent for Oncotype DX testing), which predominantly showed biopsy site associated fibrosis (**E**, H&E, x40). Ki-67 stain showed significant reactivity in the stroma and scattered inflammatory cells (**F**, x200).

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