GENOMIC TESTING IN INTERNATIONAL GUIDELINES

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ABSTRACT

Human breast cancer was solely classified based on clinical and immunohistochemical (IHC) findings in the past. A growing body of evidence suggests that these categorisations are rendered more precisely by intrinsic subtyping with the aim of an introduction of personalised medicine. Especially in breast cancer with the uncertain potential of disease spread, such as T1-2, Grade 2 and oestrogen receptor-positive (ER+ve) tumours, the value of chemotherapy applied to every patient has been questioned and the need for additional information on the tumour´s specific risk of recurrence is overt. It is estimated that the average risk for recurrence is 15% at 10 years in hormone-receptor-positive breast cancer. Thus, a relatively small proportion of these patients would need chemotherapy, and the main task is to stratify which patients of this cohort are at high-risk and will benefit from cytotoxic agents. Ki67, as a proliferation marker classifying high-risk tumours, has been demonstrated as a continuous marker, but not as a clear cut risk-defining instrument in recent publications. Thus, the difficulties are perceived especially at the threshold of the low to high-risk area of this marker. Reproducibility of Ki67 is to some extent uncertain considering there is inter and intra-institutional variability of up to 30% of the results. Several multigene arrays, such as MammaPrint®, Oncotype DX®, Endopredict®, and PAM50 have demonstrated clinical utility and experienced validation. The aim of this review is the description of the implementation of genomic testing in international guidelines (North American and European), with regard to incorporation of multigene arrays into the decision-making process in different clinical settings (including tumour size and IHC status). Data cut-off was 1st October, 2013. It seems that North America and some European countries have initiated a shift towards a personalised medicine with multigene arrays based on RT-PCR or microarrays.

Keywords: Breast cancer, gene array, guidelines, Oncotype DX®, MammaPrint®, Rotterdam signature-prognosis, prediction-chemotherapy response.

INTRODUCTION

After a century of predicting the prognosis of early human breast cancer solely on clinical and immunohistochemical findings, Sorlie et al.[1] initiated at the transition of the millennium a change of paradigm in deciphering breast cancer prognosis with their milestone paper on intrinsic subtypes. Furthermore, within their defined two groups of oestrogen receptor-positive (ER+ve) breast cancers (Luminal A and B), a large variety of risk population is allocated. These two subtypes have been subject to repeated attempts of differentiation and approximation immunohistochemically by grading (St. Gallen, 2009)[2] or Ki67 (St. Gallen, 2011)[3] with a shift of from ≥15% to ≥20% in the threshold from a low to high Ki67 from 2011 to 2013. Denkert et al.[4] however, published in their current analysis of pre-therapeutical core biopsies of 1,166 early breast cancer patients that Ki67 is a continuous marker with regard to the clinical endpoints of disease-free survival (DFS) in a range of 6-46% and overall survival (OS) of 4-58%. Thus, the cut-off range defined by the

latest St. Gallen consensus lies in the midst of a continuous field of risk points. Absolute borders to differentiate Luminal A from Luminal B on the basis of an immunohistochemical approximation may be defined for practical reasons, but not strictly on biologically founded grounds.

Given this obscurity in determining the actual risk profile of hormone receptor-positive (HR+ve) breast cancer, and also other breast cancer subtypes, we set out to analyse whether National North American (American Society of Clinical Oncology [ASCO] guidelines)[5] and European guidelines provide recommendations for physicians in this zone of ambiguity of clinical management. The commercially available genomic tests are MammaPrint® (prognostic: lymph node [N]0-1), Oncotype DX® (prognostic and predictive: N0-1, ER+ve), Endopredict® (prognostic, postmenopausal, N0-1, ER+ve, HER2-ve), and PAM50 (prognostic subtype classifier, N0-1) (Table 1).

