Input from patient representatives, external expert and manufacturer on the **2nd draft assessment** “MammaPrint - Added value of using gene-expression signature for adjuvant chemotherapy decisions in early breast cancer”

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA JA3 WP4 - Other technologies, OTCA04
Comments on the 2nd draft rapid assessment on MammaPrint
Added value of using gene-expression signature for adjuvant chemotherapy decisions in early breast cancer

The objective of this reviewer form is to standardise the process of reviewing rapid relative effectiveness assessments.

The 2nd version of the Rapid Assessment on MammaPrint – Added value of using gene-expression signature for adjuvant chemotherapy decisions in early breast cancer was open to review by external reviewer(s) between **between 29/09 and 20/10/2017**.

Comments received from

Patient Representatives
NFK BVN: Nederlandse Federatie Kankerpatientenverenigingen, Borstkanker Vereniging Nederland (Dutch Federation for Cancer Patients, Dutch Breast Cancer Organisation)
Clinical experts
NVMO: Nederlandse Vereniging van Medische Oncologie (Dutch Society for Medical Oncology)
Manufacturer
Agendia, NL

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution disclosed.

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b “minor”: the comment does not necessarily have to be answered in a detailed manner
c“linguistic“: grammar, wording, spelling or comprehensibility

Comments by Patient Representatives: NFK BVN: Borstkanker Vereniging Nederland

Comment from *Name, title and affiliation*	Page number *Or 'general'*	Line/ section number	Comment and suggestion for rewording *Please insert each new comment in a new row.*	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
Summary					
Patient organisation	7	194-196	Adjuvant systemic chemotherapy aims at treating subclinical metastatic cancer cells already present at the time of diagnosis, in order to prevent distant metastasis, ultimately prolonging survival and eventually cure the disease. If this is true than the optimal surrogate endpoint to analyse is 5 yr DMFS and not 5 yr DFS.	1	Adjuvant chemotherapy is primarily given to prevent distant metastasis but, as mentioned by the NVMO, it also prevents locoregional recurrences. Although such a recurrence is stressful to patients it is still a curable disease. Therefore, DFS is also a relevant surrogate for overall survival. In general there is no consensus on the use of surrogate endpoints to assess (added) clinical benefit of a health technology, because the relationship between a patient-relevant clinical endpoint and its various surrogates has rarely been investigated in such depth that one particular surrogate is universally accepted as a replacement. Therefore, the assessment should be based on final patient-relevant clinical endpoints whenever possible, e.g. overall survival, quality of life and/or morbidity.[1] Each HTA organisation, needs to decide individually which surrogate endpoint is considered best for their assessment. Therefore, we describe in the report the relevance of each endpoint, based on its biological plausibility and empirical evidence, providing specific information relevant for each endpoint. In summary: DMFS has a biological rationale and the MammaPrint is developed as predictor for five-year DMFS, whereas DFS is also a relevant patient related outcome, as it includes all kind of recurrences. Therefore, DFS reflects for the patient all stressful events, even when the disease is still

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					curable, potentially impacting quality of life. [1] *EUnetHTA methodological guideline for rapid relative effectiveness assessment (REA) of Pharmaceuticals – surrogate endpoints (february 2013)*
Patient organisation	8	235-238	Refraining from chemotherapy will inevitably result in no side effects and better QOL. We feel this is not ONLY to be seen as an advantage in the absence of a negative effect on OS (or on the surrogate DMFS), but there is an advantage even if there is a limited (negative) effect on efficacy endpoints (OS, DMFS, DFS). Even in that case a subgroup of all women will be prepared to accept this small increase in risk for metastasis in exchange for QOL gain.	1	We agree with you that when there is an advantage in QoL this can outweigh a limited negative effect on efficacy in overall survival (or surrogate endpoints). Furthermore, we support initiatives form scientific societies, such as the TRANSBIG consortium that involved also patients advocates, to 'set' the threshold of what is considered an acceptable increase in risk of distant metastasis potentially leading to death. We disagree with your statement that there is a limited negative effect on efficacy endpoints when following MammaPrint risk assignment. This is based on the wide 95% CI's that indicate that the absolute effect on overall survival is highly uncertain. Next to that this trade off can only be quantified if the long-term benefit in QoL is available. However, QoL is not directly measured in the MINDACT trial, but it may be argued that some aspects of QoL are reflected by other outcomes. As mentioned in the assessment report it is obvious that the QoL of patients receiving adjuvant chemotherapy will be reduced due to chemotherapy side effects during and shortly after treatment compared to patients who do not receive chemotherapy The benefit in quality of life during the administration period chemotherapy is indirectly known from empirical evidence. In addition, the MINDACT study shows that refraining from chemotherapy leads to a significant and clinically relevant worse five-year DFS. All kind of recurrences are stressful to patients even in the case of a curable disease. This distress will have its repercussions on quality of life. Because long-term QoL is not available in the MINDACT, the added value of the MammaPrint in terms of QoL in the long term cannot be quantified.

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Patient organisation	9	305-306	Although QOL and AE profile are either not measured or not reported yet, it might be self-explanatory that women not receiving any chemotherapy cannot experience many AES (at least not drug related AEs) and as a consequence their QOL will be better. This is shown also in historical data. It is strange these data are not taken into consideration in the risk benefit assessment.	1	See our reaction above.
Patient organisation	12	377-399	Looking at the data (also in table 5, page 36 and in appendix A12) it is true that the OS, DMFS and DFS are slightly better after CT based on the AO! as compared to the outcome after CT based on MP. It cannot be neglected however, that this can only be reached through a 23% increase in patients being exposed to chemotherapy with concurrent AES and loss of QOL. Patients might make different choices based on different criteria than just clinical statistical significance especially when the % of OS / DMFS / DFS is quite high already and the differences are so small. For every 3-4 out of 100 more with distant metastasis after 5 yrs there are 23/100 pats without chemo treatment (associated with AES and decrease in QOL). It is very strange this latter is not taken into account in this report and is missing in this final conclusions. The added value of MP is that 23 % of women van be offered a possibility to make their own choice between a small increase in risk for metastasis at 5 yr and increase of QOL due to refraining of chemotherapy.		The fact that possible 23% of all breast cancer patients can omit chemotherapy is also included in our assessment. However, this positive effect was not demonstrated by proven added value in terms of QoL and/or AE's in the MINDACT. We do not agree that there is a small increase in risk of distant metastasis, as in absolute numbers, omitting chemotherapy after following MammaPrint® risk assessment and not AO! can lead to 10 (of 100) more patients that will not be free of distant metastases after five years. Looking at the 95% CI of five-year DMFS, it could also lead to one (0.6) less or at worst 29 (of 100) more patients who are not free of distant metastases after five years. The CI shows that there is a lot of uncertainty and a possibility that many patients could be harmed. Furthermore, there is an on-going risk of distant recurrence after five years.
Patient organisation	14-15	472	The original PICO as discussed during the Dutch scoping meeting (see lines 503-505 on page 16) were slightly different from the ones presented here: To the 10yr OS criterion was added *(5-year Distant*		It is correct that during the Dutch scoping meeting five-year DFS was not mentioned as surrogate for 10-year OS. However, the dedicated reviewers added well-reasoned arguments for adding five-year DFS as an important surrogate outcome measure (as mentioned at the first

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			Metastasis Free Survival (DMFS) as a surrogate for OS)		comment).
Patient organisation	18	597	It is not clear why the RASTER study is not taken into consideration. Also there are various other publications on the MP like e.g. Positive Early Breast Cancer: Results of a Prospective Cohort Study. Kuijer A et all, J Clin Oncol. 2017 Aug 20;35(24):2814-2819. It is unclear whether exclusion of these articles is valid , so this should be better explained.	2	We have described in more detail why the RASTER study was excluded. In summary: Although the RASTER study provides relevant information about the impact of MP on clinical decision making, it was not informative for our assessment because the RASTER study does not provide information on the relevant outcomes as selected in this assessment: the RASTER does not report the difference in OS (or any surrogate outcomes of interest) between the discordant patients based on the MammaPrint result (not receiving chemotherapy) and the discordant patients that did receive chemotherapy (based on Adjuvant! Online). We have added a table in which is explained why literature was not included in the assessment.
Health problem and current use (chapter 4)					
Patient organisation	26-27	902-979	A number of different guidelines are cited her as well ae in Table A4. It is well known that guidelines often lag behind because they not very frequently updated. We therefore feel that it is not correct to cite guidelines from before the NEJM publication It might very well be that in a number of countries practice has been changed already base on this publication while the guidelines have not yet been updated. It is strange that the EUNETHA report comes to different conclusion as compared to a number of recently updated guidelines (ASCO, St Gallen, ESMO)	2	We agree that guidelines are not frequently updated. An overview of relevant guidelines is provided in which no selection is made if MINDACT is incorporated or not, because we cannot determine which guidelines did or did not assess the clinical utility of MammaPrint. But we now added in the Table additional information on which guidelines were published after the MINDACT publication.
Description and technical characteristics of the technology (chapter 5)					
Clinical effectiveness					
Patient organisation	35	1354-1368	EUnetHTA has chosen to analyse the PPS population and take DFS as a surrogate endpoint. Our knowledge is not sufficient to comment on the choice of population (either PP or PPS). However,	1	Our conclusion is not only based on DFS. We have explained in more detail that our conclusion is based on DFS, DMFS as well as QoL. The conclusion is based on the absence of evidence on added value in terms QoL and on the fact that non-inferiority in terms of OS (surrogates

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			with respect to the endpoint it is stated in lines 194-196 (page 7): *Adjuvant systemic chemotherapy aims at treating subclinical metastatic cancer cells already present at the time of diagnosis, in order to prevent distant metastasis, ultimately prolonging survival and eventually cure the disease.* If chemotherapy aims at prevention of distant metastasis then the most appropriate surrogate endpoint would be DMFS.		five-year DMFS, five-year DFS and five-year OS) is not shown. In case of DMFS there are concerns about the immaturity of this outcome because of the imprecision (=very wide 95% CI's). Therefore the results do not rule out the possibility of a clinically relevant increase in distant metastasis and hence risk of death. In the case of DFS the fact that the effect was significant and clinically relevant was also taken into account in our final conclusion.
Patient organisation	72 36	1937 1400-1401 and 1408-1409	5yr DMFS in PPS is 96.5% (AO!) vs 94% (MP), HR0.65, p=0.08 5yr DMFS in PP is 96.7% (AO!) vs 94.8% (MP), HR 0.65, p=0.11 If DMFS is used |(either in PPS or PP) there is a rather small difference between outcome of CT based on AO! or MP (being the MP the less favorable). However, around 23 % of patients fall in the category of high risk AO! and low risk MP, so this minor disadvantage in DMFS would be achieved with 23% of patients less receiving chemotherapy. The resulting advantage of decrease in AES and increase in QOL (see p 27-28) is not taken into consideration, which is unacceptable for the patient organization.	1	Five-year DMFS is used as a surrogate for ten-year OS. Because there is no one-on-one relation between five-year DMFS and ten-year OS, the results of five-year DMFS are considered immature. Also because the data on DMFS points to inferiority and the confidence intervals are wide, it cannot be concluded it is safe to omit chemotherapy. As the absolute numbers show (6 less or at worst 287 more patients with distant metastasis) there is a lot of uncertainty about the potential risk. It is only possible to determine the trade-off between a potential increased risk of death and possible gain in QoL if both parameters had been quantified.
Safety					
Patient organisation	36	1396-1409	Minor attention is paid on this section to the AES related to chemotherapy and the subsequent loss in QOL. This is addressed at several other points in the report but not taken into serious consideration in the benefit risk evaluation.		These outcome measures were seriously considered, but there was no direct information available to quantify in more detail the results on long-term QoL and AE's.

