# DOES THIS PATIENT NEED TO BE TESTED FOR LYNCH SYNDROME? ASSESSING THE RELIABILITY OF FAMILY HISTORY FOR ASCERTAINMENT

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## BACKGROUND

- Lynch Syndrome (LS) is a dominantly inherited cancer syndrome caused by pathogenic germline variants in mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, as well as *EPCAM*.
- Mutation carriers are candidates for more aggressive clinical management such as increased surveillance and prophylactic surgery.
- Age and family history are key components in targeted genetic testing of individuals,[1-3] but may be insufficient to identify individuals carrying pathogenic variants (PVs) prior to cancer onset.

## METHODS

- We used pedigree simulation and statistical modeling to estimate the probability that a 40 year old proband carrying a germline PV in *MLH1*, *MSH2* or *EPCAM* would meet family history requirements for genetic testing.
- Three-generational pedigrees were simulated with 2 or 4 offspring per generation per couple for a high risk and moderate risk model using published data (www.myriadpro.com), this process is shown in Figure 1.
- All analyses were performed using R version 3.1.3.

## RESULTS

- As per NCCN 2015 guidelines, we applied both Amsterdam II criteria[1] and Revised Bethesda guidelines[2] to each set of pedigree simulations.
- We evaluated a third "Relaxed Criteria" as follows; 1) colorectal or endometrial cancer under age 50, 2) any LS cancer in an individual with a 1st or 2nd degree relative with a LS associated cancer at any age, 3) two primary LS cancers at any age, and 4) any unaffected individual who has a 1st degree relative that meets one or more of the criteria above.
- The 2-sibship Amsterdam II and Revised Bethesda moderate risk models failed to detect >25% of unaffected patients, as shown in Figure 2A.
- The preliminary high risk simulation model (Figure 2B) overestimates the number of affected individuals per family as it uses lifetime risks rather than age-dependent risks.

## DISCUSSION

- Genetic testing based on family history will identify a subset of Lynch Syndrome patients prior to cancer onset.
- Simulations demonstrate that the strength of family history declines significantly for families harboring a PV with incomplete penetrance, particularly if the proband is unaffected and generation sizes are small.
- In the case of unaffected probands, particularly those with weaker family histories, clinicians should consider broad pancancer testing rather than more limited cancer specific testing.

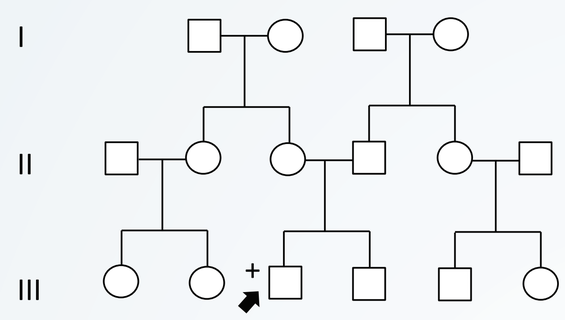
## REFERENCES

1. Vasen HF et al. Gastroenterology. 1999 Jun;116(6):1453-6. PMID: 10348829.
2. Umar A et al. J Natl Cancer Inst. 2004 Feb 18; 96(4):261–268. PMID: 14970275.
3. Kastrinos et al. Gastroenterology. 2011 Jan;140(1):73-81. PMID: 20727894.

## FIGURE 1. PEDIGREE SIMULATION AND RISK ASSESSMENT PROCESS

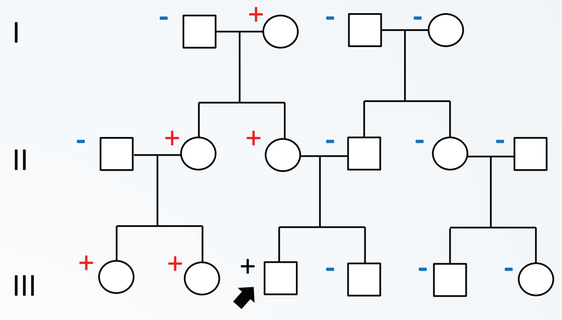
### STEP 1. PEDIGREE SIMULATION

1000 pedigrees were simulated for each pedigree structure. Gender was assigned stochastically.



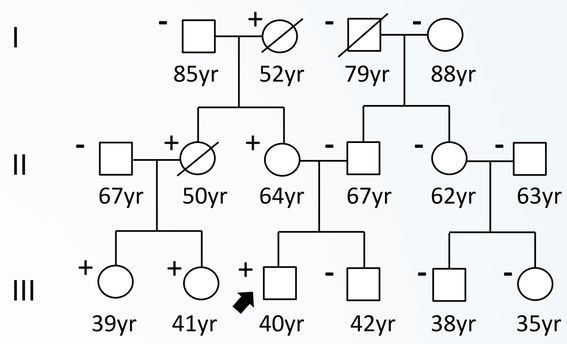

### STEP 2. DISEASE LOCUS SIMULATION

For each pedigree, a biallelic disease locus (+/-) was simulated according to Mendelian inheritance.



