The impact of cancer treatment on financial aid in a publically funded system: a retrospective cohort study on the Ontario Trillium Drug Program.

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CONTRIBUTORS STATEMENT

All authors have: 1) contributed significantly to conception and design, or acquisition of data, or analysis and interpretation or data; and 2) drafted the article or revised it critically for important intellectual content; and 3) given final approval of the version to be published; and 4) agreed to act as guarantor of the work.

CONFLICT OF INTEREST

NM is employed by Cancer Care Ontario. CCE is employed by the Canadian Partnership Against Cancer. KKC is a consultant of Cancer Care Ontario. SJS consults with the pharmaceutical industry via The HOPE Research Centre.

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ABSTRACT

BACKGROUND: The aim of this study was to characterize the demographics and investigate the cost of the Trillium Drug Program (TDP) for an oncology patient population.

METHODS: All TDP claims between April 1997 and December 2016 were ascertained from the Ontario Drug Benefit database to assess utilization and cost. Each drug was classified as a cancer treatment drug, cancer suportive therapy drug or non-cancer drug. We also identified a cohort of cancer patients with least one TDP claim, for which we examined demographics and claims-related characteristics.

RESULTS: 50,975,293 TDP claims were made over the study period, totalling $4.8 billion. Although the proportion of cancer claims among all TDP remained constant, the total annual cost of cancer treatment drugs increased nearly 50-fold from 1997 to 2016. Imatinib and lenalidomide together made up nearly half of the cost of all cancer treatment drugs. From TDP claims, we identified a cohort of 49,892 cancer patients, of which 37% enrolled in the TDP prior to their cancer diagnosis. Those who enrolled in TDP before their cancer diagnosis were more likely to be in lower income quintiles and have more chronic conditions. Significant differences were also found in the distribution of cancer diagnoses between these two groups.

INTERPRETATION: Our study characterizes TDP utilization and shows that utilization increased over time and differed across cancer diagnoses and drugs. These results have public health and policy implications as antineoplastic drug costs continue to rise and place burden on patients.

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INTRODUCTION

The Ontario Drug Benefit (ODB) is a Ministry of Health and Long-Term Care program covering approximately 28% of the Ontario population and pays for over 4,400 prescription drug products, typically oral medications, for which patients would normally have to pay for out-of-pocket.[1-3] Drugs administered in hospital, such as IV chemotherapies, are covered by other provincial drug reimbursement programs (such as the New Drug Funding Program) or the hospital's global budget and are therefore out of scope for ODB. All eligible Ontario residents qualify for the ODB upon their 65th birthday under the Seniors program, however those below the age of 65 can apply to the Trillium Drug Program (TDP). TDP funds prescription drugs that are approved and listed on the ODB formulary, which patients would otherwise have to pay out-of-pocket, and patients must spend more than 4% of the net household income on prescription drugs to be eligible.[1, 2]

Since 2004, the cost of cancer drugs has risen at a rate five times greater than the increase in cancer incidence and at a rate far beyond the rate of inflation.[4, 5] The high cost of cancer treatment is associated with considerable distress and worse outcomes, which has led to the concept of 'financial toxicity'.[6] Research has shown that financial toxicity is related to poorer health-related quality of life and decreased improvement in the two years post-cancer diagnosis.[6] In 2011, Canadian households spent an average of nearly $500 on out-of-pocket prescription drugs, which was substantially higher in older adults.[7-9] Furthermore, a 2018 study estimated that 731,000 Canadians had to borrow money to pay for prescriptions in the previous year.[10] There is also evidence that patients may decide against taking their cancer medications or reduce dosages due to high costs, leading to concerns about cost-related prescription non-adherence.[7, 11, 12] Moreover, specialty drugs are becoming increasingly common on the market, with cost per claim that is 25 times greater than traditional drugs and accounting for more than 25% of total drug costs in 2014.[13, 14] Cancer drugs, cholesterol-lowering drugs and immunosuppressant drugs combined accounted for approximately 33% of the overall growth in drug spending in Canada between 2005 and 2010 with trends suggesting that they will continue to drive drug spending in the coming years.[15] With this rise in drug spending driven by specialty drugs (including cancer drugs), the TDP is becoming increasingly important for residents who rely on the publicly funded system for their drug expenditures.

With little information on the health care utilization, demographics and costs of a financial assistance program, such as TDP, the objective of this study is to characterize the demographics and investigate the cancer drug costs among individuals with a cancer diagnosis on the TDP program.

METHODS

Data sources

The ODB database contains information on claims for prescription drugs covered under the ODB program, including those claimed through TDP. This includes: service date, drug information number (DIN) and the total amount paid (by ODB). The Ontario Cancer Registry (OCR) was used to identify

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incident cancer cases in Ontario, Canada, and patient demographics were obtained from the Registered Persons Database (RPDB).

