Consolidated stakeholder feedback

HTA report

Multigene-expression tests in early breast cancer

Stakeholders (SH; in alphabetical order) that have provided comments:

1	Agendia NV
2	Europa Donna Schweiz
3	Exact Sciences International GmbH
4	Myriad (ab 1.8.2025 Eurobio Scientific)
5	Prio.Swiss
6	Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK), Projekt Gruppe Brustkrebs
7	Schweizerischen Gesellschaft für Gynäkologie und Geburtshilfe (SGGG)
8	Schweizerische Gesellschaft für Medizinische Onkologie (SGMO)
9	Schweizerische Gesellschaft für Pathologie (SGPath)
10	Schweizerischen Gesellschaft für Senologie (SSS)
11	SVDI / ASID
12	Veracyte

SH	SH comment	Reply authors / BAG & implemented changes
1	1. The report repeatedly claims a lack of comparison between multigene tests and conventional testing, a point Agendia respectfully disagrees with. MINDACT directly compared MammaPrint (MP) to the (at the time) widely used modified adjuvant online (AOL) clinical risk algorithm for chemotherapy (CT) decisions. Later analyses, e.g. Viale2018Jan;167(1):123-131, compared MP to more modern clinical classifiers (i.e. Ki67 & PR positivity) and still found that conventional methods overclassify high risk. Across MINDACT studies, MP Low consistently shows good prognosis with no meaningful CT benefit.	This statement regarding the lack of comparison between multigene-expression tests and conventional testing is a general remark, considering the full evidence base for all tests. This holds to a lesser extent for MammaPrint. It is therefore stated in the HTA report that comparative clinical effectiveness evidence is available for MammaPrint. For example, in the conclusion: “Overall, the comparative evidence on multigene-expression tests is sparse. Of the 4 multigene-expression tests, only for MammaPrint an interim analysis of one RCT is available on the comparative clinical effectiveness of the multigene-expression test versus conventional testing for guiding adjuvant chemotherapy decisions in early breast cancer patients.” No changes to the report have been made based on this comment.
1	2. Throughout the report genomic risk (G-Risk) proportions for MP are used based on the full MINDACT population (including TNBC & HER2+). These proportions should be changed based on the MP Low vs MP High distribution in the HR+HER2- group within MINDACT. You can use Table (Tbl) S2 of the Piccart2021Apr;22(4):476-488 and the row titled ‘“Clinicopath subtype – Lum HER2–: ER+ PR+ or both”. You will find the proportions to be 85% MP low / 15% MP high in AOL Low, and 61% MP low / 39% MP High. This is especially important for section 7.1.5.1 and the inputs in Tbl 28. Here the proportions need to be adjusted for the model for accurate health economic results.	It is acknowledged that the full MINDACT population does not completely align with the target population of the HTA report, and therefore it would be more suitable to use data from the HR+/ HER2- subpopulation. Implemented change: the input parameters have been adapted to specify the distribution of the tested population over the genetic risk groups based on the data shown in Table S2 of the mentioned publication (Piccart 2021). The analysis for MammaPrint has been redone and results have been updated in the report.
1	3. Regarding the comparison in MINDACT between AOL and MP (C-high/G-low CT vs C-high/G-low no CT), we believe that the downgrading of the CT randomization evidence in Tbl 23 to ‘low certainty’ is not justified. The 1st cited reason for the downgrade was "serious risk of bias" based on Chapter 6.2.3.2, yet that chapter only notes “some concerns for bias” for these analyses in Tbl 13. This does not justify a full downgrade, making the rationale invalid. The 2nd downgrade reason—“indirectness” due to use of an intermediate measure—is, in our view, incorrect, as the CT vs no CT comparison in the C-high/G-low group directly aligns with the report’s definition of clinical effectiveness: “Evidence that compares the difference in clinical benefits and harms of using multigene tests and conventional testing versus conventional testing to support the treatment decision on adjuvant CT...” This is a direct measure of clinical effectiveness, not an intermediate outcome—patients (pts) deemed high risk by conventional criteria were randomized to CT based on C-risk or no CT based on G-risk, clearly showing the impact of using MP versus standard assessment. We therefore suggest upgrading the evidence to high certainty per GRADE criteria.	“Some concerns for bias” suggest potential issues in a specific domain that could affect the reliability of the results. In GRADE, this can lead to a downgrade by one level in the certainty of evidence. This is applied consistently for all studies. In this report, the results from the MINDACT trial are presented both in the overview of evidence on comparative clinical effectiveness (the main outcome of interest), and on predictive ability/ chemotherapy benefit. For comparative clinical effectiveness, the comparison of interest was multigene-expression tests added to conventional testing (with or without clinical prediction tools) versus conventional testing (with or without clinical prediction tools). The comparative clinical effectiveness data from MINDACT which compares the clinical outcomes from treatment based on clinical risk versus treatment based on genomic risk is not downgraded for indirectness. However, in the C-high/G-low group chemotherapy is compared to no chemotherapy, resulting in an estimate of chemotherapy benefit. This is not a direct comparison between treatment outcomes based on genomic risk and clinical risk, and therefore downgraded for indirectness. Results on intermediate measures (i.e. predictive ability/chemotherapy benefit and prognostic ability, which lack the comparison between the multigene-expression test and conventional testing, and impact on treatment management, which lacks follow-up of clinical outcomes) were consistently downgraded for indirectness.

		No changes to the report have been made based on this comment.
1	4. Tbl 30 presents CT use by G-Risk, using RASTER for adherence inputs. However, RASTER, as an early feasibility study, is less suitable for modeling. More recent studies like Kuijer et al. 2017, reflecting real-world use of MP, report 97% and 95% adherence for MP high- and low-risk, respectively. We recommend updating Tbl 30 and the model with these more relevant probabilities.	The RASTER study is the only published data that directly presents treatment decisions in each of the combined Adjuvant!Online – MammaPrint risk categories. Thereby, this source is able to directly inform the model input parameters. It is acknowledged that the data is relatively old and familiarity with the technology might have changed clinical decision making. The paper by Kuijer et al. is not suitable to inform input parameters, as it does not provide a pre-multigene expression test treatment decision for all tested patients (by including an 'uncertain' group without indicating the treatment recommendation for this group in the absence of multigene expression tests). Therefore, it is not possible to specify the adjuvant chemotherapy rate in each clinical risk group. The more recent treatment management impact study by Wuerstlein et al. (DOI: 10.1007/s10549-018-05075-x) does provide enough data to inform input parameters. However, to use this data to inform the model, the assumption has to be made that the recurrence risk in the four subgroups defined by the pre- and post-test treatment decisions are the same as those in the four clinical-genetic risk groups defined by combining Adjuvant!Online and MammaPrint. Given the difference between the MINDACT trial and the Wuerstlein paper in how the total populations are distributed over these four categories, it could be argued that this assumption does not hold. For these reasons the data from the RASTER study are considered the best available data to inform the adjuvant chemotherapy rate in each clinical-genetic risk group. However, to explore the potential impact of the treatment decision data presented in the more recent Wuerstlein paper, an additional scenario was defined based on this data (Scenario 8, described on page).
1	5. Tbl 31+32 presents the 8-yr DMFI for AOL-high G-Low pts, including TNBC and HER2+ cases, based on Tbl S5 from Piccart 2021 showing a 2.4% absolute CT benefit in the C-high/G-low group. Tbls S9 and S12 show smaller differences for HR+HER2- pts—2.2% (N0) and 1.4% (N1)—when TNBC & HER2+ are excluded. As the combined HR+HER2- N0/N1 data aren't published, but necessary for the model, this data has been prepared by the EORTC statistician for this HTA. The 8-yr DMFI probability without ET is 90.9%, and with CT + ET it is 92.6%. Official report is added as an appendix to Agendia comments. We request the 8-yr DMFI probability in Tbl 31 and the model for AOL High – MP low to be changed to 0.909 and in Tbl 32 for AOL High – MP Low to 0.926.	The preparation of this data is appreciated. However, only published data can be used in the HTA report. Therefore, the inputs based on published data are maintained.
1	6. Scenario 6 in the model is flawed: it overestimates the value of clinical factors, which lack the rigorous validation of genomic assays like MP. It adjusts CT use by clinical criteria within G-Risk groups but ignores how G-Risk is distributed across these subgroups. This leads to underestimating CT de-escalation potential, especially in pts with C-high/G-low tumors.	Many more clinical factors are incorporated in clinical practice than they are used in the model to specify clinical risk stratification. Therefore, it is to be expected that conventional testing has better prognostic abilities than the comparator in the model. Because the prognostic ability of conventional testing is not known (as it lacks the rigorous validation of genomic assays), it cannot be determined whether this leads to an underestimation of CT de-escalation potential. However, as it is deemed plausible that the base case overestimates CT de-escalation (by