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Appendix

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Comments by external reviewers: NVMO

Comment from *Name, title and affiliation*	Page number *Or 'general'*	Line/ section number	Comment and suggestion for rewording *Please insert each new comment in a new row.*	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
Summary					
			/		
Description and technical characteristics of the technology					
NVMO	12 & 23	353-357 763-766 1381-82	For the main conclusions the authors have used the Per Protocol Sensitivity (PPS) analysis, a surrogate endpoint with a observed higher absolute difference in Disease Free Survival (DFS) than in the ITT or PP analysis. This PPS analysis is in striking contrast to the analysis used in the peer reviewed article in the renowned New England Journal of Medicine as well as the ASCO Clinical Practice Guideline Update on the use of MammaPrint®. The primary end point of the MINDACT study was distant metastasis free survival at 5 years in the PP population. We therefore doubt if use of the 5 year DFS in the PPS analysis is the most reasonable, and consider this as authors's choice, while another choice could be possible as well, with a different outcome.	1	If the EUnetHTA assessment was based on the PP analysis it would have led to the same final conclusions as in the PPS. We have now added this specifically to the discussion section of the report. While setting up the MINDACT study and prespecifying the PP analysis it was not foreseen that there would be a period in which risk assessment went wrong. As a consequence it is debatable on which population the PP analysis should be based. In our opinion the PPS population is the least biased one, because all patients included in the study during this G-shift period were excluded and not only the selection of patients with a change in risk as was the case in the MINDACT PP population. As also the authors of the MINDACT mention all risk groups enrolled are somewhat biased due to incorrect risk assignment in the full

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					period (see table S5 of the MINDACT publication). Moreover, even though less events were observed and the number of patients was smaller, the effect in the PPS analysis was stronger showing a smaller p-value. In order to assess the robustness of the findings of the prespecified analyses of the study a sensitivity analysis (PPS) of the MINDACT study was performed. The sensitivity analysis is a critical way to assess potential variation and hence it is complementary and confirmative to the results of the prespecified analysis (PP) and herewith an important way to assess the final impact of the study results for clinical practice. Unfortunately, the PPS analysis points in the direction in which the MP group scores worse, thereby casting doubt on the robustness of the prespecified analysis. Our conclusion is not only based on DFS. We have explained in more detail that our conclusion is based on DFS, DMFS as well as QoL. The conclusion is based on the absence of evidence on added value in terms QoL and on the fact that non-inferiority in terms of OS (surrogates five-year DMFS, five-year DFS and five-year OS) is not

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					shown. In case of DMFS there are concerns about the immaturity of this outcome because of the imprecision (=very wide 95% CI's). In this case the results do not rule out the possibility of a clinically relevant increase risk of death. In case of DFS the fact that the effect was significant and clinically relevant was also taken into account in our final conclusion.
Health problem and current use					
NVMO	27	968	The recently published ASCO Clinical Practice Guideline Update on the use of MammaPrint® to guide decisions on the use of adjuvant chemotherapy in breast cancer clearly recommends the use of MammaPrint® for certain indications (Krop I et al, J Clin Oncol 2017; 35: 2838-28470). This evidence-based guideline by an international Expert Panel rates the evidence of this recommendation as high quality and the strength of recommendation is labelled as being strong Look at page 1241	1	The most recent guidelines of the ASCO, ESMO and the ST Gallen recommend MP based on level 1 evidence from the MINDACT study. It was not clear how the quality of the evidence was rated. From an EUnetHTA perspective however, it is mandatory to assess the quality of the evidence following EUnetHTA standards and methods and make transparent what the arguments are to rate the evidence. The fact that the evidence is derived from a large multicenter RCT does not automatically mean that the quality of the evidence is high. Differences in for example outcome measures influence the rated quality of the evidence and therefore the confidence in the results.
NVMO	12	383-385	In the clinic the MammaPrint® is not used neither indicated in clinical low risk patients.		We understand that MammaPrint is not used in clinical low risk patients in the

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					Dutch setting. However, the dedicated reviewers within the EUnetHTA network requested to add the results of the clinical high as well as the clinical low risk patient groups.
Clinical effectiveness					
NVMO	12 35	357-358 1357-1361	The conclusion of the authors that MammaPrint® is not proven non-inferior compared to Adjuvant Online for decision making of adjuvant chemotherapy is mainly based on the observation that 5 year DFS in the PPS shows a worse outcome (88,8 versus 93,3%). In the PP analysis, however, the difference is not significant. However, we think DMFS is a better outcome to use in this situation. Chemotherapy is primarily given to prevent distant metastasis, but it also prevents locoregional recurrences. Although such a recurrence is stressfull to patients it is still a curable disease, and MammaPrint® is not developed as predictor for local recurrences.	1	Also in the PP analysis the five-year DFS is significant (p=0.03). In addition, our conclusion is not only based on 5-year DFS. As mentioned in our reaction to your first comment we have explained in more detail that our conclusion is based on DMFS, DFS as well as on QoL. We also now explained this in more detail in the report.
Safety					
NVMO	general		Although health related quality of life was not measured in the MINDACTstudy , there is ample evidence that adjuvant chemotherapy does have a negative effect on quality of live. Besides the 1-2,5% chance of serious illnesses like leukemia and heart failure, several studies show a 20-30% of patients who are not able to go back to work because of fatique or psychological problems. This makes it extremely important that only patients with a poor prognosis and a high risk of the development of distant metastasis will be treated with chemotherapy to diminish the risk of distant recurrences. The benefits and risks of adjuvant chemotherapy are extensively discussed with every patient, in a process of shared decision making, while taking into account patient preferences, general life expectancy and comorbidity as well. In prospective cohort studies in the Netherlands, the use of MammaPrint® appeared to be safe with an excellent outcome for those with a low risk MammaPrint® not treated with adjuvant chemotherapy (RASTER study) and a decrease in the use of (unnecessary) adjuvant chemotherapy (Kuijer A et al, J Clin Oncol 2017;35:2814). At present, gene expression profiles on adjuvant chemotherapy in early breast		The QoL is not directly measured in the MINDACT trial, but it may be argued that some aspects of QoL are reflected by other outcomes. As mentioned in the assessment report it's obvious that the QoL of patients receiving adjuvant chemotherapy will be reduced due to chemotherapy side effects during and shortly after treatment compared to patients who do not receive chemotherapy The benefit in quality of life during the administration period chemotherapy is indirectly known from empirical evidence. In addition, the MINDACT study shows that refraining from

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			cancer are extensively used in daily clinical practice both in Europe as well as in the Unites States. Various international guidelines (ASCO, ESMO and St Gallen) advice on the use of validated gene expression profiles such as MammaPrint® for certain indications in early breast cancer (Senkus E et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26S5: v8; • Coates AS et al. Tailoring therapies-improving the management of early breast cancer: St Gallen 2015. Ann Oncol 2015;26:1533-46).		chemotherapy leads to a significant and clinically relevant worse five-year DFS. All kind of recurrences are stressful to patients even in the case of a curable disease. This distress will have its repercussions on quality of life. Because QoL is not available in the MINDACT, the added value of the MammaPrint in terms of long-term QoL in the long term cannot be quantified. In addition to that it is not yet clear what will be the effect of refraining from chemotherapy on mortality. In our opinion shared decision making should be based on information about the loss of overall survival (or surrogate) and the benefit in long-term QoL in which both patient related outcomes are measured and there is enough certainty in the results (so no wide 95% CI's). Currently, benefit in long-term QoL is not quantified and the risk of distant metastasis is not certain, as shown by the absolute numbers: omitting chemotherapy after following MammaPrint® risk assessment and not AO! can lead to 10 (of 100) more patients that will not be free of distant metastases after five years. Looking at the 95% CI five-year of DMFS, it could also lead to one (0.6) less or at worst 29 (of 100) more patients who are not free of distant metastases after five

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					years.
Appendix					
			/		

Additional feedback external reviewers: NVMO

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Methods				
1. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	x			
2. Are the quality appraisal tools appropriate?	x			
3. Is the type/presentation of evidence (e.g. Meta-analysis, qualitative synthesis, GRADE) appropriate for this analysis?	x			
4. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?				We doubt the method, comment on PPS above
5. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?	x			
6. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?	x			
7. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?				We wonder why other data were not used, especially the RASTER data
8. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?				See comment on DMFS
Comments:				

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9. Are details on sources of information and literature search strategies provided?					
Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
O	O	O	O	O	O
Comments: yes for all questions					

10. Information on basis for the assessment and interpretation of selected data and information:		
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?
O	O	O
Comments: yes for all questions		

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part II: Results (See Domain Reports)				
Description and technical characteristics of the technology				
1. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	x			
2. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	x			
3. Are the supporting references current and do they provide an international picture of the problem?	x			
Comments:				
Health problem and current use of the technology				
4. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	x			
5. Are the supporting references current and do they provide an international picture of the problem?	x			
Comments:				
Safety and effectiveness				See earlier
6. Is the risk of bias clearly reported?				

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7. Is quality of data sufficiently evaluated?				
8. Are both relative and absolute effect measures presented for each dichotomous outcome?				
9. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?				
10. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?				
11. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported?				
12. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?				
13. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?				
14. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?				
Comments:				
General				
15. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	x			
16. Can the results be applied to the intended population?	x			
17. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	x			
Comments:				
Part III: Summary of Relative Effectiveness				
18. Does the summary present a balanced representation of the content of the report?				It stresses the difference in DFS too much and looks less to other outcomes as well as QoL see comment on safety
19. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?				

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	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Comments:				
Part IV: Other Considerations				
20. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)				
Comments:				

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Comments by Manufacturer: Agendia, NL

Comment from *Name and organisation*	Page number *Or 'general'*	Line or section number	Comment and suggestion for rewording *Please insert each new comment in a new row.*	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
Summary					
Agendia			In this summary we respond to the outcome of EUnetHTA's rapid assessment of added value of using gene-expression signature MammaPrint for adjuvant chemotherapy decisions in early breast cancer. Based on the recent release of the EUnetHTA assessment of MammaPrint we would like to provide the following clarification. We appreciate the effort taken to review all data available for the MammaPrint assessment. However, we respectfully disagree with its conclusion that the current data are not sufficient to determine that it is safe to omit chemotherapy in the clinical high and genomic low population of early breast cancer patients, and questioning the approach taken by the clinicians who designed the supporting trials. We believe that the design and positive outcome of the MINDACT trial were not correctly interpreted in the assessment. **We question the validity of several key assumptions utilized by the committee for this review, and believe that this warrants re-examination of our submission.**		The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
			Our main problem with this assessment is the basis of using the secondary aim of the MINDACT study as a primary aim on the sensitivity population which was not intended to evaluate protocol deviations for the primary or secondary objective of the study. The aim of the assessment		The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of

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			was to prove clinical utility of MammaPrint and that MammaPrint in addition to clinical factors would improve adjuvant treatment recommendations; not to prove that it cannot be excluded that adjuvant chemotherapy following clinical risk assignment significantly decreases the hazard of death due to distant metastasis, as this not the aim of the assessment. No significant difference was found in 5-years DMFS in clinical high/ genomic low the patients indicating no benefit of giving chemotherapy in this group. The primary importance for reimbursement decisions should be that by adding MammaPrint to clinical factors patients would not be compromised in outcome. The primary analysis of MINDACT focused on the survival by DMFS for the discordant clin-high/MP-low group randomized to no chemo. The primary test in MINDACT was as follows: In the group of patients who have a low risk gene prognosis signature (G-Low) and high risk clinical-pathological criteria (A!O/Clin-high), and who were randomized (R-Treatment decision) to use the MammaPrint risk and thus receive no chemotherapy, a null hypothesis of a 5-year DMFS of 92% was tested. At 5 years, patients from the primary-test group had a DMFS of 94.7% (95% CI, 92.5 to 96.2); thus, the primary objective of the study was achieved. This is of direct interest for the EUnetHTA question regarding clinical utility of MammaPrint. The results indicate that there is no clinical benefit for chemotherapy, since also in the discordant group (Clin-high/G-Low), in the untreated are, the 5-year rate of survival without distant metastasis was a non-statistically significant 1.5% lower than the rate with chemotherapy. Moreover, the risk of recurrence for the indicated group without chemotherapy was considered to be sufficiently low, that by predefined criteria benefit of chemotherapy was considered not to be beneficial. Together, these data show that added benefit of chemotherapy does not outweigh the harms for MammaPrint -Low Risk patients. **Therefore, the primary aim of the MINDACT should be used in the assessment of this EUnetHTA report to prove clinical utility of MammaPrint.**		technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.

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			Secondly, we argue that 5 years of follow-up is sufficient and no 10 years follow-up is required. In the clinical community the general consensus is that chemotherapy benefit is mainly seen within the first five years (as observed in the Oxford Overview Analysis, Lancet, 2012). Moreover, five year survival data is commonly accepted by regulators as the basis for approval and implementation of novel therapies. The MINDACT trial was designed to assess the clinical utility of the MammaPrint 70-gene breast cancer recurrence test, not the effect of therapies. The clinical utility of MammaPrint and its primary intended use is determining the potential benefit of adjuvant chemotherapy for reducing the risk of metastatic disease. This information contributes to an informed shared decision-making process between the patient and her doctor. Contrary to the benefit of (extended) endocrine therapy for which the 10 year end point is generally accepted, there is a wealth of medical evidence that the benefit of chemotherapy is limited to the first 5 years after diagnosis, and therefore 10 years' follow-up would not be expected to significantly change the clinical utility of the assay. Chemotherapy in the first weeks after diagnosis of a primary tumor tends not prevent a metastatic event in the years 5-10. Specifically, the benefit of chemotherapy, in both ER+ and ER- breast cancer, is limited to reducing recurrences within the first 5 years, with no later effect. Evidence for the main effect of chemotherapy in the first five years is captured by the entire body of peer-reviewed randomized trials in Adjuvant Therapy for Breast Cancer has been periodically reviewed by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) in the so-called "Oxford Overview" and has established the standard of care for early breast cancer (Oxford Overview Analysis, Lancet, 2005 and 2012). **Therefore, in the case of the MammaPrint assay, the principle area of clinical utility is to determine the potential benefit of chemotherapy for ER+ breast cancer, a benefit which, if present, will only be observed in the first 5 years.**		The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.

