Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

DATA SUPPLEMENT #1 Lupus Healthcare Provider ETD

Question

Problem: Which health care professional should be most responsible for decision-making and care of lupus patients?

Intervention:	General rheumatologist/lupus specialty clinic or specialist
Comparison:	GP/internist
Main outcomes:	Mortality, morbidity, hospitalisations, surrogate outcomes (e.g. assessment and monitoring of morbidities)
Setting:	Outpatient
Perspective:	Population

Background: *Lupus is a complex and relatively rare disease with a wide range of disease severity and organ involvement. Family physicians and general internists may not have many patients with the disease. As well, subspecialists may be focused on specific organ involvement rather than the multi-systemic involvement seen in many patients. In addition to the variability between patients, most patients will have a fluctuating course with remissions and flares making frequent assessment and adjustment of treatment necessary, and this applies to patients with inactive disease as well[1]. Many patients may require involvement of multiple specialists depending on organ systems affected. In addition, as survival has improved over the past 50 years, the necessity of preventing long-term complications of the disease and its treatment has become increasingly important. Timely investigations and treatment are key to improved outcomes and decreased morbidity[2] . Therefore, the care of lupus patients is complex, perhaps more so than other chronic diseases, and patients may have better outcomes if their care is managed by a rheumatologist or lupus specialty clinic.*

Currently, many of the studies published about caring for lupus patients come from large tertiary care lupus clinics, with relatively little data about lupus patients managed in the community setting. The Lupus Outcomes Study is a longitudinal prospective study of patients with lupus living in the United States that was started in 2002 and continues currently. There are approximately 800-900 patients who are contacted annually to complete a telephone interview. Patients have been recruited from academic rheumatology offices (23%), community rheumatology offices (11%), and community-based sources such as lupus support groups, the Internet, and media advertisements (66%)[3]. Most SLE patients are managed by a rheumatologist, based on data from Lupus Outcomes Study, with 76.6% identifying a rheumatologist as primarily responsible for their SLE compared with 4.2% naming a nephrologist, 11.3% naming an internist, and 6% naming a family practitioner. A small number of patients identified other specialists as primarily responsible for their SLE (dermatologist, haematologist, neurologist, respirologist, orthopaedist, gastroenterologist and endocrinologist). Overall, 78% had seen a rheumatologist in the past year, though of the patients with a severe flare in the past 3 months, this only increased to 81.5%. Another study used the data from the National Ambulatory Care Survey (NAMCS) to identify physician visits and medications prescribed for lupus patients between 1993 and 2010[4]. They found that 43% of outpatient physician visits for SLE patients were to rheumatologists, with 22.2% to internal medicine specialists, 11.2% to general/family practice and 8.2% to dermatology.

	Criteria	Judgement	Research evidence	Additional considerations

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Problem	**Is the problem a priority?**	○ No ○ Probably no ○ Probably yes x Yes ○ Varies ○ Don't know	Our survey and discussion identified the primary lupus caregiver as an important consideration[5]. The 1999 American College of Rheumatology (ACR) guidelines for referral and management of SLE[6] list the major tasks of the primary care physician "to be alert to the possibility of SLE and to make a diagnosis as soon as possible, to manage and monitor patients with SLE who have mild and stable disease, to recognize when referral to a rheumatologist is indicated and to collaborate with the specialist in monitoring disease activity and therapy in patients with moderate to severe SLE" and list reasons for referral to a rheumatologist which include confirm a diagnosis, assess disease activity and severity, provide general disease management, manage uncontrolled disease, manage organ involvement or life-threatening disease, manage and prevent toxicities, and other specific circumstances, including antiphospholipid syndrome, pregnancy and surgery. These guidelines were based on expert opinion from the members of the Ad Hoc committee who were all rheumatologists, but "were reviewed by primary care physicians who concurred with their content". However, it was not addressed in most other lupus guidelines, including the EULAR guidelines[7],[8] ACR lupus nephritis guidelines[9], ACR neuropsychiatric lupus recommendations[10], Asian nephritis guidelines[11]. The Treat2Target guidelines state in their over-arching principles that "management of SLE requires an understanding of its many aspects and manifestations, which may have to be targeted in a multidisciplinary manner"[12]. A recent review on lupus treatment goals recognized the importance of the early suspicion of SLE by PCPs and prompt referral to 'the lupus specialist'.[13] Overall, most groups looking at care of lupus patients focused on specific tests and treatments rather than which physician should be managing the patients[14],[15].	Since the 1999 ACR guidelines, more patients are using a nurse practitioner as their primary health care provider so should be included in any recommendations.
Desirable effects	**How substantial are the desirable anticipated effects?**	○ Trivial ○ Small ○ Moderate x Large ○ Varies ○ Don't know	We found no randomized controlled trials comparing care by different providers for outcomes of mortality, or morbidity. Most of the research evidence is from observational data, predominantly retrospective. From the literature search, over 1200 abstracts were reviewed, and this was supplemented with hand searching the references of key articles of interest. Evidence of benefits for lupus patients to be managed by experienced physicians includes:	Panel discussion of moderate vs large, voted as large.

	Criteria	Judgement	Research evidence	Additional considerations
Undesirable effects	**How substantial are the undesirable anticipated effects?**	○ Large ○ Moderate ○ Small x Trivial ○ Varies ○ Don't know	lower mortality for lupus patients admitted to hospital when patients were cared for by physicians who saw more lupus admissions per year, based on over 15000 patients with SLE admitted to hospital in New York or Pennsylvania in 2000-2002: 4.1% mortality if the physician saw less than 1 SLE admission per year, vs 3.5% among physicians who treated 1-3 per year and 2.5% among physicians who treated more than 3 patients per year[16]. In a study using the California Hospital Discharge Database which included almost 10,000 patients with SLE hospitalized between 1991-1994, there was a marked decreased in-	Panel discussion and vote that harms were trivial.

	Criteria	Judgement	Research evidence	Additional considerations
	What is the overall certainty of the evidence of effects?	Very low ○ Low X○ Moderate ○ High ○ No included studies	hospital mortality for emergency hospitalizations in hospitals with more than 50 urgent or emergent SLE admissions per year compared with hospitals with less experience patients with SLE (1.7% vs 10% if the cause of admission was SLE, 4.2% vs 11.3% for emergency admission)[17]. Earlier referral of lupus patients to a specialized lupus clinic was shown to be associated with lower risk of renal insufficiency (n=281, 46 developed renal insufficiency, relative risk 1.25 (1.05-1.5) per 5 years of disease before referral)[18]. Another group showed fewer hospitalizations after establishment of a lupus clinic (5 years pre and post lupus clinic establishment, for the same 218 patients, rate of hospitalization dropped from 31.1% to 11.7%)[19] . However, a study from London, ON of 102 patients hospitalized for SLE over 3.5 years showed 71% had a rheumatologist, and there was no difference in hospitalizations whether patients had a rheumatologist or not[20] . The Lupus Outcome study also showed no difference in emergency department visits based on primary lupus physician[21]. They did show that better quality of care, assessed by pass rate of quality indicators, was associated with decreased damage[22] . Diagnosis: poor diagnostic accuracy for GPs and PCPs based on subsequent assessment in Autoimmune Disease Center [23] (273 referred for SLE with only 138 confirmed to have disease (kappa 0.34) and of 76 with ANA positivity and no SLE, 39 had been treated with prednisone up to 60 mg/day), referral accuracy of patients referred to an academic rheumatology clinic (kappa 0.46 for SLE referrals)[24] , clinical scenario responses by 51 GPs[25] . Surrogates: Antimalarial use is higher for rheumatologists than other specialists or primary care providers. Lupus patients in Oslo, Norway are largely all referred to a specialist, with management by a rheumatologist alone, or in collaboration with other specialists in 291/325 (90%), and other specialists managing lupus patients in 10%[26]. Patients managed by rheumatologists were more frequently taking hydroxychloroquine (246/291, 84.5%) compared with those managed by non-rheumatologists (4/34, 12%). Similarly, in the Lupus Outcomes study, HCQ users were much more likely to report having a rheumatologist as their main SLE doctor and more likely to have seen a rheumatologist at least once in the past 12 months (88% vs 66%, P<0.0001)[27]. In insured SLE patients in Puerto Rico, more patients followed by rheumatologists than primary care physicians were prescribed hydroxychloroquine (32.6% vs 18.5%)[28] which was similar to data from a German cohort (36.5% for rheumatologists vs 17% for non-rheumatologists)[29]. 4 Osteoporosis: In a German cohort, osteoporosis prevention was more frequently addressed by rheumatologists than non-rheumatologists (55% vs 15% of 1248 patients)[29] . Similarly, in an academic centre cohort from Boston, (34/58, 59% had BMD testing, 36/58, 62% were on calcium and vitamin D supplements, and 6/7, 86% met quality indicators for anti-resorptive or anabolic osteoporosis medications. Having a primary care physician in	**Panel discussion:** Experience of GPs with lupus is very low and some rheumatologists also see very few SLE patients. The experienced lupus caregiver is typically a rheumatologist; however, there are experienced lupus caregivers who are not rheumatologists. Some rheumatologists are not experienced in lupus caregiving and there are some other physicians who are experienced in lupus (eg. nephrologists, dermatologists, immunologists, etc). The panel distinguished between outcomes specific to lupus and outcomes due to comorbidities and related preventive care. Overall benefits were seen for lupus specific outcomes, but potential for harms associated with other comorbidities due to lower screening of these diseases by lupus specialists. Evidence from non-randomised studies showed large effects for critical outcomes leading to moderate quality evidence overall.

	Criteria	Judgement	Research evidence	Additional considerations
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?**	○ Important uncertainty or variability ○ Possibly important uncertainty or variability x Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes		
Balance of effects	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?**	○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison x Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel agreed that benefits probably outweigh harms when rheumatologists manage the specific aspects of lupus care. The panel agreed that for management and prevention of complications and co-morbidities the balance may not favour either the lupus specialist or the PCP, but rather having both involved.
Resources required	**How large are the resource requirements (costs)?**	○ Large costs ○ Moderate costs x Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		**Panel discussion:** SLE is a rare disease so overall costs are generally low even if rheumatologists cost more than primary care providers.

	Criteria	Judgement	Research evidence	Additional considerations
Certainty of evidence of required costs	**What is the certainty of the evidence of resource requirements (costs)?**	○ Very low ○ Low ○ Moderate ○ High x No included studies	No direct cost comparison. Inferred cost savings if you can prevent severe flares as those drive most of the costs, especially with hospital admissions. Also costs of misdiagnosis (ineffective treatment) offset costs of additional outpatient visits. Systemic Autoimmune Rheumatic Diseases in British Columbia: direct costs of SLE patients (27 566 936) divided to 37% hospitalization, 34% prescriptions, 27% outpatient care[37].	
Cost-effectiveness	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?**	○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison x Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		
Equity	**What would be the impact on health equity?**	○ Reduced ○ Probably reduced x Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	From the US data in the Lupus Outcome Study, lupus patients of older age, milder disease and lower socioeconomic status were less likely to follow with a rheumatologist[3]. Previously, lower referral rates to rheumatologists for elderly patients in general have also been shown[38]. This may not accurately reflect the situation in Canada due to differences in insurance in the US, and the larger geographic distances to travel to see a rheumatologist in Canada. In the Canadian Network of Improved Outcomes (CaNIOS) cohort, the most common barrier to care was the distance to a rheumatologist or lupus clinic, identified by 30% of patients[39].	**Panel discussion:** Accessing the lupus caregiver can vary according to geography and access to funds. However, this does not create inequity, but it highlights the inequity issue that may already exist. There are also provincial differences in coverage of travel to see a specialist.

	Criteria	Judgement	Research evidence	Additional considerations
Acceptability	**Is the intervention acceptable to key stakeholders?**	○ No ○ Probably no ○ Probably yes x Yes ○ Varies ○ Don't know	**Primary care:** 1999 ACR guidelines recommended GPs could manage mild SLE so they may not want to refer[6]. However, in a German study, over 60% of SLE patients are referred to rheumatology within 6 months[40]. Almost all SLE patients in Norway are referred**Error! Bookmark not defined.**, 90% of insured lupus patients in Puerto Rico are followed by a rheumatologist**Error! Bookmark not defined.**, and 80% of SLE patients in the Lupus Outcome Study see a rheumatologist. **Patients:** Patients may prefer to see physicians in their community. Significant number of SLE patients were reconnected with rheumatology via general rheumatology outreach clinic to First Nations community (5/144, 3.5%)[41]. **Rheumatologists:** In a survey of lupus specialists who were members of SLICC and/or BILAG "there is a will to practice preventative cardiology among lupus specialists but the details need to be addressed by establishing consensus guidelines."[42] However, more recently such guidelines have been developed and quality assessment studies show that lupus clinics are not as good as primary care in documenting their cardiovascular assessments and treatment[43] with 298 RA or SLE patients, the found an odds ratio of 5.04 (1.57-16.17) for hyperlipidemia screening by a primary care physician compared a rheumatologist, and an odds ratio of 4.54 (1.54-13.39) for diabetes mellitus screening by a PCP compared with a rheumatologist.	**Panel discussion:** Given that the data shows that the majority of patients are seeing a rheumatologist, it is most likely acceptable to primary care providers. It was also felt to be acceptable to patients and rheumatologists. The panel agreed that periodic assessment with disease activity and damage indices are generally beyond the scope of most primary care physicians
Feasibility	**Is the intervention feasible to implement?**	○ No ○ Probably no ○ Probably yes x Yes ○ Varies ○ Don't know	SARDS in BC: 4322 SLE patients (2010), 50 rheumatologist = 86 or 87 lupus patients/rheumatologist which seems quite feasible. In the NACMS study, they found an average of 143.2 visits for SLE per rheumatologist per year.[4] **Survey of rheumatologists in US:** 46% mild, 37% moderate, 17% severe disease so of the 87 patients, almost half may be mild and not need frequent follow-up.	

