Answering reviewers

Reviewer's code: 06110595

SPECIFIC COMMENTS TO AUTHORS

Most patients with CRC are diagnosed at an advanced stage. The high morbidity and mortality of advanced CRC indicates an urgent need for clinical improvements in early CRC detection and individualized management. The liquid biopsy includes blood, the most commonly used human fluid sample, as well as other fluids, such as urine, ascites, pleural effusion, cerebrospinal fluid, and saliva. With the development of high-throughput sequencing technology and single-cell gene amplification technology, new types of circular cell-free DNA have been discovered such as extrachromosomal circular DNA. This study was designed to build a multi-parameter diagnostic model based on the commonly used clinical detection indicators and the 4 eccDNA markers for early detection of CRC which is urgently needed in clinical practice. The manuscript is very well designed and the manuscript is very well written. The inclusion criteria is reasonable, and the samples size is enough. Comments: 1. There are some minor language polishing, which should be corrected. 2. The figure 3 is too small, please update the images. 3. How about the limit of the study? Please make a short discussion about it.

Response to Reviewer

Thanks for the suggestions. We have polished the language. The Figure 3 was updated , and we have added the limitation in the discussion section.

Reviewer's code: 06110615

SPECIFIC COMMENTS TO AUTHORS

This is an interesting study of early detection of CRC based on circular DNA and common clinical detection indicators. The study is well performed and the results are very interesting. The reviewer recommends the publication of the manuscript. No specific comments.

Response to Reviewer

Thanks for the suggestions.

Reviewer's code: 06143370

SPECIFIC COMMENTS TO AUTHORS

ccDNA refers to a closed circular DNA located outside the chromosome in the form of single-stranded or double-stranded DNA, which is widely found in eukaryotes, including humans. Compared with free linear DNA, eccDNA is not easily degraded by nucleases, and its structure is more stable. In this study, the authors built a multi-parameter diagnostic model for early detection of CRC. This study is very interesting, and the findings are important. Minor comments: Please add the "5' ends of the primers were modified with a FAM fluorophore, and the 3' ends were modified with a BHQ1 quenching group" into a table.

Response to Reviewer

Thanks for the suggestions. We have added the sentence in the table.