Submitted Abstracts EHTG 2022

page	DAY	TIME	PART	FUNCTION	NAME	FIRST NAME	TITLE presentation	FROM
1	THU	11:30-01:30	Plenary Session 1	Speaker 6	Robbe	Julie	Clinical description and fi	France
2	THU	11:30-01:30	Plenary Session 1	Speaker 5	Kloor	Matthias	Immune surveillance and	Germany
3	FRI	08:00-09:00	PLSD Meeting	ABSTRACT 1	Møller	Pål	Lynch Syndrome: Which	Norway
4	FRI	08:00-09:00	PLSD Meeting	ABSTRACT 2	Møller	Pål	The four Lynch syndrome	Norway
5	FRI	08:00-09:00	PLSD Meeting	ABSTRACT 3	Møller	Pål	An additional carcinogen	Norway
	FRI	WG 8	F2F					
6	FRI	09:00-11:00	WG 8 - Surgery ar	ABSTRACT 1	D'Hooge	Marion	Is there a correlation bet	France
7	FRI	09:00-11:00	WG 8 - Surgery ar	ABSTRACT 2	Truscott	Becky	Duodenal disease in 579	UK
8	FRI	09:00-11:00	WG 8 - Surgery ar	ABSTRACT 3	Colletti	Gaia	Small bowel cancer in pat	Italia
9	FRI	09:00-11:00	WG 8 - Surgery ar	ABSTRACT 4	Pellino	Gianluca	Ileoanal pouch cancers in	Italy
10	FRI	09:00-11:00	WG 8 - Surgery ar	ABSTRACT 5	Seppälä	Toni	Metachronous CRC after	Finland
11	FRI	09:00-11:00	WG 8 - Surgery ar	ABSTRACT 6	Mira	Daniel	Functional Outcome Diffe	Sweden
12	FRI	09:00-11:00	WG 8 - Surgery ar	ABSTRACT 7	Hüneburg	Robert	Real-time use of artificial	Germany
	FRI	WG 1	VIRTUAL					
13	FRI	09:00-11:00	WG 1 - Carcinoger	ABSTRACT 1	Suárez Sánchez	Aida	Clinicopathological Featu	Spain
14	FRI	09:00-11:00	WG 1 - Carcinoger	ABSTRACT 2	Dardenne	Antoine	Constitutional MLH1 met	France
15	FRI	09:00-11:00	WG 1 - Carcinoger	ABSTRACT 3	Mäki-Nevala	Satu	Genome-wide methylom	Finland
16	FRI	09:00-11:00	WG 1 - Carcinoger	ABSTRACT 4	Valle	Laura	Germline MBD4 mutation	Spain
17	FRI	09:00-11:00	WG 1 - Carcinoger	ABSTRACT 5	Hernandez Sanchez	Alejandro	HLA-specific immunogeni	Germany
18	FRI	09:00-11:00	WG 1 - Carcinoger	ABSTRACT 6	Ahadova	Aysel	Molecular carcinogenesis	Germany
19	FRI	09:00-11:00	WG 1 - Carcinoger	ABSTRACT 7	Nielsen	Maartje	APC mosaicism is a releva	Netherlands
	FRI	WG 3	VIRTUAL					
20	FRI	09:00-11:00	WG 3 - Epidemiol	ABSTRACT 1	Dominguez Valentin	Mev	Cancer mortality by organ	Norway
21	FRI	09:00-11:00	WG 3 - Epidemiol	ABSTRACT 2	Huntley	Catherine	Central Amalgamation of	UK
22	FRI	09:00-11:00	WG 3 - Epidemiol	ABSTRACT 3	Turnbull	Clare	Germline Mismatch Repa	UK
23	FRI	09:00-11:00	WG 3 - Epidemiol	ABSTRACT 4	Herrero Belmonte	Patricia	Implementation of popul	UK
24	FRI	09:00-11:00	WG 3 - Epidemiol	ABSTRACT 5	Monahan	Kevin	The English National Lync	UK
25	FRI	09:00-11:00	WG 3 - Epidemiol	ABSTRACT 6	Díaz Vico	Tamara	Universal Testing of Astur	Spain
	FRI	11:00-11:30	COFFEE BREAK					
	FRI	WG 9	F2F					
26	FRI	11:30-01:30 p	WG 9 - Systemic t	ABSTRACT 4	Hallermayr	Ariane	Combined somatic copy n	Germany
27	FRI	11:30-01:30 p	WG 9 - Systemic t	ABSTRACT 1	Lewis	Samantha	A Demonstration of Micr	United States
28	FRI	11:30-01:30 p	WG 9 - Systemic t	ABSTRACT 2	Eikenboom	Ellis	Analysis of plasma cell-fre	Netherlands	genome-wide meth
29	FRI	11:30-01:30 p	WG 9 - Systemic t	ABSTRACT 3	Sievänen	Tero	Associations of circulating	Finland
30	FRI	11:30-01:30 p	WG 9 - Systemic t	ABSTRACT 5	Romic-Pickl	Julia	Highly sensitive Liquid Bio	Germany
31	FRI	11:30-01:30 p	WG 9 - Systemic t	ABSTRACT 6	Kauma	Iiro	Whole-exome sequencing	Finland
	FRI	WG 6	VIRTUAL					
32	FRI	11:30-01:30 p	WG 6 - Risk and C	ABSTRACT 1	Kohut	Kelly	The Person-Based Approa	UK
33	FRI	11:30-01:30 p	WG 6 - Risk and C	ABSTRACT 2	Zeilmann	Alexander	Uncertainty quantificatio	Germany
34	FRI	11:30-01:30 p	WG 6 - Risk and C	ABSTRACT 3	Monje-Garcia	Laura	From Diagnosis of Colore	UK
	FRI	11:30-01:30 p	WG 6 - Risk and C	ABSTRACT 3	Koziel	Ana	with Monje-Garcia	UK
35	FRI	11:30-01:30 p	WG 6 - Risk and C	ABSTRACT 4	Bauerfeind	Peter	Improvement of IAFLD un	Switzerland
36	FRI	11:30-01:30 p	WG 6 - Risk and C	ABSTRACT 5	Backman	Ann-Sofie	Mesalamine for Colorecta	Sweden
37	FRI	11:30-01:30 p	WG 6 - Risk and C	ABSTRACT 6	Zalevskaja	Kristina	Clinical characteristics of	Finland
	FRI	WG 2	VIRTUAL					
38	FRI	11:30-01:30 p	WG 2 - Early onset	Speaker	Cavestro	Giulia Martina C	DIRECT: Delphi initiative	Italy
39	FRI	11:30-01:30 p	WG 2 - Early onset	ABSTRACT 2	Farelly	Solenne	Genetic testing in early o	FRANCE
40	FRI	11:30-01:30 p	WG 2 - Early onset	ABSTRACT 3	Puzzono	Marta	Young-onset gastric canc	Italia
41	FRI	11:30-01:30 p	WG 2 - Early onset	ABSTRACT 4	Dominguez Valentin	Mev	Comprehensive character	Norway
42	FRI	11:30-01:30 p	WG 2 - Early onset	ABSTRACT 5	Grolmusz	Vince Kornél	Germline pathogenic vari	Hungary
	FRI	01:30-02:30	LUNCH					

Submitted Abstracts EHTG 2022

page	DAY	TIME	PART	FUNCTION	NAME	FIRST NAME	TITLE presentation	FROM
	FRI	*WG 4*	*F2F*					
43	FRI	02:30-04:30	WG 4 - Genetics &	ABSTRACT 1	McRonald	Fiona	A national picture of mol	UK
44	FRI	02:30-04:30	WG 4 - Genetics &	ABSTRACT 2	Langford	Lora	A NURSE LED GENETIC CL	UK
	FRI	02:30-04:30	WG 4 - Genetics &	ABSTR:2/2.	Proserpio	Mauro	*with Langford*	UK
45	FRI	02:30-04:30	WG 4 - Genetics &	ABSTRACT 3	Aretz	Stefan	APC-specific ACMG/AMP	Germany
46	FRI	02:30-04:30	WG 4 - Genetics &	ABSTRACT 4	Wendlandt	Martin	Targeted short-read RNA	Germany
47	FRI	02:30-04:30	WG 4 - Genetics &	ABSTRACT 5	Eriksen	Elin O.	Existing with a cancer gh	Norway
48	FRI	02:30-04:30	WG 4 - Genetics &	ABSTRACT 6	Torra I Benach	Maria	Mutational and transcript	UK
49	FRI	02:30-04:30	WG 4 - Genetics &	ABSTRACT 7	Monje-Garcia	Laura	Psychological well-being	UK
	FRI	*WG 5*	*VIRTUAL*					
50	FRI	02:30-04:30	WG 5 - Novel asso	ABSTRACT 1	Reznick Levi	Gili	High Prevalence of MUTY	Israel
51	FRI	02:30-04:30	WG 5 - Novel asso	ABSTRACT 2	Mannucci	Alessandro	LYNCH SYNDROME IS ASS	Italia
52	FRI	02:30-04:30	WG 5 - Novel asso	ABSTRACT 3	Roht	Laura	Oligodontia-colorectal ca	Estonia
53	FRI	02:30-04:30	WG 5 - Novel asso	ABSTRACT 4	Lubinski	Jan	The Impact of Oophorect	Poland
54	FRI	02:30-04:30	WG 5 - Novel asso	ABSTRACT 5	Haupt	Saskia	Why the combination of	Germany
55	FRI	02:30-04:30	WG 5 - Novel asso	ABSTRACT 6	Aretz	Stefan	Clinically relevant combin	Germany
	FRI	*WG 7*	*VIRTUAL*					
56	FRI	02:30-04:30 p	WG 7 - Screening	ABSTRACT 1	Perez-Lopez	Maria-Eva	Hypercalcemic Ovarian ca	Spain
57	FRI	02:30-04:30 p	WG 7 - Screening	ABSTRACT 2	Ryan	Neil	The prevalence of misma	UK
58	FRI	02:30-04:30 p	WG 7 - Screening	ABSTRACT 3	Buchanan	Dan	The genomic and clinico-	Australia
59	FRI	02:30-04:30 p	WG 7 - Screening	ABSTRACT 4	Phelps	Rachel	Detection of mismatch re	UK
60	FRI	02:30-04:30 p	WG 7 - Screening	ABSTRACT 5	Ryan	Neil	Distinguishing the molecu	UK
61	FRI	02:30-04:30 p	WG 7 - Screening	ABSTRACT 6	Jimenez Ruiz	Francisco Javier	NON-BRCA MUTATION PF	Spain
62	SAT	03.15-03.45	best of abstract	Speaker	Dueñas Cid	Nuria	Assessment of the ability	Spain
63	SAT	03.15-03.45	best of abstract	Speaker	Jansen	Marnix	Mutation rate evolution c	UK

Title: Clinical description and first estimates of age-associated cancer risk and survival in the context of constitutional mismatch repair system deficiency (CMMRD syndrome): report from the European database of the European consortium C4CMMRD.

Author: Robbe, Julie

Author Institution: 1 Curie Institute, Genetic Department, Paris, France; 2 Centre Léon Bérard, Département Prévention et Santé Publique, Lyon, F-69008, France Université de Lyon, CNRS UMR 5558 LBBE, Villeurbanne, F-69622 France; 3 Department of Pediatric and Adolescents Oncology, Gustave Roussy Cancer Center, Paris-Saclay University, Villejuif, France.; 4 Gustave Roussy Cancer Center, Unite Mixte de Recherche 8203, Centre National de la Recherche Scientifique, Paris-Saclay University, Villejuif, France.; 5 CHU Charles Nicolle, Rouen, France; 6 CHU Purpan, Toulouse, France; 7 Curie Institute, SIREDO Cancer Center (Care, innovation and research in pediatric, adolescents and young adults oncology), Paris, France; 8 Hôpital Universitaire Reine Fabiola (HUDERF), Genetic department, Université Libre de Belgique (ULB), Brussels, Belgium; 9 Centre Léon Bérard, Département Prévention et Santé Publique, Lyon, F-69008
10 Department of Hemato-Oncology, Hôpital Universitaire Reine Fabiola (HUDERF), Université Libre de Belgique (ULB). Brussels - Belgium.; 11 Pédiatrie Onco-Hématologie-Pédiatrie III-CHRU Hautepierre UdS-EA 3430, Strasbourg, France; 12 CHU Dijon Bourgogne, Dijon, France; 13 Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC Genetica Medica, Rome, Italy Dipartimento di Scienze della Vita e Salute Pubblica, Università Cattolica del Sacro Cuore, Rome, Italy; 14 Raphael Recanati Genetics Institute, Beilinson Hospital, Rabin Medical Center, Petach Tikva, Israel; 15 Poznań University of Medical Sciences, Poznań, Poland; 16 University Hospital, Prague, Czech Republic; 17 Department of Pediatric Oncology, University Children´s Hospital, Hematology and Clinical Immunology Duesseldorf, Germany; 18 Hospital Universitario Doce de Octubre, Unidad de Oncología Pediátrica, Madrid, Spain; 19 Hospital 12 de Octubre, Madrid, Spain; 20 Fundación Pública Galega de Medicina Xenómica (FPGMX) SERGAS, Grupo de Medicina Xenómica, IDIS, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERer), Santiago de Compostela, Spain; 21 CHU Hôpitaux de Bordeaux, Bordeaux, France; 22 Centre Hospitalier Universitaire Vaudois, Division of Genetic Medicine, University of Lausanne, Lausanne Switzerland.; 23 Department of Pediatric Oncology, UZ Leuven, Leuven, Belgium; Department of Oncology, KU Leuven, Leuven, Belgium; 24 Department of Clinical Genetics, Erasmus MC Cancer Institute, University Medical Center Rotterdam, 3000CA Rotterdam, The Netherlands.; 26 Institute of Human Genetics, Medical University Innsbruck, Innsbruck, Austria; 27 Curie Institute, Genetic Department, Paris, France, INSERM U830, Paris, France / Université de Paris, France

Co-Authors: Julie Robbe1, Youenn Drouet2, Lea Guerrini-Rousseau3,4, Stéphanie Baert-Desurmont5, Delphine Bonnet6, Franck Bourdeaut7, Karin Dahan8, Francoise Desseigne9, Christine Devalck10, Natacha Entz-Werle11, Laurence Faivre12, Maurizio Genuardi13, Yael Goldberg14, Danuta Januszkiewicz-Lewandowski15, Edita Kabickova16, Michaela Kuhlen17, Vanessa Perez-Alonso18, Daniel Rueda19, Clara Ruiz-Ponte20, Julie Tinat21, Sheila Unger22, Anne Uyttebroeck23, Anja Wagner24, Christine Lasset2, Katharina Wimmer26, Laurence Brugières3, Chrystelle Colas27on behalf of the C4CMMRD consortium

Abstract text:

Introduction: Constitutional Mismatch Repair Deficiency (CMMRD) is a rare childhood cancer predisposition syndrome due to biallelic germline pathogenic variants in one of the MMR genes. Patients affected with this syndrome have a high risk of developing early onset tumors. Although improvement of the clinical description of CMMRD, due to the scarcity of the disease, age-associated cancer risk and survival remain largely unknown. The aim of this study is to estimate the tumor risks in the context of CMMRD syndrome and to explorer genotype-phenotype correlations.

Method: Data of 100 CMMRD patients were extracted from the C4CMMRD European consortium database. Overall survival and cumulative risks (CR) of cancers were estimated using Kaplan-Meier method. Subgroup analyses were conducted according to the mutated gene and the variant type.

Results: These 100 patients developed 178 tumors of which 40% were brain tumors, 31% hematological malignancies and 26% Lynch syndrome related tumors. PMS2 is the main gene involved followed by MSH6, MSH2 and MLH1. The tumor spectrum varies according to the mutated gene. The median age of onset of the first tumor is 7 years (0,1- 33,6) and is significantly different according to the germline mutated gene (p<0,001) as is the cumulative risk of any tumor (p<0,0001). The highest risk is observed for biallelic MLH1 patients with 75% CR at 5 years of age. The median overall survival was 13,2 years (1,2-46,8), with 71% of the patients deceased at last news. Survival was highly correlated to the mutated gene (p<0,001) : median age at death was 6 y for MLH1, 7y for MSH2, 13 for MSH6 and 20 for PMS2 biallelic carriers.

Conclusion: This is the largest reported series of CMMRD patients, providing the first estimates of age-associated cancer risk and survival to date. These data provide evidence-based arguments for a more accurate management of CMMRD patients according to their genotype.

Title: Immune surveillance and immune prevention in Lynch syndrome – new evidence for the feasibility of cancer-preventive vaccines

Author: Kloor, Matthias

Author Institution: 1Department of Applied Tumor Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany; 2Cooperation Unit Applied Tumor Biology, German Cancer Research Centre (DKFZ), Heidelberg, Germany; 3Molecular Medicine Partnership Unit (MMPU), European Molecular Biology Laboratory (EMBL), Heidelberg, Germany ; 4Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany; 5German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Heidelberg, Germany ; 6Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany ; 7National Center for Hereditary Tumor Syndromes, University Hospital Bonn, Bonn, Germany; 8Translational and Clinical Research Institute, Newcastle University, International Centre for Life, Central Parkway, Newcastle upon Tyne, NE1 3BZ, UK; 9Institute of Pathology, University Hospital Bonn, Bonn, Germany; 10Department of Nephrology, Klinikum Stuttgart – Katharinenhospital, Stuttgart, Germany; 11Department of Medical Oncology, National Centre for Tumor Diseases, Heidelberg University Hospital, Heidelberg, Germany; 12Institute of Pathology, University Hospital Leipzig, Leipzig, Germany; 13Department of Surgery, Ev. Krankenhaus Bethesda Hospital, Duisburg, Germany; 14Department of Gastrointestinal Surgery, Helsinki University Central Hospital, Helsinki, Finland; 15Applied Tumor Genomics Research Program, University of Helsinki, Helsinki, Finland ; 16Department of Molecular Pathology, Central Finland Hospital Nova, Jyväskylä, Finland; 17Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland; 18Department of Surgery, Central Finland Hospital Nova, Jyväskylä, Finland; 19Division of Hematology and Immunology, Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK

Co-Authors: Matthias Kloor1,2,3, Lena Bohaumilitzky1,2,3, Klaus Kluck4,5, Robert Hüneburg6,7, Richard Gallon8, Jacob Nattermann6,7, Martina Kirchner4, Glen Kristiansen9, Oliver Hommerding9, Pauline Pfuderer1,2,3, Lelia Wagner1,2,3, Fabian Echterdiek1,2,3,10, Svenja Kösegi1,2,3, Nico Müller1,2,3, Konstantin Fischer1,2,3, Nina Nelius1,2,3, Ben Hartog8, Gillian Borthwick8, Elena Busch11, Georg Martin Haag11, Hendrik Bläker12, Gabriela Möslein13, Magnus von Knebel Doeberitz1,2,3, Toni T. Seppälä14,15, Maarit Ahtiainen16, Jukka-Pekka Mecklin17,18, D Timothy Bishop19, John Burn8, Albrecht Stenzinger4,5, Jan Budczies4,5, Aysel Ahadova1,2,3

Abstract text:

Introductio: Due to defects of DNA mismatch repair, Lynch syndrome (LS)-associated tumors are characterized by a high load of frameshift mutations and immunogenic frameshift neoantigens. Thus, immune surveillance may play a critical role in controlling tumor outgrowth in LS carriers. Systemic neoantigen-specific immune responses have been previously reported in healthy LS carriers. Here, we asked whether mucosal immune surveillance can be detected in LS carriers and influence their colorectal cancer (CRC) risk.

Method: Quantitative analysis of immune cell populations was performed in 233 colonic mucosa tissue sections from 132 individuals and in 26 LS CRC using immunohistochemistry (IHC) with antibodies specific for CD3, CD8, and FOXP3. The NanoString nCounter gene expression platform was used to perform in-depth immune cell profiling in a subset of patients.

Results: LS carriers presented with higher mucosal CD3-positive T cell counts than non-LS individuals. Significantly elevated T cell densities were detected in the normal mucosa of healthy LS carriers compared to LS CRC patients. Notably, gene expression analysis revealed distinct immune profiles in the colonic mucosa of LS carriers with and without cancer manifestation. The mucosa of healthy LS carriers was characterized by an overrepresentation of CD45+, exhausted CD8+, NK, mast and B cells. Long-term follow-up of LS carriers within the CAPP2 trial showed a significant correlation between rectal mucosal CD3+ T cell infiltrate and time to subsequent CRC occurrence.

Conclusions: The immune profile of the colorectal mucosa may act as a tumor risk modifier in LS. Monitoring local immune profiles and modulation of the existing immune responses by vaccination hold potential for dynamic CRC risk assessment and primary cancer prevention in LS carriers. The latest results on the clinical translation of frameshift neoantigen-based vaccine approaches to boost immune surveillance in LS will be presented at the meeting.

Title: An additional carcinogenetic mechanism for colon cancer in Lynch syndrome

Author: Møller, Pål

Author Institution: 1Department of Tumor Biology, Institute of Cancer Research, The Norwegian Radium Hospital, 0379 Oslo, Norway; 2Engineering Mathematics and Computing Lab (EMCL), Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University, Heidelberg, Germany, and Data Mining and Uncertainty Quantification (DMQ), Heidelberg Institute for Theoretical Studies (HITS), Heidelberg, Germany; 3 Department of Applied Tumour Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany; and Clinical Cooperation Unit Applied Tumour Biology, German Cancer Research Center (DKFZ), Heidelberg, Germany; 4 University of Newcastle and the Hunter Medical Research Institute, Callaghan, Australia; 5 Translational & Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne NE1 3BZ; 6Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Center, Tampere University Hospital; 7Department of Gastrointestinal Surgery, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland;8Applied Tumor Genomics, Research Program Unit, University of Helsinki, Helsinki, Finland; 9Institute of Medical Genetics, Division of Cancer and Genetics, Cardiff University School of Medicine, Heath Park, Cardiff CF14 4XN, UK; 10Department of Clinical Genetics, Aalborg University Hospital, 9000 Aalborg, Denmark; 11Department of Biomedicine, Aarhus University, DK-8000 Aarhus, Denmark

Co-Authors: Saskia Haupt2, Aysel Ahadova3, Vincent Heuveline2 , Matthias Kloor3 , Rodney J Scott 4 , John Burn5, Toni Seppala6,7,8, Julian R. Sampson9, Lone Sunde10,11 , Eivind Hovig1 and Mev Dominguez-Valentin1

Abstract text:

Background: Both the CIN and mutator/MSI/dMMR carcinogenic pathways assume accumulations of somatic mutations causing progression to colon cancer cellsPath_MLH1 carriers may have > 1,000 dMMR crypts in colon at any given time1. Both dMMR crypts and colon cancers are infiltrated with immunocompetent cells2. Colon cancer rarely occurs before 25 years of age. Colonoscopy may over-diagnose colon cancer indicating that not only precursor lesions but infiltrating cancers as well may be rejected by the host immune system. In contrast to path_BRCA1/2, founder variants are few.

Methods: The Prospective Lynch Syndrome Database3 reports observed annual incidence rates (CC_AIR) by age of colon cancer in path_MLH1 carriers.

Results: CC_AIR in path_MLH1 carriers increases from close to zero at age 25 up to 2% at age 50, after which it plateaus, see figure.

Discussion: Both the CIN and mutator pathways should lead to linear or logarithmic increasing CC-AIR from early in life onwards, which was not the observed results. The observed CC-AIRs may indicate an additional carcinogenetic mechanism: If the somatic events leading to cancer are frequent bordering on infinite, the limiting factor may be the host's ability to control mutated cells. Is there other evidence of the adult immune system functioning less well than in the child or adolescent? The answer is yes, as exemplified in viral infections among which measles and Covid19 are examples. The flattening-out of the AIRs in older age may be associated with lower mitotic activity and/or the individuals were selected survivors because of constitutional abilities to destroy cancers. The effect of immunotherapy to help a surrendering immune system dispose of cancer cells would be in keeping with the hypothesis. High mutation rates and low fitness may explain few founder variants. Future studies may test the hypothesis.

