

# The Impact of a Population-Based Screening Program on Income- and Immigration-Related Disparities in Colorectal Cancer Screening

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## Abstract

**Background:** A population-based program promoting the Fecal Occult Blood Test (FOBT) for colorectal cancer screening was introduced in 2008 in Ontario, Canada, where opportunistic screening with colonoscopy had been increasing in frequency. We evaluated the impact of the program on income and immigration-related disparities in screening.

**Methods:** We used linked administrative data to calculate colorectal cancer screening rates for eligible Ontarians in each year between 2001/02 ( $n = 2,852,619$ ) and 2013/14 ( $n = 4,139,304$ ). We quantified disparities using an "inequality ratio" of screening rates in the most disadvantaged group relative to the most advantaged group. We performed segmented logistic regression analyses stratified by screening modality and adjusted for age, sex, rurality, comorbidity, and morbidity.

**Results:** Between 2001/02 and 2013/14, the income and immigration inequality ratios narrowed from 0.74 to 0.80 and 0.55 to 0.69, respectively. Before the screening program, the

income inequality ratio was widening by 1% per year (95% CI 1% to 1%); in the year it was introduced, it narrowed by 4% (95% CI 2% to 7%) and in the years following, it remained stable [0% decrease (95% CI 1% decrease to 0% decrease) per year]. Results were similar for immigration-related disparities. After program introduction, disparities in receiving FOBT were narrowing at a faster rate while disparities in receiving colonoscopy were widening at a slower rate.

**Conclusions:** Introduction of a population-based screening program promoting FOBT for colorectal cancer was associated with only modest improvements in immigration and income-related disparities.

**Impact:** Reducing immigration and income-related disparities should be a focus for future research and policy work. Disparities in Ontario seem to be driven by a higher uptake of colonoscopy among more advantaged groups. *Cancer Epidemiol Biomarkers Prev*; 26(9); 1401–10. ©2017 AACR.

## Introduction

Colorectal cancer is the third most common cancer and fourth leading cause of cancer-related death worldwide (1). Mortality and morbidity can be reduced through regular screening with a Fecal Occult Blood Test (FOBT) every 2 years (2, 3). In some jurisdictions, screening every 10 years via colonoscopy is recommended as an alternative to FOBT (4), but other guidelines recommend against colonoscopy, citing lack of evidence (5).

Screening for colorectal cancer has been recommended for more than a decade, yet disparities in screening persist. Patients living in low-income neighborhoods (6–9), racial and ethnic minority groups (9–11), and foreign-born and immigrant populations (12, 13) are less likely to be screened. These disparities have been persistent over time and have been well-documented in

a number of high-income countries, including those with universal health care (6, 9) as well as in subpopulations with insurance coverage (14). Targeted clinic-based outreach to underscreened populations shows promise (15, 16), but it is still unclear how disparities can be addressed at the larger system level.

International evidence suggests that population-based screening programs can reduce inequities in screening (17). Ontario introduced Canada's first provincial population-based colorectal cancer screening program, Colon Cancer Check, in April 2008. The program primarily promoted FOBT for patients of average risk with a central role for family doctors who were asked to counsel and order tests for patients. Early evidence suggests that Colon Cancer Check increased uptake of FOBT (18), but its impact on screening inequities in Ontario is less clear (13).

We conducted a retrospective analysis to determine the impact of Ontario's population-based screening program for colorectal cancer on disparities related to income and immigration.

## Materials and Methods

### Setting

Ontario is Canada's largest province with a population of approximately 13.8 million in 2015 (19). All permanent residents are fully insured for necessary health care services through the Ontario Health Insurance Plan (OHIP). Physician services and cancer screening investigations are free at the point-of-care with no copayments or deductibles.

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Ontario introduced a province-wide, population-based screening program for colorectal cancer, Colon Cancer Check, in April 2008 (20). The program recommended biennial FOBT for persons aged 50 to 74 who were at average risk of colorectal cancer and colonoscopy for those at higher risk. Initially, the Colon Cancer Check program relied on family physicians to identify eligible patients and recommend the appropriate screening test, or patients to self-identify and visit their family physician to discuss screening. Patients who did not have a family physician could obtain an FOBT screening kit from a local pharmacy or by calling an information line. In the months preceding the program launch, there was a multi-faceted awareness campaign for both family physicians and the public about the screening program. In late 2010, Colon Cancer Check began mailing invitation letters to newly eligible adults turning 50 and recall letters to adults with a previous negative FOBT who were due for repeat testing. Although the program promoted FOBT as the recommended screening test for average risk individuals, opportunistic screening via colonoscopy also occurs and predated introduction of the program.

### Study design and patient population

We conducted a retrospective analysis using linked administrative claims data held at the Institute for Clinical Evaluative Sciences (ICES). For all Ontarians eligible for health care, data is available dating back to 1991 for all publicly funded health services as well as some services outside health. Data are linked at the individual level using unique, encoded identifiers and analyzed at ICES. This study was approved by the Research Ethics Board of Sunnybrook Research Institute in Toronto, Ontario.

We performed a patient-level analysis and included all Ontarians eligible for colorectal cancer screening in any year between 2001/02 and 2013/14. 2001/02 was the first year we had complete data for our study outcomes. Ontarians were eligible for colorectal cancer screening if they were between the ages of 50 and 74 per Ontario's health care registry. They were excluded if they had a history of inflammatory bowel disease, as noted by physician and lab service claims, or known colorectal cancer, as determined by physician service claims and data from the provincial cancer registry.

We determined whether patients eligible for colorectal cancer screening in a given year were up-to-date with screening. Patients were considered up-to-date if they received at least one FOBT in the previous 30 months or colonoscopy in the previous 10 years based on physician and laboratory service claims. We measured FOBT completion but did not assess whether a patient was offered an FOBT kit but chose not to complete it. Our analyses focused on overall screening participation because opportunistic screening with colonoscopy predated introduction of the screening program and FOBT participation alone would underestimate colorectal cancer screening participation. We stratified all of our analyses by type of screening test to understand their contribution to overall screening participation. This approach is consistent with internal evaluations of the screening program by Cancer Care Ontario (21). Flexible sigmoidoscopy is also a recommended screening test for colorectal cancer, however we did not include it in our analysis as examination of OHIP billing data revealed that they occur in less than 0.5% of the screen-eligible population and rates were declining during the study time period from 23,590 in 2001 to 18,497 in 2014.

