CMAJ Open 2019-0148 Reviewer comments and author responses

Title: The frequency of repeat antinuclear antibody (ANA) testing in Ontario, Canada: a population-based descriptive study			
AUTHORS: Shirley Lake MD MSc, Zhan Yao MD MS, Natasha Gakhal MD MSc, Amanda Steiman MD MSc, Gillian Hawker MD MSc, Jessica Widdifield PhD			
	Reviewer 1: Dr. Elizabeth Arkema This was a nicely written and straightforward descriptive study about the frequency of ANA testing in Ontario. I have no major comments for revisions, but a few questions for clarification.	**Author's comments**	
1	The authors write that the ANA test results were collected – is this marked as positive or negative or was the actual titre available? What was the cutoff used for "positive"?	As it is difficult to standardize the ANA tests between laboratories, we used each lab's reported interpretation (positive or negative). We have clarified this in the discussion as follows: "As it is difficult to standardize the ANA tests between laboratories, we used each laboratory's reported interpretation (positive or negative) and thus were unable to assess ANA titres which could potentially influence physicians' repeat testing."	12

2	Is it just one type of ANA test used throughout the period?	We only assessed one type of ANA test (in Serum); We did not assess ANA tests done on other body fluids e.g. plueral, peritoneal, pericardial fluids.	
	Reviewer 2: Natalie McCormick, Ph.D. Post-Doctoral Research Fellow, Mongan Institute, Department of Medicine, Massachusetts General Hospital, Boston MA USA Thank you for preparing this manuscript on the population-level frequency and correlates of repeat ANA testing. The topic is relevant to current efforts in addressing low-value healthcare consumption and reducing costs. You have leveraged a rich source of data for assessing these testing patterns on a large scale and illustrating the magnitude of this problem. The figure is effective at showing the distribution of repeat tests since the index test and declining proportion of preceding positive results. 1. However, I think it would be even more effective to report the impact of redundant testing in monetary terms. These tests may not cost much individually, but it adds up. Such an estimate was made in the BC ANA testing protocol, where the per-test cost was $23.82, but total annual spending exceeded $2.2 million. Of course, a small proportion of the tests (and spending) would be appropriate, but even a general estimate would help convey the scale of this issue. 2. I also think it would be helpful to include more background information about the clinical guidelines for ANA testing. It was explained well in the Introduction about when an ANA test should be ordered (i.e. clinical suspicion of SLE) and the problems stemming from its high sensitivity but low specificity for SLE. But it was not clear when a repeat test would be warranted, and if it makes a difference whether the initial result was negative or positive. I inferred that repeat testing within 12 months of a positive test was not useful, but what about repeat tests several years after the initial	1. Regarding impact of testing in monetary terms, Dr. McCormick makes an excellent suggestion and we have added this statement to the discussion, Paragraph 4: "It is difficult to extrapolate exact costs associated with repeat testing. In Ontario, an ANA test alone costs $6.85 per test equating to $1,129,654.05 associated with the 164,913 repeat tests performed during the study period. However, in addition to the direct costs related to the test itself, there are immediate direct labour costs (e.g. Phlebotomists), indirect labour costs (e.g. administrative), direct material costs (e.g. collection needles, tubes), and indirect material costs (e.g. facilities, analyzer). Furthermore, the direct physician component includes the time spent by the physician to analyze and interpret the results, and communicate with the patient. Potential downstream costs could be incurred, such as unnecessary specialist consultations." 2. We have added additional background to the introduction about the indications for ANA testing. We cannot draw conclusions as to <u>why</u> repeat testing was done throughout the study (rather that repeat testing does occur, which may be potentially redundant). Given the heterogeneous makeup of the study population, our inability to link ANA testing with detailed clinical diagnoses and underlying symptoms (i.e. reasons for testing), and it's expected than up to 20% of the healthy population have a positive ANA, it's difficult to draw further inferences beyond what our study aimed to address. 3. The nature of our laboratory data source limits our ability to accurately assess temporal trends (the provincial coverage of OLIS increased over time so earlier time period would be weighted differently).	10-11, 3

