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ARTICLE

Primary care providers' responses to unsolicited Lynch syndrome secondary findings of varying clinical significance

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PURPOSE: How primary care providers (PCPs) respond to genomic secondary findings (SFs) of varying clinical significance (pathogenic, uncertain significance [VUS], or benign) is unknown.
METHODS: We randomized 148 American Academy of Family Physicians members to review three reports with varying significance for Lynch syndrome. Participants provided open-ended responses about the follow-up they would address and organized the SF reports and five other topics in the order they would prioritize responding to them (1 = highest priority, 6 = lowest priority).
RESULTS: PCPs suggested referrals more often for pathogenic variants or VUS than benign variants (72% vs. 16%, $p < 0.001$). PCPs were also more likely to address further workup, like a colonoscopy or esophagogastroduodenoscopy, in response to pathogenic variants or VUS than benign variants (43% vs. 4%, $p < 0.001$). The likelihoods of addressing referrals or further workup were similar when PCPs reviewed pathogenic variants and VUS (both $p > 0.46$). SF reports were prioritized highest for pathogenic variants (2.7 for pathogenic variants, 3.6 for VUS, 4.3 for benign variants, all $p \leq 0.014$).
CONCLUSION: Results suggest that while PCPs appreciated the differences in clinical significance, disclosure of VUS as SFs would substantially increase downstream health-care utilization.

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INTRODUCTION

Increasingly, primary care providers (PCPs) will have to manage genomic test results. PCPs are already encountering genetic risk information that their patients have obtained from direct-to-consumer (DTC) services,[1] and numerous health systems are offering genomic screening to patients as an elective service.[2–4] In addition, a growing number of research initiatives are performing genome-based testing and are returning individual genomic research results to their participants with expectations that PCPs will manage follow-up.[5,6] When patients receive genome or exome sequencing based on personal or family histories of disease, the American College of Medical Genetics and Genomics recommends the return of highly actionable secondary findings that may be unrelated to test indications.[7] As frontline providers, PCPs will need to help patients manage genomic information that they have not ordered.

These developments raise concerns about how PCPs will respond. Only about 60% of PCPs report receiving formal genetics training during their medical education.[8] In surveys, only half of PCPs reported being at least somewhat knowledgeable about genetics[9,10] and approximately 41% rate their genetics knowledge as very poor.[11] Limitations in PCPs preparedness to practice genomic medicine may lead to inappropriate medical follow-up and increased downstream medical costs.[12,13] Moreover, providers may also be reluctant to act on this information altogether, possibly leading to missed opportunities to improve the way they manage their patients' health-care and prevent disease.[14–16]

PCPs' abilities to manage genomic test results may be especially challenging when the health implications of the findings are unclear, such as variants of uncertain significance (VUS).[17] Generally, clinical laboratories report VUS from exome/genome sequencing only for results pertaining to the test indications, but practices are at the discretion of individual laboratories and can vary greatly.[18] A majority of nongenetic specialists and a minority of genetic specialists in a recent study reported that laboratories should be obligated to report VUS when patients had an associated family history of disease.[14]. Individuals can also receive genomic information, including VUS, through direct-to-consumer testing apps that allow consumers to query their genomes themselves, or by requesting their raw genetic data from DTC companies, like 23andMe, Ancestry.com, and others and having them interpreted by third-party interpretation services.[19] Consumers receiving these results may ask their PCPs for guidance about how to respond.

At present, most research on PCPs' responses to unsolicited genetic test results has come from observational studies that have examined the disclosure of pathogenic variants as secondary findings.[14,16,20–22] We expand upon this literature by asking PCPs how they would respond to various results related to secondary findings for Lynch syndrome. We hypothesized that providers who viewed reports for pathogenic variants or VUS would be more

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likely to consider clinical follow-up and referrals than providers who viewed reports for benign variants. We also hypothesized that providers would assign a higher priority to act upon a secondary finding characterized as a pathogenic variant than a finding characterized as VUS or benign. The goal of this study was to provide insight to policymakers about potential provider responses to genomic information of varying clinical importance.

MATERIALS AND METHODS

Participants and study design

We invited 4,000 members of the American Academy of Family Physicians (AAFP) in 2014 to complete a web-based survey. Eligible participants were prespecified as providers with active licenses who provided direct patient care. AAFP staff sent email invitations to a random sample of their members who met eligibility criteria. Invitations provided an overview of the study purpose and presented a link to a web-based survey hosted by Qualtrics software (Qualtrics, Provo, UT), with two reminders sent approximately two weeks apart. Consent was implied by survey completion. Respondents were provided a $25 Amazon gift card upon completing the survey. The study protocol was developed by a multidisciplinary team with experience in clinical and molecular genetics, primary care, and public health. A convenience sample of five physicians and five genetic counselors reviewed and pilot tested the survey for usability prior to launch. The study protocol was approved by the AAFP and the Institutional Review Board of Mass General Brigham (formerly Partners HealthCare).

Figure 1 summarizes the flow of survey participation. The survey included a description of the study's purpose, procedures, and definitions of terms. It then presented a scenario where a new 30-year-old female patient requested help interpreting a secondary genomic finding in a gene associated with Lynch syndrome (Supplementary Fig. 1). The survey platform randomly assigned participants in equal proportions to arms that presented one of three genetic test reports: a pathogenic variant (NM_000179.2[MSH6]: c.1784delT), a VUS (NM_000249.3[MLH1]: c.25C>T), or a benign variant (NM_000249.4[MLH1]: c.1151T>A). The layout of reports was based on prior work that tested different formats for summarizing genetic testing findings for PCPs.[23] A section that provided additional information such as clinical characteristics of Lynch syndrome, population prevalence, and testing sensitivity and specificity was omitted during pilot testing due to concerns that the survey was too long. Content was developed with assistance from a genetic counselor and medical geneticist and reviewed by a medical oncologist.