We constructed an "inequality ratio" to quantify disparities related to income and recent residence, an approach used by

others studying inequities (22). The inequality ratio is calculated by dividing the percentage of individuals up-to-date with screening in the most disadvantaged group by the percentage up-to-date in the most advantaged group. A ratio of 1 denotes perfect equality, a ratio above 1 means the most disadvantaged group is more likely to receive the test, and a ratio below 1 means they are less likely to receive the test.

We calculated the income inequality ratio by dividing the percentage up-to-date in the lowest neighborhood income quintile by those up-to-date in the highest neighborhood income quintile. We linked patient residential postal code, obtained from the health care registry, with 2006 census data to determine neighborhood income quintile for the dissemination area, the smallest census area that contained socioeconomic data. We calculated the immigration inequality ratio by dividing the percentage up-to-date among recent residents (those who registered with the provincial health plan within the last 10 years) by those up-to-date among long-term residents (those who registered with the provincial health plan more than 10 years ago). Recent registration has been shown previously to be a good proxy for recent immigration in Ontario (23).

### Other data sources

Age and sex were determined from the health care registry. We used the Rurality Index of Ontario (RIO) to categorize patients as living in major urban areas (RIO score, 0–9), smaller cities (RIO score, 10–39), or rural areas (RIO score, 40+; ref. 24). We measured comorbidity using Adjusted Diagnosis Groups (ADG) derived from the Johns Hopkins Adjusted Clinical Group (ACG) Case-Mix System (25). The ACG system is a disease-based risk adjustment system and is based on the observation that patients with certain groups of conditions have similar health care use. The system uses ICD-9 and ICD-10 codes to assign Individuals to one of 32 diagnostic clusters (ADGs) based on five clinical dimensions: duration of the condition, severity of the condition, diagnostic certainty, etiology of the condition, and specialty care involvement. ADGs provided us with a measure of comorbidity and were also used to assign patients to a Resource Utilization Band based on similar expected health care use (1 = low, 5 = high), a measure of morbidity. We used validated algorithms based on physician billings and/or hospital records to assess whether patients had diabetes (26), hypertension (27), congestive heart failure (28), an acute myocardial infarction (29), asthma (30), chronic obstructive pulmonary disease (31), or mental illness (32). We measured the number of primary care visits using physician billings. We determined whether a patient was attached to a primary care physician based on whether he or she was either formally enrolled to a primary care physician or made any primary care visit in the preceding two years.

### Analysis

For each year of the study period, we determined which patients were screen-eligible, their characteristics, and whether they were up-to-date for screening (based on whether they had received FOBT or colonoscopy in the specified time frame). We used descriptive statistics to examine the characteristics of individuals eligible for and up-to-date for colorectal cancer screening at the start and end of the study time period. For 2013/14, we determined the crude percentage of patients up-to-date with screening stratified by patient sex, neighborhood income quintile, and immigration. We then constructed a logistic regression model to

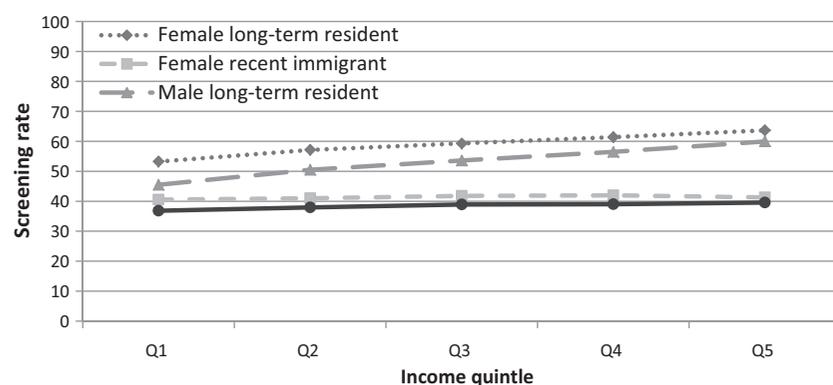
**Table 1.** Characteristics of Ontarians receiving colorectal cancer screening by modality, 2001/2002 and 2013/14