		underestimating prognostic ability of conventional testing), exploring this effect in a scenario analysis is warranted (see HTA report scenario analysis 6). No changes to the report have been made based on this comment.
2	Europa Donna Schweiz ist Teil eines europaweiten Netzwerks, das sich für die Rechte, die Versorgung und die Stimme von Brustkrebspatientinnen einsetzt. Wir begrüßen ausdrücklich die Evaluation der vier multigene-expression Tests (Oncotype DX, MammaPrint, EndoPredict, Prosigna) durch das Bundesamt für Gesundheit im Rahmen des Health Technology Assessments (HTA). Im Sinne einer betroffenenorientierten Versorgung möchten wir zu den Ergebnissen Stellung nehmen. • Personalisierung der Therapie ist ein Fortschritt – auch bei Unsicherheiten Die Möglichkeit, durch multigene-expression Tests die Indikation für eine adjuvante Chemotherapie differenzierter zu beurteilen, stellt einen bedeutenden Fortschritt dar. Der mögliche Verzicht auf eine Chemotherapie stellt für viele Betroffene eine enormen- nicht nur psychologischen Gewinn- dar. Auch wenn der HTA-Bericht die klinische Evidenz insbesondere für drei der vier Tests als begrenzt einstuft, erkennen wir das Potenzial für eine individualisierte Behandlungsentscheidung an. Translation: Europa Donna Switzerland is part of a Europe-wide network that advocates for the rights, care, and voice of breast cancer patients. We expressly welcome the evaluation of the four multigene-expression tests (Oncotype DX, MammaPrint, EndoPredict, Prosigna) by the Federal Office of Public Health as part of the Health Technology Assessment (HTA). In the interest of patient-centered care, we would like to comment on the results. • Personalization of therapy is a step forward – even in cases of uncertainty. The possibility to more accurately assess the indication for adjuvant chemotherapy through multigene-expression tests represents significant progress. The potential avoidance of chemotherapy constitutes an enormous benefit – not just psychological – for many affected individuals. Even though the HTA report considers the clinical evidence for three of the four tests as limited, we acknowledge the potential for individualized treatment decisions.	This comment has been noted. No changes to the report have been made based on this comment.
2	• Der Zugang zu Tests darf nicht eingeschränkt werden Wir sind besorgt, dass die eingeschränkte Evidenzlage und hieraus fehlende Kostenübernahme zu einer Einschränkung der Testverfügbarkeit führen könnte. Dies würde gerade jene Patientinnen treffen, für die konventionelle Testverfahren keine klare Therapieentscheidung ermöglichen. Wir fordern daher, dass die Tests weiterhin unter den bestehenden Voraussetzungen im Rahmen der Pflichtversicherung verfügbar bleiben – insbesondere für die definierte „unklare“ Zielpopulation (ER+, HER2-, LN0–3), für die die Entscheidung über eine Chemotherapie besonders herausfordernd ist. Translation: • Access to the tests must not be restricted. We are concerned that the limited evidence base and the resulting lack of cost coverage could lead to a reduction in test availability. This would particularly affect those patients for whom conventional testing methods do not provide a clear treatment decision. We therefore demand that the tests continue to be available under the existing conditions within the framework of mandatory health insurance	This comment has been noted. No changes to the report have been made based on this comment.

	– especially for the defined "uncertain" target population (ER+, HER2-, LN0–3), for whom the decision regarding chemotherapy is particularly challenging.	
2	• Information und Einbindung der Patientin stärken die Entscheidung für oder gegen eine Chemotherapie und ist eine hochkomplexe, persönliche Abwägung, die im shared decision making gemeinsam mit dem Behandlungsteam (PatientIn, Senologe, Onkologie, interdisziplinäres Tumorboard) getroffen wird. Multigene-expression Tests können hierbei als Entscheidungsgrundlage in kritischen Fällen dienen. Es braucht transparente, verständliche Informationen über den Nutzen, die Limitationen und die Unsicherheiten der Tests. Die Perspektive und Präferenz der Patientin muss ein zentraler Bestandteil dieses Entscheidungsprozesses sein. Translation: • Strengthening information and patient involvement. The decision for or against chemotherapy is a highly complex, personal consideration that is made together with the treatment team (patient, breast specialist, oncology, interdisciplinary tumor board) as part of shared decision making. Multigene-expression tests can serve as a basis for decision-making in critical cases. There is a need for transparent, understandable information about the benefits, limitations, and uncertainties of the tests. The perspective and preferences of the patient must be a central part of this decision-making process.	This comment has been noted. Shared decision making and patient involvement are discussed in Chapters 8.2.6 and 8.2.7. No changes to the report have been made based on this comment.
2	• Chancengleichheit sicherstellen Der HTA-Bericht weist auf soziale und organisatorische Hürden beim Zugang zu den Tests hin. Europa Donna Schweiz fordert daher: o die konsequente Sicherstellung des Zugangs unabhängig von Einkommen, Wohnort oder Bildungsgrad, o die Einbindung von verordnenden GynäkologInnen und OnkologInnen in Schulungen zu den Tests, o und die stärkere Berücksichtigung von Diversität (z. B. Alter, Geschlecht, Migrationshintergrund) in zukünftiger Forschung und Anwendung. o Forschung weiterführen – Betroffene einbeziehen Translation: • Ensuring equal opportunities. The HTA report highlights social and organizational barriers to accessing the tests. Europa Donna Switzerland therefore demands: o the consistent assurance of access regardless of income, place of residence, or level of education, o the involvement of prescribing gynecologists and oncologists in training on the tests, o and greater consideration of diversity (e.g., age, gender, migration background) in future research and application. o Continue research – involve those affected	This comment has been noted. In Chapters 8.2.4 through 8.2.7 issues of diversity and minority representation, age of the patient, and clinicians' influence are discussed. No changes to the report have been made based on this comment.
2	Wir unterstützen die Weiterentwicklung der Evidenzlage durch klinische Studien ausdrücklich. Künftige Forschung muss jedoch: • Patientinnenperspektiven gezielt erfassen (z. B. zu Lebensqualität, psychischer Belastung, Entscheidungskonflikten), • die Zielpopulation wie im Schweizer Versorgungskontext definieren (die „unklare" Gruppe), • und Patientinnenorganisationen systematisch in die Studiengestaltung und Bewertung einbeziehen.	This comment has been noted. No changes to the report have been made based on this comment.

	Fazit Multigene-expression Tests bieten Chancen – aber sie bedürfen einer verantwortungsvollen, evidenzbasierten und patientinnenzentrierten Anwendung. Eine Einschränkung des Zugangs oder eine Rücknahme der Kostenübernahme wäre aus Sicht von Europa Donna Schweiz nicht gerechtfertigt. Die Testverfahren sollen weiterhin im Leistungskatalog bleiben, begleitet durch Aufklärung, Forschung und eine Stärkung der Entscheidungskompetenz der betroffenen Frauen. Translation: We expressly support the further development of the evidence base through clinical studies. However, future research must: • specifically capture patients' perspectives (e.g., on quality of life, psychological stress, decision conflicts), • define the target population as in the Swiss healthcare context (the "uncertain" group), • and systematically involve patient organizations in study design and evaluation. Conclusion Multigene-expression tests offer opportunities – but they require responsible, evidence-based, and patient-centered application. Restricting access or withdrawing cost coverage would not be justified from the perspective of Europa Donna Switzerland. The test procedures should remain included in the benefit catalog, accompanied by education, research, and strengthening the decision-making competence of affected women.	
3	Multigene-expression tests (MGT) in early breast cancer can have two purposes: inform on clinical outcome (prognosis) or the response to a specific treatment (prediction). In clinical practice, and in line with the Swiss reimbursement text, MGT are applied when "conventional tests" of clinical-pathological features have been exhausted and do not allow a clear decision regarding chemotherapy. To guide the treatment decision in such ("unclear") cases, it is imperative that the received MGT result is valid and reliable – emphasizing the importance to define the prognostic and predictive capability of each test. Unfortunately, the current report fails to provide new insights or a reliable assessment. This is mainly due to the comparison of MGT against "conventional testing" issued in PICO 1, contradicting medical reality as MGT are used in an unclear setting of conventional parameters. Not surprisingly, only "sparse" evidence is then identified for PICO 1, leading to invalid conclusions.	A preliminary review of published HTAs indicated that evidence is lacking on the population as defined in the policy question of this HTA, i.e. the population for whom it is unclear based on conventional testing whether to prescribe adjuvant chemotherapy. Therefore, the population in the PICOs was broadened to additionally include early breast cancer patients whose diagnosis most closely matched the intended study population. Except for a small number of studies on the impact of multigene-expression tests on treatment management, none of the studies included the population for whom it was unclear based on conventional testing whether to prescribe adjuvant chemotherapy. No changes to the report have been made based on this comment.
3	The methodology is also not compelling, as the comparator Adjuvant!Online misses relevant factors (like Ki67) and the tool been discontinued for years.	The comparator of interest for this HTA was conventional testing with or without clinical prediction tools. Adjuvant!Online was mentioned as an example of such a tool. Since the highest level of evidence for MammaPrint (the MINDACT trial) compares the multigene-expression test to clinical decision-making based on Adjuvant!Online, the latter was chosen as the comparator for MammaPrint. To clarify that Adjuvant!Online is just mentioned as an example of a clinical prediction tool (rather than a specific comparator), the PICO section has been revised. The examples of clinical prediction tools are now mentioned in a footnote rather than in the main text.
3	This issue is also reflected in the economic review ("[…] insufficient [for] a robust […] analysis of [MGT]. In particular, data on […] conventional testing is lacking"). Still, an undifferentiated speculative conclusion is drawn at the end ("most likely will […] increase […] costs"), inconsistent from a scientific point.	The conclusions of the economic evaluation in Chapter 11 as well as the executive summary and summary statements at the beginning of Chapter 7 have been revised to clarify the distinction between the conclusions of the analysis as conducted, and its value to answer the research and policy questions.

