Review of *KRAS* testing in patients with metastatic colorectal cancer in France in 2011

Flash Kras

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Conflicts of interest

Consulting activity or remunerated participation in an expert group for Merck Serono.

Abstract

Introduction:
Cetuximab is an anti-EGFR monoclonal antibody indicated for the treatment of metastatic colorectal cancer (mCRC). The presence of somatic *KRAS* mutations has been identified as a predictor of resistance to anti-EGFR therapy. *KRAS* mutation detection is thus required prior to prescribing anti-EGFR therapy and was integrated in cetuximab MA in 2008. The objective of the Flash-*KRAS* study was to review *KRAS* genotyping in 2011 as part of the initial management of mCRC.

Patients and Methods:
This epidemiological, national, retrospective, non-interventional study was performed from 28 March to 8 April 2011. During this period, 538 patients with mCRC were included in 160 hospital centers spread all over France. The primary endpoint was to assess the frequency at which *KRAS* testing was requested for patients having started a first line treatment (L1) of mCRC. The secondary endpoints consisted in describing the time required and the methods used for *KRAS* testing, the possible reasons for not performing this test, and in describing and analyzing the clinical characteristics of patients as well as the L1 treatments planned and that received.

Results:
A total of 319 men and 218 women were included in this investigation with a mean age of 67.1 ± 11.3 years. CRC had been diagnosed for 12.0 ± 20.7 months, with synchronic metastases in 69.9% of cases. Colic / rectal localization: 76.3% / 23.3%, with exeresis of primary tumor: 66.7%. L1 treatment was administered less than 2 months (1.7 ± 2.5 months) after diagnosis of metaastases. L1 regimens used were: Folfiri: 41%, Folfox: 31.1%, combined with biotherapy for 54.3%. *KRAS* genotyping was performed in 433 patients (81.1%). The request rates according to the type of establishment were 87.7% (private), 83.3% (CAC), 81.6% (CHG), 72.9% (CHU), 73.1% (other structure) and varied according to the region from 56.5% to 100%. *KRAS* genotyping was not performed in 101 patients out of the 538 questionnaires received (18.9%). The main reasons for not requesting a *KRAS* test were: non-prescription of anti-EGFR (n=58), one recruitment for surgery (n=6), available equipment not exploitable (n=5), patient age (n=3), time required too long (n=2), peri-surgical chemotherapy (n=2), technical impossibility (n=1), other (n=12), missing (n=14). The genotyping report was available for 370 patients (87%) after an average time of 23.6 ± 28.2 days. The time required was heterogeneous within the regions (time required to receive the report ranging from 8.3 ± 7.2 days to 38.8 ± 101.8 days). Genotyping was requested by oncologists (48%), gastroenterologists (33.6%) or surgeons (14.5%), about 15 days (median) after diagnosis of metastases, and 15 days (median) prior to L1 treatment initiation. *KRAS* status was not received before L1 selection for 56.6% of patients. Genotyping showed a wild-type *KRAS* gene in 223 (66.6%) patients. In case of wild-type *KRAS* gene and change in the patient's treatment, the latter corresponded to the prescription of an anti-EGFR in 77.8% of cases.

Conclusion:
The Flash-*KRAS* study is the first study reviewing *KRAS* genotyping practice in France. It shows that in 2011 *KRAS* testing is an integral part of the management of patients with mCRC. Nevertheless, there are some discrepancies within the French territory as to the rate at which *KRAS* testing is requested and also as to the time required to obtain the mutational status which must be compatible with the treatment.

Introduction / Context

- Cetuximab and panitumumab are anti-EGFR monoclonal antibodies indicated for the treatment of metastatic colorectal cancer (mCRC).
- The presence of a somatic mutation in codons 12 and 13 of the *KRAS* gene has been identified as a predictor of resistance to anti-EGFR therapy1-3.
- *KRAS* mutation detection (*KRAS* test) is thus required prior to prescribing anti-EGFR therapy and was integrated in the MA of both anti-EGFR drugs.
- *KRAS* testing is thus an integral part of the assessment prior to any therapeutic decision.

