VOLUME 27 · NUMBER 8 · MARCH 10 2009

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Twenty-One–Gene Assay: Challenges and Promises in Translating Personal Genomics and Whole-Genome Scans Into Personalized Treatment of Breast Cancer

TO THE EDITOR: In the September 1 issue of *Journal of Clinical Oncology*, Goldstein et al[1] conclude that the 21-gene assay is a better recurrence predictor than the currently used Adjuvant!—a validated algorithm based on classical clinicopathologic features—and that it can be used for tailoring chemotherapy among individual patients with hormone receptor (HR) –positive operable breast cancer.

The use of genomic markers for treatment decision making without consideration of standard conventional factors is not realistic.[2] Personalized cancer treatment in an environment of personalized medicine is one of the major goals of clinical research in oncology. Personal genomics, pharmacogenomics, and whole-genome scans have stimulated major interest by national anticancer organizations, industry, academia, and the general public and have contributed to intensive, internationally collaborative research efforts. But despite these global efforts, only a few robust prognostic and predictive biomarkers, like HR and human epidermal growth factor receptor 2 (HER-2), have been validated and widely used in clinical practice.[2-4] Although the 21-gene assay represents one, and perhaps the most promising, gene expression profiling marker to reach the level of testing in a large-scale randomized controlled trial (Trial Assigning Individual Option for Treatment [TAILORx]),[5] the translation of genomics research into evidence-based clinical use faces multiple challenges.[2-4,6,7]

In addition to its strengths,[5] the study by Goldsteinet al has several limitations: First, it is a retrospective, relatively small study of 465 patients that compared the predictive utility of the 21-gene assay with that of Adjuvant! Second, the study population, including both node-negative and node-positive patients who all received chemohormonal therapy, differs from the original population—HR-positive, node-negative patients who received tamoxifen—in whom the 21-gene assay recurrence score (RS) was developed.[8] Third, despite methodological strengths, there are several weaknesses[6] in the techniques used to assess the predictive value of the original RS with regard to chemotherapy benefit.[9] Fourth, and perhaps most important, neither the original RS study [8,9] nor the present study[1] have considered the new standard targeted agents: aromatase inhibitors for HR-positive, postmenopausal patients and trastuzumab for HER-2–postitve patients.[10] Because therapeutic strategy is changing, markers developed in tissues of patients who had not received current standard agents have limited value in current clinical practice.[11] Therefore, the utility of RS for postmenopausal HR-positive and/or HER-2–positive patients is unknown.

Two randomized trials test the efficacy of the 21-gene assay (TAILORx) and the 70-gene signature[12] (Microarray in Node-Negative Disease Avoids Chemotherapy [MINDACT] trial). Genomics research in collected biospecimens (biobanks) will add important new information.

It was once thought that simply stratifying individual patients into subgroups at high or low risk for developing breast cancer or recurrence and tailoring the most effective preventive or therapeutic intervention would revolutionize management of breast cancer. However, given the heterogeneity and complexity of breast cancer, this goal now appears elusive. Indeed, some individual primary tumors contain small cancer cell subpopulations, like breast cancer stem cells, that vary in metastatic ability and treatment response. Moreover, different deregulated signaling pathways and various biologic processes, including angiogenesis, tumor microenvironment, and dormancy, prove that individualized treatment approaches in solid cancers will require extremely hard work and sophisticated protocols.[13]

There is promise that the next-generation sequencing technology will provide newer genotyping platforms with more than 1 million single-nucleotide polymorphisms and copy number variants. Genome-wide association studies that used platforms with smaller number of single-nucleotide polymorphisms/copy number variants have discovered novel genetic risk variants. Although each risk variant confers only a small effect on cancer risk, and thus it is irrelevant, their combination may have clinical implications.[14,15] Completion of breast cancer genetic mapping and functional studies to define the role of key genes and signaling pathways will enable future personalized studies. Comparison of whole-genome scans from relapsed nonresponders and relapse-free responders in large-scale, prospective, unbiased studies that record both "classic" clinicopathologic features and novel genetic risk variants might result in the development of individualized therapeutic approaches preventing both locoregional and distant recurrences.[3,7,16,17]

The results of the two currently underway randomized trials on genomic biomarkers, TAILORx and MINDACT, will substantially contribute to evidence-based decisions in the treatment of early breast cancer.

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ACKNOWLEDGMENT

There is no research support for this article.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

1. Goldstein LJ, Gray R, Badve S, et al: Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features. J Clin Oncol 26:4063-4071, 2008

2. Bustin SA: Molecular medicine, gene-expression profiling and molecular diagnostics: Putting the cart before the horse. Biomark Med 2:201-207, 2008

3. Roukos DH: Personal genomics and genome-wide association studies: Novel discoveries but limitations for practical personalized medicine. Ann Surg Oncol doi: 10.1245/s10434-008-0109-6 [epub ahead of print on August 23, 2008]

4. Roukos DH, Murray S, Briasoulis E: Molecular genetic tools shape a roadmap towards a more accurate prognostic prediction and personalized management of cancer. Cancer Biol Ther 6:308-312, 2007

5. Paik S, Tang G, Fumagalli D: An ideal prognostic test for estrogen receptor–positive breast cancer? J Clin Oncol 26:4058-4059, 2008

