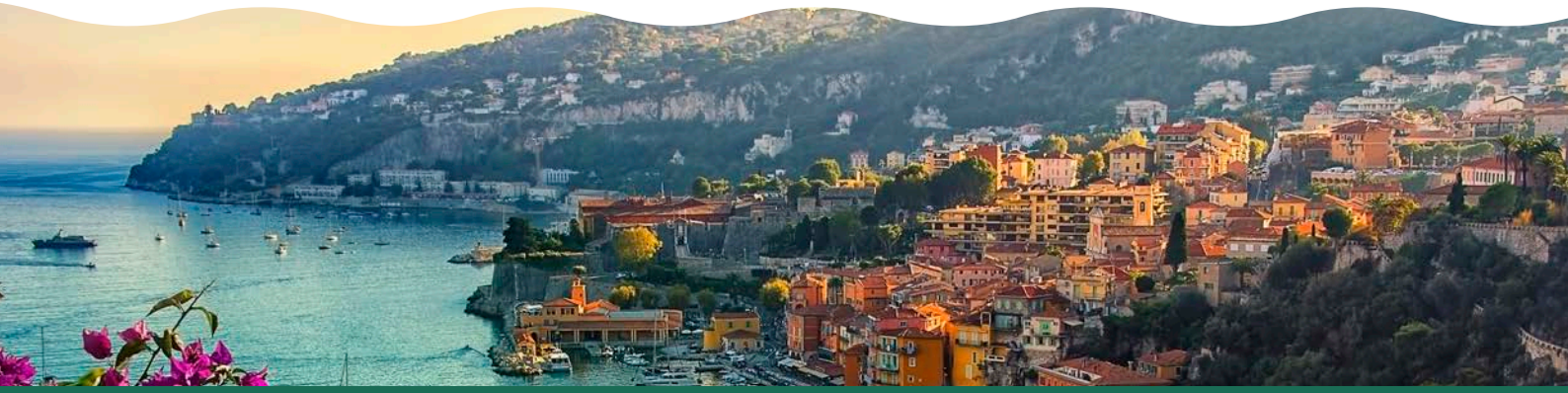

Final Programme

Third Meeting of the European Hereditary Tumour Group (EHTG) Nice, France

Sunday 23 – Tuesday 25 September 2018

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Meeting Overview

Sunday 23 September 2018

Time	Mistral
13:00 – 15:30	**EHTG Membership Meeting – Update and Vision** Election of EHTG representatives Road map
15:30 – 16:00	**Coffee Break**
16:00 – 19:00	**Registries Working Group**
19:00 – 19:45	**Welcome Reception for all delegates in the Poster and Exhibition area**

Monday 24 September 2018

07:45 - 08:45 **CAPP3 Collaborators Meeting (invitation only) - Restaurant Le 223**
08:00 - 09:00 **Annual PLSD Business Meeting - for PLSD contributors and other interested parties - Galion**

Time	Baie des Ange	Clipper	Fregate
09:00 – 12:30	**Genetics Working Group**	**Gastroenterology Working Group**	**Clinical Working Group**
	Coffee Break 10:30 – 11:00	**Coffee Break** 11:00 – 11:30	**Coffee Break** 10:30 – 11:00
	Meeting continues	**Meeting continues**	**Meeting continues**
12:30 – 13:30	**Lunch Break**		
13:30 – 17:00	**EMMR Working Group**	**EHTG Living Guidance Working Group**	
	Coffee Break 15:20 – 15:40		
17:15 – 18:00	**Closed EMMR Meeting**	**Coffee Break** 15:00 – 15:30	
		Meeting continues	

Tuesday 25 September 2018

Time	Baie des Ange	Clipper	Fregate
08:00 – 10:30	08:30 - 12:30 **Surgery Working Group: The Devil is in the Detail: Ileoanal Pouches**	**Pathology and Immunology Working Group**	10:00 – 10:45 **International Prospective Study of Duodenal Disease in MAP**
11:00 – 12:30		**Coffee Break** 11:00 – 11:30	
	Coffee Break 10:30 – 11:00	**Gene Panel Working Group**	
	Meeting continues		
12:30 – 13:30	**Lunch Break**		
13:30 – 15:00	**Systematic Gene Panel Testing for Hereditary GI Cancers in Europe - Guidance Debate**		
16:15 – 16:45	**Coffee Break**		
15:00 – 18:20	**State of the Art Lectures**		
18:20 – 19:30	**Farewell Reception**		
19:45 – 21:30	**Informal Dinner**		

Tuesday Informal Dinner at 19:45
Immediately after farewell drinks

Join us to wind down after a successful meeting!
Still need to buy a ticket? See us at Registration by 14:00 on Monday! Further details on page 19.

Visit www.ehtg.org for more information about the European Hereditary Tumour Group and how to become a member.

Welcome to the Third Meeting of the EHTG (now incorporated!)

On behalf of the directors of the European Hereditary Tumour Group (EHTG), we are delighted to welcome you to the 2018 EHTG meeting being held just ahead of the annual meeting of the European Society of Coloproctology (ESCP). Nice is nice!

We will start Sunday morning with a patient meeting where we plan to launch "Eurolynch". This is an open invitation to all parties interested in patient advocacy, better communication and networking for and with patients and their families. EHTG's vision is to provide a platform for patient networking in the area of hereditary cancer. Hosting meetings in different countries and back to back with other societies provides excellent opportunities to grow from year to year.

Don't miss the membership meeting on Sunday afternoon and contribute to shaping the Society for the future; we will appoint the Steering Committee and structure specific committees. World-wide registries recently have contributed enormously to our knowledge and are key to understanding better the syndromes that we believed we understood but were wrong about! The scientific program is jam-packed with the most up-to-date scientific and clinical topics that we will discuss during the meeting.

Tuesday morning will be devoted to two very topical sessions: Immunology, pathology and genetics on one hand and in parallel a most high-end video session on ileal pouches with the world's experts addressing their technical details and discussing the pros and cons of procedural steps that make the difference.

Keeping up the Mallorca Group tradition, we put importance to the social encounters and nice evening dinners. Nice is the ideal place to go out for a stroll, a walk on the beach with plenty of beautiful locations, restaurants and excellent food. The town is small enough to move around easily, big enough to be on your own if you like and again small enough to bump into nice people.

We would like to thank all of our sponsors for their support this year. Without their involvement, this meeting would not have been possible. We ask you to support their investment by taking time to speak with them during the coffee and lunch breaks. Our particular thanks go to our Gold Sponsor Promega, Silver Sponsor Invitae, Bronze Sponsor SLA Pharma and Educational Sponsor Bowel Cancer UK, EACR and Inomed.

Wishing you a very fruitful meeting, with updated scientific knowledge, inspiring discussions, new collaborations and new friends.

Prof. Gabriela Möslein, Chair / Secretary

EHTG Directors:
Prof. Sir John Burn
Prof. Pål Møller
Prof. Gabriela Möslein
Prof. Julian Sampson

Monday will be an entire day dedicated to cutting edge specialized topical discussion and identification of most needed collaborative studies.

"The Devil is in the Detail: Ileoanal Pouches" will address innovation in the field including TaTME for benign conditions, reassess the value of continent ileostomies and learn tips and tricks from the videos of leading world experts.

Tuesday afternoon will be a plenary with a consensus session for European gene panel testing (!). The last session gives an update on the newest aspects in hereditary GI predisposition to cancer syndromes in state of the art lectures from world experts.

"Living Guidance for gene panel testing and clinical management" - join the debate and help make sure that the EHTG living guidance that will be hosted on the website for members is always up to date. The final Delphi voting will take place on Monday afternoon – be sure to join!

Opening Times

	Registration	Presentation Check In	Poster Desk
Sunday	09:00 – 19:30	09:00 – 19:30	09:00 – 19:30
Monday	07:00 – 18:00	07:00 – 18:00	07:00 – 10:00
Tuesday	07:00 – 16:00	07:00 – 14:00	

EHTG Programme Committee

Sir John Burn / EHTG Director
Pål Møller / EHTG Director
Gabriela Möslein / EHTG Director
Julian Sampson / EHTG Director
Francesc Balagauer
Lucio Bertario
Gabriel Capella
Evelein Dekker
Mev Dominguez Valentin
Ian Frayling
Elke Holinski-Feder
Roel Hompes
Andrew Latchford
Finlay Macrae
Monika Morak
Marta Pineda Riu
Luigi Ricciardiello
Sanne ten Broeke

Secretariat

C/o Integrity International Events Ltd,
The Coach House, 7 St Alban's Rd, Edinburgh, EH9 2PA, UK
T: **+44 131 624 6040**
E: ehtg@integrity-events.com

Contact phone number during the meeting:
+44 7734 425 210 – Lindsey Whitehouse

About Meeting Sessions

The official meeting language is English.

Questions: sessions may vary as to whether questions are invited at the end of all presentations or after each speaker. Chair persons will direct you. Audience microphones will be located at fixed points. Please make your way to the nearest microphone and wait for the Chair to take your question.

Speaker/Presentation Check-In Information

The Presentation Check-In area is at the Registration Desk in the hotel lobby. All speakers are requested to check in presentations in advance.

Please note that it will not be possible to use your own laptop during your presentation.

Presentations will be made available on the member area of the EHTG website after the meeting, together with videos of Tuesday's sessions.

Scientific Programme

Sunday 23 September 2018

Time	Session
13:00 – 15:30 Mistral / Ground Floor	**EHTG MEMBERSHIP MEETING – UPDATE AND VISION** **Chairs:** *John Burn (UK), Pål Møller (Norway), Gabriela Möslein (Germany), Julian Sampson (UK)*
	Election of EHTG representatives
	Road map
15:30 - 16:00	**Coffee Break**
16:00 – 19:00 Mistral / Ground Floor	**WORKING GROUP – REGISTRIES**
16:00 – 17:00	**POPULATION BASED REGISTRIES** **Chairs:** *Mark Jenkins (Australia), Jukka-Pekka Mecklin (Finland)*
16:00 – 16:10	**Australian/New Zealand registries** – *Mark Jenkins (Australia)*
16:10 – 16:20	**N60: Lynch syndrome registries in South America** – *Mev Dominguez (Norway)*
16:20 – 16:30	**N01: The German HNPCC Consortium: aims, structure, methods and data** – *Christoph Engel (Germany)*
16:30 – 16:40	**N88: The Finnish Registry** – *Toni Seppälä (Finland)*
16:40 – 17:00	**Discussion**
17:00 – 18:15	**INTERNATIONAL RESEARCH REGISTRIES** **Chairs:** *Pål Møller (Norway), Lone Sunde (Denmark)*
17:00 – 17:15	**C4CMMRD** – *Chrystelle Colas (France)*
17:15 – 17:30	**CCFR** – *Mark Jenkins (Australia)*
17:30 – 17:45	**N09: Worldwide study of cancer risks for Lynch syndrome: International Mismatch Repair Consortium (IMRC)** – *Mark Jenkins (Australia)*

Sunday 23 September 2018

Time	Session
17:45 – 18:00	**N39: The Prospective Lynch Syndrome Database** – *Pål Møller (Norway), Toni Seppälä (Finland), Julian Sampson (UK), Mev Dominguez (Norway)*
18:00 – 18:15	**Discussion**
18:15 – 19:00	**GENE-SPECIFIC VARIANT DATABASES** **Chairs:** *Stefan Aretz (Germany), Finlay Macrae (Australia)*
18:15 – 18:30	**MMR variant database** – *Finlay Macrae (Australia)*
18:30 – 18:40	**APC** – *Stefan Aretz (Germany)*
18:40 – 18:50	**SMAD4/BMPR1A** – *Karl Heinimann (Switzerland)*
18:50 – 19:00	**Discussion**
19:00 - 19:45	**Welcome Reception for all delegates in the Poster and Exhibition area**

Monday 24 September 2018

Time	Session
09:00 – 12:30 Baie des Ange / Level -2	**WORKING GROUP - GENETICS** **Chairs:** *Gabriel Capella (Spain), Mev Dominguez (Norway)*
09:00 – 09:10	**The algorithms used for analysing the PLSD data** – *Pål Møller (Norway)*
09:10 – 09:30	**N33: Validation and updating of Path_MLH1 in cases with class 4 and 5 genetic variants; a Prospective Lynch Syndrome Database (PLSD) report** – *Toni Seppälä (Finland)*
09:30 09:50	**N40: Validated and updated risks for and survival after cancer by age and gender in Path_MSH2 carriers; a Prospective Lynch Syndrome Database (PLSD) report** – *Pål Møller (Norway)*
09:50 – 10:10	**N07: Cancer risks by age and gender and survival after cancer in Path_MSH6 carriers: a Prospective Lynch Syndrome Database (PLSD) report** – *Julian Sampson (UK)*
10:10 – 10:30	**N37: Cancer incidences by age in Path_PMS2 carriers: a report from the Prospective Lynch Syndrome Database (PLSD)** – *Mev Dominguez (Norway)*
10:30 – 11:00	**Coffee Break in the Poster and Exhibition area**

Monday 24 September 2018

Time	Session
11:00 – 12:10	**GENETIC ABSTRACTS** (5 mins for presentation + 2 mins for questions) **Chairs:** *Chrystelle Colas (France), Lene Rasmussen (Denmark)*
11:00 – 11:07	**N66: The ICCON Australian database of mismatch repair variants** – *Finlay Macrae (Australia)*
11:07 – 11:14	**N69: Interpretation of inheritable DNA variation: room for error across genetic services?** – *Finlay Macrae (Australia)*
11:14 – 11:21	**N08: The apparent genetic anticipation in PMS2-associated Lynch syndrome families is explained by birth-cohort effect** – *Sanne W. ten Broeke (The Netherlands)*
11:21 – 11:28	**N24: Systematic linkage of all diagnostic hereditary cancer genotypes to the National Cancer Registry** – *Fiona McRonald (UK)*
11:28 – 11:35	**N50: Age-related efficiency of BRAF V600E mutational testing for the exclusion of Lynch syndrome in MSI colorectal cancers** – *Aysel Ahadova (Germany)*
11:35 – 11:42	**N72: CSTF2T and ACTB discern sporadic from FAP-associated colon carcinomas at various stages of carcinogenesis on the proteomic level** – *Timo Gemoll (Germany)*
11:42 – 11:49	**N19: Colorectal cancer risk is not increased in NTHL1 heterozygous mutation carriers** – *Abi Ragunathan (Australia)*
11:49 – 11:56	**N55: A genetic variant in telomerase gene modifies cancer risk in Lynch syndrome patients harbouring MSH2 mutations** – *Bente Talseth-Palmer (Australia)*
11:56 – 12:03	**N59: Highly sensitive MLH1 methylation analysis in blood allows the identification of low-level epigenetic mosaicism** – *Gabriel Capella (Spain)*
12:03 – 12:10	**N18: Deciphering the contribution of recently proposed polyposis predisposing genes** – *Mariona Terradas (Spain)*
12:10 – 12:30	**COLLABORATIVE STUDIES**
12:10 – 12:20	**Collaborative study for a better estimation of cancer risks in rare digestives predispositions (CTNNA11 family project)** – *Chrystelle Colas (France)*
12:20 – 12:30	**Initiatives and strategies of ESBB (European, Middle Eastern & African Society for Biopreservation & Biobanking) for empowering biosharing accross EMEA** – *Jens Habermann (Germany)*

Monday 24 September 2018

Time	Session
09:00 – 12:30 Clipper / Level -2	**WORKING GROUP – GASTROENTEROLOGY** **Chairs:** *Francesco Balagaur (Spain), Luigi Ricciardiello (Italy)*
09:00 – 09:20	**Chemoprevention of hereditary GI cancers: state of the art (15' + 5' discussion) –** *Luigi Ricciardiello (Italy)*
09:20 – 09:40	**How should we design the next chemopreventive trials (15' + 5' discussion)** – *Evelein Dekker (The Netherlands)*
09:40 – 10:00	**Quality in endoscopy: does chromoendoscopy help in managing LS?** – *Francesc Balaguer (Spain)*
10:00 – 11:00	**Roundtable discussion of cases (on clinical/endoscopic management)** – *Andrew Latchford (UK)* **Cases: Duodenal polyposis; serrated polyposis; juvenile polyposis**
11:00 – 11:30	**Coffee Break in the Poster and Exhibition area**
11:30 – 12:00	**HI-SPEED ABSTRACT PRESENTATIONS** (3 mins for presentation + 2 mins for questions) **Chairs:** *Evelein Dekker (The Netherlands), Andrew Latchford (UK)*
11:30 – 11:35	**N31: Identification of clinical, genetic and endoscopic predictors of incident colorectal cancer in Lynch syndrome** – *Ariadna Sanchez Garcia (Spain)*
11:35 – 11:40	**N80: An international study of duodenal disease in MAP: incidence of polyposis and cancer** – *Laura Thomas (UK)*
11:40 – 11:45	**N41: Small bowel neoplasia detection in Lynch syndrome using video capsule endoscopy** – *Raffaella Alessia Zuppardo (Italy)*
11:45 – 11:50	**N82: Endocuff-assisted colonoscopy versus standard colonoscopy in the surveillance of serrated polyposis syndrome. A randomized, controlled and multicenter study** – *Liseth Rivero Sánchez (Spain)*
11:50 – 11:55	**N45: High-definition white-light colonoscopy versus chromoendoscopy for surveillance of lynch syndrome. A multicenter, randomized and controlled study (EndoLynch Study)** – *Liseth Rivero Sánchez (Spain)*
11:55 – 12:00	**N36: Back to back comparison of colonoscopy with virtual chromoendoscopy using third generation narrow band imaging system to chromoendoscopy with indigo carmine in Lynch syndrome patients** – *Elia Samaha (France)*

Monday 24 September 2018

Time	Session
12:00 – 12:30	**COLLABORATIVE STUDIES**
12:00 - 12:15	**N02: Opportunities for collaboration: analysis of longitudinal data in Lynch syndrome carriers to inform development and calibration/validation of a new LS screening model – "Policy1-Lynch"** – *Yoon-Jung Kang (Australia)*
12:15 - 12:30	**N03: Prevalence, phenotype and clinical consequences of mosaicism in APC and other colorectal cancer and polyposis associated genes** – *Manon Suerink (The Netherlands)*
12:30 – 13:30	**Lunch Break**
09:00 – 12:30 Fregate / Level -2	**WORKING GROUP - CLINICAL**
09:00 – 10:30	**CLINICAL ABSTRACTS** (8 mins for presentation + 2 mins for questions) **Chairs:** *Laura Renkonen-Sinisalo (Finland), Ingrid Winship (Australia)*
09:00 – 09:10	**N35: An assessment of endometrial cancer risk markers in lynch syndrome patients** – *Angel Alonso Sanchez (Spain)*
09:10 – 09:20	**N81: Genomic and transcriptomic profiling of duodenal adenomas in familial adenomatous (FAP) and MUTYH-associated polyposis (MAP)** – *Elena Meuser (UK)*
09:20 – 09:30	**The phenotype of POLE and POLD1** – *Ingrid Winship (Australia)*
09:30 – 09:40	**N87: SELINA – clinical trial on lowering the risk of malignancies by optimizing selenium levels in females from families with hereditary breast cancer** – *Jan Lubinski (Poland)*
09:40 – 09:50	**N38: Yield of Lynch syndrome surveillance for individual MMR genes** – *Anja Wagner (The Netherlands)*
09:50 – 10:00	**N43: Hide and seek with hereditary cancer: testing the effectiveness and cost-effectiveness of implementation approaches for translating Lynch syndrome evidence into practice** – *Natalie Taylor (Australia)*
10:00 – 10:10	**N83: Surveillance recommendations for first-degree relatives of patients with unexplained multiple colorectal adenomas: a nationwide survey of UK regional genetic services** – *Bianca Desouza (UK)*

Monday 24 September 2018

Time	Session
10:10 – 10:20	**N58: The cost of identifying Lynch syndrome carriers in Australia** – *Mary Dillon (Finland)*
10:20 – 10:30	**N11: A dominantly inherited 5'UTR variant causing methylation associated silencing of BRCA1 as a novel cause of breast and ovarian cancer** – *Gareth D. Evans (UK)*
10:30 – 11:00	**Coffee Break in the Poster and Exhibition area**
	Chairs: *Gareth D. Evans (UK), Zohar Levi (Israel)*
11:00 – 11:20	**N27: The management of gynaecological cancers in Lynch syndrome: the Manchester International Consensus Meeting** – *Emma Crosbie (UK)*
11:20 – 11:40	**N42: Improving triaging of patients with sebaceous neoplasia for the identification of Muir-Torre/ Lynch syndrome** – *Ingrid Winship (Australia)*
11:40 – 12:00	**N67: Penetrance for carriers of a DNA mismatch repair gene specific variant** – *Aung Ko Win (Australia)*
12:00 – 12:30	**HIGH SPEED ABSTRACTS** (3 mins for presentation + 2 mins for questions)
12:00 – 12:05	**N47: Prevalence of mismatch repair deficiency in small bowel carcinomas and neuroendocrine tumours** – *Manon Suerink (The Netherlands)*
12:05 – 12:10	**N84: Mutations in MutYH gene among Russian patients with colorectal polyps** – *Alex Tsukanov (Russian Federation)*
12:10 – 12:15	**N63: Clinical and molecular characterization of Lynch-like syndrome** – *Maria Dolores Picó (Spain)*
12:15 – 12:20	**N61: Physical activity and the risk of colorectal cancer in Lynch syndrome** – *S Ghazaleh Dashti (Australia)*
12:20 – 12:25	**N68: A Multidisciplinary approach to familial pancreatic cancer enriches the proportion of patients with pancreatic cancer susceptibility** – *Giulia Martina Cavestro (Italy)*
12:25 – 12:30	**N05: Exogenous and endogenous associated factors to early onset colorectal cancer** – *Raffaella Alessia Zuppardo (Italy)*
12:30 – 13:30	**Lunch Break**