Diagnosis information found in the following administrative databases were used to determine patient comorbidities: Discharge Abstract Database (DAD) contains inpatient hospital discharges, Same Day Surgery dataset (SDS) contains ambulatory surgery, National Ambulatory Care Reporting System (NACRS) for ambulatory care visits and Ontario Health Insurance Plan (OHIP) for physician billing and diagnosis information. Using validated algorithms and the diagnoses found in the aforementioned databases, we identified patients who were prevalent with the following chronic conditions: asthma[16], congestive heart failure[17], hypertension[18], diabetes[19], rheumatoid arthritis[20], and Crohn's and colitis[21]. The Johns Hopkins ACG System Resource Utilization Bands (RUBs) describes predicted resource use: 0 – no utilization or invalid diagnoses, 1 – healthy user, 2 – low user, 3 – moderate user, 4 – high user, 5 – very high user.

All datasets were linked using unique encoded identifiers and analyzed at ICES.

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Analysis

We identified all TDP claims between April 1, 1997 and December 31, 2016. Using the DIN available in this TDP utilization data, we classified each drug claim as a cancer treatment, cancer supportive therapy, or other. Cancer treatment medications were further grouped as: cytotoxic chemotherapy, luteinizing hormone-releasing hormone (LHRH) agonist, aromatase inhibitor, antiandrogen, or a specific antineoplastic treatment drug (ex. tamoxifen, imatinib, capecitabine). Further details on drug classification can be found in eTable 1. Without information on indication, somatostatins, though could be used to treat some malignancies, were categorized as supportive therapy to remain conservative in estimating treatment costs. We examined the year-over-year changes in distribution of the number of TDP drug claims and costs across drug groups. In a sensitivity analysis, costs were inflated using the Consumer Price Index (CPI).[22]

From the TDP utilization, we then identified a retrospective cohort of individuals who were also diagnosed with an index (first) primary cancer between April 1, 1997 and December 31, 2017, using the OCR. The following exclusions were applied: non-Ontario residents, patients diagnosed with cancer prior to age 18 and after age 65 (due to eligibility into the Seniors ODB program), and patients who died prior to cancer diagnosis. We classified each patient as having enrolled in the TDP before or after their index cancer diagnosis based on the timing of their first TDP claim. Demographic variables including age, sex, average neighborhood income quintile, rural residence, and comorbidities were examined at cancer diagnosis. We described patients' baseline demographics and cancer characteristics using descriptive statistics (e.g., mean and standard deviation, median and interquartile range for continuous variables and proportions for categorical variables). Patients with missing or unknown demographic information were reported as such, and values were not imputed. Differences between groups were assessed using χ^2 tests and *t*-tests.

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The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. Statistical analyses were performed using SAS Enterprise Guide version 6.1 (2013, SAS Institute Inc., Cary, NC).

RESULTS

In the 20-year study period, 50,975,293 claims to the TDP were identified, with a total value of $4,448,411,177. Figure 1 illustrates the trend over time for the total number of TDP claims and the average paid per claim from 1997 to 2016. In the first year that TDP data became available (April 1997), there were only 312,276 claims to the TDP, of which, only 0.6% were for cancer treatment drugs. Although the proportion of cancer claims among all TDP remained constant, the total annual cost of cancer treatment drugs increased from $823,900 (4.3% of total TDP cost) in 1997 to $40.1 million (7.9% of total TDP cost) in 2016, a nearly 50-fold increase, and the average amount paid per claim increased from $479 to $2,106 within the same time period. This is largely due to the by the introduction of high-cost biologic drugs in recent years. For more details on year-over-year cancer treatment drug costs can be found in eFigure 1. Adjusting for CPI did not change the cost trend over time (eFigure 2).

In total, there were 216,968 TDP claims for cancer treatment drugs totaling over $250 million CAD. As seen in Figure 2, different treatment drugs dominated total annual TDP costs throughout our study period: interferon and LHRH agonists in the first several years (80% of the annual total), imatinib and temozolomide throughout the 2000s (70% of the annual total) and finally dasatinib and lenalidomide upon their introduction in the last several years (40% of the annual total).

From the TDP utilization data, we retrospectively identified a cohort of 49,892 cancer patients among claimants, of which the majority (63.2%) had their first TDP claim after their cancer diagnosis. Those who had been enrolled in the TDP prior to cancer diagnosis were significantly older (median age 59 vs. 54), male (44.2% vs 40.6%), had lower income (50.4% vs. 43.2% in the two lowest quintiles) and lived in rural residences (18.7% vs. 14.1%). These patients also had significantly higher resource utilization and more chronic conditions at cancer diagnosis (Table 1).

The distribution of cancer diagnoses also varied significantly between the two patient groups. Among those who were enrolled in the TDP before being diagnosed with cancer, 15% were diagnosed with breast cancer and 13% with lung cancer. However, among those who enrolled in the TDP after their cancer diagnosis, a much larger proportion were breast cancer patients (27%) followed by prostate cancer (9%), colorectal cancer (7%), lymphoma (6%) and lung cancer (6%) (Figure 3).

INTERPRETATION

This retrospective cohort study showed that the majority of all TDP claims were for drugs unrelated to cancer treatment or supportive therapy, however, over the past 20 years, the total annual cost of TDP claims increased significantly, far outpacing the increase in the number of claims. The average amount

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paid per claim was highest for cancer treatment drugs. Among cancer treatment drugs, the introduction of immunotherapies has greatly contributed to the rising TDP cost to fund cancer treatment over the observation period. Those who were already enrolled in the TDP prior to their cancer diagnosis had more comorbidities, and the majority of those who enrolled in TDP after, were diagnosed with breast cancer.

