Consolidated stakeholder feedback

HTA protocol

Multigene-expression tests in early breast cancer

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

1	Agendia NV
2	Curafutura
3	Exact Sciences International GmbH
4	Krebsliga Schweiz
5	Myriad Genetics GmbH
6	SAKK (Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung)
7	Santésuisse
8	SGGG (Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe)
9	SGMO (Schweizerische Gesellschaft für Medizinische Onkologie)
10	SGPath (Schweizerische Gesellschaft für Pathologie)
11	SGS (Schweizerische Gesellschaft für Senologie)
12	SVDI (Schweizerischer Verband der Diagnostikindustrie)
13	Swiss Cancer Screening
14	Veracyte

SH	SH comment	Reply authors / BAG & implemented changes
1	The policy and research question are both very specific to testing on surgical resection specimen / after surgical resection and does not recognize that multigene-expression tests can be performed on core needle biopsies. At least for MammaPrint, the concordance between surgical resection and core needle biopsy specimens has been specifically studied by Crozier and colleagues, and found very good concordance for MammaPrint results of matched samples of 90.9% (k = 0.817). Full Reference: Crozier JA et al. High concordance of 70-gene recurrence risk signature and 80-gene molecular subtyping signature between core needle biopsy and surgical resected specimen in early-stage breast cancer. Journal of Surgical Oncology 2022; 125:596-602. We propose to change the policy and research question (and other references to this topic throughout the protocol) in a manner where testing can be performed on both specimen types. In many cases it is already clear that a patient is candidate for chemotherapy based on the clinical stage of the tumor (pre-surgery); within criteria and the intended use of multigene-expression tests. In these instances, ordering on the core needle biopsy allows the test to be performed while awaiting surgery, facilitating the results to be available straight after surgery, with the benefit of starting the adequate systemic therapy earlier.	We are aware that multigene-expression tests can be performed on specimens other than those obtained by surgical resection. The scope of the current health technology assessment (HTA) is not limited based on the method of specimen collection (that is, evidence based on samples collected using core needle biopsy is eligible for inclusion). However, in line with the current reimbursement text for multigene-expression tests in Switzerland, this HTA only concerns the use of these tests for decisions on adjuvant chemotherapy. Therefore, the phrase “after surgical resection” in the Population, Intervention, Comparator, Outcome (PICO) and throughout the protocol refers to the treatment, not to the moment of sampling. The protocol was not adapted based on this comment.
1	Furthermore, with a global trend of treatment moving slightly more towards the neo-adjuvant setting, particularly in patients with tumors with 1-3 positive nodes, it is important for multigene-expression tests to remain available for the chemotherapy de-escalation questions when this happens. Neo-adjuvant therapy is often prescribed to down-stage surgery, but when this is done with neo-adjuvant chemotherapy, it could lead to overtreatment as multigene-expression tests indicate (depending on which one) that most tumors with 1-3 positive nodes are genomically low risk and do not derive clinically meaningful benefit from chemotherapy. The goal of down-staging surgery can also be achieved by prescribing neo-adjuvant endocrine therapy, sparing genomically low risk patients of chemotherapy. With no evidence of differential efficacy of chemotherapy in the neo-adjuvant or adjuvant setting, and a trend to more neo-adjuvant treatment, we believe it is imperative that the HTA would consider testing on both core needle biopsy and surgical resection.	The use of multigene-expression tests to inform treatment decisions in the neo-adjuvant setting is outside the scope of this HTA. This is based on the current reimbursement text for multigene-expression tests in Switzerland. The protocol was not adapted based on this comment.
1	With regards to Chapter 4.2, Agendia would like to comment that with the ongoing research on the hallmarks of cancer, the relation of the MammaPrint genes to the hallmark of cancer has been more recently studied, than the Tian paper referenced. We suggest to change that the sentence about the relation of 70 MammaPrint genes to the 6 hallmarks of cancer, to be changed to the 10 hallmarks of cancer as described in the paper of Haan et al. 2022. Full Reference: Haan J.C., et al. MammaPrint and BluePrint comprehensively capture the cancer	Agreed. The sentence is rephrased**,** and the reference replaced with the more recent reference.

	hallmarks in early-stage breast cancer patients. Genes Chromosomes Cancer 2022; 61(3): 148-160	
1	Furthermore, we would like to inform you that MammaPrint is no longer commercially performed on Fresh Frozen tissue. The reference to Fresh Frozen can therefore be removed from paragraph 4.2, as MammaPrint is solely commercialized for FFPE samples.	Agreed. The reference to fresh frozen tissue is removed from the HTA protocol.
1	Lastly, we request to accurately reflect that MammaPrint Index scores of 0 are part of the High Risk category: "Samples with a MammaPrint index value greater than 0 are classified as Low Risk, and samples with a value less than or equal to 0 are classified as High Risk."	Agreed. This is rephrased.
2	We thank the authors for this well-founded HTA-protocol. a. As also in the expert group discussion protocol stated, multigene expression tests are not interchangeable and have different levels of evidence. There appear to be numerous difficulties in evaluating the 4 tests as a whole, particularly when it comes to drawing conclusions regarding clinical effectiveness/efficacy/safety. Even though the expert group states they would not attempt to compare tests, this limitation seems to be prominent. Additionally, the experts "agreed that the type of test that is used usually depends on the institution, as it is more related to the facilities than the individual patient characteristics" (question 5, page 32), what is raising further questions. b. Another question is, if the evaluation of Swiss registry data has been discussed? Based on SEER data for example, (Hortobagyi et al., 2018) a study evaluated the prognostic value of a multigene expression test. Are such registry data, i.e. real life data, available in Switzerland and could they also be analyzed? Thank you for taking note of our comments.	a. Indeed, the 4 multigene-expression tests will not be assessed as a whole. Rather, all 4 tests will be individually assessed against the standard of care without multigene-expression test. A sentence further clarifying this has been added to the research question section. b. Performing a new study based on Swiss registry data is outside the scope of this HTA. Any previously conducted and published study based on Swiss (or other) registry data will be identified in the systematic literature search. Swiss registry data might be used to inform parameters for the economic evaluation (Section 7.2).
3	1) In line with independent HTA institutions, the gold-standard for evidence-based decision-making are prospective Randomized Controlled Trials (RCTs).	Agreed. The protocol was not adapted based on this comment.
3	2) Since MGTs are not interchangeable, we support to follow the recommendation to report the level of evidence by test.	Agreed. A sentence further clarifying this has been added to the research question section.
3	3) Modify policy question: “Do the MGTs Oncotype DX®, MammaPrint®, EndoPredict® and Prosigna® meet the effectiveness, appropriateness and economic efficiency (WZW) criteria to help guide decision making on chemotherapy treatment in patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) and early breast cancer with up to 3 positive lymph nodes?”	The policy question as it is in the protocol reflects the current reimbursement text for multigene-expression tests in Switzerland. Therefore, the suggested changes (i.e. a) delete the term ‘adjuvant’ prior to chemotherapy; b) rephrase ‘oestrogen receptor positive (ER+)’ in ‘hormone receptor positive (HR+)’; c) delete ‘after surgical resection’; and d) delete ‘for whom it is unclear based on conventional testing whether to prescribe adjuvant chemotherapy’) are not implemented. The protocol was not adapted based on this comment.
3	4) PICO criteria a. P.7,Population: BAG mentions „early“ breast cancer without definition. Add the following definition: “Stage I to IIIA breast cancer refers to invasive	4a. Since the definition of early breast cancer is not uniform across studies, it was decided not to add this definition to the protocol. Instead, the definitions as applied in