3	Additionally, some generic assumptions and simplifications used within the base case of the model lead to bias. E.g. it is clearly proven that patients with a high Oncotype RS receive a much larger benefit than assumed in the current prognostic scenario. As a result, outcomes and economic benefits (at least for Oncotype) in base case are substantially underestimated.	The clinical review concluded that there is limited evidence on the predictive ability of Oncotype. Based on this conclusion predictive effects were not included in the base case, but explored in a scenario analysis. No changes to the report have been made based on this comment.
3	In addition, central references used for model input (e.g. Harnan, TransATAC) are outdated and do not consider new essential data (e.g. refined thresholds for Oncotype).	Newer evidence or evidence more relevant to the Swiss setting that was identified in the literature reviews was incorporated. However, such data could not be incorporated if it did not match with the model structure or definition of input parameters. For example, not all required data based on newer Oncotype thresholds was available for the entire modelled population. For that reason, a scenario was included where the best available data using revised Oncotype thresholds was used in the subgroup for which such data is available. No changes to the report have been made based on this comment.
3	Overall, the report applies a rigorous methodology to evaluate and rate the available evidence but does not answer the key question. The current comparison with “conventional tests” in PICO 1 is not suitable to evaluate, if it is reasonable from an evidence and cost effectiveness perspective to use MGT in “unclear” cases.	The comparison addressed in PICO1 is conventional testing with multigene-expression test versus conventional testing only, and not multigene-expression tests versus conventional testing. In the Swiss clinical practice, multigene-expression tests are used when the decision, whether to prescribe adjuvant chemotherapy, is unclear based on conventional testing, as confirmed by the panel of Swiss clinical experts at the start of the project (see HTA Protocol Appendix A). Furthermore, PICO1 includes the “unclear setting” but is not restricted to it. The fact that multigene-expressions tests are used in a setting where conventional testing does not provide sufficient information for clear clinical decision making indicates that conventional testing is the appropriate comparator in the Swiss setting. No changes to the report have been made based on this comment.
3	In addition, a critical analysis of diverging results within the report is sometimes absent, leading to unbalanced conclusions. We suggest a revision of the report to evaluate the prognostic and predictive capability of each MGT to reflect their clinical use after inconclusive conventional testing. This would allow for an evidence-based differentiation of MGT, as illustrated by other HTA procedures and guideline recommendations. Only Oncotype and MammaPrint are supported by RCT clinical utility data leading to higher evidence levels (AGO, ASCO) and sometimes exclusive reimbursement of these two tests (e.g. in BE and NL). Oncotype is the only strongly recommended and “preferred” test (ASCO, NCCN) and the only MGT with a proven additional benefit for patients (IQWIG), demonstrating its prognostic and predictive value. Cost effectiveness analyses in different countries regularly show an advantage for (some) MGT. E.g., NICE concludes that “EndoPredict, Oncotype DX and Prosigna are likely cost effective”. This is contrary to the base case result of the “Swiss Model”, but in line with the scenario analyses #8 and #9 where Oncotype dominates, when test-specific high-quality data from the practice-changing RCTs RxPONDER and TAILORx and its proven predictive ability are considered. Modelling suggests that Oncotype can spare 594 out of 1,000 tested patients from chemotherapy (NICE), reducing overtreatment and potential side effects while providing a quantifiable measure for the individual expected benefit. We suggest a re-evaluation to differentiate the	The review of the clinical evidence aimed to present the prognostic and predictive capability of each multigene expression test in their clinical application after inconclusive conventional testing, and due to an absence of evidence also in a broader population. In choosing evidence to inform the input parameters of the economic model a trade-off occurs between assessing each test using the best available evidence for that test, and using a consistent methodology for all tests using data sources providing data for multiple tests. No changes to the report have been made based on this comment.

	evidence base and benefit for each MGT, considering their clinical application in Switzerland.	
4	Folgende Ergänzungen zum EndoPredict-Test (EP) führen wir an: Für die Validierung von Biomarkern können gut konzipierte prospektive Studien, die den natürlichen Krankheitsverlauf unter realistischen Bedingungen abbilden, eine wertvolle Alternative darstellen (Simon et al., 2009; Ziegler et al. 2012). Prospektive Studien führen in der Regel zu weniger Verzerrungen als retrospektive Studien, die anfällig für Selektionseffekte und schlechte Reproduzierbarkeit sind. Prospektive, nicht-randomisierte Studien sind insbesondere bei der Evaluierung prognostischer Biomarker ausreichend, da sie den Krankheitsverlauf unbeeinflusst von therapeutischen Interventionen abbilden und belastbare Ergebnisse liefern, ohne die ethischen und finanziellen Herausforderungen retrospektiver Studien (Ziegler et al. 2012; Simon et al., 2009). Translation: We provide the following additions regarding the EndoPredict test (EP): For the validation of biomarkers, well-designed prospective studies that reflect the natural course of the disease under realistic conditions can be a valuable alternative (Simon et al., 2009; Ziegler et al. 2012). Prospective studies generally result in less bias than retrospective studies, which are susceptible to selection effects and poor reproducibility. Prospective, non-randomized studies are particularly sufficient for evaluating prognostic biomarkers, as they depict the course of the disease unaffected by therapeutic interventions and provide robust results without the ethical and financial challenges of retrospective studies (Ziegler et al. 2012; Simon et al., 2009).	To answer the policy- and research questions of this HTA, comparative data is needed. This can be obtained either from studies that randomise between treatment based on a multigene-expression test and treatment based on conventional testing, or comparative non-randomized studies. In the latter, comparative data included results reported for the concordant and discordant combinations of the risk categories of multigene-expression tests and conventional testing, i.e. low clinical risk–low genomic risk, low clinical risk–high genomic risk, high clinical risk–low genomic risk, and high clinical risk–high genomic risk. Due to a lack of comparative data, the studies by Ziegler et al 2012 and Simon et al 2009 were out of scope for inclusion. A more elaborate discussion of the required evidence to answer the policy question and optimal study designs to gather this data was included in Chapter 10. No changes to the report have been made based on this comment.
4	Real-World-Evidenz untermauert den Wert des EndoPredict-Tests zur präzisen Risikoabschätzung bei Patientinnen mit 1 bis 3 positiven Lymphknoten. Ergebnisse wurden durch weitere Register-Studien an deutschen Kliniken wie der TUM und der Charité bestätigt – die finale Publikation der Charité Studie ist jedoch noch ausstehend. In diesen Studien liefert EndoPredict exzellente prognostische Ergebnisse und zeigt, dass Patientinnen mit einem niedrigen genomischen Risiko gemäß EndoPredict tatsächlich ein geringes Rezidivrisiko hatten - unabhängig davon, ob sie Lymphknotenmetastasen aufwiesen oder nicht. Gleichzeitig hatten Patientinnen mit einem hohen genomischen Risiko gemäß EndoPredict ein signifikant höheres Risiko für Fernmetastasen als Patientinnen mit einem niedrigen Risiko (Klein, 2024). Translation: Real-world evidence supports the value of the EndoPredict test for precise risk assessment in patients with 1 to 3 positive lymph nodes. Results have been confirmed by further registry studies at German clinics such as TUM and Charité – however, the final publication of the Charité study is still pending. In these studies, EndoPredict delivers excellent prognostic results and shows that patients with a low genomic risk according to EndoPredict actually had a low risk of recurrence – regardless of whether they had lymph node metastases or not. At the same time, patients with a high genomic risk according to EndoPredict had a significantly higher risk of distant metastases than those with a low risk (Klein, 2024).	The study by Klein et al 2024 was newly screened based on the selection criteria but was deemed not eligible, because it did not report comparative data. However, for the purposes of this HTA report, the primary interest was on comparative data about prognostic ability and other outcomes. Only studies comparing conventional testing combined with multigene-expression test versus conventional testing alone or studies comparing chemotherapy with no chemotherapy in different risk groups defined by the multigene-expression tests were included. No changes to the report have been made based on this comment.
4	Die randomisiert kontrollierte UNIRAD-Studie (Penault-Llorca, 2024) zeigt, dass der EPclin-Score auch bei Patientinnen mit lymphknotenpositivem (LK+) Brustkrebs eine entscheidende Rolle bei der Risikostratifizierung spielt. Obwohl LK-positive Patientinnen generell ein erhöhtes Rückfallrisiko haben, kann der EPclin-Score präzise zwischen Patientinnen mit einem niedrigen und einem hohen molekularen Risiko unterscheiden.	The primary interest for prognostic ability was comparative data. Only studies comparing conventional testing combined with multigene-expression test versus conventional testing alone or studies comparing chemotherapy with no chemotherapy in different risk groups defined by the multigene-expression tests were included. Comparative data included results

	In der Studie zeigten LK-positive Patientinnen mit einem niedrigen EPclin-Risiko eine ausgezeichnete Prognose, sodass eine Chemotherapie auf Basis der EndoPredict- Validierungsdaten hätte vermieden werden können. Im Gegensatz dazu zeigen LK-positive Patientinnen mit hohem EPclin-Risiko ein erhöhtes Rezidivrisiko, was eine intensivere Nachsorge oder ergänzende Therapieansätze rechtfertigt. Zusätzlich zeigt die Studie, dass das molekulare Risiko, gemessen durch den EPclin-Score, auch nach Abschluss einer Chemotherapie von hoher klinischer Relevanz bleibt. Patientinnen mit einem niedrigen EPclin-Risiko weisen eine 100-prozentige 5-Jahres-fernmetastasenfreie Überlebensrate (DMFS) auf, während Patientinnen mit einem hohen EPclin-Risiko nur eine 93-prozentige 5-Jahres-DMFS erreichen. Diese Daten verdeutlichen, dass auch nach einer erfolgreichen Chemotherapie ein Restrisiko für ein Rezidiv bei Patientinnen mit hohem molekularem Risiko besteht. Das molekulare Risikoprofil sollte daher im Follow-up-Management berücksichtigt werden, um potenzielle Spätrezidive frühzeitig zu erkennen und gegebenenfalls durch gezielte Therapiestrategien zu adressieren. Translation: The randomized controlled UNIRAD study (Penault-Llorca, 2024) shows that the EPclin score also plays a crucial role in risk stratification for patients with lymph node-positive (LN+) breast cancer. Although LN-positive patients generally have an increased risk of recurrence, the EPclin score can accurately distinguish between patients with low and high molecular risk. In the study, LN-positive patients with a low EPclin risk showed an excellent prognosis, so that chemotherapy could have been avoided based on EndoPredict validation data. In contrast, LN-positive patients with a high EPclin risk showed an increased risk of recurrence, justifying more intensive follow-up or additional therapeutic approaches. Additionally, the study shows that the molecular risk, measured by the EPclin score, remains of high clinical relevance even after completion of chemotherapy. Patients with a low EPclin risk have a 100% 5-year distant metastasis-free survival rate (DMFS), while patients with a high EPclin risk achieve only a 93% 5-year DMFS. These data illustrate that even after successful chemotherapy, a residual risk of recurrence remains for patients with high molecular risk. The molecular risk profile should therefore be taken into account in follow-up management in order to recognize potential late recurrences early and, if necessary, address them with targeted therapeutic strategies.	reported for the concordant and discordant combinations of the risk categories of multigene-expression tests and conventional testing, i.e. low clinical risk–low genomic risk, low clinical risk–high genomic risk, high clinical risk–low genomic risk, and high clinical risk–high genomic risk. The UNIRAD study did not report comparative data. No changes to the report have been made based on this comment.
4	Internationale Leitlinien beschränken sich nicht ausschließlich auf die Evidenz aus randomisierten kontrollierten Studien, sondern erkennen diese zusätzliche Evidenz an und empfehlen den Einsatz von Genexpressionstests wie Oncotype DX, MammaPrint und EndoPredict, um die Entscheidung über eine adjuvante endokrine Therapie und Chemotherapie bei Patientinnen mit ER-positivem, HER2-negativem Brustkrebs zu unterstützen – unabhängig davon, ob keine Lymphknotenbeteiligung vorliegt oder bis zu drei Lymphknoten betroffen sind. AGO LL: LoE 2B für EndoPredict ESMO guidelines: Level of evidence 1A (LoE1A) The ESMO guidelines for early breast cancer recognize genomic tests such as EndoPredict at level 1A*. * Loibl et al. Annals of Oncology, 2024 (v. supplement, table S5) Translation: International guidelines are not limited exclusively to evidence from randomized controlled trials, but also recognize this additional evidence and recommend the use of gene expression	Indeed, for this reason prospective RCTs, retrospective/re-analyses of RCTs and comparative non-randomised studies were included in the HTA. No changes to the report have been made based on this comment.