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			In addition, we argue that the chosen endpoint in this assessment, DFS, is not the appropriate endpoint. Distant metastases account for majority breast cancer deaths and are the major threat to patient survival. This is why choosing DMFS as the primary endpoint is so relevant for the chemotherapy question. It focuses on the events that are distant in nature which is the primary reason chemotherapy is prescribed. A major problem with DFS is lack of specificity for disease-specific outcome, leading to a loss of power. DMFS on the other hand excludes ipsilateral breast tumor recurrence, regional invasive recurrences, contralateral breast cancer, and all in situ carcinomas, as these events are potentially nonlethal. **Therefore, the outcome in this assessment of MammaPrint should be DMFS, as this focuses on the events that are distant in nature which is the primary reason chemotherapy is prescribe in breast cancer**		The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We believe this comment is not related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the patient organisation and the NVMO. Based on these comments we have clarified the text.
			Also we argue the use ESMO-MCBS for defining the assumption of the threshold used in the assessment as it is not intended to be used for a diagnostic device. The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a standardized, generic, validated tool to stratify the magnitude of clinical benefit that can be anticipated from anticancer therapies (“Grading derived from the ESMO-MCBS provides a backbone for value evaluations for cancer medicines”). It is not intended to be used for a diagnostic device. The choosing of these thresholds is essential to the outcome of the assessment. The importance of the choosing of a valid threshold has been acknowledged by having all stakeholders (a pan-European exercise) determine the MINDACT objectives. The current assessment is neglecting the MINDACT, BIG, EORTC joined efforts in determining the appropriate endpoints for assessing MammaPrint’s clinical utility. We sincerely regret the lack of trust (and respect) in such highly valued committees, dedicated to provide best clinical practice to breast cancer patients.		The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We believe this comment is not related to a factual inaccuracy and therefore we did not change the text based on this comment.

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			Therefore, we highly question the applied methodology of ESMO-MCBS and strongly encourage the assessment committee to consult with the ESMO-MCBS working group to discuss applicability and methodology for using the ESMO-MCBS tool for determining "MammaPrint benefit".		
			Furthermore, we disagree with the authors that they used results from the sensitivity analysis as their main result (Table S5 in MINDACT NEJM paper). Sensitivity analyses play a crucial role in assessing the robustness of the findings or conclusions based on primary analyses of data in clinical trials. They are a critical way to assess the impact, effect or influence of key assumptions or variations—such as protocol deviations, missing data, and outliers—on the overall conclusions of a study. Consistency between the results of primary analysis and the results of sensitivity analysis strengthens the conclusions or credibility of the findings and indicates the primary analysis (thus on the whole MINDACT PP population) is valid and is the preferred population. **Therefore, sensitivity analysis are meant to verify the main results and when this is confirmed results of the primary analysis on PP population should be used as main study results.**		The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the NVMO. Based on these comments we have clarified the text.
			The MINDACT trial was designed by leading European clinicians and conducted by 112 institutions, to answer the question: can genomic profiling of breast cancers with high-risk clinical and pathological features identify women who can safely avoid adjuvant chemotherapy? MINDACT was coordinated and sponsored by the European Organisation of Research and Treatment of Cancer (EORTC) as part of an extensive partnership with the BIG (Breast International Group) and other partners including patient advocate groups. The trial endpoint, after consensus by key opinion leaders involved in the trial's design, was Distant Metastasis Free Survival (DMFS) at five years. The MINDACT trial identified there was no significant benefit of		The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore. However, a reaction on this

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			chemotherapy at five years in clinical high-risk patients, classified by MammaPrint as low-risk. The excellent survival outcome of these patients, usual candidates for adjuvant chemotherapy, showed no statistically significant difference whether treated with chemotherapy or not (94.8% without versus 96.7% with chemotherapy), confirming the prognostic ability to identify a large group of women who may safely forego chemotherapy. The patient impact of the side effects of chemotherapy are widely documentedi and the MINDACT study results show that by using the MammaPrint test a 46% reduction in use of chemotherapy can be achieved in this patient population. As a result the number of women having to endure needless chemotherapy with accompanied adverse events and toxicity, but without beneficial effect, will be substantially reduced. An additional five year follow-up will be performed but based on experience in previous trials we do not expect a change in outcome. Postponing the use of gene expression based tests for another five years will lead to thousands of patients in Europe potentially receiving unnecessary chemotherapy. **Overall, the assessment of this EUnetHTA report is solely based on evidence of clinical effectiveness of one RCT, the MINDACT study. Besides the fact that we think that there is additional evidence available to prove and support the clinical utility of MammaPrint we are convinced that the whole MINDACT study is not being used appropriately in this assessment as clarified above.**		topic is found at one of the comments of the patient organisation and the NVMO. Based on these comments we have clarified the text.
Scope					
Agendia	Page 13	Line 443	In the following sentence, "*The randomized study (the MINDACT) provided direct evidence on the clinical utility on 5-year follow-up data (interim analysis)*", please remove (interim analysis). As can be read in the MINDACT paper by Cardoso et al 2016, the primary endpoint was survival without distant metastasis (event-free rate at 5 years) and not 10 years. The 5y analysis is thus by no means an interim analysis as	2	We have removed the words interim analysis. However, our critical endpoint remains 10-year OS.

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			suggested by the authors of this assessment. Indeed, patients will be followed for at least 10 years (and those receiving endocrine therapy will be followed for a minimum of 15 years) but this does not change the primary endpoint of the study.		
Agendia	Page 14	Table	Please remove (*and possibly as replacement*). from the first section in the Intervention column. The reason for this sentence being there is unclear.	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text. However, a reaction on this topic is found at one of the comments of the NVMO.
Methods and Evidence included					
Agendia	Page 17	Line 568	The assessment should include retrospective analyses of prospectively randomized trials such as the Stockholm 3 (STO-3) tiral (Esserman et al, JAMA Oncology 2017, van 't Veer et al, BCRT 2017) as well as the RASTER study.	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". This comment address another domain. But a reaction on this topic is found at one of the comments of the patient organisation and the NVMO. We have added a table in which is explained why literature was not included in the assessment.

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Agendia	Page 18	Figure 1	It is not clear which 53 records were identified. More information should be given on what these records were. Based on P15, 472 under study design **' If evidence from randomized controlled studies is limited, prospective observational studies will be considered to be included to get more stable estimates on the clinical utility'** based on the statement above there are more studies available to prove and support clinical utility. We don't see any reasons not to include RASTER (Drukker, Int J Cancer, 2013).	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". This comment address another domain. But a reaction on this topic is found at one of the comments of the patient organisation and the NVMO. Based on these comments we have clarified the text.
Agendia	Page 18	Section 3.6, line 598	Reason for excluding RASTER incorrect. The authors state that no OS or surrogate was reported for the discordant groups. The aim of the RASTER study, sponsored by CVZ, now ZIN, was to assess patient's preference for treatment decision when MammaPrint information low or high risk is added to clinical risk assessment, and to evaluate 5- and 10-year outcome in concordant as well as discordant risk assessed groups. On the basis of in/ exclusion criteria the Raster study could and should be included. The RASTER study was the first prospective study to report 5 year outcome data for patients treated on the basis of a breast cancer gene assay.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text. However, a reaction on this topic is found at one of the comments of the patient organisation and the NVMO. Based on these comments we have clarified the text.

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Agendia	Page 21	Section 3.7	Direct comparison required. As in the PICO of this assessment as well as in MINDACT, the first comparator was modified Adjuvant! Online (A!O). The authors should then use A!O as first and only comparator and not only assess the effect of chemotherapy in the discordant groups which was the secondary objective of MINDACT though not powered for. In fact both the primary and secondary objective of MINDACT address the utility of chemotherapy. The primary test in MINDACT was as follows: In the group of patients who have a low risk gene prognosis signature (G-Low) and high risk clinical-pathological criteria (A!O/Clin-high), and who were randomized (R-Treatment decision) to use the 70-gene risk and thus receive no chemotherapy, a null hypothesis of a 5-year DMFS of 92% was tested. At 5 years, patients from the primary-test group had a DMFS of 94.7% (95% CI, 92.5 to 96.2); thus, the primary objective of the study was achieved. This is of direct interest for the EUnetHTA question regarding clinical utility of MammaPrint. The results indicate that there is no clinical benefit for chemotherapy, since also in the discordant group (Clin-high/G-Low), in the untreated are, the 5-year rate of survival without distant metastasis was a non-statistically significant 1.5% lower than the rate with chemotherapy. Together, these data show that added benefit of chemotherapy does not outweigh the harms in when MammaPrint -Low Risk is indicated..	1	The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
Agendia	Page 21	Line 660-661	The authors correctly state that the primary analysis of the study (MINDACT) does not address the current (EUnetHTA) question when wanting to compare the two arms directly. However, the primary objective of the trial does evaluate clinical utility of chemotherapy in the discordant group clin-high/genomic-low	1	The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.

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Agendia	Page 22	Line724	"*This 3% difference in 10-year OS was also mentioned …. in the literature"* We would like to point out that the reference that is being referred to cannot be considered a sound peer reviewed statistical representation of how the MINDACT trial should be assessed. It is an opinion article in a Dutch medical journal. Moreover, the HR in MINDACT is based on 5 year DMFS and this HR cannot be directly extrapolated to 10 year DFS or OS as is done by the authors of this specific article.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy but we assume the manufacturer misinterpreted the text. We made minor changes to the text.
Agendia	Page 22		The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a standardized, generic, validated tool to stratify the magnitude of clinical benefit that can be anticipated from anticancer therapies ("Grading derived from the ESMO-MCBS provides a backbone for value evaluations for cancer medicines"). **It is not intended to be used for evaluation of a diagnostic test.** We highly question the applied methodology of ESMO-MCBS and strongly encourage the assessment committee to consult with the ESMO-MCBS working group to discuss applicability and methodology for using the ESMO-MCBS tool for determining "MammaPrint benefit". The form used in the current assessment (2C), *is not intended for a device such as MammaPrint: "Evaluation form 2c: for therapies that are not likely to be curative with primary end point other than OS or PFS or equivalence (non-inferiority) studies."* *Thresholds for the assessment were determined as follows: To determine non-inferiority, a non-inferiority boundary is needed. There is no international consensus about this non-inferiority threshold. For that reason we used the GRADE B threshold of the ESMO-MCBS (form 1). The ESMO describes the highest level of clinical benefit (GRADE A), as an improvement of survival >5% at ≥3 years follow up and an*	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text based on this comment.

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			improvement of survival between 3% and 5% as GRADE B level of clinical benefit. In case mature survival data are not available GRADE A level of clinical benefit is assigned when improvements in DFS are found in which the Hazard Ratio (HR) is smaller than 0.65 (in studies without mature survival data), and GRADE B clinically relevant is assigned when the HR is in between the 0.65 and 0.80. In both cases the HR threshold refers to the lower extreme of the 95% CI to take into account the variability of the estimate. Because the threshold will be used as a non-inferiority threshold the 3% difference in OS or the HR<0.8 is used to assess if the MammaPrint® is non inferior in case of 10-year OS (or a surrogate). **The choosing of these thresholds is essential to the outcome of the assessment. The importance of the choosing of a valid threshold has been acknowledged by having all stakeholders (a pan-European exercise) determine the MINDACT objectives. The current assessment is neglecting the MINDACT, BIG, EORTC joined efforts in determining the appropriate endpoints for assessing MammaPrint clinical utility. We sincerely regret the lack of trust (and respect) in such highly valued committees, dedicated to provide best clinical practice to breast cancer patients.**		
Agendia	Page 23	Section 3.8.2	The sensitivity analysis was performed to test whether leaving out the patients enrolled during the G-shift period of the MINDACT trial would have any impact on outcome for the total population. As you can see from the table below derived from Cardoso et al., 2016, the PP, PPS and ITT analyses come to essentially the same conclusions, for which reason confidence in the study results is excellent. The authors continue with using only the results from the PPS population, whereas the incentive for the PPS analysis was different and incorrect to be used for making conclusions since the study was powered not for the PPS population. Moreover, DMFS is a widely accepted relevant endpoint in breast cancer as, distant recurrence is the main threat to patient survival (Hudis et al., JCO 2007) and where the main benefit for CT is observed. DFS on the	1	The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We believe this comment is not related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the NVMO. Based on this comment we have clarified the text.

