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Risk estimations and treatment decisions in early stage breast cancer: Agreement among oncologists and the impact of the 70-gene signature



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Abstract Background: Clinical decision-making in patients with early stage breast cancer requires adequate risk estimation by medical oncologists. This survey evaluates the agreement among oncologists on risk estimations and adjuvant systemic treatment (AST) decisions and the impact of adding the 70-gene signature to known clinico-pathological factors.

Methods: Twelve medical oncologists assessed 37 breast cancer cases (cT1–3N0M0) and estimated their risk of recurrence (high or low) and gave a recommendation for AST. Cases were

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presented in two written questionnaires sent 4 weeks apart. Only the second questionnaire included the 70-gene signature result.

Results: The level of agreement among oncologists in risk estimation ($\kappa = 0.57$) and AST recommendation ($\kappa = 0.57$) was ‘moderate’ in the first questionnaire. Adding the 70-gene signature result significantly increased the agreement in risk estimation to ‘substantial’ ($\kappa = 0.61$), while agreement in AST recommendations remained ‘moderate’ ($\kappa = 0.56$). Overall, the proportion of high risk was reduced with 7.4% (range: 6.9–22.9%; $p < 0.001$) and the proportion of chemotherapy that was recommended was reduced with 12.2% (range: 5.4–29.5%; $p < 0.001$).

Conclusion: Oncologists’ risk estimations and AST recommendations vary greatly. Even though the number of participating oncologists is low, our results underline the need for a better standardisation tool in clinical decision-making, in which integration of the 70-gene signature may be helpful in certain subgroups to provide patients with individualised, but standardised treatment.

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1. Introduction

Clinico-pathological guidelines are used to guide adjuvant systemic treatment (AST) decisions in early stage breast cancer patients. These guidelines combine clinico-pathological factors such as age, tumour size, grade, hormone-receptor status and nodal status to estimate the risk of recurrence and provide an AST advice. Commonly used clinico-pathological guidelines are Adjuvant! Online (AOL), the Sankt Gallen expert panel recommendations and the Nottingham Prognostic Index (NPI) [1,2]. In the Netherlands, the Dutch Institute of Healthcare Improvement (CBO) guidelines are used most often [3]. Nevertheless, correctly estimating whether an individual patient has a high risk of recurrence and is likely to benefit from AST remains challenging [4]. Most of the guidelines consider only a small proportion of patients at a low risk of recurrence. This may result in a substantial number of patients being treated with AST while they are unlikely to derive significant benefit [5]. Each guideline mentioned above defines a partly non-overlapping group of patients at a low or high risk, which indicates that predictive accuracy for the individual patient is not high [1,6–8]. Also, online tools such as AOL that provide a survival probability instead of a low/high risk estimation can be used with different cut offs. Therefore, a variation in risk estimations made by oncologists who are guided by different guidelines is expected. The extent of this variation remains unclear.

To refine risk estimations and provide a more tailored AST recommendation for the individual patient, gene expression prognosis classifiers have been developed [9]. One of these gene expression classifiers is the 70-gene signature (MammaPrint™, Agendia Inc., Amsterdam, The Netherlands) [10]. The first prospective study, in which the 70-gene signature was used in addition to clinical guidelines, was conducted in the Netherlands between 2004 and 2006. This microarRAY prognostics

in breast cancer (RASTER) study showed discordance in risk estimation between the 70-gene signature and clinico-pathological guidelines in one third of the patients [11]. In daily clinical practice, medical oncologists are using the 70-gene signature the same way as it was used in the RASTER study, i.e. in addition to clinico-pathological guidelines [1,11]. However, the impact of the 70-gene signature on risk estimations and AST decisions in daily clinical practice is unknown. The aim of this survey was to determine the agreement among oncologists’ risk estimations and AST recommendations based on clinico-pathological factors as are used in clinical guidelines, and to assess the impact of the 70-gene signature.

