

**Disparity in public funding of systemic therapy for metastatic renal cell carcinoma within Canada**Emily Jackson<sup>1</sup>, Sebastien J. Hotte<sup>2</sup><sup>1</sup>BC Cancer Vancouver Centre, University of British Columbia, Vancouver, BC, Canada; <sup>2</sup>Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada

**Cite as:** Jackson E, Hotte SJ. Disparity in public funding of systemic therapy for metastatic renal cell Carcinoma within Canada. *Can Urol Assoc J* 2022 June 9; Epub ahead of print.  
<http://dx.doi.org/10.5489/cuaj.7846>

Published online June 9, 2022

**Corresponding author:** Dr. Emily Jackson, BC Cancer Vancouver Centre, University of British Columbia, Vancouver, BC, Canada; [emily.jackson@bccancer.bc.ca](mailto:emily.jackson@bccancer.bc.ca)

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**Abstract**

**Introduction:** There have been significant advances in systemic therapies for metastatic renal cell carcinoma (mRCC). There are currently 11 drugs approved by Health Canada: sunitinib, sorafenib, pazopanib, axitinib, everolimus, temsirolimus, nivolumab, ipilimumab, cabozantinib, lenvatinib, and pembrolizumab. These novel medications have dramatically altered the prognosis and patient experience. Despite proven benefits and recommendations for funding of most of these drugs, public access has been uneven across Canadian provinces.

**Methods:** We describe the provincial differences and timelines in public funding for approved systemic therapies for mRCC in Canada. Drug funding data was collected from the pan-Canadian Oncology Drug Review (pCODR) database and provincial drug formularies. Missing information was obtained from provincial cancer center pharmacists or drug formulary managers. We compared these dates to data available through regulatory bodies in the U.S., Europe, and Australia.

**Results:** There have been significant differences in the dates of approval for public funding among the provinces, with lags spanning between 17 and 57

**Key Messages**

- The landscape of treatment for advanced and mRCC has changed dramatically; fortunately, therapeutic options are plentiful and survival has improved.
- Once an oncology drug is approved by Health Canada, it undergoes a rigorous review by the pan-Canadian Oncology Drug Review program, which issues a recommendation to all provinces (except Quebec) regarding reimbursement. Ultimately, the final decision is left to the individual provinces to determine funding and implementation.
- Careful review of clinical and pharmacological evidence at all levels of government is intended to keep Canadians safe by providing objective evaluation and maximizing use of limited resources. This can also lead to significant delays in drug access.
- Certain provinces trended towards granting earlier public funding for mRCC drugs, while others more typically experienced delays in reimbursement and implementation. This leads to an uneven patient experience across Canada.
- The cost of oncology drugs is mounting, and tensions between providing novel beneficial drugs and balancing provincial budgets will continue to grow.

months. Funding approval was typically earlier in western provinces and those with denser populations, and most delayed in smaller, eastern provinces. Approval timelines in Canada were similar to those in the U.S., Europe, and Australia.

**Conclusions:** Most drugs approved for use in mRCC are publicly funded for specific patient populations across Canada. However, we illustrate considerable disparities in public funding implementation across the Canadian provinces. These funding lags may create inequities and differences in the patient experience across the Canadian healthcare system.

## Introduction

Metastatic renal cell carcinoma (mRCC) is incurable and accounts for approximately 1950 deaths in Canada per year.<sup>1-2</sup> Prior to 2006, interferon-alpha was the only approved systemic therapy for patients with mRCC in Canada. Since then, there have been massive advances in systemic therapies for mRCC, and this has dramatically changed both the patient experience and the prognosis for individuals living with mRCC.

Modern management of mRCC is complex and evolving at a rapid pace. There are currently 11 drugs approved by Health Canada for treatment of mRCC which fall into three broad categories: vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) such as sunitinib, sorafenib, pazopanib, axitinib, cabozantinib (which is a dual VEGFR and AXL inhibitor), and lenvatinib; mammalian target of rapamycin (mTOR) inhibitors such as temsirolimus and everolimus; and immunotherapy such as nivolumab, ipilimumab and pembrolizumab. All have been demonstrated to improve outcomes in patients living with mRCC, and their toxicity profiles and tolerability are favourable compared to historical treatment with interferon therapy.