Title:	Lynch Syndrome: Which cancer comes first?
Author:	Møller, Pål

Author Institution: 1Department of Tumor Biology, Institute of Cancer Research, The Norwegian Radium Hospital, 0379 Oslo, Norway; 2Institute of Medical Genetics, Division of Cancer and Genetics, Cardiff University School of Medicine, Heath Park, Cardiff CF14 4XN, UK; 3Department of Clinical Genetics, Aalborg University Hospital, | 9000 Aalborg, Denmark; 4Department of Biomedicine, Aarhus University, DK-8000 Aarhus, Denmark; 5Translational & Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne NE1 3BZ; 6Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Center, Tampere University Hospital; 7Department of Gastrointestinal Surgery, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland;8Applied Tumor Genomics, Research Program Unit, University of Helsinki, Helsinki, Finland

Co-Authors: Mev Dominguez-Valentin1, Julian R. Sampson2, Eivind Hovig1, Lone Sunde3,4, John Burn and Toni Seppala6,7,8

Abstract text:

Background: The question of which cancer comes first in Lynch syndrome is of practical interest with respect to early diagnosis aiming at early treatment to improve survival.

Methods: The Prospective Lynch Syndrome Database (PLSD) was examined for how frequent cancer in the organs in which path_MMR carriers reported to have increased cancer incidence, were the first cancer to be diagnosed.

Results: Cancer in colon was the first cancer to be diagnosed in 68% of cases with colon cancer (avg age at diagnosis 46.8, 95% CI ±1.2 years), endometrial cancer in 55% (49.7 ±1.3 years) and ovarian cancer in 60% (45.5± 2.6 years). This in contrast to the 10 other organs in which the cancers less frequently were the first ones: stomach 22% (55.9 ±5.1years), small intestine 31% (48.7 ±3 years), bile duct 31% (60.3 ±4.2 years), pancreas 28% (49.1 ±6.3 years), rectum 30% (47.8 ±3 years), urinary bladder 17% (54.5 ±6.6 years), ureter 18% (58.2 ±3.1 years), prostate 18% (57.7 ±3.6 years), brain 24% (45.0 ±11.4 years) and osteosarcoma 18% (44.5 ±17.3 years). With bile duct cancer as the only exception, average age when first cancer was lower than when subsequent cancer in the same organ: the less frequent cancers occurring as first cancer could not be explained as absence or late onset of colon or endometrial cancers. The results reflect the average of all carriers followed-up at the reporting centre and were not weighted on the relative prevalence of carriers of the different pathogenic variants of the genes.

Discussion: Ovarian cancer grouped with endometrial cancer as the first cancers to occur. Rectal cancer grouped with the less frequent cancers usually diagnosed as subsequent cancers. Average age was < 50 years when as first cancer diagnosing cancers in small intestine, pancreas, rectum, brain and osteosarcoma, all of which having serious prognoses. The findings may be of interest when considering which cancers to screen for in which age groups in healthy path_MMR carriers.

Title:	The four Lynch syndromes
Author:	Møller, Pål
Author Institution:	1Department of Tumor Biology, Institute of Cancer Research, The Norwegian Radium Hospital, 0379 Oslo, Norway; 2Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Center, Tampere University Hospital; 3Department of Gastrointestin
Co-Authors:	Toni Seppala2,3,4, John Burn5, Julian R. Sampson6, Lone Sunde7,8 Eivind Hovig1, and Mev Dominguez-Valentin1

Abstract text:

The Prospective Lynch Syndrome Database now includes sufficient information to describe the four Lynch Syndromes. They are different and should be kept apart because averages for all are not valid for anyone.

1. The MLH1 syndrome is a dominantly inherited cancer syndrome including high incidence of colon and endometrial cancer, and a substantial risk for upper gastro-intestinal cancers with severe prognosis. Colon cancer is more frequent in males than in females. Colonoscopy overdiagnoses colon cancer. Founder variants are infrequent – fitness is low.

2. The MSH2 syndrome is a dominantly inherited multiorgan cancer syndrome in colon, endometrium, ovaries, rectum, stomach, small intestine, bile duct, pancreas, ureter, urinary bladder, prostate, brain and osteosarcoma. Most cancer deaths are associated with non-colorectal cancers, particularly in endometrium, rectum, urinary tract, prostate and brain. Colonoscopy overdiagnoses colon cancer. No founder variants – fitness is low.

3. The MSH6 syndrome is a sex-limited dominantly inherited cancer syndrome presenting as endometrial and ovarian cancer in females, with a low but increased gender-equal incidence of colon cancer. Because it often escapes identification by family history and incident endometrial cancers are infrequently tested for genetic cause, the recognized prevalence is artificially low.

4. The PMS2 syndrome is dominantly inherited and includes late onset colon and endometrial cancer. Delineation from normal variation is difficult, and identification by family history close to impossible. Current knowledge is biased by selection artifacts. Lack of colon cancer at younger ages reported to the PLSD may indicate that colon cancer is prevented by colonoscopy, while the simultaneous lack of endometrial cancer may indicate that risks for both endometrial and colon cancer at young ages have been overestimated in retrospective studies.
More details will be given.

Title:	Is there a correlation between genotype and duodenal phenotype in Familial Adenomatous Polyposis?
Author:	D'Hooge, Marion
Author Institution:	Cochin Teaching Hospital, AP-HP Centre, Université Paris Cité
Co-Authors:	N. Hamzaoui, E. Pasmant, F. Maksimovic, M. Barret, A. Belle, R. Coriat, E. Abou Ali, S. Chaussade.

Abstract text:

Introduction: Familial Adenomatous Polyposis (FAP) is an autosomal-dominant colorectal cancer syndrome, caused by germline variations in the APC gene. Some location of the mutation on the APC gene are correlated with attenuated forms of colonic polyposis (genotype-phenotype correlation). Duodenal adenocarcinomas are the second cause of death in FAP. There is also an increased risk of gastric cancer in these patients.
The aim of our study was to search for a correlation between genotype and duodenal phenotype and to describe the associated gastric phenotype in these patients.

Patients and Methods: We included all patients followed for FAP in our local follow-up network. We collected data's about genotype, Spigelman score, history of ampullectomy, gastric phenotype and colonic phenotype.
Duodenal adenomatosis was classified as mild (Spigelman 0/I, no ampullectomy), intermediate (Spigelman II or ampullectomy) or severe (Spigelman III/IV).

Results: 70 patients from 48 families were included, 63 with a point mutation and 7 with a copy number variant (CNV) of the APC gene.
Among the families studied there was a similar profile of duodenal adenomatosis between relatives.
There was no severe impairment in the 28 patients with a mutation upstream exon 15.
There was great heterogeneity in duodenal impairment in the 35 patients with mutations in exons 15 and 16 (15 severe, 7 moderate and 13 mild injuries).
Three patients presented severe early duodenal involvment with an attenuated colonic phenotype.
Of the 39 patients with mild duodenal involvement, 16 had florid or complicated gastric polyposis.

Conclusion: It appears from this serie that no severe duodenal involvement was found in patients with point mutations upstream exon 15, duodenal phenotype seemed reproducible inside families, there could be severe and early adenomatosis in patients with attenuated colonic polyposis and severity of duodenal involvement did not appear to be correlated with gastric phenotype.

Title: Duodenal disease in 579 individuals with MUTYH-associated polyposis: updated findings from an international prospective observational study

Author: Truscott, Becky

Author Institution: 1 Institute of Medical Genetics, Division of Cancer and Genetics, Cardiff University, School of Medicine, Cardiff, UK; 2 Department of Gastroenterology, Royal Glamorgan Hospital, Llantrisant, UK; 3 GI Department, Complejo Hospitalario de Navarra, Pamplona, Spain; 4 Hereditary Cancer Unit, Cancer Division, Karolinska University Hospital, Stockholm, Sweden; 5 Institution of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; 6 Hereditary Cancer Program, Catalan Institute of Oncology, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain; 7 The Polyposis Registry, St Marks Hospital, Watford Road, Harrow, UK; 8 Department of Surgery and Cancer, Faculty of Medicine, Imperial College, London, UK; 9 Department of Genetics, Curie Institute, Paris, France; 10 Amsterdam UMC location University of Amsterdam, Department of Gastroenterology and Hepatology, Amsterdam, The Netherlands; 11 Division of Population Medicine, Cardiff University School of Medicine, Cardiff, UK; 12 Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands; 13 Institute for Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland; 14 Centrum Medische Genetica UZ, Brussels, Belgium; 15 Leiden University Medical Center (LUMC), Department of Clinical Genetics, Leiden, The Netherlands; 16 Section of Gastroenterology, Hepatology and Nutrition, University of Chicago, Chicago, USA; 17 Department of Gastroenterolgy, Hepatology and Nutrition, Division of Internal Medicine, UT MD Anderson Cancer Center, Houston, Texas; 18 Clinical Cancer Genetics Program, UT MD Anderson Cancer Center, Houston, Texas; 19 Department of Digestive Surgery, Hôpital Saint-Antoine AP-HP, Sorbonne Université, Paris, France; 20 Unit of Hereditary Digestive Tract Tumors, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 21 Digestive Department, Edouard Herriot Hospital, Lyon, France; 22 Department of Clinical Cancer Prevention, UT MD Anderson Cancer Center, Houston, Texas, USA; and 23 Institute of Life Science 1, Swansea University Medical School , Swansea, UK. 24 Department of Gastroenterology and Hepatology, Netherlands Cancer Institute, Amsterdam, The Netherlands, 25 Division of Gastroenterology and Hepatology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.

Co-Authors: The Collaborative Group on Duodenal Polyposis in MAP: Becky Truscott,1 Joanna J. Hurley,1,2 Arthur S Aelvoet,10 Angel Alonso Sanchez,3 M. Rosario Aznárez,3 Ann-Sofie Backman,4,5 Jan Bjork,4,5 Gabriel Capella,6 Susan K. Clark,7,8 Chrystelle Colas,9 Evelien Dekker,10 Sunil Dolwani,11 Christine Drogan,16 Zeinab Ghorbanoghli,12 Mark Gonn,4,5 S. Gonzalez Romero,6 Karl Heinimann,13 Frederik J. Hes,14,15 Hala Jundi,1 Bryson Katona,25 Kalaikshiga Kengadaran,7,8 Sonia S. Kupfer,16 Andrew R. Latchford,7,8 Helena Leon Brito,3 Patrick M. Lynch,17 Derek Mann,25 Julie Metras,19 Elena Meuser,1 Maureen E. Mork,18 Matthew Mort,1 M. Navarro Garcia,6 Maartje Nielsen,15 Yann Parc,19 Laura Reyes-Uribe,22 Maria T. Ricci,20 Jean-Christophe Saurin,21 Karin van der Tuin,15 Monique E. van Leerdam,12,24 Hans Vasen,12 Eduardo Vilar,18,22 Olivier Vinet,21 Marco Vitellaro,20 Sarah-Jane Walton,7,8 Hannah D. West,1, Julian R. Sampson*1 and Laura E. Thomas*,23.
*These authors contributed equally

Abstract text:

Introduction: The characteristics and progression of duodenal disease in MAP are poorly understood.

Methods: Our prospective study collates standardised demographic and genotype information and details of endoscopic surveillance findings from collaborating centres to address knowledge gaps and inform future upper gastrointestinal surveillance recommendations.

Results: In this 2022 update, data relating to 579 patients with genetically confirmed MAP who had undergone one or more upper GI endoscopies are presented. 81/579 MAP patients had one or more duodenal adenomas at index endoscopy (14%) at a median age of 54 years (range; 22-81): this was Spigelman stage I in 66.7%, stage II in 19.8%, stage III in 12.3% and stage IV in 1.2% of patients. 357 patients had follow-up endoscopies providing 2986 follow up years (1523 additional years since our previous report). Of the patients who had no adenomas at initial endoscopy, 26% (76/295), developed adenomas during follow up (median follow up 11.3 years, range 0.7 to 29.2). The cumulative incidence of polyposis was 27.2% by the age of 80.
Among patients with no adenomas at initial endoscopy, E480* homozygotes were at higher risk of subsequently developing adenomas than G396D homozygotes (P=0.01) or Y179C/G396D compound heterozygotes (P=0.03), despite similar follow up. Limited prospective data on Y179C homozygotes, who were more likely to have adenomas at initial endoscopy than patients with other frequently reported genotypes, precluded longitudinal statistical analysis.
Twenty-eight adenomas had high grade dysplasia, and of these 42% (n=12) were <10mm in size. Spigelman stage IV disease was uncommon (n=9, 1.6%, at a median age of 54 years) and six patients (1%) developed duodenal cancer.

Conclusions: Our results contribute to a better understanding of duodenal disease and its progression in MAP and suggest that current guidelines for surveillance and management, that were devised for FAP, should be revisited for MAP.

Title:	Small bowel cancer in patients with Familial Adenomatous Polyposis – report of two clinical cases and review of literature.
Author:	Colletti, Gaia
Author Institution:	1 Center for Hereditary Tumours, Evangelisches Bethesda Krankenhaus, Heerstraße 219, 47053 Duisburg, Germany 2 General Surgery Residency Program, University of Milan, Via Festa del Perdono 7, 20122 Milan, Italy
Co-Authors:	Gloria Zaffaroni1,2, Gabriela Möslein1

Abstract text:

Background: A 46-year-old and 67-year-old female patient with Familial Adenomatous Polyposis (FAP) adhering to regular follow-up were admitted to our surgical department because of sudden abdominal pain. Diagnostic assessment revealed jejunal cancer with liver metastases. The clinical condition deteriorated rapidly, being lethal in both within 3 months of the diagnosis. Regular small bowel examinations do not form part of our screening recommendation for FAP. We performed a review of literature for small bowel cancer in FAP investigating incidence and screening recommendations.

Methods: Descriptive case report and review of literature (articles indexed in Pubmed).

Results: Only 18 cases of jejunal and 2 cases of ileal cancer have been described in literature and were predominantly characterized by poor prognosis. The prevalence of jejunal and ileal adenomas is reported to be 30-75% in FAP patients, while the real incidence of cancer is unknown, but seems to be rare (<2%). A predictor for detecting adenomas in the non-duodenal small bowel could be the severity of duodenal polyposis, especially in patients >50. Therefore, videocapsule endoscopy (VCE) could be recommended as an additional routine diagnostic tool, whereas double-balloon endoscopy could have a role in prophylactic resection of polyps > 10 mm and in symptomatic patients. VCE has higher diagnostic yield for small polyps than CT-Enterography and Magnetic Resonance Enterography, which are indicated assessment of big polyps and tumours. When surgery for advanced duodenal polyposis is recommended, a preoperative study with VCE could guide the extent of resection.

Conclusion: Limited evidence on cancer in the small bowel is available, however it may have an unfavourable prognosis. To improve its detection and the chances of preventive management, VCE may be suggested for older patients with advanced Spigelman stage. Prospective collaborative documentation of non-duodenal cancers in FAP must be discussed.

Title:	Ileoanal pouch cancers in Ulcerative Colitis and Familial Adenomatous Polyposis: A systematic review and meta-analysis
Author:	Pellino, Gianluca
Author Institution:	1. Department of Medicine, Northwick Park Hospital, London North West University Healthcare NHS Trust, Watford Road, Harrow, HA1 3UJ, United Kingdom 2. Department of Surgical Science, University Tor Vergata, Viale Oxford 81, 00133 Rome, Italy 3. Departmen
Co-Authors:	Danujan Sriranganathan 1, Danilo Vinci 2, Gianluca Pellino 3,4, Jonathan P Segal 5,6

Abstract text:

Introduction: Restorative proctocolectomy results in the formation of a pouch that adapts to a more colonic phenotype. The incidence of cancer of the pouch is thought to be low with most societal guidelines differing on their recommendations for surveillance. We conducted a systematic review with meta-analysis to report the incidence of cancer in all pouch patients.

Methods: The Embase, Embase classic and PubMed databases were searched between June 1979– June 2021. A random effects model was performed to find the pooled incidence of pouch cancer. In addition, we also looked for risk factors for pouch cancers.

Results: Forty-six studies were included. In 19,964 patients with Ulcerative Colitis (UC) the pooled incidence of pouch cancer was 0.0030 (95% CI: 0.0016 -0.0055). In 3741 patients with Familial Adenomatous Polyposis (FAP) the pooled incidence of pouch cancer was 0.01 (95% CI: 0.01 – 0.02) (Figure 1). In UC most pouch cancers were found to occur in the pouch body (0.59 (95% CI: 0.29-0.84)). With the incidence data for both UC and FAP pooled; mixed effects regression did not suggest an association between the year of publication of the study and the size of effect (14.9 95% CI: 158.3-188.2) (P =0.86) (Figure 2).

Conclusions: The findings suggest that the pooled incidence of pouch cancer in UC is similar to that which was previously published, and this is the first meta-analysis to report a pooled incidence for pouch cancer in FAP.

Title: Metachronous CRC after surgery in Lynch Syndrome

Author: Seppälä, Toni

Author Institution: Helsinki University Hospital, University of Heidelberg, Oslo Radium Hospital, Cardiff University, Oslo Radium Hospital,

Co-Authors: Kalle Ojala, Saskia Haupt, Mev Dominguez-Valentin, Julian Sampson, Pål Moller, on behalf of Prospective Lynch Syndrome Database (PLSD) contributors

Abstract text:

Background: Current Lynch syndrome (LS) guidelines for extended surgery are based on information that the risk of subsequent colorectal cancer (CRC) is about similar to the risk of first CRC due to stochastic probability.

Method: Prospective Lynch Syndrome Database (PLSD) version 5 was analyzed to study the risk of metachronous CRC risk at prospective observation after previously treated CRC. The cumulative incidence was stratified by the extent of previously performed bowel resection.

Results: In path_MLH1, path_MSH2 and path_MSH6, respectively, 1310, 1216 and 532 had previous bowel surgery for CRC before prospective observation, whereas 1948, 2061 and 1207 did not. The cumulative incidence of subsequent CRC was increased for path_MSH6 carriers with earlier CRC, whereas the risk for metachronous CRC was similar to first CRC in path_MLH1 and path_MSH2 carriers.
The cumulative incidence of metachronous CRC at 75 years was 57% after segmental resection (n=697) and 21% after subtotal colectomy (n=180). Path_MLH1 and path_MSH2 carriers were more likely to have undergone subtotal colectomy.

Conclusions: Despite previous bowel resection, path_MMR carriers with a prior CRC operated with standard oncological resections are at increased prospectively observed risk of metachronous CRC compared to those with no prior cancer, which may be attributed to modifiers increasing their risk. This increased risk applies also to path_MSH6 carriers, which may favor extended surgery for management of their first CRC. Subtotal colectomy with ileosigmoid or ileorectal anastomosis for LS-associated CRC was now shown in a prospective study design to substantially decrease the risk of metachronous CRC compared to standard surgery.

Title: Functional Outcome Differences between Males and Females Who have Undergone Reconstructive Surgery with Ileorectal Anastomoses (IRA) or Ileal Pouch-Anal Anastomoses (IPAA) due to Familial Adenomatosis Polyposis - A Prospective Cohort Study

Author: Mira, Daniel

Author Institution: Department of Medicine, Karolinska Institute, Stockholm, Sweden

Co-Authors: Daniel Mira, Jan Björk, Johan Reutfors, Rolf Hultcrantz, Ann Sofie Backman

Abstract text:

Background and aim: Familial adenomatous polyposis (FAP), an inherited polyposis syndrome causes ~1% of colorectal cancers (CRC). Patients develop 100-100000 polyps which may develop into CRC. Colectomy is inevitable. Pan-proctocolectomy with incontinent ileostomy was the recommended prophylactic surgery for decades. Ileorectal Anastomoses (IRA) was introduced in 1950s; However, IRA patients remained at risk of CRC. Ileal Pouch-Anal Anastomoses (IPAA) was introduced 1984 in Sweden as an alternative. Functional outcome was better after IRA vs IPAA in follow-up studies. Outcome differences have not been studied between males and females. Long-term studies of functional outcome, and CRC risk after IRA or IPAA are needed. The aim of the study is to compare postoperative functional outcome up to 45 years after IRA or IPAA and identify sex differences.

Method: Structured protocols between 2001-2021 were used to evaluate anal function at Hereditary Gastrointestinal unit at Karolinska university hospital.

Results: 71 patients had at least one protocol. Females (n=44) were on average 2 years older than males (21.5 vs 23.5) at first surgery. Higher fraction of females with IPAA had daily bowel movements (61.9% female-IPAA, 40% male-IPAA, 13.6% female-IRA), nighttime bowel movements (76.2%, 46.7%, 40.9%), nighttime incontinence (40%, 20%, 0%), and daytime incontinence (21.1%, 0%, 0%) compared to IPAA males and IRA females. Six females had secondary surgery (27%) and one male (8%) post-IRA. Median duration to conversion, 26y (4-41y) for females and 34y for the male.

Conclusions: IPAA females had worse functional outcome compared to IPAA males and IRA females. Females were overrepresented in incidence of secondary surgery after IRA.

Title:	Real-time use of artificial intelligence (CADEYE) in colorectal cancer surveillance of patients with Lynch syndrome – a randomized controlled pilot trial (CADLY)
Author:	Hüneburg, Robert
Author Institution:	1. University Hospital Bonn, National Center for Hereditary Tumor Syndromes, Bonn, Germany. 2. University Hospital Bonn, Department of Internal Medicine I, Bonn, Germany. 3. University of Leipzig, Institute for Medical Informatics, Statistics and Epidemiology, Leipzig, Germany. 4. University of Bonn, Institute of Human Genetics, Bonn, Germany. 5. University Hospital Bonn, Institute of Pathology, Bonn, Germany.
Co-Authors:	Hüneburg, Robert1, 2; Bucksch, Karolin3; Schmeißer, Friederike1, 2; Heling, Dominik1, 2; Marwitz, Tim1, 2; Aretz, Stefan1, 4; Kaczmarek, Dominik J.1, 2; Kristiansen, Glen1, 5; Hommerding, Oliver1, 5; Strassburg, Christian P.1, 2; Engel, Christoph3; Nattermann, Jacob1, 2

Abstract text:

Background and study arms: Lynch syndrome (LS), an autosomal dominant disorder caused by pathogenic germline variants in DNA mismatch repair (MMR) genes, represents the most common hereditary colorectal cancer (CRC) syndrome. LS patients are at high risk of CRC despite regular endoscopic surveillance. The present study investigates Artificial intelligence (AI)-assisted colonoscopy (CAD-EYE; Fujifilm, Japan) in comparison to HD white-light endoscopy (HD-WLE) for the first time.

Patients and methods: Patients ≥ 18 years, with pathogenic germline variant (MLH1, MHS2, MSH6), and at least one previous colonoscopy (interval 10-36 months) were eligible. Patients were stratified by previous CRC and affected MMR gene with a 1:1 allocation ratio (AI-assisted vs. HD-WLE).

Results: Between Dec-2021 and Dec-2022, 101 patients were randomised and 96 patients analysed (5 excluded due to insufficient bowel preparation). In the HD-WLE arm, adenomas were detected in 12/46 patients compared to 18/50 in the AI arm (26.1% [95% CI 14.3-41.1] vs. 36.0% [22.9-50.8]; p=0.379). The increased ADR was due to identification of flat adenomas (Paris classification 0-IIb and 0-IIc). By HD-WLE, 4/20 flat adenomas compared to 17/30 in the AI arm (p=0.018) were detected, the number of examinations with detection of flat adenomas was higher in the AI arm (3/46 [6.5%] vs. 10/50 [20%]; p=0.07). The median withdrawal time was not statistically different between HD-WLE and AI (14 vs. 15 min; p=0.170).

Conclusion: We here present first data suggesting that real-time AI-assisted colonoscopy is a promising approach to optimize endoscopic surveillance, in particular to improve the detection of flat adenomas.

