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Biomarker-based tests to support the decision for or against adjuvant systemic chemotherapy in primary breast cancer[1]

Extract

1 Translation of Chapters 1 to 6 of the final report *Biomarkerbasierte Tests zur Entscheidung für oder gegen eine adjuvante systemische Chemotherapie beim primären Mammakarzinom* (Version 1.0; Status: 27 October 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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The responsibility for the contents of the report lies solely with IQWiG.

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Key statement

Research question

The aim of the present investigation is

- to assess the benefit of a biomarker-based strategy to support the decision for or against adjuvant chemotherapy compared with a biomarker-independent decision strategy or a second biomarker-based decision strategy

in each case in patients with primary, hormone receptor-positive, human epidermal growth factor receptor (HER2)-negative breast cancer and 0 to 3 affected lymph nodes. The focus of the investigation is on patient-relevant outcomes.

Conclusion

There is currently no hint of a benefit or harm of a biomarker-based strategy to support the decision for or against adjuvant chemotherapy in primary breast cancer. The data from 6 of the 8 studies included could not be used for the present benefit assessment due to the high proportion of patients not considered in the analyses. Thus only data from 2 randomized controlled trials (RCTs) could be used.

The study by Martin 2014 (10-year follow-up period) investigated the interaction between biomarkers and the type of chemotherapy regimen administered and did not show a benefit of the EndoPredict test for the choice between 2 chemotherapies.

The still ongoing MINDACT study is investigating the use of chemotherapy versus no chemotherapy in patients for whom the clinical-pathological assessment and the biomarker test result led to different recommendations (discordant results). The 5-year interim results do not indicate a benefit of a biomarker-based treatment decision by means of the MammaPrint test.

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List of abbreviations

Abbreviation	Meaning
BCI	Breast Cancer Index
C-low/C-high	clinical risk assessment using a modified version of Adjuvant! Online low: chemotherapy not indicated high: chemotherapy indicated
DFS	disease-free survival
DMFS	distant metastasis-free survival
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
ER	(o)estrogen receptor
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
G-low/G-high	genomic risk assessment using the 70-gene-signature test (MammaPrint) low: chemotherapy not indicated high: chemotherapy indicated
HER	human epidermal growth factor receptor
HrQoL	health-related quality of life
IHC	immunohistochemistry
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
OS	overall survival
RCT	randomized controlled trial
RNA	ribonucleic acid

1 Background

On 22 April 2014 the Federal Joint Committee (G-BA) wrote to the Institute for Quality and Efficiency in Health Care (IQWiG) to commission the assessment of biomarker-based tests to support the decision for or against adjuvant systematic chemotherapy in primary breast cancer.

Disease definition

Breast cancer (ICD-10 C50[3]) is a malignant neoplasm that originates from the mammary gland and progresses over different stages: Loco-regionally limited primary disease is restricted to a limited area of the mammary gland, potentially extending to a few regional lymph nodes. In locally advanced breast cancer, the cancer has spread to large parts of the breast and/or to the chest wall or skin without yet metastasizing [1]. A local or loco-regional recurrence is the recurrence of breast cancer in, for instance, the breast, the chest wall, and the regional lymph nodes of the axilla [1]. It can be isolated or also occur in combination with distant metastasis in other organ systems. In the event of distant metastasis, long-term cure can only be achieved in exceptional cases. A relatively favourable course of disease can be expected in the event of solitary distant metastasis affecting only the bones and/or skin [1].

Intrinsic subtypes of breast cancer

According to the Consensus Conference St. Gallen 2011 [2], breast cancer is classified into 4 intrinsic subtypes:

- Luminal A: hormone receptor-positive (for oestrogen and/or progesterone), human epidermal growth factor receptor (HER)2-negative, Ki-67 low
- Luminal B:
  - hormone receptor-positive, HER2-negative, Ki-67 high or
  - hormone receptor-positive, HER2-positive, any Ki-67 score
- HER2-positive, non-luminal: hormone receptor-negative, HER2-positive
- Triple negative: hormone receptor-negative (for oestrogen and progesterone), HER2-negative

This report focuses on patients with primary, hormone receptor-positive, HER2-negative breast cancer (corresponds to the intrinsic subtypes Luminal A and Luminal B, HER2-negative) with 0 to 3 affected lymph nodes. This is because it is unclear only for this subgroup whether they benefit from adjuvant chemotherapy or whether, on the basis of a biomarker-based test result, they can avoid chemotherapy, which could be indicated following established clinical-pathological criteria.

