The MAGIC survey in hormone receptor positive (HR+), HER2-negative (HER2−) breast cancer:

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Novel tools, such as multigene assays, may help to guide treatment decisions for these patients by providing prognostic and predictive information beyond traditional parameters. The global MAGIC (Multidisciplinary Application of Genomics in Clinical Practice) survey evaluated physicians on the following criteria: general practice patterns, chemotherapy decision criteria and treatment decisions for simulated breast cancer patients. Physicians with ≥5 years' of experience in breast cancer treatment working in multidisciplinary teams were invited to complete the survey.

This study reports the survey results of 911 respondents (879 clinicians, 32 pathologists) from 52 countries. Data indicated an overall tendency to administer chemo-endocrine treatment rather than endocrine treatment alone. However, a substantial degree of uncertainty in treatment recommendations was observed for 52% of the analysed patient profiles. A high proportion of these patient profiles had intermediate risk features based on traditional parameters. The majority of physicians indicated they wanted to use multigene assays clinically. The lack of reimbursement and availability were indicated as the main reasons for non-usage. These findings highlight the need for additional markers that are both prognostic and predictive of chemotherapy benefit that may support more-informed treatment decisions in HR+, HER2– patients with early disease.

The MAGIC survey in Hormone Receptor Positive (HR+), HER2-Negative (HER2–) breast cancer: When might multigene assays be of value?

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List of abbreviations

ASCO, American Society of Clinical Oncology

BCI, Breast Cancer Index

ER, estrogen receptor

ESMO, European Society for Medical Oncology

FDA, US Food and Drug Administration

HER2, human epidermal growth factor receptor 2

HR, hormone receptor

MAGIC, Multidisciplinary Application of Genomics in Clinical Practice

N0, lymph node negative

N1, 1–3 affected lymph nodes

NCCN, National Comprehensive Cancer Network

PR, progesterone receptor

ROR, risk of recurrence

RT-PCR, reverse transcription polymerase chain reaction

Abstract

Background

A modest proportion of patients with early stage hormone receptor-positive (HR+), HER2-negative (HER2–) breast cancer benefit from adjuvant chemotherapy. Traditionally, treatment recommendations are based on clinical/pathologic criteria that are not predictive of chemotherapy benefit. Multigene assays provide prognostic and predictive information that can help to make more informed treatment decisions. The MAGIC survey evaluated international differences in treatment recommendations, how traditional parameters are used for making treatment choices, and for which patients treating physicians feel most uncertain about their decisions.

Methods

The MAGIC survey captured respondents' demographics, practice patterns, relevance of traditional parameters for treatment decisions, and use of or interest in using multigene assays. Using this information, a predictive model was created to simulate treatment recommendations for 672 patient profiles.

Results

The survey was completed by 911 respondents (879 clinicians, 32 pathologists) from 52 countries. Chemo-endocrine therapy was recommended more often than endocrine therapy alone, but there was substantial heterogeneity in treatment recommendations in 52% of the patient profiles; approximately every fourth physician provided a different treatment recommendation. The majority of physicians indicated they wanted to use multigene assays clinically. Lack of reimbursement/availability were the main reasons for non-usage.

Conclusions

The survey reveals substantial heterogeneity in treatment recommendations. Physicians have uncertainty in treatment recommendations in a high proportion of patients with intermediate risk features using traditional parameters. In HR+, HER2– patients with early disease the findings highlight the need for additional markers that are both prognostic and predictive of chemotherapy benefit that may support more-informed treatment decisions.

Keywords: Hormone receptor-positive, HER2-negative early breast cancer, adjuvant chemotherapy, multigene assay, treatment decision

Introduction

Breast cancer is the malignancy with the highest incidence among women in the Western world[1] but mortality rates have been improving over many years due to a combination of improved therapies and screening programs leading to detection in earlier stages of disease.[2]

For patients with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–) early breast cancer, adjuvant chemotherapy is beneficial for only a modest proportion of patients.[3] Despite this, a high proportion of patients are recommended adjuvant chemotherapy when using traditional parameters such as age, nodal status, tumor size, tumor type, grade, and ER status. Some of these parameters are prognostic but not predictive of chemotherapy benefit.[4] International treatment guidelines, including the St. Gallen consensus and the European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) guidelines, do acknowledge that many patients do not benefit from chemotherapy, but do not provide clear guidance on treatment recommendations for the large group of patients who are characterized as having intermediate risk.[5-8] In the absence of such guidance, there is substantial heterogeneity in the treatment recommendations for this patient population, although the extent of this heterogeneity across different geographic regions is unknown.

Multigene assays can provide prognostic information beyond traditional parameters, and in some cases predictive information that can help physicians and patients make more-informed adjuvant chemotherapy treatment decisions.[9, 10] Accordingly, studies have shown that the use of multigene assays can lead to an overall reduction in chemotherapy utilization.[11-13] Despite this, the health-economic value of assays has been challenged by many payers in Europe.[11,14,15] It is therefore important to establish the breast cancer patient population in which multigene assays are most useful.

The worldwide Multidisciplinary Application of Genomics in Clinical Practice (MAGIC) survey aimed to assess which treatments are recommended to patients across different countries and how physicians use different clinical and pathologic parameters for their decisions. In addition, the MAGIC survey aimed to identify breast cancer patient populations for which there is an uncertainty regarding treatment recommendations and where multigene assays may be of particular value.

Methods

Questionnaire

An international panel of 8 breast cancer experts developed the MAGIC survey with input from Genomic Health (Geneva, Switzerland) and TRM Oncology (The Hague, The Netherlands). An online survey Web module was developed by the SKIM Group (Rotterdam, The Netherlands).

The survey questionnaire (see **supplementary material**) consisted of single-select, numeric, and multiple-select questions capturing respondents' demographics, general practice patterns, relevance of clinical and pathologic criteria for adjuvant chemotherapy decisions, and the usage of multigene assays. Each respondent was also asked to indicate treatment recommendations for 24 breast cancer patient profiles, randomly selected from a pool of 896 different patient profiles generated by all possible combinations of 7 patient characteristics: age (>50, >60, >70, >80 years), tumor size (>1, >2, >3, >4, >5 cm), tumor grade (Grade ≥ 1, Grade ≥ 2, Grade 3) ER expression (<1%, <10%, <30%), PR expression (yes vs no), Ki67 expression(≥ 14%, >20%, >30%), and lymph node status (0 or any positive node; 1, including isolated tumor cell or micrometastases; 2; 3; ≥4). Patient profiles with >20% Ki67+ tumor cells combined with a Grade 1 were excluded, as they were judged as biologically implausible by the expert panel and>20% Ki67+ tumor cells combined with a Grade 2 were also excluded. . For each patient profile, respondents could choose from the following 3 recommendations: chemotherapy in addition to endocrine treatment, endocrine treatment alone, and a request for more information.

Eligible respondents and survey distribution

The survey was conducted between August 2013 and January 2014. Practicing clinicians and pathologists who actively participated in a multidisciplinary breast cancer team, had >5 years' experience in breast cancer, and personally treated >20 new breast cancer patients per year (practicing clinicians) or ran immunohistochemistry for progesterone receptor (PR), ER, or HER2 for >20 breast cancer patients per year (pathologists) were eligible to complete the survey. Practicing clinicians also had to be personally involved in adjuvant treatment decisions for breast cancer patients. A link to the survey was distributed via email by breast cancer organizations, breast cancer study groups, and an international network of breast cancer physicians (acknowledgment in the **Appendix**).

Data analysis

Descriptive statistical analyses of the data were performed using SPSS (IBM) and Excel (Microsoft).

Country-specific trends were analyzed in countries with >30 respondents. A conjoint analysis was used to analyze practicing clinicians' preferences and their sensitivity for different patient features when making treatment decisions by ranking the relevance of the 7 patient characteristics.[16] Interaction effects between the patient characteristics were disregarded in this univariate analysis.

A predictive model was developed to simulate the likelihood of each treatment recommendation for all 896 possible breast cancer patient profiles. For this multivariate analysis, the survey data were analyzed using hierarchical Bayes analysis to calculate a physician-level model for each treatment choice. When simulating a patient profile, the corresponding utilities to the patient features were added and converted to a preference share for each treatment option. The preference share was then aggregated to identify the probability of each treatment for the simulated patient.

Results

Respondent demographics and general practice patterns

In total, 911 respondents (96% practicing clinicians, 4% pathologists) from 52 countries completed the MAGIC survey, of which the majority (74%) resided in Europe; 14 countries had ≥30 respondents and qualified for analysis of country-specific trends. Over half of the respondents (54%) were medical oncologists, followed by surgical oncologists (21%), gynecologists (16%), radiation oncologists (4%), and pathologists (4%). The respondent characteristics are summarized in **Table 1**.[6,7, 17-21]

The majority of respondents used tools/nomograms to estimate prognosis. The usage was highest among the radiation oncologists (97%) and lowest among the gynecologists (74%). Adjuvant! Online was used most frequently by gynecologists and medical, radiation, and surgical oncologists, whereas Nottingham Prognostic Index was more common among pathologists and practicing clinicians of other specialties. Predict was the third most common nomogram, used by approximately 12% of the respondents. In total, 98% of respondents indicated they always or often consulted internationally accepted guidelines for breast cancer treatment.

Consideration of clinical and pathologic criteria for treatment recommendations

Although most respondents always or often adhered to internationally accepted breast cancer guidelines, simulated treatment recommendations by practicing clinicians showed that the likelihood of receiving adjuvant chemotherapy varied substantially across countries (**Figure 1**). Overall, 65% of the patient profiles had >50% probability of an adjuvant chemotherapy recommendation; this proportion was highest in Greece and Mexico (72%) and lowest in Germany (59%) and Switzerland (58%). Part of this heterogeneity among countries may be explained by differences in the cutoff of clinical and pathologic criteria at which adjuvant chemotherapy is recommended (**Table 2**). Although many differences were observed between countries, a high proportion of respondents strongly considered using adjuvant chemotherapy in patients with: a tumor size of >2 cm (35%), or a tumor grade of 3 (70%), or <10% ER+ tumor cells (47%), >20% Ki67+ tumor cells (34%), or at least 1 positive lymph node (39%).

The relevance of individual patient characteristics for adjuvant chemotherapy recommendations was also evaluated by a conjoint analysis. Using the recommendations for random patient profiles, the impact of patient characteristics on practicing clinicians' treatment recommendations could be determined, providing insight into what drives their decisions. Outcomes of this analysis showed that age was the most important patient characteristic for adjuvant chemotherapy decisions,

followed by tumor grade, tumor size, lymph node status, and Ki67, ER, and PR expression (**Figure 2**). However, the conjoint analysis did not consider potential interactions between patient characteristics, while these were shown to be relevant in the individual treatment recommendations. For example, patients with high-risk characteristics (eg, 1–3 positive lymph nodes or a Grade 3 tumor) had a high predicted probability (>75%) of receiving endocrine treatment alone if they were older or had small (<2 cm) tumors. Conversely, patients with small, Grade 1 tumors were likely (>75% predicted probability) to be recommended adjuvant chemotherapy if they were young or had positive lymph nodes.

Breast cancer profiles where a multigene assay might be of value

To explore the heterogeneity in treatment recommendations for patients with breast cancer, patient profiles were ranked on a heat map according to their predicted likelihood for an adjuvant chemotherapy or endocrine treatment alone recommendation (**Figure 3**). This analysis showed substantial heterogeneity in the simulated treatment decisions for 52% of the patient profiles, with at least every fourth physician recommending a different treatment. There was a particularly high level of uncertainty regarding treatment decisions for 15% of the patient profiles (as detailed below), with <50% probability for a recommendation of both chemotherapy and endocrine therapy alone.

For patients with only high-risk characteristics, the general consensus was to advise adjuvant chemotherapy; 42% of the patient profiles had ≥75% probability of receiving adjuvant chemotherapy. Substantially fewer patient profiles (6%) had a ≥75% probability for an endocrine treatment alone recommendation. The 15% of patient profiles with the greatest heterogeneity in treatment recommendations had predominantly intermediate-risk features by traditional parameters (**Figure 3**).