Conclusions

Type of recommendation	We recommend against the intervention or for the comparison	We suggest against the intervention or for the comparison	We suggest either the intervention or the comparison	We suggest the intervention	We recommend the intervention

	○	○	○	○	x
Recommendation	***We recommend that all adult patients suspected of systemic lupus erythematosus be referred to a lupus specialist, most often a rheumatologist, to confirm diagnosis and be involved in ongoing care [strong recommendation; moderate quality evidence].*** This recommendation considers that the primary care physician continues to provide overall care to the patient, including monitoring for and managing comorbidities**.**				
Justification	There is moderate quality evidence that caregivers with more experience treating SLE (typically the rheumatologist) likely results in accurate diagnosis of SLE when compared with primary care physicians. There is also moderate quality evidence for lower mortality and hospitalization when a lupus specialist is involved in the care of people with SLE. Moreover, recommendations of this committee for monitoring SLE patients include periodic assessment with disease activity and damage indices that are beyond the scope of most primary care physicians (see Disease activity and Damage recommendations). Regardless of care provider, engaging the patient as a member of the care team and participating in shared care models is important.				
Subgroup considerations	We excluded pediatric patients and pregnant patients from the literature search and the discussion.				
Implementation considerations					
Monitoring and evaluation					
Research priorities	Evaluating the pediatric care team for SLE patients.				

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Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

DATA SUPPLEMENT #2 DISEASE ACTIVITY ETD

Question: What are the minimum studies (including disease activity, damage & patient-reported outcomes) that should be obtained at diagnosis and follow up and how frequently should this be collected for the following SLE patients: a. Active lupus patient; b. Stable lupus patient (clinically quiescent)

ETD #1 : DISEASE ACTIVITY STUDIES

Patients: SLE patients

Intervention: SLE disease activity scores

Comparison: SLE disease activity scores or regular clinical monitoring

Main outcomes: Mortality, Damage, SLE Flares, PRO

Setting: Rheumatology clinics in Canada

Background Affecting over 17,000 Canadians (Arthritis Society), SLE is an important rheumatic disease associated with significant morbidity and mortality in Canada (1-3).Given the heterogeneity of the disease, significant variability exists between the main caregivers of SLE (primarily rheumatologists) in diagnosing and managing these patients over time, with lack of consensus on what measures are most useful in monitoring both active and clinically quiescent disease. A recent practice pattern survey of SLE management in Canada confirmed this lack of consensus (4). Applicability of these measures between the clinical and research settings must be considered. Frequency of assessment for active and clinically quiescent SLE patients and attention to possible differences between clinically and serologically concordant or discordant SLE patients, and between the pediatric and adult SLE patients should be paid.

Perspective: Clinical	Basic laboratory testing of SLE is considered part of good clinical practice. Serologic tests at baseline for SLE are typically ordered by the rheumatologist to assist in making the diagnosis. Subsequent lab parameters, including serologic and non-serologic, that may be ordered are included in existing disease activity indices; therefore, a separate search of independent lab parameters was not included in this review. The performance of disease activity and disease damage measures in a clinical setting to quantify the extent of disease is required to help a physician make an informed decision regarding which treatment(s) to choose for a particular lupus patient and for appropriate management of comorbidities. International organizations including EULAR (European League Against Rheumatism) and the American College of Rheumatology (ACR) have identified the need to establish clearer guidelines for the monitoring of SLE with on-going work focussing on different aspects of SLE (5, 6). The current treat-to-target approach in rheumatoid arthritis is also being proposed in SLE, with various panels working to define what these treat-to-target goals should be and what is needed to define remission (7, 8). Existing measures of disease activity include the following: Physician Global Assessment (PGA) of disease activity, BILAG (British Isles Lupus Assessment Group) (9), SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) (10), ECLAM (European Consensus Lupus Activity Measurement) (11, 12), SLAM (Systemic Lupus Erythematosus Activity Measure) (13, 14), , LAI (Lupus Activity Index) (15),, RIFLE (Responder Index For Lupus Erythematosus) (16) and SIS (SLE Activity Index score) (17). Disease damage indices are limited to: SLICC (Systemic Lupus International Collaborating Clinics) /ACR Damage Index (SDI) (18, 19) (Table 1: Instruments). **Subgroup considerations**: (1) Diagnosis/classification; (2) Follow-up/monitoring; (3) Clinically active disease; (4) Clinically quiescent disease; (5) Serologically Active/Quiescent disease, (6) Pediatric versus adult and(7) Damage

	Criteria	Judgement	Research evidence	Additional considerations

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Problem	**Is the problem a priority?**	○ No ○ Probably no ○ Probably yes X ○ Yes ○ Varies ○ Don't know	In Canada, the prevalence of SLE is 51 cases per 100,000 individuals with a 7:1 to 10:1 female sex bias depending on age category (20, 21). Life expectancy in SLE is much shorter (despite overall improvements) than the general population, most evident in patients under the age of 45 (22, 23). Outcome Measures in Rheumatology (OMERACT) recommended the assessment of the following domains in patients with SLE in clinical trials and research settings: (1) lupus disease activity (reversible), (2) damage (irreversible) that has occurred since the onset of SLE in different organ-systems that may have resulted from lupus disease activity leading to organ damage or failure (e.g. renal failure) or lupus therapy (e.g. glucocorticoids induced diabetes) or intercurrent illness (e.g. cancer), (3) adverse events of drugs, (4)health-related quality of life and (5) economic impact (24).	The Canadian Rheumatology Association (CRA) has identified the need to develop recommendations for the diagnosis and monitoring of SLE and established this as a priority with its Guidelines Subcommittee. A 63-question survey of 155 members of the Canadian Rheumatology Association (CRA) recently showed that validated measures of SLE disease activity and damage were regularly used by less than 50% of responders. (4). Twelve percent of responders reported completing the SLICC/ACR damage index. This variation in practice pattern may impact health care delivery to lupus patients (4).

	Criteria	Judgement	Research evidence	Additional considerations
Desirable effects	**How substantial are the desirable anticipated effects?**	○ Trivial ○ Small ○ Moderate X ○ Large ○ Varies ○ Don't know	Table #3: Outcomes of higher disease activity in SLE patients over time The largest data available for mortality and morbidity outcomes in disease activity include the SLEDAI (and associated versions) and the BILAG A systematic literature review "Measuring Disease Activity and Damage with Validated Metrics: A Systematic Review and Meta-analysis on Mortality and Damage Accrual in Systemic Lupus Erythematosus" was performed from which Table #3 data is derived. Further studies which were not meta-analyzable but met the PICO and described the impact of measuring disease activity and damage on outcomes of mortality and damage are available in Table 1 of this manuscript. [submitted to J Rheum for peer review] Table #4: Summary of disease activity measures in SLE **e) Frequency of monitoring in SLE** We performed a systematic review of the literature to evaluate the impact of	While the majority of panel members voted that the desirable effects would be large, a few panel members suggested moderate desirable effects.
Undesirable effects	**How substantial are the undesirable anticipated effects?**	○ Large ○ Moderate ○ Small ○ Trivial ○ Varies X ○ Don't know		Due to the small chance that there could be undesirable effects from overtreatment from measuring disease activity scores, most panel members (12) did not know if there were potential harms while some (6) panel members felt this would be trivial. No intervention studies relating to harms of measuring disease activity exist.

	Criteria	Judgement	Research evidence	Additional considerations
Certainty of the evidence	**What is the overall certainty of the evidence of effects?**	○ Very low X○ Low ○ Moderate ○ High ○ No included studies	different frequency of monitoring for SLE patients (active and clinically quiescent). No articles were found to recommend optimal frequency of monitoring SLE patients to impact prognosis. Flare and persistently active disease are common disease states in SLE (25, 26). A recent study showed that flare or persistently active disease in a year can be present in almost 50% of the followed patients. Moreover,the most commonly involved organ systems were musculoskeletal, cutaneous, renal, immunologic or the nervous system. Hematologic, serosal, vasculitis, and fever manifestations were less common (26). Time to recovery of individual lupus manifestations on standard of care therapy varies among organ systems. The tempo of recovery from proteinuria in LN is slow; in 212 patients studied, 52% recovered from proteinuria within 2 years and an additional 22% recovered within 5 years, for a total of 74% and the level of proteinuria at baseline visit along with other factors predict the time to complete recovery in proteinuria (27).	The heterogeneity of lupus presentations amongst patients prevents projections of rates of disease progression and severity over time, limiting the ability to prescribe a specific frequency of physician visits and therefore predict how patients would perceive this frequency of visit(s). The clinical phenotype of patients with SLE help to determine which patients incur a closer follow up to control their disease activity and flares, e.g. patients with renal replacement therapy continue to be at risk for extrarenal lupus activity. In this group of patients the most common flare was hematologic and those with low C4 levels and younger age at the beginning of renal replacement were risk factors (28) The panel agreed that regular performance of disease activity and damage measures in rheumatology clinics across Canada to manage SLE patients may facilitate earlier treatment choices for patients to prevent damage.
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?**	○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance or values of the main outcomes of interest:** Mortality Critical Damage Critical Morbidity – PRO's such as fatigue, function Flare rate Critical	Research is required to evaluate the importance of patient reported outcomes (PRO's) (eg. fatigue) and the value that people may place on these particular outcomes.

	Criteria	Judgement	Research evidence	Additional considerations
Balance of effects	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?**	○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention X○ Favors the intervention [disease activity measurement] ○ Varies ○ Don't know		The panel was split regarding the balance of effects, with 9 voting that the balance favoured the intervention (disease activity score) whereas 8 voted that the balance *probably* favors the intervention (disease activity score).
Resources required	**How large are the resource requirements (costs)?**	○ Large costs ○ Moderate costs X○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Performance of various disease activity and damage measures vary according to time burden, cost burden, or self-administered by the patient versus performed by clinician, (Table #1). Data collected within disease activity and damage indices include standard questions that are part of the history-taking and physical exam performed in the rheumatology assessment. Presentation in an organized standardized format may in fact organize the clinical encounter to improve clinical efficiency. Uncontrolled disease activity also incur more visits to the specialists, and laboratory/imaging tests which is associated with higher cost in SLE (30). Studies have shown that patients with flares incur higher direct and indirect costs when compared to patients without flares. Moreover, major organ flares (which usually requires hospitalization) are associated with higher disease costs. Thus, treatments that effectively control disease activity and prevent flares may reduce the costs related to flare in SLE and may reduce damage in its costs in SLE (3, 29).	Time: range of time depending on instrument used; real-time delay in labs Training: Initial training required for several disease activity indices; adoption of scoring system may vary depending on practice Labs: certain disease activity scores require some labs beyond good clinical practice (*Good clinical practice room survey:* Complete blood count, routine urinalysis, liver tests, creatine kinase, antinuclear antibody, double-stranded DNA, extractable nuclear antigens, C-reactive protein, erythrocyte sedimentation, C3, C4)

	Criteria	Judgement	Research evidence	Additional considerations
Certainty of evidence of required costs	**What is the certainty of the evidence of resource requirements (costs)?**	○ Very low ○ Low ○ Moderate ○ High X○ No included studies	No cost effectiveness studies located.	
Cost-effectiveness	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?**	○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies X○ No included studies		
Equity	**What would be the impact on health equity?**	○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased X○ Varies ○ Don't know	As of 2008, there were 350 rheumatologists in Canada, or about 1.2 rheumatologists per 100,000 Canadians, about half the number of rheumatologists needed to provide adequate care. As many as 1/3 of Canada's rheumatologists will retire before 2018 (26-27). Increased monitoring of SLE patients with use of disease activity and damage measures may impact the following: (a) demand of rheumatologist's time per patient which slows down patient volume seen; (b) concerns of co-managers of SLE patients (e.g. internists, family physicians) in adapting these measures in regular practice; (c) increased demand for laboratory monitoring which may be limited by health region and lab test availability.	The panel felt that the impact on health equity would vary. Inequity might be increased (1) if there is lack of access to a rheumatologist in particular areas (eg. rural) and/or (2) a rheumatologist did not have experience utilizing a disease activity score. Equity might be increased (1) with increased access to educational tools for disease activity scores and (2) implementation of this recommendation to "level the playing field" with standardized disease activity assessment.

