# Prevalence and Phenotypes of *APC* and *MUTYH* Mutations in Patients With Multiple Colorectal Adenomas

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**Context** Patients with multiple colorectal adenomas may carry germline mutations in the *APC* or *MUTYH* genes.

**Objectives** To determine the prevalence of pathogenic *APC* and *MUTYH* mutations in patients with multiple colorectal adenomas who had undergone genetic testing and to compare the prevalence and clinical characteristics of *APC* and *MUTYH* mutation carriers.

**Design, Setting, and Participants** Cross-sectional study conducted among 8676 individuals who had undergone full gene sequencing and large rearrangement analysis of the *APC* gene and targeted sequence analysis for the 2 most common *MUTYH* mutations (Y179C and G396D) between 2004 and 2011. Individuals with either mutation underwent full *MUTYH* gene sequencing. *APC* and *MUTYH* mutation prevalence was evaluated by polyp burden; the clinical characteristics associated with a pathogenic mutation were evaluated using logistic regression analyses.

**Main Outcome Measure** Prevalence of pathogenic mutations in *APC* and *MUTYH* genes.

**Results** Colorectal adenomas were reported in 7225 individuals; 1457 with classic polyposis (≥100 adenomas) and 3253 with attenuated polyposis (20-99 adenomas). The prevalence of pathogenic *APC* and biallelic *MUTYH* mutations was 95 of 119 (80% [95% CI, 71%-87%]) and 2 of 119 (2% [95% CI, 0.2%-6%]), respectively, among individuals with 1000 or more adenomas, 756 of 1338 (56% [95% CI, 54%-59%]) and 94 of 1338 (7% [95% CI, 6%-8%]) among those with 100 to 999 adenomas, 326 of 3253 (10% [95% CI, 9%-11%]) and 233 of 3253 (7% [95% CI, 6%-8%]) among those with 20 to 99 adenomas, and 50 of 970 (5% [95% CI, 4%-7%]) and 37 of 970 (4% [95% CI, 3%-5%]) among those with 10 to 19 adenomas. Adenoma count was strongly associated with a pathogenic mutation in multivariable analyses.

**Conclusions** Among patients with multiple colorectal adenomas, pathogenic *APC* and *MUTYH* mutation prevalence varied considerably by adenoma count, including within those with a classic polyposis phenotype. *APC* mutations predominated in patients with classic polyposis, whereas prevalence of *APC* and *MUTYH* mutations was similar in attenuated polyposis. These findings require external validation.

*JAMA. 2012;308(5):485-492* www.jama.com

THE PRESENCE OF MULTIPLE COlorectal adenomas may be attributable to familial adenomatous polyposis (FAP), an autosomal dominant polyposis syndrome resulting from germline mutations in the adenomatous polyposis coli (*APC*) gene (NCBI Entrez Gene 324).[1] Individuals with *APC* mutations may present with "classic" polyposis (≥100 adenomas) and develop thousands of adenomas in the second or third decade of the disease. Approximately 10% of individuals with *APC* mutations may have milder disease, with 20 to 99 adenomas at an older age of onset. Multiple colorectal adenomas may also arise secondary to mutations in the mutY homolog (*MUTYH*) gene (NCBI Entrez Gene 4595).[2,3] Individuals with *MUTYH*-associated polyposis (MAP) are at an increased risk of colorectal cancer that may develop in the presence of few polyps.[4]

Although it is established that the clinical presentation of FAP and MAP may overlap, 2 important issues war-

**For editorial comment see p 514.**

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rant further study. First, the relative contribution of biallelic *MUTYH* mutations to *APC* mutations in individuals with multiple adenomas is unknown. Current estimates have been derived from highly selected clinic-based patients with multiple adenomas and no *APC* mutation.[5-8] Studies evaluating the prevalence of both *APC* and *MUTYH* mutations in attenuated polyposis have been small, and their findings have not been validated.[9,10] Second, guidelines for when genetic evaluation should be performed in individuals with multiple colorectal adenomas vary, and data to support such guidelines are limited.[11-14]

We evaluated the frequency of *APC* and *MUTYH* mutations by the number of colorectal adenomas among individuals who had undergone clinical genetic testing. We also studied the relationship between the number of adenomas and age at diagnosis of adenoma and colorectal cancer and the prevalence of pathogenic *APC* or *MUTYH* mutations to inform future guidelines for genetic testing in individuals with multiple adenomas.

## METHODS

### Study Population

This cross-sectional study was conducted among 8903 individuals whose clinicians (physicians, physician assistants, or nurse practitioners) submitted blood samples for genetic testing for *APC* and *MUTYH* mutations to a commercial laboratory (Myriad Genetic Laboratories Inc) between 2004 and 2011 as part of clinical care because of the patient's personal or family history of colorectal cancer, colorectal polyps, or both. Clinicians, genetic counselors, or other members of the clinical staff completed a prespecified test order form that included age at testing, ancestry (Western/Northern European, Central/East European, Ashkenazi, Latin American/Caribbean, African, Asian, Near East/Middle Eastern, Native American, other), cancer history (colorectal cancer, endometrial cancer, other), age at cancer diagnosis, age at colorectal adenoma diagnosis and adenoma count (1, 2-5, 6-9, 10-19, 20-99, 100-999, and ≥1000), and family history of cancer (relative, cancer site, age at diagnosis) and colorectal adenomas in first-, second- and third-degree relatives. From the original 8903 individuals, we excluded 227 individuals for whom personal as well as family histories were missing, for a final study cohort of 8676.