Access to Genomic Testing

After numerous studies on genomic testing, also combined with other endocrine and chemotherapy regimens,[6] genomic tests have been entered into clinical practice as Abu-Khalf et al.[7] published

Table 1. Genomic tests and their evaluation in the German AGO-guidelines (Version 2013.1)[13]

	MammaPrint®	Oncotype DX®	Endopredict®	PAM50
Provider	Agendia	Genomic Health	Sividon	NanoString
Type of assay	70-gene assay	21-gene RS	11-gene assay	50-gene assay
Type of tissue	Fresh frozen	FFPE	FFPE	FFPE
Technique	DNA microarrays	qRT-PCR	qRT-PCR	qRT-PCR
Central lab	yes	yes	no	yes
Indication and population studied	Prognostic N0-1	Prognostic N0-1 ER+ve	Prognostic postmenopausal N0-1 ER+ve HER2-ve	Prognostic subtype classifier N0-1
Analytical validation	no	yes	yes	no
Clinical validation	yes	yes	yes	yes
Clinical utility	no	yes	yes	no
Prospective-retrospective evidence		NSABP B-14 NSABP B-20 ECOG 9127 SWOG 8814 ATAC	ABCSG 6 ABCSG 8	MA.12 MA.5
Prospective evidence (pending)	MINDACT	TAILORx RxPONDER		

RS: Recurrence Score; FFPE: formalin-fixed paraffin-embedded; qRT-PCR: quantitative reverse transcription polymerase chain reaction; ER: oestrogen; HER2: human epidermal growth factor receptor 2; N: node; NSABP: National Surgical Adjvant Breast and Bowel Project; ECOG: Eastern Cooperative Oncology Group; SWOG: Southwest Oncology Group; ATAC: Arimidex, Tamoxifen, Alone or in Combination; ABCSG: Austrian Breast and Colorectal Cancer Study Group; MA: mammary.

most recently. The authors asserted that today 30%, 13% and 1% of Stage I, II and III ER+ve breast cancers are tested and that among those who are tested, genomic testing changed the recommendation in approximately 25-30% of cases. Almost all cost-effectiveness studies, the authors concluded, demonstrated a positive result when the tests are used under current guidelines. However, the main reason for not having access to genomic testing is not driven by the personal economic situation, but the fact that the treating physician did not offer it (80%), as Defrank et al.[8] analysed. Defrank also found, by interviewing (n=123) patients eligible for the 21-gene array test, that those having received such a test described their decision-making style with regard to chemotherapy as active (75%), whereas only a minority who received the test described their style as passive (12%) ($p<0.01$).

Given the cost-effectiveness and the empowerment of patients for a more active role in decision-making, pondering the pro or cons of chemotherapy in early breast cancer, and the obstacle of missing offers of genomic testing by physicians, we scrutinised whether more recent and precise national guidelines of the genomic testing of North America and Europe exist.

METHODS

Published North American and European guidelines were analysed with regard to implementation of directives on genomic testing in the management of early breast cancer. Data cut-off was 1st October, 2013.

RESULTS

ASCO Guidelines Update 2007

As early as in 2007, the ASCO guidelines were the first international guidelines to be published by Harris et al.,[5] incorporating multigene arrays into their panel of 'Recommendation on the Use of Tumour Markers in Breast Cancer.' These guidelines commented on four multigene arrays in node-negative (N-ve), ER+ve breast cancer: Oncotype DX® assay (21-gene array), Amsterdam signature (MammaPrint®, 70-gene array), Rotterdam signature (76-gene array), and the Breast Cancer Gene Expression ratio. Out of these, Oncotype DX® and MammaPrint® attracted the main focus of the ASCO panel, however for 'newly diagnosed patients with N-ve, ER+ve breast cancer,' only the Oncotype DX® assay was approved 'to be used to predict the risk of recurrence in patients treated with tamoxifen and to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy.' In addition, patients with high Oncotype DX® Recurrence Scores (RS) were recognised 'to achieve relatively more benefit from adjuvant chemotherapy (specifically (C)MF) than from Tamoxifen.'

However, the ASCO panel considered that there was 'insufficient data at that time to comment on whether these conclusions generalise to hormonal therapies other than Tamoxifen, or whether this assay applies to other chemotherapy regimens.' The precise clinical utility and appropriate application for other multi-parameter assays, such as the MammaPrint® assay, the 'Rotterdam Signature,' and the Breast Cancer Gene Expression Ratio were classified as being 'still under investigation,' which meant no positive consideration so far in the ASCO guidelines.