	test? How many tests would you have anticipated be positive? Half the tests you identified were conducted more than 12 months after the previous one. Is there an expectation that negative results would turn positive? This information would help readers interpret the findings. 3. In addition, with the study period spanning 2008-2016, I'm wondering if there were any temporal changes in testing patterns. Perhaps redundant testing has slowed down? The Choosing Wisely recommendations were developed and released over the later part of the study period, and increased uptake of EMRs may have made it easier for physicians to access the results of previous tests. I see year of testing was included in the regression models as a covariate, but I think it could be useful to perform an exploratory analysis comparing patterns across two or three subsets of the study period. Please see some additional comments and questions below:		
1	Introduction: The BC Ministry of Health published an ANA testing protocol in June 2013 (https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/ana-testing) which was cited in the CRA Choosing Wisely recommendation about ANA testing. Is there similar guidance/protocols for Ontario physicians?	The Ontario Ministry of Health has not published guidance/protocols for Ontario physicians. We cite the BC testing protocol as it's a valuable resource that Canadian physicians may be accessing.	
2	Methods, page 10, Covariates: Could you please give more detail on how CTD diagnoses were defined? Was only one code required? From inpatient or outpatient? You provide more detail in the footnote of Table 2; if there isn't enough room in the main manuscript, perhaps you could direct readers to this table.	We determined whether patients had at least 1 OHIP code 710 (connective tissue disease) or 695 (lupus) from 1 year prior to 6 months after the test date as a proxy for testing or confirmation of connective tissue disease. OHIP codes are not very specific to different types of connective tissue diseases (710 covers all). Like all diagnosis codes in billings claims data, these codes may reflect testing for these conditions or individuals confirmed to have a connective tissue disease. We have added addition detail under Covariates and updated the description in Table 2.	5

3	Methods, page 10, Covariates: How was academic vs. community practice setting defined? Could some physicians have fallen under both?	We have clarified under covariates: "academic or community settings (determine by each physician's primary practice location based on postal codes linked to an academic hospital location)." Physicians can have more than one practice location; however we are only able to assess primary practice location.	5
4	Methods, top of page 11: For readers who may not be familiar with the term "marginal logistic regression", could you please provide a short explanation? You could perhaps add "population-averaged" or "which informs about the population-average" in parentheses.	To the methods we have added: "The results of the regression analysis are expressed as odds ratios (ORs) and their 95% confidence intervals (CIs), representing the population-averaged effects of covariates on each outcome of interest."	6
5	Methods, top of page 11: Assuming this is true, I think it would be worthwhile to point out that the GEE models accounted for repeated measures (tests performed) within patients and within providers?	We have made this correction. Please see detailed response above to Editorial Comment #21.	6
6	Results, page 12, paragraph 1, final sentence: This sentence is not entirely clear to me but suggests that 100% of people who initially tested negative and had a repeat test were also negative on the repeat test. Is that correct?	We have revised this statement: "Among 91,684 patients who received multiple ANA tests, 61,684 (67.3%) patients had their first test reported as negative, and among these, only 4,641 (7.5%) patients had a subsequent positive test result at a later date."	8
7	Results, page 12, paragraph 2 "presence of a query or confirmed diagnoses of connective tissue diseases": Did you have a means of differentiating queries for CTD diagnoses from confirmed diagnoses, or is this wording just acknowledging that the diagnosis may have been recorded but not confirmed?	Like all diagnosis codes in billings claims data, these codes may reflect testing for these conditions or individuals confirmed to have a connective tissue disease.	5
8	Results: When the repeat test was ordered by a different provider than the first, how often was it a referral from a family physician to a rheumatologist, vs. one family physician to another?	We have added the following to the results to address this question (keeping in mind that we do not have access to referral information in administrative data): "In our analysis among those patients with only two ANA tests (n=63,084), we identified 43,706 patients in which a family physician ordered the initial test, with 5,461(12.5%) patients having their repeat test done by a rheumatologist and 30,168 (69.0%) patients having a subsequent test done by a family physician."	8