[3] 10th revision of the International Statistical Classification of Diseases and Related Health Problems, malignant neoplasms of breast.

Treatment of the disease after primary surgery

After successful primary surgery it is the aim of adjuvant systemic therapy to treat and cure potential, but not verified, micrometastisis, thus preventing a recurrence. Adjuvant systemic therapy is conducted as

- chemotherapy
- endocrine therapy
- antibody therapy or
- as a combination of these therapy forms

This can reduce the recurrence and mortality rate [1,3-6].

The decision for adjuvant systemic therapy is based on various factors: for instance, patients with hormone-sensitive breast cancer receive endocrine therapy and patients with HER2-positive breast cancer receive targeted anti-HER2-positive chemotherapy (e.g. with trastuzumab) [1,7]. Established factors considered in the decision for or against chemotherapy are, for example, age, lymph node status, and grading. However, in patients with primary hormone receptor-positive HER2-negative breast cancer and 0 to 3 affected lymph nodes, this decision cannot be made solely on the basis of these established factors. Even without chemotherapy, a large proportion of these patients will not suffer a recurrence (approx. 80% after 10 years, according to an unpublished subanalysis provided by R. Kreienberg on the study by Wolters et al. [8]). This means that only a limited proportion of these women would actually benefit from chemotherapy. Currently neither a clear guideline recommendation nor a uniform standard of care exists for this subgroup with regard to decision-making for or against chemotherapy; thus this is a group for which no clear treatment recommendation can so far be provided.

The role of predictive markers in treatment decisions

To improve the situation described above of an unclear treatment recommendation for the subgroup relevant here, several molecular-biological markers have been identified and tested with regard to whether, in addition to the established markers, they allow making further statements on the course of disease and on the benefit of different treatment concepts. In this context, prognostic markers allow statements on the individual course of disease to be expected in terms of disease-free survival (DFS) or overall survival (OS) if a patient is either not treated or treated with a standard treatment [9]. A predictive marker allows statements on the differential benefit of treatment based on the marker status: For example, patients who express a certain marker are highly likely to benefit from a specific treatment, whereas patients who do not express this marker are not [10].

As a large part of the relevant subgroup will possibly not benefit from chemotherapy, it is of particular interest to identify via a predictive marker those patients who are highly likely to benefit from chemotherapy and those who are highly unlikely to do so.

Measurement of biomarkers in patients with breast cancer

Biomarker-based tests are based on different methods, for example, immunohistochemistry (IHC), gene expression analysis or an enzyme-linked immunosorbent assay (ELISA). With some methods, the detection and quantitative measurement of a biomarker works via the use of marked reagents. In this context, different types of labelling (e.g. with fluorescent dyes or enzymes) are possible. Biomarkers are determined in samples of resected tumour tissue, which for this purpose must be available either as shock-frozen fresh tissue or as a formalin-fixed paraffin-embedded tissue block.

IHC is a method for detecting proteins in tissue slices [11]. For this purpose, chromogens are used that are also detectable with an optical microscope. ICH can be used to identify and classify tumour cells that express certain proteins.

ELISA is based on the principle of an antibody-linked enzymatic colour reaction. In this context, one also exploits the characteristic of specific antibodies to bind to the structure to be detected, whereby the antibody is marked with an enzyme beforehand; this enzyme catalyses a chemical reaction in which a certain colour is created by a substrate. By means of ELISA, among other things, proteins are detected that are associated with the metastasizing potential of a tumour [12,13].

Gene expression analysis is a further method of tumour classification in which the expression or activity of different genes is measured. The principle is based on the detection of messenger RNA [14]. If the sequence of a DNA or RNA fragment to be analysed is complementary to a sequence of a sample, then the 2 sequences can hybridize to each other; this hybridization can be detected by labelling with (fluorescent) dyes.

2 Research question

The aim of the present investigation is

- to assess the benefit of a biomarker-based strategy to support the decision for or against adjuvant chemotherapy compared with a biomarker-independent decision strategy or a second biomarker-based decision strategy

in each case in patients with primary, hormone receptor-positive, HER2-negative breast cancer and 0 to 3 affected lymph nodes. The focus of the investigation is on patient-relevant outcomes.

