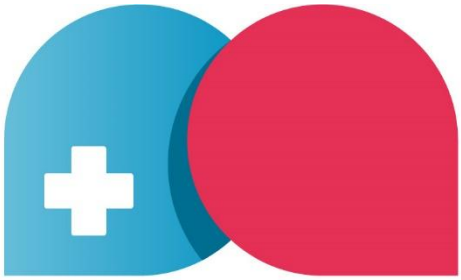
A report on the treatment options for patients with hormone receptor-positive, HER2-negative early primary breast cancer (HR+/HER2-):

endocrine therapy alone or additional chemotherapy?



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SHARE TO CARE. Patientenzentrierte Versorgung GmbH

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LIST OF ABBREVIATIONS

AE	Adverse events
AGO	Arbeitsgemeinschaft Gynäkologischer Onkologen
AMNOG	Arzneimittelmarktneuordnungsgesetz
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
DA	Decision aid
dDFS	Distant disease free survival
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
FAQ	Frequently asked question
HR	Hazard ratio
HrQoL	Health-related quality of life
IQWiG	Institute for Quality and Efficiency in Health Care
MA	Meta-analysis
MD	Mean difference
n.a.	Not applicable
NMA	Network meta-analysis
n.r.	Not reported
n.s.	Not specified
OR	Odds ratio
PICOS	Participants, intervention, comparators, outcomes, and study design
PRISMA	Preferred Reporting of Systematic Reviews and Meta-Analyses
QoL	Quality of life
RCT	Randomised controlled trial
RR	Risk ratio
SDM	Shared decision-making
SD	Standard deviation
SEAE	Serious adverse events
SMD	Standardised mean difference
SR	Systematic review
TRAE	Treatment-related adverse events
UKSH	Universitätsklinikum Schleswig-Holstein
WSG	West German Study Group

1. PROJECT OBJECTIVES

A key aim of the present project is to inform patients with primary breast cancer (HR+/HER2-) on different therapy options as part of shared decision-making (SDM). In a teamwork with clinical experts from four German university medical centres and patients from two patient organizations, we developed an evidence-based online decision aid (DA).

For each of SHARE TO CARE's decision aids we prepare and regularly update evidence reports, that cover the relative effects of interventions defined in the inclusion criteria (PICOS).

This evidence report has been updated in July 2025 as a reaction to user feedback and a new IQWiG report [1]. We used the opportunity for some editorial revisions for clarification (see below for details).

2. METHODS

2.1 INCLUSION CRITERIA

The frequently asked questions (FAQs) underpinning the literature searches were developed in collaboration with the patients and clinical experts during the scoping-process. These questions pertain to the relevant characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1.

The decision for or against additional chemotherapy in this patient group depends largely on the expected risk of recurrence after completion of primary therapy. The higher this risk, the more likely it is that the benefits of chemotherapy outweigh its side effects. It is generally assumed that this is the case with a risk of distant recurrence over 10% within ten years [2].

The field of methods used to assess this risk is heterogeneous, ranging from clinical factors (e.g. TNM, grading) to biomarkers (e.g. HER2-neu, Ki67), which are calculated into a risk estimation using various algorithms [3].

In addition, the methods for validating diagnostic tests and prognostic algorithms are versatile, ranging from simple diagnostic tests to multivariate prognostic tests and randomized trials that examine, for example, the effects of two different tests on treatment decisions and ultimately on patient outcomes [4].

This report therefore does not primarily examine the question of chemotherapy versus no chemotherapy. The question of which test or which combination of tests is better for predicting risk is also beyond the scope of this paper. The aim of this report is to translate the method and results of the WSG algorithm into a patient-understandable language. We will extract data on absolute risk of endocrine therapy and chemoendocrine therapy for the different subgroups of the algorithm, so patients can estimate the potential benefits of additional chemotherapy. Potential risks of additional chemotherapy will also be described.

The WSG algorithm has been developed and validated in Germany by the West German Study Group (WSG) in a series of studies [3,5,6]. This algorithm is meanwhile used in many oncology centres in Germany. The aim of this decision aid is therefore to explain the WSG algorithm and its components to patients in a generally understandable way. This also includes communicating the results in accordance with the rules of risk communication.

We are aware that the WSG algorithm is based on the sole use of the OncotypeDX test [7,8]. In Germany, other genomic tests are also available and used in healthcare (Breast Cancer Index, EndoPredict, EPclin, IHC4, Prosigna and Mammaprint, …) [9]. However, the determination of the probability of recurrence will be explained here using the WSG algorithm as an example. The validity of the other tests will be described on the basis of an IQWiG report.

Another specific feature of the WSG algorithm is that it also takes into account the endocrine response in the context of induction endocrine therapy. Induction therapy is not used across the board. However, it is becoming increasingly popular for hormone receptor-positive breast cancers. It will probably represent the German standard of care in near future.

The aim of this decision aid is to use the evidence-based methodological standard of the WSG algorithm to explain the diagnostic pathway to patients so that they can get an idea of their individual risk of relapse. This knowledge should enable them to understand further diagnostic workflows with other genomic tests than OnoctypeDX or without induction endocrine therapy.

