Development of a gene expression-based test for the detection of endometrial cancer in uterine aspirates.

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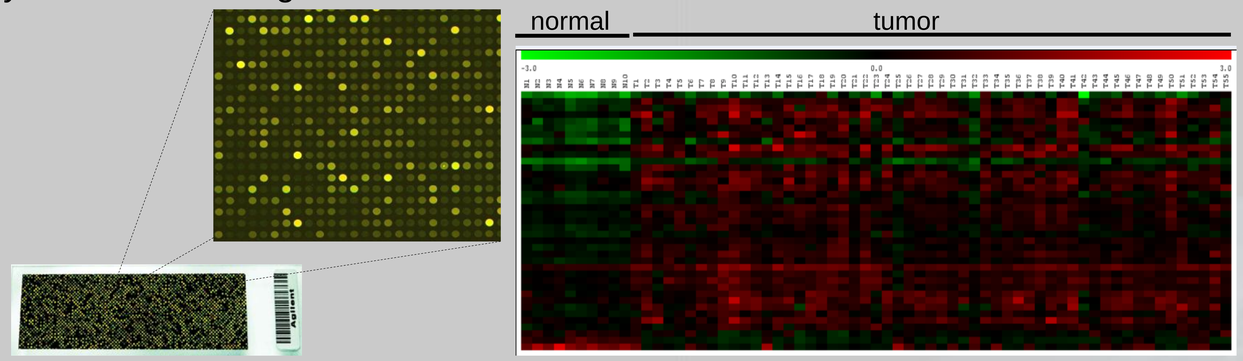
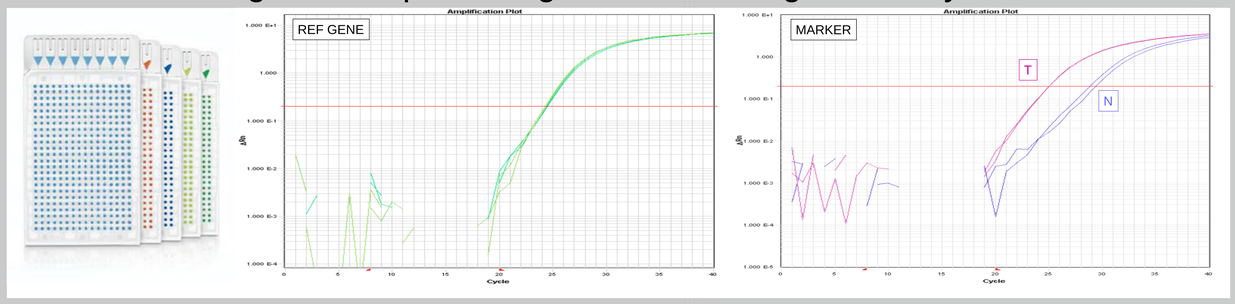
We report the development of a gene expression (GE) based test to detect endometrial cancer (EC). Validation of the test in a multicenter validation study conducted in over 10 different hospitals in Spain is ongoing.

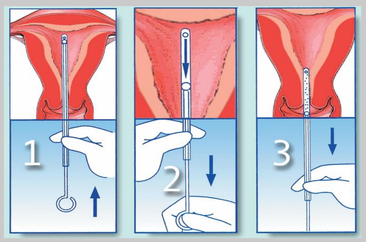
Discovery: Seventy tissue samples (60 EC + 10 normal) were collected from women with abnormal uterine bleeding (AUB) that were submitted to biopsy or tumor resection. Microarray based GE analysis was performed at Oryzon to yield a candidate gene set.

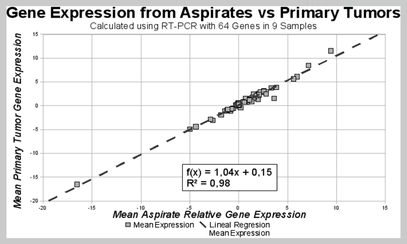


Initial validation: An independent cohort of normal (n = 20) and tumor tissue (n = 20) samples as well normal (n = 48) and tumor (n = 33) uterine aspirate samples was obtained for validation. GE analysis was performed using TaqMan LDAs containing an EC-specific signature in a 64-gene assay format.



