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A factorial randomised trial investigating factors influencing general practitioners' willingness to prescribe aspirin for cancer preventive therapy in Lynch syndrome: a registered report

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Supplementary material: 6 tables, 1 figure, and 1 questionnaire.

Abstract

Background: The National Institute for Health and Care Excellence (NICE) recommends aspirin for colorectal cancer prevention for people with Lynch syndrome. Strategies to change practice should be informed by understanding the factors influencing prescribing.

Aim: To investigate the optimal type and level of information to communicate with GPs to increase willingness to prescribe aspirin.

Design and setting: We recruited GPs in England and Wales (*n*=672) to an online survey with a 2^3 factorial design. GPs were randomised to one of eight vignettes describing a hypothetical patient with Lynch syndrome recommended to take aspirin by a clinical geneticist.

Method: Across the vignettes, we manipulated the presence or absence of three types of information: 1) existence of NICE guidance; 2) results from the CAPP2 trial; 3) information comparing risks/benefits of aspirin. We estimated the main effects and all interactions on the primary (willingness to prescribe) and secondary outcomes (comfort discussing aspirin).

Results: There were no statistically significant main effects or interactions of the three information components on willingness to prescribe aspirin or comfort discussing harms and benefits. In total, 80.4% (540/672) of GPs were willing to prescribe, with 19.7% (132/672) unwilling. GPs with prior awareness of aspirin for preventive therapy were more comfortable discussing the medication than those unaware (*p*=0.031).

Conclusion: It is unlikely that providing information on clinical guidance, trial results and information comparing benefits and harms will increase aspirin prescribing for Lynch Syndrome in primary care. Alternative multilevel strategies to support informed prescribing may be warranted.

Key words: Preventive therapy; chemoprevention; decision-making; primary care; aspirin; NSAID

How this fits in: National Institute for Health and Care Excellence (NICE) guidance for England and Wales recommends daily aspirin for colorectal cancer prevention in people with Lynch syndrome, and it is likely that prescribing will occur in primary care. GPs may be reluctant to prescribe due to concerns about the side-effects, supporting evidence and lack of awareness of the NICE guidance. In a randomised factorial trial, providing GPs with information on these factors did not increase willingness to prescribe, or comfort discussing harms and benefits. Alternative strategies targeting multiple levels of prescribing behaviour among unwilling GPs may support prescribing.

Introduction

Lynch syndrome (LS) is an inherited condition that increases the risk of developing several cancers, including colorectal cancer[1]. Aspirin has been investigated as a preventive therapy for colorectal cancer[2]. The CAPP2 trial observed a reduced risk of colorectal cancer among people with LS randomised to 600mg aspirin versus placebo at 10 years (hazard ratio: 0.65, 95% CI=0.43-0.97)[3]. In 2020, the National Institute for Health and Care Excellence (NICE) NG151 guideline for colorectal cancer management recommended to consider daily aspirin to reduce colorectal cancer risk in people with LS[4]. NICE did not recommend a dose, but 150-300mg are commonly used in practice[4].

Aspirin prescribing is likely to occur in primary care, but general practitioners (GPs) may be reluctant to do so[5]. Ideally, strategies to change clinical practice should be informed by an understanding of the barriers to prescribing behaviour[6]. An Australian interview study identified several barriers amongst healthcare professionals to aspirin prescribing for colorectal cancer prevention for the public, including concerns about side-effects, limited awareness of the national guidance, and uncertainties about the strength of evidence[7]. In addition, a large UK survey found GPs who were more aware of aspirin's cancer preventive benefits were more willing to prescribe the medication to a patient with LS[5]. In the present study, we evaluated the relative effects of these different, potentially modifiable influences on decisions to prescribe aspirin for patients with LS in light of the new NICE guidance.

We investigated the optimal type and level of information to communicate with GPs to increase their willingness to prescribe aspirin to a patient with LS. We presented GPs with one of eight versions of a patient vignette, manipulating the presence or absence of three types of information on the effectiveness of aspirin for colorectal cancer prevention: existence of NICE guidance [NG151][4]; results from the CAPP2 trial[3]; and information comparing the risks and benefits of aspirin[8]. We hypothesised main effects of each manipulation on willingness to prescribe aspirin, and comfort with discussing aspirin. As exploratory research, we investigated two-way and three-way interactions between these main factors on the outcomes, and examined barriers and facilitators to prescribing aspirin among GPs.

