Burden of Unresectable/Metastatic Melanoma (u-mMel) and Advanced/Metastatic Colorectal Cancer (mCRC), and its associated *BRAF* mutations in Four Latin American (LA) Countries: A Targeted Literature Review of Epidemiological and Economic Evidence

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KEY HIGHLIGHTS

- There is a significant gap in the existing literature to understand the true nature of the clinical and economic burden of u-mMel and mCRC and its associated *BRAF* mutations in the countries under scope. In addition, the national cancer registries and local databases offered no details on *BRAF* mutations and none of the countries had publicly available databases with information on melanoma.
- CRC is among the 3 most common cancers in AR, CR, nonetheless no *BRAF* mutation status was identified. *BRAF* V600E mutation was present in 32% of melanoma cases in AR. A single LA study from Venezuela reported the prevalence of *BRAF* mutations in melanoma (50% of patients had presence of a *BRAF* mutation).
- There is a great opportunity to raise awareness on the clinical and economic burden of both diseases in the region to promote disease prioritization and the generation of local evidence. To close these gaps and ensure equitable access to precision medicine and *BRAF* testing , future research in the region should focus on characterizing the epidemiology of mCRC and m-uMel (including *BRAF*) with special focus on the economic and humanistic impact of these disease subpopulations.

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INTRODUCTION

- In **Latin America and the Caribbean (LAC),** cancer is the leading cause of morbidity and mortality (annually approximately 1.5m new cases and 700,000 deaths); this burden is expected to increase up to 67% by 2040 (2.4m new cases annually).[1-3]

The population of Latin America (LA), as well as governments and healthcare systems are facing significant challenge from the burden originated from CRC and Melanoma.[4]

Colorectal cancer (CRC) is the 5th most common cancer in LA (>130,000 new cases/year and >69,000 deaths/year)[4] where approximately 20-50% of patients progress to mCRC.[5]

Although CRC is among the most expensive cancers (i.e., direct costs and mainly from inpatient care), indirect costs derived from productivity loss are high. [6]

Advanced melanoma, is one of the most aggressive and deadliest cancers worldwide (in LAC >18,000 new cases/year and >5000 deaths/year).[4,7] u-mMel is associated with a short life expectancy and poor prognosis.[7-9]

Melanoma is also one of the costliest cancers to treat,[10] and affects a high proportion of young individuals (comparted to other cancers, it has one of the highest indirect costs from premature death).[11]

- The ***MAPK**** **cascade** plays a crucial role in tumor cell proliferation, tumor progression and survival.[12,13] *BRAF* is an oncogene that encodes for a serine/threonine-protein kinase involved in the *MAPK* pathway.[14] *BRAF* mutation can lead to a constitutive activation of this pathway promoting cancer growth,[13] *BRAF* mutations are commonly seen in melanomas and CRC (50% of malignant melanoma 10% of CRC).[4,15]
- Molecular advances in u-mMel and mCRC characterization have shown that patients with *BRAF* mutations are indicators for poor prognosis (survival)[13,16,18,19] poor response to standard chemotherapy (e.g., V600E-positive mCRC),[16] and in increased risk of metastasis and reoccurrence (i.e., in mCRC).[17] Nonetheless, the presence of this biomarker also creates the opportunity of improved survival and response rates thanks to combination of targeted therapies (e.g., *BRAF* + MEK inhibitors in u-mMel and BRA inhibitor + anti-EGFR in mCRC).[4,20]

V600E is the most common mutation in mCRC (95% of *BRAF* mutations) and occurs between 8-12% of patients.[15,16]

V600E (predominantly) and V600K are the two most common *BRAF* mutations in u-mMel.[21,22]

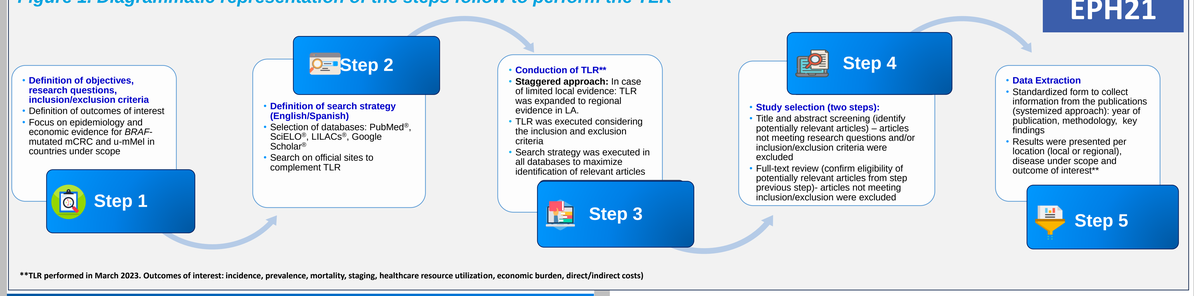
- LAC has a great opportunity to enhance molecular testing and access to new therapies to maximize and improve the treatment and outcome of *BRAF*-mutated mCRC and u-mMel.[4] To do this, it is important to gain more insight into the economic and epidemiological impact of both disease subgroups in the region to inform the relevant stakeholders and decision makers about their significance.

