Familial colorectal* cancer syndromes: The importance of registries and databases

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@ITSR_Group  
* & related
Acknowledgements

• No conflicts

• Travel support from the National Centre for Colorectal Disease, St Vincent’s University Hospital, Dublin, Ireland
Registries and Databases in Familial CRC

- Registries and Databases are complementary
- **Registries** come in different forms:
  - **Patient**, e.g. Family Registries
  - **Case**, i.e. Cancer Registries
- They can be local and national

- **Databases** are an integral component of Registries, but may also be separate
- They may be local, national or international
Registries and Databases in Familial CRC

- Registries & Databases are critical for:
  - Helping those at potential increased risk, because assessing familial risk needs information
  - Maintaining ongoing records on those affected
  - Checking records on those affected in the past
  - Rubbish in = Rubbish out
Registries and Databases in Familial CRC

• What is a Patient Registry?

• The oldest: St Marks Hospital Polyposis Registry, est. 1924

• Dr Cuthbert Dukes and his assistant Dick (later Dr) Bussey.

1958: “It would be difficult to find a more promising field for the exercise of cancer control than a polyposis family, because both diagnosis and treatment are possible in the precancerous stage and because the results of surgical treatment are excellent.”

Dr Basil Morson became the Consultant Pathologist at St Mark’s when Dr Dukes retired and, like Dr Dukes, he was fascinated by polyps. The Polyposis Registry flourished and grew.”

@PolyposisRegUK  https://www.polyposisregistry.org.uk/about/history/
Registries and Databases in Familial CRC

• What is a Patient Registry?

• “The Polyposis Registry is run by a team of specialists consisting of Colorectal Surgeons, Gastroenterologists, Nurse Practitioners, Nurse Specialists and Administrators. The team works together to ensure prompt diagnosis and surveillance of patients with or at risk of a Polyposis Syndrome.”

• Naturally, they also have close links with pathologists and geneticists!

@PolyposisRegUK  https://www.polyposisregistry.org.uk/
Registries and Databases in Familial CRC

- **What does a Patient Registry do?**
- “We look after people with a polyposis syndrome and their relatives throughout the patient journey. We also provide education for healthcare professionals and the public and actively carry out research.”
- **The patient journey** – the “rare disease odyssey”, counselling, long-term support, patient groups
- **Education** – staff, public, online resources
- **Research** – local, national, international

@PolyposisRegUK  https://www.polyposisregistry.org.uk/
## Familial Adenomatous Polyposis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chargelaigue</td>
<td>1859</td>
<td>2 isolated cases</td>
</tr>
<tr>
<td>Cripps</td>
<td>1882</td>
<td>sib pair</td>
</tr>
<tr>
<td>Smith</td>
<td>1887</td>
<td>3 sibs</td>
</tr>
<tr>
<td>Bickersteth</td>
<td>1890</td>
<td>parent &amp; child</td>
</tr>
<tr>
<td>Lockhart-Mummery</td>
<td>1925</td>
<td>&gt;2 generations</td>
</tr>
<tr>
<td>Dukes</td>
<td>1925</td>
<td>“simple tumours and cancer”</td>
</tr>
<tr>
<td>Cockayne</td>
<td>1927</td>
<td>Mendelian dominant</td>
</tr>
<tr>
<td>Dukes</td>
<td>1939</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Gardner</td>
<td>1955</td>
<td>Gardner’s syndrome</td>
</tr>
<tr>
<td>Dukes, Bussey &amp; Morton</td>
<td>1958</td>
<td>adenoma-carcinoma sequence, staging</td>
</tr>
<tr>
<td>Herera</td>
<td>1986</td>
<td>del 5q</td>
</tr>
<tr>
<td>Bodmer &amp; Solomon, Leppert</td>
<td>1987</td>
<td>linkage 5q</td>
</tr>
<tr>
<td>Fearon &amp; Vogelstein</td>
<td>1990</td>
<td>del 5q in sporadic CRCa</td>
</tr>
<tr>
<td>Kinzler, White et al.</td>
<td>1991</td>
<td>APC gene</td>
</tr>
<tr>
<td>Spirio et al.</td>
<td>1993</td>
<td>Attenuated FAP</td>
</tr>
</tbody>
</table>
Registries and Databases in Familial CRC

