Final Programme

1st Meeting of the European Hereditary Tumour Group (EHTG)
Palma de Mallorca, Spain
12 – 14 May 2016

Supported by Gold Sponsor

Visit www.mallorca-group.org for more information about The Mallorca Group
Bowel Cancer UK, the UK’s leading bowel cancer research charity

We are determined to save lives and improve the quality of life for all those affected by bowel cancer.

We support and enable research, educate patients, public and professionals about bowel cancer and campaign for early diagnosis and best treatment and care for all those affected.

Our research is focussed on four key areas:

**Investigating the gaps in bowel cancer research** - we’re bringing together 100 leading bowel cancer scientists and clinicians from across the UK to identify gaps in current research into bowel cancer.

**Understanding bowel cancer in younger people** - supporting research that allows us to better identify people with hereditary and other risk factors that put them at higher risk.

**Improving surgery for bowel cancer patients** - working with the Royal College of Surgeons to establish a Colorectal Cancer Surgical Research Chair in England, establishing seven new independent professorial chairs in surgical trials and developing a network of Bowel Cancer UK Surgical Research Fellows.

**Putting patients at the heart of research** - developing a Patient and Public Involvement (PPI) strategy and training programme to develop a strong network of patient advocates.

Find out more at [bowelcanceruk.org.uk](http://bowelcanceruk.org.uk)

@Bowel_Cancer_UK /charitybcuk

Registered charity number 1071038 (England & Wales) and SCO40914 (Scotland) and a company limited by guarantee number 3409832
Welcome to the 1st Meeting of the EHTG!

Dear Colleagues

On behalf of the Mallorca Group, we are excited to welcome you to the 1st Meeting of the European Hereditary Tumour Group (EHTG). This event marks a very significant point, and we hope provides an interesting, informative and high quality forum that establishes EHTG for the future. I would like to take this opportunity to thank my colleagues on the Programme Committee for their commitment and support, and making this first meeting a reality.

We will begin on Thursday morning with Working Groups; delegates are encouraged to attend and contribute to the difference specialties involved. Friday’s Plenary session will feature a host of abstracts submitted by your peers. On Saturday, delegates are invited to propose and discuss ongoing on new collaborative studies in the Reporting Back and Collaborative Studies session.

It was vital that in this, our first year, we obtain educational grant funding, and we particularly thank our principal sponsors Bowel Cancer UK (gold sponsor), LS Cancer Diag (silver sponsor) and SLA Pharma (bronze sponsor) for their most valuable contribution. Our thanks also to Tillots, and the Barbour Foundation for their support. Representatives of these organisations will be with us and we hope you find time to talk to them.

Finally, our thanks to you personally for attending the event; we look forward to the networking time we will have together as colleagues, and wish you all a very successful meeting.

Gabriela Möslein
Chair/Secretary

MALLORCA GROUP / EHTG
PROGRAMME COMMITTEE
Gabriela Möslein (Chair/Secretary)
Sir John Burn
Gabriel Capellá
Ian Frayling
Maurizio Genuardi
Magnus von Knebel-Doeberitz
Pål Møller (Treasurer)
Rolf Sijmons

SECRETARIAT
c/o Integrity International Events Ltd
The Coach House, 7 St Alban’s Road,
Edinburgh EH9 2PA, UK
T: +44 131 624 6040
F: +44 131 624 6045
E: events@integrity-events.com
Contact mobile during the meeting: +44 7734 425 210

Opening Times

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<th></th>
<th>REGISTRATION</th>
<th>POSTER DESK</th>
<th>PRESENTATION CHECK IN</th>
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<tr>
<td>Wednesday</td>
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<tr>
<td>Thursday</td>
<td>07:30 – 18:00</td>
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<td>Friday</td>
<td>08:00 – 19:00</td>
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<tr>
<td>Saturday</td>
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Supported by Gold Sponsor

BOWEL CANCER UK

Supported by Silver Sponsor
Supported by Bronze Sponsor
and Educational Sponsors

LS CancerDiag
SLA Pharma

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 and 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.

Speakers must be aware of the times allocated for their presentations: “OR” is a time of 6 + 2 min and “S” is a time of 2+1 min.

Chairs will not allow for more than the time assigned!

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 of their presentation.

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

### WORKING GROUPS - THURSDAY 12 MAY

<table>
<thead>
<tr>
<th>LOCATION/TIME</th>
<th>MEETING</th>
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</table>
| **ATENEA** 08:30 – 10:30 | **REGISTRIES AND BIOBANKS**  
*Chairs: Pål Møller, Toni Seppala, Mark Jenkins*  
**Local/Original Registries**  
- Melbourne, Australia  
- German LS consortium  
- LUMC  
- Milan, Italy  
- Finland  
- Newcastle Upon Tyne, UK  
- French database  
- Sweden  
- Cardiff, UK  
- Catalan Institute of Oncology, Spain  
- Manchester, UK  
- Denmark  
- Oslo, Norway  
- Reporting to LOVD – Finlay Macrae  
- Discussion  
**Collated MMR Registries**  
- CCFR  
- IMRC  
- PLSD (Prosp LS database)  
- LUMC_collated_PMS2_monoallelic  
- LUMC_CMMRD relatives_monoallelic  
- De Novo monoallelic mutations  
- European CMMRD database  
- Discussion  
**Proposals for Collaboration** |
| **FOYER TAPICES** 10:30 – 11:00 | **COFFEE BREAK** |
| **ATENEA** 11:00 – 12:30 | **MMR EUROPEAN GROUP**  
*Chairs: Elke Holinski-Feder, Gabriel Capellá*  
- Standardisation of cDNA analysis – Moni Morak, Marta Pineda  
- Minigene assays – Alexandra Martins  
- Lessons learned from BRCA cDNA analysis in the ENIGMA consortium – Gabriel Capellá  
- Joint discussion on future collaborative efforts |
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<thead>
<tr>
<th>TIME</th>
<th>SECTION</th>
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<tbody>
<tr>
<td>11:00 – 12:30</td>
<td>PLUTON</td>
<td><strong>SURGERY &amp; ENDOSCOPY</strong>&lt;br&gt;<strong>Chairs:</strong> John Karagiannis, Gabriela Mösllein&lt;br&gt;• Current guidelines of endoscopic treatment and follow-up of patients with hereditary polyp syndromes - John Karagiannis&lt;br&gt;• Acceptable adenoma detection rate in LS - Robert Hübner&lt;br&gt;• Extended prophylactic surgery for CRC in Lynch syndrome - Laura Renkonen Sinisalo&lt;br&gt;• Small bowel and urothelial surveillance in Lynch syndrome - Elia Samaha&lt;br&gt;• Joint discussion on future collaborative efforts” (no name assigned)</td>
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<tr>
<td>12:30 – 13:00</td>
<td>FOYER TAPICES</td>
<td><strong>LUNCH</strong></td>
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<td>13:00 – 14:30</td>
<td>ATENEA</td>
<td><strong>CHEMOPREVENTION FOR POLYPOSIS SYNDROMES</strong>&lt;br&gt;<strong>Chair:</strong> Andy Latchford, Patrick Lynch&lt;br&gt;• IPSS and beyond - Patrick Lynch&lt;br&gt;• Synopsis EPA study for Horizon 2020 - Dora Colussi&lt;br&gt;• OR13: Surveillance of duodenal polyposis in familial adenomatous polyposis: should the Spigelman score be modified? - Yann Parc&lt;br&gt;• Quality assessment of UGI endoscopy in the adenomatous polyposis syndromes - Andy Latchford&lt;br&gt;• Colorectal cancer prevention by using prebiotic functional foods - Felipe Lombó</td>
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<td>13:00 – 14:30</td>
<td>PLUTON</td>
<td><strong>VIC: VARIANT INTERPRETATION COMMITTEE</strong>&lt;br&gt;<strong>Chairs:</strong> Finlay Macrae, John Paul Plazzer, Maurizio Genuardi&lt;br&gt;• Modus operandi of the VIC - How do we formalize the membership of the VIC, what criteria, terms of reference, covering Participation-based membership and Qualification for membership? - Finlay Macrae&lt;br&gt;• Interactions with InSiGHT database and European national databases. Interactions with InSiGHT and the Prospective Lynch Syndrome database (Moller et al) Interaction with ClinGen and ClinVar - John Paul Plazzer&lt;br&gt;• Governance Committee membership altered – Maurizio Genuardi, Mike Woods, Rolf Sijmons, Finlay Macrae.&lt;br&gt;• Quest negligence suit for variant misclassification – Finlay Macrae&lt;br&gt;• New InSiGHT database and features - John Paul Plazzer&lt;br&gt;<strong>Penetration of path_MMR variants</strong>&lt;br&gt;• Suggested nomenclature for penetrance - Pål Møller&lt;br&gt;• Penetration of path_PMS2 variants - Maartje Nielsen&lt;br&gt;• Degrees of imperfect splicing - Alexandra Martins&lt;br&gt;<strong>VIC Classification criteria updates -</strong> Finlay Macrae, John Paul Plazzer&lt;br&gt;• Initiation codon variants&lt;br&gt;• Nonsense/frameshift variants in the last exon&lt;br&gt;• 5’UTR variant guidelines&lt;br&gt;• Possibility of an “update” publication on the rules</td>
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<tr>
<td>14:30 – 15:00</td>
<td>FOYER TAPICES</td>
<td><strong>COFFEE BREAK</strong></td>
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<tr>
<td>15:00 – 17:00</td>
<td>PLUTON</td>
<td><strong>VIC: VARIANT INTERPRETATION COMMITTEE (continued)</strong></td>
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</table>
**ATENEA**
15:00 – 17:00

**CHEMOPREVENTION & IMMUNOTHERAPY**

*Chair: John Burn*

- Progress towards a peptide based vaccine based on commonly mutated coding microsatellites - Magnus von Knebel Doeberitz, Matthias Kloor
- Targeted dendritic cells as a weapon of mass destruction – Nijmegen team
- Development of cell based immunity based on multiple epitopes: lessons from Ebola - Elisa Scarselli
- Bioinformatic approaches to vaccine design – Jon Timmis
- PD-1 Blockade – an effective treatment and a guide to vaccine development – Magnus von Knebel Doeberitz, Matthias Kloor
- The role of the patient in research design and project development – Pauline Skarrott
- Add two additional talks:
  - Towards Precision medical care in the UK for people at high genetic risk of bowel cancer - Deborah Alsina
  - Panel Discussion

**FOYER TAPICES**
17:00 – 18:30

**WELCOME RECEPTION**

19:30 – 22:00

**TAPAS MEAL AT QUINA CRUE** - ticket required

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**YOUR SAMPLES MAKE A DIFFERENCE!**

We are collecting material for test validation. Please, join our efforts by submitting clinical samples!

Submit at [www.lscancerdiag.com](http://www.lscancerdiag.com)

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LS CancerDiag Ltd has developed the novel DiagMMR™ assay, a functional test for the diagnosis of MMR deficiency. Our vision is to see DiagMMR™ as the new testing standard in Lynch Syndrome diagnostics.
<table>
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<tr>
<th>LOCATION/TIME</th>
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</table>
| ATENEA 09:00 – 11:00 | **CHEMOPREVENTION AND IMMUNOTHERAPY**  
*Chairs: Magnus von Knebel Doeberitz, John Burn*  
- Towards a vaccine against MSI cancer - Matthias Kloor, Magnus von Knebel Doeberitz  
- Dendritic cell therapy with mutant gene products in MSI cancers – Gerty Schreibelt  
- Development of viral delivery systems for cancer vaccines - Elisa Scarselli  
- The role of PD1L inhibition in MMR deficient tumours – Matthias Kloor  
- Chemoprevention and ASS - John Burn  
- Role of environmental modifiers in the risk of colorectal cancer for Lynch syndrome - Aung Ko Win  
- OR9: Frameshift mutations in microsatellite unstable colorectal cancers: from immune signature to personalized immunotherapy - Jean-Baptiste Latouche  
- Applying simulation modelling in cancer vaccine development – Mark Coles  

| FOYER TAPICES 11:00 – 11:30 | **COFFEE BREAK** |

| ATENEA 11:30 – 13:00 | **POLYPOSIS SYNDROME AND INHERITED COLORECTAL CANCER**  
*Chairs: Ian Tomlinson, Ian Frayling*  
- PPAP and NAP – Ian Tomlinson  
- Hot topic: a new polyposis gene! – Stefan Aretz  
- Update JPS – Robert Blatter, Karl Heinimann  
- NGS panel testing - Gabriel Capellá  
- OR4: Molecular diagnosis of inherited colorectal cancer using NGS panel - Stéphanie Baert-Desurmont  
- OR3: Functional assays and bioinformatics predictions reveal a high contribution of splicing mutations in the most frequent forms of hereditary cancer - Alexandra Martins  
- SO4: Targeted NGS of 22 mismatch repair genes identifies LS families - Bente Talsø-Telseth-Palmer  
- SO8: Identification of novel causal genes of hereditary colorectal cancer - Laura Valle  
- SO10: Identification of genetic biomarkers for clinical management of familial colorectal cancer - Merv Domínguez Valentin  
- SO9: Elucidating the molecular basis of MSH2-deficient tumours in Lynch syndrome suspected patients - Marta Pineda |

| FOYER TAPICES 13:00 – 13:30 | **LUNCH** |

| ATENEA 13:30 – 15:30 | **REGISTRIES AND GUIDELINES**  
*Chairs: Rolf Sijmons, Pål Møller, Maurizio Genuardi*  
- Carriers of path_MMR variants: penetrance, expressivity and survival - Pål Møller  
- Health economic principles – Ian Frayling  
- In vitro testing – Moni Morak, Elke Holinski  
- Potential of International Mismatch Repair Consortium (IMRC) collaboration – Aung Ko Win, Mark Jenkins  
- LOVD and big data management – John Paul Plazzer, Finlay Macrae  
- OR2: The LynCE study (the pilot): an assessment of endometrial cancer progression markers in Lynch syndrome – Angel Alonso Sanchez  
- OR7: Age stratified surveillance strategies Lynch syndrome - associated cancer according to mismatch repair mutation – Neil Ryan  
- Discussion: Pathway for inclusion of lacking variant and mutation information into the LOVD – Finlay Macrae, Pål Møller |
<table>
<thead>
<tr>
<th>FOYER TAPICES</th>
<th>COFFEE BREAK</th>
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<tr>
<td>15:30 – 16:00</td>
<td>16:00 – 18:00</td>
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**SURGERY, ENDOSCOPY AND MISCELLANEOUS**  
*Chairs: Jukka Pekka Mecklin, Gabriel Capellá, Finlay Macrae*