Method

Setting and participants

We recruited GPs in England and Wales to a cross-sectional online survey. A market research company (M3 Global Research) advertised the survey to their network of over 240,000 GPs. We

excluded GPs not currently practising, and those outside England and Wales. GPs from Scotland and Northern Ireland were excluded. We preregistered the stage one registered report on Open Science Framework (https://doi.org/10.17605/OSF.IO/B5SFH). We followed CONSORT reporting guidelines[9].

Experimental design

We used a 2^3 factorial trial design, with participants randomised evenly across the eight conditions (i.e. minimisation) by the survey platform Qualtrics. All vignettes described a hypothetical scenario where a clinical geneticist recommends that the GP prescribes aspirin to a patient with LS (Supplementary Table 1S). Three factors were manipulated to form the eight conditions (Table 1). These factors were selected and designed using our interview data with UK healthcare providers and people with LS (preregistered: https://osf.io/3efg7), the Theoretical Domains Framework[10], existing evidence[5,7,11], and expert opinion from healthcare professionals and a patient representative. The three factors were:

1) NICE guidance [NG151] recommending aspirin for people with LS[4] (vs. no information);
2) Results from the CAPP2 trial investigating the effectiveness of aspirin for people with LS[3] (vs. no information);
3) Information comparing the risks and benefits of aspirin[8] (vs. no information).

Participant blinding was not possible, but we only informed participants about the three factors across the vignettes after survey completion.

Measures

Participant characteristics

Participants self-reported their gender, status in practice, number of years qualified, and their specialism (Supplementary Materials 1).

Willingness to prescribe

We asked GPs how willing they would be to prescribe aspirin to this patient with LS[11]. Response options ranged from 'not at all willing' to 'definitely willing'.

Comfort discussing aspirin

GPs were asked how comfortable they would feel discussing the benefits and harms of aspirin with this patient[11]. Response options ranged from 'very uncomfortable' to 'very comfortable'.

Barriers and facilitators to prescribing

We asked participants how much they agree or disagree that 14 factors affected their willingness to prescribe. The factors were based on a similar survey[11], with additional items included relevant to LS and aspirin. Example factors included the dose of aspirin being prescribed[5], and the patient's age[7].

Previous experience

Participants were asked questions on their professional experience, such as if they have ever prescribed aspirin for colorectal cancer prevention to a patient with LS.

Awareness

We asked participants if they were aware, before taking the survey, that aspirin can be used to reduce the risk of colorectal cancer, how they first became aware of this, and if they were aware of the NICE guidance [NG151][4].

Sample size calculation

We calculated the smallest expected main effect size[12]. A UK survey of GPs found willingness to prescribe aspirin to patients with LS was as low as 62%[5]. After considering effect size data from reviews of interventions targeting prescribing behaviour[13,14], we determined the smallest expected effect size is a 10% absolute increase in willingness to prescribe aspirin. We calculated an increase of willingness from 62% to 72% as an odds ratio of 1.58 (~Cohen's D of 0.25). With this effect size, power of 90%, *alpha*=0.05, and an equal number of participants per condition, the required sample size was 672 participants. The sample size calculation is available as an R Script here: https://osf.io/mgxc4/.

Analysis

We described the data using proportions and frequencies. The primary outcome was willingness to prescribe, and the secondary outcome was comfort discussing the harms and benefits of aspirin. We used an ANOVA to estimate the main effects and all interactions on the primary and secondary outcomes. We used effect coding (-1, 1) to enable interpretation of the main and interaction effects simultaneously[15].

The outcomes of willingness and comfort were also be dichotomised at mid-point. We conducted multivariable logistic regression models assessing the relationship between GPs' characteristics, awareness, and previous experience on willingness to prescribe (willing vs. unwilling), and comfort discussing aspirin (comfortable vs. uncomfortable). We also reported the proportion of GPs who agreed that each of the 14 factors influenced their willingness to prescribe.