The study was investigator initiated and approved by the Dana-Farber Cancer Institute institutional review board.

### Laboratory Methods

Clinical genetic testing consisted of full gene sequencing and large rearrangement analysis of the *APC* gene. Full gene sequence determination was performed in the forward and reverse direction of approximately 8532 base pairs comprising 15 exons and 420 adjacent noncoding intronic base pairs. For large rearrangement analyses, all exons of *APC* were examined for evidence of deletions and duplications by standard Southern blot methods. All individuals also underwent DNA sequence analysis of specific portions of *MUTYH* exons 7 and 13 designed to detect the 2 most common *MUTYH* mutations (Y179C, G396D). Full *MUTYH* gene sequencing was performed if 1 of the 2 most common mutations was identified. Individuals with deleterious or suspected deleterious mutations were defined as mutation-positive. Suspected deleterious mutations included genetic variants for which the available evidence indicated likelihood, but not proof, that the mutation is deleterious. Genetic testing techniques did not change during the study period (2004-2011).

### Statistical Methods

The primary outcome was the prevalence of pathogenic *APC* or pathogenic biallelic *MUTYH* mutations. Covariates of interest included the number and age at diagnoses of adenomas, the presence of and age at colorectal cancer diagnosis, and the presence of colorectal cancer in a first-degree relative. In individuals diagnosed with the same cancer more than once, the age at diagnosis was defined as the youngest age at diagnosis. Age was categorized a priori into 4 categories (<30, 30-39, 40-49, and ≥50 years). For individuals with adenomas identified more than once, a cumulative adenoma count was computed. Adenoma count was analyzed as an ordinal variable (<10, 10-19, 20-99, 100-999, and ≥1000 adenomas).

Bivariable analyses were used to assess the association between mutation status and covariates of interest. $\chi^2$ tests were performed for categorical variables and *t* tests for continuous data. Results were reported as odds ratios with 95% confidence intervals. $P<.05$ (2-sided) was considered statistically significant.

Multiple imputation was used to obtain estimates of missing data for adenoma count (398/7225 [6%]), age at adenoma diagnosis (1912/7225 [26%]), and age at colorectal cancer diagnosis (67/2306 [3%]).[15] The coefficients of 5 rounds of imputation (performed in R using the AregImpute function) were combined to obtain the final estimates for missing data. Multivariable logistic regression analysis was performed on the imputed data set to assess the independent associations of the presence of a pathogenic mutation (*APC* or biallelic *MUTYH*) and covariates of interest. Multinomial logistic regression analyses were used to examine the differences in phenotypic characteristics between individuals with a pathogenic *APC* mutation and biallelic *MUTYH* mutations and to derive the probability of these mutations based on clinical characteristics.

Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc) and R version 2.11.0 (R Foundation for Statistical Computing).

## RESULTS

Of the 8676 individuals included in the study, 4324 (50%) were male and 6323 (73%) were of European ancestry (**TABLE 1**). Of the included individuals, 1508 (17%) had a pathogenic *APC* mutation, 422 (5%) had biallelic pathogenic *MUTYH* mutations, 168 (2%) had a monoallelic pathogenic *MUTYH* mutation, and 6578 (76%) had a nonpatho-

genic *APC* or *MUTYH* alteration or no alteration in either gene.

Overall, 7225 individuals (83%) were reported to have a history of adenomas, with a median age of 47 years at adenoma diagnosis, and 517 (6%) were reported to have extraintestinal manifestations associated with a familial polyposis syndrome. Of the remaining 1451 individuals (17%) without a history of adenomas, 527 (36%) had a personal history of colorectal cancer and 184 (13%) had a history of either a cancer that was not colorectal cancer or an extraintestinal manifestation associated with familial polyposis. A personal history of colorectal cancer was reported in 2306 individuals (27%); of these, 1779 (77%) had a history of both colorectal cancer and adenomas. Approximately one-third of the study population reported having a first-degree relative with a history of colorectal cancer.

