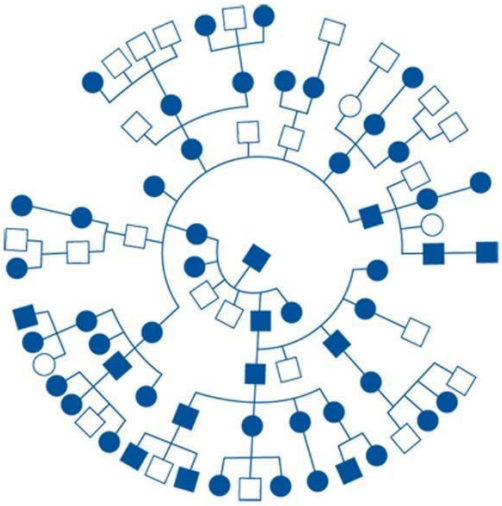
Annual Report

2019

The Netherlands Foundation for the Detection of Hereditary Tumors

Stichting Opsporing Erfelijke Tumoren (StOET)



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MISSION

The mission of the Foundation for the Detection of Hereditary Tumors is to prevent unnecessary death by early detection of hereditary tumors. To achieve this, the national registry offers its support in the management of patients genetically predisposed to the development of cancer. The registry helps to identify all persons within an affected family and to provide information regarding their greatly increased risk of cancer and the importance of preventive surveillance examinations. It also monitors the quality of care and adherence to the necessary lifelong surveillance. In addition, the Foundation is a port of call for patients and families. The registry promotes scientific research with the joint aims of improving screening programs and increasing our understanding of hereditary tumors. All activities described in this annual report were designed to help accomplish the above mission.

1. GENERAL ISSUES

Monique van Leerdam as the new Medical Director

As of January 1, 2019, Hans Vasen retired as medical director. Monique van Leerdam MD, PhD, and gastroenterologist, has become the new medical director. She has a long record of excellent research in Lynch syndrome and polyposis syndromes. Dr van Leerdam is head of the Department of GI-Oncology at the National Cancer Institute (Antoni van Leeuwenhoek) in Amsterdam. In addition to her appointment as Medical Director of the registry, she is the head of the Family Cancer Clinic at Leiden University Medical Center.

Protection of privacy in accordance with new European legislation: AVG

The Registry keeps a record of medical data relating to patients and risk-bearing family members. The processing of such data has been subject to the General Data Protection Regulation (AVG) since May 25, 2018. The AVG sets out the conditions under which personal and medical data can be processed and also defines the rights of subjects involved. In agreement with the AVG, the STOET will only initiate registration once the person concerned has given written permission. In 2018 the Supervisory Committee for the Protection of Privacy was abolished and instead a privacy officer was appointed at the StOET, with a mandate to ensure that the rules on privacy are adhered to. If a person registered with the StOET wishes to exercise his or her rights in accordance with the AVG, this can be done by sending a message to the following email address: privacy@stoet.nl.

Secure communication solutions

E-mail is an indispensable part of communication for the StOET and the specialists (and in some cases with patients). In 2019 ZorgMail Secure e-mail has been implemented which means that the StOET can receive and deliver e-mails with privacy-sensitive information in a the most secure environment possible.

European Society for Gastrointestinal Endoscopy (ESGE) guidelines

In 2019 the European Society for Gastrointestinal Endoscopy (ESGE) initiated two new guidelines regarding endoscopic surveillance of hereditary gastrointestinal tumors. The medical director of the StOET, Monique van Leerdam, was head of both guidelines. A pan-European group of experts performed the literature search, made a summary of the literature and wrote the guidelines.
1. Endoscopic Management of Lynch syndrome and familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) guideline.
2. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline.