- St Marks Polyposis Registry predated HNPCC and Lynch Syndrome (LS)
- It has a separate Family Cancer Clinic which incorporates a Registry for LS
  - Dr Kevin Monaghan, Gastroenterologist
  - Previously the FCC Clinical Research Fellow

@StMarksFCC  https://familycancerclinic.wordpress.com/
Registries and Databases in Familial CRC

- Not all Patient Registries do all functions
- Elsewhere in the UK, other Regional Genetics Services have, or have what amounts to, a Registry
- Worldwide there are now many Registries

https://www.bsgm.org.uk/healthcare-professionals/list-of-genetic-clinics/
Registries and Databases in Familial CRC

- **Evidence base for Efficacy of Patient Registries**


    Compliance with surveillance guidance (BSG): “For FAP, 33 of 33 studies described a significant reduction of CRC incidence and mortality with registration and screening. For LS, nine of ten studies described a reduction of CRC incidence and mortality with registration and screening. Five studies (FAP, 2; LS, 3) provided evidence for complete prevention of CRC-related deaths during surveillance.”


    “… demonstrated a decreased prevalence of colorectal cancer from 60% to 27% (p<0.0001), and an increased use of colectomy from 52% to 93% (p<0.00001). The cumulative crude survival in FAP showed substantial improvement with time (p<0.00001).”


https://www.bsg.org.uk/
Registries and Databases in Familial CRC

- International Cooperation & Coordination
- InSiGHT

[Image of InSiGHT website]

https://www.insight-group.org/
https://www.insight-group.org/syndromes/
Registries and Databases in Familial CRC

- **International Cooperation & Coordination**
- **Other Patient Registries and Groups, e.g.**
  - Lynch Syndrome International: [https://lynchcancers.com/](https://lynchcancers.com/)
  - Lynch Syndrome UK: [https://www.lynch-syndrome-uk.org/](https://www.lynch-syndrome-uk.org/)
  - Denmark: [https://polypose.dk/the-danish-polyposis-register](https://polypose.dk/the-danish-polyposis-register) & [https://www.hnpcc.dk](https://www.hnpcc.dk)
  - USA, Canada, Australasia: Colon CFR [https://www.coloncfr.org/](https://www.coloncfr.org/)
Registries and Databases in Familial CRC

- **Databases**
- Essential part of Patient Registries

- **National & International**
- Compilations of local and national data
- Extremely informative
Registries and Databases in Familial CRC

- **Case Registries**
- Cancer Registries have a prime role in case confirmation and national statistics
  - Pathology
  - Genetics
- In UK, all cancer diagnostic data is collected centrally by Public Health England
  - The National Cancer Registration and Analysis Service (NCRAS)
Registries and Databases in Familial CRC

- National Cancer Registration and Analysis Service Data Protection

Information Governance Arrangements for the National Cancer Registration and Analysis Service (NCRAS) in England.

Jem Rashbass, National Director for Disease Registration, Public Health England
Fiona McDonald, Genomics Programme Manager
Tariq Malik, Lead for Office for Data Release (ODR)

Revised October 2018

The NCRAS data release register is available online at:

https://www.ndrs.nhs.uk
Vision for NCRAS in the Genomic Era

NCRAS: National Cancer Registration and Analysis Service

ENCORE Local Feeds (from NHS Trusts)

