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Genetic testing for prevention and treatment of cancer

PERSPECTIVES

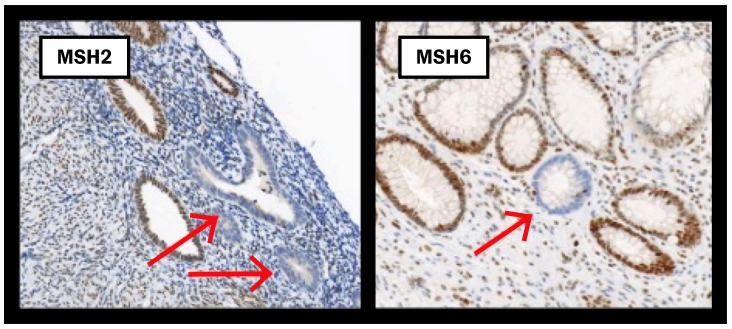
PÅL MØLLER

moller.pal@gmail.com
Pål Møller, MD PhD, specialist in medical genetics, senior scientist at Department of Tumour Biology, Institute of Cancer Research, the Norwegian Radium Hospital, part of Oslo University Hospital. He initiated the Prospective Lynch Syndrome Database (www.plsd.eu) in 2012, which he headed until 2023. He is a co-founder and honorary member of the European Hereditary Tumour Group (www.ehtg.org).
The author has completed the ICMJE form and declares no conflicts of interest.

EIVIND HOVIG

Eivind Hovig, scientist and group leader at Department of Tumour Biology, Institute of Cancer Research, the Norwegian Radium Hospital, part of Oslo University Hospital, and professor emeritus at the Department of Informatics, University of Oslo.
The author has completed the ICMJE form and declares no conflicts of interest.

Screening for early diagnosis may not always prevent cancer, but early treatment may improve its outcome. New knowledge indicates that all cancers should be genetically tested for proper treatment selection, independently of personal or family history of disease.



Immunohistochemical identification of colonic MSI crypts that lack the gene product (dMMR cells) of MSH2 and MSH6 respectively in carriers of genetic mutations in MSH2 and MSH6. dMMR results in microsatellite instability, leading to colorectal cancer. Immunotherapy improves the prognosis of this type of colorectal cancer. All colorectal cancers should be investigated for this cause to select the best possible treatment. Multidisciplinary Digital Publishing Institute, Switzerland / CC BY 4.0 / Adapted by the Journal of the Norwegian Medical Association

Most cases of microsatellite instable (MSI) cancers are not inherited. However, dominantly inherited MSI cancers – the four Lynch syndromes – are the most frequently inherited cancers. They are caused by inherited pathogenic DNA variants in the four mismatch-repair (MMR) genes, referred to as *path_MLH1, path_MSH2, path_MSH6 and path_PMS2, respectively*. They may cause cancer in many different organs. Immunotherapy may be indicated for both inherited and non-inherited MSI cancers. All cancers should be genetically tested for proper treatment selection, irrespective of the disease being inherited.

How does cancer initiate?

The usual way of thinking (paradigm) is that carcinogenesis is triggered by a mutation in a cell causing the cell to escape normal control, resulting in an increased number of cellular divisions, and subsequently more new mutations. This may cause further loss of control of cell division, and the development of a cancer with invasive growth. This is commonly referred to as the adenoma-carcinoma paradigm. Inherited genetic variants causing such events to occur more often are the causes of inherited cancers. More cellular divisions in infiltrating cancers may cause more mutations, in turn causing distant spread of the tumour. Screening may demonstrate an adenoma, and cancer may be prevented by removing the adenoma. Early diagnosis of a cancer may improve prognosis by early treatment.

A different paradigm is that cancer is caused by a stochastic coincidence of events, and that inherited cancer increases the risk of this. Such events may occur in random order. There may be no pre-invasive adenoma before an invasive cancer occurs, and an adenoma may not be the precursor of a cancer. In this case, what we know about the prevalence of adenomas and cancers, and how they develop, are group averages. These averages may not be used to predict prognosis for single cases. Without an adenoma precursor to invasive cancer, screening for and removal of adenomas may not prevent cancer.

However, early diagnosis and treatment may improve prognosis. Incidences of cancer when screening may therefore not be a good surrogate marker for monitoring the effect of screening.

Both paradigms may be true at the same time: One single person may have two (or more) tumours following different pathways, and two parts of the same tumour may follow different pathways. The question is when a tumour follows which pathway. This is relevant for the expected outcome of screening for breast cancer, and for colonoscopy screening for colorectal cancer, for example. Both these screening programmes are based on the paradigm that initially a local tumour is found that can be removed before it becomes cancerous, that a cancer can be detected and removed before it spreads, and/or that a cancer can be detected before it becomes resistant to drug therapy.

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As we now know, neither of these screening programmes have prevented all cancers, or cured all cancers. This questions the validity of the adenoma-carcinoma paradigm for carcinogenesis. Overdiagnosis in cancer screening has made it difficult to assess its utility. If the goal is to improve prognosis, one should monitor survival.