Our study found that both the total and average amount paid per claim for cancer treatment drugs had increased significantly compared to non-cancer and supportive drugs. These results are supported by the literature which show an increasing burden of high-cost biologic drugs on the TDP[23] and where the overall economic burden of cancer care in Canada is substantial.[24] In 2016, the global cost of cancer treatment drugs increased by nearly 15% (approximately $90 billion USD) where cancer drugs were found to be one of the fastest growing components in pharmaceutical spending. [15, 25]

The increase in oncology-related costs and number of TDP claims over time can be attributed to the uptake of newer therapies, which are not offset by the use of generic medications as older brands are used more often with increasing number of patients receiving treatment and increasing length of treatment durations.[15, 25, 26] This is further evidenced by our results showing the year-over-year increase in expenditure as closely mirrored by the introduction and approval of new oral treatment drugs, such as imatinib in 2001, dasatinib in 2008 and lenalidomide in 2009, which are some of the highest cost cancer drugs in the market.[27] The availability of generic imatinib in 2013 was reflected in a slight decline in total TDP costs, which was not sustained, as claims for abiraterone, lenalidomide, ruxolitinib and other new drugs increased through to the end of our observation period. Although the vast majority of TDP claims were for non-cancer drugs, the amount paid by TDP for each cancer treatment drug far exceeds those of non-cancer drugs.

Not surprisingly, we found that those who were already enrolled in TDP prior to their cancer diagnosis had more comorbidities at the time of cancer diagnosis, which may make them vulnerable to conditions requiring costly out-of-pocket prescription medication treatment even before their cancer diagnosis. The distribution of cancer diagnoses among patients who had already been enrolled in TDP before their diagnosis, mirrored the distribution of newly diagnosed cancer cases in the province.[28] However, among patients who enrolled in TDP after their cancer diagnosis, some cancer sites were over-represented compared to 2013 Ontario statistics (breast cancer, thyroid cancer, and brain cancer), while others were under-represented (colorectal and lung cancer). While a recent study by de Oliveira et al., showed that many of these cancers did in fact incur the largest financial burden during the first year after cancer diagnosis, (approximately $480 million for colorectal, $450 million for lung, $270 million for breast and $240 for prostate cancers[29]), the drivers of cost varied. Cancers that we found were over-represented in our TDP cohort tended to include treatment protocols that would require patients to pay, out-of-pocket, for oral medications that are costly and/or with long (and sometimes lifetime) treatment windows.

The burden of cancer is increasing as approximately 1 in 2 Canadians are expected to be diagnosed with cancer in their lifetime.[30] As such, the cost of treating cancer is a significant problem, especially within a growing, aging society, where access to increasingly expensive interventions adds to the rising societal

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costs of cancer care.[31, 32] This is akin to financial toxicity, as rising cancer costs can reduce quality of life incurring severe emotional and family distress, reduces patients' access to care and can lead to financial bankruptcy, treatment abandonment, and impede delivery of the highest quality of care.[31-33] Research has shown that even insured cancer patients experienced considerable financial burden and altered their care to reduce out-of-pocket costs, such as taking less than the amount of medication prescribed, partially filling prescriptions, or opting to not fill prescriptions at all, as well as spending less on food, clothing and leisure activities.[34] As the number and availability of oral cancer treatment drugs continues to increase, coupled with patients' preference for oral administration over intravenous drugs, cancer treatment may move away from hospital cancer centres, thereby transferring treatment costs more directly to the patient.[35-37] This can, in turn, exacerbate the issue of financial toxicity for patients in the future as cancer drug prices continue to steadily rise. However, it is our hope that improved access to TDP will positively affect patient outcomes and reduce their burden of financial toxicity.

Our rich comprehensive provincial data allowed us to link population-based samples of cancer patients to health administrative databases and objectively assess their TDP claims and costs associated with these claims, as well as objectively determine their cancer diagnosis and drugs dispensed for each patient. Our study also has some limitations worth noting. For example, the research team was not able to access income at the household level and the corresponding TDP deductible incurred by the household. We also lack information on the indication for drug use, household composition and which individual within the household initiated enrollment in the TDP.

Our results show that cancer treatment drugs are highly costly, however the TDP program, available to all Ontarians regardless of their income, can help benefit those with high financial burden of cancer treatment by significantly offsetting those costs. In fact, research has shown that TDP recipients are increasingly using the program for high cost and biologic drugs.[23] As the projected cost of cancer treatment drugs continue to steadily rise with the introduction of novel therapies at higher costs, the TDP is an available resource and support system to aid in managing these debilitating costs and prevent financial toxicity often experienced from a cancer diagnosis. Budget projections may benefit from the consideration of cancer drug claims to obtain a more wholesome picture of the funding required to sustain this program. Further research is needed to understand the barriers to TDP enrollment and promote greater awareness of the availability of this program to vulnerable populations.

