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Review Article

Prevalence of *KRAS* G12C Mutation and Co-mutations and Associated Clinical Outcomes in Patients With Colorectal Cancer: A Systematic Literature Review

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Abstract

Purpose: A systematic literature review was conducted to estimate the global prevalence of Kirsten rat sarcoma virus gene (*KRAS)* mutations, with an emphasis on the clinically significant *KRAS* G12C mutation, and to estimate the prognostic significance of these mutations in patients with colorectal cancer (CRC).

Design: Relevant English-language publications in the Embase, MEDLINE, and the Cochrane Library databases (from 2009 to 2021) and congress presentations (from 2016 to 2021) were reviewed. Eligible studies were those that reported the prevalence and clinical outcomes of the *KRAS* G12C mutation in patients with CRC.

Results: A total of 137 studies (interventional [*n* = 8], post hoc analyses of randomized clinical trials [*n* = 6], observational [*n* = 122], and longitudinal [*n* =1]) were reviewed. Sixty-eight studies reported the prevalence of *KRAS* mutations (*KRASm*) in 42 810 patients with CRC. The median global prevalence of *KRASm* was 38% (range, 13.3%-58.9%) and that of the *KRAS* G12C mutation (*KRAS* G12C) 3.1% (range, 0.7%-14%). Available evidence suggests that *KRASm* are possibly more common in tumors that develop on the right side of the colon. Limited evidence suggests a lower objective response rate and inferior disease-free/relapse-free survival in patients with *KRAS* G12C compared with patients with *KRASwt* or other *KRASm*.

Conclusion: Our analysis reveals that *KRAS* G12C is prevalent in 3% of patients with CRC. Available evidence suggests a poor prognosis for patients with *KRAS* G12C. Right-sided tumors were more likely to harbor *KRASm*; however, their role in determining clinical outcomes needs to be investigated further.

Key words: *KRASm*; *KRAS* G12C; prevalence; prognosis; colorectal cancer; systematic literature review; global.

Implications for Practice

Our systematic literature review of 68 studies from around the globe, reporting on 42 810 patients with colorectal cancer (CRC), revealed a median prevalence of 3.1% (range, 0.7%-14%) for the *KRAS* G12C mutation. Overall, patients with *KRAS* G12C had shorter overall survival, progression-free survival, and disease-free survival compared to patients with wild-type *KRAS* or other non-G12C mutations. The variation in *KRAS* G12C prevalence across different geographies and the poor prognosis associated with this mutation suggests that *KRAS* G12C prevalence is an important factor that needs to be considered during patient recruitment in clinical trials of CRC therapies targeting this mutation.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide.[1] In 2020, CRC accounted for around 1.9 million new diagnoses and 935 000 deaths globally.[2] The 5-year survival rate for patients with CRC ranges from 91% for those with localized disease to a dismal 15% for those with metastatic disease.[3]

A number of genes have been implicated in the transformation process from benign neoplasia to invasive

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carcinoma and metastatic colorectal cancer (mCRC). The development of mutations in the Kirsten rat sarcoma virus gene (*KRAS*) is an early event in tumorigenesis, which marks the progression from the adenoma to the carcinoma stage.[4]

KRAS is a proto-oncogene that encodes the 21 kDa guanosine triphosphate (GTP)/guanosine diphosphate (GDP)-binding RAS protein. RAS functions as a molecular switch regulating receptor tyrosine kinase signal transduction by alternating between an active GTP-bound and an inactive GDP-bound states. Mutations in *KRAS* disrupt this guanine exchange cycle, locking the RAS protein in an active GTP-bound form. The constitutively activated RAS protein can drive uncontrolled cell proliferation, suppress apoptosis, upregulate glucose uptake, promote angiogenesis, and improve cell survival.[5] More than 80% of these mutations are located in codon 12 and around 14% are located in codon 13 of *KRAS*.[6,7]Mutations in other codons are relatively rare.[8-10]

For patients with mCRC, first- and second-line treatment approaches typically include chemotherapy combinations with a fluoropyrimidine-based doublet (folinic acid, fluorouracil, and oxaliplatin/folinic acid, fluorouracil and irinotecan [FOLFOX/FOLFIRI]) or triplet (folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan [FOLFOXIRI]) regimen combined with therapies that target either tumor angiogenesis (bevacizumab) or the epidermal growth factor receptor (EGFR) (panitumumab or cetuximab).[11-15] However, patients with *KRAS* mutations (*KRASm*) or neuroblastoma-RAS (*NRAS)* mutations are unlikely to benefit from treatment with anti-EGFR therapy and, therefore, have more limited treatment options.[16-18] Nonetheless, recently developed KRAS-specific inhibitors offer hope for cancers with certain *KRASm*. Sotorasib and adagrasib are small-molecule *KRAS* G12C inhibitors that covalently bind to mutant cysteine residues and lock the G12C-mutated KRAS protein in a non-activated GDP-binding state causing irreversible inhibition of the proliferative activity of the tumor cell.[19] Sotorasib and adagrasib have received US FDA approval for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), and are currently being evaluated in patients with mCRC either as monotherapy or in combination with other therapeutic agents. Other inhibitors that are currently being evaluated for their activity against *KRAS* G12C-positive solid tumors include JNJ-74699157 (NCT04006301), LY3499446 (NCT04165031), JAB-21822 (NCT05002270), YL-15293 (NCT05119933), GDC-6036 (NCT04449874), BI 1823911 (NCT04973163), and MK-1084 (NCT05067283).

Given the emerging clinical actionability in patients with *KRASm,* there is a valid need for understanding the prevalence and clinical significance of these mutations in CRC to design appropriate treatment strategies in clinical trials and testing approaches. Additionally, the prognostic significance of these mutations, particularly the "druggable" *KRAS* G12C mutation in the context of currently approved therapies for CRC has not been definitively established.

The objective of this systematic literature review (SLR) was to assess the prevalence of the *KRAS* G12C mutation, the prevalence of co-existing mutations, and characterize the clinical outcomes in patients with *KRAS* G12C-mutated CRC based on robust methodology.

Methods

This SLR was conducted using a standardized approach that was compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines.[20]

Search Strategy

Search strategies were developed around a Population, Intervention, Comparator, Outcomes (PICO) framework in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The 2 central questions that formed the basis of the literature review were:

1. What is the prevalence of *KRAS* G12C in patients with CRC and what are the mutations that have been reported to co-exist with it?
2. What are the clinical outcomes among patients with CRC who have *KRAS* G12C-positive tumors?

Searches were carried out in Embase, MEDLINE, and the Cochrane Library databases. A detailed list of the literature sources is provided in Supplementary Table S1. The search timeframe was from January 2009 to July 2021.