	tests such as Oncotype DX, MammaPrint, and EndoPredict to support the decision on adjuvant endocrine therapy and chemotherapy in patients with ER-positive, HER2-negative breast cancer – regardless of whether there is no lymph node involvement or up to three lymph nodes are affected. AGO LL: LoE 2B für EndoPredict ESMO guidelines: Level of evidence 1A (LoE1A) The ESMO guidelines for early breast cancer recognize genomic tests such as EndoPredict at level 1A*. * Loibl et al. Annals of Oncology, 2024 (v. supplement, table S5)	
5	Die Ausführungen im HTA-Bericht zeigen deutlich, dass kaum Evidenz zur Wirksamkeit und Zweckmässigkeit von Multi-Gene-Expression Tests im Vergleich zusätzlich zur konventionellen Diagnostik besteht. Gleichzeitig wird ausführlich aufgezeigt, dass die Anwendung der vier Tests (Oncotype DX, MammaPrint, EndoPredict, Prosigna) nach erfolgter adjuvanter Therapie gemäss aktuellem Stand der Evidenz nicht nachweislich zu einer Erhöhung der Lebenserwartung bei Patientinnen mit frühem ER+/HER2− Brustkrebs führt. Diese Erkenntnisse spiegeln sich auch in den verschiedenen erwähnten HTA-Berichten sowie in den Leitlinien wider, welche uneinheitliche Empfehlungen abgeben – insbesondere in Bezug auf die definierte Patientengruppe (z.B. Abgrenzung nach Lymphknotenbefall) sowie auf die Auswahl des einzusetzenden Tests (einige Tests werden nicht empfohlen). Die Beurteilung der Wirtschaftlichkeit der vier Tests im HTA-Bericht ist methodisch korrekt und adressiert alle notwendigen Aspekte. Die Bewertung der Wirtschaftlichkeit der vier untersuchten Multigenexpressionstests ergibt ein insgesamt kritisches Bild. Die Evidenzlage erweist sich als schwach und widersprüchlich. Zahlreiche Studien kommen zu unterschiedlichen und teils gegensätzlichen Ergebnissen hinsichtlich der Kosten-Nutzen-Beurteilung. Zudem zeigt sich, dass durch den Einsatz dieser Tests tendenziell zusätzliche Gesundheitskosten entstehen, ohne dass ein gesicherter gesundheitlicher Nutzen belegt werden kann. Die Beurteilung der Wirtschaftlichkeit dieser Tests ist zudem stark abhängig von verschiedenen Faktoren, insbesondere vom individuellen Rückfallrisiko der Patientinnen, der Häufigkeit des Testeinsatzes und der jeweils gewählten Therapiestrategie. Zusammenfassend kann festgehalten werden, dass die aktuelle Vergütung der vier Tests durch die OKP (in Evaluation bis Ende 2025) kritisch hinterfragt werden darf. Es fehlt die klare Evidenz für die klinische Wirksamkeit in der gemäss KLV definierten Patientenpopulation sowie Indikation, - ein Punkt, der auch von den einbezogenen Expertinnen kritisch bewertet wurde. Darüber hinaus kann die Wirtschaftlichkeit der vier Tests nicht nachgewiesen werden. Seit 2011 werden Multi-Gene-Expressionstests gemäss KLV vergütet. Aus Sicht von prio.swiss lässt die heutige Datenlage rund 15 Jahre später den Schluss zu, dass diese Tests nicht länger durch die OKP vergütet werden sollten. Falls die Vergütung dennoch beibehalten wird, fordert prio.swiss, dass die Leistung weiterhin als in Evaluation befindlich gilt - mit der Auflage, die erforderlichen Daten zum Nachweis der Wirksamkeit, Zweckmässigkeit und Wirtschaftlichkeit (WZW) zu liefern. Zudem soll künftig nur noch der Test mit dem besten Kosten-Nutzen-Verhältnis eingesetzt werden (Oncotype DX), wie dies in einzelnen Leitlinien bereits ansatzweise berücksichtigt wird.	This comment has been noted. No changes to the report have been made based on this comment.

	Darüber hinaus ist die Patientenpopulation, die potenziell von diesen Tests profitieren kann, erneut im Detail zu evaluieren (z.B. LN-positiv, LN-negativ, Geschlecht etc.). Translation: The statements in the HTA report clearly show that there is little evidence regarding the effectiveness and appropriateness of multi-gene expression tests in comparison to conventional diagnostics. At the same time, it is extensively demonstrated that the use of the four tests (Oncotype DX, MammaPrint, EndoPredict, Prosigna) after adjuvant therapy—according to the current state of evidence—does not demonstrably increase life expectancy in patients with early ER+/HER2− breast cancer. These findings are also reflected in the various HTA reports and in the guidelines, which give inconsistent recommendations—especially with regard to the defined patient group (e.g., differentiation by lymph node involvement) and the choice of test to be used (some tests are not recommended). The assessment of the cost-effectiveness of the four tests in the HTA report is methodologically correct and addresses all necessary aspects. The evaluation of the cost-effectiveness of the four examined multi-gene expression tests presents an overall critical picture. The evidence is weak and contradictory. Numerous studies arrive at different and partly contradictory results regarding cost-benefit assessment. In addition, it appears that the use of these tests tends to generate additional healthcare costs without a proven health benefit. The assessment of the cost-effectiveness of these tests is also highly dependent on various factors, in particular the individual risk of recurrence of the patients, the frequency of test use, and the therapy strategy chosen in each case. In summary, it can be stated that the current reimbursement of the four tests by the OKP (under evaluation until the end of 2025) may be critically questioned. There is a lack of clear evidence for clinical effectiveness in the patient population and indication defined according to the KLV—a point that was also critically evaluated by the involved experts. In addition, the cost-effectiveness of the four tests cannot be proven. Since 2011, multi-gene expression tests have been reimbursed according to the KLV. From the perspective of prio.swiss, the current data situation about 15 years later leads to the conclusion that these tests should no longer be reimbursed by the OKP. If the reimbursement is nevertheless maintained, prio.swiss demands that the service continues to be considered as under evaluation—with the requirement to provide the necessary data to demonstrate effectiveness, appropriateness, and cost-effectiveness (WZW). In addition, in the future, only the test with the best cost-benefit ratio should be used (Oncotype DX), as is already partly considered in some guidelines. Furthermore, the patient population that can potentially benefit from these tests should be re-evaluated in detail (e.g., LN-positive, LN-negative, gender, etc.).	
6	We respectfully disagree with several conclusions presented in the report. Multigene-expression tests (METs) are essential for clinical practice! The report has some fundamental problems: 1. Misunderstanding of what the technology is supposed to do In section 3.1, "Technology Description", the report states: “In practice, METS are used to identify those patients for whom the survival and quality of life benefit from adjuvant chemotherapy.” This is not consistent with current knowledge nor clinical practice. These tests are used to identify patients unlikely to benefit from chemotherapy, thereby sparing them unnecessary	The description of the purpose of multigene-expression tests in Switzerland and their use in the prevention of unnecessary chemotherapy has been further clarified in Chapter 3.1. The discussion (Chapter 10) also elaborates on the findings of this HTA with respect to the value premise of multigene-expression tests in avoiding unnecessary chemotherapy.

