A REVIEW OF LYNCH SYNDROME PATIENTS WITH COLON CANCER WITH LITTLE OR NO FAMILY HISTORY BY AGE: A DIAGNOSTIC LABORATORY'S EXPERIENCE

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BACKGROUND

- Current guidelines for Lynch syndrome (LS) testing for patients with colorectal cancer (CRC) are based on tumor testing (using immunohistochemistry or microsatellite markers to monitor genome instability) or personal and family history (FHX) of the LS associated cancers.
- Patients diagnosed with colon cancer under age 50 are often considered appropriate for genetic testing without additional family history.
- Since the mean age for colon cancer diagnosis is 61, we examined rates for positive mutations by five year intervals.

METHODS

- A commercial laboratory database was queried for patients with a personal diagnosis of colorectal cancer and tested for LS from September 2006 to October 2013 (N=15,469) to assess how age of the colon cancer diagnosis affected the likelihood of a patient having a mutation in a mismatch repair gene, specifically focusing on patients with little or no additional reported family history.
- All patients underwent full sequence and large rearrangement analysis of *MLH1* and *MSH2*, and full sequence analysis of *MSH6*.
  - Some patients also underwent full sequence and large rearrangement analysis of *PMS2* and large rearrangement analysis of *MSH6* and *EPCAM*.
- Patients tested for only one of the MMR genes, or for a known family mutation, were excluded from this analysis.

RESULTS

- The majority of all pathogenic mutations were identified in the *MLH1* and *MSH2* genes (78.9% combined) with the remaining mutations identified in *MSH6*, *PMS2* and *EPCAM* (Figure 1).
- The proportion of mutations in at least one of the genes is statistically significantly different (Pearson's chi-square test, $P < 0.001$) between the two age groups (Figure 2).
- Positive rates for patients in the 50-54 and 55-59 age ranges with no FHX, or only one 1st or 2nd degree relative with CRC or endometrial cancer (EC) over 50, were similar to positive rates of patients in the 40-44 and 45-49 age ranges (Table 1).

FIGURE 1 • Gene Mutation Distribution for All Positive Patients

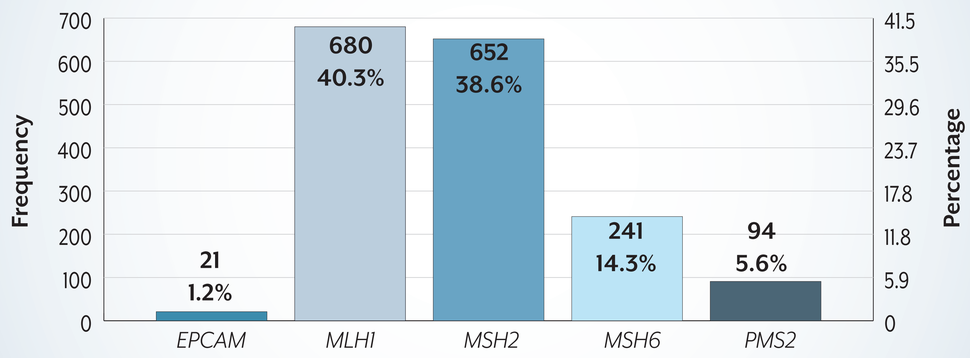
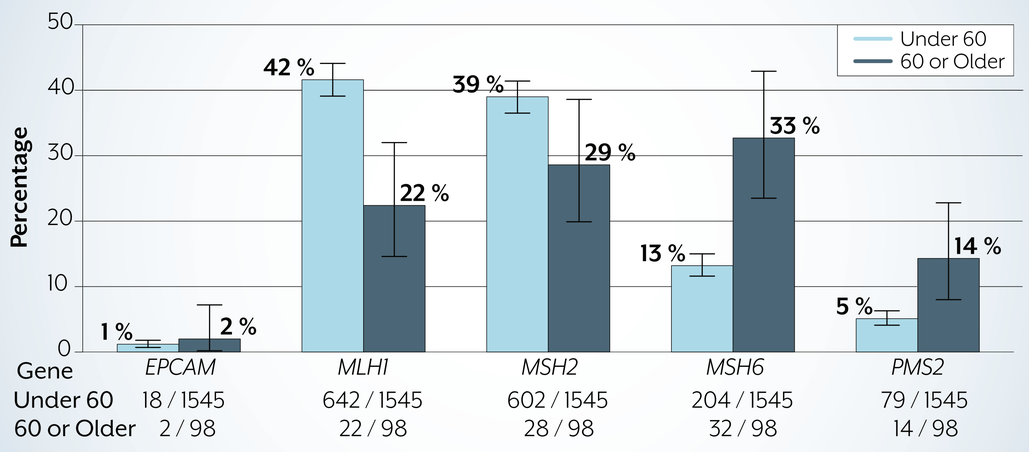


FIGURE 2 • Gene Mutation Distribution by Age Group



Exact 95% confidence limits for binomial proportions are displayed as bars surrounding each proportion.

TABLE 1 • Positive Rate by Age for Patients with No/Limited Family History

	No FHX/Insignificant FHX (no CRC/EC)			FHX: One CRC/EC >50		
Min Age CRC Dx	Tested Patients	LS Positive	Positive Rate	Tested Patients	LS Positive	Positive Rate
30 - 34	608	55	9.0%	163	19	11.7%
35 - 39	1060	53	5.0%	400	33	8.3%
40 - 44	1410	74	5.2%	573	42	7.3%
45 - 49	1686	72	4.3%	795	45	5.7%
50 - 54	633	35	5.5%	447	25	5.6%
55 - 59	290	22	7.6%	257	16	6.2%
60 - 64	212	12	5.7%	187	5	2.7%
65 - 69	138	4	2.9%	101	4	4.0%
70 - 74	92	2	2.2%	57	2	3.5%

CONCLUSIONS

- The majority of pathogenic mutations were identified in the *MLH1* and *MSH2* genes, however patients with older onset colon cancer (diagnosed at 60 or older) are more likely to have mutations in *MSH6* or *PMS2* than those diagnosed at younger ages. This is consistent with the less severe LS phenotype previously reported for these genes.
- These data suggest that the fall off in mutation rates as a function of age occurs later than the age of 50. Patients with LS are at a high risk for a 2nd cancer in the colon or endometrium as well as cancers in other organs. Identifying these patients can allow physicians to make medical management changes to reduce these risks.

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