INAHTA Brief Issue 2023/12

Title Assessment of the Endotest® saliva test in complex endometriosis diagnosis situations

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Reference ISBN number: 978-2-11-172117-3, link to full report in French: https://www.has-sante.fr/jcms/p_3486036/fr/evaluation-du-test-salivaire-endotest-dans-les-situations-complexes-de-diagnostic-d-endometriose

Aim

- To assess the self-referral by the HAS in July 2023 relating to the clinical utility of the Endotest® saliva test for complex endometriosis diagnosis situations.
- The objective is to inform the HAS Board's decision with a view to determining whether reimbursement of the test by the French national health insurance system is valid in a relevant indication.
- At the time of the assessment, this 109-miRNA saliva signature test using a sophisticated next-generation sequencing method is in the validation phase and is the only test currently with CE marking in endometriosis.

Conclusions and results

- The not yet published data supplied by the manufacturer and deemed to be acceptable in view of the clinical question concerns a subgroup from the EndomiARN SALIVA test validation study (NCT05244668), financed by the manufacturer, Ziwig, of 237 patients with suspected endometriosis, with inconclusive imaging on radiology and an indication for laparoscopy validated at a multidisciplinary team meeting (complex clinical situations).
- The risks of bias and clinical applicability of the study are uncertain according to the QUADAS 2 tool.
- The available data does not directly demonstrate a favourable clinical impact of the test on patient management.
- The diagnostic performance of the test is high for the disease prevalence of 49% (in the study) : sensitivity: 0.95 95% CI [0.89 – 0.98]; specificity: 0.94 95% CI [0.88 – 0.98] negative predictive value: 0.95 95% CI [0.91 – 0.99]; negative likelihood ratio: 0.05.
- This performance remains stable despite several robustness tests (sensitivity analyses using an imputation method). However, the risk of diagnostic error must nonetheless be taken into account for a negative test in the case of a plausible theoretical high prevalence of 75% (14% false negatives in this case).
- The method for modelling the clinical impact on patient management used Decision Curve Analysis (DCA) and shows that the strategy with Endotest® is superior to the default strategies (without Endotest®). The Endotest® strategy involves performing from three (in the case of a prevalence of 50%) to five tests (in the case of a prevalence of 75%) in order to (possibly) avoid an unnecessary laparoscopy for a patient (indirect evidence based on diagnostic performance).
- According to the advisory panel of external experts, there are numerous clinical elements that are not - or are inadequately - documented in the validation study, meaning that it is not possible to reach a confident conclusion with respect to the effective applicability of the results to routine practice.

Recommendations

- While Endotest® is undeniably innovative, with strong potential highlighted by the experts and a validated diagnostic performance, an interventional (comparative) diagnostic study of the impact of the test before and after the result on the same patient concerning decision-making and patient management (particularly in terms of reducing the number of unnecessary laparoscopies) is now needed to demonstrate the clinical utility of the test and thus be able to meet the high expectations of patients and clinicians regarding its use in practice.
- Although the long-term reimbursement of Endotest® cannot yet be envisaged at this stage, Endotest® is nonetheless likely to meet the eligibility criteria of the French *"forfait innovation"* innovation and research funding programme. This programme could thus authorise safe and early access to the test for patients included in the clinical impact study. In the context of its support actions, the HAS will be able to provide methodological assistance for the preparation of the clinical impact study.

Methods

This assessment is based on:

- early consultation of French patient associations (need to cover, current medical context);
- a critical analysis of the full clinical data (not yet published) from the single ENDOmiARN saliva test validation study (NCT05244668), supplied by the manufacturer, without the need for another systematic review (in the absence of other tests at

comparable level identified on the European market);
- consultation of external experts (gynaecologists, radiologist, medical biologist) to put the study results in French context;
- the written reactions of stakeholders concerning the assessment work (professional bodies, patient associations);

The conclusions have been reviewed by the Diagnostic, Prognostic and Predictive Health Technologies Evaluation Committee, the HAS specialised appraisal committee then validated by the HAS Board.

Further research/reviews required

In addition to its decision to fund Endotest® in the temporary clinical research context (*"Forfait Innovation"* procedure), the HAS proposes collection of the following elements:

- access to data on the repeatability and reproducibility of test results in the same patient at different times in the hormonal cycle, and the observation of normalisation of the test results following complete surgical resection;
- performance, within the context of the *"Forfait Innovation"* procedure, of a clinical impact study assessing the decision-making impact on patient management before and after the test result in the same patient in which all patients would have the saliva test (change-in-management study);
- the primary endpoint of this confirmation study would be the reduction in the number of unnecessary laparoscopies as a result of the final decision, medically shared with the patient, and on a sufficient number of patients, with other informative data to confirm the diagnostic performance and analytical data, and to obtain patient-reported experience measures (PREMs) relating to satisfaction and quality of life;
- at the time the protocol of the next clinical search will be build, the discussions and expectations by the search for consensus of the professionals, patients in addition to the manufacturer may relate to the context of care (level 3 centre, meeting with medical and surgical experts), the target population and its clinical profile, as well as the imaging to be performed prior to the test, the relevant endpoints, and the decisional algorithm for the test (downstream consequences) in the event of a positive or negative test result;
- a survey to estimate the volume of tests prescribed in the HAS' target population (before laparoscopy) and beyond this restricted context (following an "inconclusive imaging" in large);
- an acceptability survey of the test results (in the event of a negative or positive test) concerning both doctors and patients "MRI negative or equivocal" (with the help of a patient association, for example).

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