shortreport

Regione Emilia-Romagna
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
osservatorio regionale per l'innovazione

n. 5

TECHNOLOGY

In vitro test, based on a *microarray* methodology, that measures the level of activity of genes in a sample of surgically removed breast of women treated for breast cancer. The test is used to predict individual risk of developing metastasis. The test classifies the patients in two categories: low and high risk of metastasis.

COMMERCIAL TECHNOLOGY NAME

MammaPrint®

PRODUCER / SUPPLIER

Agendia (NL)

USE

☐ therapeutic

■ diagnostic

■ other: prognostic

CATEGORY

Diagnostic / prognostic *in vitro* device.

THERAPEUTIC OR DIAGNOSTIC FIELD OF APPLICATION

Oncology (breast cancer).

PATIENTS / CLINICAL CONDITION

In Europe[1] eligible patients are women surgically treated for stage 1 or stage 2 breast cancer (infiltrating carcinoma) with tumour size less than 5.0 cm, lymph node (LN) status negative or positive (up to 3 nodes), either ER+ or ER-. In USA[2] the test has been approved only for patients with negative lymph node. While ER+ and LN negative women treated with tamoxifene have a 10-year absolute risk of metastasis of about 15%[3], LN 1-3 women can have a risk of up to 50%, depending on other prognostic factors[3]. Manufacturer estimates that "at 5-10 years, up to or over 30% of patients with early stage breast cancer develop metastases"[4]. By treating with adjuvant chemotherapy, risk of developing metastasis can be reduced by an absolute 3% in ER+ and LN negative women, and by as much as 25% in ER- and LN positive women[3].

TECHNOLOGY DESCRIPTION

MammaPrint® is a *in vitro* test based on microarray methodology. After processing the RNA extracted from specimens of breast cancer tissue, the microarray chip technology enables the assessment of 70-gene profile involved in the molecular *pathway* related to the metastatic process of breast cancer.

THE REPORT

A brief presentation of a technology, providing sufficient information to decide whether to undertake a comprehensive assessment process.

The reported information derives from:

- the consultation of web materials supplied by the producer and of current national and/or regional registries
- the search of secondary studies on HTA databases and of primary studies, indexed on Medline.

! The report does not represent a definitive assessment of the technology.

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The tumour sample is collected at room temperature within 60 minutes from the surgical removing, and sent in a fixative solution (freezing of tissue not required) for the centralyzed analysis to the Agendia laboratory in Amsterdam (Netherlands), which processes the sample from RNA extraction to the reading of microarray results. Finally, an individual risk of distant metastasis is attributed: either "high" (corresponding to a 29% risk at 10 years, without any treatment) or "low" (corresponding to a 10% risk at 10 years, without any treatment)[5].

TARGET PATIENTS

In the year 2005 according to the Emilia-Romagna Region Registry, the number of incident cases of women surgically treated for stage 1 or stage 2 breast cancer was 2 630 (LN negative were 1 950; LN 1-3 were 680) (data source: Registro Tumori Emilia-Romagna, 2005).

STANDARD TREATMENT / METHOD

In standard practice the physician makes an estimate of the individual risk for metastasis, on the basis of which an indication for adjuvant chemotherapy is placed. Information used for this decision making process include clinical, pathologic and molecular data. Guidelines criteria or validated electronic calculators[6-8]- incorporating the presence or absence of some prognostic factors - can assist the clinician in assigning the individual risk of metastasis. As these tools can provide different estimates for the same patient and do not cover all known prognostic factors, physicians do not rely solely on them.

MAIN EXPECTED BENEFITS

MammaPrint® is proposed as a more accurate test than guideline criteria or electronic calculators for the estimate of individual risk for metastasis, for a better identification of low and high risk patients. Among the benefits, the producer emphasises an expected decrease in number of women undergoing unnecessary adjuvant chemotherapy and adverse effects, because wrongly assigned to the high risk group[9].