Monday 24 September 2018

Time	Session
13:30 – 17:15 Baie des Ange / Level -2	**WORKING GROUP - EUROPEAN MMR GROUP** **Chairs:** *Gabriel Capella (Spain), Elke Holinski-Feder (Germany), Monika Morak (Germany)*
13:30 – 14:35	**RNA AND SPLICING ANALYSES**
13:30 – 13:55	**Introduction: splicing variants and methods of analysis** – *Alexandra Martins (France), Monika Morak (Germany)*
13:55 – 14:10	**Standardization of a high throughput cDNA analysis and generation of SOPs** – *Elke Holinski-Feder (Germany)*
14:10 – 14:35	**Interpretation rules for cDNA results** – *Marta Pineda (Spain)*
14:35 – 15:40	**SELECTED ABSTRACT PRESENTATIONS**
14:35 – 14:45	**N57: Comprehensive constitutional (epi)genetic characterization of Lynch-like patients** – *Marta Pineda (Spain)*
14:45 – 14:55	**N65: Etiology and characterization of Lynch-like syndrome patients** – *Mar Giner Calabuig (Spain)*
14:55 – 15:20	**Tumour signatures and variant classification** – *Gabriel Capella (Spain)*
15:20 – 15:40	**Coffee Break in the Poster and Exhibition area**
15:40 – 16:15	**FUNCTIONAL PROTEIN TESTS**
15:40 – 16:15	**Functional analyses of protein variants and promoter variants: strengths and limitations** – *Guido Plotz (Germany)*
16:15 – 17:15	**SELECTED ABSTRACT PRESENTATIONS**
16:15 – 16:27	**N34: A functional assay-based procedure to classify mismatch repair gene variants in Lynch syndrome** – *Lene Juel Rasmussen (Denmark)*
16:27 – 16:37	**N53: Discordant IHC MMR staining and MSI results in tumors of MSH6 mutation carriers** – *Manon Suerink (The Netherlands)*
16:37 – 16:47	**N54: Characterisation of mismatch repair variants submitted to the International Mismatch Repair Consortium (IMRC)** – *Jeanette Reece (Australia)*
16:47 – 17:15	**Discussion**

Monday 24 September 2018

Time	Session
17:15 – 18:00 Baie des Ange / Level -2	**Closed EMMR meeting – by invitation only**
13:30 – 18:00 Clipper / Level -2	**WORKING GROUP EHTG LIVING GUIDANCE** **DELPHI VOTING SESSION (BRING YOUR SMARTPHONE!)**
13:30 – 15:00	**SYSTEMATIC GENE PANEL TESTING** **Chairs:** *John Burn (UK), Ian Frayling (UK)*
15:00 – 15:30	**Coffee Break in the Poster and Exhibition area**
15:30 – 18:00	**CLINICAL MANAGEMENT** **Chairs:** *Andrew Latchford (UK), Gabriela Möslein (Germany) Toni Seppälä (Finland)*

Tuesday 25 September 2018

Time	Session
08:30 – 12:30 Baie des Ange / Level -2	**EHTG SURGERY SESSION** **THE DEVIL IS IN THE DETAIL: ILEOANAL POUCHES**
	Chairs: *Sue Clark (UK), Emmanuel Tiret (France)*
08:30 – 09:00	**PRO-CON: TATME-POUCH**
08:30 – 08:45	**TaTME-Pouch: what are the advantages?** – *Roel Hompes (The Netherlands)*
08:45 – 09:00	**TaTME-Pouch: what are the disadvantages?** – *Peter Kienle (Germany)*

Tuesday 25 September 2018

Time	Session
09:00 – 10:00	**TECHNICAL CONSIDERATIONS**
09:00 – 09:15	**Mucosectomy and hand-sewn anastomosis: the Japanese long-term experience** – *Nagahide Matsubara (Japan)*
09:15 – 09:30	**IPAA: does size matter?** – *Willem Bemelman (The Netherlands)*
09:30 – 09:45	**Vascular supply: dissect ileocolic vessels as a routine?** – *Peter Kienle (Germany)*
09:45 – 10:00	**Intraoperative monitoring of pelvic autonomic nerves during pouch surgery to prevent urogenital and anorectal dysfunction: any evidence?** – *Werner Kneist (Germany)*
10:00 – 10:30	**WHAT CAN WE LEARN FROM COLLECTIVE EXPERIENCE?**
10:00 – 10:15	**Does volume of cases make a difference? - data from the ACPGBI pouch registry** – *Baljit Singh (UK)*
10:15 – 10:30	**What can we learn from the TaTME registry on benign disease?** – *Roel Hompes (The Netherlands)*
10:30 – 11:00	**Coffee Break in the Poster and Exhibition area**
11:00 – 12:00	**COMPLICATIONS: PREVENTION AND TREATMENT** **Chairs:** *Antonio Lacy (Spain), Antonino Spinelli (Italy)*
11:00 – 11:15	**Diagnosis and treatment options for the failing pouch** – *André d'Hoore (The Netherlands)*
11:15 – 11:30	**Redo anastomosis for cancer in a previous proctocolectomy patient** – *Antonio Lacy (Spain)*
11:30 – 11:45	**What to do with the leaking pouch** – *Willem Bemelman (The Netherlands)*
11:45 – 12:00	**Is continent ileostomy an option?** – *Gabriela Möslein (Germany)*
12:00 – 12:30	**PRO-CON: PLANE OF DISSECTION**
12:00 – 12:07	**TME plane of dissection is better** – *Antonino Spinelli (Italy)*
12:07 – 12:15	**Close dissection is better** – *Roel Hompes (The Netherlands)*
12:15 – 12:30	**Pouch: can fluorescence angiography be of any help?** – *Antonino Spinelli (Italy)*
12:30 – 13:30	**Lunch**

Tuesday 25 September 2018

Time	Session
08:00 – 10:30 Clipper / Level -2	**WORKING GROUP – PATHOLOGY AND IMMUNOLOGY** **Chairs:** *Matthias Kloor (Germany), Philip Quirke (UK)*
08:00 – 08:30	**N49: A mouse model for proof of concept of a vaccine against Lynch syndrome-associated cancers** *– Magnus von Knebel Doeberitz (Germany)*
08:30 – 09:00	**N30: Life-long immune surveillance and immunoediting – evidence from Lynch syndrome cancers** *– Matthias Kloor (Germany)*
09:00 – 09:30	**The balance between cytotoxic T-cell lymphocytes and immune checkpoint expression determines prognosis in colon tumours** *– Alex Duval (France)*
09:30 – 09:40	**Discussion**
09:40 – 10:30	**PATHOLOGY AND IMMUNOLOGY ABSTRACTS** (8 mins for presentation + 4 mins for questions)
09:40 – 09:52	**N29: New treatment possibilities for Lynch syndrome-associated cancer?** *– Christina Therkildsen (Denmark)*
09:52 – 10:04	**N78: In contrast to subjects with Lynch syndrome, the adenomatous polyps from subjects with sporadic MSI-high tumours have normal expression of MMR proteins** *– Zohar Levi (Israel)*
10:04 – 10:16	**N48: Molecular tumor testing in Lynch-like patients reveals de novo mosaic DNA mismatch repair gene pathogenic variants transmitted to offspring** *– Chrystelle Colas (France)*
10:16 – 10:28	**N51: A novel tool for quantitative analysis of microsatellite mutations and frameshift neoantigens** *– Alexej Ballhausen (Germany)*
10:30 – 11:00	**Coffee Break in the Poster and Exhibition area**
11:00 – 12:30 Clipper / Level -2	**WORKING GROUP – GENE PANEL SESSION**
11:00 – 12:30	**GENE PANEL ABSTRACTS** (8 mins for presentation + 4 mins for questions) **Chairs:** *Angel Alonso Sanchez (Spain), Dan Buchanan (Australia)*
11:00 – 11:12	**N13: Identification of genetic variants in early-onset and familial cancers by targeted next generation sequencing** *– Mev Dominguez (Norway)*

Tuesday 25 September 2018

Time	Session
11:12 – 11:24	**N26: Consensus for genes to be included on cancer panel tests offered by UK Genetics Services: Guidelines of the UK Cancer Genetics Group** – *Amy Taylor (UK)*
11:24 – 11:36	**N06:The effectiveness and the cost-effectiveness of systematic testing for Lynch syndrome in incident colorectal cancer cases in Australia** – *Yoon-Jung Kang (Australia)*
11:36 – 11:48	**N56: Incorporating somatic sequencing into current molecular testing strategies for Lynch syndrome** – *Bianca Desouza (UK)*
11:48 – 12:00	**N20: A new approach in panel testing for hereditary cancer: phenotype-derived with opportunistic screening of mismatch repair genes and BRCA1 and BRCA2** – *Gabriel Capella (Spain)*
12:00 – 12:30	**Discussion**
12:30 – 13:30	**Lunch**
13:30 – 15:00 Baie des Ange / Level -2	**SYSTEMATIC GENE PANEL TESTING FOR HEREDITARY GI CANCERS IN EUROPE - GUIDANCE DEBATE** **Chairs:** *John Burn (UK), Rolf Sijmons (The Netherlands)*
	The appropriate panel: UK Consensus - *Amy Taylor (UK)*
	The appropriate panel: European view – *Ian Frayling (UK)*
	The appropriate panel: US approach and perspective – *Robert Nussbaum (USA)*
	Podium: *Gareth Evans (UK), Ian Frayling (UK), Robert Nussbaum (USA), Ingrid Winship (Australia)*
15:00 – 18:20 Baie des Ange / Level -2	**STATE OF THE ART LECTURES** **Chairs:** *Pål Møller (Norway), Julian Sampson (UK)*
15:00 – 15:18	**Systematic Testing: A Pathologists viewpoint** – *Philip Quirke (UK)*
15:18 – 15:36	**Does fast cheap targeted DNA testing have a future?** – *John Burn (UK)*
15:36 – 15:54	**The potential of liquid biopsies in hereditary disease** – *Jesus Garcia Foncilla (Spain)*
15:54 – 16:12	**PMS2-associated Lynch syndrome: the odd one out** – *Sanne ten Broeke (The Netherlands)*
16:15 – 16:45	**Coffee Break in the Poster and Exhibition Area**
	Chairs: *Finlay Macrae (Australia), Gabriela Möslein (Germany)*
16:45 – 17:03	**MUTYH mutations, polyposis and cancers: what we know so far** – *Aung Ko Win (Australia)*

Tuesday 25 September 2018

Time	Session
17:03 – 17:21	**Update on serrated polyposis** – *Dan Buchanan (Australia)*
17:21 – 17:39	**CMMRD and young LS** – *Chrystelle Colas (France)*
17:39 – 17:57	**Primary and secondary prevention in Lynch syndrome – clinical lessons from molecular pathology** – *Aysel Ahadova (Germany)*
17:57 – 18:15	**Genomics and surgery** – *Dion Morton (UK)*
18:15 – 18:20	**Invitation to InSight 2019** – *Finlay Macrae (Australia)*
	Meeting Closes
18:20 – 19:30	**Farewell Drinks Reception** See page 19 for more information
19:45 – 21:30	**EHTG Informal Dinner at the Radisson Blu Hotel**

MEETING INFORMATION

Posters

Posters are available to view from 18:00 on Sunday to the end of the meeting. They are located immediately outside the *Baie des Anges* main plenary room on level -2 (in the corridor adjacent, and the main foyer area).

If you are presenting a poster, please check in with us at the Registration Desk (hotel lobby). Adhesives will be provided (you may not use your own). Posters should be left up through to Farewell Drinks on Tuesday, and should then be removed at 20:00 prompt.

Badges

Delegates are asked to wear name badges at all times during the meeting.

Delegate Feedback and Certificate of Attendance

You will be emailed a feedback form after the conference. Once you have completed the form, you will be emailed a Certificate of Attendance.

Internet Access

Free WiFi is available to all delegates for use on your own device. The WiFi details are available from the Registration Desk.

GENERAL INFORMATION

Medical and Safety Information

The emergency number to dial in France in the event that an ambulance is needed is 112.

First Aid at the Radisson Blu Hotel

If you require First Aid Assistance please contact a member of the Radisson Blu Hotel reception/event team, who will dispatch a qualified Occupational First Aider. Alternatively, please contact us at Registration and we will contact them for you.

Emergencies and Evacuation Procedure

An automatic fire detection and warning system (smoke / heat detection) together with an automatic fire suppression system is installed throughout the venue. In any emergency situation, please contact Radisson Blu reception or speak to a member of the hotel team so that services can be accurately directed to the incident to ensure it is dealt with promptly and safely. If circumstances make it necessary to leave the building an evacuation message will be broadcast. Please follow the instructions of hotel staff. For your own safety, everyone must leave the building by the nearest exit and gather at the Assembly Point in front of the main hotel entrance of the hotel. Information will also be given regarding arrangements for returning into the building by the Hotel.

Medical Centres and Pharmacies near to the Radisson Blu Hotel

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122 Avenue de la Californie, 06200 Nice
Tel: **+33 4 93 86 50 33**

Lost Property

If you have lost anything at the Radisson Blu, please contact us at Registration and we will try to assist. Should you find any lost property, please bring it to Registration.

EHTG/ESCP Joint Symposium at ESCP

Date: Wednesday 26 September 2018

Time: 10:00 – 11:00

If you have selected to attend the joint symposium, you will be able to collect your name badge from the registration area in the Acropolis.
Acropolis address:

EVENING EVENTS

Welcome Drinks Reception at the Radisson Blu Hotel

Date: Sunday 23 September 2018

Time: 19:00 – 19:45

Cost: included for delegates. Additional tickets: €30

All delegates are invited to attend this event which is included in the registration fee. Additional tickets may be purchased online if you wish to bring a guest. It will take place in the poster and exhibition area following the close of meeting sessions; delegates are then free to make their own arrangements for dinner after the reception.

Farewell Reception

Date: Tuesday 25 September 2018

Time: 18:20 – 19:30

Cost: included for delegates. Additional tickets: €30

Do join us for drinks to mark the close of EHTG's third meeting with a relaxing drink or two!

See also details regarding dinner which is available at the Radisson immediately after this reception!

EHTG Informal Dinner at the Radisson Blu Hotel

An invitation to all EHTG attendees and to ESCP delegates joining EHTG on Tuesday, or simply arriving for ESCP – all are welcome!

Date: Tuesday 25 September 2018

Time: 19:45 – 21:30

Cost: €65 (reduced cost for trainees) for a 3 course meal with wine

Follows on immediately after the EHTG farewell reception.

We look forward to relaxing and talking over dinner as we unwind after three days of stimulating discussion, and welcome those arriving for ESCP who we hope will join us too.

After dinner, there is the option to go up to the **Radissons's rooftop terrace bar**, with its superb views of the Nice Promenade des Anglais and the Mediterranean, to continue conversations.

If you haven't purchased a ticket but would like to join us at any of these evening events, please ask at Registration. A few tickets may be available until Monday 24 September at 13:30.

Dietary requirements: if you have any dietary requirements that were not notified as part of your registration record, please advise Registration immediately.

Oral Presenter Abstracts

N01

Title: The German HNPCC Consortium: Aims, Structure, Methods and Data

C. Engel[1], S. Aretz[2] - on behalf of the German HNPCC Consortium

Please visit the EHTG website for Author Institutions

Aim: The German HNPCC Consortium, founded in 1999, is a joint network of currently 14 clinical university centers, a reference pathology, and a central documentation facility aiming to provide structured interdisciplinary care and research for individuals suspected of having an inherited predisposition for colorectal cancer. In the past, the consortium has focused on Lynch Syndrome (LS) but aims to cover also the broad spectrum of other familial colorectal cancer entities.

Method: Families are ascertained based on the established Amsterdam and Bethesda criteria. Interdisciplinary care comprises genetic counseling, molecular pathological tumour analyses for mismatch repair deficiency, germline testing of predisposing genes, and structured intensified surveillance measures. Research goals are e.g. search for new disease causing genes, genotype-phenotype correlations and tumour risks, tumour immunology, and efficacy of intensified surveillance.

Results: The consortium has established a central research database, which is populated by the clinical centres using a web-based remote online data capture application based on standardized documentation. The scope of the retro- and prospective data collection comprises fully structured pedigrees, familial tumour history, detailed results of diagnostics and results of surveillance.

Conclusion: Currently, approx. 8,800 individuals (patients, asymptomatic mutation carriers, relatives at risk) from 5,500 families are centrally registered (2,100 LS patients).

N02

Title: Opportunities For Collaboration: Analysis Of Longitudinal Data In Lynch Syndrome Carriers To Inform Development And Calibration/Validation Of A New LS Screening Model – "Policy1-Lynch"

Y. J. Kang[1], M. Caruana[1], N. Taylor[1], I. Frayling[2], A. Boussioutas[3,5,6], P. Møller[4,7,8], G. Mitchell[5], F. Macrae[6], K. Canfell[1]

Please visit the EHTG website for Author Institutions

Aim: POLICY1-Lynch" is a comprehensive health economic model platform to simulate pathways for testing, diagnosis, surveillance and prophylaxis for Lynch syndrome (LS). POLICY1-Lynch has several core components, including a model of cancer-specific natural history that needs to be calibrated/validated using good quality data with a large sample size. Therefore, we propose a collaborative study with members of the EuropeanHereditaryTumourGroup to: i) estimate the underlying natural history of colorectal cancer (CRC) and other LS-related cancers; and ii) use the information for calibration/validation of the detailed natural history model in LS carriers.

Method: Additional data, if available, from each centre currently contributing to the ProspectiveLynchSyndromeDatabase will be collated to estimate the: i) prevalence of pre-invasive/invasive lesions by histopathology/size at baseline colonoscopy; ii) cumulative incidence of adenoma/CRC, taking into account the effect of colonoscopic surveillance and surveillance interval; and iii) cumulative incidence of non-colonic LS-related cancers/pre-cancerous lesions in LS, accounting for participation in a surveillance program and prophylactic options. The outcome measured will be stratified by MMR gene, sex, age group and site(colon/rectum) wherever possible.

Results: N/A

Conclusion: Significance: The calibrated model will allow accurate estimates of the effectiveness and cost-effectiveness of optimal screening and management options for LS in Australia and other countries.

N03

Title: Prevalence, Phenotype And Clinical Consequences Of Mosaicism In APC And Other Colorectal Cancer And Polyposis Associated Genes

M. Suerink[1], S. Aretz[2,3], A. Wagner[4], M. Nielsen[1], T. van Wezel[5], H. Morreau[5]

Please visit the EHTG website for Author Institutions

Aim: APC mosaicism is identified in ~25% of previously unexplained polyposis patients with >20 adenomas. Prevalence of APC mosaicism in more mildly affected polyposis patients is currently unknown. Furthermore, surveillance advice is now the same for germline and mosaic APC patients, while a milder phenotype in the latter is expected. In the LUMC in Leiden, The Netherlands, a new study will start this year examining the prevalence of APC mosaic mutations in mildly affected polyposis patients as defined below. All mosaic patients will be recorded meticulously to determine phenotype.

Method: FFPE material of colorectal neoplasms (adenomas and/or colorectal cancers) of patients meeting the following criteria will be collected:

- >5 adenomas and aged <50
- >10 adenomas and aged <70y
- >20 adenomas and aged >70ymeta- or synchronous CRC <70y
- 10-20 adenomas, between ages 55-75y, identified by population-based screening

We expect inclusion to start in the second half of 2018. DNA will be isolated from the neoplasms (n≥2) and a gene panel (including the following genes: APC, POLE/D1, MUTYH, NTHL1, MSH3, MLH1, MSH2, MSH6, PMS2, SMAD4, BMPR1A, ENG, RNF43, STK11, TP53, BRCA1, BRCA2, PALB2 and PTEN) will be run to identify APC mosaic cases as well as other (mosaic) causes of polyposis/colorectal cancer. Identification of the same mutation in multiple samples of the same patient will be considered to be indicative of mosaicism. Whenever possible, DNA isolated from leucocytes, buccal mucosa and urine will then be analyzed to see whether the variant can be identified in these tissues as well. Eligible patients will need to provide written consent before they are included.

Results: The main outcome will be prevalence of mosaic mutations in the above mentioned patient groups. Furthermore, mutation patterns and clinical phenotype will be recorded to study the mechanisms behind mosaicism and provide data to adapt surveillance guidelines.

Conclusion: A new study is starting this year at the LUMC in Leiden with the aim of further clarifying the prevalence, phenotype and clinical consequences of APC mosaicism. We invite attendees of the EHTG who have several cases that meet the selection criteria to contact us to discuss participation. We require tissue from multiple tumors from well described cases and can accommodate the NGS gene panel.

N04

Title: Breast Cancer Pathology And Stage Are Better Predicted By Risk Stratification Models Including Mammographic Density And Common Genetic Variants

D. G. Evans[1,2,6,7,8], E. Harkness[2,3,4], A. Brentnall[5], E. van Veen[1], S. Astley[2,3,4,8], H. Byers[1], S. Sampson[2], J. Southworth[2], P. Stavrinos[2], S. Howell[2,6,8], A. Maxwell[2,3,4,8], A. Howell[2,6,8], W. Newman[1,7,8], J. Cuzick[5]

Please visit the EHTG website for Author Institutions

Aim: To better stratify breast cancer risks to enable more targeted early detection/prevention strategies particularly to balance the risks/benefits of population

Method: Data from 9,362 women unaffected by breast cancer at study entry who provided a DNA sample for polygenic-risk-score (PRS) were analysed from the 57,902 women in the PROCAS study. The PRS score was analysed along with mammographic density (density residual-DR) and standard risk factors to assess future risk of breast cancer pathological type and hormonal receptor status

Results: For the 195 prospective breast cancers a predictor based on Tyrer-Cuzick/DR/PRS was informative for subsequent cancer overall and more so for stage 2+ cancers and calibrated (0.99) for predicting cancers across all risk groups. Although DR was most predictive for HER2+ and stage 2+ cancers it did not discriminate as well between poor prognosis cancers and extremely good prognosis cancers as Tyrer-Cuzick or the PRS, with the PRS providing the highest OR for post-prevalent stage 2+ cancers IQR OR=1.79 (95%CI:1.30-2.46).

Conclusion: A combined approach using Tyrer-Cuzick, mammographic density and a PRS provides accurate risk stratification not only overall but also for worse prognosis cancers. This provides support for reducing screening intervals in the high and increasing them in the low risk groups.

N05

Title: Exogenous And Endogenous Associated Factors To Early Onset Colorectal Cancer

R. Zuppardo[1], M. Di Leo[2], A. Mannucci[1], F. Azzolini[1], D. Esposito[1],

L. Fanti[1], G. Mazzoleni[1], C. Notaristefano[1], E. Viale[1], R. Rosati[3], P. Testoni[1], G. M. Cavestro[1]

Please visit the EHTG website for Author Institutions

Aim: Early onset colorectal cancers (eoCRC < 50 years), is projected to increase by as much as 90% and 140%, respectively by 2030, and germline mutations appear to account for only about 20%. We investigate the role of exogenous and endogenous risk factors as associated factors in eoCRCs.