**Table 1.** Patient Characteristics

| Characteristics | No. (%) | | | | |
|---|---|---|---|---|---|
| | | *MUTYH* | | | |
| | *APC* (n = 1508) | Biallelic (n = 422) | Monoallelic (n = 168) | Nonpathogenic/ No Alteration (n = 6578) | Total (N = 8676) |
| Male | 765 (51) | 211 (50) | 79 (47) | 3269 (50) | 4324 (50) |
| Ancestry[a] | | | | | |
| European | 1022 (68) | 307 (73) | 140 (83) | 4854 (74) | 6323 (73) |
| Non-European | 525 (35) | 91 (22) | 27 (16) | 1549 (24) | 2192 (25) |
| None specified | 210 (14) | 75 (18) | 20 (12) | 1105 (17) | 1410 (16) |
| Adenoma count, No. | 1380 (92) | 401 (95) | 135 (80) | 5309 (81) | 7225 (83) |
| ≥1000 | 95 (7) | 2 (0.5) | 0 | 22 (0.4) | 119 (2) |
| 100-999 | 756 (55) | 94 (23) | 15 (11) | 473 (9) | 1338 (19) |
| 20-99 | 326 (24) | 233 (58) | 74 (55) | 2620 (49) | 3253 (45) |
| 10-19 | 50 (4) | 37 (9) | 12 (9) | 871 (16) | 970 (13) |
| <10 | 44 (3) | 19 (5) | 28 (21) | 1056 (20) | 1147 (16) |
| Missing | 109 (8) | 16 (4) | 6 (4) | 267 (5) | 398 (6) |
| Age at first colorectal adenoma diagnosis, median (IQR), y | 30 (20-41) | 47 (39-52) | 47 (39-55) | 50 (39-58) | 47 (34-55) |
| History of colorectal cancer | 328 (22) | 162 (38) | 64 (38) | 1752 (27) | 2306 (27) |
| Colorectal cancer and adenoma | 286 (87) | 149 (92) | 48 (75) | 1296 (74) | 1779 (77) |
| Colorectal cancer alone | 42 (13) | 13 (8) | 16 (25) | 456 (26) | 527 (23) |
| Age at colorectal cancer diagnosis, median (IQR), y | 36 (27-45) | 46 (39-52) | 47 (41-59) | 48 (38-58) | 46 (36-56) |
| First-degree relative with colorectal cancer | 600 (40) | 102 (24) | 51 (30) | 1907 (29) | 2660 (31) |

Abbreviations: *APC*, adenomatous polyposis coli; IQR, interquartile range; *MUTYH*, mutY homolog.
[a]More than 1 ancestry reported by 1097 individuals.

### Prevalence of *APC* and *MUTYH* Mutations Among Individuals With Colorectal Adenomas

Of the 7225 individuals with a reported history of colorectal adenomas, 1457 (21%) had a classic polyposis phenotype (≥100 adenomas [1338 with 100-999 adenomas and 119 with ≥1000 adenomas]) and 3253 (45%) had an attenuated phenotype (20-99 adenomas) (TABLE 2).

Of the 119 individuals with 1000 or more adenomas, 95 (80% [95% CI, 71%-87%]) had a pathogenic *APC* mutation and 2 (2% [95% CI, 0.2%-6%]) had biallelic *MUTYH* mutations. In contrast, among 1338 individuals with 100 to 999 adenomas, 756 (56% [95% CI, 54%-59%]) had an *APC* mutation and 94 (7% [95% CI, 6%-8%]) had biallelic *MUTYH* mutations. The presence of a first-degree relative with colorectal cancer did not significantly influence *APC* or *MUTYH* mutation prevalence in individuals with 1000 or more adenomas.

Of the 3253 individuals with 20 to 99 polyps, 326 (10% [95% CI, 9%-11%]) had a pathogenic *APC* mutation and 233 (7% [95% CI, 6%-8%]) had biallelic *MUTYH* mutations. In these patients with an attenuated FAP phenotype, having a first-degree relative with colorectal cancer was associated with a higher *APC* mutation prevalence than if no such history existed (15% [95% CI, 13%-17%] and 8% [95% CI, 7%-9%], respectively).

Of the 970 individuals with 10 to 19 adenomas, *APC* and biallelic *MUTYH* mutations were present in 50 (5% [95% CI, 4%-7%]) and 37 (4% [95% CI, 3%-5%]), respectively. The majority of mutation carriers did not report a family history of colorectal cancer.

Overall, the prevalence of *APC* and *MUTYH* mutations varied with adenoma count, with *APC* mutation rate progressively increasing with increasing polyp burden and *MUTYH* mutation rates remaining relatively constant across different categories (FIGURE).