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<table>
<tr><td></td><td></td><td></td><td>other hand includes all deaths, local relapses and secondary primaries for which chemotherapy is not primarily intended.
Focusing the main research question of this assessment on a sensitivity analysis of MINDACT (PPS) and taking DFS as endpoint from this analysis is therefore not correct.

<table><tr><td>High C-risk, Low G-risk</td><td>PP-Per Protocol (tabel 2)</td><td></td><td>PPS-Sensitivity (ta</td></tr><tr><td>DMFS</td><td>0.65 (0.38 – 1.10)</td><td>0.11</td><td>0.60 (0.34 – 1.06)</td></tr><tr><td>DFS</td><td>0.64 (0.43 – 0.95)</td><td>0.03</td><td>0.57 (0.37 – 0.87)</td></tr><tr><td>OS</td><td>0.63 (0.29 – 1.37)</td><td>0.25</td><td>0.54 (0.23 – 1.26)</td></tr></table></td><td></td><td></td></tr>
<tr><td>Agendia</td><td>Page 23</td><td>Section 3.9</td><td>In this section it is stated that the Scientific Advice Committee of ZIN is not included within this assessment for the reason that they will be involved with the Dutch reimbursement assessment that will be based on this report. In the same paragraph however, Prof Bossuyt, chairman of the same Scientific Advice Committee of ZIN is put forward as a contributor for this current assessment. This is contradictory and implies a conflict of interest for ZIN in the Dutch assessment with Prof Bossuyt being the chairman within the same institute, ZIN.</td><td>1</td><td>The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.</td></tr>
<tr><td colspan="6">Health problem and current use</td></tr>
<tr><td>Agendia</td><td>Page 24</td><td>Line 814-815</td><td>Choosing the right endpoint when assessing prognosis and benefit of treatment for patients is very important. As line 814-815 states correctly; Distant metastases account for majority breast cancer deaths [20], and was also noted by Hudis et al., JCO 2007, distant recurrence is the threat to patient survival. This is why choosing DMFS as the primary endpoint is so relevant for the chemotherapy question. It focuses on the events</td><td>1</td><td>The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We</td></tr>
</table>

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			that are distant in nature which is the primary reason chemotherapy is prescribed. It also includes deaths by all causes, which is why DMFI, also is found in the Supplementary data of the MINDACT publication (Cardoso et al., 2016) is an even more specific end-point and includes distant recurrence and breast cancer specific deaths only. We would like to specifically address why using disease-free survival as well as Overall Survival in adjuvant studies are not the most appropriate, since these endpoints include all deaths, even those that are unrelated to the cancer being treated, and some definitions of disease-free survival also include the occurrence of unrelated new cancers at other sites. A major problem with these endpoints is lack of specificity for disease-specific outcome, leading to a loss of power. For breast cancer, only about 30% of women will die from their disease and less than 20% for stage I disease. (Cuzick, JNCI 2014). Moreover, it is known that chemotherapy is not given to prevent secondary primary (42% of events) or local recurrence (16%), the key drivers of DFS in MINDACT.		believe this comment is not related to a factual inaccuracy and therefore we did not change the text. However, a reaction on this topic is found at one of the comments of the patient organisation and the NVMO.
Agendia	Page 27	Line 966	We would like to specifically address the referencing and quoting of guidelines on page 27, starting at line 962. The guidelines mentioned in Table A4 are not a representative collection of guidelines and their appropriateness in the different countries. Certain very important guidelines are not referred to at all (such as AGO in Germany), other inappropriate and/or outdated guidelines *are* included and used merely to state "that certain guidelines state that "MammaPrint is 'only for research purposes'". Guideline referencing is a very sensitive matter, since in each country different rules apply. For instance in Spain, reimbursement of breast cancer genomic signatures is very complex since there is no National plan. It is managed and decided in each of the 17 Autonomous Communities. Some regions have set public tenders to choose only one platform, others allow all platforms and let hospitals decide which to use and some Communities haven't authorized these tests yet. Recently, there has been a growing trend towards public tenders, in which both the clinical evidence of the	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. The main text of paragraph 4.2.5. is already based on ESMO and St Gallen recommendations and we have added their recent revisions with regard to the MammaPrint also in 4.2.5. as we already did in table A4.

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			test as well as the economic offer are weighted equally. Regarding ESBC Guidelines, the most accepted and followed in Spain are ASCO, NCCN & ESMO, although the St. Gallen's consensus is also important. The Spanish Society of Medical Oncology (SEOM) Guidelines (attached) are not truly relevant. There are no universal guidelines for all specialists, each one follows which considers appropriate. The AETSA & UETS reports that are included in the table are not considered guidelines in Spain at the moment, they are obsolete and under review (in fact, in Andalusia and Madrid all 4 tests are available, the decision depends on each hospital). It is mentioned that ASCO has been updated when looking at table A4, Appendix 1, not the latest version of the guidelines are included which actually have included MammaPrint to be the only GEP that can be used in lymphnode positive patients.. The EUnetHTA assessment repeatedly states that the assessment is a European exercise, so we wonder why the most important European guidelines (ESMO and St Gallen) are so ill represented, whereas these guidelines do provide a positive recommendation for using MammaPrint in the adjuvant breast cancer setting.		
Description and technical characteristics of the technology					
Agendia	Page 29	Line1064	"with a median follow-up of 8 years" → Of the 78 patients, 44 patients remained free of disease after their initial diagnosis for an interval of at least 5 years (good prognosis group, mean follow-up of 8.7 years), and 34 patients had developed distant metastases within 5 years (poor prognosis group, mean time to metastases 2.5 years).	2	The citation is literally copied from the MINDACT protocol as referenced. We will add your reference, and change follow-up in 8.7 years.
Agendia	Page 29	Line 1066	"recurrence in less than 5 years" → recurrence within 5 years	2	The citation is literally copied from the MINDACT protocol as referenced. We will change recurrence in less than 5 years in recurrence within 5 years.

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Agendia	Page 29	Line 1066	Reference 62 → *Veer, Laura J Van et al. 2002. "Gene Expression Profiling Predicts Clinical Outcome of Breast Cancer." Nature 415: 530–36.*	2	We will add this reference.
Agendia	Page 29	Line 1072	Add text: "This numerical score is overlaid with a binary Low Risk / High Risk clinical classification system. A breast cancer tumour with a MammaPrint index below or equal to zero is classified as High Risk and a tumour with a MammaPrint index higher than zero is classified as Low Risk."	2	We will add this text.
Agendia	Page 29	Starting Line 1092	The section "Validation of the 70-gene profile (MammaPrint®)" is based on the report of the KCE which is adapted from the publication of Ward et al. (2013) that only includes references from January 2009 through May 2011, is very UK-minded and focused on ER+, LN- patients. The main critic of Ward et al. (2013) on MammaPrint® is that validation is based on observational data (small cohort studies) rather than randomized data. The KCE report even states that the results of the report should be considered preliminary until the data from randomized controlled trials, like MINDACT, are made public. In 2016 the results from the MINDACT study were published in the New England Journal of Medicine.[1] The prospective, randomized controlled trial showed that patients identified as high risk by conventional risk classifiers and re-classified by MammaPrint® as Low Risk, have an excellent survival without chemotherapy. To further show that the "validation of the 70-gene profile" is poorly referenced, we provide you with a list of both retrospective and prospective validation studies[1-23]: 1. *Cardoso, F. et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N. Engl. J. Med. 375, 717–729 (2016).* 2. *Vijver, M. J. van de et al. A gene-expression signature as a predictor of survival in breast cancer. N. Engl. J. Med. 347, 1999–2009 (2002).* 3. *Buyse, M. et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J. Natl.*	1	We have replaced the conclusions of the KCE report/Ward with the conclusions of the systematic reviews as described in chapter 2.1 (lines 419-423 and 443-446 of the consultation version of the assessment). For the sake of completeness we have added a reference to this (and the next) comments for all literature concerning validation of the MammaPrint. However, we want to emphasize that validation studies cannot be used as supportive evidence for clinical utility. It was not in the scope of this assessment to assess the validation of the MammaPrint.

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			Cancer Inst. 98, 1183–1192 (2006). *4. Bueno-De-Mesquita, J. M. et al. Validation of 70-gene prognosis signature in node-negative breast cancer. Breast Cancer Res. Treat. 117, 483–495 (2009).* *5. Sapino, A. et al. MammaPrint Molecular Diagnostics on Formalin-Fixed, Paraffin-Embedded Tissue. J. Mol. Diagn. 16, 190–197 (2014).* *6. Delahaye, L. J. Performance characteristics of the MammaPrint breast cancer diagnostic gene signature. Per. Med. 10, 801–811 (2013).* *7. Drukker, C. A. et al. Long-term impact of the 70-gene signature on breast cancer outcome. Breast Cancer Res. Treat. 143, 587–592 (2014).* *8. Wittner, B. S. et al. Analysis of the mamma print breast cancer assay in a predominantly postmenopausal cohort. Clin. Cancer Res. 14, 2988–2993 (2008).* *9. Mook, S. et al. The 70-gene prognosis signature predicts early metastasis in breast cancer patients between 55 and 70 years of age. Ann. Oncol. 21, 717–722 (2009).* *10. Mook, S. et al. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. Breast Cancer Res. Treat. 116, 295–302 (2009).* *11. Mook, S. et al. Metastatic potential of T1 breast cancer can be predicted by the 70-gene MammaPrint signature. Ann. Surg. Oncol. 17, 1406–1413 (2010).* *12. Knauer, M. et al. Identification of a low-risk subgroup of HER-2-positive breast cancer by the 70-gene prognosis signature. Br. J. Cancer 103, 1788–1793 (2010).* *13. Ishitobi, M. et al. Clinical utility of the 70-gene MammaPrint profile in a Japanese population. Jpn. J. Clin. Oncol. 40, 508–512 (2010).* *14. Esserman, L. J. et al. Impact of mammographic screening on the detection of good and poor prognosis breast cancers. Breast Cancer Res. Treat. 130, 725–734 (2011).* *15. Grant, K. A. et al. Mammaprint Pre-screen Algorithm (MPA) reduces*		

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			chemotherapy in patients with early-stage breast cancer. South African Med. J. 103, 522–526 (2013). *16. Espinel, C. F. et al. MammaPrint Feasibility in a Large Tertiary Urban Medical Center: An Initial Experience. Scientifica (Cairo). 2012, 941507 (2012).* *17. Kok, M. et al. Additional value of the 70-gene signature and levels of ER and PR for the prediction of outcome in tamoxifen-treated ER-positive breast cancer. Breast 21, 769–778 (2012).* *18. Saghatchian, M. et al. Additional prognostic value of the 70-gene signature (MammaPrint) among breast cancer patients with 4-9 positive lymph nodes. Breast 22, 682–690 (2013).* *19. Drukker, C. A. et al. Mammographic screening detects low-risk tumor biology breast cancers. Breast Cancer Res. Treat. 144, 103–111 (2014).* *20. Drukker, C. A. et al. Optimized outcome prediction in breast cancer by combining the 70-gene signature with clinical risk prediction algorithms. Breast Cancer Res. Treat. 145, 697–705 (2014).* *21. Drukker, C. a et al. Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Breast Cancer Res Treat 148, 599–613 (2014).* *22. Nunes, R. et al. Genomic profiling of breast cancer in African-American women. Breast Cancer Res. Treat. 159, 481–488 (2016).* *23. Yao, K. et al. Molecular subtyping improves diagnostic stratification of patients with primary breast cancer into prognostically defined risk groups. Breast Cancer Res. Treat. 154, 81–88 (2015).* Please also find detailed table with the most important references for published MammaPrint validation studies below (MammaPrint Evidence Overview).		
Agendia	Page 29	Conituna tion line 1092	MammaPrint Evidence Overview		See reaction above.