2. Methods

Two written questionnaires were developed (C.A.D., S.C.L., H.C.v.d.H., M.K.S.) and reviewed by an independent oncologist (G.S.S.). Thirty-seven cases of breast cancer patients were presented to 29 medical oncologists specialised in breast cancer in Europe. The oncologists were chosen because of their area of expertise and the country they work in. We included oncologists from all over Europe to not only demonstrate the situation among oncologists in one country, but for an entire continent. The oncologists were asked to indicate their use of clinical guidelines and to give their risk estimation (high/low) and recommendation of AST (none, endocrine therapy, chemotherapy, trastuzumab or a combination) for each case. Several weeks later, the same cases were presented in a randomly changed order in a second questionnaire. In this second questionnaire, the 70-gene signature result was provided along with clinical characteristics.

2.1. Cases

To provide a reflection of true clinical practice, 37 cases of breast cancer patients were selected from the

database of the RASTER study, with a 70-gene signature result. All cases involved women under 61 years, with unilateral, histological proven, operable breast cancer (cT1–3N0M0). Of each patient tumour size, histo-pathological grade, histological type, mitotic index, hormone-receptor status and human epidermal growth factor receptor 2 (HER2) status were described ([Supplementary Table 1](#)). The actually received treatments were not mentioned in the questionnaire.

2.2. Clinical risk estimation based on Adjuvant! Online

Hereafter, risk estimations using clinico-pathological factors will be referred to as ‘clinical risk’. In this survey, the clinical risk estimation was first assessed using AOL version 8.0. Patients were assigned to a high clinical risk if their AOL 10-year survival probability was less than 90% based on ‘minor problems’ regarding overall health status, which is the default item of the online programme [11]. Of the 37 cases, 10 cases were concordant high, 12 concordant low and 15 discordant with the 70-gene signature result. The cases are a random selection from stratification of concordant low risk, discordant and concordant high risk with the 70-gene signature result.

2.3. Clinical risk estimations by other guidelines

Additional risk estimations according to the St. Gallen expert panel recommendations of 2003, NPI and CBO 2004 (all versions were used at the time of the RASTER study) were assessed previously [6,11–13]. Differences among clinico-pathological guidelines, tool and expert panel recommendations are summarised in [Table 1](#).

Risk estimations were concordant with the 70-gene signature and all clinical guidelines in 12 cases, six were concordant high risk and six concordant low risk. There was discordance between the 70-gene signature and at least one of the guidelines in 25 cases (68%).

2.4. Statistical analysis

All data were analysed using SPSS 20.0 (SPSS Inc.). Agreement among the oncologists as well as between each oncologist and the 70-gene signature result (low risk versus high risk) was assessed using kappa statistics. A kappa of 0 means random, 0.01–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, 0.81–0.99 almost perfect agreement and a kappa of 1 is perfect agreement. The paired samples *t*-test was conducted to compare the kappa means between the oncologists’ risk estimations in the first and second questionnaire. Logistic regression models were used to assess the likelihood of the 70-gene signature result leading to changes in risk

estimations and AST recommendations. Co-variants included in this model were age, tumour size, grade, histological type, oestrogen receptor (ER) and HER2 status. In case of an unanswered question in either the clinical risk estimation or the estimation based on the 70-gene signature, these risk estimations were both excluded from the analyses. A significant finding was defined as a two-sided *p*-value below 0.05.

3. Results

3.1. Participants and case characteristics

Nineteen oncologists completed the first questionnaire (66%). Twelve oncologists (41%) also completed the second questionnaire. Mean age of these oncologists was 49 years (36–66 years) and they were practicing their current profession on average for 18 years (2–35 years). Six of the oncologists came from the Netherlands and six from other European countries (Germany, France, Italy and Portugal). Patient- and tumour-characteristics of the 37 cases included in the analyses as well as their risk estimations according to the 70-gene signature, AOL and other clinical guidelines are summarised in [Supplementary Table 1](#). On average, for each case two risk estimations and three AST recommendations were missing per oncologist, i.e. not answered in the two questionnaires.

