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A nationwide survey on current clinical practices for diagnosis and treatment of patients with BRAF-mutated melanoma and BRAF-mutated colorectal cancer in Argentina

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Abstract

Background: v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation occurs in approximately 50% of cutaneous melanoma and in 10% of patients with colorectal cancer (CRC). BRAF testing is recommended as good clinical practice, since it is critical for decision-making regarding adjuvants and treatment selection. In Argentina, there is a considerable knowledge gap with respect to how often BRAF testing is indicated, the delay between the time points at which the test is ordered and the results are received, how much external factors influence this delay, and how diagnosis, treatment and follow-up of melanoma and CRC are affected. Thus, the aim of this project was to provide insight into current clinical practices for diagnosis and treatment of patients with melanoma and CRC in Argentina.

Methods: A nationwide digital survey directed at clinical oncologists in private and public institutions across the country.

Results: Twenty-five percent of the oncologists answered the survey (115/462), from 16 out of 24 provinces. Over 95% of oncologists consider the test as standard of care, but there are considerable delays in the time to obtain the results depending on the jurisdictions, which significantly affect decision-making in diagnosis, treatment and follow-up.

Conclusion: BRAF testing is considered useful for the diagnosis and treatment of melanoma and CRC. The survey results highlight the need to optimise available resources to ensure quality care.

Keywords: *epidemiology, B-Raf proto-oncogene, melanoma, colorectal cancer, public health*

Introduction

Melanoma and colorectal cancer (CRC) are leading causes of cancer-related deaths around the world, and their incidence is increasing. Both types of cancer have some of the highest mutation rates among all solid tumours [1, 30]. Specific oncogenes are involved in these mutations, leading to alterations in cell cycle regulation, proliferation and apoptosis [37]. In particular, v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation

Research

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ecancer 2026, **20**:2187
https://doi.org/10.3332/ecancer.2026.2187

Published: 18/08/2026
Received: 27/11/2025

Publication costs for this article were supported by *ecancer* (UK Charity number 1176307).

occurs in approximately 50% of cutaneous melanoma [28] and in 10% of patients with CRC [21], commonly due to the V600E substitution. BRAF mutations are frequently associated with poor prognosis and reduced response to treatment [15]. The identification and characterisation of BRAF mutations led to the development of highly specific drugs that substantially improved survival in patients with melanoma [4]. Unfortunately, similar clinical responses were not observed in BRAF-mutated CRC, proposing a distinct mechanism of carcinogenesis, which will require new therapeutic agents to improve outcomes in these patients [5, 8].

Melanoma is a tumour that presents epidemiological rates different from any other tumour. The annual increase in incidence rates varies between 3% and 7% in different Caucasian countries. Thus, it is estimated that every 10 to 20 years the incidence doubles, being for these reasons one of the malignant tumours that has increased the most in the white population. In Latin America, the incidence varies throughout the region with a relatively low incidence of 1% to 5% [26]. This finding may be related to the scarce systematic collection of data in the region, in addition to large differences in ethnicities throughout the territory. However, mortality is high in this subcontinent due to this pathology, a fact that could be associated with the low socioeconomic resources in most of the countries of the region [36, 39].

With regard to CRC, it is the third leading diagnosis and the fourth most common cause of cancer-related deaths worldwide [34]. The main risk factors for CRC are poor diet, lack of exercise and tobacco and alcohol consumption, among others [9]. Whereas the incidence of CRC in developed countries has stabilised or declined in the past five decades, countries transitioning to higher levels of human development (such as those in Central and South America) have seen an increase in the incidence of CRC [6]. Here, it is estimated that CRC explains almost 80,000 new cancer cases and 44,000 cancer deaths per year, and it is expected to increase by almost 80% by 2030. However, these estimations rely on high-quality cancer incidence and mortality data, which are still lacking in the region.

Argentina is a large and heterogeneous country with 46 million people, and it has remarkable socioeconomic and cultural differences among its population. In Argentina, available cancer data are scarce and incomplete, and it often comes from external sources, making it difficult to analyse local issues. With respect to melanoma, it is known that the risk could be related in part to skin colour, which is genetically determined. The composition of the Argentinian population is a mixture of European descendants, native peoples and African immigrants in smaller proportions [19]. A case-control study conducted in Argentina shows that individuals with European grandparents have a similar risk of melanoma as those living in southern Europe. However, those with Argentinean grandparents have a lower risk of melanoma, which could be related to a darker skin tone [20].

