



Time to move forward from "first-generation" prognostic gene signatures in early breast cancer

Christine Desmedt, Stefan Michiels, Benjamin Haibe-Kains, Sherene Loi,
Christos Sotiriou

► To cite this version:

Christine Desmedt, Stefan Michiels, Benjamin Haibe-Kains, Sherene Loi, Christos Sotiriou. Time to move forward from "first-generation" prognostic gene signatures in early breast cancer. *Breast Cancer Research and Treatment*, 2010, 128 (3), pp.643-645. 10.1007/s10549-010-1213-4 . hal-00615381

HAL Id: hal-00615381

<https://hal.science/hal-00615381>

Submitted on 19 Aug 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Time to move forward from “first generation” prognostic gene signatures
in early breast cancer**

Christine Desmedt¹, Stefan Michiels¹, Benjamin Haibe-Kains², Sherene Loi¹ and
Christos Sotiriou^{1*}

Author Affiliation:

¹ Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Brussels, Belgium

² Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, and
Department of Biostatistics, Harvard School of Public Health, Boston, USA

**Corresponding author:*

Christos Sotiriou, M.D., Ph.D.

Breast Cancer Translational Research Laboratory

Institut Jules Bordet

Universite Libre de Bruxelles

121 Boulevard de Waterloo

1000 Bruxelles, Belgium

e-mail: christos.sotiriou@bordet.be

For clinicians, it has been clear for many years that breast cancer patients with the same clinical and pathological characteristics can have diverse clinical outcomes. The advances in the annotations of the genome and the emergence of high through-put gene expression technologies during the last decade have offered researchers powerful means to investigate breast cancer biology and to determine the mechanisms of this clinical heterogeneity [1,2]. For this purpose, several research groups have developed “first-generation” gene expression signatures that could help to better identify which breast cancers are at high or low risk of cancer recurrence, such as MammaPrint [3], the Oncotype Dx [4] and the Gene Expression Grade Index [5]. The prognostic value of these 3 scores have all stood the test in independent validation series [6-8] and are reported to provide further prognostic information to standard clinical and pathological factors, although their precise added value needs to be studied [9]. For two of these prognostic scores, prospective worldwide clinical trials are ongoing to estimate their impact on clinical practice for the prescription of adjuvant chemotherapy [10,11].

In this article, Naoi et al. developed a 95-gene score to predict recurrences in node-negative (N0) patients with ER-positive tumors. They developed their score using publicly available gene expression data from 549 node negative (N0) breast cancer patients with ER-positive disease and validated their predictor in a Japanese cohort of 105 N0 with ER-positive disease. They reported that their 95-gene score was the most significant factor in a multivariate analysis which included the classical clinical and pathological characteristics, including other proliferation markers such as Ki-67, as well as the previously identified gene expression grade signature (GGI), another gene expression prognostic score [5]. The authors deserve credit for their study which investigated if currently available prognostic gene

expression signatures derived from Caucasian breast cancer patients are also be applicable to the Japanese population.

However, there are some limitations to their study that should be highlighted. First, there exists heterogeneity in the treatment of the patients selected for the training and validation set. In other words, some patients did and did not receive adjuvant hormonal treatment. This could have considerably affected the clinical outcome of some of these patients. Additionally, although the type of endocrine therapy seems to be quite homogeneous in the training set, a variety of different hormonal agents were administered to patients in the validation set. This issue could have been addressed by adjustment in the statistical models or by using other publicly available datasets of systemically untreated N0 ER+ patients [12].

Secondly, the validation set of Japanese patients used comprised of only 24 relapse events. Even if we assume that the validation set only was used in the multivariate analyses (as including the training set would provide an overoptimistic advantage to the new 95-gene score), such a small number of events is really too small to draw definitive conclusions. More importantly, in order to show that the new 95-gene score could add prognostic information to established clinical or pathological factors (and GGI), further statistical methods are required. It is not sufficient to just perform a multivariate regression analysis comparing the effects of the established prognostic factors and of the gene score under study, and to show that the new gene score is 'more significant' than the others factors in this model [13]. A new gene score is of interest only if it provides additional prognostic value, over and above that of easy-to-measure clinico-pathological characteristics (nodal involvement, tumour size, age, histological grade and immunochemistry markers) or gene signatures. The gain in prognostic ability should therefore be quantified by comparing the predictive accuracy of two multivariate models -one with and one without the newly developed gene score-, using specific statistical measures such as the concordance index [14,15].