NCCN Guidelines 3.2013

National Comprehensive Cancer Network (NCCN) has more precisely updated its recent guidelines - Version 3.2013[9] - on the use of genomic testing (Figure 1). In HR+ve, HER2-HER2-ve early breast cancer of Stages pT1-3 N0 or $N1_{mic}$ (<2 mm), the guidelines recommend for tumours of >5 mm to consider a 21-gene RT-PCR array (Oncotype DX®). Depending on the RS, the NCCN stratifies the clinical management pathway as follows: RS <18 (low RS) recommending adjuvant endocrine therapy only, RS 18-30 (intermediate RS) suggesting potentially (+/-) additional adjuvant chemotherapy and >31 (high RS) definitely recommending additional chemotherapy. In N+ve disease (one or two ipsilateral lymph node metastasis >2 mm) adjuvant chemotherapy is unequivocally recommended.

St. Gallen 2013 International Expert Consensus

Guidelines of the St. Gallen 2013 International Expert Consensus on the Primary Therapy of Early Breast Cancer declared that intrinsic subtypes should determine whether chemotherapy should be applied but not which type of chemotherapy. In ER+ve, HER2-ve, N-ve breast cancer a slim, but definite majority of experts of the panel voted in favour of requesting a

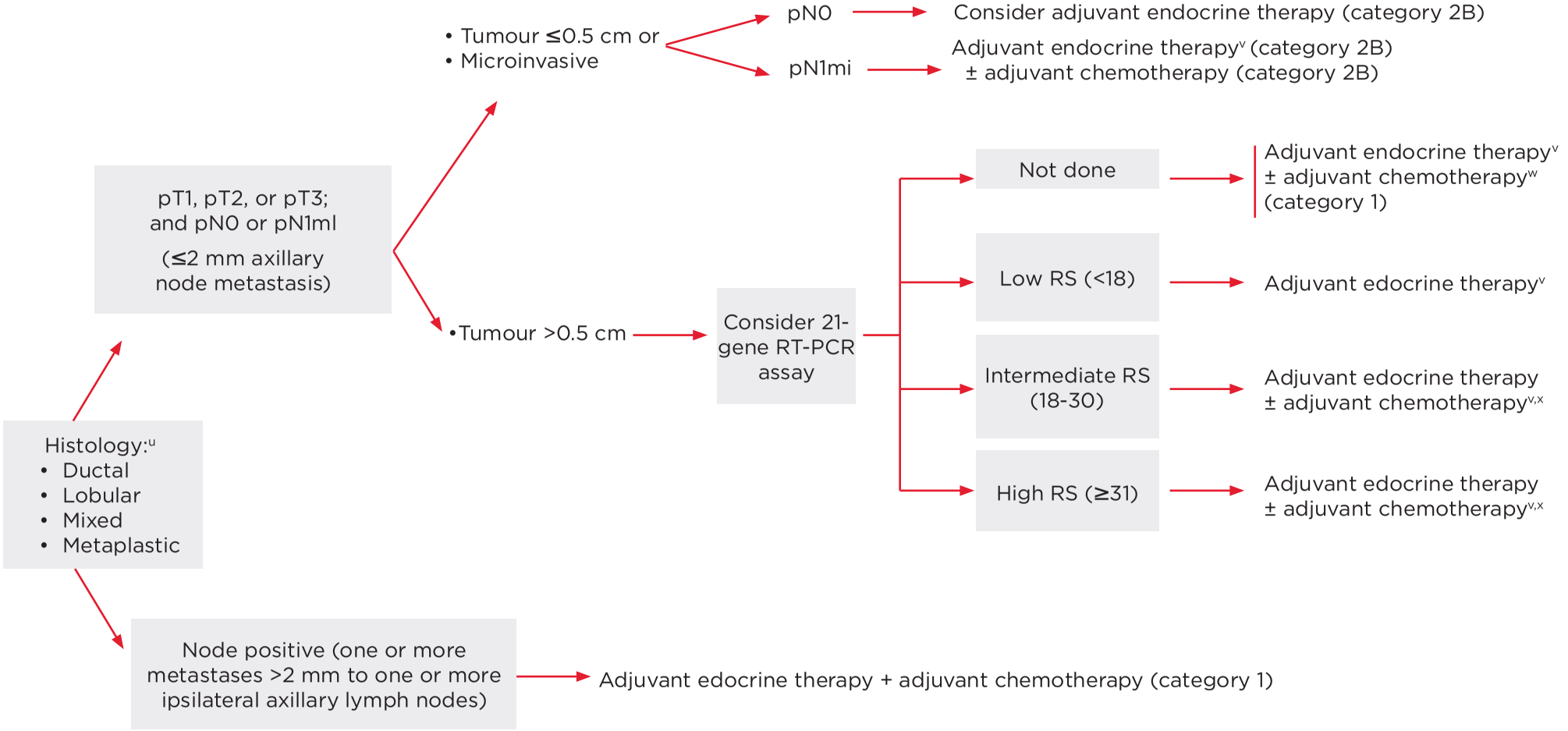

Figure 1. NCCN-guidelines 3.2013 (adapted).

[u] Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

[v] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. Early evident suggests similar benefits from ovarian suppression (ie, Luteinising hormone-releasing hormone) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

[w] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

[x] There are limited data to make chemotherapy recommendations for those >70 yr old. Treatment should be individualised with consideration of comorbid conditions.

multigene array. The 21-gene RS was judged to be predictive of chemotherapy responsiveness by the majority of panel members; however this was not the case for PAM50 or the EPClin. For the 70-gene signature it was a split vote of 25% in favour, and 25% in opposition, and the rest of the panel voted for abstention.

At tumour size ≤1 cm – contrary to the NCCN guidelines 3.2013 which also cover tumour sizes of 5-10 mm as eligible for genomic testing – request for a gene array was deemed unnecessary by the St. Gallen panel members. On the other end, with tumour size >5 cm, inflammatory breast cancer, cases of >4 positive lymph nodes or very low ER positivity (e.g. 5%) required chemotherapy without use of gene arrays as decision assistance due to the St. Gallen panel 2013. This however, was felt to be different for selected patients with one to three positive lymph nodes and patients aged <35 years.[10]