On the other hand, CRC caused 6,816 deaths in Argentina in 2010, 11.7% of all deaths from malignant tumours, ranking second only to lung cancer. More than 90% of CRC occur in people over 50 years of age, so the increase in life expectancy and the decrease in the birth rate observed in the country, with the consequent aging of the population, will generate an increase in the population vulnerable to this disease in the coming decades. Argentina has implemented a national CRC prevention and early detection program to reduce incidence and mortality, but it should be complemented with further actions to improve the diagnosis, treatment and follow-up of the disease in all its stages.

In Argentina, the costs of BRAF mutation testing are completely covered by the pharmaceutical industry, which is centralised in Buenos Aires. Additionally, Argentina's vast territory presents a challenge for the efficient management of BRAF testing. Since testing is concentrated in a single geographic location, turnaround times for obtaining results may vary depending on the province from which the request originates. In this context, there is a considerable knowledge gap with respect to how often testing is indicated by clinical oncologists, what is the delay between the time points at which the test is ordered, and the results are received, how much do external factors (such as geographical distance to the testing laboratory) influence this delay and how diagnosis, treatment and follow-up of melanoma and CRC cancer are consequently affected. Within this framework, the aim of this work was to describe current clinical practices for diagnosis and treatment of patients with BRAF-mutated melanoma and BRAF-mutated CRC in Argentina.

Materials and methods

Participants

The survey was directed to clinical oncologists in Argentina. It was intended to have a nationwide outreach, so we aimed to obtain responses from all 24 jurisdictions, i.e., the 23 provinces and the Autonomous City of Buenos Aires (CABA).

Survey design

This descriptive study was designed to collect information about the current clinical practices for diagnosis and treatment of patients with BRAF-mutated melanoma and BRAF-mutated CRC in Argentina. The survey was elaborated by the clinical oncologist in our research group (V.V.). Before implementing the survey, we conducted a pilot test involving two oncologists, with the aim of checking the clarity and usability of the questionnaire. Respondents were interviewed after completing the survey to get their opinions about the questions and the web interface where the survey was implemented.

The survey consisted of four sections: 1. Referred to oncologists ("*Zip code of the city where you work regularly,*" "*Do you work in private or public institutions or both?*" "*How many people do you have on your staff?*" and "*Number of patients per day*"); 2. Referred to BRAF testing in melanoma ("*How many melanoma patients do you see per month*?" "*How many BRAF tests do you perform per month?*" "*Do you consider BRAF a SOC (Standard of Care) test in your clinical practice?*" "*Do you make decisions based on BRAF result in melanoma?*" and "*At what point in time do you perform BRAF testing?*"); 3. Referred to BRAF testing in CRC (the same questions as in the previous section but referring to the CRC) and 4. Referred to the BRAF test ordering procedure ("*Does the execution of the test change depending on the workplace?*" "*Who completes the administrative questions?*" "*Do you agree with the following statement: 'The current procedure for ordering the BRAF test is satisfactory'?*" "*How long is the average time between ordering the test and sample pick-up?*" and "*How long is the time between the exam request and the result on average?*"). The survey was sent to 462 oncologists nationwide via email and telephone, and the goal was to have at least five responses from each province. The survey was resent 3 and 6 weeks after the first contact to those oncologists who had not responded the first time.

Survey implementation

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the National University of Entre Ríos [16, 17]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for data integration and interoperability with external sources. Furthermore, REDCap also provides tools to ensure the anonymity of the responders.

Data analysis and statistics

Descriptive statistics were performed to summarise the data. Postal codes were used to discriminate physicians by jurisdiction. Missing data were not imputed.

Results

Response rate and demographic data

The survey was sent to 462 clinical oncologists: 31.0% (143/462) accessed the survey, 24.9% (115/462) completed only the first section, 23.6% (109/462) completed up to the second section, 22.5% (104/462) completed up to the third section and 22.1% (102/462) completed all sections of the survey. Table 1 shows the distribution of responses by province, with 115 responses obtained in 16 of the 24 jurisdictions.

Of the 115 completed surveys, it can be observed that 70.4% (81/115) worked with a team of more than three people, 21.7% (25/115) worked with two or three people and 7.9% (9/115) worked alone (Figure 1, left). Team members (n = 99, seven persons did not answer this question) were asked who completed the administrative tasks for the test order: 74.7% (74/99) answered that they completed them themselves, 19.2% (19/99) answered that the tasks were completed by administrative staff and 6.1% (6/99) answered that the questions were completed by resident physicians (Figure 1, right).