3.2. Risk estimations and AST recommendations

On average, the oncologists classified 51% (range 24–65%) cases as clinically low risk and 47% (range 32–76%) as clinically high risk. After adding the 70-gene signature result, the oncologists classified 59% (range 22–78%) of the cases as low risk and 38% (range 22–78%) as high risk ([Fig. 1](#)). On average, an oncologist changed the given clinical risk estimation in 14.2% of the cases. In 10.8% of the cases high risk changed to low risk and in 3.4% of the cases low risk changed to high risk ([Table 2](#)). This leads to a net reduction of 7.4% (range 6.9–22.9%) in high risk classifications. In the 12 cases in which all guidelines and the 70-gene signature were concordant significantly less changes in risk estimations were made (3.5%) compared to the 25 cases in which one or more of the guidelines and the 70-gene signature were discordant (18%) ($p < 0.0001$).

The oncologists recommended AST based on clinico-pathological factors in 95% (range 76–100%) of the cases, chemotherapy (alone or combined) in 48% (range 30–70%) and endocrine therapy (alone) in 46% (range 0–70%) of the cases ([Table 2](#), [Fig. 2](#)). After adding the 70-gene signature result to the clinico-pathological factors provided in the first questionnaire, they recommended AST in 93% (range 78–100%) of the cases, chemotherapy (alone or combined) in 37% (range 22–68%)

Table 1
Clinico-pathological factors used by breast cancer guidelines and risk estimation tools to define patients at a low risk of recurrence.

Guideline/tool	Age	Size	Grade	Hist. type	ER/PR	HER2	Ki67	Nodal status	Other factors	Low risk is defined as
AOL [8]	Continuous	Yes	Yes	Ductal, in case of other hist. type, information is available online	ER	No	No	Yes	Co-morbidities, CT regimen	Not specified
St. Gallen 2003 [7,12]	<35 or ≥35	Yes	Yes	Not used	ER and PR	No	No	Node-negative	None	ER+ and PR+, grade I, ≤2 cm and age ≥35 years
St. Gallen 2009 [12]	Not used	Yes	Yes	Not used	ER and PR	No	Yes	Yes	PVI, multigene assays	High ER and PR, grade I, low Ki67, node-negative, absence of PVI, ≤20 mm, low score on multigene assay
St. Gallen 2011 [20]	Pre- or post menopausal	No	Yes	Not used	ER and PR	Yes	Yes	Yes, more than 3+ nodes is high risk	Biological subtype	Luminal A; ER+ and PR+, HER2-, low Ki67
NPI [6]	Not used	Yes	Yes	Not used	No	No	No	Yes	None	[0.2 × Size] + Number of nodes + Grade; low risk = score lower than 3.4
CBO 2004 [13]	<35 or ≥35	Yes	Yes	Not used	No	No	No	Yes	None	N0, ≥35 years, grade I tumour ≤1 cm OR >35 years, grade 1 ≤30 mm OR grade 2, ≤20 mm OR grade 3 ≤10 mm
CBO 2012 [3]	<35 or ≥35	Yes	Yes	Not used	No	Yes	No	Yes	None	10-years survival probability ≥85%. N0, <35, grade I tumour ≤1 cm OR ≥35 years, grade I tumour ≤2 cm.
PREDICT [21]	Yes	Yes	Yes	Not used	ER	Yes	Yes	Yes	Method of detection, CT regimen	Not specified. Suggested: <3% survival benefit in 10-years no chemotherapy; 3–5% chemotherapy discussed as possible option

AOL = Adjuvant! Online; NPI = Nottingham Prognostic Index; CBO and NABON = Dutch guidelines; ER = oestrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; CT = chemotherapy; PVI = peritumoural vascular invasion.