	Criteria	Judgement	Research evidence	Additional considerations
Acceptability	**Is the intervention acceptable to key stakeholders?**	○ No X○ Probably no [Rheumatologist] ○ Probably yes X○ Yes [Patients] ○ Varies ○ Don't know	No consensus exists for the "best" measure for disease activity while one main damage index (SDI) has been used for damage assessment. Different groups suggest using different disease activity measures (e.g. versions of SLEDAI in North American sites compared to versions of BILAG in the United Kingdom) depending on factors including where the original tools were developed and how local practice evolved. Existing measures in SLE for disease activity, damage and heterogenous patient reported outcomes vary in ease of use, time taken, accessibility and all validation parameters (Table 1). . **The Wait Time Alliance of Canada**: Perceived current wait times for patients with suspected or potential SLE were < 1 month (17% respondents), 1-2 months (22%), 3-5 months (13%), and "other" (26%). Comments pertaining to "other" included suggestions that wait times relied heavily on information about disease severity, organ involvement, call and triage responsibilities. An equal number of respondents reported using (43%) and not using (43%) a system for determining mild, moderate and severe SLE and some (13%) chose not to answer the question. Organ involvement and pregnancy was felt to influence the wait time. Based on this, the ideal wait time for new SLE patient was < 1 month. No further consensus or discussion regarding follow up intervals or differentiating between active and clinically quiescent lupus patients. Frequent physician visits in active lupus are standard of care (31)	Change in practice to using a regular composite measure for disease activity/damage (and possibly patient reported outcome) may not be as acceptable to some rheumatologists who perceive this as less feasible in their daily practice. Recommending regular use of disease activity and damage indices may be newer in community and/or rural rheumatology practises or in primary care/internal medicine offices. This may be viewed as prohibitive to busy practises with less support, and long waiting lists.
Feasibility	**Is the intervention feasible to implement?**	○ No ○ Probably no ○ Probably yes X○ Yes ○ Varies ○ Don't know	Performance of current existing disease activity measures (Table 1) varies with respect to feasibility in the clinic setting. Many were developed in research settings also utilized for clinical trials to group or stratify patients and stage their degree of disease activity and damage	Centres collecting outcomes data for SLE research are currently more likely to utilize at least one measure for disease activity/damage/patient-reported outcomes compared to non-research oriented centres. The panel agreed that implementation of a disease activity and damage score for clinical practice is feasible to implement. Education for rheumatologists on a convenient, easy-to-use score (eg. SLEDAI) would be required.

Conclusions

Type of recommendation	We recommend against the intervention or for the comparison	We suggest against the intervention or for the comparison	We suggest either the intervention or the comparison	We suggest the intervention	We recommend the intervention
	○	○	○	X	○
Recommendation	Best clinical practice dictates that all adult and pediatric patients with SLE have a complete history, physical and lab evaluation at baseline and during each follow-up visit. Careful interpretation of the clinical and laboratory findings is required to ensure proper attribution of the signs, symptoms and investigation results towards SLE or other co-morbid conditions. *Remarks:* Best clinical practice includes a complete history and physical examination at baseline, lab monitoring possibly including but not limited to complete blood count (CBC), liver enzymes, creatine kinase (CK), creatinine and glomerular filtration rate (eGFR), urine routine/microscopic (urinalysis), urine protein-creatinine ratio, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complements (C3, C4), anti-double stranded DNA (ds-DNA), antinuclear antibodies (ANA), antibodies to extractable nuclear antigens (ENA), antiphospholipid antibodies (lupus anticoagulant (LAC), anticardiolipin (aCL), and anti-beta-2-glycoprotein-1 (anti-b2GP1) and lipid profile. Follow-up lab monitoring will depend on the patient's clinical status and may include CBC, creatinine and glomerular filtration rate (eGFR), urine routine/microscopic (urinalysis), urine protein-creatinine ratio, CRP and/or ESR, C3, C4, and anti- dsDNA antibodies. *Justification:* Justification: There is no current evidence which compares outcomes when specific tests are performed or not performed at baseline or at follow-up. This best practice statement is therefore based on the utility of results to inform subsequent care of the patient with SLE. For some tests, there is evidence that the results may also be predictive of other health risks (see the following recommendations). ***For adult and pediatric patients with SLE, we suggest assessing disease activity with a validated instrument of disease activity during baseline and follow up visits.*** *Remarks:* This recommendation does not specify what validated instrument should be performed; however, examples of validated instruments that may be used include: SLE Disease Activity Index-2K (SLEDAI)(27) , British Isles Lupus Assessment Group score (BILAG)(28), SLE Activity Measure (SLAM)(29) and others. Several factors influence the choice of a particular instrument including physician preference and expertise, cost, time burdens, and applicability to paediatric populations. All variables in each instrument are derived from a complete history and physical and lab examination which is good clinical practice.				

Justification	The evidence showing that measuring disease activity with validated instruments result in better outcomes compared to best clinical practice (complete history, physical and lab examinations) is low to moderate quality; however, studies show that higher disease activity is associated with small increases in the risk of death and disease damage, and adverse cardiovascular outcomes(30). (see Cardiovascular Recommendations). The guideline panel agreed that using validated instruments may organise the clinical encounter with the patient, incur negligible costs, and be acceptable to patients; however, the use of disease activity instruments may lead to variable equity in sites due to inaccessibility to an experienced user of the tool. The panel expressed concern that disease activity measurement with validated tools could still lead to over-measurement and therefore overtreatment of patients with low disease activity. The recommendation considers resource requirements to be negligible but recognizes variability depending on what score is used. Performing disease activity scores pose a minimal resource burden as they incorporate low costing aspects of clinical care many of which are best practice. While there is some variation on the specific laboratory tests included in the disease activity scores, this variation is minor and performance of specific labs which are part of the disease activity score are standard of care and not resource intensive. Patients would find the performance of disease activity scores acceptable while many rheumatologists probably would not. The lower acceptability to rheumatologists reflects the burden of time in learning the scores and performing them in the clinic setting. Educational tools to facilitate learning of these scores in rheumatology offices is feasible.
Subgroup considerations	Active versus clinically quiescent – not evaluated separately. Pediatric versus adult – not separate between pediatric and adult patients with SLE.
Implementation considerations	Training modules for disease activity score; training by lupus experts; facilitation via lupus centers; dissemination with Canadian Rheumatology Asscociation
Monitoring and evaluation	Evaluation of best practice in rheumatology should be evaluated. Canadian rheumatologists can be monitored to identify what disease activity scores are used and the logistics of implementation in their clinics.
Research priorities	Comparison of outcomes in clinics utilizing various disease activity scores. Why are more rheumatologists NOT completing disease activity scores; pre- and post-CRA surveys Evaluate patient reported outcomes that are more feasible – BILD/LupusQol and determine if these predict outcome and clarify logistics in clinic of utilizing these.

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Table 1. INSTRUMENTS USED IN THE ASSESSMENT OF DISEASE ACTIVITY AND DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS (32, 33)

Tool	Score range	Time frame	Reliability (33, 34)	Validity (34, 34)	Responsiveness (33, 34)	Administrative burden (34)	Refs
Disease activity							
Original instrument: SLEDAI **Derivations[1]:** SLEDAI-2K SLEDAI-2K 30 days SELENA-SLEDAI	0-105 0-105 0-105 0-105	Last 10 days Last 10 days Last 30 days Last 10 days	X	X	X	Cost[2] Time: 15 minutes Requirements: -Training[4] -Laboratory test including hematology (white blood count, platelets), renal (24-hour proteinuria, urine sediment), serologic (Anti dsDNA, C3, C4, CH50), musculoskeletal (myositis: CK or aldolase) -Diagnostic tests and imaging as determined by physician (e.g. echocardiography, ECG for pericarditis)	(10) (35) (36, 37) (38)
Original instrument: BILAG **Derivations:** BILAG-2004	Categories: A = Active, B = Beware, C = Contentment, D = Discount, E = No evidence Response scale: Each question is answered as: 0 = not present, 1 = improving, 2 = same, 3 = worse, and 4 = new	Previous month	X	X	X	Cost[3] Time: 50 minutes Requirements: -Training[4] (glossary) -Laboratory tests including: hematology (hemoglobin, white blood count, neutrophils, lymphocytes, platelets), TTP, direct coomb, hemolysis studies, renal (urine albumin, urine protein, urine creatinine, 24-hours proteinuria) -Diagnostic tests and imaging as determined by physician -Computer	(9, 39) (40,41, 42)
Original instrument: SLAM **Derivations[5]:** SLAM-R	0-86 0-81	Previous month	X	X	X	Cost[3] Time: 15 minutes Requirements: -Training[4] -Laboratory results including: hematology (hematocrit, white blood cell count, lymphocyte count, platelet count), Erythrocyte Sedimentation Rate, renal (serum creatinine, urine sediment, 24-hour proteinuria) -Diagnostic tests and imaging as determined by physician	(14) (43,44)
Damage							
SDI	0-49	Last year[6]	X	X	X	Cost[2]	(19)

						Time: 15 minutes Requirements: -Training[4] (glossary) -Laboratory and diagnostic tests as determined as physician	

ABBREVIATIONS

"X" Confirms that the psychometric properties (validity, reliability or responsiveness) for the instrument have been studied
SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; **SLEDAI-2K** = Systemic Lupus Erythematosus Disease Activity Index 2000; **SELENA-SLEDAI** = Safety of Estrogens in Lupus Erythematosus-National Assessment Trial-SLEDAI; **BILAG** = British Isles Lupus Assessment Group; **SLAM** = Systemic Lupus Activity Measure; **SLAM-R** = Systemic Lupus Activity Measure-Revised; **SDI** = Systemic Lupus Collaborating Clinics (SLICC) - American College of Rheumatology (ACR) Damage Index.

NOTES

1. Adjusted Mean SLEDAI (AMS): AMS was developed to summarize disease activity over time (43). SLEDAI-2K Responder Index 50 (SRI-50): It was developed to identify partial improvement, ≥ 50% in each of the 24 descriptors of the SLEDAI-2K (46).
2. Cost related to the use of the instrument: There is no cost for using the instrument.
3. Cost related to the use of the instrument: There is no cost for using the instruments unless the computerized version is needed; the cost of this version depends on the use of the instrument (academic vs. commercial)(34).
4. Training: Physicians must be trained on the use of the instrument.
5. The Systemic Lupus Activity Questionnaire (SLAQ) was developed based on the SLAM. The SLAQ purpose is to follow on SLE patients who may be at a distance from a center. The SLAQ is filled by the patients as a screening tool for flares requiring further assessment (47).
6. SDI: Damage occurring since diagnosis of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated.

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Question: What is the association of health outcomes with disease activity in systemic lupus patients over time? **Setting**: Adult and pediatric SLE patients
Bibliography: Becker-Merok 2006, Ibanez 2007, Liang 2010, Telles 2013, Wu 2014, Wu 2014, Lin 2012, Nossent 1993, Pons-Estel 2004, Zonana-Nacach 2007, Ibanez 2005, Nossent 2010, Gilboe 2001, Lilleby 2005, Lin 2012, Mikdashi 2004, Mok 2006, Lopez 2012, Stoll 2004, Alarcon 2004, Karlson 1997, Peschken 2009, Toloza 2004
Author(s): Touma, Medina, Pope, Nevskaya, Alabdurubalnabi, Keeling

№ of studies	Quality assessment						Impact	Quality	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Higher SLEDAI predicts mortality (follow up: mean 11.9 years; assessed with: SLEDAI)									
6	observational studies	not serious	not serious	not serious	serious [a]	none	High SLEDAI score was associated with mortality HR 1.14 (95% CI 1.06, 1.22) Number of deaths = 247 Number of patients = 1716 [b,c,d]	⊕⊕⊕◯ MODERATE	CRITICAL
Higher SLEDAI and relationship with SLE disease damage (follow up: mean 8 years; assessed with: SLEDAI)									
3	observational studies	not serious	serious [e]	not serious	serious [f]	none	Higher SLEDAI score at baseline or over time was associated with greater damage (SLICC > 0): HR 1.15 (0.97, 1.38) Number of deaths = 124 Number of patients = 933 [e,g,h]	⊕⊕◯◯ LOW	CRITICAL
Mean total BILAG predicts mortality in SLE patients (assessed with: BILAG)									
1	observational studies	not serious	not serious	not serious	very serious [i]	none	Mean total BILAG score associated with mortality: HR 1.15, p=0.008	⊕⊕◯◯ LOW	CRITICAL
Mean total BILAG predicts damage in SLE patients (assessed with: BILAG)									
1	observational studies	not serious	not serious	not serious	serious [i]	none	Mean total BILAG score associated with new organ damage (SDI > 0) (95% CI 1.02, 1.14) [j]	⊕⊕⊕◯ MODERATE	CRITICAL
SLAM predicts damage in SLE patients (assessed with: SLAM)									
3	observational studies	not serious	not serious	not serious	serious [i]	none	Higher SLAM scores were associated with increased risk of damage (SDI > 0): OR 1.06 (95% CI 1.04,1.08) Number of patients = 1916 [k]	⊕⊕⊕◯ MODERATE	CRITICAL

1. a. Total number of events (deaths) = 247
2. b. 5/6 studies had a Newcastle Ottawa Score of 8, and the remaining 1 study had a Newcastle Ottawa Score of 7.