- TaTME for ileoanal pouch surgery in FAP – potential short and long-term benefits – Antonino Spinelli
- Surgical strategies for pouch surgery: can we improve? - Gabriela Möslein
- SO31: Do we still need surgery for treating small bowel polyps in Peutz-Jeghers syndrome? A 13-years follow-up cohort – Elia Samaha
- SO33: Assessment of MUTYH Associated Polyposis (MAP) phenotype in order to refine testing guidelines – Kate Simon
- OR11: Risk factors for the presence of pathogenic APC and biallelic MUTYH mutations in patients with multiple adenomas – Maartje Nielsen
- SO30: Compliance and impact of colonoscopy in familial adenomatous polyposis and MYH-associated polyposis – Carmen Guillén-Ponce
- SO34: A reassessment colonoscopy increases the diagnostic yield for serrated polyposis syndrome in a Faecal Immunochemical Test (FIT)-based colorectal cancer screening population – María Pellisé
- SO35: DNA-diagnostics of familial adenomatous polyposis and Peutz-Jeghers syndrome among Russian patients – Natalia Pospekhova
- SO1: Germline mutations in MMR genes among Russian patients with Lynch syndrome – Alexey Tsukanov
- SO6: Impact of an optimized colonoscopic screening program for patients with Lynch syndrome. Four years results of a specialized French network – Elia Samaha
- OR12: Chromocolonoscopy with indigo carmine facilitates high adenoma detection in Lynch syndrome patients - Robert Hüneburg
- OR5: Non-polyposus colorectal cancer – a distinct tumour type in Lynch syndrome? – Aysel Ahadova
- SO11: Endoscopic surveillance of the upper gastrointestinal tract in Lynch syndrome patients - Robert Hüneburg
- SO2: DNA mismatch repair genes deficiency is a frequent phenomenon in small intestine adenocarcinoma - Adriana Sanchez Garcia
- SO22: Colon polyps prevention and associated gut microbiota changes in a colorectal cancer animal model fed with functional meat foods containing prebiotics – Felipe Lombó
- OR6: DiagMMR: functional Lynch syndrome carrier testing from skin – Minttu Kansikas
- OR1: Universal screening Of colorectal cancers for Lynch syndrome by reflex immunohistochemistry – a single centre 9 year experience – Des Winter
- SO5: Selective and universal screening strategies for Lynch syndrome: a perspective from the Royal Marsden Hospital – Bianca Desouza
- SO29: Screening of 274 familial colorectal cancer patients using a multi-gene panel – Wenche Sjursen
- OR10: Technological innovation in hereditary cancer risk assessment – Anju Kulkarni
- OR8: Young adult colorectal cancer incidence trends in Europe: an important clinical and research opportunity for the European Hereditary Tumour Group and meeting report – Thomas Weber

20:00  
**CONFERENCE DINNER AT BAHIA MEDITERRANEO** - ticket required
### COLLABORATIVE STUDIES - SATURDAY 14 MAY

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<tr>
<td><strong>ZEUS</strong> 07:30 – 08:30</td>
<td>CAPP3 INTERNATIONAL For CaPP3 collaborators only</td>
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<tr>
<td><strong>MEMPHIS</strong> 08:30 – 10:30</td>
<td>REPORTING BACK SESSION FROM WORKING GROUPS AND COLLABORATIVE STUDIES (ongoing and new) Chairs: Julian Sampson, John Burn</td>
</tr>
<tr>
<td><strong>AFRODITA</strong> 09:00 – 12:00</td>
<td>PATIENT ADVOCACY AND EDUCATION WORKING GROUP UK, Spain, Germany, USA</td>
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<tr>
<td><strong>FOYER MEMPHIS</strong> 10:30 – 11:00</td>
<td>COFFEE BREAK</td>
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<tr>
<td><strong>MEMPHIS</strong> 11:00 – 12:00</td>
<td>REPORTING BACK SESSION FROM WORKING GROUPS &amp; COLLABORATIVE STUDIES (ongoing and new) (ctd) Chairs: Fiona Lalloo, Gabriel Capellá</td>
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<tr>
<td><strong>MEMPHIS</strong> 12:00 – 12:30</td>
<td>REPORTING BACK FROM PATIENT ADVOCACY AND EDUCATION</td>
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<tr>
<td><strong>RESTAURANT</strong> 12:30 – 13:15</td>
<td>LUNCH</td>
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<tr>
<td><strong>MEMPHIS</strong> 13:15 – 16:00</td>
<td>FORMER MALLORCA GROUP MEETING</td>
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<tr>
<td><strong>20:00</strong></td>
<td>DINNER AT RIFIFI - ticket required</td>
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MEETING INFORMATION

ABSTRACT / POSTER INFORMATION
Abstracts will be published in the Familial Cancer Journal after the meeting. Abstracts have been evaluated by the Programme Committee based on merit; they are on display at the meeting at the Welcome Reception and during the Friday coffee and lunch breaks in the Foyer Tapices.

POSTER LOCATIONS AND ACCESS TO SET UP/REMOVE
Posters may be put up between 16:30 – 19:00 on Thursday; please check-in at the Poster Check-In desk located at the registration desk (hotel lobby). You will be given a ticket which confirms your poster number, along with a supply of pins to use to hang your poster. Posters must be removed by 18:30 on Friday, as soon as the meeting concludes for the day. Any posters remaining after this time will be disposed of.

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

BADGES FOR THE WELCOME RECEPTION ON THURSDAY
This is not a ticketed event but all attendees are required to wear a name badge for this event.

CATERING
For each day of your registration, you are entitled to the following:
- Welcome reception on Thursday
- Coffee breaks from Thursday morning to Saturday afternoon
- A light buffet lunch on Thursday and Saturday
- A standing canapés lunch on Friday

DELEGATE FEEDBACK
You will find a delegate feedback form in your Registration Pack. Please complete the form and return it to the Registration Desk in the lobby.

INTERNET ACCESS
Free WiFi is available to all delegates for use on your own device. The WiFi details are as follows:
Username: HEREDITARY16 Password: PALMA

GENERAL INFORMATION

MEDICAL AND SAFETY INFORMATION
The emergency number to dial in Spain in the event that an ambulance is needed is 112.

FIRST AID AT MELIA PALAS ATENEA HOTEL
If you require First Aid Assistance please contact a member of the Melia Palas Atenea Hotel reception/event team, who will dispatch a qualified Occupational First Aider to deal with the incident. 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 Melia Palas Atenea reception or speak to a member of the event team. That way the services can be correctly 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 at the main hotel entrance through the lobby of the hotel. Information will also be given regarding arrangements for returning into the building by the Officers in Charge of the Incident.

MEDICAL CENTRES AND PHARMACIES NEAR TO MELIA PALAS ATENEA HOTEL
Nearest Medical Centres to Melia Palas Atenea Hotel:

- MRI Group
  Carrer de Porto Pi, 8, Palma, Illes Balears Spain
  Tel: +34 971 919 244
  www.mri-group.es

- Farmacia Murillo-Ribot C.B.
  Calle del Marqués de la Sénia, 40, 07014 Palma, Illes Balears, Spain
  Tel: +34 971 73 18 25
  www.hanovermedical.ie

LOST PROPERTY
If you have lost anything at the Melia Palas Atenea, please contact us at Registration and we will try to assist. Should you find any lost property, please bring it to Registration.
**EUROPEAN HEREDITARY TUMOUR GROUP (EHTG)
Mallorca Group**

**EVENING EVENTS**

**WELCOME DRINKS AT THE MELIA PALAS ATENEA HOTEL**

**Thursday 12 May**

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<td>Cost: Included for delegates</td>
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All delegates are invited to attend this event which is included in the registration fee. The event will take place in Foyer Tapices following the close of meeting sessions.

**THURSDAY: TAPAS AT A LOCAL RESTAURANT – QUINA CRUE**

<table>
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<th>Time: 19:30</th>
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<td>Cost: €25 / reduced cost for trainees</td>
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**How to get there:**
Carrer de la Corderia, 24, 07001 Palma, Illes Balears

Quina Crue is located in the Old Town, just 35 minutes’ walk from the Melia Palas Atenea. Alternatively, the journey by taxi is approximately 15 minutes.

Walking directions from the Melia Palas Atenea: Exit the hotel and take a left onto Avinguda de Gabriel Roca. After 1.6 km turn left onto Carrer del Consolat. Turn right onto Plaça de la Drassana. Turn right onto Carrer dels Apuntadors. At the roundabout, take the 1st exit onto Av. d’Antoni Maura. Turn left onto Plaça de la Reina and then continue onto Carrer del Conquistador. Slight left onto Carrer Sant Domingo and Slight right onto Carrer de Jaume II. Turn right onto Carrer de les Monges and then left onto Plaça del Marquès del Palmer. Turn right onto Carrer de la Bosseria and continue straight onto Plaça d’En Coll. Continue onto Carrer de la Galera and turn left onto Carrer de la Corderia. The restaurant will be on the right.

**FRIDAY: CONFERENCE DINNER AT BAHIA MEDITERRANEO**

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<th>Time: 20:00</th>
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<td>Cost: €65 / reduced cost for trainees</td>
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**How to get there:**
5º, Paseo Marítimo, 33, 07014 Palma, Illes Balears

Bahia Mediterraneo is located 3 minutes’ walk from the hotel.

Walking directions from the Melia Palas Atenea: turn right when you exit the hotel onto Avinguda de Gabriel Roca. Continue walking for three minutes and the hotel will be located on the right hand side.

**SATURDAY: EVENING MEAL AT RIFIFI**

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<th>Time: 20:00</th>
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<td>Cost: €50 / reduced cost for trainees</td>
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**How to get there:**
Avinguda Joan Miró, 182, 07015 Palma, Illes Balears

Rififi restaurant in located 1.5 km from the hotel.

Walking directions from the Melia Palas Atenea: turn right when you exit the hotel onto Avinguda de Gabriel Roca. After a kilometre, slight right onto Carrer de Porto Pi. After 280 meters, turn left onto Avinguda de Joan Miró. The restaurant will be on the right.

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

Venue
- Meliá Palas Atenea

Evening Events
- Quina Creu Tapas & Restaurant
- Restaurante Bahía Mediterráneo
- Restaurante Rifí
**OR01**

**Title:** Universal screening of colorectal cancers for Lynch syndrome by reflex immunohistochemistry – a single centre 9 year experience

D. Winter, E. Ryan
St Vincent’s University Hospital, Dublin

**Background:** Up to 15% of colorectal cancer (CRC) exhibit microsatellite instability (MSI), where errors in replication go unchecked due to deficient mismatch repair (dMMR). Many institutions now advocate universal tumour screening via either polymerase chain reaction for MSI or immunohistochemistry (IHC) for dMMR to help identify Lynch syndrome. The majority of MSI is caused by MLH1 promoter hypermethylation and occurs sporadically. BRAF mutation may be used as a proxy marker for MLH1 promoter hypermethylation. We describe a series of 1753 consecutive CRCs subjected to reflex IHC for dMMR in our institution, and the resulting follow up with BRAF and germline testing.

**Design:** Retrospective analysis of the pathological features of CRCs identified on a prospectively maintained database at St Vincent’s University Hospital (SVUH) from January 2004 to December 2013 inclusive. IHC was used to identify mismatch repair (MMR) status. Molecular analysis for the BRAFV600E mutation hotspot was carried out selectively on MLH1 deficient tumours. Tumours with absent MLH1 and who were BRAF mutation negative and tumours with absent MSH2, MSH6 or PMS2 were referred for genetic testing.

**Results:** Of the 1753 CRCs in the SVUH database during the study period 1753 had IHC for dMMR. 13.69% (n=183) exhibited dMMR. The median age was 69 (range 26-96) 22.4% (n=39) had a genetics referral during the study period. BRAF testing was undertaken in 29.5% (n=54) individuals. Once MLH1 absent tumours with BRAF mutation were excluded 27% (41/151) of patients with dMMR were referred for genetic testing. 1.2% (n=21) of the total CRCs screened were diagnosed with Lynch syndrome. 60.1% (n=110) of MMRd tumours were not referred. Those not referred or who declined further testing had a median age of 77 years.

**Conclusions:** Universal IHC for Lynch syndrome results in increased detection of dMMR tumours. BRAF testing can reduce the number of genetic referrals if performed in specimens with MLH1 loss. Additional testing for MLH1 hypermethylation on BRAF wild type tumours may distinguish sporadic from germline MSI cases. When Universal IHC for Lynch syndrome is introduced there is a need for appropriate planning and resources to fully investigate abnormal IHC results to ensure patients are appropriately referred for genetic testing.