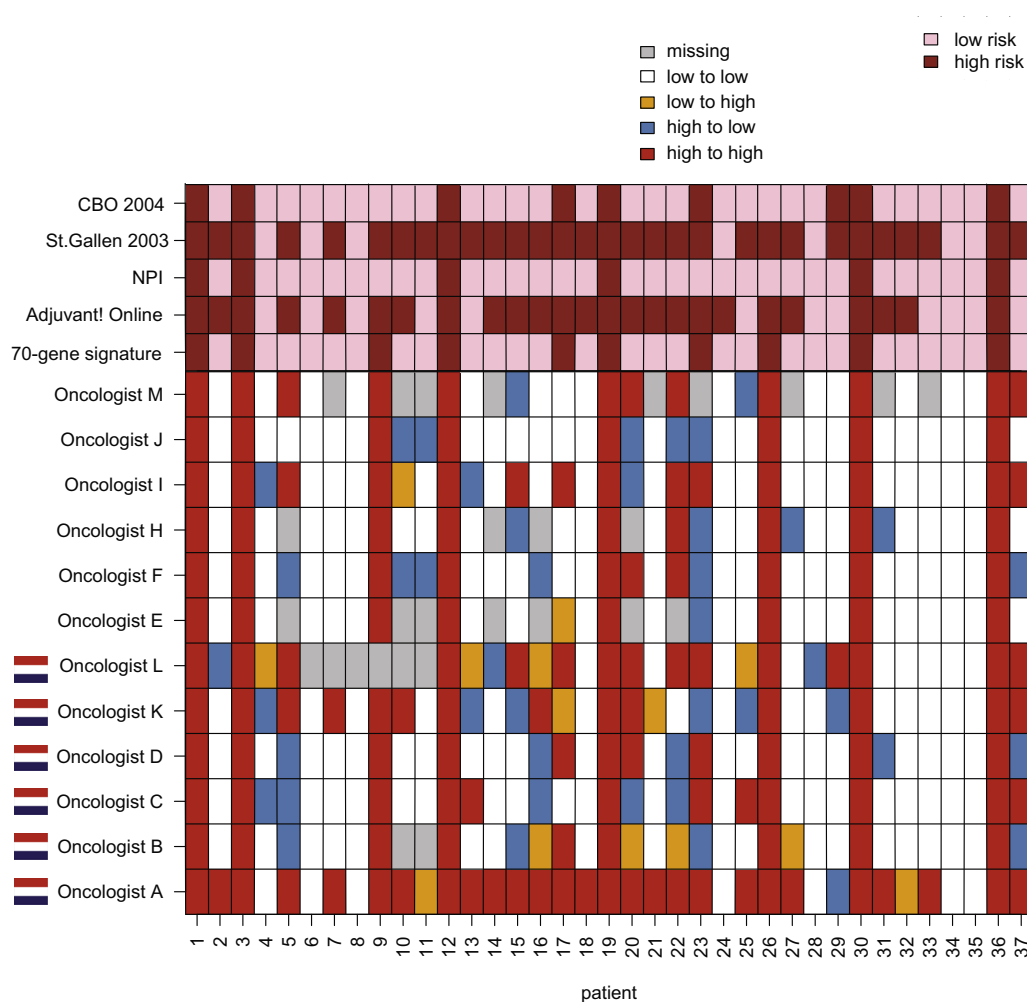


Fig. 1. Changes in risk estimations per oncologist per case and risk estimations by clinico-pathological guidelines and the 70-gene signature.

Table 2

Changes in risk estimation and adjuvant systemic treatment (AST) recommendation after providing 70-gene signature result.