ENCORE National Feeds

Integration of genotype and phenotype data

Data Extraction

Patient ID and Tumour Data

Family history confirmation

Haematology molecular and cytogenetics Labs

Regional NHS Cytogenetics and Molecular Genetics Labs

Molecular Pathology Labs

Regional NHS Clinical Genetics Services

Precision Oncology

Cancer predisposition

ENCORE Local Feeds

ENCORE National Feeds

Somatic Mutation Data

Germline Mutation Data

NEW DATA FEEDS

Radiotherapy

Chemo-therapy

Cancer Waiting Times

ONS Deaths

PAS

Radiology

Audit

Pathology Reports

COSD / MDT

Radio-therapy

Chemo-therapy

Cancer Waiting Times

ONS Deaths

NCRAS: National Cancer Registration and Analysis Service

Courtesy: Dr Fiona McRonald, PHE
Registries and Databases in Familial CRC

- **Databases**
- **Within Patient Registries**

- **National & International**
- Compilations of local and national data
- Extremely informative
Registries and Databases in Familial CRC

- **International Databases**
- InSiGHT LOVDs
- Prospective Lynch Syndrome Database (PLSD)
- Colon CFR

Registries and Databases in Familial CRC

- **InSiGHT** Leiden Open Variation Databases
- **Variant Interpretation Committee (VIC): MMR Gene variants**
- First peer-reviewed system of variant classification, predates ACMG/AMP
- Public, Transparent, Curated and Quantitative, based on Bayesian probability


https://www.insight-group.org/criteria/

- Uses a database of prior probabilities of pathogenicity for all possible missenses
  - Calculated from evolutionary conservation http://hci-lovd.hci.utah.edu/home.php?action=switch_db

- Being mapped to ACMG as part of FDA-recognition of VIC as the ClinVar **Variant Curation Expert Panel**


Registries and Databases in Familial CRC

- **Leiden Open Variation Databases**

- **Variant Interpretation Committee (VIC): MMR Gene variants**

- **The International Reference Database for MMR Variants**
  - ~3,000 variants, of all Classes
  - ~16,000 entries

- Curator: Dr John Paul Plazzer, Royal Melbourne Hospital Foundation
  Johnpaul@variome.org

Registries and Databases in Familial CRC

- ~3,000 variants, of all Classes
- ~16,000 entries

Johnpaul@variome.org

https://databases.lovd.nl/shared/genes/MSH2/graphs
Registries and Databases in Familial CRC

- Cases of Databases working together
InSiGHT database and 100KGP

<table>
<thead>
<tr>
<th>Class</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>511</td>
<td>92</td>
<td>259</td>
<td>27</td>
<td>52</td>
</tr>
<tr>
<td>MSH2</td>
<td>494</td>
<td>78</td>
<td>235</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>MSH6</td>
<td>170</td>
<td>14</td>
<td>212</td>
<td>25</td>
<td>46</td>
</tr>
<tr>
<td>PMS2</td>
<td>60</td>
<td>11</td>
<td>34</td>
<td>6</td>
<td>31</td>
</tr>
</tbody>
</table>

| Total | 1235| 195| 740| 88 | 174|

4 x 100,000 + NHS

ClinVar

Genomics England
Registries and Databases in Familial CRC

- **Case:control comparison in gene variant interpretation**
- *MSH6* variant found by mistake (robot error) in organ donor being tested for something else - ?pathogenic
- How many UK labs have tested persons with LS-associated cancers, i.e. performed *MSH6* diagnostic tests and found this variant?
  - = 1/4300
- Checking this case reveals it to have been a case of sporadic cancer ("female age 73, sigmoid colon, MMR IHC tumour testing showed no loss of expression"), so eliminated as not LS-associated,
  - = 0/4299
- Population frequency from gnomAD = 4/102,672 non-Finnish European non-cancer controls
- Fisher’s Exact probability = 1, so odds of association = 1 – 1 = 0, i.e. this variant is not significantly increased in those with LS-associated cancers, which is evidence against pathogenicity: conditional = 0.001
- The variant’s prior probability of pathogenicity as a missense = 0.153
- The Bayesian posterior probability of pathogenicity = 0.00018, which being <0.001 = Class 1 (Benign)