3. c. Lin et al. (2012) found that a SLEDAI at diagnosis (OR of 1.13 (P=0.003) (95% CI 1.06, 1.22)) was an independent predictor of mortality
4. d. Three studies (Nossent 1993, Pons-Estel 2004, Zonana-Nacach 2007) found a mean SLEDAI score of 7.01 (95% CI 4.11,9.92) in dead SLE patients versus alive SLE patients
5. e. The 95% CI for this meta-analysis which used a random effects model crosses 1; explanations are most likely mathematical as each independent study had HRs with significant 95% CI's; one explanation might be the very tight 95% CI of the Ibanez study in comparison to the other 2 studies.
6. f. Number of deaths was lower
7. g. Three pooled studies (Gilboe 2001, Lilleby 2005, Lin 2012) demonstrated OR 1.08 (95% CI 1.03,1.12) for mortality in patients with higher SLEDAI's
8. h. Two studies confirmed that the mean SLEDAI was higher in dead versus alive patients (mean difference 7.53 (95% 1.35, 13.70)
9. i. No explanation was provided
10. j. Stoll et al 2004 demonstrated an OR of 1.62 (95% CI 1.22, 2.16) for damage using a total BILAG
11. k. Toloza et al. 2004 showed that the mean difference in the SLAM was 2 (95% CI 0.30,3.70) between dead and alive SLE patients

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Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

DATA SUPPLEMENT #3 DAMAGE ETD

Question: What are the minimum studies (including disease activity, damage & patient-reported outcomes) that should be obtained at diagnosis and follow up and how frequently should this be collected for the following SLE patients: a. Active lupus patient; b. Stable lupus patient (clinically quiescent)

ETD #2 : DISEASE DAMAGE STUDIES

Patients: SLE patients

Intervention: SLE Damage scores

Comparison: regular clinical monitoring

Main outcomes: Mortality
Damage
Patient reported QOL

Setting: Rheumatology clinics in Canada

Background Affecting over 17,000 Canadians (Arthritis Society), SLE is an important rheumatic disease associated with significant morbidity and mortality in Canada (1-3). Given the heterogeneity of the disease, significant variability exists between the main caregivers of SLE (primarily rheumatologists) in diagnosing and following these patients over time, with lack of consensus on what measures are most useful in monitoring both active and clinically quiescent disease. A recent practice pattern survey of SLE management in Canada demonstrated this lack of consensus (4). Applicability of these measures between the clinical and research work must be considered. Frequency of assessment for active and clinically quiescent SLE patients and attention to possible differences between the pediatric and adult SLE patients should be paid.
Basic laboratory monitoring of SLE is considered part of good clinical practice. Serologic tests at baseline for SLE are typically ordered by the rheumatologist to assist in making the diagnosis. Subsequent lab

Perspective: Clinical	parameters that may be ordered are included in existing disease activity indices; therefore, a separate search of independent lab parameters was not included in this review. The performance of disease activity and disease damage measures in a clinical setting to define the extent of disease is required to help a physician make an informed decision regarding which treatment(s) to choose for a particular lupus patient. International organizations including EULAR (European League Against Rheumatism) and the American College of Rheumatology (ACR) have identified the need to establish clearer guidelines for the monitoring of SLE with on-going work focussing on different aspects of SLE (5, 6). The current treat-to-target approach in rheumatoid arthritis is also being proposed in SLE, with various panels working to define what these treat-to-target goals should be and what is needed to define remission (7, 8). Disease damage indices are limited to: SLICC-DI/SDI (Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI, SDI), LDIQ (Lupus Damage Index Questionnaire) and the BILD (Brief Index of Lupus Damage) (see Table 1 for descriptions of each measure). Given the large amount of data surrounding the SLICC-DI, and relatively recent development of the BILD/LDIQ, the damage score used for these recommendations will focus on the SLICC-SDI. SLE damage is defined as irreversible change in an organ or system that has been present for at least six months since the diagnosis of SLE. In 1996, the SLICC group and American College of Rheumatology developed this clinical index consisting of 41 items involving 12 organ systems (9). Only items occurring after SLE onset are recorded, but contrary to disease activity, attribution is not evaluated. **Subgroup considerations**: (1) Diagnosis/classification; (2) Follow-up/monitoring; (3) clinically active disease; (4) Clinically quiescent disease; (5) Pediatric versus adult

	Criteria	Judgement	Research evidence	Additional considerations

	Criteria	Judgement	Research evidence	Additional considerations
Problem	**Is the problem a priority?**	○ No ○ Probably no ○ Probably yes X○ Yes ○ Varies ○ Don't know	In Canada, the prevalence of SLE is 51 cases per 100,000 individuals with a 7:1 to 10:1 female sex bias depending on age category (10, 11). Life expectancy in SLE is much shorter (despite overall improvements) than the general population, most evident in patients under the age of 45 (12, 13). Outcome assessment in SLE can be divided into the well-recognized domains of disease activity (reversible), disease damage (irreversible) and the health-related quality of life (HRQoL) that reflects a person's sense of well-being associated with the disease or treatment (14, 15). With standardized mortality (SMR) ratios reduced from 12.6 in the 1970's to 3.5 in the 2000's, attribution of mortality includes both disease activity and organ damage from the disease and medications used (16, 17) and lack of standardized approach which may impact health care delivery to lupus patients (4).	The Canadian Rheumatology Association (CRA) has identified the need to develop recommendations for the diagnosis and monitoring of SLE and established this as a priority with its Guidelines Subcommittee. A 63-question survey of 155 members of the Canadian Rheumatology Association (CRA) recently showed that validated measures of SLE disease activity and damage were regularly used by less than 50% of responders. (Table 1). Twelve percent (12%) of responders reported completing the SLICC/ACR damage index. This variation in practice pattern reflects a lack of consistent evaluation of disease damage suggesting possible suboptimal evaluation of the lupus patient.
Desirable effects	**How substantial are the desirable anticipated effects?**	○ Trivial ○ Small X○ Moderate ○ Large ○ Varies ○ Don't know	Table #2: Outcomes of higher disease damage in SLE patients over time (12, 18-24) A systematic literature review "Measuring Disease Activity and Damage with Validateds Metrics: A Systematic Review and Meta-analysis on Mortality and Damage Accrual in Systemic Lupus Erythematosus" was performed from which Table #2 data is derived. Further studies which were not meta-analyzable but met the PICO and described the impact of measuring disease activity and damage on outcomes of mortality and damage are described here. [submitted to J Rheum for	

	Criteria	Judgement	Research evidence	Additional considerations
Undesirable effects	**How substantial are the undesirable anticipated effects?**	○ Large ○ Moderate ○ Small X○ Trivial ○ Varies ○ Don't know	peer review] Impaired HRQoL is more common in SLE patients than controls (regardless of age, sex, education, poverty) → pre-exsiting damage is associated with poorer HRQoL; new damage predicts further decline in HRQoL. Patients place considerable value on the outcomes reflecting HRQoL (eg. Physician domain of SF36, fatigue, physical function) (28) Damage (as measured by the SLICC) is associated with physical function (PF) and social function subscales of the SF-36 (29)	The panel could not identify any disadvantage in assessing damage annually.

	Criteria	Judgement	Research evidence	Additional considerations
Certainty of the evidence	**What is the overall certainty of the evidence of effects?**	○ Very low X○ Low ○ Moderate ○ High ○ No included studies	Accrual of damage is faster in children with SLE (eg. 2x the damage scores reported in adults at 5 years) (26) The pediatric version of the SDI (Ped-SDI) has been developed to include growth failure and delayed puberty. Other aspects of the original SDI remain the same except for the indication that in younger children proteinuria is adjusted for height and weight. Some forms of damage are deemed potentially reversible in pediatric patients (27) Overall, damage accumulation is slow. Multiple cohort studies report that a minority of patients experience early damage (eg. SDI scores >0); however, these rates worsen over time. Specific cohort examples: *SLICC:* 11.1% damage in 1st year, 43.4% had damage at 5 years (25) *Toronto:* 28% damage (SDI>0) at 1 year (20), *UK:* 90% no damage at 1 year; 55% damage at year 5 (19) (232 patients) Annual evaluation of damage using the SLICC/ACR DI is embedded in the score, largely accounting for the need to ensure that irreversible change in an organ/system is present for at least six months. **Frequency of monitoring in SLE** We performed a systematic review of the literature to evaluate the impact of different frequency of monitoring for SLE patients (active and clinically quiescent). No articles were found to prescribe optimal frequency of monitoring damage in SLE patients to impact prognosis.	The panel acknowledged that changes in the SDI in the pediatric population may not have enough validity; however, the tool is still used in pediatric lupus patients every 6 to 12 months.

	Criteria	Judgement	Research evidence	Additional considerations
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?**	○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability X○ No important uncertainty or variability ○ No known undesirable outcomes	**Important outcomes:** Mortality Critical Damage Critical Physical function Important Fatigue Important Lupus stakeholders (physicians, patients) place great value in the critical outcomes of mortality and damage.	

	Criteria	Judgement	Research evidence	Additional considerations
Balance of effects	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?**	○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention X○ Favors the intervention ○ Varies ○ Don't know		No downside to measuring damage annually

	Criteria	Judgement	Research evidence	Additional considerations
Resources required	**How large are the resource requirements (costs)?**	○ Large costs ○ Moderate costs X○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Performance of disease damage measures vary according to time taken (self-administered versus performed by clinician). Data collected within the damage scores include standard questions that are part of the history-taking and physical exam performed in the rheumatology assessment.	Prescribing annual disease damage measurement may be newer in community and/or rural rheumatology practises or in primary care/internal medicine offices. This may be viewed as prohibitive to busy practises with less support, and long waiting lists. Additional nursing support with training to complete these scores may be required. Patients with greater disease damage and disease duration will require more time for completion of the SLICC/ACR SDI. For rheumatologists who care for SLE patients and are not currently performing these measures, the cost may be marginally increased – ie. increased time spent with the patient may impact cost in the health care system for those physicians who perform direct billing and bill for more time. Formal measurement of time spent has not been assessed. Time spent in the rheumatologist office may increase for a proportion of patients who are spending slight increased time to complete the assessment as they may require increased parking, time off of work, etc.

	Criteria	Judgement	Research evidence	Additional considerations
Certainty of evidence of required costs	**What is the certainty of the evidence of resource requirements (costs)?**	○ Very low ○ Low ○ Moderate ○ High X○ No included studies	A systematic review from 2012 identified 14 articles with economic data (3 Canadian; 7 USA; 1 Taiwan; 2 Hong Kong; 1 Germany). Focussing on disease damage, higher direct healthcare costs were reported in patients with renal damage(30). A tri-nation study (USA, Canada, UK) compared costs & quality of life in SLE patients with/without damage(31). Seven hundred and fifteen patients enrolled between July 1995 and February 1998 at 6 tertiary care SLE clinics in Canada (231), USA (269), UK (215) found that the mean 4-year cumulative direct costs per patient ranges from $20,337 in those with SLICC/ACR DI (renal item) = 0 compared to $99,544 in SLICC/ACR DI = 3. Much of the renal subscale of 3 costing reflected hospitalisation and dialysis. A retrospective observational study using Medicare medical claims data (5% random sample) from 2003-2007 matched 6,707 SLE and 13,414 non-SLE patients and found that SLE cohort had on average 2.4 times more physician visits, 2.7 times more hospitalizations, 2.2 times more outpatient visits, and 2.1 times more emergency room visits. A medical cost surplus of ~ $10,229 per patient per year in the SLE cohort relative to the non-SLE cohort was seen (driven largely by in-hospital costs ($p<0.001$). Details as to the reasons for hospitalizations/health utilization were not identified in the study (32).	

