BACKGROUND Lynch syndrome (LS) is a well-known cause of hereditary colon cancer. Alu insertions are the most abundant retrotransposon in the human genome and have been shown to cause disease by either disrupting a coding region or splice signal. There have been previous reports of Alu insertions in families with LS. We report a 16-year-old female who was diagnosed with stage 4 colon cancer and was posthumously found to have an *MSH2*/Alu insertion. Past medical history was unremarkable, and she passed away 10 months later. Her colon tumor showed abnormal microsatellite instability and loss of protein expression of MSH-2 and MSH-6 by immunohistochemistry (Fig. 1). Prior to her passing, multiple genes, including *MSH2,* were analyzed without identifying a causal variant. One year following, whole genome sequencing (WGS) was performed in her mother which also did not reveal a causal variant.

RESULTS Eight years later, testing on the patient's banked DNA using a commercial laboratory's custom panel on a Next-Generation sequencing (NGS) platform observed a c.1442_1443insAlu likely pathogenic variant in the *MSH2* gene. The mobile element (ME) detection software Mobster and the commercial laboratory's in-house developed software was used to detect unaligned and soft-clipped reads from the BAM file, and the variant was confirmed by sanger sequencing. The patient's parents underwent confirmatory testing. The father's results were negative. The mother was positive for the *MSH2*/Alu insertion.

METHODS The mother's WGS BAM file data were again reviewed and reads covering this insertion were not identifiable. Mobster was implemented to run on the maternal WGS, and split reads were detected in the same variant location. Upon further review, standard WGS BWA alignment did not map the reads which contained more than 50% Alu reads and trimmed the reads with less than 50% Alu reads (Fig. 2). This splice site was not detected by standard variant calling as reads are assessed for small variants and structural variation, the *MSH2*/Alu insertion was undetected by conventional NGS variant calling methods.

CONCLUSION There is a subset of patients with a phenotype strongly suggestive of LS and no identifiable causal variant. In conclusion, this case demonstrates the importance of critically assessing the testing methodologies previously performed in this patient cohort and reanalyzing short-read sequencing data for retroelement events for cases that have not been previously diagnosed.