Epidemiology

The Prospective Lynch Syndrome Database (PLSD) was a Norwegian initiative for European collaboration which has become a worldwide ongoing effort (1). PLSD has published colorectal cancer and cancer incidences in any organ in carriers of pathogenic MMR variants, and survival when cancers occur, in carriers subjected to follow-up and treatment as internationally advocated, including regular colonoscopy (1). In the InSiGHT variant database (2) all known MMR variants scored as pathogenic or non-pathogenic are included (see also 'MMR CANCER RISK' in the database, or directly at www.plsd.eu.

The four inherited MSI cancer syndromes are different at the group level with respect to penetrance (incidence of disease), expressivity (cancer in which organ), mortality and sex (1). No one has an 'average sex' and/or a pathogenic variant of an 'average gene'. Consequently, averages for penetrance, incidences and survival in the four different forms of dominantly inherited MSI cancer syndromes and without taking account of sex, are valid for no one. The four hereditary MSI cancer syndromes entail an increased risk of cancer in 13 different organs: The colon, rectum, small bowel, stomach, bile duct, pancreas, prostate, endometrium, ovaries, urinary bladder, ureter, brain and for osteosarcomas. Colorectal cancer is not the most frequent cause of death. Gynaecological cancer is frequent in women, while urinary tract/prostate cancer is frequent in men. Ovarian cancer is thought to be a variant of endometrial cancer.

The PLSD collaboration has reported that survival in the inherited MSI cancers that have onset relatively early in life, such as colorectal cancer, endometrial and ovarian cancer, has been improved due to early diagnosis and better treatment. In addition to this, we now have immunotherapy. Patients who are cured may live on to contract cancers in other organs. Such later cancers in other organs often result in poorer survival than in patients who were previously cancer-free, and this means that most fatalities in inherited MSI cancers are observed in other organs than the colon, endometrium and ovaries (1). Cancer in persons with pathogenic MMR variants will generally entail stochastic variables (1): those who have had cancer previously do not appear to have a significantly increased risk of new cancer, either in the same or other organs.

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Colonoscopy has not substantially reduced the incidence of inherited MSI cancer. If the adenoma-carcinoma paradigm were true, then removing adenomas detected on colonoscopy should lead to reduced incidence of colorectal cancer in the risk groups. This is reportedly what happens in *path_PMS2* carriers, but not in *path_MLH1, path_MSH2* and *path_MSH6* carriers (1,3). This may reflect the fact that healthy carriers have microscopic precursors of MSI cancer in the colonic crypts. These precursors produce neopeptides which attract immune cells, and the precursor is removed by the immune response. On the other hand, MSI cancer gives rise to neopeptides which prevent the HLA system and the immune cells from 'seeing' the tumour. Modern immunotherapy can inhibit 'unbeneficial' neopeptides from the MSI cancer tumours so that the HLA system is not prevented from removing the tumour. The fact that the immune system may also be able to remove established colorectal cancer may explain why in some groups colonoscopy does not lead to a reduced incidence of colorectal cancer. Some of the cases identified through screening may have been removed by the patient's own immune system before the cancer led to clinical symptoms if it had not been removed. This may have offset the preventive effect of removing some precursors of cancer. Immunotherapy facilitates the host immune system's ability to remove MSI tumours and research is now focusing on how the host HLA system may participate in this process with a view to developing vaccines against MSI cancers.

Recent research indicates that colonoscopy at least every third year prevents cancer that develops through a detectable adenoma in the colonic mucosa. However, not all cancers have a macroscopically detectable early stage without infiltrating cell growth, and this may explain why not all cancers can be prevented by screening. When the occurrence of cancer is not reduced by colonoscopy, the reason may be that some of the tumours that are removed by colonoscopy would have been later removed by the patient's immune system unnoticed by the patient.

Genetic testing as a health measure

Genetic testing for diagnosis and selection of treatment for cancer has been implemented in Norway since 1988 (4-6). Recommended guidelines related to inherited MSI cancers were published as European guidelines in 2021 (7). From the outset in 1988, the pathogenic variants causing inherited cancers were not known, and the testing was based on cancer in a family and/or early-stage cancer in particular organs of an individual patient. Both these approaches are suboptimal as they have neither high positive nor high negative predictive value to identify inherited cancer (8). Family history is not sufficient to indicate which tumours should be genetically tested for what. It is also resource-intensive to collect the necessary information, including safeguarding personal data, the requirement for informed consent and good record-keeping. There are not enough clinicians to increase the capacity for this to any real extent.

Genetic testing to select treatment is generally described as personalised medicine and is performed by machines whose capacity can be increased (and precision improved), without the use of specialist personnel and working hours. In the same way that blood samples are tested through machine analysis, the rapid technical developments in genetic testing are now making this available also for genetic testing of cancers.