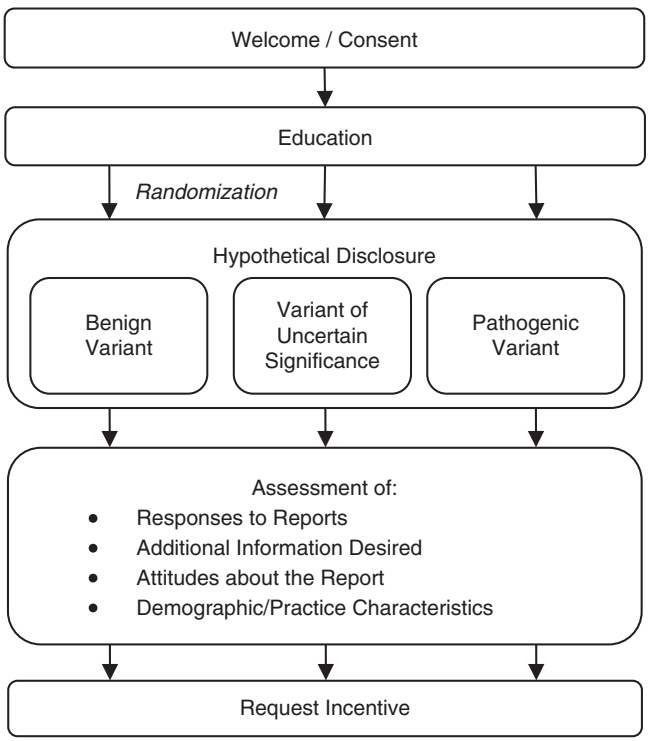

Fig. 1 Flow of survey participation. After brief education about genetic testing terminology, participants were randomized to review one of three hypothetical scenarios about a secondary genomic finding in a gene associated with Lynch syndrome.

We used a clinical reporting format for all variant types, including VUS and benign variants, to maximize perceptions about the analytic validity of reported findings. We included the benign variant to determine how providers might interact with a genomic report where the variant was not pathogenic or associated with Lynch syndrome. The survey also asked about the actions they would take in response to the reports. We collected demographic and practice information at the end of the survey as well. Respondents were then directed to a separate website unlinked to their survey responses where they could provide contact information for delivery of the study incentive.

Survey domains

Response to report

The survey asked for open-ended responses for up to five actions that would be taken and referrals that would be made based on the test report received. Actions and referrals were collected as open-ended responses to avoid prompting participants to endorse actions they may not have actually considered. If participants would not take any actions or make any referrals, they were prompted to specifically list "no action" or "none."

Participants also organized six topics that may be addressed during an initial patient encounter. These topics were the genomic results, personal history of disease, family history of disease, blood pressure, lipid levels, and immunizations. Participants used a drag-and-drop interface to organize the topics such that the most important topic was at the top of the list and the least important topic was at the bottom of the list. Topics were then assigned a 1–6 value according to their final position (1 = the most important topic, 6 = the least important topic).

The survey also asked participants to rate the importance of eight factors relevant to interpreting the reports: family health history, personal medical history, existing symptoms, cancer surveillance history, medication use, smoking, exposures, and laboratory tests. Response options for each of the factors included not at all important, somewhat unimportant, somewhat important, and extremely important.

Attitudes about the report

The survey included six statements to assess the respondents' attitudes toward the genetic test report, including burden on the provider, harm to the patient, laboratory obligation to report findings, provider understanding, and importance of results on patient care. Response options included strongly disagree, disagree, agree, and strongly agree. Respondents also rated their confidence about understanding genomic information on a six-item self-efficacy scale, which were aggregated to create a final score from 6 to 24 with higher scores indicating greater confidence.[24]

Data analysis

Survey responses from one respondent who did not confirm specialization in family practice were omitted from analyses. Open-ended responses about actions and referrals were classified using approaches developed for coding qualitative data.[25] First, one study team member (K.D.C.) proposed an initial codebook based on review of responses. Two study team members (L.N.G. and C.L.P.) then coded each response set independently. In instances where interrater reliability metrics were suboptimal, codebooks were revised and data were recoded until agreement was strong (Cohen's $\kappa > 0.8$).[26] Final differences in coding were reconciled by a single study team member (L.N.G.). Final codes were then combined into parent codes for analysis, which can be found in the appendices. Available case analyses where missing data were not imputed were conducted using R version 4.0.3.

Respondents' genders were compared against AAFP member files using a one-sample test of proportions. Respondents' ages were also compared, although formal comparisons could not be conducted because distributions of ages were not available about AAFP membership. We used chi-squared tests to compare the rates of actions and referrals by randomization status. We used Wilcoxon rank sum tests to compare whether randomization arms differed in the way they prioritized different topics, the additional information they wanted to help interpret reports, and their attitudes toward the reports. We used Friedman tests to compare

whether preferences for the return of secondary findings varied by finding or disease characteristics. Statistical significance was set at a two-sided p value of 0.017 to account for testing of three primary a priori hypotheses at an overall $\alpha = 0.05$: providers who viewed reports for pathogenic variants or VUS would be more likely to address (1) clinical follow-up and (2) referrals than providers who viewed reports for benign variants, and (3) providers would assign higher priorities to act upon pathogenic variants than VUS or benign variants. We estimated 108 total respondents were needed to achieve 80% power to test the first and second hypotheses, and 162 total respondents were needed to achieve 80% power to test the third hypothesis.

