

RESPONSES TO REVIEWERS

REVIEWER 00503561:

Please add the concept of "genometastasis" is a new idea (according to the reference 79) in the abstract. This is very interesting, provocative, and newly twisted idea, possibly raise an argument in the community. I love this kind of statement in a review article and hope the text should be gradual and introductory (junctional part in the section 2.4, and 3 in the flow of the manuscript).

AUTHORS' RESPONSE:

In order to highlight the revolutionary approach of the theory of genometastasis, we have incorporated the terms of "recently discovered", "innovative" and "unprecedented" in Abstract section (lines 10, 11 and 19). We have also added an extra paragraph after section 2.4 named "Gathering pieces" (page 13) to joint both parts of the article.

We finally would like to thank to Reviewer 00503561 for his/her encouraging comments.

REVIEWER 00503399:

*In this manuscript the authors discuss the uses of liquid biopsies in cancer diagnosis and metastases detection and they focus in their theory (genometastases) which supports that tumor DNA can enter normal cells genetic material leading to the introduction of genetic changes leading to cancer. In more than half of the paper the authors are focused in explaining the uses of liquid biopsies similarly to other reviews and editorials in the literature. "Karachaliou, Niki et al. "Real-Time Liquid Biopsies Become a Reality in Cancer Treatment." *Annals of Translational Medicine* 3.3 (2015): 36. PMC. Web. 6 July 2017. Pancreatic cancer: Are "liquid biopsies" ready for prime-time? Alexandra R Lewis, Juan W Valle, Mairead G McNamara *World J Gastroenterol*. 2016 Aug 28; 22(32): 7175–7185. Circulating tumor DNA as a liquid biopsy target for detection of pancreatic cancer Erina Takai, Shinichi Yachida *World J Gastroenterol*. 2016 Oct 14; 22(38): 8480–8488. Circulating tumor cells versus circulating tumor DNA in lung cancer—which one will win? Silvia Calabuig-Fariñas, Eloísa Jantus-Lewintre, Alejandro Herreros-Pomares, Carlos Camps *Transl Lung Cancer Res*. 2016 Oct; 5(5): 466–482." In the other half of the paper the authors try to present their theory of free tumor DNA that can enter normal cells and can lead to metastases and they suggest that the DNA detected from liquid biopsies may be a useful tool to predict metastases (the "genometastases" phenomenon). In my personal opinion the primary target of this group is to prove the genometastases phenomenon since there are many holes in our knowledge in this aspect and then write a review of how to detect it.*

AUTHORS' RESPONSE:

We sincerely appreciate Reviewer 00503399 his/her thorough review and observations. Regarding the first comment (related to the similarity of the first part to other reviews), we wish to argue that our aim was not to simply explain the uses of liquid biopsies but rather gathering several pieces in the text that authors frequently analyze separately. In addition, we have highlighted the complexity and the variety of mechanisms by which cfNA can be present in circulation to

emphasize that cfNA may be released in blood due to a biological phenomenon (genometastasis) and not only by chance.

We will consider your suggestions for next articles. In the current manuscript, we have not applied any concrete change, since no specific suggestion is given.

REVIEWER 0058446

This a very good review for application of liquid biopsy, it not only constitutes a promising tool for cancer diagnostic and patient follow-up but also it may help in the comprehension of metastasis. With this technique, it was found that CTCs are limited in blood, and circulating nucleic acids are much more abundant. Together with the demonstrated capability of circulating nucleic acids to transform susceptible cells, strongly support the theory of genometastasis which sustains that cancer propagation relies on gene transfer from malignant cells to normal cells.

AUTHORS' RESPONSE:

We certainly acknowledge Reviewer 0058446 for such encouraging comments, and we admire his awareness on the field.