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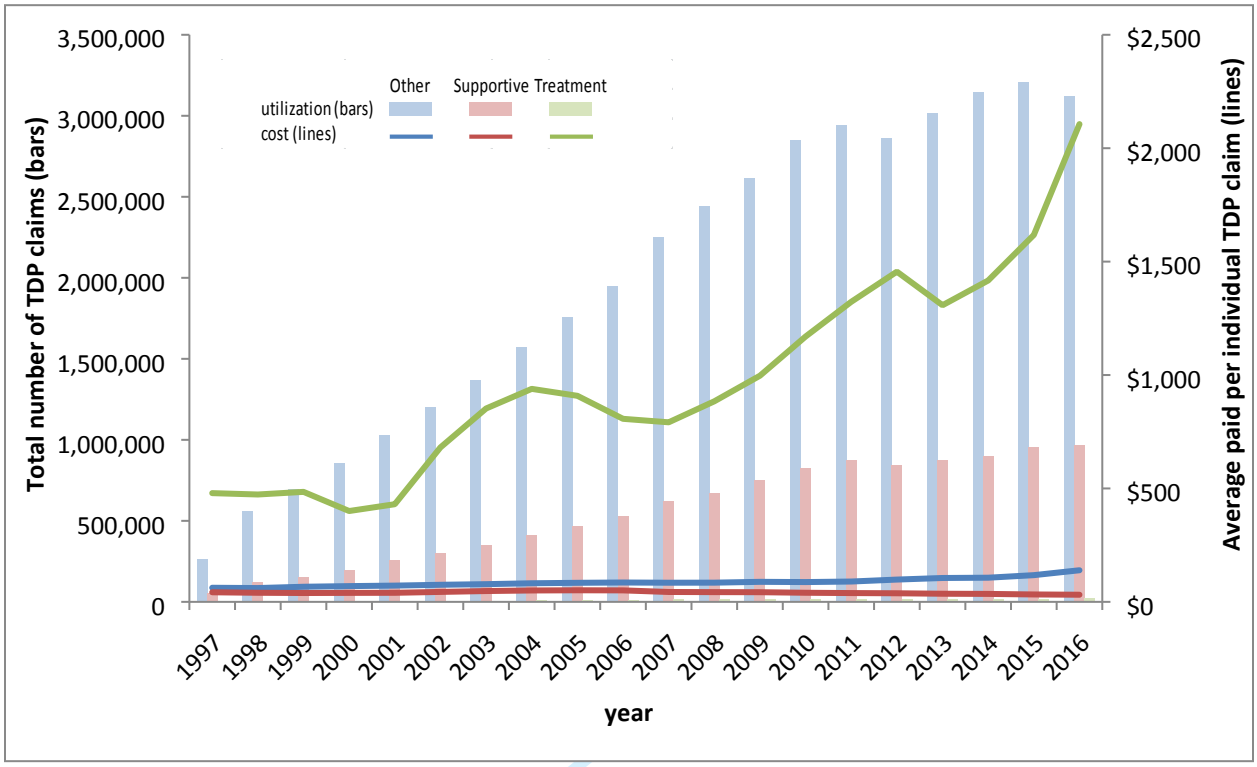
Figure 1: Total number of TDP claims and average paid per claim, by drug group, 1997-2016.



* TDP data available starting April 1997

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Figure 2: Total amount paid for TDP cancer treatment drugs, overall and selected drugs, 1997-2016.

