Colorectal cancer in young adults: The focus on hereditary cancer syndromes

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Incidence of CRC in USA (1975-2010)

- Increasing annual percentage change for:
  - 20-34y ~2%
  - 35-49y ~0.5%

- Similar trend for:
  - Localised
  - Regional
  - Distant
  - Colon and rectosigmoid disease

Prediction is more worrisome

Annual percentage change-based predicted incidence rates of rectosigmoid and rectal cancers by age compared with incidence rate in 2010

May be attributed to behavioural factors

- Obesity
- Western diet
- Lack of physical activity
- No screening

High prevalence of hereditary cancer syndromes in young adults

- Retrospective study from MDACC:
  - 193 individuals referred for genetic counselling
  - 2009-2013

- 1 in 3 (35%) had an identifiable syndrome:
  - 23 Lynch syndrome
  - 22 mutation-negative Lynch syndrome
  - 16 AFP
  - 2 MAP
  - 1 Li-Fraumeni

- One in five (19%) had no family history!

# Hereditary CRC syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Acronym</th>
<th>Alternate Name</th>
<th>Associated Gene(s)</th>
<th>Key Phenotypic Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch syndrome</td>
<td></td>
<td>Hereditary nonpolyposis colorectal cancer, Muir-Torre syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Risk of other cancers (endometrial, ovarian, gastric, small bowel, urothelial, hepatobiliary, pancreatic, brain), sebaceous adenomas/carcinomas</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>FAP</td>
<td>Gardner syndrome</td>
<td>APC</td>
<td>Duodenal/ampullary neoplasia, thyroid neoplasia, desmoid tumors, brain tumors, fundic gland polyps, osteomas</td>
</tr>
<tr>
<td>MUTYH-associated polyposis</td>
<td>MAP</td>
<td></td>
<td>MUTYH</td>
<td>Autosomal recessive inheritance; variable degree of polyposis; colorectal cancers/polyps may be more likely to harbor KRAS G12C mutations</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td></td>
<td></td>
<td>STK11</td>
<td>Mucocutaneous pigmentation, Peutz-Jegher hamartomas in small and/or large bowel, risk of other cancers (breast, pancreatic)</td>
</tr>
<tr>
<td>Juvenile polyposis coli</td>
<td></td>
<td></td>
<td>SMAD4, BMPR1A</td>
<td>Large and/or small bowel juvenile polyps, gastric cancer risk, some patients with congenital heart defects and/or hereditary hemorrhagic telangiectasia</td>
</tr>
<tr>
<td>PTEN hamartoma tumor syndrome</td>
<td></td>
<td>Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome</td>
<td>PTEN</td>
<td>Macrocephaly, colorectal hamartomas, trichilemmomas, risk of other cancers (breast, thyroid, uterine, kidney)</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td></td>
<td></td>
<td>TP53</td>
<td>Risk of multiple early-onset cancers (leukemia, sarcoma, premenopausal breast cancer, adrenal cancer, brain tumors)</td>
</tr>
<tr>
<td>Polymerase proofreading-associated polyposis</td>
<td>PPAP</td>
<td></td>
<td>POLD1, POLE</td>
<td>Not fully defined; low-level colorectal polyposis; may increase risk of endometrial cancer; cancers may be preferentially microsatellite stable</td>
</tr>
<tr>
<td>Familial colorectal cancer type X</td>
<td>FCCX</td>
<td></td>
<td>Likely numerous genes; mostly unknown</td>
<td>Microsatellite-stable CRC involving multiple generations; absence of gastrointestinal polyposis</td>
</tr>
</tbody>
</table>

Abbreviation: CRC, colorectal cancer.
Genetics of CRC

- Sporadic (65%–85%)
- Familial (10%–30%)
- Rare CRC syndromes (<0.1%)
  - Lynch syndrome (Hereditary nonpolyposis colorectal cancer - HNPCC) (3%)
  - Familial adenomatous polyposis (FAP) (1%)
  - MYH associated polyposis (MAP) (1%)
- Genetics of CRC
Individual with colorectal cancer <50y

Polyposis (adenomatous)

100s of polyps

APC testing

1-100 polyps

APC & MUTYH testing
Colorectal polyps

- ~50% of adults will be found to have at least one colorectal polyp during their lifetime