Multigene assay utilization

Of the respondents, only around half (54%) of the practicing clinicians used multigene assays (**Figure 4A**). The most common reason for not using assays was lack of reimbursement, price, and lack of availability (**Figure 4B**; country-specific data are displayed in **Supplementary Table 1**).

There was a pronounced difference in usage of multigene assays between respondents from different countries, ranging from 91% of respondents in Greece using them to 0% in Sweden (**Figure 4A**). Onco*type* DX® Breast Cancer Assay was used most frequently (81%), followed by MammaPrint® (35%), EndoPredict (7%), FEMTELLE® (5%), Prosigna™ (2%), and Mammostrat® (1%) (**Figure 4C**;

country-specific data are displayed in **Supplementary Table 2**). In all countries except Germany (50%), the majority of physicians currently not using multigene assays wanted to use these tests.

Discussion

The MAGIC survey showed that treatment recommendations in ER+, HER2– patients are highly heterogeneous internationally and that there is substantial uncertainty for a large proportion of patients. However, there was an overall strong tendency to recommend chemotherapy rather than endocrine therapy alone. For the majority (52%) of ER+, HER2– early breast cancer patient profiles, there was substantial heterogeneity in treatment recommendations, with at least every fourth physician recommending a different treatment. The probability of receiving chemo-endocrine or endocrine treatment alone was ≤ 50% for both in 15% of patients, indicating a very high uncertainty regarding treatment decisions. These patient profiles often had a combination of intermediate-risk features by traditional parameters. Using further prognostic and predictive markers such as multigene assays may be particularly useful to help make more-informed treatment decisions in these patients, although it should be emphasized that such markers may provide useful information also in other patients.

Additionally, the survey revealed large differences between countries in the use of available multigene assays. The Onco*type* DX Breast Cancer Assay was the most frequently used assay except in the Netherlands and Spain, where MammaPrint was the most commonly used multigene assay. This is in line with results from a recent ESMO-supported survey showing that Onco*type* DX Breast Cancer Assay was selected most frequently as a multigene assay to determine adjuvant chemotherapy benefit for breast cancer patients.[22] The differences seen in the use of available multigene assays is likely due to differences in data supporting prediction of chemotherapy benefit that only exist for the Onco*type* DX assay,[9] and differences in the level of evidence supporting the different assays in relevant patient populations, as well as the different status of multigene assays in international guidelines (**Table 3**).[5-7, 23]

Although most internationally accepted guidelines include multigene assays, there is no clear consensus on the precise characteristics of breast cancer patients for whom these assays should be used and this is a likely reason to at least some of the differences seen.[5-7, 23] In the ESMO guidelines it is suggested that multigene assays may be considered for ER+, HER2– breast cancer patients who are node negative with stage 2 tumors (>2 cm tumor without extension to the chest wall and/or skin, and without distant metastases).[6] Meanwhile, the 2013 St. Gallen consensus recommended usage of multigene assays in selected patients with ER+, HER2− node-negative disease, those with 1–

3 positive nodes, and patients aged more than 35 years, as adjuvant chemotherapy was thought to be of uncertain indication in these patients.[17] These characteristics are not clearly outlined in the more recent recommendations from the 2015 St. Gallen consensus.[5] Genomic testing was felt to be unnecessary for low-risk or high-risk patients by clinicopathologic parameters, although it is acknowledged that the interobserver variability for grade and Ki67 is high. In the NCCN guidelines the usage of the Onco*type* DX assay is considered for node-negative, ER+, HER2− breast cancer patients with primary tumors of 0.6−1 cm with unfavorable features or tumors >1 cm.[7] NCCN does not currently consider Prosigna, EndoPredict, Breast Cancer Index (BCI), or MammaPrint as having sufficient evidence to support their clinical use.[7] In contrast, the panel of 2015 St. Gallen consensus voted in favor of acknowledging that Prosigna, EndoPredict, BCI and MammaPrint and Onco*type* DX have a prognostic value in the first 5 years.[5] The NCCN guidelines, the ASCO recommendations, and the 2013 St. Gallen consensus also all acknowledge that the Onco*type* DX assay has predictive value in determining the benefit of adjuvant chemotherapy.[7, 17, 23] The lack of data from prospective studies and real life outcome data from patients where multigene assays have been used for treatment decisions have for a long time been a key weakness in the evidence supporting multigene assays. Many physicians and reimbursement bodies have also chosen to wait with including multigene assays in their clinical care until such data is available. Recently, prospective outcome data from studies and real outcome data from large cohorts of patients where Oncotype DX has been included when making treatment decisions have now been reported: Data from the TAILORx study has recently been published.[24] This study prospectively stratified the use of chemotherapy on the basis of the Onco*type* Dx assay. This study has reported that 99.3% of the patients with low Onco*type* Dx assay Recurrence Scores between 0-10, treated with endocrine therapy alone, were free of distant recurrence at 5 years further demonstrating the utility of the Onco*type* Dx assay to identify a group of patients with an exceptionally good prognosis in the absence of chemotherapy.[24] The Plan B adjuvant study in high risk node negative and node positive patients was also recently published.[25] The Clalit registry in Israel containing data from more than 2000 patients with node

negative disease reported a risk of recurrence of 0.7% at 5 years follow up for patients with low Recurrence scores (less than 18) where 98% had been treated with endocrine therapy alone[26] and the SEER database analysis including more than 40 000 pts corroborates these data with breast cancer specific mortality rate that is exceptionally low- only 49 events in more than 20 000 patients with low Recurrence Scores (less than 18).[27] It should be emphasized that real life data may be affected by selection bias regarding in which patients the assay is ordered however.

Prospective data for the MammaPrint assay from the MINDACT trial have been presented and published in 2016. In this randomized, phase 3 study, 6693 women with early-stage breast cancer were enrolled and their genomic risk was determined using the 70-gene signature and their clinical risk with a modified version of Adjuvant! Online. The primary goal was to assess whether, among patients with high-risk clinical features and a low-risk gene-expression profile who did not receive chemotherapy, the lower boundary of the 95% confidence interval for the rate of 5-year survival without distant metastasis would be 92% (i.e., the noninferiority boundary) or higher. A total of 1550 patients (23.2%) were deemed to be at high clinical risk and low genomic risk. At 5 years, the rate of survival without distant metastasis in this group was 94.7% (95% confidence interval, 92.5 to 96.2) among those not receiving chemotherapy. The absolute difference in this survival rate between these patients and those who received chemotherapy was 1.5 percentage points, with the rate being lower without chemotherapy. The authors conclude that these findings suggest that approximately 46% of women with breast cancer who are at high clinical risk might not require chemotherapy.[28]

Published before the above mentioned trials, the ASCO Biomarkers guidelines panel found sufficient evidence of clinical utility for the biomarker assays Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, and urokinase plasminogen activator and plasminogen activator inhibitor type 1 in specific subgroups of breast cancer. [29] The panelists indicate also that treatment decisions should consider disease stage, comorbidities, and patient preferences.Parameters such as nodal status, tumor size

have been shown to add prognostic value to genomic information generated in both Oncotype DX, Endopredict and PAM50 .[30-32]

The MAGIC survey results are based on respondents' answers indicating certain trends and not on objective analyses of actual treatment recommendations, which may be considered a limitation of this study. In addition, some of the subgroup analyses are based on small group sizes. Nevertheless, the large number of respondents varying in their specialty, level of experience, and country of origin provided a unique opportunity to compare physician subgroups. Insights into the current differences in general practice patterns may be valuable when developing international guidelines for breast cancer treatment

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In conclusion, the MAGIC survey provides valuable insight into worldwide treatment recommendations for early breast cancer patients and the clinical and pathologic criteria used for these decisions. The overall findings indicate that there is substantial heterogeneity in how patients are treated and a substantial uncertainty in treatment recommendations for a large proportion of patients, highlighting an unmet need for broadly available markers, such as multigene assays, that can help to make more-informed treatment decisions by predicting a patient's likelihood of benefit from adjuvant chemotherapy.

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Appendix. Breast cancer organizations and study groups that participated in distribution of the link to the MAGIC survey.

Arbeitsgemeinschaft Gynäkologische Onkologie e.V.

Breast International Group

Berufsverband Niedergelassener Gynakologischer Onkologen

Breast International Group

European Society of Breast Cancer Specialists

European Organisation for Research and Treatment of Cancer

Grupo Español de Investigación en Cáncer de Mama

Gruppo Italiano Mammella (GIM)

Hellenic Society of Breast Surgeons

International Breast Cancer Study Group

International Collaborative Cancer Group

Italian Trials in Medical Oncology

National Cancer Research Institute

The Netherlands Association for Medical Education

Priv-Doz Dr Med Marc Thill

The Swedish Association of Breast Oncologists

Grupo Español de Estudio, Tratamiento y Otras Estrategias Experimentales en Tumores Sólidos

United Kingdom Breast Intergroup

Central and Eastern European Oncology Group

European Society of Surgical Oncology

Austrian Breast & Colorectal Cancer Study Group

West German Study Group

Sociedad Mexicana de Oncología

Asociación Mexicana de Mastología

Sociedad Argentina de Mastología

Sociedade Brasileira de Oncologia Clínica

Figure Legends

Figure 1. Likelihood of adjuvant chemotherapy recommendations stratified by country. Each practicing clinician was asked to make treatment recommendations for 24 randomly selected patient profiles (chemotherapy, endocrine treatment alone, or a request for more information). Based on their treatment recommendations a simulation model was generated to predict the probability for each treatment recommendation for 896 simulated patient profiles.

Figure 2. Graphic representation of a conjoint analysis of adjuvant chemotherapy recommendations. The *y*-axis depicts a ranking of importance of various clinical and pathologic characteristics with regard to recommendation of chemotherapy. The *x*-axis depicts the index of importance for each patient characteristic. The relative distance between the levels indicates the relative impact on the recommendation. Interaction effects between the characteristics have not been considered in these analyses. ER, estrogen receptor; N0, lymph node negative; N1, 1–3 affected lymph nodes; PR, progesterone receptor.

Figure 3. Ranking of 672 simulated breast cancer patient profiles according to their likelihood for an adjuvant chemotherapy or endocrine treatment alone recommendation. Patient profiles having the biologically uncommon combination of low ER expression and high PR expression or >20% Ki67+ tumor cells in a Grade 1 or 2 tumor were excluded from this analysis. Grey cells (n=43) show patient profiles with ≥75% probability to be recommended endocrine treatment alone. Orange cells (n=99) show patient profiles with 50%–75% probability to be recommended endocrine treatment alone. Purple cells (n=104) show patient profiles with <50% probability to be recommended endocrine treatment alone AND <50% probability to be recommended chemotherapy. Green cells (n=145) show patient profiles with 50%–75% probability to be recommended chemotherapy. Blue cells (n=281) show patient profiles with ≥75% probability to be recommended chemotherapy. ER, estrogen receptor; HR, hormone receptor; N0, lymph node negative; N1, 1–3 affected lymph nodes; PR, progesterone receptor.

Figure 4. (A) Usage of multigene assays and desire to use multigene assays for practicing clinicians by country. **(B)** Type of multigene assays that were used (multiple answers were allowed; only practicing clinicians who indicated to use multigene assays were considered). **(C)** Reasons for not using multigene assays (multiple answers were allowed; only practicing clinicians who indicated to not use multigene assays were considered).

Tables

Table 1. Demographics and general practice patterns of MAGIC survey respondents.