	2001/2002			2013/2014				
	Number eligible for screening	Percentage up-to-date			Number eligible for screening	Percentage up-to-date		
		Overall	FOBT within 30 months	Colonoscopy within 10 years		Overall	FOBT within 30 months	Colonoscopy within 10 years
All	2,852,619	20.58	10.14	12.55	4,139,304	55.70	27.67	35.10
Sex								
Female	1,458,751	21.31	10.38	13.17	2,109,911	58.53	29.73	36.39
Male	1,393,868	19.81	9.90	11.90	2,029,393	52.75	25.53	33.76
Age								
50-54	830,064	15.96	7.64	9.62	1,136,951	41.99	21.32	24.09
55-59	661,795	19.74	9.61	12.01	990,500	55.58	26.62	35.28
60-64	513,835	22.39	11.22	13.55	823,368	60.77	29.36	39.72
65-69	445,920	24.31	12.30	14.85	691,980	65.07	32.80	42.29
70-74	401,005	25.03	12.42	15.63	496,505	65.85	34.38	42.24
Income quintile								
Missing	16,392	15.76	6.72	10.46	24,195	38.14	18.52	23.52
Q1 (lowest)	506,380	17.66	8.26	11.12	731,193	48.76	26.63	28.09
Q2	560,295	19.39	9.63	11.74	794,761	53.3	28.49	31.59
Q3	571,592	20.38	10.36	12.12	814,635	55.76	28.60	34.34
Q4	573,381	21.39	10.84	12.76	874,766	58.21	28.27	37.41
Q5 (highest)	624,579	23.57	11.38	14.69	899,754	61.44	26.63	42.63
Long-term resident								
Yes	2,617,455	21.35	10.38	13.20	3,897,864	56.73	27.62	36.41
No	235,164	11.92	7.57	5.34	241,440	38.98	28.46	13.82
Rurality (RIO)								
Major urban (0-9)	1,948,251	20.66	10.76	12.09	2,860,546	55.38	27.54	34.96
Nonmajor urban (10-39)	598,799	21.20	9.72	13.64	867,224	57.52	28.68	36.26
Rural (40+)	270,175	19.12	7.10	13.60	365,531	55.39	27.12	34.44
Adjusted diagnostic groups								
No utilization	274,071	2.29	0.52	1.81	428,225	11.44	3.85	7.97
1-4 (low comorbidity)	969,691	12.74	7.59	5.82	1,555,111	50.8	28.05	27.46
5-9	1,208,537	25.05	12.65	14.95	1,667,328	66.77	32.65	43.47
10+ (high comorbidity)	400,320	38.57	15.35	28.94	488,640	72.28	30.36	54.60
Resource Utilization Band								
0 (no utilization)	274,030	2.29	0.52	1.81	427,318	11.32	3.82	7.87
1	87,137	8.06	4.79	3.58	127,096	38.95	20.44	21.29
2	314,426	11.68	7.00	5.28	521,456	47.59	26.19	25.42
3	1,554,706	21.95	11.56	12.48	2,245,056	62.73	32.14	38.64
4	426,247	31.17	13.54	21.72	563,188	68.46	31.12	48.06
5 (high utilization)	196,073	32.04	12.43	23.78	255,190	64.89	27.32	47.51
Comorbidities:								
Diabetes	360,015	22.09	10.50	13.93	771,284	60.08	30.42	37.90
Hypertension	1,065,753	24.06	11.88	14.82	1,701,298	63	31.42	40.37
CHF	76,371	24.86	9.80	17.94	97,082	56.6	26.1	38.08
AMI	65,159	20.97	9.50	13.66	101,079	55.09	26.59	35.3
Asthma	252,201	26.41	11.63	17.80	470,927	61.78	28.05	42.36
COPD	301,578	24.86	10.52	17.09	506,450	59.09	27.56	39.59
Mental health	526,862	26.40	11.98	17.48	627,444	61.71	28.65	41.71
Psychotic	31,528	22.94	9.20	16.47	61,819	54.26	25.98	35.27
Nonpsychotic	480,215	26.84	12.16	17.82	554,412	62.75	28.95	42.71
Number of primary care visits:								
0	385,569	5.92	1.66	4.58	595,352	20.03	8.27	13.14
1-4	624,313	14.63	7.21	8.40	1,273,370	54.03	27.08	32.25
5-9	729,858	22.17	11.68	12.55	1,160,581	64.97	32.83	40.51
10+	1,112,879	27.95	13.72	17.64	1,110,001	67.05	33.36	44.47
Attachment to primary care physician								
Yes	2,491,482	22.83	11.42	13.80	3,775,789	59.81	29.80	37.65
No	361,137	5.05	1.35	3.95	363,515	13.02	5.58	8.56

understand the association between patient characteristics and being up-to-date for screening. Model variables included age, rurality, Adjusted Diagnosis Groups (comorbidity), and Resource Utilization Band (morbidity). For all analyses, our primary outcome was being up-to-date for colorectal cancer screening but we also examined associations for FOBT and colonoscopy separately.

For each year of the study, we calculated the inequality ratio related to (i) income and (ii) recent residence by dividing the percentage of screen-eligible individuals up-to-date in the most disadvantaged group by the percentage up-to-date in the most advantaged group. We also examined changes in the proportion of individuals up-to-date for screening after standardizing for age

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**Figure 1.** Colorectal screening rates stratified by sex, immigration, and income quintile 2013/14.

and sex, stratified by neighborhood income quintile and recent residence.

We performed a longitudinal segmented regression analyses to assess the changes in the level and slope of the inequality ratio related to (i) income and (ii) recent residence after introduction of the Colon Cancer Check program in April 2008 (33). The analyses assessing changes in income inequality was stratified by immigration and vice versa. We used logistic regression to model whether individuals were up-to-date with colorectal cancer screening. We used the Generalized Estimation Equation method with an AR(1) covariance structure to account for repeated measures over time. The regression analyses adjusted for age, sex, rurality, comorbidity (Adjusted Diagnosis Groups), and morbidity (Resource Utilization Band). All analyses were performed using Unix SAS Enterprise Guide 6.1.

## Results

The percentage of adults up-to-date with colorectal cancer screening increased from 20.6% ( $n = 587,068$ ) in 2001/02 to 55.7% ( $n = 2,305,592$ ) in 2013/14 (Table 1). Recent immigrants and individuals living in low income neighborhoods had lower rates of colonoscopy and overall screening. Males, younger individuals, those not attached to primary care, those with fewer primary care visits, and lower comorbidity or morbidity also had lower overall screening rates.

In 2013/14, male recent residents living in low income neighborhoods had the lowest colorectal cancer screening rate at 35.6% and female long-term residents in high income neighborhoods had the highest screening rate at 65.0% (Fig. 1). Individuals living in the lowest income neighborhood were less likely to be up-to-date with screening compared those in the highest income quintile and this association was stronger for long-term residents than for recent immigrants, even after adjustment for other patient characteristics (Table 2). For example, after adjustment, the odds of males in the lowest income quintile being up-to-date compared with males in the highest income quintile was 0.55 [95% confidence interval (CI), 0.54–0.56] for long-term residents and 0.79 (95% CI, 0.75–0.82) for recent immigrants. Those living in lower income neighborhoods were much less likely to receive colonoscopy than those living in higher income neighborhoods, but there was little difference in FOBT rates by income quintile.

The income inequality ratio for colorectal cancer screening narrowed from 0.74 to 0.80 between 2001–02 and 2013–14 (Fig. 2A) with a narrowing of the ratio for FOBT from 0.71 to

1.01 but a widening of the ratio for colonoscopy from 0.74 to 0.66. The immigration inequality ratio for colorectal cancer screening narrowed from 0.55 to 0.69 between 2001–02 and 2013–14 (Fig. 2A) with a narrowing of the ratio for FOBT from 0.72 to 1.02 and a widening of the ratio for colonoscopy from 0.40 to 0.37. Figure 2B and C shows the change in age and sex standardized FOBT, colonoscopy, and overall colorectal screening rates in Ontario between 2001 and 2013, stratified by neighborhood income quintile and immigration, respectively. Colonoscopy and overall colorectal screening rates increased over the time period whereas FOBT rates seemed to peak in 2008/09.