Titles and abstracts of identified studies were screened in a double-blind manner by 2 researchers to determine whether they met the predefined inclusion and exclusion criteria (Table 1). Uncertainties regarding the inclusion of studies were resolved by a full-text review carried out in a single-blind manner by the first reviewer, and 10% of these decisions were spot-checked by a second reviewer. All decisions on inclusion and exclusion at title/abstract screening and full-text review, including the reasons for these decisions, were documented. Data were extracted from the identified publications into a data extraction table by the 1st reviewer and independently checked for errors against the original publication by a 2nd reviewer. Discrepancies were resolved through discussion or with the intervention of a 3rd reviewer and the data were qualitatively synthesized. The methodological quality of each individual study was assessed using the Cochrane quality assessment tools. The Risk of Bias (RoB) 2 tool was used to assess the RoB in randomized controlled trials (RCTs), and the Risk of Bias in Non-Randomized Studies—of Interventions (ROBINS-I) tool was used to assess RoB in single-arm trials and observational studies.[21,22] Risk of bias assessments was carried out in a single-blind manner by 1 researcher.

The search was carried out in 2 phases: The searches for the 1st SLR (phase I) were performed on July 24, 2019, and covered the years from 2009 to 2019. Searches for phase II of the SLR, which was an update of phase I SLR, were conducted on March 10, 2021, and covered the years from 2019 to 2021. The 2 phases of the search were performed simultaneously for both NSCLC and CRC. The search strings that were used in the different databases are shown in Supplementary Table S2.

Selection Criteria

Studies describing treated (any stage, any anticancer drug or line of treatment with the exception of radiotherapy, or surgery unless a relevant comparator arm was included) or untreated patients with CRC (any stage) and harboring the *KRAS* G12C mutation were included. Non-English publications, editorials, and reviews were excluded. Articles

Table 1. PICO framework used for study selection.

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with colorectal cancer (any stage, any line of treatment) carrying a *KRAS* G12C mutation	Tumor types other than colorectal cancer
Intervention	Any anticancer drugs, any line of treatment, or no treatment	Radiotherapy or surgery (unless a relevant comparator arm)
Comparator	Any or none	Not applicable
Outcome	Outcome reported by *KRAS* G12C mutation status *Epidemiological evidence* • Prevalence of *KRAS* G12C mutation • *KRAS* mutation and subtypes *Clinical evidence* • Overall survival • Progression-free survival • Disease-free survival • Adverse events • Objective response rate • Time to response • Duration of response	Not applicable
Study design	Any randomized controlled trial, single-arm trial, observational study	Exclude animal/in vitro studies, case studies, and case reports
Date restrictions	• Published since 2009 • Congress abstracts published since 2016	Published before 2009
Language restrictions	English language	Non-English language
Publication type	All publication types, except editorials and reviews, but including systematic reviews	Editorials and reviews
Country	Not restricted	Not applicable

Abbreviations: *KRAS*, Kirsten rat sarcoma virus gene; *KRAS* G12C, *KRAS* with mutation at codon 12 that results in the substitution of glycine with cysteine; PICO, Population, Intervention, Comparator, Outcome.

published between January 2009 and June 2021 and conference abstracts published between January 2016 and June 2021 were included for title and abstract review. RCTs, single-arm trials, and observational studies published since 2009 that met the SLR inclusion criteria were included. The PICO framework and the detailed selection criteria are described in Table 1. Data from publications reporting the incidence and prevalence of *KRAS* G12C were extracted only when the total study population comprised ≥100 patients, or when the primary aim of the study was to examine the prevalence of *KRASm*. Data from all publications reporting clinical outcomes for the *KRAS* G12C were extracted. SLR articles were identified and listed separately; however, data were not extracted from these papers. The reference lists from SLRs were cross-checked against the lists of included references to ensure that no relevant references were omitted.

Studies reporting clinical outcome data, including overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease-free survival (DFS), relapse-free survival (RFS), and duration of response, were extracted. Epidemiological data extracted included prevalence of *KRAS* G12C, other *KRASm*, and co-mutations.

Results

The 2 phases of the search, which were performed simultaneously for both NSCLC and CRC, returned 7549 hits. After removing duplicates and filtering by the pre-specified exclusion criteria, 2038 publications were considered for full manuscript review. Following a full-text review, 185 CRC publications were identified for further review; from these, 48 publications reporting on <100 patients were excluded. Finally, 137 publications were selected for data extraction; of these, 8 were interventional (6 single-arm trials, 2 RCTs), 6 were post hoc analyses, 122 were observational, and 1 was longitudinal. In total, 90 publications reported only epidemiological data, 37 reported epidemiological and clinical outcomes data, and 10 publications reported only clinical outcomes data. Flow diagrams summarizing the study selection process for phases I and II of the SLR are shown in Fig. 1A, 1B, respectively.

Geographical Prevalence of KRASm

Sixty-eight studies that reported on unselected patient populations (participants not chosen for having any particular characteristic other than being adults with CRC) were included. The studies originated from the following countries: China (13 studies); US (8 studies); Italy (6 studies); Japan (4 studies); Iran (4 studies); Australia, South Korea, Spain, Taiwan (3 studies each); Belgium, Brazil, France, India, Mexico, Saudi Arabia (2 studies each); Austria, Denmark, Pakistan, Peru, Russia, Tunisia, Turkey, and the United Kingdom (1 study each). One study reported on mutations from patients from different countries. The country-wise prevalence of *KRAS* G12C is shown in detail in Supplementary Table S3. Of these, 11 studies had sample sizes > 1000 and 8 had sample sizes 500-1000 (Table 2). Collectively, these 68 studies reported the frequency of *KRASm* in 42 810 patients.

