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LynchRisk:
Taking into account biological testings in a Mendelian risk model for the Lynch syndrome

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Context and problematic

- **Context:** Screening for Lynch syndrome (LS) in all cases of colorectal cancer (CRC) and endometrial cancer (EC), i.e. immunostaining for the four MMR proteins and/or microsatellite instability testing is often recommended. However the relevance of conducting further testing is guided by a thorough analysis of the age at diagnosis and the Family History (FH) to avoid a cascade of tests with an eventual negative (no Lynch), or ambiguous (Lynch-like) result with no clear impact on patients and relatives.
- **Objective:** We are developing an innovative mathematical prediction model called LynchRisk that estimates the probability of LS in a patient by combining the FH of cancer with rigorous survival analysis (time to event analysis) and Mendelian transmission of the alleles in the whole family, as well as immunostaining, microsatellite, BRAF mutation and MLH1 promoter hypermethylation results.
  LynchRisk will be useful for clinicians at each stage of the process as a tool for estimating the relevance of a screening for LS and the utility to conduct further testing as well as a help for clinical recommendations when germline results do not allow for clear conclusions.

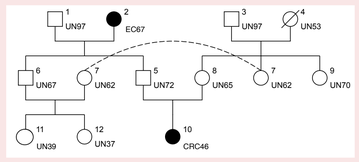
State of art

- Models computing LS risk and tumoral risk:
  - The only Mendelian one : MMRpro (Chen et al., 2006)
  - Other (non Mendelian) models : PREM$_{1,2,6}$ (Kastrinos et al., 2011), MMRpredict (Barnetson et al., 2006)
- Limitations of MMRPro:
  - No update since 2008
  - Ignore PMS2 gene
  - Ignore BRAF mutation & MLH1 promoter hypermethylation.
  - Statistical limitations (no linkage disequilibirum, limitations when several laboratory testing, etc.)
- Our model: Mendelian model with up to date parameters referenced by InSiGHT which combines family history (FH) of cancer, MSI, IHC per gene, BRAF mutation and MLH1 promoter hypermethylation testing.

Data structure and model

Pedigree (family structure)

G1, G2, G3, G4: set of unobserved genotypes for MLH1, MSH2, MSH6 and PMS2 respectively.



Individual data

- $\mathrm{FH} = \{\mathrm{PH}_i\}_{i=1,\dots,n}$: set of personal histories of CRC and EC (status and age at first diagnosis or censoring).
- MSI, IHC, BRAF, methH1: set of testings in tumor results.

- **Modelization** in a *Bayesian network* (Koller and Friedman, 2009):

$$\mathbb{P}(G1, G2, G3, G4, \mathrm{FH}, \mathrm{MSI}, \mathrm{IHC}, \mathrm{BRAF}, \mathrm{methH1}) =$$
$$\prod_{i=1}^{n} \mathbb{P}\left(G1_i | G1_{\mathrm{par}_i}\right) \mathbb{P}\left(G2_i | G2_{\mathrm{par}_i}\right) \mathbb{P}\left(G3_i | G3_{\mathrm{par}_i}\right) \mathbb{P}\left(G4_i | G4_{\mathrm{par}_i}\right) \times$$
$$\mathbb{P}(\mathrm{PH}_i | G1_i, G2_i, G3_i, G4_i) \times$$
$$\mathbb{P}(\mathrm{MSI}_i, \mathrm{IHC}_i, \mathrm{BRAF}_i, \mathrm{methH1}_i | G1_i, G2_i, G3_i, G4_i)$$

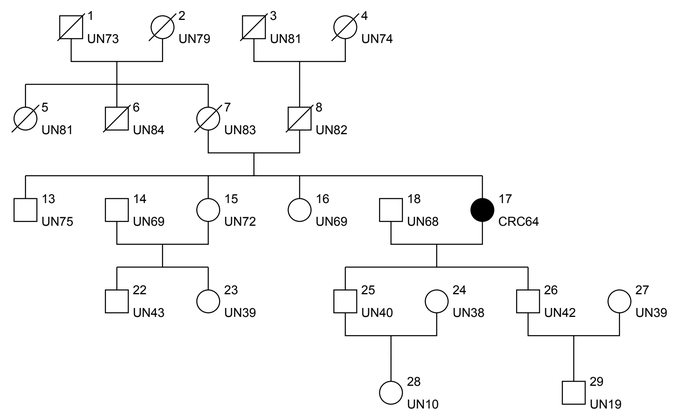
  where n denotes the number of individuals and par_i denotes the parents of individual i (empty for founders).
- **Complexity** for the computation of the posterior probability of LS for an individual i:
  Let data = {FH, MSI, IHC, BRAF, methH1}, then:
  $\mathbb{P}(G1_i, G2_i, G3_i, G4_i | \mathrm{data}) =$

$$\frac{\sum_{G1,G2,G3,G4 \setminus G1_i,G2_i,G3_i,G4_i} \mathbb{P}(G1, G2, G3, G4, \mathrm{data})}{\sum_{G1,G2,G3,G4} \mathbb{P}(G1, G2, G3, G4, \mathrm{data})}$$

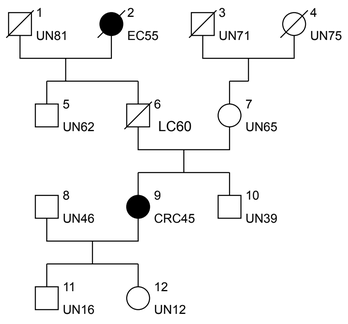
  - naive approach (brut force) : Complexity = $\mathcal{O}(81^n)$
  - sum-product or Elston-Stewart algorithm: Complexity = $\mathcal{O}\left(n \times 81^3\right)$

Example with two case reports

- **First case report (different stages of investigations):**
  - Female patient with CRC diagnosed at the age of 64. No history of cancer in her large family.
  - Routine MMR immunostaing on surgical specimen -> MLH1 & PMS2 loss.
  - Prescription of MLH1 promoter hypermethylation testing on surgical specimen + germline testing for the four MMR genes -> No germline MMR mutation nor MLH1 promoter hypermethylation.