- ~30% of adults will be found to have at least one colorectal adenoma during their lifetime

- Colorectal polyps are ‘pre-cancerous polyps’
  That have the potential to develop into invasive colorectal adenocarcinoma

Colorectal cancer syndromes associated with polyps

- Adenomatous polyposis syndromes:
  - Familial Adenomatous Polyposis (FAP)/Attenuated FAP (AFAP)
  - MYH-Associated Polyposis (MAP)

- Hamartomatous polyposis syndromes:
  - Peutz-Jeghers syndrome (PJS)
  - Juvenile polyposis syndrome
  - Cowden syndrome

- Mixed polyposis and other rare syndromes

Mutation identification in patients with adenomatous polyposis syndromes

- **APC** germline mutations:
  - Account for >70% of clinically diagnosed FAP
  - And for ~25% of clinically diagnosed AFAP

- Biallelic **MYH** germline mutations:
  - Account for ~25-30% of patients with 10-100 adenomas and in 5-30% of patients with >100, who are tested negative for **APC** mutation

Lipton L and Tolimson I. Fam Cancer. 2006;5:221-6.
FAP/AFAP – De novo mutations

- Up to 30% of individuals with APC mutations have de-novo mutations – neither parent is found to have the mutation

- De novo mutation assumed to have occurred during formation of the germ cell

- Somatic mosaicism (mutation occurs in early embryo leading to two cell populations) accounts for up to 20% of de novo cases – variable phenotype and challenging detection

MAP – Mutation spectrum

- Two founder mutations in Caucasian Northern European population:
  - Y165C and G382D
  - Account for 73% of MYH mutations in the Northern European population

- There are common mutations in individuals of varied ethnicities of Italian, Finnish and Portuguese ancestry

“Red flags” for adenomatous polyposis syndromes

- ≥10 cumulative colorectal adenomas
- Colorectal cancer associated with multiple adenomas
- Previously identified adenomatous polyposis mutation(s) in the family
- Red flags identify individuals at risk for hereditary adenomatous polyposis syndromes for whom genetic counselling is warranted before proceeding with genetic testing!
## Adenomatous polyposis syndromes

### Presentation

<table>
<thead>
<tr>
<th>Condition</th>
<th>FAP</th>
<th>AFAP</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>APC</td>
<td>APC</td>
<td>MYH</td>
</tr>
<tr>
<td>Inheritance Pattern</td>
<td>Autosomal Dominant</td>
<td>Autosomal Dominant</td>
<td>Autosomal Recessive</td>
</tr>
<tr>
<td>Adenoma number</td>
<td>100 or more</td>
<td>Sometimes 1000s</td>
<td>0 to hundreds</td>
</tr>
<tr>
<td>Additional information</td>
<td>20-30% of cases will be first affected individuals in the family</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SIDENOTE: Variable presentation and clinical overlap necessitates testing for all three genes!

Increased colorectal cancer risk

### Familial adenomatous polyposis

#### LIFETIME CANCER RISKS

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Risk Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Duodenal/periampullary</td>
<td>4-12%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Gastric</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Adrenal</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>CNS (most often medulloblastoma)</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>1.6% (to age 5)</td>
</tr>
</tbody>
</table>

Lipton L. Fam Cancer 2006;5:221-6.
### ADDITIONAL EXTRA-COLONIC CANCER RISKS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundic gland polyps of the stomach</td>
<td>26-61%</td>
</tr>
<tr>
<td>Desmoid tumours</td>
<td>15%</td>
</tr>
<tr>
<td>Duodenal adenomas</td>
<td>80-100%</td>
</tr>
<tr>
<td>Osteomas (1-2% in general population)</td>
<td>20%</td>
</tr>
<tr>
<td>Dental abnormalities (supernumerary or impacted teeth)</td>
<td>17%</td>
</tr>
<tr>
<td>Cutaneous findings: epidermal cysts, fibromas, lipomas, leiomyomas, neurofibromas, pigmented skin lesions</td>
<td>up to 50%</td>
</tr>
<tr>
<td>CHRPE (congenital hypertrophy of the retinal pigmented epithilium)</td>
<td>20%</td>
</tr>
</tbody>
</table>