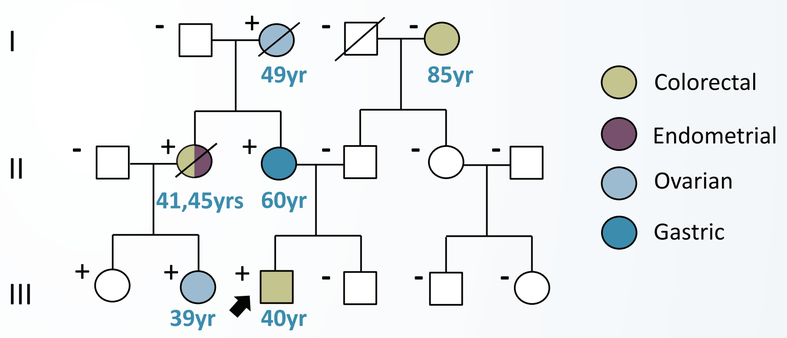

### STEP 3. AGE SIMULATION

Family member age or age of death were stochastically determined conditional on US population data for birth age and mortality. In all pedigrees, the proband was assumed to be alive.




### STEP 4. AFFECTION STATUS

For each pedigree member, cancer phenotype(s) or unaffected status were assigned considering published cancer risks (www.myriadpro.com), gender, and PV carrier status. This example used cancer risks from Model 2 (High Risk).




| Gender | Cancer Phenotype | MODEL 1: Moderate Risk to 70 yrs | MODEL 2: High Risk to 70 yrs | Population Risk to 70 yrs |
|---|---|---|---|---|
| Female | Ovarian | 4% | 12% | 0.7% |
| | Endometrial | 25% | 60% | 1.6% |
| Male and Female | Colorectal | 52% | 82% | 1.9% |
| | Pancreatic | 1% | 6% | 0.5% |
| | Gastric | 6% | 13% | 0.3% |
| | Small Bowel | 3% | 6% | 0.1% |
| | Hepatobillary | 1.4% | 4% | 0.4% |
| | Ureter/Renal Pelvis | 1% | 4% | <1%* |
| | Central Nervous System | 1% | 3% | 0.4% |
| | Sebaceous Neoplasm | 1% | 9% | <1%* |

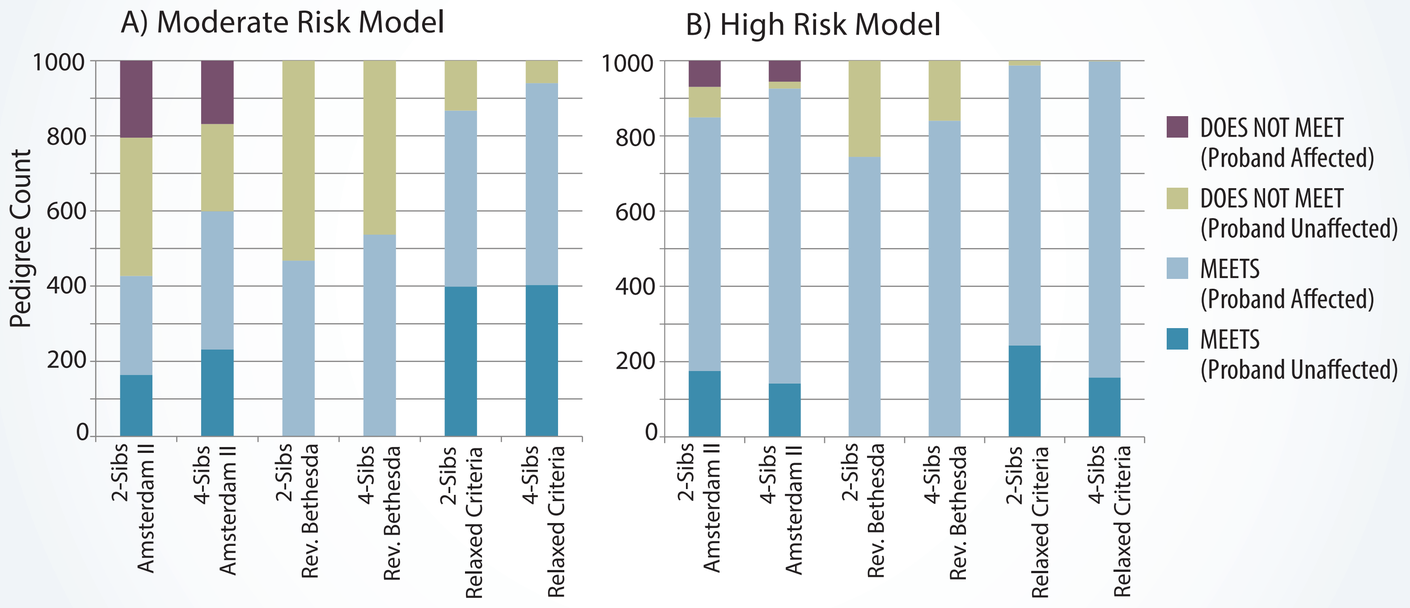
www.myriadpro.com/myrisk/why-myriad-myrisk/gene-selection/
*Assumed as 1% for the purpose of this analysis

### STEP 5. DETERMINATION OF ELIGIBILITY

The eligibility for each pedigree was determined using LS family history criterion.

✓ Positive

## FIGURE 2. Pedigree Models and Family History Criteria




Presented at ASHG - October 9, 2015