**OR02**

**Title:** The LynCE study (The pilot): An assessment of endometrial cancer progression markers in Lynch syndrome

R. Guach Troyas1,2, M. Arias Alonso1, S. Moreno Laguna1,2, E. Recari Elizalde1,2, A. Alonso Sánchez1,2,3
1 - Complejo Hospitalario de Navarra, 2 - Oncogenetics and Hereditary Cancer Group, IDISNA (Biomedical Research Institute of Navarre)

**Aim:** Abnormal Mismatch Repair (MMR) proteins Immunohistochemistry (IHC) and Microsatellite Instability (MSI) has been observed both in tumoural and normal endometrial biopsies in patients carrying mutations predisposing to Lynch syndrome (LS). The potential use of these findings as potential markers for progression to endometrial cancer is to be clarified in a prospective multicentric study: the LynCE study. These are the results of its pilot study.

**Method:**
- 72 endometrial biopsy samples from 51 Lynch Syndrome (LS) carriers: (MLH1=22; MSH2=21; MSH6=8), with different pathology diagnoses: Normal Endometrium (NELS=34); Complex Endometrial Hyperplasia (CEHLS=4) and Endometrial Carcinoma (ECLS= 13).
- 17 Normal Endometrium biopsy samples from control population (NELS).
- 72 endometrial biopsy samples from 51 Lynch Syndrome (LS) carriers: (MLH1=22; MSH2=21; MSH6=8), with different pathology diagnoses: Normal Endometrium (NELS=34); Complex Endometrial Hyperplasia (CEHLS=4) and Endometrial Carcinoma (ECLS= 13).

**Results:**
- 100% (13/13) of the Endometrial Cancer (ECLS) and Endometrial Hyperplasias (CEHLS) (4/4) in Lynch syndrome patients showed absent IHC concordant with the underlying genetic defect, and 75% of ECLS and 83% of CEHLS had MSI.
- 64% (19/30) of Normal Endometrium biopsies from Lynch patients (NELS) and 0% of control population (NE) showed abnormal IHC (χ² p<0.01**).
- +46% (7/15) of LS carriers whose biopsy showed normal endometrium (NELS) with normal IHC, progressed to endometrial cancer (median time=38,4 months) vs 0% (0/19) of those with normal IHC (Log-Rank; Kaplan Meier p<0.001**).

**Conclusion:** Abnormal MMR IHC and MSI is an abnormal finding in normal endometrium biopsies from Lynch Syndrome patients. In the pilot study these markers were able to predict the progression to endometrial cancer. A multicentric study, the LynCE, is now on its way to prospectively validate these results which could improve the medical evidence for recommendations (surveillance vs. prophylactic hysterectomy) in Lynch syndrome patients.

**OR03**

**Title:** Functional assays and bioinformatics predictions reveal a high contribution of splicing mutations in the most frequent forms of hereditary cancer

P. Gaillard1,2, O. Soukarieh1,2, G. Castelain1,2, H. Tubeuf1,2, S. Krieger1,2, S. Baert-Desurmont1,2,4, D. Di Giacomo1,2, M. Hamelie1,2, S. Caputo1, A. Jabbad1, A. Killian1,2, J. Thery1,2, I. Tourrier1,2, C. Bonnet1,2, S. Alliké1,2, A. Drouet1,2, M. Vezain1,2, E. Rouleau1, T. Houdayer1, T. Frebourg1,2, M. Tos1, A. Mart1,2 in collaboration with the French Oncogenetics Network

**Aim:** The identification of a causal mutation is essential for molecular diagnosis and clinical management of hereditary cancers. Even if DNA-seq has greatly improved the detection of nucleotide changes, the biological interpretation of most variants remains challenging.

**Method:** We performed splicing assays to evaluate the impact on RNA splicing of more than 600 variants identified in genes implicated in Lynch syndrome or in hereditary breast and ovarian cancer syndrome, notably MLH1/MSH2(MMR), BRCA1/BRCA2 (BRCA).

**Results:** We found that more than 25% of variants of unknown significance in the MMR/BRCA genes have an impact on RNA splicing. Furthermore, our targeted studies on “model-exons”, including MLH1 exon 10 and BRCA2 exon 7, revealed an unexpected large number of variants altering potential exonic splicing regulatory elements (ESR), an effect that could be predicted by two newly developed ESR-dedicated in silico tools, but not by commonly used bioinformatics approaches.

**Conclusion:** This work revealed the important contribution of splicing mutations in hereditary cancer, contributed to the clinical classification of several variants, and pinpointed the potential of new prediction methods as filtering tools for prioritizing variants for functional analyses.

**OR04**

**Title:** Molecular diagnosis of inherited colorectal cancer using NGS panel

S. Baris-Baucico1,2,4, F. Charbonnier, S. Coutant, M. Vezain, R. Lanos, J. Bou, E. Bouvignies, S. FOURNOIS, S. MANASE, S. Vasseur, G. BOUGEARD, J. MAUILLON, I. TOURNIER, T. FREBOURG
Department of Genetics Rouen University Hospital and Inserm U1079, Rouen University, Normandy Centre for Genomics and Personalized Medicine, Rouen, France

**Aim:** We have developed and optimized a massive parallel sequencing strategy for the diagnosis of inherited forms of colorectal cancer (CRC).

**Method:** This strategy is based on (1) a panel of 10 genes involved in Mendelian forms of CRC (MLH1, MSH2, MSH6, PMS2, APC, MUTYH, STK11, SMAD4, BMPRIA, PTEN), (2) a quick capture of exonic and intronic sequences using Sureselect Agilent OXT, (3) sequencing on MiSeq and NextSeq 500 illumina platforms, (4) double bioinformatics pipelines including CASAVA (Illumina) and BWA-GATK (Broad Institute) softwares for alignment and variant calling, Alamut Batch (Interactive BioSoftware) for annotation, completed by CANOES software for the rearrangement detection, (5) automatically generated quality reports and (6) systematic control of the genotypes, using Sanger sequencing or QMPSF for the positive cases and Multiplex SNAPsiShot analysis of SNPs for the negative cases.

**Results:** Analysis of 1200 index cases allowed us to identify a deleterious mutation in 18% of the patients and the mutation detection rate reached 32% in Lynch syndrome suspected by tumour analyses.

**Conclusion:** The main advantages of this strategy are the reduction of molecular diagnosis delay, the correction of the diagnosis in cases of overlapping phenotypes (MUTYH biallelic mutations mimicking Lynch syndrome) and the detection of mosaics and cryptic alterations.

**OR05**

**Title:** Non-polypous colorectal cancer – a distinct tumour type in Lynch syndrome?
A. Ahadova1, M. von Knebel Doberthä2, H. Bläker3, M. Kloos1 Please see Mallorca Group website for Author Institutions

Aim: Regular colonoscopy is recommended for colorectal cancer (CRC) prevention in Lynch syndrome. However, a significant part of interval cancers develop in mutation carriers under surveillance. These cancers could be derived from endoscopically invisible non-polypous precursors such as the recently described mismatch repair-deficient crypt foci. We here aimed to analyze the frequency and mutation pattern of CRCs derived from non-polypous precursors in Lynch syndrome.

Method: We analyzed the histological appearance of 46 Lynch syndrome-associated CRCs and profiled them for mutations by fragment length analysis and Sanger sequencing.

Results: Among 40 analyzable cancers, 25 (62.5%) lacked evidence of polypous growth. CTNNB1 mutations, which were strongly associated with lack of polypous growth, were detected in 8/46 (17.4%) of Lynch syndrome-associated cancers. CTNNB1 mutations were not found in sporadic MSI-H colorectal cancers (n=34).

Conclusion: A significant proportion of Lynch syndrome-associated CRCs, characterized by a distinct mutation profile, appear to develop as immediate invasive cancers from non-polypous precursors. This is of high clinical significance, because it may explain interval cancer formation in Lynch syndrome. In addition, colonoscopy efficacy data in the general population cannot be directly extrapolated to Lynch syndrome. Active, primary preventive measures should be considered in Lynch syndrome mutation carriers to tackle non-polypous precursors.

OR06 Title: DiagMMR: Functional Lynch syndrome carrier testing from skin M. Kansikas1, J. Kantelinen1, M. Kasa1a, P. Palowita1, J. Mecklin1,2, P. Peltomäki1, M. Nyström1,3 Please see Mallorca Group website for Author Institutions

Aim: Our aim is to optimize the specificity and sensitivity of the predictive DiagMMR functional test for Lynch syndrome (LS) diagnostics.

Method: The DiagMMR method recognizes reduced DNA mismatch repair (MMR) by quantitatively assessing the MMR efficiency of cells derived from normal skin tissue and hence allows inherited cancer predisposition to be diagnosed from healthy LS mutation carriers without mutation sequencing.

Results: Using samples obtained from known LS mutation carriers and their unaffected family members, the DiagMMR method has been optimized to distinguish MLH1, MSH2 and MSH6 mutation carriers from non-affected individuals. The clinical validation of the test is commencing.

Conclusion: This prominent method for recognizing LS without the onset of cancer is now ready for clinical validation which can only be accomplished with the broad support of LS clinicians, as LS mutation carrier skin samples representing a variety of different MMR-gene mutations is required. In order to apply the DiagMMR test to the clinical screening of LS carriers a rigorous validation of the method needs to be completed.

OR07 Title: Age stratified surveillance strategies Lynch syndrome-associated cancer according to mismatch repair mutation N. Rydz4, K. Green3, E. Croebel5, G. Evans5 Please see Mallorca Group website for Author Institutions

Aim: Lynch syndrome is a dominantly inherited germline mutation that predisposes individuals to colorectal (CRC), endometrial (EC) and other cancers through inactivation of the cellular mismatch repair system. This in turn leads to a loss of DNA fidelity during replication. Colorectal surveillance is well established for Lynch patients and has been shown to save lives. There is a growing consensus that women with Lynch syndrome who choose to avoid hysterectomy should also be offered EC surveillance. The age at which cancer surveillance should start is disputed. Our work aims to explore the association between the age of cancer diagnosis and the mutational profile of the patient.

Method: This was a retrospective study of subjects with Lynch syndrome-associated EC and/or CRC. The database is clinical data set of a large region within the UK. Data quality is ensured by the use of lateral data source collaboration utilising the National Cancer Registry and death certification among others. Subjects were stratified by mutated gene (MLH1, MSH2 & MSH6) and the age of diagnosis. Statistical analysis was investigated using one-way analysis of variance (ANOVA) with post hoc Newman-Keuls multiple comparison test and Student's t-test.

Results: In total, 226 women with EC and 228 men and women with CRC were identified. Women with EC, MSH2 mutations were most common (n=114), followed by MLH1 (n=70) and MSH6 (n=62). In CRC, MLH1 mutations (n=121) were most common, followed by MSH2 (n=80), MSH6 (n=21) and PM2 (n=6) mutations. When stratified by mutation, mean age of EC diagnosis was 50 years for MLH1, 48 years for MSH2 and 54 years for MSH6 mutation (p=0.0001). For CRC, the mean age at diagnosis was 44, 45, 53 and 47 years for MLH1, MSH2, MSH6 and PM2 mutations, respectively. Mutations in MSH6 presented significantly later with CRC than mutations in the other genes (p=0.0014). When stratified by type of mutation (truncating, splicing or large rearrangement), no significant difference was found for EC. However, in the CRC cohort, truncating mutations presented earlier than other types of mutations (p=0.04). In these data, CRC and not EC was the most common sentinel cancer.

Conclusion: Our data indicate that women with known Lynch syndrome could be risk stratified by age and type of mutation and offered tailored surveillance programmes. Specifically, individuals with an MSH6 non-truncating mutation could be offered cancer surveillance from a later age.

OR08 Title: Young adult colorectal cancer incidence trends in Europe: an important clinical and research opportunity for the European Hereditary Tumour Group T. Weber1, D. Ahnhen2, C. Sardo-Molmenti3, D. Alsin4, A. Win5, C. Lieu6 Please see Mallorca Group website for Author Institutions

Aim: To evaluate young adult (<50 years) colorectal cancer (CRC) incidence trends across Europe and assess the potential impact of that data on the clinical and research priorities of the European Hereditary Tumour Group.

Method: We searched PUBMED and the WHO Mortality Database for current literature on young adult (YA) CRC incidence across 34 European Countries.

Results: Multiple references including a recent United European Gastroenterology report indicate that YA CRC accounts for over 10% of CRC cases in Europe affecting 45,000 individuals annually. YA CRC incidence is increasing including in Britain where Cancer U.K. reports a 40% increase since 2004. Over 80% of cases are symptomatic at diagnosis. Importantly, less than 20% of cases are associated with the known hereditary CRC syndromes.

Conclusion: YA CRC represents a significant and growing percentage of CRC cases in Europe, consistent with global trends. While the majority of these cases do not overtly fit the hereditary CRC paradigm, the optimal clinical practice and translational research questions are similar and clearly compliment existing efforts. We believe the collective clinical expertise and scientific resources of the European Hereditary Tumour Group are exquisitely well positioned to support investigations into this emerging young adult cancer control issue.