Understanding the individual risk of relapse is an important prerequisite for being able to weigh up the benefits of additional chemotherapy against its adverse effects in order to make an informed decision.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Women with hormone receptor-positive, HER2-negative early primary breast cancer (HR+/HER2-) for whom endocrine therapy is planned and the indication for additional chemotherapy is unclear	Triple negative or HER2-positive BC or clear indication for chemotherapy and/or no endocrine response [with induction ET], ...
Intervention	Chemotherapy with consecutive endocrine therapy	n.a.
Comparator	Endocrine therapy only	n.a.
Outcomes	Life expectancy Recurrent disease (metastases, …) Quality of life (physical activity / social participation, …) Treatment related time and burden Adverse events: e.g. hair loss, fatigue, hospitalization, peripheral nerve damage, heart problems	n.a.

	Included	Excluded
	long-term adverse effects	
Study design	Data primarily extracted from the WSG-ADAPT trial [3,5,6] and the TAILORx trial [7,8,10]	n.a.
BC= breast cancer; ET = endocrine therapy; n.a.= not applicable		

2.2 Frequently asked questions

The following FAQs were identified:

1. What is my chance of staying free from a distant recurrence in the next 5 years with only endocrine therapy?
2. What does the additional chemotherapy involve (including treatment related time and burden)?
3. Will the additional chemotherapy be capable of preventing relapses/metastases?
4. How will the additional chemotherapy impact my quality of life?
5. What are the risks or side effects of additional chemotherapy?
6. Are there long-term negative effects of additional chemotherapy to be expected?
7. What effects can I expect on my everyday life?

2.3 Literature searches

For this report, publications from the WSG-ADAPT study were used specifically to extract the prognostic data for the algorithm [5,6]. Further data from the TAILORx study [7,8,10] was used to shed light on questions not covered by WSG-ADAPT. The state of validation of the genomic tests was extracted from IQWiG report D19-01. Data on the side effects of the different chemotherapy regimens were taken from the WSG-ADAPT study [11], the EBCTCG-meta-analyses[12,13], the SPUPEO-Project [14] and the German Cancer Information Service ("Krebsinformationsdienst") [15]. No systematic search for primary literature was conducted.

Systematic reviews and guidelines

In addition to the specific sources, relevant guidelines from national and international professional societies were used [2,16–18].

Update July 2025

After publication of the first version of the decision aid we received feedback from a medical professional and patient advocate. The person sent us a cohort study in breast cancer survivors which reports treatment regrets after chemotherapy [19]. We deemed this information relevant for the treatment decision and included the source in our evidence report. We also noted that an update to the IQWiG report on biomarkers in primary breast cancer [1] changed conclusions for premenopausal women. Therefore, we decided to modify our tables to better differentiate the data for intermediate risk groups. We did not, however, conduct a systematic literature search.

3. Results

3.1 Overview of included Sources

Table 2 summarises the sources of evidence used to answer the seven FAQs.

Table 2: Evidence sources (primary studies)

Study/year reference	**Evidence source**	**Intervention(s)**	FAQ1: What is my chance of staying free from a distant recurrence in the next 5 years?	FAQ2: What does the additional chemotherapy involve?	FAQ3: Will the additional chemotherapy be capable of preventing relapses/ metastases?	FAQ4: How will the additional chemotherapy impact my quality of life?	FAQ5: What are the risks or side effects?	FAQ6: Are there long-term negative effects?	FAQ7: What effects can I expect on my everyday life?
WSG-ADAPT	[3,5,6,20,21]	WSG-Algorithm (diagnostic)	✓	✓					
WSG-ADAPT (endocrine sub-study)	[6]	Endocrine therapy in different risk groups	✓	✓	✓				
WSG-ADAPT (high risk HR+/HER2- sub-study)	[11]	Endocrine therapy versus chemoendocrine therapy	✓	✓	✓	✓	✓	✓	
TAILORx	[7,8,10]	Oncotype DX	✓	✓	✓				
MINDACT	[22]	MammaPrint	✓	✓	✓				
SPUPEO	[14]	Different forms of chemotherapy					✓	✓	
RCT = randomized controlled trial									

Table 3: Evidence sources (validity of genomic tests)

Test	**Evidence source**	Genomic test	Highest level of study evidence	10-year dDFS < 10 % with negative test result	Quality of evidence
IQWiG D19-01	[9]	Oncotype DX, Breast Cancer Index, EndoPredict, EPclin, IHC4, Prosigna and Mammaprint	✓	✓	✓
dDFS = Distant disease free survival					

3.2 FAQ 1: 1. What is my chance of staying free from a distant recurrence in the next 5 years with only endocrine therapy?

Based on data from the TailorX-study [10] and the RxPonder-study [23] we built a table with absolute numbers for 10-years recurrences in the different RS-subcategories. To be able to give numbers for 10 years, we had to model the results based on two assumptions:

1. The rate of recurrences is constant over time (proportional growth)
2. Most of the recurrences occur within the first ten years after BC surgery.

Update 2025: As a reaction to a new IQWiG report [1], we modified Table 4 to differentiate the data for intermediate risk groups for premenopausal women with nodal-negative breast cancer. We recalculated the numbers and reported data separately for RS 11-15, 16-20 and 21-25, as well as for low and high clinical risk, respectively. Data for postmenopausal women and women with nodal-positive breast cancer remained unchanged. The results are shown in Table 5.