### Association Between Phenotypic Characteristics and a Pathogenic Mutation in Either Gene

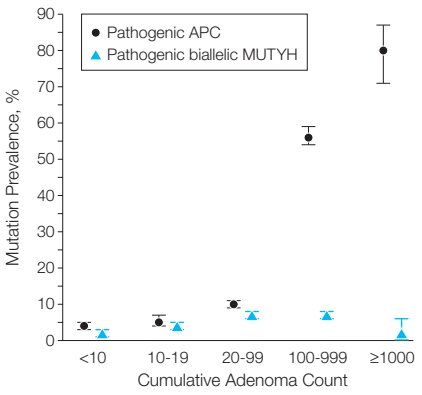
We performed bivariable and multivariable logistic regression analyses to evaluate the association of a pathogenic mutation in either gene with clinical characteristics (TABLE 3). In the multivariable logistic regression analysis, controlling for a family history of colorectal cancer in a first-degree relative, individuals with 10 to 19 adenomas were significantly more likely to have pathogenic *APC* mutations or biallelic *MUTYH* mutations than those with fewer than 10 adenomas (odds ratio [OR], 2.7 [95% CI, 1.9-3.7]). The odds of a mutation increased with adenoma count (20-99: OR, 6.4 [95% CI, 4.9-8.4]; 100-999: OR, 30.7

**Table 2.** Prevalence of Mutations by Adenoma Count

| Mutation | No./Total (%) [95% CI] Adenoma Count <10 (n = 1147) | 10-19 (n = 970) | 20-99 (Attenuated Polyposis) (n = 3253) | 100-999 (Classic Polyposis) (n = 1338) | ≥1000 (Classic Polyposis) (n = 119) | Missing Adenoma Count (n = 398) | Total, No. (%) (N = 7225) |
|---|---|---|---|---|---|---|---|
| Pathogenic *APC* | 44 (4) [3-5] | 50 (5) [4-7] | 326 (10) [9-11] | 756 (56) [54-59] | 95 (80) [71-87] | 109 (27) [23-32] | 1380 (19) |
| Colorectal cancer in first-degree relative | | | | | | | |
| Yes | 19/372 (5) [3-8] | 18/287 (6) [4-10] | 142/954 (15) [13-17] | 295/457 (65) [60-69] | 36/44 (82) [67-92] | 39/121 (32) [24-41] | 549 (40) |
| No | 25/775 (3) [2-5] | 32/683 (5) [3-7] | 184/2299 (8) [7-9] | 461/881 (52) [49-56] | 59/75 (79) [68-87] | 70/277 (25) [20-31] | 831 (60) |
| Biallelic *MUTYH* | 19 (2) [1-3] | 37 (4) [3-5] | 233 (7) [6-8] | 94 (7) [6-8] | 2 (2) [0.2-6] | 16 (4) [2-6] | 401 (6) |
| Colorectal cancer in first-degree relative | | | | | | | |
| Yes | 4/372 (1) [0.3-3] | 5/287 (2) [0.6-4] | 52/954 (5) [4-7] | 25/457 (5) [4-8] | 2/44 (4) [0.6-15] | 6/121 (5) [2-10] | 94 (23) |
| No | 15/775 (2) [1-3] | 32/683 (5) [3-7] | 181/2299 (8) [7-9] | 69/881 (8) [6-10] | 0/75 (0) [0-5] | 10/277 (4) [2-7] | 307 (77) |
| Monoallelic *MUTYH* | 28 (2) [2-3] | 12 (1) [0.6-2] | 74 (2) [2-3] | 15 (1) [0.6-2] | 0 (0) [0-3] | 6 (2) [0.6-3] | 135 (2) |
| Nonpathogenic/ no mutation | 1056 (92) [90-94] | 871 (90) [88-92] | 2620 (81) [79-82] | 473 (35) [33-38] | 22 (18) [12-27] | 267 (67) [62-72] | 5309 (73) |

Abbreviations: *APC*, adenomatous polyposis coli; *MUTYH*, mutY homolog.

**Figure.** Prevalence of *APC* and *MUTYH* Mutations by Adenoma Count




Numbers of participants in each adenoma count group and mutation prevalence numbers and percentages are reported in Table 2. Error bars indicate 95% CIs. *APC* indicates adenomatous polyposis coli; *MUTYH*, mutY homolog.

[95% CI, 23.4-40.3]; ≥1000: OR, 77.5 [95% CI, 45.3-132.4]). Colorectal adenomas prior to age 50 years were associated with an increased likelihood of pathogenic *APC* or biallelic *MUTYH* mutations, which increased progressively with earlier age at diagnosis (40-49 years: OR, 2.4 [95% CI, 2.0-2.8]; 30-39 years: OR, 4.2 [95% CI, 3.5-5.2]; <30 years: OR, 8.7 [95% CI, 7.1-10.6]).