It has previously been shown that cancer associated with pathogenic variants in the *BRCA1/2* genes may be inherited or occur somatically only, both forms having survival benefit from treatment with PARP inhibitors. More recent enhanced knowledge has shown that MSI cancer, the most common form of inherited cancer, is most often not inherited and all MSI cancers have prognostic improvement with immunotherapy. Genetic testing of cancerous tumours is therefore rapidly increasing in order to give cancer patients the best possible treatment. When such tumour testing indicates that the cancer may be inherited, blood tests are also performed with a view to the risk of new tumours in other organs. When an inherited cause of cancer is found in this way, the patient may be recommended genetic counselling as well as being offered cascade testing of relatives so that they may also be given acceptable healthcare provision.

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The laboratory machines can now test many genes simultaneously. Because of both cost-efficiency and quality control, two different lines of machine-testing in cases of cancer are being developed: One for testing the tumour for all relevant genes to select treatment (9), and one to test blood for inherited gene variants that can lead to relatives also being offered a health intervention (10) where indicated by the result of the oncological examination. The machines analyse and report the test results automatically by assessing the results against open international databases developed for the purpose (11-13). The written analysis results are in general twofold, one version formatted for the treating doctor, and one for the patient. The contribution of specialists in medical genetics primarily consists of findings of new, unknown gene variants. Assessment of hitherto unknown variants will depend on continued research. The healthcare offered to individuals and their families was initially research-based, but is now evidence-based with consensus-based methods for determination of inherited variants that result in disease (7).

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Conclusion

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Personalised treatment based on genetic testing improves survival in the case of both inherited and non-inherited pathogenic variants in both *BRCA1/2* and MSI cancers. Family history is insufficient to indicate when a cancer is inherited. Oncologists will increasingly perform genetic tests to select the proper treatment, irrespective of personal or family history of cancer. Today's laboratory machines for genetic testing identify who may have an inherited cancer. When the test results give rise to suspicion of inherited cancer, the patient should be referred for blood tests to determine or exclude this, in accordance with the guidelines for investigation of potentially inherited cancer (7).

The progress is driven forward by increased knowledge, increased laboratory capacity, lower cost of testing and more personalised treatment, and is unstoppable. The question is when and how it is to be implemented in Norway as well. Cost-efficient genetic testing to prevent and/or improve prognosis can now be offered to all adults with or without cancer, if so wished.

The illustration is from Walker R, Mahmood K, Como J et al. DNA Mismatch Repair Gene Variant Classification: Evaluating the Utility of Somatic Mutations and Mismatch Repair Deficient Colonic Crypts and Endometrial Glands. Cancers (Basel) 2023; 15: 4925. doi: 10.3390/cancers15204925.

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REFERENCES

1. Prospective Lynch Syndrome Database (www.plsd.eu) and The European Hereditary Tumour Group (www.ehtg.org). Dominantly inherited micro-satellite instable cancer - the four Lynch syndromes - an EHTG, PLSD position statement. Hered Cancer Clin Pract 2023; 21: 19. [PubMed] [CrossRef]

2. InSiGHT. InSiGHT variants databases https://www.insight-group.org/variants/databases/ Accessed 15.1.2024.

3. Møller P, Haupt S, Ahadova A et al. Incidences of colorectal adenomas and cancers under colonoscopy surveillance suggest an accelerated "Big Bang" pathway to CRC in three of the four Lynch syndromes. Hered Cancer Clin Pract 2024; 22: 6. [PubMed][CrossRef]

4. Børresen AL, Brøgger A, Møller P et al. Genteknologi i bekjempelse av kreft. Tidsskr Nor Lægeforen 1989; 109: 3430–4. [PubMed]

5. Calmettes C, Ponder BA, Fischer JA et al. Early diagnosis of the multiple endocrine neoplasia type 2 syndrome: consensus statement. European Community Concerted Action: Medullary Thyroid Carcinoma. Eur J Clin Invest 1992; 22: 755–60. [PubMed][CrossRef]

6. Møller P. Helsetilbud ved arvelig kreft. Hva står vi overfor? Tidsskr Nor Lægeforen 1995; 115: 1213–4. [PubMed]

7. Seppälä TT, Latchford A, Negoi I et al. European Hereditary Tumour Group (EHTG) and European Society of Coloproctology (ESCP). European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender. Br J Surg 2021; 108: 484–98.

8. Sjursen W, Haukanes BI, Grindedal EM et al. Current clinical criteria for Lynch syndrome are not sensitive enough to identify MSH6 mutation carriers. J Med Genet 2010; 47: 579–85. [PubMed][CrossRef]

9. Myriad genetics. MyRisk Hereditary Cancer Test. https://myriad.com/genetic-tests/myrisk-hereditary-cancer-risk-test/ Accessed 15.1.2024.

10. Myriad genetics. Precise Tumor Molecular Profile Test. https://myriad.com/genetic-tests/precise-tumor/ Accessed 15.1.2024.

11. Nakken S, Saveliev V, Hofmann O et al. Cancer Predisposition Sequencing Reporter (CPSR): A flexible variant report engine for high-throughput germline screening in cancer. Int J Cancer 2021; 149: 1955–60. [PubMed] [CrossRef]

12. Orphanet. https://www.orpha.net/consor/cgi-bin/index.php Accessed 15.1.2024.

13. Lynch Syndrome UK. https://www.lynch-syndrome-uk.org/ Accessed 15.1.2024.

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