MYH-associated polyposis

<table>
<thead>
<tr>
<th>LIFETIME CANCER RISKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
</tr>
<tr>
<td>Duodenal/periampullary</td>
</tr>
<tr>
<td>Sebaceous gland tumours</td>
</tr>
<tr>
<td>&gt;80%</td>
</tr>
<tr>
<td>~4%</td>
</tr>
<tr>
<td>~2%</td>
</tr>
</tbody>
</table>

- FAP-like features:
  - Duodenal polyposis present in ~17% of MAP patients
  - Incidence of other FAP-like features appears to be low and described as part of case reports

Managing cancer risk in adenomatous polyposis syndromes

- Markedly improved outcome with proven medical interventions:
  - Surveillance
  - Chemoprevention
  - Risk reduction surgeries

## Surveillance guidelines for colon and rectum

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>PROCEDURE</th>
<th>AGE TO BEGIN</th>
<th>INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP</td>
<td>Sigmoidoscopy or colonoscopy</td>
<td>12-14 years</td>
<td>2 years (until polyps develop and surgery is indicated)</td>
</tr>
<tr>
<td>AFAP</td>
<td>Colonoscopy</td>
<td>18-20 years</td>
<td>1-2 years (based on adenomas burden)</td>
</tr>
<tr>
<td>MAP</td>
<td>Colonoscopy</td>
<td>18-20 years</td>
<td>2 years (based on adenomas burden)</td>
</tr>
</tbody>
</table>

# FAP/AFAP: Extra-colonic screening

<table>
<thead>
<tr>
<th>CANCER RISK</th>
<th>SCREENING</th>
<th>AGE AND INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal, gastric, peri-ampullary</td>
<td>Upper GI endoscopy with and side-viewing examination</td>
<td>Begin 25-30 and repeat every 5 years until adenomas develop</td>
</tr>
<tr>
<td>Small bowel</td>
<td>Consider small bowel visualisation</td>
<td>Based on symptoms and duodenal polyps status</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Clinical exam and u/s</td>
<td>Late teens and repeat annually</td>
</tr>
<tr>
<td>Desmoid tumours</td>
<td>CT abdomen and pelvis</td>
<td>Family history and prior surgery</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>Consider AFP and u/s</td>
<td>Every 3-6 months for the first 5 years of life</td>
</tr>
<tr>
<td>Pancreas and others</td>
<td>No recommendation (adjust to family history)</td>
<td></td>
</tr>
</tbody>
</table>

[www.nccn.org](http://www.nccn.org) (last assessed 31/8/2015)
Chemoprevention has been studied in an effort to reduce polyp burden:

- COX-2 inhibitors and aspirin mostly investigated
- Primary chemoprevention has never been demonstrated to delay appearance of FAP
- Secondary prevention reduce and number and extension of colorectal adenomas and less duodenal adenomas
- Note: consider cardiovascular side effects

Significant reduction in the number of colorectal polyps with celecoxib 400 mg x 2

Adenomatous polyposis: Surgical issues

- **FAP** (severe polyposis):
  - Colectomy or proctocolectomy (consider age, disease burden, risk for desmoid tumours)
  - Secondary chemoprevention (optional)
  - Post-surgical surveillance for rectal and extra-colonic tumours

- **AFAP**: Colectomy essential necessary in two-thirds of individuals, depending on the polyp burden

Individual with colorectal cancer <50y

Polyposis (adenomatous)
- 100s of polyps
  - APC testing
- 1-100 polyps
  - APC & MUTYH testing

Few or no polyps
- IHC or MSI testing
  - MMR genes testing

In case of negative genetic testing treat the case as a familial one!!!
Lynch Syndrome

- **MLH1**: GI cancers predominate. Highly penetrant.
- **MSH2**: Higher rates on non-GI cancers than in MLH1; GYN, urothelial, sebaceous, breast, prostate.
- **MSH6**: A bit like MSH6; Higher endometrial than colon ca in women & later age at diagnosis in men than in women.
- **PMS2**: Lower overall penetrance but the highest rate of biallelic constitution al dMMR.
- **EPCAM**: Silences MSH2 but spectrum is different with less endometrial due to tissue specific expression.