To minimise missing data, participants were required to answer all survey questions, unless a question was not applicable due to a previous answer. We used RStudio (version 4.1.2) for the analysis, with $p<0.05$ statistically significant. The dataset and analysis scripts were made available on the Research Data Leeds Repository (https://doi.org/10.5518/1184).

Results

Out of 2,200 GPs approached, 867 (39.4%) started the survey. After excluding 195 ineligible participants, 672 GPs were included (Supplementary Figure 1S). Recruitment was open between March to April 2022. Table 2 summarises participant characteristics, which were comparable across the eight conditions (Supplementary Table 2S).

Awareness of aspirin for colorectal cancer prevention

Nearly half (300/672, 44.6%) of GPs reported prior awareness of aspirin for colorectal cancer prevention in people with LS, while 17.4% (117/672) were aware of NICE guidance NG151 recommending aspirin. GPs who were aware of aspirin for LS selected all applicable information sources which made them first aware of using the medication for preventive therapy. The most common sources of information were training days/educational meetings (136/300, 45.3%), GP magazines (65/300, 21.7%), academic journals (55/300, 18.3%), and national guidelines (49/300, 16.3%) (Figure 1). Prior awareness of the NICE guidance was comparable across the eight conditions (Table 2S).

Previous professional experience

In total, 46.3% (311/672) of GPs reported previously consulting a patient with LS, while 16.7% (112/672) were unsure. A smaller proportion of GPs recalled having discussed aspirin for prevention (61/672, 9.1% had discussed; 28/672, 4.2% were unsure), or prescribing aspirin to a patient with LS (73/672, 10.9% had prescribed; 40/672, 6.0% were unsure).

Willingness to prescribe aspirin

Most (390/672, 58.0%) GPs were 'probably willing' to prescribe aspirin for the hypothetical patient with LS, while 22.3% (150/672) were 'definitely willing' to prescribe. In total, 19.7% of GPs were unwilling to prescribe (112/672, 16.7% probably not willing; 20/672, 3.0% not at all willing). Willingness to prescribe among GPs was comparable across the three information components (NICE guidance; CAPP2 results; risk and benefit information) (Table 3). There were no significant main effects or interactions of these three components on willingness to prescribe aspirin (Table 3S).

In the multivariable logistic regression model, GPs who were unsure whether they had previously prescribed aspirin for colorectal cancer prevention were significantly more willing to prescribe aspirin than those who had not prescribed, however confidence intervals were wide (OR=5.67, *p*=0.032, 95% CI=1.37–34.71). Furthermore, there was no significant relationship between GPs who recalled previously prescribing aspirin and willingness to prescribe (*p*=0.183). No other factors were associated with willingness to prescribe (Table 4).

Discussing the harms and benefits of aspirin

Most GPs felt comfortable discussing aspirin harms and benefits with the hypothetical patient (361/672, 53.7% quite comfortable; 150/672, 22.3% very comfortable), while 24.0% were uncomfortable with these discussions (130/672, 19.4% quite uncomfortable; 31/672, 4.6% very uncomfortable). GPs' comfort discussing aspirin harms and benefits was comparable across the three components (NICE guidance; CAPP2 results; risk and benefit information; Table 4S). There was no statistically significant main effects or interactions of the components on comfort discussing aspirin (Table 3S).

In the multivariable logistic regression model, GPs who reported awareness of aspirin for colorectal cancer prevention in people with LS were more comfortable discussing benefits and harms than those who were unaware prior to the survey (OR=1.68, 95% CI=1.06–2.72, *p*=0.031). GPs who were unsure whether they had previously prescribed aspirin were more comfortable discussing harms and benefits than those who had not prescribed aspirin (OR=6.30, *p*=0.019, 95% CI=1.61-36.67). However, confidence intervals were wide, and GPs who recalled previously prescribing aspirin were not more comfortable discussing the medication (*p*=0.823). No other factors were significantly associated with comfort discussing aspirin (Table 5S).