3 Methods

The target population of the benefit assessment comprised patients with primary hormone receptor-positive, HER2-negative breast cancer and 0 to 3 affected lymph nodes. The test intervention was a biomarker-based strategy to support the decision for or against adjuvant chemotherapy. This includes not only strategies for deciding between a chemotherapy regimen and no chemotherapy, but also strategies for deciding between 2 different chemotherapy regimens. The control intervention was a biomarker-independent decision strategy or a second biomarker-based decision strategy.

The following patient-relevant outcomes were considered in the assessment:

- OS
- DFS (the patient relevance of this outcome was evaluated by means of the specific operationalization in the corresponding studies; see below)
- health-related quality of life (HrQoL)
- adverse events, both as a consequence of the diagnostic test and as a consequence of the subsequent measures taken

Since patients in the subgroup relevant here were treated with a curative therapeutic approach and in most cases it can be assumed that after completion of primary therapy they were actually in remission, any recurrence discovered during regular follow-up examinations represented a patient-relevant event [15]. Accordingly, DFS was specified as an outcome relevant for the present assessment. In the individual case it was to be evaluated whether, for example, examinations conducted during a study were consistent with the usual recommendations or whether they deviated from regular follow-up care (e.g. because of more frequent examinations or unusual diagnostic procedures). Analyses exclusively restricted to distant or local disease recurrence were evaluated as supplementary information.

Subjective outcomes (e.g. HrQoL) were only considered if they had been recorded with valid measurement instruments (e.g. validated scales).

The benefit assessment of a biomarker-based decision for or against adjuvant chemotherapy was conducted on the basis of randomized controlled trials (RCTs). For the outcomes OS and DFS, a follow-up period of at least 10 years was defined so as to be able to derive a benefit from the result. Against the background of the results of the preliminary report, namely, that at the time of its production neither robust evidence from completed studies was available nor would it become available in the near future from ongoing studies, 5-year interim analyses of ongoing RCTs are presented as supplementary information to provide an estimation of the results to be expected for the relevant 10-year period.

In addition, the benefit of a biomarker-based decision for or against adjuvant chemotherapy was also investigated by means of prognostic studies (prospectively planned cohort studies) with a follow-up period of at least 10 years.

If, on the basis of RCTs, positive conclusions on benefit could be drawn for at least one biomarker (reference biomarker), it was also to be evaluated whether the conclusion on benefit from these studies could also be applied to further biomarkers. For this purpose, studies investigating the concordance of diagnostic conclusions on the biomarkers validated in RCTs with further, still unvalidated, biomarkers were to be systematically searched for and analysed. These studies are referred to as "concordance studies".

A systematic search for primary literature was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In addition, a search for relevant systematic reviews was conducted in MEDLINE and Embase parallel to the search for relevant primary studies as well as by means of a search in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. The last searches were conducted on 5 November 2015 (for RCTs) and on 9 November 2015 (for prognostic studies). In addition, data on ongoing studies submitted by the manufacturers were considered up to the end of August 2016.

Systematic reviews and publicly available trial registries were also searched. Furthermore, publicly accessible documents from regulatory authorities, documents sent by the G-BA, and publications that had been provided in the hearing procedure on the preliminary report plan (protocol) and preliminary report were also screened. Finally, manufacturers and the authors of relevant study publications were contacted in order to clarify important questions.

The selection of relevant studies was performed by 2 reviewers independently of each other. Data were extracted into standardized tables. To evaluate the qualitative certainty of results, the risk of bias at study and outcome level was assessed and rated as low or high. The results of the individual studies were described, organized by outcomes.

If the studies were comparable regarding the research question and relevant characteristics and no relevant heterogeneity was observed, the individual results were to be pooled quantitatively by means of meta-analyses.

The present report describes and compares the results on the patient-relevant outcomes reported in the studies, and, if applicable, on positive or negative concordance (concordance studies).

In certain cases, individual results from the studies on an outcome or on concordance were not considered in the benefit assessment. This applied in particular to cases where many patients were not included in the analysis. In general, results were not considered in the benefit assessment if they were based on less than 70% of patients to be considered in the analysis, that is, if the proportion of patients not considered in the analysis was more than 30%.

