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Comments on "Association between breast cancer risk and disease aggressiveness: Characterizing underlying gene expression patterns"

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Dear Editor,

As trainees within the T32-funded Cancer Prevention and Control Program at the University of Alabama at Birmingham, we read with interest the article "Association between breast cancer risk and disease aggressiveness: Characterizing underlying gene expression patterns" by Emilio Ugalde-Morales et al. [1] We congratulate the authors on their successful publication, and heartily endorse the need to develop prognostic measures of cancer aggressiveness. However, we raise several issues that may require further thought.

First, given that luminal A breast cancer is the most common subtype, it is likely that any tools developed to predict risk will bias towards this type of breast cancer [2]. The Tyrer-Cuzick (TC) score is no exception, so expression profiles based on a high TC score will likely be associated with the Luminal-A subtype [3]. As a result, it is not surprising that there was a significant departure from this TC expression profile in the less common but more aggressive basal-like and HER2+ tumors. Although the authors' previous work addressed this point, we question whether they have adequately addressed the tendency for ER+ bias in the TC score in their current study.

Next, the authors' application of well-validated markers of disease risk to serve as indicators of disease severity/aggressiveness is novel, but largely unrealized in this research. It is important to note that although they are not represented in this study design, there are far more women with low TC-scores who never go onto develop any form of breast cancer. Indeed, the inclusion of appropriate low-risk, non-cancer controls would be a worthwhile step in filtering "signal-from-noise" in building an aggressiveness signature based upon differential gene expression patterns versus healthy controls.

An additional concern is that although differential gene signatures for TC-Gx were created for low versus high risk groups, and 10 year survival by group was evaluated, the survival effect of individual signature genes was not examined. A cursory analysis of three signature genes: CYP2A7, LALBA, and PGC in TCGA shows some differential expression as compared to normals, but no survival effect was identified for any of these genes based

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Conflict of Interest

The authors declare no conflicts of interest.

on high versus low expression. Thus, the actual molecular mechanisms underlying these differences remain unclear and warrant additional validation.

Finally, the relatively low mortality (39/661 individuals total) indicates that resources may be better allocated elsewhere when it comes to improving overall breast cancer patient survival. Other studies have noted that increases in genetic screening are likely only worth the increased cost in high-risk individuals [4].

Overall, this is an excellent paper that addresses an important gap in our understanding of the risks involved with aggressive subtypes of breast cancer. As stated earlier, risk assessment tools are likely to be inherently biased towards the more common variants of a disease. It is also important to note that the TC score lacks important factors in its risk calculation, including alcohol consumption and radiation exposure. We agree with the authors' conclusion that more work should be done to understand the risk determinants for the less common but more life-threatening forms of breast cancer.

Abbreviations

CYP2A7	cytochrome P450, family 2, subfamily A, polypeptide 7
HER2	human epidermal growth factor receptor 2
LALBA	lactalbumin alpha
PGC	progastricsin
TC	Tyrer-Cuzick
TCGA	The Cancer Genome Atlas
TC-Gx	Tyrer-Cuzick Gene Expression

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