9	Discussion: It was intriguing how being an international medical graduate was a significant (negative) correlate of repeat testing. Is there any other literature on international medical school graduates and provision of redundant/potentially low-value care available for comparison?	See response to Editorial Comment #16; Due to word limits, we are not able to comment on the literature for each correlate of repeat testing.	n/a
10	Table 1: Could you please list some of the specialties of the "Other Practitioners" who ordered ANA tests most frequently? Were ER physicians and OB-GYNs included? Altogether, this category accounted for a non-negligible percentage of providers (28%), though I realise the contribution from individual specialties may have been small.	All other physicians were grouped into the other category (including ER and OB). In the results we have added this statement: "The top specialties within the Other category (Table 1) who ordered ANA tests in descending order were: gastroenterology (n=22,239, 3.8% tests), neurology (n=20,120, 3.4% tests); dermatology (n=16,331, 2.8% tests); and nephrology (n=14,484, 2.5%)."	7
11	Table 2: It says on page 10 and in Table 3 that hospitalisations were counted within the six months before index date, but here it says within two years. Could you please clarify?	We assessed the n (%) who were Hospitalized in the 6 months prior to entry (use DAD); and we computed the Charlson index with a 2-year look period.	5
	Reviewer 3: Dr. Cheryl Barnabe, University of Calgary, Medicine The research team has studied a very pertinent question in the Canadian healthcare system and has taken advantage of linking several datasets in Ontario for their analysis.		
1	Introduction: The rationale for the study is well presented and justified. The 4th sentence of the 1st paragraph has a structural issue that requires correction.	We have corrected this sentence as follows. "Inappropriate overuse of laboratory tests reflects a wasteful clinical practice that may threaten the value of health care, may result in medical errors, and contribute to potential morbidity from follow-up investigations and interventions"	3
2	Methods: Verify that your ICD edition is correct (should it be ICD-9-CM) which is the Canadian Modification?	Ontario billing claims use OHIP codes which are slightly modified from the ICD8/9 versions.	4
3	Methods: Can you share/further justify why you chose your primary outcome to be repeat testing within 12 months specifically, as opposed to any repeat testing during the study period? There is no mention of excluding people who did not have 1 year of	While there are no endorsed quality indicator metrics for ANA testing yet, repeat testing within 12 months was chosen based on this outcome used in previous studies. Such as:	5

	registration in the Ontario system in your participant eligibility, wouldn't this be important with that outcome determination? In the Covariates paragraph there is an error with brackets to be corrected. I also wonder if the understanding of this situation might be advanced by including a specific outcome of ANA re-testing due to hospitalization, rather than hospitalization in the 6 months prior to testing as a covariate. What about year of testing as a covariate? There may be important shifts related to changing rheumatology practice paradigms, institution of triage protocols, Choosing Wisely that could account for changes in ANA testing over the study period.	Lesuis, N., Hulscher, M.E.J.L., Piek, E., Demirel, H., van der Laan-Baalbergen, N., Meek, I., van Vollenhoven, R.F. and den Broeder, A.A. (2016), Choosing Wisely in Daily Practice: An Intervention Study on Antinuclear Antibody Testing by Rheumatologists. Arthritis Care & Research, 68: 562-569. doi:10.1002/acr.22725 Additionally, based on clinical judgement, tests repeated outside a 12-month span may reflect the onset of new clinical signs and symptoms and thus may not be redundant. However we report both the number of repeat tests within <12 months and without this cut off. Our primary outcome definition was any repeat test within a 12-month period. We did not exclude “people who did not have 1 year of registration in the Ontario system” as this eligibility criteria would have been important if we used an inception cohort design. In the Covariates paragraph, we have added the missing bracket. We used hospitalization in the 6 months prior to testing as a proxy of re-testing due to hospitalization. We have added year of testing (as a covariate) to Table 3.	
4	Results: I would suggest major revisions to this section to improve the presentation of results.	We have made revisions to the results (based on all reviewer feedback), and revised the headings to ANA testing-level results, and patient-level results.	7
5	Results: With regards to the first sentence, could this data be presented in a flow diagram-type figure to make it more clear to follow? I'm also wondering if there is a denominator issue in the presentation of your results - for example it would make your results much more striking to show the proportion of repeated tests that we knew were already positive (which I interpret as 74848 of 126322 - 59.3%) a significantly higher proportion than 17.1% which is in the text. I think it is more logical to then follow that descriptive section with the number of repeat tests within the different time periods from a previous test, then to move on to the	While it’s an excellent point, we opted not to include a flow diagram as it would be redundant presentation of data in the text. Under statistical analysis, we have edited a statement to add clarity to the different denominators being used in the analyses: “For ANA testing-level results, percentages were expressed using the denominator for the total number of ANA tests. For patient-level results, the denominator includes the total number of patients with ANA tests.”	7