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Publication	Objective	Details	Results
Gene-expression signature as a predictor of survival in breast cancer. **van de Vijver** MJ, He YD, van't Veer LJ, et al. N Engl J Med 2002; 347:1999-2009	First validation of MammaPrint in consecutive series of breast cancer patients. (<53 yrs)	295 patients (151 patients LN0; 5% adj treatment; 7.3 yrs follow-up)	Metastasis-free survival by MammaPrint at 10 yrs for LN- patients: good prognosis signature 87%; poor prognosis signature 44% (at 5 yrs: 93% and 56% respectively)
Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. **Buyse** M, Loi S, van't Veer L, Viale G, et al. J Natl Cancer Inst 2006; 98:1183-1192	Independent validation of MammaPrint; (LN0, <61 yrs)	302 patients; no adj treatment; 13.6 yrs follow-up	Metastasis-free survival by MammaPrint at 10 yrs: good prognosis signature 88%; poor prognosis signature 71%; (at 5 yrs: 96% and 83% respectively)
Analysis of the MammaPrint Breast Cancer Assay in a Predominantly Postmenopausal Cohort. **Wittner** BS, Sgroi DC, Ryan PD, et al. Clin Cancer Res 200; 814(10): 2988-2993	Independent US validation of MammaPrint in postmenopausal women; (median age 63 yrs)	105 patients; 45% adj treatment; 11.3 yrs follow-up	Metastasis-free survival by MammaPrint at 10 yrs: good prognosis signature 100%; poor prognosis signature 90%; (at 5 yrs: 100% and 90% respectively)
The 70-gene prognosis signature predicts early metastasis in breast cancer patients between 55 and 70 years of age. **S. Mook**, M. K. Schmidt, B. Weigelt, et al. Ann of Oncol 2009; 21(4):717-722	Independent validation of MammaPrint; (T1-2, LN0, 55-70yrs)	148 patients; 18% adj BT; 12.3 yrs follow-up	Metastasis-free survival by MammaPrint at 10 yrs: good prognosis signature 80%; poor prognosis signature 67%; (at 5 yrs: 93% and 72% respectively)
Validation of 70-gene prognosis signature in node-negative breast cancer. **Bueno-de-Mesquita** JM, Linn SC, Keijzer R, et al. Breast Cancer Res Treat 2009; 117(3):483-495	Independent validation of MammaPrint; (LN0, <55 yrs)	123 patients; 37% adj treatment; 5.6 yrs follow-up	Metastasis-free survival by MammaPrint at 5 yrs: good prognosis signature 98%; poor prognosis signature 78%
The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1–3 positive lymph nodes in an independent validation study. **Mook** S, Schmidt MK, Viale G, et al. Breast Cancer Res Treat 2009; 116(2):295-302	Independent validation of MammaPrint; (LN1-3)	241 patients; 91% adj treatment; 7.8 yrs follow-up	Metastasis-free survival by MammaPrint at 10 yrs: good prognosis signature 91% poor prognosis signature 76%; (at 5 yrs: 98% and 80% respectively)
Identification of a low-risk subgroup of HER-2-positive breast cancer by the 70-gene prognosis signature. **Knauer** M, Cardoso F, Wesseling J, et al. Br J Cancer 2010; 103(12):1788-1793	HER2-positive subgroup analysis	168 HER2+ patients of which 89 chemotherapy-naive	In non chemo treated HER2+ patients, MP classified 20 (22%) as good prognosis, with 10-year DDFS of 84%, compared with 69 (78%) poor prognosis patients with 10-year DDFS of 55%. HR 4.5 (95% confidence interval (CI) 1.1–18.7, P=0.04)
Additional value and potential use of the 70-gene prognosis signature in node-negative breast cancer in daily clinical practice. **Bueno-de-Mesquita** JM, Sonke GS, van de Vijver MJ, Linn SC. Ann Oncol. 2011 Sep;22(9):2021-30.	Re-evaluation of MP in pts from vd Vijver (n=151), Bueno-de-Mesquita (n=123), RASTER (427),	total n=701; sub-analyses for ER-positive adj untreated pts	Only patients with both clinical risk scores (low risk and a MammaPrint low-risk score) had a 10-year distant recurrence risk below 10%.
Clinical Utility of the 70-gene MammaPrint profile in a Japanese population. **Ishitobi** M, Goranova TE, Komoike Y, et al. Jpn J Clin Oncol. 2010; 40(6):508-512	Japanese patients	Japanese patients (n=102; 7.1 yrs FU)	MP accurately identified Japanese breast cancer patients at low risk of developing recurrences. 100% of the individuals in the low-risk category remained metastasis-free at 5 year follow-up.
Additional prognostic value of the 70-gene signature (MammaPrint(®)) among breast cancer patients with 4-9 positive lymph nodes. M. **Saghatchian**, S. Mook, G. Pruneri, et al. Breast. 2013 Jan 21.	MP in pts with LN 4-9	173 samples; 40% MP LR; 60% MP HR (median FU 7.9 yrs)	In breast cancer patients with 4-9 positive lymphnodes, DMFS at 5 years was 87% for MP Low Risk patients and 63% for MP High Risk patients (p< 0.01)
A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. C.A. **Drukker**, J.M. Bueno-de-Mesquita, V.P. Retel, et al. Int J Cancer. 2013 Jan 31.	5 year outcome of MP in RASTER	pts (n=427) treated according to MP	DRFI by MammaPrint at 5 year: Low Risk: 97%, High Risk: 91.7%
Optimized outcome prediction in breast cancer by combining the 70-gene signature with clinical risk prediction algorithms. **Drukker** CA, Nijenhuis MV, Bueno-de-Mesquita JM, et al. Breast Cancer Res Treat. 2014 Apr 24.	RASTER re-evaluation	In this cohort (RASTER; n=427), the PREDICT plus tool combined with MP provided the best risk prediction.	5-year outcome of systemic therapy-naive patients with a low risk 70-gene signature

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			<table><tr><th>Publication</th><th>Objective</th><th>Details</th><th>Results</th></tr><tr><td>Molecular subtyping improves diagnostic stratification of patients with primary breast cancer into prognostically defined risk groups. Yao K, Goldschmidt R, Turk M, et al. Breast Cancer Res Treat. 2015 Nov;154(1):81-8.</td><td>MammaPrint and BluePrint classification</td><td>(n=373) from 2 US centers (NorthShore and Fox Chase; median follow-up time of 9.5 years.)</td><td>MammaPrint low-risk patients 10-year DMFS of 96% (95% CI 92.8–99.4), MammaPrint high-risk patients had a 10-year DMFS of 87% (95% CI 81.9–92.1) HR 3.62. (95% CI 1.38–9.50) (p = 0.005). A sub-analysis of MammaPrint in patients with IHC/FISH HR-positive and Her2-negative disease also significantly predicted 10-year DMFS with a HR of 2.91 (95% CI 0.97–8.68; p = 0.045).</td></tr><tr><td>The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Knauer M, Mook S, Rutgers EJ, et al. Breast Cancer Res Treat 2010;120(3):655-661</td><td>Pooled analysis of all MP validation studies. Shows "predictiveness".</td><td>Pooled study series includes 541 pts treated with adj ET, stratified with MP.</td><td>For patients treated with adj ET only: MammaPrint Low Risk patients have a 10 yr DDFS 98%; MammaPrint High Risk patients have a 10yr DDFS 76%.</td></tr><tr><td>The 70-gene signature as a response predictor for neoadjuvant chemotherapy in breast cancer. Straver ME, Glas AM, Hannemann J, et al. Br Cancer Res Treat 2009; 119(3):551-558</td><td>MammaPrint in neo-adjuvant patient series</td><td>n=167</td><td>pCR was measured (n=167). 14% of pts were MP LR with no pCR. And 100% 3 yr DFS.</td></tr><tr><td>Molecular subtyping of early-stage breast cancer identifies a group of patients who do not benefit from neoadjuvant chemotherapy. Glück S, de Snoo F, Peeters J, et al. Breast Cancer Res Treat. 2013 Jun;139(3):799-67</td><td>MammaPrint in neo-adjuvant patient series</td><td>Data were analyzed from 4 neoadjuvant chemotherapy trials (n=487).</td><td>21% of patients was MammaPrint Low Risk with low pCR (6%) and 93% 5 yr DMFS.</td></tr><tr><td>Chemosensitivity and Endocrine Sensitivity in Clinical Luminal Breast Cancer Patients in the Prospective Neoadjuvant Breast Registry Symphony Trial (NBRST) Predicted by Molecular Subtyping. Whitworth P, Beitsch P, Mislowsky A, et al. Ann Surg Oncol. 2017 Mar;24(3):669-675.</td><td>MammaPrint in neo-adjuvant patient series</td><td>Prospective neo-adj study for MP and BP, reassigning more responsive patients to the HER2 and Basal categories while reassigning less responsive patients to the Luminal category.</td><td>The MammaPrint index is positively associated with the likelihood of pCR (p<0.001), suggesting that patients who are at the highest risk of recurrence are more likely to have chemotherapy benefit.</td></tr><tr><td>Molecular subtyping predicts pathologic tumor response in early-stage breast cancer treated with neoadjuvant docetaxel plus capecitabine with or without trastuzumab chemotherapy. Bayraktar S, Royce M, Stork-Sloots L, et al. Med Oncol. 2014 Oct;31(10):168</td><td>MammaPrint in neo-adjuvant patient series</td><td>Molecular subtyping data were analyzed on samples from XeNA neoadjuvant trial (n=122). Better stratification than PAM50.</td><td>Low pCR in MammaPrint Low Risk patients versus high in other subgroups.</td></tr><tr><td>70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. Cardoso F, van't Veer LJ, Bogaerts J, et al. N Engl J Med. 2016 Aug 25;375(8):717-29</td><td>Prospective randomized clinical trial</td><td>Level 1A evidence</td><td>Suppl dat: ER+/HER2-/LN0 pts MammaPrint Low Risk have a 5 yr DMFS of 96.7%</td></tr><tr><td>Genomic profiling of breast cancer in African-American women using MammaPrint. Nunes RA, Wray L, Mete M, et al. Breast Cancer Res Treat. 2016 Oct;159(3):481-8</td><td>Prospective comparative study</td><td>Prospective study of MammaPrint in African American patients (n=100)</td><td>High Risk MammaPrint was present in 68% of patients and in 32% of patients with Stage I disease</td></tr><tr><td>Use of Molecular Tools to Identify Patients With Indolent Breast Cancers With Ultralow Risk Over 2 Decades. Laura J. Esserman, MD, MBA; Christina Yau, PhD; Carlie K. Thompson, MD;, JAMA Oncology 2017</td><td>To determine if a multigene classifier is associated with indolent behavior of invasive breast cancers in women followed for 2 decades.</td><td>Secondary analysis of a randomized clinical trial, with more than 20-year follow-up</td><td>The ultralow-risk threshold of the 70-gene MammaPrint assay can identify patients whose long-term systemic risk of death from breast cancer after surgery alone is exceedingly low.</td></tr><tr><td>Tamoxifen therapy benefit for patients with 70-gene signature high and low risk. van 't Veer, Christina Yau, Nancy Y. Yu BCRT 2017</td><td>to evaluate long-term 20-year benefit of endocrine therapy within prognostic risk classes of the 70-gene prognosis signature that was developed on adjuvantly untreated patients.</td><td>BCSS and 10-year distant metastasis-free survival (DMFS) were assessed on STO-3 trial patients with retrospectively ascertained 70-gene prognosis classification.</td><td>Patients with ER-positive breast cancer, regardless of high or low 70-gene risk classification, receive significant survival benefit lasting over 10 years from adjuvant tamoxifen therapy, even when given for a relatively short duration.</td></tr></table>		
Agendia	Page 29	Line 1095	As can be seen from the MammaPrint Evidence Overview most of the sample sizes are larger than the mentioned *"….developing but is based*	1	See reaction above

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			on small sample sizes (≤ 272)." It includes validation series of 295, 302, 105, 148, 123, 241 etc etc patients. The statement by Ward et al., is therefore incorrect. In addition, the MINDACT study included 6,693 patients, thus the argument that the prognostic ability of the test is based on small sample sizes is not valid to date.		
Agendia	Page 30	Line 1097	Data from the Oxford Overview conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) confirm that the benefit of adjuvant chemotherapy for reducing breast cancer recurrence is primarily seen within the first 5 years, with no additional increase in benefit observed beyond 5 years.[1] Therefore, studies on the benefit of chemotherapy will focus on 5 year follow-up data. Also, we argue with the authors that only prognostic data for 5 years is available. As can be seen from the MammaPrint Evidence Overview, as well from the below mentioned studies, most validation studies have follow-up for 10 years instead of 5 years. Retrospective analysis of prospective STO trial shows MammaPrint Low Risk patients have sufficient low risk to forgo chemotherapy at 93% DMFI at 10 year and breast cancer specific survival of 90% at 20 years with only Tamoxifen as adjuvant treatment. [2] Moreover, the below studies also confirm MammaPrint Low Risk patients have excellent metastasis free survival at 10 years: ○ Homogeneously untreated patients showed a 90% DMFS at 10 years for MammaPrint Low Risk patients. [3] ○ Subgroup of MammaPrint Low Risk patients who did not receive chemotherapy had a 98% 10-year DMFS. [4] ○ Non-homogeneously treated, post-menopausal, MammaPrint Low Risk patients had no (0/27) metastases at 10 years. [5] ○ Non-homogenously treated population of lymph node positive patients showed 91% DMFS at 10 years. [6]	1	See reaction above