With thanks to: Dr Fiona McDonald, Programme Manager - Molecular, Genomic and Research Data, National Disease Registration, Public Health England

Registries and Databases in Familial CRC

- **InSiGHT** Leiden Open Variation Databases
- **Variant Interpretation Committee (VIC):** *Adenomatous Polyposis Gene variants*
- **APC**
- **MUTYH**
- Others, e.g. *POLE, POLD1, NTHL1* etc.
- Seeking FDA-recognition as ClinVar Variant Curation Expert Panel (VCEP)
- **STK11, BMPR1A, SMAD4, GREM1** ...

Registries and Databases in Familial CRC

- **International Databases**
- InSiGHT LOVDs
- **Prospective Lynch Syndrome Database (PLSD)**
- Colon CFR

Registries and Databases in Familial CRC

• **The Prospective Lynch Syndrome Database (PLSD)**
  - Collects data on LS patients worldwide
  - On surveillance
  - On what tumours, where, when
  - Follows each individual (family irrelevant)
  - Links to the InSiGHT MMR variant database – only Class 4 & 5 variants
    - Phenotype linked to Genotype
  - Held and curated in Oslo, Norway
    - Prof. Pål Møller
    - Dr Mev Dominguez Valentin
  - Now >50,000 patient-years

• [www.PLSD.eu](http://www.PLSD.eu)  [www.lscarisk.org](http://www.lscarisk.org)

  [https://databases.lovd.nl/shared/genes](https://databases.lovd.nl/shared/genes)  [https://www.plsd.eu](https://www.plsd.eu)
Registries and Databases in Familial CRC

- PLSD

https://www.plsd.eu
### Registries and Databases in Familial CRC

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database</td>
</tr>
<tr>
<td>2016</td>
<td>Incidence of and survival after subsequent cancers in carriers of pathogenic MMR variants with previous cancer: a report from the prospective Lynch syndrome database</td>
</tr>
<tr>
<td>2017</td>
<td>Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database</td>
</tr>
</tbody>
</table>
Registries and Databases in Familial CRC

- PLSD

Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age; a report from the prospective Lynch syndrome database

Pål Møller,1,2,34 Toni Seppälä,3 Inge Bernstein,4,5 Elke Holinski-Feder,6,7 Paola Sala,8 D Gareth Evans,9,10 Annika Lindblom,11 Finlay Macrae,12,13 Ignacio Blanco,14 Rolf Sijmons,15 Jacqueline Jeffries,16 Hans Vasen,17 John Burn,18 Sigve Nakken,2 Eivind Hovig,2,19,20 Einar Andreas Rødlund,2 Kukatharmini Tharmaratnam,21 Wouter H de Vos tot Nederveen Cappel,22 James Hill,23 Juul Wijnen,24 Mark Jenkins,25 Kate Green,9 Fiona Laloo,9 Lone Sunde,4,26,27 Miriam Mints,28 Lucio Bertario,8 Marta Pineda,14 Matilde Navarro,14 Monika Morak,6,7 Laura Renkonen-Sinisalo,29,30 Ian M Frayling,16 John-Paul Plazzer,12 Kirsi Pylvänäinen,31 Maurizio Genuardi,32 Jukka-Pekka Mecklin,31,33 Gabriela Möslin,34 Julian R Sampson,16 Gabriel Capella,14 in collaboration with The Mallorca Group (http://mallorca-group.org)