Method: Clinical, anamnestic and pathological data were retrieved on eoCRC patients from 06/2017 to 04/2018, and compared with a group of late onset CRC (loCRC) of the same period.

Results: We enrolled 33 eoCRCs and 48 loCRCs, mean age 40.7 +/- 7.3 and 66.1 +/- 9.8, respectively (p<0.001), prevalence of females (54.5% in eoCRCs and 52.1% in loCRCs). Diagnostic delay was higher in eoCRC group: 42.4% of eoCRCs diagnosed in the 6th months from symptoms onset versus 100% of loCRC patients (p<0.001). Lynch syndrome was more frequent in eoCRC (12%) than loCRC group (0%) p=0.02. A statistically significant difference was found in alcohol habit, 66.7% of no-drinker in eoCRCs and 41.7% of loCRCs (p=0.04), and a trend through significance for no-smokers in eoCRCs.

Conclusion: CRC should be considered earlier for differential diagnosis in young patients. We confirmed alcohol as cofactor in development of eoCRC and we underlined that familiar history should be collected to identify mutations carriers.

N06

Title: The Effectiveness And The Cost-Effectiveness Of Systematic Testing For Lynch Syndrome In Incident Colorectal Cancer Cases In Australia

Y. J. Kang[1], J. Killen[1], M. Caruana[1], K. Simms[1], N. Taylor[1], I. Frayling[2], A. Boussioutas[3,4,5], G. Mitchell[4], F. Macrae[5], K. Canfell[1]

Please visit the EHTG website for Author Institutions

Aim: The study aims to evaluate the effectiveness and cost-effectiveness of Lynch syndrome (LS) screening in incident colorectal cancer (CRC) cases diagnosed in 2017 in Australia via universal germline gene panel testing compared to no screening.

Method: A micro-simulation model was used to estimate health and resource outcomes under two different assumptions: i) colonoscopic surveillance reduces the CRC incidence and down stages (scenario 1); or ii) colonoscopic surveillance down stages only (scenario 2). A range of sensitivity analysis was also performed.

Results: LS screening for CRC cases of all ages with annual colonoscopic surveillance in confirmed LS carriers till age 70 years will cost from $66,557/life-year saved (LYS, scenario 1) to 111,143/LYS (scenario 2). An additional 35,948 to 36,476 colonoscopies will be generated in a given year but 136 to 208 CRC deaths will be averted per 1,000 LS carriers. The cost-effectiveness improves if: i) the gene panel testing cost is reduced from $1,200 capturing 11 gene variants related to hereditary CRC to $450 capturing MMR genes only ($38,665/LYS); or ii) a maximum age for screening is applied.

Conclusion: Our preliminary results indicate that LS screening via universal gene panel testing can be cost-effective if the testing cost is reduced.

N07

Title: Cancer Risks By Age And Gender And Survival After Cancer In Path_MSH6 Carriers: A Prospective Lynch Syndrome Database (PLSD) Report

J. Sampson[1], J. P. Plazzer[2], M. Dominguez-Valentin[3,4], S. Nakken[4], T. Seppälä[5], C. Engel[6], S. Aretz[6], H. K. Schackert[6], W. Schmiegel[6], N. Rahner[6], M. von Knebel Doeberitz[6], M. Loffler[6], E. Holinski-Feder[6] I. Bernstein[7], L. Sunde[7], M. Jenkins[8], D. G. Evans[9], J. Burn[9], L. Bertario[10], G. M. Cavestro[10], A. Lindblom[11], A. Della Valle[12], R. H. Sijmons[13], W. H. de Vos tot Nederveen Cappel[13], L. Katz[14], N. Gluck[14], K. Heinimann[15], C. A. Vaccaro[16] F. Lopez-Koestner[17], F. Balaguer[18], E. Hovig[4], F. Macrae[19], G. Möslein[6], J. P. Mecklin[5], G. Capella[18], Members of the PLSD project[20], P. Møller[4,21]

Please visit the EHTG website for Author Institutions

Aim: To determine cancer risks by age and gender and cancer survival in carriers of path_MSH6 variants.

Method: An independent cohort of class 4 or 5 path_MSH6 carriers was used to validate findings reported previously by PLSD. Data for individuals in the previous and validation cohorts who carried class 4 or 5 variants listed in the InSIGHT variant database were then combined and analysed by age and gender, deriving more precise risk and survival estimates to inform management.

Results: The validation cohort (N=425) provided 2,367 prospective observation years and confirmed previously reported cumulative risks for any cancer: 14% vs 18% at fifty years and 48% vs 53% at 70 years. The combined series of 841 carriers of class 4/5 path_MSH6 variants provided 5,205 prospective observation years. Cumulative risks at 75 years in males/females were: any cancer 42%/60%; colorectum 18%/20%; endometrium NA/41%; ovary NA/11%; stomach, duodenum, bileduct, pancreas 8%/4%; ureter,_kidney 2%/6%; bladder 8%/1%; prostate 9%/NA; breast NA/14%; brain 2%/1%. Ten-year crude survival following cancer was: colon 100%; rectum 86% and endometrium 90%. See www.PLSD.eu to calculate risks for individual patients by age and gender.

Conclusion: MSH6-associated Lynch syndrome has distinct characteristics with a high risk of endometrial cancer compared to other organs.

N08

Title: The Apparent Genetic Anticipation In PMS2-Associated Lynch Syndrome Families Is Explained By Birth-Cohort Effect

S. W. ten Broeke[1], M. Rodríguez-Girondo[2], M. Suerink[1],

S. Aretz[3,4], I. Bernstein[5,6], G. Capellá[7], C. Engel[8], E. Gomez Garcia[9] L. P. van Hest[10], M. von Knebel Doeberitz[11,12], K. Lagerstedt-Robinson[13], T. G.W. Letteboer[14], P. Møller[15,16,17], T. A. van Os[18], M. Pineda[7], N.Rahner[19], M. J. W. Olderode-Berends[20], J. von Salomé[13], H. K. Schackert[21], L. Spruijt[22], V. Steinke-Lange[23], A. Wagner[24], C. M. J. Tops[1], M. Nielsen[1]

Please visit the EHTG website for Author Institutions

Aim: PMS2-associated Lynch syndrome is characterized by a relatively low colorectal cancer (CRC) penetrance compared to other Lynch syndromes. However, age at CRC diagnosis varies widely and a strong genetic anticipation effect has been suggested for PMS2 families. In this study we examined proposed genetic anticipation in a sample of 230 European PMS2 families.

Method: The 152 families (637 family members) that were eligible for analysis were mainly clinically ascertained via clinical genetics centers. We used weighted Cox-type random effects model, adjusted by birth-cohort and sex, to estimate the generational effect on the age of onset of CRC. Probands and young birth-cohorts were excluded from the analyses. Weights represented mutation probabilities based on kinship coefficients, thus avoiding testing bias.

Results: Family data across three generations, including 123 CRCs, were analyzed. When compared to the first generation, the crude Hazard Ratio (HR) for anticipation was 2.242 (95%CI: 1.162-4.328) for the second and 2.644 (95%CI: 1.082-6.464) for the third generation. However, after correction for birth-cohort and sex the effect vanished (HR=1.302 (95%CI: 0.648-2.619) and HR=1.074 (95%CI: 0.406-2.842) for second and third generations, respectively).

Conclusion: Our study did not confirm previous reports of genetic anticipation in PMS2-associated Lynch syndrome. Birth-cohort effect seems the most plausible explanation for observed younger CRC diagnosis in subsequent generations, particularly since there is currently no commonly accepted biological mechanism that could explain genetic anticipation in Lynch syndrome.

N09

Title: Worldwide Study Of Cancer Risks For Lynch Syndrome: International Mismatch Repair Consortium (IMRC)

M. Jenkins[1], J.C. Reece[1], G. Lee[1], R. Haile[2], G. Moslein[3], F. Macrae[4], A. Win[1]

Please visit the EHTG website for Author Institutions

Aim: The International Mismatch Repair Consortium (IMRC) was established to determine cancer risks by geographic region.

Method: Pedigree data for 6,436 Lynch syndrome families from 22 countries were submitted by researchers/clinicians throughout the world to the analysis team at the University of Melbourne. We estimated the cumulative risks (penetrance) by geographic region. We used a modified segregation analysis and adjusted for any ascertainment of families.

Results: Preliminary analysis suggest that for MLH1 mutations, the risk of colorectal cancer to age 70 is highest for carriers in Australasia (68% males, 55% females) and North America (61% males, 48% females) and lowest for carriers in South America (12% males, 10% females) and East Asia (20% males, 14% females). For MSH2, the patterns were similar, except for South America which had a high estimated average risk (82% males, 75% females).

Conclusion: Collection of MMR family data from many international sites has progressed well despite the challenges faces by sites to establish databases for epidemiological research with varying resources. Preliminary results suggest that cancer risks for people with Lynch syndrome differ by geographic region which is consistent with environmental modifiers for the disease and might justify region specific screening guidelines.

N10

Title: Breast Cancer Risk In Neurofibromatosis Type 1 Is A Function Of The Type Of NF1 Gene Mutation: A New Genotype-Phenotype Correlation.

I. Frayling[1], V. F. Mautner[2], R. van Minkelen[3], R. A. Kallionpää[4], S. Aktaş[5], D. Baralle[6], S. Ben-Shachar[7], A. Callaway[8], H. Cox[1], D. M. Eccles[6], S. Ferkal[9], H. LaDuca[10], C. Lázaro[11], M. T. Rogers[1], A. J. Stuenkel[10], P. Summerour[10], A. Varan[12], Y. S. Yap[13], J. Peltonen[4], D. G. Evans[14,15], P. Wolkenstein[16], M. Upadhyaya[1]

Please visit the EHTG website for Author Institutions

Aim: NF1 predisposes to breast cancer (BC), but no genotype-phenotype correlations have been described.

Method: Constitutional NF1 mutations in 78 NF1 patients with BC (NF1-BC) were compared to the NF1 LOVD (N=3432).

Results: There are no gross relationships with mutation position. No cases were observed with large deletions (HR=0.10; 95%CI: 0.006–1.63; p=0.014, Fisher's exact (FE)) 64.3% of the 70 different mutations have p<0.05 (FE), while 74.3% are significant when adjusted for multiple comparisons (Benjamini-Hochberg p≤0.125). Two pairs of patients shared the same predicted effects on neurofibromin, but had different mutations at the DNA level. 6/14 (43%) of the missenses (MS) were located in the CSRD (p=0.093; FE). 10/11 (91%) of MS cases with known age of BC occurred <50y (p=0.041; FE). 18 had BRCA1/2 testing, revealing one BRCA2 mutation.

Conclusion: This demonstrates that certain heritable mutation types, and indeed certain specific mutations in NF1 confer different risks of BC. The observation that NF1 amplification does not always occur with, and can occur independently of ERBB2 amplification, supports the concept that BC risk in NF1 may be due to gain of function mutations. A prospective NF1-BC study needs to be established. Regardless of NF1 mutation status NF1-BC patients warrant testing of other BC-predisposing genes.

N11

Title: A Dominantly Inherited 5'UTR Variant Causing Methylation Associated Silencing of BRCA1 As A Novel Cause Of Breast And Ovarian Cancer

D. G. Evans[1,2,3,4,8], E. M. van Veen[1,5,8], H. J. Byers[1,5], A. J. Wallace[5], J. M. Ellingford[1,5], G. Beaman[1,5], J. Santoyo-Lopez[6], T. J. Aitman[6], D. M. Eccles[7], F. I. Lalloo[5], M. J. Smith[1,5,8], W. G. Newman[1,4,5,8]

Please visit the EHTG website for Author Institutions

Aim: Pathogenic variants in BRCA1/BRCA2 are identified in ~20% of families with multiple individuals with early-onset breast/ovarian cancer. Extensive searches for additional highly penetrant genes/alternative mutational mechanisms altering BRCA1/2 have not explained the missing heritability. For the first time, we report a dominantly inherited 5'UTR variant associated with epigenetic silencing of BRCA1 due to promoter hypermethylation in two families with breast/ovarian cancer.

Method: BRCA1 promoter methylation of ten CpG dinucleotides in breast/ovarian cancer families without germline BRCA1/2 pathogenic variants was assessed by pyrosequencing and clonal bisulfite sequencing. BRCA1 RNA/DNA sequencing from lymphocytes was undertaken to establish allelic expression and germline variants.

Results: BRCA1 promoter hypermethylation was identified in 2/49 families with multiple women affected with grade-3 breast/high-grade-serous ovarian cancer. Soma-wide BRCA1 promoter hypermethylation was confirmed in blood/buccal mucosa/hair follicles. Methylation levels were ~50%, consistent with complete silencing of one allele. RNA sequencing revealed allelic BRCA1 expression loss in both families segregating with a novel heterozygous variant c.-107A>T in 5'UTR.

Conclusion: Our results indicate a novel mechanism for familial breast/ovarian cancer, caused by an in cis 5'UTR variant associated with epigenetic silencing of BRCA1 promoter. We propose methylation analyses are undertaken to establish the frequency of this mechanism in families affected by early onset breast/ovarian cancer without a BRCA1/2 pathogenic variant.

N12

Title: The Role Of RNF43 In Serrated Polyposis And Colorectal Cancer Predisposition

M. Lorans[1], K. Mahmood[1], M. Clendenning[1], B. Pope[1], D. J. Park[1], S. Joseland[1], V. Vijay[2], J. Arnold[2], K. Sweet[3], K. Semotiuk[4], M. Aronson[4], S. Holter[4], S. Gallinger[4], P. Newcomb[5], F. Hutchinson[5], A. Win[1], M. Jenkins[1], F. Macrae[6], I. M. Winship[6], C. Rosty[7], S. Parry[2], D. D. Buchanan[1]

Please visit the EHTG website for Author Institutions

Aim: Rare germline truncating variants in the RNF43 gene have been implicated in Serrated Polyposis Syndrome (SPS), a condition with an increased risk of colorectal cancer (CRC). We screened individuals with SPS and a cohort of CRC-affected probands for germline variants in RNF43 to determine prevalence and clinicopathological features of carriers.

Method: 418 probands with SPS and n=1951 CRC-affected probands and n=1208 controls were screened by targeted multiplex-PCR and sequencing (Hi-Plex) for coding variants within RNF43. Single nucleotide variants and short indels were classified as predicted pathogenic if they were: 1) novel or present in gnomAD at <5.0E-05 minor allele frequency; and 2) were truncating, frameshift or splice site variants or a non-synonymous change predicted to be deleterious on protein function (CADD or REVEL).

Results: Six carriers of predicted pathogenic variants in RNF43 were identified in 418 SPS probands (1.4%); these particular variants were significantly enrichment in the SPS cohort compared with gnomAD (odds ratio=4.4, 95%CI=1.7-9.1, p=0.0003). A single predicted pathogenic variant in RNF43 was identified in one of the CRC-affected probands tested. Clinicopathological findings and segregation in the carrier families will be presented.

Conclusion: Rare germline RNF43 predicted pathogenic variants were significantly enriched in individuals with SPS.

N13

Title: Identification Of Genetic Variants In Early-Onset And Familial Cancers By Targeted Next Generation Sequencing

M. Dominguez-Valentin[1], S. Nakken[1], H. Tubeuf[2], D. Vodak[1], P. O. Ekstrøm[1], A. M. Nissen[3,4], M. Morak[3,4], E. Holinski-Feder[3,4], A. Holth[5], B. Davidson[5,6], A. Martins[2], P. Møller[7,8], E. Hovig[1]

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Aim: To study the potential contribution of genes other than BRCA1/2, PTEN, TP53 and MMR to the biological and clinical characteristics of early-onset and familial cancers in Norwegian families.

Method: The Hereditary Cancer Biobank from the Norwegian Radium Hospital was used to identify early-onset families and individuals with a high risk of developing breast, gynecological and colorectal cancers. Forty-four cancer susceptibility genes were selected and analyzed by our in-house designed TruSeq amplicon-based assay for targeted sequencing. Protein- and RNA splicing-dedicated in silico analyses were performed for all variants of unknown significance (VUS). Variants predicted as the more likely to affect splicing were experimentally analyzed by a minigene assay (PMID: 29458332, 29371908, 28608266).

Results: We analyzed 176 early onset and familial cases who harbored 5% (8/175) class 5 variants in the genes ATM (3), CHEK2 (2), MSH6, MUTYH and MAP3K1. Out of the 18 VUS tested in the minigene splicing assay, ATM c.3806A>G, NOTCH3 c.14090C>T and MSH2 c.815C>T showed a significant effect on RNA splicing.

Conclusion: Our study provides new information on genetic loci that may affect the risk of developing cancer in these patients and their families, demonstrating that genes presently not routinely tested in molecular diagnostic settings may be important for capturing cancer predisposition in these families.

N14

Title: Identification And Characterization Of An Alu Element Insertion In BRCA2 In A Spanish Family Associated To Prostate Cancer

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Aim: Pathogenic Alu element insertions are rarely reported because this type of insertions are undetectable with the classical screening methods. The aim of this work has been the identification and characterization of an Alu element insertion in a Spanish family with a history of breast/ovarian cancer.

Method: Molecular analysis was carried out using the BRCA MASTRDx (Multiplicom) and Massively Parallel Sequencing (Illumina). The Alu insertion was identified and characterized by fragments analysis, genotyping, PCR amplification and Sanger sequencing (ABI3130).

Results: We have identified and characterized a heterozygous pathogenic variant c.5007_5008ins174 located at the exon 11 of the BRCA2 gene in a patient with prostate cancer. The variant identified is a pathogenic Alu element insertion (AluYb8BRCA2) of about 174 bp long.

Conclusion: NGS has been incorporated into clinical genetic testing for hereditary cancer risk. NGS-based techniques and the standard bioinformatic pipelines, however, are unable to detect and precissely characterize ALU element insertions. In this work, we report, by using classical screening methods and bioinformatic programs, BLAST and RepeatMasked, the identification of the AluYb8BRCA2 insertion in BRCA2 coding region. This insertion could generate a framesift resulting in the abrogation of BRCA2 protein function that has been associated with oxidative stress involved in carcinogenesis.

N16

Title: Colorectal Cancer Risk Susceptibility Loci In A Swedish Population

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Aim: Around 30% of all colorectal cancer has a genetic contribution. Less than 5% have an inherited mutation in a known high-risk colorectal cancer (CRC) gene. A germline mutation in cancer predisposing genes is known to increase the risk of more than one tumor type. In order to find loci associated with CRC, a genome-wide association study (GWAS) was conducted.

Method: The study used haplotype analysis instead of single SNP analysis in order to find putative founder effects. Logistic Haplotype association studies was conducted. 2,637 Swedish CRC cases and 4,780 healthy controls were analyzed for 219,114 SNPs.

Results: Logistic Haplotype association studies identified three risk loci associated with CRC risk, on chromosomes 2q24.2 (OR= 0.45 and p= 1.59 x10-9), 2q14.3 (OR= 0.61 and p= 9.39 x10-9) and 16q23.3 (OR= 2.77 and p= 1.10 x10-9). Some of the candidate loci hold several cancer genes, suggesting that the risk associated with one locus could involve more than one gene associated with CRC risk.

Conclusion: In summary, this study identified three novel candidate loci associated with CRC risk. It was also suggested that cancer risk at one locus could depend on multiple contributing risk mutations/genes.

N17

Title: BRF1, A Novel Gene Associated With Hereditary Colorectal Cancer

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Aim: The identification of genes associated with hereditary colorectal cancer (CRC) facilitates the management of families and individuals carrying pathogenic mutations, having a direct impact in the processes of genetic testing and counseling. However, much of the genetic predisposition to CRC remains unexplained.

Method: We performed whole-exome sequencing in 3 CRC-affected relatives of an Amsterdam I CRC family.

Results: Variants located in 38 genes were shared by all affected relatives. A splice-site mutation in BRF1 (subunit of RNA polymerase III transcription initiation factor), stood up as potential causal mutation. BRF1 mutational screening was performed in 547 additional familial CRC cases using pooled DNA and targeted next generation sequencing. Ten novel or rare (population MAF<1%) BRF1 variants were identified in 11 independent CRC families. The deleterious nature of the identified BRF1 mutations were demonstrated for seven of them (1 detected in two families): BRF1 c.1459+2T>C and 6 missense variants, p.T12M, p.V75M, p.S81T, p.C140S, p.P405R and p.R572G, which led to the alteration of protein function and/or protein expression in functional studies carried out in yeast and/or human CRC cell lines. The frequency of mutations in familial CRC cases was significantly higher to the frequency observed in control population.

Conclusion: Germline heterozygous mutations in BRF1 may contribute for at least 1.4% of unexplained familial colorectal cancer cases. If validated in independent series, BRF1 mutation carrier families could benefit in the future from a clinical management based on carrier status and personalized risk assessment.

N18

Title: Deciphering The Contribution Of Recently Proposed Polyposis Predisposing Genes

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Aim: The genetic defect responsible for colorectal polyposis remains unknown in much of the cases with adenomatous polyposis. Recently, MCM9 (recessive), FOCAD (recessive or dominant) and POLQ (dominant) have been identified as putatively new polyposis genes. Here we aim at providing a more definitive answer about the contribution of germline mutations in these genes to adenomatous polyposis.

Method: A total of 182 unrelated polyposis patients were screened for MCM9, FOCAD and POLQ mutations using PCR amplification in pooled DNAs combined with targeted parallel sequencing. Variants detected in the pooled samples were validated by genotyping and/or Sanger sequencing.

Results: While no homozygotes or compound heterozygotes where identified in MCM9 and FOCAD, a predicted deleterious missense variant (c.911A>G; p.N304S) was identified in heterozygosis in MCM9 in an individual with adenomatous polyposis, and 4 were identified in the FOCAD gene: c.401C>T (p.P134L), c.1393G>A (p.G465R), c.2861C>T (p.P954L) and c.3041A>G (p.Y1014C). A stop-gain variant (c.7537C>T; p.Q2513*) located in the DNA-polymerase domain and a predicted deleterious missense variant (c.4684G>T; p.D1562Y), were identified in POLQ.

Conclusion: Additional studies are currently being performed in order to elucidate the association of the identified variants with the predisposition to polyposis in the carrier families.

N19

Title: Colorectal Cancer Risk Is Not Increased In NTHL1 Heterozygous Mutation Carriers

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Aim: Bilallelic loss-of-function germline mutations in the base excision repair gene NTHL1 result in an increased risk of colorectal polyps and different cancer types, resulting in the inclusion of this gene on many multi-gene cancer predisposition panels. However, the impact of heterozygous germline NTHL1 mutations on colorectal cancer (CRC) risk is unclear.