Presented by Noralane Lindor at 2014 ASCO Annual Meeting
Clinical features of Lynch Syndrome

- Early onset of CRC (~45 years)
- Proximal colon predominantly
- Lymphocytic infiltration
- Endometrial and other cancers: any abdominal organ but RCC, PLUS sebaceous skin and brain tumours
- Second CRC primaries (~50%)
Amsterdam II criteria

- 3 or more relatives with verified HNPCC associated tumour (CRC, endometrial, ovarian, gastric, small bowel, urinary tract) in family AND
- One case a first-degree relative of the other two AND
- Two or more generations involved AND
- One or more cancer diagnosed by age 50 AND
- FAP excluded

Failure to meet these criteria does *not* rule out HNPCC
Revised Bethesda Guidelines

- CRC < age 50
  - OR
- Patient with 2 HNPCC related tumours
  - OR
- Patient with CRC < age 60 with MSI-H histology
  - OR
- Patient with CRC and 1st degree relative with HNPCC related cancer; one of the cancers at < 50 years
  - OR
- Patient with CRC and 2 or more relatives with HNPCC-related cancer regardless of age

A classic Lynch family tree

CRC dx 50s

CRC dx 45
CRC dx 52
CRC dx 48
CRC dx 61
CRC dx 75
Ovarian Ca, dx 64

Endometrial Ca, dx 59
45
CRC dx 42
Immunohistochemistry

Abnormal Gene (MSH2)

Abnormal or missing MSH2 protein

Lack of MSH2 expression, negative IHC staining for MSH2 protein

Normal tissue

Tumour tissue

MSH2+

MSH2−
Colorectal cancer

MIN (MSI+)
(Microsatellite Instability)

15%

Lynch Syn
Germline Mutation
MMR genes
MLH1, MSH2,
MSH6 & PMS2

Sporadic MSI(+)
Epigenetic silencing of MLH1
by hypermethylation of its
promoter region

13%

CIN
(Chromosome Instability)

85%

FAP
Germline Mutation
APC

<1%

Sporadic
Acquired
APC, p53,
DCC, kras,
LOH,...
Frequency of loss of MLH1 expression in CRC increases with advancing aging

Trend of MLH1 loss of expression with age at diagnosis of colorectal carcinoma in males and females combined (solid line; solid circles are point estimates)

95% Confidence Intervals are represented by dotted trend lines and open symbols around the point estimates

A pair of tumour tests can distinguish non-LS from LS tumours

- **Assay for MLH1 promoter hypermethylation**
  - Should be *methylated* in all non-LS MSI tumours
  - But MLH1 methylation can be present in LS tumours as the second hit

- **BRAF somatic mutation assay (practically V600E)**
  - Found ~75% of in non-LS MSI tumours
  - But if there it essentially rule out LS CRC
Recommended LS screening protocol

Any new colorectal cancer

IHC abnormal

MLH1 missing

MLH1 promoter methylation or BRAF V600E

+ Likely sporadic CRC

Consider other syndromes

MLH1 missing

Missing: PMS2 (MLH1+) MSH2 or MSH6

- Genetic testing

Family history suggestive of LS but:
No personal history of cancer
No known family mutation
Tumour tissue unavailable

Predictive model

>5% probability

Consider other syndromes

≤5% probability
Columbus area HNPCC study (1999-2005)

- Age at diagnosis – 51.4 (range 23-87)
- 50% diagnosed over age 50
- 25% did not meet either Amsterdam or Bethesda criteria
- Mutations
  - 20.5% MLH1
  - 52.3% MSH2
  - 13.6% MSH6
  - 13.6% PMS2

2.8% of CRC probands with deleterious mutations (n=44)

Family studies of 35/44 CRC probands

- 35 CRC probands have had genetic counselling

<table>
<thead>
<tr>
<th>Degree of kinship</th>
<th>Tested</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>99</td>
<td>52</td>
</tr>
<tr>
<td>Second</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>&gt;Second</td>
<td>86</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>249</td>
<td>109</td>
</tr>
</tbody>
</table>

Cumulative cancer risk of CRC and GYN cancers for all genes

Increased cancer risk for any organ of the abdomen

Table 4. Cumulative Risks of Other Hereditary Nonpolyposis Colorectal Cancer Localizations According to the Mutated Gene

