

Format for ANSWERING REVIEWERS

March 12, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8612-review.doc).

Title: Clinical Application of DNA Ploidy to Cervical Cancer Screening: a Review

Author: David Garner

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 8612

The manuscript has been improved according to the suggestions of reviewers:

1 Reference list has been updated and re-formatted

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer 2527607:

'...according to author stated that "to detect aneuploid cells is to detect cancer cells", aneuploid detection may do not has ability to identify tumor types, it can just only show the existence of tumor cells.'

This comment is correct and the manuscript has been edited to include this point. Generally, in the context screening, definitive diagnosis (including identification of tumour type) comes from a pathological assessment of a biopsy, rather than from the screening test.

'...author said that "aneuploidy is the cause of cancer", obviously, aneuploidy is not the sole cause of cancer, maybe it's just one of the reasons'

'...author mentioned that "Recent work shows that aneuploidy can be both a promoter and an inhibitor of cancer", so the author's conclusion "aneuploidy is the cause of the cancer" is still correct?'

This is a review article that attempts to place this technology into a historical scientific context. That "aneuploidy is the cause of cancer" is my simple re-statement of the theory of Boveri from 1902 and the preceding sentence begins "In essence, the theory is...". The next statement on recent work on aneuploidy is my simple summary of recent research papers on the subject. While the theory of Boveri from so long ago has proven to be remarkably and substantially correct, of course it does not correctly explain everything; the role of aneuploidy in cancer is now known to be somewhat more nuanced than the simple Boveri theory. A small change has been made to the wording to make this more clear.

'...author mentioned that "if present, sperm cell nuclei are stained", because sperm cells only have one basic set of chromosomes while the nuclei of epithelial cells and white blood cells have two, so whether the existence of sperm cells will lead to the results of DNA ploidy looks like "mosaic"?'

The presence of sperm cells can only cause confusion when they are found on top of epithelial cell nuclei, thereby giving the appearance of epithelial cell false aneuploidy. However, this is



why the putatively aneuploid cell images (and possibly the cells themselves) are reviewed. The DNA in sperm cells is very condensed and compact and easily identified, and so such epithelial cells overlaid with sperm cells are easily rejected on review. The same situation can occur with white blood cells overlaying epithelial cells. The text has been edited to clarify this point. As discussed in detail later in the article, cells with DNA Index >2.5 are clearly identified as aneuploid by this technique, but cells with DNA Index >1.25 but <2.5 are in a different category and so would not lead to a "false positive" result.

(2) Reviewer 2687374:

"As the length of this paper is too long, it is best to make some streamlined. Adequately modified in accordance with the requirements of submission and publication of papers would be necessary."

This was written as an invited review article with no length limit requirement. The general comment that it is too long is well taken and some revisions have been made with this in mind. However, without specific editorial suggestions, this review comment is as helpful as it should be.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Clinical Oncology*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'DMG', followed by a horizontal flourish.

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