The Frequency of Repeat Anti-Nuclear Antibody (ANA) Testing in a Single-payer universal healthcare system: A population-based study

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Abstract:	Background: Our aim was to assess the frequency and correlates of repeat ANA testing in the setting of a single-payer universal healthcare system. Methods: We identified all ANA tests performed over 2008-2016, and repeat testing within 12 months, among adults within the Ontario Laboratories Information System, a nearly population-wide laboratory database linked with administrative data. To assess correlates of repeat testing, and repeat testing after a positive test, we fit marginal logistic regression models by means of generalized estimating equations. Results: In total, 587,357 ANA tests were performed on 437,966 patients between 2008 and 2016, 23% were positive and 28% were repeats. Family physicians ordered 358,422 tests (61%) and rheumatologists ordered 65,071 tests (11%). Among 164,913 total repeat tests, 49%

	were ordered within 12 months of the previous test. Among 81,058 tests repeated within 12 months, 33,574 (41%) had a preceding positive result. Rheumatologists performed more repeat tests within 12 months (36% vs 11% other physicians). In the multivariable analyses, rheumatologists were more likely to order repeat tests and repeat testing after a positive test than other practitioners, and patients with connective tissue diseases were 4-5 times more likely to undergo repeat testing. Interpretation: Over a quarter of ANA tests were repeats, many of which were performed on patients with prior positive tests. Family physicians ordered more tests than other care providers, however rheumatologists are most likely to perform repeat testing. Our findings may be useful to inform quality improvement initiatives related to the appropriateness of ANA testing.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3-4
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Study design	#4	Present key elements of study design early in the paper	4
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Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	5
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Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4
Bias	#9	Describe any efforts to address potential sources of bias	5-6
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Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5-6
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Statistical methods	#12e	Describe any sensitivity analyses	6
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Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	6-7

		eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	7
Participants	#13c	Consider use of a flow diagram	N/A
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7-8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	6-7
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
Main results	#16b	Report category boundaries when continuous variables were categorized	N/A
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	7-8
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Generalisability	#21	Discuss the generalisability (external validity) of the study results	10
Other Information			
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ABSTRACT

Background:
Our aim was to assess the frequency and correlates of repeat ANA testing in the setting of a single-payer universal healthcare system.

Methods:
We identified all ANA tests performed over 2008-2016, and repeat testing within 12 months, among adults within the Ontario Laboratories Information System, a nearly population-wide laboratory database linked with administrative data. To assess correlates of repeat testing, and repeat testing after a positive test, we fit marginal logistic regression models by means of generalized estimating equations.

Results:
In total, 587,357 ANA tests were performed on 437,966 patients between 2008 and 2016, 23% were positive and 28% were repeats. Family physicians ordered 358,422 tests (61%) and rheumatologists ordered 65,071 tests (11%). Among 164,913 total repeat tests, 49% were ordered within 12 months of the previous test. Among 81,058 tests repeated within 12 months, 33,574 (41%) had a preceding positive result. Rheumatologists performed more repeat tests within 12 months (36% vs 11% other physicians). In the multivariable analyses, rheumatologists were more likely to order repeat tests and repeat testing after a positive test than other practitioners, and patients with connective tissue diseases were 4-5 times more likely to undergo repeat testing.

Interpretation:
Over a quarter of ANA tests were repeats, many of which were performed on patients with prior positive tests. Family physicians ordered more tests than other care providers, however rheumatologists are most likely to perform repeat testing. Our findings may be useful to inform quality improvement initiatives related to the appropriateness of ANA testing.

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INTRODUCTION

Laboratory testing is the highest volume procedure in medicine[1] and testing volumes are growing each year[2 3]. Previous research has shown that approximately 20% of tests are ordered unnecessarily and at least 15% of tests are repeated unnecessarily[4 5]. Misuse of laboratory tests is a major challenge impacting sustainability of health care[6 7]. Inappropriate overuse of laboratory tests reflects a wasteful clinical practice that threatens the value of health care, may result in medical errors, potential morbidity from follow-up investigations and interventions[4]. Thus, understanding the frequency and correlates of potentially redundant laboratory testing is useful to identify areas for quality improvement initiatives.