Table 4: Recurrence Score (RS): patients without distant recurrence within 10 years (previous version of the evidence report)

N0*			
RS	0-10	11-25	26-100
≤50 y	**98 of 100** No benefit from CTx shown*	**93 of 100** No benefit from CTx shown*	**83 of 100** Estimated benefit of CTx: **5 of 100**
>50 y	**96 of 100** No benefit from CTx shown*	**94 of 100** No benefit from CTx shown*	**79 of 100** Estimated benefit of CTx: **6 of 100****
N1***			
RS	0-10	11-25	26-100
≤ 50 y	**86 of 100** Significant benefit of CTx: **7 of 100*****		No data High benefit from CTx
>50 y	**89 of 100** No benefit from CTx shown***		No data High benefit from CTx

*Data were extracted from the TailorX study ([10], table 1); and extended to 10 years (assumption of linear increase in recurrence rates over time; (see [8]).

** In the TailorX study, all patients were treated with chemoendocrine therapy. Therefore, the recurrence rates are lower than they would be with anti-hormone therapy alone. For this reason, 25% of recurrences were added according to the results of the EBCTCG meta-analysis (mean of 20-30% RR).

***Data were extracted from the RxPonder study (Kalinsky 2021 [23]; Fig 2E/F); and extended to 10 years.

Table 5: Patients without distant recurrence within 10 years (baseline risk) according to recurrence score (RS) (current version)

N0*					
RS	0-10	11-15	16-20	21-25	26-100
≤50 y	**98 of 100** No benefit from CTx shown*	**97 of 100** No benefit from CTx shown*	**93 of 100** Hint for benefit from CTx for high clinical risk*	**85 of 100** Hint for benefit from CTx*	**83 of 100** Estimated benefit of CTx: **4 of 100****
>50 y	**96 of 100** No benefit from CTx shown*	**94 of 100** No benefit from CTx shown*			**79 of 100** Estimated benefit of CTx: **5 of 100****
N1***					
RS	0-10	11-15	16-20	21-25	26-100
≤ 50 y	**86 of 100** Significant benefit of CTx: **7 of 100*****				No data High benefit from CTx
>50 y	**89 of 100** No benefit from CTx shown***				No data High benefit from CTx

*Data were extracted from the TailorX study ([10], Table 1 and Table 2, respectively); and extended to 10 years (assumption of linear increase in recurrence rates over time; (see [8]). Table 2 reports subgroup data only for RS groups 16-20 and 21-25. Data for RS group 11-15 were extracted from [7], Table 3. For RS groups 16-20 (high clinical risk) and 21-25 (high and low clinical risk), data suggest a benefit, although not all differences between chemotherapy and no chemotherapy are statistically significant. Therefore, we decided not to quantify the benefit.

** In the TailorX study, all patients were treated with chemoendocrine therapy. Therefore, the recurrence rates are lower than they would be with anti-hormone therapy alone. For this reason, 25% of recurrences were added according to the results of the EBCTCG meta-analysis (mean of 20-30% RR).

***Data were extracted from the RxPonder study (Kalinsky 2021 [23]; Fig 2E/F); and extended to 10 years.

In addition to the clinical and biochemical markers, the evidence based algorithm based on the WSG-ADAPT studies [3,6,20] takes into account the response to induction anti-hormone therapy and the result of the Oncotype DX test when assessing the individual risk of relapse. A recommendation for endocrine or chemoendocrine therapy is given for each cell in the tables (Table 6 and Table 7).

Table 6: Algorithm based on the WSG-ADAPT studies (NO) [3]

N0				
RS	0-15	16-20	21-25	>25
≤ 50 years	ET	With endocrine response: ET*	CHT → ET Consider ET alone if clinical risk is low and endocrine response.	CHT → ET
> 50 years	ET			
*Chemotherapy benefit in this RS group after 12 years: clinical low risk 0%; clinical high-risk 3%				
Recommended endocrine therapy: - Premenopause: ET: TAM +/- GnRH for low risk; otherwise, TAM/AI + GnRH analogs - Postmenopause: AI or AI --> TAM or TAM --> AI - Preoperative endocrine anti-hormone therapy recommended to predict the effectiveness of AI				
NO = lymph node negative; RS = risk score (Oncotype DX); ET = endocrine therapy; CHT = chemotherapy; TAM = tamoxifen; AI = Aromatase Inhibitor; GnRH = gonadotropin-releasing-hormone				

Table 7: Algorithm based on the WSG-ADAPT studies (N1) [3]

N1			
RS	0-11	12-25	>25
≤ 50 years no endocrine response	CHT → ET*	CHT → ET	CHT → ET
≤ 50 years endocrine response	based on ADAPT: ET* at low clinical risk CHT --> ET for high clinical risk to be discussed		
> 50 years	ET		CHT → ET
*Excellent survival in the ADAPT study with ET alone; however, small number of cases			
Recommended endocrine therapy: - Premenopause: ET: TAM/AI + GnRH analogs - Postmenopause: AI or AI --> TAM or TAM --> AI - Preoperative endocrine anti-hormone therapy recommended to predict the effectiveness of AI			
N1 = 1-3 affected nodes; RS = Risk score (Oncotype DX); ET = endocrine therapy; CHT = chemotherapy; TAM = tamoxifen; AI = Aromatase Inhibitor; GnRH = gonadotropin-releasing-hormon			

In order to be able to make an informed decision, patients should know what their initial risk is with endocrine therapy alone, for example, and by how much it could be reduced with additional chemotherapy. Patients should also understand the criteria doctors use to decide whether additional chemotherapy is beneficial. In this way, they can compare the medical criteria with their own assessments of benefits and harms and actively participate in decisions. This requires a precise assessment of the level of risks and their potential reduction. To this end, we have extracted the absolute risks and the risk reduction from the available studies. These should be made available to patients.

