**Author's response to reviews**

**Title:** Molecular Apocrine Breast Cancer: Gene Expression Meta-Analysis with Network Reconstruction Supports a Causal Role for Androgen Receptor and Implies Interactions with the ErbB Family

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To the Editor:

We submit “Molecular Apocrine Breast Cancer: Gene Expression Meta-Analysis with Network Reconstruction Supports a Causal Role for Androgen Receptor and Implyes Interactions with the ErbB Family” for review. This paper touches on many topics, including bioinformatics, systems biology, cancer, and considerations for targeted therapeutic interventions. We chose Medical Genomics because it is a journal whose readers have this diverse subject expertise.

The paper tells a long but connected story. First we establish that two small separate studies of breast cancer actually discover the same tumor subset, and we propose criteria for establishing what we call molecular equivalence—that is, two separately described subsets of a breast cancer (in this case) represent the same phenotype from a transcriptional point of view. Once we have achieved this, we use two network inference methods to establish androgen receptor and estrogen response signal genes as fundamental to the phenotype. Finally, we build a signature from the meta-analysis and generate an even larger pool of data to study. This time it would be biased to establish that androgen receptor and estrogen response as networks operating in the data since we used a classifier that includes androgen receptor and estrogen response genes to classify the new data from published series. Instead, Brad Broom collaborated with us and used Gene Shaving with Robust Bayesian Network Analysis to identify important gene clusters that interact with AR. We conclude that AR interacts with ErbB1 and ErbB2 in the data. While we surveyed the literature for support from cell lines experiments, our point is that this is a novel discovery in data generated from human tumors. It is an important discovery because it points to the need to consider combinatorial targeted therapy. In addition, it also demonstrates how useful network inference methods applied to gene expression array data can be—we can hypothesize networks and their interactions from actual tumor data and use it to drive cell lines experiments to study the interactions and their response to therapy in vitro, instead of continuing to discover these networks and their interactions in a slow "blinded" approach.

We have included suggested reviewers whom we feel will have the combined expertise in pathways and the biology of breast cancer along with a knowledge of gene expression array analysis to review this paper. We note that a portion of this research was recently presented as a platform at the United States and Canada Association of Pathology 2009 Conference in Boston, MA where it was well received. A shorter version of this paper in which we tried to separate the meta-analysis as a stand-alone manuscript was rejected because it did not contain sufficient original results. We combined then our results and lessons learned in the meta-analysis with our network inference studies. This paper was deemed to have too much informatics to be appropriate for the BMC Breast Cancer Journal and equally not appropriate for BMC Genome Biology because of a lack of genomics. We feel that the combination of bioinformatics and clinical implications then are best suited to BMC Medical Genomics and we hope that you will submit this manuscript for review as such.

Thank you for your kind attention to this submission. We look forward to hearing from you and until then we remain

Sincerely yours,

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