	breast cancer that is contained within the breast and may or may not have spread to the axillary lymph nodes." b. P.7,Intervention: BAG has included not only MGTs, but also other procedures. Only MGTs are the intervention. Otherwise, it is misleading. c. P.7,Comparator: Comparator is only clinical pathological factors. Inclusion of MGTs as a comparator (to MGTs) would be methodologically incorrect. d. P. 7, Outcomes i. Overall survival (OS) to be added ii. Include „concordance" similar to assessments by other HTA institutions iii. „Freedom of recurrence" is scientifically named „recurrence-free-survival (RFS)" and would need to be further differentiated in: 1) invasive Disease-Free Survival (iDFS) and 2) Distant Recurrence-Free Survival (DRFS) e. Economics i. QALY and life-years are per definition no economic parameters. It is suggested to delete these parameters as both measures are statistical modelling outcomes. ii. Within the economic outcomes parameters, a focus should be put on (incremental) cost-effectiveness and (incremental) cost per QALY. iii. "Total cost" is not a measure to be taken when considering different health outcomes between interventions. Delete outcome „total cost".	the included studies will be extracted. A footnote explaining this is added to the PICO tables. 4b. The multigene-expression tests could also be evaluated together with co-interventions, such as clinical prediction tools, as long as these co-interventions are applied also in the comparator arm. Application of prediction tools reflects clinical practice in other countries as well as some key clinical studies of multigene-expression tests. The protocol was not adapted based on this comment. 4c. In the PICOs on page 7 the comparator indeed does not include multigene-expression tests . The protocol was not adapted based on this comment. 4di. Overall survival is already listed as an outcome of interest. The protocol was not adapted based on this comment. 4dii. Concordance studies will not be included in the systematic review for the clinical evaluation. These studies will be discussed shortly in the section "Additional issues". The protocol was not adapted based on this comment. 4diii. Agreed. This is rephrased in the HTA protocol. 4ei. For the economic parameters we look at all parameters that are generally reported in economic evaluations and that are relevant in determining the cost-effectiveness of the intervention in a particular setting. These obviously include incremental cost-effectiveness ratios (ICERs) and quality-adjusted life-years (QALYs). The protocol was not adapted based on this comment. 4eii. As mentioned in section 7.5.2, the ICERs of the included studies are a main focus of the data analysis and synthesis. The protocol was not adapted based on this comment. 4eiii. For the economic parameters we look at all parameters that are generally reported in economic evaluations and that are relevant in determining the cost-effectiveness of the intervention in a particular setting. Total costs are presented in almost all health economic evaluations. The protocol was not adapted based on this comment.
3	5) Clear definition of „impact on treatment management" in PICO2 required a. iDFS, DRFS and OS (prognostic) and b. Guide treatment decisions by providing information on a patient's estimated benefit from a chemotherapy (predictive value) c. Clinical impact according to the test result on the proportion of patients to receive chemotherapy.	a/b. These outcomes are captured in PICO 1. The concept of prognostic and predictive is mentioned as a footnote below the PICO 1 table. The protocol was not adapted based on this comment. c. The definition of treatment management is added: clinical impact according to the test result on the proportion of patients to receive adjuvant chemotherapy.
3	6) Research questions (p. 8): a. Question 3 to be deleted as only cost-effectiveness or cost per QALY should be decision-relevant from a health economic perspective. b. Question 6 might be of relevance; it is however not yet included in any of the PICOs suggested by the BAG. Suggestion to be updated accordingly.	a. Question 3 is deleted. b. Question 6 refers to the exploration of the ethical, legal, social and organisational (ELSO) domains. As this is related to the intervention and can be explored in a broader context than the specific comparison defined in the PICO, it is not reflected in the PICOs. The general objective and