Trial registration number: DRKS00023157

Title:	Clinicopathological Features of Deficient Mismatch Repair (dMMR) Protein Expression Patterns in Colorectal Cancer in a Spanish Cohort.
Author:	Suárez Sánchez, Aida

Author Institution:	(1) Division of General Surgery, Department of Colorectal Surgery, Hospital Universitario Central de Asturias (HUCA), Oviedo, Asturias, Spain. (2) Department of Medical Oncology, Hospital Universitario Central de Asturias (HUCA), Oviedo, Asturias, Spain.
Co-Authors:	Aida Suárez Sánchez (1), Tamara Díaz Vico (1), Pilar Blay Albors (2), Milagros Balbín Felechosa (2), Luka Mihic Góngora (2), María Fernández Hevia (1), José E. Granero Trancón (1) , Luis J. García Flórez (1)

Abstract text:

Introduction: Around 5% of colorectal cancers (CRC) are due to mutations within DNA MMR genes, producing microsatellite instability (MSI), which leads to Lynch syndrome (LS). This study aimed to provide the clinicopathological features of dMMR CRCs in an Asturian cohort.

Method: We conducted a retrospective review of patients diagnosed with LS who have developed CRC from January 1, 2017 to December 31, 2020 in our genetic counseling department, a reference center in the region of Asturias. Diagnosed dMMR CRC patients were classified according to their mutation (MLH1, MSH2, MSH6, PSM2) for the analyses and compared among groups.

Results: We enrolled 23 (34.3%) dMMR CRCs patients out of 65 LS individuals. 26.1% of the tumors in the Asturian LS cohort were diagnosed under age 40. None of the patients were identified preoperatively; however, 12 (52.2%) were referred to genetic counseling following surgery. Eight (34.8%) patients presented with additional second and third tumors, such as colon (17.4%, of which one was synchronous), ovarian (8.7%), gastric (4.3%), urological (4.3%), and central nervous system (4.3%) tumors. MSH2 (34.8%) and MSH6 (26.1%) were the most repeated patterns, presenting more frequently, in the case of MSH2, in the ascending colon (50.0%), and usually showing typical distal location (sigma and rectum), in the case of MSH6 (83.3%). MLH1 and MSH2 CRCs were usually diagnosed at younger ages (p = 0.005), and significant positive association was also found between MLH1 and MSH2 with advanced stages of CRC (p < 0.001) and perineural invasion (p < 0.001).

Conclusion: The identification of dMMR genes provides opportunities for the detection of cancer at an early stage, as well as the introduction of proper, more effective treatment and surveillance for the patients and relatives, which will result in increased patient survival and reduced costs of medical care.

Title: Constitutional MLH1 methylation, frequency and mode of identification

Author: Dardenne, Antoine

Author Institution: APHP, Paris, France

Co-Authors: A Choquet, G Martin,P Cervera, S Magali,J Metras, Y Parc

Abstract text:

Introduction: Most of MSI colorectal cancers (CRC) are explained by epigenetic phenomena: acquired MLH1 promoter hypermethylation. However, constitutional hypermethylation of MLH1 has been described. The aims of our study were to evaluate the rate of germline MLH1 epimutation and determine variables which could help us to identify them.
Patients and Methods:All patients operated in our institution demonstrating a loss of expression of MLH1 in their CRC between 2011 and 2017 were included. Patients were referred for germline hypermethylation testing if patients were young or with multiples cancers. Comparison of patient variable with germline MLH1 epimutation to germline mutation and somatic hypermethylation was performed.

Results: 121 patients were included, 20 were excluded. 4 patients had constitutional MLH1 promoter hypermethylation,23 germline MLH1 mutation and 74 somatic MLH1 promoter hypermethylation. Patients with constitutional hypermethylation were younger as those with germline mutation (47,50, and 72 years, respectively; $p<0.0001$) and had sex ratio equivalent (50%, 78% and 23%, respectively; $p<0.0001$). Family history was more likely to be poor as somatic hypermethylation patient. Patients with somatic hypermethylation had more frequently right sided colon cancer (86%, $p=0.005$) than the other groups. Somatic genetic alterations were also different, BRAF mutation being inexistant in the group of patients with constitutional methylation and very few somatic alterations being observed in this group ($p<0.0001$).

Conclusion: Constitutional methylation of MLH1 is a rare event but represent 4% of colorectal cancer with a loss of expression of MLH1.Young patients with CRC demonstrating hypermethylation of MLH1 should be referred to oncogenetician for constitutional search, especially if the cancer is not right sided and the tumor is not demonstrating somatic alteration of BRAF and/or KRAS.

Title:	Genome-wide methylome of Lynch syndrome and Familial adenomatous polyposis-associated colorectal tumors
Author:	Mäki-Nevala, Satu
Author Institution:	1 University of Helsinki, Helsinki, Finland; 2 Institute for Molecular Medicine Finland, Helsinki, Finland; 3 Helsinki University Hospital, Helsinki, Finland; 4 University of Jyväskylä, Jyväskylä, Finland; 5 Central Finland Central Hospital, Jyväskylä, Fi
Co-Authors:	Satu Mäki-Nevala1 (presenting author), Päivi Lahermo2, Toni Seppälä3, Laura Renkonen-Sinisalo3, Anna Lepistö3, Jukka-Pekka Mecklin4,5, Päivi Peltomäki1

Abstract text:

Introduction: Lynch syndrome (LS) and Familial adenomatous polyposis (FAP) are both hereditary cancer predisposition syndromes characterized with early-onset colorectal cancer. LS is caused by germline mutations in DNA mismatch repair genes (MLH1, MSH2, MSH6 and PMS2) and FAP by inherited mutation in APC gene. FAP patients tend to have abundant polyps in the colon since the early adulthood, whereas LS patients develop adenomas more occasionally. Our aim is to study genome-wide DNA methylation changes in precancerous tumors, i.e. adenomas, and carcinomas compared to paired normal colonic mucosa samples. We aim to characterize the methylomes associated with MMR haploinsufficiency (LS) vs. constitutionally inactive APC (FAP) -driven tumorigenesis.

Method: Our study cohort is consisted of 100 LS patients and 30 FAP patients who went through the colonic mucosa sampling during the colonoscopy screenings. Sampling was done in three rounds, i.e. three sample sets for each patients were collected at different time points, whenever possible. Normal colonic mucosa was sampled at least from one colonic location (mostly three locations from LS patients), and polyps and carcinoma samples were collected whenever there was enough material after diagnosis purposes. All samples were flash frozen in liquid nitrogen at time of the collection. For this study, we analyzed 28 adenomas and 5 carcinomas with paired normal mucosa of LS samples. Of FAP patients, all 30 paired polyp and normal colonic mucosa samples from the first sampling round were selected.

Results and Conclusion: Genome-wide methylation was studied with Illumina Infinium MethylationEPIC array. Illumina GenomeStudio software and the SeSaMe package in R were used for data analysis. The investigation is ongoing, and initial results will be available for presentation and discussion.

Title:	Germline MBD4 mutations in cancer predisposition
Author:	Valle, Laura
Author Institution:	1. Hereditary Cancer Program, Catalan Institute of Oncology; Oncobell Program, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain. 2. Cancer Immunotherapy (CIT) Group-iPROCURE, Catalan Institute of Oncology; Oncobell Program, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain. 3. Medical Oncology Department, Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain. 4. Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain. 5. Catalan Insitute of Oncology, IDIBGi, Girona, Spain.
Co-Authors:	Mariona Terradas (1), Sandra García-Mulero (2), Noemi Gonzalez-Abuin (1), Gemma Aiza (1), Josep M. Piulats (2,3,4), Joan Brunet (1,4,5), Gabriel Capellá (1,4), Laura Valle (1,4).

Abstract text:

Introduction: Biallelic loss-of-function germline variants in the base excision repair (BER) gene MBD4 cause a cancer syndrome characterized by increased risk to adenomatous polyposis, colorectal cancer (CRC), acute myeloid leukemia (AML) and uveal melanoma (UVM). To expand the knowledge on this syndrome, we performed studied MBD4 in individuals affected with tumors that fit the syndrome's phenotypic spectrum.

Methods: Germline predicted damaging (population MAF<0.1%, REVEL score >0.5) variants in MBD4 were interrogated in individuals diagnosed with CRC (n=543), adenomatous polyposis (n=192), UVM (n=88), or with personal/familial history of CRC or polyposis and hematologic malignancies (n=10). Sequencing of MBD4 coding regions was performed polyposis patients and patients with personal/familial history of CRC/polyposis and hematologic malignancies. For CRC and UVM patients, MBD4 information was obtained from TCGA (exome sequencing data). Somatic 2nd hit information, including somatic mutations, copy number alterations and promoter hypermethylation, was obtained from TCGA; tumor mutational burden (TMB) and signatures were calculated with MuSiCa and Signal, respectively.

Results: A homozygous missense variant in MBD4, c.181T>C; p.C61R, was identified in a CRC patient. Eight patients were heterozygotes for MBD4 predicted pathogenic variants. For all nine patients, tumor molecular features were analyzed. High TMB and the MBD4-associated mutational signature SBS96 were detected in the CRC developed by the homozygous patient, and in the UVM of a patient with a germline canonical splice-site variant and somatic MBD4 loss (2nd hit).

Conclusions: Biallelic germline pathogenic variants in MBD4 are rare among CRC, polyposis and UVM patients. Monoallelic pathogenic MBD4 variants may also predispose to cancer when a 2nd hit occurs in the target organ. The presence of high TMB and SBS96 may be used for MBD4 variant interpretation and to know the MBD4-related etiology.

Title: HLA-specific immunogenicity of Lynch Syndrome associated frameshift peptide neoantigens – towards next-generation cancer vaccines

Author: Hernandez Sanchez, Alejandro

Author Institution: Clinical Cooperation Unit Applied Tumor Biology, DKFZ, Heidelberg, Germany
Department of Applied Tumor Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany

Co-Authors: Hernandez-Sanchez Alejandro, Litau German, Urban Katharina, Gebert Johannes, Hämmerling Günter, Ahadova Aysel, von Knebel Doeberitz Magnus, Kloor Matthias

Abstract text:

Introduction: Lynch Syndrome (LS) is caused by inactivation of the DNA mismatch repair system. Insertion/deletion mutations that accumulate in coding microsatellites (cMS) result in a shift of the translational reading frame and thus in the generation of frameshift peptide (FSP) neoantigens. Manifest tumors share a similar cMS mutation profile and therefore potentially immunogenic FSPs. As such, LS represents a unique model for the evaluation of cancer-preventive vaccines. Here, were assess the immunological properties of candidate FSPs as potential vaccine targets.

Method: Splenocytes from FSP-vaccinated HLA-A2 transgenic mice were used to analyze peptide-specific T cell responses. A competition-based binding assay to HLA-A2 was performed with predicted FSP and their correct processing and presentation to CD8+ T cells was assessed by epitope-specific restimulation in an IFNg ELISpot assay. Ex vivo killing assays to confirm vaccination-induced tumor cells killing by T cells are underway.

Results: FSP-specific T cells were induced after FSP-vaccination suggesting processing and presentation of immunogenic epitopes. The competition-based binding assay identified multiple HLA-A2 strong binders for 3 FSPs. Multiple epitopes within 2 FSPs were able to elicit epitope specific CD8+ T cells after in vitro re-stimulation of splenocytes, confirming correct processing and presentation.

Conclusion: Here, we have established a pipeline for the identification of relevant HLA-specific epitopes within potential neoantigens. We have identified multiple strong binder epitopes within 2 FSPs that are able to elicit epitope-specific CD8+ T cells. The killing capacity of elicited T cells against HLA-A2-specific epitopes presented on the surface of target cancer cells will be analyzed to provide a proof-of-concept. Our results highlight the potential of FSP vaccination for LS cancer prevention and advance clinical translation of the next-generation FSP-based preventive vaccines.

Title:	Molecular carcinogenesis pathway of MLH1-associated Lynch syndrome colorectal cancer unraveled: "two-in-one hit" model
Author:	Ahadova, Aysel

Author Institution:	1Department of Applied Tumor Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany
	2Cooperation Unit Applied Tumor Biology, German Cancer Research Centre (DKFZ), Heidelberg, Germany
	3Department of General Pathology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany
	4Department of Internal Medicine I, University Hospital Bonn, and National Center for Hereditary Tumor Syndromes, University Hospital Bonn, Bonn, Germany
	5Institute of Pathology, University Hospital Leipzig, Leipzig, Germany
Co-Authors:	Aysel Ahadova1,2, Volker Endris3, Jan-Niklas Wittemann1,2, Leonie Gerling1,2, Johannes Witt1,2, Robert Hüneburg4, Jacob Nattermann4, Magnus von Knebel Doeberitz1,2, Matthias Kloor1,2 and Hendrik Bläker5

Abstract text:

Introduction: Clinical and molecular manifestation of colorectal cancer (CRC) in Lynch syndrome (LS) varies depending on the affected MMR gene. Whereas MSH2 carriers present with a high risk of colorectal adenoma, MLH1 carriers have low adenoma risk. On the molecular level, MSH2-LS CRC commonly show somatic APC mutations, whereas MLH1-LS CRC display somatic CTNNB1 mutations. Except from MLH1-LS, CTNNB1 mutations are rare in CRC, most likely because biallelic CTNNB1 mutations seem to be required for causing an oncogenic effect in the colorectum. The mechanistic reason behind the specific association of CTNNB1 somatic mutations with MLH1 germline predisposition has been unknown. Here we describe a new pathway of LS CRC formation specific for MLH1-LS carriers.

Method: We analyzed MLH1-LS CRC for CTNNB1 mutation status and Loss of Heterozygosity (LOH) by Sanger sequencing. Using single nucleotide polymorphisms (SNP) within the chromosomal segment between MLH1 and CTNNB1, LOH was determined in CTNNB1-mutant MLH1 LS cancers. Whole Exome Sequencing (WES) was performed to validate LOH and analyze copy number alterations.

Results: CTNNB1 mutations were found in 47% (17/36) of MLH1-LS CRCs. In 15 out of 16 (93.75%; 95% CI: 69.69-99.99%) analyzable samples, evidence for LOH spanning the entire region between MLH1 and CTNNB1 was detected. WES confirmed for all analyzed samples copy number-neutral LOH (cnLOH) events of >49 Mbp in the chromosomal region 3pter–p21 including MLH1 and CTNNB1 genes. This indicates that one single cnLOH event causes two simultaneous hits: loss of MLH1 and CTNNB1 wild type alleles, resulting in MLH1 loss-of-function and beta-catenin gain-of-function at the same time.

Conclusion: CTNNB1 being a neighbor of MLH1 on chromosome 3 reduces the number of somatic events required for CRC formation in MLH1 compared to MSH2 carriers. The "two-in-one hit" model provides a plausible explanation for the clinico-pathological differences between MLH1 and MSH2 carriers.

Title:	APC mosaicism is a relevant explanation in (mild) polyposis phenotypes
Author:	Nielsen, Maartje
Author Institution:	1 Department of Pathology, Leiden University Medical Centre, Leiden, the Netherlands
	2 Department of Clinical Genetics, Leiden University Medical Centre, Leiden, the Netherlands
	3 Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, the Netherlands
	4 Department of Clinical Genetics, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
	3 Department of Pathology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
Co-Authors:	D. Terlouw1,2, M. Suerink2, A.M.J. Langers3, M.E van Leerdam3, A. Wagner4, F.J.H Hes2, F.H. Groenendijk5, D. van Egmond1, D. Ruano1, C.M. Tops2, Tom van Wezel1, H. Morreau1, Maartje Nielsen2

Abstract text:

Introduction: Mosaic APC mutations have been identified as a common cause (>25%) for unexplained colonic polyposis in patients with >20 adenomas. Nevertheless, this remains an undervalued and understudied genetic cause in diagnostics. The frequency of APC mosaicism in milder phenotypes, such as <10 adenomas or development of adenomas above the age of 70, is still unknown.

Method: We analysed APC in multiple lesions of polyposis patients using target Next Generation Sequencing.

Results: The mosaicism detection rate was 2% (1/47) in patients with <10 adenomas, 3% (4/147) in those with 10-20 adenomas and 18% (33/188) in patients with >20 adenomas. Furthermore, mosaicism was detected in 2% (1/51) of patients aged >70. Besides 'true' mosaicism cases, 21% (81/388) showed a so called hybrid mosaicism, where multiple, but not all lesions share an identical variant. Moreover, while testing for APC mosaicism we identified extraordinary mosaic cases. For instance, we found a family with two mosaic patients and a patient with a mosaic variant in 15-17% in semen DNA while this variant was detected in 6% in leukocyte DNA.

Conclusions: Our findings suggest again show a pivotal role of APC mosaicism in unexplained polyposis patients. Looking at our detection rates, we recommend APC mosaicism testing for at least all patients with >20 adenomas below the age of 70. Also, analyses of APC mosaicism has revealed interesting cases which might be of interest for other genetic mosaicisms or point to so far unknown genetic causes.

Title: Cancer mortality by organ, gene and gender in carriers of pathogenic mismatch repair gene variants receiving surveillance for early diagnosis and treatment: A report from the Prospec-tive Lynch Syndrome Database

Author: Dominguez Valentin, Mev

Author Institution: 1Department of Tumor Biology, Institute of Cancer Research, The Norwegian Radium Hospital, 0379 Oslo, Norway; 2Engineering Mathematics and Computing Lab (EMCL), Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University, Heidelberg, Germany; 3Data Mining and Uncertainty Quantification (DMQ), Heidelberg Institute for Theoretical Studies (HITS), Heidelberg, Germany; 4Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Center, Tampere University Hospital; 5Department of Gastrointestinal Surgery, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland; 6Applied Tumor Genomics, Research Program Unit, University of Helsinki, Helsinki, Finland; 7Institute of Medical Genetics, Division of Cancer and Genetics, Cardiff University School of Medicine, Heath Park, Cardiff CF14 4XN, UK; 8Department of Clinical Genetics, Aalborg University Hospital, 9000 Aalborg, Denmark; 9Department of Biomedicine, Aarhus University, DK-8000 Aarhus, Denmark; 10Department of Surgical Gastroenterology, Aalborg University Hospital, Aalborg University, 9100 Aalborg, Denmark; 11Department of Clinical Medicine, Aalborg University Hospital, Aalborg University, 9100 Aalborg, Denmark; 12Melbourne School of Population and Global Health, Centre for Epidemiology and Biostatistics, The University of Melbourne, Parkville, 3010 Victoria, Australia; 13Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, 04107 Leipzig, Germany; 14Institute of Human Genetics, National Center for Hereditary Tumor Syndromes, University of Bonn, 53127 Bonn, Germany; 15Department of Clinical Genetics, Leids Universitair Medisch Centrum, 2300RC Leiden, The Netherlands; 16Hereditary Cancer Program, Institut Català d'Oncologia-IDIBELL, L Hospitalet de Llobregat, 08908 Barcelona, Spain; 17Gastroenterology Department, Hospital Clínic de Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain; 18Manchester Centre for Genomic Medicine, Manchester University NHS Foundation Trust, Manchester M13 9WL, UK; 19Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne NE1 7RU, UK; 20Campus Innenstadt, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, 80336 Mu-nich, Germany; 21Center of Medical Genetics, 80335 Munich, Germany; 22Division of Cancer Prevention and Genetics, IEO, European Institute of Oncology, Fondazione IRCCS Instituto Nazionale dei Tumori, IRCCS, 20141 Milan, Italy; 23Department of Molecular Medicine and Surgery, Karolinska Institutet, 171 76 Stockholm, Sweden; 24Service High Risk GI Cancer Gastroenterology, Dept Rabin Medical Center, Israel; 25Colorectal Medicine and Genetics, The Royal Melbourne Hospital, Melborne, Australia; Department of Medi-cine, Melbourne University, Melborne, Australia; 26 Department of Medicine, University of Melbourne, Melbourne, Australia; 27Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; 28Laboratory of Molecular Gastroenterology, IRCCS Humanitas Research Hospital, and Dept. of Medicine and Surgery, University of Parma, Parma, Italy; 29Hospital Fuerzas Armadas, Grupo Colaborativo Uruguayo, Investigación de Afecciones Oncológicas Heredi-tarias (GCU), Montevideo, Uruguay; 30Medical Genetics, Institute for Medical Genetics and Pathology, University Hospital Basel, Switzerland; 31Department of Genetics and Pathology, International Hereditary Cancer Center, ul. Unii Lubelskiej 1, 71-252 Szczecin; 32Department of Medicine and Surgery, University of Milan Bicocca, A.O. San Gerardo, Clinic of Obstetrics and Gynecology, Via Pergolesi 33, Monza (MB), Italy; 33Programa Cáncer Heredo Familiar Clinica Universidad de los Ande, Santiago, Chile; 34Department of Gastroenterology, Hadassah, Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Israel; 35Hadassah Medical Center, Israel; 36Hereditary Cancer Program (PROCANHE) Hospital Italiano de Buenos Aires, Argentina; 37 Clinical and Functional Genomics Group, A.C.Camargo Cancer Center, Sao Paulo, Brazil; 38Lynch Syndrome & Family Cancer Clinic, St Mark's Hospital, Harrow HA1 3UJ, London, United Kingdom; 39Gastrointestinal Cancer Prevention Unit, Gastroenterology Department, Rambam Health Care Campus, Haifa, Israel; 40St Vincent's University Hospital, Ireland; 41Department of Gastroenterology, Tel-Aviv Souraksy Medical Center and Sackler Faculty of Medicine, Tel-Aviv University, Israel; 42Foundation for Research in Genetics and Endocrinology, Institute of Human Genetics, FRIGE House, Ah-meda-bad, India- 380015; 43Soroka University Medical Center, Ben-Gurion University of the Negev, Beer Sheva, Southern Israel; 44University of Vermont, Larner College of Medicine, Burlington, VT 05405, USA; 45Hospital Sirio Libanes, Sao Paulo, Brazil; 46University of Tolima, Tolima, Colombia; 47Gastroenterology and Gastrointestinal Endoscopy Unit, Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, 20132 Milan, Italy; 48Surgical Pathology, Instituto Nacional de Cancerologia, Mexico City, Mexico ; 49Department of Visceral and Transplantation Surgery, University Hospital of Zurich (Switzerland) and Depart-ment of Surgery, Universitätsmedizin Mainz (Germany) 50Ospedale di Circolo ASST Settelaghi, Centro di Ricerca tumori eredo-familiari, Università dell'Insubria, Va-rese, Italy; 51Universidade Federal de Bahia, Bahia, Brazil; 52St Mark's Hospital, Department of Surgery and Cancer, Imperial College London, London, UK; 53 Fundación para el Progreso de la Medicina" y "Sanatorio Allende", Córdoba, Argentina ; 54Hospital Universitário Oswaldo Cruz, Universidade de Pernambuco, Recife, Brazil & SEQUIPE, Recife, Bra-zil55Semmelweis University. 1st Dept. of Surgery; 56Department of Medical Oncology, University Clinical Hospital of Santiago de Compostela (SERGAS); Trans-ational Medical Oncology Group (Oncomet), Health Research Institute of Santiago de Compostela (IDIS);Ge-nomes and Disease, Centre for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela (USC), 15706 Santiago de Compostela, Spain & Centro de Investigación Biomédica en Red Cáncer (CIBERONC), 28029 Madrid, Spain.; 57Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland & Department of Surgery, Central Finland Health Care District, Jyväskylä, Finland; 58Department of Education and Science, Central Finland Health Care District, jyväskylä, Finland; 59Department of Medical and Clinical Genetics, University of Helsinki, Helsinki, Finland; 60The Danish HNPCC register, Clinical Research Centre, Copenhagen University Hospital, Hvidovre, Denmark; 61Department of Urology, Aarhus University Hospital, Denmark; 62Department of Surgery and Transplantation, Rigshospitalet, Copenhagen University Hospital, Denmark; 63Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The Universi-ty of Melbourne, Parkville, Victoria, Australia; 64Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University, USA; 65Department of Health Science Research, Mayo Clinic Arizona, USA; 66Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Canada; 67University of Hawaii Cancer Center, USA; 68Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109-1024; 69Colorectal Oncogenomics Group, Department of Clinical Pathology, The University of Melbourne, Parkville, Victoria, Australia ; 70University of Melbourne Centre for Cancer Research, Victorian Comprehensive Cancer Centre, Parkville, Victoria, Australia; 71Genomic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Parkville, Victoria, Australia; 72Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, 55905, USA; 73Department of Applied Tumour Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany; and Cooperation Unit Applied Tumour Biology, German Cancer Research Center (DKFZ), Heidel-berg, Germany; 74Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany; 75Institute of Human Genetics, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany ; 76National Center for Tumor Diseases (NCT), Partner Site Dresden, Dresden, Germany: German Cancer Consor-tium (DKTK) Dresden and German Cancer Research Center (DKFZ) Heidelberg, Heidelberg, Germany; Institute for Clinical Genetics, Faculty of Medicine and University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany; Hereditary Cancer Syndrome Center Dresden, Faculty of Medicine and University Hospital Carl Gus-tav Carus, TU Dresden, Dresden, Germany. ; 77Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, Munich, Germany; Center of Medical Genetics, Munich, Germany; 78Department of Medicine, Knappschaftskrankenhaus, Ruhr-University Bochum, Bochum, Germany; 79Department of Internal Medicine, University Hospital Bonn, Bonn, Germany; 80Institute of Human Genetics, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany ; 81Institute of Pathology, Faculty of Medicine and University Hospital Cologne, Cologne, Germany ; 82Technische Universität Dresden, Dresden, Germany; 83Universitat de Barcelona & Centre de Recerca en Economia i Salut (CRES-UPF), Barcelona, Spain; 84Centre for bioinformatics, Department of Informatics, University of Oslo, Oslo, Norway; 85Centre for Cancer Cell Reprogramming (CanCell), Institute of Clinical Medicine, Faculty of Medicine, Uni-versity of Oslo, Oslo, Norway; 86Department of Surgery, Central Manchester University NHS Foundation Trust and University of Manchester, London, UK; 87Gynaecological Oncology Research Group, Manchester University NHS Foundation Trust, Manchester, UK and Division of Cancer Sciences, University of Manchester, Manchester, UK; 88Department of Women's and Children's health, Division of Obstetrics and Gynaecology, Karolinska Institutet, Karolinska University Hospital, Solna, Stockholm, Sweden; 89Head Adult Genetic Service, Raphael Recanati Genetic Institute, Rabin Medical Center-Bellinson Hospital, Petach Tikva, Israel; 90Colorectal Medicine and Genetics, The Royal Melbourne Hospital, Melbourne, Australia; Department of Med-icine, Melbourne University, Melbourne, Australia; 91Leids Universitair Medisch Centrum, Leiden, Netherlands; 92Sushrut Hospital, Mumbai, India 93Zydus Hospital, Ahmedabad, India; 94Instituto de Medicina Traslacional e Ingeniería Biomedica (IMTIB), CONICET IU, Hospital Italiano de Bue-nos Aires, Buenos Aires, Argentina.94; 95Hospital Privado Universitario de Córdoba, Córdoba, Argentina; 96Surgical Center for Hereditary Tumors, Ev. Bethesda Khs Duisburg, University Witten-Herdecke, Germany