	All respondents (n=911)	Medical oncologists (n=495)	Gynecologists (n=147)	Radiation oncologists (n=38)	Surgical oncologists (n=192)	Pathologists (n=32)[a]	Other (n=7)
Region of residence, n(%)[b]							
Europe	672 (74)	392 (79)	85 (58)	32 (84)	132 (69)	25 (78)	6 (86)
Latin America	157 (17)	44 (9)	62 (42)	4 (11)	45 (23)	1 (3)	1 (14)
Russia	56 (6)	46 (9)	0 (0)	0 (0)	5 (3)	5 (16)	0 (0)
Rest of World	26 (3)	13 (3)	0 (0)	2 (5)	10 (5)	1 (3)	0 (0)
Experience, n (%)							
≥10 Years of experience[c]	720 (79)	392 (79)	111 (76)	34 (89)	157 (82)	23 (72)	3 (43)
Chemotherapy prescriber	613 (67)	492 (99)	66 (45)	19 (50)	32 (17)	2 (6)	2 (29)
Number of new patients/year[d]	113 (150)	104 (97)	97 (73)	125 (125)	146 (266)	641 (719)	76 (58)
Involvement of multidisciplinary team, n(%)[a]							
Always	756 (83)	407 (82)	113 (77)	34 (89)	172 (90)	25 (96)	5 (71)
In some cases	140 (15)	86 (17)	27 (18)	4 (11)	20 (10)	1 (4)	2 (29)
Never	9 (1)	2 (0.4)	7 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Guidelines adherence, n(%)[a]							
Always	496 (55)	251 (51)	86 (59)	19 (50)	123 (64)	14 (54)	3 (43)
Often	389 (43)	234 (47)	60 (41)	16 (42)	64 (33)	12 (46)	3 (43)
Sometimes	15 (2)	8 (2)	0 (0)	3 (8)	4 (2)	0 (0)	0 (0)
Never	5 (1)	2 (0.4)	1 (1)	0 (0)	1 (1)	0 (0)	1 (14)
Guidelines used, n(%)[a,e]							
St. Gallen[17]	353 (71)	179 (71)	63 (73)	18 (95)	82 (67)	11 (79)	0 (0)
ESMO[6]	205 (41)	131 (52)	21 (24)	10 (53)	35 (28)	7 (50)	1 (33)

ASCO[18]	218 (44)	115 (46)	38 (44)	9 (47)	45 (37)	9 (64)	2 (67)
NCCN[7]	272 (55)	138 (55)	42 (49)	10 (53)	74 (60)	7 (50)	1 (33)
Tools/nomograms used, n(%)[a]							
Nottingham Prognostic Index[19]	209 (23)	86 (17)	23 (16)	9 (24)	69 (36)	17 (65)	5 (71)
Adjuvant! Online[20]	644 (71)	363 (73)	96 (65)	32 (84)	135 (70)	15 (58)	3 (43)
Predict[21]	109 (12)	59 (12)	15 (10)	9 (24)	23 (12)	2 (8)	1 (14)
No use of tools/nomograms	134 (15)	73 (15)	38 (26)	1 (3)	19 (10)	2 (8)	1 (14)
Consideration of Ki67, n(%)[a]							
Strong consideration	265 (29)	156 (32)	48 (33)	6 (16)	46 (24)	8 (31)	1 (14)
Not a predominant consideration	497 (55)	275 (56)	78 (53)	21 (55)	108 (56)	13 (50)	2 (29)
Little influence	48 (5)	20 (4)	14 (10)	2 (5)	10 (5)	1 (4)	1 (14)
Not considered	34 (4)	13 (3)	7 (5)	2 (5)	7 (4)	4 (15)	1 (14)
No access to Ki67 testing	61 (7)	31 (6)	0 (0)	7 (18)	21 (11)	0 (0)	2 (29)

ASCO, American Society of Clinical Oncology; ER, estrogen receptor; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; PR, progesterone receptor.

Due to rounding of the numbers, total percentages may not equal 100%.

[a]For the categories "Involvement of multidisciplinary team," "Guidelines adherence," "Guidelines used," "Tools/nomograms used," and "Consideration of Ki67," data were missing for 6 pathologists.

[b]Countries with more than 30 respondents were: Argentina, Belgium, Switzerland, Germany, Spain, France, Greece, Hungary, Italy, Mexico, The Netherlands, Russia, Sweden, and the United Kingdom.

[c]For practicing clinicians, the number of years of experience in treating breast cancer was considered. For pathologists, the number of years in which they were involved in running diagnostic tests for breast cancer patients was considered.

[d]For practicing clinicians, the number of new breast cancer patients per year treated by the respondent was considered. For pathologists, the number of breast cancer patients per year for which the respondent runs ER/PR/HER2 immunohistochemistry was considered. For both, "mean (standard deviation)" are shown.

[e]Only respondents who indicated to always use breast cancer treatment guidelines were considered.

Table 2. Consideration by practicing clinicians of traditional patient characteristics for adjuvant chemotherapy recommendations. Practicing clinicians indicated at which level of the respective clinical or histopathologic markers they would strongly consider to recommend adjuvant chemotherapy to HR+, HER2– early breast cancer patients.

	All N=879	AR N=66	BE N=45	CH N=29	DE N=54	ES N=75	FR N=63	GR N=45	HU N=28	IT N=103	MX N=52	NL N=27	RU N=52	SE N=31	UK N=67
In a node-negative context, is there a specific tumor size above which you would strongly consider using adjuvant chemotherapy?															
>1 cm	14	39	0	3	6	11	8	11	11	4	37	22	8	10	3
>2 cm	35	39	42	10	26	49	48	36	50	31	31	52	29	32	34
>3 cm	14	8	16	10	9	16	14	24	14	17	8	15	2	23	31
>4 cm	5	6	7	7	0	1	6	7	11	1	4	0	2	3	12
>5 cm	9	5	11	38	11	8	3	4	0	6	15	4	12	26	7
Tumor size does not affect decision	22	3	24	31	48	15	21	18	14	42	6	7	48	6	12
In a node-negative context, is there a specific tumor grade above which you would strongly consider using adjuvant chemotherapy?															
Grade ≥1	1	0	0	0	0	0	0	0	0	0	0	0	4	0	0
Grade ≥2	21	6	16	10	13	25	25	42	32	10	29	44	35	19	24
Grade 3	70	86	80	79	81	71	68	53	64	79	56	56	44	81	73
Tumor grade does not affect decision	8	8	4	10	6	4	6	4	4	12	15	0	17	0	3
What percentage of ER+ cells would you consider low and would make you strongly consider using adjuvant chemotherapy in addition to hormonal therapy?															
<1%	26	61	16	28	52	19	17	24	11	22	25	22	25	0	12
<10%	47	30	49	38	35	45	65	44	54	45	44	56	44	84	43
<30%	20	6	27	34	4	29	10	24	32	25	17	11	15	10	39
Percentage of ER+ cells does not affect decision	7	3	9	0	9	7	8	7	4	8	13	11	15	6	6
At which Ki67 percentage would you strongly consider giving adjuvant chemotherapy?															
≥14%	27	28	36	10	13	43	18	33	14	20	35	17	40	6	21

>20%	34	31	36	48	56	31	44	36	46	37	21	17	28	45	11
>30%	32	31	27	38	26	27	31	29	39	39	38	17	21	42	53
Ki67 expression does not affect decision	7	10	2	3	6	0	8	2	0	4	6	50	11	6	16
What number of positive axillary nodes would make you <u>strongly</u> consider giving chemotherapy?															
Lymph node negative	4	0	0	3	2	5	2	2	0	4	10	4	4	6	6
1[a]	39	61	27	3	22	43	40	42	39	23	48	59	58	48	34
2	21	17	27	14	20	25	22	24	29	18	10	15	8	35	34
3	11	12	16	31	22	3	14	7	7	15	13	0	10	0	6
≥4	21	8	29	45	31	13	19	22	21	33	19	15	13	6	10
Number of positive lymph nodes does not affect decision	5	3	2	3	2	11	3	2	4	7	0	7	8	3	9
Is there an upper age limit above which you would <u>strongly</u> consider <u>not</u> giving adjuvant chemotherapy?															
>50 years	1	3	0	0	2	1	0	2	0	5	0	0	2	0	0
>60 years	1	0	0	3	0	0	3	2	4	0	0	4	0	0	0
>70 years	17	29	11	7	11	12	21	13	14	8	15	52	15	6	19
>80 years	48	52	53	62	39	60	41	36	57	51	33	33	38	77	61
Age does not affect decision	33	17	36	28	48	27	35	47	25	36	52	11	44	16	19

AR, Argentina, BE, Belgium; CH, Switzerland; DE, Germany; ER, estrogen receptor; ES, Spain; FR, France; GR, Greece; HER2, human epidermal growth factor receptor; HR, hormone receptor; HU, Hungary; IT, Italy; MX, Mexico; NL, The Netherlands; RU, Russia; SE, Sweden; UK, United Kingdom.

Due to rounding of the numbers, total percentages may not equal 100%. Country-specific data are shown for countries with ≥30 respondents.

[a]Including isolated tumor cells or nodal micrometastases.

Table 3. Multigene assays – guideline recommendations.

Source	Oncotype DX (21-gene RT-PCR assay)	MammaPrint (70-gene expression profile)	Other multigene assays
NCCN[7]	• An option when evaluating patients with primary tumors characterized as – 0.6 to 1.0 cm – Unfavorable features or >1 cm – Node negative, HR+, and HER2– (category 2A) • The RS may assist in estimating likelihood of recurrence and benefit from chemotherapy	• FDA-approved for identifying patients with ER+ or ER− breast cancer as having a high or low risk of recurrence • Not approved for predicting benefit from adjuvant systemic therapy	• Currently insufficient evidence to warrant inclusion in the guidelines
ESMO[6]	• Recommended for obtaining extra prognostic and/or predictive information that is used to complement pathology assessment • May be used to predict response to adjuvant chemotherapy		• Not specifically addressed
St. Gallen[5]	• Provides prognostic and predictive information (years 1–5 and >5) regarding usefulness of adjuvant chemotherapy in patients with luminal	• Has prognostic utility regarding adjuvant chemotherapy in years 1–5. Panel rejected the prognostic value	• PAM-50 ROR score, EndoPredict, and the Breast Cancer Index considered to be prognostic in years 1–5. The panel was equally

	disease. Beyond 5 years, the Panel was divided almost equally on the prognostic value of Oncotype DX	beyond 5 years	divided with regard to the prognostic value for EndoPredict, Breast Cancer Index in years 5-10 but acknowledged the prognostic value of PAM-50 ROR in years 5-10.
ASCO[23]	• For use in newly diagnosed patients with node-negative, ER+ breast cancer • Can identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy • High RS appears to be predictive of benefit with adjuvant chemotherapy	• The clinical utility of other assays is under investigation	

ASCO, American Society of Clinical Oncology; ER, estrogen receptor; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NCCN, National Comprehensive Cancer Network; RS, recurrence score; ROR, risk of recurrence; RT-PCR, reverse transcription polymerase chain reaction.

Supplementary Table 1. Reasons for not using multigene assays, stratified by country.

	All N=389	AR N=13	BE N=28	CH N=13	DE N=6	ES N=16	FR N=37	GR N=3	HU N=12	IT N=82	MX N=11	NL N=3	RU N=34	SE N=31	UK N=42
Lack of reimbursement	45%	0%	68%	85%	67%	63%	70%	67%	67%	60%	9%	33%	15%	6%	33%
Price	44%	92%	43%	8%	33%	25%	49%	67%	75%	33%	91%	0%	15%	39%	52%
Lack of availability	39%	31%	25%	15%	0%	31%	14%	67%	33%	38%	55%	0%	71%	29%	60%
Not in relevant guidelines	20%	0%	21%	0%	67%	6%	32%	0%	8%	17%	0%	0%	32%	45%	21%
Lack of evidence	17%	8%	29%	38%	67%	6%	22%	0%	8%	12%	0%	67%	3%	39%	19%
Other	2%	0%	4%	8%	0%	0%	3%	0%	0%	0%	0%	0%	0%	10%	0%

AR, Argentina, BE, Belgium; CH, Switzerland; DE, Germany; ES, Spain; FR, France; GR, Greece; HU, Hungary; IT, Italy; MX, Mexico; NL, The Netherlands; RU, Russia; SE, Sweden; UK, United Kingdom.

