Peer Review of "Nicholson, J., 2013. Will we cure cancer by sequencing thousands of genomes? Molecular Cytogenetics 6, 57"

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Abstract

The following are pre-publication peer reviews received on the manuscript: Will we cure cancer by sequencing thousands of genomes (Nicholson 2013), which was initially rejected and later resubmitted and published in Molecular Cytogenetics

the WINNOWER

BIOLOGICAL SCIENCES

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ABSTRACT

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INITIAL REJECTION

"I'm able to get back to you sooner than I thought. I had consulted with a colleague who works in cancer research, and the combination of our opinions is, I'm afraid, not so positive. We both feel that the essay needs more structure (and that the writing needs improving); but more importantly, we both detect a lot of the already extant debate in the essay: it covers almost all aspects of the debate: that is not in doubt. However, it does not go significantly far enough into new directions to make it stand out as key work that will be of influence. That is, of course, your aim also as an author, so we should be thinking along the same line there. I'd like to think that there's more to this topic, and there might well be, but that would mean going much further in the direction of solving the existing problem rather than describing it (i.e. what's wrong with just carrying on with ever more sequencing projects aimed at finding ever more cancer-related mutations, translocations etc, etc,). So, I trust you don't mind my honesty in this regard: the essay needs a great deal of development and shifting away from the more well-trodden and widely acknowledged - if perhaps not accepted - criticisms of traditional cancer genomics (to paraphrase)."

LATER ACCEPTED BASED ON THE FOLLOWING REVIEWS:

REVIEWER 1 REVIEW & RESPONSE:

The article is mostly a Commentary which is a narrowly focused article of contemporary interest and a discussion of an issue that is relevant to the scope of the journal.

1. It addresses an important and timely issue.

2. It is well reasoned.

3. It is relatively balanced.

4. The standard of writing acceptable.

ADVISE

- Accept after minor essential revisions

LEVEL OF INTEREST

- An article whose findings are important to those with closely related research interests

QUALITY OF WRITTEN ENGLISH

- Acceptable

DECLARATION OF COMPETING INTERESTS

I declare that I have no competing interests' below.

1. IS THE QUESTION POSED ORIGINAL, IMPORTANT AND WELL DEFINED?

The research question posed by the authors is easily identifiable and understood. The question posed original, important and well defined.

2. ARE THE DATA SOUND AND WELL CONTROLLED?

The data sound and well controlled

3. IS THE INTERPRETATION (DISCUSSION AND CONCLUSION) WELL BALANCED AND SUPPORTED BY THE DATA?

The interpretation discusses the relevance of all the results in an unbiased manner. Conclusions drawn from the study are valid and result directly from the data shown, with reference to other relevant work as applicable. The author provided references wherever necessary with minor abovementioned exceptions.

4. ARE THE INCLUDED ADDITIONAL FILES (SUPPLEMENTARY MATERIALS) APPROPRIATE?

The appropriateness of the additional file is doubtful for publication with the final article. It is enough to limit this only by reference on the corresponding articles or on the appropriate web site.

MINOR REVISIONS

1) "I PREFER TO HAVE THE TITLE MORE MODEST"

I have changed the title from "Cancer genome sequencing: a quixotic view of carcinogenesis" to "Rethinking Cancer Genomes." I am however still open to hearing other suggestions for the title.

2)"IN THE PART ALTERNATIVE THEORIES OF CANCER, "THE CANCER GENE CENSUS CURRENTLY LISTS 487 CANCER GENES" ARE THE OLD DATA. THE NEW, SEPTEMBER 2013 RELEASE: 507 CANCER GENES)"

I have updated the text and the figure to reflect the new data. Thank you for pointing this information out.

3) "PAGE 2: ... ISOCITRATE DEHYDROGENASE (IDH1), [3], WAS FOUND TO BE..."

"PAGE 2: ... MUTATED IN ONLY IN 12% OF GLIOBLASTOMA"

I have changed the following sentence to "isocitrate dehydrogenase (*IDH1*) (Sjoblom et al. 2006), was found to be mutated in only 12% of glioblastoma multiforme (Parsons et al. 2008) and 8% of AML (Mardis et al. 2009)"

4) PAGE 3: "INITIAL TESTS OF ONCOGENES AND TUMOR SUPPRESSOR GENES AS TRANSFORMING AGENTS WERE LARGELY PERFORMED IN THE HIGHLY ANEUPLOID MOUSE CELL LINE NIH/3T3" - NOT ONLY "IN THE HIGHLY ANEUPLOID MOUSE CELL LINE NIH/3T3" BUT MOST OF THE

EXPERIMENTS DETECTING TRANSFORMING ABILITY OF GENES OVEREXPRESSED AND/OR MUTATED IN TUMORS (ONCOGENES) WERE PERFORMED USING MOUSE EMBRYONIC FIBROBLASTS (MEFS), NIH3T3 MOUSE FIBROBLAST CELL LINE, HUMAN EMBRYONIC KIDNEY 293 CELL LINE (HEK293), AND HUMAN MAMMARY EPITHELIAL CELL LINES (MAINLY HMECS AND MCF10A). THESE CELL LINES HAVE ABNORMAL KARYOTYPES AND ARE PRONE TO PROGRESS TO MALIGNANTLY TRANSFORMED CELLS [STEPANENKO A.A., KAVSAN V.M. (2012) IMMORTALIZATION AND MALIGNANT TRANSFORMATION OF EUKARYOTIC CELLS. CYTOL. GENET., 46 (2), 96-129].