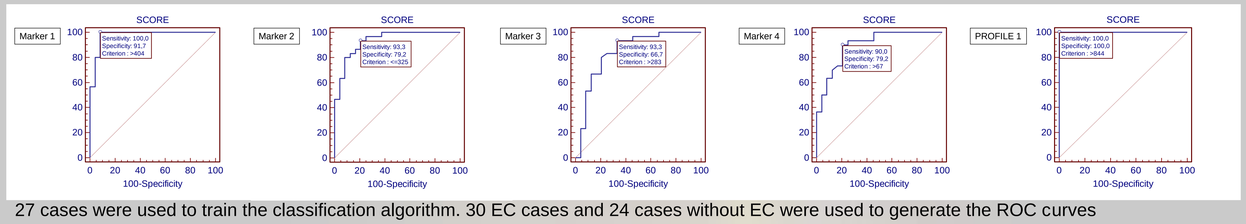
Translation: Expression profiles from 9 tumor tissue and aspirates from the same patients were compared in Taqman LDAs and showed high correlation.





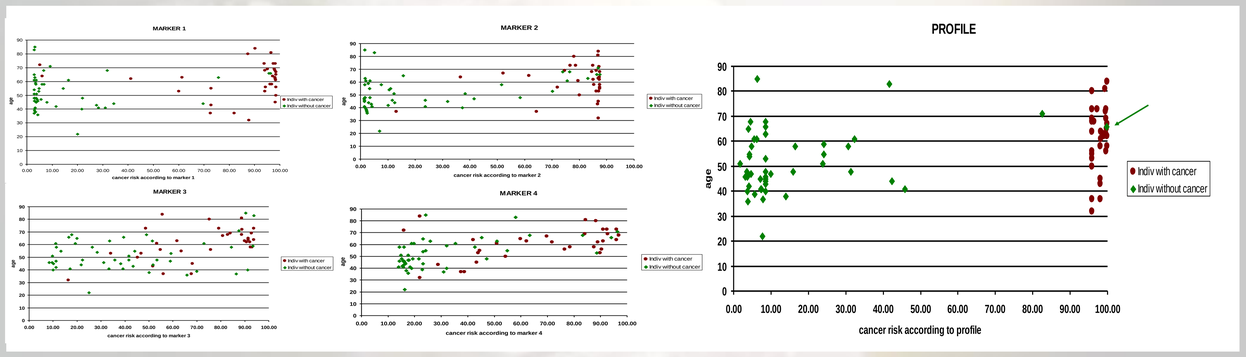
This opened the possibility to perform the GE analysis on a sample type which can be obtained by a procedure that is considerably less invasive than hysteroscopy.

ROC scores of the individual markers as secretory / proliferative and/or tumor/ no tumor markers were assessed. The best markers and endogenous controls were selected and 5 test score algorithms (4, 5, 6, 12, 20 genes) developed.



27 cases were used to train the classification algorithm. 30 EC cases and 24 cases without EC were used to generate the ROC curves

The 5 scoring algorithms classified the 81 aspirates from subjects in the validation cohort as positive or negative for EC with high specificities and sensitivities (near 100%). Inclusion of markers that distinguish between secretory and proliferative phase is essential to correctly diagnose pre or perimenopausal women. One sample recorded as negative on histologic basis was classified as a tumor sample according to our algorithms. The histological revision of the EC-negative sample led to a reclassification of the sample, which may indicate that the GE assay could reduce diagnostic errors.



Multi-center validation: a cohort of 350-500 patients with AUB (20% is expected of being affected by EC) is being enrolled in a multicentric double blind study to evaluate 5 test algorithms. The LDA assay is being evolved to a small profile to produce a cost-effective assay.

Conclusion: The uterine aspirate based GE test shows high diagnostic potential. Inclusion of EC subtype specific and prognostic marker is expected to further increase the utility of the proposed diagnostic method.

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