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			*1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. Lancet **379,** 432–44 (2012).* *2. van 't Veer, L. J. et al. Tamoxifen therapy benefit for patients with 70-gene signature high and low risk. Breast Cancer Res. Treat. (2017). doi:10.1007/s10549-017-4428-9* *3. Buyse, M. et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J. Natl. Cancer Inst. 98, 1183–1192 (2006).* *4. Yao, K. et al. Molecular subtyping improves diagnostic stratification of patients with primary breast cancer into prognostically defined risk groups. Breast Cancer Res. Treat. 154, 81–88 (2015).* *5. Wittner, B. S. et al. Analysis of the mamma print breast cancer assay in a predominantly postmenopausal cohort. Clin. Cancer Res. 14, 2988–2993 (2008).* *6. Mook, S. et al. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. Breast Cancer Res. Treat. 116, 295–302 (2009).*		
Agendia	Page 30	Line 1099	Unlike concluded by Ward et al., there is substantial evidence of change in the management of patients by use of MammaPrint®. This has been assessed in several studies, one of which was one of the first in its kind, the RASTER study[1]. The RASTER study is a prospective community-based feasibility study on the use of the 70-gene signature to predict prognosis of patients with node-negative breast cancer. On average, MammaPrint® changes treatment decision in 30% of the cases.[1-12] The most recent impact studies conducted in the Netherlands[3] and Germany[4] even showed very high adherence (96% and 93%, respectively) to the MammaPrint® test results. *1. Bueno-de-Mesquita, J. M. et al. Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: a*	1	See reaction above.

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			prospective community-based feasibility study (RASTER). Lancet Oncol. ***8,*** *1079–1087 (2007).* *2. Drukker, C. A. et al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. Int. J. Cancer* ***133,*** *929–936 (2013).* *3. Kunz, G. Use of a genomic test (MammaPrint) in daily clinical practice to assist in risk stratification of young breast cancer patients. Arch. Gynecol. Obstet.* ***283,*** *597–602 (2011).* *4. Rutgers, E. et al. The EORTC 10041/BIG 03-04 MINDACT trial is feasible: Results of the pilot phase. Eur. J. Cancer* ***47,*** *2742–2749 (2011).* *5. Kuijer, A. et al. Impact of 70-Gene Signature Use on Adjuvant Chemotherapy Decisions in Patients With Estrogen Receptor-Positive Early Breast Cancer : Results of a Prospective Cohort Study. J Clin Oncol* ***35,*** *(2017).* *6. Gevensleben, H. et al. Comparison of MammaPrint and TargetPrint results with clinical parameters in German patients with early stage breast cancer. Int. J. Mol. Med.* ***26,*** *837–843 (2010).* *7. Cusumano, P. G. et al. European inter-institutional impact study of MammaPrint. The Breast* ***23,*** *423–428 (2014).* *8. Drukker, C. A. et al. Risk estimations and treatment decisions in early stage breast cancer: Agreement among oncologists and the impact of the 70-gene signature. Eur. J. Cancer* ***50,*** *1045–1054 (2014).* *9. Exner, R. et al. The multigene signature MammaPrint impacts on multidisciplinary team decisions in ER+, HER2- early breast cancer. Br. J. Cancer* ***111,*** *837–42 (2014).* *10. Retèl, V. P. et al. Association between genomic recurrence risk and well-being among breast cancer patients. BMC Cancer* ***13,*** *295 (2013).* *11. Pohl, H. et al. Impact of MammaPrint on clinical decision-making in South African patientsw with early-stage breast cancer. Breast J.* ***22,*** *442-446 (2016).* *12. Wuerstlein, R. et al. Impact of MammaPrint and BluePrint on early*		

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			breast cancer treatment decisions : WSG PRIMe study results. Poster St. Gall. (2017).		
Agendia	Page 30	Line 1102	The clinical utility, in other words the predictiveness of the chemotherapy benefit has been studied in several studies. [1-10] The most recent study to prove clinical utility is the MINDACT study[10]. This study shows that withholding chemotherapy in clinically high risk, but MammaPrint® Low Risk patients does not compromise outcome where distant metastasis free survival at five years is 94.7% in the patient group not treated with chemotherapy. All patients had such a good prognosis in this group that the toxicity of chemotherapy may outweigh the marginal survival benefit due to chemotherapy. *1. Straver, M. E. et al. The 70-gene signature as a response predictor for neoadjuvant chemotherapy in breast cancer. Breast Cancer Res. Treat. 119, 551–558 (2009).* *2. Knauer, M. et al. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Breast Cancer Res. Treat. 120, 655–661 (2010).* *3. Glück, S. et al. Molecular subtyping of early-stage breast cancer identifies a group of patients who do not benefit from neoadjuvant chemotherapy. Breast Cancer Res. Treat. 139, 759–767 (2013).* *4. Groenendijk, F. H. et al. Estrogen receptor splice variants as a potential source of false-positive estrogen receptor status in breast cancer diagnostics. Breast Cancer Res. Treat. 140, 1–10 (2013).* *5. Krijgsman, O. et al. A diagnostic gene profile for molecular subtyping of breast cancer associated with treatment response. Breast Cancer Res. Treat. 133, 37–47 (2012).* *6. Whitworth, P. et al. Chemosensitivity predicted by BluePrint 80-gene functional subtype and MammaPrint in the Prospective Neoadjuvant Breast Registry Symphony Trial (NBRST). Ann. Surg. Oncol. 21, 3261–7 (2014).* *7. Bayraktar, S. et al. Molecular subtyping predicts pathologic tumor response in early-stage breast cancer treated with neoadjuvant docetaxel*	1	See reaction above.

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			plus capecitabine with or without trastuzumab chemotherapy. Med. Oncol. 31, 163 (2014). *8. Baron, P. et al. Impact of Tumor Size on Probability of Pathologic Complete Response After Neoadjuvant Chemotherapy. Ann. Surg. Oncol. 23, 1522–1529 (2015).* *9. Beitsch, P. et al. Genomic Impact of Neoadjuvant Therapy on Breast Cancer: Incomplete Response is Associated with Altered Diagnostic Gene Signatures. Ann. Surg. Oncol. 23, 3317–3323 (2016).* *10. Cardoso, F. et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N. Engl. J. Med. 375, 717–729 (2016).*		
Agendia	Page 30	Line 1105	The authors of the assessment seem to be unaware of the FDA clearance and the multitude of validation studies for MammaPrint that have not been limited to premenopausal patients only. Please see below, as well as the FDA clearances. Clinical validation studies of MammaPrint® have been published proving additional prognostic ability in all age, groups, small primary tumors, up to 3 positive lymph nodes (LN+), ER+/-, HER2+/- and ethnic groups.[1,2,3,4,5,6] MammaPrint® is predictive for both pre- and postmenopausal women.[6,7] *1. Drukker, C. A. et al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. Int. J. Cancer 133, 929–936 (2013).* *2. Cardoso, F. et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N. Engl. J. Med. 375, 717–729 (2016).* *3. Buyse, M. et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J. Natl. Cancer Inst. 98, 1183–1192 (2006).* *4. Bueno-de-Mesquita, J. M. et al. Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: a prospective community-based feasibility study (RASTER). Lancet Oncol. 8, 1079–1087 (2007).*	1	See reaction above.

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Agendia	Page 30	Line 1113-1116	Agendia claims that patients at high risk according to the current clinicopathological criteria but who are defined as Low Risk using MammaPrint® can safely forgo chemotherapy without deterioration of the clinical outcome.	2	We have changed safely spare in safely forgo.
Agendia	Page 31	Section starting at 1157	FDA-status: The authors have not taken the latest information regarding FDA approvals for the MammaPrint into account. Please adapt the text to the following: The MammaPrint test is a laboratory developed test (LDT) which falls into the class of *In Vitro* Diagnostic Multivariate Index Assays (IVDMIA). MammaPrint received the first 510(k) IVDMIA clearance in 2007 by the FDA in a *De Novo* Classification Process (Evaluation of Automatic Class III Designation). MammaPrint® FFPE received a Predicate Device 510(k) clearance in 2015. The FDA label indicates that MammaPrint® and MammaPrint® FFPE can be used as a prognostic risk stratification tool for early stage breast cancer patients. Agendia's FDA clearances for MammaPrint are publicly available at fda.gov (k062694, k070675, k080252, k081092, k101454, k141142).	1	We have updated the FDA status.
Agendia	Page 31	1163	In case the above sentence is not taken over, at least the untrue fact ….”*less than 61 years old,* ….”should be removed. As can be seen from the FDA clearances, MammaPrint is valid for women above the age of 61 years as well.	2	See reaction above
Clinical Effectiveness and Safety					
Agendia	Page 32	Section 6.2.1	**Direct evidence on clinical effectiveness in this assessment is based solely on one RCT, the MINDACT study**. We agree that prospective RCT data is ideally preferred, but clinical effectiveness can	1	The manufacturer was asked to check factual accuracy of the domains “Description and

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			also be provided by non-level 1A evidence studies and should not be taken out of the equation. Simon Level 1B evidence has been provided by retrospective analysis of prospective studies such as presented in the STO trial (vh Veer Br Can Res 2017) that shows MammaPrint Low Risk patients have sufficient low risk to forgo chemotherapy at 93% DMFI at 10 year and breast cancer specific survival of 90% at 20 years with only Tamoxifen as adjuvant treatment. The prospective RASTER trial showed that MammaPrint identified more low risk patients than clinicopathological factors alone, potentially reducing chemotherapy by 20% without detrimentally affecting survival (Drukker 2013). ○ At 5 years, the MammaPrint Low Risk and High Risk patients had a DRFI of 97.0% and 91.7% respectively. ○ At 10 years MammaPrint Low Risk patients who did forego chemotherapy had a 94% DRFI.(Poster presentation by S.Vliek ESMO 2017) Moreover, 3 Simon level of evidence category C studies confirm MammaPrint Low Risk patients have excellent metastasis free survival at 10 years: ○ Homogeneously untreated patients showed a 90% DMFS at 10 years for MammaPrint Low Risk patients.(Buyse 2006) ○ Subgroup of MammaPrint Low Risk patients who did not receive chemotherapy had a 98% 10-year DMFS.(Yao 2015) ○ Non-homogeneously treated, post-menopausal, MammaPrint Low Risk patients had no (0/27) metastases at 10 years.(Wittner 2008)		technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text. However, a reaction on this topic is found at one of the comments of the patient organisation and the NVMO.
	Page 33	Line 1209	We would like to point out that the authors should take the following into consideration, as they state themselves: "*As a starting point for determining the non-inferiority threshold in the MINDACT there was consensus in the TRANSBIG consortium 2014 (a 21-country network associated with the Breast International Group [BIG]) that among every hundred women….".* We are very surprised by the decision of the authors to deviate from this starting point and that the authors have decided to use a non-peer reviewed opinion article as a starting point (page 22, line 724) instead of	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy but a misinterpretation.

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			this 21-country network TRANSBIG Consortium.		Therefore we tried to clarify the text.
Agendia	Page 34	1283	With regards to the following statement: "Different thresholds for clinical relevance are being used by different scientific societies and individual countries. As described in the Method's section we used the ESMO-MCBS threshold of HR 0.80 to determine imprecision in GRADE. This HR thresholds refers to the lower extreme of 95% CI." This committee has not sufficiently proven that the ESMO-MCBS threshold use for this assessment is justified. They should provide a more robust and thorough overview of the different thresholds used for clinical relevance. Bypassing the ESMO breast cancer guidelines and choosing a tool that is per definition not intended for gene expression assays for chemotherapy decision making is not doing justice to physicians and patients in Europe.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text based on this comment.
Agendia	Page 34	Section 6.2.3.1	The MINDACT study had three pre-defined patient populations, and it is incorrect to state that these included protocol violations. Deviations from assigned treatment allocation was envisioned, though only observed for a small subset, less the 5-10% per category. The following test populations were pre-defined (Cardoso, 2016): The primary analysis was conducted in the primary-test population. This population included patients at high clinical risk and low genomic risk, who were randomly assigned to use the genomic risk for the decision to forgo chemotherapy and who adhered to the treatment assignment of no chemotherapy. Patients with changes in clinical or genomic risk were excluded from the primary-test population. Treatment-randomization analyses for the groups with discordant clinical and genomic risks were performed with the use of the risk at enrollment (intention-to-treat population). In the intention-to-treat population, patients were analyzed according to the randomized group, irrespective of adherence. The treatment-randomization analyses were repeated in the per-protocol population, which excluded patients who were ineligible, had a change in their clinical or genomic risk, or were non-adherent to the treatment assignment.	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the NVMO. Based on this comment we have clarified the text.