RESULTS

Participant characteristics

Of 4,000 AAFP members who were invited, 148 (3.7%) responded. Six (4.1%) started the survey but discontinued it so their data were omitted. Of the remaining 142 respondents, 46 (31.1%) reviewed a pathogenic variant, 47 (31.8%) reviewed a VUS, and 55 (37.2%) reviewed a benign variant ($p = 0.61$). Characteristics of respondents who provided demographic and practice information are summarized in Table 1. Survey respondents were more likely to be female than the overall AAFP membership (54.2% vs. 40.7%, respectively, $p = 0.001$), although mean ages appeared similar (50.3 vs. 48.4, respectively). Most respondents identified themselves as non-Hispanic white (78.9%) and 89.4% reported that they spent more than 75% of their time providing direct patient care.

Mean genetics self-efficacy scores were moderate (15.7 on the 6–24 scale), but respondents were more likely to agree than disagree with individual statements that they could interpret genetic sequencing results (58.6% vs. 42.4%). Respondents tended to be unfamiliar and inexperienced with genetics and Lynch syndrome. Only 15 respondents (10.6%) reported being very or extremely familiar with Lynch syndrome, although 29 (20.4%) reported having patients with the condition. Only three respondents (2.1%) reported ordering a genetic test for Lynch syndrome in the past year.

Table 1. Characteristics of survey respondents.

Characteristic	$n = 142$ (%), unless noted
Mean age (SD)	50.3 (10.6)
Gender	
Male	65 (45.8%)
Female	77 (54.2%)
Non-Hispanic white	112 (78.9%)
Mean years since medical school graduation (SD)	22.7 (11.1)
Practice	
Hospital-based	8 (5.6%)
Individual	27 (19.0%)
Small group	44 (31.0%)
Large group	44 (31.0%)
Other	19 (13.4%)
Percent time in direct patient care	
Less than 10%	2 (1.4%)
11–50%	5 (3.5%)
51–75%	8 (5.6%)
More than 75%	127 (89.4%)
Degree[a]	
MD	126 (89.4%)
DO	15 (10.6%)
Medical school	
US medical school	127 (89.4%)
Foreign medical graduate	15 (10.6%)
Mean genetics self-efficacy score (SD)	15.7 (3.4)
Number of times genomic sequencing was ordered or received by respondents in the past 12 months	
0	90 (63.4%)
1 to 5	44 (31.0%)
6 to 10	2 (1.4%)
11 or more	6 (4.2%)
Number of times genetic tests were ordered or received by respondents in the past 12 months	
0	65 (45.8%)
1 to 5	66 (46.5%)
6 to 10	5 (3.5%)
11 or more	6 (4.2%)

No differences were observed by randomization arm on any provider characteristics. Six respondents did not provide demographic and practice characteristics.
[a]One additional participant did not provide information about her or his medical degree.

Response to report

Providers were more likely to state that they would act on the information if they received a report with the pathogenic variant or VUS than the benign variant. Twenty-four respondents who reviewed the benign variant report (44%) overtly stated that they would neither take action nor refer patients for follow-up, compared to none of the respondents who received the pathogenic variant report (0%; $p < 0.001$ vs. benign arm) and three who received the VUS report (6%; $p < 0.001$ vs. benign arm). Four who received the benign variant report (8%) indicated that they would not review the report with the patient during the initial visit, compared to only one provider who received the pathogenic variant report (2%; $p = 0.004$ vs. benign arm) and three providers who received the VUS report (6%; $p = 0.060$ vs. benign arm).

As hypothesized, respondents were more likely to address further workup when they reviewed either a pathogenic variant or VUS than a benign variant (43% for pathogenic or VUS, 4% for benign, $p < 0.001$). Regarding additional workup, 30% of respondents who received the pathogenic variant or VUS reports stated that they would consider a colonoscopy, and 4% reported that they would consider an esophagogastroduodenoscopy (all $p \leq 0.003$). Respondents who reviewed a pathogenic variant or VUS were also more likely than respondents who reviewed a benign variant to address reviewing family histories of disease, cancer screening, testing family members, and documenting the finding (Fig. 2; Supplementary Table 1; all $p \leq 0.017$). Conversely, respondents were more likely to address reassuring patients in response to report of a benign variant than reports for a VUS or pathogenic variant (all $p < 0.002$). Also, as hypothesized, respondents were more likely to address referrals when they reviewed either a pathogenic variant or VUS than a benign variant (72% for pathogenic or VUS, 16% for benign, $p < 0.001$). More specifically, these PCPs were more likely to refer patients to genetic specialists or to gastroenterology (all $p \leq 0.002$). Notably, differences between respondents who received the pathogenic variant and VUS reports did not achieve statistical significance on aggregated or specific measures of actions or referrals.

Similarly, respondents rated the importance of most types of additional information for interpreting reports lower when they

