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Title Clinical utility of genomic signatures in early-stage breast cancer

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Aim

Evaluate the clinical utility of four genomic signatures (GS)[1], currently and temporarily funded on a conditional basis as part of a specific funding program for research and innovation (known in France as RIHN). The aim of the evaluation is to assess funding eligibility for the traditional reimbursement schemes offered by the National Health Insurance Fund.

The four GS are decision-making aids for the prescribing of adjuvant chemotherapy (ACT) in certain cases of early breast cancer.

Conclusions and results

The HAS report concludes that GS are not intended to replace standard clinicopathological criteria (SCPC), which are considered to play a crucial role in the prescribing of ACT for early breast cancer.

In light of inadequate[2] and/or lack of clinical data respectively found in first and second generation tests, the HAS considers it to be premature to recommend routine use of GS in early breast cancer. Thus, the HAS does not recommend reimbursement by the National Health Insurance Fund at this current juncture.

Furthermore, the HAS identified a small yet well-defined population of interest that may particularly benefit from the use of GS in addition to SCPC: cases at intermediate risk for breast cancer recurrence, with no major clinicopathological discordance and *uncertain* prescribing decision-making on ACT use.

These patients should present with the following characteristics:

- invasive adenocarcinoma with a diameter of 1 to 5 centimetres (pT1c-2), predominantly ductal, with a hormone-receptor-positive (HR+) and HER2 negative phenotype status;
- lymph node involvement : absent or microscopic (pN0-N1mi);
- tumour with intermediate proliferation (tumor grade 2);
- exclusion of a clear indication for ACT based on other available SCPF, such as young age (less than 35-40 years old) or lymphovascular invasion;
- informed patient consent with regards to treatment (GS testing is not indicated in case of patient refusal of one of the two available treatment options);

Taking into consideration the potential benefit to be gained by this specific subgroup, the HAS highlights the need to collect prospective and comparative data in this small, well-defined population of interest through the RIHN funded-program. Generation of this data, combined with the results of current, ongoing international clinical studies, will enable an HAS reassessment for traditional reimbursement purposes and eligibility.

Therefore, the HAS recommends that temporary and conditional funding within the RIHN program be maintained for the four GS thus far assessed. The HAS also recommends elaboration of a national, consensus-based clinical guideline on SCPC to reduce heterogeneous decision-making with respect to ACT prescribing in HR+/HER2- early breast cancer.

Methods

A systematic literature search to identify prospective and comparative clinical impact studies was performed, followed by a critical analysis of the resulting and available data for the specified target population[3]. Of the four studies selected, two clinical impact studies (TAILORx/MINDACT) and one decision-making concordance study (OPTIMA Prelim) were contributory to the assessment. Study results (validity, clinical applicability) and future prospects were discussed with a multidisciplinary expert working group[4].

[1] *Oncotype Dx*, *Mammaprint* (first generation GS tests), *Endopredict*, *Prosigna* (second generation GS tests).
[2] Relatively uninformative data due to a major risk of bias and/or an inappropriate study population included in trials in relation to usual care in France.
[3] Patients presenting with HR+/HER2- breast cancer staged pT1c-2 pN0-1, and who are likely to receive ACT in usual care on the basis of true uncertainty or established recommendation.
[4] The working group was composed of 12 health professionals specialising in medical oncology, breast surgery, pathology,

Stakeholders were consulted during the document review phase (professional organisations, patient associations, National Cancer Institute). Conclusions and recommendations were reviewed by the Medical Device and Health Technology Assessment Committee and further validated by the HAS Board.

Further research/reviews required

The HAS strongly recommends that temporary and conditional funding (within the RIHN program) be maintained and truly conditioned to the collection of exhaustive and relevant data in the context of a prospective, comparative clinical study for the four GS assessed; and in accordance with methodological and population requirements described in the report. The awaited results of ongoing international trials—in patients with lymph node involvement (pN+: RxPONDER trial) and in those presenting with ACT indications (OPTIMA trial or WSG ADAPT HR+/HER2- trial) —will allow HAS to update its analysis and report. HAS also recommends validating a risk prediction model in the French clinical context to optimise prescribing decision-making of ACT in case of complex uncertainty related to major clinicopathological discordance.

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