OR09 Title: Frameshift mutations in microsatellite unstable colorectal cancers: from immune signature to personalized immunotherapy P. Roccabernardi1,2, H. Korai2, J. Touguer2,1, D. Bransch6, B. Bläker1,2, H. Angell1, T. Fredriksen1, N. Elie2, J. Leprince2, J. Maullion2,6, F. Le Pessot10, R. Sesboüé2, T. Frebourg4,1, J. Galon5, J-B. Lafouge6,1 Please see Mallorca Group website for Author Institutions

Aim: In colorectal cancers with microsatellite instability (MSI-CRCs), overall tumour-infiltrating lymphocyte (TIL) density and survival rate are known to be higher than in microsatellite stable CRCs (MSS-CRCs). However, the clinical links between DNA mismatch repair (MMR) machinery deficiency, TIL density and prognosis remain to be established.

Method: Starting from 141 MSI-CRCs, we studied tumour microenvironment by gene expression profiling and immunohistochemistry, tumour frameshift mutations (FSMs) by multiplex PCRs, and tumour-specific autologous T cell responses using artificial antigen presenting cells developed in the laboratory.

Results: MSI-CRCs, compared to MSS-CRCs, expressed more immune-related genes and were infiltrated with more in situ proliferative T cells, functional CD8+ T cells, B cells and macrophages, which correlated with prolonged survival. Moreover, CD8+ TIL density was associated with the total number of FSMs, and was especially higher when a FSM was present in ASTE1, HNF1A or TCF7L2 gene. Finally, starting from peripheral blood of MSI-CRC Lynch patients, we could mount in vitro efficient CD8+ T cell responses against neoantigens derived from FSMs present in their tumour.

Conclusion: Altogether, our results allow us to describe, for the first time to our knowledge, the precise immune signature of MSI-CRCs, and pave the way for developing personalized immunotherapy strategies in these cancers.

OR10 Title: Technological innovation in hereditary cancer risk assessment
A. Kulkarni1, A. Kenney2, V. Tripathi2, C. Compton2, S. Rose1, D. Ruddy1, L. Izatt1, E. Haque1, A.C. Shaw1.

Aim: To develop an accessible information technology solution for hereditary cancer risk assessment and referral guidance for clinicians, thereby improving patient access to our service by targeting several factors; clinicians’ limited understanding of hereditary cancer, lack of time, confusion about where to refer patients, use of outdated guidance.

Method: Guy’s Cancer Genetics guidelines are used across a population of 5 million in Southeast England and updated in line with national standards. However they are presented in ‘non-interactive’ pdf format and it is difficult to ensure clinicians are using the most recent version.

The Cancer Genetics App contains a risk assessment tool and reference guide, enabling clinicians to decide who requires genetic assessment and who can be managed in primary or secondary care.

Results: Patients thereby have quicker access to cancer surveillance, genetic counselling and testing, chemoprevention and surgical options. Cancer Genetics is freely available via iOS, android and web-based platforms. It is certified as a Class 1 medical device, CE marked, and a secure content management system allows central updates.

Conclusion: We will present the development process, user feedback and integration into primary and secondary care. Our goal is that Cancer Genetics will promote timely, evidence-based management of those at risk of hereditary cancer.

OR11

Title: Risk factors for the presence of pathogenic APC and biallelic MUTYH mutations in patients with multiple adenomas
M. Nielsen1, S. ten Broeke1, S. Badal1, T. van Wezel1, H. Morreau2, F.J. Hes1, H. Vasen1, C. Tops1.

This study was supported by the Dutch Cancer Society

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Aim: Patients with multiple colorectal adenomas may carry germline mutations in APC or MUTYH, but mutation detection rate seems to be declining. The aims of this study were (1) to assess the proportion of these mutations in patients with multiple adenomas and (2) to identify risk factors that predict mutation detection.

Method: We performed mutation analysis of APC and/or MUTYH in a Dutch cohort of 1933 patients ascertained from family cancer clinics between 1992 and 2015. Risk factors were examined using (multinomial) logistic regression analyses.

Results: The overall detection rate declined from 54% before to 14% after 2004. The proportion of APC/MUTYH carriers in patients with >20 polyps was low (3.5%;25/722). Only one mutation was identified in the patient group (n=198) of 10-19 adenomas diagnosed at age 60+. A younger age at adenoma diagnosis and a first degree relative (FDR) with polyps was associated with higher odds of finding an APC mutation, but CRC in a FDR was not. Having CRC was only predictive of finding biallelic MUTYH mutations.

Conclusion: Adenoma count and younger age at adenoma detection are the main predictive factors of finding a mutation, but a FDR with CRC is not. For patients over age 60 with less than 20 adenomas testing does not seem justifiable. Our findings have an important impact on referral policy.

OR12

Title: Chromocolonoscopy with indigo carmine facilitates high adenoma detection in Lynch syndrome patients
R. Hünemur1,2, P. van Heteren1, S. Aretz1, D. Pantelis2, C. Strassburg2, J. Nattermann1,4.

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Aim: The risk of colorectal cancer (CRC) in Lynch syndrome is up to 70% by the age of 70 years. Progression from adenoma to carcinoma is believed to be faster than in sporadic CRC. In a previous study, we demonstrated chromocolonoscopy to significantly increase adenoma detection rate (ADR) compared to standard and NBI colonoscopy (28% vs. 15%). Here, we studied the diagnostic performance of chromoendoscopy in Lynch patients in daily clinical routine.

Method: Between 08/2006 and 02/2016 Lynch syndrome patients with a proven germline mutation in a mismatch repair gene were included. All patients were examined using pan-colonic chromoendoscopy with indigo carmine and high-definition endoscopes.

Results: A colonoscopy was performed in 152 patients with proven germline mutation (68 MLH1 (45%), 69 MSH2 (45%), 14 MSH6 (9%) und 1 EPCAM (1%)). Mean age was 45 years (+/- 12). In 84 patients (55%) a prior surgery due to CRC was documented. At least one adenoma was detected in 59 patients (38%). Hyperplastic polyp(s) were found in 70 patients (45%).

Conclusion: Chromoendoscopy is feasible and effective in routine care of Lynch syndrome patients.

OR13

Title: Surveillance of Duodenal Polyposis in Familial Adenomatous Polyposis: Should the Spigelman score be modified?
I. Sourrouille1, J. Lefèvre1, C. Shields2, C. Colas1, J. Bellanger4, B. Desaint1, E. Trelat5, Y. Parc6.

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Aim: Duodenal polyposis (DP) is a manifestation of Adenomatous Polyposis (AP) which predisposes to duodenal or ampullary adenocarcinoma (ADC). DP is monitored by upper GI endoscopies (UGIE) and may require iterative resections and prophylactic radical surgical treatment (RST), when malignancy is threatening. Evaluate severity scoring for surveillance and treatment in a large series of DP.

Method: From 1982 to 2014, every patient surveyed by UGIE for DP was included.

Results: We performed 1912 UGIE in 437 patients (median 3, IQR [2-6]). Genes involved were APC (n=274, 62.7%) and MYH (n=21, 4.8%). First UGIE (median age 32±[21,44]) revealed DP in 190 (43.5%). Rates of low grade dysplasia (LGD), high grade dysplasia (HGD), and ADC at 5 years were 65%(61.7-66.9), 12.1%(10.3-13.9) and 2.4%(1.5-3.3) respectively while 10 year rates were 75.8%(73.1-78.5), 20.8%(18.2-23.4) and 5.4%(3.8-7.0). The incidence of ampullary abnormalities rose during surveillance, from 18.3% at the first UGIE to 47.4% at the fourth. Predictive factors for HGD were age at first UGIE, type and age of colorectal surgery, Spigelman score, presence of an ampullary abnormality, and the number of endoscopic treatments. In multivariate analysis, only age at first UGIE and presence of an ampullary abnormality were independent predictive factors. Conservative treatment was performed in 103 patients (159 endoscopic resections, 17 surgical), while RST (Whipple procedure or duodenectomy) was required in 52 (median age 47.5±[43-57.3]) because of HGD or unrectable lesions. Histological analysis after RST showed HGD in 30 patients and ADC in 11 (4 patients had lymph node involvement).

Conclusion: Over 20% of patients develop HGD with DP after 10 years. Iterative endoscopic resections allow extended control but surgery remains necessary in 12% of the patients, and happens too late in many cases; 20% had developed ADC, while 8% exhibited malignancy with lymph node involvement. The trigger for prophylactic surgery requires a more accurate predictive score. Modifying the Spigelman score by accounting for ampullary abnormalities should be considered.

OR14

Title: The Colon Cancer Family Registry Cohort and Genetic Factors for Colorectal Cancer
M. Jenkins1, D. Buchanan1, A. Win1, N. Lindor2, S. Gallinger1, L. Le Marchand1, G. Casey2, P. Newcomb1, R. Haile3, J. Baron4, J. Potter5, F. Macrae6, T. Thibodeau1, J. Hopper1, A. Templeton7 for the Colon Cancer Family Registry.

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Aim: To investigate the genetic and environmental aetiology of colorectal cancer, the National Institutes of Health (USA) have funded (since 1997) the Colon Cancer Family Registry, which is a consortium of six institutions in Australia, Canada and the USA that have recruited approximately 13,000 population- and clinic-based colorectal cancer and control families comprising approximately 38,000 participants. Participants have completed a baseline risk factor questionnaire, donated a blood sample, and given permission to access medical records, and every 5-years they have completed a follow-up questionnaire. Participants have undergone tumour testing for mismatch repair proficiency and germline testing for variants in mismatch repair (MMR) genes and MUTYH, as well as whole exome and genome sequencing and genome-wide SNP testing.

Method: Cancer risks for carriers of germline mutations in MMR genes and MUTYH have been estimated using modified segregation analyses, conditioning on the ascertainment. Modifiers of cancer risk for MMR gene and MUTYH carriers have been studied using lifestyle factors, personal characteristics and genetic factors. Risk of metachronous cancer in Lynch syndrome has been estimated. Studies on characterisation of MMR gene variants, methods of variant detection and psychological impact of testing have been conducted. Population prevalence of mutations in each of the four MMR genes and MUTYH have been estimated, as has the proportion of MMR gene mutation carriers that are de novo. Gene discovery for colorectal cancer has been conducted using sequencing utilising the family design and conducted using genome-wide association studies utilising the
Over 450 participants from 260 families have undergone whole exome or whole genome sequencing. Approximately 10,000 cases and controls have undergone genome-wide SNP testing. Over 120 studies on Lynch syndrome, 12 studies on MUTYH, and over 120 studies on other genetic factors for colorectal cancer have been published using the Colon Cancer Family Registry resource. The resource is available, on application to investigators and has been utilised for over 300 projects (83 from investigators external to the Colon Cancer Family Registry). Policies and instructions for application to collaborate and access data, DNA or other biospecimens have been developed and are available at http://coloncfr.org/collaboration.

Conclusion: The Colon Cancer Family Registry is a large and well-characterised (in terms of genetic risk factors) prospective series of colorectal cancer cases and controls that includes detailed information on family history of cancer and recruitment of relatives. The resource has been used for many research studies on genetic syndromes for colorectal cancer including Lynch syndrome and MUTYH.

Future direction: This work was supported by grant UM1 CA167551 from the National Cancer Institute, National Institutes of Health (NIH) and through cooperative agreements with members of the Colon Cancer Family Registry (CFR) and Principal Investigators. Collaborating centers include Australasian Colorectal Cancer Family Registry (U01/U24 CA097735), Mayo Clinic Cooperative Family Registry for Colon Cancer Studies (U01/U24 CA074800), Ontario Familial Colorectal Cancer Registry (U01/U24 CA074783), Seattle Colorectal Cancer Family Registry (U01/U24 CA074794), Stanford Consortium Colorectal Cancer Family Registry (U01/U24 CA074799), and University of Hawaii Colorectal Cancer Family Registry (U01/U24 CA074806).

OR15

Title: Worldwide study of cancer risks for Lynch syndrome: International mismatch repair consortium (IMRC)

M. Jenkins1, A. Win1, J. Reece2, G. Lee3, A. Templeton3, R. Haile4, G. Mosleim4, F. Macrae1 for the IMRC.

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Aim: To bridge critical gaps in Lynch syndrome research, the International Mismatch Repair Consortium (IMRC) was formed in 2010. The IMRC comprises major international consortia involved in the research and/or clinical treatment of Lynch syndrome (cancer predisposition caused by inherited mutations in mismatch repair (MMR) genes: MLH1, MSH2, MSH6, PMS2 and EPcad). http://www.sphinx.org.au/imrc. The establishment of the IMRC was facilitated by the International Society for Gastrointestinal Hereditary Tumours (InSIGHT) and the Collaborative Group of the Americas on Inherited Colorectal Cancer (CGA). Currently, the IMRC has 205 members from 74 centres in clinics, in Africa, Australasia, Europe, North and South America, and membership is open to anyone involved in research related to Lynch syndrome and/or the treatment of Lynch syndrome families.

Accurate cancer risk estimates are needed to develop genetic counselling guidelines, and are of importance for the clinical management of mutation carriers and members within high-risk families. Risk may differ not only by age and gender and the gene that is mutated, but also by the country, ethnicity and characteristics of the carriers. The only way to thoroughly address this potential heterogeneity is to conduct comprehensive penetrance analyses on large, ethnically heterogeneous samples of persons/families segregating mutations in MMR genes.

Method: The IMRC will: (i) establish a combined data set of pedigrees from around the world for approximately 8,800 Lynch syndrome families; (ii) evaluate the age-specific cumulative risk (penetrance) of cancers at each anatomical site by sex, mismatch repair gene, type of mutation, and nationality/geographic region; and (iii) develop a personal risk tool for clinical use that provides 10-year risks of cancer based on the age, sex, mismatch repair gene, type of mutation, and nationality/geographic region.