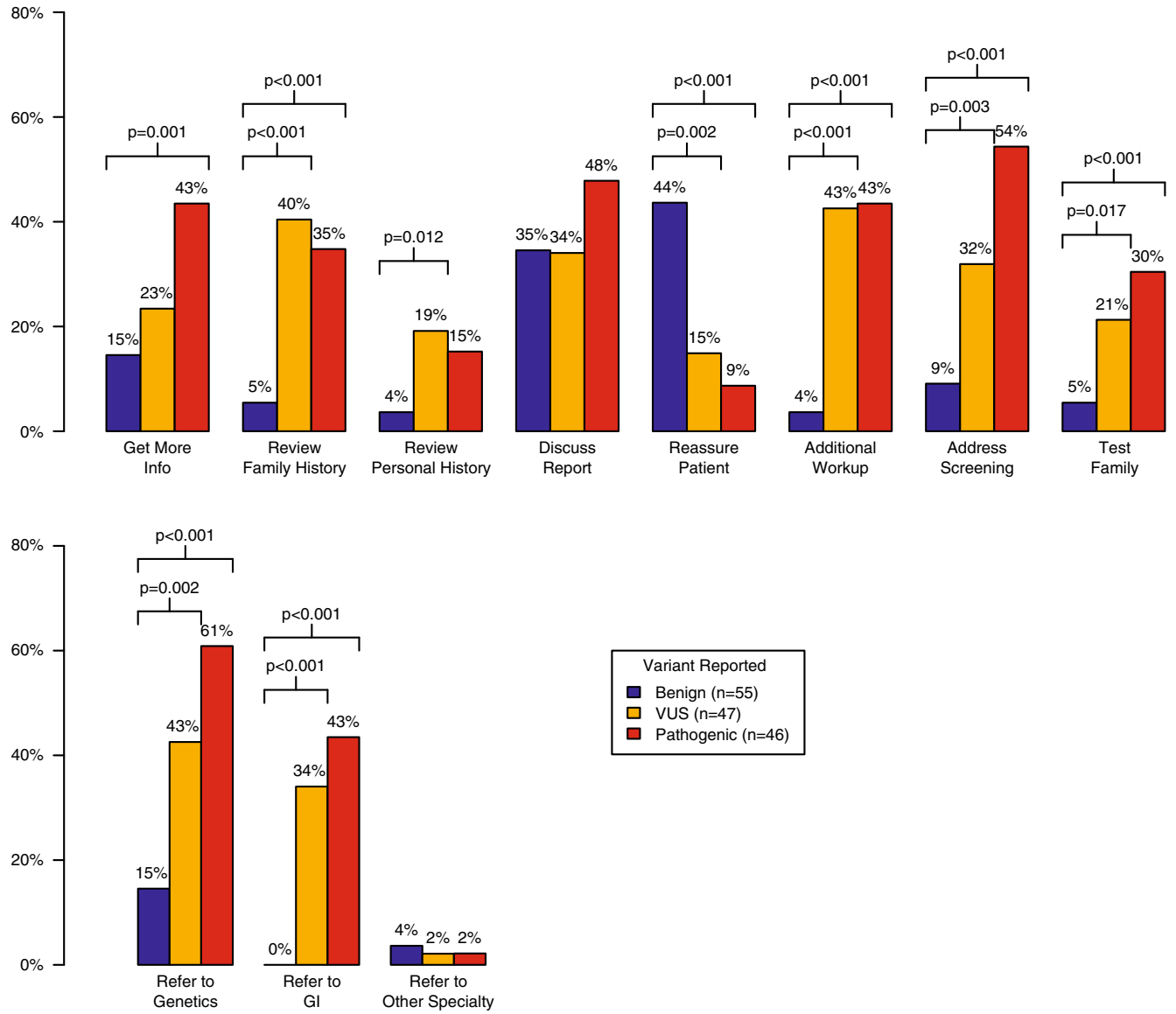

Fig. 2 Actions that participants reported they would consider in response to the secondary findings type, by variant classification. Subcategories of actions and referrals summarized in the categories above are summarized in Supplementary Tables 1 and 2. GI gastrointestinal specialist or gastroenterologist.

received a benign variant report, but differences were not observed between respondents who received pathogenic variant and VUS reports (Fig. 3). Among respondents who received reports about a pathogenic variant or VUS, over 70% reported the patient's family history, medical history, and symptoms as very important for interpreting the report, compared to less than 55% of providers who received a report about a benign variant (all $p < 0.001$).

Attitudes toward the reports were consistent across variants except for the perceived importance of the report (Fig. 4). Over 80% of respondents who received any report agreed with the statements that laboratories are obligated to report these findings and that they understood the information in the report. Regardless of what variant they reviewed, less than 35% indicated the report would be a burden to them, but the majority also stated that follow-up may harm their patient. Differences by variant were only observed on the perceived importance of the report with 96% of respondents who received a pathogenic variant report and 83% who received a VUS report stating the information would be important to the patient's health and health care, while only 49% who received a benign variant report felt this way ($p \leq 0.009$ for all pairwise comparisons).

The prioritization providers assigned to these genomic test reports varied by variant classification (Supplementary Table 3). Providers assigned greater priority to the reports when they reviewed a pathogenic variant (mean rank: 2.7) than when they reviewed a VUS (mean rank: 3.6; $p = 0.014$ vs. ranking of pathogenic variants) or a benign variant (mean rank: 4.3; $p < 0.001$ vs. ranking of pathogenic variants). Notably, the patient's history of disease received the greatest priority when respondents reviewed a VUS (mean rank: 2.0; $p = 0.008$ vs. ranking of pathogenic variants). Differences in how respondents ranked all other topics by randomization arm were not statistically significant.

DISCUSSION

Here, we summarize data about PCPs' anticipated responses to Lynch syndrome secondary findings of varying clinical significance. The majority of participants reported that they understood