Factors influencing willingness to prescribe

Among GPs willing to prescribe aspirin, the factors participants agreed were important in their decision were the benefits of aspirin (527/540, 97.6%), the geneticist recommendation to prescribe (492/540, 91.1%), patient interest in using aspirin (491/540, 90.9%), and patient awareness of aspirin harms and benefits (519/540, 96.1%; Table 5). Those GPs unwilling to prescribe felt the most important factors influencing their decision were the harms of aspirin (121/132, 91.7%), benefits (113/132, 85.6%), dose being asked to prescribe (112/132, 84.8%), and prescribing off label (110/132, 83.3%).

A higher proportion of those unwilling to prescribe aspirin wanted to speak to a colorectal cancer specialist (96/132, 72.7%) before prescribing than those who were willing (224/540, 41.5%). The patient's interest in aspirin factored less into the decision-making of those unwilling (86/132, 65.2%), than those willing (491/540, 90.9%). In an open text box, participants were able to write additional factors that influenced their decision. Among unwilling GPs, 12.1% (16/132) suggested that the clinical geneticist should make the first prescription, and 7.6% (10/132) that patients should buy aspirin from the pharmacy instead (Table 6S).

Discussion

Summary

In this online factorial experiment, we found highlighting the clinical guidance, summarising trial evidence, or giving information on aspirin's benefits and harms did not increase GPs' willingness to prescribe aspirin for colorectal cancer prevention. Reassuringly, most GPs participating in our experiment were willing to prescribe aspirin for a hypothetical patient with LS. However, a fifth of GPs were unwilling. Most GPs who were unwilling described several barriers that behavioural interventions are unlikely to affect, such as the harms of aspirin and prescribing off-label. Alternative strategies targeting multiple levels of prescribing behaviours may be warranted, including targeted support for GPs unwilling to prescribe.

Strengths and limitations

Our study design enabled us to test three different intervention components in a more efficient approach than if we had conducted individual experiments[16]. However, we highlight several limitations. First, whilst the clinical vignette described a hypothetical patient with LS, the specific patient characteristics which may affect GPs' willingness to prescribe, such as patient age and other medication use, are likely to vary widely among the LS population. Our study only measured GPs' hypothetical willingness to prescribe aspirin; prescribing behaviour may be different in clinical practice. Our sample of GPs was also derived via a market research company and may not be typical of the wider GP community. Finally, we may have encountered a ceiling effect of willingness to prescribe aspirin for preventive therapy, beyond which it becomes difficult to influence the outcome.

Comparison with existing literature

We found GPs' levels of willingness to prescribe aspirin for colorectal cancer prevention to a patient with LS were comparable to a previous cross-sectional UK survey[5]. We also observed barriers to prescribing aspirin which were consistent with previous research conducted in breast cancer prevention. In our study, several GPs unwilling to prescribe reported a preference for the clinical geneticist to initiate the prescription. Similarly, in breast cancer research, GPs have been observed to be more willing to prescribe preventive medicine to a hypothetical patient at higher risk of cancer if a clinical geneticist makes the first prescription[11]. There are several potential barriers which may prevent aspirin from being initiated in specialist care. Previous UK and Australian research into breast cancer preventive therapy has observed a resistance among hospital-based clinicians to prescribe preventive medicines, given unfamiliarity with prescribing and side-effect management[17,18], and lack of access to patients' medical history[17]. An Australian study also found that specialist clinicians typically viewed GPs as the main prescribers of aspirin for cancer prevention, while perceiving their own roles as more advisory[7].

Implications for research and practice

Multilevel strategies, targeting both patients and healthcare professionals, could be utilised to support prescribing of aspirin for preventive therapy. Our findings suggest one approach to supporting GPs' discussions with patients on the benefits and harms of aspirin for preventive therapy is increasing awareness on using aspirin for this purpose through formal training, educational events, and GP magazines. There may also be scope to change GPs' knowledge and behaviour through patient-mediated interventions[19], as patients were identified as an important information source by many GPs. One approach to increasing patients' knowledge is decision aids. This approach has been successful for breast cancer preventive therapy whereby tailored web-based decision aids have been observed to increase patients' knowledge and to support decision-making[20,21]. Similar educational tools may also be effective for some patients with LS considering aspirin. In 2020, NICE released a decision aid for people with LS considering aspirin for preventive therapy[8], however its effectiveness on patients' decision-making is unknown.

