Title	Authors' reply
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LETTERS TO THE EDITOR

HER2 overexpression of breast cancers in Hong Kong shows good concordance with *HER2* amplification by fluorescence in-situ hybridisation study

To the Editor—Yau et al[1] report that, in Hong Kong, over 25% of breast cancer cases showing *HER2* overexpression on immunohistochemistry cannot be verified by in-situ hybridisation (ISH) assays. The implication is that ISH should always be performed if anti-HER2 drug therapy is contemplated.

Our results, from tests performed at Queen Elizabeth Hospital, Hong Kong, are different. Of 260 consecutive invasive breast cancers, 57.3% scored 0 or 1 (negative) on HER2 immunostaining , 26.2% scored 2 (borderline) and 16.5% scored 3 (strong), results comparable to those reported in the literature.[2] Our correlation study using the fluorescence ISH test for *HER2* amplification (PathVysion Kit) shows *HER2* amplification in none of the 10 negative cases (score 0 or 1), four (6.9%) of 58 score 2 cases, and 12 (92.3%) of 13 score 3 cases. The single negative score 3 case showed increased copies of *HER2* gene, but since there was also chromosome 17 polysomy, the ratio of *HER2/CEP17* fell below 2.2 (negative by definition). The good concordance between strong *HER2* overexpression with *HER2* amplification supports the general recommendation that breast cancers with score 3 *HER2* overexpression do not require molecular confirmation. The differences between our results and those reported by Yau et al may be due to their inclusion of results from different laboratories, using different antibodies and different technologies.

Finally, we doubt the latest guidelines for score 3 positivity (30% instead of 10% tumour cells exhibiting strong circumferential membrane staining[3]) will improve accuracy and concordance. In our experience, the percentage of positive cells is never an issue where there is strong, thick membrane staining because this is almost always seen in practically all tumour cells (Fig).

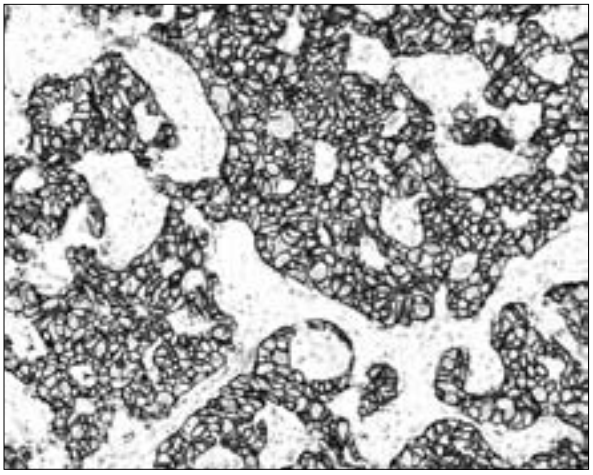

FIG. Invasive breast carcinoma showing strong overexpression of *HER2* (score 3) on immunostaining
Note that practically every tumour cell exhibits circumferential, thick cell membrane staining

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Authors' reply

To the Editor—We thank Dr Chan and his colleagues for their interest in our paper. The most critical point in this discussion is the need for accurate *HER2* tests from all laboratories because the results have such profound clinical implications. High *HER2* test accuracy can indeed be achieved in high-volume laboratories but extrapolating their results to other laboratories can be misleading. Our study, analysing private and public laboratory results, reflects the real world situation in Hong Kong. Another local series, studying 1485 Chinese women, also found a relatively high *HER2* overexpression rate (22-28% in different age-groups).[1]

Dr Chan et al's experience of a high percentage of tumour cells showing strong staining in true immunohistochemistry (IHC) 3+ cases is well recognised. The international guidelines[2] state "a cutoff of more than 30% reflects the cumulative experience of panel members that usually a high percentage of the cells will be positive if it is a true IHC 3+, published reports using cutoff values higher than 10%,[3] and the goal of the panel to decrease the incidence of false-positive 3+". Preliminary evidence suggests the revised cutoff of 30% may help improve the accuracy of poorer-performing laboratories.[4]

We advocate compliance with the latest international guidelines[2] to improve the accuracy of *HER2* testing. They clearly state that there is no need to repeat ISH testing for IHC 3+ cases and validated ISH tests should be performed for equivocal (IHC 2+) cases. Some IHC 3+ cases diagnosed using the original 10% cutoff would now be considered equivocal (2+) and hence validated ISH confirmation tests may be considered before commencement of anti-HER2 therapy, unless the laboratory can provide supporting information.

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