Ideally, this task requires data from studies that directly compare patients who receive purely endocrine therapy and those who additionally receive chemotherapy. To our

knowledge the only study that has undertaken this is the WSG-ADAPT study. However, only 5-year data are currently available for the question at hand. Furthermore, this study does not cover all fields of the WSG algorithm. It was therefore necessary to estimate data for some fields of the algorithm. The footnotes to the respective fields in Table 8 and Table 9 indicate the sources of the data.

Table 8: Absolute numbers based on the WSG-ADAPT studies [3]: patients without distant recurrence in 10 years (NO)

<table>
<tr><th colspan="5">N0</th></tr>
<tr><td>RS</td><td>0–15</td><td>16–20</td><td>21–25</td><td>26–100</td></tr>
<tr><td>≤ 50 years</td><td rowspan="2">>96 of 100[a]
No estimated benefit from CTx</td><td colspan="2">Endocrine responders:
94 of 100[b]
No benefit from CTx</td><td rowspan="2">83 of 100[d]
Estimated benefit of CTx:
4 of 100</td></tr>
<tr><td colspan="2">Endocrine non-responders:
80 of 100[c]
estimated benefit of chemotherapy:
5 of 100</td></tr>
<tr><td>> 50 years</td><td colspan="3">Endocrine responders:
90-92 of 100[b]
No estimated benefit from CTx</td><td rowspan="2">79 of 100[d]
Estimated benefit of CTx:
5 of 100</td></tr>
<tr><td colspan="3">Endocrine non-responders:
88 of 100[b]
No estimated benefit from CTx</td></tr>
<tr><td colspan="5">Recommended endocrine therapy:
- Premenopause: ET: TAM +/- GnRH for low risk; otherwise, TAM/AI + GnRH analogues
- Postmenopause: AI or AI --> TAM or TAM --> AI
- Preoperative endocrine anti-hormone therapy recommended to predict the effectiveness of AI</td></tr>
<tr><td colspan="5">NO = lymph node negative; RS = Risk score (Oncotype DX); ET = endocrine therapy; CHT = chemotherapy; TAM = tamoxifen; AI = Aromatase Inhibitor; GnRH = gonadotropin-releasing-hormone; RR = relative risk</td></tr>
</table>

a: Data were extracted from the TailorX study Sparano 2019 [10] (table 1). Nitz et al. 2022 [6] show rates for distant recurrence-free survival of 96.8%. However, the cut-off value of RS ≤ 11 was chosen somewhat lower here. This also explains the slightly lower recurrence rates. The figures were extended to 10 years.

b: Data were extracted from Nitz 2022 [6] and extended to 10 years.

c: The Nitz paper reports a dRFS of 92.5% after 5 years (recurrence rate = 7.5%). Extrapolated to 10 years, this corresponds to a dRFS rate of 85% (relapse rate of 7.5% x 2 = 15%). These patients were all treated with chemoendocrine therapy in the study. With endocrine therapy alone, the risk of relapse should therefore be correspondingly higher. We have therefore added 25% (EBCTCG) to the 15% risk of relapse (15/0.75=20). We therefore estimate the risk of relapse with endocrine therapy alone to be 20% (dRFS = 80). The effect of chemotherapy in this group is therefore about 5 percentage points (25% risk reduction of 20% = 5%). (Assumption of linear increase in recurrence rates over time; (see Sparano 2015)).

d: These figures are from the TailorX study (Sparano 2019 [10] ; table 1). The risks of women > 50 years of age were taken as a basis here.

Table 9: Absolute numbers based on the WSG-ADAPT studies [2]: patients without distant recurrence in 10 years (N1) [3]

N1			
RS	0-11	12-25	≥26
≤ 50 years Endocrine non-responders:	86 of 100[a]	80 of 100[b] estimated benefit of chemotherapy: 5 of 100	No data High benefit from CTx
≤ 50 years Endocrine responders	94 of 100[a]*	94 of 100[a]*	
> 50 years	92 of 100[a]*	90 of 100 [a]	No data High benefit from CTx
*Excellent survival in the ADAPT study with ET alone; however, small number of cases			
Recommended endocrine therapy: - Premenopause: ET: TAM/AI + GnRH analogs - Postmenopause: AI or AI --> TAM or TAM --> AI - Preoperative endocrine anti-hormone therapy recommended to predict the effectiveness of AI			
N1 = 1-3 affected lymph nodes; RS = Risk score (Oncotype DX); ET = endocrine therapy; CHT = chemotherapy; TAM = tamoxifen; AI = Aromatase Inhibitor; GnRH = gonadotropin-releasing-hormon			

a: Data extracted from Nitz 2022 [6] (text and table A1, figures A3A and A3B: no differences between N0 and N1)
b: In the WSG study, these patients were treated with chemoendocrine therapy. In order to estimate the recurrence rates with endocrine therapy alone, 25% was added to the measured recurrence rates (7.5%/0.75=10; DRFS = 90). These values were doubled for the 10-year estimate (RR 20%; DRFS 80%). The efficacy of chemotherapy is estimated accordingly at (25% RR) 5%.

