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Title 2023 update: clinical utility of genomic signatures in early-stage HR-positive/HER2-negative breast cancer

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Aim

In 2019, the French National Authority for Health (HAS) evaluated the clinical utility of four genomic signatures (Oncotype Dx, Mammaprint, Prosigna, Endopredict) in early-stage hormone-receptor-positive (HR+) breast cancer with HER2-negative status (HER2-). Genomic signatures could be used as a guide to safely de-escalate adjuvant chemotherapy (ACT) in certain patient profiles in situations of clear decision-making uncertainty, with a low or favourable genomic score enabling the avoidance of unnecessary decisions to administer ACT. Based on the data available and the consultations carried out at the time, the HAS had returned an unfavourable opinion for coverage of testing for these four genomic signatures. But it issued a favourable opinion for temporary funding as part of a specific funding program for research and innovation (RIHN) to maintain access to these innovative tests in a potential population of interest. In 2021 and 2022, the publication of new intermediate data led to changes being made to several international guidelines, reporting a risk of loss of chance in terms of oncological outcome in some premenopausal patients aged 50 or under linked to genomic signatures. At the end of 2022, in view of this risk of loss of chance in terms of oncological outcome, the HAS decided to update its assessment of the four genomic signatures and to redefine the scope of the eligible target population to guarantee the oncological safety of patients and limit the risk of misuse by healthcare professionals.

Conclusions and results

In 2023, taking into consideration the new data, the HAS concluded that it was necessary to modify its definition of the patient population eligible for genomic signatures, on the basis of menopausal status and patient age, in particular.

This assessment led it to the conclusion that there was a **risk of loss of chance in terms of oncological outcome** for some premenopausal patients (or aged ≤ 50 years). It is for this reason that **the use of genomic signatures in premenopausal patients (or aged ≤ 50 years) HR positive/HER2 negative is now restricted, on the advice of experts, to two specific subpopulations**:

- **pT2 grade 2 N0 patients**. For these patients, in the event of a tumour measuring more than 3 cm, the decision to use genomic signatures should be taken carefully at a multidisciplinary team meeting;
- **pT1c grade 2 N0 patients.** For these patients, before prescribing tests for genomic signatures, prescribers should carefully use the NHS PREDICT algorithm to check that the potential improvement in 10-year overall survival induced by ACT is more than 2% with the aim of preventing the risk of genomic-induced ACT. (https://breast.predict.nhs.uk/tool).
- **Since relevant and reassuring data in premenopausal patients (or aged 50 or under) are only available with the Oncotype DX® genomic signature**, only this genomic signature may be used in the two defined subpopulations (Recurrence Score ≤ 15 to avoid ACT).

Outside these two subpopulations, the use of genomic signatures is not indicated in premenopausal patients (or aged ≤ 50 years) due to a risk of loss of chance in terms of oncological outcome.

Furthermore, **in postmenopausal women (or aged over 50 years)**, new data lead to:

- extension of the four genomic signatures to **pT2 grade 2 N0, pT1c-T2 grade 2 N1/N1mi and pT2 grade 1 N1** patients;
- restriction of the four genomic signatures **to patients under 70 years of age**. This is because there are **no specific data in favour of the use of genomic signatures in patients over 70 years of age, for whom the prescription of ACT in the event of an HR+/HER2- tumour remains optional, uncommon, case-dependent, and with a marginal or uncertain benefit**. In these women, the relevant research question with these tests is therefore whether it is appropriate **to escalate ACT in the event of an unfavourable genomic signature** rather than to guide towards therapeutic de-escalation (see non-conclusive ASTER 70s study, NCT0156405).

Other intermediate results relative to clinical utility

As regards the first-generation signatures[1] (Oncotype DX® and Mammaprint®), the inconclusive or intermediate data from three randomised studies (TAILORx, RxPONDER, MINDACT), along with the inappropriate study designs for the assessment of predictive tests in view of the requirements of the HAS guide[2] do not make it possible to demonstrate in 2023 that these signatures are able to reliably predict the efficacy or lack of efficacy of adjuvant chemotherapy. Moreover, they were not intrinsically and originally designed as predictive tests. Consequently, these signatures should be strictly considered as prognostic. As regards the second-generation signatures[3] currently used in France (Prosigna® and Endopredict®), no conclusive evidence was identified in 2023. Therefore, the situation remains the same as in 2019. The four genomic signatures do not have the same gene panel. As in 2019, the data analysed in 2023 confirmed the existence of inconsistent results between signatures for the same tumour. The risk of heterogeneous treatment decisions between healthcare facilities or analysis laboratories depending on the signature performed therefore needs to be highlighted.

Recommendations

The HAS decided that the temporary funding of these tests be maintained in the context of innovation programmes (RIHN) and in a redefined population taking into account the loss of chance observed in terms of oncological outcome in some premenopausal patients and the risk of misuse of these tests in some postmenopausal patients (tumour profile and age restricted to under 70 years for these reasons). It will be possible to conduct a reassessment of the coverage decision once finalised data from the OPTIMA and RxPONDER clinical trials have been reported.

Methods

Since this is an update of the 2019 assessment, the 2023 methodological requirements and assessment criteria are the same as for the previous assessment. The critical analysis of the literature focused on randomised trials published between January 2018 and June 2023 assessing the clinical utility of genomic signatures and studies assessing the level of consistency between signatures in the same patients. External experts from a range of different disciplines (medical oncology, anatomical pathology, medical biology, oncological surgery) were consulted. The reactions of stakeholders (professional organisations, patient associations) and the French National Cancer Institute (INCa) to this scientific update were also collected.

Further research/reviews required

A reassessment of the decision coverage will be scheduled following the publication of two ongoing randomised trials: final analysis of RxPONDER in an N1 population (NCT01272037, Oncotype Dx® signature) and results of OPTIMA trial expected in 2026 in a population at intermediate/high (stage 1-2) and high clinical risk (stage 3) (ISRCTN42400492, Prosigna®). The results of the OFSET trial in a premenopausal N0/N1 population (NCT05879926, Oncotype Dx®) started in 2023 will not be available for several years. The mature results of the TAILORx trial after 5 years and 10 years in the premenopausal and postmenopausal patients at intermediate/high clinical risk according to Adjuvant! with HER2 (high clinical risk) and comparative clinical data in a population aged 70 years or over are also required (in TAILORx and RxPONDER trials). Analyses of French databases or prospective registries of breast cancer patients with archived tumour samples will be necessary. The prognostic added value of genomic signatures beyond a well-established clinical predictive model (NHS PREDICT) would be useful in order to propose a useful clinico-genomic model. In addition, reassuring oncological safety data in high clinical risk patients ≤ 50 years of age or premenopausal without receiving ACT guided on a favourable genomic signature will be required. Prescribing data (FRESH registry) or prognostic data from the CANTO registry (UNICANCER) will also be necessary.

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[1] Technological development between 2002 and 2004 (genomic data only)

[2] METHODOLOGICAL GUIDE. February 2014. Companion diagnostic test associated with a targeted therapy: definitions and assessment method https://www.has-sante.fr/upload/docs/application/pdf/2014-11/companion_diagnostic_test_associated_with_a_targeted_therapy_-_definitions_and_assessment_method_2014-11-18_16-09-49_75.pdf

[3] Technological development between 2009 and 2011: Prosigna® (Veracyte) and Endopredict® (Myriad) [genomic data incorporating two clinical factors: tumour size (T) and lymph node status (N)]