		methodology used to address question 6/ the ELSO domains are presented in section 7.3. The protocol was not adapted based on this comment.
3	7) Non-systematic reviews and data of evidence levels below prospective/retrospective RCTs for test validation and below prospective RCTs for clinical utility, respectively, should be excluded.	Agreed, non-systematic reviews will be excluded during the title/abstract selection. The focus of HTAs conducted by the FOPH is to search for the highest quality of available scientific evidence provided by randomised controlled trials (RCTs). Exclusion of data of evidence levels below prospective RCTs will depend on the output of the first step of the stepwise systematic literature search approach for PICO 1. In case less than one prospective RCT is found for a multigene-expression test for the clinical outcomes, an additional systematic literature search for retrospective/reanalyses of RCTs and comparative non-randomised studies will be conducted. A rationale on prospective and retrospective RCTs is added to section 7.1.1 of the protocol: For this HTA topic, prospective RCTs as well as retrospective or re-analyses of RCTs have been conducted. The primary interest is in prospective RCTs, which use the multigene-expression test prospectively to guide the treatment decision on adjuvant chemotherapy. These trials will provide the highest quality of the available evidence. In contrast, in retrospective RCTs multigene-expression tests are performed on stored resected breast tissue samples.
3	8) Limiting systemic literature search (SLR) to 15 years will miss relevant Oncotype DX studies. Change the protocol to no time restrictions.	Multiple articles, on for example Oncotype DX, are published with different follow-up times. Only the article with the longest follow-up or largest sample size will be included, since the goal is to obtain data from long-term follow-up. **I**t is regarded as unlikely that important data will be missed, given that the multigene-expression tests were approved in the years 2007-2012. Reference lists of systematic reviews identified during the title and abstract screening and reference lists of the included studies will be checked for potentially missed relevant references of primary studies. The protocol was not adapted based on this comment.
3	9) Search strategy improvements a. Sentence break separators are included in the search protocols and can lead to misinterpretations, e.g., the spelling "Onco-type DX" is not correct. b. Search queries are not sensitive enough. This can be remedied by adding "OR (multigene assay[tiab] AND gene*[tiab])" c. Health economic search is not capturing all relevant search terms for "budget impact/cost-effectiveness": Keywords “cost saving”, “budget impact analysis” and “health economics” should be included.	9a. Agreed. To avoid misinterpretations the formatting of the search strategy tables is changed, without using sentence break separators. 9b. Since the HTA is aimed at 4 specific multigene-expression tests, it was decided to use targeted search terms for these tests and not include the less specific general terminology for multigene-expression tests. In addition, reference lists of systematic reviews identified during the title and abstract screening and reference lists of the included studies will be checked for potentially missed relevant references of primary studies. The protocol was not adapted based on this comment. 9c. “Cost-saving” would seem a term related to a specific conclusion of an analysis, and thereby not a valid search term. The keyword “health economics” is less specific than the terms for specific health economic study types included, and therefore expected to result in a lot of additional irrelevant papers. Therefore, these 2 suggested search terms are not included in the queries. The keyword “budget impact analysis” is a valuable addition to the search and is added to the health economic outcomes search string.

3	10) Table 3, protocol: “inclusion criteria >5 year follow-up“ is not state of the art for SLRs in health economic studies. Specification of 5-year time horizon including acceptance of modelled and extrapolated outcomes would be acceptable.	The minimal follow-up time for inclusion is the same in the systematic review of economic studies as in the systematic review of clinical studies. This relates to the follow-up time point of the clinical study that the economic study is based on, and it is done to prevent inclusion of economic studies based on data that does not meet the required quality criteria for clinical studies. A footnote was included in the table for clarification.
3	11) RCTs should be the basis for health economic models as the results could otherwise be biased. Modelling outcomes including lifetime results and direct as well as indirect cost are acceptable.	The focus of HTAs conducted by the FOPH is to search for the highest quality of available scientific evidence provided by RCTs. In case less than one prospective RCT is found for a multigene-expression test for the clinical outcomes, an additional systematic literature search for retrospective/reanalyses of RCTs and comparative non-randomised studies will be conducted. The protocol was not adapted based on this comment.
4	Vielen Dank, wir sind mit dem Protokoll weitgehend einverstanden und es entspricht den gängigen Guidelines. Für uns stellt sich einzig die Frage, ob die auf klinische oder ökonomische Fragestellungen ausgelegten Studien aus den systematischen Literatursuchen ausreichen, um ethische, legale, soziale und organisatorische Aspekte abzubilden. Translation Thank you very much, we largely agree with the protocol, and it complies with the common guidelines. The only question for us is whether studies designed for clinical or economic issues from the systematic literature searches are sufficient to address ethical, legal, social, and organizational aspects.	In addition to clinical or economic issues from the systematic literature searches, targeted non-systematic searches will be conducted to identify ethical, legal, social and organisational issues in PubMed (MEDLINE) and on relevant websites, such as the websites of the European Society of Breast Cancer Specialists (eusoma.org), the Schweizerische Gesellschaft für Senologie (senologie.ch), the Union for International Cancer Control (uicc.org), and other websites that may be identified. This is outlined in Section 7.3. The protocol was not adapted based on this comment.
5	We would like to draw attention to the following aspects and request that they be taken into account: p.3 In addition to the 2021/23 St. Gallen recommendations mentioned in the protocol, we would like to refer to the ESMO guidelines currently specified in 2024 (Loibl S et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2024;35(2):159-182), which in our view will also influence further HTA processes, not only in CH: No Preferred Test. Emphasizing the guideline's impartial stance on test preference. EndoPredict got Level of Evidence 1A (LoE 1A) recommendation.	A sentence and the reference to the European Society for Medical Oncology (ESMO) guidelines is added in Chapter 1. The ESMO guidelines are in line, so there is no further change needed to the protocol.
5	p.5 Please make sure that EndoPredict is described correctly and completely in the technology description to avoid later discussions. Indeed, EndoPredict is intended for in vitro analysis of FFPE resection and biopsy specimens of primary female invasive breast cancer (estrogen receptor positive, HER2 negative (ER+/HER2-)), for the determination of the 10-year risk of distant recurrence (metastatic disease), the likelihood of distant recurrence 5-15 years after diagnosis, and the estimated absolute benefit of chemotherapy at 10 years. The different description of Oncotype and EndoPredict is not correct . The first sentence 4.1 on Oncotype also applies to EndoPredict. Please also insert this in its entirety under 4.3 for EndoPredict. p.5 We are wondering about the following statement: "however ER, PR, and HER2 status are not included, contrary to the Oncotype DX and PAM50 assays". Please correct this.p.5 The description of EndoPredict should	The technology description of EndoPredict (Section 4.3) and the overview table with test characteristics are adapted based on the stakeholder feedback: - “that assesses the risk of 10-year distant recurrence from the time of initial diagnosis“ is rephrased in “that assesses the risk of 10-year distant recurrence (metastatic disease) from the time of initial diagnosis assuming 5 years of endocrine therapy, the likelihood of distant recurrence 5-15 years after diagnosis, and the estimated absolute benefit of chemotherapy at 10 year“. - “FFPE tissue sample“ is specified as “FFPE resection and biopsy tissue samples“. - “however ER, PR, and HER2 status are not included, contrary to the Oncotype DX and PAM50 assays” is deleted. - The applications indicated by the manufacturer in Table 1 is changed from “Recurrence risk“ in “Recurrence risk and chemotherapy benefit“.