6. Ioannidis JP: Gene expression profiling for individualized breast cancer chemotherapy: Success or not? Nat Clin Pract Oncol 3:538-539, 2006

7. Roukos DH, Lykoudis E, Liakakos T: Genomics and challenges toward personalized breast cancer local control. J Clin Oncol 26:4360-4361, 2008

8. Paik S, Shak S, Tang G, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351:2817-2826, 2004

9. Paik S, Tang G, Shak S, et al: Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 24:3726-3734, 2006

10. Goldhirsch A, Wood WC, Gelber RD, et al: Progress and promise: Highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 18:1133-1144, 2007

11. Roukos DH: HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med 358:197, 2008

12. van de Vijver MJ, He YD, van't Veer LJ, et al: A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 347:1999-2009, 2002

13. Roukos DH: Innovative genomic-based model for personalized treatment of gastric cancer: Integrating current standards and new technologies. Expert Rev Mol Diagn 8:29-39, 2008

14. Hunter DJ, Khoury MJ, Drazen JM: Letting the genome out of the bottle: Will we get our wish? N Engl J Med 358:105-107, 2008

15. Pharoah PD, Antoniou AC, Easton DF, Ponder BA: Polygenes, risk prediction, and targeted prevention of breast cancer. N Engl J Med 358:2796-2803, 2008

16. Roukos DH: Genetics and genome-wide association studies: Surgery-guided algorithm and promise for future breast cancer personalized surgery. Expert Rev Mol Diagn 8:587-597, 2008

17. Roukos DH: Assessing both genetic variation (SNPs/CNVs) and gene-environment interactions may lead to personalized gastric cancer prevention. Expert Rev Mol Diagn 9:1-6, 2009

DOI: 10.1200/JCO.2008.20.2812; published online ahead of print at www.jco.org on February 2, 2009

In Reply: We appreciate the comments by Dimitrios H. Roukas concerning our report recently published in *Journal of Clinical Oncology*.[1] We found that the 21-gene assay (Oncotype DX Recurrence Score [RS]; Genomic Health Inc, Redwood City, CA) was a more accurate predictor of recurrence than classical clinicopathologic features in patients with operable breast cancer and zero to three positive axillary nodes who were treated with adjuvant doxorubicin-containing chemotherapy in trial E2197.[2] The 21-gene assay also provided information that was complementary to an integrator algorithm modeled after Adjuvant! that was adjusted for 5-year outcomes rather than 10-year outcomes (by multiplying the projected 10-year recurrence rate by one half). As we pointed out in the report, the purpose of including the integrator analysis was not to determine which method for estimating recurrence was superior, but rather to provide a more stringent test of the prognostic utility of the 21-gene assay in the population studied. To emphasize and clarify the point that the integrator used in our analysis and Adjuvant! are not equivalent, we have requested that the editors replace the term "Adjuvant!" (which appeared in Figs 2 through 5 and the running title in the original version of this publication) with the term "integrator" to ensure consistent terminology throughout the publication. Nevertheless, our results with the integrator do recapitulate the findings of Bryant et al with Adjuvant! that were presented at the ninth International Conference on the Primary Therapy of Early Breast Cancer in 2005 (http://www.oncoconferences.ch/2005/home/home.htm); that analysis demonstrated that RS likewise provides information that is complementary to Adjuvant!, in this case using 10-year outcomes in patients with node-negative disease who were treated with a 5-year course of tamoxifen.

Roukos pointed out several limitations of our analysis, including its retrospective nature and other methodologic issues, the study population, and changing standards of care that now often include aromatase inhibitor (AI) therapy rather than tamoxifen. First, although this was retrospective study, it was a prospectively planned analysis that used specimens from a completed trial whose methods were consistent with the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines.[3] Second, consistent with our findings, Albain et al[4] have reported that the 21-gene assay provides prognostic information in postmenopausal patients with node-positive disease treated with adjuvant tamoxifen; this study also confirmed that high RS predicts benefit from adjuvant cyclophosphamide, doxorubicin, and fluorouracil chemotherapy in node-positive disease, as had previously been shown for cyclophosphamide, methotrexate, fluorouracil chemotherapy in node-negative disease.[5] Third, regarding the limited use of AI therapy in the E2197 trial, it was performed before AIs had been shown to be an acceptable alternative to tamoxifen. A recent analysis presented at the 2008 San Antonio Breast Cancer Symposium demonstrated the prognostic utility of RS in patients with adjuvant AI therapy.[6]

We agree with Roukus that the successful completion of prospective, randomized trials such as Trials Assigning Individualized Options for Treatment (TAILORx) and Microarray in Node-Negative Disease May Avoid Chemotherapy (MINDACT) is critical for moving the field forward. We also agree that newer technologies offer opportunities to improve the prognostic and predictive utility of somatic multigene markers, and that host genetic markers are also likely to play an important role in the creation of individualized therapeutic approaches in the near future.

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ACKNOWLEDGMENT

Supported in part by the US Department of Health and Human Services, by National Cancer Institutes of Health grants (CA23318 to the Eastern Cooperative Oncology Group [ECOG] statistical center, CA66636 to the ECOG data management center, CA21115 to the ECOG coordinating center, CA25224 to the North Central Cancer Treatment Group, CA32291 to Cancer and Leukemia Group B, and CA32012 to the Southwest Oncology Group), and by a grant from Sanofi-aventis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