Method: 1953 CRC-affected individuals and 1207 controls from the Colon Cancer Family Registry Cohort were screened for coding single nucleotide and short indels variants in NTHL1 using a targeted multiplex PCR-based sequencing approach (Hi-PLEX). Variants were filtered on sequencing depth and allele proportions. Variants were predicted to be pathogenic if they were novel or rare (gnomAD < 0.05%), protein truncating variants or missense variants predicted to be deleterious (based on CADD>20 or REVEL>0.5).

Results: We detected 22 (1.13%) predicted pathogenic variants in cases and 17 (1.41%) in controls (OR=0.79, 95% CI=0.42-1.48, p=0.51), all carriers were heterozygotes. The loss-of-function variants identified were not different in frequency between CRC cases (n=5, 0.26%) and controls (n=5, 0.41%; OR=0.62, 95%CI=0.18-2.14, p=0.52), and of similar frequency to rare NTHL1 loss-of-function variants observed in gnomAD (0.199%).

Conclusion: The effect of heterozygous NTHL1 predicted pathogenic variants on CRC risk, if any, is not likely to be more than 1.5 fold.

N20

Title: A New Approach In Panel Testing For Hereditary Cancer: Phenotype-Derived With Opportunistic Screening Of Mismatch Repair Genes And BRCA1 And BRCA2

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Aim: Multigene panels provide a powerful tool for analyzing several genes simultaneously. We evaluated the frequency of pathogenic variants (PVs) in customized pre-defined phenotype-based panels and compared it to the yield obtained in the analysis of an extended 24-gene panel. We also investigated the mutational yield of opportunistic screening of mismatch repair (MMR) and BRCA1/2 genes.

Method: A total of 1205 unrelated probands with clinical suspicion of hereditary cancer were screened for germline mutations using next generation sequencing panels: 205 HNPCC-suspected, 883 HBOC-suspected, 73 polyposis-suspected and 44 with other/multiple clinical suspicion.

Results: Our phenotype-driven panel identified 150 carriers of PVs (12%). Opportunistic screening additionally identified 5 MSH6, 1 BRCA1 and 1 BRCA2 carriers. The additional analysis of our extended 24-gene panel provided 26 additional PVs (3%), including 4 out of 51 individuals harboring MMR-proficient tumors (2 CHEK2 and 2 ATM). Multiplex panel unmasked discrepancies between MMR immunohistochemistry pattern and the germline mutation.

Conclusion: Comprehensive panels increase the mutational yield by 3% over a phenotype-approach. Opportunistic screening of highly penetrant genes leads to a significant straightforward identification of MMR and BRCA1/2 mutation carriers, and endorses the model of opportunistic testing of genes with clinical utility under a standard genetic counseling process.

N21

Title: Detection Of A Pathogenic Promoter And Localiser BRCA 2 (PALB 2) Variant

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Aim: A 48 year old woman was referred to the West of Scotland Genetic Services with a diagnosis of metastatic breast cancer and was subsequently shown to have a maternal family history of bowel cancer fulfilling the Amsterdam criteria. The pathology of the breast tumour was oestrogen receptor negative, progesterone receptor negative and HER 2 negative. Previously at the age of 44 years the woman had been diagnosed with oestrogen receptor positive and progesterone receptor positive breast cancer.

Method: The patient was offered mutation analysis of the highly penetrant BRCA 1 gene and BRCA 2 gene and panel testing.

Results: Analysis detected a heterozygous pathogenic PALB 2 variant c.1592_1593delInsA, p.(Leu531fs). A variant resulting in the same frameshift c.1592ddel, p.(Leu531fs) is a known pathogenic variant that has been shown to result in a truncated unstable protein which is associated a significant risk of breast cancer. No pathogenic variants were detected on BRCA1, BRCA 2, ATM, CHEK 2, MLH1, MSH2, MSH 6, MUTYH, PTEN, STK11 and TP53 genes. Inheritance was determined by accessing stored tumour tissue from the time of her mother's surgery for rectal cancer in 1991. Analysis confirmed the presence of the PALB2 variant.

Conclusion: Predictive testing is now available to the wider family.

N22

Title: Family Case Of Rare MSH6 Variant Identified As Secondary Finding - Shall We Screen For Lynch?

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1 - Geneton Ltd. 2 - Comenius University Science Park. 3 - Faculty of Natural Sciences.

Aim: In Slovakia, the incidence of colorectal cancer is one of the highest worldwide and could be a result of higher incidence of cancer predisposing syndromes, such as Lynch syndrome. Novel large gene panel, exome or whole genome tests become less costly and widely available which allow detection of cancer predisposing genetic variants. In addition, novel non-invasive methods for tumor screening (liquid biopsy) become available as well.

Screening for genetic cancer predisposing syndromes and accordingly adjusted cancer screening regimes with inclusion of liquid biopsy methods could be viable options but the implementation and social aspects need to be studied.

Method: A clinical exome test was carried out in 20yo male. Identification of variants relevant for secondary findings was carried out too. Identified variants were verified by Sanger sequencing. A family follow-up included clinical exome test as well as Sanger confirming tests.

Results: We identified a rare potentially pathogenic variant in MSH6 gene in 20yo male as secondary finding. In addition a rare BRCA2 variant was also detected and confirmed. Despite family cancer history did not meet used criteria it was tested for these variants.

A suspected case of metastatic breast cancer in the family was confirmed in 65yo female bearing the in 12/2017 and a suspected case od CRC was identified in 67yo male bearing the MSH6 variant.

All family members adherred to required medical procedures after genetic testing.

Conclusion: Genomic tests and their wider availability with novel liquid biopsy methods offer novel cancer screening algorithm options. A case of family with two detected variants in both BRCA2 and MSH6 a secondary finding shows possible benefits but social aspects have to be considered for wider implementation.

N23

Title: Digestive Burden Of CMMRD (Constitutional Mismatch Repair Deficiency) Patients And Overlap With Lynch Syndrome: Report From The European Care4CMMRD Consortium

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Aim: Constitutional Mismatch Repair Deficiency (CMMRD), due to biallelic germline mutations in one MMR gene, is characterized by multiple and very early-onset malignancies including Lynch-related tumors. We describe the digestive burden of these patients with their phenotypical presentation, somatic datas and phenotype-

genotype correlations.

Method: Digestive phenotype was reported in 45/78 patients registered in the C4MMRD database.

Results: Overall, 37 digestives cancers (DC) were observed in 27 patients (35 colorectal, 1 stomach,1 duodenal, 1 small bowel cancer). Median age at first DC was 17,5 (7-33). DC was the first tumor for 14 patients. Thirteen patients are alive at last follow-up, 7 patients died because of their DC and 7 of other cancers.

32 patients (including 23 with DC) had multiple colic adenomas at a median age of 16 (9-33).

Conclusion: CMMRD patients have severe digestive burden with early-onset multiple adenomas and cancers in upper and lower digestive tract. An early and intensive screening of those lesions is required as some of them could be removed to prevent cancer.

Some data also support the existence of a clinical overlap between CMMRD and Lynch Syndrome. This is suggestive of a genetic continuum whose mechanism is still unknown. We discuss several hypotheses and propose collaborations.

N24

Title: Systematic Linkage Of All Diagnostic Hereditary Cancer Genotypes To The National Cancer Registry

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1 - Public Health England. 2 - Health Data Insight CiC, Cambridge. 3 - Northern Genetics Service, Newcastle.

Aim: To create a national service collecting pseudonymised germline cancer-predisposing genotypes, and link these to the National Cancer Registration and Analysis Service for individuals with a prior or subsequent cancer diagnosis.

Method: NHS molecular genetics laboratories submit patient-level genotype data through a secure online portal. Unique patient demographics are pseudonymised using a one-way hash function that generates an irreversible pseudoID; additional identifiers are secondarily encrypted. The same hash function applied to cancer registration records, where patient identity is already known, enables linkage of the genotype data; decryption of additional identifiers is then possible. We can thus obtain accurate variant counts nationally, and identify those who develop cancer, without compromising patient privacy.

Results: Pilot work has focused upon BRCA1 and BRCA2 genes; we are now commencing collection of colorectal cancer predisposition gene data. To date, ten laboratories have submitted BRCA1/2 data, covering a time period from 2001 onwards, and including ~1300 different gene variants. Initial linkage to cancer registry records showed a 68% match rate.

Conclusion: This robust, secure system collects depersonalised but linkable genotypes on all individuals tested. Record-level linkage to the rich phenotype, treatment and outcome data in the national cancer registry provides allelic frequency and associated phenotype data, and facilitates variant interpretation.

N25

Title: Frequency Of Germline Pathogenic Variants Of Cancer Susceptibility Genes For Japanese Ovarian Cancer Patients

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Aim: The aim of our study was to reveal the prevalence of pathogenic germline variants of candidate genes associated with genetic predisposition to ovarian cancer (OC) in Japanese OC patients.

Method: Germ-line DNA samples from 230 unselected OC patients were recruited from the Keio Women's Health Biobank at Keio University School of Medicine. Germ-line DNA was enriched using the SureSelect XT Target Enrichment System (Agilent Technologies) designed for 75 or 79 genes as a custom OC panel, followed by sequencing using MiSeq (Illumina). Detected variants were classified according to the American College of Medical Genetics and Genomics recommendations. Furthermore, BRCA1/2 variants were interpreted using resources from Myriad Genetic Laboratories.

Results: Of 230 patients, 19 (8.3%) and 8 cases (3.5%) carried germline BRCA1 and BRCA2 pathogenic variants, respectively. No variant of uncertain significance (VUS) of BRCA1/2 genes was detected in our analysis according to the database of Myriad Genetics. Six (2.6%) carried pathogenic germline variants of mismatch repair genes. Carriers of BRCA1/2 or pathogenic variants of any other genes tested were more likely to be diagnosed younger, have first or second-degree relatives with OC, and have OC classified as high-grade serous carcinoma (HGSC).

Conclusion: Our data can facilitate genetic predisposition prediction in Japanese OC patients and referring high-risk patients for genetic counseling and testing.

N26

Title: Consensus For Genes To Be Included On Cancer Panel Tests Offered By UK Genetics Services: Guidelines Of The UK Cancer Genetics Group

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Aim: Genetic testing for hereditary cancer predisposition has evolved rapidly in recent years with the discovery of new genes, but there is debate over the clinical utility of testing genes for which there is currently limited data regarding the degree of associated cancer risk. To address discrepancies that have arisen in the provision of these tests across the UK, the UK Cancer Genetics Group (UK-CGG), facilitated a workshop with representation from the majority of NHS Clinical Genetics Services.

Method: We administered a pre-workshop survey to canvas opinion on genes to be included on panels for familial breast, ovarian, or colorectal cancer/polyposis. Participants then presented arguments for and against inclusion of genes without prior majority agreement, and this was followed by focused discussion.

Results: We achieved consensus for panels of cancer genes with sufficient evidence for clinical utility, to be adopted by all NHS Genetics Services. To support consistency in the delivery of these tests and advice given to families across the country, we also developed management proposals for individuals who are found to have pathogenic mutations in these genes.

Conclusion: We have recommended genes to be included on panels for investigating familial breast, ovarian, or colorectal cancer/polyposis. However, we fully acknowledge that the decision regarding what test is most appropriate for an individual family rests with the clinician, and will depend on factors including specific phenotypic features and the family structure.

N27

Title: The Management Of Gynaecological Cancers In Lynch Syndrome: The Manchester International Consensus Meeting

E. J. Crosbie[1], N. A. J. Crosbie[1], D. G. Evans[1], Manchester International Consensus Group[2]1 - University of Manchester. 2 - Manchester International Consensus Group.

Aim: There are no internationally agreed clinical guidelines as to how best to manage the risk, prevention and treatment of gynaecological cancers in women with Lynch syndrome. The Manchester International Consensus Group was convened in April 2017 to develop clear and comprehensive clinical guidance regarding the management of the gynaecological sequelae of Lynch syndrome based on existing evidence and expert opinion from medical professionals and patients.

Method: Stakeholders from Europe and North America worked together over a two-day workshop to achieve consensus on best practice. Stakeholders included patients, patient support groups, gynaecologists, clinical geneticists, medical oncologists, colorectal surgeons, gastroenterologists, histopathologists, genetic pathologists, health economists, epidemiologists, gynaecology nurse specialists and genetic counsellors.

Results: Guidance was developed in four key areas: 1) whether women with gynaecological cancer should be screened for Lynch syndrome and 2) how this should be done; 3) whether gynaecological surveillance was of value for women with Lynch syndrome; and 4) what preventive measures should be recommended for women with Lynch syndrome to reduce their gynaecological cancer risk.

Conclusion: The Manchester International Consensus Guideline provides comprehensive clinical guidance that can be referenced by both patients and clinicians so that women with Lynch syndrome can expect and receive appropriate standards of care.

N28

Title: Awareness Of Lynch Like Syndrome Within Clinical Genetics –Results From A UK Survey

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Aim: UK NICE guidelines (2017) recommend screening of all new colorectal cancers with either immunohistochemistry (IHC) or Microsatellite instability (MSI) testing. Following an abnormal IHC or MSI result, up to 70% of individuals may have no identifiable germline mutation. This group constitutes Lynch-like syndrome (LLS), estimated to represent 3% of colorectal cancer cases.

Evidence suggests the majority of LLS cases are caused by somatic variants in the tumour. Colorectal and extracolonic cancer risks in LLS are increased in comparison to population risks. UK guidelines suggest 2 yearly colonoscopies for individuals with LLS and their first degree relatives; assuming there may be an unknown hereditary cause.

Method: We conducted a survey amongst clinicians practising in regional clinical genetics departments within the UK. We aimed to explore clinicians' understanding and management of LLS families. The survey was disseminated by the cancer lead clinician within each department, through a "surveymonkey" link.

Results: We received 44 responses from 19 centres. 40% of participants were aware of the definition of LLS while 27% would offer 2 yearly colonoscopies. There were variations in practice within and between departments.

Conclusion: These results emphasize the importance of increasing awareness of LLS, and contribute towards the need for clear management guidelines.

N29

Title: New Treatment Possibilities For Lynch Syndrome-Associated Cancer?

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Aim: Recent advances within immunotherapy have proven highly effective in microsatellite instable tumors, which offer promising treatment options for Lynch syndrome patients. However, different immune evasion mechanisms may influence the response rate and call for further investigation in Lynch syndrome tumors.

Method: We examined the immunological tumor microenvironment and potential immune-escape mechanisms and ana-lyzed their prognostic value in 169 Lynch syndrome-associated colorectal cancers with comparison to 101 mi-crosatellite stable tumors.

Results: Lynch syndrome cancers where dominated by increased infiltration of CD3+ T cells, CD8+ cytotoxic T cells and CD68+ macrophages and showed up-regulation of pro-inflammatory genes suggestive of an immune-mediated surveillance and potential tumor-killing. Interestingly, two escape mechanisms were also found up-regulated in Lynch syndrome tumors, which related to loss of the MHC class I subunit, Beta-2-microglobulin (B2M), and T cell exhaustion through up-regulation of PD-L1. Immune evasive tumors showed up-regulation of genes involved in natural killer cell-mediated cytotoxicity and cell death indicating that additional immunological cell types may aid in the eradication of tumor cells. This was supported by survival analyses showing improved survival in patients with PD-L1 positive and B2M negative tumors.

Conclusion: These data suggest that detailed immunological characterization could predict immunotherapy response and should be performed prior to immune therapy.

N30

Title: Life-Long Immune Surveillance And Immunoediting – Evidence From Lynch Syndrome Cancers

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Aim: Lynch syndrome-associated cancers accumulate a high load of immunogenic frameshift peptide neoantigens as a consequence of DNA mismatch repair (MMR) deficiency. MMR-deficient cells can therefore be recognized by the immune system. We aimed to comprehensively characterize the immune phenotype of MSI cancers, accounting for somatic mutations inducing immune evasion and for immune cell infiltration.

Method: We combined the analysis of our own cohort of MSI cancers with mutation data of MSI cancers of the TCGA/DFCI cancer collections. Immune cell infiltration was quantified by immunohistochemistry, using antibodies specific for T cell subtypes, including CD3, FOXP3, and PD-1.

Results: 72% of MMR-deficient colorectal cancers of the DFCI database harbored alterations affecting genes involved in HLA class I-mediated antigen presentation. The most common alterations were truncating mutations affecting the Beta2-microglobulin (B2M) gene. B2M mutations were related to a higher density of activated T cells infiltrating the tumor, and to a lower frequency of regulatory T cells in the tumor environment.

Conclusion: The extraordinarily high prevalence of immune evasion phenomena in MSI cancer most likely reflects life-long immune surveillance and suggests that most MSI pre-cancers are eliminated by the immune system if they fail to evade the immune attack.

N31

Title: Identification Of Clinical, Genetic And Endoscopic Predictors Of Incident Colorectal Cancer In Lynch Syndrome

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Aim: Lynch syndrome (LS) families have a high risk of colorectal cancer (CRC) during their lifetime. Colonoscopy every <3 years decreases incidence and mortality of CRC. However, recent studies show that up to 40% of carriers develop CRC during colonoscopy follow-up at the age of 70. It is crucial to identify the factors that predict CRC development in this setting to further improve prevention in LS. Endoscopy quality indicators in the setting of Lynch screening have been poorly studied.

This study is designed to assess the clinic-pathological, genetic and endoscopy factors that predict the development of CRC during colonoscopy surveillance in LS mutation carriers.

Method: Multicenter nation-wide study in Spain, with retrospective collection of prospectively observed data in the setting of organized high-risk clinics. A centralized online database was used, including demographic, genetic, family and personal cancer history, and surveillance protocol and treatments, from September 2015 to October 2017. First prospectively complete colonoscopy planned as LS screening was considered as date of inclusion. Cumulative incidence of the first CRC diagnosed under screening was calculated by mutated gene and gender. For this analysis, CRCs diagnosed prior or within the first colonoscopy (prevalent cancers) were excluded. Additionally, endoscopic predictor factors of CRC have been analyzed.

Results: We included 1,108 LS cases, 631 female (56.9%), with a median age of 53 year (SD 15.4), and a median follow-up of 50.85 months (SD 47.6). Distribution per gene was: 449 (40.5%) MLH1, 371 (33.6%) MSH2, 197 (17.9%) MSH6, 68 (6.1%) PMS2 and 23 (2.1%) EPCAM. The prevalence of CRC was 41.42% (459). Five-hundred-thirty-eight healthy carriers with proven endoscopic surveillance were selected from all the healthy carriers (666) from whom we could obtain endoscopic reports. Seventeen (17/538) incident CRC were diagnosed during endoscopic screening in healthy carriers: 7/191 MLH1, 9/192 MSH2, 1/113 MSH6, 0/37 PMS2 and 0/5 EPCAM. Inadequate endoscopic follow-up was present in 7/17 incident CRC including longer than 3 years interval (n=4) or inadequate bowel cleansing (n=3) (Table.1). Cumulative CRC incidence at 70 years under endoscopic follow-up was calculated per gen (Figure.1): 13.8% (95%CI:5.9-30.3%) for MLH1; 18.5% (95%CI: 8.8-36.4%) for MSH2 and 1% (95%CI: 0.15-7.1%) for MSH6; and per gender (Figure.2): 16.7% (95%CI: 8-32.1%) for males and 8.7% (95% CI: 3.9-19%) for females.

Conclusion: In this large Spanish multicenter study, a preliminary analysis reveals that cumulative incidence of the first CRC under screening colonoscopy is lower than previously published. Our results suggest that colonoscopy is highly effective for CRC prevention in LS, and that high quality endoscopic standards are key for its effectiveness.

N32

Title: A Novel Mainstreaming Model For Lynch Syndrome Genetic Testing In Colorectal Cancer Patients

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Aim: New NICE guidance (2017) recommends universal tumour screening for Lynch syndrome (LS) in all patients with newly diagnosed colorectal cancer (CRC). Identifying CRCs with deficient DNA mismatch repair (dMMR) will guide further diagnostic testing for LS. Establishing a diagnosis of LS has important implications for the management of CRC patients. All CRC patients with suspected LS should have access to appropriate diagnostic testing performed within a suitable time frame. Based on the anticipated rapid increase in clinical need, we have developed and implemented a novel mainstreaming model for LS genetic testing.

Method: Reflex IHC testing is undertaken in all newly diagnosed CRC cases; abnormal results are reviewed at the colorectal MDM, and eligible patients offered germline testing at their routine cancer appointments by appropriately trained cancer clinicians (i.e. oncologists and surgeons). Genetic results are fed back to patients by the cancer team, and all patients with a pathogenic variant or a variant of unknown significance are referred to clinical genetics for further management.

Results: We present the pathway as adopted at St Marks Hospital and the outcomes from the first year post implementation.

Conclusion: This pathway was effective at our hospital.

N33

Title: Validation And Updating Of Path_MLH1 In Cases With Class 4 And 5 Genetic Variants; A Prospective Lynch Syndrome Database (PLSD) Report

T. Seppälä[1], J. P. Plazzer[2], M. Dominguez-Valentin[3], S. Nakken[4], C. Engel[5], S. Aretz[5], M. A. Jenkins[6], L. Sunde[7], I. Bernstein[7], F. Balaguer[8], A. Lindblom[9], D. G. Evans[10,]L. Bertario[11], J. Burn[12], E. Holinski-Feder[13], F. Lopez-Koestner[14], A. Della Valle[15], K. Heinimann[16], C. A. Vaccaro[17], W. H. de Vos tot Nederveen Cappel[18], R. H. Sijmons[19], N. Gluck[20], L. Katz[20], G. M. Cavestro[11], E. Hovig[4], F. Macrae[21], G. Möslein[22], J. Sampson[23], G. Capella[8], J. P. Mecklin[1], P. Møller[24]

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Aim: Determine average risks for and survival after cancer in path_MLH1 carriers.

Method: Previously reported results were validated in an independent series of path_MLH1 carriers followed-up by colonoscopy. Combined results merging former and present series included only carriers with pathogenic class 4 or 5 variants listed in the InSiGHT database.