These newer agents are costly, and provincial funding decisions and implementation timelines have been uneven. Following approval by Health Canada, these medications undergo analysis by the Canadian Agency for Drugs and Technologies in Health (CADTH) pan-Canadian oncology drug review (pCODR). pCODR is an evidence-based review program that objectively reviews the clinical evidence, economic impact, and patient-important aspects of cancer drugs that have been approved by Health Canada.<sup>3</sup> Following this thorough assessment, pCODR makes funding recommendations to the provinces (with the exception of Quebec, who does not participate in pCODR). The provincial agencies then must make a final decision regarding drug coverage, taking into consideration CADTH recommendations and other province-specific economic and logistical realities.

In this paper, we describe the highly specific and dynamic landscape of public funding for systemic mRCC therapies across Canada. The ultimate objective is to identify any interprovincial disparities in drug access for mRCC, to explore potential barriers or challenges these disparities may introduce, and to highlight possible inequities in the patient experience across Canada.

## Methods

Information regarding public drug funding and specific patient criteria necessary to access funding was obtained through the provincial oncology drug formularies. This data was cross-

referenced with the pCODR database. Data for Quebec was obtained from its provincial health organization, the Institut national d'excellence en santé et en services sociaux (INESS) where possible. We described the funding policies of each province, and which populations may be left without drug coverage. Data for the Canadian territories was reported when available.

We also compared the temporal differences between date of clinical trial research publication, the date of approval by Health Canada, the date the funding recommendation was issued by pCDOR, and the date of approval for public funding in each province where available. The date of approval by Health Canada was obtained from the Health Canada Notice of Compliance online database. The date of each pCODR report is published online. The dates for funding decisions and implementation for each drug in each province was collected from individual provincial drug formularies. Missing information was corroborated by employees in leadership positions of either a provincial cancer centre pharmacy, or a provincial drug formulary. Finally, we compared these dates to timelines for funding in the US, Australia and Europe.

## Results

Dates of publication from randomized controlled trials (RCT), Health Canada approval, funding recommendations and provincial implementation are detailed in Table 1.<sup>4-27</sup> An overview of the current funding landscape by province is shown in Table 2. Overall, the lag between first and last provincial approvals ranged from 2-57 months (median 20.5 months). More comprehensive information about timelines for each drug is available in Appendix 1.

## Discussion

The landscape of treatment for advanced and metastatic renal cell carcinoma has changed dramatically since sunitinib was first approved by Health Canada in 2006. With now 11 medications approved by Health Canada, therapeutic options are plentiful and survival of Canadians with mRCC has improved.<sup>2</sup> However, public access to these medications has been variable across Canada (Tables 1 and 2), sometimes with lags in funding between provinces stretching multiple years (Figure 1).

Combined, this data shows that there are clearly provinces with more comprehensive and earlier access to drug funding, and conversely those with relatively limited access. In our study, western provinces (particularly BC) and provinces with higher populations (ON, QC) tended to be early funders, while smaller and more eastern provinces (particularly PEI) tended to have significant delays until funding implementation. This trend was similarly documented in a 2018 study by Woon D, *et al.* detailing interprovincial disparities in public funding of drug therapies in metastatic castrate-resistant prostate cancer.<sup>28</sup> This paper demonstrates how restrictive funding criteria differ by province, with greater access trending in western and more populace provinces. Our study approaches this similar theme from a unique perspective, documenting lags in funding implementation through the lens of mRCC.

It is important to note that despite a positive funding decision of a given drug, some patients with mRCC may receive only partial funding if they do not meet the demographic requirements of the provincial publicly funded drug programs. For example, in Ontario patients under 65 often do not have Ontario Drug Benefits (ODB) coverage and must qualify through other social assistance programs such as Trillium, Ontario Works or the Ontario Disability

Support Program for coverage of oral drugs. This can lead to delays in treatment initiation, and sometimes in costly out-of-pocket co-pays from patients.