With regard to the workplace-related questions, 12.9% (13/115) of the physicians worked only in the public sector, 38.6% (47/115) worked only in the private sector and 48.5% (55/115) worked in both sectors (Figure 2, left). Those working in both sectors (n = 51, four people did not answer this question) were asked if the execution of the test changed according to the place of work: 84.3% (43/51) answered that it did not, whereas 15.7% (8/51) answered that it did (Figure 2, right).

The median number of patients seen per day was 20. In relation to the diseases treated (n = 104, nine did not complete the section), 6.7% (7/104) reported treating only CRC, 3.8% (4/104) reported treating only melanoma and 89.9% (93/104) reported treating both diseases. The median number of patients seen per month was 3 and 10 for melanoma and CRC, respectively. The median value of BRAF tests ordered per month for melanoma was 1 and for CRC 3 (the ratio of patients seen to the number of BRAF tests ordered is similar).

Table 1. Distribution of responses by jurisdiction.

Province	No. of responses	Province	No. of responses
CABA	27	Misiones	3
Buenos Aires	24	Chubut	2
Santa Fe	21	Mendoza	2
Córdoba	11	Río Negro	1
Entre Ríos	7	La Pampa	1
Formosa	6	Neuquén	1
Salta	4	Tucumán	1
Corrientes	3	Santa Cruz	1

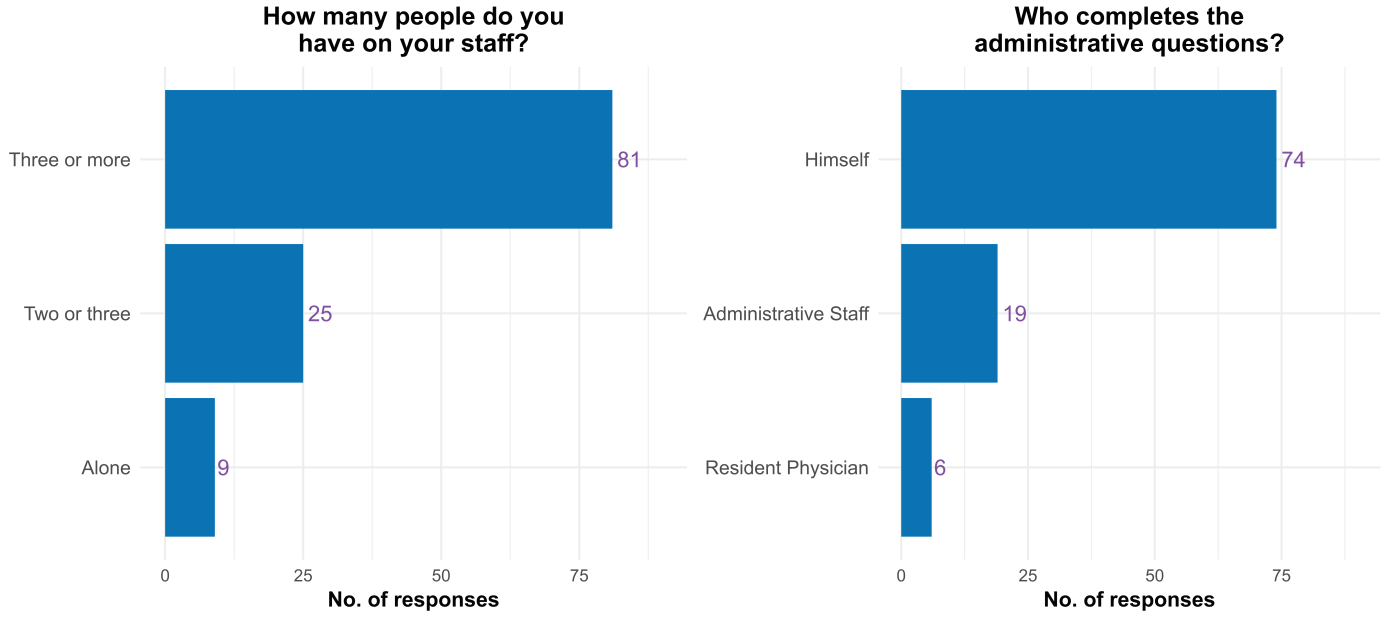

Figure 1. Staff. Left: Number of people on staff. Right: Person responsible for completing administrative questions.