Results: The validation series including 10,037 observation years confirmed previously published cumulative risk for any cancer: at fifty years, 37% in the validation series compared to 40% in the previous series, and at 75 years, 78% compared to 76%. The combined series of path_MLH1 variant carriers included 24,297 observation years. Cumulative risk for cancer in specific organs or group of organs at 75 years were (males/females): Any cancer 70%/80%; colon_rectum 56%/47%; endometrium -/37%; ovaries -/11%; stomach_duodenum_bileduct_pancreas 21%/11%; ureter_kidney 4.7%/3.6%; urinary bladder 6.4%/4.9%; prostate 12%/-; breast -/12%; brain 0.7%/1.6%. Ten-year crude survival after cancer in different organs were: colon 86%; endometrium 90%; ovaries 82%; ureter_kidney 61%; urinary bladder 54%; prostate 90%, breast 80%; brain 0%.

Conclusion: PLSD reports average risks for and survival after cancer in path_MLH1 carriers of variants classified as clinically actionable in the InSiGHT database. See www.PLSD.eu for risk determination in any single patient by age and gender.

N34

Title: A Functional Assay-Based Procedure To Classify Mismatch Repair Gene Variants In Lynch Syndrome

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Aim: Determining pathogenicity of the increasingly prevalent Variants of Uncertain Significance (VUS) in cancer-predisposing genes provides a major challenge to clinical geneticists. Lynch syndrome is a prevalent cancer predisposition syndrome caused by a germ line defect in one of four DNA mismatch repair (MMR) genes. Thus far, the large majority of missense variants identified in MMR genes cannot be classified. As clinical multi-gene testing increases, many more VUS are being identified, emphasizing the need of a calibrated and validated classification method.

Method: Here we calibrate and validate an assay that rapidly quantifies the biochemical activity of variants in MMR proteins MLH1 and MSH2.

Results: We show that Bayesian integration of functional assay results with in silico analysis correctly classifies ~85% of missense variants, and we demonstrate inter-laboratory assay reproducibility.

Conclusion: This integrated diagnostic procedure provides a paradigm for the assessment of pathogenicity of VUS in disease-predisposing genes.

N35

Title: An Assessment Of Endometrial Cancer Risk Markers In Lynch Syndrome Patients

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Aim: Assesment of a set of markers to anticipate endometrial cancer occurence in healthy female Lynch syndrome (LS) carriers.

Method: Materials: 242 biopsy specimens obtained during the prospective annual follow-up of 79 Lynch syndrome (LS) carriers from 4 different Spanish Centers.

Investigated markers were (High Microsatellite Instability MSI-H; abnormal mismatch repair proteins (MMR-IHC) or PTEN (PTEN-IHC) inmunohistochemistry; LINE sequences (LINE-CIN) or MMR genes CpG islands abnormal methylation (MMR-MMR), and somatic mutations in a custom panel of 27 genes related to type 1 endometrial carcinogenesis (Panel-27).

Results: Simultaneous presence of abnormal MMR and PTEN-IHC anticipated the occurrence of the precursor lesion “focal hyperplasia” in a median time of 19,63 months (CI95=17,55-21,71) with a Hazard Ratio HR= 3,97 (CI95=1,32-11,9) vs the no markers group. Panel-27 somatic mutations rate was also higher (75x10-6 mutations per Mb vs. 12x10-6 mutation per Mb, p<0,05) in these samples.

Conclusion: These findings provide a basis for recommending to introduce the investigation of these markers in biopsy specimens from LS patients, as a supportive tool for selecting the most appropriate management option in these patients (prophylactic hysterectomy vs surveillance).

N36

Title: Back To Back Comparison Of Colonoscopy With Virtual Chromoendoscopy Using Third Generation Narrow Band Imaging System To Chromoendoscopy With Indigo Carmine In Lynch Syndrome Patients

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Aim: Colonoscopic screening with indigo carmine chromoendoscopy (ICC) in Lynch Syndrome (LS) patients improves adenoma detection rate and is widely used nowadays. Nevertheless, it is a time- and-money-consuming technique which requires a dedicated training. Narrow band imaging (NBI) is a well-known virtual chromoendoscopy technique that highlights superficial mucosal vessels and improves contrast for adenomas. We conducted a prospective multicenter study in a back-to-back fashion to compare 3rd generation NBI to ICC for detecting colonic adenomas in LS patients.

Method: One hundred and thirty eight patients underwent a double colonoscopy, first with NBI, followed by ICC, in a back-to-back fashion. All polyps detected in either pass were removed for histopathological analysis. The primary outcome measure was the number of patients with at least one adenoma after NBI compared with the number of patients with at least one adenoma after NBI and ICC. Proportions were compared with the paired exact test (McNemar’s test). Continuous variables were compared with the Wilcoxon signed-rank test.

Results: All of the 138 patients were proven MMR mutation carriers (MLH1 = 33%, MSH2 = 47%, MSH6 = 15%, PMS2 = 4%, EPCAM = 1%). Mean age (standard deviation [SD]) was 40.5 (14.7) years, 64 (46.4%) were male. The median time for an NBI procedure was 8 minutes (interquartile range [IQR] 6–11) compared to 13 minutes (IQR 8–17) for ICC. At least one adenoma was detected during the initial NBI pass in 28 (20.3%) of 138 patients. ICC detected additional adenomas in 25 (18.1%) of 138 patients. Forty-two patients (30.4%) had at least one adenoma detected after both NBI and ICC; this represents an increase of 50.0% of the adenoma detection rate (ADR) (p=0.0001). The total number of adenomas increased from 39 after NBI pass to 75 after ICC pass with a mean number of adenomas detected per patient of 0.3 (0.7) after NBI pass vs 0.5 (1.1) after both NBI and ICC passes (p<0.0001). The ADR for flat adenomas was 10.9% after NBI vs 23.2% after ICC (p<0.0001). The ADR increased for right sides adenomas (10.9% after NBI vs 16.7% after ICC, p=0.0078) as well as for diminutive adenomas ≤5mm (16.7% after NBI vs 28.3% after ICC, p<0.0001). Detection of both sessile adenomas (11.6% NBI vs 13.8% ICC, p=0.25) and adenomas > 5mm (6.5% NBI vs 8.0% ICC, p=0.5) did not differ significantly between the 2 techniques. After adding white light detected adenomas, the total ADR of the study was 33.3%.

Conclusion: Colonoscopy with indigo carmine chromoendoscopy detects significantly more adenomas than 3rd generation NBI in LS patients, whereas sessile and > 5mm adenomas are equally detected. Although less time consuming, NBI colonoscopy cannot be recommended to replace indigo carmine chromoendoscopy in LS patients.

N37

Title: Cancer Incidences By Age In Path_PMS2 Carriers: A Report From The Prospective Lynch Syndrome Database (PLSD)

M. Dominguez-Valentin[1], S. W. Ten Broeke[2], J. P. Plazzer[3], T. Seppälä[4], S. Nakken[1], M. A. Jenkins[5], R. H. Sijmons[6], G. Capella[7], C. Engel[8], S. Aretz[9], L. Sunde[10], I. Bernstein[11], D. G. Evans[12], J. Burn[13], M. Greenblatt[14], F. Balaguer[15], M. Grazia Tibiletti[16], E. Holinski-Feder[17], H. K. Schackert[18], W. Schmiegel[19], N. Rahner[20], M. Löffler[8], F. Macrae[3], J. Sampson[21], H. Thomas[22], A. Lindblom[23], W. H. de Vos tot Nederveen Cappel[24], F. Lopez-Koestner[25], A. Della Valle[26], E. Hovig[1], G. Mösslein[27], J. P. Mecklin[28], M. Nielsen[2], P. Møller[1, 29, 30]

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Aim: Determine average risks for cancer in path_PMS2 carriers.

Method: Prospectively observed cancers in carriers of PMS2 variants classified as pathogenic (class 4/5) in the InSiGHT database.

Results: 407 carriers were prospectively observed for 2239 years and they underwent regular surveillance and if needed polypectomies. Cumulative incidences for cancer at 50/75 years of age were: Any cancer 8% (95% CI 0%-19%)/32% (95% CI 14%-50%); colorectal- 0% /9% (95% CI 0%-21%); endometrial 0%/13% (95% CI 1%-25%); ovarian 0%/3%(95% CI 0%-9%); and urinary tract 0%/3% (95% CI 0%-9%) cancer.

Conclusion: Neither colorectal, endometrial, ovarian nor urinary tract cancer was observed before 50 years of age. The point estimates for colorectal and endometrial cancers at age 75 were, however, higher than expected despite undergoing regular surveillance . The patients examined were mostly selected from cancer kindreds, and the late onset cancers might not necessarily have been caused by the path_PMS2 variants. Clinical guidelines for monoallelic path_PMS2 carriers should be revised.

N38

Title: Yield Of Lynch Syndrome Surveillance For Individual MMR Genes

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Aim: To assess the yield of Lynch syndrome (LS) surveillance for MLH1, MSH2, MSH6 and PMS2 mutation carriers.

Method: Data on colonoscopy surveillance was collected for all LS mutation carriers in our center. We compared the development of adenomas and CRC between the different gene mutation carrier groups.

Results: Colonoscopy data was available for 264/314 (84%) patients; 55 MLH1, 44 MSH2, 143 MSH6 and 22 PMS2 mutation carriers. Median age was 44 years (IQR 35-56 years) and median follow-up time 6 years (IQR 2-10 years). At first colonoscopy CRC was found in eight patients and during 916 follow-up colonoscopies in nine patients. No CRC was found in MSH6 or PMS2 mutation carriers. There were no significant differences in the number of colonoscopies with adenomas or advanced adenomas between the different gene mutation carrier groups. In MSH6 mutation carriers advanced neoplasia (advanced adenoma or colorectal carcinoma) was found after a longer follow-up time than in the other mutation carrier groups.

Conclusion: Since no CRC was found during follow-up in MSH6 mutation carriers and advanced neoplasia was found in shorter follow-up time in MLH1 and MSH2 mutation carriers, the colonoscopy interval in MSH6 mutation carriers might be less stringent than for MLH1 and MSH2 mutation carriers.

N39

Title: The Prospective Lynch Syndrome Database (PLSD)

P. Møller

PI to the PLSD

Aim: Compile existing prospective data on carriers of pathogenic MMR variants.

Method: Inclusion: 1) Demonstrated monoallelic germline carriers of pathogenic variant of either of the genes MLH1, MSH2, MSH6 or PMS2 listed in the InSiGHT database. 2) Determined to be at risk for Lynch Syndrome for any reason. 3) Inclusion point: First planned and carried out prospective colonoscopy. 4) One or more follow-up years.

Patient information: Age, gender, pathogenic variant, reporting centre, age and ICD9 diagnoses of all cancers (before, at or after inclusion), organs removed when.

Events scored: All prospectively diagnosed cancers after inclusion by ICD9 code and age at diagnosis. Age at death.

Information not yet analysed: polyps removed, stage at colorectal cancer and time since last colonoscopy.

For detailed protocol see https://ehtg.org/

Results: Incidences of cancer by age, genetic variant and gender. Survival after cancer. Results of intervention (international guidelines).

Conclusion: The reports migrate knowledge on Lynch syndrome from expert opinions based mainly on retrospective studies to assumption-free empirical observations in carriers subjected to follow-up according to accepted clinical guidelines. The interactive website www.PLSD.eu returning risk for any single case when indicating age, gender and gene is referred to for clinical use by InSiGHT and others.

N40

Title: Validated And Updated Risks For And Survival After Cancer By Age And Gender In Path_MSH2 Carriers; A Prospective Lynch Syndrome Database (PLSD) Report

P. Møller[1], J. P. Plazzer[2], T. Seppälä[3], M. Dominguez-Valentin[4], S. Nakken[5], C. Engel[6], S. Aretz[7], H. K. Schackert[8], W. Schmiegel[9], N. Rahner[10], M. von Knebel Doeberitz[11], M. Löffler[12], I. Bernstein[13], L. Sunde[13], M. Jenkins[14], D. G. Evans[15], F. Balaguer[16], E. Holinski-Feder[17], J. Burn[18], L. Bertario[19], A. Lindblom[20], A. Della Valle[21], R. H. Sijmons[22], L. Katz[23], W. H. de Vos tot Nederveen Cappel[24], K. Heinimann[25], N. Gluck[23], C. A. Vaccaro[26], F. Lopez-Koestner[27], G. Martina Cavestro[19], E. Hovig[5], F. Macrae[28], G. Möslein[29], J. P. Mecklin[3], J. Sampson[30], G. Capella[16]

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Aim: Determine average risks for and survival after cancer in path_MSH2 carriers.

Method: Previously reported results were validated in an independent series of path_MSH2 carriers followed-up by colonoscopy. We combined results merging former and present series including only carriers with pathogenic class 4 or 5 variants listed in the InSiGHT database.

Results: The validation series including 11,684 observation years confirmed previously published cumulative risk for any cancer: at fifty years 35% compared to 37%, and at 75 years 79% compared to 80%. Combined series of carriers of path_MSH2 variants included 19,888 prospective observation years. Cumulative risk for cancer in specific organs or group of organs at 75 years in males/females were: Any cancer 73%/82%; colon_rectum 49%/45%; endometrium -/47%; ovaries -/17%; stomach_duodenum_bileduct_pancreas 19%/12%; ureter_kidney 17%/18%; urinary bladder 12%/8%; prostate 22%/-; breast -/14%; brain 7%/3%. Ten-year crude survival after cancer in different organs were: colon 94%; endometrium 86%; ovaries 81%; ureter_kidney 65%; urinary bladder 72%; prostate 51%, breast 74%; brain 18%. See www.PLSD.eu for risk determination in any single patient by age and gender.

Conclusion: The PLSD and InSiGHT databases are complementary: PLSD reports prospectively observed average risks and survival in carriers of variants determined to be pathogenic by InSiGHT.

N41

Title: Small Bowel Neoplasia Detection In Lynch Syndrome Using Video Capsule Endoscopy

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Aim: Screening for small-bowel cancer (SBC) is not yet included in surveillance guidelines for LS. In 2016 Mallorca group advised may be appropriate in MSH2 and MLH1 mutation carriers, after 40 years. Aim of the study was to determine SBC incidence in asymptomatic LS patients by means of video capsule endoscopy (VCE).

Method: Two prospective VCE databases were retrospectively reviewed to identify consecutive asymptomatic LS patients, compared with a group of patients who underwent VCE for obscure gastrointestinal bleeding (OBS).

Results: 25 LS patients and 280 OBS patients were enrolled by two Italian centers. In 91.5%, caecal visualization was achieved. SBC was detected in two LS patients and three OBS patients (p=0.06). The two groups have a significant statistically different mean age (SD): 41.3 ys± 14.0 ys in LS group and 62.9 ys ± 17.2 ys in OBS group. Besides SBC, LS patients and OBS patients have statistically significant difference in incidence of vascular lesion, angiectasia and minute polyps.

Conclusion: The prevalence of SBC in asymptomatic patients with LS was 8% vs 1.1%. Although the incidence of SMC did not reach statistical significance difference, a trend through statistically significant difference was observed and this suggests further multicentric studies are needed.

N42

Title: Improving Triaging Of Patients With Sebaceous Neoplasia For The Identification Of Muir-Torre/Lynch Syndrome

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Aim: Loss of expression of mismatch repair (MMR) proteins is frequently observed in sebaceous skin lesions, but the positive predictive value of MMR-deficiency for identifying a germline MMR gene mutation is low. Determining which sebaceous neoplasms should be tested for MMR protein expression and of those with MMR-deficiency, which should undergo subsequent germline MMR gene mutation testing, currently presents significant clinical challenges.

Method: An audit between January 2009 and April 2014 was undertaken of a single pathology practice in Queensland, Australia of all sebaceous lesions where pathologist-initiated MMR IHC had been performed comprising 928 lesions from 882 individuals. A subset of 125 participants provided a blood sample for germline MMR and MUTYH gene testing. Individuals and their lesions were further characterised for differences in gender, age at diagnosis, lesion type and anatomic location, personal and family history of cancer, and stratified by MMR status.

Results: MMR-deficiency, observed in 282 of the 919 lesions included (30.7%), and was most common in sebaceous adenomas (210/282; 74.5%). Loss of MSH2/MSH6 protein expression was the most common (187/282; 66.3%). Characteristics of germline MMR mutation carriers will be presented.

Conclusion: Further elucidation of genotype-phenotype correlations in sebaceous neoplasia should result in improved triaging for MMR testing and clinical decision making.

N43

Title: Hide And Seek With Hereditary Cancer: Testing The Effectiveness And Cost-Effectiveness Of Implementation Approaches For Translating Lynch Syndrome Evidence Into Practice

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Aim: Evidence indicates that hospitals face infrastructural, psychosocial and environmental barriers to detecting Lynch Syndrome (LS) patients. In Australia, less than half of all high-risk colorectal cancer (CRC) patients are being referred for LS genetic testing. This study aims to compare the effectiveness and cost-effectiveness of two implementation approaches for increasing the proportion of CRC patients with risk-appropriate completion of the LS testing and referral pathway.

Method: This randomised controlled trial will test the Theoretical Domains Framework Implementation approach against a non-theory-based implementation approach in eight large Australian hospitals. Site based healthcare professionals will be trained to lead the following process: 1) Baseline audits, 2) Form Implementation Teams, 3) Identify practice change behaviours, 4) Identify/confirm barriers to change, 5) Generate intervention strategies, 6) Support intervention implementation, 7) Evaluate practice/culture change. Theoretical and non-theoretical components are distinguished in 4-5.

Results: Progress to date of baseline data analysis will be presented. Plans for the analysis of health and economic outcomes of each implementation approach to be estimated using "POLICY1-Lynch" will be provided.

Conclusion: This will be a world first study to compare theory-based and non-theory based approaches to evidence translation in healthcare, and to incorporate these findings into existing microsimulation models to accurately assess implementation cost-effectiveness.

N44

Title: Genetic And Clinical Characteristics Of Registry-Validated Pedigrees Of Lynch Syndrome Families In Slovenia – First Report

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Aim: The aim of this study was to assess genetic and clinical characteristics of Slovenian Lynch syndrome (LS) families, as such evaluation has not yet been performed for our population.

Method: We analyzed the results of genetic testing performed in 2008-2018 for probands fulfilling LS testing criteria. LS spectrum cancers identified in confirmed,

obligate and assumed carriers of mismatch repair (MMR) gene mutations were verified in Slovenian cancer registry and analyzed according to site, age of onset, and genes involved.

Results: 25 probands out of 251 tested carried a MMR mutation. 22 different mutations, 2 of which were recurrent, were identified. Mutation detection rate was 9.9%. 48% of probands harbored MLH1, 36% MSH2, 8% MSH6 and 8% PMS2 mutations. Of 120 cancers identified, 84 were colorectal (average age of onset: 42.2y) and 14 were endometrial carcinomas (average age of onset 52.4y).

Conclusion: We had very few referrals for LS testing in the 10-year period analyzed considering its prevalence in the population. LS is therefore likely to be drastically underdiagnosed in Slovenia. Screening of all colorectal and possibly endometrial cancers with immunohistochemical test should be performed in order to systematically identify LS families and offer them adequate treatment and familial risk assessment in the future.

N45

Title: High-Definition White-Light Colonoscopy Versus Chromoendoscopy For Surveillance Of Lynch Syndrome. A Multicenter, Randomized And Controlled Study (Endolynch Study)

L. Rivero-Sánchez[1,2,3,4], C. Arnau[4], F. Balaguer[1,2,3,4,5], J. Herrero[6], D. Remedios[6], V. Alvarez[7], E. Albéniz[8], P. Calvo[8], J. Gordillo[9], I. Puig[10], J. López Vicente[11], A. Huerta[12], M. López-Cerón[13], I. Salces[13], B. Peñas[14], S. Parejo[14], M. Herraiz[15], A. Gimeno[16], E. Saperas[17], C. Alvarez[18], L. Moreno[4], C. Rodriguez de Miguel[13], M. Diaz[4], T. Ocaña[12], L. Moreira[1,2,3,4,5], M. Cuatrecasas[1,19], S. Carballal[1,2,3,4,5], A. Sánchez[1,2,3,4,5], J. Llach[1,2,3], M. Pellisé[1,2,3,4,5]

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Aim: The use of pan-chromoendoscopy (CE) for surveillance in Lynch syndrome is currently recommended despite low evidence. We aimed to demonstrate that high-definition white-light endoscopy (WLE) is not inferior to CE for detection of adenomas.

Method: Patients with confirmed germline mismatch repair mutation were prospectively randomized 1:1 to WLE or CE performed by endoscopists devoted to high-risk conditions of colorectal cancer. The main outcome was the adenoma detection rate.

Results: 256 patients (60% women; age 47±14y) were included in 14 centers. The detection rate of lesions in WLE versus CE group were: adenomas 28.1% versus 34.4% respectively (p=0.281), total polyps 50.0% versus 57.7% (p=0.004), proximal serrated lesions (SL) 10.2% versus 11.7% (p=0.689), sessile SL 5.5% versus 3.9%(p=0.554) and advanced adenomas 7.8% (4.3%-13.7%) versus 3.9% (1.6%-3.9%) (p=0.183) respectively. The mean (standard deviation) of lesions per patient for WLE versus CE were: adenomas 1.04 (1.37) versus 0.86 (1.04) (p=0.670),proximal SL 0.25 (0.56) versus 0.25 (0.61) (p=0.426),sessile SL 0.10 (0.31) versus 0.11 (0.67) (p=0.660),left-sided SL 0.21 (0.55) versus 0.53 (1.04) (p=0.002) respectively.The withdrawal time (minutes) for WLE and CE were 13.5 (5.63) versus 18.37 (7.57)(p<0.001) respectively.

Conclusion: In a scenario with expert endoscopists, WLE is an optimal and efficient endoscopic technique for surveillance of Lynch syndrome patients.

N46

Title: The Role Of Immunohistochemistry (IHC) Testing In The Tumor Spectrum Of The Lynch Syndrome (LS)

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Aim: To validate the performance of IHC testing of Mismatch Repair (MMR) proteins in patients with LS spectrum cancers.

Method: We analyzed MicroSatellite Instability (MSI) on 461 cancers (378 colorectal, 64 gynecologycal, 19 other sites). IHC analysis of MMR proteins was performed in all samples, irrespective of the MSI status. IHC results were classified as proficient-IHC (normal expression), deficient-IHC (loss of expression), borderline-IHC ("patchy" expression); borderline-IHC cases with MSI were classified as deficient-IHC.

Excluding samples with BRAF mutation or MLH1 promoter hypermetilation (MLH1-Hy), deficient-IHC cases were addressed to germline MMR gene testing.