A. Changes in risk estimation (%)

CR	70GS		
	High risk	Low risk	Total CR
High risk	149 (35.8)	45 (10.8)	194 (46.6)
Low risk	14 (3.4)	208 (50)	222 (53.4)
Total 70GS	163 (39.2)	253 (60.8)	416 ^C (100)

B. Changes in AST recommendation (%)

CR	70GS			
	No AST	Chemotherapy ^A	Endocrine therapy ^B	Total CR
No AST	16 (3.9)	1 (0.2)	5 (1.2)	22 (5.3)
Chemotherapy ^A	2 (0.5)	144 (34.8)	57 (13.8)	203 (49)
Endocrine therapy ^B	10 (2.4)	8 (1.9)	171 (41.3)	189 (45.7)
Total 70GS	28 (6.8)	153 (37)	233 (56.3)	414 ^C (100)

CR = clinical risk, estimations based on clinico-pathological factors, 70GS = 70-gene signature, result included in the questionnaire.

^A Chemotherapy alone or combined with endocrine therapy and/or trastuzumab.

^B Endocrine therapy alone.

^C Missing values not included.

and endocrine therapy (alone) in 57% (range 11–78%). In 24% of the cases the oncologist adjusted the AST recommendation (Table 2). Adding the 70-gene signature

resulted in 14.3% of the cases in a change from chemotherapy to either endocrine therapy or no AST at all. Only one oncologist advised more chemotherapy after