We found evidence to suggest that individual guidance and advice from specialist clinicians, especially in colorectal cancer, may help increase the prescribing of aspirin among unwilling GPs. Local pathways setting out roles and responsibilities of GPs, pharmacists, and specialist clinicians are warranted, and should be clearly described in GP training materials that discuss the use of aspirin for colorectal cancer prevention. Furthermore, these training and educational materials should clarify the role of GPs when asked to prescribe off-label medication, as well as highlighting the importance of ensuring medications obtained over-the-counter are recorded on patients' medical records.

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Ethical approval: Ethical approval was awarded by the University of Leeds School of Medicine Research Ethics Committee (MREC 20-075). The study was conducted in accordance with the Declaration of Helsinki.

Informed consent: Informed consent was obtained from all individual participants included in this study, and no confidential information was collected that could identify the participants.

Competing interests: Robbie Foy is a member of the NICE Implementation Strategy Group. All other authors declare no conflicts of interest.

Data availability: The dataset and analysis scripts generated during the study are publicly available in the Research Data Leeds Repository, (https://doi.org/10.5518/1184).

Authors' contributions: Conceptualisation: K.E.L, S.G.S, R.F, L.H.H, and L.Z. Methodology: K.E.L, S.G.S, R.F, L.H.H, L.Z, D.G.T, M.M., and G.M.B. Supervision: S.G.S, R.F, L.H.H, and L.Z. Funding acquisition: S.G.S, D.G.T, M.M, and G.M.B. Investigation: K.E.L. Formal analysis: K.E.L. Data Curation: K.E.L. Writing – original draft: K.E.L. Writing – review and editing: all authors.

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Table 1. Description of the eight experimental conditions (i.e. vignettes) in the study, and the three factors across the conditions.

Experimental condition	NICE guidance [NG151]	CAPP2 trial results	Risks/ benefit information
1	Yes	Yes	Yes
2	Yes	Yes	No
3	Yes	No	Yes
4	Yes	No	No
5	No	Yes	Yes
6	No	Yes	No
7	No	No	Yes
8	No	No	No

Table 2. Demographic and professional characteristics of the GP sample (*n* = 672)

	***n* (%)**
Country	
England	651 (96.9%)
Wales	21 (3.1%)
Gender	
Female	373 (55.5%)
Male	290 (43.2%)
Non-binary	1 (0.15%)
Another identity	1 (0.15%)
Prefer not to say	7 (1.0%)
GP status	
Salaried/locum GP	389 (57.9%)
GP partner	233 (34.7%)
GP specialist trainee	44 (6.6%)
GP retainers	3 (0.5%)
Other	3 (0.5%)
Years qualified	
0-4 years	24 (3.6%)
5-9 years	151 (22.5%)
10-14 years	174 (25.9%)
15-19 years	143 (21.3%)
20+ years	180 (26.8%)
Specialism	
Cancer	37 (5.5%)
Family history	28 (4.2%)
Genetics	4 (0.6%)
Preventive medicine	87 (13.0%)
Other	132 (19.6%)
N/A - no speciality	384 (57.1%)

Figure 1. Proportion of GPs (%) who learnt about the use of aspirin for colorectal cancer prevention in people with Lynch syndrome from the following information sources (*n* = 300)