<table>
<thead>
<tr>
<th>Localization</th>
<th>Cumulative Cancer Risk at 70 Years, % (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MLH1</td>
</tr>
<tr>
<td>Stomach</td>
<td>6 (0.2-17)</td>
</tr>
<tr>
<td>Urothelium</td>
<td>0.2 (0-2.6)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>0.4 (0.1-3)</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>1.9 (0-15)</td>
</tr>
</tbody>
</table>

\(^a^\)See eTable 4 (available at http://www.jama.com) for the number of affected individuals and the number of family members contributing to the likelihood for risk estimation.
# Recommended screening management for members at risk of LS families

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
<th>Quality of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>Every 1-2 years from 20-25 y (age 30 in MSH6 families)</td>
<td>Well-designed and conducted studies</td>
<td>Strongly recommended</td>
</tr>
<tr>
<td>Endometrial Sampling</td>
<td>Every year beginning at age 30-35 y</td>
<td>Insufficient to assess the effect on health outcome</td>
<td>Insufficient evidence to recommend for or against</td>
</tr>
<tr>
<td>TVUS</td>
<td>Every 1-2 years beginning at age 25-35 y</td>
<td>Insufficient to assess the effect on health outcome</td>
<td>Insufficient evidence to recommend for or against</td>
</tr>
<tr>
<td>Urinalysis with cytology</td>
<td>Every 1-2 years beginning at age 25-35 y</td>
<td>Insufficient to assess the effect on health outcome</td>
<td>Insufficient evidence to recommend for or against</td>
</tr>
<tr>
<td>History and Physical</td>
<td>Every 1-2 years beginning at age 21 y</td>
<td>Insufficient to assess the effect on health outcome</td>
<td>Insufficient evidence to recommend for or against</td>
</tr>
</tbody>
</table>

## Risk-reduction surgeries for LS families

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
<th>Quality of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal resection</td>
<td>Without colorectal neoplasia</td>
<td>Insufficient to assess the effect on health outcome</td>
<td>Insufficient evidence to recommend for or against</td>
</tr>
<tr>
<td>(segmental vs. subtotal colectomy vs. complete proctocolectomy)</td>
<td>Generally not recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnosed cancer or polyps not resectable by endoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal colectomy is favoured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysterectomy of BSO</td>
<td>Discuss as an option after childbearing is completed</td>
<td>Good - fair</td>
<td>No recommendation for or against</td>
</tr>
</tbody>
</table>

Adjust your screening and prophylactic surgery recommendations to family history!!
Impact of screening for CRC in HNPCC families

66% reduction in the risk of death!!!
No survival difference between mutation-carriers and mutation-negative family members

![Bar chart showing cancers and deaths](chart.png)

- 242 mutation +, 367 mutation - : >95% screening compliance

Aspirin: A bullet for LS?

- CAPP2 (Colorectal Adenoma/Carcinoma Prevention Programme), UK

- 1071 carriers of Lynch Syndrome
  - 34 centres, 17 countries (not USA)
  - 600 mg Aspirin and/or 30 grams of resistant starch
  - 2x2 placebo controlled randomised trial over 2 to 4 years
  - 82% enrolees identified based on genetic testing
  - The world’s first large scale genetically targeted trial!
Burn J, *et al.*, Results of the CAPP-2-trial (Aspirin and resistant starch) in HNPCC gene carriers. NEJM 2008

- No significant cancer reduction
- Biologic possibility that the impact would be delayed and CAPP2 maintained follow-up
Stunning results for the LS community

Colorectal cancers

Aspirin in red
Placebo in blue

HR 0.41 (95% CI 0.19–0.86)
p=0.02

Stunning results for the LS community

Other cancers besides CRC

HR 0.45 (95% CI 0.26–0.79)
p = 0.005

CAPP2: 4 years from randomisation

- More than **50% reduction** in the development of new Lynch Syndrome related cancers, an effect which persists for at least five years after the cessation of aspirin therapy

- What would be the effect with continuous treatment?
Theoretical Population Health Benefit