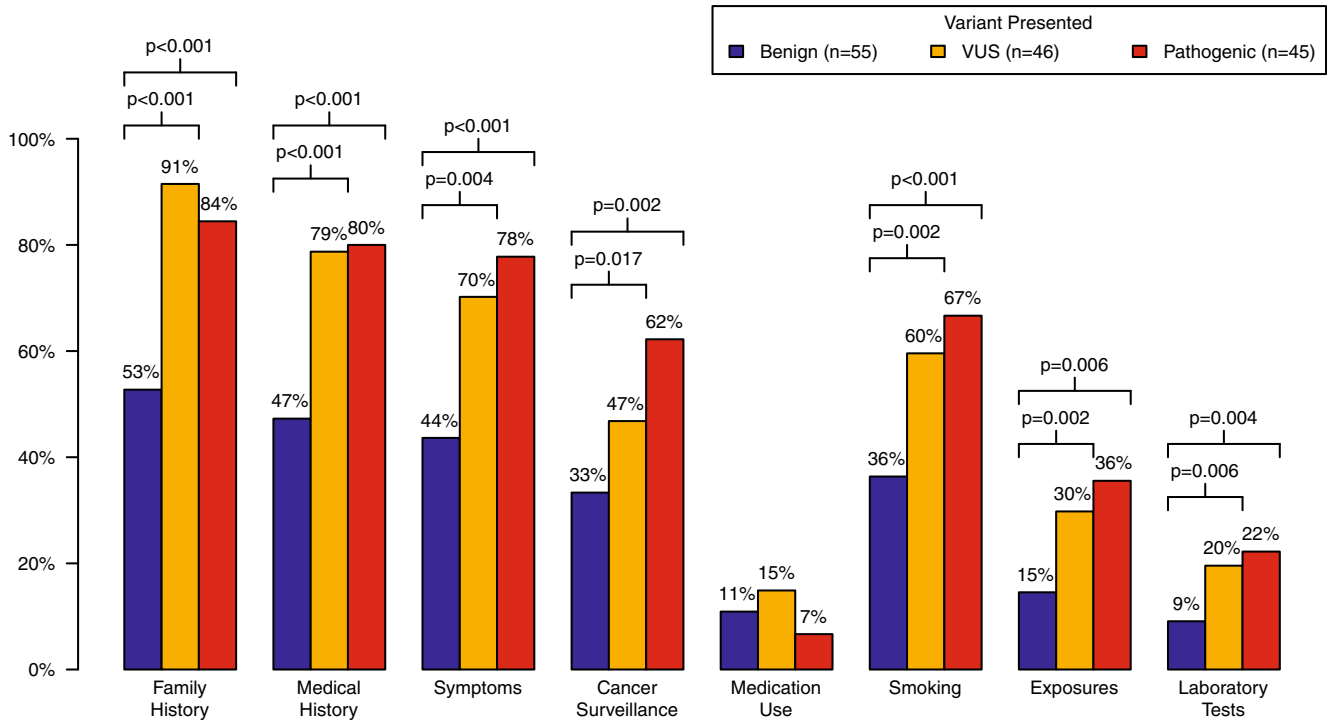

Fig. 3 Additional information needed, by variant classification. Bars indicate the percentage of participants who reported the importance of a factor as "very important" for interpreting the secondary findings report.

the information contained in the reports they received, regardless of SF result. PCPs prioritized highest responding to the reports when they presented pathogenic variants and lowest when they presented benign variants. Few differences were observed between PCPs who reviewed VUS and pathogenic variants about the actions they would consider. Overall, our findings suggest that respondents were sensitive to the types of variants they reviewed but were likely to manage VUS similar to the ways they would manage pathogenic variants.

Results are simultaneously encouraging about the ability of PCPs to understand secondary findings reports while raising concerns about the impact of disclosing results, such as VUS. The rates for additional workup and referrals we observed suggest that the PCPs would request health-care interventions in response to VUS and pathogenic variants similarly. Although similarities in responses to VUS and pathogenic findings have been observed in studies of diagnostic testing,[27] the likelihood that VUS are clinically significant as secondary findings are substantially lower.[28] It is possible that respondents misunderstood the meaning of VUS and the likelihood that they may not be pathogenic. Even cancer specialists often struggle with the meaning of VUS findings in the absence of clinical decision support.[29] The mere act of issuing a secondary findings report may have heightened such perceptions, as PCPs may have assumed that the variants would not be reported unless they warranted clinical response. Yet, our data also showed important differences in attitudes after PCPs reviewed VUS and pathogenic variants. PCPs assigned less priority to responding to VUS compared to pathogenic variants. Over 90% of PCPs who reviewed VUS rated family history information as very important, and these PCPs also assigned greater priority to addressing family history information than PCPs who reviewed pathogenic reports. Taken together, these data suggest that PCPs recognized that other clinical information would be critical to judging the significance of the VUS. It is likely that PCPs were sensitive to the meaning of VUS reports, but also felt that they need to act defensively in response to them. A growing body of literature addresses potential legal liabilities associated with secondary genomic findings, including implications if physicians fail to act on these results.[30–32] As a result, the disclosure of VUS could lead to unnecessary medical follow-up for patients such as prophylactic surgery that not only increases downstream costs, but potentially harms patients as well. There are also the additional risks that patients may experience of psychological distress from the disclosure of VUS or, conversely, feel false reassurance that they do not carry pathogenic variants.[33] Moreover, the benefits and risks of genetic information disclosure can be compounded by the responses of family members who seek cascade screening for the same VUS.

Importantly, results suggested that respondents were generally familiar with the implications of Lynch syndrome variants for colorectal cancer risk, but unfamiliar about the increased risks for other cancers, including less common conditions such as urothelial cancer and those that affect women such as endometrial cancer. While 43% of respondents who viewed pathogenic reports addressed referrals to gastroenterologists, only 13% of respondents addressed referrals to gynecologists. Similarly, far fewer respondents addressed pelvic exams or endometrial biopsies than colonoscopies, even though mock reports communicated a 20–60% risk for endometrial cancer. Results add weight to existing calls for robust clinical decision support for genomic information, particularly for PCPs, to help ensure they manage surveillance and follow-up of patients appropriately.[34]

Our results also provide insight about how PCPs may respond to genomic findings received by unselected populations. The condition of focus in our study, Lynch syndrome, is considered by the Centers for Disease Control and Prevention to be a tier 1 genomic application with the greatest potential to benefit patients if implemented as population screening.[35] Moreover, healthy patients may already obtain genetic information about Lynch syndrome from elective clinical testing, DTC services, or through third-party interpretation programs.[19,36] PCPs are likely to be called upon to answer their patients' questions about such