Results: Fifty-three patients (11.5%) had deficient-IHC: 1 for all proteins, 1 for three proteins, 41 for two proteins (32 MLH1-PMS2, 9 MSH2-MSH6), 10 for 1 protein. IHC deficiency rate was significantly different among sites: 10% colorectal, 23% endometrial/ovarian cancer, 0% in other sites (p<0.001).

Twenty-five samples had BRAF mutation or MLH1-Hy. Twenty-eight patients, including 6 borderline-IHC, were addressed to genetic testing (16 ongoing) and mutations were found in 9 patients (4 in MLH1, 4 in MSH2 and 1 in MSH6), including one borderline-IHC with MSI.

Conclusion: We support the systematic evaluation of MMR proteins in colorectal and gynecological cancers to select patients with LS. MSI could be useful to manage borderline-IHC cases.

N47

Title: Prevalence Of Mismatch Repair Deficiency In Small Bowel Carcinomas And Neuroendocrine Tumours

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Aim: Mismatch repair (MMR) deficiency in tumours is caused by biallelic loss of one of the MMR genes. Carriers of a heterozygous germline mutation in an MMR gene have Lynch syndrome and consequently a ~4% lifetime risk of developing small bowel cancer. Previous studies on prevalence of MMR deficiency in small bowel cancer have shown varying results, likely due to small sample size and differences in selection criteria. We aimed at establishing MMR deficiency prevalence in a large, unbiased cohort of small bowel cancers.

Method: A cohort of 308 (adeno)carcinomas and 43 neuroendocrine tumours was collected. MMR deficiency was analysed by performing immunohistochemical staining for PMS2 and MSH6.

Results: 16.9% of small bowel (adeno)carcinomas and 0% of neuroendocrine tumours was MMR deficient.

Conclusion: MMR deficiency prevalence of 16.9% is similar to that observed in colorectal cancers (CRC). ~3% of all CRC cases is caused by Lynch syndrome and universal screening of all CRC cases below age 70 for MMR deficiency is common in many countries. Similar MMR deficiency rates for small bowel cancers suggest similar Lynch prevalence. To further evaluate this, staining of MLH1 and MSH2 will be performed in the MMR deficient tumours and the MMR genes will be sequenced in tumour DNA.

N48

Title: Molecular Tumor Testing In Lynch-Like Patients Reveals De Novo Mosaic DNA Mismatch Repair Gene Pathogenic Variants Transmitted To Offspring

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Aim: Lynch-like syndrome (LLS) patients have tumors with Microsatellite Instability but no germline variant in Mismatch Repair genes (MMR) or somatic methylation of the MLH1 promoter. Double somatic hits are the usual explanation for these cases. Our purpose was to find other explanations, such as mosaicism, that could explain LLS and have an impact on genetic counselling.

Method: We analysed the MMR genes in frozen tumor tissue samples by NGS for 28 LLS patients. When a tumoral variant was found, we performed a targeted re-examination of the germline NGS results with lower detection rates and targeted Sanger analysis in normal adjacent tissue DNA and lymphocytes DNA from offspring when available.

Results: Eight patients had double somatic hits in their tumors. Two patients had a germline de novo mosaic variant of MSH2 with low variant allele frequency (9% and less than 2%). Those variants were missed by NGS analysis in lymphocytes DNA. Their identification in tumors allowed a targeted NGS reanalysis. In both cases, these variants were found to be heterozygous in one of the offspring.

Conclusion: These mosaic cases confirm that identification of the mechanism that causes tumors in LLS is crucial for genetic counselling and guiding screening of patients and their relatives.

N49

Title: A Mouse Model For Proof Of Concept Of A Vaccine Against Lynch Syndrome-Associated Cancers

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Aim: Microsatellite-unstable (MSI) cancers occurring in Lynch syndrome elicit pronounced immune responses directed against frameshift peptide (FSP) neoantigens. Our group could demonstrate the existence of shared FSP neoantigens in MSI cancer and detected spontaneous FSP-specific immune responses in affected patients. To further develop the concept of a cancer-preventive vaccine in Lynch syndrome, we aimed to establish a preclinical mouse model.

Method: A systematic database search was performed to identify coding microsatellites (cMS) and potential neoantigens in Lynch syndrome mice (Msh2flox/floxVpC+/+). After mutation analysis of murine tumors, most promising FSP neoantigens were evaluated for immunogenicity by ELISpot after vaccination of C57BL/6 mice.

Results: Four FSP neoantigens derived from common cMS mutations in the genes Nacad, Maz, Xirp1, and Senp6 elicited strong antigen-specific cellular and humoral immune responses. Based on the cMS mutation data, a vaccine with these four FSP neoantigens is predicted to cover about 75% of cancers in Lynch mice.

Conclusion: We have identified four immunogenic FSP neoantigens derived from commonly mutated cMS in murine Lynch syndrome colorectal cancers. This allows evaluating the concept of cancer-preventive neoantigen vaccines in mouse models of Lynch syndrome, including longitudinal monitoring of immune responses and combination with different adjuvants and chemoprevention approaches.

N50

Title: Age-Related Efficiency Of BRAF V600E Mutational Testing For The Exclusion Of Lynch Syndrome In MSI Colorectal Cancers

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Aim: For distinguishing Lynch syndrome patients from sporadic microsatellite unstable (MSI) patients, BRAF V600E testing has become one of the most important tools. In order to analyze the discriminatory power of BRAF mutations in different age groups, we looked at the age distribution of BRAF mutations in MSI colorectal cancers.

Method: Age at diagnosis and BRAF mutation status were retrieved for unselected series of MSI colorectal cancers (n=151) from publicly available databases (DFCI) and the DACHS cohort.

Results: The prevalence of BRAF V600E mutations in MSI cancers strongly increased with age at diagnosis, with 87% of BRAF mutations occurring after the age of 65. There was no patient with a BRAF mutation under the age of 50, and the youngest patient with a BRAF mutation was 52 year old.

Conclusion: Our data demonstrate that BRAF mutation testing to exclude Lynch syndrome has very limited value in patients younger than 50, as the likelihood of detecting BRAF mutation in a patient under 50 is close to 0%. Reports of BRAF mutations in 1-2% of cancers from proven Lynch syndrome mutation carriers call into question the role of BRAF mutations as a bona-fide exclusion marker for Lynch syndrome.

N51

Title: A Novel Tool For Quantitative Analysis Of Microsatellite Mutations And Frameshift Neoantigens

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Aim: Lynch syndrome cancers are caused by DNA mismatch repair (MMR) deficiency. MMR deficiency leads to microsatellite instability (MSI) and to a high mutational load. Insertion/deletion mutations (indels) of coding microsatellites are drivers of MSI cancer development and responsible for the accumulation of immunogenic frameshift neoantigens. Next-generation sequencing has a limited sensitivity for detecting such indels. We have developed a novel tool to provide a high-resolution map of the MSI cancer mutation and neoantigen landscape.

Method: The 'qMSI' algorithm processes fragment length analysis data, removing stutter band artifacts using a linear matrix. QMSI allows the quantification of the true allele frequency of mutations and the distinction of different mutation types that give rise to distinct frameshift neoantigens.

Results: Using qMSI for 40 target genes in MSI colorectal cancers (n=139) we demonstrate that most indels in MSI cancer are single-nucleotide deletions (77%) followed by two-nucleotide deletions and single-nucleotide insertions (21%). Neoantigen-inducing mutations were surprisingly similar across different MSI cancers.

Conclusion: The qMSI algorithm is a powerful tool to identify driver genes and mutational neoantigens in MSI cancer. The identification of shared, recurrent neoantigen-inducing mutations indicates that a vaccine for tumor prevention in Lynch syndrome is highly promising.

N52

Title: MMR Deficiency Is An Early Event In Lynch Syndrome Colorectal Cancer Pathogenesis

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Aim: The onset of mismatch repair (MMR) deficiency in Lynch syndrome-associated tumors has been discussed to be a late event of pathogenesis. Since the time point of MMR deficiency onset and its consequences have a direct impact on the selection of suitable therapeutic and preventive measures, we aimed to reconstruct the sequence of mutational events in Lynch syndrome cancers.

Method: MMR protein expression and mutational signatures were analyzed to address the time point of MMR deficiency in Lynch syndrome adenomas and carcinomas from public databases and our own cohort.

Results: 77% of Lynch syndrome adenomas (n=640) were MMR-deficient. Mutational signatures of MMR deficiency were reflected in canonical CRC gene mutations, demonstrating that 100% of KRAS and more than 60% of APC mutations likely occurred after the onset of MMR deficiency. A substantial proportion of Lynch syndrome-associated colorectal cancers lacked evidence of polypous growth. These tumors showed a distinct molecular pattern enriched for TP53 and CTNNB1 mutations.

Conclusion: There is more than one pathway of CRC development in Lynch syndrome. MMR deficiency commonly occurs early during Lynch colorectal carcinogenesis. Non-polypous cancers developing from MMR-deficient crypts may be missed by colonoscopy, strengthening the need for additional primary prevention measures in Lynch syndrome.

N53

Title: Discordant IHC MMR Staining And MSI Results In Tumors Of MSH6 Mutation Carriers

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Aim: Diagnosing Lynch Syndrome caused by a MSH6 mutation can be challenging due to the relatively frequent occurrence of discordant immunohistochemistry staining (i.e. MSH6 positive staining) and microsatellite stable phenotype. The aim of this study is to describe to what extent discordant phenotypes occur in colorectal and endometrial carcinomas (CRC/EC) in MSH6 families.

Method: Data were collected from 192 MSH6 families with a confirmed segregating pathogenic germline variant ascertained from Dutch family cancer clinics.

Results: The data consists of 9719 family members and 838 proven mutation carriers. MSH6-mutation carriers with CRC or EC (n=306) were included in the study, accounting for 219 CRCs and 122 ECs. Of the tested tumors, discordant staining for MSH6 was reported in 10 out of 68 CRCs (14.7%) and 3 out of 26 ECs (11,5%). Six out of 62 CRCs (9.7%) and 5 out of 25 (20.0%) ECs appeared to be microsatellite stable. Fifteen germline MSH6 mutation carriers also displayed negative staining for MSH2 in addition to negative MSH6 staining, but did not harbor a germline MSH2 mutation.

Conclusion: Germline MSH6 mutation carriers can be missed using reflex IHC MMR testing as is currently standard in most western countries. MSH6 germline or tumor DNA analysis - preferably as part of a larger gene panel - should therefore be considered, especially in patients fulfilling the Bethesda criteria.

N54

Title: Characterisation Of Mismatch Repair Variants Submitted To The International Mismatch Repair Consortium (IMRC)

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Aim: The IMRC contains data from 4624 Lynch families from 22 countries. We examined the geographical distribution of MMR mutations.

Method: Pedigree data includes: country, MMR mutation and cancer history. Frequency of each variant was calculated by geographical region.

Results: Of the 1578 unique MMR variants (MLH1=568, MSH2=582, MSH6=293, PMS2=135), the two most commonly reported variants were:

Gene: Variant (number of families with variant):

MLH1:
North America: c.350C>T (26), c.1852_1854del (22)
Europe: c.1489dup (48), c.676C>T (28)
South America: c.350C>T (6), c.1276C>T (6)
Asia: c.381_453del (11), c.1852_1854del (4)
Australasia: c.1852_1854del (12), c.350C>T (10)
MSH2:
North America: c.942+3A>T (88), c.(?_-125)_1076+?del (67)
Europe: c.942+3A>T (130), c.1165C>T (25), c.1786_1788del (25)
South America: c.942+3A>T (2), c.1077-?_1276+?del (2)
Asia: c.1457_1460del (19), c.942+3A>T (5)
Australasia: c.942+3A>T (16), c.2502_2508del (8)
MSH6:
North America: c.3261dup (18), c.2731C>T (12)
Europe: c.3261dup (29), c.2731C>T (16)
South America: c.1519dup (2)
Asia: c.3261dup (2)
Australasia: c.3261dup (7), c.1571dup (5)
PMS2:
North America: c.137G>T (28), c.736_741delins11 (19)
Europe: c.736_741delins11 (14), c.1882C>T (6)
South America: c.2186_2187del (2), c.2192_2196del (2)
Asia: c.1572del (2), c.861_864del (2)
Australasia: c.736_741delins11 (11), c.989-296_1144+706del (4)

Conclusion: Some variants are frequently identified across geographical regions but heterogeneous distribution was found for other common variants. The IMRC has the potential to increase our understanding of the geographic distribution of Lynch syndrome.

N55

Title: A Genetic Variant In Telomerase Gene Modifies Cancer Risk In Lynch Syndrome Patients Harbouring MSH2 Mutations

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Aim: In this study chosen to genotype 3 SNPs in telomerase reverse transcriptase (TERT), as common genetic variants of the TERT gene are influencing telomere length and have been associated with a wide range of cancers, including colorectal cancer and Lynch syndrome (LS).

Method: We genotyped 1895 LS patients samples for rs2075786 (G>A) and 1241 LS

patient samples for rs2736108 (C>T) and rs7705526 (C>A). Risk of LS cancer with each SNPs genotype was estimated using simple- and mixed-effects logistic regression adjusting for gene, gender and country of origin.

Results: We see an increased risk of LS cancers for patients carrying MSH2 mutations and heterozygous genotype (GA) for rs2075786 (OR=1.84, confidence interval (CI) =1.15-2.94), p=0.01). This association is even stronger if we divide the group into LS cancer <45 years of age at diagnosis and compare it to LS cancer free patients ((MSH2 and AA genotype) OR=2.53, CI=1.43-4.49, p=0.002).

Conclusion: Both MLH1 and MSH2 mutation carrier's starts off with the same risk of cancer, but a SNP in TERT is associated with a differential risk of developing cancer for MSH2 mutation carriers. By including modifier gene/loci in risk algorithms it should be possible to tailor surveillance options for individual patients, allowing for better disease outcome.

N56

Title: Incorporating Somatic Sequencing Into Current Molecular Testing Strategies For Lynch Syndrome

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Background: UK guidelines recommend that all newly diagnosed colorectal cancers (CRCs) be screened for mismatch repair deficiency (MMR-D) that may be indicative of Lynch syndrome (LS). Current diagnostic approaches, will fail to detect MLH1 promoter hypermethylation or a germline mutation in approximately 60% of suspected LS cases. In most cases the diagnosis of LS can be excluded by somatic sequencing through the demonstration of double somatic mismatch repair (MMR) mutations.

Method: We have used our clinical data from over 1100 families to model costs for different diagnostic strategies for LS that integrate germline and somatic testing. Outcomes were correlated to family history category of either revised Bethesda guidelines or modified Amsterdam criteria.

Results: Modelling shows that for Bethesda families, performing concurrent germline and somatic testing would be more cost-effective than sequential germline and somatic testing (£523 vs. £940 per proband). For Amsterdam families, however, performing sequential testing would be more cost-effective than concurrent testing (£617 vs. £1256 per proband).

Conclusion: LS diagnostic strategies for CRC cases could be accelerated and simplified by concurrent germline and somatic testing. Moreover, our data suggests that this approach is more cost-effective than sequential testing in Bethesda families.

N57

Title: Comprehensive Constitutional (Epi)Genetic Characterization Of Lynch-Like Patients

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Aim: In ~50% of Lynch syndrome (LS)-suspected patients (also called Lynch-like syndrome, LLS), the causal mechanism for cancer predisposition remains unknown. Our aim was to elucidate the constitutional basis of MMR-deficiency in LLS patients throughout a comprehensive (epi)genetic analysis.

Method: One hundred and fifteen LLS patients harboring MMR deficient tumors and no pathogenic germline mutations identified in MMR genes were included in this study. Pathogenicity of MMR VUS was assessed by mRNA analysis and multifactorial likelihood calculations. Mutational analysis of 26 CRC-associated genes was performed by a customized NGS panel. Methylome analysis was perfomed by Infinium 450K array.

Results: NGS analysis revealed the presence of two MMR truncating mutations not previously found. Five out of 15 MMR VUS were reclassified as pathogenic. Methylome analysis identified one case harboring a constitutional MLH1 epimutation. In addition, 12 predicted deleterious variants in other CRC-predisposing genes were found. Differentially methylated regions were not identified in samples from LLS patients compared to LS or healthy individuals.

Conclusion: In conclusion, the use of subexome gene panels combined with pathogenicity assessment of VUS allows the identification of MMR mutations as well as new LLS-candidate genes. Constitutional epimutations outside MMR genes are not responsible for the MMR-deficient phenotype observed in LLS patients.

N58

Title: The Cost Of Identifying Lynch Syndrome Carriers In Australia

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Aim: We estimated the cost of different screening strategies to identify Lynch syndrome (LS) mutation carriers in Australia.

Method: We used a microsimulation to model costs of DNA mismatch repair gene mutation testing for five target population subgroups: i) incident colorectal cancers (CRCs) diagnosed under age 50; ii) under age 70; iii) at any age; iv) unaffected people aged 20-50 years; and v) unaffected people aged 20-80 years. For the incident CRC subgroups, three strategies were considered: multi-gene panel testing; immunohistochemistry (IHC) followed by a multi-gene panel test; and IHC followed by MLH1 methylation testing and a multi-gene panel test. For the strategies targeting the general population (no CRC), only multi-gene panel testing was considered.

Results: IHC followed by panel testing yielded the lowest cost per mutation carrier identified at AU$2,529, AU$6,331, and AU$11,182 for the approaches targeting incident CRCs under age 50, 70 and any age, respectively. For the general population approaches, testing unaffected people aged 20-50 years was the cheapest option (AU$112,282 per carrier identified). Testing incident CRCs under age 50 identified the highest number of carriers (11,774 per 100,000 probands).

Conclusion: Testing incident CRC cases under age 50 years appears as the most effective and cheapest strategy to identify LS mutation carriers.

N59

Title: Highly Sensitive MLH1 Methylation Analysis In Blood Allows The Identification Of Low-Level Epigenetic Mosaicism

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Aim: Constitutional MLH1 epimutations are a rare cause of Lynch syndrome. Low methylation levels (<10%) have been occasionally described. The aim of this study was the identification of patients with low levels of epigenetic mosaicism in MLH1 gene.

Method: Eighteen patients with MLH1 hypermethylated tumors and undetectable methylation in blood as assessed by Methylation-Specific (MS) Multiplex Ligation-Dependent Probe Amplification were included. Highly sensitive MS-Melting Curve Analysis (MS-MCA) at MLH1 promoter was used to screen for epigenetic mosaicism. Constitutional methylation was confirmed by other methods. Mutational analysis of hereditary cancer genes including MLH1 was performed.

Results: MS-MCA analysis identified one case (5.6%) with low levels of methylation (1-2%) in blood DNA. The patient had developed 3 gastrointestinal tumors at ages 22, 24 and 25, sharing MLH1 promoter hypermethylation and loss of heterozygosity associated with c.655A allele. The presence of low MLH1 methylation levels was confirmed by clonal bisulfite sequencing, evidencing the association with c.-93G allele. The extension of the hypermethylated region overlaps with the reported in constitutional MLH1 epimutation carriers. No rare germline variants were identified.

Conclusion: The use of highly sensitive techniques such as MS-MCA has demonstrated to be useful for the detection of low levels of methylation in blood.

N60

Title: Lynch Syndrome Registries In Latin America

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Aim: Despite significant advances in cancer genetics research in Latin America, the access to routine medical care for hereditary cancer patients is still limited.

Aim: To assess clinical resources for Lynch syndrome (LS) management across Latin American countries.

Method: International survey including selection criteria, clinical and genetic information was sent out to the 26 recently described LS programs from 10/33 countries of Latin America (Vaccaro et al. submitted).

Results: Amsterdam or Bethesda guidelines were mostly used to select patients for a tumor screening test and/or genetic MMR sequencing in 15/26 LS programs from public (n=7) or private (n=8) hospitals located in large urban areas from Argentina, Brazil, Chile, Colombia, Mexico, Peru and Uruguay. 717 LS carriers have been identified with a mean age of 42.5 years (range 32-50.9) and a mean of 3.7 follow-up years (range 1-9.6).

Conclusion: Several research projects and publications have been implemented, generating knowledge of MMR variants in these populations to bring additional awareness to medical professionals and public health leaders. Participation in PLSD and international collaborations have been initiated to support the implementation of genetic testing and research in most of the countries of Latin America.

N61

Title: Physical Activity And The Risk Of Colorectal Cancer In Lynch Syndrome

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Aim: The association between physical activity and colorectal cancer risk for DNA mismatch repair (MMR) gene mutation carriers is not well understood. We investigated this relationship in a cohort of 2,042 MMR gene mutation carriers (807 diagnosed with colorectal cancer) from the Colon Cancer Family Registry.

Method: Physical activity was self-reported in three age periods (20-29, 30-49, and ≥50 years). This information was used to calculate the average metabolic equivalent of task hours per week (MET-h/week) during the age-period of cancer diagnosis or censoring (near-term exposure), and across all age-periods preceding cancer diagnosis or censoring (long-term exposure). Hazard ratio (HR) and 95% confidence intervals (CI) for the association were estimated using a weighted Cox regression approach.

Results: A small reduction in colorectal cancer risk was observed in relation to the near-term physical activity (HR ≥35 vs. <3.5 MET-h/week, 0.71; 95% CI, 0.53 – 0.96). For long-term physical activity, the strength of direction of the association was similar, but the association was not nominally significant.

Conclusion: Our results suggest that physical activity may reduce colorectal cancer risk in MMR gene mutation carriers. If replicated, this information could be useful for risk prediction and counselling advice for lifestyle modification in this high-risk population.

N62

Title: Genetic And Clinical Features In Russian Patients With Lynch Syndrome

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Aim: Up to 3% of all colorectal cancers are connected with Lynch syndrome (LS), which is caused by mutations in mismatch repair (MMR) genes. According to the literature the main manifestations of LS are tumors of right colon, endometrium, ovary, kidhey and ureter, stomach ets. at the age of <45.

Method: Between 2012 and 2017 ninety seven patients with primary tumors at the age of <45y.o. and/or with familial history were included in the study. All the tumors were analyzed for microsatellite instability (MSI). In patients with MSI the genes of MMR were examined.

Results: LS was diagnosed in thirty three (34%) out of 97 patients. Twenty of them (60%) had MLH1-gene mutation, 11 (34%) had MSH2-gene mutation, 2 (6%) – MSH6-gene mutation. The median age of primary tumor appearance in patients with LS was 38±7y.o. The primary tumor site was colorectum in 24 (73%) patients, uterus – in 8 (24%) patients, thyroid – in 1 (3%). Among the patients with colorectal cancer right colon lesions were registered in 5 (24%) cases and left colon – in 19 (76%).

