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Comment on: Tan WJ, Cima I, Choudhury Y, Wei X, Lim JCT, Thicke AA, Tan MH, Tan PH. A five-gene reverse transcription-PCR assay for pre-operative classification of breast fibroepithelial lesions. Breast Cancer Research 2016;18:31

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See related research by Tan et al. http://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-016-0692-6

I read with interest the article by Tan et al. [1] describing a five-gene reverse transcription-PCR assay for pre-operative classification of breast fibroepithelial lesions (FELs).

I would like to raise three points, however: one regarding the presentation of the statistics in this paper, and two about the practical application of this assay.

Firstly, it is not clear whether the test group is representative of the prevalence of phyllodes tumours (PT) in their population. Because the rate of cases diagnosed as fibroadenoma (FA) on core biopsy with a subsequent diagnosis of PT on excision in their test group is more than four times that which they reported previously as part of a multi-centre study on a series of 4163 consecutive such cases [2], it would appear more likely that the test group is not representative. If this is the case, their calculation of the positive predictive value (PPV) and the negative predictive value (NPV) (which are dependent on disease prevalence) is in error and leaves it unclear how this assay would perform in practice.

Secondly, in relation to Tan et al.'s indeterminate FELs on core biopsy, because 21 of the 22 of these in their test group turned out to be PTs on excision, their histological classification as indeterminate FELs on core biopsy performed better than their five-gene assay at predicting PTs on excision (94.5 % vs 82 %). Again, however, this is likely to be a selected group, as the authors quote a rate of 41–63 % for these cases in their previous publication [2].

Finally, regarding the rare cases which on excision turn out to be PT following a histological diagnosis of FA on core biopsy—there were only 16 such cases in their previous study of 4163 consecutive cases—the practicality of applying this molecular assay in identifying these cases is questionable. To identify one true positive, 260 cases would need to be tested, and it is likely that testing would generate more false positive than true positive results.

While it remains an interesting avenue of investigation for these challenging lesions, the general applicability of the findings in this study appears limited by its design and by the practical difficulties inherent in identifying very rare events. It may be that, as yet, what we know of the molecular characteristics of this complex group of tumours does not add enough to be of practical value in their pre-operative classification.

Authors' response

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We appreciate the comments offered by Dr Joseph Loane on our publication [1]. To address the issues raised, it is important to describe the cohort involved in our paper and that of the multi-centre study [2]. Our assay was developed using an initial test set of 48 samples of FAs and PTs, including paired core biopsies with subsequent excisions. This was then validated on 230 core biopsies, of which 131 were diagnosed as FAs with event-free follow-up of at least 2 years, and on 99 FAs and PTs ($n = 58$ and $n = 41$, respectively) concluded by surgical excisions with corresponding pre-operative core biopsies, including 22 cases in which the core biopsy diagnosis was indeterminate. A large proportion of core biopsies with subsequent excisions serving as the reference diagnosis was selected. In contrast, the multi-centre study reviewed consecutive core biopsies diagnosed as unequivocal FAs which would not ordinarily be excised, determining the likelihood of subsequent occurrence of PT on follow-up as 0.38 %. This study concluded that a firm diagnosis of unambiguous FA on core biopsy was reliable and safe with adequate imaging and follow-up [2]. It is therefore not unexpected that the rate of subsequent diagnosis of PT among core biopsies in our validation cohort was substantially higher than in the multi-centre study, as the aim and selection criteria were different. The PPV and NPV calculated in our study were based on the validation cohort used, and we agree that an optimal PPV and NPV could be derived from application of the assay in a prospective hospital-based cohort evaluating key outcomes including recurrence. This would be best addressed by a follow-up study. Notably, PTs are more common in Asian women [3].

The indeterminate FELs diagnosed pre-operatively were histologically inconclusive; it is unclear how indeterminate calls could be compared or inferred as performing better than the assay. Discordance (4/22; 18 %) between the assay and reference diagnosis among FELs may reflect tumour heterogeneity because the assay was performed on limited core biopsy material, while the reference diagnosis was based on surgical excisions.

Distinguishing cellular FELs on core biopsy into FA vs PT remains challenging, with multiple studies attempting to use a variety of microscopic parameters, none of which are uniformly predictive [4, 5]. An adjunctive objective practical assay such as ours to aid decision-making will be helpful, especially if further validated in larger studies in a multi-centre prospective setting.

Abbreviations

FA, fibroadenoma; FEL, fibroepithelial lesion; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value; PT, phyllodes tumour

Authors' contributions

JL conceived and wrote this letter. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

JL hereby gives consent for publication.

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