- **Second case report (different stages of investigations):**
  - Female patient with CRC diagnosed at the age of 45. Her paternal grandmother died of EC diagnosed at the age of 55 (no other details provided) and her father died of lung cancer at the age of 60 but he was a heavy smoker. Her family is small.
  - Routine MMR immunostaining on surgical specimen + MSI testing -> MSH2 & MSH6 loss and microsatellite instability.
  - Prescritpion of germline analysis + somatic sequencing for the four MMR genes -> No MMR mutation identified neither germline nor in the tumor itself.
  - Complementary germline panel of CCR susceptibility genes is also normal.



Results for both case reports:

	LynchRisk	MMRPro
No data	0.23	0.23
PH	1.54	0.75
FH	0.08	0.04
PH + IHC	6.24	7.84
FH + IHC	0.26	0.4
PH + IHC + Hyp.meth	61.48	7.84
FH + IHC + Hyp.meth	5.92	0.4

Table 1: Posterior probability of a Lynch syndrome (in percent) for Individual 17 given the different stages of investigations in the first case report.

	LynchRisk	MMRPro
No data	0.23	0.23
PH	5.38	17.82
FH	26.48	47.45
PH + IHC	22.50	71.20
FH + IHC	72.29	91.08
PH + IHC + MSI	82.00	71.20
FH + IHC + MSI	97.61	91.08

Table 2: Posterior probability of a Lynch syndrome (in percent) for Individual 9 given the different stages of investigations in the second case report.

Comments:

- Case report 1:
  - The large family with no history of cancer in the Lynch spectrum dramatically decreases the probability of a Lynch syndrome for Individual 17 at any stage of the investigations. Ignoring the FH and considering the PH alone critically affects the conclusions.
  - Results of MLH1 promoter hypermethylation is critical in addition of FH + IHC.
  - The probability of a Lynch syndrome given the FH only for Individual 17 is 0.08%, before any investigation.
- Case report 2:
  - The family history of cancer increases the probability of a Lynch syndrome for Individual 9 at any stage of the investigations.
  - The additional MSI testing along with IHC is critical.
  - The probability of a Lynch syndrome given the FH alone is 26.48 % for Individual 9. IHC and MSI testing along with FH lead to a conditional posterior probability of 97.61 % of a Lynch syndrome.

Parameters

- Sensitivity and specificity of laboratory testing (Assasi et al., 2016).
- Genetic distances from Genome Data Viewer (https://www.ncbi.nlm.nih.gov/genome/gdv/) and 1000 Genomes Project (http://www.internationalgenome.org).
- Allele frequencies in general population from MMRPro (Chen et al., 2006).
- Incidences in non-carriers in the French population (Binder-Foucard et al., 2013).
- Incidences in carriers for MLH1, MSH2, MSH6 (Møller et al., 2018) and PMS2 (Sanne et al., 2014). Instant hazards derived from penetrances assumed piecewise linear. Therefore, instant hazards are assumed piecewise constant and computed penetrances are piecewise exponential.
  Cf Figures 1 and Table 3.

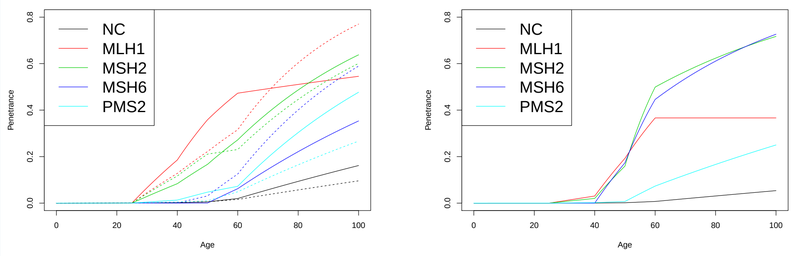


Figure 1: Penetrance of CRC (left) and EC (right) per gender (plain lines for men and dashed lines for women) and per gene (NC for non-carriers).

Age at diag.	20	30	40	50	60	70
EC	0.23	14.37	23.51	11.54	0.89	0.78
CRC fem.	0.23	11.70	5.65	1.38	1.67	1.37
CRC male	0.23	14.00	7.00	1.67	0.46	0.42

Table 3: Posterior probability of a Lynch syndrome (in percent) given the personal history.

Perspectives

- Add Germline testing (sensitivity and specificity of sequencing).
- Include Variants of Uncertain Significance and the probability of pathogenicity of a sequenced variant (InSiGHT class) as a prior.
- Include other localizations in the Lynch spectrum and reccurence with multistate models and competing events.
- Add localization of CRC (proximal / distal), Hystopathology of tumor (Type of ovarian cancer, etc.)

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