	Criteria	Judgement	Research evidence	Additional considerations
Cost-effectiveness	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?**	○ Favors the comparison ○ Probably favors the comparison X○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		

	Criteria	Judgement	Research evidence	Additional considerations
Equity	**What would be the impact on health equity?**	○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased X○ Varies ○ Don't know	As of 2008, there were 350 rheumatologists in Canada, or about 1.2 rheumatologists per 100,000 Canadians, about half the number of rheumatologists needed to provide adequate care. As many as 1/3 of Canada's rheumatologists will retire before 2018 (33, 34). Increased monitoring of SLE patients with use of disease damage measures may impact the following: (a) demand of rheumatologist's time per patient which slows down patient volume seen; (b) concerns of co-managers of SLE patients (eg. internists, family physicians) in adapting disease damage measures in regular practice; (c) increased demand for laboratory monitoring which may be limited by health region and lab test availability.	The panel recognized that if a patient does not have damage, they are less likely to have a medical visit. Patients with less access to a rheumatologist will have less opportunity for disease activity and damage evaluation. Education to facilitate damage assessment with online modules, awareness of the issue of damage to primary care, general internal medicine and subspecialists may reduce this inequity potential. While access to supportive investigations to assess organ-specific damage may vary between health regions (eg,creatinine for renal function), these laboratory tests are good clinical practice and would not increase the burden to the health care system both regarding demand and cost.
Acceptability	**Is the intervention acceptable to key stakeholders?**	○ No X○ Probably no [Rheumatologists] ○ Probably yes X○ Yes [Patients] ○ Varies ○ Don't know	One main damage index (SLICC/ACR SDI) has been used for damage assessment. The CRA survey (Table 1) confirms the current state where a large majority of rheumatologists do no perform the SDI.	Centres collecting outcomes data for SLE research are currently more likely to utilize a disease damage measure compared to non-research oriented centres. Change in practice to a regular composite measure for disease damage may not be as acceptable to some rheumatologists who perceive this as less feasible in their daily practice. The panel was concerned about the potential disengagement of rheumatologists from performing disease damage measures.

	Criteria	Judgement	Research evidence	Additional considerations
Feasibility	**Is the intervention feasible to implement?**	○ No ○ Probably no ○ Probably yes X○ Yes ○ Varies ○ Don't know	No included studies.	Performance of disease damage is feasible to perform in clinic. Since damage is slow to accumulate over time, this measure differs from disease activity scores in that it is required either semi-annually or annually at a maximum in order to detect a change in damage. The panel identified several barriers largely reflecting access to care.

Conclusions

Type of recommendation	We recommend against the intervention or for the comparison	We suggest against the intervention or for the comparison	We suggest either the intervention or the comparison	We suggest the intervention	We recommend the intervention
	○	○	○	X	○
Recommendation	***For adult and pediatric patients with systemic lupus erythematosus, we suggest assessing disease damage annually with a validated measure. [conditional recommendation; moderate quality evidence].*** *Remarks:* This recommendation does not specify what disease damage tool to use; however, the SLICC/ACR damage index (SDI)(31) is the only validated physician completed measure to evaluate damage. The components of damage are derived from the full patient assessment as per best clinical practice including a complete history, physical and lab examination. The SDI measures damage from any cause, including but not limited to SLE since the diagnosis of SLE.				
Justification	The evidence showing better outcomes for SLE patients (beyond the full history, physical and lab examination) by measuring damage with a validated instrument is moderate to low quality; however, studies show that early and late damage from SLE is associated with small to moderate increases in mortality and future damage which may lead to lower function and quality of life. Higher disease damage is also likely associated with small increases in cardiovascular outcomes. The panel acknowledged that validated damage instruments provided extra value by allowing for quantification of disease damage in a standardized way that can be followed over time. The panel did not identify any harm from using a validated tool or significant resource requirements. The panel agreed that the tool would be feasible to implement as it is performed infrequently (eg. annually) over time and adds minimal time burden. The panel agreed that use of a validated instrument might be more acceptable to patients than rheumatologists due to possible unfamiliarity performing disease damage measures by rheumatologists and the perception of increased time required for completion. The panel could not identify significant resource requirements but could not demonstrate a cost savings.				
Subgroup considerations	Active versus clinically quiescent – Disease damage is slow to progress and annual assessment appropriate and feasible for active and clinically quiescent patients. Pediatric versus adult – Disease damage may accrue faster in pediatric SLE patients and should be evaluated annually.				
Implementation considerations	Dissemination of disease damage score (SLICC/ACR DI) in rheumatology clinics across Canada requires education to encourage uptake.				
Monitoring and evaluation	Evaluate the administration of disease damage scores amongst Canadian rheumatologists as well as frequency of use.				
Research priorities	Comparison of outcomes in clinics measuring disease damage over time. Evaluate damage tools that are more feasible – eg. BILD and determine if it predicts outcome and its ease of use in clinic.				

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TABLE 1. Summary of Practice Patterns in Diagnosing and Monitoring SLE in Canada

Questionnaire Items	Mode (%)	Strategies (%)
a) Use revised ACR 1997 criteria for diagnosis	Usually (39)	Always (35), Sometimes (15), Never (10)
(b) Laboratory investigations for initial patient visit	CBC (100)	**76 - 99%** Creatinine (99); Urinalysis (99); WBC & differential (98); ds-DNA (96); ANA (96); Antibodies against extractable nuclear antigens (95); Complement (C3/C4 or functional assay) (94); Liver enzymes (91); CRP (86); ESR (84) **50 -74%** Anticardiolipin/antiphospholipid antibodies (64); Lupus anticoagulant/ inhibitor (58) **11 - 49%** INR/PTT (49); Urine Protein: Creatinine ratio (47); Hepatitis B/C (39); Quantitative immunoglobulins (35); Anti-beta 2 glycoprotein antibody (22); CH50 or CH100 (15); Other (17) **≤10%** 24 hr urine protein (9); ANCA (8); 24 hr urine creatinine (7); HIV (5)
(c) Tests always used to evaluate disease activity, damage or co-morbidity on a regular basis	Swollen joint count (77)	**50 - <77%** Tender joint count (70); BMD (56) **11 - 50%** MD global assessment of disease activity (42); Patient global assessment of disease activity (31); SLEDAI (any Version) (16); Other (14); SLICC/ ACR damage index (12) **≤10%** SLAM (2); BILAG (any version) (1); Charlson Comorbidity Index (1)
(d) Tests used to monitor disease activity over time	CBC (98)	**76 to <98%** Creatinine (97); WBC differential (95); Urinalysis (94); Complement C3, C4 or functional assay (82) **51% to 75%** CRP (75); ESR (72); ds-DNA (72); Liver enzymes (59) **11% to <50%** Urine Protein: Creatinine ratio (44); ANA (18); Antibodies against nuclear antigens (17); 24 hr urine protein (14); Anticardiolipin/ antiphospholipid antibodies (14); INR/PTT (11) **≤10%** Lupus anticoagulant/ inhibitor (10); Quantitative immunoglobulins (10); Other (9); 24 hr urine creatinine (8); CH50 or CH100 (7); Anti-beta 2 glycoprotein antibody (4); ANCA (1); Hepatitis B/C (0); HIV (0)
(e) Frequency of monitoring disease activity with laboratory studies in a stable SLE patient	Every 6 months (39)	Every 3-4 months (35); Once a year (12); Every 2-3 months (10); Other (2); Every month (1); Never formally request laboratory monitoring (1)

Question: What is the association of disease damage scores with health outcomes in systemic lupus patients over time?
Setting: Adult and pediatric patients with systemic lupus erythematosus
Bibliography: Cardoso 2008, Chambers 2009, Lopez 2012, Rahman 2001, Telles 2013, Alarcon 2001, Gilboe 2001,
Author(s): Touma, Medina, Pope, Nevskaya, Alabdurubalnabi, Keeling

№ of studies	Quality assessment						IMPACT	Quality	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
The impact of disease damage (as measured by the SLICC/SDI) on mortality in SLE patients (assessed with: SLICC (1 or greater))									
5	observational studies	not serious	not serious	not serious	serious [a]	none	Mortality in patients with higher SLICC scores at baseline and/or immediately prior to death: Hazard ratio 1.53 (95% CI 1.28, 1.83) Number of deaths = 128; Number of patients = 1158 [b,c,d,e]	⊕⊕⊕◯ MODERATE	CRITICAL
The impact of disease damage (as measured by the SLICC/SDI) on early damage in SLE patients (assessed with: SLICC (1 or greater)) (assessed with: SLICC score)									
2	observational studies	not serious	serious [f]	not serious	serious [g]	none	Damage at baseline or early disease (SLICC > 0) increased the odds of future damage: OR 1.20 (95% 0.87,1.66); Number of patients = 832	⊕⊕◯◯ LOW	CRITICAL

a. Number of events (deaths) = 128
b. 4 out of 5 studies evaluated the initial SDI (early disease) and 1 study (Chambers 2009) evaluated last available damage score at death; Newcastle Ottawa quality score per study was 8
c. Heterogeneity in this meta-analysis was moderate (I2 60%)
d. Pons-Estel 2004 confirmed OR 2.80 (95% 1.21,6.47) of death in patients with higher SLICC scores
e. 4 studies (Gladman 2000, Liang 2010, Pons-Estel 2004, Zonana-Nacach 2007) confirmed that the mean difference in the SDI between dead and alive patients was 0.93 (95% CI 0.36,1.49)
f. The heterogeneity of this meta-analysis is moderately high (66%); The Alarcon study introduces a tight point estimate which may impact the heterogeneity and cross the confidence interval of no-effect
g. Few events

Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

DATA SUPPLEMENT #4: Cardiovascular Risk ETDs

Question

Should **demographic data (age, sex, race, positive family history)** vs. **no documentation** be used for **assessing the risk for atherosclerotic heart disease in SLE**?

POPULATION:	SLE patients in Canada
INTERVENTION:	demographic data (age, sex, race, positive family history)
COMPARISON:	no documentation
MAIN OUTCOMES:	CV and subclinical CV outcomes
SETTING:	outpatients
PERSPECTIVE:	population

BACKGROUND: Accelerated atherosclerosis leading to premature coronary artery disease (CAD) represents one of the major causes of death in patients with systemic lupus erythematosus (SLE); in particular, the standardized mortality ratio due to cardiovascular disease was the only one that did not appear to diminish overtime in the largest lupus cohort ever assembled [1]. Since the initial description of the bimodal pattern of mortality in SLE by Urowitz et al [2], several large epidemiological studies have demonstrated that atherosclerotic CAD affects a significant proportion of these patients [3, 4]. It is noteworthy that the relative risk for myocardial infarction in young, pre-menopausal, female patients was estimated to exceed 50-fold that of age-matched healthy controls [5]. More recent studies confirmed these findings, as lupus patients aged 20-39 years had a 16-fold increased risk of death from CAD in a population-wide study from Sweden [6]. Increased morbidity for CAD has been confirmed even during the first year after diagnosis (relative risk for myocardial infarction of approximately 5) [7], as well as two years preceding SLE diagnosis [8].

The pathophysiology of premature atherosclerosis in SLE is still incompletely understood and involves a complex interplay between both traditional and disease-related risk factors [9, 10]. Among the latter, SLE itself has been demonstrated to confer the greater risk for premature cardiovascular disease, as disease activity, cumulative damage, autoantibodies, soluble inflammatory factors and medications seem to play a significant role [11]. Nevertheless, the importance of traditional risk factors should not be underestimated, as early detection and management may improve long-term prognosis.

Certain demographic variables such as age and male sex have been demonstrated to substantially affect CV risk, as well as positive family history for premature CAD.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Atherosclerotic cardiovascular events (CVEs) occur in 6 to 11% of SLE patients, 3 to 5 times higher than the age-matched general population. The first CVE is more likely to develop between the age of 48 and 50 years [1-5]. Furthermore, premenopausal women have an excess risk for developing clinical premature CAD (i.e. myocardial infarction) [5, 6]. Recent research has demonstrated an increased risk for CVEs in the first year after disease diagnosis or, even, in the two years preceding diagnosis [7, 8].	The panel agreed that care providers may not be consistently assessing CV risk factors in SLE patients and it was important to review the evidence for the common CV risk factors in people with SLE to determine if there are differences.

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	**Age, particularly over 48 or immediate post-menopausal state,** is a significant independent predictor for CAD events [4] with a reported hazard ratio (HR) of 1.04 - 5.1 for all age groups. From a meta-analysis of 19 studies (15 prospective, 4 retrospective, 5, 12-29), the respective HR per year was 1.045 [95%CI 1.041-1.049]. **Male gender** was also an independent predictor for CVEs with a HR = 1.92 [95%CI=1.87-1.97]; data derived from the same meta-analysis (12-29).**Positive family history, defined by the presence of a CVE in a first-degree relative under the age of 55 for males or 65 for females**, family history was assessed in five studies and was not found to be independently associated with CVEs. **Subgroup considerations**: Peri- or immediate post-menopausal SLE patients, patients with more than 1 atherosclerotic risk factors, patients with nephritis or increased disease severity. **Subclinical disease considerations:** Age was associated with endothelial dysfunction [31, 32] as assessed with flow-mediated dilatation of the brachial artery, arterial stiffness (HR = 1.13) [33-37] as assessed with pulse wave velocity of the carotid artery, arterial wall thickening and/or plaque formation (HR = 1.11 - 4.1) [38-57] as assessed with carotid Doppler ultrasound, coronary artery calcification or non-calcified plaques (HR=1.08-8.5) [58-65] and angiographically-defined plaques (HR=2.22) [66, 67]. Male gender was associated with aortic stiffness [37], atherosclerotic plaques in the carotid and femoral arteries (HR = 8.78) [46], coronary artery calcification [53] and angiographic findings (HR = 2.38) [66].	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies		The evidence for the association of demographic characteristics and CV risk was moderate quality in people with SLE, further supported by evidence in the general population.
VALUES	**Is there important uncertainty about or variability in how**	No research evidence was identified.	

	much people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes		
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Documentation of demographic type data is not anticipated to have significant impact on cost. Besides documentation, no additional action is required that could have an effect on cost.	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no included studies but it is anticipated this would be negligible	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention		

	○ Varies ● No included studies		
EQUITY	**What would be the impact on health equity?** ● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No anticipated impact.	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes	Such documentation is currently performed in most SLE expert centres and/or rheumatology private practices.	Recruitment of primary care physicians and/or registered nurses for the regular assessment of CV risk in SLE patients may be feasible but costly.