Disparities in drug access across Canada is well documented.<sup>28-31</sup> This current study uses the mRCC treatment landscape to illustrate these discrepancies, but they are not unique to this disease site. For example a 2007 study by Verma S, *et al.* documented the interprovincial differences in funding and patient-specific criteria for adjuvant aromatase inhibitors (AIs) in breast cancer treatment across Canada.<sup>29</sup> Only Manitoba and Quebec had open unrestricted access to funded AIs at that time, with restricted or limited use in all other provinces. A recent 2022 narrative review gives a detailed high-level overview of the current status of disparate drug funding in Canada, similarly identifying relatively poorer access to oral cancer medications in the Atlantic provinces and in Ontario.<sup>31</sup>

Delays in funding and inequitable access to medications across Canada, even if only temporary, is an unfortunate reality that brings stress and uncertainty into the lives of many Canadians living with cancer. We argue that this likely has a significant impact on the patient experience, and may lead to disparities in quality of life or patient outcomes. Gotfrit J *et al.* recently published a thought provoking analysis demonstrating substantial potential life-years lost in Canada as a result of lengthy delays between proof of efficacy and public availability of 21 cancer medications used to treat lung, breast and colorectal cancer.<sup>32</sup> Another recent study evaluating the impact of delays in Canada's regulatory and reimbursement reviews of medications for lung cancer revealed a significant decrease in person-years of life, quality-adjusted life-years and productivity losses.<sup>33</sup> How the inequities identified in the present study affect regional differences in survival with mRCC is beyond the scope of this paper but does raise an important question for future studies.

New agents for treatment of mRCC are expensive, potentially influencing funding decisions and delays. For example based on the list price quoted in the pCODR reviews, a 28-day course of pembrolizumab plus axitinib costs \$17,172, and nivolumab plus ipilimumab costs \$16,302. The mounting costs of cancer care is not unique to mRCC, and will continue to stress provincial health care budgets for the foreseeable future.

The FDA tends to be the first major jurisdiction to approve new therapies for mRCC. Health Canada generally follows with a similar approval within less than one year (mean 6 months, range from 3-9 months for drugs discussed herein). EMA and TGA approval dates tend to be relatively similar to Health Canada. There is a trend for slightly earlier approval by EMA and later approval by TGA relative to Health Canada. It is important to note that approval by FDA leads to automatic and immediate funding through Medicaid and private insurers nationally. Whereas after Health Canada approval there are multiple added layers of assessment and decision making which must occur prior to a positive funding decision in the Canadian context.

This study has several key limitations. The accuracy of quoted funding decisions and dates is more limited for some provinces (particularly Quebec and the Territories) as not all data was published for these regions or represented in pCODR data. We have attempted to reduce these uncertainties by cross-referencing accessible information to data published by Kidney Cancer Canada, pCODR provincial funding summaries, and contacting drug formulary managers when possible. Furthermore, this paper is a descriptive analysis of funding discrepancies, and we hypothesize that this negatively impacts the patient experience. What remains unknown is if

these interprovincial differences actually translate into significantly different patient quality of life. Impacts on survival are outside the scope of this study.

### **Conclusions**

Most drugs approved for use in mRCC are publicly funded for specific patient populations across Canada. However, we illustrate how the drug analysis and approval process can be lengthy and lead to considerable disparities in public funding implementation across the Canadian provinces. Owing to these therapies, patients with mRCC are living longer. But the cost of publicly providing these drugs is high, and tensions between providing novel beneficial drugs and balancing the provincial budgets will likely continue to grow.

Ultimately, funding lags create inequities across the Canadian health care system which impacts patient experience, and may lead to disparities in quality of life.