3.1.1 FAQ 2a: What if my Breast Centre doesn't use the WSG-algorithm?

The WSG algorithm is explained here, because, in our opinion, it is the most advanced and best validated prognostic algorithm. Furthermore, to our knowledge, it is the most frequently used in Germany. Only if women understand the algorithm and if they are able to quantify the absolute risk of distant recurrence in their individual subcategory, they will be able to make informed decisions with their doctors.

This does not mean that other prognostic strategies are inferior or less accurate. The leading prognostic principle – combining as many different markers as possible in a systematic way to enable the most accurate prediction of distant recurrence – is the same in all algorithms. What you should not do, however, is to use a second genomic test if you are still unsure after the first genomic test result [16].

Each of the components of such an algorithm provides valuable prognostic information on its own. For example, genomic tests can predict recurrence independently of biochemical or clinical factors. The accuracy of this prediction for the genomic tests available in Germany was examined in an HTA report by the Institute for Quality and Efficiency in Health Care (IQWiG). The results are summarized in the next section.

3.1.2 FAQ 2b: How valid are genomic tests beside Oncotype DX?

IQWiG has searched for clinical studies worldwide for all genomic tests approved in Germany and systematically summarized their results [9]. Relevant characteristics of these studies (size, patient population, etc.) and potential biases (e.g. loss to follow-up) were examined. The results of this analysis are summarized in Table 10.

For this report, we have assigned 3 categories of validity: green, yellow and red. Green was assigned to the best validated tests (RCTs, multiple consistent prognostic studies, low risk of bias), yellow to genomic tests with medium quality (multiple consistent prognostic studies) and red to those with few, highly biased or inconsistent prognostic studies. For each of these tests, we extracted the risk of distant recurrence in 10 years with a negative test result (low risk).

Table 10: Study characteristics, prognostic yield, and overall rating for genomic tests

Genomic test	Number of studies (n RCTs)	Certainty of results of individual studies	10 years risk of distant recurrence with negative test result (cut-off: %)	Overall rating of validity
Oncotype DX	5 (1)	high	RS < 11: 2 – 3.2 RS < 18: 3 – 6.8 RS < 26: 5 – 5.5	green
Breast Cancer Index	1 (0)	low	5.9	red
Endopredict	2 (0)	low	3	yellow
EPclin	2 (0)	low	4.5 – 6.6	yellow
IHC4	1 (0)	low	6.2	red
MammaPrint	1 (1)	high	n.a.[a]	yellow
Prosigna	3 (0)	medium	4.9 – 12.5	yellow

a: no prognostic data for distant disease-free survival available

Reading aid using the example of IHC4: For this test, one prognostic study on the endpoint distant disease-free survival (dDFS) at 10 years was identified in the IQWiG report. No RCT was available. The certainty of the results of this study was low. If the test result is negative, the risk of distant recurrence at ten years is 6.2%. Our overall assessment of this test is "red".

3.1.3 FAQ 2c: What is the difference between a prognostic and a predictive test?

A prognostic test provides information about the likely outcome or course of a disease regardless of treatment. It helps estimate the patient's overall prognosis, including survival time or likelihood of disease recurrence. A predictive test provides information about how likely a patient is to respond to a specific treatment. It helps tailor treatment decisions by identifying patients who are most likely to benefit from a particular therapy.

A test can have both prognostic and predictive qualities. In order to determine the quality of the test for prognostic questions, single-arm observational studies are usually carried out (cohort studies). A controlled intervention study is required to determine the predictive

validity, ideally a randomized controlled study (RCT). Such RCTs have already been carried out for two of the tests listed here (MammaPrint [22,24] and Oncotype DX [7,10]).

An eight-year exploratory analysis of the MINDACT-trial showed that additional chemo-therapy might reduce distant recurrences of women < 50 years by ≥ 5% what makes it possibly beneficial. Therefore, the MammaPrint test doesn't clearly differentiate between patients, who would benefit from chemotherapy and patients who won't in this age subgroup, according to the prospectively defined cut-off criteria. The authors recommend Shared Decision Making (SDM) with these patients [22]. However, in our opinion doctors should make SDM with all patients, not only in situations, where clinical benefit of a test is unclear.

The TailorX study investigated the effect of additional chemotherapy in patients with hormone receptor positive HER2 negative tumours without affected lymph nodes in the intermediate risk categories of the Oncotype DX test (RS 11–25). It was shown that the risk of recurrence within 9 years did not exceed the 5% mark if patients guided by the RS score did not undergo chemotherapy [10].

Both tests are therefore predictive. In relation to the limit of 5% distant recurrences in 8 or 9 years set at the beginning of both studies, a predictive benefit was found for the Oncotype DX test. This was not the case for the MammaPrint. However, the difference in predictive value of these tests is only small.

3.2 FAQ 2: What does the additional chemotherapy involve (including treatment related time and burden)?

This section describes the treatment procedure of endocrine therapy and chemoendocrine therapy and their side effects.