The European Hereditary Tumor Group

In 2006, the so-called Mallorca group was initiated by Hans Vasen and Gabriela Möslein. This group successfully developed an active network of specialists working in different fields, all of whom were involved in the prevention, diagnosis and treatment of hereditary GI tumor syndromes. The main aims of the group were (1) to conduct collaborative studies, (2) to establish guidelines and (3) to set up databases. Over the years these collaborations have led to numerous publications and guidelines, focusing mainly on Lynch syndrome and polyposis. Recently, this group (P. Møller et al.) established a prospective database of individuals with Lynch syndrome (PLSD) which is now the main resource worldwide for accurate estimates of cancer risk in Lynch syndrome patients (www.lscarisk.org). The group also initiated the "Three Country Study" (3CS) (Christoph Engel et al.), which evaluated the effectiveness of colonoscopic surveillance by collecting the results of screening from LS registries in Germany, Finland and the Netherlands (see later in this report). Ten years into its existence, a decision was taken to formalize and transform the Mallorca group into a more open group which now also addresses other GI hereditary cancers. This group was named the European Hereditary Tumor Group (Chair: Gabriela Möslein). In September 2018, the Medical Director of StOET attended the third meeting of this new group in Nice. In October 2019 this meeting was organized at the same time as the UEGW and attendance was not possible. Attendance at the annual meetings of the EHTG (www.ehtg.org) is highly recommended for all who wish to increase their knowledge of hereditary GI cancer.

2. REGISTRATION

2.1 Registration of new family members

The number of subjects referred for registration has been stable for many years. Table 1 shows the current numbers of registered individuals, listed according to hereditary cancer syndrome.

Table 1. Number of individuals registered at the StOET on January 1st, 2019

Syndrome	Number of individuals registered 01-01-2019
Lynch syndrome	3664
Familial Adenomatous Polyposis	3082
Familial Atypical Multiple Mole Melanoma	4632
Hereditary prostate cancer	1323
Peutz-Jeghers syndrome	50

2.2. Reminder system

The StOET has a reminder system with the aim of guaranteeing the progress of lifelong screening. In practice this entails the sending of a message from the StOET to the treating specialist in which it is made clear that a certain patient is (again) eligible for screening examinations. The specialist then sends the result of the examination to the registry (or a copy of the letter to the general practitioner) and informs the StOET regarding scheduling of the next screening round.

In 2019 all specialists caring for persons registered at the StOET were informed in this way. If it emerged that a particular individual had withdrawn from screening, action was taken. First the patient received a reminder to attend the examination from the specialist. In case of no response, the general practitioner was then asked to remind the patient of the importance of periodic examinations. This approach helps prevent the loss of patients from screening who might later present with complaints that in many cases are due to a carcinoma.

2.3 Information about the different hereditary syndromes.

All information about the different hereditary syndromes has been updated on the website (www.stoet.nl) in 2019. This information is meant both for treating physicians as well as for patients. Updated information about hereditary prostate cancer will follow in 2020.

3. EVALUATION OF SURVEILLANCE

As stated in our mission, the registry promotes scientific research with the aim of improving screening programs. Below you will find studies related to surveillance conducted or published in 2019.

3.1. Lynch syndrome

3.1.1. Carriers of pathogenic MLH1, MSH2, and MSH6 germline variants show differences in adenoma and colorectal cancer development and molecular tumor characteristics (C. Engel et al.)

Lynch syndrome (LS) is caused by inherited pathogenic variants in mismatch repair (MMR) genes and is primarily associated with an increased risk of colorectal cancer (CRC). Recent studies suggest that LS-CRC can develop through different pathways. We assessed MMR gene-specific patterns of adenoma and CRC risk, as well as frequencies of somatic APC and CTNNB1 mutations characterizing different CRC development pathways. A total of 2,747 LS patients with pathogenic germline variants in MLH1, MSH2, or MSH6 gene were followed prospectively regarding adenoma and CRC development. Somatic mutation data from 48 CRCs were re-evaluated by grouping tumor characteristics by the affected MMR gene. Advanced adenoma risk was higher in MSH2 vs. MLH1 carriers, as was the frequency of somatic APC mutations in MSH2- vs. MLH1-associated CRCs. In contrast, MLH1-associated CRCs presented more frequently with somatic CTNNB1 mutations compared to MSH2-associated CRCs. Both MLH1 and MSH2 carriers showed higher frequencies of incident cancer than MSH6 carriers. Of the three MSH6-associated CRCs none carried a somatic CTNNB1 mutation, but all three samples presented with a somatic APC mutation.