Patients with suspected autoimmune inflammatory disease often undergo a diagnostic serologic work-up that may include anti-nuclear antibody (ANA) testing. ANA is a sensitive test for systemic lupus erythematosus (SLE), thus it is appropriate to order this test to screen in the presence of signs or symptoms of SLE or other systemic autoimmune rheumatic diseases (SARDs)[8]. However, ANA has a low specificity and can be seen in other SARDs, other conditions, and healthy individuals, making its interpretation challenging[8]. Inappropriate ANA testing may cause confusion and anxiety among patients, and may even lead to over diagnosis, over treatment, unnecessary consultations, and avoidable costs to patients and payers[9-13]. ANA tests are useful only as an adjunct to support the clinical impression and are not useful in monitoring disease or relapse, thus it may also be inappropriate to order repeat ANA tests, especially if the previous test was already positive[7 14]. Recommendations to limit repeat ANA testing have been endorsed[15-17]. Moreover, given the rare incidence of SARDs[18-20], and previous research suggesting that ANA tests are often ordered serially and/or in the setting of low pretest probability[9 21 22], understanding the patterns of ANA testing in both primary and specialty care will be useful to inform quality improvement initiatives assessing

the appropriateness of ANA testing. Therefore, our aim was to assess the frequency and correlates of repeat ANA testing in the setting of a single-payer universal healthcare system.

METHODS

Design and Setting. We performed a retrospective study using linked health administrative databases in Ontario from 2008 to 2016. Ontario is a large, diverse province that constitutes approximately 40% of Canada's population, with 13 million residents in 2015[23 24]. All residents are covered by a universal, single-payer, public health insurance that includes hospital care and physicians' services.

Sources of Data. ANA tests (including dates, tests results and ordering physician) were identified using Logical Observation Identifiers Names and Codes (LOINC) from the Ontario Laboratories Information System (OLIS), a nearly population-wide database of laboratory test results in Ontario. Patients with ANA tests were linked to the Ontario Health Insurance Plan (OHIP) Claims History Database to identify diagnoses (according to a modification of the 8th revision of the International Classification of Diseases (ICD)) associated with physician services, and to the Canadian Institute for Health Information Discharge Abstract Database to identify hospital admissions. We identified patient demographic information from the OHIP Registered Persons Database. Ordering physician specialty was identified by linking with the ICES Physician Database (IPDB), which is a validated physician registry.

These datasets are linked using unique, encoded patient and physician identifiers and are securely held and analyzed at ICES (www.ices.on.ca). ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act (PHIPA). This study was authorized under section 45 of PHIPA, which does not require review by a Research Ethics Board.

Participant Eligibility. Patients were excluded if they were <18 years of age, had missing patient or physician identifiers, lived out of province, or died on the date of their first ANA test.

Outcome Measures. Tests were classified as potentially redundant if they were repeated within 12 months of a previous test or repeated subsequent to a previous positive test result. Our primary outcome was any test performed within 1 year of a previous test. Our secondary outcome was any repeat test in which the previous test was positive.

Covariates. Patient-level covariates included age, sex, income quintile as a proxy for socioeconomic status based upon patients' postal code and census neighbourhood income quintile), rural versus urban residence, regional health services planning areas (Local Health Integration Networks, year of testing, hospitalization in the 6 months prior to testing, Charlson comorbidity score, and diagnoses codes for connective tissue diseases (OHIP codes 710 or 695). Physician-level covariates included specialty (rheumatologist, internal medicine, family medicine or other), age, sex, whether they were international medical graduates, and if they practiced in academic or community settings.

Statistical Analysis. We assessed the frequency of health system-level, patient-level and provider-level ANA testing, as well as repeat testing for individual patients within 12 months of a previous test. The frequency of total ANA tests performed, positive test results, and repeat ANA tests performed with 12 months of a previous test was determined overall and by ordering physician type (stratified by family physicians, rheumatologists, internal medicine, and all other practitioners). Repeat testing overall (regardless of who performed the previous test) and repeat testing by the same provider who performed the previous test were separately determined. Percentages were expressed using the denominator for the total number of ANA tests, and the total number of patients with ANA tests, separately. Time intervals between repeated ANA testing were assessed in relation to preceding negative or

positive test results. We assessed patient characteristics for those with multiple ANA testing to those who only received one test.