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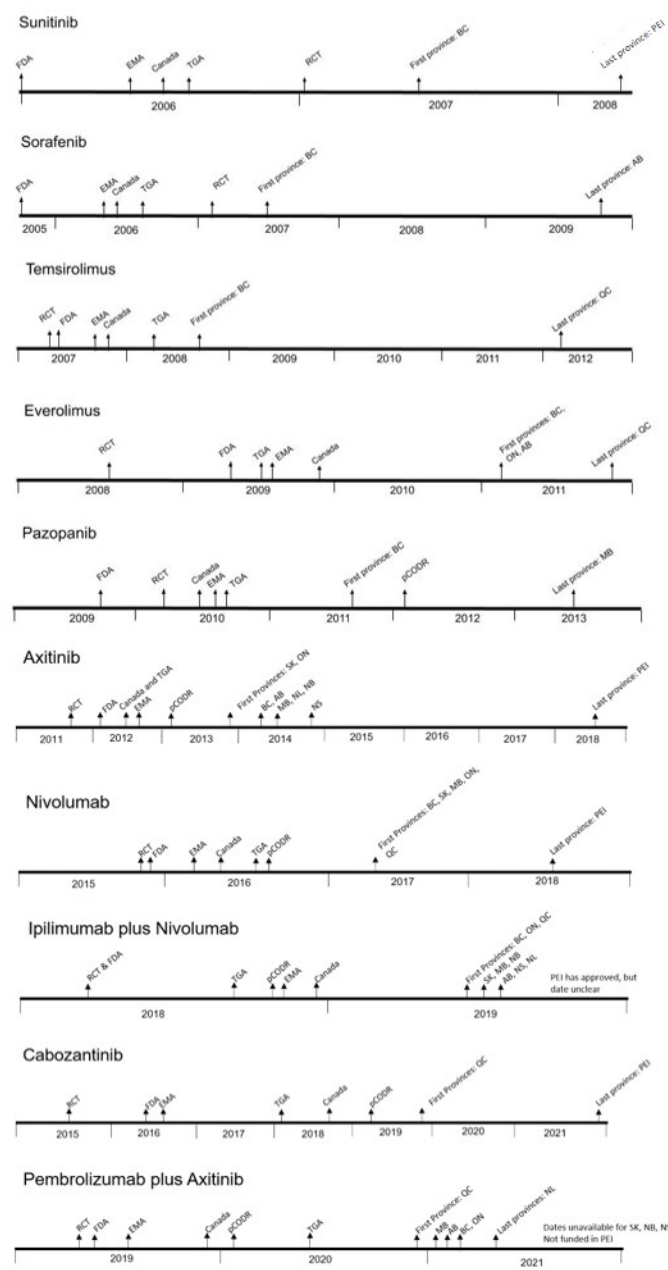
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## Figures and Tables

**Figure 1.** Timeline of drug evaluation and funding decisions for Health Canada-approved medications for metastatic renal cell carcinoma in Canada. Details the time of phase 3 trial publication (denoted RCT); approved by regulatory bodies FDA in the U.S., EMA in Europe, TGA in Australia, and Health Canada. Plus the temporal differences between first and last provinces to announce funding.



