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Fulvestrant response prediction from transcriptome data obtained from primary breast cancer biopsies

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Background
Fulvestrant is a highly selective estrogen receptor (ER) antagonist used in the treatment of postmenopausal patients with ER-positive advanced breast cancer. To identify patients who are sensitive to fulvestrant we applied a multigene mRNA-based Drug Response Predictor (DRP®) broadly validated by Wang et al (1) and for fulvestrant by Knudsen et al (2).
The DRP® is based on measuring the full transcriptome in cell lines sensitive and cell lines resistant to a drug compared with expression patterns in tumors.

Method
To evaluate patients' transcriptomes from primary biopsies and response to therapy at relapse, a total of 545 consecutive patients with advanced disease were included from five participating hospitals. After patient informed consent mRNA was extracted and assayed on Affymetrix Gene Chip U133p2 arrays from formalin fixed paraffin embedded diagnostic biopsies.
Of these 545 patients, 112 patients with ER-positive breast cancer received fulvestrant in one of the first three lines of treatment for advanced disease between November 2008 and November 2015 Patients were during treatment evaluated every 3 to 4 months using CT scans and clinical examination.

The primary analysis was a Cox regression model of the prediction scores stratified by treatment line and time to disease progression calculated from the start of treatment and until the start of a new treatment.

Results
Of 112 patients treated with fulvestrant 75 progressed within 6.4 months median (1.0-38.9 months). Of the 112 patients 81 had received prior adjuvant antihormone therapy and 30 had not. One patient was without accessible data about prior adjuvant antihormone therapy.

	Hazard ratio	95% confidence limits	P-value
No prior adjuvant antihormone therapy	0.31	0.10-0.97	0.044
Prior adjuvant antihormone therapy	0.88	0.38-2.04	0.76

Conclusion
In a real world setting mRNA from the original diagnostic biopsy can be used to predict a later fulvestrant response only if the patients are unexposed to previous adjuvant endocrine therapy.
Such transcriptome data supports the hypothesis that development of clinical resistance pathways can be detected and followed.

Wang et al JNCI (2013) 105 (17): 1284-1291
Knudsen et al PLoS ONE 9(2): e87415