Co-Authors: Mev Dominguez-Valentin1, Saskia Haupt2,3, Toni T. Seppälä4,5,6 , Julian R. Sampson7, Lone Sunde8,9, Inge Bernstein10,11, Mark A. Jenkins12, Christoph Engel13, Stefan Aretz14, , Maartje Nielsen15, Gabriel Capella16, Francesc Balaguer17, Dafydd Gareth Evans18, John Burn7,19, Elke Holinski-Feder20,21, Lucio Bertario22, Bernardo Bonanni22, Annika Lindblom23, Zohar Levi24, Finlay Macrae25, Ingrid Winship25,26, John-Paul Plazer25, Rolf Sijmons27, Luigi Laghi28, Adriana Della Valle29, Karl Heinimann30, Tadeusz Dębniak31, Robert Fruscio32, Francisco Lopez-Koestner33, Karin Alvarez-Valenzuela33, Lior H Katz34, Ido Laish34, Elez Vainer35, Carlos Vacca-ro36, Dirce Maria Carraro37, Kevin Monahan38, Elizabeth Half39, Aine Stakelum40, Des Winter40, Rory Kennelly40, Nathan Gluck41, Harsh Sheth42, Naim Abu-Freha43, Marc Greenblatt44, Benedi-to Mauro Rossi45, Mabel Bohorquez46, Giulia Martina Cavestro47, Leonardo S. Lino-Silva48, Karoline Horisberger49, Maria Grazia Tibiletti50, Ivana do Nascimento51, Huw Thomas52, Norma Teresa Rossi53, Leandro Apolinário da Silva54, Attila Zaránd55, Juan Ruiz-Bañobre56, Vincent Heuveline2,3, Jukka-Pekka Mecklin57, Kirsi Pylvänäinen58, Laura Renkonen-Sinisalo5,6, Anna Lepistö5,6, Päivi Peltomäki59, Christina Therkildsen60, Mia Gebauer Madsen61, Stefan Kob-belgaard Burgdorf62, John L. Hopper63, Aung Ko Win63, Robert W. Haile64, Noralane Lindor65, Steven Gallinger66, Loïc Le Marchand67, Polly A. Newcomb68, Jane Figueiredo68, Daniel D. Bu-chanan69-71, Stephen N. Thibodeau72, Magnus von Knebel Doeberitz73, Markus Loeffler74, Nils Rahner75, Evelin Schröck76, Verena Steinke-Lange77, Wolff Schmiegel78, Deepak Vangala78, Claudia Perne14, Robert Hüneburg79, Silke Redler80, Reinhard Büttner81, Jürgen Weitz82, Marta Pineda16, Nuria Duenas16, Joan Brunet Vidal16, Leticia Moreira17, Ariadna Sánchez17, Miquel Serra83, Eivind Hovig1,84, Sigve Nakken1,84,85, Kate Green18, Fiona Lalloo18, James Hill86, Emma Crosbie87, Miriam Mints88, Yael Goldberg89, Douglas Tjandra90, Sanne W. ten Broeke91, Revital Kariv41, Guy Rosner41, Suresh H Advani92, Liyana Thomas92, Pankaj Shah93, Mithun Shah93, Florencia Neffa29, Patricia Esperon29, Walter Pavicic94, Giovana Tardin Torrezan37, Thiago Bas-saneze45, Claudia Alejandra Martin95, Gabriela Moslein96, Pål Moller1

Abstract text:

Background and aim: The Prospective Lynch Syndrome Database collates information on carriers of pathogenic or likely pathogenic MMR variants (path_MMR) who are receiving medical follow-up, including colonoscopy surveillance that aims to the achieve early diagnosis and treatment of cancers. Here, using the most recently updated PLSD cohort that is larger and has wider geographical representation than previous versions, we aimed to determine mortality following cancer diagno-sis, by organ gene and gender, to update previous estimates of cancer risks by age, gene and gender and to determine median ages at cancer diagnoses.

Methods: International, multi-center prospective observational data were collected from 8,500 carriers of path_MMR variants from 25 countries, providing 71,713 years of follow up. Crude mortality by organ, gene and gender was calculated at 75 years of age for death from any cause, including synchronous or subsequent cancers in the same or any other organ. Cumulative cancer inci-dences and median ages at cancer diagnosis were calculated for carriers who had no cancer prior to inclusion.

Results: Path_MMR carriers undergoing colonoscopic surveillance, particularly path_MSH2 carriers, were more likely to die following diagnosis of non-colorectal Lynch syndrome (LS)-associated cancers than colorectal cancer, despite its high incidence during surveillance. Although relatively uncommon, pancreatic, brain and biliary tract cancers had much higher mortality and Lynch syndrome associated cancers other than colorectal cancers posed a greater threat to survival.

Conclusions: Extracolonic cancers pose the greatest threat to survival for path_MMR carriers undergoing co-lonoscopic surveillance. These cancers represent a current area of unmet need and research pri-ority in LS.

Title:	Central Amalgamation of a nationally complete registry of Lynch Syndrome carriers in England
Author:	Huntley, Catherine
Author Institution:	1) Division of Genetics and Epidemiology, The Institute of Cancer Research, Sutton, UK 2) National Disease Registration Service, NHS Digital, London, UK
Co-Authors:	C Huntley (1), RE Bethell (2), S Hardy (2), C Turnbull (1)

Abstract text:

Introduction: Lynch Syndrome (LS) is a common genetic cancer susceptibility syndrome that is under-ascertained and under-studied. Efforts to understand the cancer risk and effectiveness of preventive interventions in LS carriers have been hampered by a lack of representative study populations and longitudinal data. We aimed to compile a nationally representative LS registry to support patient care and research.

Methods: We designed a minimum dataset to capture epidemiological and genomic data on LS carriers across England. We iterated our dataset, applying feedback from clinicians, data scientists, laboratory representatives, and service commissioners to create a common data model. We wrote to all Genomic Medicine Service Alliances (GMSAs) in England requesting submission of the entirety of their positive LS analyses in the common data model by (i) searching their Laboratory Information Systems (LIMS) and (ii) supplementing this with a manual search of clinical records. These data are collected under Section 254 of the Health and Social Care Act, and amalgamated within the National Disease Registration Service (NDRS).

Results: Data submissions were received from all 18 NHS genomic laboratories. Each laboratory submitted the totality of their positive Lynch testing results for which data were accessible. Fields submitted include: date of birth, sex, date of LS diagnosis, gene affected, genetic variant, and NHS number. Data on >7000 MMR mutation carriers have been submitted.

Conclusions: This registry provides the architecture for regular prospective submissions of data and is an important platform for future research. Housing the data within NDRS affords opportunity for linkage to the National Cancer Registry and Hospital Episodes Statistics (records of risk-reducing surgeries and screening episodes) to explore outcomes and opportunities for preventive intervention in LS carriers. Once complete, this may represent the world's first near-complete national LS registry.

Title:	Germline Mismatch Repair (MMR) gene analyses from English NHS regional molecular genomics laboratories 1996-2020: development of a national resource of patient-level genomics laboratory records
Author:	Turnbull, Clare

Author Institution: 1) Division of Genetics and Epidemiology, The Institute of Cancer Research, Sutton, UK; 2) National Disease Registration Service, NHS Digital, London, UK; 3) Health Data Insight CIC, Fulbourn, Cambridge, UK; 4) Centre for Cancer, Society & Public Health, King's College London, London, UK; 5) Central and South Genomic Laboratory Hub, West Midlands Regional Genetics Laboratory, Birmingham Women's Hospital, Birmingham, UK; 6) West Midlands, Oxford and Wessex Genomic Laboratory Hub, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; 7) North East and Yorkshire Genomic Laboratory Hub, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; 8) East Midlands and East of England Genomics Laboratory, Nottingham University Hospitals NHS Trust, Nottingham, UK; 9) North Thames Genomic Laboratory Hub, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; 10) East Genomic Laboratory Hub, Cambridge University Hospitals Genomic Laboratory, Cambridge University Hospitals, Cambridge, UK; 11) Manchester Centre for Genomic Medicine and North West Genomic Laboratory Hub, Manchester University NHS Foundation Trust, Manchester, UK; 12) Bristol Genetics Laboratory, Southmead Hospital, Westbury-on-Trym, Bristol, UK; 13) Wessex Regional Genetics Laboratory, Salisbury Hospital NHS Foundation Trust, Salisbury, UK; 14) Sheffield Diagnostic Genetics Service, North East and Yorkshire Genomic Laboratory Hub, Sheffield Children's NHS Foundation Trust, Sheffield, UK; 15) Cancer Genetics Unit, The Royal Marsden NHS Foundation Trust, Sutton, London, UK; 16) North West Genomic Laboratory Hub (Liverpool), Manchester Centre for Genomic Medicine, Liverpool Women's Hospital, Liverpool, UK; 17) Yorkshire and North East Genomic Laboratory Hub, Leeds Teaching Hospitals NHS Trust, Leeds, UK; 18) The Ethox Centre and Wellcome Centre for Ethics and Humanities, Nuffield Department of Population Health, University of Oxford, Oxford, UK ; 19) Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK; 20) Human Genetics and Genomic Medicine, Faculty of Medicine, University of Southampton, Southampton, UK; 21) Department of Medical Genetics, National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK; 22) Division of Evolution & Genomic Sciences, The University of Manchester; 23) South East Genomic Laboratory Hub, Guy's and St Thomas' NHS Foundation Trust, London, UK; 24) Nuffield Department of Population Health, University of Oxford, Oxford, UK; 25) Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

Co-Authors: C. Turnbull (1), , C. Huntley (1), L. Loong (1), F. McRonald (2), F. Santaniello (2 , 3) , J. Pethick (2), B. Torr (1), S. Allen (1) , O.Tulloch (2, 3), S. Goel (2, 3), B. Shand (2, 3), T. Rahman (2, 3), M. Lüchtenborg (2, 4), A. Garrett (1), R. Barber (5), T. Bedenham (6), D. Bourn (7), K. Bradshaw (8), C. Brooks (9), J. Bruty (10), G. Burghel (11), S. Butler (5), C. Buxton (12), A. Callaway (13), J. Callaway (13), J. Drummond (10), M. Durkie (14), J. Field (8), L. Jenkins (9), T. P. McVeigh (1, 15), R. Mountford (16), R. Nyanhete (14), E. Petrides (6), R. Robinson (17), T. Scott (17), V. Stinton (16), J. Tellez (7), A. Wallace (11), L. Yarram-Smith (12), K. Sahan (18), N. Hallowell (18), D. Eccles (19, 20), P. Pharoah (21), M. Tischkowitz (21), A. C. Antoniou (21), DG. Evans (11, 22), F. Lalloo (11), G. Norbury (23), E.J.A. Morris (24), J. Burn (25) , S.A. Hardy (2)

Abstract text:

Introduction: We aimed to describe national patterns of NHS analysis of mismatch repair genes in England using individual-level data submitted to the National Disease Registration Service (NDRS) by the NHS regional molecular genetics laboratories.

Method: Laboratories submitted individual level patient data to NDRS against a prescribed data model, including (i) patient identifiers (ii) test episode data (iii) per-gene results and (iv) detected sequence variants. Individualised per-laboratory algorithms were designed and applied in NDRS to extract and map the data to the common data model. Laboratory-level MMR activity audit data from the Clinical Molecular Genetics Society/Association of Clinical Genomic Science was used to assess early years' missing data.

Results: Individual-level data from patients undergoing NHS MMR germline genetic testing were submitted from all 13 English laboratories performing MMR analyses, comprising in total 16,722 patients (9,649 full-gene, 7,073 targeted), with the earliest submission from 2000. The NDRS dataset is estimated to comprise >60% of NHS MMR analyses performed since inception of NHS MMR analysis, with complete national data for full-gene analyses for 2016 onwards. 2,724/9,649 full-gene tests had an abnormal result, approximately 70% of which were (likely) pathogenic. Data linkage to the National Cancer Registry demonstrated the majority of full-gene analyses were performed in patients with colorectal cancer.

Conclusion: The NDRS MMR dataset is a unique national pan-laboratory amalgamation of individual-level clinical and genomic patient data with pseudonymised identifiers enabling linkage to other national datasets. This growing resource will enable longitudinal research and can form the basis of a live national genomic disease registry.

Title:	Implementation of population-wide effective CRC screening for Lynch syndrome using the MSI-Plus Assay
Author:	Herrero Belmonte, Patricia
Author Institution:	Newcastle Health Innovation Partners, Newcastle upon Tyne, UK
Co-Authors:	Patricia Herrero, Richard Gallon, Lizzie Sollars, Gillian Borthwick, Michael Jackson, Mauro Santibanez Koref, Peh Sun Loo, John Burn, Ciaron McAnulty

Abstract text:

Introduction: In 2017, the UK National Institute for Clinical Excellence (NICE) made MMR testing colorectal cancers (CRCs) mandatory to help identify Lynch Syndrome. Most LS cases continue to be missed.

Methods: The MSI-Plus assay combines highly sensitive MSI markers with BRAFV600E plus driver Ras mutations in a single assay amenable to next gen sequencing and a machine-generated report. Using molecular inversion probes, the assay was introduced into routine practice in the Northern region of England, covering a population of 3 million people, in July '21. All hospitals were asked to send 3 curls from biopsy blocks.

Results: 2172 were tested, rising to over 200 samples /month when the service officially replaced histochemistry for screening, equivalent to all CRCs in this population.

An independent survey revealed positive professional responses but noted challenges with the median 9 day turnaround. Variable quality fixation meant that 176 cases did not generate the minimum 5ng/ml of DNA needing a salvage pathway used traditional fragment length analysis. The improved assay (launching August) uses more sensitive markers and multiplex PCR design needing only 1 ng/ml DNA. The single technologist will perform 3 MiSeq runs/week. Software allows direct reporting facilitating up to 400 results per month/staff member in <7 days. Further automation and adaptation to bigger platforms is underway.

A total of 351(16.2%) cases were microsatellite unstable. The new assay does not have an "MSI Low" category. Of these, 149 were BRAF wild type. The proportion of these which completed the pathway to a germline test will be reported.

The assay also includes a panel of KRas/NRas driver mutations of relevance to chemotherapy. A total of 718 (33%) had one or more driver mutations.

Conclusion: The number reaching the stage of being eligible for germline testing in our region (pop. 3m) is now greater than those referred across England (pop. 60 million) in 2019.

Title:	The English National Lynch syndrome transformation project: An NHS Genomic Medicine Service Programme
Author:	Monahan, Kevin
Author Institution:	1 - St Mark's Hospital Centre for Familial Intestinal Cancer, Imperial College London, North Thames GMSA, London, UK
	2 - South East Genomic Medicine Cancer Alliance, London, UK
	3 - North Thames Genomic Medicine Cancer Alliance, London, UK
Co-Authors:	Adam Shaw (2), Laura Monje-Garcia (1), Fracesca Faravelli (3), Frances Elmslie (2), Anna Kim (2), Simone Gelinas (2)

Abstract text:

Introduction: In the UK, the NICE guidelines recommend universal testing of newly diagnosed colorectal and endometrial cancer for Lynch syndrome (LS), however there is strong evidence of variation in delivery of these guidelines by clinical services. In England, through 7 Genomics Medicine Service Alliances (GMSA), a transformation project aims to establish robust pathways to improve compliance

Methods: A national oversight group was formed in May 2021, with membership drawn from 21 Cancer Alliances (CA), 7 GMSA, charities and stakeholders. Each CA was tasked with identifying a 'Lynch syndrome champion' within each cancer team, and we performed a baseline survey to identify barriers to the testing pathway. Workforce training focused on overcoming barriers to testing, identification of eligible patients and mainstreamed constitutional gene testing. This training is delivered via online modules, workshops, and face-to-face peer-support and co-consultation. Data analysis is performed in conjunction with the National Disease Registration Service (NDRS)

Results: Baseline data from NDRS and the survey demonstrates that although cancer teams self report that 71% offer universal testing for LS, in 2019 only 41% of colorectal or endometrial cancer patients received any form of MMR testing. The main barriers to testing identified relate to funding streams and systematic approaches to testing. Now LS nurses are being appointed in each GMSA to support workforce development. Subgroups have been established in primary care, nursing, pathology, training, and to pilot testing in other Lynch-related tumour types. Each GMSA has identified LS patients diagnosed via their service, which will be used to ascertain people for a Nationally coordinated screening programme from 2023, and the development of a National LS Registry

Conclusions: Despite barriers, significant quality improvement has been implemented, facilitating systematic delivery of universal testing for LS nationally, with reduction in variation in care

Title: Universal Testing of Asturian Population Diagnosed with Lynch Syndrome.

Author: Díaz Vico, Tamara

Author Institution: (1) Division of General Surgery, Department of Colorectal Surgery, Hospital Universitario Central de Asturias (HUCA), Oviedo, Asturias, Spain.
(2) Department of Medical Oncology, Hospital Universitario Central de Asturias (HUCA), Oviedo, Asturias, Spain.

Co-Authors: Tamara Díaz Vico (1), Aida Suárez Sánchez (1), Pilar Blay Albors (2), Milagros Balbín Felechosa (2), Luka Mihic Góngora (2), María Fernández Hevia (1), José E. Granero Trancón (1), Luis J. García Flórez (1)

Abstract text:

Introduction: Lynch syndrome (LS) is a cancer syndrome which is inherited in an autosomal dominant manner, and accounts for 3-5% of all colorectal cancer (CRC) cases. Patients carry deleterious germline mutations in one of the five mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS1 and PMS2). The aim of this retrospective study was to assess the frequency of germline pathogenic variants in our cohort. Additionally, we evaluated the tumor phenotype, as well as the frequency of CRC and extra-colonic tumors of patients suspected of LS within the Asturian population.

Method: We performed a retrospective review of Asturian patients diagnosed with LS of a prospectively collected database from a single and reference center institution from January 1, 2017 to December 31, 2020. Data collection included type of genetic mutations and associated tumors, anatomopathological characteristics of the specimens, and the review Bethesda and Amsterdam criteria.

Results: A total of 65 patients diagnosed with LS were analyzed. Thirty-four (52.3%) patients were male and 32 (49.2%) patients were healthy carriers at the time of data collection. From our cohort, 42 were mutation carriers in MSH2 and MSH6, 23 (35.4%) and 19 (29.2%), respectively. Among the remaining 23 patients, we identified 11 (16.9%) in MLH1 and 12 (18.5%) in PSM2 carriers of pathogenic mutations. Mutations in the MSH2 and MSH6 genes represented 64.6% of all mutations. Sixteen (24.6%) patients met Bethesda criteria, while another 10 (15.4%) met both Bethesda and Amsterdam criteria. Pathogenic mutations are represented in Table 1.

Conclusion: Understanding the specific differences in carcinogenesis for each LS subgroup will aid in the further optimization of guidelines for diagnosis, surveillance and treatment. In addition, the low percentage of patients diagnosed with LS who meet Bethesda and Amsterdam criteria is striking; thus, we recommend, at least, an immunohistochemical study of all CRC patients to rule out LS.

Title: Combined somatic copy number alteration and fragmentation analysis for treatment monitoring in colorectal cancer patients using liquid biopsy

Author: Hallermayr, Ariane

Author Institution: (1) MGZ – Medizinisch Genetisches Zentrum, Munich, Germany; (2) Pettenkofer School of Public Health, Munich, Germany; (3) Institute for Medical Information Processing, Biometry, and Epidemiology –IBE, LMU Munich, Munich, Germany; (4) Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, Munich, Germany; (5) Institute of Neurogenomics, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany; (6) Institute of Human Genetics, Diagnostic and Research Center for Molecular Biomedicine (Austria), Medical University of Graz, Graz, Austria.; (7) BioTechMed-Graz, Graz, Austria.; (8) Christian Doppler Laboratory for Liquid Biopsies for Early Detection of Cancer, Graz, Austria.; (9) Department of Oncology and Hematology, Barmherzige Brüder, Klinikum St. Elisabeth, Straubing, Germany; (10) Department of Hematology, Oncology and Palliative Medicine, Vivantes Klinikum Neukoelln, Berlin, Germany; (11) Department of Oncology, Vivantes Auguste-Viktoria-Klinikum, Berlin, Germany; (12) Department of General, Visceral, Thoracic and Endocrine Surgery, Klinikum Garmisch-Partenkirchen, Teaching Hospital, Ludwig Maximilian University Munich, Garmisch-Partenkirchen, Germany; (13) Department of General, Visceral and Thorax Surgery, Klinikum Ingolstadt, Ingolstadt, Germany; (14) Department of General, Visceral, Vascular and Transplant Surgery, University Hospital Munich, Ludwig-Maximilians University of Munich, Campus Großhadern, Munich, Germany

Co-Authors: Ariane Hallermayr (1,2,3), Tobias Wohlfrom (1), Verena Steinke-Lange (1,4), Anna Benet-Pagès (1,5), Florentine Scharf (1), Ellen Heitzer (6,7,8), Ulrich Mansmann (3), Christopher Haberl (9), Maike de Wit (10,11), Holger Vogelsang (12), Markus Rentsch (13,14), Elke Holinski-Feder (1,4), Julia MA Pickl (1,4)

Abstract text:

Introduction: Liquid biopsy for non-invasive disease monitoring of cancer patients is progressing towards routine clinical practice. So far, the main focus is on circulating tumor DNA (ctDNA) analysis, targeting actionable somatic hotspot variants to support therapy decisions. Whole-genome sequencing (WGS) of ctDNA provides a promising tool for real-time monitoring of treatment response, as well as early diagnosis for all cancer patients.