	treatment. Conversely, a high-risk genomic result does not necessarily imply chemotherapy benefit. The tests are primarely used to avoid chemotherapy! A clear understanding of this distinction is essential for accurately evaluating clinical utility.	Based on the Swiss reimbursement text as well as the description of the clinical practice in Switzerland provided by the panel of Swiss clinical experts at the start of the project (see HTA Protocol Appendix A), the target patient population of the multigene-expression tests is defined as patients 'for whom the treatment decision is not clear based on conventional testing'. This can include both patients who would be and who would not be advised to use adjuvant chemotherapy in the absence of multigene-expression tests. As a result, the most appropriate description of the multigene-expression tests' use is assessing the benefit, or lack of benefit, of adjuvant chemotherapy for each patient, thereby supporting personalised treatment decisions.
6	2. Omission of Relevant Evidence Several key data sources were excluded from the report: o The WSG-ADAPT trial (Nitz UA, J Clin Oncol. 2022; 40: 2557) was dismissed as having an "out of scope comparator." However, its comparator was chosen using a sophisticated methodology similar to the primary endpoint in MINDACT with a non-inferiority design. This trial enables chemotherapy de-escalation, including premenopausal patients. With this approach 67% of 2116 patients with intermediate recurrence risk, who would otherwise have received chemotherapy, could safely forgo this treatment. A meaningful evaluation of METs is not possible without considering this publication.	The study by Nitz et al 2022 was based on the WSG-PlanB trial. The WSG-PlanB trial began as a chemotherapy trial comparing anthracycline-containing chemotherapy with anthracycline-free chemotherapy. During the trial this was amended, and endocrine therapy alone was recommended for pN0/pN1, locally HR+ patients with RS≤11. Patients with RS≥12, pN2-3, or HR-/HER2- disease were randomised to anthracycline-containing or free chemotherapy. This study design does not provide any evidence on the difference in clinical outcomes between patients treated based on a multigene-expression test versus conventional testing. It also does not provide evidence on the chemotherapy benefit in patients with a certain recurrence score. As a result, it does not provide any clinical evidence that can be used to determine the comparative clinical benefit of multigene-expression tests and was thus considered out of scope. No changes to the report have been made based on this comment.
6	o A secondary analysis of TAILORx (Sparano JA, N Engl J Med. 2019; 380: 2395) was excluded on the grounds that it was not a primary analysis. Yet this analysis is highly relevant because it integrates clinical and genomic risk, improving the identification of patients who may safely avoid chemotherapy.	Sparano et al 2019 integrated clinical risk and genomic risk, i.e. in patients with an intermediate genomic risk the risk of recurrence is compared for patients with low or high clinical risk. The opposite comparison is of interest: difference in recurrence risk between genomic risk groups within in a certain clinical risk group. No changes to the report have been made based on this comment.
6	o Although the Swiss SAKK 26/10 study (Pestalozzi BC, BMC Cancer 2017; 17: 265) was briefly mentioned in the report, its findings were not adequately considered even though it is the only study on this topic in Switzerland. It was able to show that about 40% of the patients who would have received chemotherapy based on clinical features, were spared chemotherapy after taking into account the Oncotype result. This provides important national context on how the use of METs affects treatment decisions in everyday practice.	The study characteristics of Pestalozzi et al 2017 are described in Table 6 and the results are shown in Forest plots 28-32. The study is used as input for the economic model, see Table 30 and Table 42. No changes to the report have been made based on this comment
6	3. Limitations in Economic Analysis The report attempts to assess financial impact using data from international settings. However, chemotherapy prescribing practices differ substantially across healthcare systems. As a result, cost-effectiveness and budget impact analyses must be context-specific to be meaningful for national decision-making. Despite acknowledging that " The evidence base is insufficient to conduct a robust cost-effectiveness analysis of the multigene-expression tests " (p. 188), the report comes to the conclusion that "The effect of	As it is correctly pointed out, chemotherapy prescribing practices and healthcare system structures differ substantially between countries, which may limit the applicability of our findings to the Swiss context. Swiss data was incorporated in the model wherever possible. In the discussion chapter, executive summary, and summary statements the need for Swiss-specific data to enable robust, context-specific

	adding multigene-expression tests to conventional testing on costs and health outcomes are very uncertain, though most likely will result in no change in health outcomes and an increase in healthcare costs" (p. viii). This statement is not backed by the data compiled in the report.	analyses to inform national decision-making is discussed and emphasised. The conclusions of the economic evaluation in Chapter 11 as well as the executive summary and summary statements at the beginning of Chapter 7 have been revised to clarify the distinction between the conclusions of the analysis as conducted, and its value to answer the research and policy questions. No changes to the report have been made based on this comment
6	Conclusion and Offer of Expertise 1. Both claims in the conclusion of the report, that the use METs will 1. most likely result in increase in healthcare costs and 2. most likely there will be no change in health outcomes are unsubstantiated! 2. The report with its huge emphasis on cost-utility misses the fundamental question: Do these tests help avoid unnecessary chemotherapy? The answer is clearly yes, supported by evidence such as MINDACT, WSG-ADAPT, SAKK 26/10 and our real-world experience in tumorboards. SAKK has experience in clinical research of METs. We would be pleased to make one of our experts available to the authors of the report to provide further insight into the clinical relevance of WSG-ADAPT, MINDACT, TAILORx and RxPONDER	1. The conclusions of the economic evaluation in Chapter 11 as well as the executive summary and summary statements at the beginning of Chapter 7 have been revised to clarify the distinction between the conclusions of the analysis as conducted, and its value to answer the research and policy questions. 2. besides the economic evaluation which takes the form of a cost-utility analysis, the report presents an extensive review of the clinical evidence base and discusses ethical, legal, social, and organisational aspects. Additionally, a cost-utility analysis is a suitable methodology to assess whether multigene-expression tests avoid unnecessary chemotherapy. Studies such as WSG-ADAPT, SAKK 26/10, TAILORx and RxPONDER do not provide comparative clinical effectiveness evidence, and can therefore not be used to conclude that using multigene-expression tests to inform the decision to use adjuvant chemotherapy leads to better health outcomes when compared to a decision without multigene-expression tests. No changes to the report have been made based on this comment.
7/10	We respectfully challenge several of the conclusions drawn in the report. Multigene expression tests (METs) are an indispensable part of clinical practice. The conclusions presented in the HTA report are unsubstantiated, primarily due to fundamental misunderstandings of the technology's application, the omission of relevant and impactful evidence, and the drawing of economic conclusions not supported by the data or appropriate context. Misunderstanding of Clinical Application: The report inaccurately states METs are used to identify those patients who benefit from chemotherapy. In fact, their primary role is to identify patients who can safely avoid chemotherapy—sparing them toxicity and burden. This critical nuance impacts the assessment of their utility.	The description of the purpose of multigene-expression tests in Switzerland and their use in the prevention of unnecessary chemotherapy has been further clarified in Chapter 3.1. The discussion (Chapter 10) also elaborates on the findings of this HTA with respect to the value premise of multigene-expression tests in avoiding unnecessary chemotherapy. Based on the Swiss reimbursement text as well as the description of the clinical practice in Switzerland provided by the panel of Swiss clinical experts at the start of the project (see HTA Protocol Appendix A), the target patient population of the multigene-expression tests is defined as patients 'for whom the treatment decision is not clear based on conventional testing'. This can include both patients who would be and who would not be advised to use adjuvant chemotherapy in the absence of multigene-expression tests. As a result, the most appropriate description of the multigene-expression tests' use is assessing the benefit, or lack of benefit, of adjuvant chemotherapy for each patient, thereby supporting personalised treatment decisions.
7/10	Flawed Comparison Leading to "Sparse Evidence": The HTA compares METs to "conventional testing," even though METs are used precisely when conventional methods are inconclusive. Furthermore, "Adjuvant!Online"—used as a comparator—is outdated and no longer available. The	See answer to previous comment regarding the conventional testing comparator. Since the highest level of evidence for MammaPrint (the MINDACT trial) compares the multigene-

	repeated description of RCTs - representing the best available multinational prospective evaluation of METs - as “low certainty” and “very low certainty evidence” is misleading and irritating for us as academic professionals, having contributed to the vast body of evidence. In contrast, “conventional testing” has neither been evaluated nor confirmed in comparable quality evidence – so as very often in HTAs (and also in clinical trials), the quality of the standard comparator is a major issue.	expression test to clinical decision-making based on Adjuvant!Online, the latter was chosen as the comparator for MammaPrint. It has to be taken into consideration that adding new prognostic factors such as Ki67 to conventional testing (e.g. Adjuvant!Online) improves its prognostic ability, thereby potentially reducing the added benefit of multigene-expression tests. It is agreed that conventional testing has not been included in the rigorous analysis of multigene-expression tests, as this would both provide evidence on the quality of conventional testing, as well as the comparative clinical effectiveness of multigene-expression tests. No changes to the report have been made based on this comment.
7/10	Omission of Relevant Studies: Several pivotal studies were overlooked or underweighted: 1) WSG-ADAPT (Nitz UA, J Clin Oncol. 2022): Demonstrated that 67% of 2,116 patients with intermediate recurrence risk could avoid chemotherapy—critical evidence to consider. 2) TAILORx secondary analysis (Sparano JA, NEJM 2019): Excluded due to being a secondary analysis, yet it significantly improved treatment decisions by integrating clinical and genomic data. 3) The Swiss SAKK 26/10 study (Pestalozzi BC, BMC Cancer 2017): Only briefly mentioned and not adequately considered: Ca. 40% of patients who would have received chemotherapy based on clinical features were spared chemotherapy after considering Oncotype DX results, providing an important Swiss context on how the use of METs affects treatment decisions in clinical practice.	1) The study by Nitz et al 2022 was based on the WSG-PlanB trial. The WSG-PlanB trial began as a chemotherapy trial comparing anthracycline-containing chemotherapy with anthracycline-free chemotherapy. During the trial this was amended, and endocrine therapy alone was recommended for pN0/pN1, locally HR+ patients with RS≤11. Patients with RS≥12, pN2-3, or HR-/HER2- disease were randomised to anthracycline-containing or free chemotherapy. This study design does not provide any evidence on the difference in clinical outcomes between patients treated based on a multigene-expression test versus conventional testing. It also does not provide evidence on the chemotherapy benefit in patients with a certain recurrence score. As a result, it does not provide any clinical evidence that can be used to determine the comparative clinical benefit of multigene-expression tests and was thus considered out of scope. 2) Sparano et al 2019 integrated clinical risk and genomic risk, i.e. in patients with an intermediate genomic risk the risk of recurrence is compared for patients with low or high clinical risk. The opposite comparison is of interest: difference in recurrence risk between genomic risk groups within patients in a clinical risk group. 3) The study characteristics of Pestalozzi et al 2017 are described in Table 6 and the results are shown in Forest plots 28-32. The study is used as input for the economic model, see Table 30 and Table 42. No changes to the report have been made based on this comment.
7/10	Unsubstantiated and Biased Economic Conclusions: Despite stating that the evidence is insufficient for robust cost-effectiveness analysis, the report paradoxically concludes that METs increase costs and do not impact outcomes. This contradicts both clinical experience and available data. In the cited studies, in a third of all patients, treatment recommendations were altered and in a quarter this meant omission of chemotherapy. Chemotherapy impact cannot only be measured in survival and drug cost figures, but causes a significant number of additional outpatient consultations, side effects with additional cost and often long-term complications for this relevant number of patients in our daily clinical routine. International assessments, such as NICE (UK), found METs to be cost-effective. „The EAG’s economic model predicted that using Oncotype DX® would result in 594 fewer women having	It is acknowledged that the evidence is limited and that multigene expression tests can significantly impact treatment decisions, including the omission of chemotherapy. The HTA report emphasizes the high uncertainty of economic conclusions and the need for Swiss-specific data to fully capture these broader clinical and economic effects. The conclusions of the economic evaluation have been revised to clarify the distinction between the conclusions of the analysis as conducted, and its value to answer the research and policy questions.