Table 11: Description of treatments

Endocrine therapy
Endocrine therapy is a cornerstone in the treatment of hormone receptor-positive (HR+) primary breast cancer. Key features of endocrine therapy are: Hormone Receptor Targeting: Some endocrine therapies target hormone receptors, specifically estrogen receptor (ER) and/or progesterone receptor (PR), which are commonly found in breast cancer cells. It aims to block the effects of estrogen on cancer cells or reduce estrogen levels in the body, thus slowing down or stopping cancer growth. E.g. Selective Estrogen Receptor Modulators (SERMs), drugs like tamoxifen, bind to estrogen receptors and thus prevent estrogens from binding to them. Aromatase Inhibitors (AIs): These drugs, such as anastrozole, letrozole, and exemestane, work by blocking the enzyme aromatase, which converts androgens into estrogen. They reduce the amount of estrogen produced in the body. The medication is suitable for postmenopausal women. Gonadotropin-Releasing Hormone (GnRH) analogs: These drugs, such as goserelin and leuprolide, suppress ovarian function, reducing estrogen production. The medication is suitable for premenopausal women. Added in update 2025: GnRH analogs can be used as an alternative to tamoxifen in premenopausal women when tamoxifen is not suitable. According to the S3

guideline for diagnosis and treatment of breast cancer [17], GnRH analogs ought to be given additionally to tamoxifen or aromatase inhibitors in premenopausal women with high clinical risk.

Endocrine therapy can be used as adjuvant therapy after surgery to reduce the risk of cancer recurrence, or as neoadjuvant therapy to shrink tumours before surgery or to test hormone-sensitivity of the tumour.

The duration of endocrine therapy may vary depending on the individual patient's risk factors, menopausal status, and type of endocrine therapy used. Typically, treatment may last for 5 to 10 years.

Side effects: While generally well-tolerated, endocrine therapy may cause side effects such as hot flashes, vaginal dryness, mood swings, bone thinning (osteoporosis), and increased risk of blood clots. Some breast cancers may develop resistance to endocrine therapy over time, leading to disease progression. Research is ongoing to understand mechanisms of resistance and develop strategies to overcome it, such as combination therapies or novel endocrine agents. Patients undergoing endocrine therapy are regularly monitored for response to treatment and any potential side effects. This may involve imaging studies, blood tests, and clinical assessments.

Chemoendocrine therapy

Chemoendocrine therapy, also known as combination therapy, involves the sequential use of chemotherapy and endocrine therapy for the treatment of primary breast cancer. Key features of chemoendocrine therapy are:

Chemoendocrine therapy combines the cytotoxic effects of chemotherapy with the hormone-suppressing effects of endocrine therapy. This dual approach targets both hormone receptor-positive (HR+) breast cancer cells and hormone receptor-negative (HR-) or less hormone-sensitive cells, providing a more comprehensive treatment strategy. Combining chemotherapy with endocrine therapy has been shown to improve treatment outcomes compared to using either treatment alone, particularly in patients with HR+ breast cancer. Added in update 2025: Chemotherapy can be given either before surgery (neoadjuvant setting) or after surgery (adjuvant setting).

The chemotherapy may consist of different regimens, including anthracycline-based, taxane-based, or combination regimens such as AC-T (doxorubicin/cyclophosphamide followed by paclitaxel) or FEC-T (fluorouracil/ epirubicin/ cyclophosphamide followed by paclitaxel). Newer regimes contain 8 weeks of dose-dense solvent-based (SB)-taxane or nanoparticle-albumin-bound (nab)-paclitaxel followed by four cycles of epirubicin [11].

The current German AGO-guideline recommends [25]:

Dose-dense regimes:

- A_{60} x 4 → Pac_{175} x 4 → C_{600} x4 q2w*
- $A_{60}C$ q2w x 4 → Pac_{175} q2w x 4
- $E_{90}C$ q2w x 4 → Pac_{175} q2w x 4
- $E_{90}C$ q2w x 4 → Pac_{80} q1w x 12
- $NabPac_{125}$ x 8-12 → $E_{90}C$ q2(3)w x 4

*__Reading aid:__ 60 mg anthracycline for 4 weeks followed by 175 mg paclitaxel for 4 weeks, followed by 600 mg cyclophosphamide every second week for 2 times (4 weeks).

The endocrine component is identical to the one described above.

Chemotherapy may cause side effects such as hair loss, nausea, vomiting, fatigue, and increased risk of infections (see 3.5 and 3.6). Endocrine therapy-related side effects, such as hot flashes, mood swings, and bone thinning, may also occur.

Patients undergoing chemoendocrine therapy are closely monitored for response to treatment, toxicity, and disease progression. This may involve imaging studies, blood tests, and clinical assessments.

3.3 FAQ 3: Will the additional chemotherapy be capable of preventing relapses/metastases?

The efficacy of chemotherapy in primary breast cancer according to the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has been extensively studied through meta-analyses of multiple clinical trials [13,26]. The EBCTCG conducts analyses pooling data from various randomized controlled trials (RCTs) to assess the impact of different treatments on breast cancer outcomes.

Reduction in Recurrence Risk: Chemotherapy has been shown to significantly reduce the risk of breast cancer recurrence, particularly in patients with early-stage breast cancer. The EBCTCG meta-analyses have demonstrated that adjuvant chemotherapy reduces the risk of recurrence by approximately one-third across different patient populations [13]. A recent meta-analysis showed that anthracycline-containing regimens reduced risks of recurrence more than only taxane-containing regimens. It also showed that a higher cumulative dose and more dose-intense schedules were more efficacious [26].