Data show the percentage of practicing clinicians who indicated to not use multigene assays (multiple answers were allowed). Country-specific data are shown for countries with ≥30 respondents.

Supplementary Table 2. Multigene assays used, stratified by country (multiple answers allowed).

	All N=471	AR N=52	BE N=16	CH N=16	DE N=48	ES N=59	FR N=26	GR N=41	HU N=15	IT N=20	MX N=41	NL N=24	RU N=10	UK N=22
Onco*type* DX® Breast Cancer Assay	81%	94%	56%	94%	77%	69%	88%	100%	93%	70%	78%	17%	50%	100%
MammaPrint®	35%	25%	31%	19%	4%	73%	8%	7%	7%	50%	73%	96%	20%	9%
EndoPredict®	7%	0%	13%	25%	44%	0%	0%	0%	0%	0%	2%	0%	10%	0%
FEMTELLE®	5%	0%	0%	0%	38%	0%	15%	2%	0%	0%	0%	0%	10%	0%
Prosigna™	2%	0%	0%	0%	0%	10%	4%	0%	0%	5%	2%	0%	20%	0%
Mammostrat®	1%	4%	0%	0%	0%	0%	0%	0%	7%	0%	5%	0%	0%	0%
Other multigene assay	2%	0%	31%	6%	2%	0%	0%	0%	0%	0%	0%	0%	0%	0%

AR, Argentina, BE, Belgium; CH, Switzerland; DE, Germany; ES, Spain; FR, France; GR, Greece; HU, Hungary; IT, Italy; MX, Mexico; NL, The Netherlands; RU, Russia; SE, Sweden; UK, United Kingdom.

Data show the percentage of practicing clinicians who use multigene assays who indicated to use the described multigene assay. Country-specific data are shown for countries with ≥30 respondents. Sweden was not included in this analysis as none of the Swedish respondents indicated to use multigene assays.

The MAGIC survey in Hormone Receptor Positive (HR+), HER2-Negative (HER2–) breast cancer: When might multigene assays be of value?

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List of abbreviations

ASCO, American Society of Clinical Oncology

BCI, Breast Cancer Index

ER, estrogen receptor

ESMO, European Society for Medical Oncology

FDA, US Food and Drug Administration

HER2, human epidermal growth factor receptor 2

HR, hormone receptor

MAGIC, Multidisciplinary Application of Genomics in Clinical Practice

N0, lymph node negative

N1, 1–3 affected lymph nodes

NCCN, National Comprehensive Cancer Network

PR, progesterone receptor

ROR, risk of recurrence

RT-PCR, reverse transcription polymerase chain reaction

Abstract

Background

A modest proportion of patients with early stage hormone receptor-positive (HR+), HER2-negative (HER2–) breast cancer benefit from adjuvant chemotherapy. Traditionally, treatment recommendations are based on clinical/pathologic criteria that are not predictive of chemotherapy benefit. Multigene assays provide prognostic and predictive information that can help to make more informed treatment decisions. The MAGIC survey evaluated international differences in treatment recommendations, how traditional parameters are used for making treatment choices, and for which patients treating physicians feel most uncertain about their decisions.

Methods

The MAGIC survey captured respondents' demographics, practice patterns, relevance of traditional parameters for treatment decisions, and use of or interest in using multigene assays. Using this information, a predictive model was created to simulate treatment recommendations for 672 patient profiles.

Results

The survey was completed by 911 respondents (879 clinicians, 32 pathologists) from 52 countries. Chemo-endocrine therapy was recommended more often than endocrine therapy alone, but there was substantial heterogeneity in treatment recommendations in 52% of the patient profiles; approximately every fourth physician provided a different treatment recommendation. The majority of physicians indicated they wanted to use multigene assays clinically. Lack of reimbursement/availability were the main reasons for non-usage.

Conclusions

The survey reveals substantial heterogeneity in treatment recommendations. Physicians have uncertainty in treatment recommendations in a high proportion of patients with intermediate risk features using traditional parameters. In HR+, HER2– patients with early disease the findings highlight the need for additional markers that are both prognostic and predictive of chemotherapy benefit that may support more-informed treatment decisions.

Keywords: Hormone receptor-positive, HER2-negative early breast cancer, adjuvant chemotherapy, multigene assay, treatment decision

Introduction

Breast cancer is the malignancy with the highest incidence among women in the Western world[1] but mortality rates have been improving over many years due to a combination of improved therapies and screening programs leading to detection in earlier stages of disease.[2]

For patients with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–) early breast cancer, adjuvant chemotherapy is beneficial for only a modest proportion of patients.[3] Despite this, a high proportion of patients are recommended adjuvant chemotherapy when using traditional parameters such as age, nodal status, tumor size, tumor type, grade, and ER status. Some of these parameters are prognostic but not predictive of chemotherapy benefit.[4] International treatment guidelines, including the St. Gallen consensus and the European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) guidelines, do acknowledge that many patients do not benefit from chemotherapy, but do not provide clear guidance on treatment recommendations for the large group of patients who are characterized as having intermediate risk.[5-8] In the absence of such guidance, there is substantial heterogeneity in the treatment recommendations for this patient population, although the extent of this heterogeneity across different geographic regions is unknown.

Multigene assays can provide prognostic information beyond traditional parameters, and in some cases predictive information that can help physicians and patients make more-informed adjuvant chemotherapy treatment decisions.[9, 10] Accordingly, studies have shown that the use of multigene assays can lead to an overall reduction in chemotherapy utilization.[11-13] Despite this, the health-economic value of assays has been challenged by many payers in Europe.[11,14,15] It is therefore important to establish the breast cancer patient population in which multigene assays are most useful.

The worldwide Multidisciplinary Application of Genomics in Clinical Practice (MAGIC) survey aimed to assess which treatments are recommended to patients across different countries and how physicians use different clinical and pathologic parameters for their decisions. In addition, the MAGIC survey aimed to identify breast cancer patient populations for which there is an uncertainty regarding treatment recommendations and where multigene assays may be of particular value.

Methods

Questionnaire

An international panel of 8 breast cancer experts developed the MAGIC survey with input from Genomic Health (Geneva, Switzerland) and TRM Oncology (The Hague, The Netherlands). An online survey Web module was developed by the SKIM Group (Rotterdam, The Netherlands).

The survey questionnaire (see **supplementary material**) consisted of single-select, numeric, and multiple-select questions capturing respondents' demographics, general practice patterns, relevance of clinical and pathologic criteria for adjuvant chemotherapy decisions, and the usage of multigene assays. Each respondent was also asked to indicate treatment recommendations for 24 breast cancer patient profiles, randomly selected from a pool of 896 different patient profiles generated by all possible combinations of 7 patient characteristics: age (>50, >60, >70, >80 years), tumor size (>1, >2, >3, >4, >5 cm), tumor grade (Grade ≥ 1, Grade ≥ 2, Grade 3) ER expression (<1%, <10%, <30%), PR expression (yes vs no), Ki67 expression(≥ 14%, >20%, >30%), and lymph node status (0 or any positive node; 1, including isolated tumor cell or micrometastases; 2; 3; ≥4). Patient profiles with >20% Ki67+ tumor cells combined with a Grade 1 were excluded, as they were judged as biologically implausible by the expert panel and>20% Ki67+ tumor cells combined with a Grade 2 were also excluded. . For each patient profile, respondents could choose from the following 3 recommendations: chemotherapy in addition to endocrine treatment, endocrine treatment alone, and a request for more information.

Eligible respondents and survey distribution

The survey was conducted between August 2013 and January 2014. Practicing clinicians and pathologists who actively participated in a multidisciplinary breast cancer team, had >5 years' experience in breast cancer, and personally treated >20 new breast cancer patients per year (practicing clinicians) or ran immunohistochemistry for progesterone receptor (PR), ER, or HER2 for >20 breast cancer patients per year (pathologists) were eligible to complete the survey. Practicing clinicians also had to be personally involved in adjuvant treatment decisions for breast cancer patients. A link to the survey was distributed via email by breast cancer organizations, breast cancer study groups, and an international network of breast cancer physicians (acknowledgment in the **Appendix**).

Data analysis

Descriptive statistical analyses of the data were performed using SPSS (IBM) and Excel (Microsoft).

Country-specific trends were analyzed in countries with >30 respondents. A conjoint analysis was used to analyze practicing clinicians' preferences and their sensitivity for different patient features when making treatment decisions by ranking the relevance of the 7 patient characteristics.[16] Interaction effects between the patient characteristics were disregarded in this univariate analysis.

A predictive model was developed to simulate the likelihood of each treatment recommendation for all 896 possible breast cancer patient profiles. For this multivariate analysis, the survey data were analyzed using hierarchical Bayes analysis to calculate a physician-level model for each treatment choice. When simulating a patient profile, the corresponding utilities to the patient features were added and converted to a preference share for each treatment option. The preference share was then aggregated to identify the probability of each treatment for the simulated patient.

Results

Respondent demographics and general practice patterns

In total, 911 respondents (96% practicing clinicians, 4% pathologists) from 52 countries completed the MAGIC survey, of which the majority (74%) resided in Europe; 14 countries had ≥30 respondents and qualified for analysis of country-specific trends. Over half of the respondents (54%) were medical oncologists, followed by surgical oncologists (21%), gynecologists (16%), radiation oncologists (4%), and pathologists (4%). The respondent characteristics are summarized in **Table 1**.[6,7, 17-21]

The majority of respondents used tools/nomograms to estimate prognosis. The usage was highest among the radiation oncologists (97%) and lowest among the gynecologists (74%). Adjuvant! Online was used most frequently by gynecologists and medical, radiation, and surgical oncologists, whereas Nottingham Prognostic Index was more common among pathologists and practicing clinicians of other specialties. Predict was the third most common nomogram, used by approximately 12% of the respondents. In total, 98% of respondents indicated they always or often consulted internationally accepted guidelines for breast cancer treatment.

Consideration of clinical and pathologic criteria for treatment recommendations

Although most respondents always or often adhered to internationally accepted breast cancer guidelines, simulated treatment recommendations by practicing clinicians showed that the likelihood of receiving adjuvant chemotherapy varied substantially across countries (**Figure 1**). Overall, 65% of the patient profiles had >50% probability of an adjuvant chemotherapy recommendation; this proportion was highest in Greece and Mexico (72%) and lowest in Germany (59%) and Switzerland (58%). Part of this heterogeneity among countries may be explained by differences in the cutoff of clinical and pathologic criteria at which adjuvant chemotherapy is recommended (**Table 2**). Although many differences were observed between countries, a high proportion of respondents strongly considered using adjuvant chemotherapy in patients with: a tumor size of >2 cm (35%), or a tumor grade of 3 (70%), or <10% ER+ tumor cells (47%), >20% Ki67+ tumor cells (34%), or at least 1 positive lymph node (39%).

The relevance of individual patient characteristics for adjuvant chemotherapy recommendations was also evaluated by a conjoint analysis. Using the recommendations for random patient profiles, the impact of patient characteristics on practicing clinicians' treatment recommendations could be determined, providing insight into what drives their decisions. Outcomes of this analysis showed that age was the most important patient characteristic for adjuvant chemotherapy decisions,

followed by tumor grade, tumor size, lymph node status, and Ki67, ER, and PR expression (**Figure 2**). However, the conjoint analysis did not consider potential interactions between patient characteristics, while these were shown to be relevant in the individual treatment recommendations. For example, patients with high-risk characteristics (eg, 1–3 positive lymph nodes or a Grade 3 tumor) had a high predicted probability (>75%) of receiving endocrine treatment alone if they were older or had small (<2 cm) tumors. Conversely, patients with small, Grade 1 tumors were likely (>75% predicted probability) to be recommended adjuvant chemotherapy if they were young or had positive lymph nodes.