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Agendia	Page 34	Line 1295-1296	It is incorrect to state that a sensitivity analyses was performed to evaluate the effect of the protocol violations as defined by the authors in 6.2.3.1. The sensitivity analysis was performed to evaluate a period of small test calibration deviation which had affected only 165 patients. This sensitivity analysis confirmed no difference in outcome of results. It is therefore incorrect to use this sensitivity data as the main outcome of the trial.	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the NVMO. Based on this comment we have clarified the text.
Agendia	Page 35	1342	We disagree with the following: "DFS is widely accepted as surrogate for OS in adjuvant cancer treatments, for example in the scientific guidelines of the EMA and FDA." Again, as explained in the comment regarding page 24 sentence 814-815, the primary endpoint of 5 yr DMFS is a better and more acceptable outcome when evaluating a genomic test that is designed to determine the risk of distant recurrences.	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the patient organisation and the NVMO. Based on these comments we have clarified the text.
Agendia	Page 35	1354	We disagree with how the authors are re-doing and re-interpreting the MINDACT analysis with the following reasoning: "Because of the temporary change in risk all risk groups as enrolled are somewhat biased due to incorrect risk assessment. Therefore the results of the PPS	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of

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			population, in which all patients enrolled during this period of change in risk are excluded, are the less biased and therefore most conservative analysis." The authors continue with using only the results from the PPS population, whereas the incentive for the PPS analysis was different and incorrect to be used for making conclusions since the study was powered not for the PPS population.		technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the NVMO. Based on these comments we have clarified the text.
Agendia	Page 35	Footnote	The data that are needed to assess the value of MammaPrint by ZIN are available through the MINDACT publication. These analyses were conducted by independent and highly skilled statisticians. Instead of doing a point estimate, the authors could have reached out to the MINDACT statisticians to verify why they were unable to reproduce certain numbers. The publication of this assessment, which is essentially implying flaws in data analysis by the EORTC, is potentially damaging. Moreover, this conclusion is again based on the wrong endpoint, namely, DFS and the impact of this invalid conclusion could be detrimental for patients wellbeing. ' Moreover, the authors shift their 10y OS target to the 5 year DFS. The 10year OS HR >0.8 (also based on incorrect use of the ESMO-MCBS tool) is now being used as target for 5year DFS and then falsely state that this 10year OS HR falls within the 95% CI of 5y DFS. This is in our eyes, incorrect use of statistics.	1	Because we based our conclusions on the data available through the MINDACT publication, there is no need to clarify why some results are slightly different. However, we would be pleased if Agendia could provide a clarification for these differences. If we receive this clarification before the 8th of December we will add this to the EUnetHTA assessment report.
Agendia	Page 35	table	In the MINDACT manuscript it is very clearly described why the PPS analysis was done, and why it is in the supplementary data, and not in the main manuscript. Not only was this a reasonable statistical methodology, also it has been reviewed and accepted by the NEJM, as well as by ASCO guidelines. It is doing unjust to all patients physicians, statisticians etc etc who have been involved in the MINDACT trial (which has an external review as well) to disregard the well supported defined	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not

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			etc primary endpoint of the trial.		related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the NVMO. Based on this comment we have clarified the text.
Agendia	P36	1386 Figure 3	See comments P67, line 1887 figure A2	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
Agendia	Page 36	1406	"Short term and long term side effects were measured during the MINDACT trial but not published in the publication of Cardoso et al. (2016), the 10 year-analysis have to be awaited. On the other hand, already is known that complications of chemotherapy are leukaemia and cardiovascular and other side-effects as described in 4.2.6." The authors imply that indeed the 10 yr outcome is not a necessary outcome of the trial as this information is already available from other literature.	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy but a misinterpretation, and therefore we tried to clarify the text.
Agendia	Page 37	1415	"However, we did not find controlled observational studies that provide evidence on clinical utility." Please note our earlier overview with clinical utility studies for MP.	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of

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					technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the patient organisation and the NVMO. Based on these comments we have clarified the text.
Agendia	Page 38	Line 1484-1485	Although these subgroup analyses were predefined, of note, they were considered 'exploratory'.	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". But, we felt this was a factual inaccuracy. Therefore, we have added that these predefined subgroup analyses were exploratory.
Discussion					
Agendia	Page 40	Starting line 1584	In line 1584, *"First, now the current MINDACT data are available it can be concluded that the lower boundary of the CI of the 5-years DMFS in the clinically high genomic low risk group receiving chemotherapy is 94,1% which is higher than the predefined threshold of 92%".,* the authors again illegitimately use the PPS calculation to proof their point. They should refer to the PP population. In this sentence, also remove *current*. Furthermore, the authors imply that added value for MammaPrint is only achieved when the lower boundary of the 95% cI is higher than the lower	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy but a misinterpretation, and

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			boundary 95% CI of the treated arm (94.1 in the PPS population and 94.7 in the PP population). However, the proven benefit of MammaPrint should always be determined before the start of the study to ensure statistically sound data analysis. It was determined that the lower boundary 95% CI should be at least 92% to meet the primary objective of the trial. Adapting this on hind sight would be considered statistically incorrect. Moreover, as can be seen from the p-value, the differences between the treated and untreated arm is non-significant, indicating that it is safe to omit chemotherapy in C-high/G-low patients and harms would outweigh the benefit.		therefore we tried to clarify the text.
Agendia	Page 40	Starting line 1590	"*Third, Thewes and Prins et al. (2016) wrote a comment on the MINDACT [68] that most patients with breast cancer are willing to accept adjuvant chemotherapy for very small survival gains (≤1%). Also Hamelinck et al. (2014) conclude that most patients judged small to moderate benefits sufficient to consider adjuvant systemic therapy worthwhile, but individual preferences varied widely."* However, elsewhere in the assessment it is mentioned that a 3% threshold for clinical relevance is considered relevant. **Point three in this section is therefore arbitrary**. Ultimately, the decision to receive or forgo chemotherapy (or any other treatment) lies with each patient who is properly informed about the potential side effects and the potential benefits of such treatment. For the same risk–benefit scenario, different patients may make different decisions. In the development phase of MINDACT, a survey amongst women and their physicians was held to identify how much benefit chemotherapy must provide in order to be willing to undergo such therapy. At least 2% benefit turned out to be the minimal benefit needed to be worth the toxicity. MINDACT showed a non-significant difference of 1.5% between CT/No CT and is well below the at least 2% reduction in survival due to chemotherapy induced toxicities and below the 2% required benefit of CT as indicated by the survey.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. Therefore we did not change the text.
Agendia	Page 40	Line 1597	*The PPS population provides the least biased and most conservative estimate of overall survival which is the safety outcome in the current assessment.* -> PPS population is derived from the sensitivity analysis (Table S5 in MINDACT NEJM paper). Sensitivity analyses play a crucial	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of

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			role in assessing the robustness of the findings or conclusions based on primary analyses of data in clinical trials. They are a critical way to assess the impact, effect or influence of key assumptions or variations—such as protocol deviations, missing data, and outliers—on the overall conclusions of a study. Consistency between the results of primary analysis and the results of sensitivity analysis strengthens the conclusions or credibility of the findings and indicates the primary analysis (thus on the whole MINDACT PP population) is valid and is the preferred population. In summary: sensitivity analysis are meant to verify the main results and when this is confirmed results of the **primary analysis on PP population should be used as main study results.**		technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the NVMO. Based on this comment we have clarified the text.
Agendia		Section 7.2	**We argue that the chosen endpoint DFS, is not the appropriate endpoint for this analysis.** It is generally accepted that distant recurrence (metastasis) trumps other events because it is a threat to patient survival. Indeed, it is the main predictor of death in all end point definitions. Our proposed definition for distant DFS (DDFS) preserves this focus. Therefore, it excludes ipsilateral breast tumor recurrence, regional invasive recurrences, contralateral breast cancer, and all in situ carcinomas, as these events are potentially nonlethal. The separation of distant as a specific end point is also very important for developing genetic panels for use in determining prognosis and/or response to treatment. In these situations, distant disease recurrence is often used as a marker for survival to increase statistical power because there is such a strong correlation between these end points and because there will be more distant events than deaths. Using a combined regional/distant end point would dilute the correlation. (see also earlier comment in this document).	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. However, a reaction on this topic is found at one of the comments of the patient organisation and the NVMO. Based on these comments we have clarified the text.
Agendia	P41	Line 1617	**We argue that the assessment is based on the secondary aim of the MINDACT study.** The primary importance for reimbursement decisions should be that by adding MammaPrint to clinical factors patients would not be compromised in outcome. The primary analysis of MINDACT focused on the survival by DMFS for the discordant clin-high/MP-low group randomized to no chemo. This is of direct interest for the	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We

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			EUnetHTA question of clinical utility to prescribe chemotherapy. The results indicated that there is no clinical utility for chemotherapy, as survival is 95% and the added benefit of chemotherapy does not outweigh the harms in this situation.		believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
Agendia	Page 42	Line 1668	**In this section the authors say: "***As the confidence interval shows there is a lot of uncertainty and possibly many patients could be harmed*". In their analyses, the authors involve absolute numbers when interpreting the wide 95% CI for the HR of all different endpoints. However, the 95% CI is already an estimate (and not very accurate because as there is not enough power because MINDACT was not set up for this question). By translating the wide 95% CI into absolute numbers, the result seems very bad. While the p-value is non-significant. This latter point is however, completely neglected. Also, the authors should also ask themselves whether, if the analysis would be turned around, and MammaPrint the gold standard, whether A!O or the use of standard clinical pathological factors for determining treatment decisions would succeed to prove clinical utility.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
Agendia	Page 42	Line 1688	However, when it is concluded that non-inferiority is questionable (see the blue line in figure 2), quality of life data will be mandatory to conclude if the positive effects on toxicity and/or quality of life outweigh a possible inferior effect on overall survival. Quality of life data was assessed in the first 800 patients enrolled in MINDACT, this paper (Retel et al. BMC Cancer 2013) was published but not taken into account by the authors. As the authors also state elsewhere, quality of life data after chemotherapy is available, but if so, why did the authors not incorporate these findings into their analyses? As they also assume these side effects not to be different after MammaPrint testing. Please find here the reference for longterm toxic effects: H. A. Azim Jr, E. de Azambuja, M. Colozza, J. Bines & M. J. Piccart. Long-term toxic effects of adjuvant chemotherapy in breast cancer. Annals of Oncology 2011, 22: 1939–1947 http://annonc.oxfordjournals.org/content/early/2011/02/02/annonc.mdq683.full	1	The manufacturer was asked to check factual accuracy. We believe this comment is not related to a factual inaccuracy but for the sake of completeness we clarified why the study of Retel et al. was not included in the assessment. See also our reaction on comment P63. Azim et al was used in chapter 4 but we referenced the references in the Azim overview, but we have added Azim in the main text of chapter 4.

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Agendia	Page 42	Last sentence section 7.3	**We strongly argue against the necessity of 10 year follow-up based on the following literature:** the entire body of peer-reviewed randomized trials in Adjuvant Therapy for Breast Cancer has been periodically reviewed by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) in the so-called "Oxford Overview" and has established the standard of care for early breast cancer. It has been established as fact by the published data from the Oxford Overview conducted by the EBCTCG, that the benefit of adjuvant therapy in early breast cancer varies by the type of intervention and the time period of risk. Specifically, the benefit of chemotherapy, in both ER+ and ER- breast cancer, is limited to reducing recurrences within the first 5 years, with no later effect. This has been documented in both the 2005 and 2012 overview summaries, which reviewed trials involving over 30,000 patients, with 15-20 years of follow-up, treated with chemotherapy regimens ranging from CMF to anthracycline and taxane containing regimens (1, 2). The specific observations relevant to the benefit of chemotherapy are stated here (Ref 1, p 1699): "Among younger women the main divergence in recurrence [between chemotherapy and no chemotherapy] takes place just during the first 5 years, when the absolute recurrence rate is high and the recurrence rate ratio is most favorable. This produces an absolute difference of 12% (37% vs 25%) in the 5-year recurrence probability, and *this absolute difference of about 12% then persists after year 5* …Among older women, the main divergence in recurrence takes *place just within the first 2 years of starting chemotherapy*…". It has therefore been established by extensive data that the benefit of adjuvant chemotherapy for reducing breast cancer recurrence is seen only within the first 5 years, with no additional increase in benefit observed beyond 5 years. The MINDACT study identified, in a prospective, randomized trial of nearly 7000 women, a cohort of women with a Low Genomic Risk in the MammaPrint Assay, who show no evidence of benefit from chemotherapy within the first 5 years. The data from the Oxford Overview confirm that no further benefit from	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.