***MAPK= mitogen-activated protein kinase; EFGR: anti-epidermal growth factor receptor**

Objectives

- Assess the epidemiological and economic burden of u-mMel and mCRC in adult patients with *BRAF* mutated (+) in Argentina (AR), Costa Rica (CR), Panama (PA), and Dominican Republic (DR).

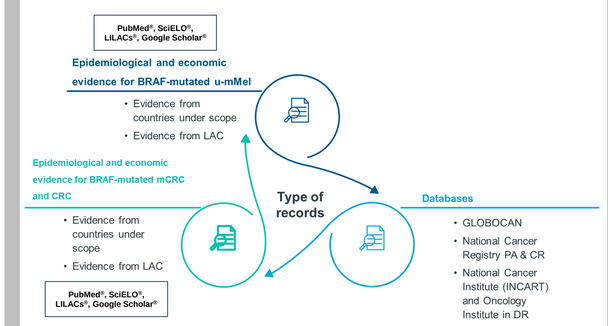
Figure 1. Diagrammatic representation of the steps follow to perform the TLR



Methods

- **Figure 1.** presents a diagrammatic representation of the methodology used to perform the **targeted literature review (TLR)**, while **Figure 2.** provides a closer look into the types of records/ sources that were explored of each of the diseases of interest.
- An epidemiological and an economic **TLR was conducted for each condition of interest**.
- Selection of databases including **PubMed®, LILACS®, SciELO®, and Google Scholar®** (literature published in English or Spanish).
- A **staggered methodology was followed (i.e., expanding the search to LA studies in case no local information was found and considering data from CRC or Mel not describing mutation status or staging).** Epidemiological and economic TLRs included narrative studies, literature reviews, and observational studies from **2004-2023**. The search was expanded to include LA studies due to lack of local publications on *BRAF*-mutated mCRC and u-mMel in the countries under scope (CR, DR, PA and AR).
- Review of official sites, including GLOBOCAN[23] and National Cancer Registries /Institutes[24-27] for the countries under scope was performed to complement the information obtained from published articles obtained through the TLR (see more details on **Figure 1 and Figure 2.**

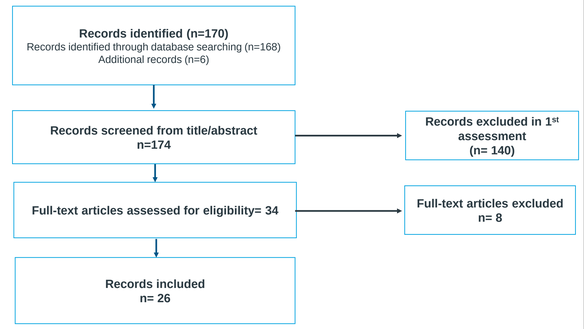
Figure 2. Types of records/sources explored for the TLR



Results

- **Figure 3.** provides an overview of the TLR flowchart and results.
- From 2004 to 2023 there was an **absence of economic evidence for u-Mel and mCRC (with or without *BRAF* mutations)** in the countries within scope and LA.
- Based on available evidence in the countries of interest, AR had the highest incidence rate of melanoma (annual incidence of 3.1/100,000-males and 2.8/100,000-females), followed by CR (2.5-100,000-males and 2.2/100,000-females).[28]
- CRC is among the 3rd/4th most common cancers in AR, CR, DR and PA (2020).[23] AR's age-standardized incidence rate (25.1/100,000) is higher than CR's, LA's, PA's, and DR's (17.2, 16.6, 13.9, and 12.9/100,000, respectively).[23,29]

Figure 3. Flowchart of the TLR and results



- All countries except for AR have CRC reports.[24-27] None of the countries have available databases with information on melanoma.[24-27]
- Although no specific information was found on *BRAF*-mutated u-mMel or mCRC in the 4 countries, the TLR was able to identity some studies in LA which provided some insights on both disease subpopulations in the region.
- A regional study on melanoma provided evidence on the association between of mutations of the *BRAF* gene and presence of metastases.[30] Meanwhile, a single LA study from Venezuela provided evidence about the prevalence of *BRAF* mutations, reporting that up to 50% of the Venezuelan patients with melanoma had presence of a *BRAF* mutation.[31] Additionally, a Colombian study found that 61% of patients with lentiginous melanoma had *BRAF* mutations.[32]
- A review article found that *BRAF* V600E mutation was present in 32% of melanoma cases in AR (in contrast with 30.1% in Mexico and 39% in Brazil).[33]

Discussion

- There is a significant evidence gap on the epidemiological and economic burden of u-mMel and mCRC and its associated BRAF mutations in the four countries and LA, ultimately hindering the development of local public health strategies/policies. In addition, there was an absence of *BRAF*-mutation status in the available databases or national cancer registries in the 4 countries. This scarcity of local data on *BRAF* mutations was also been raised as one of the perceived barriers for optimal care on BRAF-mutated melanoma/CRC by a group of experts in LA. [4]
- LA region could be facing under-reported epidemiological indexes for CRC and Melanoma. Future research efforts should focus on estimating the cost of illness and burden of disease both to raise awareness and address these evidence gaps to promote equitable access to precision medicine and to incorporate economic burden implications in the decision-making and disease prioritization process.

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