	mention in a clear way that EndoPredict provides not only prognostic information but also an individual estimate of absolute chemotherapy benefit (ABCSG6/8,GEICAM/9906, GEICAM/2003-02). Please add tissue sample from biopsy or surgical resection as from ODx. p.6 (Overview of test characteristics, Table 1) Please complete “Applications indicated by manufacturer” with “Distant recurrence risk and chemotherapy benefit".	
5	p.8 (HTA research questions) Q1-What is the comparator technology?	The HTA research questions are formulated according to the standard format of the FOPH. The comparator is defined in the PICOs. The protocol was not adapted based on this comment.
5	Throughout the document, we have 3 definitions of comparator:p.7: “Conventional testing (including clinical prediction tools such as Adjuvant!Online)”. p.10-11: “Conventional testing: with or without clinical prediction tools such as Adjuvant!Online”. p.18: “The comparison for the intervention is conventional testing only, without the use of any clinical prediction tools (i.e. the current standard of care in Switzerland). This includes of the following tests and examinations: ...”We are not quite sure why the use of clinical prediction tools should be considered as a comparator (in combination with conventional testing), as part of the clinical and economic evaluations when it’s not the case for the Economic Model protocol. It is clearly stated page 18, that conventional testing only, without the use of any clinical prediction tools, is the current standard of care in Switzerland. This statement is consistent with the latest ESMO recommendations (2024 recommendation above).	To avoid confusion, we better aligned the definitions of the comparator in the PICOs (p.7) and p.10-11, by using the definition presented at p.10-11 also in the PICO at p.7. The definition of the comparator in the economic model is narrower than that in the systematic literature search, as the model should reflect the current Swiss clinical practice. In contrast, the clinical literature search aims to capture all applications in which the multigene-expression tests under consideration have been evaluated. This includes settings in which they are implemented as an add-on to clinical prediction tools.
5	p.10 (Table 2. Inclusion criteria for clinical studies) We miss including meta-analyses, prospective non comparative studies and prospective-retrospective studies in compliance with the criteria of Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 4 nov 2009;101(21):1446-52. p.21	Meta-analyses are covered with the study design systematic reviews. Non-comparative studies are not within the scope of the HTA. Prospective-retrospective studies, i.e. prospective RCTs using archived samples or retrospective analyses of RCTs, are also covered in the stepwise search approach. The RCTs are further specified as prospective RCTs or retrospective/re-analyses of RCTs in section 7.1.1 and Table 2.
5	We wonder why there is no part dealing and struggling with the legal challenge of out-of-country testing for Oncotype because there is a legal framework in CH that clearly denies sent-out solutions in the case there are Swiss in-country solutions (ProSigna, EndoPredict). In our view, the existing exception in Annex 1 KLV cannot be a long-term exemption.	Acknowledged. This will be incorporated in the ELSO domains in the HTA report. The protocol was not adapted based on this comment.
6/8/10/11	Dies ist ein gemeinsames Statement der SAKK, der SGS, der SGGG und der SGPath. Das vorliegende HTA Protokoll beschreibt das geplante Vorgehen, eine Bewertung der vier bekannten und in der Schweiz zugelassenen Genexpressions-Test, die zur Behandlungsentscheidung beim frühen HR+ Brustkrebs eingesetzt werden, durchzuführen. Die für die Erstellung einer Meta-Analyse geplante Methodik wird dargestellt und Schlüsselfragen werden formuliert. Das FPOH ist beauftragt, mit der aktuellen Beurteilung die Genexpressions-Tests zu reevaluieren und deren weitere Erstattungsfähigkeit zu prüfen. Das vorliegende Protokoll beschreibt präzise die geplante HTA Analyse, die sowohl klinische, als auch ökonomische Outcomes beinhalten wird. Die vorgeschlagene HTA Analyse plant, unter	We acknowledge the points of view by these stakeholders. Collecting Swiss input data for the cost-effectiveness analysis is expected to be challenging. The best available cost inputs will be collected, while the uncertainty will be addressed. The protocol was not adapted based on this comment.