Breast cancer profiles where a multigene assay might be of value

To explore the heterogeneity in treatment recommendations for patients with breast cancer, patient profiles were ranked on a heat map according to their predicted likelihood for an adjuvant chemotherapy or endocrine treatment alone recommendation (**Figure 3**). This analysis showed substantial heterogeneity in the simulated treatment decisions for 52% of the patient profiles, with at least every fourth physician recommending a different treatment. There was a particularly high level of uncertainty regarding treatment decisions for 15% of the patient profiles (as detailed below), with <50% probability for a recommendation of both chemotherapy and endocrine therapy alone.

For patients with only high-risk characteristics, the general consensus was to advise adjuvant chemotherapy; 42% of the patient profiles had ≥75% probability of receiving adjuvant chemotherapy. Substantially fewer patient profiles (6%) had a ≥75% probability for an endocrine treatment alone recommendation. The 15% of patient profiles with the greatest heterogeneity in treatment recommendations had predominantly intermediate-risk features by traditional parameters (**Figure 3**).

Multigene assay utilization

Of the respondents, only around half (54%) of the practicing clinicians used multigene assays (**Figure 4A**). The most common reason for not using assays was lack of reimbursement, price, and lack of availability (**Figure 4B**; country-specific data are displayed in **Supplementary Table 1**).

There was a pronounced difference in usage of multigene assays between respondents from different countries, ranging from 91% of respondents in Greece using them to 0% in Sweden (**Figure 4A**). Onco*type* DX® Breast Cancer Assay was used most frequently (81%), followed by MammaPrint® (35%), EndoPredict (7%), FEMTELLE® (5%), Prosigna™ (2%), and Mammostrat® (1%) (**Figure 4C**;

country-specific data are displayed in **Supplementary Table 2**). In all countries except Germany (50%), the majority of physicians currently not using multigene assays wanted to use these tests.

Discussion

The MAGIC survey showed that treatment recommendations in ER+, HER2– patients are highly heterogeneous internationally and that there is substantial uncertainty for a large proportion of patients. However, there was an overall strong tendency to recommend chemotherapy rather than endocrine therapy alone. For the majority (52%) of ER+, HER2– early breast cancer patient profiles, there was substantial heterogeneity in treatment recommendations, with at least every fourth physician recommending a different treatment. The probability of receiving chemo-endocrine or endocrine treatment alone was ≤ 50% for both in 15% of patients, indicating a very high uncertainty regarding treatment decisions. These patient profiles often had a combination of intermediate-risk features by traditional parameters. Using further prognostic and predictive markers such as multigene assays may be particularly useful to help make more-informed treatment decisions in these patients, although it should be emphasized that such markers may provide useful information also in other patients.

Additionally, the survey revealed large differences between countries in the use of available multigene assays. The Onco*type* DX Breast Cancer Assay was the most frequently used assay except in the Netherlands and Spain, where MammaPrint was the most commonly used multigene assay. This is in line with results from a recent ESMO-supported survey showing that Onco*type* DX Breast Cancer Assay was selected most frequently as a multigene assay to determine adjuvant chemotherapy benefit for breast cancer patients.[22] The differences seen in the use of available multigene assays is likely due to differences in data supporting prediction of chemotherapy benefit that only exist for the Onco*type* DX assay,[9] and differences in the level of evidence supporting the different assays in relevant patient populations, as well as the different status of multigene assays in international guidelines (**Table 3**).[5-7, 23]

Although most internationally accepted guidelines include multigene assays, there is no clear consensus on the precise characteristics of breast cancer patients for whom these assays should be used and this is a likely reason to at least some of the differences seen.[5-7, 23] In the ESMO guidelines it is suggested that multigene assays may be considered for ER+, HER2– breast cancer patients who are node negative with stage 2 tumors (>2 cm tumor without extension to the chest wall and/or skin, and without distant metastases).[6] Meanwhile, the 2013 St. Gallen consensus recommended usage of multigene assays in selected patients with ER+, HER2− node-negative disease, those with 1–

3 positive nodes, and patients aged more than 35 years, as adjuvant chemotherapy was thought to be of uncertain indication in these patients.[17] These characteristics are not clearly outlined in the more recent recommendations from the 2015 St. Gallen consensus.[5] Genomic testing was felt to be unnecessary for low-risk or high-risk patients by clinicopathologic parameters, although it is acknowledged that the interobserver variability for grade and Ki67 is high. In the NCCN guidelines the usage of the Onco*type* DX assay is considered for node-negative, ER+, HER2− breast cancer patients with primary tumors of 0.6−1 cm with unfavorable features or tumors >1 cm.[7] NCCN does not currently consider Prosigna, EndoPredict, Breast Cancer Index (BCI), or MammaPrint as having sufficient evidence to support their clinical use.[7] In contrast, the panel of 2015 St. Gallen consensus voted in favor of acknowledging that Prosigna, EndoPredict, BCI and MammaPrint and Onco*type* DX have a prognostic value in the first 5 years.[5] The NCCN guidelines, the ASCO recommendations, and the 2013 St. Gallen consensus also all acknowledge that the Onco*type* DX assay has predictive value in determining the benefit of adjuvant chemotherapy.[7, 17, 23] The lack of data from prospective studies and real life outcome data from patients where multigene assays have been used for treatment decisions have for a long time been a key weakness in the evidence supporting multigene assays. Many physicians and reimbursement bodies have also chosen to wait with including multigene assays in their clinical care until such data is available. Recently, prospective outcome data from studies and real outcome data from large cohorts of patients where Oncotype DX has been included when making treatment decisions have now been reported: Data from the TAILORx study has recently been published.[24] This study prospectively stratified the use of chemotherapy on the basis of the Onco*type* Dx assay. This study has reported that 99.3% of the patients with low Onco*type* Dx assay Recurrence Scores between 0-10, treated with endocrine therapy alone, were free of distant recurrence at 5 years further demonstrating the utility of the Onco*type* Dx assay to identify a group of patients with an exceptionally good prognosis in the absence of chemotherapy.[24] The Plan B adjuvant study in high risk node negative and node positive patients was also recently published.[25] The Clalit registry in Israel containing data from more than 2000 patients with node

negative disease reported a risk of recurrence of 0.7% at 5 years follow up for patients with low Recurrence scores (less than 18) where 98% had been treated with endocrine therapy alone[26] and the SEER database analysis including more than 40 000 pts corroborates these data with breast cancer specific mortality rate that is exceptionally low- only 49 events in more than 20 000 patients with low Recurrence Scores (less than 18).[27] It should be emphasized that real life data may be affected by selection bias regarding in which patients the assay is ordered however.

Prospective data for the MammaPrint assay from the MINDACT trial have been presented and published in 2016. In this randomized, phase 3 study, 6693 women with early-stage breast cancer were enrolled and their genomic risk was determined using the 70-gene signature and their clinical risk with a modified version of Adjuvant! Online. The primary goal was to assess whether, among patients with high-risk clinical features and a low-risk gene-expression profile who did not receive chemotherapy, the lower boundary of the 95% confidence interval for the rate of 5-year survival without distant metastasis would be 92% (i.e., the noninferiority boundary) or higher. A total of 1550 patients (23.2%) were deemed to be at high clinical risk and low genomic risk. At 5 years, the rate of survival without distant metastasis in this group was 94.7% (95% confidence interval, 92.5 to 96.2) among those not receiving chemotherapy. The absolute difference in this survival rate between these patients and those who received chemotherapy was 1.5 percentage points, with the rate being lower without chemotherapy. The authors conclude that these findings suggest that approximately 46% of women with breast cancer who are at high clinical risk might not require chemotherapy.[28]

Published before the above mentioned trials, the ASCO Biomarkers guidelines panel found sufficient evidence of clinical utility for the biomarker assays Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, and urokinase plasminogen activator and plasminogen activator inhibitor type 1 in specific subgroups of breast cancer. [29] The panelists indicate also that treatment decisions should consider disease stage, comorbidities, and patient preferences.Parameters such as nodal status, tumor size

have been shown to add prognostic value to genomic information generated in both Oncotype DX, Endopredict and PAM50 . [30-32]

The MAGIC survey results are based on respondents' answers indicating certain trends and not on objective analyses of actual treatment recommendations, which may be considered a limitation of this study. In addition, some of the subgroup analyses are based on small group sizes. Nevertheless, the large number of respondents varying in their specialty, level of experience, and country of origin provided a unique opportunity to compare physician subgroups. Insights into the current differences in general practice patterns may be valuable when developing international guidelines for breast cancer treatment

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In conclusion, the MAGIC survey provides valuable insight into worldwide treatment recommendations for early breast cancer patients and the clinical and pathologic criteria used for these decisions. The overall findings indicate that there is substantial heterogeneity in how patients are treated and a substantial uncertainty in treatment recommendations for a large proportion of patients, highlighting an unmet need for broadly available markers, such as multigene assays, that can help to make more-informed treatment decisions by predicting a patient's likelihood of benefit from adjuvant chemotherapy.

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Appendix. Breast cancer organizations and study groups that participated in distribution of the link to the MAGIC survey.

Arbeitsgemeinschaft Gynäkologische Onkologie e.V.

Breast International Group

Berufsverband Niedergelassener Gynakologischer Onkologen

Breast International Group

European Society of Breast Cancer Specialists

European Organisation for Research and Treatment of Cancer

Grupo Español de Investigación en Cáncer de Mama

Gruppo Italiano Mammella (GIM)

Hellenic Society of Breast Surgeons

International Breast Cancer Study Group

International Collaborative Cancer Group

Italian Trials in Medical Oncology

National Cancer Research Institute

The Netherlands Association for Medical Education

Priv-Doz Dr Med Marc Thill

The Swedish Association of Breast Oncologists

Grupo Español de Estudio, Tratamiento y Otras Estrategias Experimentales en Tumores Sólidos

United Kingdom Breast Intergroup

Central and Eastern European Oncology Group

European Society of Surgical Oncology

Austrian Breast & Colorectal Cancer Study Group

West German Study Group

Sociedad Mexicana de Oncología

Asociación Mexicana de Mastología

Sociedad Argentina de Mastología

Sociedade Brasileira de Oncologia Clínica

Figure Legends

Figure 1. Likelihood of adjuvant chemotherapy recommendations stratified by country. Each practicing clinician was asked to make treatment recommendations for 24 randomly selected patient profiles (chemotherapy, endocrine treatment alone, or a request for more information). Based on their treatment recommendations a simulation model was generated to predict the probability for each treatment recommendation for 896 simulated patient profiles.

Figure 2. Graphic representation of a conjoint analysis of adjuvant chemotherapy recommendations. The *y*-axis depicts a ranking of importance of various clinical and pathologic characteristics with regard to recommendation of chemotherapy. The *x*-axis depicts the index of importance for each patient characteristic. The relative distance between the levels indicates the relative impact on the recommendation. Interaction effects between the characteristics have not been considered in these analyses. ER, estrogen receptor; N0, lymph node negative; N1, 1–3 affected lymph nodes; PR, progesterone receptor.

Figure 3. Ranking of 672 simulated breast cancer patient profiles according to their likelihood for an adjuvant chemotherapy or endocrine treatment alone recommendation. Patient profiles having the biologically uncommon combination of low ER expression and high PR expression or >20% Ki67+ tumor cells in a Grade 1 or 2 tumor were excluded from this analysis. Grey cells (n=43) show patient profiles with ≥75% probability to be recommended endocrine treatment alone. Orange cells (n=99) show patient profiles with 50%–75% probability to be recommended endocrine treatment alone. Purple cells (n=104) show patient profiles with <50% probability to be recommended endocrine treatment alone AND <50% probability to be recommended chemotherapy. Green cells (n=145) show patient profiles with 50%–75% probability to be recommended chemotherapy. Blue cells (n=281) show patient profiles with ≥75% probability to be recommended chemotherapy. ER, estrogen receptor; HR, hormone receptor; N0, lymph node negative; N1, 1–3 affected lymph nodes; PR, progesterone receptor.