The global median prevalence of *KRAS* G12C in patients with CRC was 3.1% (range, 0.7% to 14.0%) (**Fig. 2A**). The reported median prevalence was 3.8% (range, 1.3% to 7.8%)

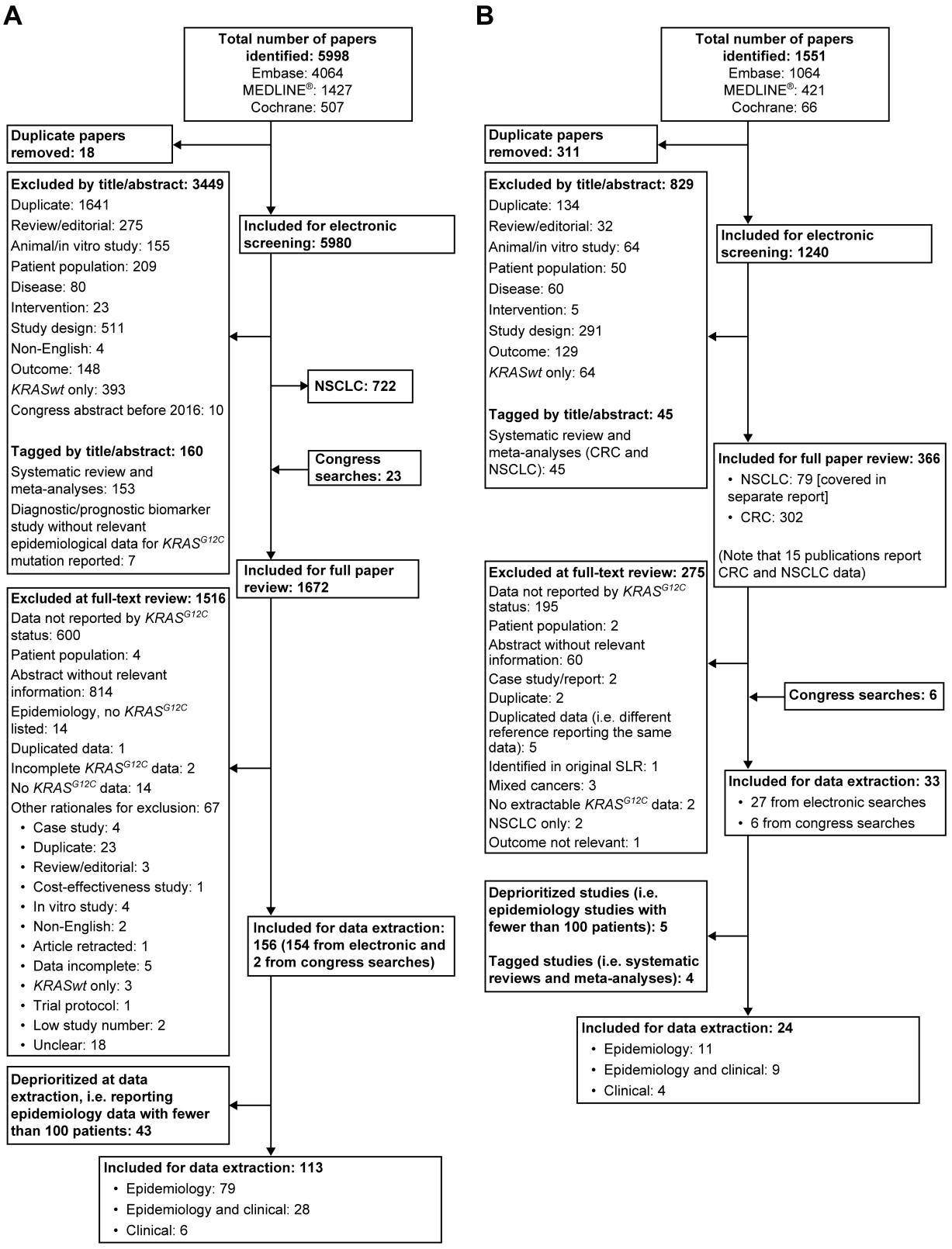

Figure 1. (**A**) Flow diagram depicting the screening and selection process for study selection in phase I (2009-2019) of the systematic literature search. (**B**) Flow diagram depicting the screening and selection process for study selection in phase II (2019-2021) of the systematic literature search. Abbreviations: CRC, colorectal cancer; *KRASwt*, wild-type Kirsten rat sarcoma virus gene; NSCLC, non-small cell lung cancer; SLR, systematic literature review.

Table 2. List of publications reporting the geographical prevalence of the *KRAS* mutation in >500 patients with colorectal cancer.

Study	Country	Patients tested[a] for *KRASm* (*N*)	Study type	Patients with the *KRAS* G12C mutation (*n*)	*KRAS* G12C mutation prevalence within tested[a] population, % (*n/N*)	Median *KRAS* G12C prevalence, % (*n/N*)	Patients with *KRASm* (*N1*)	*KRAS* G12C mutation prevalence within *KRASm* % (*n/N1*)	Median *KRAS* G12C prevalence/ region % (*n/N1*)	*KRASm* prevalence % (*N1/N*)	Median *KRASm* prevalence/ region *KRASm* % (*N1/N*)
European Union											
Gvaldin et al (2019)[23]	Russia	744	Obs/NR	19	2.6	3.5	238	8.0	8.9	32.0	36.5
Palomba et al (2016)[24]	Italy	1284	Obs/retrospective	64	5	(2.6-5.0)	457	14.0	(8.0-14.0)	35.6	(32.0-39.7)
Malapelle et al (2012)[25]	Italy	1691	Obs/retrospective	64	3.8		671	9.5		39.7	
Marchetti et al (2011)[26]	Italy	2519	Obs/prospective	78	3.1		940	8.3		37.3	
Intercontinental region											
Gil Ferreira at. (2014)[27]	Brazil	7797	Obs/retrospective	206	2.6	2.6	2623	7.9	7.9	33.6	33.6
Japan and Asia-Pacific region											
Price et al (2020)[28]	Australia	1605	Obs/retrospective	63	3.9	2.5 (1.5 to 4.3)	658	9.6	5.9 (3.6 to 9.6)	41.0	42.1 (35.9 to 51.5)
Wong et al (2020)[29]	Australia	1308	Obs/prospective	56	4.3		674	8.3		51.5	
Li et al (2019b)[30]	China	526	Obs/retrospective	9	1.7		253	3.6		48.1	
Li et al (2019a)[31]	China	1164	Obs/retrospective	29	2.5		490	5.9		42.1	
Loong et al (2020)[32]	China	1114	Obs/retrospective	28	2.5		545	5.1		48.9	
Luo et al 2020[33].	China	655	Obs/retrospective	13	2.0		305	4.3		46.6	
Shen et al, 2013[34]	China	674	Obs/retrospective	10	1.5		242	4.1		35.9	
Fu et al, 2019[35]	China	5495	Obs/retrospective	127	2.3		2070	6.1		37.7	
Won et al, 2017[36]	South Korea	1092	Obs/retrospective	31	2.8		401	7.7		36.7	
North America											
Nash et al (2010)[37]	USA	531	Obs/retrospective	15	2.8	4.1 (2.8 to 4.2)	190	7.9	10.0 (7.9 to 10.4)	35.8	39.0 (35.8 to 39.7)
Paulino A (2014)[38]	US	577	Obs/retrospective	23	4.0		229	10		39.7	
Maus et al (2014)[39]	US	838	Obs/retrospective	34	4.1		327	10.4		39.0	
Nusrat et al (2020[40]	US	3469	Obs/retrospective	146	4.2		NR	NR		NR	
Greater than 1 geographical region											
Smith et al (2013b)[41]	> 1	599	Obs/retrospective	17	2.8	2.8	258	6.6	6.6	43.1	43.1

[a]Patients with an evaluable test result.
Abbreviations: *KRAS*, Kirsten rat sarcoma virus gene; *KRASm*, *KRAS* mutation(s); *KRAS* G12C, *KRAS* with mutation at codon 12 that results in the substitution of glycine with cysteine; NR, not reported; Obs, observational; UK, United Kingdom; US, United States of America.