	○ Varies ○ Don't know		

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	

	JUDGEMENT							IMPLICATIONS
			intervention or the comparison					
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should demographic data (age, sex, race, positive family history) vs. no documentation be used for assessing the risk for atherosclerotic heart disease in SLE?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●
RECOMMENDATION	***Best practice dictates that a cardiovascular (CV) risk assessment be performed in adult patients upon diagnosis of systemic lupus erythematosus.*** The assessment includes documentation of characteristics of patients that are non-modifiable, but predictive of cardiovascular events, such as age, gender, and family history of premature coronary artery disease (males < 55 years old, females < 65 years old) in the general population (33). These characteristics and assessments in the complete history, physical, and lupus-related laboratory examinations provided at baseline and follow-up visits can inform the overall assessment of cardiovascular risk (see Best Practice Statement for General Assessment).				
. JUSTIFICATION	The aforementioned demographic variables have been shown to be independent predictors of atherosclerotic CVEs in several SLE cohorts and in the general population. This best practice statement is based on evidence from the general and SLE populations that have demonstrated the independent association between demographic variables and cardiovascular events (CVEs). Although positive family history for premature coronary artery disease (CAD) has not been shown to be an independent predictor for cardiovascular events (CVEs) in studies of lupus patients, it is included as part of this best practice statement and as a basis for strong recommendation due to its significance in the general population, and the low associated cost. There are no issues with equity, acceptability or feasibility regarding the collection of these				

	demographic cardiovascular risk factors.
SUBGROUP CONSIDERATIONS	Peri-menopausal patients, male patients, patients with positive family history for premature CAD.
IMPLEMENTATION CONSIDERATIONS	No significant implementation issues are anticipated, since suggested documentation is routinely performed in most dedicated SLE centres and rheumatology practices.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Further research is warranted to delineate the possible association between SLE and premature CAD in cases with late-onset SLE and in patients with an SLE diagnosis shortly after a major CVE.

Author(s): Konstantinos Tselios, Dafna D Gladman, Murray B Urowitz
Question: What is the association of demographic data (age, sex, race, positive family history) with the risk for atherosclerotic heart disease in SLE?
Setting: outpatient

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**demographic data (age, sex, race, positive family history)**	**Follow-Up**	**Relative risk (95% CI)**	**Absolute (95% CI)**		
Age (follow up: mean 9,4 years; risk per year)												
16	observational studies	not serious	not serious	serious [a]	not serious	none	9382	9.4±7.6 years	**HR 1.045 [95%CI 1.041-1.049]**		⊕⊕⊕◯ MODERATE	CRITICAL
Male gender (follow up: mean 9,4 years)												
4	observational studies	not serious	not serious	serious [a]	not serious	none	263/3536 (7.4%)	9.4±7.6 years	**RR 1.92** (1.87 to 1.97)		⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

a. Included studies did not enrol SLE patients exclusively

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Question

Should **monitoring of smoking habits and body weight** vs. **no monitoring** be used for **assessing CV risk in SLE patients**?

POPULATION:	SLE patients in Canada
INTERVENTION:	monitoring of smoking habits and body weight
COMPARISON:	no monitoring
MAIN OUTCOMES:	Smoking;
SETTING:	outpatients
PERSPECTIVE:	population

BACKGROUND: Accelerated atherosclerosis leading to premature coronary artery disease (CAD) represents one of the major causes of death in patients with systemic lupus erythematosus (SLE); in particular, the standardized mortality ratio due to cardiovascular disease was the only one that did not appear to diminish overtime in the largest lupus cohort ever assembled [1]. Since the initial description of the bimodal pattern of mortality in SLE by Urowitz et al [2], several large epidemiological studies have demonstrated that atherosclerotic CAD affects a significant proportion of these patients [3, 4]. It is noteworthy that the relative risk for myocardial infarction in young, pre-menopausal, female patients was estimated to exceed 50-fold that of age-matched healthy controls [5]. More recent studies confirmed these findings, as lupus patients aged 20-39 years had a 16-fold increase risk of death from CAD in a population-wide study from Sweden [6]. Increased morbidity for CAD has been confirmed even during the first year after disease diagnosis (relative risk for myocardial infarction of approximately 5) [7], as well as two years preceding disease diagnosis [8].
The pathophysiology of premature atherosclerosis in SLE is still incompletely understood and involves a complex interplay between both traditional and disease-related risk factors [9, 10]. Among the latter, SLE itself has been demonstrated to confer the greater risk for premature cardiovascular disease, as disease activity, cumulative damage, autoantibodies, soluble inflammatory factors and medications seem to play a significant role [11]. Nevertheless, the importance of traditional risk factors should not be underestimated, as early detection and management may improve long-term prognosis.
Among the latter, obesity and smoking have been associated with the development of cardiovascular events (CVEs). Obesity affects 28-50% of the patients, depending on definition [12] whereas approximately 16% of lupus patients are smokers at diagnosis [13]. Management of obesity and guidance for smoking cessation is recommended by the 2006 Canadian Obesity Network clinical practice guidelines [14] and the Canadian Smoking Cessation clinical practice guidelines [15].

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Atherosclerotic cardiovascular events (CVEs) occur in 6 to 11% of SLE patients whereas the first event is more likely to develop between the age of 48 and 50 years [1-5]. Furthermore, premenopausal women have an excess risk for developing clinical premature CAD (i.e. myocardial infarction) [5, 6]. Recent research has demonstrated an increased risk for CVEs in the first year after disease diagnosis or, even, in the two years preceding diagnosis [7, 8].	The panel agreed that care providers may not be consistently assessing CV risk factors in SLE patients and it was important to review the evidence for risk factors in people with SLE to determine if there are differences.

	○ Don't know		
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Smoking was independently associated with the development of CVEs [HR=1.87, 95%CI=1.80-1.94], according to our meta-analysis in SLE patients [5, 16-33]. Obesity, as measured through Body Mass Index, was not an independent predictor for CVEs for SLE patients (data from 6 prospective and 3 retrospective studies) (19, 24, 27-33). Considerations for no association between obesity and risk included a lack of power due to low numbers of patients compared to general population studies evaluating obesity as a contributor to CV risk. **Subclinical disease considerations:** Lupus patients with BMI>30 demonstrated endothelial dysfunction, assessed by brachial artery flow mediated dilation [35], increased carotid IMT and plaque formation (HR = 1.06 - 6.16) [36-40] and coronary artery calcification [41, 42]. Also, an abnormal waist-to-hip ratio was predictive of increased carotid IMT [43]. Obesity was among the major predictors of IMT progression over 3 years in pediatric SLE patients [34]. Smoking was associated with carotid plaque (HR=7.7) [44, 45] and coronary artery calcification (HR=3.8) [46-48].	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies		The panel agreed that the evidence for the association of the risk factors with CV risk is high and would remain high after considering the link with treatment for CV risks.
VALUES	**Is there important**	The relative importance or values of the main outcomes of interest:	

	uncertainty about or variability in how much people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	**Outcome** — **Relative Importance** Coronary Artery Disease (angina, myocardial infarction, acute coronary syndrome, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, congestive heart failure) — CRITICAL	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		Additional costs will depend on the actions taken for counselling towards weight loss and smoking cessation when necessary.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	There is no direct evidence on smoking/obesity and resource requirements in SLE	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention	No research evidence was identified.	Despite no direct evidence in SLE for obesity, the panel felt that the impact of obesity on CVE's in the general population would favor the evaluation and management of obesity in SLE patients. The panel felt that the evaluation of smoking and management of smoking cessation was important due to the impact of smoking on CVE's in SLE and the general population; this was felt to incorporate the cost benefits of reducing CVE's.

	○ Varies ○ No included studies		
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No anticipated impact.	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No direct evidence.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no	No research evidence was identified.	

	○ Probably yes ● Yes ○ Varies ○ Don't know		

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF	Very low	Low	Moderate	High			**No included studies**	

	JUDGEMENT							IMPLICATIONS
REQUIRED RESOURCES								
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should monitoring of smoking habits and body weight vs. no monitoring be used for assessing CV risk in SLE patients?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●

RECOMMENDATION

For adults, we recommend that indicators of obesity, smoking status, diabetes, arterial hypertension and dyslipidemia be measured upon diagnosis of systemic lupus erythematosus, and be reassessed periodically according to current recommendations in the general population and be used to inform the cardiovascular risk assessment. [strong recommendation, high quality evidence].

i) Indicators for obesity include measurement and documentation of body weight and body mass index. The 2006 Canadian Obesity Network clinical practice guidelines provide recommendations for action after assessment (http://www.cmaj.ca/content/suppl/2007/09/04/176.8.S1.DC1/obesity-lau-onlineNEW.pdf)

ii) For smoking, the Canadian Smoking Cessation clinical practice guidelines provide recommendations for action

	after assessment (http://www.strokebestpractices.ca/wp-content/uploads/2012/04/CAN-ADAPTT2.pdf).
JUSTIFICATION	This recommendation places high value on the association of smoking and CVE's in the general population as well as association of smoking with clinical and subclinical coronary artery disease in lupus patients. Although, there is low quality evidence for no association of obesity (BMI >30) with atherosclerotic CVEs in SLE patients, obesity has been associated with subclinical cardiovascular disease in SLE, and one longitudinal study in paediatric patients showed that obesity is associated with progressive increase of carotid IMT, as well as an association in the general population. There no issues with equity, acceptability or feasibility regarding the documentation of obesity or smoking. Subsequent reassessment of smoking is important as it can change for the SLE patient over time.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	No significant implementation issues are anticipated, since suggested actions are routinely performed in most dedicated SLE centres and rheumatology practices.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	

Author(s): Tselios, Sheane, Gladman, Urowitz
Question: What is the association of smoking habits and body weight with CV risk in SLE patients?
Setting: outpatients

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Smoking**	**Follow-up**	**Relative (95% CI)**		
Smoking (follow up: mean 9,4 years)											
6	observational studies	not serious	not serious	not serious	not serious	none	7567	9.4±7.6 years	**RR 1.87** (1.80 to 1.94)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

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Question

Should **blood pressure monitoring** vs. **no monitoring** be used for **assessing CV risk in SLE patients**?

POPULATION:	SLE patients in Canada
INTERVENTION:	blood pressure monitoring
COMPARISON:	no monitoring
MAIN OUTCOMES:	Arterial Hypertension and other subclinical CV outcomes; CV outcomes
SETTING:	outpatients
PERSPECTIVE:	population

BACKGROUND: Accelerated atherosclerosis leading to premature coronary artery disease (CAD) represents one of the major causes of death in patients with systemic lupus erythematosus (SLE); in particular, the standardized mortality ratio due to cardiovascular disease was the only one that did not appear to diminish overtime in the largest lupus cohort ever assembled [1]. Since the initial description of the bimodal pattern of mortality in SLE by Urowitz et al [2], several large epidemiological studies have demonstrated that atherosclerotic CAD affects a significant proportion of these patients [3, 4]. It is noteworthy that the relative risk for myocardial infarction in young, pre-menopausal, female patients was estimated to exceed 50-fold that of age-matched healthy controls [5]. More recent studies confirmed these findings, as lupus patients aged 20-39 years had a 16-fold increase risk of death from CAD in a population-wide study from Sweden [6]. Increased morbidity for CAD has been confirmed even during the first year after disease diagnosis (relative risk for myocardial infarction of approximately 5) [7], as well as two years preceding disease diagnosis [8]. The pathophysiology of premature atherosclerosis in SLE is still incompletely understood and involves a complex interplay between both traditional and disease-related risk factors [9, 10]. Among the latter, SLE itself has been demonstrated to confer the greater risk for premature cardiovascular disease, as disease activity, cumulative damage, autoantibodies, soluble inflammatory factors and medications seem to play a significant role [11]. Nevertheless, the importance of traditional risk factors should not be underestimated, as early detection and management may improve long-term prognosis.
Among the latter, arterial hypertension has been associated with the development of cardiovascular events (CVEs) and it has been estimated to burden up to 74% of lupus patients [12]. With regard to the general population in Canada, screening for arterial hypertension is recommended in all individuals (regardless of age, gender, other cardiovascular risk factors etc) with blood pressure measurement at each clinic visit. Further diagnostic approach and therapy are thoroughly described by the 2015 Canadian Hypertension Education Program [13].