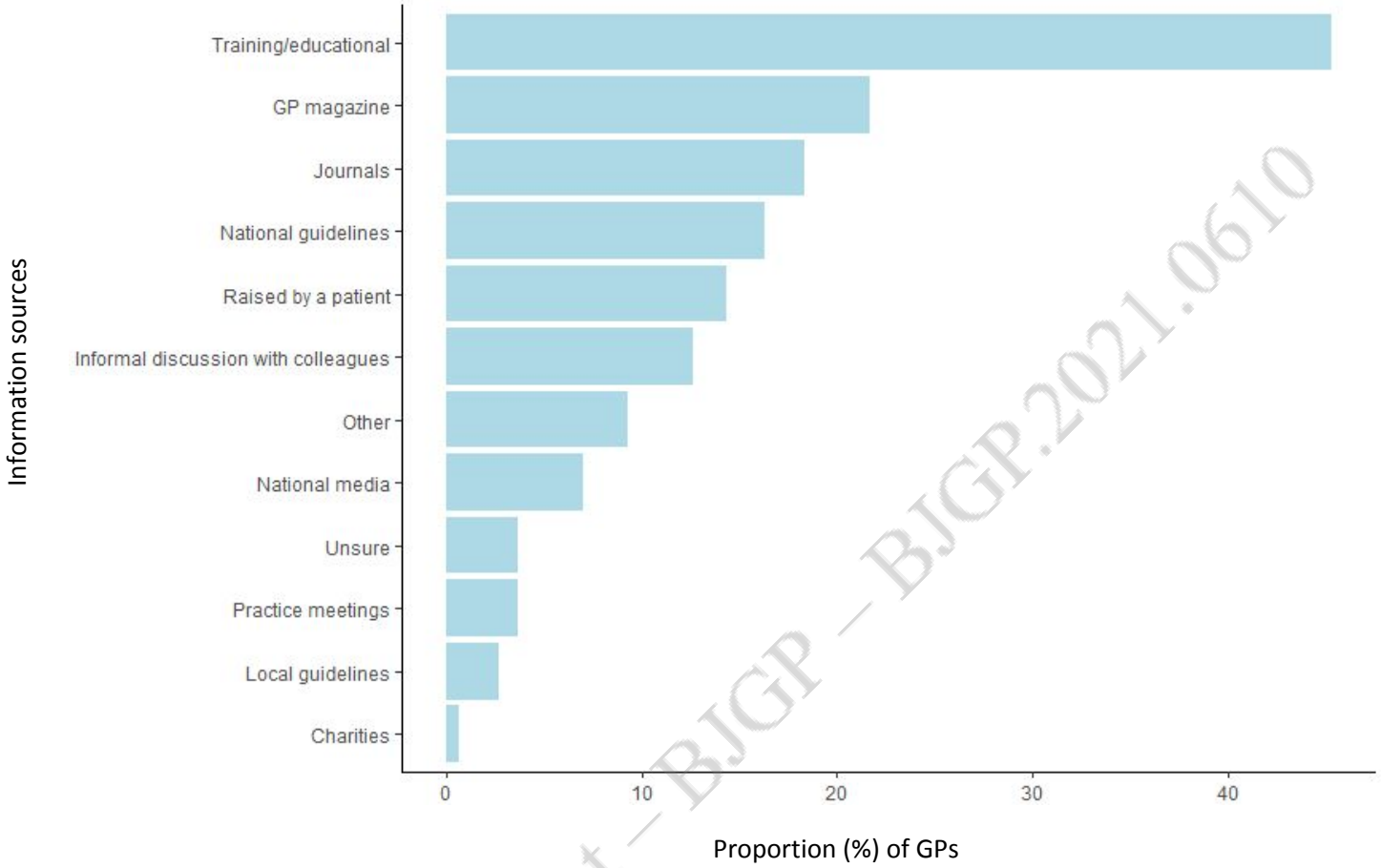

Table 3. Willingness to prescribe aspirin among GPs across the three information components (*n* = 672)

	NICE guidance ***n* (%)**	**CAPP2 results** ***n* (%)**	**Risks/ benefits** ***n* (%)**
Definitely willing	80 (53.3%)	72 (48.0%)	74 (49.3%)
Probably willing	188 (48.2%)	194 (49.7%)	196 (50.3%)
Probably not willing	52 (46.4%)	59 (52.7%)	59 (52.7%)
Not at all willing	15 (75.0%)	11 (55.0%)	8 (40.0%)

Table 4. GPs' willingness to prescribe aspirin by participant characteristics, previous experience, and awareness (*n* = 672)

