Background
Colorectal cancer (CRC) occurring in the setting of Inflammatory Bowel Disease (IBD) is relatively uncommon. Compared to sporadic CRC, the molecular pathogenesis of IBD-associated CRC has some distinctive features, particularly the timing of acquisition of genetic changes during progression through high-grade dysplasia. DNA mismatch repair (MMR) deficient sporadic CRC is a well-defined entity comprised of Lynch syndrome-associated cancers and cancers characterized by a CpG island methylator phenotype (CIMP). The latter cancers characteristically arise in sessile serrated adenomas/polyps. The role of MMR deficiency in IBD CRC is less well-established. We undertook this study to determine the frequency and clinical pathologic associations of MMR deficiency in IBD-associated neoplasia.

Methods
Patients with CRC were selected from the pathology database of Miraca Life Sciences. The database includes demographic and clinical information, summary of the endoscopic report, biopsy location, and the histopathologic report for each biopsy specimen. Cases of CRC with a report date from 11/1/2007 to 11/30/2011 were extracted. From these cases, patients with a history of Ulcerative Colitis (UC) and Crohn Disease (CD) were extracted. Immunohistochemical (IHC) staining for MMR proteins MLH1, MSH2, MSH6 and PMS2 were performed on the CRC and interpreted as intact (positive staining) or deficient (loss of staining).

Results
Biopsies from 917,599 colonoscopies were interpreted on 878,835 patients (51% female, 49% male) during the study period. Of these, 16,631 unique patients (48% female, 52% male) had histological and clinical features of UC while 5,736 patients had histological and clinical features of CD. During this period, 6,211 CRCs were diagnosed (52% male, 48% female). Of these CRCs, 22 occurred in patients with UC (prevalence of 22/16,631 = 0.13%), and 5 occurred in patients with CD (prevalence of 5/5,736 = 0.09%). 19 IBD patients were male (70.4%) and 8 were female (29.6%). The mean age was 58 years (median 56 years, standard deviation 13.5 years, range 33 to 84 years). Of these tumors, 14 (51.9%) were moderately differentiated (MD) and 13 (48.1%) were poorly differentiated (PD). IHC staining for MMR proteins showed MLH1 and PMS2 deficiency abnormalities in 3/27 (11%) patients, all of whom had UC. These 3 patients were 65, 77 and 79 years old and had CRC in the cecum, rectum and left colon, respectively. MSH2 and MSH6 expression were intact in all cases.

Conclusions
• MMR protein deficiency in the setting of IBD associated CRC appears to be less frequent than in the sporadic setting.
• Demographic characteristics suggest that it is likely due to MLH1 promoter methylation.
• Additional studies are needed to further define the mechanism.
• CRC occurring in the setting of IBD is rare, occurs predominantly in males and tends to be PD.

Reference