

April 7, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format with corrections highlighted in yellow

**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 16129**

**Columns: ORIGINAL ARTICLE**

*Prospective Study*

**Title:** Tissue Resonance Interaction Accurately Detects Colon Lesions: a Double-blind Pilot Study

**Author:** Maria P. Dore, Marcello O. Tufano, Giovanni M. Pes, Marianna Cuccu, Valentina Farina, Alessandra Manca, David Y. Graham,

**Short Title:** Screening of colon lesions

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

1 Format has been updated

Reviewer 00070894

This article reported the Tissue Resonance Interaction Method (TRIM) used to detect colon polyps and cancers. TRIM presents highly sensitivity and specificity. TRIMprob scanning is a valuable tool in diagnosing carcinoma of prostate, breast, gastric, rectal and so on. In this study, the authors compared TRIMprob with colonoscopy. It's of clinical significance and convincing.

1 In my opinion, the instruction about TRIM need to be simplified properly. TRIM was applied to study more than 10 years.

We agree with the suggestion proposed by the reviewer 00070894, revised the text to summarize the section relative to TRIMprob function and use. We attempted to simplify the physical concepts. (see Pages 6-7)

2. In this study, all colon cancer (12 patients) were identified. Please supply the tumor size (T stage) of these patients.

We provided this information in the paper: 3 were Tis; 4 were T1N0 M0; 2 were T2 N0 M0; 2 Any T N M0; Any T Any N M1b respectively

3. The format of Tables and references should be modified.

In the revised manuscript we have modified Table 1 and Table 2 according to the reviewer's suggestions. In particular we have replaced asterisks with superscript letters and made the tables self-explanatory.

**Reviewer 00053417**

The Tissue Resonance Interaction Method (TRIM) is a new non-invasive device for the diagnosis of many kinds of cancers including prostate, breast, bladder cancers, thyroid, gastric cancer and rectal cancer. Some papers have been published in this field, but the technique has not been accepted widely. In this prospective operator-blinded study with big sample size (n=281), the authors revealed that TRIM provides a rapid and accurate diagnosis in comparison to colonoscopy. The results are extraordinary good (sensitivity 98.7%, specificity 96.2%, diagnostic accuracy 97.5%). Study methods are innovative and systemic.

As the results are extraordinary good, it is suggested to provide the data of relative studies on this topic and give an explanation in the discussion section.

The only previous paper published on this topic is: *Diagnosis of rectal cancer by Tissue Resonance Interaction Method* by Vanelli et al. This is discussed in the introduction and discussion sections. See page 15

**Reviewer 00044333**

The authors presented the performance of new non-invasive method (TRIM) to detect colon polyps and cancer. They showed very interesting and promising results using Tissue Resonance Interaction Method. I have just a minor suggestion. If you can suggest the possible explanation for false negative in detection or discordant lesion in histologic evaluation, it will be helpful to improve the manuscript.

Two patients had hyperplastic polyps that went undetected. Both were between 6 and 9 mm and located in the sigmoid colon. One possible speculation could be a difficult niche, or the small size. This is discussed on Page 14.

**Reviewer 00071725**

This is an interesting study. Please comment on:

1. Whether the authors think the sample size is enough? Are the number of lesions enough for you to make your conclusions?

Answer to the reviewer#00071725. As regard to the sample size of 281 patients, we considered it adequate since the statistical power (beta) calculated for the values of Table 2 is 100% for all contingency tables assuming an alpha threshold of 0.05

2. How do you know that your probe is detecting only colonic lesions and not other lesions in the same region? 3. Should patient selection be only those who are only performed for screening?

The TRIMprob method proved to be a valuable diagnostic tool in the diagnosis of premalignant lesions and CRC, mainly owing to its high sensitivity, and deserves to be recommended in the routine screening of GI cancers. However, it requires a high degree of skill for the interpretation of multifrequency patterns generated by the device during the assay, as well the ability to recognize subtle abnormalities of the signal arising from the presence of multiple lesions or with complex tridimensional structure. As with any technology, training is required. An additional side benefit of the test is the possibility to detect other potential malignant lesions located in the scanned areas, regardless to their origin in the GI tract.

However, and as noted, before TRIMprob can be used as a routine method for CRC screening additional studies will be needed to confirm the results in larger multicenter clinical series. Large cohort studies are necessary in order to better define the diagnostic accuracy of the TRIMprob especially for those subjects that cannot effort the torture of bowel preparation. Development of software should also reduce the need for a high level of training.

References and typesetting were corrected

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



Sincerely yours,

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