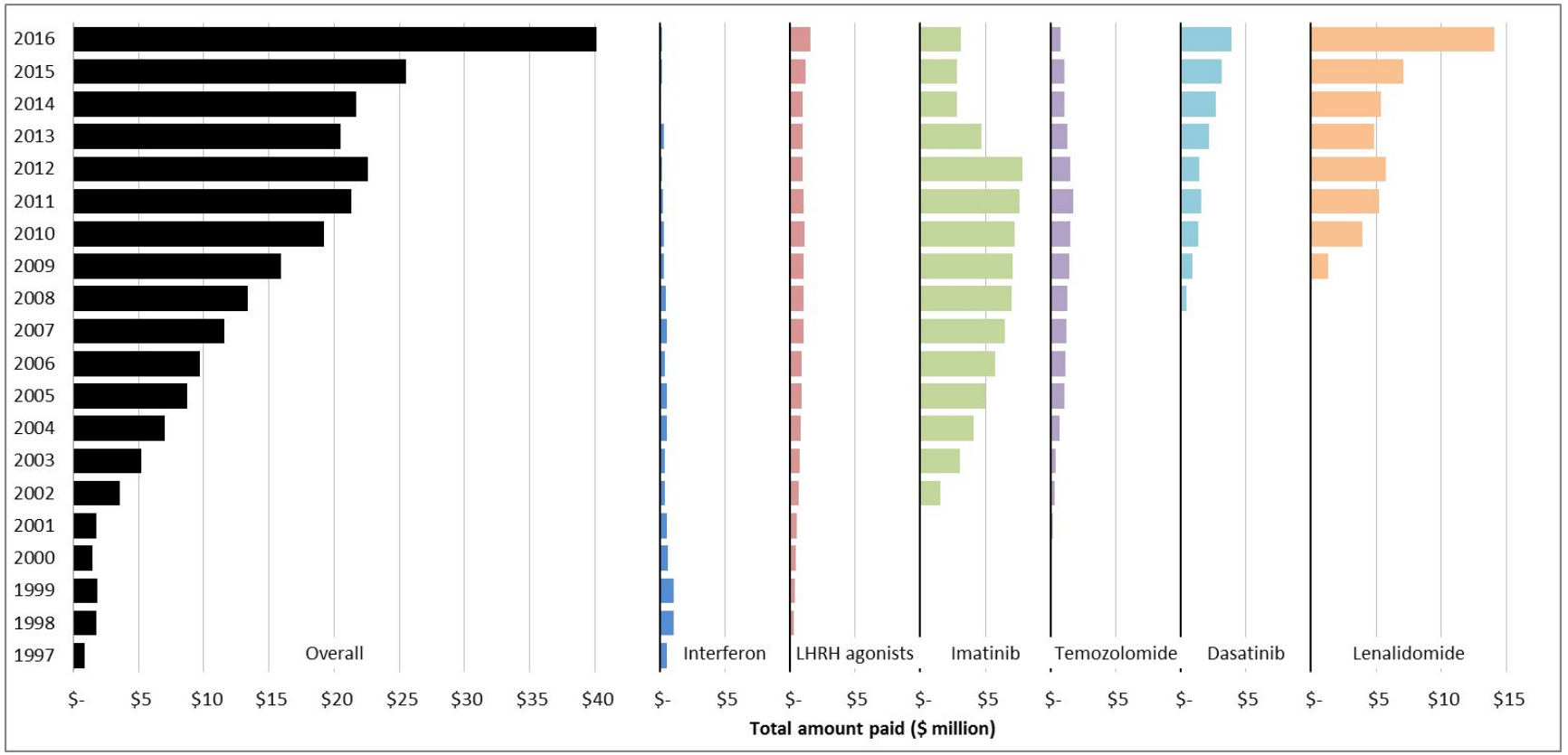

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Table 1. Baseline characteristics of patients who enrolled in the TDP before and after their cancer diagnosis.

	TDP claims began before cancer diagnosis	TDP claims began after cancer diagnosis	Overall	p-value	Standardized difference
	N=18,631	N=31,261	N=49,892		
Age at diagnosis date (years) (Mean ± SD)	56.23 ± 8.14	51.33 ± 9.73	53.16 ± 9.47	<.001	0.55
Age at diagnosis date (years) (Median (IQR))	59 (53-62)	54 (46-59)	56 (49-60)	<.001	0.63
Age group at cancer diagnosis (years), # (%)					
< 25	134 (0.7%)	636 (2.0%)	770 (1.5%)	<.001	0.11
25-44	1,572 (8.4%)	5,858 (18.7%)	7,430 (14.9%)		0.3
45-64	16,925 (90.8%)	24,767 (79.2%)	41,692 (83.6%)		0.33
Sex, # (%)					
Female	10,387 (55.8%)	18,559 (59.4%)	28,946 (58.0%)	<.001	0.07
Male	8,244 (44.2%)	12,702 (40.6%)	20,946 (42.0%)		0.07
Income quintile, # (%)					
1 (lowest)	5,009 (26.9%)	6,713 (21.5%)	11,722 (23.5%)	<.001	0.13
2	4,385 (23.5%)	6,798 (21.7%)	11,183 (22.4%)		0.04
3	3,656 (19.6%)	6,253 (20.0%)	9,909 (19.9%)		0.01
4	3,144 (16.9%)	6,030 (19.3%)	9,174 (18.4%)		0.06
5 (highest)	2,379 (12.8%)	5,381 (17.2%)	7,760 (15.6%)		0.12
Unknown/missing	58 (0.3%)	86 (0.3%)	144 (0.3%)		0.01
Rurality, # (%)					
Urban residence	15,138 (81.3%)	26,853 (85.9%)	41,991 (84.2%)	<.001	0.13
Rural residence	3,490 (18.7%)	4,393 (14.1%)	7,883 (15.8%)		0.13
Unknown/missing	<=5	<=20	<=20		0.02
Chronic conditions, # (%)					
Asthma	3,269 (17.5%)	3,349 (10.7%)	6,618 (13.3%)	<.001	0.2
Congestive heart failure	1,383 (7.4%)	476 (1.5%)	1,859 (3.7%)	<.001	0.29
Chronic obstructive pulmonary disease	4,336 (23.3%)	3,215 (10.3%)	7,551 (15.1%)	<.001	0.35
Hypertension	10,583 (56.8%)	9,925 (31.7%)	20,508 (41.1%)	<.001	0.52
Diabetes	6,356 (34.1%)	4,512 (14.4%)	10,868 (21.8%)	<.001	0.47
Rheumatoid arthritis	641 (3.4%)	397 (1.3%)	1,038 (2.1%)	<.001	0.14
Crohn's and colitis	441 (2.4%)	288 (0.9%)	729 (1.5%)	<.001	0.11