Conclusion: Adenoma and CRC development in patients with distinct pathogenic MMR gene variants are attributable to different molecular pathways, potentially explaining the variation in the efficacy of colonoscopy. These differences indicate that LS screening and management guidelines should be revisited and tailored to the MMR gene affected.

3.1.2 Effect of chromoendoscopy in the proximal colon on colorectal neoplasia detection in Lynch syndrome: a multicenter randomized controlled trial (J. Haanstra et al.)

Patients with Lynch syndrome (LS) undergo regular surveillance by colonoscopy because of an increased risk of colorectal neoplasia, particularly in the proximal colon. Chromoendoscopy (CE) has been reported to improve neoplasia detection compared with conventional white-light endoscopy (WLE) but evidence is limited. Our aim was to investigate the effect of CE in the proximal colon on detection of neoplastic lesions during surveillance in LS. A multicenter prospective randomized controlled trial of 246 LS patients who were randomly assigned (1:1) to conventional WLE or colonoscopy with CE in the proximal colon, stratified for previous colorectal adenomas, and enrolling center. Two years after baseline colonoscopy, patients underwent colonoscopy with CE in the proximal colon. The primary outcome was the proportion of patients with at least one neoplastic lesion at baseline and after 2 years. Neoplasia detection rates at baseline colonoscopy were 27% for WLE versus 30% for CE. In the proximal colon, neoplasia detection rates were 16% for WLE versus 24% for CE. Total procedure time was 9 minutes longer in the CE group. At follow-up after 2 years, neoplasia detection rates were similar in both groups: 26% for the original WLE group versus 28% for the CE group.

Conclusion: CE in the proximal colon for LS surveillance was not superior to WLE with respect to the initial detection of neoplasia, and not associated with reduced neoplasia detection rates after 2 years. The value of CE remains to be established.

3.1.3. We evaluated the effects of family history on relative and absolute risks for colorectal cancer by performing a systematic Review and meta-Analysis. (Roos et al.)

Guidelines recommend that individuals with familial colorectal cancer undergo colonoscopy surveillance instead of average-risk screening. However, these recommendations vary widely. To substantiate appropriate surveillance strategies, precise and valid evidence-based risk estimates are needed for individuals with a family history of colorectal cancer (CRC). We screened 4417 articles and identified 42 eligible case-control and 20 cohort studies. In case-control studies, the RR for CRC in patients with 1 first-degree relative (FDR with CRC) was 1.92 (95% CI, 1.53-2.41) and 1.37 (95% CI, 0.76-2.46) for cohort studies. For individuals with 2 or more FDRs with CRC, the RR was 2.81 in case-control studies (95% CI, 1.73-4.55) and 2.40 in cohort studies (95% CI, 1.76-3.28). For individuals having a FDR diagnosed with CRC at an age younger than 50 years, the RR for CRC in their FDRs was 3.57 in case-control studies (95% CI, 1.07-11.85) and 3.26 in cohort studies (95% CI, 2.82-3.77). The cumulative absolute risks for CRC at 85 years in Western Europe were 4.8% for persons with 1 FDR with CRC (95% CI, 2.7%-8.3%), 8.2% for individuals with 2 or more FDRs (95% CI, 6.1%-10.9%), and 11% for persons with a FDR diagnosed with CRC at an age younger than 50 years (95% CI, 9.5%-12.4%).

Conclusion: In this systematic review and meta-analysis, we found that the RR of CRC among FDRs is lower than previously expected, especially based on cohort studies. Risk estimates are affected by the number of relatives with CRC and their age at diagnosis. Intensified colonoscopy surveillance strategies could be considered for high-risk groups.