Figure 4. (A) Usage of multigene assays and desire to use multigene assays for practicing clinicians by country. **(B)** Type of multigene assays that were used (multiple answers were allowed; only practicing clinicians who indicated to use multigene assays were considered). **(C)** Reasons for not using multigene assays (multiple answers were allowed; only practicing clinicians who indicated to not use multigene assays were considered).

Tables

Table 1. Demographics and general practice patterns of MAGIC survey respondents.

	All respondents (n=911)	Medical oncologists (n=495)	Gynecologists (n=147)	Radiation oncologists (n=38)	Surgical oncologists (n=192)	Pathologists (n=32)[a]	Other (n=7)
Region of residence, n(%)[b]							
Europe	672 (74)	392 (79)	85 (58)	32 (84)	132 (69)	25 (78)	6 (86)
Latin America	157 (17)	44 (9)	62 (42)	4 (11)	45 (23)	1 (3)	1 (14)
Russia	56 (6)	46 (9)	0 (0)	0 (0)	5 (3)	5 (16)	0 (0)
Rest of World	26 (3)	13 (3)	0 (0)	2 (5)	10 (5)	1 (3)	0 (0)
Experience, n (%)							
≥10 Years of experience[c]	720 (79)	392 (79)	111 (76)	34 (89)	157 (82)	23 (72)	3 (43)
Chemotherapy prescriber	613 (67)	492 (99)	66 (45)	19 (50)	32 (17)	2 (6)	2 (29)
Number of new patients/year[d]	113 (150)	104 (97)	97 (73)	125 (125)	146 (266)	641 (719)	76 (58)
Involvement of multidisciplinary team, n(%)[a]							
Always	756 (83)	407 (82)	113 (77)	34 (89)	172 (90)	25 (96)	5 (71)
In some cases	140 (15)	86 (17)	27 (18)	4 (11)	20 (10)	1 (4)	2 (29)
Never	9 (1)	2 (0.4)	7 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Guidelines adherence, n(%)[a]							
Always	496 (55)	251 (51)	86 (59)	19 (50)	123 (64)	14 (54)	3 (43)
Often	389 (43)	234 (47)	60 (41)	16 (42)	64 (33)	12 (46)	3 (43)
Sometimes	15 (2)	8 (2)	0 (0)	3 (8)	4 (2)	0 (0)	0 (0)
Never	5 (1)	2 (0.4)	1 (1)	0 (0)	1 (1)	0 (0)	1 (14)
Guidelines used, n(%)[a,e]							
St. Gallen[17]	353 (71)	179 (71)	63 (73)	18 (95)	82 (67)	11 (79)	0 (0)
ESMO[6]	205 (41)	131 (52)	21 (24)	10 (53)	35 (28)	7 (50)	1 (33)

ASCO[18]	218 (44)	115 (46)	38 (44)	9 (47)	45 (37)	9 (64)	2 (67)
NCCN[7]	272 (55)	138 (55)	42 (49)	10 (53)	74 (60)	7 (50)	1 (33)
Tools/nomograms used, n(%)[a]							
Nottingham Prognostic Index[19]	209 (23)	86 (17)	23 (16)	9 (24)	69 (36)	17 (65)	5 (71)
Adjuvant! Online[20]	644 (71)	363 (73)	96 (65)	32 (84)	135 (70)	15 (58)	3 (43)
Predict[21]	109 (12)	59 (12)	15 (10)	9 (24)	23 (12)	2 (8)	1 (14)
No use of tools/nomograms	134 (15)	73 (15)	38 (26)	1 (3)	19 (10)	2 (8)	1 (14)
Consideration of Ki67, n(%)[a]							
Strong consideration	265 (29)	156 (32)	48 (33)	6 (16)	46 (24)	8 (31)	1 (14)
Not a predominant consideration	497 (55)	275 (56)	78 (53)	21 (55)	108 (56)	13 (50)	2 (29)
Little influence	48 (5)	20 (4)	14 (10)	2 (5)	10 (5)	1 (4)	1 (14)
Not considered	34 (4)	13 (3)	7 (5)	2 (5)	7 (4)	4 (15)	1 (14)
No access to Ki67 testing	61 (7)	31 (6)	0 (0)	7 (18)	21 (11)	0 (0)	2 (29)

ASCO, American Society of Clinical Oncology; ER, estrogen receptor; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; PR, progesterone receptor.

Due to rounding of the numbers, total percentages may not equal 100%.

[a]For the categories "Involvement of multidisciplinary team," "Guidelines adherence," "Guidelines used," "Tools/nomograms used," and "Consideration of Ki67," data were missing for 6 pathologists.

[b]Countries with more than 30 respondents were: Argentina, Belgium, Switzerland, Germany, Spain, France, Greece, Hungary, Italy, Mexico, The Netherlands, Russia, Sweden, and the United Kingdom.

[c]For practicing clinicians, the number of years of experience in treating breast cancer was considered. For pathologists, the number of years in which they were involved in running diagnostic tests for breast cancer patients was considered.

[d]For practicing clinicians, the number of new breast cancer patients per year treated by the respondent was considered. For pathologists, the number of breast cancer patients per year for which the respondent runs ER/PR/HER2 immunohistochemistry was considered. For both, "mean (standard deviation)" are shown.

[e]Only respondents who indicated to always use breast cancer treatment guidelines were considered.

Table 2. Consideration by practicing clinicians of traditional patient characteristics for adjuvant chemotherapy recommendations. Practicing clinicians indicated at which level of the respective clinical or histopathologic markers they would strongly consider to recommend adjuvant chemotherapy to HR+, HER2– early breast cancer patients.

	All N=879	AR N=66	BE N=45	CH N=29	DE N=54	ES N=75	FR N=63	GR N=45	HU N=28	IT N=103	MX N=52	NL N=27	RU N=52	SE N=31	UK N=67
In a node-negative context, is there a specific tumor size above which you would strongly consider using adjuvant chemotherapy?															
>1 cm	14	39	0	3	6	11	8	11	11	4	37	22	8	10	3
>2 cm	35	39	42	10	26	49	48	36	50	31	31	52	29	32	34
>3 cm	14	8	16	10	9	16	14	24	14	17	8	15	2	23	31
>4 cm	5	6	7	7	0	1	6	7	11	1	4	0	2	3	12
>5 cm	9	5	11	38	11	8	3	4	0	6	15	4	12	26	7
Tumor size does not affect decision	22	3	24	31	48	15	21	18	14	42	6	7	48	6	12
In a node-negative context, is there a specific tumor grade above which you would strongly consider using adjuvant chemotherapy?															
Grade ≥1	1	0	0	0	0	0	0	0	0	0	0	0	4	0	0
Grade ≥2	21	6	16	10	13	25	25	42	32	10	29	44	35	19	24
Grade 3	70	86	80	79	81	71	68	53	64	79	56	56	44	81	73
Tumor grade does not affect decision	8	8	4	10	6	4	6	4	4	12	15	0	17	0	3
What percentage of ER+ cells would you consider low and would make you strongly consider using adjuvant chemotherapy in addition to hormonal therapy?															
<1%	26	61	16	28	52	19	17	24	11	22	25	22	25	0	12
<10%	47	30	49	38	35	45	65	44	54	45	44	56	44	84	43
<30%	20	6	27	34	4	29	10	24	32	25	17	11	15	10	39
Percentage of ER+ cells does not affect decision	7	3	9	0	9	7	8	7	4	8	13	11	15	6	6
At which Ki67 percentage would you strongly consider giving adjuvant chemotherapy?															
≥14%	27	28	36	10	13	43	18	33	14	20	35	17	40	6	21

>20%	34	31	36	48	56	31	44	36	46	37	21	17	28	45	11
>30%	32	31	27	38	26	27	31	29	39	39	38	17	21	42	53
Ki67 expression does not affect decision	7	10	2	3	6	0	8	2	0	4	6	50	11	6	16
What number of positive axillary nodes would make you <u>strongly</u> consider giving chemotherapy?															
Lymph node negative	4	0	0	3	2	5	2	2	0	4	10	4	4	6	6
1[a]	39	61	27	3	22	43	40	42	39	23	48	59	58	48	34
2	21	17	27	14	20	25	22	24	29	18	10	15	8	35	34
3	11	12	16	31	22	3	14	7	7	15	13	0	10	0	6
≥4	21	8	29	45	31	13	19	22	21	33	19	15	13	6	10
Number of positive lymph nodes does not affect decision	5	3	2	3	2	11	3	2	4	7	0	7	8	3	9
Is there an upper age limit above which you would <u>strongly</u> consider <u>not</u> giving adjuvant chemotherapy?															
>50 years	1	3	0	0	2	1	0	2	0	5	0	0	2	0	0
>60 years	1	0	0	3	0	0	3	2	4	0	0	4	0	0	0
>70 years	17	29	11	7	11	12	21	13	14	8	15	52	15	6	19
>80 years	48	52	53	62	39	60	41	36	57	51	33	33	38	77	61
Age does not affect decision	33	17	36	28	48	27	35	47	25	36	52	11	44	16	19

AR, Argentina, BE, Belgium; CH, Switzerland; DE, Germany; ER, estrogen receptor; ES, Spain; FR, France; GR, Greece; HER2, human epidermal growth factor receptor; HR, hormone receptor; HU, Hungary; IT, Italy; MX, Mexico; NL, The Netherlands; RU, Russia; SE, Sweden; UK, United Kingdom.

Due to rounding of the numbers, total percentages may not equal 100%. Country-specific data are shown for countries with ≥30 respondents.

[a]Including isolated tumor cells or nodal micrometastases.

Table 3. Multigene assays – guideline recommendations.

Source	Oncotype DX (21-gene RT-PCR assay)	MammaPrint (70-gene expression profile)	Other multigene assays
NCCN[7]	• An option when evaluating patients with primary tumors characterized as – 0.6 to 1.0 cm – Unfavorable features or >1 cm – Node negative, HR+, and HER2– (category 2A) • The RS may assist in estimating likelihood of recurrence and benefit from chemotherapy	• FDA-approved for identifying patients with ER+ or ER− breast cancer as having a high or low risk of recurrence • Not approved for predicting benefit from adjuvant systemic therapy	• Currently insufficient evidence to warrant inclusion in the guidelines
ESMO[6]	• Recommended for obtaining extra prognostic and/or predictive information that is used to complement pathology assessment • May be used to predict response to adjuvant chemotherapy		• Not specifically addressed
St. Gallen[5]	• Provides prognostic and predictive information (years 1–5 and >5) regarding usefulness of adjuvant chemotherapy in patients with luminal	• Has prognostic utility regarding adjuvant chemotherapy in years 1–5. Panel rejected the prognostic value	• PAM-50 ROR score, EndoPredict, and the Breast Cancer Index considered to be prognostic in years 1–5. The panel was equally

	disease. Beyond 5 years, the Panel was divided almost equally on the prognostic value of Oncotype DX	beyond 5 years	divided with regard to the prognostic value for EndoPredict, Breast Cancer Index in years 5-10 but acknowledged the prognostic value of PAM-50 ROR in years 5-10.
ASCO[23]	• For use in newly diagnosed patients with node-negative, ER+ breast cancer • Can identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy • High RS appears to be predictive of benefit with adjuvant chemotherapy	• The clinical utility of other assays is under investigation	

ASCO, American Society of Clinical Oncology; ER, estrogen receptor; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NCCN, National Comprehensive Cancer Network; RS, recurrence score; ROR, risk of recurrence; RT-PCR, reverse transcription polymerase chain reaction.

Supplementary Table 1. Reasons for not using multigene assays, stratified by country.