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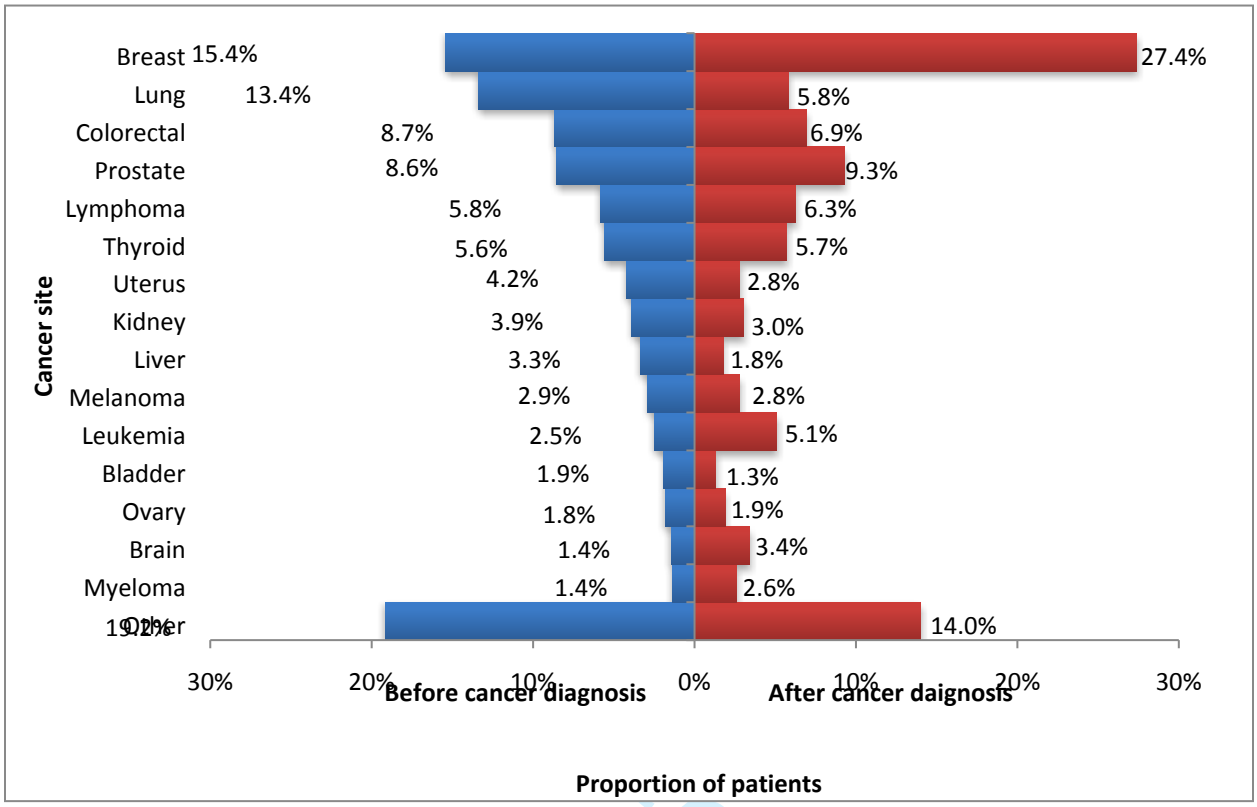
Figure 3: Distribution of cancer site by TDP enrollment timeframe.



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APPENDIX

eTable 1. TDP drugs by drug groups.

Cytotoxic Chemotherapy	LHRH agonist	Aromatase inhibitor	Antiandrogen	Supportive therapy
asparaginase busulfan carmustine chlorambucil cladribine cyclophosphamide cytarabine dacarbazine daunorubicin epirubicin estramustine etoposide fludarabine fluorouracil hydroxyurea irinotecan lomustine mechlorethamine melphalan mercaptopurine methotrexate mitomycin mitotane procarbazine thioguanine thiotepa vinblastine	buserelin goserelin leuprolide triptorelin	aminoglutethimide anastrozole exemestane letrozole	bicalutamide cyproterone flutamide nilutamide	Antidiarrheals Antiemetics Bisphosphonates Corticosteroids Erythropoiesis-stimulating agents (ESA) Granulocyte colony-stimulating factors (GCSF) Iron Laxatives Adjunct paint medications Opiates Somatostatins

