

# Incidences of colorectal adenomas and cancers under colonoscopy surveillance suggest an accelerated “Big Bang” pathway to CRC in three of the four Lynch syndromes

Pal Moller,<sup>1</sup> Saskia Haupt,<sup>2,3</sup> Aysel Ahadova,<sup>4,5</sup> Matthias Kloor,<sup>4,5</sup> Julian R. Sampson,<sup>6</sup> Lone Sunde,<sup>7,8,9</sup> Toni Seppälä,<sup>10,11,12</sup> John Burn,<sup>13</sup> Inge Bernstein,<sup>14,15</sup> Gabriel Capella,<sup>16</sup> D. Gareth Evans,<sup>17</sup> Annika Lindblom,<sup>18,19</sup> Ingrid Winship,<sup>20,21</sup> Finlay Macrae,<sup>21</sup> Lior Katz,<sup>22</sup> Ido Laish,<sup>23</sup> Elez Vainer,<sup>22</sup> Kevin Monahan,<sup>24</sup> Elizabeth Half,<sup>25</sup> Karoline Horisberger,<sup>26</sup> Leandro Apolinário da Silva,<sup>27</sup> Vincent Heuveline,<sup>2,3</sup> Christina Therkildsen,<sup>28</sup> Charlotte Lautrup,<sup>34</sup> Louise L Klarskov,<sup>29,30</sup> Giulia Martina Cavestro,<sup>31</sup> Gabriela Möslein,<sup>32</sup> Eivind Hovig,<sup>1,33</sup> and Mev Dominguez-Valentin<sup>1</sup>

<sup>1</sup>Department of Tumour Biology, Institute of Cancer Research, The Norwegian Radium Hospital, Oslo, 0379 Norway

<sup>2</sup>Engineering Mathematics and Computing Lab (EMCL), Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University, Heidelberg, Germany

<sup>3</sup>Data Mining and Uncertainty Quantification (DMQ), Heidelberg Institute for Theoretical Studies (HITS), Heidelberg, Germany

<sup>4</sup>Department of Applied Tumour Biology, Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany

<sup>5</sup>Clinical Cooperation Unit Applied Tumour Biology, German Cancer Research Centre (DKFZ), Heidelberg, Germany

<sup>6</sup>Institute of Medical Genetics, Division of Cancer and Genetics, Cardiff University School of Medicine, Heath Park, Cardiff, CF14 4XN UK

<sup>7</sup>Department of Clinical Genetics, Aalborg University Hospital, Aalborg, 9000 Denmark

<sup>8</sup>Department of Biomedicine, Aarhus University, Aarhus, DK-8000 Denmark

<sup>9</sup>Clinical Cancer Research Center, Aalborg University Hospital, Aalborg, Denmark

<sup>10</sup>Faculty of Medicine and Health Technology, Tays Cancer Center, Tampere University, Tampere University Hospital, Tampere, Finland

<sup>11</sup>Department of Gastrointestinal Surgery, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland

<sup>12</sup>Applied Tumour Genomics, Research Program Unit, University of Helsinki, Helsinki, Finland

<sup>13</sup>Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, NE1 7RU UK

<sup>14</sup>Dept. of Quality and Coherence, Aalborg University Hospital, Aalborg, 9000 Denmark

<sup>15</sup>Department of Clinical Medicine, Aalborg University Hospital, Aalborg University, Aalborg, 9100 Denmark

<sup>16</sup>Hereditary Cancer Program, Institut Català d'Oncologia-IDIBELL, L; Hospitalet de Llobregat, Barcelona, 08908 Spain

<sup>17</sup>Manchester Centre for Genomic Medicine, Division of Evolution, Infection and Genomic Sciences, University of Manchester, Manchester University NHS Foundation Trust, Manchester, M13 9WL UK

<sup>18</sup>Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, 171 76 Sweden

<sup>19</sup>Dept Clinical Genetics, Karolinska University Hospital, Solna, Sweden

<sup>20</sup>Genomic Medicine, The Royal Melbourne Hospital, Melbourne, Australia

<sup>21</sup>Department of Medicine, University of Melbourne, Melbourne, Australia

<sup>22</sup>Department of Gastroenterology, Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Hadassah, Israel

<sup>23</sup>Gastroenterology institute, Sheba medical center and Faculty of medicine Tel Aviv university, Tel Aviv, Israel

<sup>24</sup>Lynch Syndrome & Family Cancer Clinic, Centre for Familial Intestinal Cancer, St Mark's Hospital, London, UK

<sup>25</sup>Gastrointestinal Cancer Prevention Unit, Gastroenterology Department, Rambam Health Care Campus, Haifa, Israel

<sup>26</sup>Department of Surgery, Universitätsmedizin Mainz, Mainz, Germany

<sup>27</sup>Hospital Universitário Oswaldo Cruz, Universidade de Pernambuco, Recife, Brazil & SEQUIPE, Recife, Brazil

<sup>28</sup>Gastro Unit, The Danish HNPCC Register, Copenhagen University Hospital – Amager and Hvidovre, Copenhagen, Denmark

<sup>29</sup>Dept of Pathology, Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark

<sup>30</sup>Dept of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

<sup>31</sup>Gastroenterology and Gastrointestinal Endoscopy Unit, Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, 20132 Milan, Italy

<sup>32</sup>Surgical Center for Hereditary Tumors, University Düsseldorf, Ev. Bethesda Khs, Duisburg, Germany

<sup>33</sup>Centre for bioinformatics, Department of Informatics, University of Oslo, Oslo, Norway

<sup>34</sup>Department of Clinical Genetics, Aarhus University Hospital, DK 8000 Aarhus, Denmark

## Abstract

---

### Background

Colorectal cancers (CRCs) in the Lynch syndromes have been assumed to emerge through an accelerated adenoma-carcinoma pathway. In this model adenomas with deficient mismatch repair have an increased probability of acquiring additional cancer driver mutation(s) resulting in more rapid progression to malignancy. If this model was accurate, the success of colonoscopy in preventing CRC would be a function of the intervals between colonoscopies and mean sojourn time of detectable adenomas. Contrary to expectations, colonoscopy did not decrease incidence of CRC in the Lynch syndromes and shorter colonoscopy intervals have not been effective in reducing CRC incidence. The prospective Lynch Syndrome Database (PLSD) was designed to examine these issues in carriers of pathogenic variants of the mis-match repair (*path\_MMR*) genes.

## Materials and methods

We examined the CRC and colorectal adenoma incidences in 3,574 *path\_MLH1*, *path\_MSH2*, *path\_MSH6* and *path\_PMS2* carriers subjected to regular colonoscopy with polypectomy, and considered the results based on sojourn times and stochastic probability paradigms.

## Results

Most of the *path\_MMR* carriers in each genetic group had no adenomas. There was no association between incidences of CRC and the presence of adenomas. There was no CRC observed in *path\_PMS2* carriers.

## Conclusions

Colonoscopy prevented CRC in *path\_PMS2* carriers but not in the others. Our findings are consistent with colonoscopy surveillance blocking the adenoma-carcinoma pathway by removing identified adenomas which might otherwise become CRCs. However, in the other carriers most CRCs likely arised from dMMR cells in the crypts that have an increased mutation rate with increased stochastic chaotic probabilities for mutations. Therefore, this mechanism, that may be associated with no or only a short sojourn time of MSI tumours as adenomas, could explain the findings in our previous and current reports.