Method: We established LIquid biopsy Fragmentation, Epigenetic signature and Copy Number Alteration analysis (LIFE-CNA) using WGS with ~6x coverage in 259 plasma samples collected from healthy individuals and colorectal cancer (CRC) patients.

Results: Based on 55 healthy controls, we established distinct cutoffs for the detection of ctDNA based on global and regional fragmentation patterns, transcriptionally active chromatin and somatic copy number alterations for the analytical validation of LIFE-CNA. We further combined global and regional cfDNA fragmentation into a machine learning classifier for the accurate prediction of ctDNA. By following individual patients treated with surgery and / or chemotherapy throughout their course of disease we were able to show that changes in ctDNA signals enable the reliable prediction of response or resistance to treatment.

Conclusion: In conclusion, we developed and validated a sensitive and cost-effective method for untargeted ctDNA detection at diagnosis or recurrence, as well as treatment monitoring expanding the advantages of liquid biopsy to all cancer patients. The high sensitivity and cost-effectiveness of our approach form the basis of the implementation of LIFE-CNA into clinical practice.

Title:	A Demonstration of Microsatellite Instability Analysis with Circulating Tumor DNA in Endometrial Cancer
Author:	Lewis, Samantha
Author Institution:	Promega Corporation, Palatine, United States
Co-Authors:	Samantha Lewis, Martin Ensenberger, Kathryn Oostdik.

Abstract text:

Introduction: Microsatellite instability (MSI) analysis requires both a tumor and normal (non-tumor derived) genetic profile for the most sensitive detection of acquired changes in tumor tissue. However, in many cases adjacent tissue can be contaminated with tumor cells or non-tumor tissue simply may not be available. Without the use of a reference profile from the same individual, subtle changes in tumor alleles may be missed especially in difficult sample types. In this work, we present a way to obtain sensitive results with ccfDNA and matched buffy coat or whole blood from the same sample using two MSI panels, one containing the gold standard markers, and the other containing novel markers optimized for alternative sample type assessment.

Methods: A cohort of samples from individuals with MSI-high endometrial adenocarcinomas with associated staging at time of collection were used. High quality DNA was obtained from matched FFPE normal, FFPE tumor, circulating tumor DNA from plasma samples for all individuals. A subset of samples also had associated matched buffy coat for comparison.

Results: High concordance was shown between profiles obtained in circulating tumor DNA and DNA isolated from the solid tumor of origin. Limit of detection for selected representative samples were calculated for differing shift sizes to demonstrate the sensitivity of this technique with each tissue type.

Conclusions: PCR followed by capillary electrophoresis has several advantages for MSI testing in circulating DNA and other limited or precious sample types. The very low DNA requirement of this technique uniquely allows for targeted MSI analysis even in very degraded or small samples. In this study we show a valuable and effective tool for MSI analysis with challenging samples and across tissue types.

Title:	Analysis of plasma cell-free DNA genome-wide methylation in colorectal cancer and adenoma patients - Towards a cell-free DNA-based surveillance
Author:	Eikenboom, Ellis

Author Institution:	1 Department of Clinical Genetics, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; 2 Department of Gastroenterology & Hepatology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; 3 Department of Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; 4 Department of Developmental Biology, Erasmus University Medical Center, Rotterdam, The Netherlands; 5 Department of Pathology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands;
Co-Authors:	Ellis L. Eikenboom1,2, Saskia M. Wilting3, Teoman Deger3, Gosia I. Srebniak1, Ruben G. Boers4, Agnes Reijm2, Sophia van Baalen-van Daalen2, Peggy Atmodimedjo5, Hendrik J. Dubbink5, John W.M. Martens3, Manon C.W. Spaander2, Anja Wagner1

Abstract text:

Introduction: Surveillance for colorectal cancer (CRC) by colonoscopy is effective, but is burdensome, especially for genetically predisposed patients, who are advised colonoscopies regularly. Previously, analysis of cell-free DNA (cfDNA) has emerged as a promising, non-invasive tool for disease management. We hypothesized that a cfDNA-based blood test might also be used in CRC screening and surveillance.

Methods: For this prospective, longitudinal cohort study (trial ID NL8695), patients with a colonoscopy in the Erasmus MC Cancer Institute Rotterdam, in the context of Lynch syndrome (LS) surveillance or the Dutch National Colorectal Cancer screening program (SP), were approached between July 19th 2020 and June 16th 2022. Blood was drawn from consenting patients and in case advanced adenoma (AA; adenoma with villous component, high-grade dysplasia, at least 10 mm in size) or CRC was detected, patients were included for cfDNA genome-wide methylation (MeD-seq) analyses. Analyzed cfDNA samples were subsequently compared to healthy blood donors using hierarchical clustering on the most differentially methylated regions (DMRs).

Results: A total of ten patients (two LS carriers, eight SP patients) were included for analyses: five having CRC (stage I-IV, one sporadic being microsatellite instable) and five with AA. Until now, eight have been analyzed with MeD-seq.: patients with CRC/AA cluster separately from healthy blood donors, indicating clear differences in their cfDNA methylation profiles.

Conclusion: Patients with AA/CRC could be discriminated from healthy blood donors based on their cfDNA methylation profile. Based on these results, cfDNA methylation profiling might have additional value for CRC screening and surveillance, but further studies are needed.

Title:	Associations of circulating microRNAs with body mass index, waist circumference, and physical activity in Lynch syndrome
Author:	Sievänen, Tero
Author Institution:	1. Gerontology Research Center and Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland
	2. Department of Education, Central Finland Health Care District, Jyväskylä, Finland 3. Department of Surgery, Central Finland Health Care
Co-Authors:	Tero Sievänen1, Kirsi Pylvänäinen2, Tiina Jokela1, Sarianna Sipilä1, Jukka-Pekka Mecklin3,4, Toni T. Seppälä5,6, Elina Sillanpää1,7 & Eija K. Laakkonen1

Abstract text:

Introduction: Circulating microRNA (c-miR) expression associates with body composition, serum lipids and carcinogenesis. We showed that body weight and physical activity (PA) contribute to cancer risk in Lynch syndrome (LS). However, the mechanism how these lifestyle factors may contribute to LS carcinogenesis is unknown. Here we explored associations of c-miR expression and lifestyle factors.

Materials & methods: Healthy LS-carriers without (n=18) or with cancer history (n=18) were paired based on sex, age, and pathogenic gene variant. Wilcoxon signed rank test was used to inspect if the groups differed in c-miR expression, body mass index (BMI [kg/m2], n=8), waist circumference (WC [cm], n=8) and PA ([MET-h/d], n=8). Pair differences in c-miR expression, BMI, WC, and PA were computed and used in downstream analyses. Correlation analysis between c-miRs and lifestyle variables was conducted. Multiple linear regression models were used to study if BMI, WC, and PA difference predict c-miR expression difference. Functional enrichment was performed on c-miR target genes.

Results: The expression of 14 c-miRs out of 228 differed among the paired groups (nominal p<.05) whereas BMI, WC and PA did not. c-miR-625 expression difference correlated strongly with differences in BMI (r=.81, p=.02), WC (r=.78, p=.02) and PA (r=-.92, p<.00). C-miR-625 expression was higher in LS carriers without cancer history. The first regression model (BMI, B=-.01, p=.93; PA, B=-.15, p=.06; r2=.84) did not indicate BMI and PA difference to have combined contribution to c-miR-625 expression difference. The second regression model (WC, B=-.02, p=.89; PA, B=-.14, p=.04; r2=.84) showed that if WC difference was constant, higher PA difference predicts lower c-miR-625 expression difference. c-miR-625 targets genes enriched in Wnt-signaling, metabolism and development.

Conclusion: Physical activity could affect LS cancer risk through c-miR-625, which is known negative regulator of carcinogenic processes.

ABSTRACTS – Meeting Palma de Mallorca, Sept.30 – Oct.1, 2022

Title:	Highly sensitive Liquid Biopsy Duplex Sequencing complements tissue biopsy to enhance detection of clinically relevant genetic variants
Author:	Romic-Pickl, Julia
Author Institution:	1 MGZ – Medizinisch Genetisches Zentrum, Munich, Germany 2 Pettenkofer School of Public Health, Munich, Germany 3 Institute for Medical Information Processing, Biometry, and Epidemiology – IBE, LMU Munich, Munich, Germany 4 Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, Munich, Germany 5 Limbus Medical Technologies GmbH, Rostock, Germany
Co-Authors:	Ariane Hallermayr1,2,3, Teresa M. Neuhann1, Verena Steinke-Lange1,4, Florentine Scharf1, Andreas Laner1, Roland Ewald5, Ben Liesfeld5, Elke Holinski-Feder1,4 and Julia MA Pickl1,4

Abstract text:

Background: Liquid biopsy is a promising complement to tissue biopsy for identification of clinically relevant variants in tumor and mosaic diseases. A combined workflow for tissue and plasma analysis is likely to increase the diagnostic yield.

Methods: We developed and validated a cost-efficient combined NGS workflow for both tissue and liquid biopsy analysis, and applied Duplex Sequencing technology for highly accurate detection of very low frequency variants in plasma.

Results: Liquid biopsy Duplex Sequencing was established with 100% sensitivity and 92.3% precision for SNVs, and 91.7% sensitivity and 100% precision for InDels in clinically relevant hotspots with 0.5-5% allele frequency (VAF) in plasma. Clinically relevant cut-offs for reporting variants (i.e. Limit of Blank, LOB) at 0.25% VAF and for accurate quantification of variants (i.e. Limit of Quantification, LOQ) at 5% VAF in plasma were defined. Using liquid biopsy as complement to tissue biopsy enabled identification of the molecular cause of a clinically confirmed asymmetric overgrowth syndrome in a 10-year old child, which would have remained undetected with tissue analysis only.

Conclusion: Our flexible and cost-efficient workflow allows analysis of both tissue and liquid biopsy samples. Complementation of tissue analysis by liquid biopsy increases the diagnostic yield for patients with tumor and mosaic diseases.

Title:	Whole-exome sequencing of cell-free DNA reveals mutational signatures associated with Lynch syndrome
Author:	Kauma, Iiro
Author Institution:	1 Applied Tumor Genomics Research Program, Research Programs Unit, University of Helsinki, Finland 2 Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Center, Tampere University Hospital, Finland 3 Department of Molecular Pathology, Jyväskylä Hospital Nova, Jyväskylä, Finland 4 Department of Gastrointestinal Surgery, Helsinki University Hospital and University of Helsinki, Finland 5 Department of Sports and Health Sciences, University of Jyväskylä, Finland 6 Department of Medical and Clinical Genetics, University of Helsinki, Finland
Co-Authors:	Riku Katainen1, Erdogan Pekcan Erkan2, Maarit Ahtiainen3, Teijo Kuopio3, Anna Lepistö1,4, Auli Karhu1, JP Mecklin5, Lauri Aaltonen1,6 , and Toni Seppälä1,2,4

Abstract text:

Introduction: Cell-free DNA (cfDNA) based assays have emerged as a potential method for detecting cancer in surveillance setting. Several mutational single base substitution (SBS) signatures have been associated with mismatch repair deficiency (dMMR). We studied if cfDNA dMMR signatures can be detected in Lynch syndrome (LS) carriers by whole-exome sequencing (WES) of plasma samples.

Method: Plasma was collected during LS surveillance. From path_MMR carriers, we selected roughly equal amounts of individuals with current and future LS-related cancers, advanced adenomas, and no clinical findings, 29 in total. 9 patients with sporadic CRCs and 6 healthy controls were added to analysis. Deep sequencing was performed on Illumina platform, and the SigProfiler algorithm with de novo mutation signature extraction was applied.

Results: The mean sequencing coverage was 192. On average, 281, 362 and 208 SBS mutations per patient were detected in the LS, sporadic CRC and control group, respectively, with low allelic fractions (1-10%).

We detected SBS1, 2, 5, 6, 15, and 17a signatures. Previously, SBS6 & 15 have been linked with dMMR. SBS6 had 100% specificity and 28% sensitivity for LS, SBS15 67% and 24%, and the combination of SBS6 & 15 67% and 52%, respectively. Within the LS group, SBS6 & 15 were found only in patients with current or near-future cancer, or advanced adenoma. The combination of SBS6 & 15 had 100% specificity and 65% sensitivity for LS-related neoplasia.

Conclusion: LS associated dMMR-related signatures can be detected from WES of cfDNA. SBS6 & 15 were specific in detecting patients with current and near-future advanced neoplasia in LS population. The study included future LS cancer cases where abnormal cfDNA signature analysis preceded diagnosis, some of these are not currently screened by clinical guidelines. Signature-based cfDNA assay shows promise as an additional risk stratification tool with potential for clinical applications in LS surveillance.

Title:	The Person-Based Approach to optimising a personalised, interactive patient decision aid for people with Lynch syndrome
Author:	Kohut, Kelly
Author Institution:	University of Southampton, Southampton, United Kingdom
Co-Authors:	Kate Morton, Lesley Turner, Chloe Grimmett, Diana Eccles, Claire Foster

Abstract text:

Introduction: Patient decision aids (PtDAs) increase knowledge and confidence about decisions in keeping with personal values. As genetic testing for Lynch syndrome becomes a priority in mainstream care, we are co-designing a PtDA for people with Lynch, working closely with patients and an international stakeholder group. The Person-Based Approach will be used to develop and iteratively optimise the content and delivery of our PtDA to complement shared decision-making for people with Lynch making choices about cancer risk management together with their healthcare professionals.

Methods: We have co-designed the first PtDA modules focussing on hysterectomy and aspirin decision-making. These were evaluated by patients with Lynch in semi-structured think-aloud interviews. Patients were invited from a clinical genetics service, and by working with patient groups, charities and community leaders to promote diversity and inclusivity. Health literacy and demographic data were captured to help inform purposive sampling. Transcripts were analysed using the Table of Changes from the Person-Based Approach to identify optimisations to the PtDA. Results: Important barriers to engaging with the PtDA were identified, such as risk perception and preferences for values-based activities. Optimisations were made to overcome these barriers.

Conclusion: Engagement with patient and stakeholder partners throughout the development of a PtDA ensures possible barriers to engagement and implementation can be addressed, to maximise patient benefit and sustainability of the PtDA.

Title:	Uncertainty quantification in oncology - How do uncertain data influence model results and clinical decision making?
Author:	Zeilmann, Alexander
Author Institution:	(1) Engineering Mathematics and Computing Lab (EMCL), Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University, Heidelberg, Germany (2) Data Mining and Uncertainty Quantification (DMQ), Heidelberg Institute for Theoretical Studies (HITS), Heidelberg, Germany (3) Department of Applied Tumor Biology, University Hospital Heidelberg and Cooperation Unit Applied Tumor Biology, German Cancer Research Center (DKFZ), Heidelberg, Germany
Co-Authors:	Alexander Zeilmann (1,2), Saskia Haupt (1,2), Aysel Ahadova (3), Magnus von Knebel Doeberitz (3), Matthias Kloor (3), Vincent Heuveline (1,2)

Abstract text:

Uncertainty in medical data is a common challenge in cancer research as many measurements cannot be determined precisely due to experimental restrictions, measurement errors or ethical guidelines. Even more, other parameters may not be measured at all. However, current research results and clinical guidelines heavily rely on data. Thus, quantifying these uncertainties and estimating the impact on cancer outcome and clinical procedures are essential for profound cancer research.

This is true for any kind of cancer research but is analytically feasible in particular when using mathematical models as considered in the fast growing field of mathematical oncology. Here, the aim is to support the clinician by describing medical phenomena through mathematical equations that cannot be observed in vivo. By using state-of-the-art mathematical techniques, we are able to adequately incorporate the data uncertainties in the computations and by this, reflect these in the simulation results.

In the presentation, using the mathematical Kronecker model [Haupt et al, PLOS Comp Bio, 2021] of the three main pathways [Ahadova et al., IJC, 2018] of Lynch syndrome colorectal carcinogenesis, we explain why a sensible modeling of uncertainties is essential and should be considered for any mathematical model in cancer research and beyond. We will discuss common sources and types of data uncertainty and how we can represent them in mathematical computations. Using examples from carcinogenesis modeling, we explain how these uncertainties can be propagated in order to get a reliable quantification of the uncertainties in the model results. Finally, we will give a few recommendations from a mathematical side on medical and clinical data acquisition and processing that support the uncertainty quantification of mathematical models in cancer research.

Title:	From Diagnosis of Colorectal cancer to Diagnosis of Lynch Syndrome: The RM Partners Quality Improvement Project
Authors:	Monje-Garcia, Laura & Koziel, Ana
Authors' Institutions:	1 - St Mark's Hospital Centre for Familial Intestinal Cancer, Imperial College London, London, UK 2 - RM Partners Cancer Alliance, London, UK 3 - North West Thames Regional Genetics Service, London, UK 4 - The Royal Marsden Hospital Cancer Genetics Unit, London, UK 5 - South West Thames Centre for Genomics, London, UK 6 - St Mark's Hospital Centre for Familial Intestinal Cancer, Imperial College London, North Thames GMSA, London, UK
Co-Authors:	Kevin Monahan (1), Laura Monje Garcia (1), Timothy Bill (2), Lindsay Farthing (2), Nate Hill (2), Ricki Ostrov (2), Emma Kipps (2), Angela Brady (3), Zoe Kemp (4), Katie Snape (5), Anna Koziel (6)

Abstract text:

Introduction: The UK NICE DG27 guidelines recommends universal testing for Lynch syndrome (LS) in all newly diagnosed Colorectal Cancer (CRC) cases. However, implementation of the guidelines varies significantly by geography. This Quality Improvement Project (QIP) was developed to measure variation and deliver an effective diagnostic pathway within the RM Partners (RMP) cancer alliance geography

Methods: RMP covers a population of 4 million people and incorporates 9 CRC multidisciplinary teams (MDT) overseen by a Pathway Group, and 3 regional genetic services, managing approximately 1500 new CRC cases annually. A LS champion was nominated within each MDT. A project manager and nurse practitioner were appointed to support the LS champions, to develop online training packages and consultation workshops. MDTs were supported to develop an 'in-house' mainstreaming service to offer genetic testing in their routine oncology clinics. Baseline data was collected by auditing the pathway in each MDT. This information identified areas for improvement

Results: Baseline results showed that tumour MMR testing was performed in 93% of 270 CRC patients. However, only 23% (7/30) of eligible patients underwent methylation testing, and only 9% (2/22) eligible for constitutional testing were referred to a genetics service, with high levels of variation between each MDT. During the QIP we developed new mainstreaming services and demonstrated implementation of systematic and robust testing pathways across RMP

Conclusions: The LS project was completed in April 2022. This work has led to the development of a new NICE standard QS30 in England which recommends local leadership within cancer teams to ensure delivery of diagnosis of LS. We have implemented a systematic approach with workforce transformation to facilitate identification and 'mainstreamed' genetic diagnosis of LS. This programme has now evolved to be one of the UK national genomics transformational projects which will integrate genomics into clinical practice

Title:	Improvement of IAFLD under Teduglutide in a patient with familiary adenomatous polyposis (FAP) and short bowel syndrome
Author:	Bauerfeind, Peter
Author Institution:	1)Gastroenterologie, St Anna Spital Luzern, Switzerland 2)University of Zürich, Switzerland 3)Department für Endokrinologie, Universitätsspital Zürich, Switzerland
Co-Authors:	H.Heinrich 1,2, P. Gerber 3, P. Bauerfeind 1,2

Abstract text:

We report the case of a 53-year-old male patient diagnosed with FAP in his adolescence. He underwent proctocolectomy and temporary ileostomy. After ileostomy reversal the patient required multiple small bowel resections over a course of seven years ending in definitive enterostomy due repetitive small bowel obstructions caused by adhesions and desmoid tumours. The patient developed short bowel syndrome with malnutrition and required parenteral nutrition. Elevated liver enzymes and cholestatic parameters were first noted in 2013 with elevated fibroscan values and a diagnosis of intestinal failure associated liver disease was made. In 2016 an interdisciplinary decision was made to start off label revestive in order to avoid progression of IAFLD. In the follow-up, liver and fibroscan values showed a marked improvement. The patient was able to reduce and completely stop parenteral nutrition in 2018. He regularly underwent enteroscopies with removal of small bowel adenomas - none of them showing malignancy. Repetitive imaging studies were able to rule out tumor or desmoid development.

Revestive is a Glucagon like petide 2 analogon applied in patients with short bowel syndrome in order to increase resorptive capacity of the remaining small bowel. It is formally contraindicated in patients with a history of malignant disease within the last 5 years as it seems to induce bowel mucosa malignancy. However, there is little data on adequate treatment of patients with short bowel syndrome after surgery for hereditary colon cancer syndromes. Small bowel transplantation is a high-risk procedure which is not ubiquitary available and would have required immunosuppression with added risk of further desmoid development. To best of our knowledge this is the first case of a patient with FAP, short bowel syndrome and associated IAFLD treated successfully under consequent endoscopic and radiologic surveillance with Revestive in the literature.

Title:	Mesalamine for Colorectal Cancer Prevention Program in Lynch Syndrome (MesaCAPP)
Author:	Backman, Ann-Sofie
Author Institution:	Karolinska institutet Sahlgrenska university Umeå university Centrum Wsparcia Badań KlinicznychPomorski Uniwersytet Medyczny w Szczecinie Gastroenheden, Hvidovre Hospital University of Bologna
Co-Authors:	Ann-Sofie Backman, Annika Lindblom, Rolf Hultcrantz, David Ljungman, Gustav Silander, Luigi Ricciardiello, Jan Lubinski, Christina Therklidsen, Lars Joachim Lindberg, Luigi Ricciardiello

Abstract text:

In vitro, mesalamine (5-ASA), a well-tolerated drug that had been used for over 30 years in ulcerative colitis, and reduces MSI via improvement of replication fidelity . 5-ASA activates a replication checkpoint thereby allowing more time for cells to pass through S-phase leading to less replications errors . Such a chemopreventive effect was not observed upon aspirin/ASA, which has no effect on MSI either.

5-ASA has minimal toxicity as it is delivered to the colon through slow release formulations and immediately inactivated (N-acetylated) within the colonic mucosa. The drug is not systemically active. Thereby it would fulfill all requirements for a designer drug for CRC prevention in LS and an alternative to aspirin. In addition epidemiological data support its chemopreventive properties in humans as it reduces the risk of CRC in patients with ulcerative colitis

This is a multicenter, multinational, randomized, 2-arm, double-blind, phase II clinical study with 2000mg mesalamine (5-ASA) or placebo in LS patients for a 2-year treatment. 260 tumor free carriers of a known genetic mutation in a major MMR gene will be randomized 1:1 to receive 2000mg mesalamine or placebo. Tumor free patients, assessed by white light high resolution colonoscopy, will be randomized to the study. Blood and stool samples will be collected for analysis of microbiota, ctDNA and potential biomarkers. Biopsies of the normal tissue of ascending colon and rectum will be taken at the first and the last colonoscopy.

The aim of the study is to investigate the effect of regular treatment with mesalamine (5-ASA) on the occurrence of any colorectal neoplasia, tumor multiplicity (the number of detected adenomas/carcinomas) and tumor progression in LS patients.

The study is including patients in Sweden at the moment and will start to include patients in Denmark, Italy and Poland during the autumn 2022. Newcastle is investigating possibilities to participate. Interested partners are welcome.