1- Lièvre et al. J Clin Oncol 2008 ; 26: 374-9 2- Amado et al. J Clin Oncol 2008 ; 26: 1626-34 3- Karapetis et al. N Eng J Med 2008 ; 359: 1757-65

Study objectives

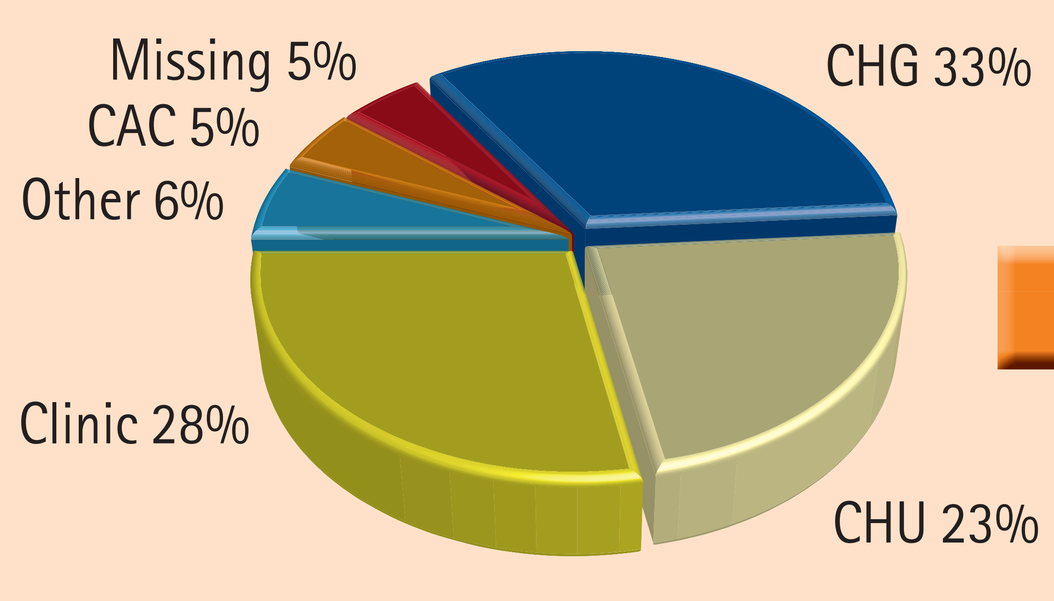
- **Primary objective**
  - To assess the rate of *KRAS* test prescription in patients starting a 1st line (L1) treatment for mCRC.
- **Secondary objectives**
  - To describe the possible reasons for not prescribing this test.
  - To describe and analyze the clinical characteristics of patients and the planned L1 treatments and those finally received.
  - To describe and analyze the time to obtain the *KRAS* test results and the process (who makes the request, when) as well as the therapeutic approach adopted during this period.
  - To analyze the impact of *KRAS* test availability and its result on the treatment chosen by the physician.
  - To describe the method used for the analysis, the type of mutation (if available) and the way of reporting results to clinicians (report of results).

Patients and methods

Observational, national, retrospective study performed from 28 March to 8 April 2011

- Patients initiating a 1st line mCRC treatment between 01/01/2011 and 28/03/2011 (date of study start). Questionnaires (physicians).