### Phenotypic Differences Between Individuals With *APC* and Biallelic *MUTYH* Mutations

To examine the differences between the phenotypic characteristics of individuals with a pathogenic *APC* mutation and biallelic *MUTYH* mutations, we performed multinomial logistic regression analysis (logistic regression for a categorical dependent variable with ≥2 categories [*APC*, biallelic *MUTYH*, nonpathogenic *APC*, or *MUTYH* alteration/no *APC* or *MUTYH* alteration/monoallelic *MUTYH*)] (Table 3). The odds of carrying a pathogenic *APC* mutation were significantly increased in patients with more than 10 adenomas (10-19: OR, 2.4 [95% CI, 1.6-3.6]; 20-99: OR, 6.0 [95% CI, 4.3-8.2]; 100-999: OR, 40.1 [95% CI, 29.2-55.1]; ≥1000: OR, 124.0 [95% CI, 69.7-220.7]). Age at adenoma diagnosis was also associated with an *APC* mutation (<30 years: OR, 15.4 [95% CI, 12.2-19.5]; 30-39 years: OR, 6.1 [95% CI, 4.8-7.8]; 40-49 years: OR, 2.7 [95% CI, 2.2-3.4]). Individuals with 10 to 19 adenomas were significantly more likely to have biallelic *MUTYH* mutations than no mutation or a monoallelic *MUTYH* mutation. The odds of biallelic *MUTYH* mutations increased with increasing number of adenomas (10-19: OR, 2.9 [95% CI, 1.7-5.1]; 20-99: OR, 6.6 [95% CI, 4.1-10.6]; 100-999: OR, 12.5 [95% CI, 7.6-20.6]).

### Predicted Probability of *APC* and Biallelic *MUTYH* Mutations

The multinomial logistic regression model (eSupplement, available at http://www.jama.com) was also used to derive the predicted probability of pathogenic *APC* and *MUTYH* mutations based on phenotypic characteristics and family history of colorectal cancer. The C statistic was 0.81 (95% CI, 0.73-0.89) for *APC* and 0.59 (95% CI, 0.49-0.68) for *MUTYH* when the model included the number of adenomas alone, 0.88 (95% CI, 0.82-0.95) for *APC* and 0.59 (95% CI, 0.49-0.69) for *MUTYH* when the model included the number and age at adenoma diagnoses, 0.89 (95% CI, 0.82-0.95) for *APC* and 0.65 (95% CI, 0.55-0.74) for *MUTYH* when the pres-

ence of colorectal cancer and age at colorectal cancer diagnosis were added to the model, and 0.89 (95% CI, 0.82-0.95) for *APC* and 0.66 (95% CI, 0.56-0.75) for *MUTYH* when the presence of a first-degree relative with colorectal cancer was also included in the model.

To illustrate how the prediction probabilities derived from these models may be used in a clinical setting and the differences in *APC* and *MUTYH* mutation probability based on clinical characteristics, 20 clinical scenarios with their respective predicted mutation probabilities are reported in TABLE 4. For example, for an individual with multiple adenomas diagnosed at age 20 years and no history of colorectal cancer in a first-degree relative, the probabilities of *APC* and biallelic *MUTYH* mutations range from 97% (95% CI, 93.4%-100.0%) for *APC* and 0.5% (95% CI, 0.0%-1.9%) for *MUTYH* with 1000 or more adenomas to 89% (95% CI, 83.0%-95.2%) for *APC* and 3% (95% CI, 0.0%-6.9%) for *MUTYH* with 100 to 999 adenomas, to 59% (95% CI, 49.3%-68.6%) for *APC* and 8% (95% CI, 2.7%-13.4%) for *MUTYH* with 20 to 99 adenomas, and 38% (95% CI, 28.6%-47.7%) for *APC* and 6% (95% CI, 1.4%-10.7%) for *MUTYH* with 10 to 19 adenomas.

## COMMENTS

We evaluated the relative frequencies of mutations in the *APC* and *MUTYH* genes in a large number of individuals who had undergone genetic testing. Our results help further inform the understanding of the genetic epidemiology of the classic hereditary colorectal cancer syndrome FAP and shed some light on the important differences in disease patterns between carriers of *APC* mutations vs those with biallelic *MUTYH* mutations.

The clinical syndrome of FAP was first reported in 1847. In 1975, Bussey[16] described the clinical characteristics of patients with hundreds to thousands of colorectal polyps. In 1991, the *APC* gene was cloned and found to be mutated in patients with FAP.[1,17,18] *MUTYH*-associated polyposis was described in 2002 when Al-Tassan et al[2] noted biallelic germline mutations in the base excision repair gene *MUTYH* in a family with recessive inheritance of multiple colorectal adenomas and colorectal cancer.

Previous studies (predating the discovery of MAP) have reported widely varying prevalence of pathogenic *APC* mutations among individuals with a classic polyposis phenotype (52%-82%), likely attributable to varying mutation analysis techniques and patient selection.[19-24] However, these studies primarily involved small cohorts that