Title: Clinical characteristics of pancreatic and billiary tract cancers in Lynch sysdrome: a retrospective analysis from the finnish national Lynch Syndrome Reseach Registry

Author: Zalevskaja, Kristina

Author Institution: 1 Department of Gastrointestinal Surgery, Helsinki University Hospital, Helsinki, Finland.
2 Department of Education & Research, Jyväskylä Hospital Nova, Jyväskylä, Finland; Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland.
3 Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Center, Tampere University Hospital

Co-Authors: Kristina Zalevskaja1, Jukka-Pekka Mecklin2, Toni Seppälä1,3

Abstract text:

Introduction: Patients with Lynch syndrome have increased lifetime risk of pancreatic (PC) and biliary tract cancer (BTC). These cancers have notoriously pessimistic prognosis due to late diagnosis and limited therapeutic options. There are limited data based on small cohorts reviewing PC and BTC in LS patients.

Methods: In this retrospective study of Finnish National LS-research Registry we identified genetically verified Lynch syndrome patients diagnosed with pancreatic or biliary tract cancer between 1982 and 2020.

Results: Forty patients were included: tumor(s) was located in pancreas in 27 patients, biliary tract in 10 and ampulla of Vater in 3. Pathogenic germline variant was in MLH1 in 33/40 patients. Curative surgery was attempted in 17/40 patients. Twenty-three pancreatic ductal adenocarcinomas (PDAC), 5 neuroendocrine tumors (NET) and 1 sarcoma metastasis were identified. The median age at diagnosis of PC was 64 years (range 38-81). In PC, the 5-year overall survival (OS) rate was 19% and with PDAC 13%. Ten patients with BTC were diagnosed: 2 intrahepatic, 5 perihilar, 2 distal extrahepatic cholangiocarcinomas and 1 gallbladder carcinoma. Eight patients were male and the median age at diagnosis was 54 years (range 34-82). The 5-year OS rate in BTC was 30%. Metachronous tumors were diagnosed in 29 patients (72.5%). Colorectal cancer was the most common metachronous cancer, diagnosed in 20 patients (50%), and prior to PC or BTC in all cases. For 30 patients (88%), the cause of death was PC or BTC. Three patients died from another LS-associated cancer and 1 patient from stoke.

Conclusion: Although survival of LS patients with PC or BTC is better than in sporadic cancers, it is still poor, and may be reflected by the relatively higher surgical resectability accounted for by earlier age of onset. More studies on analyses of the molecular and immune profile, screening and management for LS-associated pancreaticobiliary cancers are warranted.

Title: DIRECT: Delphi initiative for EoCRC. CGA-IGC, EHTG, AIFET Guidelines for the Management of Early-Onset Colorectal Cancer

Author: Cavestro, Giulia Martina Cavestro

Author Institution: 1. Gastroenterology and Gastrointestinal Endoscopy Unit, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy; 2. Department of Gastroenterology, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; 3. Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), University of Barcelona, Barcelona, Spain; 4. Department of Medical Oncology & Therapeutics Research, City of Hope National Medical Center, Duarte, California, USA; 5. Department of Medicine, Section of Gastroenterology, Hepatology, and Nutrition, University of Chicago Medicine, Chicago, Illinois, USA; 6. Gastrointestinal Endoscopy Unit, Humanitas University, Humanitas Research Hospital, Rozzano, Italy.; 7. Clinical Molecular Oncology Unit, Department of Hematology, Oncology and Molecular Medicine, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Università degli Studi di Milano, Milan, Italy.; 8. University of Tampere, Arvo Ylpön katu, Tampere, Finland; 9. Unit of Gastroenterological Surgery, Tampere University Hospital, Elämänaukio, Tampere, Finland; 10. Applied Tumor Genomics Research Program and Dept of Surgery, Helsinki University and Helsinki Univerity Hospital, HUS, Finland; 11. Department of Radiology, Radiation Oncology and Hematology, Università Cattolica del Sacro Cuore di Roma, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy; 12. Department of Medicine, Division of Gastroenterology, University of California San Diego, CA, USA; 13. Division of Gastroenterology, Hepatology & Nutrition, University of Pittsburgh, Pittsburgh, PA, USA; 14. Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy; 15. Oncology Unit, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy; 16. Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, University of Amsterdam, the Netherlands; 17. Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy; 18. Department of Tumor Biology, Institute of Cancer Research, The Norwegian Radium Hospital, Oslo, Norway ; 19. Division of Digestive and Liver Diseases, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center and the Vagelos College of Physicians and Surgeons, New York, USA. ; 20. Surgical Center for Hereditary Tumors, Ev. BETHESDA Khs. Duisburg, Academic Hospital University of Düsseldorf Germany ; 21. School of Public Health, University of Texas Health Science Center at Houston, Houston, USA. ; 22. Gastrointestinal Cancer Center, Young-Onset Colorectal Cancer Center, Harvard Medical School Dana Farber Cancer Institute, Boston, MA, USA; 23. Medical Oncology, AULSS 5 Polesana, Santa Maria Della Misericordia Hospital, Rovigo, Italy.; 24. Centro Scienze della Natalità- IRCCS San Raffaele Scientific Institute. Milano, Italy; 25. University of Colorado Anschutz Medical Center and Rocky Mountain Regional Veterans Affairs Medical Center, Aurora, Colorado, USA; 26. Pathology Unit, Mater Salutis Hospital, ULSS9, Legnago, 37045 Verona, Italy.; 27. Department of Medical and Surgical Sciences, Universita degli Studi di Bologna, Bologna, Italy.; 28. Department of Onco-Haematology, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy.; 29. Brigham and Women's Hospital, Harvard Medical School, Dana Farber Cancer Institute, Boston, MA, USA; 30. Department of Anesthesiology, Vita-Salute University, IRCCS San Raffaele Scientific Institute, Milan, Italy; 31. Chirurgia Generale 3, Department of Surgical, Oncological and Gastroenterological Sciences (DiSCOG), University Hospital of Padova, Padova, Italy.; 32. Hereditary Cancer Program, Catalan Institute of Oncology; Oncobell Program, Bellvitge Biomedical Research Center (IDIBELL), Hospitalet de Llobregat, Barcelona, Spain; 33. Centro de Investigación Biomédica en Red en Cáncer (CIBERONC), Madrid, Spain; 34. Division of Gastroenterology and Hepatology, Department of Internal Medicine and Rogel Cancer Center, University of Michigan Medical School, Ann Arbor, Michigan, USA

* These authors equally contributed to this document

§ Chairs of the Working Panels

Co-Authors: Cavestro GM1*, Mannucci A1*, Balaguer F2,3,§, Hampel H4,§, Kupfer S5,§, Repici A6,§, Sartore-Bianchi A7,§, Seppälä TT8,9,10,§, Valentini V11,§, Boland CR12, Brand RE13, Caccialanza R14, Cascinu S15, Danese S1, Dekker E16, Daca-Alvarez M2, Deni F17, Dominguez-Valentin M18, Houwen BBSL16, Kastrinos F19, Meldolesi E11, Moslein G20, Murphy CC21, Nass K16 , Ng K22, Oliani C23, Papaleo E24, Patel SG25, Puzzono M1, Remo A26, Ricciardiello L27, Ripamonti CI28, Syngal S29, Turi S30, Urso ED31, Valle L32,33, Zuppardo RA1, Stoffel E34, on behalf of the Associazione Italiana Familiarità Ereditarietà Tumori, the Collaborative Group of the Americas on Inherited Gastrointestinal Cancers, and the European Hereditary Tumor Group.

Abstract text:

Introduction: Patients with early-onset colorectal cancer (eoCRC) are managed according to CRC guidelines that are not specific for this age group. A multidisciplinary international group (DIRECt), comprised of 39 experts (T1), was convened to develop the first evidence-based consensus recommendations for eoCRC.

Methods: After reviewing the published literature, a Delphi methodology was employed to draft and respond to clinically relevant questions. Each statement was submitted to two rounds of voting and reached a consensus level of agreement of >80%.

Results: The DIRECt group produced 34 statements in 7 areas of interest: diagnosis, screening, genetics, pathology-oncology, endoscopy, therapy, and supportive care (T2-T7). There was a strong consensus that all individuals younger than 50 should receive prompt risk assessment when symptomatic. All newly diagnosed eoCRC patients should receive germline genetic testing, ideally before surgery. Currently, endoscopic, surgical, and oncologic treatments of eoCRC should not differ from older onset CRC, except for individuals with pathogenic germline variants. The evidence on chemotherapy is still not strong enough to recommend changes to established therapeutic protocols. Fertility preservation is important to address in eoCRC survivors.
The DIRECt group highlighted areas with knowledge gaps, including age at first screening for the general population, neoadjuvant/adjuvant chemotherapy, and endoscopic therapy for eoCRC patients. We suggest that these areas receive research priority.

Conclusion: The DIRECt group produced the first evidence-based consensus recommendations on eoCRC. All statements should be considered together with the accompanying comments and literature discussions. We highlighted areas where research should be prioritized. These guidelines represent a useful tool for clinicians caring for patients with eoCRC.

Title:	Genetic testing in early onset colo-rectal cancer: experience of an oncogenetic consultation in the era of NGS sequencing
Author:	Farelly, Solenne
Author Institution:	(1) Hôpital Cochin, APHP Centre, Université Paris Cité (2) Hôpital Européen Georges Pompidou, APHP Centre, Université Paris Cité (3) Centre Léon Bérard
Co-Authors:	M. Dhooge (1), B. Terris (1), P.A. Just (1), A. Rouquette (1), K. Leroy (2), Q. Wang (3), R. Coriat (1), E. Pasmant (1), N. Hamzaoui (1), and S. Chaussade (1).

Abstract text:

Introduction: Patients with Early Onset Colo-Rectal Cancer (EOCRC) are often referred for genetic counselling. Like many genetic society, the French Genetic and Cancer Group (GGC)-Unicancer have established a list of 14 genes relevant in this context and made recommendations for their analysis. We here report results of NGS testing for EOCRC in our consultation.

Materials and Methods: We collected data from all patients referred for EOCRC since April 2016 (additional tumor analyses, synchronous digestive lesions, personal and familial history).
Our NGS panel included the MMR genes, APC, MUTYH, STK11, SMAD4, BMPR1A, PTEN, POLE, POLD1 and CDH1 (GGC genes panel). MSH3, NTHL1, RNF43, GREM1 and AXIN2 genes were added since 2018.

Results: Between April 2016 and August 2021, 103 index patients were referred for EOCRC. All tumors had determination of MMR tumoral status except in polyposis. 34 patients had dMMR tumors and 41 had significant synchronous colonic lesions, including 14 patients fulfilling the criteria for multiple adenomas defined by the GGC and 6 with serrated polyposis.
We did not perform genetic testing in 7 patients (patients older than 40 with pMMR tumors and without synchronous colonic lesions or familial history).
A deleterious variation was identified on a gene of interest in 27 patients among the 96 tested.
In the 55 patients with pMMR tumors and without criteria for multiple adenomas, 48 had nevertheless benefited from a genetic testing (ages 27 to 48 years, average: 36.3 years). Six had OMS criteria for serrated polyposis. No deleterious variation was found in these 48 patients.

Conclusion: In 103 individuals referred for oncogenetic counselling for EOCRC, a relevant genetic variation was identified in 27 patients. No deleterious variants were found in the 55 patients with pMMR tumors without criteria for multiple adenomas or hamartomatous polyposis. This confirms the relevance of GGC criteria for NGS digestive gene panel testing.

Title: Young-onset gastric cancers ar often early gastric cancers

Author: Puzzono, Marta

Author Institution: 1. Gastroenterology and Gastrointestinal Endoscopy, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy
2. Pathology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

Co-Authors: Puzzono, Marta 1; Mannucci, Alessandro 1; Grannò, Simone 1; Poliani Laura 1; Albarello, Luca 2; Cavestro, Giulia Martina 1

Abstract text:

Introduction: The incidence of young-onset gastric cancer (YOGC), defined as GC before 50, is rising. Previous works claimed that YOGC has a worse prognosis than in the elderly. The underlying cause of YOGC remains unclear and the clinicopathological characteristics are incompletely understood

Methods: We conducted a cohort study of patients with YOGC diagnosed from 2015 to 2021. We collected clinical and familial data and performed multi-gene panel testing on all. We evaluated the histological subtype and the presence of H.Pylori (HP) from available samples

Results: We included 51 patients with YOGC (52.9%M, 47.1%F; median age 42±7.5y). HP status was evaluated on 31 patients (66.6%): 31% had HP, 9.6% eradicated HP. 54.8% were HP-negative and presented with a more advanced stage than HP-positive YOGC (mean stage: III vs I, $p<0.05$, F1). 27.5% drank alcohol daily (2.5±1.66 alcoholic unit/day), 23.5% sometimes, and 49% never; 25.5% were smokers, 23.5% former smokers (overall average cigarette consumption: 17,6±12,1/day), and 51% were non-smokers. 13.7% were both drinkers and smokers (F2). 15.8% had a germline pathogenic variant (4 CDH1; 1 EPCAM; 1 PTEN; 2 TP53) (F3a). 64.7% had no family history of GC, 25.4% reported a first-degree relative with GC and 13.7% a second-degree relative with GC (F3b). 25.4% of YOGC were in the gastric body, 23.5% in the antrum, and 23.5% in the cardia. 66.6% of lesions were diffuse-type adenocarcinoma and 19.6% intestinal-type. 23.5% of YOGC were early gastric cancers (EGC), and 54.3% had tumor staging of T3 and above. 50% of EGC had a family history of GC and 16.6% had a germline pathogenic variant (T1)

Conclusions: YOGC more often presents as diffuse-type adenocarcinoma. One in six patients with YOGC has a germline pathogenic variant, suggesting all patients should receive panel testing at diagnosis. One in four patients with YOGC presents with early gastric cancer, possibly implying that younger age does not entail worse outcomes

Title: Comprehensive characterization of hereditary cancer cases from Peru: Bringing precision medicine to a low-resource setting city

Author: Dominguez Valentin, Mev

Author Institution: 1Instituto de Investigación, Universidad Católica los Ángeles de Chimbote (ULADECH-Católica), Chimbote, Perú., 2Universidad Católica los Ángeles de Chimbote (ULADECH-Católica), Chimbote, Perú., 3Research Department of Primary Care and Population Health, University College London, London, UK, 4Escuela de Medicina, Universidad Cesar Vallejo, Trujillo, Peru, 5Independent Researcher, Lima, Peru., 6Department of Medical Genetics, Institute of Clinical Medicine, University of Oslo and Oslo University Hospital, 0424 Oslo, Norway, 7Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway., 8Institute for Informatics, University of Oslo, Oslo, Norway, 9Universidad de Los Andes, Santiago, Chile., 10Centre for Cancer Cell Reprogramming, Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway.

Co-Authors: Elizabeth Zavaleta1, Nelly Solis1, Maria Palacios Palacios2, Liz Zevallos Escobar2, Edisson Vásquez Corales2, Juan Carlos Bazo-Alvarez3,4, Constantino Dominguez-Barrera5, Anthony Campos5, Patrik Wernhoff6, Per Olaf Ekstrøm7, Møller P7, Hovig E7,8, Karin Alvarez-Valenzuela9, Sigve Nakken7,8,10, Mev Dominguez-Valentin7

Abstract text:

Background: Genetic testing for hereditary cancers is inconsistently applied within the healthcare systems in Latin America. The prevalence and spectrum of cancer-predisposing germline variants is thus poorly characterized in these populations.

Purpose. To determine the spectrum and prevalence of cancer-predisposing germline variants and variants of uncertain significance (VUS) in Peruvian high-risk individuals.

Methods: Study population included individuals with early onset cancer and unaffected individuals with family history of cancer. Samples from a total of 84 individuals were subjected to a high-throughput DNA sequencing assay that targeted a set of n = 94 cancer predisposition genes. Pathogenicity of detected germline variants were classified according to established ACMG criteria.

Results: We identified a total of eight pathogenic variants, found in 19 of 84 individuals (23%). Pathogenic variants were identified mostly in unaffected individuals with family history of cancer (10/19) and were located in five genes: RET (1), BRCA1 (2), SBDS (2), SBDS/MLH1 (2), MLH1 (2) and FANCD2 (1). Followed by colon cancer individuals (5/19) with pathogenic variants in MLH1 and SDBS genes. RET c.1900T>C were identified in two thyroid cancer individuals, and a double heterozygous pathogenic variant in DDB2 and FANCG genes were identified in a patient with endometrial cancer while a breast cancer patient (1/19) had a pathogenic variant in TP53 gene. Overall, an individual presented at least 17 VUS, totalizing 1926 VUS for the total study population.

Conclusion: We describe the first genetic characterization in a low-resource setting population where genetic testing is not yet implemented. We identified multiple pathogenic germline variants in clinically actionable predisposition genes, that has an impact on providing an appropriate genetic counselling and clinical management for individuals and their relatives who carry these variants.

Title: Germline pathogenic variants detected in microsatellite-instable cancers: a two-year prospective experience from a Hungarian center

Author: Grolmusz, Vince Kornél

Author Institution: 1 Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary
2 Hereditary Cancers Research Group, Eötvös Loránd Research Network – Semmelweis University, Budapest, Hungary
3 Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary
4 National Tumorbiology Laboratory, Budapest, Hungary
5 Department of Surgical and Molecular Pathology, National Institute of Oncology, Budapest, Hungary

Co-Authors: Vince Kornél Grolmusz1,2,3,4, Henriett Butz1,2,3,4, Anikó Bozsik1,2, János Papp1,2, Tamás Strausz5, Erika Tóth5, Attila Patócs1,2,3,4

Abstract text:

Introduction: Molecular pathological diagnosis of microsatellite instability (MSI-H) in solid tumors is becoming more important as it directly effects treatment. In addition to the consideration of applying immmunotherapies, individuals with MSI-H or mismatch repair-deficient tumors are advised to be referred to genetic counseling to investigate their possible involvement with Lynch syndrome (LS). LS is one of the most frequent genetic predisposition to cancer resulting in elevated risk to a variety of neoplasms, among which colorectal (CRC) and endometrial (EC) cancers are the most common. LS is caused by germline pathogenic variants (gpath) in genes coding key elements of the DNA mismatch repair machinery (MLH1, MSH2, MSH6, PMS2). In the present study, our aim was to investigate that to what extent do LS occur in MSI-H cancers.

Method: Patients referred to genetic counseling based on the MSI-H status were consecutively enrolled between January 1, 2020 and December 31, 2021. Folowing genetic counseling, germline DNA was isolated from peripheral blood and was subjected to multi-gene testing (Sanger sequencing, multi-gene next generation sequencing panel and multiple ligation-dependent probe amplification) to detect LS.

Results: In total, 47 patients were enrolled, among which 27 presented MSI-H CRC and 20 presented MSI-H EC. Gpath mutations were found in 34% of patients with MSI-H tumors (37% of CRC, 30% of EC). In total 6, 6, 3 and 1 individuals harboured gpath variants in MLH1, MSH2, MSH6 and PMS2, respectively.

Conslusion: We found gpath variants resulting in LS in a large proportion of this relatively small cohort of MSI-H tumors. In accordance with international guidelines, all individuals with MSI-H tumors are advised to be referred to genetic counseling.

Title: A national picture of molecular testing for Lynch syndrome in England highlights gaps in testing and opportunities for improved diagnosis

Author: McRonald, Fiona

Author Institution: National Disease Registration Service; NHS Digital, Leeds, UK (FM, JP, FS, AT, BS, OT, ML, SG, JR, SH)
Health Data Insight CIC, Cambridge, UK (FS, BS, OT, SG, JR)
Institute Of Cancer Research, Sutton, UK (CT)
Institute Of Genetic Medicine; Newcastle University, Newcastle, UK (GB, JB)

Co-Authors: Fiona McRonald, Joanna Pethick, Francesco Santaniello, Adele Tyson, Brian Shand, Oliver Tulloch, Margreet Lüchtenborg, Shilpi Goel, Clare Turnbull, Gill Borthwick, John Burn, Jem Rashbass, Steven Hardy

Abstract text:

Introduction: Lynch syndrome (LS) is massively underdiagnosed, representing a missed opportunity for earlier cancer detection, screening of at-risk relatives, and predictive prevention. In England, the National Cancer Registration and Analysis Service (NCRAS) collects and curates National Health Service (NHS) cancer data for the population of 55 million. In 2019, 37,090 people had 37,662 colorectal cancers (CRC) and 8077 people had 8081 endometrial cancers (EC). NHS guidelines recommend testing all CRC and EC for mismatch repair (MMR) deficiency; however it is not known how well the guidance is implemented.

Methods: We collected germline MMR testing data from all English NHS genomic diagnostic laboratories, and matched this to individual NCRAS records for tumours diagnosed in 2019. Concurrently, we undertook systematic registration of all MMR immunohistochemistry (IHC) and microsatellite instability (MSI) tests performed on tumours.

Results: Only 43% CRC and 15% EC were screened for MMR deficiency; these figures varied over four-fold with respect to geography. Of those screened and identified as MMR deficient, only 44% CRC / 28% EC were given follow up testing. Overall, only 1% of patients diagnosed with CRC or EC in 2019 had a germline MMR test performed, of which 39% (for CRC) and 27% (for EC) were appropriately referred via the tumour testing pathway, as opposed to being members of known LS families or arising from tumour referrals outside the guidelines.

Conclusions: The low rates of molecular diagnostic testing in both CRC and EC supports the premise that LS is underdiagnosed, with significant leakage identified at all stages of the testing pathway. Data in future years will be examined to investigate wider implementation of testing guidelines. We estimate that, were guidelines to be properly applied in all cases of CRC/EC, up to 1000 additional LS index cases could be diagnosed per year; others could then be identified through familial testing and screening.

Title:	A nurse led genetic clinik for Lynch syndrome testing in colorectal cancer 1 year later
Authors:	Langford, Lora / Proserpio, Mauro
Author Institution:	Imperial College Healthcare NHS Trust
Co-Authors:	NONE

Abstract text:

Background: Lynch syndrome is an inherited genetic condition caused by a variation in one of five DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6, PMS2 and EPCAM.
It is essential that MMR tests are completed on the first tumour sample to ensure timely diagnosis.
NICE guidance recommends all people with colorectal cancer are tested for Lynch syndrome.
In the past, there has been no 'in house' genetic clinic, due to this referrals were made to external providers which caused delays in testing and results.
In May 2021, we set up and established a new nurse led genetic clinic, in order to streamline the Lynch Syndrome testing pathway.

Aim: Review the in house nurse led genetic clinic, to demonstrate what improvements have been made since starting the clinic.
Highlight the impact of establishing genetic champions within the Multi Disciplinary Team (MDT).

Methods: Review all patients who have been assessed in the in house nurse led genetic clinic, within the first 12 months.
Review the first 30 patients in the MDT meeting during November 2021 when genetic champions were established, to assess whether MMR was documented and referrals made accordingly.
Compare to November 2020 where genetic champions were not present.

Conclusion: We have successfully implemented the in house nurse led genetic clinic and assessed 20 patients over a 12 month period.
We have shown an improvement in discussing MMR results of patients and referring as needed, during the MDT.

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I consent to publication of the abstract on the EHTG website
I consent to publication of my abstract in Familial Cancer

Title: APC-specific ACMG/AMP variant classification guideline alleviates the burden of variants of uncertain significance in ClinVar and locus-specific databases

Author: Aretz, Stefan

Author Institution: 1 Department of Colorectal Medicine and Genetics, Royal Melbourne Hospital, Parkville, Australia 2 Department of Medicine, University of Melbourne, Parkville, Australia 3 Institute of Human Genetics, Medical Faculty, University of Bonn, Bonn, Germany 4 Na

Co-Authors: Xiaoyu Yin1,2,3,, Isabel Spier3,4,5, Marcy Richardson6, Marta Pineda5,7,8, Deborah Ritter9,10, Tina Pesaran6, Gabriel Capellá5,7,8, Sean V. Tavtigian11,12, John-Paul Plazzer1,2, Andreas Laner13, Julie Boyle12, Pilar Mur7,8, Thomas V. O. Hansen14 , Xuemei

Abstract text:

Background and Aim: The APC subcommittee of the ClinGen - InSiGHT Hereditary Colon Cancer/ Polyposis Variant Curation Expert Panel (VCEP) established gene-specific variant classification criteria based on the ACMG/AMP framework. The criteria were externally reviewed and refined through a pilot study. To lay the groundwork for prospective expert panel approval for the substantial number of uncertain germline APC variants (VUS) in ClinVar, this study adopted a large-scale classification approach using the APC-specific guidelines.