4 Results

4.1 Results of information retrieval

4.1.1 Results of information retrieval for RCTs

After the exclusion of duplicates, the systematic literature search in bibliographic databases yielded a total of 4477 hits for screening. 4388 hits were excluded as "not relevant" in the title and abstract screening. 89 potentially relevant hits, which were screened in full text, thus remained from the bibliographic literature search: 74 of these hits were excluded due to a lack of relevance; 13 hits represented relevant systematic reviews, which were screened for relevant studies. In the opinion of both reviewers, the remaining 2 publications on 2 RCTs fulfilled the criteria for study inclusion defined for this report.

No additional relevant study was identified by the search in further search sources (systematic reviews, publicly accessible trial registries, publicly accessible documents of regulatory authorities, documents sent by the G-BA, documents of manufacturers, information from the hearings on the preliminary report plan and the preliminary report). The search in trial registries identified 8 ongoing studies whose relevance could in part not be conclusively clarified. Information from enquiries to authors was considered in the assessment.

The 5-year data from a further, ongoing, relevant RCT, the MINDACT study, were provided by the manufacturer and have in the meantime been published.

A total of 3 RCTs were thus identified as relevant for the research question of the present benefit assessment.

4.1.2 Results of information retrieval for prognostic studies

After the exclusion of duplicates, the systematic literature search in bibliographic databases yielded a total of 6024 hits for screening. 5393 hits were excluded as "not relevant" in the title and abstract screening. 631 potentially relevant hits, which were screened in full text, thus remained from the bibliographic literature search: 611 of these hits were excluded due to a lack of relevance; 15 hits represented relevant systematic reviews, which were screened for relevant studies. In the opinion of both reviewers, the remaining 5 publications on 4 prognostic studies fulfilled the criteria for study inclusion defined for this report.

No additional relevant study was identified by the search in further search sources (systematic reviews, publicly accessible trial registries, publicly accessible documents of regulatory authorities, documents sent by the G-BA, documents of manufacturers, information from the hearings on the preliminary report plan and the preliminary report). As already noted in Section 4.1.1, the search in trial registries identified 8 ongoing studies whose relevance could in part not be conclusively clarified.

The manufacturer provided a previously announced publication on the 10-year data from a further relevant prognostic study (Buus 2016, TransATAC).

A total of 5 prognostic studies were thus identified as relevant for the research question of the present benefit assessment.

4.1.3 Results of information retrieval for concordance studies

Concordance studies were not searched for since, on the basis of RCTs, no positive conclusions on benefit could be drawn for at least one biomarker.

4.2 Characteristics of the studies included in the assessment

4.2.1 Characteristics of the RCTs included in the assessment

Paik 2006 [16] prospectively investigated the interaction between the result of the Oncotype DX recurrence score and the variable "treatment with adjuvant chemotherapy". For this purpose, archived tumour samples of the NSABP-B20 study were analysed retrospectively. The primary outcome was specified as freedom from distance recurrence (distant metastasis-free survival, DMFS).

In the underlying randomized controlled NSABP-B20 study [17], hormone therapy alone (tamoxifen) was compared with tamoxifen plus chemotherapy (methotrexate and fluorouracil or cyclophosphamide, methotrexate and fluorouracil). Between 1988 and 1993, 2363 patients with, oestrogen receptor(ER)-positive, lymph node-negative breast cancer were included. Tumour samples of 670 of the patients originally included were available for the analysis of the biomarker; the other samples were either never archived or were exhausted from use in prior studies. Successful application of the Oncotype DX test was reported for 651 tumour samples.

After a request for information by IQWiG, the manufacturer provided a subgroup analysis of 472 patients with HER2-negative tumours.

The prospective-retrospective study by **Martin 2014** [18] investigated the interaction of the EndoPredict test result with the variable "type of chemotherapy regimen".

The analysis of the biomarker was performed using archived tumour samples of the GEICAM-9906 study [19]; DMFS was the primary and OS the secondary outcome. After a request for information by IQWiG, the study authors did not provide unpublished data on all recurrences (i.e. on the patient-relevant outcome DFS specified for the present assessment). In the randomized, controlled GEICAM-9906 study, 2 chemotherapy regimens (fluorouracil, epirubicin, and cyclophosphamide with or without paclitaxel) were compared in 1246 patients with lymph node-positive disease, who were included between 1999 and 2002. Tumour samples of 800 of the patients originally included were available for the analysis of the biomarker. The tumour samples of the other patients were either not available in the central laboratory or no consent for sample analysis was given. The biomarker could be successfully determined in 555 ER-positive, HER2-negative tumour samples.

