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, 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 and Revised Bethesda guidelines 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 unaffacted 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 cancer testing rather than more limited cancer specific testing.

REFERENCES