Methods: Building off the ClinGen VCEP approval process, a streamlined algorithm using the current VCEP gene-specific codes was developed consisting of population, variant type, and splice prediction criteria to comprehensively re-classify all APC variants in ClinVar. The results were compared to the ClinVar classifications to assess the efficacy of the preliminary classification criteria.

Results: The 9121 APC variants on ClinVar consisted of 1790 (Likely) Benign (20%), 1258 (Likely) Pathogenic (14%), and 6074 VUS (66%). Using the VCEP defined cut-offs, 3908 variants were classified as (Likely) Benign (43%), and 1169 variants were classified as (Likely) Pathogenic (13%), which included 2072 VUS, respectively. A prioritised list of promising causative APC variants that remained at VUS by the algorithm alone were identified from the remaining 4044 variants (44%), which will be subjected to a data mining-driven work-up to collect clinical and experimental evidence.

Conclusion: The application of the APC-specific classification criteria substantially reduced the number of VUS on ClinVar. This study highlights the importance of a systematic approach built into the current APC-specific guidelines. In the future, lists of prioritised APC variants will be classified by the VCEP regularly and made available to the public through ClinVar, with detailed evidence housed in the ClinGen Evidence Repository.

Title: Targeted short-read RNA sequencing as supplement to DNA germline testing to increase diagnostic yield

Author: Wendlandt, Martin

Author Institution: 1MGZ – Medizinisch Genetisches Zentrum, Munich, Germany
2Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, Munich, Germany

Co-Authors: Elen Samadashvili1, Taisya Volodina1, Verena Steinke-Lange1,2, Florentine Scharf1, Tobias Wohlfrom1, Elke Holinski-Feder1,2 and Julia MA Pickl1,2

Abstract text:

Background: Accurate classification of variants in patients with hereditary tumor syndromes is crucial in the clinical management of patients and their relatives. With ~50% of variants submitted to ClinVar being of uncertain significance there is a great need for additional functional evidence. RNA sequencing (RNA-Seq) as supplement to DNA diagnostic enables detection of aberrant splicing, aberrant gene expression and allelic imbalance, and provides additional information, which helps reclassifying VUS as well as identifying disease-causing variants missed by routine diagnostics.

Methods: We developed a cost-efficient targeted NGS-based approach to enrich and analyse the transcripts of 123 cancer-associated genes from PAXgene RNA samples.

Results: We achieved ultra-high coverage sequencing data with over 19,000 mean target coverage and up to 93% of exons covered with >50 read depth. As proof-of principle, we analysed the samples of eight Lynch syndrome patients with known pathogenic mismatch repair variants. We were able to successfully identify and quantify the effect of seven variants that lead to reduced gene expression through exon skipping and loss of splice acceptor site, and confirmed pathogenicity of a variant, which results in reduced protein activity.

Conclusion: Our cost-efficient workflow provides high quality RNA-Seq data, which allow the assessment of splicing events, gene expression levels as well as allelic imbalance, and can be automated for high sample throughput. This work represents the basis for future implementation of targeted RNA-Seq in routine cancer diagnostics.

Title:	Existing with a cancer ghost in the back of my mind- Written narratives of living with Lynch syndrome
Author:	Eriksen, Elin O.
Author Institution:	1. Western Norway Familial Cancer Center, Haukeland University Hospital, Bergen, Norway, 2. VID Specialized University, Faculty of Health Studies, Norway
Co-Authors:	Elin O. Eriksen 1, 2, Hildegunn Høberg Vetti 1, 2, Cathrine Bjorvatn 1, 2, Oddgeir Synnes 2

Abstract text:

Introduction: In genetic counselling, patients' stories are usually not fully told. The aim of this study was to shed light on how individuals with Lynch syndrome tell their story of cancer in their family. How do they understand information about a gene mutation and how do they reflect about cancer risk?

Method: Fifty patients with Lynch syndrome were invited to write a narrative about the gene mutation and cancer in their family. In these narratives, they had the opportunity to put their experiences and memories into words without disturbing questions from an interviewer. While writing a narrative they have the possibility to reflect over their experiences and perhaps get a better understanding of themselves. We have used a qualitative content analysis in analyzing the narratives.

Results: Eight patients, four men and four women, returned their narratives. Six had been treated for cancer, two of them twice. They were between 49 and 69 years. The stories ranged from half a page to four and a half pages.
Three themes emerged in the narratives:
1) Experiences with cancer and cancer treatment
2) Having an optimistic view on life, but still being vulnerable
3) Concerns for their children

Conclusion: Through the written narratives we got a better understanding of how patients experienced the cancer diseases in their families. These experiences influenced how they coped with their own diseases. Two of the participants had cancer twice, still they were grateful and had an optimistic view of life.
The burden of the knowledge is related to the carrier status of their children. All expressed concerns about the risk of transferring the mutation to their children. However, they were comforted by the regular surveillance mutation carriers are offered and overall, they felt positive about genetic testing.

Keywords; Lynch syndrome, cancer risk, written narratives, genetic counselling

Title:	Mutational and transcriptomic landscape and somatic evolution in Li-Fraumeni Syndrome-associated tumourigenesis
Author:	Torra I Benach, Maria
Author Institution:	Maria Torra I Benach - University of Cambridge & Wellcome Sanger Institute
	Rashesh Sanghvi - Wellcome Sanger Institute
	Lia Chappell - Wellcome Sanger Institute
	My Ha Pham - University of Cambridge & Wellcome Sanger Institute
	Mette Jorgensen - Great Ormond Street Hospital NHS Foundation Trust
	Joseph Christopher - Cambridge Univeristy Hospitals NHS Foundation Trust & Wellcome Sanger Institute
	Raheleh Rahbari - Wellcome Sanger Institute
Co-Authors:	Maria Torra I Benach, Rashesh Sanghvi, Lia Chappell, My Ha Pham, Mette Jorgensen, Joseph Christopher and Raheleh Rahbari
	Maria Torra I Benach - mt26@sanger.ac.uk - presenting author ; Joseph Christopher - jc27@sanger.ac.uk ; Raheleh Rahbari - rr11@sanger.ac.uk

Abstract text:

Li-Fraumeni Syndrome (LFS) is a hereditary cancer predisposition disorder associated with germline TP53 variants. Indeed, lifetime risk of cancer development in LFS is ~80% for men and ~100% for women. Of particular interest are adrenocortical carcinomas (ACCs), since they present poor outcome, a strong correlation with LFS, and a high prevalence of germline TP53 variants in childhood.

Thus, this study aims to perform a comprehensive investigation of the mutational and transcriptomic landscape of LFS-associated ACC, to later compare it to sporadic ACC formation and Beckwith-Wiedemann Syndrome (BWS)-associated ACC. A recently developed and unpublished combined DNA and RNA laser-capture microscopy (LCM) protocol will be employed to better understand the germline impact on tumorigenesis and tumour heterogeneity. Furthermore, by sampling multiple subclones within a single tumour, the timing of key driver events will be elucidated at unprecedented resolution. So far 6 ACCs, 1 anaplastic astrocytoma, and 2 ACC metastatic samples from 8 different patients have been collected. These include 5 LFS, 2 BWS, and 1 tp53 wild-type patients. We have sequenced 31 whole-genomes from 5 tumour samples and their respective matched normal blood and are aiming to increase our cohort to 10 whole genomes per tumour, with further patient recruitment ongoing. Moreover, matched RNA from each microbiopsy is also being generated.

Preliminary analysis of drivers, mutation burden, mutational signatures, copy number alterations and structural variants has already highlighted the structural complexity of ACCs, and the importance of p53, Rb-cell-cycle, and Wnt alterations. As more sequencing results are received, we expect our study to provide insight into the different evolutionary routes of sporadic and hereditary ACC formation, which could directly impact patient care through identification of novel therapeutic avenues in a disease with significant unmet clinical need.

Title: Psychological well-being of people living with a colorectal cancer predisposition syndrome: evidence from a systematic review

Author: Monje-Garcia, Laura

Author Institution: 1 - St Mark's Hospital Centre for Familial Intestinal Cancer, Imperial College London, London, UK;

2 - Imperial College London, London, UK

Co-Authors: Jai Vairale (2), Hilary Watt (2), Sondus Hassounah(2), Heidi Lai(2), Kevin Monahan(1), Laura Monje-Garcia (1)

Abstract text:

Introduction: About 5-10% of newly diagnosed colorectal cancers have a genetic cause. Early detection is key to facilitate effective treatments and prevent future cancers. Genetic and genomic health information increasingly informs routine clinical care. However, some health care professionals have concerns about the potential for genetic information to inflict psychological harm on patients

Method: A systematic review was carried out using PRISMA guidelines. Six relevant databases were searched. Inclusion criteria followed those in our Prospero-published protocol: peer-reviewed quantitative and qualitative studies on the psychological well-being of adult asymptomatic individuals living with inherited colorectal cancer

Results: The search strategy yielded 1590 studies of which 33 were eligible. Eight studies were qualitative interviews and 25 were quantitative. Psychological distress, anxiety, depression, cancer worry, risk perception, quality of life, resilience, coping, and hopelessness were assessed using psychometric scales. Quantitative studies showed that there is a transient increase in anxiety, worry, and depression following genetic results which drop back to baseline level one year after the genetic results are given. Baseline is defined as immediately prior to genetic testing, when related worries may already be present. Overall, important factors that influence individuals' psychological well-being are decision making, risk perception, cancer worry, family relationships and coping mechanisms. Related positive outcomes are hopefulness, optimism, good communication within the family, and positive attitude

Conclusion: Risk factors, such as experience of nursing a relative through colorectal cancer, significant family history, lack of close family connections, poor family dynamics, and 'feeling' alone in the genetic diagnosis, can help clinicians to identify patients that are more likely to need additional support

Title: High Prevalence of MUTYH Associated Polyposis Among Minority Populations in Israel, due to Rare Founder Pathogenic Variants

Author: Reznick Levi, Gili

Author Institution: 1. The Genetics Institute, Rambam Health Care Campus, Haifa, Israel
2. Raphael Recanati Genetic Institute, Rabin Medical Center, Petach Tikva, Israel
3. Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
4. Gastroenterology Department, Rambam Medical Center, Haifa, Israel
5. Gastroenterology Institute, Chaim Sheba Medical Center, Tel-Hashomer, Israel
6. Division of Gastroenterology, Rabin Medical Center, Petach Tikva, Israel
7. Institute of Medical Genetics, Meir Medical Center, Kfar Saba, Israel
8. The Institute of Gastroenterology and Hepatology, Beer Sheva, Israel
9. Soroka University Medical Center, Faculty of Health Sciences, Beer Sheva, Israel
10. Baruch Padeh Medical Center, Poriya, Israel
11. Faculty of Medicine, Bar Ilan University, Galilee, Israel
12. Clalit National Cancer Control Center and Personalized Medicine Program, Haifa, Israel
13. Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel
14. The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
15. The Genetics Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Co-Authors: Gili Reznick Levi[1], Yael Goldberg[2,3], Hanna Segev[1], Itay Maza[4], Yuri Gorelik[4], Ido laish[5,3], Zohar Levi[6,3], Inbal Kedar[2], Sonia Naftali Nathan[2], Nitzan Sharon Swartzman[7], Naim Abu Freha[8,9], Maya Paritsky[10,11], Gad Rennert[12,13,14], Hagit Baris Feldman[15,3], Tamar Paperna[1], Karin Weiss[1,14], and Elizabeth E. Half[4,14].

Abstract text:

Background: Autosomal recessive conditions are common in consanguineous populations. As consanguinity is common among the Israeli Arab population, we evaluated the rate of MUTYH polyposis (MAP) among polyposis patients in this population and studied Pathogenic Variants (PVs) spectrum.

Methods: We reviewed health records of all Arab and Druze polyposis patients referred for counseling between 2013-2020, who fulfilled the Israeli Genetic Society criteria for MUTYH/APC testing in a tertiary center in Northern Israel, and four additional gastro -genetic clinics in Israel.

Results: The Northern cohort included 37 patients from 30 unrelated families. Eight families (26.6%) carried bi-allelic MUTYH PVs; The major variant p.Glu452del was detected in 6/8 Druze and Muslim families, who shared the same haplotype. Other PVs detected in Israel included p.Tyr56Ter, p.His57Arg, c.849+3A>C, p.Ala357fs and p.Tyr151Cys. Among bi-allelic carriers, 88% reported consanguinity, 100% had positive family history for polyposis or colorectal cancer (CRC). Generally, the age of CRC was 10 years younger than the age reported in the general MAP population.

Conclusions: MAP accounts for 27% of polyposis cases in the Arab population in Northern Israel. Mutation spectrum is unique, with high frequency of the founder p.Glu452del. Our results impact the genetic testing strategy in the Israeli Arab population.

Title:	LYNCH syndrome is associated with fecal and salivary dysbiosis
Author:	Mannucci, Alessandro
Author Institution:	1. Gastroenterology and Gastrointestinal Endoscopy, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy 2. Microbiology and Virology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy
Co-Authors:	Mannucci, Alessandro 1 (presenting author); Massimino, Luca 1; Puzzono, Marta 1; Ferrarese, Roberto 2; Danese, Silvio 1; Ungaro, Federica 1; Mancini, Nicasio 2; Cavestro, Giulia Martina 1.

Abstract text:

Introduction: The oral and fecal microbiota of Lynch syndrome patients (LSP) may differ from healthy controls (HC).

Method: We compared the fecal microbiota of 17 LSP (14 MSH2, 2 MLH1, 1 MSH6) vs 21 HC, and the oral microbiota of 37 LSP (9 MLH1, 23 MSH2, 2 MSH6, 3 PMS2) vs 11 HC. 16 LSPs had CRC, 2 gastric cancer, 1 pancreatic cancer, and 1 neuroendocrine tumor. On average, 9.2 years had elapsed from cancer treatment to microbiota collection. We purified and amplified the V3-V4 region of the 16s rRNA gene and discriminated microbial from human reads with BMTagger. For species/family/order level analysis, reads were mapped to the collection of all available genomes with Kraken2 for exact alignment of k-mers and accurate read classification. Relative abundances were calculated with Pavian. Differential abundances were performed with DESeq2 upon variance-stabilizing transformation.

Results: UMAP analysis could differentiate oral samples from fecal samples at the order, family, and species level (F1).
Fecal beta-diversity (but not alpha-diversity) differentiated LSP vs HC (F2). LSPs demonstrated a significant reduction in the abundance of fecal Firmicutes, including 8 bacterial orders, 16 bacterial families, and 51 bacterial species. LSPs also showed an increase in fecal Bacteroidetes: these included 23 bacterial orders, 36 bacterial families, and 98 bacterial species (F3-4)
Salivary alpha and beta diversity differentiated LSP vs HC (F2). LSPs demonstrated a significant reduction in salivary Proteobacteria (including 4 bacterial orders, 12 bacterial families, and 96 bacterial species) and an increase in salivary Firmicutes, with a higher expression of 5 bacterial orders, 8 bacterial families, and 39 bacterial species (F5-6).

Conclusion: LSP demonstrated a significant disruption of both the oral and fecal microbiota. Firmicutes became the dominant salivary phylum over Proteobacteria. The increase in fecal Bacteroidetes led to a significant decrease in fecal Firmicutes.

Title:	Oligodontia-colorectal cancer syndrome with cleft palate as a possible new feature in a cohort of 13 AXIN2 variant carriers
Author:	Roht, Laura
Author Institution:	(a)Department of Clinical Genetics, Genetic and Personalized Medicine Clinic, Tartu University Hospital, Tartu, Estonia (b) Department of Clinical Genetics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia (c) Department of Medical Genetics, Oslo University Hospital, Oslo, Norway (d) Norwegian National Resource Centre for Oral Health in Rare Diagnosis, Lovisenberg Diaconal Hospital, Oslo, Norway (e)Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands (f) Department of Clinical Genetics and Genomics, Mayo Clinic, Jacksonville, United States of America (g) Department of Radiology, Tartu University Hospital, Tartu, Estonia (h) Broad Institute of MIT and Harvard, Cambridge, MA, USA (i) Divisions of Genetics and Genomics and Newborn Medicine, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
Co-Authors:	Hanne K. Hyldebrandt (c), Astrid T. Stormorken (c), Hilde Nordgarden (d), Rolf H. Sijmons (e), Dennis K. Bos (e), Douglas Riegert-Johnson (f), Sarah Mantia-Macklin (f), Pilvi Ilves (g), Kai Muru (a,b), Monica H. Wojcik (h,i), Tiina Kahre (a,b), Katrin Õunap (a,b)

Abstract text:

Introduction: AXIN2 pathogenic variants are known to be connected to tooth agenesis, colon polyps and colon cancer. As the phenotype is quite rare and not fully known, our aim was to collect additional genotypic and phenotypic information.

Methods: Here we report 13 individuals with a heterozygous AXIN2 disease-causing variant who have a diverse phenotype of oligodontia-colorectal cancer syndrome (OMIM 608615) or oligodontia-cancer predisposition syndrome (ORPHA 300576).

Results: Three individuals from one family also had cleft palate, which might be a new clinical feature of AXIN2 phenotype, besides AXIN2 polymorphisms have been associated with oral clefting in population studies. AXIN2 gene is already on multigene cancer panel tests, further research should be done to decide if it should be included in cleft lip/palate multigene panels.

Conclusion: More clearness about oligodontia-colorectal cancer syndrome, about the variable expression and associated cancer risks is required to enhance clinical management and to establish guidelines for surveillance. We gathered information about the guided surveillance, which might contribute to clinical management of these patients.

Title: The Impact of Oophorectomy on Survival from Breast Cancer in Patients with CHEK2 Mutations

Author: Lubinski, Jan

Author Institution: 1 International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University Poland; 2 Department of Clinical Genetics and Pathology, University of Zielona Góra, Zielona Góra, Poland 3 West Pomeranian Oncology Center, Radia

Co-Authors: Monika Cieszynska 1, Wojciech Kluzniak 1, Dominika Wokołorczyk 1, Cezary Cybulski 1, Tomasz Huzarski 1,2, Jacek Gronwald 1, Michał Falco 3, Tadeusz Dẹbniak 1, Anna Jakubowska 1,4, Róza Derkacz 1,5 , Wojciech Marciniak 1,5 , Marcin Lener 1, Karolina Woron

Abstract text:

Introduction: The number of survivors of breast cancer is increasing worldwide due to wide-scale screening programs and effective therapies. A diagnosis of breast cancer increases the risk of psychosocial distress, cardiovascular disease, and second primary cancers, including those of the contralateral breast, endometrium, ovary, colon, lung, and thyroid. It is important to consider the risk of secondary primary cancers in the follow-up of breast cancer survivors and to identify those at the highest risk
The positive association between breast and thyroid cancers suggests a possible common genetic susceptibility in some cases. The goal of this study was to estimate the risk of thyroid cancer following breast cancer and to identify therapeutic and genetic risk factors for the development of thyroid cancer after breast cancer.

Methods: We followed 10,832 breast cancer patients for a mean of 14 years for new cases of thyroid cancer. All women were genotyped for three Polish founder mutations in BRCA1 (C61G, 4153delA, 5382insC) and four mutations in CHEK2 (1100delC, IVS2 + 1G/A, del5395, I157T). Information was collected on chemotherapy, radiotherapy, hormonal therapies, and oophorectomy.

Results: Of the 10,832 women, 53 (0.49%) developed a second primary thyroid cancer. Based on Polish population statistics, the expected number was 12.4 (SIR = 4.3). The ten-year risk of developing thyroid cancer was higher
in women who carried a CHEK2 mutation (1.5%) than in women who carried no mutation (0.9%). The age-adjusted hazard ratio for developing thyroid cancer was 1.89 (0.46–7.79; p = 0.38) for those with a CHEK2 protein-truncating mutation and 2.75 (1.29–5.85; p = 0.009) for those with a CHEK2 missense mutation.

Conclusion: The risk of thyroid cancer in women with a (truncating or missense) mutation in CHEK2 is approximately nine times that of the general population of Poland. Approximately 19% of thyroid cancers after breast cancer are attributable to CHEK2 mutations.

Title:	Why the combination of modeling and machine learning could be the future direction in mathematical oncology
Author:	Haupt, Saskia
Author Institution:	(1) Engineering Mathematics and Computing Lab (EMCL), Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University, Heidelberg, Germany (2) Data Mining and Uncertainty Quantification (DMQ), Heidelberg Institute for Theoretical Studies (HITS), Heidelberg, Germany (3) Department of Applied Tumor Biology, University Hospital Heidelberg and Cooperation Unit Applied Tumor Biology, German Cancer Research Center (DKFZ), Heidelberg, Germany
Co-Authors:	Saskia Haupt (1,2), Alexander Zeilmann (1,2), Aysel Ahadova (3), Magnus von Knebel Doeberitz (3), Matthias Kloor (3), Vincent Heuveline (1,2)

Abstract text:

In recent years, oncology has become an interdisciplinary field including experts from many medical disciplines but also mathematicians, computer scientists, and bioinformaticians.
Especially the field of mathematical oncology has expanded successfully with the aim of developing mathematical models and approaches to simulate cancer development and by this, better understand the underlying biological processes and improve current clinical procedures. Mathematical models are built based on medical expertise and the current understanding or hypotheses of cancer development making them explainable. However, the validation with clinical data is often challenging.

Besides mathematical modeling, artificial intelligence and machine learning are very prominent fields in data analysis and pattern recognition of various omics data and histological images. Here, machine learning algorithms are trained to learn the underlying rules of a system by using a large amount of data. Although machine learning algorithms are not fully understandable, they often outperform mathematical models in terms of accuracy.

Thus, a combination of mathematical modeling and machine learning while using the advantages of both fields seems very promising. In this talk, we will elaborate on this possible future direction of mathematical oncology with the example of Lynch syndrome cancer development, the most common inherited cancer predisposition syndrome. We show our recent advances in modeling Lynch syndrome colorectal carcinogenesis at different physical scales ranging from the DNA over the cell and crypt to the population level. Coming from the modeling side, we will point to the possibilities of adding machine learning to these models. We emphasize why this could be a very promising future research direction leading to explainable models of cancer development that are calibrated and validated by biomedical and clinical data in a straightforward and efficient way.

Title:	Clinically relevant combined effect of polygenic background, rare pathogenetic germline variants, and family history on colorectal cancer incidence
Author:	Aretz, Stefan

Author Institution:

1 Institute of Human Genetics, Medical Faculty, University of Bonn, Germany; National Center for Hereditary Tumor Syndromes, University Hospital Bonn, Germany; European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) / 2 Institute for Genomic Statistics and Bioinformatics, University Hospital Bonn, Germany / 3 Institute for Genomic Statistics and Bioinformatics, University Hospital Bonn, Germany; Institute for Medical Biometry, Informatics and Epidemiology, Medical Faculty, University Bonn, Germany / 4 Institute of Human Genetics, Medical Faculty, University of Bonn, Germany; / 5 Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg/ 6 Catalan Institute of Oncology-IDIBELL, ONCOBELL, Hospitalet de Llobregat, Barcelona, Spain; Biomedical Research Centre Network for Oncology (CIBERONC), Instituto Salud Carlos III, Madrid, Spain / 7 Department of Internal Medicine I, University Hospital Bonn, Germany; National Center for Hereditary Tumor Syndromes, University Hospital Bonn, Germany; European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) / 8 Catalan Institute of Oncology-IDIBELL, ONCOBELL, Hospitalet de Llobregat, Barcelona, Spain; Biomedical Research Centre Network for Oncology (CIBERONC), Instituto Salud Carlos III, Madrid, Spain; Hereditary Cancer Program, Catalan Institute of Oncology-IDBIGI, Girona, Spain; European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) / 9 Catalan Institute of Oncology-IDIBELL, ONCOBELL, Hospitalet de Llobregat, Barcelona, Spain; Biomedical Research Centre Network for Oncology (CIBERONC), Instituto Salud Carlos III, Madrid, Spain; European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) / 10 Institute of Human Genetics, Medical Faculty, University of Bonn, Germany; Centre for Human Genetics, University of Marburg, Germany; Institute of Neuroscience and Medicine, Research Center Jülich, Germany / 11 Institute for Medical Biometry, Informatics and Epidemiology, Medical Faculty, University Bonn, Germany / 12 Institute for Genomic Statistics and Bioinformatics, University Hospital Bonn, Germany; Centre for Human Genetics, University of Marburg, Germany

Co-Authors:	Stefan Aretz1, Emadeldin Hassanin2, Hannah Klinkhammer3, Friederike David4, Dheeraj Bobbili5, Rana Aldisi2, Nuria Dueñas6, Claudia Perne1, Markus M. Nöthen4, Robert Hüneburg7, Peter Krawitz2, Joan Brunet8, Gabriel Capella9, Patrick May5, Andreas Forstner10, Andreas Mayr11, Isabel Spier1, Carlo Maj12

Abstract text:

Introduction: Polygenic risk scores (PRS) can be used for CRC risk stratification in the general population and among individuals predisposed for hereditary CRC. The study aims to investigate to which extent PRS, high-impact monogenic variants for Lynch syndrome and polyposis, and family history (FH) affect CRC risk.