The prospective, randomized **MINDACT** study [20] included 6693 patients from 9 European countries. In all patients, the clinical-pathological risk with regard to breast cancer-specific survival was determined using a modified version of Adjuvant! Online, that is, considering information on ER status, HER2 status, tumour stage and size, as well as the number of affected lymph nodes. In addition, the genomic risk was determined using the 70-gene-signature test (MammaPrint). Patients with a low risk score in both tests (C-low/G-low) did not receive chemotherapy. Patients with a high risk score in both tests (C-high/G-high) received chemotherapy. Patients with discordant results, that is, C-low/G-high (n = 690) or C-high/G-low (n = 1497) were randomized to treatment with or without chemotherapy. The outcomes DMFS, DFS and OS were investigated. So far only results for a follow-up period of 5 years have been reported. Conclusions on the benefit of a biomarker-based strategy with regard to the outcomes named above can only be drawn from a follow-up period of 10 years (see Section A.4.4.3 of the full report). However, as this is the only prospective, randomized study published so far on the question of a biomarker-based decision to avoid chemotherapy, the results are presented as supplementary information in order to obtain an estimation of the results to be expected after 10 years.

4.2.2 Characteristics of the prognostic studies included in the assessment

The retrospective study by **Buus 2016** [21] investigated the EndoPredict test and the Oncotype DX recurrence score to determine the risk of distant recurrence using conserved tumour samples of the TransATAC database. These samples were collected in the ATAC study [22] between 1996 and 2000. This study was a 3-arm RCT conducted in 21 countries. It compared different adjuvant hormone therapy regimens in 9366 postmenopausal women with histologically proven operable invasive breast cancer who were not receiving chemotherapy. Of the 5880 patients in the 2 monotherapy arms (anastrozole and tamoxifen), results on 2006 tumour samples were collected retrospectively in a database from the year 2002 onwards [23]. The analysis by Buus 2016 included samples of 931 ER-positive and HER2-negative patients from the United Kingdom. The biomarker test results were related to the results on DMFS stored in the database.

In the retrospective analysis by **Filipits 2011** [24], the EndoPredict test was applied using conserved tumour samples from the ABCSG-6 and ABCSG-8 studies. The ABCSG-6 study [25], an RCT, compared tamoxifen alone versus tamoxifen in combination with aminoglutethimide. From 1990 to 1995, 2021 patients were randomized, of which 1004 were randomized to the tamoxifen arm; this arm was used for the analysis of the EndoPredict test. 443 tumour samples were available for this analysis, including 395 ER-positive, HER2-negative samples; the test was successfully applied in 378 of the latter samples.

In the ABCSG-8 study, an Austrian RCT comparing 2 adjuvant hormone therapy regimens, 3714 postmenopausal patients up to 80 years of age with hormone receptor-positive early breast cancer were randomized between 1996 and 2004 [26,27]. Of 1421 tumour samples

available, the analysis by Filipits 2011 considered 1324 samples with ER-positive, HER2-negative tumours.

The results of the biomarker-based test were then related to the results from the 2 RCTs for the outcome DMFS in order to determine the prognostic value of the test.

Fitzal 2015 [28] conducted a retrospective analysis of archived tumour samples of the ABCSG-8 study and used the same samples previously used in Filipits 2011. In this context, Fitzal 2015 related the EndoPredict test results to the outcome of local recurrence-free survival (LRFS).

Gnant 2014 [29,30] conducted a retrospective analysis of archived tumour samples of the multi-centre ABCSG-8 study (see previous page). They included 1478 available and evaluable tumour samples from the control arm of the ABCSG-8 study (without adjuvant chemotherapy), which were analysed using the PAM50 risk-of-recurrence score. In other contexts, this test has also been referred to as the Prosigna Breast Cancer Prognostic Gene Signature Assay. The data of those patients who had already died at the time of analysis (435 of 2255 in the database) were almost completely considered in the analysis. Those patients from the original RCT who were still alive were again asked for their consent. The results of the biomarker-based test were then related to the results on the outcomes DFS and DMFS recorded in the RCT in order to determine the prognostic value of the test in 1397 HER2-negative patients.

