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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology
ESPS manuscript NO: 27814
Title: Role of circulating free DNA in colorectal cancer
Reviewer's code: 02505493
Reviewer's country: Greece
Science editor: Xue-Mei Gong
Date sent for review: 2016-06-18 09:00
Date reviewed: 2016-06-20 08:21

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

It is a very interesting review of the work concerning the clinical value of circulating free DNA in colorectal cancer. The m/s is suitable for publication.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology
ESPS manuscript NO: 27814
Title: Role of circulating free DNA in colorectal cancer
Reviewer's code: 02534438
Reviewer's country: Croatia
Science editor: Xue-Mei Gong
Date sent for review: 2016-06-18 09:00
Date reviewed: 2016-07-01 02:55

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

1. Abstract is not informative and serves no purpose, it contains no data, no conclusions. Needs rewriting. 2. Rationale for prognostic and predictive biomarkers is not given. Authors try to impress with percentages, but all mentioned incidences are irrelevant. What is important is that we don't know which patients harbour occult metastases (those are ones that will 'relaps'). So it is important that we know which patients already have occult metastases at the time of initial diagnosis, and those patients need to receive maximal treatment (e.g. adjuvant therapy). The practice today is that we determine risks of relaps based on Dukes' classification (i.e. positivity of lymph nodes and some other hystological findings such as vascular invasion etc.), but that is not sufficient. See comments 6 and 8. 3. Liquid biopsy is not explained. How is it different from normal biopsy ? How it "...addresses these pressing requirements"? 4. What is "Asymptomatic screening" ? Can we talk about screening in patients with symptoms ? Screening is always asymptomatic, if patients have symptoms, we talk about diagnostic workup. 5. "Colonoscopy is regarded as the preferred technique, since it clearly improves disease specific survival, it doesn't require additional therapeutic interventions..." Colonoscopy is gold standard, and how is it advantageous that it "doesn't require additional

therapeutic interventions"? What does it mean? I would delete that. 6. "In a high risk population with positive fecal occult blood test that subsequently underwent colonoscopy, Perrone et al demonstrated that the quantification of cfDNA by qPCR was predictive for CRC but not premalignant lesions" this sentence is pivotal for your work, I would give it more focus. 7. "otherwise clinically insignificant malignancies"? What would that be? Malignant = capable of metastasizing. How can it be insignificant? Maybe you meant neoplasia? 8. "Following curative surgery for localized CRC, approximately 50% of stage III patients according to the American Joint Committee on Cancer (node-positive disease) and 20% of stage II patients (T3N0 and T4N0) are expected to experience disease relapse without adjuvant chemotherapy." This is another pivotal sentence I would focus on. 9. "Also, several ethical issues will need to be considered, such as the management of healthy subjects with detectable cfDNA at presymptomatic screening and the possibility of barriers regarding the access to certain agents despite their regulatory approval (as an example of a possible scenario, the use of anti-EGFR treatment is not reimbursed for a patient with a RAS WT tumor and KRAS mutant cfDNA)." Why would there be such an ethical issue? You have cfDNA on screening, you undergo further diagnostic workup or enhanced monitoring (consider e.g. prophylactic mastectomy for MCIS or Brca+). As for reimbursements, cfDNA testing might actually turn the tables and force insurances to reimburse as it might eventually be cheaper than treatment of advanced disease. I would not go into that line of thinking.