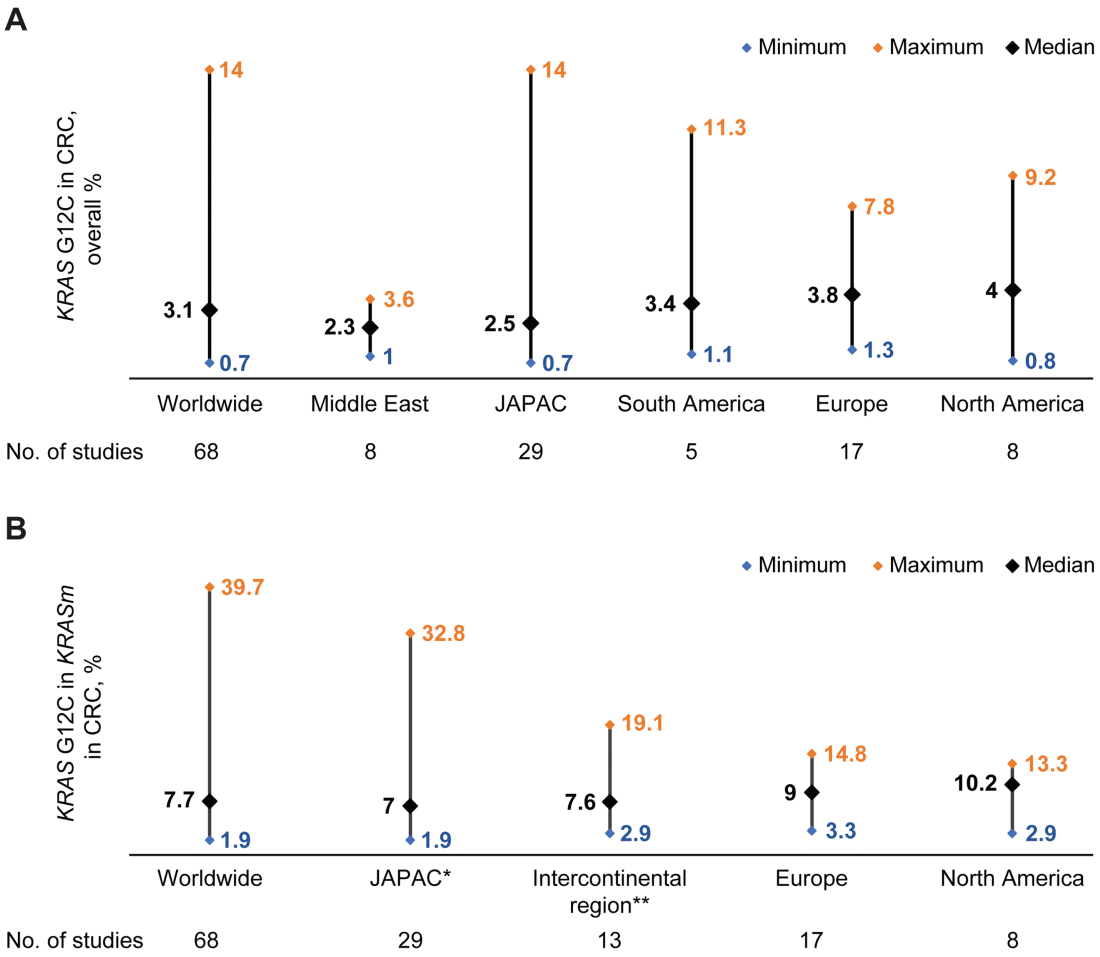

Figure 2. (**A**) Worldwide prevalence of *KRAS* G12C mutations in the entire cohort of included populations with colorectal cancer. (**B**) Worldwide prevalence of *KRAS* G12C mutations within the *KRASm* population in patients with colorectal cancer. *JAPAC, Japan & Asia-Pacific regions; **Intercontinental region: South America, Middle East. Abbreviation: *KRASm*, Kirsten rat sarcoma virus gene mutations.

in Europe, 2.9% in the intercontinental region (range, 1.0% to 11.3%) (Middle East: 2.3% [range, 1.0% to 3.6%]; South America: 3.4% [range, 1.1% to 11.3%]), and 4.0% in North America (range, 0.8% to 9.2%). The median of reported prevalence estimates in Japan and the Asia-Pacific region (JAPAC) was 2.5% (range, 0.7% to 14.0%). When a study describing a large outlying prevalence of 14.0% in Indian patients with CRC[42] was removed from the analysis, the median prevalence was 2.3% (0.7% to 6.9%).

The reported median prevalence of *KRASm* in CRC in the included studies was 38.0% (range, 13.3% to 58.9%), with the median prevalence on a regional level ranging from 38.0% (range, 17.0% to 55.2%) in Europe to 40.7% (range, 13.3% to 51.5%) in JAPAC. The median prevalence of *KRAS*m in CRC in studies from the intercontinental region was 38.2% (range, 16.7% to 58.9%) (Middle East: 37.3% [range, 26.0% to 50.9%]; South America: 41.4% [range, 16.7% to 58.9%]), and 37.4% in North America (range, 23.1% to 50.0%).

Among patients with *KRASm*, the median global prevalence of *KRAS* G12C in patients with CRC was 7.7% (range, 1.9% to 39.7%) (**Fig. 2B**). The median regional prevalence was 9.0% in Europe (range, 3.3% to 14.8%), 10.0% in North America (range, 2.9% to 13.3%), 7.0% in JAPAC (range, 1.9% to 32.8%), although this was reduced to 6.5% (range, 1.9% to 21.2%) when a study with a large outlier prevalence[42] was excluded, and 7.6% in the intercontinental region (range, 2.9% to 19.1%) (Middle East: 5.1% [range, 2.9% to 8.6%]; South America: 7.9% [range, 6.7% to 19.1%])

Tumor sidedness, KRAS mutations, and outcomes

Five studies that reported on tumor sidedness noted that tumors on the right side of the colon were more likely to have *KRASm* than those that developed on the left side of the colon.[43-47] Three of the five studies reported *KRASm* prevalence in the rectum separately,[45-47] even though the rectum is anatomically considered a part of the left colon.[48] Two studies did not specify which parts of the colon were included for assessing tumor sidedness.[43,44]

Multivariate analysis from one study reported that survival was significantly lower in patients with right-sided tumors, however, the association between the presence of *KRASm* and tumor location was not studied.[49] Multivariate analyses from another study reported that patients with tumors on the left side had a lower risk of death compared with those with tumors on the right side (hazard ratio [HR], 0.699; 95% CI: 0.350, 1.398; P = .312) although the risk of death between the groups was more similar if the left-sided tumors were positive for *KRAS* G12C (HR: 0.812; 95% CI: 0.131, 5.053; P = .823).[50] However, none of these findings was statistically significant.