**Table 3.** Association Between Phenotypic Characteristics and *APC* and Biallelic *MUTYH* Mutation Status

| Covariate of Interest (No.) | OR (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| | *APC* or Biallelic *MUTYH* (n = 1930) | | *APC* (n = 1508) | | Biallelic *MUTYH* (n = 422) | |
| | Bivariable | Multivariable[a,b] | Bivariable | Multinomial[b,c] | Bivariable | Multinomial[b,c] |
| Adenoma count, No. | | | | | | |
| <10 (1218) | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| 10-19 (1020) | 1.6 (1.2-2.2) | 2.7 (1.9-3.7) | 1.2 (0.84-1.9) | 2.4 (1.6-3.6) | 2.3 (1.3-4.0) | 2.9 (1.7-5.1) |
| 20-99 (3420) | 3.5 (2.7-4.5) | 6.4 (4.9-8.4) | 2.7 (2.0-3.6) | 6.0 (4.3-8.2) | 4.6 (2.9-7.3) | 6.6 (4.1-10.6) |
| 100-999 (1437) | 28.9 (22.2-37.7) | 30.7 (23.4-40.3) | 31.0 (23.0-42.0) | 40.1 (29.2-55.1) | 4.3 (2.7-7.1) | 12.5 (7.6-20.6) |
| ≥1000 (130) | 76.3 (45.8-127.2) | 77.5 (45.3-132.4) | 98.1 (58.3-165.0) | 124.0 (69.7-220.7) | 0.94 (0.22-4.0) | 5.3 (1.2-24.2) |
| Age at adenoma diagnosis, y | | | | | | |
| <30 (1236) | 11.6 (9.9-13.7) | 8.7 (7.1-10.6) | 22.3 (18.3-27.2) | 15.4 (12.2-19.5) | 0.36 (0.23-0.57) | 0.93 (0.57-1.5) |
| 30-39 (1092) | 5.0 (4.2-5.9) | 4.2 (3.5-5.2) | 7.5 (6.1-9.2) | 6.1 (4.8-7.8) | 1.5 (1.1-2.0) | 2.2 (1.6-3.0) |
| 40-49 (1837) | 2.7 (2.3-3.2) | 2.4 (2.0-2.8) | 3.1 (2.5-3.8) | 2.7 (2.2-3.4) | 1.9 (1.5-2.4) | 2.0 (1.6-2.6) |
| ≥50 (3060) | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| History of colorectal cancer | | | | | | |
| Yes (2306) | 0.92 (0.82-1.0) | 1.7 (1.3-2.2) | 0.73 (0.64-0.83) | 1.2 (0.83-1.6) | 1.8 (1.4-2.2) | 2.8 (2.0-3.8) |
| No (6370) | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Age at colorectal cancer diagnosis, y | | | | | | |
| <30 (270) | 4.3 (3.1-5.9) | 0.83 (0.52-1.3) | 8.4 (5.8-12.3) | 1.2 (0.70-2.1) | 0.40 (0.18-0.90) | 0.60 (0.20-1.8) |
| 30-39 (479) | 2.7 (2.0-3.5) | 1.2 (0.85-1.8) | 3.9 (2.7-5.6) | 1.5 (0.94-2.4) | 1.2 (0.75-1.8) | 1.3 (0.77-2.2) |
| 40-49 (634) | 2.3 (1.7-3.0) | 1.8 (1.3-2.6) | 2.5 (1.8-3.6) | 1.9 (1.2-2.9) | 1.7 (1.2-2.5) | 1.8 (1.2-2.8) |
| ≥50 (923) | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |

Abbreviations: *APC*, adenomatous polyposis coli; *MUTYH*, mutY homolog; OR, odds ratio.
[a] Multivariable logistic regression analysis performed on imputed data set.
[b] Model includes the following variables: number of adenomas, age at adenoma diagnosis, history of colorectal cancer, age at colorectal cancer diagnosis, and family history of colorectal cancer in a first-degree relative.
[c] Multinomial logistic regression analysis performed on imputed data set.

were geographically and ethnically homogeneous. After the discovery of *MUTYH, APC* mutation–negative probands with classic FAP were screened for *MUTYH* mutations. These relatively small studies reported *MUTYH* mutation prevalence rates ranging from 7.5% to 20% in individuals with classic polyposis.[5,7]

The results of our study, in which all individuals were tested for both *APC* and *MUTYH* mutations, indicate significant heterogeneity in mutation prevalence, even among individuals with a classic polyposis phenotype. Among individuals with 1000 or more adenomas, 80% (95% CI, 71%-87%) had a pathogenic *APC* mutation, and *MUTYH* played a minor role (2% [95% CI, 0.2%-6%]). The distribution and prevalence of mutations was markedly different, however, in individuals with 100 to 999 adenomas (still considered classic polyposis)—only 56% (95% CI, 54%-59%) were *APC* carriers, and a higher proportion (7% [95% CI, 6%-8%]) had biallelic *MUTYH* mutations. No pathogenic *APC* or *MUTYH* mutations were detected in 18% (95% CI, 12%-27%) of individuals with 1000 or more adenomas and in 35% (95% CI, 33%-38%) with 100 to 999 adenomas, a finding potentially attributable in part to genes that have not been identified.