3.2. Hereditary Melanoma and Pancreatic cancer

3.2.1. Dilatation of the main pancreatic duct as first manifestation of small pancreatic ductal adenocarcinomas detected in a hereditary pancreatic cancer surveillance program (H. Vasen et al.)

MRI surveillance in a cohort of CDKN2A-p16-Leiden mutation carriers with a 20% lifetime risk of PDAC led to increased resection rates and improved survival. Patients with screen-detected PDAC were evaluated for main pancreatic duct (MPD) abnormalities in this retrospective review. Since 2000 annual MRI and optional EUS was performed in mutation carriers. Data of patients with screen-detected PDAC was collected including gender, age at diagnosis, site of tumor, size, outcome of surgery, pathology findings and survival. All MRIs were re-evaluated for MPD abnormalities. 23 PDAC were detected in 22 (10%) of 217 mutation carriers, 10 (45%) males and 12 (55%) females. The mean age at diagnosis was 59.8 years (range 39.2-74.3 years). Revision of the MRI/MRCP revealed a lesion and dilatation of the MPD in 8 of the 22 patients. In 5 of 7 patients with PDAC detected during follow-up, the previous MRI showed MPD dilatation without evidence of tumor. The mean size of PDAC was 12.3 mm (range 5-19 mm). All tumors were respectable.

Conclusion: MPD dilation is common in patients with screen-detected PDAC. Abnormalities on MRI during surveillance of high-risk individuals requires intense follow-up or prompt treatment, as early treatment results in a better prognosis.

3.2.2. Surveillance for familial melanoma: recommendations from a national center of expertise. (A. Halk et al.)

The department of Dermatology at the Leiden University Medical Center, is a national center of expertise for the management of individuals with familial and hereditary melanoma. In collaboration with the department of Clinical Genetics and Gastroenterology & Hepatology, they

published the current surveillance recommendations for the various syndromes in the British Journal of Dermatology.

3.2.3. Incidental findings in pancreas screening programs for high-risk individuals: results from three European expert centers (I. Ibrahim et al.)

Widespread abdominal imaging has led to a substantial increase in the detection of incidentaloma. Currently, an increasing number of centers offer surveillance of the pancreas, to individuals at high risk (IAR) of pancreatic cancer (PDAC). The aims of this study were to evaluate the frequency and type of incidental findings in an MRI-based surveillance program for high-risk individuals for PDAC, and to discuss the benefit of detecting these lesions. The outcome of MRI screening was reviewed in 568 individuals from three long-term pancreas surveillance programs conducted in three large European expert centers. All MRI´s were studied in detail for the presence of incidental lesions. The most common lesions were liver cysts, renal cysts and liver hemangioma, which together comprised 75% of all lesions. Only five (0.9%) patients underwent surgery for a benign lesion. Cancer was detected in eleven patients (2.0%), and early detection of tumors was beneficial in at least five cases.

Conclusion: The present study demonstrates that extrapancreatic incidentaloma is a common finding in IAR for PDAC, but rarely requires additional treatment. CDKN2A-p16-Leiden mutation carriers were the only patient group found to harbor a substantial number of cancers, and detection resulted in benefit in several cases.

3.3. Hereditary prostate cancer

3.3.1. Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in BRCA2 Mutation Carriers. (Page et al.)

Mutations in BRCA2 cause a higher risk of early-onset aggressive prostate cancer (PrCa). The IMPACT study is evaluating targeted PrCa screening using prostate-specific-antigen (PSA) in men with germline BRCA1/2 mutations. We report the utility of PSA screening, PrCa incidence, positive predictive value of PSA, biopsy, and tumor characteristics after 3 yr of screening, by BRCA status.

Men aged 40-69 yr with a germline pathogenic BRCA1/2 mutation and male controls testing negative for a familial BRCA1/2 mutation were recruited. Participants underwent PSA screening for 3 yr, and if PSA>3.0 ng/ml, men were offered prostate biopsy.