AVAILABLE EVIDENCE AND RESULTS

Literature search

The key words used to search the electronic databases described the disease (*Breast Neoplasms [mesh], breast cancer, breast neoplasm, breast tumour*) and the technology (*Gene Expression Profiling [mesh], PAM50, Breast Bioclassifier, Theros H/I, Oncotype dx, Mapquant, Mammaprint, Mammostra*t). In February 2010 442 eligible records were found. A further search was carried out in November 2011 and further 115 records were found. Nineteen pertinent primary studies and four secondary studies were selected and analysed.

N° and type of studies

Four secondary studies (2 HTA reports[10,11] and 2 systematic reviews[12,13]-including a total of 9 primary studies) and further 10 primary studies were found, for a total of 19 primary studies. Fifteen of these evaluated the technical performance of the test. Prognostic value (estimating hazard ratios) was explored by 11 studies and 7 studies explored individual predictive values (estimating sensitivity, specificity, overall accuracy) of risk classification according to MammaPrint®. This latter group included cohort studies with low methodological quality due to the retrospective re-construction of the cohort. No study evaluates the "clinical utility".

Outcomes

TECHNICAL PERFORMANCE

The test showed a good within-laboratory test-retest reproducibility[10,11]; however a variability in between-laboratory reproducibility of the RNA labelling phase was found. For this reason the test analyses are centralized at the manufacturer base.
Six studies (1 395 patients)[16-21] reported a technical failure of the test in 13-28% of cases. Time for implementation of the procedures resulted in a median duration of 1.2 months (range 0.2-9.4) in 15 oncologic centres in Netherland[20].

The prognostic value of classification according to MammaPrint® results has been explored in 11 retrospective cohort studies[14,17,21-29] (for a total of 2 174 patients). Most studies presented risks of bias due to lack of blinding of investigators, uncertainty about patients lost to follow up, heterogeneity in populations (age, LN involvement, ER status, prevalence of metastasis). Considering these limitations real estimates of prognostic hazard ratios may be over or underestimated.

EFFICACY – CLINICAL VALIDITY

Individual predictive values of MammaPrint® for metastasis and death, in terms of sensitivity and specificity have been evaluated in 7 retrospective cohort studies[14,17,21,29,31-33], including 882 patients (predominantly LN- women with age less than 60 years). In 4 studies[29,31-33] no comparison against existing test is performed or reported. Three studies[14,17,21], using guidelines criteria or validated electronic calculators as comparator, do not find statistical significant differences in predictive values (sensitivity and specificity) between MammaPrint® and these diagnostic tools.
In the above cited studies sensitivity estimates for predicting metastasis ranged from 72% to 100% (median 90.5%) and specificity estimates from 21% to 77% (median 50.5%).

EFFICACY – CLINICAL UTILITY

No available study.

SAFETY

MammaPrint® does not carry any procedural risk. However, test application can lead patients to misunderstand or misinterpret results. One study[20] carried out on 77 women undergoing MammaPrint® reported the following misconceptions: between 50 and 87% of women erroneously thought the test to be totally reliable, that treatment is *always* decided on the basis of results of microarray test and that in case of positive results (i.e. high risk classification) the risk of metastasis for the next 10 years is over 50%. An important psychological impact has also been documented, with women showing significantly more negative emotions when receiving a high risk result or no result from MammaPrint®, irrespective of the clinical evaluation.

COSTS

According to the manufacturer the cost of a single test is 2 675 euros[34].

PRESUMED IMPACT

Clinical issues

Genetic signature according to MammaPrint® is an independent prognostic risk factor for distant metastasis. Nevertheless the test does not seem to have an individual predictive value superior to that of other available predictive tools, such as guidelines criteria or electronic calculators.
Moreover MammaPrint® has not been compared with best current practice, which involves an assessment of risk for distant metastasis based on several criteria and information and not solely on guidelines criteria or electronic calculators. Therefore, if MammaPrint® was to be compared with best clinical practice the presumed benefit – reduction in number of women wrongly assigned to the high risk group – would probably be overturned.
An analysis of the data from the Emilia-Romagna 2005 tumour registry shows that, out of the 2 630 women with breast cancer eligible for MammaPrint®, 887 (33.7%) had been assigned to the high risk of metastasis and treated with adjuvant chemotherapy. A simulation carried out, using MammaPrint® predicting performance on the same sample of women, assuming a pre-test probability for developing metastases[3] at 5-10 years of 30%, resulted in an increase of expected number of women assigned to the high risk group and thus potentially referred for chemotherapy (range between 1 212 and 2 022 with best and worst MammaPrint® predicting performance respectively).