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes	Atherosclerotic cardiovascular events (CVEs) occur in 6 to 11% of SLE patients whereas the first event is more likely to develop between the age of 48 and 50 years [1-5]. Furthermore, pre-menopausal women have an excess risk for developing clinical premature CAD (i.e. myocardial infarction) [5, 6]. Recent	

	○ Varies ○ Don't know	research has demonstrated an increased risk for CVEs in the first year after disease diagnosis or, even, in the two years preceding diagnosis [7, 8].	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Arterial hypertension (HTN), defined as systolic blood pressure>140mmHg and/or diastolic blood pressure>90mmHg, was found to be independently [HR = 1.72, 95%CI=1.68-1.75) associated with increased rates of CVEs [5, 14-31] based on our meta-analysis in lupus patients. In a different meta-analysis, HTN was found to be an independent predictor for CVEs in lupus patients [HR=3.52, 95%CI=1.62-7.54], [32]. **Subgroup considerations**: SLE patients with renal involvement, high disease activity, receiving high doses of corticosteroids, NSAIDs abuse, having other risk factors (e.g. diabetes) [12]. **Subclinical disease considerations:** HTN was related to impaired endothelial dysfunction [33, 34] and arterial stiffness [35-37], increased carotid IMT and plaque formation (HR = 1.04 - 3) [35, 38-42], coronary artery calcification [43] and angiographically proven CAD [44]. HTN was an independent risk factor for myocardial perfusion defects (HR = 2.11 - 2.53) [45, 46].	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies		The panel agreed that the evidence for the association of the risk factors with CV risk is high and would remain high after considering the link with treatment for CV risks.
VALUES	**Is there important uncertainty about or variability in how much**	***The relative importance or values of the main outcomes of interest:***	

	people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	**Outcome** Coronary Artery Disease (angina, myocardial infarction, acute coronary syndrome, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, congestive heart failure) **Relative Importance** Critical	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		Minimal requirements since all practices are likely equipped with a sphygmomanometer.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	No studies specifically focus on the cost implications of standard blood pressure screening in SLE patients and resource requirements.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No studies specifically focus on the cost implications of standard blood pressure screening in SLE patients and resource requirements.	The panel acknowledged that additional costs will depend on the necessary actions for patients with abnormal blood pressure.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	The panel did not think there would be a significant impact on health equity.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	Measuring blood pressure regularly is acceptable to both physicians and patients since the test is non-invasive, non-time consuming and has minimal cost.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**				

	JUDGEMENT							IMPLICATIONS
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should blood pressure monitoring vs. no monitoring be used for assessing CV risk in SLE patients?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●

RECOMMENDATION	***For adults, we recommend that indicators of obesity, smoking status, arterial hypertension, diabetes and dyslipidemia be measured upon diagnosis of systemic lupus erythematosus, and be reassessed periodically according to current recommendations in the general population and be used to inform the cardiovascular risk assessment. [strong recommendation, high quality evidence].*** The 2015 Canadian Hypertension Education Program (CHEP) (http://guidelines.hypertension.ca/diagnosis-assessment) provides information about the measurement and documentation of blood pressure, re-assessment and treatment.
JUSTIFICATION	This recommendation places great importance on the association of arterial hypertension and atherosclerotic CVEs in SLE patients based on cohort studies. Despite a lack of direct cost-effectiveness studies on hypertension screening in SLE, the panel felt that blood pressure measurement was available to the majority of SLE patients, acceptable to SLE patients and physicians and feasible to implement.
SUBGROUP CONSIDERATIONS	Subgroups with greater risk of hypertension include those with lupus nephritis as well as patients with high disease activity who are administered high doses of corticosteroids [12].
IMPLEMENTATION CONSIDERATIONS	While blood pressure assessment is routinely performed in most dedicated SLE centres and rheumatology practices, dissemination of this recommendation to primary care and other caregivers of lupus (eg. internal medicine subspecialties) may increase blood pressure monitoring for lupus patients.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Further research is warranted to delineate the most appropriate treatment for lupus patients with hypertension.

Author(s): Tselios, Sheane, Gladman, Urowitz
Question: What is the association of blood pressure with CV risk in SLE patients?

Setting: outpatient
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Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SLE patients**	**Follow-up**	**Relative RIsk (95% CI)**		
Arterial Hypertension (follow up: mean 9,4 years; Scale from: 3 to 37)											
6 (14,21,22,25,28,31)	observational studies	not serious	not serious	not serious	not serious	none	7899	9.4±7.6 years	**HR = 1.72 [95%CI=1.68-1.75]**	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval

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Question

Should **screening for diabetes** vs. **no screening** be used for **assessing CV risk in SLE patients**?

POPULATION:	SLE patients in Canada
INTERVENTION:	screening for diabetes
COMPARISON:	no screening
MAIN OUTCOMES:	Diabetes; CV and subclinical CV outcomes
SETTING:	outpatients
PERSPECTIVE:	population

BACKGROUND:

Accelerated atherosclerosis leading to premature coronary artery disease (CAD) represents one of the major causes of death in patients with systemic lupus erythematosus (SLE); in particular, the standardized mortality ratio due to cardiovascular disease was the only one that did not appear to diminish overtime in the largest lupus cohort ever assembled [1]. Since the initial description of the bimodal pattern of mortality in SLE by Urowitz et al [2], several large epidemiological studies have demonstrated that atherosclerotic CAD affects a significant proportion of these patients [3, 4]. It is noteworthy that the relative risk for myocardial infarction in young, pre-menopausal, female patients was estimated to exceed 50-fold that of age-matched healthy controls [5]. More recent studies confirmed these findings, as lupus patients aged 20-39 years had a 16-fold increase risk of death from CAD in a population-wide study from Sweden [6]. Increased morbidity for CAD has been confirmed even during the first year after disease diagnosis (relative risk for myocardial infarction of approximately 5) [7], as well as two years preceding disease diagnosis [8].

The pathophysiology of premature atherosclerosis in SLE is still incompletely understood and involves a complex interplay between both traditional and disease-related risk factors [9, 10]. Among the latter, SLE itself has been demonstrated to confer the greater risk for premature cardiovascular disease, as disease activity, cumulative damage, autoantibodies, soluble inflammatory factors and medications seem to play a significant role [11]. Nevertheless, the importance of traditional risk factors should not be underestimated, as early detection and management may improve long-term prognosis.

Diabetes mellitus has been associated with clinical and subclinical CAD in lupus patients [12-18] and affects approximately 4% of the patients at diagnosis [19]. The Canadian Diabetes Association recommends screening with fasting plasma glucose (FPG) and/or HbA1c every 3 years in individuals older than 40 years of age or those at high risk [20].

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Atherosclerotic cardiovascular events (CVEs) occur in 6 to 11% of SLE patients whereas the first event is more likely to develop between the age of 48 and 50 years [1-5]. Furthermore, premenopausal women have an excess risk for developing clinical premature CAD (i.e. myocardial infarction) [5, 6]. Recent research has demonstrated an increased risk for CVEs in the first year after disease diagnosis or, even, in the two years preceding diagnosis [7, 8].	

	○ Don't know		
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Diabetes mellitus was associated with adverse CVEs in our meta-analysis in lupus patients [HR=1.8, 95%CI=1.77-1.84]. Moderate-to-high doses of corticosteroids may increase the risk of diabetes in lupus patients. **Subclinical disease considerations:** Increased insulin and glucose levels, without a formal diagnosis of diabetes, have been related to increased arterial stiffness (HR=1.54) [13] and McMahon et al recently reported a 60-fold increase for carotid IMT progression in lupus patients with diabetes [14]. In addition, DM was independently related to coronary artery calcification [15, 16] and a 4-fold increased risk of myocardial perfusion defects [17].	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies		The panel agreed that the evidence for the association of the risk factors with CV risk is high and would remain high after considering the link with treatment for CV risks.
VA LU	**Is there important**	***The relative importance or values of the main outcomes of interest:***	

	uncertainty about or variability in how much people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	**Outcome** — **Relative importance** Coronary Artery Disease (angina, myocardial infarction, acute coronary syndrome, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, congestive heart failure) — Critical	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	No research evidence was identified.	

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Fasting plasma glucose (FPG) assessment costs less than 1 CAD.	The panel discussed that despite including more patients for diabetes screening than is typically screened in the general population, this would include only a small number of more patients to screen given the rarity of lupus overall.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence was identified.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the	No research evidence was identified.	The panel acknowledged that the low cost of screening compared to the benefits of earlier diagnosis and management of diabetes in the lupus population would favor diabetes screening.

	intervention ● Favors the intervention ○ Varies ○ No included studies		
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No anticipated impact.	The panel acknowledged that given the relative risk of MI and increased risk of death from cardiovascular disease in SLE patients starting at a young age (see Background), screening for cardiovascular risk factors like diabetes earlier may improve equity.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No direct evidence for this criterion.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes	No research evidence was identified.	

	● Yes ○ Varies ○ Don't know		

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should screening for diabetes vs. no screening be used for assessing CV risk in SLE patients?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●
RECOMMENDATION	***For adults, we recommend that indicators of obesity, smoking status, arterial hypertension, diabetes and dyslipidemia be measured upon diagnosis of systemic lupus erythematosus, and be reassessed periodically according to current recommendations in the general population and be used to inform the cardiovascular risk assessment. [strong recommendation, high quality evidence].*** *Remarks:* Initial diabetes screening includes fasting plasma glucose (FPG) and/or glycosylated hemoglobin (HbA1c). The Canadian Diabetes Association 2013 clinical practice guidelines for patients with ≥ 1 risk factor provides additional information about reassessment, monitoring, and treatment [20].				

JUSTIFICATION	This recommendation is based on the evidence confirming an association between diabetes in the general population and SLE patients and adverse CV events. Diabetes mellitus has been shown to be an independent predictor of atherosclerotic CVEs in two large retrospective studies. The contribution of diabetes to subclinical cardiovascular disease further strengthens the effect of diabetes on CVEs in SLE. Additionally, other SLE-specific factors including corticosteroids to diabetes risk supports the certainty of the value of this effect. The resource requirement for diabetes screening was felt to be negligible compared to the effect of diabetes on CVEs in SLE. The panel had no concerns regarding equity, acceptability or feasibility in implementing diabetes screening over time.
SUBGROUP CONSIDERATIONS	Lupus patients on moderate-to-high doses of corticosteroids are at increased risk.
IMPLEMENTATION CONSIDERATIONS	No significant implementation issues are anticipated since suggested assessment is widely available in Canada.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Further research could delineate the optimal frequency of FPG monitoring for minimizing CV risk.

Author(s): Tselios, Sheane, Gladman, Urowitz
Question: What is the association of diabetes with CV risk in SLE patients?
Setting: outpatient

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**screening for diabetes**	**Follow Up**	**Relative (95% CI)**		
Diabetes (follow up: mean 9,4 years)											
2 (12,18)	observational studies	not serious	not serious	not serious	not serious	none	340/4661 (7.3%)	12.4 years	**1.80** (95% CI 1.77 to 1.84)	⊕⊕⊕⊕ HIGH	Critical

CI: Confidence interval

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Question

Should **lipid profile monitoring** vs. **no monitoring** be used for **assessing CV risk in SLE patients**?

POPULATION:	SLE patients in Canada
INTERVENTION:	lipid profile monitoring
COMPARISON:	no monitoring
MAIN OUTCOMES:	Total cholesterol; Triglycerides; HDL; cardiovascular and subclinical cardiovascular outcomes
SETTING:	outpatient
PERSPECTIVE:	

BACKGROUND:

Accelerated atherosclerosis leading to premature coronary artery disease (CAD) represents one of the major causes of death in patients with systemic lupus erythematosus (SLE); in particular, the standardized mortality ratio due to cardiovascular disease was the only one that did not appear to diminish overtime in the largest lupus cohort ever assembled [1]. Since the initial description of the bimodal pattern of mortality in SLE by Urowitz et al [2], several large epidemiological studies have demonstrated that atherosclerotic CAD affects a significant proportion of these patients [3, 4]. It is noteworthy that the relative risk for myocardial infarction in young, pre-menopausal, female patients was estimated to exceed 50-fold that of age-matched healthy controls [5]. More recent studies confirmed these findings, as lupus patients aged 20-39 years had a 16-fold increase risk of death from CAD in a population-wide study from Sweden [6]. Increased morbidity for CAD has been confirmed even during the first year after disease diagnosis (relative risk for myocardial infarction of approximately 5) [7], as well as two years preceding disease diagnosis [8].

The pathophysiology of premature atherosclerosis in SLE is still incompletely understood and involves a complex interplay between both traditional and disease-related risk factors [9, 10]. Among the latter, SLE itself has been demonstrated to confer the greater risk for premature cardiovascular disease, as disease activity, cumulative damage, autoantibodies, soluble inflammatory factors and medications seem to play a significant role [11]. Nevertheless, the importance of traditional risk factors should not be underestimated, as early detection and management may improve long-term prognosis.

Among the latter, dyslipidemia has been associated with the development of cardiovascular events (CVEs). The prevalence of dyslipidemia in SLE ranges from 36.3%, at the time of diagnosis, to 60% or even higher after three years of follow up in the SLICC cohort of 918 patients [12, 13]. The Canadian Cardiovascular Society recommends screening for men >40 years and women >50 years or post-menopausal or for all patients with chronic inflammatory diseases with total cholesterol, triglycerides, HDL and LDL [14].

