Changes made to the manuscript according to the peer-reviewers' comments

Peer-reviewers' comments	**Changes made to the manuscript**
*"…the first half mentioned molecular role of NOD2 gene could be a little bit tedious (too many possible explanations) and should be **more concise**"*	Section: The Expanding NOD2 Role (pages **7,8 and 9** of the manuscript) The following paragraph was **SHORTENED AND ADAPTED** to be more concise: "According to *in vitro* studies, *NOD2*-deficient animals showed an increased susceptibility to several viral infections~~. This has been shown to occur in *NOD2*-deficient animals~~ [18]. The response to certain parasite infections may be compromised as well, due to reduced production of IFN-γ [16, 19]. ~~Even though it is classically described as a part of the innate immune system, there are some indicia that innate receptors such as *NOD2* are direct regulators of T-cell function. This was shown by the reduced capacity of *NOD2*-deficient T-cells to produce IFN-γ following infection with certain parasites. Once again, the hypothesis of a PGN-independent *NOD2*-activation seems to have solid basis. Interestingly, *NOD2* may also contribute to the maintenance of intestinal homeostasis and in restricting bacterial translocation through Peyer's patches (PPs).~~" The following paragraph was **REMOVED** from the manuscript: "The complex effects of NOD2 activation on the immune system have even led to the use of muramyl dipeptide (MDP) synthetic derivatives as anticancer drugs. Synthetic MDP is approved in high-grade, nonmetastasizing, resectable osteosarcoma following complete surgical removal (Mifamurtide). The rationale

	behind its use is that MDP simulates a bacterial infection by binding to NOD2, leading to the activation of monocytes and macrophages. This results in an increased production of TNF-α, interleukins 1, 6, 8, and 12, and other cytokines that will target cancerous cells. If NOD2 activation by MDP may elicit anticancer properties, then NOD2 polymorphisms that lead to loss of function may have the opposite effect, eventually leading to increased cancer susceptibility."
*"I would prefer to know more about the **practical applications** in the **treatment of IBD** and CRC"*	Section: NOD2 mutations and other malignant and non-malignant conditions (pages 19 and 20) The following paragraphs were **ADDED** to the manuscript: "The effect of NOD2 as a risk factor for disease is best established in CD. After an etiologic role was consolidated for these mutations in CD, further investigation was undertaken to find out if these mutations influenced the behavior, prognosis and response to treatment as well. The presence of one mutation increased the risk for structuring or penetrating disease by 8% and this effect was largely increased if two NOD2 mutations were present (41% risk increase) [38]. An Australian study revealed as well that carriers have a more aggressive disease, needing more frequent and more precocious surgery [50]. A recent European multicenter cohort study recently revealed that NOD2 mutations and early use of immunomodulatory drugs are the most relevant predictors of the course of disease [51]. It was speculated as well that certain disease phenotypes and their response to treatment could be influenced by NOD2 mutations. The development of perianal fistulas is thought to depend on the proliferation of luminal bacteria. As such a possible connection between NOD2, a

	regulator of host response to microbial agents, and perianal fistulas was evaluated in recent literature. These fistulas showed significantly worse response to antibiotics in NOD2 mutation carriers [52], probably due to impaired recognition of intestinal bacteria and a decreased ability to mount an effective innate immune response. This kind of studies emphasizes the importance of gene mapping and corresponding phenotypic correlations in order to predict disease severity and optimize treatment strategies."
*"I would prefer to know more about the practical applications in the treatment of IBD **and CRC**"*	Section: Case-Control Studies on NOD2 polymorphisms (pages 17) The following paragraph was **ADDED**: "Routine detection of NOD2 mutations is still not being offered in the management of CRC patients. However, there is a new simple and cost-effective tool for the genetic screening of CRC [45]. Besides well-known mutations in MLH1, MSH2 and MSH6 genes, the DNA microarray assay also searches the 3020insC polymorphisms in the NOD2 gene. This may be a useful tool in clinical practice in colorectal cancer screening programs."
"Recent meta-analysis results of Liu J 2014 quoted in table 2 are inconclusive as there is gross **heterogeneity** of the included studies."	Section: Case-Control Studies on NOD2 polymorphisms (page 18) The following paragraph was **ADDED**: "The studies included in this meta-analysis showed no obvious heterogeneity was observed (I^2<50%). The exclusion of each single study did not significantly change the overall outcome, suggesting that the results of the meta-analysis were robust [40]."
"…studies included in table 1 I would like to suggest to assess the quality of the included studies and a pooled analysis if the studies can be pooled"	The studies included in Table 1 were subject to analysis of quality according to the Newcastle-Ottawa quality assessment scale and the National Institutes of Health tool for case-control studies. The results from the two meta-analysis already include pooled analysis of such studies.