BAISHIDENG PUBLISHING GROUP INC
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology
ESPS manuscript NO: 21008
Title: Multiple primary colorectal cancer: individual or familial predisposition?
Reviewer's code: 03001734
Reviewer's country: Italy
Science editor: Ze-Mao Gong
Date sent for review: 2015-07-01 09:04
Date reviewed: 2015-08-17 19:00

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

COMMENTS TO AUTHORS

Reviewer's name: Luca Morandi (l.morandi@ausl.bo.it)
Title
Multiple primary colorectal cancer: individual or familial predisposition?
Version: 1 Date: August 16th, 2015
Reviewer's report:

This work by Pajares et al. investigated and reviewed previousy reports about multiple primary colorectal carcinomas, in relation with individual or familial predisposition.
The report is well written and highly interesting. However, there are some points remaining to be included in this review to complete the manuscript:

Major points:
MPCRC may derive from the same cell of origin or from different clones at different time. SCRC and MCRC are clinical entities and sometimes may not reflect the condition of the tumor at the molecular

level. Genetic heterogeneity plays a fundamental role in this case.

A proposed role of genetic heterogeneity in individual predisposition to CRC has been described by Galvan A et al. Trends in Genetics 2010 March. Either a single genetic defects or the polygenic conditions produce a cancer - prone condition in the human normal tissue. Individual risk of cancer might be further modulated by environmental factors, leading to somatic mutations and ultimately to cancer.

A section discussing tumor heterogeneity in CRC should be added to the text citing for instance the following papers:

Zauber P et al. J Mol Diagn. 2013 Sep;15(5):652-60 who evaluate by a set of 6 different markers (LOH for APC, DCC, and mutations of KRAS, BRAF, MSI methylation of MMR genes) 50 patients with synchronous and 5 metachronous CRC. They found that genetic changes may vary considerably, particularly when the tumors are found in different colon segments. Frequent differences in the molecular findings are also seen between synchronous tumors sharing the identical microenvironment of the same colon segment. These findings support the hypothesis that synchronous and metachronous colorectal cancers may follow different pathways of carcinogenesis in the same patient.

Siravegna G et al Nature Med 2015 Jul. They evaluate ctDNA mutations after EGFR antibodies treatments

Siegmund KD PLoS One. 2011;6(6):e21657 they performed a population genetics approach to human somatic cancer cell populations by measuring genomic diversity within and between small colorectal cancer (CRC) glands.

- Rosty et al. Am J Surg Pathol. 2013 Mar; 37(3): 434–442. They found that the majority of CRCs arising in individuals with Serrated Polyps do not harbor molecular hallmarks of serrated pathway CRCs but show a diverse range of molecular profiles.

Graham TA Gastroenterology. 2011 Apr;140(4):1241-1250 who developed a technique to follow changes in intestinal stem cell dynamics in human epithelial tissues that might be used to study premalignant disease by using the methylation pattern as a marker.

- Kamiyama H et al. Oncolgene 2012 Nov 29. This work pointed out the stronger association of demethylation in normal mucosa with multiple CRC risk from younger patients also suggests an inherited predisposition for the apparent field cancerization effect of somatic demethylation.

- Vakiani E J Clin Oncol. 2012 Aug 20;30(24):2956-62 they check for mutations KRAS, NRAS, BRAF, PIK3CA, and TP53 genes in 615 patients for both primary and metastatic sites. They found for most cases the same mutations.

- Huang CS et al. Hepatogastroenterology. 2015 Mar-Apr;62(138):286-90. They scan a large cohort with 5346 patients with synchronous, metachronous and solitary CRC. They found similar clinicopathological features between synchronous and metachronous CRC.

Minor points:

there are several grammatical errors (I detected 18 errors), and this is unacceptable. A mother

toungue revision is needed before accepting the manuscript.
In section “familial predisposition”, lane 8, after “Win et al” the reference must be cited.