A total of 3027 patients (2932 unique individuals) were recruited (919 BRCA1 carriers, 709 BRCA1 noncarriers, 902 BRCA2 carriers, and 497 BRCA2 noncarriers). After 3 yr of screening, 527 men had PSA>3.0 ng/ml, 357 biopsies were performed, and 112 PrCa cases were diagnosed (31 BRCA1 carriers, 19 BRCA1 noncarriers, 47 BRCA2 carriers, and 15 BRCA2 noncarriers). Higher compliance with biopsy was observed in BRCA2 carriers compared with noncarriers (73% vs 60%). Cancer incidence rate per 1000 person years was higher in BRCA2 carriers than in noncarriers (19.4 vs 12.0; p= 0.03); BRCA2 carriers were diagnosed at a younger age (61 vs 64 yr; p= 0.04) and were more likely to have clinically significant disease than BRCA2 noncarriers (77% vs 40%; p= 0.01). No differences in age or tumor characteristics were detected between BRCA1 carriers and BRCA1 noncarriers. The 4 kallikrein marker model discriminated better (area under the curve [AUC]=0.73) for clinically significant cancer at biopsy than PSA alone (AUC=0.65).

Conclusion: We demonstrate that after 3 yr of prostate-specific antigen (PSA) testing, we detect more serious prostate cancers in men with BRCA2 mutations than in those without these mutations. We recommend that male BRCA2 carriers are offered systematic PSA screening.

4. EDUCATION, PUBLICATIONS AND PATIENT INFORMATION

In the course of 2019 several presentations were given on various hereditary forms of cancer. In addition, many articles were published with the aim of increasing knowledge regarding hereditary cancer (see below). The leaflets produced by the StOET on various hereditary forms of cancer were updated where necessary. The StOET website is updated regularly by Magdalena van Heck.

5. OTHER STUDIES

5.1 Lynch syndrome and CMMRD

5.1.1. An alternative approach to establishing unbiased colorectal cancer risk estimation in Lynch syndrome (Suerink et al.)

Biallelic pathogenic variants in the mismatch repair (MMR) genes cause a recessive childhood cancer predisposition syndrome known as constitutional mismatch repair deficiency (CMMRD). Family members with a heterozygous MMR variant have Lynch syndrome. We aimed at estimating cancer risk in these heterozygous carriers as a novel approach to avoid complicated statistical methods to correct for ascertainment bias.

Cumulative colorectal cancer incidence was estimated in a cohort of PMS2- and MSH6-associated families, ascertained by the CMMRD phenotype of the index, by using mutation probabilities based on kinship coefficients as analytical weights in a proportional hazard regression on the cause-specific hazards. Confidence intervals (CIs) were obtained by bootstrapping at the family level.

The estimated cumulative colorectal cancer risk at age 70 years for heterozygous PMS2 variant carriers was 8.7% (95% CI 4.3-12.7%) for both sexes combined, and 9.9% (95% CI 4.9-15.3%) for men and 5.9% (95% CI 1.6-11.1%) for women separately. For heterozygous MSH6 variant carriers these estimates are 11.8% (95% CI 4.5-22.7%) for both sexes combined, 10.0% (95% CI 1.83-24.5%) for men and 11.7% (95% CI 2.10-26.5%) for women.

Conclusion: Our findings are consistent with previous reports that used more complex statistical methods to correct for ascertainment bias. These results underline the need for MMR gene-specific surveillance protocols for Lynch syndrome.

5.1.2. CD31-positive microvessel density within adenomas of Lynch Syndrome patients is similar compared to adenomas of non-Lynch patients (Vleugel et al.)