Conclusion: In contrast to European patients, Russian patients with LS have MLH1-gene mutation in 60% cases, early-age appearance of colorectal cancer and preferable left-side lesions.

N63

Title: Clinical And Molecular Characterization Of Lynch-Like Syndrome

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Aim: The aim of this study is to know the clinical and molecular characteristics of LLS and to analyze if there are clinical, pathology or molecular characteristics that could suggest a hereditary or sporadic origin.

Method: This is a multicenter nation-wide study (25 Spanish hospitals). Patients were included when CRC tumors showed immunochemical loss of MSH2, MSH6, PMS2 or loss of MLH1 with BRAF-WT and/or no MLH1 methylation and absence of pathogenic mutation in these genes.

Results: Our study included 160 LLS patients. Loss of MLH1/PMS2 was found in 48% of CRC, loss of MSH2/MSH6 in 25%, loss of MSH6/PMS2 in 2%, isolated loss of MSH6, PMS2 and MSH2 was found in 11%, 9% and 2% respectively. In 3% of patients no gene loss of expression was found. 5 patients (3%) developed CRC during the follow up time since diagnosis, (median time of 7 years (SD 3.95)); 20 patients (12.5%) had personal history of non-CRC, and only 5 (3%) patients had LS-related cancer history.

Conclusion: In this LLS cohort, the largest until now, there are no clinical, molecular or pathological characteristics that could help distinguish between probably sporadic and hereditary patients. These results support the need of homogeneous follow-up for this group of patients.

N64

Title: Peritoneal And Abdominal Wall Metastasis Following Colectomy In A Patient With Lynch Syndrom. Is It Time To Rethink The Non-Metastatic Theory?

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Aim: Hereditary non-polyposis colorectal cancer defines the development of colorectal cancer within the spectrum of presentation of Lynch syndrome. A major characteristic of CRC in Lynch individuals is the failure to metastasize despite the large tumor size. Herein we present a case of metastatic CRC in a patient with a pathogenic MSH2 / MSH 6 mutation.

Method: A 68 year old Caucasian male patient with a history of right nephrectomy 25 years after a uretheral cancer. Mismatch repair analysis confirmed MSI-H for MSH2 / MSH6. The patient now presented with a rectal cancer and to date he had not been recommended genetic testing. He underwent an anterior rectal resection with a protective loop ileostomy in December 2017 for colorectal cancer of the rectosigmoidal junction (pT3N0pV0pL0G2R0). An abdominal wall mass was found 10 months after surgery at the former ileostomy site during follow-up, which was completely excised with negative margins. Five months later, computed tomographic scans of the abdomen suspected recurrent metastasis including a peritoneal mass. Surgical exploration was performed.

Results: The abdominal wall mass was completely removed with negative margins. Equally, limited peritonectomy was performed during the second exploratory laparotomy. Histopathology confirmed the presence of metastasis from a colorectal cancer with loss of MSH 2 / MSH 6 proteins on immunohistochemistry. The patient was discussed at the interdisciplinary oncologic board after which adjuvant checkpoint inhibitor therapy was recommended However, the insurance was not willing to pay for this treatment.

Conclusion: Histopathologic features including loss of MSH 2 / MSH6 protein expression on immunohistochemistry in both the primary tumor as well as the metastatic lesions confirms the presence of metastatic seeding. This provides evidence for a metastasis of CRC in a patient with Lynch syndrome and disapproves the currently accepted non-metastatic theory. We conclude, that we cannot rely on the theory and are mandated to adhere to all principles of oncological surgery and also of stringent follow-up.

N65

Title: Etiology And Characterization Of Lynch-Like Syndrome Patients

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Aim: Lynch-like Syndrome patients are younger at diagnosis and had a higher prevalence of cancer in their families than individuals with sporadic cancers. These characteristics suggest the presence of an underlying hereditary condition.

The aim of this study is to characterize the molecular bases of LLS.

Method: We performed whole exome sequencing in a cohort of 27 LLS patients. We performed an analysis to identify rare likely pathogenic variants that could be predisposing to cancer. Only high-quality called variants, present with a population frequency <2.10-5 were included.

Based on the fact that the mutations in the MMR genes could be passenger mutations that drive further instability, a targeted analysis including a comprehensive list of DNA repair genes was also included.

We also performed tumor exome analysis from the matching samples to search for somatic hits.

Results: We identified 4 LLS patients with rare germinal variants in the following genes: AXIN1, PIWIL3, CD109, RECQL5 and GEN1. No somatic second hit was found in any of these genes. 2/8 cases where we could evaluate somatic events had a somatic mutation in one MMR gene and 1 showed LOH of the other copy. One tumor had a single mutation in a MMR gene and in one case I did not identify any somatic alterations.

Conclusion: Based on these results we hypothesize that there is a group of patients with predisposition to CRC due to a germinal variant in one allele that triggers genomic inestability. But there is also another group of patients where it could be due to a biallelic somatic mutation in MMR genes.

N66

Title: The ICCon Australian Database Of Mismatch Repair Variants

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Aim: To systematically collect DNA mismatch repair variants identified by clinical testing in Australian families.

Method: Initial attempts through the HVP sourced variants from laboratories by streamlining with Laboratory Information Management Systems. Subsequently, a grant was awarded from the New South Wales Cancer Council to build a database of pathogenic (Class 4 and 5) variants identified in the cancer genes through the familial cancer clinics (FCCs); a collaboration across the clinics (ICCon) was formed to facilitate this.

Results: The ICCon database holds information about MMR gene pathogenic variants in adult carriers as follows: MLH1 124 (90 unique), MSH2 121 (94), MSH6 68 (50), PMS2 36 (25); totalling 349 (259). Ten discordant interpretations between clinics and/or InSiGHT's classifications were resolved as part of the ICCon process. Importantly, clinical and other data to assist VUSs was accessible from the FCCs.

Conclusion: Sourcing variants via the FCCs has proved feasible. The ICCon database has contributed to variant interpretation internationally, including InSiGHT's Variant Interpretation Committee and, in part, the PLSD. ICCon is working to achieve governance around transforming the variant database to a national registry, to permit changes in counselling, and clinical management, such as when new information emerges through contemporary experience or research.

N67

Title: Penetrance For Carriers Of A DNA Mismatch Repair Gene Specific Variant

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Aim: Previous estimates of colorectal cancer risk for Lynch syndrome are averages over hundreds of different mutations in these genes. Reason for heterogeneity of cancer risk within specific variants in each gene is unknown.

Method: We estimated colorectal cancer risk for MSH2 c.942+3A>T variant using 234 families from the International Mismatch Repair Consortium. Age-specific cumulative risks (penetrance) and 95% confidence intervals were estimated using a modified segregation analysis with appropriate ascertainment conditioning and allowing for risk to vary between families by fitting a polygenic effect.

Results: The estimated average cumulative risks to age 70 years (95% confidence intervals), were 56% (38%-78%) for males carriers and 45% (28%-67%) for female carriers. However, the lifetime risks for different people were estimated to vary widely about these average risks (p=0.001). For carriers of this specific variant, 26% of males and 16% of females had colorectal cancer risk less than 20%; and 24% of males and 37% of females had risk greater than 70%.

Conclusion: Even for a specific variant in a DNA mismatch repair gene, there is a wide range of colorectal cancer risks. This is consistent with the existence of strong modifiers of risk, that if known, could be used to provide personalized risk of colorectal cancer for Lynch syndrome.

N68

Title: A Multidisciplinary Approach To Familial Pancreatic Cancer Enriches The Proportion Of Patients With Pancreatic Cancer Susceptibility

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Aim: Life-time risk of pancreatic cancer (PC) is 1.3%. Familial PC (FPC) have over 5% risk, due to family history and/or germline mutations. FPC accounts for 4-10% of all PCs, and germline mutations are detected in 5-10% of FPCs.

Method: Clinical and pathological data were retrieved during a single-session visit in gastroenterology and genetics from 2016 to 2017. FPC underwent either pancreatic endoscopic ultrasound (eUS) or magnetic resonance (MR) and Next Generation Sequencing analysis.

Results: 57FPC were evaluated; 17 had a personal diagnosis of PC.

29(50,9%) had ≥2 relatives affected, of whom ≥1 was a first-degree relative (FDR); 11(37,9%) had PC.

11(19,3%) had ≥3 relatives affected (1 had PC). 6(10,5%) had Lynch Syndrome with ≥1 FDR (1 had PC). 2(3,5%) had hereditary pancreatitis and 9(15,8%) BRCA1/2 mutation with 1 FDR affected (5 had PC).

17(29,8%) were genetically confirmed: 6 LS (35,3%), 2 PRSS1 (11,8%), 6 BRCA2 (35,3%), 1 BRCA1 (5,9%), 2 PALB2 (11,8%). 8 showed a Variant of Unknown Significance (VUS). 21(36,8%) underwent eUS, revealing 8 PC, 3 intraductal mucinous neoplasias, 1 pseudopapillary lesion. 16(28,1%) underwent MR, revealing 7 CP, 1 IPMNs, and 3 cystadenoma.

Conclusion: A multidisciplinary approach enriches the proportion of patients with genetically confirmed FPC from 5-10% to about 30% of all FPC.

N69

Title: Interpretation Of Inheritable DNA Variation: Room For Error Across Genetic Services?

M. Daly[1], J. P. Plazzer[2,3], F. Macrae[2,3]

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Aim: We aimed to evaluate the frequency of conflicts in interpretation of pathogenicity for gene variants in the mismatch repair genes MLH1, MSH2, MSH6 and PMS2 between InSiGHT's Variant Interpretation Committee (VIC) and those provided by submissions from primary sources to ClinVar.

Method: Variant interpretation submissions for the four genes within ClinVar were compared and with those of the InSiGHT VIC. Factors that could account for the discordance were assessed including classification guidelines, evidence sources, research only interpretations.

Results: A total of 9,921 unique variant submissions were assessed. 584 interpretation conflicts were identified when compared to the VIC's classifications. 98 of the conflicts were considered clinically significant. 5,862 variant interpretations have only one submitter. Methods of interpretation by submitters were heterogeneous and included clinical testing, research, and literature searching, accounting for much of the discordance.

Conclusion: Discordant interpretations between submitters represent opportunity for inconsistent counselling for families with the same variant, with potentially serious clinical consequences. Improvements in data sharing, increased support, coupled with increased awareness of the limitations of current generic methods for variant interpretation, and greater utilisation of expert panels who have access to comprehensive information and use clear gene specific criteria, are essential for optimal interpretation and safe clinical counselling.

N72

Title: CSTF2T And ACTB Discern Sporadic From FAP-Associated Colon Carcinomas At Various Stages Of Carcinogenesis On The Proteomic Level

T. Gemoll[1], A. Masche[1], U. J. Roblick[1], F. Bader[1], A. Unger[1], S. Becker[2], G. Möslein[3], U. Hellmann[4], H. Jörnvall[5], H. P. Bruch[1], G. Auer[2], J. K. Habermann[1]

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Aim: Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease with a germline mutation of the APC gene. In spite of this specific genetic alteration early diagnosis in young patients without polyposis onset and lack of family history can be difficult and finally letal. Thus, additional sensitive diagnostics are required. We aimed at identifying and validating a protein expression signature in macroscopically unaffected colon mucosa that allows identifying genetic carriers of the FAP-syndrome.

Method: Protein profiling by 2-D gel electrophoresis was performed on samples obtained from 15 different patients (FAP, n=8; sporadic colorectal cancer, n=7). Analysis was performed for normal mucosa, adenoma, and carcinoma while comparing FAP-associated tissue with the sporadic counterpart. Analysis aimed at identifying proteins that were expressed in FAP tissue but not in the corresponding sporadic tissue, comparing particularly FAP associated normal mucosa versus sporadic normal mucosa. Target validation was performed by Western and by immunohistochemistry on clinical samples (n=189), respectively.

Results: A total of 47 proteins were present in all macroscopically unaffected FAP mucosa specimens but absent in sporadic normal mucosa. Comparing FAP polyps with sporadic colonic polyps revealed 49 polypeptides being present in FAP samples but absent in all sporadic polyps. Comparing three FAP carcinomas with seven sporadic colorectal carcinomas yielded 66 proteins with absence/ presence expression pattern. CSTF2T and ACTB were validated by Western Blot and immunohistochemistry in unaffected colon mucosa of FAP patients.

Conclusion: The data obtained demonstrate specific differences of FAP and sporadic colorectal disease on the protein expression level and could help to identify patients with FAP disease already in macroscopically "normal" colorectal mucosa.

N73

Title: The Danish HNPCC-Register From 1991 To 2018

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Aim: Presenting the story of The Danish HNPCC-register and methods used for datacollection

Method: The Danish HNPCC register was established in 1991 as a private research register, later developing into a national database financed within the National Public Health care System. Epidemiological, clinical, and genomic data generated all over the country on 6.297 CRC families hereof 443 Lynch families are registered.

Initially paper-based reports were sent to and typed into the database. Later a model for electronic exchange of data between laboratories, departments and the register in an EC co-funded project to prevent cancer by optimizing screening, digitization of data transport and combining genotype-phenotype information, sufficiently usable and generic to be implemented in other countries were developed. As medical data are heterogeneous, focuses were on integration, development of classification systems and communication standards. Identified gaps and status of usability will be presented.

Results: Data in the HNPCC register belongs to the financing Capital Region and the multidisciplinary scientific societies providing data. To achieve commitment and ownership representatives off all parties are invited into the Scientific Board and Steering Comity of the register, where rules for ownership and data delivery are decided.

Conclusion: The Danish HNPCC-register is national and comprehensive, and researchers can request data via the Scientific Board.

N74

Title: Idiopathic Pan-Colonic Varices Found Incidentally In A Young Patient With A Hepatic Flexure Tumor: A Rare Occurrence And A Challenging Surgical Management

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KFSH-D

Aim: Reporting the case of colon tumor in the presence of pancolonic varices and the surgical management we elected to do.

Method: Literature review

Results: Colonic varices is a rare entity and in majority of cases results from portal vein hypertension. It is even rarer when these lesions develop without an underlying hepatic or portal vein disease, termed, idiopathic colonic varices with less than 40 cases reported in the literature. Familial idiopathic colonic varices have also been described, where more than one family member is affected. These lesions could present an incidental finding, however, many cases presenting with lower GI bleeding were recognised in the literature, but no case was reported with a colonic tumor. Hereby we report a case of a 24 years old gentleman who presented with a history of acute abdominal pain and anemia. CT and Colonoscopy showed evidence of hepatic flexure mass, proved to be adenocarcinoma on histological examination, with an incidental finding of pancolonic varices. The patient has two relatives with pan-colonic varices on colonoscopy, but no history of colonic tumors. He underwent right hemicolectomy with uneventful recovery. To our knowledge, this is the first case reported with coexistence of extensive idiopathic colonic varices and colonic tumor.

Conclusion:

N75

Title: Hereditary Cancer Predisposition Syndromes: Evaluation On The Influence Of Personality In Predictive Genetic Testing

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Aim: Assess the psychological impact of genetic testing, evaluate changes in social life and behaviour, and estimate if personality influences the use of medical resources.

Method: Ten adults undergoing predictive genetic testing for cancer predisposition syndromes were included between January and March 2017. Demographic information, personality traits, psychological distress, behaviour in some daily activities and medical resources use were collected before testing and two months after results disclosure.

Results: High pre- and post-test psychological distress was associated to low education levels, having psychopathological history, pursuing testing for offspring, and being recruited at ICO ($p<0.05$). It was also associated with high negative affect, detachment, psychoticism and novelty seeking, and low reward dependence, self-directiveness, cooperativeness, and persistence ($p<0.05$). High post-test distress was also associated with having pre-test psychological distress ($p<0.05$). It would be important to know our counselees' personality because it gives us the opportunity to know who to offer more support and how to personalize genetic counselling.

Conclusion: Our results suggest that there are some personality traits which can influence psychological distress in individuals undergoing predictive genetic testing. Further studies need to be performed in order to extrapolate these results to this particular population.

N77

Title: Correlation Of Immunohistochemical Mismatch Repair Protein Status In Colorectal Carcinoma Endoscopic Biopsy And Resection Specimens

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Aim: Microsatellite instability (MSI) is reflective of a deficient mismatch repair system (dMMR) and occurs in 15% of all colorectal carcinomas (CRC). This most frequently occurs due to sporadic or constitutional mutations in mismatch repair genes. Mismatch repair (MMR) status is often identified by immunohistochemistry (IHC) for mismatch repair proteins (MMRPs) on CRC resection specimens. IHC testing performed on endoscopic biopsy material may be as reliable as that performed on resected specimens. We aimed to evaluate the reliability of MMR IHC staining on preoperative CRC endoscopic biopsies.

Method: A retrospective search of our institution's histopathology database was performed. Patients with CRC who had MMR IHC performed on both their preoperative endoscopic biopsy and surgical resection from 2010 - 2016 were included. Concordance of MMR staining between these specimens was assessed.

Results: 53 patients had MMR IHC performed on both their preoperative endoscopic biopsy and resection specimens; 10 patients (18.87%) demonstrated loss of 1 or more MMRP on their endoscopic tumour biopsy. The remainder (81.13%)demonstrated preservation of staining for all MMRPs. There was 100% agreement in MMR IHC status between specimens in all cases ($\kappa = 1.000$, $p < 0.000$), with a sensitivity of 100% (95% confidence interval [CI]: 69.15-100] and specificity 100% (95% CI: 91.78-100) for detection of dMMR.

Conclusion: Endoscopic biopsies may provide a suitable source of tissue for MMR IHC analysis. This could allow a number of advantages to both clinicians and patients in the management of CRC.

N78

Title: In Contrast To Subjects With Lynch Syndrome, The Adenomatous Polyps From Subjects With Sporadic MSI-High Tumors Have Normal Expression Of MMR Proteins

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Aim: Polyps from patients with Lynch Syndrome (LS) may show loss of expression of Mismatch Repair (MMR) proteins. Data about MMR expression in polyps from patients with sporadic MSI-high colorectal cancer is lacking. We investigated whether polyps form patients with sporadic MSI-High tumor may also show loss of MMR proteins expression.

Method: We performed IHC stain for four MMR proteins of adenomatous polyps from patients with sporadic MSH-high CRC vs. polyps from patients with LS. Sporadic MSI-high cancers were defined as tumors with loss of MLH1/PMS2 & BRAF V600E mutated.

Results: 70 adenomatous polyps were analyzed: 22 from patients with sporadic MSH-High (81.8% women, median age 68.0 [IQR 61.7-86.2]) and 48 from LS patients (37.5% women, median age 48.5 [IQR 39.2-63.7]). Overall, none (0/22) polyps of the sporadic MSH-High group and 45.8 % (22/48) of the LS group showed loss of MMR protein stain ($p<0.001$). Of the LS group polyps, 41.5 %(17/41) of polyps <10 mm and 71.4% (5/7) of polyps ≥10mm showed loss of protein expression $p=0.145$.

Conclusion: In contrast to LS, polyps from patients with sporadic MSI-high CRC do not show loss of MMR proteins. This may suggest that loss of MLH1 is a late event in the sporadic cases.

N79

Title: Immune Microenvironment Of Colorectal Carcinoma

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Aim: The immune system plays crucial role in the development of the neoplastic diseases. Colorectal carcinoma is one of the most frequent oncological diseases with high mortality rate also in Slovak republic. Its development is the result of environmental, genetic and epigenetic changes accumulation leading to neoplastic transformation. Tumor-specific mutations manifest by neoantigens activating the immune system. The aim of the work was to evaluate the antitumor immune microenvironment in association of tumor grading.

Method: Archival surgical specimens of CRC were evaluated and graded according to the WHO criteria. Immunohistochemically detected CD4, CD8 and CD68 positive cells were evaluated morphometrically and expressed as % of the evaluated area.

Results: Neoplastic as well as the surrounding tissues were infiltrated by the three cell types in unchanged ratios, with predomonation of CD68+ histiocytes. With the increasing grade there was significant decrease of CD4+ and CD68+ cells and a clear decrease of CD8+ cells at the edge of significance, of infiltration of the tumor tissue. Changes in the peritumoral tissue infiltration were not significant.

Conclusion: Our findings support the idea of tumor suppressing activity of the anti tumor immunological response and that it plays an important role in progression of the neoplasm.

Supported by the APVV-14-0318 grant.

N80

Title: An International Study Of Duodenal Disease In MAP: Incidence Of Polyposis And Cancer

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Aim: Duodenal polyposis and cancer represent significant disease manifestations in patients with FAP and MAP. This study aims to determine the extent and incidence of duodenal disease in patients with MAP to establish whether upper GI surveillance recommendations developed for patients with FAP are also appropriate for MAP.

Method: A long-term prospective collaboration has been established. Demographic and genotype information and details of endoscopic surveillance and therapy has been collected on 394 MAP patients to date.

Results: 63/394 had duodenal disease at index endoscopy (16%) at a median age of 54 years (range; 33-81): this was Spigelman stage I in 37 patients (58.7%), stage II in 12 (19%), stage III in 10 (15.9%), stage IV in 1 patient and three patients had cancer (4.8%). During 1417 follow up years, five further patients progressed to stage IV disease at a

median age of 63 (range; 51-67) and one patient developed cancer.

Conclusion: Patients with MAP appear to develop fewer duodenal polyps at a more advanced age than is reported in FAP. Nonetheless, progression to advanced disease and cancer may occur despite surveillance. We are collecting prospective data that may inform development of a more appropriate surveillance strategy for upper GI disease in MAP.

N81

Title: Genomic And Transcriptomic Profiling Of Duodenal Adenomas In Familial Adenomatous (FAP) And MUTYH-Associated Polyposis (MAP)

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Aim: Duodenal polyposis and cancer are important yet poorly understood causes of morbidity and mortality in FAP and MAP patients. We aimed to characterise the genomic and transcriptomic signatures associated with duodenal adenomas from patients with FAP and MAP, to better understand duodenal tumourigenesis in these hereditary disorders.

Method: A series of 67 samples from patients with a genetically confirmed diagnosis of FAP or MAP were subjected to whole transcriptome sequencing, consisting of 44 duodenal adenomas (FAP n=29, MAP n=15) and 23 duodenal normal mucosa (FAP n=15, MAP n=8). Outcomes were compared to exome sequencing data from 50 duodenal adenomas (FAP n=25, MAP n=25).