Results: Since July 2014, IMRC investigators from 63 sites were contacted and requested to submit the MMR family data from their clinics/centres. Instructions on the preferred data format were provided, including data dictionaries for personal and family history of demographical data, cancers, MMR gene mutation status, screening, surgery and mortality. As of April 2016, 28 investigators representing 38 sites of 18 countries have submitted MMR pedigree data for 4302 families including 11418 mutation carriers.

Conclusion: Collection of MMR family data from many international sites, with varying resources (many of which were not established or designed for epidemiological research) is challenging. The IMRC will be investigating ways to facilitate data collection for this project to ensure the maximum benefit is gained from this collegial and international consortium.

Funding source: Australian National Health and Medical Research Council.

Short Oral Presenter Abstracts

SO01

Title: Germline mutations in MMR genes among Russian patients with Lynch syndrome

A. Tsukanov, V. Shubin, A. Vardanyan, D. Semenov, S. Achkasov, S. Frolov, V. Kashmikov, Y. Shehlygin, N. Pospelkova

State Scientific Center of Coloproctology, Moscow, Russia

Aim: Lynch syndrome is one of the most frequent hereditary colorectal cancer syndromes. The syndrome is caused by mutation in one of the mismatch repair (MMR) genes: mainly MLH1, MSH2, MSH6. The aim of this investigation was to study frequency and spectrum of germline mutations of MMR genes among Russian patients.

Method: Microsatellite instability was studied in tumour samples of probands who corresponded to next criteria: age ≤ 45 and/or family history of colorectal cancer. Germline mutations in MMR genes of patients with MSI-H (high level) tumours were detected by PCR, conformation-sensitive electrophoresis and Sanger sequencing.

Results: Microsatellite instability of high level was found in 88 tumour samples. Twenty nine out of 88 patients had germline mutations in MMR genes. Fourteen mutations were found in MLH1, 12 mutations - in MSH2, 3 mutations - in MSH6. Ten of these mutations were frameshift, 8 - nonsense, 6 – splice sites and 5 pathogenic missense mutations.

Conclusion: Frequency of germline mutation in MMR genes among set of Russian patients was 35.4%. The using of NGS and MLPA methods is necessary for detection mutations in other MMR genes or large rearrangements.

SO02

Title: DNA mismatch repair genes deficiency is a frequent phenomenon in small intestine adenocarcinoma

A. Sanchez1, S. Carballal1, M. Cuatrecasas2, T. Ocanà1, M. Pellissié1, M. Liz Leoz1, A. Castells1, F. Balaguer1, L. Moreira1

Please see Mallorca Group website for Author Institutions

Aim: Etiological and molecular mechanisms had been poorly described in small intestine adenocarcinoma(SIA). Our aim is to describe the clinicopathological characteristics of SIA, and assess the role of DNA mismatch repair (MMR) genes deficiency in these tumours.

Method: Retrospective, descriptive study including all (21) SIA diagnosed in our center between 2004-2014. Personal, tumour-related, and family characteristics, as well as tumour MMR immunohistochemistry (IHC), and germline MMR mutational status data were reviewed.

Results: Eleven(52.4%) men, with a median age of 67(23-93) years. Median follow-up was 23.7(IQR 8.5-59.6) months with an overall 5-year survival of 45.8%. Ten(47.6%) tumours were located in duodenum, 9(42.9%) in jejunum and 2(9.5%) in ileum. Twelve(57.1%) were diagnosed in advanced stages(III-IV) and 7(33.3%) had a high histological grade. IHC revealed pathological findings in 4(19%) tumours: 2(50%) with loss of expression in MLH1/PM2 and 2(50%) in MSH2/MSH6. These patients were younger and had better survival, without statistically significant differences [age: 53.5(12) vs 65(17.5) years, p = 0.2; mortality: 25%vs 53%, p = 0.3]. Lynch syndrome was diagnosed in 2(50%) patients. No other hereditary syndromes were detected.

Conclusion: 20% of SIA present MMR deficiency. Only half of the patients were diagnosed with Lynch syndrome. These results may suggest that, as described recently in colorectal cancer, somatic inactivation of MMR genes could explain these phenomena.

SO03

Title: Evaluation of a 25-gene panel in patients with suspected Lynch syndrome: preliminary results from the FAMOSA study
Aim: The role of multigene panels for hereditary cancer risk assessment is yet to be established. We aimed at describing the prevalence of cancer predisposition gene mutations identified by a multigene panel in individuals with suspected Lynch syndrome (LS).

Method: We performed germline analysis with a next-generation sequencing 25-gene-panel (Myriad myRisk™ Hereditary Cancer) using DNA from 95 patients with suspected LS (endometrial cancer <50 y.o. and/or fulfillment of revised Bethesda criteria) from Nov-2014 through March-2015 within the FAMOSA study. We classified all identified germline variants for pathogenicity and calculated the prevalence of pathogenic mutations and variants of uncertain clinical significance (VUS). We analyzed data on patients’ personal and family history of cancer.

Results: We included 95 patients (female:46(48.5%), mean age:48.6±12); 8(8.5%) with endometrial cancer and 87(91.5%) with colorectal cancer. Multigene panel testing identified 20(21%) patients with LS syndrome mutations (BMLH1, 7MSH2, 4MSH6, 1PMS2) and 1(1%) with a mutation in BRCA2 in a 35 y.o. woman without personal/familial history of breast/ovarian cancer. In patients diagnosed with mutations in the MMR genes and prior molecular screening (n=9), two displayed MMR proficiency and 5 patients had a negative prior genetic result by conventional techniques.

Conclusion: In individuals with suspected Lynch syndrome, multigene panel testing identified unexpected high-penetration mutations in 1% of cases. Parallel sequencing also detected a meaningful number of cases with previous false negative results.

SO04
Title: Targeted NGS of 22 mismatch repair genes identifies LS families
T. Liseth-Palmer1,2, D. Bauer1, W. Sjursen3, T. Evans1,2, M. McPhilips6, A. Piroietti3, G. Otton1,4, A. Spigelman1,2,10, R. Scott1,2,10

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Aim: Causative germline mutations in mismatch repair (MMR) genes can only be identified in families with a clinical diagnosis of the inherited colorectal cancer (CRC) syndrome hereditary nonpolyposis colorectal cancer (HNPPC)/Lynch syndrome (LS). Identification of these patients are critical as they are at substantially increased risk of developing multiple primary tumours, mainly colorectal and endometrial cancer (EC), occurring at a young age. This demonstrates the need to develop new and/or more thorough mutation detection approaches.

Method: Next-generation sequencing (NGS) was used to screen 22 genes involved in the DNA MMR pathway in constitutional DNA from 14 HNPPC and 12 sporadic EC patients, plus 2 positive controls. Several softwares were used for analysis and functional annotation.

Results: We identified 5 exonic indel variants, 42 exonic nonsynonymous single-nucleotide variants (SNVs) and 1 intronic variant of significance. Three of these variants were class 5 (pathogenic) or class 4 (likely pathogenic), 5 were class 3 (uncertain clinical relevance) and 40 were classified as variants of unknown clinical significance.

Conclusion: In conclusion, we have identified two LS families from the sporadic EC patients, one without a family history of cancer, supporting the notion for universal MMR screening of EC patients. In addition, we have detected three novel class 3 variants in EC cases. We have, in addition discovered a polygenic interaction which is the most likely cause of cancer development in a HNPPC patient that could explain previous inconsistent results reported on an intronic EX01 variant.

SO05
Title: Selective and universal screening strategies for Lynch syndrome: a perspective from the Royal Marsden Hospital


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Aim: Despite colonoscopic surveillance recommendations, interval colorectal cancer (ICC) remains frequent in Lynch syndrome (LS) patients. We evaluated the impact of an optimized screening program within a dedicated network.

Method: All LS patients in our institution were prospectively offered a colonoscopy surveillance program. Starting at the age of 20 years old, colonoscopy with indigo carmine chemoendoscopy was scheduled every 2 years. Colonoscopies were considered as optimal when all quality criteria were met. We analyzed colonoscopies’ quality, polyp detection rate (PDR), adenoma detection rate (ADR) and ICC detection rate (ICDR).

Results: Between January 2010 and January 2014, 134 confirmed LS patients were included (mean age = 47.4 years [21-78] and mutations: MLH1=41%, MSH2=43%, MSH6=14%, PMS2=2%). A total of 422 colonoscopies were analyzed. Optimal colonoscopies were more often performed after program inclusion 172/217 (79%) vs 87/205 (42%) before inclusion (p<0.0001) and 92/134 (68%) had all their screening colonoscopies optimal after inclusion vs 44/119 (35%) before (p<0.0001). Comparing optimal to non-optimal colonoscopies, ICC was 1.259 (0.39%) vs 7.163 (4.29%) (p=0.006), PDR was 163/259 (62.9%) vs 58/163 (35.5%) (p<0.0001) and ADR was 72/259 (27.7%) vs 39/163 (24%) (p=0.38).

Conclusion: An optimized colonoscopic surveillance program in LS patients within a dedicated network improves colonoscopic screening quality and lesion detection rates and may reduce ICC.

SO08
Title: Identification of novel causal genes of hereditary colorectal cancer

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Aim: Inherited factors account for over 20% of all colorectal cancers (CRC), but less than 6% can be explained by rare high-penetration mutations in known genes. We aimed at identifying novel hereditary cancer genes by performing whole-exome sequencing (WES) in individual hereditary CRC families.

Method: WES was performed in 3 Amsterdam-positive families (3 CRC-affected members were studied per family). Validation studies in familial cancer cases and in silico analysis were performed as appropriate.

Results: One family harbored two mutations in the MUTYH gene –known polyposis (recessive) gene-, one recurrent in the European population and the other novel, for which functional studies demonstrated its deleterious nature. The family showed an atypical phenotype for MUTYH, characterized by the absence of polyps, apparent autosomal dominant inheritance, and presence of a mismatch repair-deficient tumour. The study of the second family allowed us to identify a novel hereditary CRC gene, FAN1. Functionally relevant mutations were identified in almost 3% of Amsterdam-positive families. The third family carried mutations in two candidate genes: a splice-site mutation in a tumour suppressor gene, and a missense mutation in a previously proposed cancer-predisposing gene.

Conclusion: In summary, the analysis of exomes in individual high-risk families allowed us to identify two novel genes for hereditary CRC, as well as mutations in previously known or previously proposed CRC-predisposing genes.
Title: Elucidating the molecular basis of MSH2-deficient tumors in Lynch syndrome suspected patients

G. Vargasi1, E. Dámaso2, T. Pons2, J. del Valle2, S. Iglesias1, Á. Velasco3, A. Solanes4, A. Valencia1, J. Brunet2, L. Felibarbaldi2, C. Lázaro2, M. Navarro2, M. Pineda1, G. Capellá1

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Aim: Mutations in POLE and MUTHY and mismatch repair (MMR) double somatic events were found in a proportion of Lynch-like syndrome (LLS) patients. The aim of this study was to elucidate the molecular basis of MSH2-deficient LLS cases by means of a comprehensive analysis of colorectal cancer (CRC) associated genes at germline and somatic level.

Method: Eighteen LLS individuals harboring MSH2-deficient tumors were included. A customized NGS subexome panel including CRC associated genes was designed. PBL and matched FFPE DNA from available tumors were analyzed.

Results: Predicted pathogenic germline heterozygous variants in MSH2, BUB1, SETD2, FAN1 and MUTHY were identified in 6 of the 18 (33%) cases analyzed. The somatic analysis of tumors demonstrated the presence of MMR double somatic hits, apparent MSH2 loss of heterozygosity and coexistence of double somatic mutations in other MMR and/or POLE/POLD1 genes. Also, somatic mutations in other cancer genes coexisted with the above mentioned alterations. In all, alterations putatively responsible for LLS were detected in 60% of the cases.

Conclusion: The evaluation of germline and somatic mutational status of CRC-associated genes by means of a subexome panel is useful for the elucidation of the molecular basis of LS-suspected cases. Funding: SAF2012-33636, AECC, 2014GR388.

Title: Identification of genetic biomarkers for clinical management of familial colorectal cancer

M. Dominguez-Valerín1, S. Nakken2, D. Vodák2, P. Mäller1,2,3, E. Hovig1,2,2

Please see Mallorca Group website for Author Institutions

Aim: To identify inherited genetic factors that influence biological and clinical characteristics of CRC developed in high-risk patients.

Method: The hereditary cancer registry from the Norwegian Radium Hospital was used to identify non-related high-risk CRC individuals (n=51) with colorectal cancer-predisposing mutations in MLH1, MSH2, MSH6 and PMS2 genes that had been found by Sanger DNA sequencing. Forty-four cancer genes reported to carry risk of familial breast or CRC were selected and analyzed by an amplicon-based assay for targeted resequencing (TSCA, Illumina, Palo Alto, CA).

Results: We identified 2 variants with a predicted deleterious mutation in CHEK2 (i.e. p.I157T and c.319+2T>A), and 7 variants of uncertain significance in CHEK2, MLH1, MSH2, MUTHY and NOTCH3. The minor allele frequencies (MAF) in these variants were very low or no frequency data have been reported. Pathogenicity prediction algorithms were applied and suggest that 6/7 (87%) of these variants were probably pathogenic and should be further studied with segregation analyses and in vitro testing. In sum 8/51 (16%) of the patients tested had pathogenic or probably pathogenic variants described.

Conclusion: Our study provides new information on variants on genetic loci that may affect the risk of developing cancer in these patients and their families.