Microsatellite instability accelerates colorectal cancer development in patients with Lynch syndrome (LS). Previous research showed that virtual chromoendoscopy increases detection of adenomas during colonoscopy surveillance of patients with LS. Because previous research revealed that Lynch patients have an increased vascular network in the oral mucosa, we hypothesized that increased vascularization of LS-associated adenomas is the cause of better detection with virtual chromoendoscopy. Patients with LS having a proven germline mutation were selected from two tertiary referral hospitals and non-LS patients from an outpatient colonoscopy center. Adenomas from patients with LS were exactly matched in size and histology with adenomas from non-LS patients. Colonoscopy of 63 patients with LS and 24 non-LS patients provided 40 adenomas that could be exactly matched in size and histology. In image-analysis, the CD31-positive microvessel density (2.49% vs. 2.47%, P = 0.96), the average size of CD31-positive structures (514 μm^2 vs. 523 μm^2, P = 0.26) nor the amount of vascular structures per mm^2 (183 vs. 176, P = 0.50) differed between adenomas of LS patients and non-Lynch patients.

Conclusion: The outcomes of this pilot case-control study did not provide further insights into the mechanism of increased adenoma detection in LS patients using virtual chromoendoscopy techniques.

5.1.3. Constitutional mismatch repair deficiency as a differential diagnosis of neurofibromatosis type 1: consensus guidelines for testing a child without malignancy (M. Suerink)

Constitutional mismatch repair deficiency (CMMRD) is a rare childhood cancer predisposition syndrome caused by biallelic germline mutations in one of four mismatch-repair genes. Besides very high tumor risks, CMMRD phenotypes are often characterized by the presence of signs reminiscent of neurofibromatosis type 1 (NF1). Because NF1 signs may be present prior to tumor onset, CMMRD is a legitimate differential diagnosis in an otherwise healthy child suspected to have NF1/Legius syndrome without a detectable underlying NF1/SPRED1 germline mutation. However, no guidelines indicate when to counsel and test for CMMRD in this setting. Assuming that CMMRD is rare in these patients and that expected benefits of identifying CMMRD prior to tumor onset should outweigh potential harms associated with CMMRD counselling and testing in this setting, we aimed at elaborating a strategy to preselect, among children suspected to have NF1/Legius syndrome without a causative NF1/SPRED1 mutation and no overt malignancy, those children who have a higher probability of having CMMRD. At an interdisciplinary workshop, we discussed estimations of the frequency of CMMRD as a differential diagnosis of NF1 and potential benefits and harms of CMMRD counselling and testing in a healthy child with no malignancy. Preselection criteria and strategies for counselling and testing were developed and reviewed in two rounds of critical revisions. Existing diagnostic CMMRD criteria were adapted to serve as a guideline as to when to consider CMMRD as differential diagnosis of NF1/Legius syndrome. In addition, counselling and testing strategies are suggested to minimize potential harms.

5.2 Familial adenomatous polyposis (FAP)

5.2.1. Optimizing the timing of colorectal surgery in patients with familial adenomatous polyposis in clinical practice (H. Vasen et al.)

Familial adenomatous polyposis (FAP) is characterized by the development of hundreds of colorectal adenomas in the second decade of life, and prophylactic colectomy is usually performed around age of 20. A common question is the appropriate timing of surgery and which endoscopic findings indicate surgery. All FAP patients known at Leiden University Medical Centre from 1985 onwards were included. The patients were then subdivided into those diagnosed before or after 2000. Patient information included age at diagnosis, colonic phenotype, age at surgery, pathological findings, and the outcome of follow-up colonoscopies in whom surgery was postponed.

The 72 FAP patients identified consisted of 33 patients diagnosed before (group A) and 39 after (group B) 2000. The median age at diagnosis for patients with classical FAP was 18 in groups A and B. All patients diagnosed before 2000 underwent colorectal surgery versus 68% of those diagnosed >2000. The median age at surgery for classical FAP patients was 19 and 24 years in groups A and B, respectively. In patients with intact colon, the number of adenomas gradually increased over many years. Although most adenomas remained <5mm, the proportion of 5-15mm adenomas slowly increased. Only one patient developed a high-grade adenoma. None of the patients developed CRC.