Economic issues

By applying the cost of the test to the eligible population, we explored how potential adoption of MammaPrint® could affect Regional Health Service budget. The impact on budget has been estimated in €€7 035 250. Additional costs would also need to be considered, such as costs of extraction and manipulation of biological samples and costs of genetic counselling service for the management and communication of test's results to patients.
In absence of robust estimates of diagnostic accuracy, it is not possible to carry out more complex analyses taking into account decrease or increase in costs of treatments, induced by test's results.

Organisational issues

Among the test procedures the rapid selection and preparation of the surgical cancer tissue by expert pathologists would have to be planned. The input from the unit of pathology need to be concomitant to surgical resection, and an efficient organization of transport from surgical theatre to dispatch would be need to set up. It would also be mandatory to plan a service of genetic counselling in order to communicate the results of the test to the patients.

Ethical-social issues

Considering results from the study that assessed women's expectations and values assigned to results of MammaPrint® [20], we can presume a deep psychological impact on a relevant number of patients due to the not negligible percentage of technical failure of the test. Finally, given the widely spreading social expectation and trust put into genetic tests, there is a high risk of inappropriate diffusion of the test to categories of not eligible patients.

ONGOING STUDIES

One ongoing study (MINDACT) has the main objective to confirm that breast cancer patients (LN 0-3) with a "low risk" molecular prognosis (i.e. according to MammaPrint®) and "high risk" clinical prognosis (i.e. according to the electronic calculator *Adjuvant! Online*) can be safely spared adjuvant chemotherapy after surgical treatment without affecting distant metastasis free survival[35]. The study started in 2006 and will be end in 2019, after recruiting 6 000 women. At October 2009 (last available update) 2 264 patients where included. The study is a noninferiority randomised controlled trial. Patients classified as "low risk" by MammaPrint® and "high risk" by *Adjuvant! Online* are randomized to adjuvant chemotherapy or no chemotherapy (expected sample 672). The tested hypothesis is that patients not referred to chemotherapy (i.e. following the indication of "low risk") have a distant metastasis free survival not inferior to that of women undergoing adjuvant chemotherapy with an absolute noninferiority margin of 3% at 5 years of follow up. Due to the choice of comparator, which does not correspond to best current practice, results from this study will not help to resolve major uncertainties regarding the predictive value of MammaPrint®.

AUTHORISATIONS

FDA Authorisation: February 2007.

CE mark: 2005.

DIFFUSION / DIFFUSION PREDICTION

The worldwide diffusion is not clear. Nowadays at least 70 European medical centres are accredited as participants to MINDACT trial; 6 of these are Italian institutions (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola; Ospedale Civile, Sondrio; Ospedale Carlo Poma, Mantova; Azienda Ospedaliera Universitaria San Martino, Genova; Arcispedale Di S. Maria Nuova, Reggio Emilia; Ospedale Civile Rimini, Rimini)[36]. Today we cannot predict an estimate of future diffusion of MammaPrint®.

BRIEF SUMMARY

The technology, providing a genetic signature of the breast cancer tissue, assigns a 10 year level of risk for distant metastasis to women - treated with surgery, LN 0-3 and potentially eligible for adjuvant chemotherapy. The main expected benefit is a more accurate individual estimate of risk for distant metastasis and a reduction in number of patients unnecessarily treated with chemotherapy. However, considering the available data on the individual predictive value of the MammaPrint® and applying them to the population of breast cancer patients of Emilia-Romagna region, the test could not actually obtain any of the expected benefits, besides presenting several important limitations, such as the not negligible amount of technical failure of the test and the difficult management of genetic information, with possible negative psychological repercussions on patients. The ongoing randomized controlled trial, which aims to evaluate the impact of the test on relevant clinical usefulness outcomes, has such serious limitations in the design and rationale that it will be difficult to transfer results to standard clinical practice.

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