The income inequality ratio was widening by 1% per year (95% CI, 1%–1%) before Colon Cancer Check (Table 3A). In the year Colon Cancer Check was introduced, the income inequality ratio narrowed by 4% (95% CI, 2%–7%) and in the years following, the ratio remained stable [0% decrease (95% CI, 1% decrease to 0% decrease) per year]. For FOBT, the income inequality ratio was narrowing at a faster rate after Colon Cancer Check compared with before; for colonoscopy, the income inequality ratio was widening at a slower rate after Colon Cancer Check compared with before. Trends were similar for both long-term residents and recent immigrants.

The immigration inequality ratio was widening by 2% per year (95% CI, 1%–3%) before Colon Cancer Check (Table 3B). In the year Colon Cancer Check was introduced, the immigration inequality ratio narrowed by 4% (95% CI, 0%–8%) and in the years following, the ratio narrowed by 1% per year (95% CI, 0%–2%). For FOBT, the immigration inequality ratio was fairly stable (95% CI, 1% decrease to 1% increase per year) before Colon Cancer Check and was narrowing by 6% per year after (95% CI, 5%–7%). For colonoscopy, the immigration inequality ratio was widening by 4% per year (95% CI, 3%–5%) before Colon Cancer Check but stabilized after (95% CI, 1% decrease to 1% increase per year). Trends were similar for both long-term residents and recent immigrants.

## Discussion

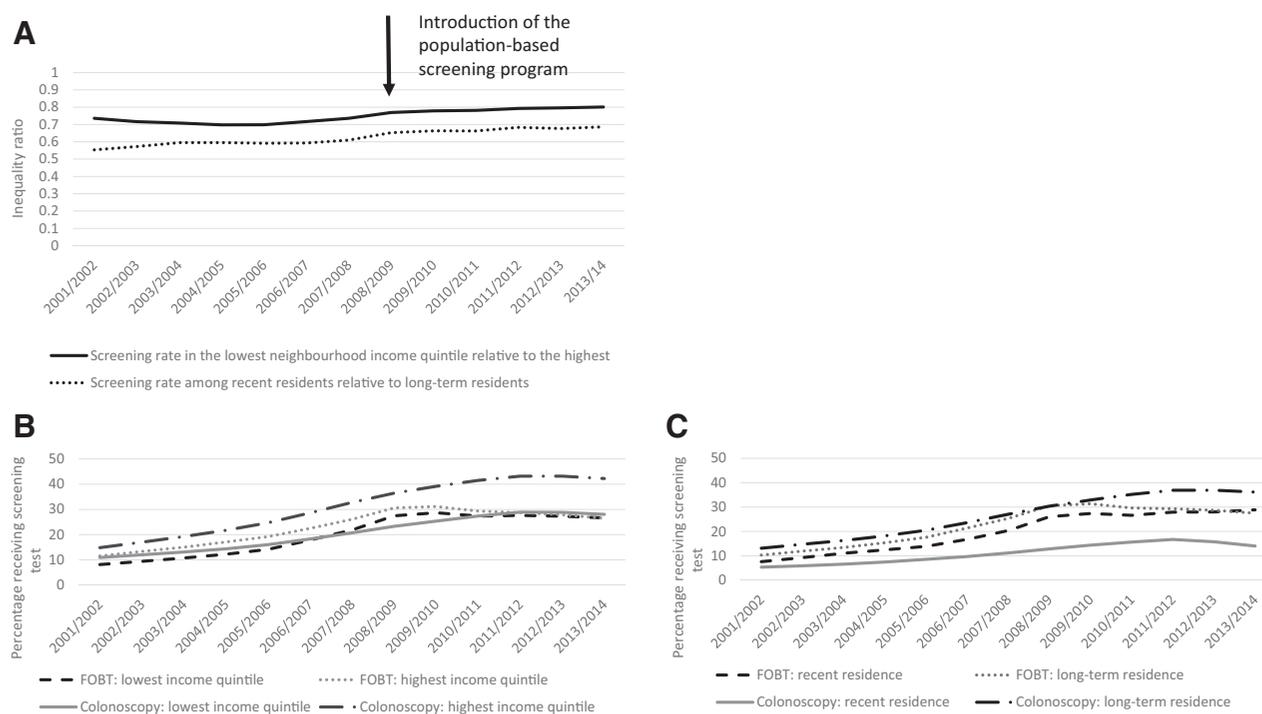
We found that a population-based screening program for colorectal cancer screening was associated with a modest narrowing of immigration and income-related disparities. Despite improvements, screening rates for male recent immigrants living in the lowest neighborhood income quintile were almost half the rate of female long-term residents living in the highest

**Table 2.** Colorectal cancer screening rates in 2013/14 stratified by age, immigration, and income quintile with and without adjustment for other patient characteristics (age, rurality, comorbidity, and morbidity)