From a clinical point of view, this signature will most likely not add important information to the existing gene scores. Previously, a pooled analysis of prognostic gene expression signatures using publicly available gene expression data from over 1000 breast cancer patients reported that proliferation and cell-cycle genes appear to be the common denominator underlying the prognostic abilities of the vast majority of the first generation prognostic signatures [16]. Notable also was the fact that they were only clinically relevant for the ER-positive/ HER2-negative breast cancers [16,17]. Since Noai et al. report that a) the new 95-gene score is significantly correlated with both the histological grade and Ki67, b) the hazard ratios of histological grade, Ki67 and GGI dramatically change in the multivariate analysis as compared to the univariate one, and c) the 95-gene score is significantly enriched in cell cycle proliferation (22 genes), it is highly likely that their gene signature is tracking the same biological mechanism as the above mentioned prognostic gene scores.

It also should be highlighted that whilst proliferation-based prognostic signatures have considerable potential to refine the risk of recurrence for breast cancer patients, they have several important limitations. Even though these signatures display high performances in identifying early relapses (up to 5 years after the initial diagnosis), their performance decreases with increasing follow-up years [18]. Despite seeming to add prognostic value to established clinical prediction systems (such as AdjuvantOnline!), there is still a lot of variation in the occurrence of distant metastases that remains unexplained (such as those that occur in the HER2 overexpressing or triple negative breast cancer populations). It is therefore hoped that the “second generation” gene signatures that will be reported in the near future can provide better fine-tuning. Advancements in the understanding of signaling, tumor microenvironment and host-tumor immune interplay are also likely to aid prognostic and therapy prescription for breast cancer patients [19].

Additionally, it has now become a standard practice for microarray data to become publicly available after publication and to provide full details of the statistical methods used. Whole genome gene expression data provides a valuable and powerful resource for breast cancer researchers worldwide and its global accessibility also acknowledges the altruism of the women that consent for their tumors to be used for the advancement of breast cancer research. Given that there are few datasets of non-Caucasian breast cancer samples available, we encourage these authors and others to publicly release their data.

Conflict of interest

Christos Sotiriou is a named inventor on the patent of the Gene Expression Grade Index (GGI).

References

1. Sotiriou C, Piccart MJ (2007) Taking gene-expression profiling to the clinic: When will molecular signatures become relevant to patient care? *Nat Rev Cancer* 7 (7):545-553.
doi:nrc2173 [pii]
10.1038/nrc2173
2. Sotiriou C, Pusztai L (2009) Gene-expression signatures in breast cancer. *N Engl J Med* 360 (8):790-800. doi:360/8/790 [pii]
10.1056/NEJMra0801289
3. van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ, Kerkhoven RM, Roberts C, Linsley PS, Bernards R, Friend SH (2002) Gene expression profiling predicts clinical outcome of breast cancer. *Nature* 415 (6871):530-536

4. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N (2004) A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 351 (27):2817-2826
5. Sotiriou C, Wirapati P, Loi S, Harris A, Fox S, Smeds J, Nordgren H, Farmer P, Praz V, Haibe-Kains B, Desmedt C, Larsimont D, Cardoso F, Peterse H, Nuyten D, Buyse M, Van de Vijver MJ, Bergh J, Piccart M, Delorenzi M (2006) Gene expression profiling in breast cancer: Understanding the molecular basis of histologic grade to improve prognosis. *J Natl Cancer Inst* 98 (4):262-272
6. Buyse M, Loi S, van't Veer L, Viale G, Delorenzi M, Glas AM, d'Assignies MS, Bergh J, Lidereau R, Ellis P, Harris A, Bogaerts J, Therasse P, Floore A, Amakrane M, Piette F, Rutgers E, Sotiriou C, Cardoso F, Piccart MJ (2006) Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst* 98 (17):1183-1192
7. Dowsett M, Cuzick J, Wale C, Forbes J, Mallon EA, Salter J, Quinn E, Dunbier A, Baum M, Buzdar A, Howell A, Bugarini R, Baehner FL, Shak S (2010) Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: A transatac study. *J Clin Oncol* 28 (11):1829-1834. doi:JCO.2009.24.4798 [pii]
10.1200/JCO.2009.24.4798
8. Haibe-Kains B, Desmedt C, Piette F, Buyse M, Cardoso F, Van't Veer L, Piccart M, Bontempi G, Sotiriou C (2008) Comparison of prognostic gene expression signatures for breast cancer. *BMC Genomics* 9:394. doi:1471-2164-9-394 [pii]
10.1186/1471-2164-9-394