Title: Endoscopic surveillance of the upper gastrointestinal tract in Lynch syndrome patients

R. Camblor1,2,3, P. van Heteren1,4, S. Aretz1,4, D. Pantelic1,2,4, C. Strassburg1,4, J. Nattermann1,4

Please see Mallorca Group website for Author Institutions

Aim: Besides increased risk for the development of colorectal cancer Lynch syndrome is also associated with an increased life-time risk for the development of gastric (up to 8%) and small bowel cancer (up to 12%), respectively. However, the diagnostic performance of esophagogastroduodenoscopy in surveillance of Lynch syndrome patients has not yet been studied and, thus, has been analyzed in the present study.

Method: Between 01/2006 and 02/2016 Lynch syndrome patients with a proven germline mutation in a mismatch repair gene were examined by esophagogastroduodenoscopy.

Results: A total of 140 patients with proven germline mutation (55 MLH1 (39%), 69 MSH2 (49%) and 16 MSH6 (12%)) were enrolled into our study. Mean age was 48 years (27-78 years). During endoscopic examination two gastric adenomas (1.4%) and one gastric cancer were found (0.8%). In one patient duodenal cancer as well as two adenomas were found. In addition, a duodenum-infiltrating pancreatic cancer was detected in one patient. Finally, 14 patients (10%) were found to display a helicobacter pylori infection.

Conclusion: Endoscopic surveillance of the upper gastrointestinal tract revealed pathologic findings in a relevant proportion of Lynch syndrome patients. Further prospective studies are needed.

Title: Colon polyps prevention and associated gut microbiota changes in a colorectal cancer animal model fed with functional meat foods containing prebiotics

J. Fernández1, E. Ledesma2, E. Milán3, P. Costa3, J. Monte2, P. Martínez-Cambor1, V. Varela3, A. Suárez2, C. Villar1, F. Lombó1

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Aim: Diet is an important environmental factor for development of colorectal cancer. We try to demonstrate if daily consumption of the prebiotic fiber inulin is able to reduce occurrence of colorectal polyps in a chemical induced animal model for colon cancer (azoxymethane 10 mg/kg combined with DSS 3%).

Method: Two different functional meat matrices have been developed: cooked ham (HAM, containing 10% inulin) and traditional chorizo sausage (TCS, containing 15.8% inulin). These functional meat foods were given to experimental animal cohorts, together with conventional rat feed. An absolute control diet (only rat feed) and two experimental control diets (feed plus normal meat matrices) were also included.

Results: After the 17 weeks study, animals were sacrificed and colons examined. Functional meat products cohorts showed increased levels of intestinal short chain fatty acids, 48.94% less tumours and 57.45% less tumour mucosal area than control groups. Microbiome analyses also showed a clear modification in the case of functional diet cohorts, with a clear increase of diverse bacterial groups belonging to Bacteroidetes and Proteobacteria phyla.

Conclusion: The prebiotic fiber inulin is able to drastically reduce the appearance and extension of colon polyps in this animal model, producing big changes in the colon microbiome composition.

Title: Renal cell carcinoma in Lynch Syndrome: a preliminary report from a Proteusica group collaborative study

M. Calichia1, T. Seppala2, J. Mecklin1, F. Hes1, M. Nielsen4, G. Evans2, E. Holinski-Feder1, M. Morak1, B. Rojer-Pokora2, M. Pineda1, G. Capellà1, L. Sunde1, C. Therkildsen2, P. Mäller1, E. Lucci-Cordisco1, M. Genuardi1

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Aim: Lynch syndrome (LS) is associated with increased risk of several extraintestinal cancers including renal cell cancer. It is not clear whether LS patients are also at increased risk of renal cell carcinoma (RCC).

Method: In order to determine if there is a link between RCC and LS, we have started a collaborative European study to collect information on the clinical, pathological, molecular and immunohistochemical characteristics of RCC associated with LS.

Results: So far, data on 35 cases have been accrued, with the following results: 17 males, 18 females; mean age at diagnosis 60 years (range 45-78); involved gene: 10 MSH2, 19 MLH1, 5 MSH6, 1 PM25; histology: 24 clear cell, 3 papillary type 1, 2 papillary type 1, 1 papillary type not specified; 10 cases tested for MSI, of these 7 were MSS and 3 MSI-H; all 11 cases tested for MMPR protein immunohistochemistry showed loss of MMPR protein signals: 6 MLH1 or MLH1/PM25, 3 loss of MSH2/MSH6, and 2 loss of MSH6 only.

Conclusion: These results indicate that RCC arising in the context of LS is associated with evidence of MMPR disruption (immunohistochemically loss variably associated with MSI). Further data submissions and collaborations are encouraged.

Title: Screening of 274 familial colorectal cancer patients using a multi-gene panel

M. Hansen1,2, J. Johansen3,4, B. Talseth-Palmer3,4, R. Scott5,6, L. A. Lavik7,8, A. Xavier1,2, F. Drablé1, W. Sjursen1

Please see Mallorca Group website for Author Institutions

Aim: The aim of this study was to find genetic causes of the increased cancer risk for patients fulfilling Amsterdam and/or Bethesda clinical criteria, but where no pathogenic MMR mutations have been identified in their samples. Methods: Custom HaloPlex gene panel targeting 112 genes (established and candidate CRC susceptibility genes), were used to generate libraries from 274 Norwegian and Australian patient samples. Sequencing was performed
on Illumina HiSeq 2500 or NextSeq 500.

Results: After in silico and manual filtering of the almost 14000 variants, less than 100 unique variants remained. About half of these variants were found in well-known CRC susceptibility genes, whereas half were pathogenetic and the other half VUS. The other half of the variants were found in genes where the association to CRC is yet to be clarified.

Conclusion: We found a clear pathogenetic explanation for the increased cancer risk for almost 10% of the patients. This percentage may increase if some of the identified VUS also prove to be pathogenic. This study demonstrates the power of using panel based screening, rather than testing one gene after the other by Sanger sequencing.

SO30

Title: Compliance and impact of colonoscopy in familial adenomatous polyposis and MYH-associated polyposis C. Guillén-Ponce1, M-T. Salazar-López1, B. Peñas1, J. Solera1, P. Martínez1, V. Pachón-Olmos1, R. Ferreiro1, J. Earl1, M-I. Humanes1.

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Aim: The aim of this study was to determine the compliance and impact of colonoscopy follow-up in individuals with familial adenomatous polyposis (FAP) and MYH-associated polyposis (MAP), in terms of the detection of cancer.

Method: Between 02/12/2011 and 12/31/2015, 27 individuals underwent regular follow-up. All patients met clinical criteria of FAP or MAP, and underwent a genetic study of APC or MUTYH genes. 13 had a pathogenic mutation; 7 had variants of unknown significance (VUS); 7 had a non-informative result. Compliance and results of the colonoscopies were evaluated annually.

Results: Of the 27 individuals, 9 (33.3%) did not perform the recommended screening. The reasons were: 3 (11.1% of 27) physician didn’t prescribe the tests; 3 (11.1%) due to the patient; 3 (11.1%) other reasons. Out of 9 patients that don’t complete the colonoscopies, there was a lost of contact in 6 of those patients (22.2% of 27). During the follow-up period, one patient was diagnosed of rectal cancer.

Conclusion: Almost one third of the patients with FAP and MAP do not meet the recommended colonoscopies. The most important limitation for compliance is either physicians or patients. 22% of individuals leave the screening. Colonoscopy can detect colorectal cancer during the follow-up.

SO31

Title: Do we still need surgery for treating small bowel polyps in Peutz-Jeghers Syndrome? A 13-years follow-up cohort.

E. Samaha1, S. Scialom1,4, G. Rahimi1, J. Edery1, C. Savale1, C-A. Cuenod1,2,4, J-M. Canadí1, G. Malatum1, P-L. Puig1,4, C. Cellier1,4. On behalf of PRED-Idf Network.

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Aim: Polypectomy during endoscopy is the first line treatment of small bowel (SB) polyps in Peutz-Jeghers syndrome (PJS). Our aim was to assess the need for surgery in a PJS cohort after joining a specialized screening network.

Method: Between 2002 and 2015, 25 PJS patients (F/M = 11/14, mean age=36, mean follow-up 60 months [2-139]), were screened every 2 to 3 years and polypectomy using device-assisted enteroscopy (DAE) was attempted each time a polyp > 1 cm was detected. In case of failure or incomplete resection, intra-operative enteroscopy (IOE) or surgical resection was performed.

Results: 23/25 patients (92%) had 42 capsule endoscopies, and 14/25 patients (57%) had 23 magnetic resonance enterography (MRE) or magnetic resonance enterography (CTE). A total of 50 DAE (42 per-oral and 8 per-anal) in all patients allowed the resection of 216 polyps. Endoscopic treatment was complete in 19/25 patients (76%). IOE was performed in another 4/25 patients (16%) allowing the resection of 58 polyps and a complete treatment in 92% of patients. SB surgical resection was finally indicated in 2/25 patients (8%), compared to 64% before screening (p=0.001).

Conclusion: DAE with IOE is sufficient in 92% of PJS patients for removing SB polyps. Surgical resection has become rare, but remains a good alternative for difficult cases.

SO33

Title: Assessment of MUTYH Associated Polyposis (MAP) phenotype in order to refine testing guidelines

K. Simon, S. Loughlin, L. Jenkins, L. Side

Great Ormond Street Hospital

Aim: To review our genetic testing criteria for MAP and improve understanding of the MAP phenotype.

Method: We reviewed patient records in those whom we requested MAP testing from 01/01/2009 to 31/12/2014. We documented the number and type of polyps and age of polyp/bowel cancer diagnosis.

Results: Common Caucasian or Asian mutation testing or a full screen was completed in 122 families. 7/122 (5.7%) patients were MUTYH compound heterozygotes for pathogenic mutations, 1/122 (0.8%) had a homozygous VUS, 2/122 (1.6%) were carriers and 105/122 (86%) had no mutations identified. 7/122 (5.7%) had another condition identified. 6/8 patients with two mutations/variants had at least one rare mutation. These 8 patients had 6 to ~30 polyps identified; mostly low grade adenomas. Average age of polyp diagnosis was 54; cancer diagnosis 55.

Those without a mutation had a broader range of polyp type. Average age of polyp/cancer diagnosis was 45. Mutations were not found in any patients with serrated polyps or with isolated bowel cancer <35 years without polyps.

Conclusion: We no longer test for MAP in isolated colorectal cancer cases <35 years or patients with ≤5 adenomas. We will offer a full screen if phenotype is classical. Serrated polyps appear to represent a phenotype distinct to MAP.

SO34

Title: A reassessment colonoscopy increases the diagnostic yield for serrated polyposis syndrome in a faecal immunochemical test (FIT)-based colorectal cancer screening population

L. Rivero-Sanchez1, 2, M. Lopez-Ceron1, 3, S. Carballal1, 3, M. Moreira1, 3, B. Bessa1, A. Serradasanfer1, 2, A. Pozo1, J. M. Augé1, T. Ocaña1, M. L. Leoz2, M. Cuatrecasas1, J. Grañ1, J. Lluch1, A. Castells1, F. Balaguer1, M. Pellissié1.

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Aim: Serrated polyposis syndrome (SPS) is underdiagnosed despite being a high risk condition for colorectal cancer. Surveillance strategies for patients with serrated lesions (SLS) remain controversial. We aim to evaluate the yield of a Reassessment Colonoscopy (RC) to detect SPS in patients with proximal-SLS.

Method: Retrospective study of all individuals with ≥5 proximal or ≥2 sessile serrated polyps ≥35 years or patients with <5 adenomas. We will offer a full screen if phenotype is classical. Serrated polyps appear to represent a phenotype distinct to MAP.

Results: From 196 patients, 71 underwent RC in 11.9±1.7 months. RC helped to diagnose 20/71 (28%) new SPS patients. Independent features associated with SPS diagnosis were the presence of ≥5 proximal-SLS (OR=4.01[1.20-13.45]; p=0.024) or ≥2 sessile serrated polyps ≥10mm (OR=6.35[1.40-28.81]; p=0.016) at index-colonoscopy and the use of BE-HD at RC (OR=4.99[1.11-22.36]; p=0.036).

Conclusion: A RC using BE-HD substantially improves SPS detection in individuals with proximal SLSs from a FIT-based screening-program. Having ≥5 proximal-SLSs or ≥2 sessile serrated polyps ≥10mm at index-colonoscopy could be thresholds to indicate a RC. Further prospective studies are required to validate these results and adjust surveillance recommendations in patients with SLSs.

SO35

Title: DNA-diagnostics of Familial Adenomatous Polyposis and Peutz-Jeghers syndrome among Russian patients

N. Pospekhova, V. Shubin, I. Sachkov, A. Kuzminov, V. Kashnikov, Y. Sheplygin, A. Tsukanov

State Scientific Center of Coloproctology, Moscow, Russia

Aim: Familial Adenomatous Polyposis (FAP) and Peutz-Jeghers syndrome (PJS) are responsible for 1% of colorectal cancer cases. FAP is caused by germline mutations in APC gene. PJS is caused by germline mutations in STK11 gene. Mutations were not found in any patients with serrated polyps or with isolated bowel cancer <35 years without polyps.

Results: We no longer test for MAP in isolated colorectal cancer cases <35 years or patients with ≤5 adenomas. We will offer a full screen if phenotype is classical. Serrated polyps appear to represent a phenotype distinct to MAP.
with FAP and PJS were 72% and 71% respectively. Twenty two mutations in both genes are described for the first time.