	chemotherapy per 1,000 tested, whereas with EndoPredict® or Prosigna® the reduction was around 40.“ and with that – most likely saving healthcare cost.	
7/10	Conclusions: 1) The HTA report’s conclusions about cost and lack of outcome benefit are not substantiated. 2) METs help prevent unnecessary chemotherapy, improving patient quality of life and reducing healthcare burden—clearly shown in trials and daily practice.. 3) The board of the multidisciplinary Swiss Society of Senology therefore clearly demands to keep the recommendation in place for reimbursement of METs for the previously specified population of breast cancer patients in Switzerland	These points have been addressed in previous responses. Your remarks have been noted. No changes to the report have been made based on this comment.
8	Adjuvant treatment decisions in early breast cancer rely on anatomical stage for prognosis and biological features for both prognosis and treatment prediction. Many patients fall into an intermediate-risk group. Historically, many received chemotherapy to prevent relapse, though a significant number were likely overtreated, without means to identify them. Multigene-expression tests (MET) enhance prognostic assessment and mainly identify patients unlikely to benefit from chemotherapy; those who can safely avoid it despite traditional features suggesting otherwise. This core role is insufficiently acknowledged in the HTA report, limiting its conclusions. Multiple studies, including a Swiss trial, show MET reduce chemotherapy use. MET are now routine in clinical practice, with decisions made case-by-case in multidisciplinary tumor boards.	The description of the purpose of multigene-expression tests in Switzerland and their use in the prevention of unnecessary chemotherapy has been further clarified in Chapter 3.1. The discussion (Chapter 10) also elaborates on the findings of this HTA with respect to the value premise of multigene-expression tests in avoiding unnecessary chemotherapy. Based on the Swiss reimbursement text as well as the description of the clinical practice in Switzerland provided by the panel of Swiss clinical experts at the start of the project (see HTA Protocol Appendix A), the target patient population of the multigene-expression tests is defined as patients ‘for whom the treatment decision is not clear based on conventional testing’. This can include both patients who would be and who would not be advised to use adjuvant chemotherapy in the absence of multigene-expression tests. As a result, the most appropriate description of the multigene-expression tests’ use is assessing the benefit, or lack of benefit, of adjuvant chemotherapy for each patient, thereby supporting personalised treatment decisions. Nonetheless, the methodology used for the clinical and economic literature reviews, as well as the economic evaluation, is fully capable to capture all evidence and represent all clinical and economic effects associated with the use of multigene-expression tests to reduce adjuvant chemotherapy use. The central question of this HTA is not whether multigene-expression tests lead to a reduction in adjuvant chemotherapy use, but whether that in turn leads to improved clinical and economic outcomes.
8	The report cites Adjuvant! Online, which has been unavailable for years and was based on historical population data. The MINDACT trial showed that personalized MET approaches are superior. MET are now standard of care and endorsed by major guidelines, including ESMO, NCCN, ASCO, and St. Gallen.	The comparator of interest for this HTA was conventional testing with or without clinical prediction tools, such as Adjuvant!Online. Since the highest level of evidence for MammaPrint (the MINDACT trial) compares the multigene-expression test to clinical decision-making based on Adjuvant!Online, the latter was chosen as the comparator for MammaPrint. Guideline recommendations are reported in Chapter 9.3. No changes to the report have been made based on this comment.

8	The report's cost-effectiveness analysis is based on a selective literature review and overlooks the clinical and societal impacts of chemotherapy. Beyond acute toxicities (fatigue, nausea, alopecia, neutropenia, etc.), chemotherapy can cause lasting effects, neuropathy, cognitive issues, chronic fatigue, cardiac dysfunction, menopause, and fertility loss. These reduce quality of life and lead to higher healthcare use and lost productivity. Many patients face major disruptions to work, family, and social life, costs not considered in the report. The report implies that avoiding chemotherapy offers no measurable benefit. Yet, with nearly 90,000 breast cancer survivors in Switzerland, each avoided toxicity improves long-term outcomes and reduces healthcare costs and societal burden.	A healthcare system perspective is required by FOPH in economic evaluations. Therefore, effects on productivity (losses) are out of scope of the analysis. Including short term adverse effects (acute toxicities) of adjuvant chemotherapy is acknowledged as an important factor in the treatment decision. However, as discussed in the report, data on the quality of life effects are missing. This makes it challenging to include these effects in a cost-utility analysis. Better data on the disutility resulting from chemotherapy use would be very helpful in assessing the clinical impact of multigene-expression tests. Our approach in incorporating both short- and long-term negative effects of chemotherapy is in line with other HTA reports. No changes to the report have been made based on this comment.
8	The report's mention of patient anxiety over MET is misleading. While awaiting results may cause temporary stress, it is far less than the psychological and physical burden of chemotherapy. MET reduce uncertainty in intermediate-risk cases, supporting clearer decisions and ultimately easing patient anxiety.	Chapter 8.2.6 describes findings on the relationship of emotional distress, multigene-expression testing, and subsequent treatment pathways. While the chapter notes that increased clarity is associated with lower levels of anxiety, research also indicates that patients who receive high recurrence risk results experience significantly higher levels of anxiety. No literature was identified that suggests that intermediate risk results lead to improved anxiety levels. Implemented change: the first sentence of the section on emotional distress in Chapter 8.2.6 was changed. The section mentioning a particular anxiety in patients having undergone multigene-expression testing was removed.
8	While MammaPrint is valuable, it has limitations. It did not identify premenopausal patients who can safely avoid chemotherapy, unlike Oncotype DX, which some guidelines (e.g., NCCN) rank higher. Both tests, validated in large randomized trials (MINDACT, TAILORx, RxPONDER), offer strong clinical utility and should remain reimbursed to support individualized care. These trials provide top-level evidence for de-escalation strategies. Building on this, an international study now explore MET use in higher-risk patients. Early data also suggest MET may help guide chemotherapy regimen selection. MET are increasingly used to identify high-risk patients eligible for additional adjuvant therapies, such as CDK4/6 inhibitors (e.g., ribociclib in the NATALEE trial). Trials like Cambria-2 also rely on genomic tests for selection. Excluding MET from practice could deny Swiss patients access to innovative and potentially life-saving treatments or trials. We respectfully disagree with the conclusions of the HTA report. It overlooks key aspects of real-world practice and the established clinical value of MET. Adjuvant therapy decisions require careful balance between under- and overtreatment, both carrying serious human and financial costs. Ending MET reimbursement would be a major step backward, reducing personalized care, increasing uncertainty, and leading to more unnecessary chemotherapy. These unnecessary chemotherapies lead to more costs, relevant long term side effects and thereby unnecessary burdon on the healthcare system. MET have strong evidence of utility and are endorsed by all major international guidelines. Continued reimbursement is essential to ensure high-quality care and protect Swiss patient outcomes.	This comment has been noted. Cost and long-term side effects of adjuvant chemotherapy have been incorporated in the cost-utility analysis in the HTA report. In this analysis, cost-savings due to a reduction in adjuvant chemotherapy use only outweighed the cost of testing in a few high-risk subpopulations. No changes to the report have been made based on this comment.
9	Es handelt sich um einen sehr ausführlichen und präzisen, auch sorgfältigen Bericht, der jedoch mehrere prinzipielle und fundamentale Mängel aufweist:	This comment has been noted. No changes to the report have been made based on this comment.