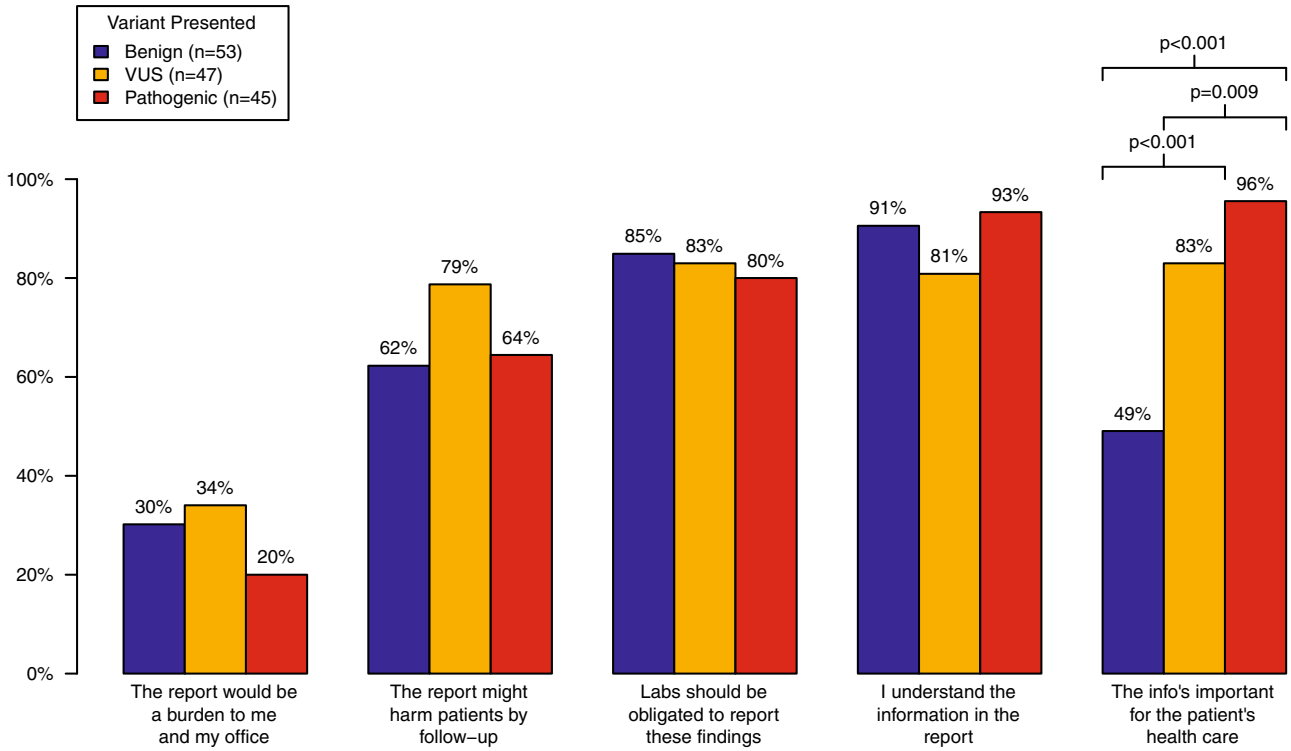

Fig. 4 Participants' attitudes toward the genetic sequencing report, by variant classification. Bars indicate the percentage of participants who agreed or strongly agreed with each statement.

results and to understand when ordering such tests themselves is appropriate.[37]

Interestingly, nearly half of respondents who reviewed a report about a benign variant reported that these sequencing reports were important for managing their patients' health. Moreover, greater than 80% of respondents felt that labs should be obligated to report these secondary findings, even when reports presented variants classified as benign or VUS. These findings are concerning because, as secondary findings, they provide nearly no insight about patient's risks for cancer but may provide false reassurance that patients do not carry genetic risk factors. PCPs often have misunderstandings about sequencing results,[38] and could be falsely reassured that their patient does not have any risk, incorrectly interpreting the variant as a true negative. The mere act of reporting a benign variant may have made some respondents think that it held some clinical significance. Although it is extremely unlikely that laboratories will begin to report VUS or benign variants as secondary findings, the potential exists for patients to receive results from alternative mechanisms, like DTC testing, elective clinical testing, or third-party interpretation services. Ongoing genomic education for providers should address the potential for providers to encounter reports of VUS and benign variants and reinforce that such results are uninformative and will likely not have an impact on the care their patient receives.

Limitations to our study include enrollment of self-selected participants who may have had a greater interest in genetic information that nonparticipants. Mock reports were formatted based on prior studies of report preferences among PCPs,[23] but do not reflect the format used by many laboratories and had limited content in comparison. These reports also included the same guidance about managing Lynch syndrome, regardless of the variant classification, which could have prompted respondents to believe follow-up was warranted. In practice, most laboratories do not report benign variants nor VUS as secondary findings, though exceptions may occur, particularly for suspicious VUS with partial evidence for pathogenicity.[39] Even then, reports may be formatted differently than reports of pathogenic variants.[40] Data on physician actions and referrals were based on open-ended responses, which cannot differentiate services that PCPs would consider and/or discuss with patients from services that PCPs would initiate. Guidelines do not exist to guide patient management in response to VUS identified as secondary findings.

Nevertheless, our study provides crucial data about how PCPs may respond to unsolicited Lynch syndrome findings of varying classifications. As genomic medicine continues to expand in all areas of patient care, systems for provider education and support will need to be sensitive about the potential for PCPs to encounter not only results about pathogenic variants, but also VUS and benign variants.