Sgroi 2013 [23] conducted a retrospective analysis using the Breast Cancer Index (BCI) in conserved tumour samples of the TransATAC database. These samples were collected in the ATAC study [22] between 1996 and 2000 (see previous page). Sgroi 2013 included samples of 915 ER-positive patients for whom informative results were available for the following 3 tests: BCI, 21-gene recurrence score (Oncotype DX), and an IHC prognostic model (IHC4). The test results were related to results stored in the database on the outcomes DMFS, OS, DFS, and breast cancer-specific mortality. Results were presented for the subgroup of 597 HER2-negative patients.

All studies identified were retrospective analyses of prospectively planned cohort studies, which at the same time represented individual arms of RCTs conducted. In the following text, the publications on these analyses are referred to as prognostic studies to improve readability.

4.3 Overview of outcomes relevant to the assessment

The results of the prospective-retrospective study by Paik 2006 were based on less than 70% of the patients to be included in the analysis. These results were therefore not used in the present benefit assessment.

The prospective-retrospective study by Martin 2014 investigated the interaction of the EndoPredict test result with the variable “type of chemotherapy regimen”, that is, the question

referring to the choice of 1 of 2 chemotherapy regimens on the basis of the biomarker-based test result. The results on DMFS and OS are presented in the following text.

Cardoso 2016 presented the prospective, randomized MINDACT study. They investigated whether patients with discordant results in the clinical-pathological assessment and genomic assessment (determined using a modified version of the Adjuvant! Online test and the MammaPrint biomarker test, respectively) could forgo chemotherapy or whether they would benefit from it. The results on DMFS, DFS and OS are presented as supplementary information in the following text, but could not be considered in the actual benefit assessment due to the short follow-up period. According to the study protocol, adverse events were also recorded; they were however not presented in the study publication. The primary outcome of the MINDACT study was DMFS in patients of the C-high/G-low group who did not receive chemotherapy. For this question too, only 5-year results were available. In contrast to the results of the randomized study, these results were not considered as supplementary information, as they refer to a purely prognostic question.

The results of the 5 prognostic studies (Buus 2016, Filipits 2011, Fitzal 2015, Gnant 2014 and Sgroi 2013) were in each case based on less than 70% of the patients to be included in the analysis, so they were not considered in the present benefit assessment.

The resulting study pool with an overview of the available relevant outcomes is presented in Table 1.

Table 1: Study pool of the benefit assessment with the matrix of outcomes

Study type	Study	Biomarker	Outcomes					
			Distant metastasis-free survival	**Local recurrence-free survival**	**Disease-free survival**	**Overall survival**	**Health-related quality of life**	**Adverse events**
RCT	Paik 2006	Oncotype DX	-	-	-	-	-	-
	Martin 2014	EndoPredict	✪	-	-	✪	-	-
	MINDACT	MammaPrint	[✪]	-	[✪]	[✪]	-	-
Prognostic study	Buus 2016	EndoPredict Oncotype DX	- -	- -	- -	- -	-	-
	Filipits 2011	EndoPredict	-	-	-	-	-	-
	Fitzal 2015	EndoPredict	-	-	-	-	-	-
	Gnant 2014	PAM50 ROR Score	-	-	-	-	-	-
	Sgroi 2013	Breast Cancer Index Oncotype DX	- -	- -	- -	- -	-	-

-: No evaluable data were available for the benefit assessment; ✪: Data extracted for the benefit assessment; [✪]: Presented as supplementary information due to the short follow-up period; ROR: risk of recurrence

4.4 Assessment of risk of bias at study and outcome level

The results of the study by Paik 2006 could not be used for the benefit assessment, as the proportion of patients not considered in the analysis was too high; the risk of bias of the results was thus not assessed.

The risk of bias at study level was rated as high for the study by Martin 2014, due, among other things, to the high proportion of patients not considered in the analysis (approx. 30%). Due to the high risk of bias at study level, the risk of bias for the outcome DMFS was also rated as high. No adequate data were available for a detailed assessment of the risk of bias for the outcome OS. The study authors merely reported that the interaction of the EndoPredict test result with the variable "type of chemotherapy regimen" was not statistically significant. As the risk of bias had already been rated as high at study level, it was also rated as high for this outcome.

The risk of bias was rated differently for the MINDACT study, depending on the population investigated. For the population of patients with the discordant risk result of C-low/G-high, the risk of bias was rated as low at study level and for the outcomes reported (DMFS, DFS and OS). For the population with the risk classification of C-high/G-low, the risk of bias was rated as high at study level and thus for all outcomes reported. The considerably high proportion of protocol violators, which differed between groups, resulted in a risk of bias, the direction of which can be assumed. For the non-inferiority question in this population, it is not conservative. In contrast, for the superiority question of the comparison in the C-low/G-high population, it is conservative.