ESMO Guidelines 2013

The most recent European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up of primary breast cancer,[11] which are also endorsed by the Japanese Society of Medical Oncology (JSMO) names two out of four commercially available genomic tests as suitable for treatment decision-making in 'some cases, such as Grade 2 ER+ve HER2-ve and N-ve breast cancer, in conjunction with all clinic-pathological factors' – these are again the 21-gene array and 70-gene array. The ESMO recommendation is irrespective of the actual size of the tumour; however the ESMO guidelines point at the awaited prospective clinical trials MINDACT, TAILORx and RxPonder to define the optimal and accurate use of these tests in the clinical setting.

UK NICE Guidelines 2013

The National Institute for Health and Care Excellence (NICE) in the United Kingdom has released its final recommendation on genomic testing in early breast cancer[12] after a long process of evaluation of the 21-gene-array, 70-gene array, IHC4 and Mammostrat. The decision, published in early September 2013, declared 21-gene array is 'recommended as an option for guiding adjuvant chemotherapy decisions for people with ER+ve, N-ve, and HER2-ve early breast cancer if:

• the person is assessed as being at intermediate-risk* and

• information on the biological features of the cancer provided by Oncotype DX® is likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing chemotherapy and

• the manufacturer provides Oncotype DX® to National Health Service (NHS) organisations according to the confidential arrangement agreed with NICE.'

(*'Intermediate-Risk' of distant recurrence was defined as a Nottingham Prognostic Index [NPI] score above 3.4. Also other decision-making tools or protocols currently used in the NHS may also be used to identify people at intermediate-risk according to NICE Guidelines.)

Other genomic tests investigated by NICE, such as MammaPrint®, IHC4 and Mammostrat, were only 'recommended for use in research in people with ER+ve, N-ve and HER2-ve early breast cancer, to collect evidence about potentially important clinical outcomes and to determine the ability of the tests to predict the benefit of chemotherapy (...). The tests are not recommended for general use in these people because of uncertainty about their overall clinical benefit and consequently their cost-effectiveness.'