Clinical outcomes with KRAS mutations

In total, 31 publications reporting clinical outcomes with *KRAS* G12C were included and comprised 6 single-arm studies (from 4 clinical trials), 4 post hoc analyses from RCTs, and 21 observational studies. No publication reported on time to response, depth of response, or treatment discontinuation in patients with *KRAS* G12C.

OS and PFS

Seventeen publications reported OS (n = 16) and/or PFS (n = 9) outcomes in patients with *KRASm*-positive CRC (**Table 3**). Most studies (11 of 17 studies) reported shorter OS and/or PFS for patients with *KRAS* G12C-positive tumors than for those with tumors harboring *KRASwt* or other *KRASm*. Of the remaining 6 studies, 2 reported outcomes in individual patients, 2 reported outcomes only for patients with *KRAS* G12C-positive tumors in studies that did not have a comparator arm. Two studies reported a higher OS rate in *KRAS* G12C-positive patients compared with those with *KRASwt* or other *KRASm*.

A study of patients with stage IV mCRC reported a significantly shorter median OS in patients with *KRAS* G12C (28.9 months [range, 24.0, 35.2]) than in those with other *KRASm* (36.7 months [range, 32.2, 41.5]).[53] Similar results were observed in an external validation cohort (patients with *KRASm*-positive CRC who were treated in a medical oncology unit of another hospital in the same timeframe as this study) that was analyzed as part of this study (median OS: *KRAS* G12C 25.9 months [range, 17.2, 37.3] vs other *KRASm* 35.8 months [range, 31.0, 42.8]). A retrospective review of genomic profiling data from patients with mCRC reported significantly shorter OS for patients with *KRAS* G12C versus patients with other *KRASm* (23 vs 27.1 months, $P < .001$).[56]

In a post hoc analysis of data from 3 clinical trials of 119 patients with mCRC who were treated with cetuximab-based first-line regimens, patients with *KRAS* G12C tumors had the shortest survival times compared with patients with other analyzed *KRASm* ($KRAS^{G12D/V/A/S/R}$).[60] The median OS for patients with *KRAS* G12C was 14.3 (95% CI: 6.7, 21.9) months and the median PFS was 4.9 (95% CI: 3.7, 6.2) months. For patients with other *KRASm*, the median OS ranged from 15.2 months (*KRAS* G12S) to 23.3 months (*KRAS* G12D) months and the median PFS from 5.3 months (*KRAS* G12R) to 9.8 months (*KRAS* G12A).

A study of patients with mCRC who were treated with standard chemotherapy, with or without an anti-angiogenic agent, reported a significantly worse OS for patients with *KRAS* G12C (7.3 months) and *KRAS* G12S (5.0 months) compared with patients harboring other *KRASm* who exhibited a median survival time ranging from 11.6 to 27.0 months.[54]

A post hoc analysis of pooled clinical data from 1239 patients from 5 randomized trials, in which patients with mCRC were treated with chemotherapy with or without bevacizumab as first-line treatment (67%), reported that patients harboring *KRAS* G12C had the shortest median OS (16.8 [95% CI: 15.6, 18.0] months).[51] Patients with other *KRASm*, including *KRAS* G12A/D/S/V and *KRAS* G13D, had OS times ranging from 17.6 to 25.2 months.[51] The median PFS for patients with *KRAS* G12C was 10.1 (95% CI: 6.4, 13.8) months and ranged from 8.8 to 10.5 months in patients with other *KRASm*. In an observational, retrospective study in Italian patients with stage IV mCRC treated with chemotherapy (most [65%] of whom had also received bevacizumab as first-line treatment), the median OS for patients with *KRAS* G12C was 24.4 months (95% CI: 10.6, 38.2) and ranged from 5.7 to 39.1 months among patients with other *KRASm*.[57]

In a retrospective analysis of data from 404 patients with mCRC who were treated with bevacizumab (80% received bevacizumab as first-line treatment), the median OS in patients with *KRAS* G12C was shorter (27.4 [95% CI: 10.0, 44.8] months) than in patients with *KRAS* G12D (28.7 months) and *KRAS* G12S (32.7 months), but longer than in those with *KRAS* G12A, *KRAS* G12V, and *KRAS* G13D (range, 16.1 to 22.8 months).[55] The median PFS was 10.6 (95% CI: 6.8, 14.3) months in patients with *KRAS* G12C, while the median PFS ranged from 3.5 to 15.1 months with other *KRASm*. In this study, the PFS and OS of patients with *KRAS* G12C tumors were comparable to those with other *KRASm* tumors (with the exception of *KRAS* G12V and *KRAS* G12A tumors which were associated with significantly shorter survival outcomes) and to those with *KRASwt* tumors.

In contrast to these reports, 2 studies noted that the clinical outcomes in patients with *KRAS* G12C were either similar or superior to the outcomes observed in patients with other *KRASm*. A retrospective review from Turkey reported no difference in the OS for patients with *KRAS* G12C and patients with other *KRASm*.[58] In another retrospective study, in which *KRAS* was identified through allele-specific polymerase chain reaction on paraffin-embedded tumor specimens, patients with *KRAS* G12C and *KRAS* G12S had the highest 2-year OS rates (both 100%); the OS rates were lower in those with other *KRASm* (OS range, 34% to 87%) and *KRASwt* (OS, 85%).[61]

The small sample sizes in each study, the difference in treatment protocols, and number of prior lines of therapy made a direct comparison of these outcomes difficult.

Objective Response Rate

At the time of the conduct of the SLR, 2 publications had reported the ORR in patients with *KRAS* G12C-positive mCRC and other gastrointestinal cancers and treated with sotorasib.[63,65] A phase I trial of sotorasib in 42 patients with CRC reported an overall ORR of 7.1% (95% CI: 1.5, 19.5) across all doses tested.[63] An ORR of 12.0% was reported for patients with CRC and other GI cancers treated with 960 mg/day of oral sotorasib.[65] However, this study lacked a comparator arm, precluding a comparison of outcomes.