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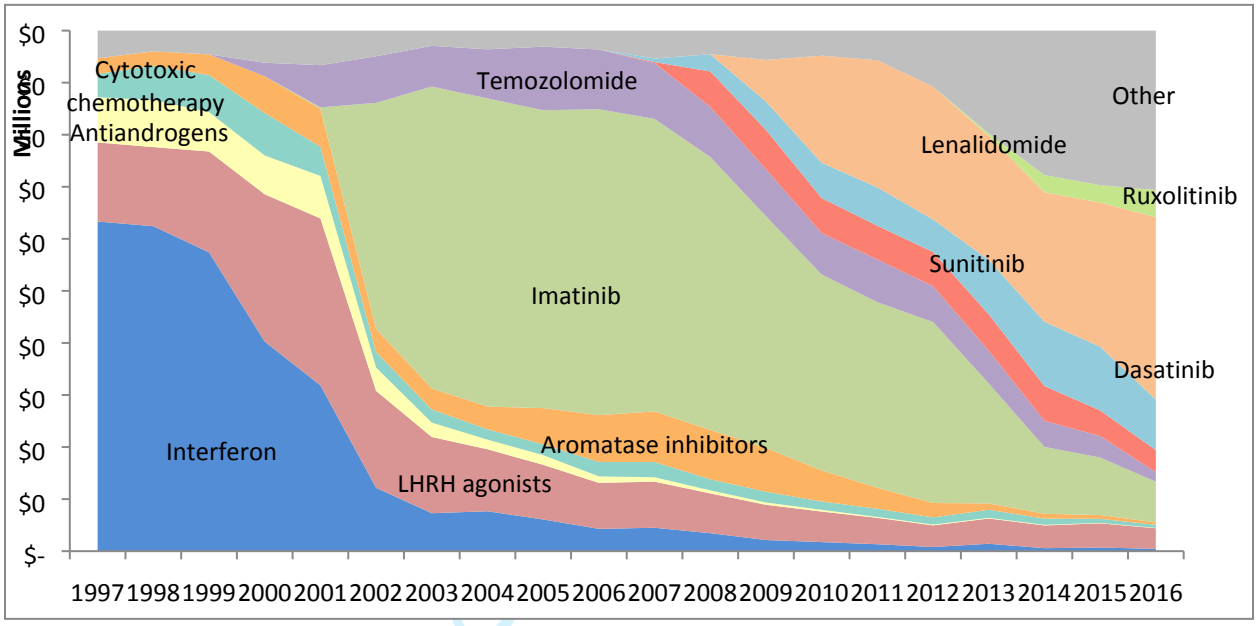
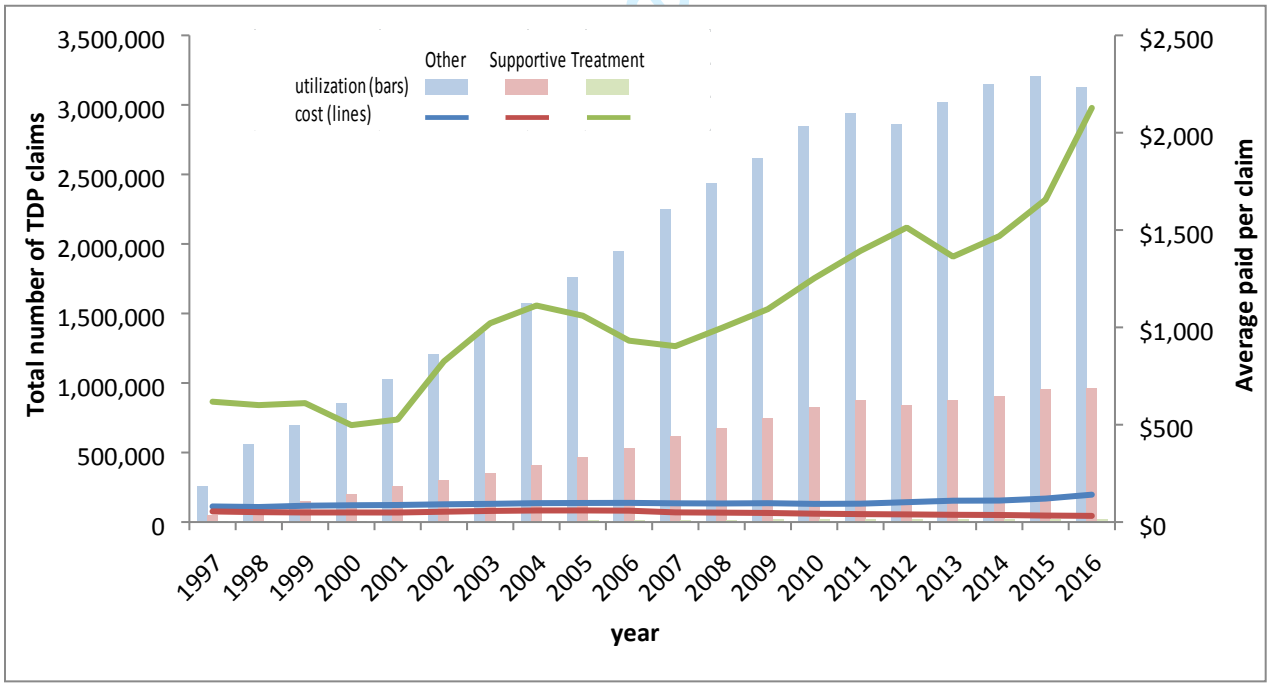
eFigure 1 – Distribution of total cost of select cancer treatment drugs in TDP, 1997-2016



eFigure 2 – Total amount paid for TDP cancer treatment drugs, overall and selected drugs, 1997-2016, adjusted for inflation.