DATA AVAILABILITY

Data will be made available at request. Inquiries can be directed to the corresponding author.

CODE AVAILABILITY

Code will be made available at request. Inquiries can be directed to the corresponding author.

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AUTHOR CONTRIBUTIONS

Conceptualization: L.N.G, H.R., M.T.S., C.H., R.G., K.D.C. Data curation: L.N.G., C.L.P., K.D.C. Formal analysis: L.N.G., C.L.P., H.R., M.T.S., C.H., R.G., K.D.C. Funding acquisition: K.D.C. Investigation: L.N.G., C.L.P., K.D.C. Methodology: C.L.P., H.R., M.T.S., R.G., K.D.C. Project administration: K.D.C. Resources: R.G., K.D.C. Supervision: L.N.G., K.D.C. Validation: H.R., M.T.S., C.H., R.G., K.D.C. Visualization: L.N.G., K.D.C. Writing—original draft: L.N.G., K.D.C. Writing—review & editing: L.N.G., C.L.P., H.R., M.T.S., C.H., R.G., K.D.C.

ETHICS DECLARATION

The study protocol was approved by the AAFP and the Institutional Review Board of Mass General Brigham (formerly Partners HealthCare). Informed consent was considered implied by survey completion.

COMPETING INTERESTS

R.C.G. has received compensation for advising the following companies: AIA, Genomic Life, Grail, Humanity, Kneed Media, Plumcare, UnitedHealth, Verily, VibrentHealth, and is co-founder of Genome Medical, Inc., a technology and services company providing genetics expertise to patients, providers, employers and care systems. The other authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41436-021-01225-7.

Correspondence and requests for materials should be addressed to K.D.C.

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Supplementary Materials

Supplementary Table 1. Specific actions addressed by respondents, stratified by variant reviewed. Findings summarized in Figure 1 are omitted here.

			Variant Reviewed			
Action	**Description**	**Sample Response**	**Benign, n (%)**	**VUS, n (%)**	**Pathogenic, n (%)**	**p [a]**
Nothing	Provider explicitly said, "no action"	"No action"	26 (47%)	3 (6%)	1 (2%)	<0.001
Discuss or explain result with patient	Providers reported that they would explain the result	"Discuss findings with patient"	19 (35%)	16 (34%)	22 (48%)	0.294
Reassure patient	Providers reported that they would reassure the patient	"Reassure the patient that this is new for all of us"	24 (44%)	7 (15%)	4 (9%)	<0.001
Get More Information						
Seek information	Providers reported that they would seek more information	"Research Lynch syndrome"	7 (13%)	8 (17%)	18 (39%)	0.004
Call lab	Providers reported that they would call the laboratory to discuss the report	"Call the phone number for additional assistance with interpretation"	1 (2%)	6 (13%)	3 (7%)	0.083
Address with colleague	Providers reported that they would confer with a colleague	"Ask colleague"	1 (2%)	0 (0%)	4 (9%)	0.057
Confirm Results	Providers reported that they would order confirmatory testing	"Get confirmatory testing for lynch syndrome"	0 (0%)	4 (9%)	3 (7%)	0.067

Review Family History	Providers reported that they would review the patient's family history of disease	"Get detailed family history"	3 (5%)	9 (40%)	16 (35%)	<0.001
Review Personal History	Providers reported that they would review the patient's personal history of disease	"Obtain a personal GI history"	2 (4%)	9 (19%)	7 (15%)	0.043
Additional Workup						
Colonoscopy	Providers reported that they would order or consider a colonoscopy	"Colonoscopy at early age"	0 (0%)	14 (30%)	14 (30%)	<0.001
EGD	Provider reported that they would order or consider an EGD	"Esophagoduodenoscopy"	0 (0%)	2 (4%)	2 (4%)	0.260
Biopsy	Providers reported that they would order or consider a biopsy	"Annual endometrial biopsy and transvaginal"	0 (0%)	1 (2%)	1 (2%)	0.530
Pelvic exam	Providers reported that they would conduct or consider a pelvic exam.	"Pelvic Exam"	0 (0%)	1 (2%)	4 (9%)	0.025
Other test	Providers reported that they would conduct or consider a procedure that was not captured in one of the above follow-up codes	"Full body skin eval"	0 (0%)	9 (19%)	7 (15%)	0.004
Continue workup	Providers reported that they would offer to continue a workup	"Offer to continue workup"	2 (4%)	2 (4%)	2 (4%)	>0.999
Test Family	Providers reported that they would discuss testing of family members	"Offer testing to other family members"	3 (5%)	10 (21%)	14 (30%)	0.004

Recommend Screening	Providers reported that they would address disease screening	"Start early colon screening"	5 (9%)	15 (32%)	5 (54%)	<0.001
Document finding	Providers reported that they would document the result in the patient's medical record	"Enter finding on problem list"	5 (9%)	15 (32%)	25 (54%)	<0.001

[a] P-value from chi-squared or Fisher's exact tests comparing all three randomization arms

Supplementary Table 2. Specific referrals addressed by respondents for categories reported in Figure 3, stratified by variant reported. Findings summarized in Figure 1 are omitted here.