Distribution of centers by type of establishment



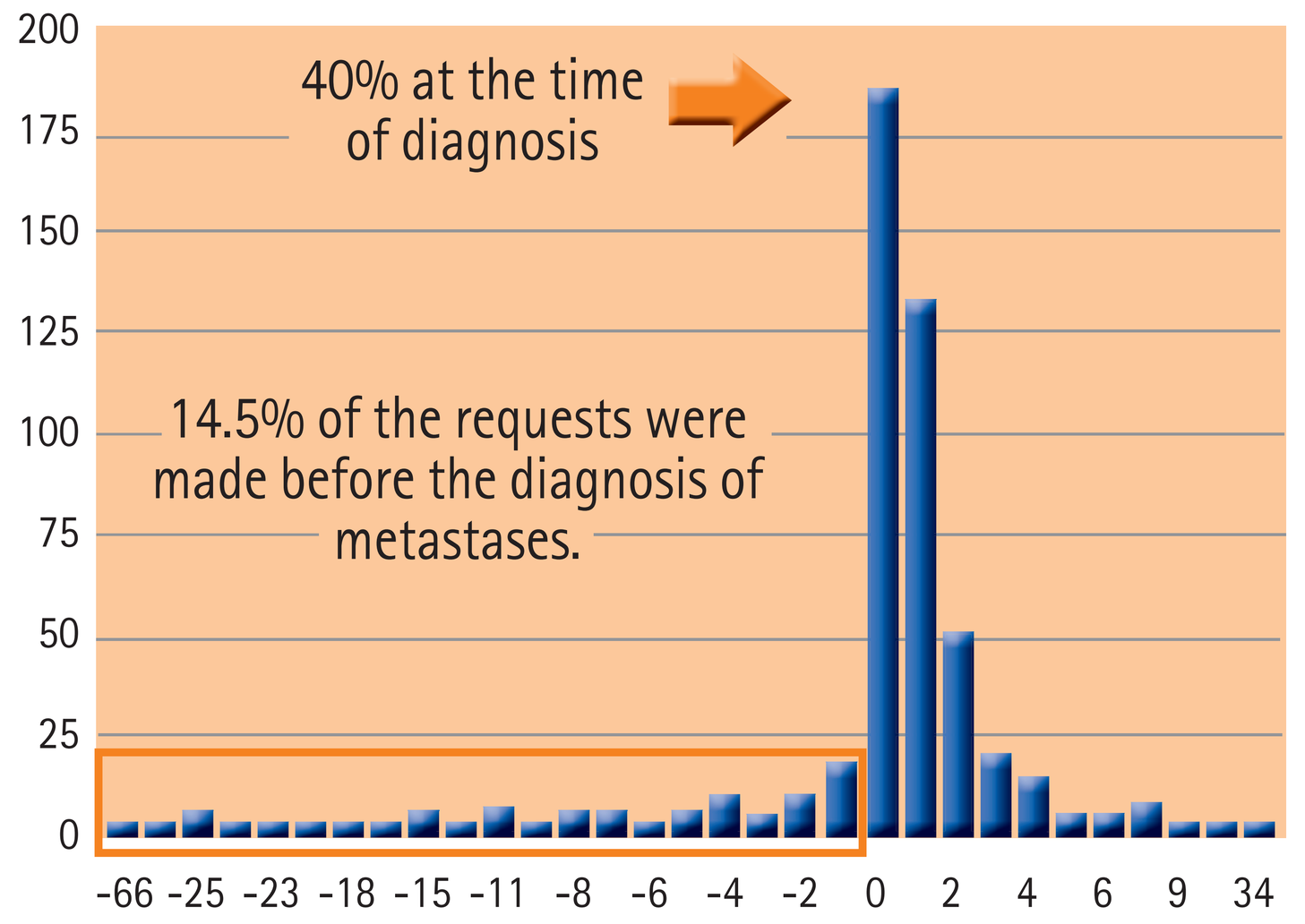
160 centers → 538 questionnaires returned