	anderem exakte Daten zur ökonomischen Bedeutung der Tests konkret in der Schweiz zu erheben. Dies ist prinzipiell interessant und nützlich, allerdings ist folgendes festzuhalten: Diese Tests werden nicht kodiert, nicht einheitlich abgerechnet, weder je Test, noch je Region (zB: ein identischer Test hat in der Schweiz je nach Versicherung der Patientin in den vergangenen Jahren verschiedene Preise gehabt, zudem sind die verschiedenen Tests unterschiedlich teuer für die Patientinnen), so dass es extrem schwierig/aufwendig sein wird, festzustellen, wie viele Tests in der Schweiz überhaupt durchgeführt wurden und wie hoch genau ihre totale monetäre Belastung im Gesundheitssystem ist. Da schlussendlich die Frage der Rückerstattung im Raume steht, besteht ein gewisses Risiko, dass die Untersuchung die Kernfrage nicht beantworten kann, oder allenfalls auch, aufgrund einer falschen/inkompletten Datenlage, falsche Konklusionen gemacht werden. Im Appendix A des zur Vernehmlassung ausgesandten Protokolls wird die Frage gestellt, wohin das Gewebe für den Oncotype geschickt wird. Aus den von der SGPath direkt überschauten Instituten sowie auch gemäss Information der Firma Exact Sciences wird das Gewebe momentan mit Versand an eine Adresse in den USA verschickt. Aus unserer Sicht ist es wichtig zu erwähnen, dass in der Schweiz bereits seit 2008 Erfahrungen mit den Genexpressions-Tests vorliegen und ihr Einsatz weit verbreitet ist. Internationale Guidelines (NCCN, ESMO, St. Gallen Konsensus, deutsche AGO Mamma) empfehlen deren Verwendung zur Indikationsstellung der adjuvanten Therapie. Die Evidenzlage für die vier Tests liegt im Level I und II. Es liegen für alle vier Tests randomisierte klinische Studien zu deren prognostischer Fähigkeit vor. Für zwei der Genexpressions-Tests (Oncotype DX und Mammaprint) gibt es grosse randomisierte Studien, die belegen, dass diese Signaturen auch den Chemotherapiebenefit vorhersagen können und damit prädiktiv sind (Level of Evidenz 1). Durch diese Entscheidungshilfen kann vielen Frauen mit Brustkrebs eine Übertherapie (= nicht wirksame Chemotherapie) erspart werden. Andererseits kann aber auch eine Untertherapie verhindert werden, wenn der Genexpressions-Tests einen Benefit einer Chemotherapie vorhersagt. Damit tragen die Genexpressions-Tests in grossem Masse zur Optimierung der Therapie bei frühem hormonrezeptor-positivem Brustkrebs bei. Aus unserer Sicht sind die Genexpressions-Tests fester Bestandteil des Therapiemanagements von Patientinnen und Patienten mit Brustkrebs in der Schweiz. Eine Erstattung dieser Genexpressions-Tests ist in jedem Falle weiterhin unbedingt zu fordern. Translation: This is a joint statement from SAKK, SGS, SGGG, and SGPath. The present HTA protocol describes the planned approach to conduct an evaluation of the 4 well-known and Switzerland-approved gene expression tests used in treatment decisions for early HR+ breast cancer. The methodology planned for conducting a meta-analysis is outlined, and key questions are formulated. The FOPH has been tasked with re-evaluating the gene expression tests and examining their broader reimbursement eligibility. The protocol precisely describes the planned HTA analysis, which will include both clinical and economic outcomes. The proposed HTA analysis	

	plans to collect exact data on the economic significance of the tests specifically in Switzerland. This is potentially interesting and useful; however, it should be noted that these tests are not encoded, billed uniformly, neither per test nor per region (for example, the same test has had different prices in Switzerland over the past years depending on the patient's insurance, and different tests vary in cost for patients). Therefore, it will be extremely difficult/time-consuming to determine how many tests have been performed in Switzerland and what their total monetary burden on the healthcare system is. Since the question of reimbursement is ultimately at stake, there is a risk that the investigation may not be able to answer the core question or, possibly, incorrect conclusions may be drawn due to incorrect/incomplete data. In Appendix A of the protocol sent for consultation, the question is raised about where the tissue for the Oncotype is sent. According to the institutes directly overseen by SGPath and information from Exact Sciences, the tissue is currently being sent to an address in the USA. It is important to mention that experiences with gene expression tests have been available in Switzerland since 2008, and their use is widespread. International guidelines (NCCN, ESMO, St. Gallen Consensus, German AGO Breast) recommend their use for determining the indication for adjuvant therapy. The evidence for the 4 tests is in Level I and II. There are randomized clinical studies for all 4 tests regarding their prognostic ability. For 2 of the gene expression tests (Oncotype DX and Mammaprint), there are large randomized studies demonstrating that these signatures can also predict chemotherapy benefit and are thus predictive (Level of Evidence 1). These decision aids can spare many women with breast cancer from overtreatment (ineffective chemotherapy). On the other hand, undertreatment can also be prevented if the gene expression test predicts a benefit from chemotherapy. Thus, gene expression tests contribute significantly to optimizing therapy for early hormone receptor-positive breast cancer. In our view, gene expression tests are an integral part of the therapy management of patients with breast cancer in Switzerland. Reimbursement for these gene expression tests is still essential in any case.	
7	The HTA protocol is clear and well structured. The following research question is addressed in this HTA protocol: What is the clinical effectiveness and cost-effectiveness of the multigene-expression tests Oncotype DX, MammaPrint, EndoPredict and Prosigna for guiding adjuvant chemotherapy decisions in patients with ER+, HER2-, LN0-3 early breast cancer after surgical resection? If santésuisse interprets correctly, it is intended that the effectiveness of the 4 multigene expression tests (Oncotype DX, MammaPrint, EndoPredict, or Prosigna) will not be assessed on a test-specific basis. Santésuisse recommends justifying the corresponding decision in the report as the discussion in the advisory board has shown that there are known differences between those different tests. Conventional tests are mentioned as comparators in the 2 PICOs. In the above mentioned context studies should also be considered in which 2 or more of the examined tests are compared with each other. This can provide information on possible and	A sentence clarifying that the 4 multigene-expression tests are each assessed individually and not directly compared with each other has been added to the section presenting the research question. A long-term assessment is part of the HTA as outlined in Section 7.2.6 of the protocol. Unless an empirical long-term assessment is meant, which is outside of the scope of the current HTA.