SO36

Title: Incidence of colonic neoplasia in patients with Serrated Polyposis Syndrome who undergo endoscopic surveillance: a multicenter study


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**Aim:** Due to the increased colorectal cancer (CRC) risk in patients with Serrated Polyposis Syndrome (SPS), annual surveillance colonoscopy is currently advised. This multicenter-study was aimed at describing the risk of advanced lesions in SPS patients undergoing surveillance and identifying which factors could predict neoplasia development during follow-up

**Method:** From March 2013 to April 2015, 296 patients who fulfilled criteria I and/or III for SPS were retrospectively recruited at 18 centers. We selected patients in which a successful clearing colonoscopy was achieved and underwent endoscopic surveillance. Advanced neoplasia (AN) was defined as CRC, advanced adenoma or advanced serrated polyp (SP >1 cm and/or with dysplasia). Cumulative incidence (CI) of AN was calculated by Kaplan-Meier survival analysis. Cox-regression analysis was performed to identify independent predictors of AN development.

**Results:** In 158 SPS patients (mean age: 53 years, 45% female) a total of 321 surveillance colonoscopies were performed (median:2, range:1-7). Four CRC were diagnosed during surveillance (3-year cumulative risk: 3%). Three-year cumulative incidence for AN was 43.7%. Fulfilling both I+III WHO criteria and the presence of advanced-SP at baseline colonoscopy were independent predictors of AN development (OR=2.1,95%CI:1.2-3.8, p=0.008 and OR=2.38,95%CI:1.2-4.0, p=0.006, respectively). During follow-up, 10(6.3%) patients were referred for surgery due to an invasive CRC(n=4, 2.5%) or severe polyposis(n=6, 3.8%)

**Conclusion:** Patients with SPS have a substantial risk of developing AN under endoscopic surveillance, whereas CRC incidence is low. Close endoscopic surveillance in SPS patients is essential, especially in those with risk factors at baseline colonoscopy

**Poster Author Abstracts**

**P7**

Title: Capsule endoscopy and magnetic resonance enterography for small bowel neoplasia screening in Lynch Syndrome


Please see Mallorca Group website for Author Institutions

**Aim:** To determine the prevalence/incidence of small-bowel neoplasia in patients with Lynch syndrome (LS) after registration to a follow-up specialized network.

**Method:** Patients with genetically proven LS were included in the PRED-Idf network, and were offered a small bowel cancer (SBC) screening using capsule endoscopy (CE), magnetic resonance enterography (MRE) or CT enteroclysis (CTE) every two years. Data were collected retrospectively.

**Results:** Between January 2010 and December 2015, 139 patients (Mean age 47 years [range 23-75], M/F=55/84, mean follow-up months 50 [range 1-105]) with proven mutations were included (MLH1 37%, MSH2 46%, MSH6 14%, PMS2 2% and EPCAM 1%). In total, 136 patients underwent 256 CE procedures, 110 patients underwent 142 MREs and 5 patients 5 CTEs. Six small bowel neoplasias were detected in 5 patients: 3 adenocarcinomas (ADK) (2 in the proximal jejunum and one ileal) and 3 adenomas (one duodenal, one jejunal and one ileal). CE detected 5/6 neoplasia (2 ADK and 3 adenomas) and missed one ADK while MRE/CTE found 2 ADK and missed one ADK and 3 adenomas. Three out of the five patients were asymptomatic (One with an ADK and two with adenomas). The number needed to diagnose one neoplasia in LS patients was 28.

**Conclusion:** The prevalence of small bowel neoplasia in patients with LS was 3.6 % in general and 2.2% in asymptomatic carriers whereas the incidence was 1% per year. CE found more neoplastic lesions than MRE or CTE.

**P13**

Title: Data from 1100 families used to model investigation strategies in familial bowel cancer

A. Shaw, L. Iazz, A. Kulkarni, D. M. Ruddy, N. Sudha, V. Tripathi, M. Green, G. Norbury.

I - Genetics Service, Guy’s & St Thomas’ Hospitals, London. 2 - Molecular Genetics, Viapath, London. 3 - Histopathology, Viapath, London.

**Aim:** We established a monthly hereditary bowel cancer multidisciplinary meeting (MDM) in 2010 with input from Clinical Genetics, Histopathology & Molecular Genetics. All individuals undergoing testing for hereditary bowel cancer are discussed to decide testing strategy, interpret results and provide surveillance recommendations for relatives. Summary reports are issued. The MDM was instituted to improve governance, but has also provided a valuable dataset for audit and service development.

**Method:** The dataset was used to model the cost of different testing algorithms. The proportion of Amsterdam and Bethesda positive families in which a pathogenic MMR mutation was ultimately identified allowed comparison of strategies, including MMR gene sequencing as an initial test.

**Results:** Over 1100 families have been assessed. Of the 208 families meeting Amsterdam criteria, 12% were found to have a MMR gene mutation compared to 4% meeting Bethesda criteria. Modelling shows that for Amsterdam positive families, performing MMR gene analysis before tumour tests would cost around £1080 per family compared with £450 in converse.

**Conclusion:** For families meeting Amsterdam criteria, the excess cost of performing MMR gene analysis as the initial test may be justified by savings in time and administration. The MDM approach promotes consistent practice and facilitates audit and service development.

**P14**

Title: Compliance and impact of screening of individuals at high risk of hereditary colorectal cancer


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**Aim:** The aim of this study was to determine the compliance and impact of screening follow-up in individuals with Lynch Syndrome (LS), in terms of the detection of polyps and cancer.

**Method:** Between 02/12/2011 and 12/31/2015, 189 individuals underwent regular follow-up. All patients met Bethesda criteria. The genetic study of mismatch repair (MMR) genes was done in 75 individuals (42 had a mutation; 7 had variants of unknown significance; 26 had no MMR gene mutation). No new colon cancers were diagnosed. Two patients were diagnosed with a lung cancer and a pancreatic neuroendocrine tumour, respectively.

**Conclusion:** Almost 14% of the patients do not meet the recommended screening for LS. The most important limitation for compliance is the physician. Adenomatous polyps in colon were detected by the screening but no colon cancer or other related cancers.

**P15**

Title: Diagnosis of Constitutional Mismatch Repair-Deficiency


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**Aim:** Bi-allelic germline mutations in mismatch repair (MMR) genes cause constitutional MMR deficiency (CMMRD) characterized by early-onset colorectal cancers, lymphomas or leukemias, and brain tumours. There is no satisfactory method for diagnosis because screening for mutations in MMR genes is often non-informative. MMR-deficient cancer cells are resistant to genotoxic agents and have microsatellite instability (MSI). We investigated whether these features could be used to identify patients with CMMRD.

**Method:** We examined MSI by PCR analysis and tolerance to methylating or ada a non-
experimental parameters that allowed discrimination of a series of 14 patients with CMMRD from 52 controls. We then used the same parameters to assess 23 patients with clinical but not genetic features of CMMRD.

**Results:** Among 23 patients suspected of having CMMRD, 6 had MSI and tolerance to methylation (CMMRD highly probable), 15 had neither MSI nor tolerance to methylation (unlikely to have CMMRD), and 2 were considered doubtful.

**Conclusion:** We identified parameters, based on MSI and LC tolerance to methylation, that detected patients with CMMRD vs controls with 100% sensitivity and specificity. These features could be used in diagnosis of patients.

P16
**Title:** Constitutive mismatch repair deficiency syndrome: clinical description in a French cohort


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**Aim:** Constitutive mismatch repair deficiency syndrome (CMMRD) is a childhood cancer predisposition syndrome involving biallelic mutations of MMR genes.

**Method:** We performed a retrospective review of 31 cases of CMMRD from 23 families diagnosed in French genetics laboratories in order to describe clinical and genetics characteristics, treatment and outcome of malignancies.

**Results:** 67 tumours were diagnosed: 17 hematologic malignancies, 22 brain tumours, 25 lymph node-associated malignancies, and 3 other tumours. Median age of onset of first tumour was 6.98 years [1.23-33.53]. 23 patients had NF1-unrelated CALMs or hypopigmented macules and 4 had brain malformative features. Adenomas were found in all 16 patients who have had colonoscopy.

18 patients died, 7 due to the primary tumour. Median survival after diagnosis of the primary tumour was 23 months [0.26-213.2]. Among the patients who survived, 20 developed a second malignancy. A familial history of LS was found in only 6 families, and consanguinity in 43% of cases. PMS2 mutations (18 patients) were more frequent than mutations of MLH1 (4), MSH2 (3) and MSH6 (6).

**Conclusion:** CMMRD is a severe condition with multiple malignancies in childhood. Its rarity warrants international collaboration to define diagnosis criteria and guidelines for surveillance and prevention in order to decrease tumour-related mortality.

P17
**Title:** Can microsatellite instability be a useful parameter for tailoring adjuvant chemotherapy? A case report.

D. Barana1, A. Vie12, M. Padovani13, C. Forni14, F. Lo Vullo15, F. Giurde16, M. Pantalena17, C. Finci18, A. Scarpa19, C. Olani20

Supported by Fondazione Peretti

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**Aim:** MSI colorectal cancers shows better stage-independent prognosis than MMR-deficient tumours and appears to be resistant to fluorouracil-based treatment. We present the case of DD, a 39 years old man, who came to our observation in February 2010 after a right hemicolectomy.

**Method:** The pathology report showed a moderately differentiated adenocarcinoma of the colon with focal infiltration of the pericolic fat, peritumoral presence of inflammatory reaction with lymphoid aggregates and absence of vascular invasion and of perineural infiltration. All the 36 examined nodes showed negative for metastatic involvement (T3NM0). The shared decision of whether to opt for adjuvant chemotherapy with fluorouracil resulted difficult. The young age, the right site of the neoplasia and the histological type prompted us to ask for a MSI analysis which showed MSI-H and deficiency for the expression of MSH2.

**Results:** The mutational analysis revealed an exon 8 deletion in MSH2. We proposed only surveillance/follow up to DD and the screening of the family has been carried out. The father resulted gene carrier and until now has developed two polys.

**Conclusion:** In clinical practice MSI may be helpful in the choice of adjuvant therapy in selected cases.

P18
**Title:** Molecular analysis of unclassified variants in MLH1 and MSH2 genes

F. D’Ippolito2, R. Icardo3, G. Battista Rosso1, M. De Rosa1, P. Izzo1

1 - Dep Molecular Medicine and Medical Biotechnology, University of Naples, "Federico II", Italy, 2 - Endoscopy Unit Research and Care Institute "Pascale" Napoli, Italy

**Aim:** In this study, we have tested two unclassified variants (UVs) detected in the 3 untranslated regions (3’UTR) of the MLH1 and MSH2 genes (c.30_32delTTC in the MLH1 gene and c.226A>G in the MSH2 gene).

**Method:** The multivariate analysis of this variants by in silico analysis, quantification of mRNA and protein level and functional luciferase assay was performed in order to assess the correlation with the disease phenotype.

**Results:** For UV in MSH2, this multivariate analysis showed increased mRNA and protein levels, as also confirmed by a functional luciferase assay. In silico analysis was performed for prediction of miRNA target sites (TargetScan and MiRanda) and transcriptional regulation factor binding sites (TRANSFAC). The region in which falls the mutation is identified as a putative target point of two miRNAs (hsa-mir-137, hsa-miR7953p), and some trans-acting protein factors, known also as transcriptional repressors.

**Conclusion:** Therefore, we hypothesized that this variant could prevent the binding of these factors with the MSH2 3’UTR leading to unregulated expression of the MSH2 gene. In agreement with several literature data showing a deleterious effect derived from overproduction of MMR protein3, it is conceivable that the variant c.226A>G in the MSH2 gene has a pathogenic role in the development of the disease.

P19
**Title:** Identification of germline FAN1 variants in MSH2-deficient Lynch-like syndrome patients


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**Aim:** In about 55% of individuals harboring mismatch repair (MMR) deficient tumours, germline mutations of MMR genes are not identified, being referred as Lynch-like syndrome (LLS) patients. Recently FAN1 germline mutations have been associated to MMR proficient colorectal cancer (CRC) and pancreatic cancer predisposition. The aim of this study was to determine whether germline FAN1 play also a role in LLS.

**Method:** Germline analysis of FAN1 was performed in 30 LLS unrelated individuals showing MSH2 loss of expression in tumours. Pathogenicity assessment of identified variants was performed using computational and cosegregation analyses.

**Results:** We identified three rare missense variants in 3 unrelated LLS patients (10% of the studied sample). Two of the 3 identified variants, c.434G>A [p.(R145H)] and c.1129C>T [p.(R377W)], cosegregated with tumourigenic features. The remaining variant, c.1856T>A [p.(M619K)], for which no cosegregation data was available, was classified as likely pathogenic based on functional and computational analyses.

**Conclusion:** The obtained results suggest the involvement of the FAN1 gene in MSH2-deficient LLS.


P20
**Title:** Characterization of the clinical phenotype associated with the POLD1-Leu747Pro mutation

E. Martín Tomás2, A. Castillejo2, E. Hernández Illán3, M. I. Castillejo2, B. Sánchez Heras4, L. L. Soto5

On behalf of the Hereditary Cancer Program of the Valencian Region

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**Aim:** We aimed to explore the clinical phenotype associated with a specific POLD1 mutation found in the Valencian Region, in order to propose an appropriate surveillance program to these families.

**Method:** Three apparent unrelated families carrying the POLD1-Leu747Pro mutation were included in this study. Clinical and molecular data from members of these families were collected. Penetration estimates as global and stratified by age and sex was calculated. Analysis of the clinical expressivity in carrier individuals was also approached.