	All N=389	AR N=13	BE N=28	CH N=13	DE N=6	ES N=16	FR N=37	GR N=3	HU N=12	IT N=82	MX N=11	NL N=3	RU N=34	SE N=31	UK N=42
Lack of reimbursement	45%	0%	68%	85%	67%	63%	70%	67%	67%	60%	9%	33%	15%	6%	33%
Price	44%	92%	43%	8%	33%	25%	49%	67%	75%	33%	91%	0%	15%	39%	52%
Lack of availability	39%	31%	25%	15%	0%	31%	14%	67%	33%	38%	55%	0%	71%	29%	60%
Not in relevant guidelines	20%	0%	21%	0%	67%	6%	32%	0%	8%	17%	0%	0%	32%	45%	21%
Lack of evidence	17%	8%	29%	38%	67%	6%	22%	0%	8%	12%	0%	67%	3%	39%	19%
Other	2%	0%	4%	8%	0%	0%	3%	0%	0%	0%	0%	0%	0%	10%	0%

AR, Argentina, BE, Belgium; CH, Switzerland; DE, Germany; ES, Spain; FR, France; GR, Greece; HU, Hungary; IT, Italy; MX, Mexico; NL, The Netherlands; RU, Russia; SE, Sweden; UK, United Kingdom.

Data show the percentage of practicing clinicians who indicated to not use multigene assays (multiple answers were allowed). Country-specific data are shown for countries with ≥30 respondents.

Supplementary Table 2. Multigene assays used, stratified by country (multiple answers allowed).

	All N=471	AR N=52	BE N=16	CH N=16	DE N=48	ES N=59	FR N=26	GR N=41	HU N=15	IT N=20	MX N=41	NL N=24	RU N=10	UK N=22
Onco*type* DX® Breast Cancer Assay	81%	94%	56%	94%	77%	69%	88%	100%	93%	70%	78%	17%	50%	100%
MammaPrint®	35%	25%	31%	19%	4%	73%	8%	7%	7%	50%	73%	96%	20%	9%
EndoPredict®	7%	0%	13%	25%	44%	0%	0%	0%	0%	0%	2%	0%	10%	0%
FEMTELLE®	5%	0%	0%	0%	38%	0%	15%	2%	0%	0%	0%	0%	10%	0%
Prosigna™	2%	0%	0%	0%	0%	10%	4%	0%	0%	5%	2%	0%	20%	0%
Mammostrat®	1%	4%	0%	0%	0%	0%	0%	0%	7%	0%	5%	0%	0%	0%
Other multigene assay	2%	0%	31%	6%	2%	0%	0%	0%	0%	0%	0%	0%	0%	0%

AR, Argentina, BE, Belgium; CH, Switzerland; DE, Germany; ES, Spain; FR, France; GR, Greece; HU, Hungary; IT, Italy; MX, Mexico; NL, The Netherlands; RU, Russia; SE, Sweden; UK, United Kingdom.

Data show the percentage of practicing clinicians who use multigene assays who indicated to use the described multigene assay. Country-specific data are shown for countries with ≥30 respondents. Sweden was not included in this analysis as none of the Swedish respondents indicated to use multigene assays.

Figure 3

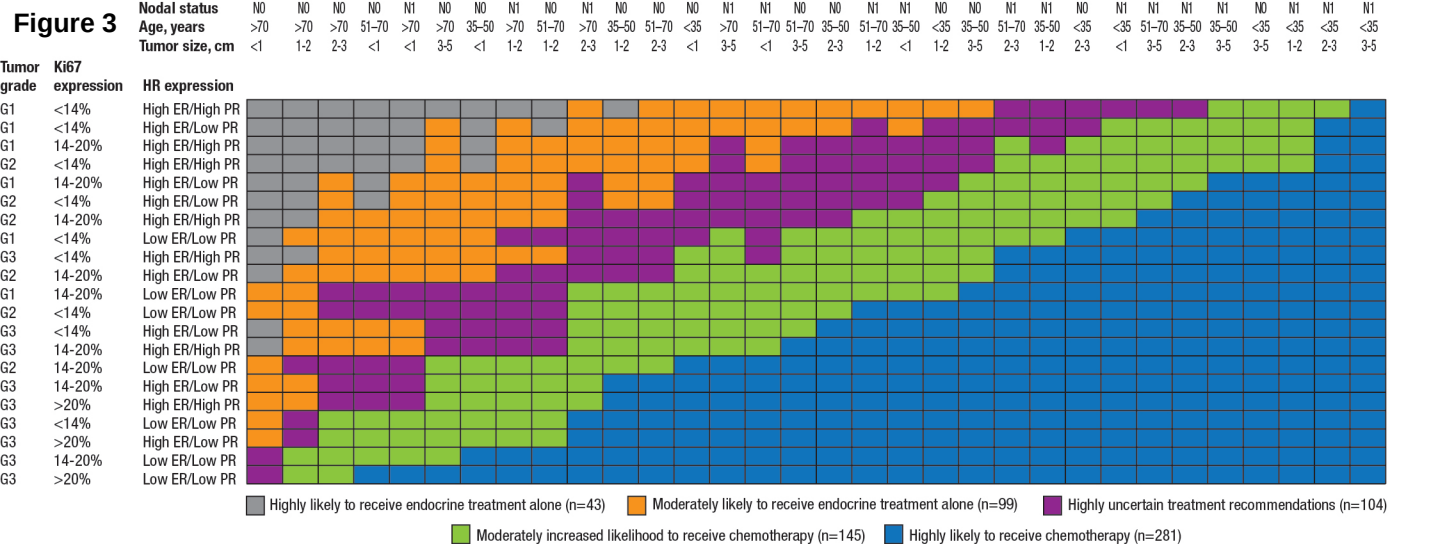

Nodal status N0 N0 N0 N0 N1 N0 N0 N1 N0 N1 N0 N0 N0 N1 N1 N0 N0 N1 N1 N0 N0 N1 N1 N0 N1 N1 N1 N1 N1 N0 N1 N1 N1
Age, years >70 >70 >70 51–70 >70 >70 35–50 >70 51–70 >70 35–50 51–70 <35 >70 51–70 51–70 35–50 51–70 35–50 <35 35–50 51–70 35-50 <35 <35 51–70 35–50 35–50 <35 <35 <35 <35
Tumor size, cm <1 1-2 2-3 <1 <1 3-5 <1 1-2 1-2 2-3 1-2 2-3 <1 3-5 <1 3-5 2-3 1-2 <1 1-2 3-5 2-3 1-2 2-3 <1 3-5 2-3 3-5 3-5 1-2 2-3 3-5
Tumor grade
Ki67 expression
HR expression
G1 <14% High ER/High PR
G1 <14% High ER/Low PR
G1 14-20% High ER/High PR
G2 <14% High ER/High PR
G1 14-20% High ER/Low PR
G2 <14% High ER/Low PR
G2 14-20% High ER/High PR
G1 <14% Low ER/Low PR
G3 <14% High ER/High PR
G2 14-20% High ER/Low PR
G1 14-20% Low ER/Low PR
G2 <14% Low ER/Low PR
G3 <14% High ER/Low PR
G3 14-20% High ER/High PR
G2 14-20% Low ER/Low PR
G3 14-20% High ER/Low PR
G3 >20% High ER/High PR
G3 <14% Low ER/Low PR
G3 >20% High ER/Low PR
G3 14-20% Low ER/Low PR
G3 >20% Low ER/Low PR
Highly likely to receive endocrine treatment alone (n=43)
Moderately likely to receive endocrine treatment alone (n=99)
Highly uncertain treatment recommendations (n=104)
Moderately increased likelihood to receive chemotherapy (n=145)
Highly likely to receive chemotherapy (n=281)

Figure 4a

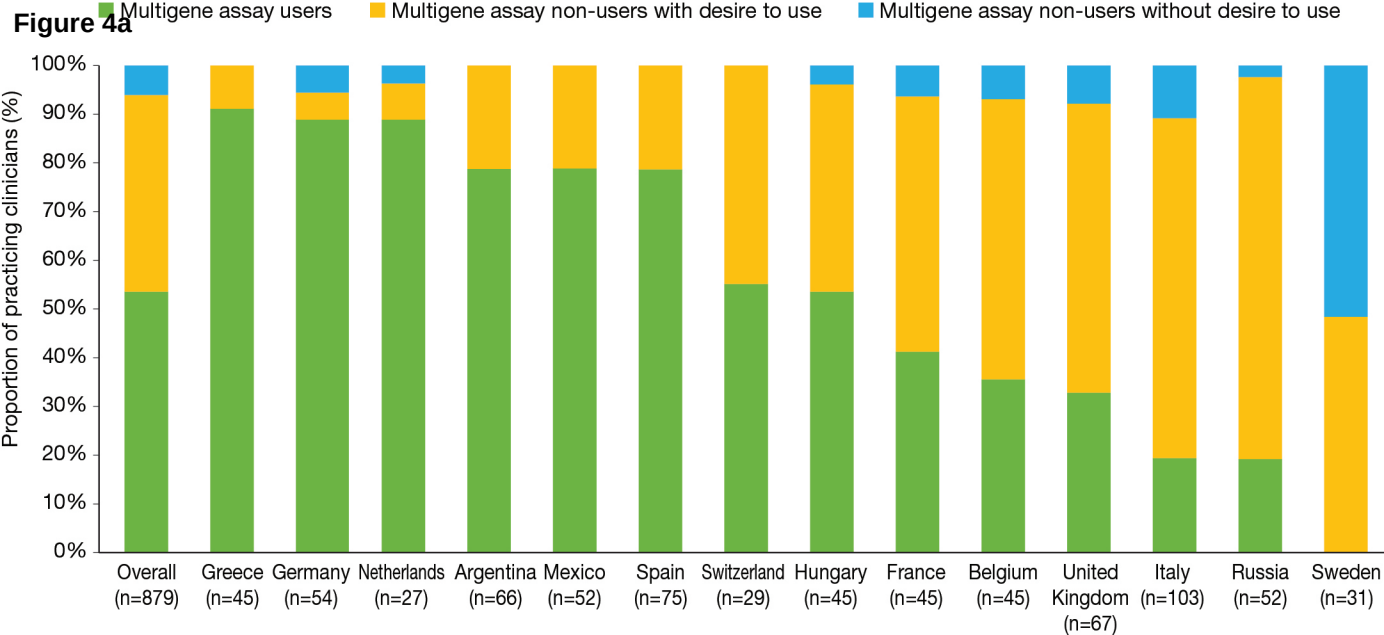

Multigene assay users
Multigene assay non-users with desire to use
Multigene assay non-users without desire to use
Proportion of practicing clinicians (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Overall (n=879)
Greece (n=45)
Germany (n=54)
Netherlands (n=27)
Argentina (n=66)
Mexico (n=52)
Spain (n=75)
Switzerland (n=29)
Hungary (n=45)
France (n=45)
Belgium (n=45)
United Kingdom (n=67)
Italy (n=103)
Russia (n=52)
Sweden (n=31)