Patient characteristics

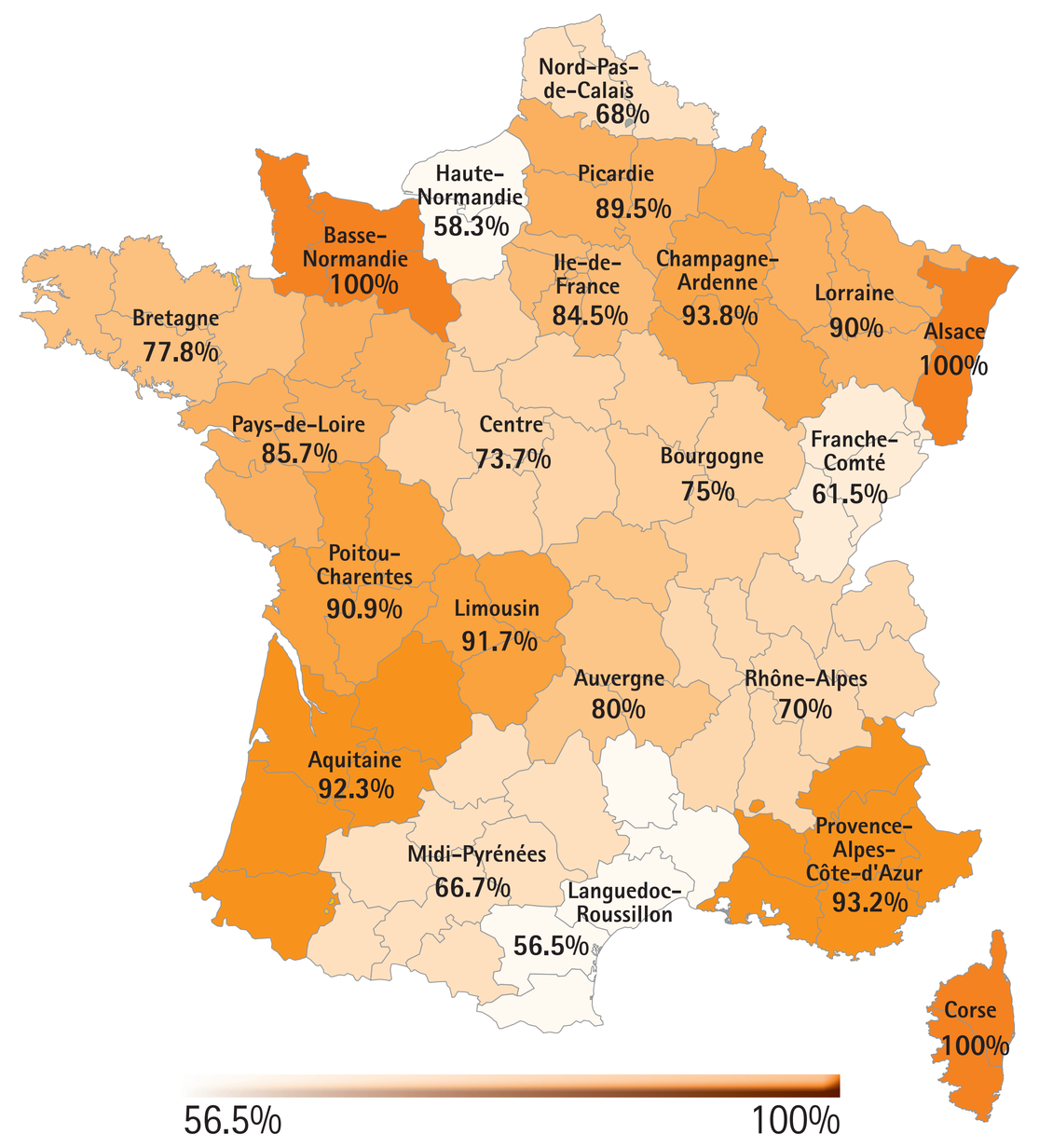
Total	n = 538	
Gender M/W (%)		59.4 / 40.6
Median age (years)		67 (25-92)
Synchronous metastases (%)		69.9
Primary tumor: colon/rectum/both (%)		76.3 / 23.4 / 0.4
Time to diagnosis-L1 treatment (months)		1.1 (0-33.8)
1st line chemotherapy (L1)		
FOLFOX/XELOX	40.5%	FOLFIRI/XELIRI 40.9%
5FU/Xeloda	9.6%	FOLFIRINOX 3.2%
Others	5.8%	Left blank 0.9%
L1 combined with targeted therapy (n,%)		289 (54.2)

Results: primary endpoint

Distribution of the time from the *KRAS* test prescription to the diagnosis of the first metastases (months)



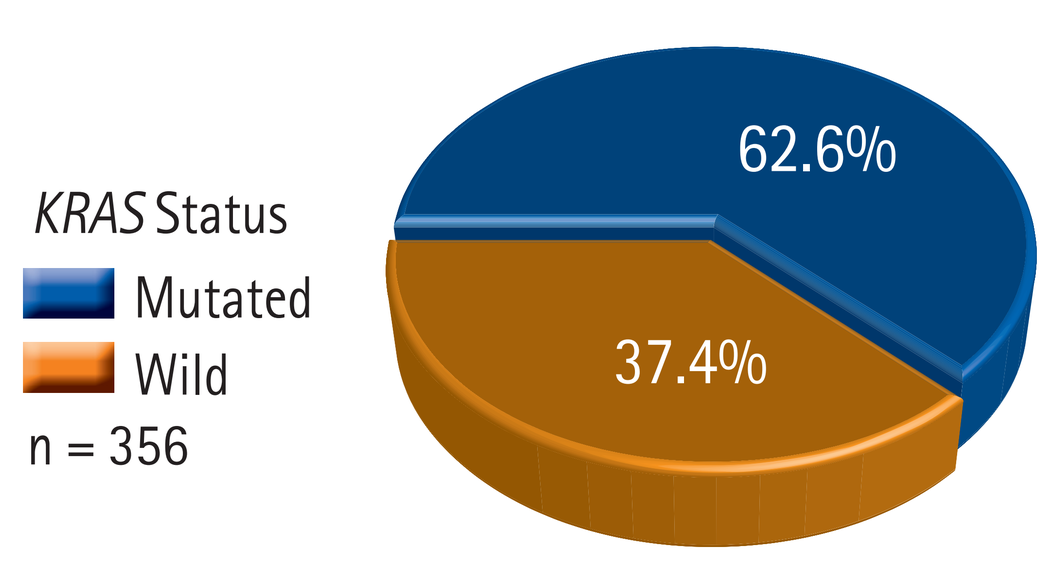
Rate of *KRAS* genotyping prescription per region



- *KRAS* status was determined in **433** patients **(81.1%)** before or during first line treatment.