**Table 2** Cost-effectiveness ratios associated with Lynch syndrome testing strategies among new diagnosed patients colorectal cancer (CRC) and testing and surveillance for CRC among their first degree relatives

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Description of testing strategy(^a)</th>
<th>Incremental costs-effectiveness ratio of universal testing relative to no testing and relative to previous strategy, dollars per life-year saved</th>
<th>Incremental costs-effectiveness ratio of age-targeted testing relative to no testing and relative to previous strategy, dollars per life-year saved</th>
<th>Incremental costs-effectiveness ratio of universal testing relative to age-targeted testing and relative to previous strategy, dollars per life-year saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IHC, <em>BRAF</em> testing and sequencing</td>
<td>$22,552 and $22,552</td>
<td>$7,832 and $7,832</td>
<td>$37,010 and $37,010</td>
</tr>
<tr>
<td>2</td>
<td>IHC testing and sequencing</td>
<td>$23,321 and $273,915</td>
<td>$7,944 and $60,569</td>
<td>$38,411 and $429,973</td>
</tr>
<tr>
<td>3</td>
<td>MSI testing and sequencing</td>
<td>$41,511 and $764,917</td>
<td>$11,680 and $168,905</td>
<td>$70,792 and $1,355,910</td>
</tr>
<tr>
<td>4</td>
<td>Genetic sequencing for 4 genes</td>
<td>$142,289 and $737,025</td>
<td>$44,902 and $252,643</td>
<td>$237,278 and $1,192,575</td>
</tr>
</tbody>
</table>

\(^a\)Sequencing includes detection of large deletions and rearrangements.

Targeting screening only to CRCs < age 50 would miss over 50% of LS cases

Known genes contribution to familial CRC

UK National study of Colorectal Cancer Genetics (NSCCG)
Cases: 646 UNRELATED samples, age at diagnosis <56 AND ≥1 FDR affected
Controls: 655 from a WTCCCIII 1958 birth control

Two thirds of cancers are due to bad luck…

We need to investigate the unknown

Moore’s Law and Genomics

“The $1,000 Genome: the $100,000 Analysis”

Baseline information
Cost of genome sequencing compared with Moore’s law for computers

<table>
<thead>
<tr>
<th>1999</th>
<th>2002</th>
<th>04</th>
<th>06</th>
<th>08</th>
<th>10</th>
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<tbody>
<tr>
<td>$ per million DNA bases</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Log scale</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>100,000</td>
<td></td>
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</tr>
<tr>
<td>10,000</td>
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<tr>
<td>1,000</td>
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<tr>
<td>100</td>
<td></td>
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<tr>
<td>10</td>
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<tr>
<td>1.0</td>
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<td>0.1</td>
<td></td>
<td></td>
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</tbody>
</table>

Source: Broad Institute

Presented by Kenneth Offit, MD, MPH at 2013 ASCO Annual Meeting
Mutations in polymerase proofreading linked to CRC/polyposis (Palles et al., Nat Genet. 2013)

**Discovery Phase:** WGS combined with pre-existing linkage data from polyposis/CRC family

- **POLE p.L424V** shared by affected family members
  - 12/3805 familial CRC/polyp pts, 0/6721 controls

- **POLD1 p.S478N** variation segregated with CRC/polyps
  - Also identified in another proband via WGS
Polymerase proofreading-associated polyposis (PPAP)

**POLE Mutation**
- AD
- Early-onset CRC, multiple or large adenomas with conventional pathology
- Tumours: MSS
- No extracolonic tumours, no non-tumour phenotypes(?)

**POLD1 Mutation**
- AD
- Early-onset CRC, multiple or large adenomas
- Tumours: MSS
- Presence of early-onset EC; 1 pt with two primary brain tumours
- No mutations identified in 386 early-onset ECs

Presented by Zsofia Stadler at 2013 ASCO Annual Meeting
Interpretation is **THE** challenge

