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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Q&A EUnetHTA MammaPrint

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What is MammaPrint?

MammaPrint® is a test that measures the activity of certain genes within the tumour cells to estimate the likelihood of the tumour to return and spread to other organs, where it becomes incurable. Based on the outcome of MammaPrint®, depending upon whether the tumour has a low or high risk of returning, and in consultation with the doctor, it can be determined whether or not additional chemotherapy is needed after surgery. By analysing the activity of 70 genes in the breast tumour, the test is a so-called tumour 'fingerprint'. Such a test is also called a 'gene expression test'. The claim of this test is that some patients can safely refrain from adjuvant chemotherapy, based on MammaPrint®. An adjuvant treatment is a treatment with drugs, such as chemotherapy and hormone treatment, which is aimed at killing tumour cells which are not detectable at the time of diagnosis because of their microscopic size, and that have already spread in the body at the time of the operation. If breast cancer is detected at an early stage, the usual treatment is to remove the tumour surgically. Breast cancer survival rates have improved over the last two decades and two out of three women with the condition survive beyond 20 years. Therefore, it is particularly difficult to ascertain and select those women in whom the potential risk of recurrence justifies adjuvant chemotherapy and its associated side effects. Known side effects of adjuvant chemotherapy during and immediately after chemotherapy are nausea and vomiting, fatigue and hair loss. In the long term there is a risk for side effects such as heart failure or haematological cancer. Although the risk is small these long-term side effects may be potentially severe.

Why is there a review of MammaPrint®?

In August 2016, the results of a study on the clinical benefits of MammaPrint® were published. This study is called the MINDACT and the results have been published in the New England Journal of Medicine (NEJM). As a result of this publication, a number of European countries have decided to jointly assess the therapeutic value of this test. The producer of MammaPrint®, Agendia, was informed of this joint assessment in advance.

Why has this assessment been carried out within the framework of the EUnetHTA project?

EUnetHTA is the European network of national and regional organizations and institutes responsible for assessing medicines, specialist medical care and other health technologies. These assessments are subsequently used to make decisions on a national or regional basis whether or not these health technologies should be reimbursed. In recent years, EUnetHTA has developed methods to assess more consistent forms of healthcare, with particular emphasis on clinical assessments. These methods are now also used to make common clinical assessments, also known as relative effectiveness assessments (REA), of new and existing health technologies, such as MammaPrint®, to increase the efficiency, consistency and quality of these assessments in Europe. This report has been written by Zorginstituut Nederland (Dutch National Health Care Institute) and organizations from other countries such as Belgium, France and Austria have participated in reviewing roles.

What is the outcome of this EUnetHTA assessment?

The EUnetHTA assessment shows that it is uncertain whether it is safe to follow MammaPrint® and to refrain from treatment with chemotherapy in patients in whom the risk for distant recurrence (also called distant metastasis) is high according to standard clinical risk-assessment but low according to the MammaPrint®. There is mainly uncertainty about the extent to which the endpoints used in the MINDACT study can be translated into outcomes that are directly relevant to the patient. In the case of cancer (in this case breast cancer), EUnetHTA believes that measurable patient-related outcomes such as the 10-year survival, quality of life and side effects of the chemo are crucial.

In the case of the MINDACT study, the distant metastasis-free survival (DMFS), the disease-free survival (DFS) and overall survival (OS) were determined after five years. In the EUnetHTA assessment, it was analysed to what extent these surrogate outcomes in the study can predict the 10-year survival, quality of life and side effects of chemotherapy. Although these surrogate parameters provide some information about the possible survival after 10 years, these data cannot simply be translated directly into the desired outcome measures. Because of these uncertainties in the data, and the direction of the results of all surrogates, the results do not rule out the possibility that more patients will be at risk of distant metastasis. Since distant metastases are incurable this means that the possibility of death due to distant metastases cannot be ruled out either. In absolute numbers 100 (out of 1000) more patients will develop distant metastasis compared with standard risk assessment (with a range of at best 6 (out of 1000) patients less, or at worst 287 (out of 1000) more patients with distant metastases). Therefore, there are concerns about whether it is safe to refrain from adjuvant chemotherapy when treatment is based on the MammaPrint® test result.

In addition, side effects and the quality of life are important parts of the assessment of whether MammaPrint® has added value compared to the standard test. It is well-known that the quality of life of patients receiving adjuvant chemotherapy will be reduced due to chemotherapy associated side effects during and shortly after chemotherapy treatment. Therefore it is reasonable to assume that patients will be spared from these burdensome side effects when refraining from adjuvant chemotherapy. On the other hand, the MINDACT study shows that refraining from chemotherapy, when following MammaPrint®, leads to a significantly worse five-year DFS. In the five-year DFS all types of recurrences, curable and incurable, are measured. It is also well-known that all types of recurrences are stressful to patients. This distress may have its repercussions on quality of life, even in the case of a curable recurrence. Although the surrogate parameter DFS provides some information about these potentially stressful disease events, this data cannot simply be translated directly into the desired outcome measures. Therefore, information about quality of life and side effects is crucial, especially in light of the uncertainty about the safety to refrain from chemotherapy based on the MammaPrint® test result. However, no results are presented in the MINDACT study based on which we can make a direct statement about whether MammaPrint has an effect on the quality of life or on side effects in the long term.

Were patients and medical specialists involved in the EUnetHTA assessment?

During this EUnetHTA assessment, patients and medical specialists were involved. In particular, they were involved in the selection of the outcomes that are directly relevant to the patient; patient associations and medical specialists indicated that they agreed with this choice at the start of the MammaPrint® assessment.

What will be the follow-up to this assessment?

National organizations will assess the extent to which MammaPrint® should be reimbursed based on this report. Depending on the timelines of the assessment process, a decision on reimbursement may follow after a few months. In the Netherlands, for example, the Zorginstituut will assess, based on this report, whether MammaPrint® should be included in the basic health insurance package. To achieve this, the added value of MammaPrint® should be demonstrated compared to the current risk assessment method. If this added value is demonstrated, the Zorginstituut will also assess, among other things, whether MammaPrint® is cost-effective.