9. Recommendations from the egapp working group: Can tumor gene expression profiling improve outcomes in patients with breast cancer? (2009). *Genet Med* 11 (1):66-73.
doi:10.1097/GIM.0b013e3181928f56
10. Cardoso F, Van't Veer L, Rutgers E, Loi S, Mook S, Piccart-Gebhart MJ (2008) Clinical application of the 70-gene profile: The mindact trial. *J Clin Oncol* 26 (5):729-735
11. Sparano JA, Paik S (2008) Development of the 21-gene assay and its application in clinical practice and clinical trials. *J Clin Oncol* 26 (5):721-728
12. Haibe-Kains B, Desmedt C, Rothe F, Piccart M, Sotiriou C, Bontempi G (2010) A fuzzy gene expression-based computational approach improves breast cancer prognostication. *Genome Biol* 11 (2):R18. doi:gb-2010-11-2-r18 [pii]
10.1186/gb-2010-11-2-r18
13. Kattan MW (2003) Judging new markers by their ability to improve predictive accuracy. *J Natl Cancer Inst* 95 (9):634-635
14. Dunkler D, Michiels S, Schemper M (2007) Gene expression profiling: Does it add predictive accuracy to clinical characteristics in cancer prognosis? *Eur J Cancer* 43 (4):745-751. doi:S0959-8049(06)01061-6 [pii]
10.1016/j.ejca.2006.11.018
15. Haibe-Kains B, Desmedt C, Sotiriou C, Bontempi G (2008) A comparative study of survival models for breast cancer prognostication based on microarray data: Does a single gene beat them all? *Bioinformatics* 24 (19):2200-2208. doi:btn374 [pii]
10.1093/bioinformatics/btn374
16. Wirapati P, Sotiriou C, Kunkel S, Farmer P, Pradervand S, Haibe-Kains B, Desmedt C, Ignatiadis M, Sengstag T, Schutz F, Goldstein DR, Piccart M, Delorenzi M (2008) Meta-analysis of gene expression profiles in breast cancer: Toward a unified understanding of

breast cancer subtyping and prognosis signatures. *Breast Cancer Res* 10 (4):R65. doi:bcr2124 [pii]

10.1186/bcr2124

17. Desmedt C, Haibe-Kains B, Wirapati P, Buyse M, Larsimont D, Bontempi G, Delorenzi M, Piccart M, Sotiriou C (2008) Biological processes associated with breast cancer clinical outcome depend on the molecular subtypes. *Clin Cancer Res* 14 (16):5158-5165.

doi:14/16/5158 [pii]

10.1158/1078-0432.CCR-07-4756

18. Desmedt C, Piette F, Loi S, Wang Y, Lallemand F, Haibe-Kains B, Viale G, Delorenzi M, Zhang Y, d'Assignies MS, Bergh J, Lidereau R, Ellis P, Harris AL, Klijn JG, Foekens JA, Cardoso F, Piccart MJ, Buyse M, Sotiriou C (2007) Strong time dependence of the 76-gene prognostic signature for node-negative breast cancer patients in the transbig multicenter independent validation series. *Clin Cancer Res* 13 (11):3207-3214

19. Reis-Filho JS, Weigelt B, Fumagalli D, Sotiriou C (2010) Molecular profiling: Moving away from tumor philately. *Sci Transl Med* 2 (47):47ps43. doi:2/47/47ps43 [pii]

10.1126/scitranslmed.3001329