**Table 1. Summary of provincial drug funding timelines by province in Canada**

Drug	Key RCT data	Health Canada Approval	International Approval	CADTH Report	Provincial Funding Implementation	Funding lag (first to last province)	Notes
Sunitinib	Jan 2007: improved quality of life (QOL), response rate, and progression free survival (PFS) with sunitinib over interferon-alpha. <sup>4</sup>	Aug 2006: based on earlier phase data, after prior cytokine therapy or likely cytokine intolerant. May 2008: first-line use.	Jan 2006: FDA Jul 2006: EMA Sep 2006: TGA	Apr 2007: recommended against funding due to cost factors and lack of evidence for the approved population.	Jul 2007: BC Nov 2007: ON Feb 2008: NS, AB Apr 2008: NB, NL Feb 2009: PEI	19 months	Unknown date for SK
Sorafenib	Jan 2007: improved PFS with sorafenib vs. placebo after failing first line systemic therapy. <sup>5</sup>	July 2006: based on earlier data after failing or intolerant of previous systemic therapy	Dec 2005: FDA Jul 2006: EMA Sep 2006: TGA	Feb 2007: recommended against public funding due to a lack of cost effectiveness. <sup>6</sup>	Jul 2007: BC Aug 2007: ON Feb 2008: NB Apr 2008: MB, NL Feb 2009: PEI Oct 2009: AB	27 months	Recent use of sorafenib has decreased given availability of more effective options, and some funding decisions have since been reversed. Sorafenib is currently unfunded in AB, SK, NB, QC and Yukon.
Temsirolimus	May 2007: improved PFS and OS compared to interferon in patients with poorer risk mRCC. <sup>7</sup>	Dec 2007: approved for first-line	May 2007: FDA Nov 2007: EMA Jun 2008: TGA	None available on record	Nov 2008: BC Mar 2010: NL Jun 2010: ON Nov 2010: AB Feb 2012: QC	40 months	Unfunded in PEI. Now rarely prescribed as more effective options available. Unknown date in SK.
Everolimus	Jul 2008: improved PFS with everolimus vs placebo after failing sunitinib or sorafenib. <sup>8</sup>	Dec 2009: second-line	Mar 2009: FDA Jul 2009: TGA Aug 2009: EMA	None available on record	Feb 2011: BC, AB, ON Jun 2011: NL Jul 2011: NB Dec 2011: QC	11 months	Unfunded in PEI. Now less frequently prescribed due to the availability of more effective options
Pazopanib	Feb 2010: improved PFS with pazopanib vs. placebo in both cytokine naive and refractory patients. <sup>9</sup> Aug 2013: PFS with pazopanib was non inferior to sunitinib as first line therapy. <sup>10</sup>	May 2010: after cytokine failure Jul 2013: first-line <sup>11</sup>	Oct 2009: FDA Jun 2010: EMA and TGA	Jan 2012: funding recommended	Sep 2011: BC Oct 2011: QC Feb 2012: NL, AB Mar 2012: SK Jul 2012: NS, NB Nov 2012: ON Jan 2013: PEI Jul 2013: MB	22 months	
Axitinib	Nov 2011: improved PFS with axitinib vs. sorafenib in second-line. <sup>12</sup>	Jul 2012: in second line after prior cytokine or TKI. <sup>13</sup>	Jan 2012: FDA Jul 2012: TGA Sep 2012: EMA	Jan 2013: funding recommended	Dec 2013: ON, SK Mar 2014: BC, AB Apr 2014: NL, MB, NB Oct 2014: NS Aug 2018: PEI	57 months	Quebec date is unclear.
Nivolumab	Nov 2015: superior response rates and OS with nivolumab vs. everolimus in the second or third line setting. <sup>14</sup>	Apr 2016: after prior anti-angiogenic therapy	Nov 2015: FDA Feb 2016: EMA Aug 2017: TGA	Sep 2016: funding recommended	Mar 2017: BC, SK, MB, ON, QC Apr 2017: NS, AB May 2017: NB Aug 2017: NL Aug 2018: PEI	17 months	
Ipilimumab + nivolumab	Apr 2018: improved OS and response rate compared to sunitinib first-line in intermediate or poor risk mRCC. <sup>15</sup>	Dec 2018: first-line in poor/intermediate performance status	Apr 2018: FDA Sep 2018: TGA Nov 2018: EMA	Nov 2018: pre-NOC recommendation for funding	May 2019: BC, ON, QC Jun 2019: SK, NB, MB Jul 2019: AB, NS, NL <sup>16-18</sup>	2+ months	PEI last to fund, but specific date unclear. <sup>19</sup>
Cabozantinib	Jul 2016: improved OS and PFS compared to everolimus in second-line and beyond. <sup>20</sup>	Sep 2018: approved second line		Feb 2019: conditional, if cost-effectiveness improved	Dec 2019: QC Jan 2020: BC Mar 2020: SK Apr 2020: MB, AB May 2020: ON Jun 2020: NS Jul 2020: NB Jan 2021: NL Dec 2021: PEI <sup>21, 22</sup>	24 months	
Lenvatinib+ Everolimus	Nov 2015: improved PFS in second-line after VEGF-targeted therapy. <sup>24</sup>	Sep 2017: second-line	May 2016: FDA Aug 2016: EMA	Jan 2019: recommended against funding.	Unfunded in all provinces		Approved by TGA, but date is unclear.
Pembrolizumab + Axitinib	Mar 2019: improved OS, PFS, response rate in previously untreated patients vs sunitinib. <sup>26</sup>	Dec 2019: first-line	Apr 2019: FDA Jul 2019: EMA Jun 2020: TGA	Jan 2020: conditional recommendation Apr 2020: final recommendation if cost effectiveness improved. <sup>27</sup>	Dec 2020: QC Jan 2021: MB Feb 2021: AB Mar 2021: ON May 2021: NL	6 months	Does not appear to be funded in PEI. Funded in SK, NB and NS but dates unclear.

Table 2. Breakdown of funding for all drugs approved for mRCC across Canada										
	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL
Sunitinib	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sorafenib	✓	✗	✗	✗	✓	✗	✓	✓	✓	✓
Temsirolimus	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓
Everolimus	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓
Pazopanib	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Axitinib	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Nivolumab	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ipilimumab + nivolumab	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cabozantinib	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lenvatinib	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Pembrolizumab + axitinib	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