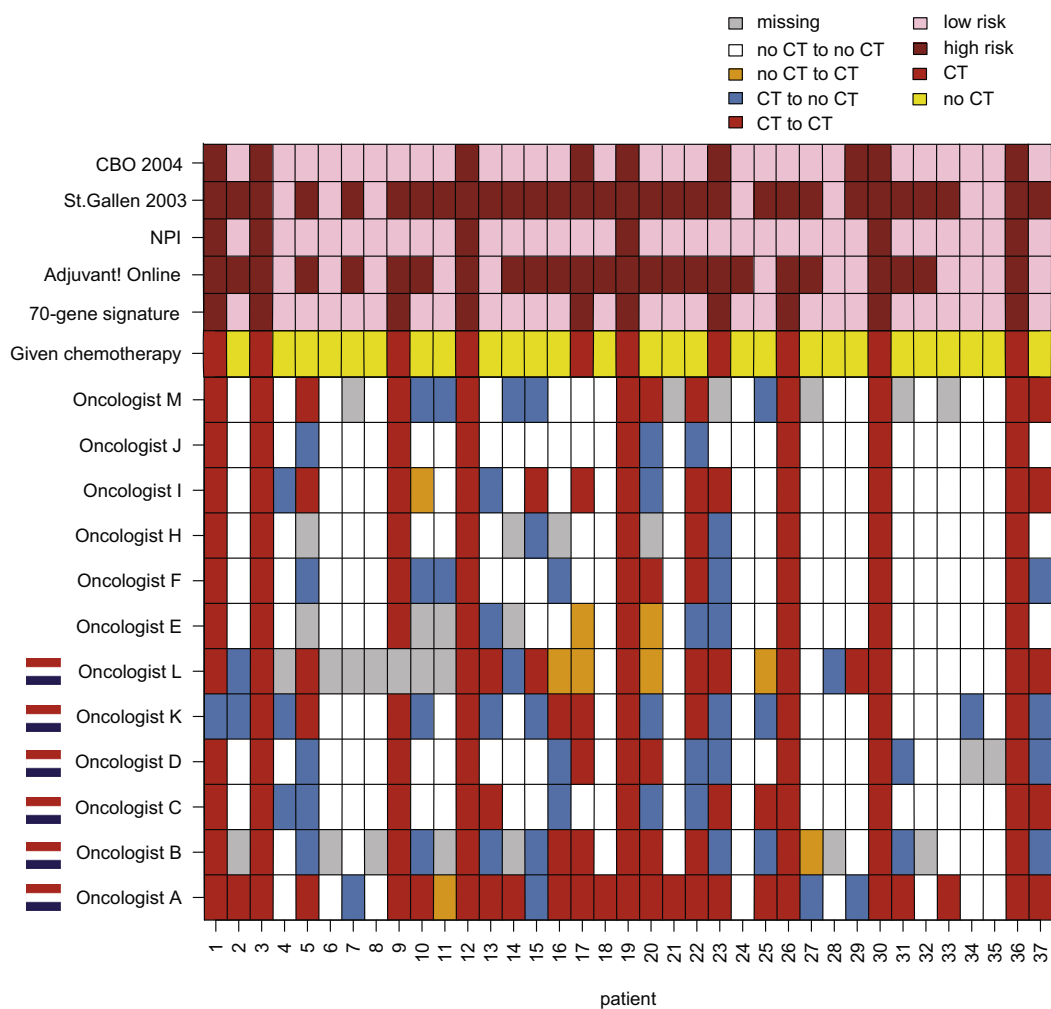


Fig. 2. Changes in adjuvant systemic treatment (AST) recommendations per oncologist per case and the actual given treatment.

knowledge of the 70-gene signature result. In 2.1% of the cases the advice of no AST or endocrine therapy only was changed to chemotherapy. This resulted in a reduction in chemotherapy use of 12.2% (range: 5.4–29.5%) after adding the 70-gene signature to known clinico-pathological factors in the second questionnaire. In the 12 cases in which all guidelines and the 70-gene signature were concordant significantly less changes in AST recommendations were made (4.2%) compared to the 25 cases in which one or more of the guidelines and the 70-gene signature were discordant (20.7%) ($p < 0.0001$).

3.3. Agreement among oncologists

There was moderate level of agreement among oncologists in risk estimations based solely on clinico-pathological factors ($\kappa = 0.57$; range: 0.20–0.88) (Table 3). The level of agreement in AST recommendation was also moderate ($\kappa = 0.57$; range: 0.24–0.84). After adding the 70-gene signature result to clinico-pathological fac-

tors, agreement in risk estimation increases slightly, but significantly to substantial ($\kappa = 0.61$; range: 0.14–1.00; $p = 0.035$), while the level of agreement regarding AST recommendations remained moderate ($\kappa = 0.56$; range: 0.18–1.00; $p = 0.59$). The agreement among oncologists after adding the 70-gene signature remained moderate for risk estimations ($\kappa = 0.44$; range: 0.05–0.84; $p = 0.39$) as well as AST recommendations ($\kappa = 0.56$; range: 0.18–1.00; $p = 0.76$).

3.4. Opinion of oncologists about the use of the 70-gene signature

Seven oncologists (58%) indicated the 70-gene signature result had additional value and adding the 70-gene signature result led to a slightly, not significantly larger decrease in the use of AST in these oncologists. On average, in 19% of the cases the result of the 70-gene signature was decisive according to the oncologists who indicated the 70-gene signature had additional value.

Table 3 (continued)

Level of agreement among oncologists in AST recommendation based solely on clinico-pathological factors												
Oncologists	1	2	3	4	5	6	7	8	9	10	11	12
1		0,53	0,37	0,30	0,28	0,30	0,26	0,37	0,24	0,42	0,44	0,34
2			0,70	0,67	0,55	0,66	0,51	0,70	0,47	0,67	0,42	0,58
3				0,69	0,69	0,71	0,62	0,84	0,65	0,66	0,50	0,47
4					0,65	0,77	0,67	0,69	0,70	0,56	0,25	0,51
5						0,79	0,79	0,69	0,83	0,48	0,52	0,56
6							0,72	0,62	0,76	0,54	0,40	0,66
7								0,70	0,84	0,66	0,65	0,66
8									0,65	0,66	0,59	0,47
9										0,43	0,35	0,60
10											0,52	0,51
11												0,41
12												

Level of agreement among oncologists in AST recommendation after providing the 70-gene signature result												
Oncologists	1	2	3	4	5	6	7	8	9	10	11	12
1		0,40	0,45	0,28	0,23	0,25	0,27	0,36	0,18	0,34	0,41	0,30
2			0,48	0,75	0,63	0,64	0,65	0,54	0,52	0,72	0,50	0,55
3				0,54	0,44	0,49	0,51	0,51	0,51	0,48	0,59	0,51
4					0,88	0,83	0,81	0,63	0,75	0,52	0,50	0,72
5						0,82	0,80	0,56	0,73	0,44	0,44	0,75
6							1,00	0,58	0,80	0,42	0,46	0,88
7								0,64	0,86	0,50	0,48	0,93
8									0,51	0,49	0,62	0,65
9										0,39	0,34	0,69
10											0,47	0,44
11												0,53
12												