In contrast, in the 3253 individuals with attenuated polyposis, prevalence rates of pathogenic *APC* and *MUTYH* mutations were similar (10% [95% CI, 9%-11%] and 7% [95% CI, 6%-8%], respectively). This *MUTYH* prevalence rate is lower than those reported in prior reports from smaller cohorts of patients with attenuated polyposis, in which estimates have ranged from 22% to 29%.[5-8,10,25-28]

We did not evaluate the genotype-phenotype correlation among individuals with *APC* mutations as has been previously reported, because this study aimed to highlight the clinical characteristics associated with a pathogenic mutation in either of the 2 familial polyposis genes (*APC* or *MUTYH*) and the differences in these characteristics between mutation carriers. Ten or more adenomas and young-onset (<50 years) adenomas were associated with a mutation in either gene (*APC* or *MUTYH*). There was an incremental increase in the odds of a mutation, with an increasing number of adenomas and earlier age at adenoma diagnosis. Individuals with 10 or more adenomas and young-onset adenomas were significantly more likely to have an *APC* mutation. The presence of 10 or more adenomas was associated with a pathogenic *MUTYH* mutation, but in contrast to individuals with an *APC* mutation, the odds of a mutation did not incrementally increase with earlier age at diagnosis and were highest at ages between 30 and 49 years.

The study population is both a weakness and strength. This was not a population-based study, and participants had undergone testing based on a personal or family history suggestive of a polyposis syndrome by clinicians (physicians, physician assistants, nurse practitioners) who may have had variable expertise in genetic evaluation; therefore, the prevalence estimates, particularly in the groups with fewer numbers of individuals, must be interpreted with caution because of potential as-

**Table 4.** Predicted Probability of Pathogenic *APC* or Biallelic *MUTYH* Mutations Based on Clinical Phenotype

| | Adenomas | | Colorectal Cancer | | | Probability (95% CI) | |
|---|---|---|---|---|---|---|---|
| Clinical Scenario | No. | Age at First Diagnosis, y | Diagnosis, Yes/No | Age at Diagnosis, y | First-Degree Relative With Colorectal Cancer | *APC* Mutation | *MUTYH* Mutation |
| 1 | 10-19 | 20 | No | | No | 38 (28.6-47.7) | 6 (1.4-10.7) |
| 2 | 10-19 | 50 | No | | No | 7 (1.8-11.7) | 6 (1.6-11.2) |
| 3 | 10-19 | 50 | Yes | 50 | No | 2 (0.0-4.7) | 6 (1.4-10.8) |
| 4 | 10-19 | 50 | No | | Yes | 11 (5.1-17.5) | 5 (0.8-9.4) |
| 5 | 10-19 | 50 | Yes | 50 | Yes | 3 (0.0-7.0) | 5 (0.7-9.3) |
| 6 | 20-99 | 20 | No | | No | 59 (49.3-68.6) | 8 (2.7-13.4) |
| 7 | 20-99 | 50 | No | | No | 15 (7.9-21.8) | 12 (5.7-18.5) |
| 8 | 20-99 | 50 | Yes | 50 | No | 5 (0.5-8.8) | 12 (6.0-18.9) |
| 9 | 20-99 | 50 | No | | Yes | 24 (15.3-32.0) | 9 (3.5-14.8) |
| 10 | 20-99 | 50 | Yes | 50 | Yes | 8 (2.7-13.3) | 10 (4.2-16.0) |
| 11 | 100-999 | 20 | No | | No | 89 (83.0-95.2) | 3 (0.0-6.9) |
| 12 | 100-999 | 50 | No | | No | 51 (41.0-60.6) | 11 (5.2-17.7) |
| 13 | 100-999 | 50 | Yes | 50 | No | 23 (14.5-30.9) | 17 (9.4-24.0) |
| 14 | 100-999 | 50 | No | | Yes | 65 (55.8-74.5) | 7 (2.0-11.9) |
| 15 | 100-999 | 50 | Yes | 50 | Yes | 35 (25.2-43.9) | 12 (5.7-18.4) |
| 16 | ≥1000 | 20 | No | | No | 97 (93.4-100.0) | 0.5 (0.0-1.9) |
| 17 | ≥1000 | 50 | No | | No | 79 (70.5-86.6) | 2 (0.0-5.4) |
| 18 | ≥1000 | 50 | Yes | 50 | No | 51 (40.8-60.4) | 5 (0.8-9.3) |
| 19 | ≥1000 | 50 | No | | Yes | 87 (79.9-93.3) | 1 (0.0-3.4) |
| 20 | ≥1000 | 50 | Yes | 50 | Yes | 64 (55.0-73.8) | 3 (0.0-6.4) |

Abbreviations: *APC*, adenomatous polyposis coli; *MUTYH*, mutY homolog.

certainment and referral bias.[29] Nonetheless, this cohort is representative of individuals for whom genetic testing for *APC* and *MUTYH* genes should be considered and reflects the characteristics of the population at risk. We did not verify the pathology of polyps or the clinical data provided on the test order form. Although data were provided by clinicians whose specific specialty or training was not reported on the form, other studies using similar methods of data collection for cohorts tested for familial colorectal cancer syndromes have been externally validated, suggesting that the data are likely to be accurate and are likely not to vary between the groups being compared.[30,31] We also used multiple imputation techniques for missing data so as to minimize selection bias, which has been demonstrated to be particularly important in genetic association studies, in which missing data may be distributed differentially and may generate spurious associations. However, results obtained from using both complete case data and imputed data were similar.