Method:. 163,516 individuals from the UK Biobank were stratified according to: 1. carrier status for germline pathogenic variants (PV) in CRC susceptibility genes (*APC, MLH1, MSH2, MSH6, PMS2*); 2. low (<20%), intermediate (20-80%), or high (>80%) PRS; and 3. FH of CRC. Multivariable logistic regression and Cox proportional hazards models were applied to compare odds ratios (OR) and lifetime incidences.

Result: Taking non-carriers with intermediate PRS as reference, we show that PV carriers with high PRS had four times higher OR than carriers with low PRS (OR = 17.5 and 3.9). CRC cumulative lifetime incidence by age 75 years for carriers of PV with low PRS is 40% and reaches 74% for carriers with high PRS, compared to 6% and 22% for non-carriers, respectively. A positive FH is associated with a further increase of the cumulative incidence reaching 98% for carriers and 26% for non-carriers. In non-carriers with a negative FH, but a high PRS, the CRC risk was doubled. The full model including PRS, carrier status, and FH improved the area under the curve for risk prediction (0.704). PRS and FH modifies the relative risk across all five genes; the effect of PRS and FH is conversely related to the penetrance of the gene.

Conclusions: Irrespective of a sporadic or monogenic background, the CRC risk is strongly influenced by the PRS. A high PRS and positive FH in non-carriers confers a CRC risk similar to a low PRS and negative FH in carriers of PV in moderate penetrance genes. The implementation of a PRS in routine patient care will likely improve individualised risk stratification for sporadic and monogenic CRC, which will guide tailored preventive strategies.

Title:	Hypercalcemic Ovarian carcinoma and mutation of SMARCA4: we need a prematurely testing
Author:	Perez-Lopez, Maria-Eva
Author Institution:	University Hospital A Coruña (Spain)
Co-Authors:	Begoña Graña, Miguel Alonso, Igor Gomez-Randulfe, Beatriz Alonso, Sofía Silva, Patricia Cordeiro, Cristina Reboredo, Rocio Lesta, Silvia Antolin and Lourdes Calvo.

Abstract text:

Introduction: Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare and aggressive form of ovarian cancer. SCCOHT tumors
have inactivating mutations in SMARCA4 (BRG1), one of the two mutually exclusive ATPases of the SWI/SNF chromatin
remodeling complex
SMARCA4 has been shown to be involved in developmental processes, transcriptional regulation, DNA repair, cell cycle control,
and cancer Inactivating mutations in SMARCA4 leads to loss of expression of protein within the nucleus and characterizes
malignancies that are related, with SMARCA-de^ciency. SMARCA4 was identi^ed as a tumor suppressor gene; however, recent
reports have revealed an oncogenic role of SMARCA4
We present a family history of cancer whose evolution lead us to need an ethical comittee evaluation and psychological support to
decide the children member treatment.

Method: The medical records of a family with four SCCOHT patients are displayed. Collected data included age, gender, family history of cancer, presenting symptoms, laboratory tests, previous malignancy, tumor characteristics, surgery type, and outcome.

Results: A fourteen years old girl underwent a prophyilactic oophorectomy because of a patogenic variant SMARCA4 in her and their 36 y
mother and 14 y sister, both of them deceased by SCCOHT. A ethic committee evaluation and psychological support was carry out previously to the surgery.

Conclusion: SCCOHT is characterized by a higher proportion of female, younger age, and agressive evolution. Patogenic variant in a family with
SMARCA4 and SCCOHT must be detected and tested prematurely because of their mortality and potential curative prophylactic
surgery.

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I consent to publication of the abstract on the EHTG website
I consent to publication of my abstract in Familial Cancer

Title:	The prevalence of mismatch repair deficiency in ovarian cancer: systematic-review and metanalysis
Author:	Ryan, Neil
Author Institution:	1. Clinical Medical School, University of Bristol, Bristol, UK. 2. Health Economics Group, University of Exeter Medical School, University of Exeter. 3. The Lancashire Women's and Newborn Centre, Burnley General Hospital, East Lancashire, UK. 4. Department of Obstetrics and Gynaecology, St Michaels Hospital, Bristol, UK. 5. Division of Evolution and Genomic Medicine, St Mary's Hospital, University of Manchester, Manchester, UK. 6. Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, St Mary's Hospital, Manchester, UK. 7. The Academic Women's Health Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
Co-Authors:	A Atwal Bsc1, T Snowsill PhD2, M Cabrera Dandy MRCOG3, T Krum BSc1 C Newton MD MRCOG4, DGR Evans MD FRCP5, EJ Crosbie PhD FRCOG6, NAJ

Abstract text:

Aims: The aim of this study is to conduct a systematic review of the literature and meta-analysis to provide an accurate estimate of the prevalence of MMRd in OC.

Background: Ovarian cancer (OC) is the most fatal gynaecological malignancy. Checkpoint inhibitors have shown clinical efficacy in mismatch repair deficient (MMRd) cancers and could be a powerful treatment in OC. However, their application in OC is limited due to limited data on the prevalence of MMRd.

Methods: We followed PRISMA guidelines throughout. Studies were identified by searches of online databases and followed by citation searching. All studies were reviewed by at least two independent reviewers. Proportions of test positivity were calculated by random and fixed- effects meta-analysis models. I2 score was used to assess heterogeneity.

Results: In total 54 studies and 17532 OCs were analysed for MMRd. The overall proportions of MMRd by immunohistochemistry, microsatellite instability analysis were 6.7% and 10.4%, respectively. MMRd was most common in endometrioid OC. We estimated that 46.7% (95% CI, 28.8 to 65.4) of OCs showing MMRd by IHC had a germline path_MMR variant identified. Lynch syndrome OC presented at an earlier age and stage. Studies however were of low quality.

Conclusions: Up to 16% of OC displays MMRd and therefore could be amenable to checkpoint inhibition therapy. However, further high-quality prospective studies are required, including trials researching the efficacy of check point inhibition in MMRd OC.

Title: The genomic and clinico-pathological characteristics of sebaceous skin lesions from people with Lynch syndrome

Author: Buchanan, Dan

Author Institution: 1 Colorectal Oncogenomics Group, Department of Clinical Pathology, The University of Melbourne, Parkville, Victoria, Australia. 2 University of Melbourne Centre for Cancer Research, Victorian Comprehensive Cancer Centre, Parkville, Victoria, Australia. 3 Genomic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Parkville, Australia. 4Sullivan Nicolaides Pathology, Herston, Queensland, Australia. 5 Melbourne Bioinformatics, The University of Melbourne, Parkville, Victoria, Australia. 6Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Victoria, Australia. 7 Department of Medicine, The University of Melbourne, Parkville, Victoria, Australia.

Co-Authors: Daniel D. Buchanan1,2,3, Khalid Mahmood1,2,5, Mark Clendenning1,2, Anita Le1,2, Jihoon E. Joo1,2, Romy Walker1,2, Peter Georgeson1,2, Julia Como1,2, Susan Preston1,2, Sharelle Joseland1,2, Liz Donaldson3, Joanne Isbister3, Kirsty Storey3, Aung K. Win2,3,6, Mark A. Jenkins5,7, Michael D. Walsh4, Ingrid M. Winship3,7

Abstract text:

Introduction: A subset of people with Lynch syndrome develop sebaceous skin lesions. Mismatch repair (MMR) deficiency is frequently observed in sebaceous lesions, but is not diagnostic for Lynch syndrome. An effective tool to aid clinical decision making for germline MMR gene testing for people with sebaceous lesions is needed.

Methods: We studied 301 people with sebaceous lesions recruited from Sullivan Nicolaides Pathology, where pathologist-initiated MMR immunohistochemistry (IHC) is performed on sebaceous lesions, or via Family Cancer Clinics across Australia. Both MMR IHC and germline testing for Lynch syndrome was completed where possible. Clinico-pathological features, personal and family history of cancer, MMR IHC status were assessed against Lynch syndrome status. In addition, whole exome sequencing (WES, n=38) of sebaceous lesions was performed to investigate the somatic mutation profiles in both Lynch and non-Lynch lesions.

Results: 283 sebaceous lesions, with mean age at diagnosis of 65.7±10.8 years, comprised 192 (68%) adenomas, 55 (19%) carcinomas and 36 (13%) sebaceomas; 76% of all lesions occurred on the head and neck region. MMR-deficiency was identified in 54% of lesions and Lynch syndrome identified in 62 (22%) of participants. Two carriers of biallelic MUTYH pathogenic variants were also identified. The tumour mutational burden of MMR-deficient Lynch lesions was significantly higher compared with MMR-proficient lesions (p<0.0001) but lower than MMR-deficient non-Lynch lesions (p<0.05). The tumour mutational signatures from Lynch lesions had low proportions of ultra-violet light exposure DNA damage signatures compared with the MMR-proficient lesions that appeared on the head and neck.

Conclusions: Further elucidation of the genotype-phenotype correlations, immune contexture and somatic mutation landscape in sebaceous neoplasia will help to improve triaging for identifying Lynch syndrome.

Title:	Detection of mismatch repair deficiency in colonoscopic biopsies and urine using a simple PCR multiplex with potential for postal urinary tumour surveillance in Lynch syndrome patients
Author:	Phelps, Rachel
Author Institution:	1. Biosciences Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK.2. Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK.
Co-Authors:	Rachel Phelps1, Richard Gallon2, Christine Hayes1, Eli Glover1, Philip Gibson3, Ibrahim Edidi3, Tom Lee4,5, Sarah Mills6, Adam Shaw7 Rakesh Heer2, Angela Ralte8, Ciaron McAnulty9 Mauro Santibanez-Koref1, John Burn2,9, Michael S. Jackson1

Abstract text:

Introduction: Microsatellite instability (MSI) analysis can identify mismatch repair (MMR) deficiency in colorectal cancers (CRCs) to screen for Lynch Syndrome (LS) and target immunotherapy. Biopsy analysis prior to tumour resection could inform surgery and therapeutics but can be limited by DNA quantity. Furthermore, analysis of voided urine samples could provide surveillance for Endometrial Cancer (EC) and Upper Tract Urothelial Cancer (UTUC), the 2nd and 3rd most common LS malignancies. Here, we develop an MSI assay suitable for low DNA quantities and assess its utility in small biopsies and voided urine.

Method: Our molecular inversion probe based MSI and BRAF c.1799T assay (PMID:31471937) was reconfigured to a two-step multiplex PCR (mPCR) using the same bioinformatics pipeline and MSI classifier. Samples analysed included 150 resected CRCs, 18 individual and composite colonoscopic CRC biopsies from 4 LS patients, as well as tumour, pre and post-op urine samples from 2 further LS patients, one with a right kidney UC, the other a suspected EC. Urine samples were self-collected and delivered by hand or post.

Results: The mPCR assay sampled >140 unique molecules per marker from <1ng of DNA. It was validated in resected CRCs, with 96%-100% sensitivity and specificity for MSI, and identified 67/68 BRAF c.1799T>A variants. Increased MSI was detected in CRC biopsies from all 4 LS patients with MSI scores comparable to their resected tumours. Clear MSI signals were apparent in pre-op urine cell free DNAs (cfDNAs) from both the UC and EC patients, with approximately 60-70% of the cfDNAs being tumour derived. The signals matched those in the resected tumours and were not detected in post-op urines.

Conclusion: Our results suggest that mPCR-based amplicon sequence analysis of MSI and mutation hotspots in CRC biopsies is viable and could facilitate pre-surgery decision making, and that postal-based urine screening has the potential to detect UCs and ECs in LS patients.

Title:	Distinguishing the molecular profile of endometrial cancer by spectroscopy: A Diagnostic Cross-Sectional Study
Author:	Ryan, Neil
Author Institution:	1. University of Manchester. 2 University of Bristol. 3. Royal Infirmary of Edinburgh 4. University of Central Lancashire. 6 University of London (Imperial College). 7 Manchester University NHS Foundation Trust. 8 Lancashire Teaching Hospitals NHS Foundation Trust
Co-Authors:	N Ryan PhD MRCOG1,2,3, Camilo Morais PhD4, Kassio Lima PhD5, Maria Paraskevaid PhD6, Ceci Pow MBChB1, Gareth Evans MD1, James Bolton FRCPath7, Piere Martin-Hirsch MD8,Raissa Silva PhD5, Francis Martin PhD4, Emma Crosbie PhD FRCOG1

Abstract text:

Background: Endometrial cancer (EC) is not a homogenous entity. Different molecular groups are amenable to different treatments allowing personalised and effective treatment. However, molecular profiling is costly and timely which often leads to a delay in actionable results. Therefore, new technologies need to be explored. One potential technology is vibrational spectroscopy.

Methods: Cases of EC were assigned to the four TCGA groups (path_POLE, Microsatellite high (MSI-H), copy number high and no-specific molecular profile) by recognised methods. Attenuated total reflection – Fourier transform infrared spectroscopy (ATR-FTIR) was used to collect ten spectra from different regions of each tissue section. Samples were divided into training (70%) and test (30%) datasets before further multivariate analysis to investigate whether spectra could be grouped in line with the established molecular phenotype. Principal component analysis linear discriminant analysis (PCA-LDA) was performed initially. This was followed by Principal component quadratic discriminant analysis (PCA-QDA) and support vector machine (SVM) analysis.

Results: Overall, 314 ECs were included and two separate analyses were conducted; for the TCGA analysis 185 ECs were analysed.
PCA-QDA performed best for the correct classification of EC into the four TCGA molecular groups with an overall accuracy of 99.1%. Lynch syndrome associated EC vs non-Lynch syndrome associated cancer (including somatic MSI-H) accuracy, sensitivity and specificity was 93% 100% and 70% respectively. In Lynch syndrome associated EC vs EC found to have MLH1 promotor region hypermethylation an accuracy, sensitivity and specificity of 83%, 100% and 75% respectively was returned by PCA-LDA analysis.

Conclusion: ATR-FTIR enabled the accurate identification of EC into the four molecular groups. It performed well in identifying Lynch syndrome associated EC. These promising findings should be evaluated prospectively in larger studies.

Title: Non-BRCA mutation prevalence in hereditary breast and ovarian cancer syndrome in out centre

Author: Jimenez Ruiz, Francisco Javier

Author Institution: (1) Hospital Juan Ramón Jiménez

Co-Authors: Laura Sánchez Escudero (1)
                 María Amor Urbano (1)
                 María Yeray Rodríguez Garcés (1)
                 Marta Amérigo Góngora (1)
                 Isabel Aragón Manrique

Abstract text:

Introduction: Hereditary breast and ovarian cancer syndrome beyond BRCA is also related to other high-risk genes such as TP53, PTEN, CDH1, PALB2; and moderate or low risk of breast cancer (BC), ATM, CHEK2, MLH1, MSH2, MSH6, PMS2 or ovarian cancer (OC), RAD51C, RAD51D, BRIP1, MLH1 and MSH2. The objective of our study is to determine the prevalence in our Centre of non-BRCA mutation involved in increasing the risk of BC and/or OC.

Method: A total of 330 families from 2015 to 2022 were studied at the Juan Ramón Jiménez Hospital with non-informative results for BRCA 1 and 2. A multi-gene panel study was performed in 288 of them using NGS. We analyzed ATM, BRIP1, CDH1, CHEK2, MLH1, MSH2, MSH6, PMS2, PALB2, PTEN, RAD51C, RAD51D, STK11 and TP53. Sanger sequencing analysis was used to confirm the non-BRCA mutation identified by NGS analysis. Statistical analysis was performed with the SPSS v.22.

Results: The median age at diagnosis of analyzed BC or OC patients was 45 years (28–73) and 59 years (56-62), respectively. Non-BRCA mutations were detected in blood sample in 43 (19.7%) families (eighteen [41.9%] in ATM, seven [16.3%] in CHEK2, five [11.6%) in MUTYH, five [11.6%] in TP53, two [4.6%] in PTEN, two [4.6%] in PALB2, one [2.3%] in RAD51C, one [2.3%] in BRIP1, one [2.3%] in CDH1 and one [2.3%] in RAD51D.

Conclusion: We support the importance of the use of multi-gene panels in the study of hereditary breast and ovarian cancer. We found high-risk non-BRCA pathogenic variations in 4.16% of cases. Non-BRCA mutations detection benefited our population and their relatives. Primary and secondary prevention was recommended based on appreciation of the early onset of the disease and family history. The high-risk genes proportion in our study (4.16%) was elevated compared to previously described (around 2.5%). We also enhance the higher prevalence of mutations in non-BRCA genes (10.76%) found in our population compared to the literature (around 6%).

Title:	Assessment of the ability of the polygenic background to refine colorectal cancer risk in Lynch syndrome
Author:	Dueñas Cid, Nuria
Author Institution:	1. Hereditary Cancer Program, Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain 2. Program in Molecular Mechanisms and Experimental Therapy in Oncology (Oncobell), IDIBELL, Hospi-talet de Llobregat, Barcelona, Spain 3. Biomedical Re
Co-Authors:	N. Dueñas*1,2,3, H. Klinkhammer*4,5, N. Bonifaci*2, I. Spier6,7,8, A. Mayr4, E. Hassanin5, A. Díez-Villanueva9,10, V. Moreno9,10, M. Pineda1,2,3, C. Maj5, G. Capellá1,2,3,8, S. Aretz**6,7,8, J. Brunet**1,2,3,8,11

Abstract text:

Introduction: LS-CRC incidences show significant variability according to gene, sex, continent and within the same family. The combined effect of single nucleotide polymorphisms (SNPs) as polygenic risk score (PRS) can stratify CRC risk in the general population, whereas its role in LS is still unclear. Our objective is to assess the ability of PRS to refine CRC risk prediction in European-descendant LS individuals.

Method: 1,465 European-descendant LS individuals (557 MLH1, 517 MSH2, 299 MSH6 and 92 PMS2) and 5,656 population controls from two independent cohorts were included. Two events were considered: CRC (712 cases and 753 CRC-free LS individuals; mean age of 56.4 and 47.1, respectively) and CRC or high-grade adenoma (hgAd) (744 cases and 721 CRC or hgAd-free LS individuals, mean age of 56.2 and 46.9, respectively). A 91-SNP weighted PRS was applied. A Cox proportional hazard regression model with "family" as a random variable (Frailty model) was performed including polypectomy as time-dependant variable. A meta-analysis combining both cohorts was conducted. All p-values were corrected for multiple testing by using False Discovery Rate (FDR) correction.

Results: Higher PRS tended to be associated with slightly higher CRC risk in the whole LS cohort, MSH6, and in LS individuals diagnosed with early-onset CRC (<50 years) when considering CRC as event (HR: 1.016 (1.003-1.030); p_FDR_corrected=0.298; HR: 1.052 (1.012-1.092); p_FDR_corrected=0.204; HR: 1.022 (1.007-1.038); p_FDR_corrected=0.204, respectively), and CRC or hgAd as event (HR: 1.019 (1.005-1.032); p_FDR_corrected=0.202; HR: 1.026 (1.004-1.049); p_FDR_corrected=0.202; HR: 1.016 (1.002-1.030); p_FDR_corrected=0.202, respectively). Moreover, PRS showed slightly higher CRC risk in MSH2 when considering CRC or hgAd as event (HR: 1.016 (1.001-1.031); p_FDR_corrected=0.202).

Conclusions: PRS might be able to refine CRC risk in European-descendant LS population. A higher sample size is needed for confirmation.

Title: Mutation rate evolution drives immune escape in mismatch repair-deficient cancer

Author: Jansen, Marnix

Author Institution: 1 UCL Cancer Institute, University College London, London, UK; 2 Centre for Medical Image Computing, University College London, London, UK; 3 Cancer and Evolution Lab, Barts Cancer Institute, Queen Mary University of London, London, UK; 4 Department of Mathematics and Geosciences, University of Trieste, Trieste, Italy; 5 Evolutionary Genomics and Modelling Lab, Centre for Evolution and Cancer, The Institute of Cancer Research, London, UK; 6 Department of Gastrointestinal Oncology, University College London Hospital, London, UK; 7 Department of Pathology, University College London Hospital, London, UK; 8 Breast Cancer Now Histopathology Core, Institute of Cancer Research, London, UK; 9 HSL-AD, London, UK; 10 Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands; 11 Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands

Co-Authors: Hamzeh Kayhanian1, Panagiotis Barmpoutis1, Eszter Lakatos3, William Cross1, Giulio Caravagna4, Luis Zapata5, Kevin Litchfield1, Christopher Steele1, William Waddingham1, Dominic Patel1 8 , Salvatore Milite4, Chen Jin2, Ann-Marie Baker3, Christopher Ross1, Daniel Alexander2, Khurum Khan6 9 , Daniel Hochhauser1,6, Marco Novelli1,7, Benjamin Werner3, Naomi Guppy8,9, Josep Linares9, Genomics England Research Consortium, Marjolijn J.L. Ligtenberg10,11, Iris D. Nagtegaal10, Andrea Sottoriva5, Trevor Graham3, Nischalan Pillay1, Manuel Rodriguez-Justo1,7, Kai-Keen Shiu1,6, Marnix Jansen1,7

Abstract text:

Introduction: Secondary mismatch repair alterations, in particular frameshift alterations in the homopolymer tracts of the minor mismatch repair (MMR) genes MSH6 and MSH3, are frequently identified in MMR-deficient tumors. Such homopolymer mutations are currently thought to constitute neutral passenger mutations. However, recent studies have highlighted distinct and non-overlapping functions of the MutSa/b and MutL modules in DNA repair. These data suggest that secondary MMR alterations may actively modulate mutation accumulation during MMR-deficient cancer progression.

Method: Here we map the clonal topography of MMR-deficient colorectal cancer to show that genomic MMR mutability co-evolves with neoantigen selection to drive intratumour diversification and immune escape. We exploit a combination of detailed molecular pathology and molecular evolution studies, bio-informatic analyses on bulk populations (Genomics England, TCGA), and mathematical modelling studies.

Results: We find that MLH1/PMS2-deficient microsatellite instability modulates subclonal DNA repair by toggling two hypermutable mononucleotide homopolymer runs (C8 and A8, respectively) through stochastic frameshift mutations in the MMR genes MSH6 and MSH3. This drives variation in subclonal mutation rate, mutation bias, and clonal HLA diversity during MMR-deficient cancer evolution. Combined experimental and simulation studies demonstrate that subclonal immune selection favors incremental MMR mutations. MMR-deficient cancers thus fuel intratumour heterogeneity by adapting subclonal mutation rate and mutation bias to immune selection, revealing a conserved co-evolutionary arms race between neoantigen selection and adaptive genomic mutability.

Conclusions: Our data reveals, surprisingly, that the complete MMR system unravels in incremental stages during MMRd cancer evolution in Lynch syndrome and sporadic patients and shows that mutation rate evolution is a key feature of MMRd cancer progression.