4.5 Results on patient-relevant outcomes

Of the 3 RCTs, only the study by Martin 2014 and the MINDACT study provided evaluable results for the present benefit assessment. In the following text, the results are presented organized by studies, as they investigated different questions.

4.5.1 Results of the study by Martin 2014

Martin 2014 investigated the benefit of the EndoPredict test for the choice between 2 chemotherapy regimens.

The interaction of the EndoPredict test result (EndoPredict score < 5 vs. ≥ 5) with the variable "type of chemotherapy regimen" (fluorouracil, epirubicin, and cyclophosphamide with or without paclitaxel) was not statistically significant for the outcome DMFS ($p = 0.71$).

For the outcome OS, without providing details on numbers, the study authors reported that the interaction of the EndoPredict test result with the variable "type of chemotherapy regimen" was not significant.

No hint of a benefit or harm of an EndoPredict-based decision on the choice of adjuvant chemotherapy in patients with primary breast cancer can be inferred from these results.

4.5.2 Supplementary presentation of the results of the MINDACT study

The MINDACT study investigated the benefit of a biomarker-based strategy versus clinical-pathological diagnostics with regard to the decision for or against chemotherapy, and thus investigated 2 questions, see Table 2 below.

Table 2: Questions of the MINDACT study

No.	Population	Comparison	Question
1	C-high/G-low	CT vs. no CT	Does omitting chemotherapy in patients identified via the biomarker (with a test result deviating from the clinical-pathological assessment) lead to non-inferiority (i.e. an at most irrelevant disadvantage) with regard to the outcome (recurrence-free, disease-free or overall) survival?
2	C-low/G-high	CT vs. no CT	Do patients identified via the biomarker (with a test result deviating from the clinical-pathological assessment) benefit from chemotherapy?
C: clinical-pathological risk assessment; CT: chemotherapy; G: genomic risk assessment; high: chemotherapy indicated; low: no chemotherapy indicated; vs.: versus			

Question 1

Question 1 is a non-inferiority question. In this context the study authors evaluated the subgroup of patients included in the study with a high clinical and low genomic risk assessment (C-high/G-low) who were randomized to the arm with chemotherapy or the arm without chemotherapy. In this subgroup, the treatment effect (estimated as the hazard ratio) in patients in the arm without chemotherapy did not suggest non-inferiority for any of outcomes analysed. No non-inferiority boundary was specified in the study. However, as the lower confidence boundaries of the estimates clearly deviated from the zero effect, depending on the outcome considered, it cannot be excluded that chemotherapy reduces the risk (hazard) of mortality and disease recurrence by up to 50% (and more).

The study authors did not discuss the relative, but the absolute treatment effect. Purely descriptively they noted that, with regard to distant recurrence, the risk difference was 1.5 percentage points and did not judge this point estimate for the increased rate in the group without chemotherapy to be a relevant difference.

However, in the evaluation of non-inferiority, not the point estimate but the lower boundary of the 95% confidence interval must be examined. This means that in the event of distant recurrence, the risk difference could also amount to 3.89 percentage points. If one looks at 2 of the patient-relevant outcomes defined for the benefit assessment (DFS and OS) the lower confidence boundaries lie at 6.09 und 2.62 percentage points.

In summary, in the MINDACT study the magnitude of the 5-year hazard ratio and risk differences for DMFS, DFS and OS does not indicate that a hint of a benefit of omitting chemotherapy can be expected after 10 years.

This assessment considers that patients can expect a relevant number of chemotherapy-related adverse events. A complete weighing of benefit and harms of chemotherapy, that is, an assessment based not only on assumptions about harms, would in principle be preferable to an assessment based only on assumptions about harms. In the case of the MINDACT study this would even be possible by comparing the differences in adverse events with the differences in recurrence rates in both groups. According to the study protocol, data on adverse events were recorded in the study; however, these data were not published. In order to be able to perform an assessment in terms of a weighing of benefit and harms, it is thus indispensable that, when publishing the 10-year analysis, data on adverse events are also published.