	important differences between the tests e.g. patient population or decisions concerning therapies. Santésuisse recommends carrying out a long-term assessment of the cost-effectiveness of the intervention.	
9	General comments: Since the 1990s, breast cancer patients outcomes have progressively improved due to advancements in adjuvant systemic therapies, including chemotherapy (JAMA.2024;331(3):233-241). However, chemotherapy benefit varies according to disease stage and biology. Two-thirds of patients have HR+/HER2- breast cancer. A substantial part of them derives little benefit from adjuvant chemotherapy, but conventional pathological parameters have limited ability to predict chemotherapy responsiveness. Genomic signatures, Oncotype Dx, MammaPrint, EPClin, and Prosigna significantly enhance patient selection for chemotherapy decisions and avoid unnecessary treatments. These signatures may also identify patients as benefiting substantially from chemotherapy despite being deemed low risk by conventional parameters. Access to these tests is important for optimizing treatment accuracy and decreasing its burden for the patients and the health system. Additionally, confirmation of chemotherapy necessity serves as motivation for the concerned patients and providers. As mentioned by the experts, establishing strict criteria for selecting patients eligible for genomic signature testing remains challenging due to the multitude of factors involved, including stage, conflicting pathological parameters, and discussion with the patients. It could be useful to mention that the chemotherapy can be administered as adjuvant (after surgery) or as neoadjuvant (before surgery). Similarly, multigene-expression tests hold relevance in both scenarios for patients with HR+/HER2- breast cancer. For instance, if a patient presents with a sizable tumor, favorable results from a multigene-expression test may lead to the recommendation of neoadjuvant endocrine therapy over chemotherapy. Maintaining an open choice between Oncotype Dx, MammaPrint, EPClin, and Prosigna is advisable. Each has been validated in diverse settings, offering flexibility for fine-tuning patient selection. Furthermore, varying accessibility across centers and avoiding dependence on a single company support this approach. Notably, the costs of these tests are comparable.	We concur with the stakeholder that it is important to identify those patients that benefit from chemotherapy. Therefore, the current HTA will carefully assess the populations included in identified studies and the extend the multigene-expression tests predict the benefit of adjuvant chemotherapy in those patient populations. The use of multigene-expression tests for decision making on neo-adjuvant therapy is outside the scope of the current HTA. The 4 multigene-expression tests will indeed be analysed individually against standard of care. It is not the aim of this HTA to compare multigene-expression tests and conclude on the superiority of a test. As sentence further clarifying this has been added to the research question section.
9	Some specific comments on the Protocol: 1. In the Protocol, you mention only ER+. The studies considered HR+ as “ER+ and/or PR+” 2. Page 3: “staging for early breast cancers … and chest radiography”. Chest radiography is not considered for staging (Loibl et al. Annals of Oncology 2024:159) 3. Page 3: “endocrine therapy is recommended … for 5 or 10 years”. It’s 5 to 10 (Cancers (Basel). 2023 Aug; 15(16): 4190). 4. Page 3: “In general, better prognosis is associated with … HER2- …”. HER2 is no more considered as a negative factor (see 8th edition AJCC staging).	1. The policy question specifies ER+ as that is part of the current reimbursement text in Switzerland. The protocol was not adapted based on this comment. 2. Chest radiography is deleted. 3. This is rephrased in 5 to 10 years. 4. HER2 is removed from this list. 5. This sentence is rephrased; 15 years is replaced with 20 years. 6. This is corrected to 9 years.

	5. Page 3: “In the last 15 years, multigene-expression …”. 15 years is short. MINDACT trial started in 2007 (17 years) and TAILORx trial in 2006 (18 years). The multigene-expression tests were developed earlier. As example Nature 2002;415:530-6 6. Page 4: “probability of distant relapse within a 10-year …”. Oncotype Dx report give the 9-year risk of distant recurrence. 8. Page 7: Adjuvant!Online does no more exist for many years 9. Page 28 Table: Family history is not a parameters influencing chemotherapy decision + it’s not “HER2 score”, but “HER2 status” 10. Page 28 / 1.1: The exact term is “lymphovascular invasion” (Loibl et al. Annals of Oncology 2024:159). 11. Page 28 / 4.1: “the size of the tumour has very little prognostic ability”. This is not exact. Size influences significantly the risk. Therefore, EPClin and Prosigna include this parameter. Also shown with Oncotype Dx (J Clin Oncol 39:557-564. © 2020) 12. Page 32: “… oncologists should be aware of mean and median Ki67 values of the pathology institutions they work with …”. There is no strong data supporting this statement. For example, in the MonarchE trial it was clearly shown that a common cutoff for all the centers is fully able to select higher risk patients (Harbeck et al. Annals of Oncology 2021: 1571	8. This is correct, but is has been included in studies. 9-12. We acknowledge the valuable information provided in these comments. However, we cannot make changes to the minutes of the clinical experts advisory panel meeting, as the reflect wat was discussed during this meeting and have been approved by all participants in their current form.
12	1. From our perspective and also in line with independent HTA institutions, the gold-standard for evidence-based decision-making are prospective Randomized Controlled Trials (RCTs).	Agreed. This is in line with the current protocol. The protocol was not adapted based on this comment.
12	2. As Multi expression tests are not interchangeable, we agree with the recommendation to report the level of evidence by test.	Agreed. The protocol was not adapted based on this comment.
12	3. Re PICO - Intervention, page 7: here, not only MGTs, but also other procedures are included. This is misleading, as the intervention should only be MGT. Otherwise, an explanation is needed. - Outcomes, page 7: further explanation is needed for „Freedom of recurrence“. - Economics: Within the economic outcome parameters, a focus should be put on (incremental) cost-effectiveness and (incremental) cost per QALY. - Clear definition of „impact on treatment management“ in PICO2 is required.	- The multigene-expression tests could also be evaluated together with co-interventions, such as clinical prediction tools, as long as these co-interventions are applied also in the comparator arm. Application of prediction tools reflects clinical practice in other countries as well as some key clinical studies of multigene-expression tests. The protocol was not adapted based on this comment. - Freedom of recurrence is rephrased in recurrence-free-survival and further differentiated in invasive disease-free survival and distant recurrence-free survival. - As mentioned in section 7.5.2, the ICERs of the included studies are a main focus of the data analysis and synthesis. The protocol was not adapted based on this comment. - Agreed. The definition of treatment management is added: clinical impact according to the test result on the proportion of patients to receive adjuvant chemotherapy.
12	4. Research questions (page 8): - Please explain why non-systematic reviews and data of evidence levels below prospective/ retrospective RCTs for test validation and below prospective RCTs for clinical utility, respectively, should be included.	- Non-systematic reviews will be excluded during the title/abstract selection. The focus of HTAs conducted by the FOPH is to search for the highest quality of available scientific evidence provided by RCTs. Exclusion of data of evidence levels below prospective RCTs will depend on the output of the first step of the stepwise systematic literature search approach for PICO 1. In case less than one prospective RCT is