Improvement in Survival: Adjuvant chemotherapy has been associated with improvements in overall survival and breast cancer-specific survival in patients with early-stage breast cancer. The EBCTCG analyses have shown that chemotherapy reduces the risk of death from breast cancer in ten years by about 20 % (relative risk) and 6.5% (risk difference), respectively [13]. Taxane-containing regimes reduced mortality at an additional 35 % (relative risk) and 4.2% (risk difference), respectively [26].

Long-term Follow-up Data: The EBCTCG continues to update its analyses with long-term follow-up data from clinical trials, providing insights into the duration of treatment effects and late treatment-related toxicities. These analyses help inform clinical practice guidelines and treatment decisions for patients with primary breast cancer.

Overall, the EBCTCG meta-analyses have consistently demonstrated the efficacy of chemotherapy in reducing the risk of recurrence and improving survival outcomes in patients with primary breast cancer, particularly in those with early-stage disease.

Conclusion for decision aid:

We estimate a relative 30% reduction in recurrence rates and a relative 20% reduction in breast cancer specific mortality for 10 years follow up in the decision aid. We assume that the probability of events is nearly equally distributed over the first ten years. Therefore, these (relative) reduction rates apply analogously for five years of follow-up.

3.4 FAQ 4: How will the additional chemotherapy impact my quality of life?

The impact of additional polychemotherapy on health-related quality of life (HrQoL) in primary breast cancer patients can vary depending on several factors, including the specific chemotherapy regimen used, individual patient characteristics, treatment-related side effects, and supportive care measures [17,27].

Treatment-Related Side Effects: Polychemotherapy can be associated with a range of side effects, including nausea, vomiting, fatigue, hair loss (alopecia), decreased appetite, diarrhoea, and increased susceptibility to infections (see FAQ 5 and 6). These side effects can have a significant impact on physical well-being and may affect daily activities, work, and social interactions. Overall quality of life seems to be worse during dose-intense treatment than during standard schedule treatment, but these differences diminish after the end of treatment [11,14].

Long-term Effects: While polychemotherapy can improve survival outcomes in breast cancer patients, some treatment-related side effects may persist beyond the completion of chemotherapy. Long-term effects such as chemotherapy-induced peripheral neuropathy (CIPN), cognitive dysfunction ("chemo brain"), cardiovascular toxicity, and risk of secondary malignancies may impact QoL in survivorship (see FAQ 5 and 6).

Psychological Impact: Coping with a breast cancer diagnosis and undergoing intensive treatment like polychemotherapy can lead to psychological distress, anxiety, depression, and emotional instability. Fear of treatment-related side effects, uncertainty about the future, and concerns about body image changes due to hair loss or weight gain may contribute to psychological distress [17].

Impact on Functional Status: Some chemotherapy side effects, such as fatigue and decreased energy levels, may affect functional status and limit the ability to perform daily tasks or engage in usual activities. Patients may experience disruptions in work, family responsibilities, and leisure activities, which can impact overall QoL [17].

Supportive Care Interventions: The provision of supportive care interventions, such as anti-nausea medications, growth factor support to prevent neutropenia-related complications, psychosocial support, nutritional counselling, and exercise programs, can help mitigate the adverse effects of polychemotherapy and improve QoL [17].

Individual Variability: It's important to recognize that individual patients may respond differently to polychemotherapy and may experience varying degrees of treatment-related side effects and QoL impact. Factors such as age, comorbidities, baseline functional status, social support, and coping mechanisms can influence individual experiences [17,27].

QoL Assessment: Regular assessment of QoL using validated tools can help healthcare providers identify treatment-related concerns, monitor patients' well-being throughout treatment, and tailor supportive care interventions to address specific needs.

Overall, while polychemotherapy is an essential component of adjuvant treatment for primary breast cancer, its impact on QoL underscores the importance of comprehensive supportive care measures to minimize treatment-related side effects and optimize patient well-being during and after chemotherapy [28,29].

Our searches found a single study that examined quality of life with and without adjuvant systemic therapy in women with hormone receptor positive primary breast cancer [30]. The study was multinationally planned and well conducted (using different validated questionnaires) and included 1,110 patients in different stages of patient journey. However, it was conducted in a cross-sectional design and possible confounders were not adjusted. In the study, the QoL scores were compared in the various subgroups (tumour stage, age, type of therapy, country, etc.) on the one hand and with the respective reference values of the healthy population on the other.

Most QoL measurements in this study showed only small differences to the reference values and the quality of life after primary therapy can therefore generally be classified as high in this group. However, there were significant losses in HrQoL in women who received adjuvant therapy compared to women after the end of adjuvant therapy or without such therapy. Differences between endocrine therapy alone and chemoendocrine therapy were not investigated in this study.

Conclusion for the decision aid:

HrQoL is a multidimensional construct and is affected by many different factors, like state of disease, impact of treatment (side effects) on functional status, psychologic factors, supportive measures (e.g. psychooncology). The additional effect of chemotherapy on HrQoL is therefore difficult to assess. Furthermore, the study situation on this question is still very thin. Patients should be informed about potential positive and negative effects of these different factors and will have to evaluate the effects in their own circumstances according to individual values and preferences.