	Overall			FOBT within 30 months			Colonoscopy within 10 years		
	Crude % up-to-date	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Crude % up-to-date	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Crude % up-to-date	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
<b>Female</b>									
Recent immigrant									
Q1	40.04	0.961 (0.926-0.998)	0.84 (0.806-0.875)	30.84	1.137 (1.092-1.184)	1.043 (0.999-1.089)	12.70	0.746 (0.708-0.785)	0.662 (0.627-0.699)
Q2	40.74	0.99 (0.952-1.029)	0.904 (0.867-0.943)	31.11	1.152 (1.105-1.201)	1.086 (1.04-1.135)	12.98	0.764 (0.724-0.806)	0.707 (0.669-0.748)
Q3	41.71	1.03 (0.991-1.071)	0.941 (0.902-0.982)	31.24	1.158 (1.11-1.208)	1.086 (1.039-1.136)	13.89	0.826 (0.784-0.873)	0.767 (0.726-0.811)
Q4	41.95	1.04 (1-1.082)	0.974 (0.933-1.016)	30.41	1.115 (1.068-1.163)	1.057 (1.011-1.106)	14.98	0.903 (0.856-0.952)	0.861 (0.815-0.909)
Q5	40.99	Reference	Reference	28.17	Reference	Reference	16.33	Reference	Reference
Long-term resident									
Q1	53.81	0.651 (0.645-0.657)	0.625 (0.619-0.631)	28.99	1.025 (1.015-1.035)	1.061 (1.05-1.072)	31.76	0.592 (0.586-0.597)	0.557 (0.551-0.562)
Q2	57.66	0.761 (0.755-0.768)	0.732 (0.725-0.739)	30.68	1.11 (1.1-1.121)	1.129 (1.118-1.14)	34.67	0.674 (0.668-0.68)	0.641 (0.635-0.647)
Q3	59.64	0.826 (0.819-0.834)	0.799 (0.792-0.807)	30.52	1.102 (1.092-1.113)	1.112 (1.101-1.123)	37.12	0.75 (0.744-0.757)	0.721 (0.714-0.728)
Q4	61.69	0.9 (0.892-0.908)	0.875 (0.867-0.883)	30.06	1.079 (1.069-1.089)	1.079 (1.069-1.09)	39.7	0.837 (0.829-0.844)	0.812 (0.805-0.82)
Q5	64.14	Reference	Reference	28.49	Reference	Reference	44.04	Reference	Reference
<b>Male</b>									
Recent immigrant									
Q1	35.58	0.884 (0.85-0.918)	0.785 (0.752-0.819)	26.66	1.122 (1.075-1.171)	1.064 (1.017-1.114)	11.88	0.643 (0.61-0.677)	0.573 (0.542-0.606)
Q2	37.11	0.944 (0.908-0.982)	0.866 (0.829-0.905)	27.19	1.153 (1.103-1.204)	1.107 (1.057-1.16)	13.15	0.722 (0.684-0.761)	0.665 (0.629-0.702)
Q3	38.30	0.993 (0.955-1.034)	0.894 (0.856-0.934)	27.98	1.199 (1.148-1.253)	1.129 (1.078-1.184)	13.83	0.765 (0.725-0.807)	0.694 (0.657-0.733)
Q4	38.34	0.995 (0.956-1.035)	0.917 (0.877-0.958)	26.84	1.132 (1.083-1.184)	1.073 (1.023-1.125)	14.77	0.826 (0.784-0.871)	0.775 (0.733-0.819)
Q5	38.46	Reference	Reference	24.47	Reference	Reference	17.34	Reference	Reference
Long-term resident									
Q1	45.41	0.542 (0.537-0.547)	0.549 (0.544-0.555)	23.81	0.951 (0.941-0.961)	1.041 (1.03-1.053)	27.00	0.481 (0.477-0.486)	0.479 (0.474-0.484)
Q2	50.68	0.67 (0.664-0.676)	0.663 (0.656-0.669)	26.09	1.075 (1.064-1.086)	1.13 (1.118-1.142)	30.89	0.582 (0.576-0.587)	0.569 (0.563-0.574)
Q3	53.69	0.756 (0.749-0.762)	0.743 (0.736-0.75)	26.46	1.096 (1.085-1.107)	1.129 (1.118-1.141)	34.03	0.671 (0.665-0.677)	0.655 (0.649-0.662)
Q4	56.62	0.851 (0.843-0.858)	0.837 (0.829-0.845)	26.36	1.09 (1.079-1.101)	1.106 (1.095-1.117)	37.56	0.783 (0.776-0.79)	0.768 (0.761-0.776)
Q5	60.54	Reference	Reference	24.73	Reference	Reference	43.45	Reference	Reference

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile.

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**Figure 2.**

**A**, Change in inequality ratios between 2001/02 and 2013/14 for the percentage of screen-eligible individuals up-to-date for colorectal cancer screening (\*), by income and recent residence. \*, Screening rates are age-sex adjusted; \*\*, Inequality ratios are calculated by dividing the percentage of up-to-date in the most disadvantaged group by the percentage of up-to-date in the most advantaged group. A ratio of 1 indicates perfect equality. **B**, Comparison of the percentage of screen-eligible individuals up-to-date for colorectal cancer screening in the lowest and highest neighborhood income quintiles, stratified by screening modality\* (\*, Screening rates are age-sex adjusted). **C**, Comparison of the percentage of screen-eligible individuals up-to-date for colorectal cancer screening among recent and long-term residents, stratified by screening modality. (\*, Screening rates are age-sex adjusted).

income neighborhood. Gaps in screening were largest for recent immigrants and seemed to relate largely to differences in screening by colonoscopy, a modality not promoted by the program. The introduction of the screening program was associated with a slight narrowing in the gap in FOBT screening between recent immigrants and long-term residents, although this change seemed to coincide with a secular decrease in FOBT screening rates. In contrast, introduction of the program was associated with a reduced widening of the gap in colonoscopy screening.

Our findings are consistent with research from the UK and Australia that has found that uptake from organized colorectal cancer screening programs is lower among patients from deprived neighborhoods (9, 34–36). These other studies did not assess the association with recent immigration, but studies from the UK have shown that patients from a nonwhite ethnic background, particularly those from the Indian subcontinent, have had persistently low colorectal screening rates (11) and lower uptake in the organized screening program (35). The population-based screening program in Australia was a pilot but the UK program has been implemented across the country. As in Ontario, these programs mailed invitations promoting FOBT screening to patients in a specific age range. In the UK, the FOBT kit itself was mailed along with the invitation, a strategy been shown to increase uptake (37).

Our findings suggest that immigration and income-related disparities in colorectal cancer screening in Ontario are largely driven by differences in use of FOBT (organized screening)

versus colonoscopy (opportunistic screening). Other Ontario studies have found that long-term residents and those living in wealthier neighborhoods are more likely to be screened by colonoscopy (38) even though colonoscopy is not recommended in Canadian clinical practice guidelines (5) and financial incentives reward FOBT but not colonoscopy (39). Screening by colonoscopy seems to be influenced by patient, physician, and system factors including more affluent patients' "normative assumptions about colonoscopy as a rite of passage" (38). That colonoscopy is a first-line screening choice in the neighboring U.S. (4) likely also influences uptake in Canada. Ontario's screening program promoted FOBT for average-risk individuals but even so, we found that the program's introduction coincided with a secular decrease in FOBT rates and an increase in colonoscopy rates.