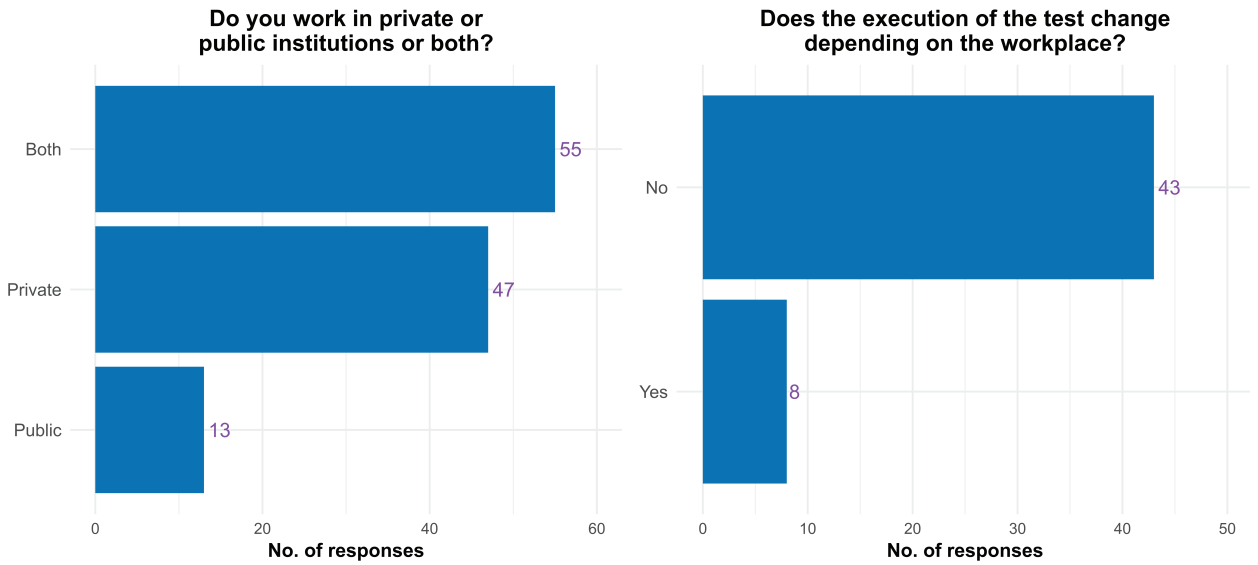

Figure 2. Workplace. Left: Institutions where physicians work. Right: Changes in text execution depending on workplace.

BRAF-test-related answers

In melanoma, 97.2% (106/109) of respondents and in CRC 94.2% (98/104) of respondents considered BRAF a standard of care (SOC) test. Of those who consider BRAF a SOC test, 1.9% (2/106) in melanoma and 8.16% (8/98) in CRC do not make decisions based on the test result. Regarding the timing of BRAF testing in melanoma, of the 95 physicians who responded to the question, 26.3% (25/95) perform it at initial histologic diagnosis regardless of stage, 33.7% (32/95) perform it at initial radiologic confirmation of advanced/metastatic disease prior to first-line treatment (1L) and 40.0% (38/95) test at diagnosis of stage 2C or greater (Figure 3, left). In CRC, of the 95 physicians who responded to the question 1.1% (1/95) do not perform the test or perform it only in clinical trials, 2.2% (2/95) perform the test in the follow-up progress of the standard 1L treatment, 22.1% (21/95) perform it at initial histologic diagnosis regardless of stage and 74.7% (71/95) perform it at initial radiologic confirmation of advanced/metastatic disease prior to first-line treatment (1L) (Figure 3, right). Of the 95 physicians who completed the CRC section, 77.9% (74/95) use tumour tissue to perform the BRAF test, and 22.1% (21/95) use both blood and tumour tissue. None of the respondents use only blood to perform the test.

The last section of the survey asked how much they agreed with the current process for ordering BRAF test (n = 102): 5.90% (6/102) reported a strong disagreement, 10.8% (11/102) reported disagreement, 11.8% (12/102) provided a neutral answer, 56.9% (58/102) reported agreement and 14.7% (15/102) reported a strong agreement (Figure 4).