In a post hoc analysis of outcomes in patients who received cetuximab in combination with FOLFOX, FOLFIRI, or capecitabine/oxaliplatin/irinotecan (XELOXIRI) as first-line treatment for mCRC, patients with *KRAS* G12C tumors had a worse ORR (17.0%) compared with patients with *KRAS* G12D (46.0%), *KRAS* G12V (44.0%), and *KRAS* G12A (42.0%) tumors, but a better ORR than patients with *KRAS G12S* (13.0%) and *KRAS* G12R (0%) tumors.[60]

Disease-Free Survival and Relapse-Free Survival

Three studies reported DFS outcomes. Overall, patients with *KRAS* G12C tumors appeared to have inferior DFS rates than those with *KRASwt* tumors. Among patients with stage III adenocarcinoma of the colon who received

Table 3. List of Publications Reporting Overall Survival and Progression-free Survival Data in Patients With *KRAS* G12C -positive Colorectal Cancers.

Study	N	Patients with the *KRAS* G12C mutation (n)	Metastatic	Study type	Treatment LoT	OS *KRASwt/ KRASm* mOS, months (95% CI)	OS *KRAS* G12C mOS, months (95% CI)	PFS *KRASwt/ KRASm* mPFS, months (95% CI)	PFS *KRAS* G12C mPFS, months (95% CI)
Wong et al, 2020[29]	1,308	56	Yes (63%)	Obs	None **Prior LoT**: 1, 2, or ≥ 3	NR	*KRAS* G12C, 31.7	NR	NR
Modest et al, 2016[51]	1,239	28	Yes	Posthoc from RCT	FUFIRI, mIROX FOLFIRI + BEV CAP + OXA + BEV; CAP + IRI + BEV; FP + BEV, BEV; XELOX/FUFOX **LoT: 1L**	[b] *KRASwt,* 26.9 (25.2, 28.5) *KRASm* 21.0 (18.5, 23.5)	*KRAS* G12C, 16.8 (15.6, 18.0)	[b] *KRASwt,* 10.3 (9.7, 10.8) *KRASm* 9.5 (8.9, 10.1)	*KRAS* G12C, 10.1 (6.4, 13.8)
De Roock et al, 2010[52] [a]	886	24	Yes	Obs	**LoT: ≥ 2** CET + CHT Prior LoT 1: n = 84 (12.9%); 2: n = 320 (49.3%); 3: n = 156 (24.0%); 4: n = 60 (9.2%); ≥ 5: n = 25 (3.9%); unknown: n = 4 (0.6%)	Reported for each patient individually	Reported for each patient individually	Reported for each patient individually	Reported for each patient individually
Schirripa et al, 2020[53]	839	145 Study cohort	Yes	Obs	None	Other *KRASm,* 36.7 (32.2, 41.5)	*KRAS* G12C, 28.9 (24.0, 35.2)	NR	NR
	329	57 External validation cohort	NR			Other *KRASm,* 35.8 (31.0, 42.8)	*KRAS* G12C, 25.9 (17.2, 37.3)	NR	NR
Ottaiano et al, 2020[54]	446	13	Yes	Obs	None Prior LoT: 1 or ≥ 2 **OS:** not defined	OS not reported for *KRASm* but for individual codon 12 mutations	*KRAS* G12C, [C] 7.3 (1.6, 12.6)	NR	NR
Jones et al, 2017[10]	392	15	Yes	Obs	Curative surgery and/or FOLFOX as 1 LoT[c]	[b]*KRASwt* 35.1 *KRASm* 25.8 (P = .006)	*KRAS* G12C, 24.9; (P < .02 vs *KRASwt*)	NR	NR
Fiala et al, 2016[55]	358	9	Yes	Obs	BEV in combination with FOLFOX, FOLFIRI, 5-FU/FA, XELOX, XELIRI or CAP, OXA or IRI alone **LoT: 1 or ≥ 2**	[b] *KRASwt,* 29.2 (26.3, 32.1) *KRASm,* 22.8 (P = .003)	*KRAS* G12C, 27.4 (10.0, 44.8)	[b]*KRASwt,* 10.8 (9.2, 12.3) *KRASm,* 9.2 (P = .30)	*KRAS* G12C 10.6 (6.8, 14.3)
George et al, 2020[56]	273	25	Yes	Obs	None	All, 26.4 *KRASm,* 25.8 *KRASm* (non- *KRAS* G12C), 27.1	*KRAS* G12C, 23 (P < .001; vs other non-*KRAS* G12C *KRASm*)	NR	NR

Table 3. Continued

Study	N	Patients with the *KRAS* G12C mutation (n)	Metastatic	Study type	Treatment LoT	OS *KRASwt/ KRASm* mOS, months (95% CI)	OS *KRAS* G12C mOS, months (95% CI)	PFS *KRASwt/ KRASm* mPFS, months (95% CI)	PFS *KRAS* G12C mPFS, months (95% CI)
Garrido-Laguna et al, 2012[45]	238	11	Yes	Obs	CET or PAN, n = 122 PI3K/Akt/mTOR inhibitors, n = 80 **Prior therapies: adjuvant CHT, anti-EGFR**	[b] *KRASm,* 57.5 (50.0, 64.8) *KRASwt,* 89.5 (63.5, 120.1) (*P* = .007)	*KRAS* G12C, 50.0 (14.3, 59.3)	**Patients treated with anti-EGFR**[b] *KRASm*, 15 weeks *KRASwt*, 22 weeks (*P* = .01)	NR
Dadduzio et al, 2016[57]	218	11	Yes	Obs	FOLFOX/XELOX ± IRI FOLFOX/XELOX ± IRI± BEV **Prior lines of systemic therapies:** **0 to ≥ 2**	[b] *KRASm* (codon 12) 32.0 (26.3, 37.7) *KRASm* (codon 13) 31.0 (24.3, 37.8)	*KRAS* G12C, 24.4 (10.6, 38.2)	*KRASm,* (codon 12) 1L: 10.8 2L: 5.9 3L: 4.6[b]	NR
Ucar et al, 2020[58]	191	7.4% in multiple mutation group	Yes	Obs	**LoT:** 1 mFOLFOX6 or FOLFIRI	[b] Single *KRASm,* 22.7 Multiple *KRASm,* 40.7 (*P* = .01)	*KRAS* G12C, 28.4	Single *KRASm,* 8.8 Multiple *KRASm,* 12.8 (*P* = .05)	NR
Renaud et al, 2015[59]	180	9	Yes	Obs	Thoracic metastasectomy Neoadjuvant and adjuvant therapy based on 5-FU	[b] *KRASwt,* 98.00 (74.21, 121.78) *KRASm,* 55.00 (28.69, 81.31)	*KRAS* G12C, 37 (15.09,58.91)	NR	NR
Modest et al, 2012[60] [a]	119	13	Yes	Posthoc analyses from RCT	CET + XELIRI CET + FOLFIRI CET + FOLFOX6 **LoT: 1L (CET-based)**	OS not reported for *KRASm* collectively, only for individual codon 12 mutations	*KRAS* G12C, 14.3 (6.7, 21.9)	PFS not reported for *KRASm* collectively, only for individual codon 12 mutations	*KRAS* G12C, 4.9 (3.7, 6.2)
Cushman-Vokoun et al, 2013[61]	111	4	Yes (Stage IV 25%)	Obs	None	2-year OS rate[a] *KRASwt,* 84.5% (75.2, 95.0)	2-year OS rate *KRAS* G12C, 100% (100.0, 100.0)	NR	NR
Andre et al, 2013[62]	65	1	Yes	Int Single arm	PAN + IRI in patients refractory to CHT **LoT: 2 or 3**	[b]*KRASwt,* 11.9 (6.8, 18.2)	*KRAS* G12C, 4.5 (1 patient)	*KRASwt* 6.3 (3.7, 8.7)	*KRAS* G12C, 3.1 (1 patient)
Hong et al, 2020[63]	42	42	Yes, or locally advanced	Int Single arm	Sotorasib **Prior LoT: ≥ 2 (98%)**	NR	NR	NR	*KRAS* G12C, 4.0 (0, 11.1)