Current patterns of screening likely perpetuate inequities and will be challenging for a population-based program to address. FOBT requires repeat testing every 2 years and a recent study estimated that only about a third of recipients received a follow-up FOBT in the recommended time frame (40). In contrast, colonoscopy provides screening clearance for 10 years, which may mean it is more advantaged recipients are more likely to stay up-to-date. Integrating colonoscopy as a choice in the screening program is likely impractical given cost-effectiveness considerations. But, the status quo is an inherently unfair situation, whereby more advantaged patients are more likely to receive a more

**Table 3.** Parameter estimates from segmented regression model assessing the change in trend for the income and immigration inequality ratio for colorectal cancer screening after introduction of a population-based screening program in Ontario in April 2008

A. Effect of program on income inequality ratio						
	Intercept (95% CI)	Trend <sup>b</sup> before screening program was introduced (95% CI)	Step change the year screening program was introduced (95% CI)	Trend <sup>b</sup> after screening program was introduced (95% CI)	Net change in trend <sup>a</sup> after screening program introduced (95% CI)	
Recent immigrants	0.81 (0.77-0.85)	-0.01 (-0.01-0.00)	0.06 (0.01-0.11)	0.01 (0.00-0.02)	0.02 (0.01-0.03)	
	0.78 (0.73-0.84)	0.01 (0.00-0.02)	0.08 (0.01-0.15)	0.02 (0.01-0.04)	0.02 (0.00-0.03)	
Long-term resident	0.96 (0.93-0.99)	-0.03 (-0.03 to -0.02)	0.04 (0.00-0.08)	0.00 (-0.01-0.01)	0.03 (0.02-0.04)	
	0.92 (0.90-0.93)	-0.01 (-0.01 to -0.01)	0.04 (0.02-0.06)	-0.01 (-0.01-0.00)	0.00 (0.00-0.01)	
	0.82 (0.79-0.85)	0.01 (0.00-0.02)	0.05 (0.00-0.09)	0.02 (0.01-0.03)	0.01 (0.00-0.02)	
	1.06 (1.04-1.08)	-0.03 (-0.03 to -0.02)	0.02 (-0.01-0.04)	-0.01 (-0.01-0.00)	0.02 (0.01-0.02)	
All residents in lowest and highest income quintiles	0.91 (0.89-0.93)	-0.01 (-0.01 to -0.01)	0.04 (0.02-0.07)	0.00 (-0.01-0.00)	0.01 (0.00-0.01)	
	0.80 (0.77-0.83)	0.01 (0.00-0.02)	0.04 (0.00-0.08)	0.02 (0.01-0.03)	0.01 (0.00-0.02)	
	1.08 (1.05-1.10)	-0.03 (-0.03 to -0.02)	0.02 (-0.01-0.05)	-0.01 (-0.01-0.00)	0.02 (0.01-0.03)	
B. Effect of program on immigration inequality ratio						
	Intercept (95% CI)	Trend <sup>b</sup> before screening program was introduced (95% CI)	Step change the year screening program was introduced (95% CI)	Trend <sup>b</sup> after screening program was introduced (95% CI)	Net change in trend <sup>a</sup> after screening program introduced (95% CI)	
Lowest income quintile	0.79 (0.75-0.82)	0.01 (-0.02-0.00)	0.05 (0.00-0.10)	0.02 (0.01-0.03)	0.03 (0.02-0.05)	
	0.88 (0.85-0.92)	0.00 (-0.01-0.01)	-0.01 (-0.06-0.03)	0.06 (0.05-0.07)	0.06 (0.05-0.07)	
Highest income quintile	0.76 (0.72-0.81)	-0.03 (-0.04 to -0.01)	0.06 (-0.01-0.12)	0.01 (0.00-0.02)	0.03 (0.02-0.05)	
	0.79 (0.75-0.82)	0.01 (-0.02-0.00)	0.05 (0.00-0.10)	0.02 (0.01-0.03)	0.03 (0.02-0.05)	
	0.89 (0.84-0.94)	0.00 (-0.01 to 0.01)	-0.05 (-0.12 to 0.02)	0.05 (0.04-0.07)	0.05 (0.04-0.07)	
	0.84 (0.82-0.87)	-0.03 (-0.03 to -0.02)	0.03 (0.00-0.06)	-0.01 (-0.01-0.00)	0.02 (0.01-0.03)	
All residents in lowest and highest income quintiles	0.81 (0.79-0.84)	-0.02 (-0.03 to -0.01)	0.04 (0.00-0.08)	0.01 (0.00-0.02)	0.03 (0.02-0.04)	
	0.80 (0.76-0.84)	0.00 (-0.01-0.01)	0.00 (-0.06-0.05)	0.06 (0.05-0.07)	0.06 (0.04-0.07)	
	0.89 (0.84-0.93)	-0.04 (-0.05 to -0.03)	0.04 (-0.02-0.10)	0.00 (-0.01-0.01)	0.04 (0.02-0.06)	

NOTE: Income inequality ratio: colorectal cancer screening rate in lowest income quintile divided by colorectal cancer screening rate in highest income quintile. Immigration inequality ratio: colorectal cancer screening rate in recent immigrants divided by colorectal cancer screening rate in long-term residents.

<sup>a</sup>Average change in inequality ratio per year (e.g., 0.01 denotes a 1% narrowing of the ratio per year; -0.03 denotes a 3% widening in the ratio per year).

<sup>b</sup>Average change in inequality ratio per year (e.g., 0.01 denotes a 1% narrowing of the ratio per year; -0.03 denotes a 3% widening in the ratio per year).

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expensive test that is perceived by some physicians and patients as the gold standard (38).

The current program relies on patients visiting their family physician and their physician counseling them appropriately. Moving to directly mailed kits could eliminate the need for a physician visit and also allow for more standardized messaging to improve uptake of FOBT (37). Use of Fecal Immunochemical Tests (FIT) instead of guaiac-based tests may further enhance uptake (41). However, to be successful, these strategies will need to explicitly address known barriers to FOBT including patients' perceived risk of handling feces (42). Other promising strategies for reducing disparities include tailored messaging (43, 44), linking invitations with primary care physicians (42, 45), telephone outreach (43, 46), and multifaceted interventions based in primary care clinics (15, 16, 47).