**Results:** We collected data from 24 genetically tested individuals from the only three families reported to date with the POLD1-Leu747Pro mutation (16 carriers and 8 non-carriers). Eleven tumours diagnosed in eight carrier patients (6 CRC, 3 endometrial cancers, a small bowel tumour and an esophageal tumour) and oligo/lymphoplasies (< 3 adenomas) in another two patients were considered. The median age of cancer onset for all POLD1 mutation carriers was 46 years (23-58 years). The observed penetrance was 50% (40% in males and 54.6% in females). The cumulative risk of cancer at age of 50 was 38.5%.
Conclusion: The clinical phenotype for this mutation is similar to that in Lynch syndrome and consequently, the recommended surveillance might be similar. Phenotype’s analysis by specific mutations might offer more accurate predictive information.

P24
Title: Improving colonoscopy quality through effective training

L. Pedersen1, J. Bernstein1, K. Lindoff-Larsen1.

1 - Aalborg University Hospital, Department of Surgery. 2 - Aalborg University Hospital, NordSim.

Aim: There is a correlation between Adenoma Detection Rate (ADR) and missed cancers. The effect of surveillance colonoscopies is dependent on optimal ADR, low complication rates and a high degree of compliance. A refined technique with minimal discomfort is essential. In Denmark surgeons traditionally perform screening colonoscopy. Surgical training programs, however, pay little attention to colonoscopy. There is an option to train on simulators, but clinical supervision is often minimal, leading to self-taught techniques.

Method: A project oriented approach to improve quality at multiple levels including consensus on technique, training programs for both trainers and trainees and exploration of the patient’s perspective. We initiated a program for trainees with a personally assigned trainer and progress evaluation using direct observation and simulator test cases. Specialists were required to participate in a trainers’ program to be eligible as supervisors.

Results: The training programs are successfully running. Data on learning curves, patient experience and essential quality parameters are pending analysis.

Conclusion: Optimal colonoscopy technique is critical for the outcome of surveillance. Insufficient attention has been paid to colonoscopy training. We aim to remedy this, and to measure the effect on essential quality parameters before and after the intervention.

P25
Title: Preliminary Epidemiological results from the first four months of a pilot interdisciplinary model in identification of GI syndromic neoplasia


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Aim: BACKGROUND: The best interdisciplinary science comes from the realization that there are pressing questions that cannot be adequately addressed by people from just one discipline. Syndromic cancer identification is one of the main interdisciplinary goals in medicine.

AIM: To apply interdisciplinary clinical work revealing the growth and influence of interdisciplinary research in high-risk patients for syndromic colorectal, gastric and pancreatic cancer. This abstract presents epidemiological results based on analysis of early scientific data returned from the first four months of a interdisciplinary model in identification of GI syndromic neoplasia.

Method: A single centre, multidisciplinary team composed by a geneticist, a surgeon, an oncologist and a pathologist is involved in the patients enrollment and decision process. The project include all individuals who have at least two first-degree relative who developed pancreatic, colorectal and gastric cancer. We propose an initial encounter contact phase with a geneticist in order to better define if the disease has a syndromic inheritance or not. The second summary phase is performed by a gastroenterologist together with the surgeon, oncologist and pathologist in order to provide all the options and decisions for the next clinical diagnostic steps.

Results: Analysis of early epidemiological data returned from the first four months of the interdisciplinary model in identification of GI syndromic neoplasia has demonstrated: 60% of the patients (n=42) were sporadic neoplasia. 22% (n=15) were Lynch syndromes, 3 (4%) patients were affected by familial polyposis and 5 patients (4%) were affected by attenuated familial pancreatic cancer and 2 (3%) patients were affected by familial gastric cancer.

Conclusion: Syndromic GI tumours are described as less than 20% of all GI tumours. An interdisciplinary approach to GI cancers can better identify syndromic patients driving researchers to ask questions and solve problems that have rarely come up before.

P26
Title: Practical therapeutic applications of ferromagnetic carbon nanotubes in colon cancer treatment


1 This work was supported by grant NCBR no. PBS2/AS/31/2013

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Aim: Nanotechnology may develop a novel therapeutic strategies for selective cancer treatment. The main goal of the study was to develop the method for hyperthermic selective destruction of human colorectal cancer cells using ferromagnetic carbon nanotube (Fe-CNTs).

Method: The chemical vapour deposition (CVD) method was used to produce nanotubes followed by their biochemical functionalization. Human colorectal cancer cells HT-29 (ATCC) and normal colon mucosal epithelial cells NCM460 (InCell) were examined in vitro. In order to evaluate biological ability, the cytotoxicity of Fe-CNTs were examined using by resazurin toxicology assay (Sigma-Aldrich).

Results: Cells were treated with Fe-CNTs at the final concentration range of 0.05-5 mg/ml. We did not find cytotoxic effect on the viability of cells treated with ferromagnetic modified CNTs (P>0.05). It was also estimated no statistical differences in the sensitivity of colon cancer HT-29 cells in comparison to control cells after using Fe-CNTs. Future, Fe-CNTs with folic acid (FA) addressed to colon cancers expressing FA receptors will be used.

Conclusion: Therefore, we conclude that Fe-CNTs may be used as non-toxic ferromagnetic molecules with their practical therapeutic applications. The final result of our study would be the demonstration of the device and methodology for the Fe-CNTs hyperthermic treatment of colon cancer.

P27
Title: Chromoendoscopy in combination with random biopsies does not improve detection of gastric cancer foci in CDH1 mutation positive patients

R. Hühnburg1, T. Marwitz1, C. van Heteren1, T. J. Weismüller1, J. Trebicika2, M. Adam3, S. Arezti2, A. Perez Bouza2, D. Pantelis2, J. C. Kalf1, H. Nattermann1, C. P. Strassburg3.

*both authors contributed equally; § shared senior authorship

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Aim: Hereditary diffuse gastric cancer (HGGC) accounts for 1-3% of gastric cancers worldwide. Patients with proven CDH1 mutation are advised to undergo prophylactic total gastrectomy (PTG) as current endoscopic surveillance protocols often fail to detect microscopic disease. Here, we studied the diagnostic performance of pan-gastric chromoendoscopy using indigo carmine combined with targeted and multiple random biopsies.

Method: Patients with a proven CDH1 germline mutation were examined using high-resolution white-light endoscopy and pan-gastric chromoendoscopy with indigo carmine combined with targeted and a minimum of 30 random biopsies prior to PTG. Postoperative histopathology was compared with endoscopic findings.

Results: Eight CDH1 germline mutation carriers underwent upper gastrointestinal endoscopy. One patient had to be excluded from further analysis due to violation of the endoscopy protocol. In the remaining seven patients 44 targeted (6.3/patient) and 225 random (32.1/patient) biopsies were taken, which identified a single focus of gastric cancer in a random biopsy. In contrast, histopathology of gastroscopy specimen revealed multiple foci of gastric carcinoma in 6 of 7 patients (86%) with a total number of 27 cancer foci.

Conclusion: Chromoendoscopy combined with random biopsies does not enable sensitive detection of gastric cancer foci in CDH1 mutation carriers.

P32
Title: Serrated Polyposis Syndrome: A multicentre cohort study


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Aim: To describe the clinical and pathological features of a cohort of patients with serrated polyposis syndrome (SPS), and to assess their colorectal cancer (CRC) risk.

Method: Patients enrolled in the PRED-IDF Network who met the criteria for SPS were identified, and their features collected retrospectively.

Results: Sixty-six cases of SPS were diagnosed (WHO Criteria: I = 30%, III = 49%, IIH = 21%). The mean follow-up was 49± 47 months. The median age at diagnosis was 55 years [IQR 63-38]. A mean of 3.8± 2 colonoscopies per patient were performed, with resection of 33± 27 serrated polyps and 43± 6 adenomas per patient. Twenty-three individuals (35%) had a familial history of CRC in first-degree relatives, and one patient had a familial history of SPS. No genetic defect was found in the cohort. Twelve CRC were diagnosed in 10 individuals (15%), at a median age of 56 years [IQR 59-31]; 1 before SPS
diagnosis, 9 at the time of diagnosis, and 2 during follow-up. The cumulative risk of CRC under surveillance was 3.4% at 4 years.

**Conclusion:** SPS predisposes patients and their relatives to CRC, suggesting its familial pattern. A close colonoscopy surveillance is recommended.

### P37
**Title:** POLE mutations – The growing cancer spectra and need for surveillance protocols

A. E. Sylvander, W. Sjursen, I. Bjørnevoll

*Please see Mallorca Group website for Author Institutions*

**Aim:** Background: Polymerase proofreading associated polyposis syndrome (PPAP) is a newly described colorectal syndrome and is caused by germline mutations in the POLE and POLD1 genes. Individuals with PPAP have a high risk of developing colorectal adenomas and carcinomas in several organs. Surveillance guidelines regarding management of mutation carriers do not yet exist. In this study we aim to investigate the clinical (phenotype) characteristics of this syndrome to help establish the clinical management.

**Method:** Participants from two Norwegian families with a mutation in the POLE gene were included in this study. Patient information such as mutation type, age at diagnosis, presence of polyps and cancer type was extracted.

**Results:** In the family described we observe a large phenotypic variation among the mutation carriers. In addition to colorectal adenomas, we report a broader cancer spectrum with cancer in colon, rectum, small intestine, pancreas and ovaries (bilateral). This study also reveals early onset uterine and pancreatic cancer and esophageal and gastric polyps.

**Conclusion:** The findings in this study present the broad cancer spectrum and complexity of clinical management in PPAP. This confirms the need for international surveillance protocols.

### P38
**Title:** High prevalence of benign and malignant thyroid disease in patients with familial adenomatous polyposis (FAP)


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**Aim:** Patients with FAP are at a high risk to develop colorectal cancer and other gastrointestinal malignancies. In retrospective series, an increased prevalence (0.4-2%) of thyroid cancer has been reported. Therefore, it is hypothesized that this mutation may be related to a higher risk of developing thyroid disease. Here, we studied the prevalence of pathological findings in FAP patients.

**Method:** Thyroid examination, consisting of palpation, ultrasound, and blood analysis (TSH, FT3 and autoantibodies), was offered to 67 FAP patients as part of their surveillance protocol.

**Results:** 57/67 patients (85%) agreed to undergo thyroid examination (33 women, 24 men; average age: 34 years (15-66 years)), and thus were included in our study. An APC mutation was known in 54/57 patients, the remaining patients had not been tested.

Papillary thyroid cancer was found in 3/57 (5%) patients, including two women (aged 19 and 28 years, respectively) and one man (23 years). Goiter was observed in 13 patients (23%), and autoimmune thyroiditis was diagnosed in six patients (10.5%).

**Conclusion:** Patients with FAP are at a high risk for benign or malignant thyroid disease independent of gender, which underscores the importance of regular thyroid examination in these patients.

### P39
**Title:** Somatic mutations in MUTYH-associated Polyposis (MAP)


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**Aim:** The KRAS gene is analyzed in metastatic CRC to predict the response of EGFR antagonists. The c.34G>T KRAS mutation is a transversion representing 8.8% of total KRAS mutations in sporadic CRC. An increased rate of this KRAS mutation in MUTYH adenomas or adenocarcinomas has been reported. Therefore, it is hypothesized that this mutation may be useful as a pre-screening test for MAP diagnosis and additionally may serve as a tool for classifying variants of uncertain significance at MUTYH.

**Method:** The study retrospectively enrolled 11 patients in two different centers during 2008 till 2013. After deparaffinization, tumour tissue was macrodissected from unstained slides, genomic DNA extracted out of normal tissue and polyps followed by Sanger sequencing.

**Results:** A total number of 11 unrelated patients with a known biallelic MUTYH mutation were included. In 8 patients a colectomy was performed due to the high number of polyps, in 2 patients due to colorectal cancer, one patient is under endoscopic treatment. In 24/66 adenomas a KRAS mutation was detected (18x p.G12C, 4x p.G13D, 2x p.G12V), in 3/7 hyperplastic polyps a p.G12C mutation and in one colorectal carcinoma a p.G12V mutation.

**Conclusion:** The somatic KRAS Gly12Cys mutation has been reported with a high specificity of MUTYH. In our study we can show the same mutation in most of the adenomas. We could identify further somatic mutations which needs further validation.

### P40
**Title:** Deep intronic mutations may explain unbalanced expression of APC alleles in familial adenomatous polyposis

T. Nieminen, W. Pavic et al.

*Please see Mallorca Group website for Author Institutions*

**Aim:** Familial Adenomatous Polyposis (FAP) is caused by germline mutations in the APC gene. We investigated 56 FAP families from Finland that had remained APC mutation-negative after traditional tests. Of particular interest were four families with allele-specific expression (ASE) of APC alleles.

**Method:** These families were interrogated by next generation sequencing of the whole genomes (WGS) and RNA (RNA-seq).

**Results:** RNA-seq raised the suspicion of a pseudoexon (inclusion of intronic sequence in the mRNA) in three families. A pseudoexon between exons 5 and 6 of the APC gene was present in one family and a pseudoexon between exons 10 and 11 in two families. By WGS, the exon 5-6 pseudoexon generated a cryptic splice site leading to a 127-bp intronic insertion in the APC mRNA. Two alternative genetic changes underlay the exon 10-11 pseudoexon and both created a new splice donor site leading to an identical 83-bp insertion in APC mRNA. All three pseudoexons were predicted to cause frameshifts and premature stop codons leading to APC protein truncation.

**Conclusion:** Pseudoexon mutations accounted for 3/4 families with APC-ASE in our study. We conclude that RNA-seq is an effective method to reveal pseudoexons and is worth considering in mutation-negative families.

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