To assess patient and provider-level factors associated with the odds of repeat testing within 12 months of a previous test, as well as any repeat test in which the previous test was positive, we fit two separate marginal logistic regression models by means of generalized estimating equations (GEE), both models accounting for physician demographics and patient demographic and clinical characteristics (the above aforementioned covariates). The primary analysis focused on all repeat testing irrespective of the provider who ordered the previous test. A sensitivity analysis was performed to assess correlates of repeat ANA testing confined to the same provider ordering the previous test.

RESULTS

Patterns of ANA Testing. In total, 587,357 ANA tests were performed between 2008 and 2016, and 82,332 (14.0%) were repeat tests within 12 months of a previous test, and 126,322 (21.5%) tests had a positive test result, table 1, with a total 74,848 (17.1%) tests being positive on their first test. We identified 7,084 physicians who performed ANA testing of which 188 were rheumatologists, and 4,643 family physicians. Family physicians ordered 358,422 tests (61%) and rheumatologists ordered 65,071 tests (11%). Compared to other care practitioners, rheumatologists had the highest frequency of positive test results and performed more repeat tests within 12 months.

Among a total 164,913 repeat tests during the study period, 28,515 (17.3%) tests were performed within 3 months of the previous test, and 81,058 (49.2%) within 12 months (Figure 1). Among 81,058 tests repeated within 12 months, 33,574 (41%) had a preceding positive result.

Patient Characteristics. The 587,357 ANA tests were performed on 437,966 patients, 346,282 (79.1%) had only 1 ANA test, and 91,684 (20.9%) patients had multiple ANA tests performed (63,084 (14.4%) had only 2 tests, 17,000 (3.9%) had only 3 tests, 5,857 (1.3%) had only 4 tests, and 5,743 (1.3%) had 5 or more tests). Of the 437,966 patients who underwent ANA testing, 294,130 (67.2%) were female with a mean (±SD) age of 52.4 (16.3) years.

Only 74,849 (17.1%) had a positive ANA on their first test. Among 61,684 (67.3%) patients who received multiple ANA tests and their initial test was negative, their subsequent ANA tests did not turn positive.

Comparing 346,282 patients with single ANA testing to 91,684 patients who had multiple repeat ANA testing (Table 2), a higher percentage of females (65.4% vs 73.9%), and presence of a query or confirmed diagnoses of connective tissue diseases (3.9% vs 11.4%) was observed among patients with multiple ANA testing.

Patient and Physician Factors Associated with Repeat ANA Testing. Table 3 provides patient and physician characteristics associated with potentially redundant ANA testing. Family physicians, internal medicine specialists, and all other care practitioners were significantly less likely to order repeat testing within 1 year, or repeat testing after a positive test result in comparison to rheumatologists. When we confined our analyses to focus on only repeat testing performed by the same physician, odds ratios (OR) remained significant. Physician demographics did not appear to be significantly associated with repeat testing, with the exception of internationally-trained medical graduates being less likely to order repeat testing within 12 months (adjusted OR 0.81 95% CI 0.70,0.93), and repeat testing after a previous positive test result (OR 0.75 95% CI 0.63,0.88).

Female patients, those with a higher socioeconomic status and greater comorbidities were more likely to undergo repeat ANA testing within 12 months. Individuals with suspected or confirmed connective tissue disease were significantly more likely to undergo repeat ANA

testing within 12 months (OR 2.20 95% CI 2.01, 2.41) for any physician, (OR 3.08 95% CI 2.70,3.51) for the same physician, and 4 to 5 times more likely to undergo repeat testing after a previous positive test result.

INTERPRETATION

We performed a population-based study assessing the frequency and correlates of repeat ANA testing in the setting of a single-payer universal healthcare system. Over a quarter of ANA tests were repeat tests, and 14% were potentially redundant repeat tests performed within 12 months of a previous test. Family physicians ordered the most ANA tests however, rheumatologists were more likely to order repeat tests and repeat testing after a positive test result than other care practitioners. Moreover, the volume of ANA testing performed in Ontario, Canada far exceeds the number of expected new cases of connective tissues diseases at the population-level raising concerns of potential overuse of ANA testing performed on patients. Future research investigating what clinical features compel physicians to order ANA could speak to the clinical appropriateness of the high number of ANAs ordered. Overall, our novel findings will be useful to inform quality improvement initiatives related to the appropriateness of ANA screening and repeat testing.