### Strengths and limitations

Our study included data for all Ontarians over a 12-year period and used several complimentary analyses to understand the interplay between a population-based screening program, income and immigration-related disparities, and mode of colorectal cancer screening. In contrast, studies from other jurisdictions have evaluated pilot programs (35), the impact of a program on a specific region (34, 35), or have been cross-sectional (9). Unlike our study, others' studies have not accounted for trends in screening disparities before program introduction or conducted longitudinal statistical analyses.

Despite these strengths, our study has two notable limitations. First, we were limited by the administrative data available to us. We used registration with the health insurance plan within 10 years as a proxy for recent immigration. This approach captures interprovincial migrants that we estimate comprise approximately 5% of recent registrants. Also, we attributed neighborhood income quintile, an area-level variable, to individuals. For all years, we assigned neighborhood income quintile based on 2006 census data, which may not have reflected true neighborhood income levels near the start and ends of the study period. However, these methods for measuring immigration and income are well accepted and have been used by several other researchers studying disparities (23, 48). In our study, recent immigrants are a heterogeneous group and we were unable to distinguish country of origin or ethnicity, both of which may influence screening attitudes.

Second, we conducted a retrospective evaluation of a natural experiment so were unable to isolate the effect of the population-based screening program and were limited in our ability to infer causation. Financial incentives were introduced for primary care physicians 2 years before the screening program was launched and may have confounded our results. A *post-hoc* evaluation of the incentive found it had only a modest impact on colorectal cancer screening rates (39), but it is unclear how it impacted equity. Our segmented regression analysis evaluated the impact of the program launch in 2008, although mailed screening invitations began in 2010. However, an increase in screening following 2010 would have influenced screening trends between 2008 and 2014, which were captured in our analyses.

### Conclusion

The introduction of a population-based screening program promoting FOBT screening for colorectal cancer was associ-

ated with modest improvements in immigration and income-related disparities. Recent immigrants experienced the greatest gaps in care. Disparities seemed to be driven by a higher uptake of opportunistic screening with colonoscopy among more advantaged groups. Addressing disparities in this context will be challenging and will require contesting normative assumptions of both patients and physicians. Promising program enhancements include direct mailing of screening kits to patients and more intensive outreach to underscreened groups. Future research should examine potential disparities in follow-up testing and access to definitive treatment for those who screen positive and ultimately evaluate whether the screening program has reduced disparities in colon cancer mortality.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Disclaimer

The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by the Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred. Parts of this material are based on data and information compiled and provided by Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors and not necessarily those of CIHI. Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, views, and conclusions reported in this article are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred.

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**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** T. Kiran