* TDP data available starting April 1997

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Reference List

1. A Guide to Understanding the Trillium Drug Program. Government of Ontario, 2013
2. De-mystifying the Trillium Drug Program (TDP). Green Shield Canada, 2017
3. 2015/16 Report Card for the Ontario Drug Benefit Program. Ontario Ministry of Health and Long-Term Care, 2016
4. Five-Year Action Plan to Address the Financial Hardship of Cancer in Canada: A Call for Action. Canadian Cancer Society, 2011
5. Gordon N, Stemmer SM, Greenberg D, Goldstein DA. Trajectories of Injectable Cancer Drug Costs After Launch in the United States. J Clin Oncol 2018;36(4):319-325.
6. Spencer J, Reeder-Hayes KE, Pinheiro LC, Carey LA, Olshan AF, Wheeler SB. Short and long term impact of financial toxicity on quality of life in the Carolina Breast Cancer study. J Clin Oncol 2017;35(15).
7. Hennessy D, Sanmartin C, Ronksley P et al. Out-of-pocket spending on drugs and pharmaceutical products and cost-related prescription non-adherence among Canadians with chronic disease. Statistics Canada, 2016
8. Survey of household spending (SHS), household spending, Canada, regions and provinces: CANSIM Table 203-0021. Statistics Canada, 2017
9. Survey of household spending (SHS), household spending, by age of reference person: CANSIM Table 203-0026. Statistics Canada, 2017
10. Kolhatkar A, Cheng L, Morgan SG et al. Patterns of borrowing to finance out-of-pocket prescription drug costs in Canada: a descriptive analysis. CMAJ Open 2018;6(4):E544-E550.
11. Law MR, Cheng L, Dhalla IA, Heard D, Morgan SG. The effect of cost on adherence to prescription medications in Canada. CMAJ 2012;184(3):297-302.
12. Doshi JA, Li P, Huo H, Pettit AR, Armstrong KA. Association of Patient Out-of-Pocket Costs With Prescription Abandonment and Delay in Fills of Novel Oral Anticancer Agents. J Clin Oncol 2018;36(5):476-482.
13. Specialty Drugs: Trends, Challenges and Solutions. Sun Life Financial, 2015
14. Prescribed Drug Spending in Canada, 2016. Canadian Institute for Health Information, 2016
15. Drivers of Prescription Drug Spending in Canada. Canadian Institute for Health Information, 2012

Confidential

For Peer Review Only

16. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. Can Respir J 2009;16(6):183-188.

17. Schultz SE, Rothwell DM, Chen Z, Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. Chronic Dis Inj Can 2013;33(3):160-166.

18. Tu K, Campbell NR, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. Open Med 2007;1(1):e18-e26.

19. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. Diabetes Care 2002;25(3):512-516.

20. Widdifield J, Bombardier C, Bernatsky S et al. An administrative data validation study of the accuracy of algorithms for identifying rheumatoid arthritis: the influence of the reference standard on algorithm performance. BMC Musculoskelet Disord 2014;15:216.

21. Benchimol EI, Guttmann A, Mack DR et al. Validation of international algorithms to identify adults with inflammatory bowel disease in health administrative data from Ontario, Canada. J Clin Epidemiol 2014;67(8):887-896.

22. Consumer Price Index, annual average, not seasonally adjusted. Statistics Canada, 2019https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000501).

23. Tadrous M, Greaves S, Martins D, Mamdani MM, Juurlink DN, Gomes T. Catastrophic drug coverage: utilization insights from the Ontario Trillium Drug Program. CMAJ Open 2018;6(1):E132-E138.

24. de OC, Weir S, Rangrej J et al. The economic burden of cancer care in Canada: a population-based cost study. CMAJ Open 2018;6(1):E1-E10.

25. Aitken M. Global Oncology Trends 2017: Advances, complexity and cost. QuntilesIMS Institute, 2017

26. Express Scripts Canada: Drug Trend Report 2016. Express Scripts Canada, 2016

27. Dusetzina SB. Drug Pricing Trends for Orally Administered Anticancer Medications Reimbursed by Commercial Health Plans, 2000-2014. JAMA Oncol 2016;2(7):960-961.

28. Ontario Cancer Statistics 2018 Report. Cancer Care Ontario, 2018

29. de OC, Bremner KE, Pataky R et al. Understanding the costs of cancer care before and after diagnosis for the 21 most common cancers in Ontario: a population-based descriptive study. CMAJ Open 2013;1(1):E1-E8.

30. Nearly 1 in 2 Canadians expected to get cancer: report. http://www cancer ca/en/about-us/for-media/media-releases/national/2017/canadian-cancer-statistics/?region=on,

Confidential

2017http://www.cancer.ca/en/about-us/for-media/media-releases/national/2017/canadian-cancer-statistics/?region=on).

31. Zafar SY, Abernethy AP. Financial toxicity, Part I: a new name for a growing problem. Oncology (Williston Park) 2013;27(2):80-1, 149.

32. Zafar SY, Abernethy AP. Financial toxicity, Part II: how can we help with the burden of treatment-related costs? Oncology (Williston Park) 2013;27(4):253-4, 256.

33. Collins SR, Rasmussen PW, Doty MM, Beutel S. The rise in health care coverage and affordability since health reform took effect: findings from the Commonwealth Fund Biennial Health Insurance Survey, 2014. Issue Brief (Commonw Fund) 2015;2:1-16.

34. Zafar SY, Peppercorn JM, Schrag D et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. Oncologist 2013;18(4):381-390.

35. Aisner J. Overview of the changing paradigm in cancer treatment: oral chemotherapy. Am J Health Syst Pharm 2007;64(9 Suppl 5):S4-S7.

36. Weingart SN, Brown E, Bach PB et al. NCCN Task Force Report: Oral chemotherapy. J Natl Compr Canc Netw 2008;6 Suppl 3:S1-14.

37. Eek D, Krohe M, Mazar I et al. Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: a review of the literature. Patient Prefer Adherence 2016;10:1609-1621.

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