<table>
<thead>
<tr>
<th>GENE</th>
<th>MUTATION</th>
<th>AMINO ACID CHANGE</th>
<th>INTERPATATION</th>
<th>DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SETX</td>
<td>c.7640T&gt;C</td>
<td>p.Ile2547Thr</td>
<td>Likely pathogenic</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>GABBR1</td>
<td>c.1465G&gt;A</td>
<td>p.Gly489Ser</td>
<td>Likely pathogenic</td>
<td>Temporal lobe epilepsy</td>
</tr>
<tr>
<td>C9</td>
<td>c.499C&gt;T</td>
<td>p.Pro167Ser</td>
<td>Likely pathogenic</td>
<td>Macular degeneration</td>
</tr>
<tr>
<td>GHRL</td>
<td>c.152G&gt;A</td>
<td>p.Arg51Gln</td>
<td>Likely pathogenic</td>
<td>Obesity of delayed onset</td>
</tr>
<tr>
<td>UGT2A1</td>
<td>c.224G&gt;A</td>
<td>p.Arg75Lys</td>
<td>Likely pathogenic</td>
<td>May increase tobacco-related cancer risk</td>
</tr>
<tr>
<td>PPP2R1B</td>
<td>c.269G&gt;A</td>
<td>p.Gly90Asp</td>
<td>Likely pathogenic</td>
<td>Increased incidence of lung and breast cancer</td>
</tr>
</tbody>
</table>
A classic Lynch family tree

CRC dx 50s

CRC dx 45
CRC dx 52
CRC dx 48
CRC dx 61
CRC dx 75
Endometrial Ca, dx 59
CRC dx 59
CRC dx 42
CRC dx 42
CRC dx 45
CRC dx 64
Ovarian Ca, dx 64
But somebody ordered MSI testing

MSI and genetic testing
And he saved lives

European Society for Medical Oncology

CRC dx 50s

75

CRC dx 45
Early stage

55

Aspirin prevention
CRC dx 52
Oophorectomy 45
Aspirin prevention

CRC dx 75
Oophorectomy
# The take home message !!!

## Potential Reduction in Cancer Through Targeted Prevention

<table>
<thead>
<tr>
<th>Cause</th>
<th>% cancer caused</th>
<th>Deaths in United States</th>
<th>Magnitude of possible reduction (%)</th>
<th>Period of time (years)</th>
<th>Evidence example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>33%</td>
<td>188,744</td>
<td>75%</td>
<td>10–20</td>
<td>Utah vs Kentucky</td>
</tr>
<tr>
<td>Overweight/obesity</td>
<td>20%</td>
<td>114,390</td>
<td>50%</td>
<td>2–10</td>
<td>Bariatric surgery</td>
</tr>
<tr>
<td>Hereditary factors (*)</td>
<td>16%</td>
<td>91,520</td>
<td>50%</td>
<td>2–10</td>
<td>Oophorectomy; MRI; Tamoxifen; Colonoscopy;</td>
</tr>
<tr>
<td>Diet</td>
<td>5%</td>
<td>28,600</td>
<td>50%</td>
<td>5–20</td>
<td>Folate, colorectal cancer</td>
</tr>
<tr>
<td>Lack of exercise</td>
<td>5%</td>
<td>28,600</td>
<td>85%</td>
<td>5–20</td>
<td>Adolescent activity</td>
</tr>
<tr>
<td>Occupation</td>
<td>5%</td>
<td>28,600</td>
<td>50%</td>
<td>20–40</td>
<td>Asbestos;</td>
</tr>
<tr>
<td>Viruses</td>
<td>5%</td>
<td>28,600</td>
<td>100%</td>
<td>20–40</td>
<td>Liver cancer, HPV vaccine</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3%</td>
<td>17,200</td>
<td>50%</td>
<td>5–20</td>
<td>Regulation</td>
</tr>
<tr>
<td>UV and ionizing radiation</td>
<td>2%</td>
<td>11,400</td>
<td>50%</td>
<td>5–40</td>
<td>Medical exposures</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>1%</td>
<td>5,720</td>
<td>50%</td>
<td>2–10</td>
<td>Hormone therapy</td>
</tr>
<tr>
<td>Reproductive factors</td>
<td>3%</td>
<td>17,200</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pollution</td>
<td>2%</td>
<td>11,400</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Total potential reduction 60%


(*) JNCI 89:287, 1997; NEJM 343:78, 2000

Presented by Kenneth Offit, MD, MPH at 2013 ASCO Annual Meeting
Genetic screening can answer life or death questions once known only to the gods. Such knowledge can be **transformative**...