	Willing to prescribe ***n* (%)**	**OR (95% CI)**	***p* value**
Country			
England	524 (80.5%)	1.17 (0.37-3.18)	0.771
Wales	16 (76.2%)	Ref	Ref
Gender			
Female	297 (79.6%)	Ref	Ref
Male	238 (82.1%)	0.94 (0.61-1.46)	0.793
Another identity*	0 (0.0%)	-	0.994
Non-binary*	1 (100.0%)	-	0.996
Prefer not to say	4 (57.1%)	0.27 (0.05-1.48)	0.105
GP status			
Salaried/locum GP	307 (78.9%)	1.00 (0.62-1.58)	0.988
GP partner	193 (82.8%)	Ref	Ref
GP retainers*	3 (100.0%)	-	0.991
GP specialist trainee	34 (77.3%)	1.22 (0.51-3.1)	0.667
Other*	3 (100.0%)	-	0.992
Years qualified			
0-4 years	20 (83.3%)	Ref	Ref
5-9 years	114 (75.5%)	0.47 (0.13-1.39)	0.205
10-14 years	133 (76.4%)	0.52 (0.14-1.51)	0.263

15-19 years	114 (79.7%)	0.61 (0.16-1.83)	0.409
20+ years	159 (88.3%)	1.04 (0.27-3.23)	0.952
Specialism			
Cancer	34 (91.9%)	1.75 (0.56-7.67)	0.387
Family history	21 (75.0%)	0.58 (0.23-1.59)	0.256
Genetics*	4 (100.0%)	-	0.989
Preventive medicine	69 (79.3%)	0.72 (0.39-1.38)	0.312
Other	104 (78.8%)	0.74 (0.44-1.26)	0.258
N/A – no speciality	308 (80.2%)	Ref	Ref
Previous experience			
Consulted a patient with LS			
Consulted - yes	261 (83.9%)	1.57 (0.99-2.5)	0.055
Consulted - unsure	90 (80.4%)	1.23 (0.69-2.27)	0.497
Consulted - no	189 (75.9%)	Ref	Ref
Discussed aspirin with a patient with LS			
Discussed aspirin - yes	57 (93.4%)	0.81 (0.21-3.57)	0.763
Discussed aspirin - unsure	23 (82.1%)	0.37 (0.10-1.53)	0.153
Discussed aspirin - no	460 (78.9%)	Ref	Ref
Prescribed aspirin to a patient with LS			
Prescribed aspirin - yes	68 (93.2%)	2.34 (0.72-9.05)	0.183
Prescribed aspirin - unsure	37 (92.5%)	5.67 (1.37-34.71)	**0.032**
Prescribed aspirin - no	435 (77.8%)	Ref	Ref
Awareness			
Prior awareness of aspirin in LS population			
Yes	261 (87.0%)	1.49 (0.91-2.49)	0.118
No	279 (75.0%)	Ref	Ref
Prior awareness of NICE guidance NG151			
Yes	107 (91.5%)	1.74 (0.80-4.07)	0.177
No	433 (78.0%)	Ref	Ref

* OR (95% CI) not reported due to insufficient cases.

Table 5. The proportion of GPs (%) who agreed that each of the 14 factors influenced their willingness to prescribe (*n* = 672)

	Willing, n (%)	Unwilling, n (%)
Benefits of aspirin	527 (97.6%)	113 (85.6%)
Harms of aspirin	472 (87.4%)	121 (91.7%)
Dose of aspirin asked to prescribe	455 (84.3%)	112 (84.8%)
Prescribing aspirin off-label	369 (68.3%)	110 (83.3%)
Geneticist recommendation to prescribe	492 (91.1%)	93 (70.5%)
Patients' interest in using aspirin	491 (90.9%)	86 (65.2%)
Patients' awareness of the harms and benefits of aspirin	519 (96.1%)	104 (78.8%)
Wanting to speak to specialist in genetics before prescribing	235 (43.5%)	86 (65.2%)
Wanting to speak to specialist in colorectal cancer before prescribing	224 (41.5%)	96 (72.7%)
Wanting to speak with another GP before prescribing	227 (42.0%)	74 (56.1%)
Patients' age	375 (69.4%)	78 (59.1%)
Confidence in aspirin in general	478 (88.5%)	92 (69.7%)
Confidence in aspirin as a form of preventive therapy	451 (83.5%)	104 (78.8%)
Prescribing budget in your practice	132 (24.4%)	28 (21.2%)