	physician-type data presentation. I also note that in the first paragraph you state there were 82332 tests repeated within 12 months of a previous test but in the current 2nd paragraph you mention 81058 tests - which is correct? I would also suggest revising the 'patient characteristics' section - you have some descriptive information (such as overall number of repeated tests at the individual level) that would fit better in your text where the overall number of repeated tests is presented. Then you could introduce the patient and physician factors associated with repeat testing as the analysis. I also note that there is a strange denominator used when looking at multiple ANA tests at the individual level (63084 had 2 tests; your denominator should be of those with multiple tests, not the entire cohort).	As different denominators are used throughout the reporting of the analyses, we have attempted to ensure denominators are consistently reported throughout the results section.	
6	Results: The significant results for physician age, and urban residence, are not presented in the text. Why?	We are confined by word limit and could only highlight some results from the text. Per CMAJ Open guidelines: “Avoid any redundant presentation of data in tables and in the text of the manuscript.” Therefore we opted to only highlight key correlates related to both repeat testing within 12 months and repeat testing after a previous positive test. Currently, we are over word limit with the additional revisions requested to add to the manuscript.	7
7	Results: I would suggest being more precise with '4 to 5 times more likely' in your final sentence of results.	We have added the OR with 95% CI within the text as follows: “Individuals with suspected or confirmed connective tissue disease were also 4 to 5 times (OR 4.18 95% CI 3.70, 4.73 for any physician, and OR 5.37 95% CI 4.69, 6.14 for the same physician) more likely to undergo repeat testing after a previous positive test result, Table 3.”	9
8	Interpretation: Key results need to be summarized in the first paragraph, not all are presented before a discussion around excess testing begins.	We have summarized more key results in the first paragraph. “We performed a population-based study assessing the frequency and correlates of repeat ANA testing in Ontario, Canada. In our sample, over a quarter of all ANA tests were repeat tests. We further identified a significant number of potentially redundant ANA testing. Among a total 164,913 repeat tests during the study period, half of these tests (49%) were performed within 12 months. Among 73,961 tests repeated within 12 months, 31% had a	9

		preceding positive result. 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. The most significant correlate of potentially redundant testing involved testing among individuals with suspected or confirmed connective tissue disease. 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."	
9	Interpretation: I would concur with the main reasons for excess testing by rheumatologists that are presented, but also consider the impact of research (ie the lupus clinic in Toronto that retests every 3-4 months using non-research labs), and also the impact of introduction of biologic therapy for a variety of immune-mediated diseases that drives pre-post ANA testing for drug-induced SLE.	We agree with this statement and have revised this sentence in our discussion: "There may be multiple reasons why rheumatologists order repeat ANA tests. This may include issues surrounding access to and perceived accuracy in previous results, as well as testing for research participants, and the introduction of biologic therapy for a variety of immune-mediated diseases that may drive pre-post ANA testing for drug-induced systemic lupus."	10
10	Figure 1: Shouldn't the 2nd and 3rd columns add up to the first? They don't.	We have added a footnote to the figure: A small proportion (0.005%-0.8%) of tests had unknown test results and therefore the number of positive and negative tests within each time interval may not add up to the cumulative total.	Figure 1
11	Table 1: Would spell out '12 months'	This correction has been made.	Table 1
12	Table 1: Again check if your denominator is appropriate for your second before last and last rows.	See response #13 below.	Table 1
13	Table 2: Row 1 numbers do not add up	There was a typo in the first row (n=) for the 2 categories which has been corrected. The text in the Results section (reporting on Table 2 was correct).	Table 2
14	Table 2: Only 1 decimal should be used for mean age and SD	The correction has been made thank you.	Table 2
15	Table 2: Please explain 'Presence of or testing for CTD from 1 year prior to 6 months after index date'	In Table 2, we have revised this footnote to state: "We determined whether patients had at least 1 OHIP code 710 (connective tissue disease) or 695 (lupus) from 1 year prior to 6 months after the test date as a proxy for testing or confirmation of connective tissue disease."	Table 2