Our study is consistent with previous studies showing that ANA testing is pervasive in the context of rheumatology practice[12 13 21 22 25-27]. We also observed similar frequencies of ANA positivity in our sample and also identified that family physicians order the majority of ANA tests[21 26]. Our findings show that rheumatologists were most likely to perform duplicate testing, which is consistent with a recent Canadian study[21]. However, the proportion of potentially redundant repeat ANA testing in our sample is higher than previous studies[21 26 28]. Potential explanations for the higher frequency of repeat ANA testing in our sample may be a

reflection of our ability to capture the majority of tests performed across providers and testing centers in Ontario, and the universal healthcare system in which this study was performed.

There may be multiple reasons why rheumatologists order repeat ANA tests, including issues surrounding access to and perceived accuracy in previous results. Yet, a recent Canadian survey identified that many rheumatologists feel that they are correctly ordering ANA, and that the Choosing Wisely lists do not apply to them since only family physicians inappropriately order ANA test[29]. However, in one Canadian city, rheumatologists were found to be the third highest laboratory spenders per physician by specialty[30] raising concerns over the volume of laboratory testing being performed on their patient populations. Improving the appropriateness of rheumatology laboratory testing is a priority of Choosing Wisely campaigns[15 17], where the American College of Rheumatology's Pediatric Choosing Wisely recommendation is to not repeat a confirmed positive ANA in patients with established SLE or juvenile idiopathic arthritis (JIA)[31]. Besides autoimmune eye disease screening in JIA, there is no evidence that ANA is valuable in the ongoing management of SLE or JIA once a diagnosis is made. This is true in adults as well, where widely established evidence shows that repeat ANA has little clinical value in monitoring disease activity or predicting a flare in SARDs[14 32 33]. Thus, serial ANA testing is not recommended in patients with a known positive ANA.

Fortunately, unnecessary test repetition is readily modifiable both through increasing education and awareness of overuse, and by enhancing access to outside health records and sharing results [5]. Targeted strategies can be highly effective in improving appropriate ANA testing[28]. There is evidence that multiple, linked interventions coupled with computerized order set modifications can affect lasting change in ordering behaviors[34]. In one study, a combination of education and feedback on ANA test ordering patterns was successful in significantly decreasing ANA testing, repeat ANA test ordering, and variation in test ordering

practices between rheumatologists[28]. Our findings will inform quality improvement initiatives related to the appropriateness of ANA testing.

The strength of our study is that it includes a large population, reflecting real-life clinical practice. A limitation is that we do not have clinical data available to comment on the reasons for repeat testing. While we were unable to determine the clinical reason to support repeat testing, many patients with suspected or confirmed connective tissue diseases had repeat testing. We were also unable to access ANA titres, subserologies, or testing which was ordered but not performed by the patient. We did not study the issue of underscreening in targeted populations, which is another form of poor quality of care that may result in unnecessary downstream health care spending associated with delayed diagnosis and undertreatment. Finally, this study was conducted in one province of Canada but over use of laboratory tests is a global issue.

In summary, we identified a significant number of potentially redundant ANA testing, with rheumatologists most likely to perform repeat testing. A large proportion of repeat ANA tests had a preceding positive and were repeatedly performed by the same physician. The possible reasons for this repeat ordering are varied but it is clear that there is a role for reducing repeat ANA ordering in clinical practice.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual contact, and all authors approved the final version to be published.
Study conception and design. Shirley Lake, Zhan Yao, Natasha Gakhal, Amanda Steiman, Gillian Hawker, Jessica Widdifield
Acquisition of data. Zhan Yao, Gillian Hawker, Jessica Widdifield
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Figure 1. Number of Repeated ANA Tests by time interval