24,475 pt.y

https://www.plsd.eu

Registries and Databases in Familial CRC

- PLSD


https://www.plsd.eu
Relative cumulative incidence (RR) of cancer in LS at 75 y by gene.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Population incidence</th>
<th>Relative cumulative Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MLH1</td>
</tr>
<tr>
<td>Small bowel</td>
<td>0.1%</td>
<td>64.7</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1.6%</td>
<td>26.7</td>
</tr>
<tr>
<td>Colon</td>
<td>2.1%</td>
<td>22.3</td>
</tr>
<tr>
<td>Bile duct and gall bladder</td>
<td>0.2%</td>
<td>18.7</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.0%</td>
<td>10.1</td>
</tr>
<tr>
<td>Ureter and kidney</td>
<td>1.3%</td>
<td>3.5</td>
</tr>
<tr>
<td>Sigmoid and rectum</td>
<td>1.4%</td>
<td>8.4</td>
</tr>
<tr>
<td>Brain</td>
<td>0.5%</td>
<td>1.9</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.8%</td>
<td>8.9</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>1.0%</td>
<td>4.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.8%</td>
<td>7.8</td>
</tr>
<tr>
<td>Prostate</td>
<td>10.0%</td>
<td>1.7</td>
</tr>
<tr>
<td>Breast</td>
<td>9.4%</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Significantly increased (p<0.05) RRs in bold. Maximum RR by gene underlined. 95% CIs omitted for clarity.

http://www.plsd.eu

Registries and Databases in Familial CRC

- PLSD
- Knowing the penetrance of LS as CRC enables us to estimate the population frequency of LS
How common is LS?

In Denmark all CRCs are tested for LS
1/17 Danes get CRC
1/30 Danish cases of CRC are due to LS
From the PLSD*, the weighted mean penetrance of LS as CRC is ¼
i.e. 1 in 4 persons with LS will present with CRC
(eliminates PMS2 from the equation)

* www.PLSD.eu
How common is LS?

0.059 \times 0.033 \times 1/0.25 = 0.0078 \ (1/128)

0.055 \times 0.034 \times 1/0.25 = 0.0075 \ (1/134)

but remember penetrance estimates from family ascertainment are always higher ...
How common is LS?

\[0.059 \times 0.033 \times 1/0.19 = 0.0104 \ (1/128) \ (1/97)\]

\[0.055 \times 0.034 \times 1/0.19 = 0.0099 \ (1/134) \ (1/101)\]
How common is LS?


Allowing for reduced penetrance of LS in those not ascertained by family history:-


would suggest correcting by a factor of 87~85% vs. 65% wrt BC in BRCA1 = x1.33
Registries and Databases in Familial CRC

- PLSD

- Regular colonoscopy is prescribed in LS, “because the tumours in LS develop more quickly from adenomas.”

- But is this actually the case?
Registries and Databases in Familial CRC

Colonoscopic surveillance in LS, 3 yrly
Reduces CRC mortality by ~50%

Registries and Databases in Familial CRC

- PLSD 2017

Colorectal cancer incidence in path\_MLH1 carriers subjected to different follow-up protocols: a Prospective Lynch Syndrome Database report

Registries and Databases in Familial CRC

• **PLSD** 2017

> Colorectal cancer incidence in *path_MLH1* carriers subjected to different follow-up protocols: a Prospective Lynch Syndrome Database report

2019

> Lack of association between screening interval and cancer stage in Lynch syndrome may be accounted for by over-diagnosis; a prospective Lynch syndrome database report

Registries and Databases in Familial CRC

### Years since last colonoscopy
- <1.5
- 1.5 – 2.5
- 2.5 – 3.5
- >3.5

### UK National Bowel Screening
Before & After

<table>
<thead>
<tr>
<th>Years since last colonoscopy</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>1.5 – 2.5</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>2.5 – 3.5</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>


Engel, Christoph, et al. "No difference in colorectal Cancer incidence or stage at detection by colonoscopy among 3 countries with different lynch syndrome surveillance policies." *Gastroenterology* 155 (2018): 1400-1409.
Registries and Databases in Familial CRC