	- Limiting the time frame to 15 years might be too short to include all relevant data / studies in the field.	found for a multigene-expression test for the clinical outcomes, an additional systematic literature search for retrospective/reanalyses of RCTs and comparative non-randomised studies will be conducted. A rationale on prospective and retrospective RCTs is added to section 7.1.1 of the protocol: For this HTA topic, prospective RCTs as well as retrospective or re-analyses of RCTs have been conducted. The primary interest is in prospective RCTs, which use the multigene-expression test prospectively to guide the treatment decision on adjuvant chemotherapy. These trials will provide the highest quality of the available evidence. In contrast, in retrospective RCTs multigene-expression tests are performed on stored resected breast tissue samples. - Multiple articles, on for example Oncotype DX, are published with different follow-up times. Only the article with the longest follow-up or largest sample size will be included, since the goal is to obtain data from long-term follow-up. **I**t is regarded as unlikely that important data will be missed, given that the multigene-expression tests were approved in the years 2007-2012. Reference lists of systematic reviews identified during the title and abstract screening and reference lists of the included studies will be checked for potentially missed relevant references of primary studies. The protocol was not adapted based on this comment.
12	5. Search strategy improvements - Search queries might need adaptation to be more sensitive. E.g. by adding "OR (multigene assay[x] AND gene*[x])" - The search terms for the health economic search should be revised. E.g. keywords such as “cost saving”, “budget impact analysis” and “health economics” should be included.	- Since the HTA is aimed at 4 specific multigene-expression tests, it was decided to use targeted search terms for these tests and not include the less specific general terminology for multi-gene-expression tests. In addition, reference lists of systematic reviews identified during the title and abstract screening and reference lists of the included studies will be checked for potentially missed relevant references of primary studies. The protocol was not adapted based on this comment. - “Cost-saving” would seem a term related to a specific conclusion of an analysis, and thereby not a valid search term. The keyword “health economics” is less specific than the terms for specific health economic study types included, and therefore expected to result in a lot of additional irrelevant papers. Therefore, these 2 suggested search terms are not included in the queries. The keyword “budget impact analysis” is a valuable addition to the search and is added to the health economic outcomes search string.
12	6. Table 3, protocol: “inclusion criteria >5 year follow-up“ is not the state of the art in health economic studies. Specification of 5-year time horizon including acceptance of modelled and extrapolated outcomes should be considered.	The minimal follow-up time for inclusion is the same in the systematic review of economic studies as in the systematic review of clinical studies. This relates to the follow-up time point of the clinical study that the economic study is based on, and it is done to prevent inclusion of economic studies based on data that does not meet the required quality criteria for clinical studies. A footnote was included in the table for clarification.
12	7. The basis for health economic models should be RCTs. The models should have a livelong time horizon. How are indirect cost included / considered?	The focus of HTAs conducted by the FOPH is to search for the highest quality of available scientific evidence provided by RCTs. In case less than one prospective RCT is found for a multigene-expression test for the clinical outcomes, an additional systematic literature search for retrospective/reanalyses of RCTs and comparative non-randomised studies will be conducted.

		Section 7.2.6.6 of the protocol addresses the time horizon of the economic model. There it is stated that: The preferred time horizon of the base-case analysis is lifetime. The feasibility of implementing a lifetime horizon will depend on the availability of data. Shorter time horizons will be considered in scenario analyses, if relevant. Section 7.2.6.3 of the protocol addresses the perspective. A healthcare payers' perspective will be taken. All costs of healthcare services covered by the Swiss mandatory health insurance will be included. The analysis will not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs. The protocol was not adapted based on this comment.
13	First of all, Swiss Cancer Screening would like to address their gratitude to the HTA Unit for giving us the chance to participate in this process. Swiss Cancer Screening represents the different Swiss breast cancer screening programs. The main objectives of the screening programs are to decrease morbidity and mortality related to breast cancer, which constitutes a public health concern in Switzerland. The impact of our programmes is mainly achieved through the detection of early-stage breast cancers, in order to improve outcomes and quality of life of the women participating. Multigene-expression tests are currently used in Switzerland, in order to determine the best outcomes in a subgroup of the population suffering from breast cancer (including the presence of up to 3 affected lymph nodes). Based on a risk analyses, the decision to provide or not adjuvant therapy will be discussed by the breast unit. As screening programs, we do not participate in clinical decisions regarding adjuvant therapies. Once a cancer is detected, the women quit the screening program and breast cancer units take in charge. However, since early-stage breast cancers constitute an important part of cancers detected through screening programs, our programs have an indirect role on the clinical decision to use multigene-expression tests. Evidence based medicine on the use of one or more multi-gene tests, will have a complementary benefit to women undergoing screening in which a cancer is diagnosed. We agree that the best and most accurate evidence needs to be available in order to determine which test and under which circumstances the multigene tests should be used. We would like to provide some complimentary information that needs to be considered: - Decision based on the best available scientific information (randomised control trials to be prioritized). Determine whether the use of multigene tests overcome the use of conventional clinical prediction tools.	The current stepwise approach of the systematic review indeed aims to base any decision on the best available scientific evidence/study designs. Determining whether the use of multigene-expression tests overcomes the use of conventional clinical prediction tools is not part of the scope of this HTA. This particular purpose of multigene-expression tests has not been identified as an important objective in the clinical experts advisory panel meeting. The protocol was not adapted based on this comment.
13	- Include clinical validation of tests by international organisations.	In case this stakeholder comment refers to test validity, this is out of scope for the current HTA. Many previous