3.5 FAQ 5: What are the risks or side effects of additional chemotherapy?

Short-Term Risks and Side Effects [11–14]:

Table 12: Side effects of chemoendocrine therapy compared to endocrine therapy alone [14]

Severe AEs	<1 of 100 more
Damage to the nerves (e.g. tingling, numbness, pain)	n.s.
Severe nausea or severe vomiting*	11 of 100 more
Other AEs	
Complete hair loss**:	37 of 100

n.s.= not stated

* Probably less common nowadays due to better anti-nausea medication

** Hair grows back after therapy

Table 13: Side effects of chemotherapy with anthracyclines compared to a combination of anthracyclines and taxanes [14]

Severe AEs	<1 of 100 more
Damage to the heart	No additional AE reported
Damage to the nerves (e.g. tingling, numbness, pain)	11 of 100 more
Severe nausea or severe vomiting*	No additional AE reported
Other AEs	
Complete hair loss**	11 of 100 more

* Probably less common nowadays due to better anti-nausea medication

** Hair grows back after therapy

3.6. FAQ 6: Are there long-term negative effects of additional chemotherapy to be expected?

Long-Term Risks and Side Effects [14,26,31]:

The EBCTCG-Mas fond a slightly higher incidence of endometrial cancer with Tamoxifen (0,1 per 100 per year) compared to aromatase inhibitors (<1 per 100 per year). On the other hand it found slightly more bone fractures with tamoxifen (0.9 per 100 per year) compared to aromatase inhibitors (0.7 per 100 per year). The latter can be reduced by the use of bisphosphonates to preserve bone density [31].

The EBCTCG meta-analysis comparing anthracycline-containing and taxane-containing chemotherapies [26] suggests that treating 1,000 women with anthracycline would cause one or two cases of acute myeloid leukaemia. No increase was apparent in cardiovascular death, or overall rates of death without recurrence in those who received an anthracycline compared to taxanes.

Update 2025: The prospective multicentre cohort study BRENDA-II [19] followed 456 patients with primary breast cancer who started therapy in the period 2009–2012. 82 % received endocrine therapy and 46 % received chemotherapy. Although this is not reported separately, most women with chemotherapy probably also received endocrine therapy. The participants answered questions about long-term problems 5 years after treatment and about decision regret. As the data about long-term outcomes were self-reported and not clinically validated and as it is also not clear, what type of chemotherapy the patients received, we decided not to use quantitative information on the frequency of long-term

problems but only to report data on decision regret: 209 patients underwent chemotherapy and were asked about treatment regret. 44 did not answer this question. 8 answered that they regret this treatment decision. This corresponds to 2 % of all patients and 4 % of all patients who responded to this question, respectively. As a worst case scenario, we report 4 % in the decision aid.

3.7. FAQ 7: What effects can I expect on my everyday life?

Once the acute treatment is over, it is not easy for many people to return to their everyday lives. Breast cancer patients in particular have to cope with the physical changes brought about by surgery, radiotherapy and hormone therapy. Nevertheless, there are ways to achieve a good quality of life. Follow-up care is therefore not only about detecting a possible recurrence at an early stage, but also about promoting general health and quality of life [9,15].

The additional chemotherapy may result in further hospital stays. The infusions will be administered there. The different treatment regimen may result in a slightly different frequency of follow-up appointments. The additional side effects require additional side effect management

Further tips and advice can be found on the websites of the Cancer Information Service, IQWiG or relevant self-help groups.

4. DISCUSSION

4.1 Summary of main findings

In this evidence report, we focused on two aspects: firstly, we wanted to translate the algorithms of the WSG for risk stratification of women with primary breast cancer into a generally understandable language; into absolute frequencies. Secondly, we wanted to present the status of validation for genetic markers that are available in Germany. Here, we wanted to differentiate between prognosis and prediction.

4.2 Strength, limitations and uncertainties

This report has several strengths that ought to be noted. These include comprehensive searches of the most-recent evidence summarized in the approval trials, clinical practice guidelines, meta-analyses and HTA-reports, as well as coverage of a wide range of FAQs and outcomes of interest. To our knowledge it is the first attempt to translate the WSG-algorithm into a patient- understandable version with absolute numbers.

Nevertheless, some limitations should also be mentioned. Firstly, it is impossible to describe all existing prognostic tools and algorithms. It is not even clear how many are in use in Germany. Secondly, in the absence of comparative studies, it is not possible to determine which of the algorithms is the most accurate. However, we can claim that the WSG algorithm presented here as an example is one of the most comprehensively developed and validated in the world.

We tried to find frequencies for 10-year distant recurrence-free survival under hormone therapy alone for all cells of this scheme in order to subsequently show the absolute increase of this target value with additional chemotherapy. The aim was to explain to patients what absolute benefit they can expect from additional chemotherapy. Unfortunately, we were unable to find data for all cells (e.g. for high-risk patients, who all received chemoendocrine therapy). In some cases, the figures given are therefore estimated.

To make an informed decision, patients should be aware not only of the potential benefits but also of the magnitude and quality of the risks and side effects. Unfortunately, these target values are difficult to determine and are very heterogeneous due to the very different treatment regimes. We have not been able to find a systematic and complete list of these results. Future studies (and registries) should focus primarily on this issue. Irrespective of this, systematic and quality-assured follow-up care with comprehensive side effect management plays an important role in the treatment and reduction of side effects.

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