This is the first Brazilian end-to-end study to carry out screening and diagnosis of families at-risk for LS. We demonstrated the effectiveness of MSI and IHC in the screening of high-risk families. Besides, we detected possible failures in the diagnosis of germline MLH1 mutation carriers when using somatic MLH1 hypermethylation to rule out LS. Furthermore, our molecular data provide new information about the spectrum of MMR mutations, which contributes to a better characterisation of LS in Brazil.

Background
Lynch syndrome (LS), is the most common hereditary colorectal cancer (CRC) syndrome. However, the characterisation of LS in Brazil is poor. Therefore, we aimed to identify families at-risk for LS and determine the spectrum of MMR mutations in a Brazilian reference cancer centre.

Methods
Patients were identified by the Oncogenetics Department and through universal tumour screening. For universal colorectal screening, IHC and MSI were performed. BRAF-V600E mutation and MLH1 promoter methylation were analysed for all MLH1-deficient tumours. Patients with IHC/MSI altered and BRAF-WT proceeded to germline genetic testing.

Results
MMR-deficient tumours were detected in 39.7% of 360 families recruited (Figure 1). The sensitivity was 98% for MSI and 100% for IHC. A significant proportion of our patients (45%) carried a pathogenic germline variant, mainly on the MLH1 (40.3%) and MSH2 (37%) genes. Twelve novel pathogenic variants were identified. Furthermore, pathogenic variants with concomitant MLH1 hypermethylation were found in 5.5% (4/58) of cases, probably as a ‘second hit’ for tumour development. CRC and extracolonic tumours were diagnosed in 78% and 28.3% of the families with LS, respectively (Figure 2).

Clinicopathological and molecular characterization of Brazilian families at risk for Lynch Syndrome
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Figure 1: Summary of universal tumour screening and germline genetic testing results. * This group included 7 cases that presented inconclusive MSI and/or IHC results. † One patient has three VUS in PMS2.

Figure 2: Extra-colonial tumours identified in the MMR mutation carriers. * Uterus not otherwise specified