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RESPONSE

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We appreciate the comments of Donna Graham et al. on our recent article (1). The first issue they raise concerns the use of an adjuvant treated patient cohort for risk scores intended to assist in decisions regarding whether or not such treatment should be administered at all. While we agree with this perception, we also contend that prognostic signatures so far have failed to provide information on likelihood of response to drugs in the adjuvant setting, which implies that they represent inherent prognostic groups, the outcome of which is not improved by therapy. This is an issue in itself, but beyond the scope of our paper. In absence of such evidence, a treated patient cohort is potentially as informative on the prognostic groups.

The second issue is the low number of stage II patients in our cohort. We agree that risk scores will be most informative in stage II patients. However, we consider a search for a very low risk subgroup in stage III colon cancer equally relevant, notably as we found evidence that such a subgroup likely exists (2). Furthermore, we currently ignore if genes making up relevant prognostic risk scores for stage II and stage III are the same, as was suggested in one study (3), or different. This is an additional justification of including stage III in an assessment of the clinical relevance of risk scores.

The third issue raised is the purported basis of our analysis on splitting the continuous score at the median. This statement is inaccurate as in fact the main analyses were done with continuous scores in survival regression (Table 2) and in time-dependent area under the curve analyses (Table 5). Median splits were only used for a Kaplan-Meier analysis (Table 3). As the PETACC III gene expression data were obtained using the same array platform as the ColDx risk score, a predefined cut-off might be meaningful. However, the other risk scores are not on the original scales. Incidentally, the advantage of an analysis based on a continuous score is that it generally summarizes well the prognostic information of a marker, and results do not show the typical large fluctuation seen with specific splits (unless the cohort would be very large) that can render statistically robust interpretations more difficult.

Regarding the comment on the general applicability of prognostic signatures for clinical practice, we reemphasize the key (and disturbing) message of our study: Application of four risk scores yielded contradictory assessment of low or high risk at the level of the individual patient because of poor correlation of genes in the respective signatures. This message is likely to be generally valid, also in gene expression profiles of stage II patients. We agree with Donna Graham et al. that robust prognostic scores are needed, and we appreciate their efforts to produce or test them. Our results suggest that such prognostic scores in colon cancer are more difficult to find than has been the case in breast cancer, where different groups quickly converged on concordant systems with proliferation markers as dominant component (4).

References

1. Di Narzo AF, Tejpar S, Rossi S, et al. Test of four colon cancer risk-scores in formalin fixed paraffin embedded microarray gene expression data. *J Natl Cancer Inst.* (2014);106(10):dju247 doi:10.1093/jnci/dju247.
2. Roth AD, Delorenzi M, Tejpar S, et al. Integrated analysis of molecular and clinical prognostic factors in stage II/III colon cancer. *J Natl Cancer Inst.* 2012;104(21):1635–1646.
3. Kennedy RD, Bylesjo M, Kerr P, et al. Development and independent validation of a prognostic assay for stage II colon cancer using formalin-fixed paraffin-embedded tissue. *J Clin Oncol.* 2011;29(35):4620–4626.
4. Wirapati P, Sotiriou C, Kunkel S, et al. Meta-analysis of gene expression profiles in breast cancer: toward a unified understanding of breast cancer subtyping and prognosis signatures. *Breast Cancer Res.* 2008;10(4):R65.