Results: We found distinct gene expression profiles in FAP and MAP duodenal adenomas which were absent from the respective normal mucosa. MAP adenomas harboured aberrations in RAS signalling and immune system stimulation, whilst evidence for dysregulation of prostanoid synthesis and NOTCH signalling were found in FAP adenomas. Whole exome analysis revealed that MAP duodenal adenomas carried more somatic mutations than FAP (p=0.0226). Recurrently mutated genes in duodenal adenomas included known drivers (APC, KRAS) and additional potential duodenal-specific tumour initiators.

Conclusion: The identification of commonly deregulated pathways contributes to our understanding of duodenal tumourigenesis in the context of FAP and MAP.

N82

Title: Endocuff-Assisted Colonoscopy Versus Standard Colonoscopy In The Surveillance Of Serrated Polyposis Syndrome. A Randomized, Controlled And Multicenter Study

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Aim: Serrated polyposis syndrome (SPS) is a high-risk condition of colorectal cancer. Endocuff device have demonstrated to improve the adenoma detection in mixed population. We aimed to ascertain if Endocuff-Assisted Colonoscopy (EAC) improves the detection of the serrated lesions (SL) during the surveillance of SPS.

Method: Patients with SPS (criteria I and/or III) and previous resection of all SL ≥4mm were consecutively randomized 1:1 to EAC or standard colonoscopy (SC) performed by endoscopists devoted to high-risk conditions of colorectal cancer. The main outcome was the number of SL per patient.

Results: 122 patients (SC n=60; EAC n=62; 59% men;age 61±7y) were included in 4 centers. Baseline characteristics (demographics,type of SPS, CRC history, last colonoscopy data) cecal intubation(100%) and withdrawal time were similar between groups. The mean (standard deviation) of lesions per patient for SC and EAC were: SL 5.0 (4.4) versus 5.8 (5.5)(p=0.361); total polyps 6.8 (4.7) versus 7.8 (5.7) (p=0.317); SL ≥5mm 2.2 (2.6) versus 3.1 (3.4) (p=0.141); adenomas 0.5 (0.9) versus 0.9 (1.6) (p=0.121) respectively. A polypectomy-related microperforation in the SC group was successfully solved with clips during the same procedure without major consequences for the patient.

Conclusion: The EAC does not significantly improve the efficacy of surveillance colonoscopy in the SPS.

N83

Title: Surveillance Recommendations For First-Degree Relatives Of Patients With Unexplained Multiple Colorectal Adenomas: A Nationwide Survey Of UK Regional Genetic Services

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Guy's Regional Genetics Service

Background: Patients with multiple colorectal adenomas (MCRA; 10-100 adenomas cumulatively) without a known genetic cause are increasingly being diagnosed in the UK. Germline monoallelic APC or biallelic MUTYH mutations are not identified in the majority of patients. Possible explanations include; APC mosaicism, cryptic mutations, mutations in other polyposis genes, and polygenic inheritance. Some guidelines have recommended regular colorectal surveillance for first-degree relatives of this patient group, but currently there is no national UK guidance.

Method: We conducted a national survey of UK regional genetic services to explore management practices for first-degree relatives of patients with MCRA without a known genetic cause. A web based-survey was sent by email to the cancer genetic lead clinicians at the 24 regional genetics services. The survey was primarily designed to assess surveillance recommendations for first-degree relatives of MRCA patients, and to determine whether recommendations varied according to the total number of adenomas and age of onset. Testing criteria and genetic investigations were also assessed for patients with MCRA.

Results: National survey results are presented.

Conclusion: The survey aims to highlight variation in the management of this patient group and their first-degree relatives in the UK.

N84

Title: Mutations In MutYH Gene Among Russian Patients With Colorectal Polyps

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Aim: MutYH-associated polyposis is one of the important inherited colorectal cancer syndromes. It is caused by germline mutations in the MutYH gene. Biallelic MutYH mutations are the genetic reason of an autosomal recessive mode of inheritance but we also observed risk of developing polyposis in monoallelic MutYH gene mutation carriers of some populations. The aim of this investigation was to study frequency of germline mutations in MutYH gene among Russian patients with different number of colorectal polyps

Method: Germline mutations in MutYH gene were detected by PCR, SSCP, Sanger sequencing and NGS among 19 patients with 100 and more colorectal polyps; 93 patients with 4-99 polyps and 150 healthy controls

Results: We found 11 germline mutations (8 biallelic and 3 monoallelic) in MutYH gene among 93 patients with 4-100 polyps and 2 mutations (1 biallelic and 1 heterozygous) in 19 patients with 100 and more colorectal polyps. We don't found heterozygous mutations among 150 healthy controls

Conclusion: Frequency of germline mutations in MutYH gene among Russian patients with 4-99 and more than 100 colorectal polyps was 11,8% and 10,5% respectively

N87

Title: SELINA – Clinical Trial On Lowering The Risk Of Malignancies By Optimizing Selenium Levels In Females From Families With Hereditary Breast Cancer

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Aim: Blood selenium (Se) levels associated with significantly lower risk of cancers has been identified in Polish females from families with hereditary breast cancers (HBC). For BRCA1 mutation carriers: 70-89 µg/l at age <50 yrs (OR~12) and 95-120 µg/l at age ≥50 yrs (OR~4); for females without detected BRCA1 mutation: 98-108 µg/l (OR~5).

The main goal of SELINA is validation of hypothesis that optimization of Se level can decrease the risk of malignancies.

Method: 7000 females (including 1200 BRCA1 carriers) from families with HBC and deficiency or excess of Se are qualified to one of the arms: "placebo", observational, supplement (Sodium Selenite) or diet modification. Blood Se level will be measured and optimized during 5 yrs.

Results: Recruitment will be closed in 2018.

Conclusion: SELINA is the first trial aimed to decrease the risk of cancers by active control of blood selenium levels . Interested scientists are welcome for collaboration.

N88

Title: The National Lynch Syndrome Registry of Finland (LSRFi)

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The nationwide Lynch Syndrome Registry of Finland (LSRFi) was founded in 1982 to organize endoscopic surveillance for high-risk families with colorectal cancer (CRC). To date, there are 298 families with confirmed pathogenic variants of mismatch repair (MMR) genes. Currently, LSRFi organises genetic counseling and predictive testing in research setting and co-ordinates endoscopic surveillance that takes place mostly in centralized public hospitals. Colonoscopy surveillance is offered from 25 years onwards, with 3-year interval for those with no prior cancer. LSRFi has access to national healthcare registries, such as registry for causes of death, parish registries and Finnish cancer registry.

About 3,000 individuals have undergone genetic testing, so far. In May 2018, there were total of 1,416 path_MMR carriers; 1,044 path_MLH1 (74%), 246 path_MSH2 (17%), 123 path_MSH6 (9%) and 3 path_PMS2 (0.2%). The mean age for live carriers was 53 years for path_MLH1, 53 years for path_MSH2, 60 years for path_MSH6 and 48 years for path_PMS2. In 2015, about two thirds of eligible children (age >18 years) of verified path_MMR carriers had undergone predictive testing. Adherence to offered surveillance is high, well over 90%. CRC incidence, stage and survival do not differ from other countries compared to independent prospective datasets in Europe.

N89

Title: Microsatellite Instability Analysis And NGS With Fragmented Sample Types

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Introduction: A significant hurdle to using fragmented DNA for genomic studies is obtaining a sample of sufficient quantity and quality for rigorous downstream applications like NGS. Having effective tools to isolate, characterize, and analyze fragmented DNA containing samples, such as circulating cell free DNA (ccfDNA) and FFPE tissues, can prevent downstream failures, ultimately saving hours of work and precious samples. Here we present optimized methods for use with even highly fragmented DNA samples. Using this toolset, we demonstrate successful NGS and microsatellite instability (MSI) workflows using matched FFPE tissues and plasma samples.

Methods: Plasma and FFPE tissue samples were obtained from three individuals with colorectal adenocarcinoma. DNA was isolated with Promega's Maxwell® RSC Instrument using the Maxwell® RSC FFPE DNA Kit for FFPE tissues and the Maxwell® RSC Circulating DNA Kit with the large volume custom protocol for plasma. DNA was then quantified with the ProNex® DNA QC Assay. Following quantitation, MSI analysis and NGS library preparation using the TruSeq Custom Amplicon Low Input Kit from Illumina was performed. NGS libraries were checked for size and quantity and then sequenced on the MiSeq® System (Illumina). Results: Full MSI profiles were obtained from DNA obtained from both ccfDNA and FFPE samples from each individual. Following successful determination of MSI-status, NGS libraries were produced from each sample. Sequencing of these libraries produced mean amplicon read depth greater than 3000x and mean coverage uniformity greater than 90%. In addition to excellent sequencing quality metrics, variants in mismatch repair genes identified in FFPE samples were also detected in matched plasma samples. Conclusions: Proper molecular tools and assays are essential to success in exacting downstream applications like NGS and multiplex PCR. This work introduces streamlined methods for DNA isolation, library preparation, and multiplex microsatellite instability analysis from fragmented sample types and demonstrates their effective use with matched FFPE and ccfDNA samples.

N90

Title: Argentinean Lynch Syndrome Registry: Experience From Rosario

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Aim: There is still no national hereditary or familial cancer registers in Argentina. With the mission of improving detection, prevention and management of high risk cancer population in Rosario, with a population of 1.198.528 inhabitants, the Asociación Civil de Estudio, Tratamiento, Investigación de Enfermedades Heredo familiares de Rosario (ACETHIER) was established as a genetic reference center in 2005.

Methods: Hospital Español is used to identify suspected Lynch syndrome (LS) families. The Amsterdam criteria (AMS) or Bethesda guidelines were mostly used to select cases for screening by immunohistochemistry (IHC) and/or microsatellite instability (MSI) analysis. Genetic testing was generally based on Sanger sequencing of MLH1, MSH2, MSH6, PMS2 and/or EPCAM. By the advent of next generation sequencing (NGS), we are recently using 17- multigene panels including: APC, BMPR1A, CDH1, CHEK2, MLH1, MSH2, MSH6, PMS2, MUTYH, POLD1, POLE, PTEN SMAD4, STK11, PT53, EPCAM and GREM1(Ambry Genetics, USA). Patients are informed about their inclusion into the registry, which generally contained data on family history, clinical information, age at onset and results of DNA testing or tumour screening in the diagnosis of LS. Written informed consent was obtained from all patients during genetic counselling sessions.

Results: From our registry, 61 suspected families fulfilled AMS criteria or Bethesda guidelines. Seventeen families (28%) had MMR deficiency and underwent genetic MMR testing. Path_ MLH1 variants was identified in 3 (21%) families, path_ MSH2/EPCAM variants in 11 (72%) families and path_ PMS2 variants in 1 family (7%). LS carriers have been identified with a mean age of 37.5 years (range 18-57) and a mean of 13 follow-up years.

Conclusion: The path_MSH2 variants are the most frequently identified in our registry and we provides support to set or improve LS genetic testing in South America. In addition, despite the small number of our registry, we described patients with a young age of onset and/or a positive family history of LS-associated cancers without an identified path_MMR variant, and may suggest the involvement of pathogenic variants in as yet undiscovered genes.

Acknowledgement: We would like to thanks Mev Dominguez-Valentin (Oslo University Hospital, Oslo, Norway), for her unconditional support and her effort, to be able to join all the research groups in Hereditary Colorectal Cancer from South America. She can lead this great Group, and we know that we will continue to grow.

N91

Title: Hereditary Cancer Program (ProCanHe): 21-Year Of Experience At A Referral Registry In Argentina

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Aim: Registries in South America were initiated in the early 90's with the help of Henry T. Lynch. The Programa de Cancer Hereditario (Pro.Can.He), is a multidisciplinary program established in 1996 at the Hospital Italiano, Argentina. The aim of the study is to update our 21-year experience to determine the applicability of genetic tests highlighting the most informative molecular findings in relation to Lynch syndrome mostly.

Materials and methods: Families undergoing genetic testing after genetic counselling between1996-2018 were included. Data were obtained from a prospective IRB approved database. Clinical-epidemiological and molecular variables were analyzed. Genetic tests were carried out after a genetic counselling session and obtaining the informed consent of the patient.Molecular testing: Until 2015, the search for variants was carried out by PCR and Sanger sequencing of exons and adjacent intronic regions of MLH1 and MSH2. Then, sequencing of *MLH1/MSH2/MSH6/PMS2/EPCAM* genes was performed by NGS and large rearrangements were detected by MLPA. The variants were classified according to international databases. Variants with uncertain or unreported clinical significance were analysed In-silico using the PolyPhen, SIFT and/or Human Splicing finder 3.0 software.

Results: A total of 83 families (49 fulfilled Amsterdam Criteria [AC] and 34 Bethesda Criteria [BC]) were analyzed. Pathogenic variants were found in 26 out of 83 (31.3%) families, been 23 pathogenic and 3 likely pathogenic.Splice site and large rearrangements represented 19.2% (5/26) and 11.5% (3/26) of the variants.23% (6/26)of them were originally described in this series and 1 was a founding mutation from Piedmont, Italy. Affected genes include MSH2, MLH1, MSH6 and PMS2 (12, 11, 2 and 1 cases respectively). Mutation detection rates in AC and BT families were 48.9% (N=24) and 5.9% (N=2), p<0.01. Among AC families, those with identified mutation had a lower median age of cancer on set and higher incidence of extra-CCR cancer than those without identified mutations. Additionally, we have also studied other genes in patients with different clinical conditions included in the registry.We identified mutations in APC, MUTYH, BMPR1A, SMAD4, CDH1, BRCA1-2, CHEK2.

Conclusion: The multidisciplinary approach and the international collaborations allowed the correct implementation of the genetic tests. To our knowledge, this study is the first Characterization of AC families according to genetic tests in South America. This allowed the identification of AC families with different ages of onset and prevalence of extra-CRC cancers, as well as several significant variant not previously reported in international databases.

N92

Title: Chilean Hereditary Colorectal Cancer Registry: Experience from Clinica Las Condes

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Aim: Considering the lack of genetic studies in our country and the benefits resulting from being able to differentiate between carrier and non-carrier individuals, in 2003 we applied for grant funds offered by the Chilean government (FONDECYT). During 2004-2006, this support enabled us to implement the MSI and IHC analyses in tumors, as well as the detection of point mutations in APC, MLH1 and MSH2 genes. In 2009, with the aim of increasing the mutation detection rate, genetic studies were supplemented with deletion/duplication analysis by MLPA for APC, MLH1, MSH2 and EPCAM genes, and the identification of point mutations in MUTYH, MSH6, PMS2, STK11, PTEN, SMAD4 and BMPR1A genes. Today, we have broadened the genetic studies into gene panels (Invitae, USA), mainly in those patients whose tumor studies do not allow us to define a candidate gene or when the definition of the hereditary syndrome becomes quite difficult.

Methods: Patients are referred to the program of hereditary colorectal cancer for evaluation. Those that meet criteria are included into the registry, which generally contained data on family history, clinical information, age at onset and results of DNA testing or tumor screening. Written informed consent was obtained from all patients during genetic counseling sessions.

: In our registry, we have an overall record of 221 suspected families (with 533 registered individuals), 107 are Lynch syndrome suspected families, 98 familial adenomatous polyposis, 11 Peutz-Jeghgers syndrome, 2 juvenil polyposis, 1 Cowden syndrome and 2 hyperplastic polyposis. In total, 88 families present a mutation or variant of uncertain significant in APC (41), MUTYH (3), MLH1 (21), MSH2 (7), MSH6 (1), PMS2 (3), EPCAM (2), STK11 (8), PTEN (1) and SMAD4 (1) genes. In those families with pathogenic or likely pathogenic mutations, we have studied 386 relatives, of which, 223 are carriers and 163 are no carriers. All families have received clinical recommendations based on the National Comprehensive Cancer Network (NCCN) guidelines. Interestingly, 25 mutations have not yet been described in other studies, clearly demonstrating the relevance of evaluating different racial/ethnic populations like ours, which include an admixture of Amerindian and European -mainly Spanish - populations.

Conclusion: Our work shows the success to integrate multidisciplinary professionals as coloproctologists, PhD in biological sciences (genetic counselor), nurses, medical doctors from various disciplines, and the constant support of a psycho-oncologist. We would like to highlight our last challenge, a pioneering initiative in Latin America, which consisted in the creation of a Course of genetic counseling in hereditary cancer aimed for health care professionals belonging to oncology units.

Acknowledgement: We would like to thanks Mev Dominguez-Valentin (Oslo University Hospital, Oslo, Norway), for her unconditional support and her effort.

N93

Title: Hereditary Gastrointestinal Cancer Mutational Registry In Uruguay

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Introduction. Since 1996, the Uruguayan Collaborative Group (UCG), a nonprofit organization is devoted to the registry, diagnosis, management and investigation of hereditary cancer. UGC is integrated by a multidisciplinary team of experts and represents in the country, a reference center for genetic counselling and risk assessment.

Objective: To present an updated Uruguayan mutation catalog for gastrointestinal (GI) hereditary cancer susceptibility.

Methodology: The UCG registry is integrated by 1536 non-related families. 548 families (35%) are defined as GI-high risk population following the National Comprehensive Cancer Network 2018 guidelines. These families were classified as: Amsterdam I-II, Bethesda, Li Fraumeni, Peutz Jeghers, Familial Adenomatous Polyposis, *MUTYH*-Associated Polyposis, or Serrated polyposis syndrome. Selected probands for genetic testing signed informed consent prior to obtain saliva or blood samples**.** Several DNA-analysis techniques were used over these 22 years, from Sanger sequencing alone (until 2010), Next Generation Sequencing of a group of genes and large rearrangements detection methods, to nowadays, panels of 30 genes.
Results: At present a total of 234 (43%) GI-high risk, non-related probands were tested and 63 families were diagnosed. We found 49 different mutations, classified according to ACMG as "Pathogenic" and distributed among the following genes: MLH1 (9), MSH2(11), PMS2(3), MSH6 (3), EPCAM(1), APC (11), STK11(2), NF1(1), FAN1(1), RAD51(1), SDHB(1), BMPR1A(1), MUTYH biallelic (3). A family carried a mutation class 4 (likely Pathogenic) in MLH1. In nine probands with a characteristic hereditary colon cancer phenotype, only MUTYH monoallelic mutations were found. An increasing number of variant of uncertain significance were found.

Conclusion: A research period of 22 years has unveiled the mutational spectrum of GI-high risk cancer of the Uruguayan population, allowing a broader vision regarding hereditary cancer profile in an understudied population. In spite of the large gene selection, only a few were involved in cancer predisposition. Lynch Syndrome, as expected, was the most frequent diagnosis, but with a relatively low pathogenic variant presentation.

Acknowledgement: Fundación Génesis Uruguay.

N94

Title: Uruguayan Hereditary Breast And Ovarian Cancer Syndrome Registry: BRCA And Non-BRCA Pathogenic Variants

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Introduction: Mutations in *BRCA1* or *BRCA2* genes are considered the most prevalent cause of hereditary breast and ovarian cancer syndrome (HBOC), although other genes also explain this kind of affection. Since 2014, the Uruguayan Collaborative Group (UCG), a nonprofit organization is devoted to the registry, diagnosis, management and research of hereditary cancer, has been recruiting high-risk family groups with HBOC.

Objective: To report about pathogenic variants in BRCA and non-BRCA genes detected in Uruguayan high-risk for HBOC population.

Methodology: From the UCG registry, 592 non-related are defined as HBOC-high risk population following the National Comprehensive Cancer Network 2018 guidelines. Selected probands for genetic testing signed informed consent prior to obtain saliva or blood samples. Different approaches for searching gene mutations have been employed. At first, Next Generation Sequencing of BRCA1 and BRCA2, then large rearrangements detection methods were used, and lately multigene panels have been employed.

Results: 330 (56%) HBOC-high risk, non-related probands were tested, 56 were found positives and 49 different pathogenic variants identified. BRCA1-2 accounted for 31 (66%) pathogenic mutations (14 BRCA1 and 17 BRCA2) while mutations in non-BRCA genes were: PALB2(3) ATM(1) CHEK2(3) BARD1(3), TP53(6), CHD1(1), NBN(1).

Conclusion: Even though only HBOC high risk probands were selected, a relatively high proportion of non-BRCA genes presented with pathogenic variants. Although multigene panels can give unexpected and uninformative results, when used with thoughtfulness, they can be a valuable tool capable of diagnose beyond the traditional boundaries of BRCA genes. Despite technological improvements, a high number of families with no molecular diagnosis still remains. Since the role of constitutive epimutations in cancer development can be underestimated, future approaches will include a methylation screening.

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AlArfaj, L. N74
Alonso, A. N35
Ambe, P. C. N64
Ballhausen, A. N51
Barca-Tierno, V. N14
Bernstein, I. N73
Buchanan, D. D. N12
Capella, G. N20, N59
Cavestro, G. M. N68
Colas, C. N23, N48
Crosbie, E. J. N27
Desouza, B. N56, N83
Dillon, M. N58
Dominguez-Valentin, M. N13, N37, N60
Engel, C. N01
Evans, D. G. N04, N11
Frayling, I. N10
Gemoll, T. N72
Georgiou, D. N28, N32
Ghazaleh Dashti, S. N61
Giner-Calbuig, M. N65
Hirasawa, A. N25
Janega, P. N79
Jenkins, M. N09
Kang, Y. J. N02, N06
Kloor, M. N30, N49
Krajc, M. N44
Levi, Z. N78
Liu, W. N16
Lubinski, J. N87
Macrae, F. N66, N69
Marabelli, M. N46
Meuser, E. N81
McRonald, F. N24
Møller, P. N39, N40
Moreno, L. N75
Mur, P. N17
Picó, M. D. N63
Pineda, M. N57
Pikunov, D. Y. N62
Ragunathan, A. N19
Rasmussen, L. J. N34
Reece, J. N54
Rivero-Sánchez, L. N45, N82
Ryan, É. N77
Samaha, E. N36
Sampson, J. N07
Sanchez Garcia, A. N31
Seppälä, T. N33, N88
Shelygin, Y. A. N84
Suerink, M. N03, N47, N53
Szemes, T. N22
Talseth-Palmer, B. A. N55
Taylor, A. N26
Taylor, N. N43
Ten Broeke, S. W. N08
Terradas, M. N18
Therkildsen, C. N29
Thomas, L. E. N80
Wagner, A. N38
Watt, C. M. N21
Win, A. K. N67
Winship, I. M. N42
Zuppardo, R. N05, N41