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## References

- Global Cancer Statistics: Centers for Disease Control and Prevention; [updated January 4, 2016]. Available from: <http://www.cdc.gov/cancer/international/statistics.htm>.
- Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst Rev* 2007;CD001216.
- Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;348:1467–71.
- US Preventive Services Task Force. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;149:627.
- Care CTfOPH. Recommendations on screening for colorectal cancer in primary care. *Canadian Med Assoc J* 2016;188:340–8.
- Singh H, Bernstein CN, Samadder JN, Ahmed R. Screening rates for colorectal cancer in Canada: a cross-sectional study. *CMAJ open* 2015;3:E149.
- Singh SM, Paszat LF, Li C, He J, Vinden C, Rabeneck L. Association of socioeconomic status and receipt of colorectal cancer investigations: a population-based retrospective cohort study. *Canadian Med Assoc J* 2004;171:461–5.
- Steele CB, Rim SH, Joseph DA, King JB, Seeff LC. Colorectal cancer incidence and screening—United States, 2008 and 2010. *MMWR Surveill Summ* 2013;62:53–60.
- Von Wagner C, Baio G, Raine R, Snowball J, Morris S, Atkin W, et al. Inequalities in participation in an organized national colorectal cancer screening programme: results from the first 2.6 million invitations in England. *Int J Epidemiol* 2011;40:712–8.
- Jerant AF, Fenton JJ, Franks P. Determinants of racial/ethnic colorectal cancer screening disparities. *Arch Int Med* 2008;168:1317–24.
- Szczepura A, Price C, Gumber A. Breast and bowel cancer screening uptake patterns over 15 years for UK south Asian ethnic minority populations, corrected for differences in socio-demographic characteristics. *BMC Public Health* 2008;8:1.
- Goel MS, Wee CC, McCarthy EP, Davis RB, Ngo-Metzger Q, Phillips RS. Racial and ethnic disparities in cancer screening. *J Gen Int Med* 2003;18:1028–35.
- Honein-AbouHaidar GN, Baxter NN, Moineddin R, Urbach DR, Rabeneck L, Bierman AS. Trends and inequities in colorectal cancer screening participation in Ontario, Canada, 2005–2011. *Cancer Epidemiol* 2013;37:946–56.
- Ananthakrishnan AN, Schellhase KG, Sparapani RA, Laud PW, Neuner JM. Disparities in colon cancer screening in the Medicare population. *Arch Int Med* 2007;167:258–64.
- Baker DW, Brown T, Buchanan DR, Weil J, Balsley K, Ranalli L, et al. Comparative effectiveness of a multifaceted intervention to improve adherence to annual colorectal cancer screening in community health centers: a randomized clinical trial. *JAMA Int Med* 2014;174:1235–41.
- Berkowitz SA, Percac-Lima S, Ashburner JM, Chang Y, Zai AH, He W, et al. Building equity improvement into quality improvement: reducing socio-economic disparities in colorectal cancer screening as part of population health management. *J Gen Int Med* 2015;30:942–9.
- Palència L, Espelt A, Rodríguez-Sanz M, Puigpinós R, Pons-Vigués M, Pasarín MI, et al. Socio-economic inequalities in breast and cervical cancer screening practices in Europe: influence of the type of screening program. *Int J Epidemiol* 2010;dyq003.
- Honein-AbouHaidar GN, Rabeneck L, Paszat LF, Sutradhar R, Tinmouth J, Baxter NN. Evaluating the impact of public health initiatives on trends in fecal occult blood test participation in Ontario. *BMC Cancer* 2014;14:1.
- Statistics Canada. Population by year, by province and territory: Government of Canada. Available from: <http://www.statcan.gc.ca/tables-tab-leaux/sum-som/l01/cst01/demo02a-eng.htm>.
- Rabeneck L, Tinmouth JM, Paszat LF, Baxter NN, Marrett LD, Ruco A, et al. Ontario's ColonCancerCheck: results from Canada's first province-wide colorectal cancer screening program. *Cancer Epidemiol Biomark Prev* 2014;23:508–15.
- Cancer Care Ontario. Ontario Cancer Screening Performance Report 2016. Toronto; 2016.
- Baker D, Middleton E. Cervical screening and health inequality in England in the 1990s. *J Epidemiol Commun Health* 2003;417–23.
- Ray JG, Vermeulen MJ, Schull MJ, Singh G, Shah R, Redelmeier DA. Results of the Recent Immigrant Pregnancy and Perinatal Long-term Evaluation Study (RIPPLES). *Canadian Med Assoc J* 2007;176:1419–26.
- Kralj B. Measuring "rurality" for purposes of health-care planning: an empirical measure for Ontario. Toronto, Ontario, Canada: Ontario Medical Association; 2005.
- The Johns Hopkins University. The Johns Hopkins ACG System Baltimore; 2012. Available from: <http://www.acg.jhsph.org/>.
- Hux J, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002;25:512–6.
- Tu K, Campbell NR, Chen X-L, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. *Open Med* 2007;1:18–26.
- Schultz S, Rothwell D, Chen Z, Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic Dis Inj Canada* 2013;33:160–6.
- Alter DA, Naylor CD, Austin P, Tu JV. Effects of socioeconomic status on access to invasive cardiac procedures and on mortality after acute myocardial infarction. *N Engl J Med* 1999;341:1359–67.
- Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. *Canadian Resp J* 2009;16:183–8.
- Gershon A, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physician diagnosed COPD in health administrative databases. *COPD* 2009;6:388–94.
- Steele L, Glazier R, Lin E, Evans M. Using administrative data to measure ambulatory mental health service provision in primary care. *Medical Care* 2004;42:960.
- Naumova EN, Must A, Laird NM. Tutorial in biostatistics: evaluating the impact of 'critical periods' in longitudinal studies of growth using piecewise mixed effects models. *Int J Epidemiol* 2001;30:1332–41.
- Ananda SS, McLaughlin SJ, Chen F, Hayes IP, Hunter AA, Skinner JJ, et al. Initial impact of Australia's national bowel cancer screening program. *Med J Australia* 2009;191:378.
- Moss S, Campbell C, Melia J, Coleman D, Smith S, Parker R, et al. Performance measures in three rounds of the English bowel cancer screening pilot. *Gut* 2012;61:101–7.
- Whynes D, Frew E, Manghan C, Scholefield J, Hardcastle J. Colorectal cancer, screening and survival: the influence of socio-economic deprivation. *Public Health* 2003;117:389–95.
- Tinmouth J, Patel J, Austin PC, Baxter NN, Brouwers MC, Earle C, et al. Increasing participation in colorectal cancer screening: Results from a cluster randomized trial of directly mailed gFOBT kits to previous non-responders. *Int J Cancer* 2015;136:E697–E703.
- Buchman S, Rozmovits L, Glazier RH. Equity and practice issues in colorectal cancer screening Mixed-methods study. *Canadian Family Physician* 2016;62:e186–e93.
- Kiran T, Wilton AS, Moineddin R, Paszat L, Glazier RH. Effect of payment incentives on cancer screening in Ontario primary care. *Ann Family Med* 2014;12:317–23.
- Paszat L, Sutradhar R, Tinmouth J, Baxter N, Rabeneck L. Interval colorectal cancers following guaiac fecal occult blood testing in the Ontario colon cancer check program. *Canadian J Gastroenterol Hepatol* 2016;2016:4768728.
- Tinmouth J, Lansdorp-Vogelaar I, Allison JE. Faecal immunochemical tests versus guaiac faecal occult blood tests: what clinicians and colorectal cancer screening programme organisers need to know. *Gut* 2015;64:1327–37.
- Palmer C, Thomas M, Von Wagner C, Raine R. Reasons for non-uptake and subsequent participation in the NHS Bowel Cancer Screening Programme: a qualitative study. *Br J Cancer* 2014;110:1705–11.
- Basch CE, Wolf RL, Brouse CH, Shmukler C, Neugut A, DeCarlo LT, et al. Telephone outreach to increase colorectal cancer screening in an urban minority population. *Am J Public Health* 2006;96:2246–53.
- Myers RE, Sifri R, Hyslop T, Rosenthal M, Vernon SW, Cocroft J, et al. A randomized controlled trial of the impact of targeted and tailored interventions on colorectal cancer screening. *Cancer* 2007;110:2083–91.

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45. Tinmouth J, Baxter NN, Paszat LF, Rabeneck L, Sutradhar R, Yun L. Using physician-linked mailed invitations in an organised colorectal cancer screening programme: effectiveness and factors associated with response. *BMJ Open* 2014;4:e004494.
46. Dietrich AJ, Tobin JN, Cassells A, Robinson CM, Greene MA, Sox CH, et al. Telephone care management to improve cancer screening among low-income women: a randomized, controlled trial. *Ann Int Med* 2006; 144:563–71.
47. Tu S-P, Chun A, Yasui Y, Kuniyuki A, Yip M-P, Taylor V, et al. Adaptation of an evidence-based intervention to promote colorectal cancer screening: a quasi-experimental study. *Implementation Sci* 2014;9:1.
48. Booth GL, Creatore MI, Moineddin R, Gozdyra P, Weyman JT, Matheson FI, et al. Unwalkable neighborhoods, poverty, and the risk of diabetes among recent immigrants to Canada compared with long-term residents. *Diabetes Care* 2013;36:302–8.

# Cancer Epidemiology, Biomarkers & Prevention

## The Impact of a Population-Based Screening Program on Income- and Immigration-Related Disparities in Colorectal Cancer Screening

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