I have added the following reference: Stepanenko A.A., Kavsan V.M. (2012) Immortalization and malignant transformation of eukaryotic cells. Cytol. Genet.,46 (2), 96-129 and text "It may be argued that other lines, such as the human embryonic kidney 293 cell line (HEK293) and mammary epithelial cell line MCF10A have been successfully used to identify oncogenes and tumor suppressor genes as transforming agents however, these lines are prone to transformation and are known to have abnormal karyotypes (Stepanenko and Kavsan 2012)."

5) IT WOULD BE GOOD IF AUTHOR MAKE A REFERENCE ON THE VIEW OF J. WATSON IN HIS RECENT ARTICLE "WE CAN CARRY ON AND SEQUENCE EVERY PIECE OF DNA THAT EVER EXISTED, BUT I DON'T THINK WE WILL FIND ANY ACHILLES HEELS. SADLY, DESPITE THE HIGH HOPES, THIS INCREDIBLE JOURNEY OF DISCOVERY, WHICH IDENTIFIED THE GENETIC MUTATIONS THAT CAUSE CANCER, HAS NOT RESULTED IN FINDING CURES". WATSON SEES NO REASON TO BELIEVE THAT CARRYING ON ENDLESSLY SEQUENCING TUMOUR DNA WILL DELIVER BREAKTHROUGH NEW TREATMENTS, HE ARGUES THAT IT IS THE PEOPLE WHO WANT TO CARRY ON WITH THE DNA SEQUENCING WHO ARE LOOKING TO GATHER KNOWLEDGE FOR ITS OWN SAKE.

I have added a quote from James Watson at the beginning of the paper. Thanks for the reference.

REVIEWER 2 AND RESPONSE

Level of interest: An article of outstanding merit and interest in its field

QUALITY OF WRITTEN ENGLISH

-Acceptable

1) MS P2, FIRST PARAGRAPH, I SUGGEST TO START WITH REVISED SECOND SENTENCE,"BY 2005 HUNDREDS OF GENE MUTATIONS ... IDENTIFIED IN INDIVIDUAL CANCERS, IT WAS UNCLEAR HOWEVER, HOW .... IN CANCERS, AND WHETHER AND WHICH WERE SPECIFIC ..... TO ANSWER THESE QUESTIONS IT WAS PROPOSED IN 2005 TO SEQUENCE THOUSANDS OF CANCERS FOR A COST OF..

I have revised this sentence to the following:

By 2005 hundreds of gene mutations had been identified in individual cancers, it was unclear however, how prevalent these gene mutations were in cancers and which were specific to a certain type of cancer, if any. To answer these questions it was proposed to sequence thousands of cancers (Miklos 2005).

2) P2, SECOND PARAGRAPH, RE "HILLS" ON THE MUTATIONAL LANDSCAPE." HERE IT WOULD BE VERY USEFUL FOR THE READER TO SEE A COPY OF ONE OF THOSE 3D-GRAPHS FROM SCIENCE OR OTHER SOURCES TO GET A FEELING FOR THIS NEW LANGUAGE LIKE "HILLS", MOUNTAINS ETC

I have included a figure of one of these graphs. It is now figure 1.

3) P2, SECOND PARAGRAPH, INSTEAD OF "WIDELY TOUTED", I SUGGEST - "ONE OF THE MOST PROMISING CANDIDATES FOR A CANCER-SPECIFIC MUTATION FROM SEQUENCING STUDIES ....

I have changed the sentence as per the reviewer's suggestion.

4) P3, LINE 2 SUGGEST A NEW PARAGRAPH BEFORE "BOZIC ET AL ...

I have reformatted the paragraph as per the reviewer's suggestion.

5) P4, FIRST PARAGRAPH, LAST SENTENCE "... BY SEQUENCERS THEMSELVES, BECAUSE ... " EXPLAIN AGAIN TO THE READER WHY.

I have deleted this last piece of text.

6) "... CONSENSUS CURRENTLY LISTS ...(TABLE 1)." GIVE EXACT REFERENCE TO THIS STATEMENT, TABLE1. AND ALSO TO FIG. 1, WHICH APPARENTLY IS FROM THE SAME SOURCE AS TABLE 1."

I have deleted Table 1 and replaced the information with a reference where Table 1 information can be found.

7) "INDEED A SINGLE TRISOMY ..." ADD CLASSICAL BIOLOGICAL REFERENCES TO THIS IMPORTANT POINT, FOR EXAMPLE, SHAPIRO, BURTON L, (1983) AM J MED GENET, 14, P241-269, 'DOWN SYNDROME - A DISRUPTION OF HOMEOSTASIS'

I have added the reference as suggested by the reviewer. Thanks for the suggestion.

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