70-gene signature validation series of untreated patients with ER-positive, node-negative breast cancer [14]. This suggests that the 70-gene signature is a useful tool to reduce the risk of falsely classifying a patient as high risk and that the 70-gene signature may help to reduce over-treatment. An important observation is the variation among oncologists in risk estimation and AST recommendation. A similar study, where the *Oncotype DX* recurrence score was used as a prognostic tool, showed comparable results, demonstrating that oncologists only have fair to moderate level of agreement when predicting the recurrence score [15]. Adding the recurrence score resulted in a decrease in chemotherapy recommendation of 10.8%, which is comparable to the 12.2% seen in our survey. In our survey, 58% of the oncologists found the 70-gene signature of additional value.

There are some limitations to this survey. The results of 12 oncologists are reported; 19 out of 29 responded to the first questionnaire and only 12 out of 29 also responded to the second questionnaire leading to a response rate of 41%. Unfortunately, because the number of participating oncologists was fairly low we were unable to perform subgroup analyses to evaluate if

oncologists are adherent to the guidelines they indicated to use. The agreement among oncologists might also be partly explained by the presence of a few cases at such a high risk that chemotherapy might be considered standard of care. Even though not all guidelines included in this survey for example identify HER2-positive patients as high risk, the majority of the oncologists consider them eligible for chemotherapy. When excluding the HER2-positive cases from the analysis, the results show a moderate agreement in risk estimation and AST recommendation based on solely clinico-pathological factors as well as after adding the 70-gene signature result. The changes in risk estimation and AST recommendations in this survey could also be due to practice patterns of oncologists and lack of adherence to guidelines in general [16]. Only oncologists in Europe were invited to participate in this survey. A larger survey, including a larger number of oncologists not only from Europe, but also from other continents would provide more detailed information on differences in breast cancer treatment between countries and continents.

In daily clinical practice, the oncologist is faced with the challenge of tailoring adjuvant systemic therapy for

each patient, taking the clinico-pathological features of the tumour, the 70-gene signature result, the patients' co-morbidities and preferences into account. Proliferation markers, like Ki67, menopausal status and co-morbidity were unknown in our case-selection and were not presented in the questionnaires. Providing this kind of extra information may have further improved the ability to discriminate between high and low risk cases and may have influenced AST recommendation. On the other hand, providing more proliferation markers and pathological characteristics may not directly result in more agreement [17]. In clinical practice, gene-expression profiles will likely be used in addition to clinico-pathological guidelines, like the way the 70-gene signature was used in the RASTER study and presented in the cases in our survey [18].

The follow-up of the RASTER study showed that patients treated according to the 70-gene signature who did not receive AST, despite poor clinico-pathological factors, had a distant recurrence free interval of 100% [18]. Based on these data, the reduction in chemotherapy resulting from knowledge of the 70-gene signature result as presented in this survey, may be justified. Especially, since in the RASTER study not only the 70-gene signature result was decisive, but also the doctors' and patients' preferences. The St. Gallen 2011 recommendations and ESMO practice guidelines include the 70-gene signature as an indicator for AST [19,20].

In conclusion, this survey shows the variability in guidelines and oncologists' risk estimations and recommendations of AST in early stage breast cancer patients. Providing the 70-gene signature result has a modest impact on risk estimation and AST recommendation. It may lead to a reduction in the classification of high risk patients and a decrease in the use of chemotherapy. Most importantly, this survey underlines the need for a better standardisation tool in clinical decision-making.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejca.2014.01.016>.

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