Conclusion: Surgery today in FAP is performed less often and at a more advanced age. Our experience also suggests that surgery can be safely postponed in selected patients. The most important endoscopic indication for surgery is substantial number of large adenomas of >5-10mm.

6. ORGANIZATION

6.1. Board

Prof. Dr. W. Bemelman, chair, surgeon, Amsterdam Medical Center, Amsterdam
Prof. Dr. R. Hofstra, Head, Department of Clinical Genetics, Erasmus Medical Center, Rotterdam
Prof. Dr. R. van Doorn, Department of Dermatology, Leiden University Medical Center, Leiden
Dr. de Vos tot Nederveen Cappel, gastroenterologist, Isala Clinics, Zwolle
Prof. Dr. M. Mourits, gynaecologist, University Medical Centre Groningen, Groningen

6.2. Registry staff

Mw. Dr. M.E. van Leerdam, gastroenterologist, Medical Director
Mw. Drs. M. van Heck, organization, communication, finances
Mw. I.S.J. van Leeuwen-Cornelisse, medical social worker
Mw. C. van der Kaa, registration Lynch syndrome
Mw. A. van Oostrum MSc, registration Lynch syndrome
Mw. I.E.M. Voncken, registration Polyposis
Mw. H.L. van Randeraad, registration Hereditary Melanoma and Hereditary Prostate cancer

6.3. Data Privacy Officer

Mr. I. de Vries

6.4. Research Commission

Dr. P. van Duijvendijk, surgeon, Gelre Hospital, Apeldoorn
Prof. dr. E. Dekker, gastroenterologist, AMC, Amsterdam
Dr. R. van Doorn, dermatologist, Leiden University Medical Centre, Leiden
Dr. A. Wagner, clinical geneticist, Erasmus Medical Center, Rotterdam

ENCLOSURES

1. Presentations

1. Antoni van Leeuwenhoek, Department of Gastroenterology: Monique van Leerdam: Update of the new ESGE polyposis guideline, June 2019

2. Publications

1. Engel C, Ahadova A, Seppälä TT, Aretz S, Bigirwamungu-Bargeman M, Bläker H, Bucksch K, Büttner R, de Vos Tot Nederveen Cappel WT, Endris V, Holinski-Feder E, Holzapfel S, Hüneburg R, Jacobs MAJM, Koornstra JJ, Langers AM, Lepistö A, Morak M, Möslein G, Peltomäki P, Pylvänäinen K, Rahner N, Renkonen-Sinisalo L, Schulmann K, Steinke-Lange V, Stenzinger A, Strassburg CP, van de Meeberg PC, van Kouwen M, van Leerdam M, Vangala DB, Vecht J, Verhulst ML, von Knebel Doeberitz M, Weitz J, Zachariae S, Loeffler M, Mecklin JP, Kloor M, Vasen HF; German HNPCC Consortium, the Dutch Lynch Syndrome Collaborative Group; Finnish Lynch Syndrome Registry. Associations of Pathogenic Variants in MLH1, MSH2, and MSH6 With Risk of Colorectal Adenomas and Tumors and With Somatic Mutations in Patients with Lynch Syndrome. Gastroenterology. 2020;158(5):1326-1333.

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7. Vleugels JLA, van Neerven SM, van Leerdam ME, Wanders LK, de Wit M, Carvalho B, Delis-van Diemen PM, Kallenberg FGJ, Vermeulen L, Beliën JA, East JE, Meijer GA, Dekker E. CD31-positive microvessel density within adenomas of Lynch Syndrome patients is similar compared to adenomas of non-Lynch patients. Endosc Int Open. 2019;7:E701-E707.

8. Adan F, Crijns MB, Dekker E, Bastiaansen BAJ, Lapid O, Snaebjornsson P, Rosenberg EH, van Leerdam ME, Bekkenk MW. A squamous cell carcinoma in a young woman with Lynch syndrome. Fam Cancer. 2019;18:193-196.

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