Table 2 shows the sample withdrawal times and BRAF test results for each region of the country: Centro (Buenos Aires, Córdoba, Entre Ríos y Santa Fe), NEA (Chaco, Corrientes, Formosa and Misiones), NOA (Catamarca, Jujuy, Salta, Santiago del Estero and Tucumán), Cuyo (La Rioja, Mendoza, San Juan and San Luis) and Patagonia (Chubut, La Pampa, Neuquén, Río Negro, Santa Cruz and Tierra del Fuego, Antártida e Islas del Atlántico Sur). The results from the CABA were separated from the Central region due to the proximity to the laboratory that processes BRAF samples, which is located in this city. It can be observed in Table 2 (n = 96) that the sample pick-up occurs in 95.8% (92/96) before 10 days in all regions. However, the BRAF results are provided within 5 days in 1.0% (1/96) of the cases, between 5 and 10 days in 55.2% (53/96) of the cases, between 10 and 15 days in 30.2% (29/96) and in more than 15 days in 2.1% (2/96) of the cases.

Discussion

The aim of the present work was to bridge the knowledge gap with respect to how often BRAF testing is indicated by clinical oncologists, the delay between the time points at which the test is ordered and the results are received, how much external factors influence this delay and

how diagnosis, treatment and follow-up of melanoma and CRC cancer are affected. A full database of clinical oncologist contacts covering the entire country does not exist; nonetheless, we obtained responses from 16 of the 24 jurisdictions. The information collected in the survey was analysed quantitatively, and we obtained descriptive results that provide an overview of the current situation of clinical practices in Argentina. We surveyed 462 clinical oncologists from an estimated total population of approximately 1,000 professionals across the country. From these, we obtained 115 partial responses and 102 full responses. We were not able to get responses from at least five oncologists from Salta, Corrientes, Misiones, Chubut, Mendoza, Río Negro, La Pampa, Neuquén, Tucumán and Santa Cruz. In these jurisdictions, there are fewer hospitals, and the number of oncologists dedicated to treating melanoma and/or CRC is consequently lower.

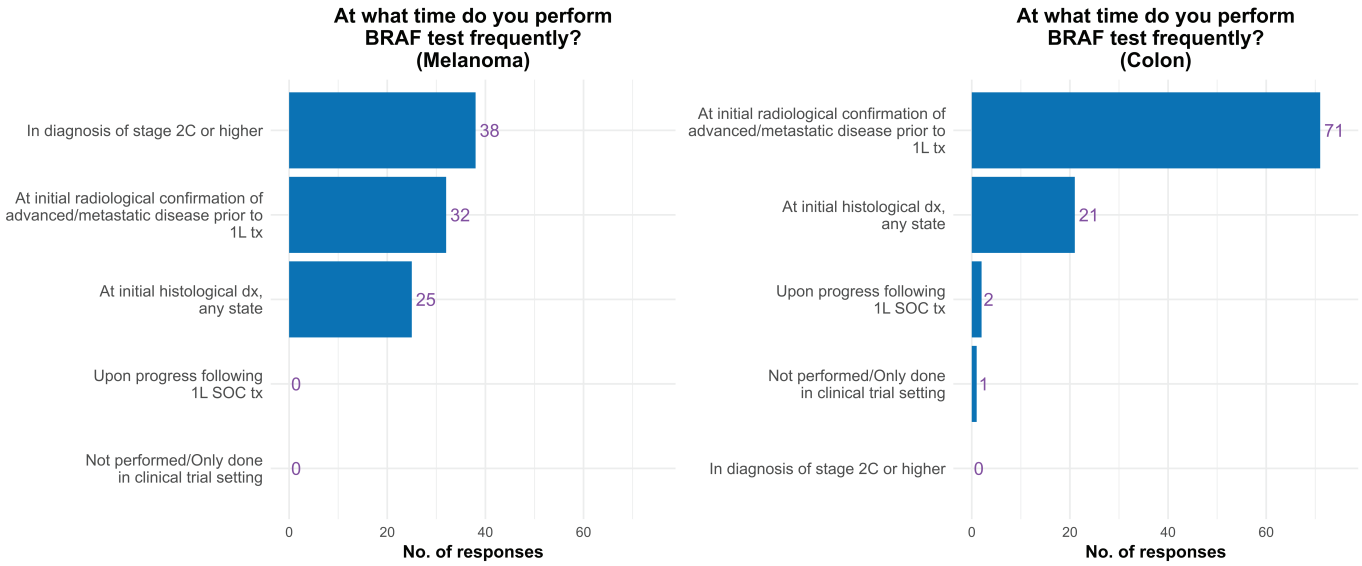

Figure 3. BRAF timing. Left: Time point at which BRAF testing is performed in melanoma. Right: Time point at which BRAF testing is performed in CRC.