Results: secondary criteria *KRAS* genotyping report

- Report available for 370 of 433 requests made (report pending or not received for 93% of unavailable cases).
- Receipt of report before 1st line treatment choice: 43.4%.



Time to receive the report (days)

Request for *KRAS* genotyping → Transmission of tumor specimens to platform → Report received by clinician: 23.7 ± 28.2 j

	Request → Transmission		Transmission → Report
N	300	N	238
Mean ± SD	9.7 ± 14.3	Mean ± SD	14 ± 11.0
Median	6	Median	11
Min. ; Max.	1 ; 121	Min. ; Max.	0 ; 85
Missing	133	Missing	124

Results: Request for and time to *KRAS* genotyping prescription

Reasons for not prescribing *KRAS* genotyping	
Total (n)	101
Anti-EGFR not prescribed	59
Candidate for metastases surgery	8
Samples not usable - technically impossible	6
Age of the patient	3
Too long time to obtain the test	2
Others (treatment refused, forgotten...)	9
Left blank	14

KRAS genotyping prescriber	N = 429
Missing	4
Oncologist	195 (45.5%)
Gastroenterologist	133 (31.0%)
Surgeon	48 (1.2%)
Anatomopathologist	31 (7.2%)
SPC	22 (5.1%)

If request for *KRAS* genotyping		n = 433
Time from *KRAS* test prescription to initiation of 1st line mCRC treatment (months)	N	418
	Mean ± SD	-1.52 ± 5.01
	Median	- 0,5
	Q1 ; Q3	- 1.1 ; - 0.1
	Min. ; Max.	- 66.9 ; 3.7
	Missing	15
Time from *KRAS* test prescription to diagnosis of first metastases (months)	N	421
	Mean ± SD	0,06 ± 5.48
	Median	0.5
	Q1 ; Q3	0.0 ; 1.2
	Min. ; Max.	- 66.5 ; 33.6
	Missing	12

Results: secondary endpoints - Impact of the result on the choice of 1st line treatment

(408 exploitable questionnaires out of 433 requests for *KRAS* testing)

Impact of *KRAS* result on therapeutic management depending on test result: YES (42.2%)

Report received	Mutated *KRAS* tumor n = 133	Non-mutated *KRAS* tumor n = 223	P-value
Impact of *KRAS*			
Result N	130	220	
Missing	3	3	
No	88 (67.7%)	112 (50.9%)	0.002 [a]
Yes	42 (32.3%)	108 (49.1%)	

[a]: Chi² test

* Prescription of anti-EGFR therapy if wild-type *KRAS* in 89.9% of cases

If impact of *KRAS* result on therapeutic management, further information depending on test result:

Report received	Mutated *KRAS* tumor n = 42	Non-mutated *KRAS* tumor n = 108
Impact N	37	108
Missing	5	0
Change in chemotherapy protocol	2 (5.4%)	5 (4.6%)
Prescription of anti-EGFR therapy*	6 (16.2%)	84 (77.8%)
Other	29 (78.4%)	6 (5.6%)
Change in chemotherapy protocol * + Prescription of anti-EGFR therapy*	0 (0.0%)	11 (10.2%)
Prescription of anti-EGFR therapy + other	0 (0.0%)	2 (1.9%)

Conclusion

- 1 st observational, retrospective study in a large cohort of patients reviewing *KRAS* genotyping practice in 2011 in France.
- *KRAS* genotyring has become routine practice (81.1% of tests in first line treatment) and is thus an integral part of the management of patients with mCRC from the first line of treatment.
- There are some discrepancies within the French territory as to the rate at which *KRAS* testing is requested and also as to the time required to obtain the mutational status (23.7 ± 28.2 days) which must be compatible with the treatment.
- This study thus demonstrates the significant impact of *KRAS* status on the choice of treatment from 1st line.

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