Figure 4b

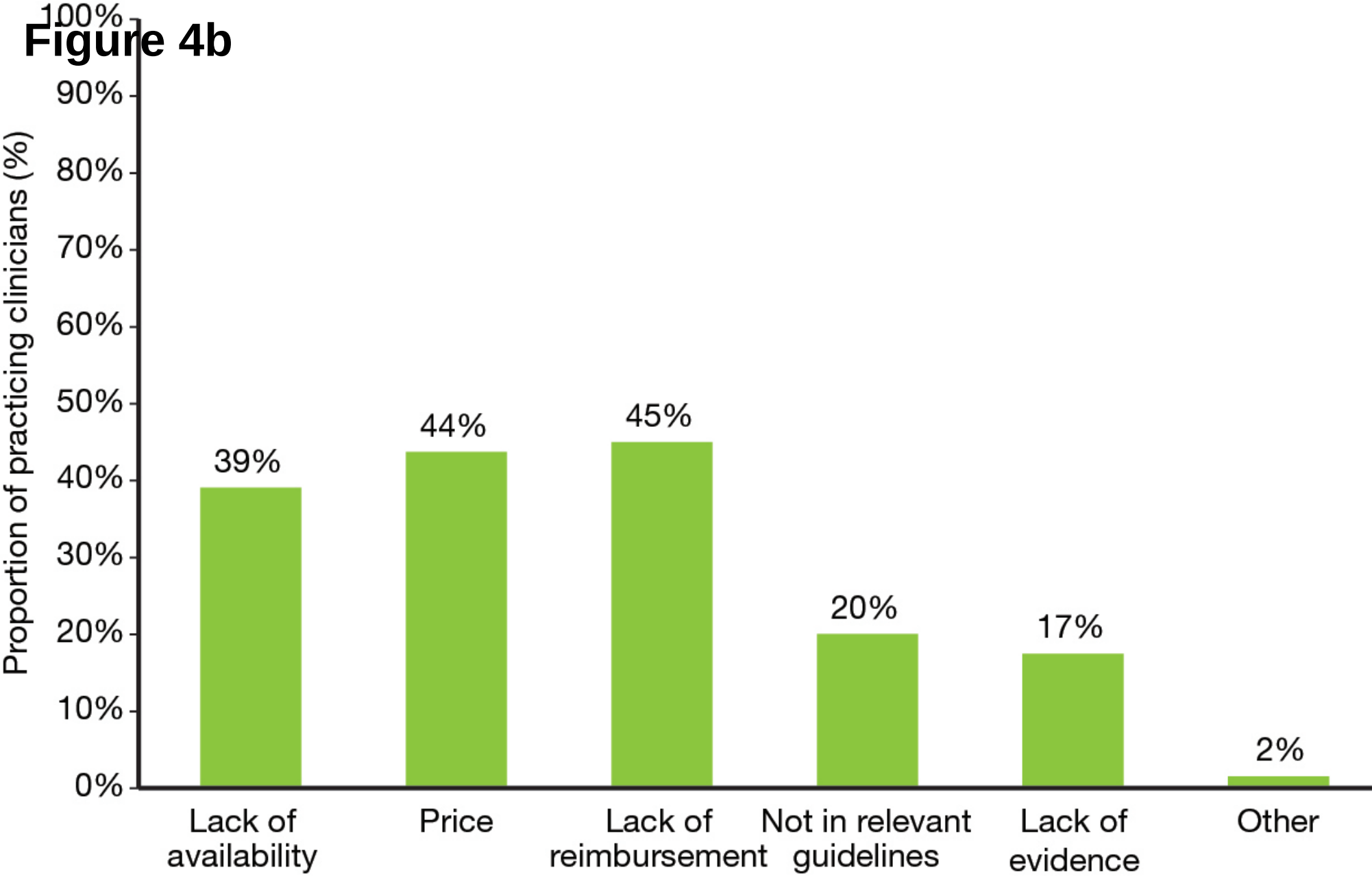
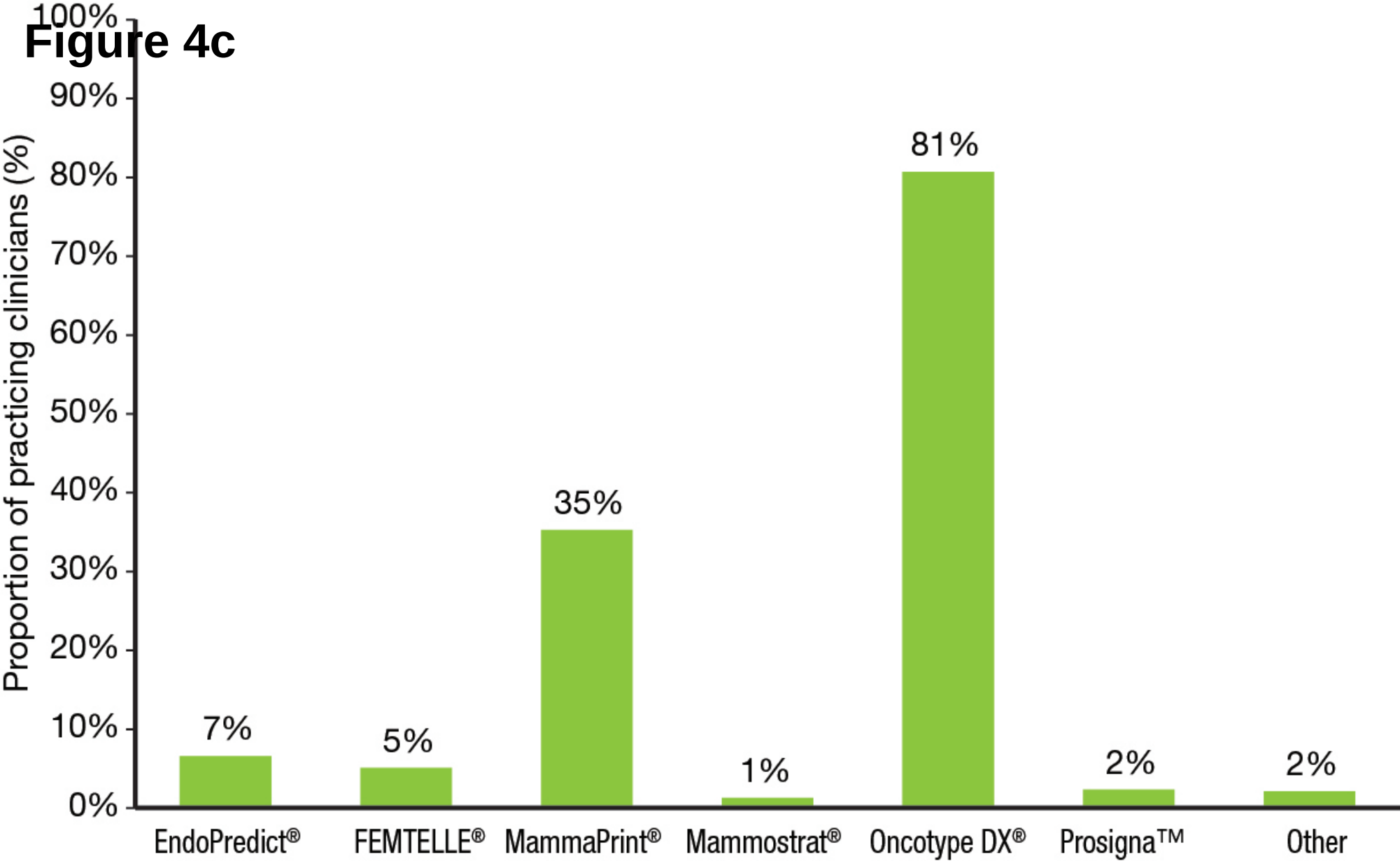
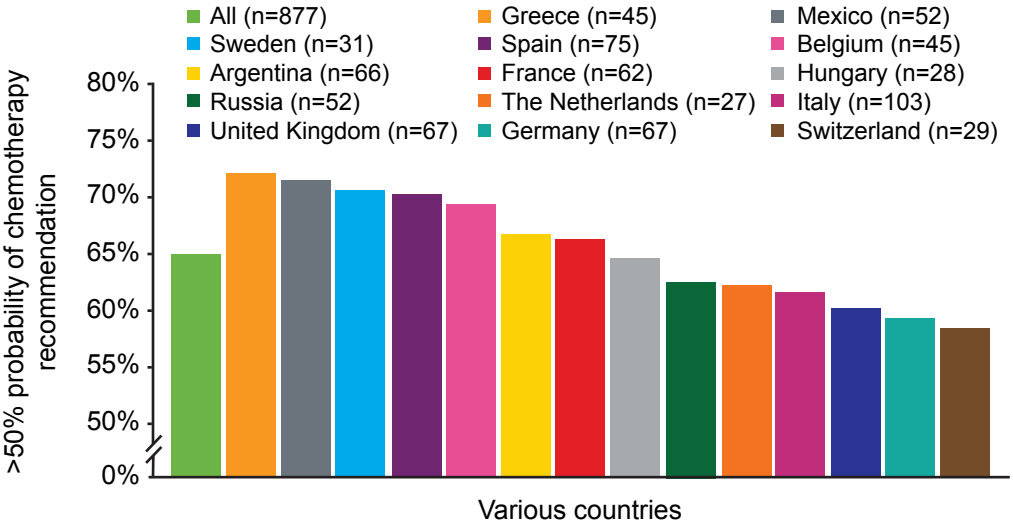

Proportion of practicing clinicians (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
39%
44%
45%
20%
17%
2%
Lack of availability
Price
Lack of reimbursement
Not in relevant guidelines
Lack of evidence
Other

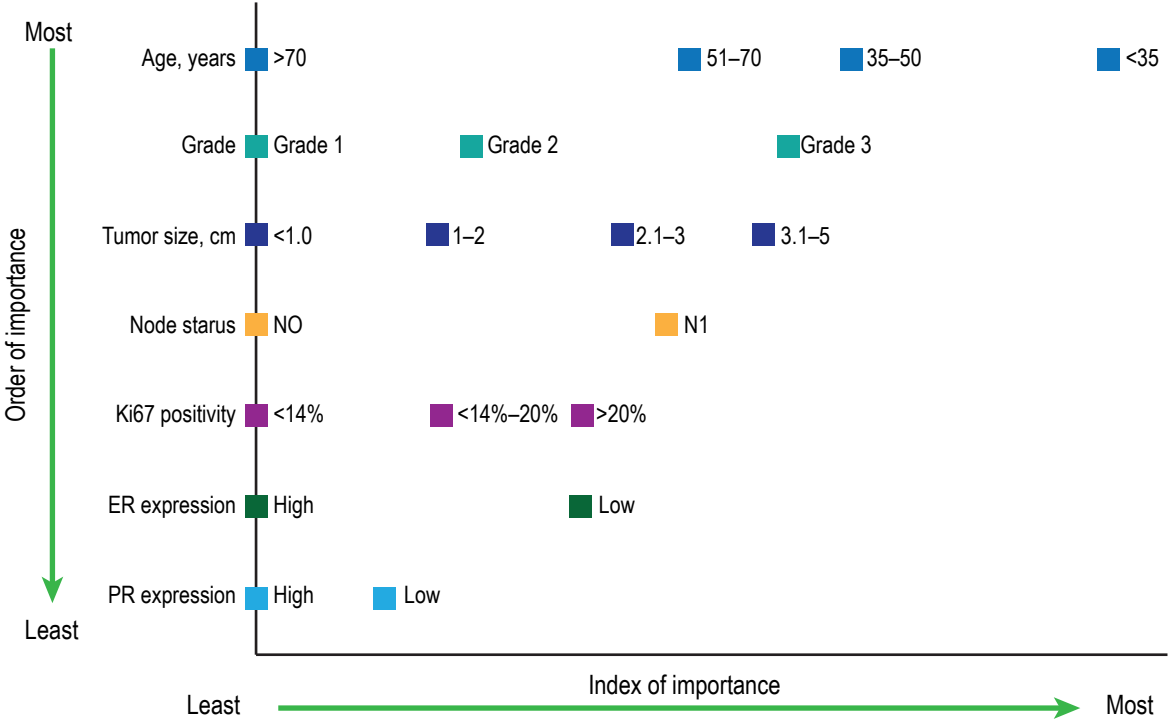
Figure 4c


Proportion of practicing clinicians (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
7%
5%
35%
1%
81%
2%
2%
EndoPredict®
FEMTELLE®
MammaPrint®
Mammostrat®
Oncotype DX®
Prosigna™
Other

Figure


All (n=877)
Sweden (n=31)
Argentina (n=66)
Russia (n=52)
United Kingdom (n=67)
Greece (n=45)
Spain (n=75)
France (n=62)
The Netherlands (n=27)
Germany (n=67)
Mexico (n=52)
Belgium (n=45)
Hungary (n=28)
Italy (n=103)
Switzerland (n=29)
>50% probability of chemotherapy recommendation
80%
75%
70%
65%
60%
55%
50%
0%
Various countries

Figure


Most
Order of importance
Least
Age, years
>70
51–70
35–50
<35
Grade
Grade 1
Grade 2
Grade 3
Tumor size, cm
<1.0
1–2
2.1–3
3.1–5
Node starus
NO
N1
Ki67 positivity
<14%
<14%–20%
>20%
ER expression
High
Low
PR expression
High
Low
Least
Index of importance
Most

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