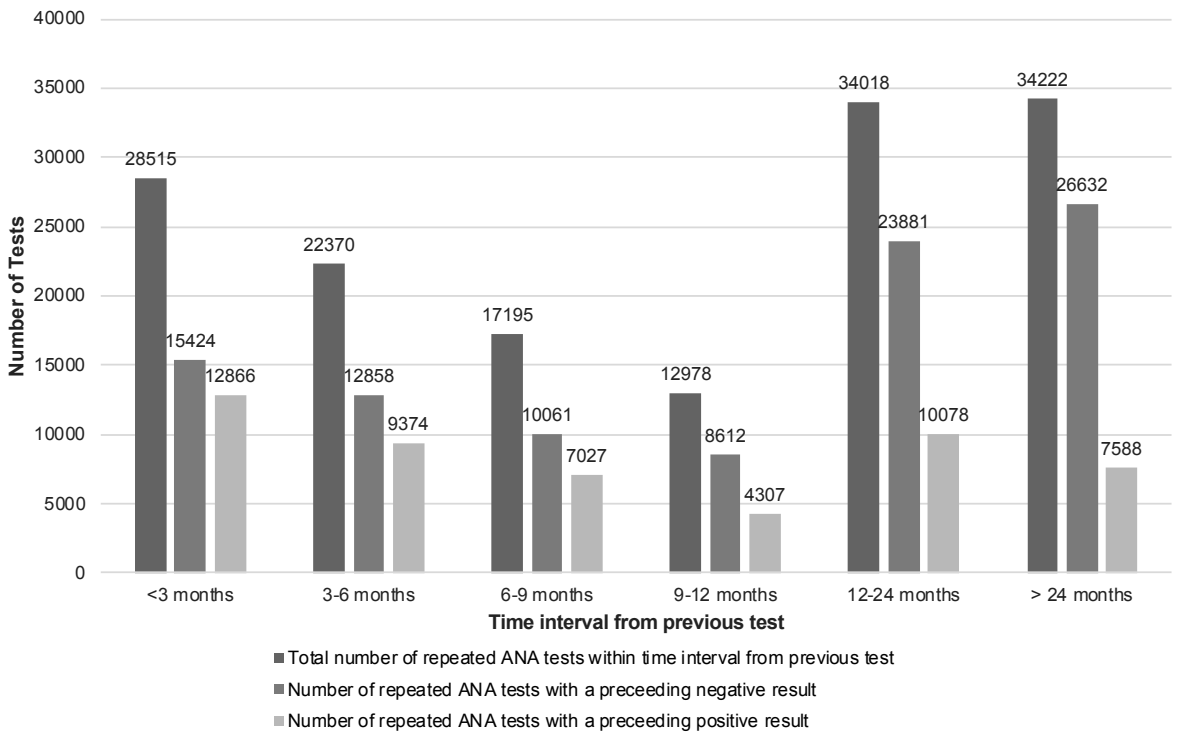

Table 1. Frequency of total and repeat ANA tests overall and by ordering physician type

	Total	Family Physicians	Rheumatologists	Internal Medicine	All other practitioners
Care Practitioners performing ANA tests					
Number	7,136	4,643	188	313	1,992
Percent of Total Number of Providers	100%	65.1%	2.6%	4.4%	27.9%
Volume of ANA Tests					
Number	587,357	358,422	65,071	26,409	137,455
Percent of Total Number of Tests	100%	61.0%	11.1%	4.5%	23.4%
Positive ANA Test Result					
Number	126,322	64,262	28,393	5,884	27,783
Percent of Positive Results out of Total Number of Tests	21.5%	17.9%	43.6%	22.3%	20.2%
Repeat ANA tests within 12mo regardless of who performed the previous test					
Number	82,332	32,994	23,507	4,707	21,124
Percent of Repeat Tests within Each Provider Type	14.0%	9.2%	36.1%	17.8%	15.4%
Repeat ANA tests within 12mo by same provider type who performed the previous test					
Number	51,411	25,213	13,093	1,656	11,071
Percent of Repeat Tests within Each Provider Type	8.8%	7.0%	20.1%	6.3%	22.3%

Table 2. Characteristics of Ontario Patients with ANA tests, n (%) unless otherwise indicated

	Total	Only 1 ANA Test	Multiple ANA Tests
Number of patients with ANA tests	437,966	346,296 (79%)	91,691 (21%)
Mean (SD) age, years	52.43 (16.30)	51.9 (16.5)	54.5 (15.3)
Female	294,130 (67.2%)	226,363 (65.4%)	67,767 (73.9%)
Connective tissue disease[1]	24,037 (5.5%)	13,610 (3.9%)	10,427 (11.4%)
Hospitalization in the preceding 2 years of index date	66,345 (15.1%)	51,204 (14.8%)	15,141 (16.5%)
Urban residence	378,822 (86.5%)	299,480 (86.5%)	79,342 (86.5%)