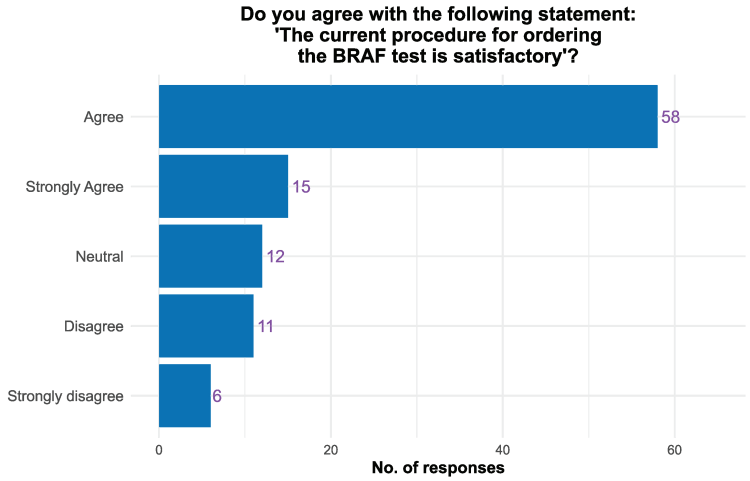

Figure 4. Satisfaction with the BRAF procedure. Level of satisfaction for the BRAF testing procedure.

Table 2. BRAF test processing times, distributed by region.

Region	Less than 5 days		5 to 10 days		10 to 15 days		Over 15 days	
	Sample pick-up	Test result	Sample pick-up	Test result	Sample pick-up	Test result	Sample pick-up	Test result
Centro	40	1	10	28	0	16	2	7
NEA	7	0	2	5	0	3	0	1
NOA	4	0	0	3	1	1	0	1
Cuyo	1	0	1	0	0	1	0	1
Patagonia	2	0	3	2	0	3	0	0
CABA	15	0	7	15	1	6	0	2

Based on the results obtained, we observe that the response rate to the survey is adequate and in line with our predictions of 20%–25% [27]. The response rate is in line with other oncology surveys in Latin America [14] but lower compared to other regions of the world [24]. Nonetheless, the absolute number of responses compared to the total population of oncologists in the country was very high. We attempted to follow some of the recommendations included in previous studies to increase the response rate, such as monetary incentives and a survey design that was easy to access and quick to fill out. However, other more impactful measures, such as follow-up phone calls, could not be implemented due to privacy concerns, and this impacted the final response rate [22]. Interestingly, physicians in cities with higher volume of patients and specialised centres answered in greater proportion than more distant cities.

With regard to the type of practice, we observed that about 75% of all surveyed professionals work in teams of more than three people, which shows a tendency towards multidisciplinary and/or teamwork [33]. A very interesting fact is that about half (48.5%) of the surveyed professionals work in both the public and private sectors, and 15.7% answered that there are differences in test implementation depending on the setting in which they work. The specific reasons for these differences were not directly evaluated in the survey; nonetheless, based on the open comments received after the survey and the knowledge of the organisational functioning of oncological institutions in Argentina, we hypothesise that this disparity reflects differences in administrative processes, logistical coordination, availability of pathological samples and human resources between public and private institutions [13, 23, 31, 32]. In particular, public institutions may rely more on individual physician initiatives than on standardised institutional circuits.

Furthermore, and going into BRAF testing in particular, we were able to observe that the professionals surveyed are clear about the usefulness of the BRAF test and most of them take it as part of their practice and for making therapeutic decisions, a fact that is not minor considering the advances in new therapies and their benefits [18]. Most physicians use tumour tissue to perform the BRAF test in CRC, although around on fifth of the sample reported using both blood and tumour tissue. In this regard, liquid biopsy from blood samples (as opposed to the traditional solid tissue biopsy) is a useful tool for early diagnosis, screening, treatment monitoring and prognosis prediction of CRC [38]. However, its use in Argentina is still limited by important aspects such as the appropriate indications for its use, limitations of the technique (particularly its sensitivity), reporting of variants, interpretation of results, cost-benefit ratio and coverage in health plans [2]. With regard to melanoma, the use of liquid biopsies is still in the research stage, showing particular promise in continuous monitoring of treatment response and disease relapse [35].