Question 2

In the comparison of chemotherapy versus no chemotherapy in patients with the risk classification of C-low/G-high, no statistically significant difference was shown for any of the outcomes investigated (Question 2 in Table 2). Thus, at the time of the 5-year analysis, the results on this superiority question cannot show that patients additionally identified via the biomarker (with a test result deviating from the clinical-pathological assessment) benefit from receiving chemotherapy. This evaluation is shared by the study authors. Here it should be noted that for this question, solely because of the lack of information on adverse events, no benefit would be derived on the basis of published results of the MINDACT study.

4.6 Ongoing studies

A brief description is given in the following text of the ongoing studies for which relevant results with regard to the present benefit assessment are to be expected within the next year. They contain both randomized and non-randomized components.

The **TAILORx study** [31] compares hormone therapy alone with hormone therapy in combination with chemotherapy in patients with primary, ER-positive, HER2-negative, lymph node-negative breast cancer. Only patients with an Oncotype DX recurrence score of 11 to 25 are randomized. Patients with a recurrence score lower than 11 receive hormone therapy alone. The results on the 5-year data of this non-randomized subgroup receiving hormone therapy were published in 2014, but are not relevant for the present report due to the short follow-up period [32].

In the **PlanB study** [33], among others, patients with hormone receptor-positive, HER2-negative breast cancer with 0 to 3 affected lymph nodes and an Oncotype DX recurrence score higher than 11 are randomized to 2 different chemotherapy regimens, as are all patients with 4 or more affected lymph nodes. Patients with hormone-receptor positive breast cancer with a recurrence score lower than 12 receive hormone therapy alone. First 3-year results of this study were published in 2016 [34], but are not relevant for the present report due to the short follow-up period.

5 Classification of the assessment result

Only results from 2 of the 8 studies included could be considered in the present report. Due to the high proportion of unconsidered data, the results of the 6 remaining studies were not used for the assessment. On the basis of the 8 studies included, the data were insufficient overall to answer the research question posed.

A total of 5 ongoing studies were identified for which relevant results with regard to the research question of the present benefit assessment can be expected in the next years. For 2 of these studies (TAILORx, PlanB) relevant results could be published within the next year. However, these results would be of only limited use for the present benefit assessment, as only results on the 5-year follow-up period are to be expected. Five-year interim results of the ongoing MINDACT study, an RCT, have already been published; they are presented in the benefit assessment as supplementary information in order to obtain an estimation of the results to be expected for the 10-year period.

Currently, the published results of the MINDACT study do not indicate that after a 10-year follow-up period a benefit could be derived for patients who omitted chemotherapy following the MammaPrint test. Data on patient preferences with regard to adjuvant chemotherapy in breast cancer have indicated that, even in the event of only a small proportion of avoidable recurrences, patients are prepared to accept the side effects of chemotherapy. If one looks at the hazard ratio and risk difference of the group difference for recurrences determined in the study, it is doubtful whether patients identified by the biomarker would opt against chemotherapy. In addition, no information on the adverse events recorded in the study has been published so far, which is indispensable for a weighing of benefit and harms that is not based on assumptions.

Apart from that, the interim results also do not otherwise support the assumed advantage that the use of biomarkers could help avoid chemotherapy. Patients who, in contrast to the clinical assessment, had a high recurrence risk based on the MammaPrint test, showed a lower recurrence risk with chemotherapy than without chemotherapy. The difference was not statistically significant, but under consideration of the confidence interval it cannot be excluded that these patients would also benefit from chemotherapy. Here too, information on adverse events is missing that is required to be able to perform a weighing of benefit and harm.

6 Conclusion

There is currently no hint of a benefit or harm of a biomarker-based strategy to support the decision for or against adjuvant chemotherapy in primary breast cancer. The data from 6 of the 8 studies included could not be used for the present benefit assessment due to the high proportion of patients not considered in the analyses. Thus only data from 2 RCTs could be used.

The study by Martin 2014 (10-year follow-up period) investigated the interaction between biomarkers and the type of chemotherapy regimen administered and did not show a benefit of the EndoPredict test for the choice between 2 chemotherapies.

The still ongoing MINDACT study is investigating the use of chemotherapy versus no chemotherapy in patients for whom the clinical-pathological assessment and the biomarker test result led to different recommendations (discordant results). The 5-year interim results do not indicate a benefit of a biomarker-based treatment decision by means of the MammaPrint test.

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See full report for full reference list

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