[1]Presence of or testing for connective tissue disease from 1 year prior to 6 months after index date

Table 3. Provider and Patient Characteristics Associated with Repeat ANA testing within 12 months, and repeat testing after a positive test presented as Adjusted Odds Ratios (ORs) with 95% Confidence Intervals (CIs)

Factors	Any Physician		Same Physician	
	Repeat Testing within 12 months of a previous test	Repeat Testing after a prior positive test	Repeat Testing within 12 months of a previous test	Repeat Testing after a prior positive test
Physician Characteristics				
Family physicians (Ref = Rheumatologists)	0.26 (0.22,0.31)	0.23 (0.20,0.28)	0.80 (0.64,1.00)	0.55 (0.44,0.69)
Internal Medicine (Ref = Rheumatologists)	0.59 (0.44, 0.79)	0.58 (0.44,0.76)	0.63 (0.47,0.85)	0.66 (0.50,0.87)
All other practitioners (Ref = Rheumatologists)	0.39 (0.32,0.48)	0.33 (0.26,0.42)	0.63 (0.47,0.84)	0.56 (0.42,0.73)
Physician age ≤ 50 years (Ref = >50 years of age)	0.98 (0.88,1.10)	0.90 (0.79,1.03)	1.29 (1.15,1.46)	1.12 (0.97,1.29)
Female physician gender (Ref = male)	0.93 (0.84,1.03)	1.05 (0.93,1.19)	0.95 (0.85,1.07)	1.10 (0.96,1.27)
Academic Centre (Ref = community practice)	1.53 (0.87,2.69)	1.32 (0.83,2.12)	1.53 (0.94,2.48)	1.33 (0.89,1.98)
International medical school graduate (Ref = Canadian)	0.96 (0.87,1.07)	0.91 (0.80,1.05)	0.81 (0.70,0.93)	0.75 (0.63,0.88)
Patient Characteristics				
Patient Age	1.01 (1.00,1.01)	1.00 (1.00,1.01)	1.01 (1.01,1.01)	1.01 (1.00,1.01)
Female Patient Sex (Ref = male)	1.29 (1.25,1.34)	1.82 (1.73,1.91)	1.29 (1.23,1.36)	1.83 (1.72,1.94)
Income quintile[1] (Ref = 1 lowest)				
2	1.03 (0.99,1.07)	1.06 (1.00,1.12)	1.05 (1.00,1.10)	1.06 (0.99,1.15)
3	1.05 (1.01,1.10)	1.12 (1.06,1.19)	1.04 (0.99,1.09)	1.10 (1.02,1.19)
4	1.07 (1.03,1.12)	1.19 (1.12,1.26)	1.04 (0.99,1.10)	1.16 (1.07,1.25)
5 (highest)	1.08 (1.03,1.12)	1.17 (1.10,1.25)	1.02 (0.97,1.07)	1.10 (1.01,1.19)
Urban residence (Ref = rural)	0.93 (0.86,0.99)	0.96 (0.89,1.05)	1.01 (0.93,1.09)	1.03 (0.94,1.13)
Connective tissue disease[2]	2.20 (2.01,2.41)	4.18 (3.70,4.73)	3.08 (2.70,3.51)	5.37 (4.69,6.14)
Hospitalization in previous 6 months	0.95 (0.89,1.00)	0.92 (0.83,1.02)	0.92 (0.84,1.01)	0.94 (0.80,1.10)
Charlson Index[3] (Ref = 0)				
1	1.17 (1.10,1.25)	1.14 (1.03,1.26)	1.20 (1.10,1.30)	1.18 (1.04,1.34)
≥ 2	1.11 (1.02,1.21)	0.97 (0.86,1.09)	1.16 (1.05,1.29)	0.98 (0.85,1.13)

Also adjusted for year of testing as a covariate;[1]Income quintile based upon subjects' postal code and census neighbourhood income quintile
[2]Suspected or confirmed connective tissue disease based on diagnosis codes;[3]Charlson comorbidity score (with a 2-year pre-index lookback period)