- The **PLSD** tells us that:
- Colonoscopy in LS definitely reduces mortality, but
- Colorectal cancers arise at the same rate in LS regardless of colonoscopy
- Colonoscopy prevents those CRCs that would have arisen from pre-existing adenomas, and finds CRCs at an earlier stage, but
- It doesn’t prevent all LS CRCs and it probably simply can’t
- Unlike the general population, stage is not strongly associated with time since last clean ‘scope
- More frequent colonoscopy in LS does not seem to be significantly more effective than less frequent
- LS is strange and different; it doesn’t behave according to the ‘rules’; something else seems to be going on ...
Matthias Kloor  Aysel Ahadova
Department of Applied Tumor Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany and Cooperation Unit Applied Tumor Biology, DKFZ (German Cancer Research Center), Heidelberg, Germany
Model of Lynch syndrome carcinogenesis

“For better visibility, pre-malignant lesions that do not develop into cancer are not included in the diagram, because their number greatly exceeds the number of carcinomas.”


Slide courtesy of Dr Matthias Kloor, Institute of Pathology, University of Heidelberg
Registries and Databases in Familial CRC

• International Databases
• InSiGHT LOVDs
• PLSD
• Colon CFR

Registries and Databases in Familial CRC

- Colon Cancer Family Registry (Colon CFR)
- International consortium: USA, Canada and Australasia
- Data and biospecimens from over 42,000 participants from more than 15,000 families ...
- Standardized protocols ...
- Both retrospective and prospective

https://www.coloncfr.org/
Registries and Databases in Familial CRC

- Colon Cancer Family Registry (Colon CFR)
- Both retrospective and prospective ...
- Risk of CRC with *PMS2* variants is very low from the PLSD
- But the Colon CFR and Dutch family data suggests it is higher
- Ascertainment bias or biology?
- PLSD tells us risks to the *relatives* of index *PMS2* cases is ~0
- Genetic modifiers of risk in index cases independent of *PMS2*?

[https://www.coloncfr.org/](https://www.coloncfr.org/)
**Colon CFR: CRC in LS: Environmental/Lifestyle Factors**

<table>
<thead>
<tr>
<th>General Population</th>
<th>LS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity</td>
<td>↓</td>
</tr>
<tr>
<td>HRT</td>
<td>↓</td>
</tr>
<tr>
<td>OCP</td>
<td>-</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>males</td>
<td>↑</td>
</tr>
<tr>
<td>females</td>
<td>-</td>
</tr>
<tr>
<td>Exercise</td>
<td>↓</td>
</tr>
<tr>
<td>Smoking</td>
<td>↑</td>
</tr>
<tr>
<td>Alcohol</td>
<td>↑</td>
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<tr>
<td>NSAIDs</td>
<td>↓</td>
</tr>
<tr>
<td>Calcium</td>
<td>↓</td>
</tr>
<tr>
<td>Multi vits</td>
<td>?</td>
</tr>
</tbody>
</table>

https://www.coloncfr.org/

*(MLH1)*
Registries and Databases in Familial CRC

• Conclusions
• Both Patient and Case Registries have a critical role in Familial CRC care
  • Evidence-based improvement; Essential for delivery of services
• Databases have an equally critical role
  • Vital in diagnosis; Enabling many scientific and clinical advances
• Data protection legislation is there to prevent abuse, not use of data
  • It is not meant to be a block to sharing data for the greater good
• Everyone has a duty to submit data for the greater good

https://www.insight-group.org/
FraylingIM@cardiff.ac.uk
WHO Classification of Tumours

ONLINE

Now available at: tumourclassification.iarc.who.int

Access to the following books:

5th edition
Digestive Tumours
Breast Tumours

4th edition
Skin Tumours Endocrine Tumours
Eye Tumours Head and Neck Tumours

Special launch rate of 100 Euros

More details from the IARC team – Booth A14, 2nd level, Agora 2 Hall
9am to 5.15pm, from Sunday 8 to Tuesday 10 September