Table 3. Continued

Study	N	Patients with the *KRAS* G12C mutation (n)	Metastatic	Study type	Treatment LoT	OS *KRASwt/ KRASm* mOS, months (95% CI)	OS *KRAS* G12C mOS, months (95% CI)	PFS *KRASwt/ KRASm* mPFS, months (95% CI)	PFS *KRAS* G12C mPFS, months (95% CI)
Cercek et al, 2014[64]	17	1	Yes	Int	Ganetespib	*KRASwt* (n = 6): median OS not calculated; individual patient OS: 26, 15, 16, 113, 11, 63 weeks	*KRAS* G12C, 22 weeks	*KRASwt*, (n = 6): median PFS not calculated, individual patient PFS: 5, 6, 4, 9, 2, 15 weeks	*KRAS* G12C, 12 weeks
				Single arm	LoT: ≥ 3		(1 patient)		(1 patient)

[a]Studies included prior or concomitant treatment with anti-EGFR therapies combined with oxaliplatin, which have been associated with either no benefit or worse outcomes in *KRASm* patients with CRC ([62]).
[b]Other *KRASm* subtypes and/or mutations reported.
[c]Unclear whether chemotherapy was used as neoadjuvant/adjuvant therapy.
Abbreviations: BEV: bevacizumab; CAP: capecitabine; CET, cetuximab; CHT: chemotherapy; EGFR: epidermal growth factor receptor; FA: folinic acid; FOLFIRI: IRI + 5-FU/FA; FOLFOX: OXA + 5-FU/FA; FP: fluoropyrimidine; 5-FU: 5-fluorouracil; FUFIRI: infusional 5-FU; FUFOX: OXA + 5-FU (bolus)/FA; Int: interventional; IRI: irinotecan; *KRAS*: Kirsten rat sarcoma viral oncogene homolog; *KRASm*: *KRAS* mutation(s); $KRAS^{G12C}$: *KRAS* with mutation at codon 12 that results in the substitution of glycine with cysteine; *KRASwt*: wild-type *KRAS*; 1L, 2L, 3L: first, second, third LoT; LoT: line of therapy; mFOLFOX: modified FOLFOX; mIROX: IRI + OXA; mOS: median overall survival; mPFS: median progression-free survival; mTOR: mammalian target of rapamycin; NR: not reported; Obs: observational; OS: overall survival; OXA: oxaliplatin; PAN: panitumumab; PFS: progression-free survival; PI3K: phosphatidylinositol-3-kinase; RCT: randomized controlled trial; XELIRI: CAP + IRI; XELOX : CAP + OXA.

adjuvant FOLFOX monotherapy or combination therapy with cetuximab, the combined 3-year DFS rate in both arms for patients with *KRAS* G12C tumors was 61.0% (95% CI: 50.0%, 73.0%) with an HR of 1.66 (95% CI: 1.14, 2.41; P = .008) compared with a 3-year DFS rate of 77% (95% CI: 75%, 80%) in patients with *KRASwt* tumors.[66] Among patients with stage II CRC, a significantly shorter DFS was noted in patients with *KRAS* G12C than in those with *KRASwt* (HR 2.03: P = .006).[43] However, it should be noted that data from only 6 patients with *KRAS* G12C tumors were available for this analysis. In another study of patients treated with cetuximab, an odds ratio of 0.95 (95% CI: 0.18, 5.15; P = .95) for DFS was reported for patients with *KRAS* G12C; however, the comparator was not clearly defined.[67]

Two studies reported RFS in patients with *KRASm*. An analysis of outcomes in Japanese patients who had undergone curative surgical resection for stage I-III CRC revealed a significantly worse 3-year RFS rate in patients with *KRAS* G12C than in patients with *KRASwt* (33.3% vs. 81.9%; HR 6.57 [95% CI: 1.90, 17.7; P < .001]).[68] In a post hoc analysis of 1404 patients with stage II or stage III colon cancer treated with irinotecan added to fluorouracil/leucovorin as adjuvant, neither *KRAS* G12C or any other *KRASm* had a prognostic value for RFS.[44]

Discussion

In this SLR, studies describing the global prevalence of the *KRASm* in patients with CRC, mutation prevalence by primary tumor sidedness, and the clinical significance of *KRASm* were identified and described. A worldwide median prevalence of 38.0% for *KRASm* was estimated based on the included studies. The observed prevalence of *KRASm* varied widely across studies, although the median prevalence in regions with the lowest prevalence (North America, 37.4%; range, 23.1% to 50.0%) and the highest prevalence (JAPAC, 40.7%; range, 13.3% to 51.5%) were not widely different and had overlapping ranges. The majority of prevalence studies for which the RoB could be estimated (46/51, 90%) had a low RoB. While it is possible that these percentages reflect actual differences in the prevalence of *KRASm*, the contribution of heterogeneity in study design and size in causing these variations cannot be discounted, even though this analysis was limited to unselected studies with > 100 patients and to studies that specifically analyzed the prevalence of this mutation in the population. The prevalence of *KRASm* noted in this SLR is comparable to that reported in a recent analysis of real-world data from 6477 adult patients with mCRC (3.7% for *KRAS* G12C and 45.5% for other *KRASm*),[69] as well as to that reported in other published databases, such as the AACR Project GENIE, which currently reports a *KRAS* G12C prevalence of 2.9% in 12 187 cases of colorectal adenocarcinoma.[70] The median prevalence of *KRAS* G12C as reported in the entire cohorts of the included populations in this study was 3.1%. The prevalence of *KRAS* G12C in CRC was much lower than that in NSCLC, where a prevalence of 14.0% has been reported.[71]