	1. Hauptproblem ist unserer Meinung nach, wie schon in unserem Stakeholder Report zum HTA Protocol befürchtet, dass die Kernfrage nicht beantwortet werden kann. Dies wird auch unmissverständlich in der Conclusion festgehalten (p vii/viii). Translation: This is a very detailed and precise, as well as careful report; however, it has several principal and fundamental shortcomings: 1. In our opinion, the main problem—as already feared in our stakeholder report on the HTA protocol—is that the core question cannot be answered. This is also clearly stated in the conclusion (p vii/viii).	
9	2. Es ist nicht ganz klar, inwiefern die ökonomischen Daten bzgl. ICER/QALY auf die Patientinnen der Schweiz 2025 anwendbar sind, oder ob man nicht hier aktuellere Quellen nutzen kann. Wirtschaftlichkeitsprüfungen, basierend auf effektiven Kosten in der Schweiz und nicht aus der Vergangenheit der EU (Lohn- und Lebenshaltungskosten in CH unterscheiden sich erheblich von EU), sollten für Entscheide, welche die Gesundheit der Schweizer Bevölkerung betreffen, herangezogen werden. Translation: 2. It is not entirely clear to what extent the economic data regarding ICER/QALY are applicable to patients in Switzerland in 2025, or whether more current sources could be used here. Cost-effectiveness analyses based on actual costs in Switzerland and not on past EU data (wage and living costs in CH differ significantly from those in the EU) should be used for decisions that affect the health of the Swiss population.	The report uses Swiss data, and the most recent data available where possible. However, as stated in the report, Swiss data is limited in particularly regarding epidemiological data. Swiss cost data was more widely available, making the input data for cost parameters relatively robust. No changes to the report have been made based on this comment.
9	3. p92: DIe effektiven Preise und Mengengerüste sollten vorhanden sein. Es wäre dann möglich, nicht nur Therapiekosten, sondern auch ICER und QALY zu diesen Kosten in Relation zu setzen. Es wäre dann auch klar, um wieviel Geld es überhaupt geht und wie häufig diese Tests überhaupt in CH gemacht werden. Translation: 3. p92: The actual prices and quantity frameworks should be available. It would then be possible not only to relate therapy costs but also ICER and QALY to these costs. It would also be clear how much money is actually involved and how often these tests are performed in Switzerland.	Costs of the multigene expression tests are presented in the report. The number of each test sold in Switzerland were not available for every test. Such data could indeed provide information relevant to the reimbursement decision. No changes to the report have been made based on this comment.
9	4. p80 unten: whs wurde Her2 Score und Her2 Status verwechselt Translation: 4. p80 bottom: probably HER2 score and HER2 status were confused.	Implemented change: Wording was corrected.
9	5. DIe Seitennummerierung muss whs überarbeitet werden. Translation: 5. The page numbering probably needs to be revised.	The page numbering has been reviewed and its has been determined that is as intended. No changes to the report have been made based on this comment.
9	Es sollten deshalb keine Entschlüsse basierend auf diesem Report gefasst werden, jedoch könnte, damit allenfalls mehr Klarheit geschaffen werden kann, der Report mit aktualisierten und vervollständigten Kostendaten rekalkuliert werden. Translation: Therefore, no decisions should be made based on this report. However, to potentially create more clarity, the report could be recalculated with updated and complete cost data.	This suggestion has been noted. No changes to the report have been made based on this comment.

9	Das Problem, dass eine in Bezug auf Prognose und Therapie-Outcome 'unklare' Patientengruppe in diesem Fall auch in Bezug auf prozentualen Anteil am Total der Patientinnen-Gruppe 'unklar' ist (und bleibt), bleibt allerdings bestehen. Die Indikation des Testes, wie vom BAG bewilligt, sowie die heutigen medizinischen Prozesse lassen den Onkologen eine gewisse Freiheit in der Nutzung dieser Tests. Abweichungen davon sollten wissenschaftlich basiert erfolgen, falls dies, wie figura zeigt, basierend auf retrospektiven Analysen nicht verlässlich möglich ist, müssten prospektive Studien in Auftrag gegeben werden. Dies erscheint aber komplett unrealistisch. Wir sind deshalb nicht überzeugt, dass mit den heute in der Schweiz zur Verfügung stehenden Mitteln und Informationen die zugrundeliegende Frage sicher objektiv geklärt werden kann. Translation: However, the problem remains that a patient group that is 'unclear' in terms of prognosis and therapy outcome is also 'unclear' (and remains so) regarding its percentage share of the total patient group. The indication for the test, as approved by the BAG, as well as current medical processes, allow oncologists a certain degree of freedom in using these tests. Deviations from this should be scientifically based; if this is not reliably possible based on retrospective analyses, as figures show, prospective studies would have to be commissioned. However, this seems completely unrealistic. We are therefore not convinced that, with the means and information currently available in Switzerland, the underlying question can be reliably and objectively clarified.	This comment has been noted. No changes to the report have been made based on this comment.
9	Erlauben Sie uns zuletzt eine andere Aussage: Es erscheint der SGPath etwas realitätsfremd, dass sich das BAG intensiv mit den Multigen-Tests Mamma auseinandersetzt, während gleichzeitig, auch vom BAG mitverantwortet, ein Tarifsystem in Kraft gesetzt wird, das ab 1.1.26 in Bezug auf Pathologie mehrheitlich negative Auswirkungen haben wird. Es ist heute (18.6.25) unklar, ob zukünftig diese Tests innerhalb von Pauschalen abgerechnet werden sollten. Innerhalb der Pauschalen, so wie das Tarifsystem am 18.06.2025 vom Bundesrat bewilligt und bekannt ist, wird es jedoch nicht möglich sein, diese Tests zu bezahlen. Man könnte deshalb etwas zynisch formulieren, dass sich dergestalt das Problem der Kosten der Multigen-Tests Mamma ab 1.1.26 sowieso gar nicht mehr stellt, man wird diese Tests, da nicht finanzierbar innerhalb der Pauschalen, gar nicht mehr durchführen (Vergütung Pauschale C09.50A Mamma-Biopsie: 1545 CHF, Pathologie-Anteil vorgesehen 46 CHF, Testkosten > 2000 CHF!!) Translation: Allow us one final comment: To SGPath, it seems somewhat detached from reality that the BAG is intensively engaging with multi-gene tests for breast cancer while, at the same time, a tariff system—also co-responsible by the BAG—is being implemented that will have predominantly negative consequences for pathology as of 1.1.26. As of today (18.6.25), it is unclear whether these tests should be billed within lump sums in the future. Within the lump sums, as the tariff system was approved and announced by the Federal Council on 18.06.2025, it will not be possible to pay for these tests. One could therefore somewhat cynically state that, in this way, the problem of the costs of multi-gene tests for breast cancer will no longer exist as of 1.1.26—since these tests, being unfinanceable within the lump sums, will simply no longer be performed (lump sum reimbursement C09.50A breast biopsy: 1545 CHF, pathology share planned 46 CHF, test costs > 2000 CHF!!).	This comment has been noted. The comment is beyond the scope of the current HTA assessment phase.
11	Allgemein: - Multigene-Expressionstests (MGT) bei Brustkrebs im Frühstadium dienen zwei zentralen Zwecken: Bereitstellung prognostischer Informationen zu klinischen Ergebnissen und	These comments have been noted. No changes to the report have been made based on this comment.

	prädiktiver Informationen zum Ansprechen auf bestimmte Behandlungen. - Gemäss den schweizerischen Erstattungsrichtlinien werden MGT dann eingesetzt, wenn konventionelle Tests der klinisch-pathologischen Merkmale ausgeschöpft sind und keine klare Entscheidung bezüglich der Chemotherapie getroffen werden kann. - In unklaren Fällen sind die Validität und Zuverlässigkeit der MGT-Ergebnisse von entscheidender Bedeutung, was die Notwendigkeit unterstreicht, die prognostischen und prädiktiven Fähigkeiten jedes Tests genau zu definieren. Translation: General -Multigene expression tests (MGT) for early-stage breast cancer serve two central purposes: providing prognostic information on clinical outcomes and predictive information on response to certain treatments. - According to Swiss reimbursement guidelines, MGT are used when conventional tests of clinical-pathological characteristics have been exhausted and no clear decision regarding chemotherapy can be made. - In unclear cases, the validity and reliability of MGT results are of crucial importance, which underlines the need to precisely define the prognostic and predictive capabilities of each test.	
11	Spezifische Kommentare zum HTA Bericht: - Für uns ist es unklar, warum Adjuvant!Online als Komparator ausgewählt wurde, da dieser Test relevante Faktoren wie Ki67 nicht einbezieht und seit Jahren nicht mehr in der Routine ist. Translation: Specific Comments on the HTA Report - For us, it is unclear why Adjuvant!Online was selected as a comparator, since this test does not include relevant factors such as Ki67 and has not been used routinely for years.	The comparator of interest for this HTA was conventional testing with or without clinical prediction tools. Adjuvant!Online was mentioned as an example of such a tool. Since the highest level of evidence for MammaPrint (the MINDACT trial) compares the multigene-expression test to clinical decision-making based on Adjuvant!Online, the latter was chosen as the comparator for MammaPrint. To clarify that Adjuvant!Online is just mentioned as an example of a clinical prediction tool (rather than a specific comparator), the PICO section has been revised. The examples of clinical prediction tools are now mentioned in a footnote rather than in the main text.
11	- Dieses Problem spiegelt sich auch in der Ökonomischen Analyse wider, der ausreichende Daten für eine robuste Analyse der MGT fehlen, jedoch spekulative Schlussfolgerungen über erhöhte Kosten ohne wissenschaftliche Konsistenz ableiten. - Vereinfachungen und generische Annahmen im Modell führen zu Verzerrungen, und die Ergebnisse und wirtschaftlichen Vorteile werden erheblich unterschätzt. - Die im Modell verwendeten Schlüsselreferenzen sind veraltet und berücksichtigen keine neuen wesentlichen Daten oder verfeinerten MGT-Schwellenwerte, die sich über die Jahre verändert haben. Translation: - This problem is also reflected in the economic analysis, which lacks sufficient data for a robust analysis of MGT, yet draws speculative conclusions about increased costs without scientific consistency. - Simplifications and generic assumptions in the model lead to distortions, and the results and economic benefits are significantly underestimated. - The key references used in the model are outdated and do not take into account new essential data or refined MGT thresholds that have changed over the years.	It is acknowledged that the evidence is limited and that multigene expression tests can significantly impact treatment decisions, including the omission of chemotherapy. The HTA report emphasizes the high uncertainty of economic conclusions and the need for Swiss-specific data to fully capture these broader clinical and economic effects. The conclusions of the economic evaluation in Chapter 11 as well as the executive summary and summary statements at the beginning of Chapter 7 have been revised to clarify the distinction between the conclusions of the analysis as conducted, and its value to answer the research and policy questions. In choosing evidence to inform the input parameters of the economic model a trade-off occurs between assessing each test using the best available evidence for that test and using a consistent methodology for all tests using data sources providing data for multiple tests. No changes to the report have been made based on this comment.
11	- Der aktuelle Bericht liefert leider keine neue Evidenz. Dies ist in erster Linie auf den fehlerhaften Vergleich von MGT mit konventionellen Tests in PICO 1 zurückzuführen, was der	The comparison addressed in PICO1 is conventional testing with multigene-expression test versus conventional testing only, and not multigene-expression