		Variant Reviewed			
Code	**Description**	**Benign, n (%)**	**VUS, n (%)**	**Pathogenic, n (%)**	**p [a]**
No Referral	Providers explicitly said, "none" or no referrals	45 (82%)	16 (34%)	6 (13%)	<0.001
Genetics					
Genetic counselor	Providers reported that they would consider a referral to a genetic counselor	3 (5%)	8 (17%)	16 (35%)	0.001
Medical geneticist	Providers reported that they would make or consider a referral to a medical geneticist	5 (9%)	12 (26%)	12 (26%)	0.047
Gastroenterology	Providers reported that they would consider a referral to a gastroenterologist or a referral for a colonoscopy	0 (0%)	16 (34%)	20 (43%)	<0.001
Other Specialty					
Gynecologist	Providers reported that they would consider a referral to a gynecologist	1 (2%)	3 (6%)	6 (13%)	0.074
Oncology	Providers reported that they would consider a referral to an oncologist	0 (0%)	1 (2%)	6 (13%)	0.003
Other	Providers reported that they would consider a referral to an unspecified specialist or a specialist that was not listed above [b]	3 (5%)	5 (11%)	11 (24%)	0.026

[a] P-value from chi-squared or Fisher's exact tests comparing all three randomization arms.

[b] Responses included developmental specialist, immunologist, and neuropsychologist.

Supplementary Table 3. Prioritization of information during the initial patient encounter, by variant classification presented in the hypothetical secondary findings report.

	Mean rank, 1-6 (SD)					
	Benign	**VUS**	**Pathogenic**	**p, pathogenic vs benign**	**p, VUS vs benign**	**p, pathogenic vs VUS**
Genomic sequencing report	4.3 (1.8)	3.6 (1.7)	2.7 (1.7)	<0.001	0.061	0.014
Personal history of disease	2.4 (1.3)	2.0 (1.1)	2.5 (1.0)	0.314	0.162	0.008
Family history of disease	3.1 (1.2)	2.9 (1.4)	2.8 (1.3)	0.298	0.261	0.874
Blood pressure	2.5 (1.6)	3.3 (1.6)	3.3 (1.7)	0.026	0.026	0.913
Lipid levels	4.0 (1.5)	4.6 (1.3)	4.5 (1.4)	0.040	0.036	0.974
Immunizations	4.6 (1.3)	4.7 (1.4)	5.0 (1.4)	0.056	0.699	0.173

Supplementary Figure 1. Example of the scenario and mock report presented to survey participants about a pathogenic variant. Participants were randomized to view a secondary finding report that presented a pathogenic variant, a variant of uncertain significance, or a benign variant.

A 30 year old female patient enters your practice for a general medical exam for the first time. She starts the encounter by mentioning that she has no specific issues that she wants to address. She does mention that she recently underwent sequencing through a CLIA-certified lab to help diagnose why her infant has developmental delays. Nothing was found that was related to developmental delays, but the patient was given report below. She would like your help interpreting it:

Pathogenic Variant Report

Test Result:	**MSH6 variant detected (1784delT) - pathogenic**
Interpretation:	Deletion of a single base pair (thymine (T) at position 1784) resulting in a frameshift mutation that is predicted to result in protein truncation and loss of function of the MSH6 gene product. This variant is suggestive of Lynch syndrome (HNPCC).

This report (including guidance) was approved by

_____ _____

John Doe, PhD
The Genetics Laboratory

Date

Guidance

- These results should be considered in the context of other clinical and family history information.
- People with Lynch syndrome have increased lifetime risks for cancer including colorectal cancer (80% for a first diagnosis and 50% for second), endometrial (20-60%), gastric (11-19%), ovary (9-12%), hepatobiliary tract (2-7%), urinary tract (4-5%), small bowel (1-4%), and brain (1-3%).
- MSH6 gene variants are transmitted as an autosomal recessive trait. First degree relatives (parents, sibling, children) of an individual with a variant have a 50% chance of having the same variant, and as a result, may be at increased risk for cancer.
- For assistance with interpretation of these test results, please call (555-555-5555).

Variant of Unknown Significance Report

Test result:	**MLH1 variant detected (25C>T) – variant of unknown significance**
Interpretation:	Substitution of a single base pair (cysteine (C) to thymidine (T) at position 25) resulting in an amino acid change that was reported in a Lynch syndrome case report and was predicted to be pathogenic in two of three bioinformatic analyses. This variant may be suggestive of Lynch syndrome (HNPCC).

This report (including guidance) was approved by:

_____ _____

John Doe, PhD — Date

The Genetics Laboratory

Guidance

- These results should be considered in the context of other clinical and family history information.
- People with Lynch syndrome have increased lifetime risks for cancer including colorectal cancer (80% for a first diagnosis and 50% for second), endometrial (20-60%), gastric (11-19%), ovary (9-12%), hepatobiliary tract (2-7%), urinary tract (4-5%), small bowel (1-4%) and brain (1-3%).
- MLH1 gene variants are transmitted as an autosomal dominant trait. First-degree relatives (parents, siblings, children) of an individual with a variant have a 50% chance of having the same variant, and as a result, may be at increased risk for cancer.
- For assistance with interpretation of these test results, please call (555-555-5555).

Benign Variant Report

Test result:	**MLH1 variant detected (1151T>A) – benign**
Interpretation:	Substitution of a single base pair (thymidine (T) to alanine (A) at position 1151) resulting in an amino acid change that is common in individuals without disease and is not predicted to be pathogenic in bioinformatic analyses. This variant is not associated with Lynch syndrome (HNPCC).

This report (including guidance) was approved by:

_____ _____

John Doe, PhD — Date

The Genetics Laboratory

Guidance

- These results should be considered in the context of other clinical and family history information.
- People with Lynch syndrome have increased lifetime risks for cancer including colorectal cancer (80% for a first diagnosis and 50% for second), endometrial (20-60%), gastric (11-19%), ovary (9-12%), hepatobiliary tract (2-7%), urinary tract (4-5%), small bowel (1-4%) and brain (1-3%).
- MLH1 gene variants are transmitted as an autosomal dominant trait. First-degree relatives (parents, siblings, children) of an individual with a variant have a 50% chance of having the same variant, and as a result, may be at increased risk for cancer.
- For assistance with interpretation of these test results, please call (555-555-5555).