Limited evidence was available to assess any link between the prevalence of *KRAS* G12C and primary tumor sidedness. The available literature indicated that tumors that develop on the right side of the colon were more likely to harbor *KRASm*. Published evidence indicates that tumors that develop on the

right side of the colon respond poorly to anti-EGFR therapies compared with left-sided colorectal tumors.[72,73] Indeed, the National Comprehensive Cancer Network (NCCN) guidelines recommend treatment with anti-EGFR therapies (eg, cetuximab and panitumumab) only for patients with left-sided tumors. The increased frequency of CpG island methylation in the *EGFR* promoter on right-sided primary tumors leading to loss of EGFR expression (and the consequent lack of response to anti-EGFR therapies) and the hypermutations observed in right-sided colorectal carcinomas may provide a possible explanation for this phenomenon.[74,75] It will be important to assess if patients with right-sided tumors, who are known to experience poorer outcomes and also have a limited range of therapeutic options, can benefit from currently available *KRAS*-targeting therapies.

When clinical outcome data were analyzed with respect to *KRASm*, most studies reported inferior survival and prognostic outcomes for patients with *KRAS* G12C. However, these studies could not be compared directly because of considerable heterogeneity in study populations, treatments, and the number of prior lines of therapy. It should also be noted that only a few studies reported prognostic data in patients with *KRAS* G12C and that these findings were inconsistent.

Studies published since the completion of this SLR continue to provide contradictory evidence regarding the prognostic significance of *KRAS* G12C. Outcome analysis from a population-based registry of Australian patients with mCRC and a real-life and population-based cohort of Nordic patients with mCRC or locally advanced untreatable CRC did not reveal any difference between patients with *KRAS* G12C and those with other *KRASm*.[76,77] In contrast, 4 recent studies from Japan, US, and China reported poorer survival rates and significantly inferior PFS in patients with *KRAS* G12C than in those with other *KRASm*.[69,78-80] These conflicting findings have been attributed to the difference in average patient age, disease stage, and data sources (selected patient populations vs population-based/real-life registries).[76] Given these findings, a deeper investigation into the biological and mechanistic role of *KRAS* G12C (vis-à-vis other *KRASm*) may possibly provide better insights into the clinical significance of this mutation.

Limited evidence was available regarding prognostic outcomes with *KRAS*-targeting therapies. However, given the number of targeted therapies that are currently in the developmental pipeline for CRC, it is expected that there will be a considerable increase in our knowledge base regarding clinical outcomes with *KRAS* G12C-positive tumors in the near future. For example, results from a recent phase I/II study of adagrasib, revealed an ORR of 19% in patients receiving adagrasib monotherapy for untreatable or metastatic tumors with *KRAS* G12C mutations.[81] The phase II CodeBreaK 100 study, the results of which were published after the conduct of this SLR, reported an ORR of 9.7% among patients who received sotorasib monotherapy for *KRAS* G12C-mutated mCRC and had progressed following fluoropyrimidine, oxaliplatin, and irinotecan treatment.[82] Recent studies have shown that treatment approaches that combine KRAS inhibitors with anti-EFGR antibodies yield considerably enhanced ORRs in patients with refractory mCRC.[83,84] These findings complement studies in preclinical models which had indicated that EGFR blockade could potentially overcome the EGFR-driven adaptive resistance to KRAS inhibitors—a phenomenon which is more pronounced in CRC in comparison to NSCLC.[85]

A major strength of this study was the inclusion of a large number of studies which enabled a robust estimate of the prevalence of *KRASm* in > 40 000 patients from different geographical regions. This information can be used to support future testing and treatment strategies. The limitations of this SLR include the analysis of data from studies that used a wide variety of techniques to estimate the prevalence of *KRASm*. This may have contributed to the outlier prevalence observed in studies from certain geographical regions. The use of standardized molecular methods to identify *KRASm* may help clarify some of these discrepancies. Another limitation was the availability of relatively few studies that investigated the role of *KRASm* with respect to tumor sidedness or studies that compared response rates and duration of response in patients with different *KRASm*. *KRASm* have not been routinely assessed in clinical trials or in real-world practice as they were considered "undruggable" until recently. Consequently, there is a limited amount of published data describing outcomes in patients with *KRAS* G12C mutations. This literature review was, therefore, not designed to definitively answer the proposed research questions but rather to summarize existing data and provide context for the interpretation of the multiple sources of existing data derived from next-generation sequencing.

Conclusions

To summarize, the prevalence of *KRAS* G12C in CRC varied widely across studies. Limited evidence was available to assess any association between the *KRAS* G12C mutation and tumor sidedness. The prognostic significance of *KRASm* could not be definitively assessed as the studies were highly variable in terms of the patient population and interventional therapies used; however, overall, the reviewed evidence suggests shorter OS, PFS, and DFS in patients with *KRAS* G12C than in those with patients with *KRASwt* and other *KRASm*. Well-designed studies with clearly delineated research questions are needed to assess the differences in clinical outcomes in patients with *KRASm* and *KRASwt* and to investigate the mechanistic link between the *KRAS* G12C mutation and tumor sidedness.

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Conflict of Interest

John Strickler reports grants or contracts to research institution from AstraZeneca, Bayer, Seagen, Amgen Inc., Daiichi-Sankyo, Nektar, Abbvie, Erasca, and Gossemer Bio, AStar D3, Curegenix, Sanofi, Roche/ Genentech, and Silverback Therapeutics, consulting fees from Abbvie, Amgen Inc., AstraZeneca, Bayer, Inivata, Natera, GlaxoSmithKline(GSK), Mereo Biopharma, Pionyr Immunotherapeutics, Seagen, Pfizer, Silverback Therapeutics, and Viatris, support for attending meetings and/or travel from Seagen, and participation on a Data Safety Monitoring Board or Advisory Board for Abbvie and Pionyr Immunotherapeutics. Takayuki Yoshino, reports research funding from Ono Pharmaceutical

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Author Contributions

Conception/design: K.S., C.S.E., M.R. Provision of study material or patients: K.S., C.S.E., M.R. Collection and/or assembly of data: K.S., C.S.E. Data analysis and interpretation: all authors. Final approval of manuscript: all authors.

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Data Availability

Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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