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			chemotherapy will be observed beyond 5 years, for both women under 50 and those from 50 to 69 years, and therefore, no more than 5 years of follow-up is needed to establish the clinical utility of the MammaPrint assay for identifying this cohort. It is also recognized, however, that late recurrences after 5 years continue to occur in ER+ breast cancer, but it is only endocrine therapy, not chemotherapy, which affects the incidence of late recurrences, from years 5 to 10, and 10 to 15. Therefore, in the case of the MammaPrint assay, the principle area of clinical utility is to determine the potential benefit of chemotherapy, a benefit which, if present, will only be observed in the first 5 years. Moreover, both also other highly respected organizations such as the ASCO (3) and AJCC consider 5 years as a mature end point for DMFS outcome in early stage breast cancer in relation to the decision to recommend or withhold chemotherapy. *References:1. EBCTCG (2005) Lancet 2005; 365: 1687–1717 2. EBCTCG (2012) Lancet 2012; 379: 432–44 (3)* Krop I et al.: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. *JCO.* 2017		
Appendix					
Agendia	P45	1730	Literature presented is not up-to date. Most recent data on Clinical validity of the test is derived from San Miguel (2015) KCE but in this document Ward from 2011 is referred concerning clinical validity. In Ward et al clinical validity is described from the year 2009! Conclusion most recent information is coming from 2009, unacceptable. See comment on P30, line 1099. IQWIG also evaluated MammaPrint.	1	The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. See our reaction on your comment on P29 (line 1092).
Agendia	P47	1738	Rationale of limit search ‘from June 2014’ ?	1	The report of KCE was used as the starting point of the search, because there was no evidence found on clinical

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					utility of the MammaPrint in the search period of the KCE. We have clarified this in the text.
Agendia	P47	1743	Rationale of limit search 'from June 2014' ?	1	See above.
Agendia	P47	1748	Rationale of limit search 'from 2015' ?	1	See above.
Agendia	P49	1778 Table A3	Table is mentioned as a reference in the main document. Source/ reference is missing	2	Thank you, we have added the source/reference.
Agendia	P51	1828	We would like to specifically address the referencing and quoting of guidelines on page 27, starting at line 962. The guidelines mentioned in Table A4 are not a representative collection of guidelines for breast cancer treatment and their appropriateness in the different countries. In addition to our comments on P27 line 966: **To further specify:** **Spain;** the most accepted and followed guidelines in Spain are ASCO, NCCN & ESMO, and St. Gallen. AETSA and UETS are NOT the right representative guidelines as being used in Spain. AETSA and UETS are obsolete and under review. Both are prior to MINDACT results and are in the process of issuing an update. **AHROQ**; unclear why this is mentioned because as MammaPrint is not a Molecular Pathological test, is issued prior to MINDACT results and is not at all relevant for EU assessment. Cancer Care Ontario does acknowledge the RASTER study but was assessed prior to the MINDACT results. **Germany;** DKG is issued in 2012. The S3 guideline (DKG) is referred to as the 'basic' guideline, but is only renewed every five years. The AGO guidelines are renewed annually and treating physicians always are interested and want to act upon the most actual recommendations. AGO should be included. **KCE;** is being part of this EUnetHTA collaborative assessment. Conclusions from Ward et al. are not representative and does not include the most recent data on MammaPrint and did not include the MINDACT study. Therefore, KCE should state that it is under review.	1	We agree that guidelines are not frequently updated. Unfortunately, we cannot determine which guidelines did or did not assess the clinical utility of MammaPrint. In the current assessment an overview of clinical practice guidelines is provided. Many guidelines and other European and international public assessments (like the AHRQ) of the mammaprint® have been published before the publication of the MINDACT trial and some of these are currently under revision. Next to the guidelines of the international associations (ESMO, ASCA, St. Gallen and NCCN) from EUnetHTA perspective is it is also relevant to provide the clinical practise guidelines of the individual countries

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			NCCN; is prior to MINDACT and under revision **ESMO** is prior to MINDACT and under revision.		irrespective of the publication date of the MINDACT. We have added which guidelines were published before and after the publication of the MINDACT.
Agendia	P57		ASCO guidelines should be updated to the latest version. Krop I, Ismaila N, Andre F, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2017:JCO2017740472. http://www.ncbi.nlm.nih.gov/pubmed/28692382.	1	We have added this ASCO guideline in the same line as the clinical practice guideline of the ASCO.
Agendia	P58	1831 Table A5	Under ' Study type' Follow up is 5 years as primary endpoint. In addition, 10 years data will be collected.	1	We have added the information that 5-year DMFS was the primary endpoint of the MINDACT.
Agendia	P58	1831 Table A5	Under ' Number of patients' number of patients in the high clinical group should be derived from Table 2 from the MINDACT study not from supplementary information Table S5. Table S5 are sensitivity analyses and are meant to confirm the results but not to be used as the main results. Numbers should be n= 592 chemo, n=636 no chemo.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text. However, a reaction on this topic is found at one of the comments of the NVMO.
Agendia	P58	1831 Table A5	Under ' Main endpoints' Primary: **5-years** distant metastasis free survival (add 5-years)	1	We have added that 5-year DMFS was the primary

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					endpoint.
Agendia	P58	1831 Table A5	Under ' Conclusion authors': the 1.5% difference in 5-years DMFS was a NOT SIGNIFICANT difference. ' not significant' should be added for completeness.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
Agendia	P60	1846 Table A7	Study Identifier NCT03080428 is cancelled and should be removed from the list.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is related to a factual inaccuracy. Therefore, we have removed this study because it was recently withdrawn because of lack of funding.
Agendia	P63	1858 Table A9	QoI is performed in the first 800 patients of the MINDACT study.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy. For sake of completeness, we have added a foot note that

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					QoL was measured but only at baseline and not during chemotherapy and in the long term. Therefore it was not included in the assessment.
Agendia	P65	1865 Table A10a	We disagree with superscript ' C' because of evidence stated in the comments on P42 of this document.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
Agendia	P65-66	1876-1877 Table A10a	'd' of footnote: We disagree with downgrading twice based on ESMO-MCBS. We don't believe that ESMO-MCBS is the right tool to test clinical relevance for MammaPrint based on the arguments stated in the report, see comment on P22 and P43 line 1283 of this document.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
Agendia	P66	1884 Table A10a	Referring to *; clarification is needed to clarify difference in numbers between this report and published papers.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not

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					related to a factual inaccuracy and therefore we did not change the text.
Agendia	P65	1865 Table A10a	QoI is measured in the MINDACT but not at all mentioned in this report but is indicated under ' importance' in this table as 'CRUCIAL' .	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text. However, a reaction on this topic is found at one of the comments of the patient organisation and the NVMO.
Agendia	P64	1865 Table A10a	Short term.... from chemo indicated as not reported. See comment on P36 line 1406 of this document.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
Agendia	P64	1865 Table A10a	Superscript ' a' and 'e' are inconsistently indicated in the table. 'e' is described in the table as being ' not serious' and serious'. Same is true for superscript ' f'.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of

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					technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy but a misinterpretation, and therefore we tried to clarify the text.
Agendia	P64	1865 Table A10a	We disagree with downgrading based on 5-years DMFS data and on imprecision based on ESMO-MCBS. See comments on P42 and P22 and P43, line 1283 of this document.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
Agendia	P64-65	1865 Table A10a	We disagree with the numbers presented on the relative effect derived from the PPS analysis. See the comment on P23 section 3.8.2 of this document.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text. However, a reaction on this topic is found at one of the comments of the NVMO.
Agendia	P67	1887	We disagree with showing this figure based on PPS –analysis as stated	1	The manufacturer was asked

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		Figure A2	in comment made on P23, section 3.8.2. As DMFS is the most representative outcome measure it can be concluded that there is no significant difference in 5-years DMFS between risk classifications based on Adjuvant Online and MammaPrint. (see table 2 MINDACT article by Cardoso et al. 2016)) Indicating that 46% of the clinical high/ genomic Low risk patients could safely omit chemotherapy without compromising outcome. Even if the PPS population is taken, DMFS should still be the endpoint to be taken into account and as you can see from Figure 2 on page 67, DMFS as well as OS show a non-significant difference between treatment decision based on either MammaPrint or A!O.		to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text. However, a reaction on this topic is found at one of the comments of the NVMO.
Agendia	P71	Table A11	Section 'comparators'; 'An update … of the MINDACT results.' Is speculative and is at this point nog relevant. Therefore this sentence should be removed.	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.
Agendia	P72	Table A12	Hazard ratio (95% CI) for High clin risk and low genomic risk (PPS) DMFS is not correct. HR should be 0.60 (0.34, 1.06)	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is related to a factual inaccuracy and therefore corrected.
Agendia	P72	Table	As stated in comment on P24, line 814-815 of this document we disagree	1	The manufacturer was asked

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		A12	with the focus on DFS as surrogate endpoint. Highlighting these numbers in the table is not optimal presenting the main data results.		to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text. However, a reaction on this topic is found at one of the comments of the patient organisation and the NVMO.
Agendia	P76	Table A14	No. of patients in Clinical low/ genomic high LN0 group is not correct. Both CT and no CT group have each n=333	2	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is related to a factual inaccuracy and therefore corrected.
Agendia	P78	1949	Section 1.1. We disagree that ***continuation*** of the use of MammaPrint will lead to NEW ethical issues. We would like to remind the authors that MammaPrint is currently part of routine basic health care as stated not only in the Dutch CBO guidelines but is also recognized in the most used (inter) national guidelines in EU and USA. MINDACT has indisputably shown that these clinical high / genomic low risk patients omitting chemotherapy have an acceptable low risk of recurrence and will have no significant survival benefit when they do get chemotherapy. The disadvantage (the side effects) will become more present than having benefit on survival of chemotherapy. Chemotherapy will do more harm than benefit.	1	The manufacturer was asked to check factual accuracy of the domains "Description and technical characteristics of technology" as well as "Health Problem and current use". We believe this comment is not related to a factual inaccuracy and therefore we did not change the text.

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Agendia	P78	1949	Section 1.2 We disagree with the whole paragraph but especially with the phrasing of *introduced prematurely*. The aim of the assessment was to prove clinical utility of MammaPrint and that MammaPrint in addition to Clinical factors would improve adjuvant treatment recommendations; not to prove that it cannot be excluded that adjuvant CT following clinical risk assignment significantly decreases the hazard of death due to distant metastasis, as this not the aim of the assessment. No significant difference was found in 5-years DMFS in clinical high/ genomic low the patients indicating no benefit of giving chemotherapy in this group. MammaPrint has been on the market for the last decade and is routinely used in clinical practice. The use of MammaPrint in early stage breast cancer patients has been recognized in many clinical guidelines and therefore, the wording *premature introduction* seems out of place and incorrect.	1	The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We believe this comment is not related to a factual inaccuracy. We have however clarified why we think introduction of the MammaPrint is too early.
Agendia	P78	1949	Section 2.1. We do not agree with the indicated YES. This should a NO as MammaPrint will not be newly introduces as it has already been on the market for over 10 years and is routinely used in clinical practice. Therefore, no changes are needed by ***continuation*** of the use of MammaPrint. MammaPrint test is centrally performed at one of the two labs of Agendia and therefore no specialized equipment or personnel at pathology labs is required as already mentioned in the main EUnetHTA report under section 5.2.1.	1	The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We believe this comment is related to a factual inaccuracy. Therefore, we have corrected it.
Agendia	P79	1949	Section of ‘Social’, 3.1; ’on the other side, more death are possible to be expected’. As this conclusion is based on incorrect use of statistical methods and tools we would like this phrase to be removed as it is illegitimate.	1	The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We believe this comment is not related to a factual inaccuracy. Therefore, we did not change the text based on this

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					comment.
Agendia	P79	1949	See comment on 3.1 of this document	2	The manufacturer was asked to check factual accuracy of the domains “Description and technical characteristics of technology” as well as “Health Problem and current use”. We believe this comment is not related to a factual inaccuracy. Therefore, we did not change the text based on this comment.

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