In the case of melanoma, the timing of BRAF testing is crucial, as its results directly influence treatment selection. While 66% of oncologists request the test at the time of the initial histological diagnosis, 40% do so at stage 2C or higher, aligning with current recommendations. On the other hand, the 26% who request it from the outset for any stage may be delaying the decision on the most appropriate treatment. However, this does not necessarily mean that oncologists in these cases do not initiate the corresponding treatment while awaiting the results to adjust their therapeutic approach. Among oncologists working independently, there is a lower tendency to request testing at stage 2C or higher, opting more frequently for other alternatives. This difference could be attributed to reduced interaction and discussion of clinical cases compared to multidisciplinary teams, where the exchange of ideas and continuous updates are encouraged. This, in turn, fosters greater confidence in requesting more complex tests. In the case of BRAF testing in CRC, the two most commonly used options align with expectations, as they do not alter the initial therapeutic approach. However, 22% of surveyed oncologists prefer to request the BRAF test at the time of histological diagnosis, suggesting that they use it not only as a diagnostic tool but also as a prognostic indicator of tumour aggressiveness. This approach allows for better long-term treatment planning.

Regarding the delay in obtaining test results, it is greater the further away from the capital of the country. This may correspond to multiple factors, which should be evaluated in future studies to overcome these difficulties and achieve equity of access throughout the country. Our findings support the need for a national biomarker testing program in Argentina in particular and Latin America in general [7, 29], following the example of similar successful programs in other countries [10–12]. This program should be oriented towards standardising molecular testing requests, improving administrative workflows and reducing geographic inequities in access to precision oncology. Furthermore, it could include the development of regional referral centres in large urban conglomerates (such as Córdoba, Rosario and Mendoza) to decentralise testing logistics and improve turnaround times, especially for patients located far from Buenos Aires.

On the other hand, the survey also revealed that, while the vast majority of oncologists (92%) work in collaboration with other professionals, a significant proportion (75%) devote time to administrative tasks related to test requests, such as completing forms and following up on results. One of the key findings of the survey is that workload overload is a significant issue for oncologists. Many of them see an average of 20 patients per day, work across multiple healthcare centres and additionally take on administrative duties, such as managing the BRAF test. This situation makes it challenging to proactively track test results, which can lead to delays in diagnosis and, consequently, postpone the initiation of timely treatments. In some cases, this overload even affects test selection, which may vary depending on the patient's care setting. From experience in clinical practice, delays in obtaining results can lead, in some cases, to the initiation of standard treatments (such as cytotoxic chemotherapy) before the complete molecular profile is available, with eventual subsequent adjustment to targeted therapies when results are available. Whereas our study was not designed to directly assess whether delays in obtaining BRAF test results actually modified treatment decisions or clinical outcomes, it has been previously shown that long turnaround times could delay access to targeted therapies in patients with advanced disease [3, 25], which merits future prospective evaluations.

Conclusion

We completed the development and implementation of a comprehensive survey to evaluate current clinical practices in the diagnosis and treatment of patients with BRAF-mutated melanoma and BRAF-mutated CRC. BRAF testing is considered useful for the diagnosis and treatment of melanoma and CRC. The survey results highlight the need to optimise available resources to ensure quality care.

Acknowledgments

We thank Dr. Marta Bader and Dr. Aldo Riso, who assisted us during the pilot phase of the survey.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflicts of interest.

Funding

This work was supported by a Pfizer Global Medical Grant (Grant No. 72134623).

Patient consent for publication

Not applicable.

Ethical approval

As this is a survey of professional practice and no confidential patient data was collected, ethical approval was not required from the local ethics committee.

Availability of data and materials

Data and materials are available upon request to the corresponding author.

Author contributions

Conceived and designed the analysis: Moglia B, Vilchez V, Biurrun Manresa J.

Collected the data: Gorbik Fornerón S.

Contributed data or analysis tools: Gorbik Fornerón S, Biurrun Manresa J.

Performed the analysis: Gorbik Fornerón S, Biurrun Manresa J.

Wrote the paper: Moglia B, Vilchez V, Gorbik Fornerón S, Biurrun Manresa J.

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