		studies and HTA reports have demonstrated test validity. The clinical validity of the multigene-expression tests was never considered controversial by the policy makers. As this is not country specific, it was considered redundant to include it again in the current HTA. The current HTA is solely aimed at assessing the clinical effectiveness and cost-effectiveness. The protocol was not adapted based on this comment.
13	- In case more than one test shows to be cost-effective, it may be useful to recommend the use of only one in order to avoid contradicting recommendations.	It is not the aim of this HTA to compare multigene-expression tests and conclude on the superiority of a test. The protocol was not adapted based on this comment.
13	- It is important that women for whom the tests are not recommended, do not lose any chances, compared to those undergoing the tests. Once again, thank you very much for this opportunity and we are looking forward for your final decision.	Acknowledged. These kinds of issues can be discussed when coming forward in the literature on the ELSO domains. The protocol was not adapted based on this comment.
14	3. a. ESMO guidelines recommend all 4 commercially available gene expression tests (GEP tests) for both lymph node -negative and -positive patients, aligning with Prosigna®'s approval designation in Europe. b. The performance of GEP tests for predicting adjuvant therapy benefit notably chemotherapy is controversial. Two of the prospective randomized clinical trials (RCTs) (MINDACT, RxPONDER) failed to demonstrate predictive performance for MammaPrint and Oncotype Dx respectively.	Acknowledged. The reference of the ESMO guidelines is added to Chapter 1. In the HTA report, guidelines will be discussed shortly in the section “Additional issues”. b. The results on predictive outcomes will be summarised and discussed in the HTA report. The protocol was not adapted based on this comment.
14	4.a. Veracyte notes some errors regarding the Prosigna® in the HTA protocol that are relevant to the evaluation: In Table 1 the technology description should read nCounter System, the manufacturer should be Veracyte and the technique RNA hybridization. b. Prosigna® has full CE marking and FDA 510K clearance ensuring high regulatory standards. BAG could consider prioritizing GEP tests that meet these requirements because of patient safety. Local sample processing endorsed by ESMO guidelines offers quicker results (DOI 10.1093/annonc/mdz173) and is in-line with recently updated (Sep-2023) Swiss data protecting law reFADP. The latter is highly relevant since Oncotype DX and MammaPrint, wholly or partly rely on shipment of human tissue and patient sensitive information to non-GDPR territories.	a. Agreed, the technique and manufacturer are adapted in the HTA protocol. b. These kinds of issues can be discussed when coming forward in the literature on the ELSO domains. The protocol was not adapted based on this comment.
14	5. The protocol draft PICO1 only considers RCTs. Yet, well-designed retrospective analyses of biomarkers in previously conducted RCTs meeting Level 1B evidence criteria (Hayes-Simon criteria DOI 10.1093/jnci/djp335) can appropriately complement the RCT evidence and contribute to answering the policy and research questions. The BAG advisory panel recommended assessing real-world evidence, yet the protocol does not reflect this. It only allows searching non-randomized studies if no RCT is found while lacking a scientific justification for it. Thus, if an RCT is found no real-world effectiveness can be assessed. This approach may lead BAG to consider only RCTs with flaws. Completing RCT data with prospective-retrospective/ prognosis evidence would aid in deriving	The focus of HTAs conducted by the FOPH is to search for the highest quality of available scientific evidence provided by RCTs. In case less than one prospective RCT is found for a multigene-expression test for the clinical outcomes, an additional systematic literature search for retrospective/reanalyses of RCTs and comparative non-randomised studies will be conducted. The RCTs are further specified as prospective RCTs or retrospective/re-analyses of RCTs in section 7.1.1 and Table 2.

	balanced conclusions within the HTA. Such studies would demonstrate the prognostic value of GEP tests in selecting adjuvant endocrine therapy and chemotherapy (DOIs): · 10.1200/JCO.20.00853 · 10.1093/annonc/mdt494 · 10.1038/s41523-022-00423-z · 10.1186/s13058-018-1012-0 · 10.1007/s10549-019-05446-y The OPTIMA trial (https://optimabreaststudy.com/) will provide RCT data to evaluate Prosigna®'s role in guiding adjuvant therapy in high-risk populations. OPTIMA includes ovarian suppression in premenopausal patients addressing a weakness of the existing prospective RCTs for evaluating the chemotherapy benefit.	
14	7.15 A justification of why "the 4 multigene-expression tests will be analysed on an individual level per test, not as one class of the 4 multigene-expression tests combined" needs to be given whilst considering that concordance data can be captured: (https://www.iqwig.de/download/d19-01_biomarker-bei-mammakarzinom_rapid-report_v1-1.pdf).	It is described more clearly that the 4 multigene-expression tests are each assessed individually. A sentence clarifying this is added to the section presenting the research question.
14	Section 7.2.6.4 and Appendix A (1.2) raise questions about cutpoints and treatment recommendations. When evaluating the RCT data and the impact on treatment recommendations in the PICO1, the BAG could consider including associated publications describing the RSClin model that incorporates clinical-pathologic factors (DOI: 10.1200/JCO.20.03007). This model is promoted as an educational tool (available only on the Exact Sciences portal) but also encouraged for clinical use by Exact Sciences (lymph-node negative disease). The model can generate markedly disparate prognostic and predictive estimates for a static RS and has not been validated by independent dataset. The PICO process should note this inconsistency and make it clear what test/model is being evaluated. Therefore, PICO1 should include RSClin as an intervention.	The current HTA only considered the 4 multigene expression tests that are currently reimbursed in Switzerland. Oncotype DX as it is included in the reimbursement text does not include the combination of genetic and clinical-pathologic factors. This is therefore outside the scope of the current HTA. The protocol was not adapted based on this comment.