

## Outcomes of PLSD and tumour biological research

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Despite agreed that the Lynch syndromes were not associated with adenomas in colon and named Hereditary Non-Polyposis Colorectal Cancer (NHPCC), colonoscopy to prevent colorectal cancer (CRC) was advocated. Some 15 years ago it became clear, however, that CRC continued to occur despite colonoscopy, and The Prospective Lynch Syndromes Database (PLSD) was designed to examine why. For a detailed history and how PLSD was designed for the purpose, see <https://plsd.eu/why-plsd>, for published PLSD reports see <https://plsd.eu/publications>.

To our surprise, the empirical observations were that colonoscopy increased, not reduced, CRC incidences in three of the four Lynch syndromes. To the obvious epidemiological interpretation that invasive CRC may spontaneously disappear, later supported by tumour biology results demonstrating the cancers to be microsatellite instable attracting immunocompetent cells, and clinical results validating that immunotherapy enabling the HLA system to recognize the tumours improved prognosis. These conclusions, however, were rejected by those believing in the hypothesis that all CRCs are preceded by non-invasive adenomas – but they had and have no valid argument for their position.

The combined observed results will be discussed to arrive at the conclusions below, close to all of which are included in the PLSD reports published but not previously published summarized like this:

**Three mechanisms** may have caused the empirical observations reported

1. Overdiagnosis: The host immune system identifies MSI cells and may, as demonstrated by immunotherapy, remove infiltrating cancers.
2. Invasive growth without an adenoma precursor lesion
3. Downstream events to the initial triggering carcinogenetic event (the second-hit in the wild-type *MMR* allele) may be circumvented by the stochastic processes leading to invasive cancer:
  - Environmental factors like chemotherapy and colonoscopy may have impact on which clones to expand as invasive cancers but have little effect on cancers to occur or not

**A brief summary of current knowledge may be:**

1. The triggering event in three of the four Lynch syndrome colorectal cancers is the second-hit in the wild-type *MMR* allele
2. Carcinogenetic events downstream to the triggering events are stochastic – not predetermined linear events - and subjected to clonal selection by internal and external factors
3. The unproven hypothesis of an accelerated adenoma-carcinoma pathway may be misleading and is not required to explain the observed incidences of CRC in *path\_MMR* carriers.