Germany

In Germany, the AGO (Working Group of Gynecological Oncology) within the German Society of Obstetrics and Gynecology and German Cancer Society, has updated its guidelines in March 2013.[13] It defined as prognostic factors in early breast cancer two validated multigene arrays in HR+ve subset of breast cancer: Oncotype DX® and EndoPredict®. The AGO ascertained the evidence as Level of Evidence (LoE) 2009 IB, Group B recommendation, and concluded that these multigene arrays may be an option (+/-). Other gene arrays like Mammostrat and PAM50 also received the same categorisation, however PAM50 and MammaPrint® in N0-1 only with LoE 2009 IIB-evidence. For response prediction in neoadjuvant chemotherapy PAM50 and MammaPrint® had a LoE 2009 of IIIC, with an optional recommendation from the AGO (+/-). For prediction of the benefit of adjuvant chemotherapy only Oncotype DX® had a LoE 2009

IB and is mentioned as the only multigene array (recommendation grade (+/-)).

The German interdisciplinary S3-guideline for diagnosis, therapy and follow-up of breast cancer Version 3.0 was issued in July 2012, and – contrary to the AGO-guidelines – did not consider gene arrays (PCR-based or microarray-based) as clinically sufficient validation to be recommended.[14]

The Netherlands

The Dutch Guidelines for Breast Cancer, Version 2.0, 2012[15] suggest three gene arrays to be eventually considered in different clinical settings: MammaPrint®, Rotterdam Signature, and Oncotype DX®, for which they state: 'It has been demonstrated for a number of gene expression profiles in retrospective studies that they are better at distinguishing subgroups with a favourable or unfavourable prognosis than traditional risk estimations.'

The Dutch guidelines attribute LoE II to these gene arrays to determine the prognosis.

For prediction of chemotherapy response, the Dutch guidelines state that the predictive value of MammaPrint® for the effect of adjuvant chemotherapy has not yet been proven, whereas this is acknowledged for Oncotype DX® according to the NSABP B20 trial. However the Dutch guidelines add that the predictive value of the gene profile has not been prospectively researched with newer therapeutic modalities such as aromatase inhibitors, other chemotherapy agents or trastuzumab.

Other European Countries

No specific guidelines were retrievable from other countries´ official national boards.

CONCLUSION

North America and some European countries have initiated a shift from mere histologically and clinically-driven risk stratification and chemotherapy response prediction towards a personalised medicine based on multigene arrays by RT-PCT or microarrays. LoE attributed to these arrays is varying due to the approach used in classifying the underlying studies. Most guidelines see a preference for Onctoype DX and MammaPrint® as validated multigene arrays (Table 2). Expert panels like St. Gallen International Expert Consensus guidelines have a preference for Oncotype DX®, especially with regard to chemotherapy response prediction. Prospective trials especially concerning these two multigene arrays are eagerly awaited, and outcomes will be presented in the near future, like trial results of the RxPONDER, TAILORx AND MINDACT trials. Refunding of multigene arrays by national health systems is implemented partly in some European countries, such as the UK and to some extent in Germany as well. The genomic era has not yet arrived, but the dawn has already begun in some parts of the world.

Table 2: Summary – genomic tests in international guidelines.

	Oncotype DX®	MammaPrint®	Rotterdam Score	PAM50	Mammostrat	IHC 4	EPClin
ASCO 2007[5]	YES	-	-	-	-	-	-
NCCN 2013[9]	YES	-	-	-	-	-	-
St. Gallen 2013[10]	YES	+/-	-	-	-	-	-
ESMO 2013[11]	YES	YES	-	-	-	-	-
UK(NICE) 2013[12]	YES	-	-	-	-	-	-
Germany (AGO) 2013[13]	YES	-	-	-	-	-	YES *
Netherlands 2012[15]	YES	YES	YES	-	-	-	-

(* EPClin restricted to postmenopausal women and only for prognosis, not for prediction of chemotherapy response)

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