The test order form did not elicit a history of hyperplastic polyps, which have been reported in small cohorts with MAP.[32] However, only a small percentage of patients with MAP present with hyperplastic polyposis, and adenomatous polyps and colorectal cancer remain the most common clinical presentation. Targeted sequence analysis was performed to detect the 2 most common *MUTYH* mutations (Y179C and G396D), and full *MUTYH* gene sequencing was performed in a small percentage of individuals. Full *MUTYH* sequencing may have led to an increase in some prevalence estimates; however, it is known that Y179C and G396D mutations account for the majority of mutant alleles in individuals of North American and European ancestry, who comprised the majority of our study participants.[7,33-35] The use of *MUTYH* gene rearrangement analysis and allele-specific *APC* analysis, which have recently been reported but are not widely available commercially, may also result in a small improvement in the yield of testing.[36]

Through evaluation of the phenotypic differences between mutation carriers in this large study, a pattern has emerged. Overall, in individuals with multiple adenomas, the *APC* mutation rate progressively increases with increasing polyp burden, whereas the *MUTYH* mutation rate remains relatively constant across different categories. Furthermore, the prevalence of *APC* mutations varies significantly among individuals with classic polyposis (≥1000 adenomas: 80% [95% CI, 71%-87%]; 100-999 adenomas: 56% [95% CI, 54%-59%]). In contrast, biallelic *MUTYH* mutations are rare in individuals with 1000 or more adenomas, and their prevalence is relatively constant among individuals with fewer than 1000 adenomas.

Our evaluation of individuals who underwent genetic testing because of a personal or family history suggestive of a familial polyposis syndrome suggests that genetic evaluation for *APC* and *MUTYH* mutations may be considered in individuals with 10 or more adenomas. However, our results are derived from a selected cohort of high-risk individuals and need to be validated in larger populations of unselected patients.

The mutation probabilities reported here may assist clinicians in their decision to recommend genetic evaluation and counsel patients undergoing genetic testing. However, it remains important to also consider the limitations of genetic testing at present, because one-third of patients with a classic FAP phenotype are found to not carry a mutation in either the *APC* or *MUTYH* gene. Such individuals should undergo periodic reevaluation as other susceptibility genes are identified.

**Author Contributions:** Drs Grover and Kastrinos had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Grover and Kastrinos, as first authors, contributed equally to the manuscript.
*Study concept and design:* Grover, Syngal.
*Acquisition of data:* Burbidge, Wenstrup.
*Analysis and interpretation of data:* Grover, Kastrinos, Steyerberg, Cook, Dewanwala, Syngal.
*Drafting of the manuscript:* Grover, Syngal.
*Critical revision of the manuscript for important intellectual content:* Grover, Kastrinos, Steyerberg, Cook, Dewanwala, Burbidge, Wenstrup, Syngal.
*Statistical analysis:* Grover, Kastrinos, Steyerberg, Cook, Syngal.
*Obtained funding:* Grover, Kastrinos, Syngal.
*Administrative, technical, or material support:* Dewanwala, Burbidge, Wenstrup.
*Study supervision:* Grover, Kastrinos, Syngal.
**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Grover reported employment with UpToDate Inc. Dr Kastrinos reported serving as a consultant for Marinabio Inc. Dr Steyerberg reported receiving a grant from the National Institutes of Health and receiving royalties from Springer for a book on clinical prediction models. Ms Burbidge and Dr Wenstrup reported holding stock options in Myriad Genetic Laboratories Inc. Dr Syngal reported serving as a consultant for Archimedes Inc, Quest Diagnostics Inc, Interquest Inc, and Cequent Inc; holding stock options from Marinabio Inc; and receiving travel/accommodations/meeting expenses unrelated to activities listed from Myriad Genetic Laboratories Inc. No other authors reported disclosures.
**Funding/Support:** This study was supported by National Cancer Institute grants R25 CA 092203 (Dr Grover) and K07 CA151769 (Dr Kastrinos) and by National Institutes of Health grant K24113433 (Dr Syngal).
**Role of the Sponsor:** The funding organizations had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.
**Independent Statistical Analysis:** Data sets were forwarded by investigators at Myriad Genetics Laboratories Inc to independent investigators at the Dana-Farber Cancer Institute, Boston, Massachusetts (Drs Grover and Syngal) and the Herbert Irving Comprehensive Cancer Center, New York, New York (Dr Kastrinos). Drs Grover, Kastrinos, and Steyerberg (Center for Medical Decision Making, Erasmus Medical Center, Rotterdam, the Netherlands) performed independent statistical analyses. All results reported in the article are from the independent statistical analyses. None of the coauthors not employed by Myriad Genetics Laboratories Inc received any funding for the study from Myriad Genetics Laboratories Inc.
**Disclaimer:** No grant support was obtained from Myriad Genetics Laboratories Inc to support the study.
**Online-Only Material:** The eSupplement is available at http://www.jama.com.

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