ANSWERING REVIEWERS

October 17th, 2013

Dear Editor,

Please find enclosed the revised manuscript according to reviewer's comments in Word format (file name: 5712-review.doc).

Title: FECAL IMMUNOCHEMICAL TEST ACCURACY IN AVERAGE-RISK COLORECTAL CANCER SCREENING

Author: Vicent Hernandez, Joaquin Cubiella, M. Carmen Gonzalez-Mao, Felipe Iglesias, Concepción Rivera, M. Begoña Iglesias, Lucía Cid, Ines Castro, Luisa de Castro, Pablo Vega, Jose Antonio Hermo, Ramiro Macenlle, Alfonso Martínez-Turnes, David Martínez-Ares, Pamela Estevez, Estela Cid, M. Carmen Vidal, Angeles López-Martínez, Elisabeth Hijona, Marta Herreros-Villanueva, Luis Bujanda, Jose Ignacio Rodriguez-Prada, for the COLONPREV study investigators.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 2429

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

Reviewer 58455:

1. The title of this manuscript is fecal immunochemical test accuracy in average-risk colorectal cancer screening. The authors provide the best cut-off point for CRC detection is 115ng/ml. However, the diagnostic data (>50ng/ml or >100 ng/ml) of FOBT may be different from vary FOBT kit in different country.

COMENTAR LOS DATOS PUBLICADOS COMPARANDO DIVERSOS KITS. VER SI SE PUEDE INTRODUCIR EN LA DISCUSION

2. The authors tried to establish the optimal number of FIT and concluded that performing two tests does not improve diagnostic accuracy. How about three test or four or more?

CREO QUE ESTO YA ESTÁ COMENTADO EN LOS MÉTODOS. SI NO, INCLUIRLO EN LA DISCUSIÓN. ESTOS DOS PUNTOS PUEDEN IR EN UN PARRAFO SOBRE LAS LIMITACIONES DEL ESTUDIO.

Reviewer 1333314:

The study conducted by Hernandez et al evaluate in a prospective study, the accuracy and cost of fecal immunochemical test (FIT) in asymptomatic average-risk to detect advanced neoplasia (AN) (defined as adenoma>10mm or villous histology or high-grade dysplasia) individuals submitted to screening colonoscopy. The authors conclude that FIT has a low sensitivity but a high specificity to detect AN. Two samples do not improve accuracy for CRC. Globally the study is well conducted and conclusions add information to current knowledge. The major limitation is the extremely low number of invasive cancer detected in the study. Because four other studies were published with similar conception (references 13 to 16) it would be of value to include a new table showing the accuracy in terms of sensitivity and specificity of AN and invasive cancer in the other 4 studies. It would be also of value to include the definition used in the other studies of advanced adenomas.

CONTESTAR QUE SOMOS CONSCIENTES DE ESTA LIMITACIÓN, QUE ES COMÚN A TODOS LOS ESTUDIOS. REVISAR QUE YA ESTE ENTRE LAS LIMITACIONES DEL ESTUDIO. RECHAZAR ELEGANTEMENTE LA SUGERENCIA DE INCLUIR UNA TABLA CON LOS DATOS DE OTROS ESTUDIOS (NO UNA REVISIÓN). INCLUIR EN LA DISCUSIÓN LA DEFINICIÓN DE NEOPLASIA

Reviewer 48752:

This is a paper of the significance of fecal immnochimical test accuracy for calorectal cancer screening. Overall, this paper is well described. # The biggest concern would be a amall number of CRC in their study. Their results are reasonable regarding of the analysis on advanced adenoma because the positive number is 97. However, It is plausible to imagene that the result of CRC would be biased by the location(eg, rectum, left sided colon ,right sided colon), and feature (eg. presence or absence of ulceration) because the number of CRC is only 5. # The cost per CRC will be half for two times method if the detected number of the CRC is same between one time method Thus, simple comparison of the cost per CRC between two methods does not make considerable sense. Because the cost of fecal test is much smaller compared with colonoscopy, it would be more important to disucuss how to decrease the CRC patient on colonoscopy with negative results on the fecal test, and this point of view is important in this study because colonoscopy was done in all subject in this study. # Please compare average value and SD of fecal results between two test to make sure that the two test was carried out in the same condition.

Reviewer 89406:

This is an interesting study that should be published. However, some changes might be of interest: The FIT test should be explained in the method section in more detail. There are some spelling errors on page 14 (e.g. and and). I would encourage to include other potential non invasive tests into the discussion section (e.g. M2PK, Mutation tests). Finally, there should be some more discussion about the fact that FIT is sensitive for CRC, however, it detects only a minority of advanced adenoma.

Reviewer 39316:

It was a real pleasure for me to review this high quality manuscript that examined the diagnostic accuracy of FIT testing in average risk CRC screening population. 1.The main limitation of the study -acknowledged by the authors- is that their sample size was not enough to reach the predetermined power of analysis. Moreover, the high AN prevalence might indicate selection bias and this must be also acknowledged in the discussion. 2. The conclusions in the abstract must include a sentence on the overall performance of FIT. 3. It will be of value to provide in the results the best cut-off value for the AN diagnosis too. Thereafter, include a paragraph in the discussion that summarizes the results of an exercise on how the adoption of the new lower cut-off would affect the performance characteristics of the test, and the cost benefit analysis. No need for details. 4. Please discuss the ref. Crotta S, et al. High rate of advanced adenoma detection in 4 rounds of colorectal cancer screening with the fecal immunochemical test. Clin Gastroenterol Hepatol. 2012;10:633-8, regarding the value of multiple FIT testing.
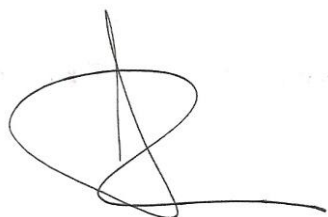
Reviewer 183459:

This is a multicentric study aimed at assessing accuracy of fecal immunochemical test (FIT) in the detection of colorectal cancer (CRC) and advanced neoplasia (AN) in patients undergoing CRC screening. The authors have compared specificity and sensitivity of two measures, one in the first sample and the other on the highest level of both samples. The authors showed a low sensitivity of FIT to detect AN, but a high specificity, which reach the highest level in the setting of average-risk CRC population. Two day sampling does not improve the accuracy for CRC, but increases the sensitivity for AN detection even though is more expensive. The study is well designed and well written and the results are interesting.
Nothing to comment.

References and typesetting were corrected

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

Yours Sincerely

Joaquín Cubiella.
Gastroenterology Department.
Complexo Hospitalario Universitario de Ourense.
Spain.