	medizinischen Realität widerspricht, da MGT für den Einsatz vorgesehen sind, wenn konventionelle Tests unklare Ergebnisse liefern. - Der Vergleich mit konventionellen Tests in PICO 1 adressiert nicht adäquat, ob die MGT in unklaren Fällen aus Evidenz- und Wirtschaftlichkeitssicht vertretbar ist. Translation: - Unfortunately, the current report does not provide new evidence. This is primarily due to the flawed comparison of MGT with conventional tests in PICO 1, which contradicts medical reality, since MGT are intended for use when conventional tests yield unclear results. - The comparison with conventional tests in PICO 1 does not adequately address whether MGT are justifiable from an evidence and cost-effectiveness perspective in unclear cases.	tests versus conventional testing. In the Swiss clinical practice, multigene-expression tests are used when the decision, whether to prescribe adjuvant chemotherapy, is unclear based on conventional testing, as confirmed by the panel of Swiss clinical experts at the start of the project (see HTA Protocol Appendix A). Furthermore, PICO1 includes the "unclear setting" but is not restricted to it. The fact that multigene-expressions tests are used in a setting where conventional testing does not provide sufficient information for clear clinical decision making indicates that conventional testing is the appropriate comparator in the Swiss setting. A preliminary review of published HTAs indicated that evidence is lacking on the population as defined in the policy question of this HTA, i.e. the population for whom it is unclear based on conventional testing whether to prescribe adjuvant chemotherapy. Therefore, the population in the PICOs was broadened to additionally include early breast cancer patients whose diagnosis most closely matched the intended study population. Except for a small number of studies on the impact of multigene-expression tests on treatment management, none of the studies included the population for whom it was unclear based on conventional testing whether to prescribe adjuvant chemotherapy. No changes to the report have been made based on this comment.
11	- Es wird eine Überarbeitung des Berichts vorgeschlagen, um die prognostischen und prädiktiven Fähigkeiten jedes MGT zu bewerten, wobei deren klinische Verwendung widergespiegelt und eine evidenzbasierte Differenzierung von MGT ermöglicht wird. Fazit: Wir möchten darauf hinweisen, dass für einige MGT RCT- oder sogar gesundheitsökonomische Daten verfügbar sind, die für eine solche Analyse beigezogen werden können. Wir empfehlen eine Neubewertung, um die Evidenzbasis und den Nutzen für jedes MGT unter Berücksichtigung seiner klinischen Anwendung in der Schweiz zu differenzieren. Translation: - A revision of the report is suggested in order to evaluate the prognostic and predictive capabilities of each MGT, reflecting their clinical use and enabling evidence-based differentiation of MGT. Conclusion We would like to point out that for some MGT, RCT or even health economic data are available that can be included in such an analysis. We recommend a re-evaluation to differentiate the evidence base and benefit for each MGT, taking into account its clinical application in Switzerland.	The main objective of the current analysis is to determine the impact of using multigene-expression tests on clinical and economic outcomes (as stated in the research question presented in Chapter 5.1). Clinical outcomes of interest are overall survival, breast cancer-specific survival, disease-free survival, recurrence risk/recurrence-free-survival, and health-related quality of life. The prognostic and predictive ability of the tests contribute to these outcomes, but are not the outcomes of interest by themselves. For this reason, referred to as intermediate measures in the report. The review of the clinical evidence aimed to present the prognostic and predictive ability of each multigene expression test. In choosing evidence to inform the input parameters of the economic model a trade-off occurs between assessing each test using the best available evidence for that test, and using a consistent methodology for all tests using data sources providing data for multiple tests. A full overview of the available RCT and economic data to be used in an assessment of the impact of using multigene-expression tests on clinical and economic outcomes is provided in the report. No changes to the report have been made based on this comment.
12	Pages vi, 3, 35, 72, 182, 208: At ESMO Breast, Prof. Stein announced that OPTIMA main RCT primary results (5-year follow-up) will be published mid-2026. Bartlett et al. 2016 and OPTIMA prelim (Stein et al 2025) show that more patients receive chemotherapy with Prosigna than with OncotypeDX (ODx). According to OPTIMA prelim Prosigna ROR was high in 22% of ODx low patients	This information which will be considered during the appraisal phase of the report. Implemented change: It is added to the respective pages where the completion date is reported that 5-year follow-up data of the OPTIMA trial is expected to be published mid-2026.

	(https://www.optimabreaststudy.com/optima/resources/admin/optima-prelim-esmo-breast2025-final.pdf) Path4Young (https://eupati.eu/path4young) generates RCT data for premenopausal patients. Regarding the soon to be published OPTIMA results, Veracyte suggest awaiting its availability before decision-making.	Path4Young is added to the ongoing trials description of the OPTIMA trial in Chapter 9.2.
12	Chapter 6.2.7: o The criterion "results not reported for combined risk categories" isn't defined in PICO1 and can't be applied to exclude studies.	This criterion is listed and defined in 'Table 5: Inclusion criteria for clinical studies' in Chapter 6.1.3 Study selection. No changes to the report have been made based on this comment.
12	Multiple studies demonstrate significant prognostic value: o Filipits et al. (2014) and Fitzal et al. (2021) o Gnant et al. (2014, 2015) o Lænkholm et al. (2018, 2020) o Nielsen et al. (2010): PAM50 shows superiority over clinical factors and IHC o Pu et al. (2020) show PAM50 prognostic value independent of menopausal status o Sestak et al. (2015): ROR score added clinically meaningful prognostic information to a Clinical Treatment Score in all patients and subgroups during late follow-up. o Wallden et al. (2015) confirm Prosigna ROR score's prognostic significance o Dowsett et al. (2013) demonstrated that the Prosigna ROR score provides more prognostic information compared to the ODx RS for HR+, lymph node negative breast cancer patients receiving endocrine therapy. o Ohnstad et al. (2024): In the EMIT-1 trial, adjuvant treatment decisions changed in 28% after Prosigna; 45% were de-escalated to endocrine therapy (ET), 12% of ET-only to chemotherapy (CT) + ET and 18% of non-adjuvant therapy to CT + ET	These studies were excluded during the full-text selection, because, for the purposes of this HTA report, the primary interest was on comparative data with regard to prognostic ability and other outcomes. Only studies comparing conventional testing combined with multigene-expression test versus conventional testing alone or studies comparing chemotherapy with no chemotherapy in different risk groups defined by the multigene-expression tests were included. The study by Ohnstad et al 2024 was published after the search date and will be considered during the appraisal phase of the report. No changes to the report have been made based on this comment.
12	Pages vi, vii, chapter 7.2: Restricting Prosigna-testing to patients assessed as clear/uncertain chemotherapy candidates is cost-effective compared to immunohistochemical (IHC) markers including Ki-67 in healthcare and societal perspectives (ICER €8.884 and €-620.170, respectively) and cost-saving from a societal perspective (Asphaug et al. 2025). Similar results from NICE 2024, Decision Forum 2024, HAS 2023, SHTG 2023 & TLV 2022.	The mentioned study by Asphaug et al. was published after the search date of the economic systematic literature search . Results of other studies mentioned published before the search date are presented in Chapter 7.2 (or chapter 9.1 for HTA reports). No changes to the report have been made based on this comment.
12	Table 33: The average list price for Prosigna assay across kit configurations is 1.360 CHF per test.	The information has been noted.
12	Page 176: The ICER of £39.357 for Prosigna is incorrect since Tappenden et al. 2023 had double counted VAT. This error has been corrected. Please refer to https://www.nice.org.uk/guidance/DG58/documents/committee-papers (p 269) for the corrected ICER which was used by NICE in their final guidance DG58 (Section 3.19): "Prosigna was likely to be a cost-effective use of NHS resources when used to help guide adjuvant chemotherapy decision making with postmenopausal women. In the EAG's base-case analysis, the probabilistic ICER for Prosigna was £24.547 per QALY gained using list price." (https://www.nice.org.uk/guidance/dg58/resources/tumour-profiling-tests-to-guide-adjuvant-chemotherapy-decisions-in-early-breast-cancer-pdf-1053878373061)	Implemented change: The ICER is adapted and a footnote is added with additional information and the reference.

12	Page 186: Attributing the comparator higher prognostic ability is just a hypothesis that does not consider that relevant factors (tumor stage, nodal stage, menopausal status, receptor status) are basis of the eligibility criteria defining study populations. Functional status balances out in RCTs.	The prognostic ability of conventional testing in Swiss clinical practice is unknown. However, as many more clinical factors are incorporated in clinical practice than there are used in the model to specify clinical risk stratification, it is to be expected that conventional testing has better prognostic abilities than the comparator in the model. The clinical factors used in the decision to take adjuvant chemotherapy are also more extensive than those used as the eligibility criteria defining study populations. Basing the treatment decision and recurrence risk from study populations defined solely by risk factors used in NPI is therefore likely to lead to an underestimation of the prognostic ability of conventional testing in Swiss clinical practice. Indeed, this is a hypothesis and there is no empirical evidence to use in an assessment. Therefore, it was included in a scenario analysis rather than the base case. No changes to the report have been made based on this comment.
12	Chapter 8.2.7: Prosigna is FDA-cleared and CE marked which is not the case for all the tests. With local processing within the Swiss healthcare system, GDPR and biobank legislation compliance is ensured. NICE, MTP Council, and the Decision Forum have required in HTAs documentation for GDPR compliance for US processed tests.	This comment about legal aspects has been noted. No changes to the report have been made based on this comment.
12	Chapter 3.1.4 (page 7): ROR-PT is obsolete. Current instructions define 1-3 or 4+ positive nodes in post-menopausal patients. Prosigna enables on-site result discussion between doctors and experienced pathologists, benefiting patient care.	The description was adapted accordingly in Chapter 3.1.4 and 3.1.5.