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes	Atherosclerotic cardiovascular events (CVEs) occur in 6 to 11% of SLE patients whereas the first event is more likely to develop between the age of 48 and 50 years [1-5]. Furthermore, premenopausal women have an excess risk for developing clinical premature CAD (i.e. myocardial infarction) [5, 6]. Recent research has demonstrated an increased risk for CVEs in the first year after disease diagnosis or, even, in the two years	

	● Yes ○ Varies ○ Don't know	preceding diagnosis [7, 8].	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	**Total cholesterol (TC)** is an independent predictor for CVEs [5, 12, 15-31] based on our-meta-analysis [HR=2.05, 95%CI=2.02-2.08]. In a different meta-analysis, TC was also found to independently predict CVEs [HR=3.91, 95%CI=1.57-9.71], [32]. Unexpectedly, low-density lipoprotein (LDL) was not an independent factor for CVEs or coronary artery calcification or angiographic CHD (13-20, 23,25, 27-31). Low levels of high-density lipoprotein (HDL) have been implicated in CVEs [28]. On the contrary, elevated triglycerides (TG) were an independent predictor for CVEs [HR = 1.17, 95%CI=1.12-1.22], based on our meta-analysis. **Subgroup considerations**: SLE patients with renal involvement, high disease activity, receiving high doses of corticosteroids. **Subclinical disease considerations:** Elevated TC is a risk factor for increased carotid IMT and plaque formation (HR = 1.2 - 3) [33-36], coronary artery calcification [37], angiographic CAD (HR=1.89) [38] and perfusion abnormalities (HR=2.51) [39]. Time-adjusted TC values may capture more precisely the increased CV risk of lupus patients, since lipid values may fluctuate over time, reflecting changes in disease activity and therapy [23]. LDL was significantly related to increased carotid IMT and plaque (HR=7.6) [40-42]. Low HDL was associated with endothelial dysfunction [43], myocardial perfusion abnormalities (HR=3.86) [44], carotid IMT and plaque (HR=4.8) [42]. TGs were related to coronary artery calcification [45] and arterial stiffness [46]. Pro-inflammatory HDL, not having the capacity of neutralizing LDL effects, was strongly associated (HR = 9.1 - 12.8) with increased carotid IMT and plaque formation [47, 48]. In addition, oxidized LDL was independently related to decreased small artery elasticity [49].	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies		The panel agreed that the evidence for the association of lipid risk factors with CV risk is high and would remain high after considering the link with treatment for CV risks.
VALUES	**Is there important uncertainty about or variability in how much**	No research evidence was identified.	

	people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability		
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	No research evidence was identified.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		Lab requirements for assessment of basic lipid profile (10-25USD/assessment).

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies		The panel felt that despite the additional cost that might be incurred by including a small group of patients (eg. the young lupus patient) who may otherwise not have been tested, this was negligible compared to the benefit of identifying a lipid profile eligible for treatment to reduce the chances of the critical outcome of cardiovascular events.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know		Minimal anticipated impact other than identifying a small number of younger SLE patients who would be eligible for lipid lowering therapies that otherwise not be identified.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
			intervention or the comparison					
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should lipid profile monitoring vs. no monitoring be used for assessing CV risk in SLE patients?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●
RECOMMENDATION	***For adults, we recommend that indicators of obesity, smoking status, arterial hypertension, diabetes and dyslipidemia be measured upon diagnosis of systemic lupus erythematosus, and be reassessed periodically according to current recommendations in the***				

	general population and be used to inform the cardiovascular risk assessment. [strong recommendation, high quality evidence]. *Remarks:* Initial dyslipidemia risk evaluation includes basic lipid profile assessment (TC, TG, HDL, LDL). In the case of normal values, periodic re-assessment is based on the effect of alterations of disease activity and administered drugs, such as corticosteroids, on lipid metabolism. The 2016 Canadian Cardiovascular Society guidelines provides information for monitoring and treating people at intermediate-to-high risk of cardiovascular outcomes. (50)
JUSTIFICATION	This recommendation demonstrates the importance of dyslipidemia, specifically total cholesterol and to a lesser extent, hypertriglyceridemia, on CVEs in SLE patients. The resource requirements are felt to be negligible given the ease of availability and general low cost of lipid screening across Canada. The panel felt that there would be little impact on health equity other than possibly improving it by increasing identification of younger SLE patients who might not have otherwise been screened but would benefit from lipid lowering therapies to reduce their intermediate to high risk.
SUBGROUP CONSIDERATIONS	Lupus nephritis patients with nephrotic syndrome, as well as patients with high disease activity who are administered high doses of corticosteroids are at increased risk.
IMPLEMENTATION CONSIDERATIONS	No significant implementation issues are expected since these tests are widely available.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Future studies evaluating the impact of close lipid monitoring in SLE patients to provide further support to these recommendations would be important.

Author(s): Tselios, Sheane, Gladman, Urowitz
Question: What is the association of the lipid profile with CV risk in SLE patients?
Setting: outpatient

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lipid Profile Monitoring**	**Follow-Up**	**Relative (95% CI)**		
Total cholesterol (follow up: mean 9,4 years; Scale from: 3 to 37)											
5	observational studies	not serious	not serious	not serious	not serious	none	5652	9.4±7.6 years	**2.047 95%CI=2.015-2.079**	⊕⊕⊕⊕ HIGH	CRITICAL
Triglycerides (follow up: mean 9,4 years; Scale from: 3 to 37)											
2	observational studies	not serious	not serious	not serious	not serious	none	755	8-37 years	**HR = 1.17 95%CI=1.12-1.22**	⊕⊕⊕⊕ HIGH	CRITICAL
HDL (follow up: 8 years)											
1	observational studies	not serious	not serious	not serious	not serious	none	1072	8 years	**0.121 [95%CI=0.041-0.358]**	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval

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Question

Should **documentation of disease activity and cumulative damage** vs. **no documentation** be used for **assessing CV risk in SLE patients**?

POPULATION:	SLE patients in Canada	**BACKGROUND:**	Accelerated atherosclerosis leading to premature coronary artery disease (CAD) represents one of the major causes of death in patients with systemic lupus erythematosus (SLE); in particular, the standardized mortality ratio due to cardiovascular disease was the only one that did not appear to diminish overtime in the largest lupus cohort ever assembled [1]. Since the initial description of the bimodal pattern of mortality in SLE by Urowitz et al [2], several large epidemiological studies have demonstrated that atherosclerotic CAD affects a significant proportion of these patients [3, 4]. It is noteworthy that the relative risk for myocardial infarction in young, pre-menopausal, female patients was estimated to exceed 50-fold that of age-matched healthy controls [5]. More recent studies confirmed these findings, as lupus patients aged 20-39 years had a 16-fold increase risk of death from CAD in a population-wide study from Sweden [6]. Increased morbidity for CAD has been confirmed even during the first year after disease diagnosis (relative risk for myocardial infarction of approximately 5) [7], as well as two years preceding disease diagnosis [8]. The pathophysiology of premature atherosclerosis in SLE is still incompletely understood and involves a complex interplay between both traditional and disease-related risk factors [9, 10]. Among the latter, SLE itself has been demonstrated to confer the greater risk for premature cardiovascular disease, as disease activity, cumulative damage, autoantibodies, soluble inflammatory factors and medications seem to play a significant role [11]. Nevertheless, the importance of traditional risk factors should not be underestimated, as early detection and management may improve long-term prognosis.
INTERVENTION:	documentation of disease activity and cumulative damage		
COMPARISON:	no documentation		
MAIN OUTCOMES:	DISEASE ACTIVITY; CUMULATIVE DAMAGE; CV and subclinical CV outcomes		
SETTING:	outpatient		
PERSPECTIVE:			

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Atherosclerotic cardiovascular events (CVEs) occur in 6 to 11% of SLE patients whereas the first event is more likely to develop between the age of 48 and 50 years [1-5]. Furthermore, premenopausal women have an excess risk for developing clinical premature CAD (i.e. myocardial infarction) [5, 6]. Recent research has demonstrated an increased risk for CVEs in the first year after disease diagnosis or, even, in the two years preceding diagnosis [7, 8].	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate	**Disease activity**, assessed by composite indices such as SLE Disease Activity Index (SLEDAI) and European Consensus Lupus Activity Measurement (ECLAM), was significantly associated with CVEs [HR=1.07, 95%CI=1.062-1.078] based on our meta-analysis [5, 12-29]. A different meta-analysis demonstrated a higher HR=1.2 [95%CI=1.2-1.2], [30].	

	● Large ○ Varies ○ Don't know	**Cumulative damage**, assessed by the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index, was strongly related to CVEs [HR=1.13, 95%CI=1.09-1.16] based on our meta-analysis [5, 12-29]. A different meta-analysis demonstrated a higher HR=1.4 [95%CI=1.09-4.44], [30].	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Subclinical disease considerations:** Disease activity was associated with increased arterial stiffness [31, 32], increased carotid IMT and plaque formation [33] and coronary artery calcification (HR=12.3) [34]. Damage Index was related to endothelial dysfunction [35], carotid IMT and plaque (HR=1.7) [36-39] and coronary artery calcification (HR=1.2) [40].	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	See Summary of Findings Table.	The panel agreed that the evidence for the association of disease activity and damage with CV risk is high and would remain high after considering the link with treatment for CV risks.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The relative importance or values of the main outcomes of interest: **Outcome** — **Relative Importance** Coronary Artery Disease (angina, myocardial infarction, acute coronary syndrome, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, congestive heart failure) — CRITICAL	

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		The panel felt that the measurement of disease activity/damage and associated role in CVEs favoured their evaluation in SLE patients.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ●Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		Additional costs need to be considered due to need for documentation and serologic evaluation (eg. double-stranded DNA, complement for SLEDAI (SLE Disease Activity Score)

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	No direct studies to evaluate certainty of resource requirements.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	It was recently shown that the direct cost of acute MI in elderly patients in Ontario, Canada is approximately 30.000CAD for a 6-year period (3 years before and 3 years after the event). Overall, heart disease and stroke cost the Canadian economy approximately 21 billion CAD per year (Conference Board of Canada, 2010).	The panel felt that the strong association of disease activity/damage with CVE's favoured the evaluation of disease activity and damage.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No direct evidence for this criterion.	No anticipated impact.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No direct evidence for this criterion.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
			intervention or the comparison					
RESOURCES REQUIRED	Large costs	Moderate costs	Moderate	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should documentation of disease activity and cumulative damage vs. no documentation be used for assessing CV risk in SLE patients?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	***For adult and pediatric patients with SLE, we suggest assessing disease activity with a validated instrument of disease activity during baseline and follow up visits. [conditional recommendation, low quality evidence] (Data Supplement #2 Disease Activity). For adult and pediatric patients with systemic lupus erythematosus, we suggest assessing disease damage annually with a validated***				

	measure. [conditional recommendation; moderate quality evidence] (Data Supplement #3 Damage)
JUSTIFICATION	This recommendation provides further evidence towards the careful evaluation of disease activity and damage for SLE patients with an emphasis on the effects of high disease activity and damage on increased CVEs. The aforementioned indices have been shown to be independent predictors of atherosclerotic CVEs in several SLE cohorts.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	No significant implementation issues, since suggested documentation is routinely performed in most dedicated SLE centres and rheumatology practices.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	

Table 1. Documentation of disease activity and cumulative damage compared to no documentation for assessing cardiovascular risk in SLE patients

Author(s): Tselios, Sheane, Gladman, Urowitz

Question: What is the association of disease activity and cumulative damage with CV risk in SLE patients?
Setting: outpatient

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SLE patients**	**Follow-up**	**Relative (95% CI)**		
DISEASE ACTIVITY (follow up: mean 9,4 years)											
5	observational studies	not serious	not serious	not serious	not serious	none	2976	9.4±7.6 years	**HR=1.07 [95%CI=1.062-1.078]**	⊕⊕⊕⊕ HIGH	CRITICAL
CUMULATIVE DAMAGE (follow up: mean 9,4 years)											
3	observational studies	not serious	not serious	not serious	not serious	none	3151	9.4±7.6 years	**1.13 [95%CI=1.09-1.16]**	⊕⊕⊕⊕ HIGH	CRITICAL

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Question

Should **documentation of renal and central nervous system involvement** vs. **no screening** be used for **assessing CV risk in SLE patients**?

POPULATION:	SLE patients in Canada
INTERVENTION:	documentation of renal and central nervous system involvement
COMPARISON:	no screening
MAIN OUTCOMES:	Lupus Nephritis (abnormal serum creatinine); NPSLE; CV and subclinical CV outcomes
SETTING:	Outpatient
PERSPECTIVE:	Population

BACKGROUND: Accelerated atherosclerosis leading to premature coronary artery disease (CAD) represents one of the major causes of death in patients with systemic lupus erythematosus (SLE); in particular, the standardized mortality ratio due to cardiovascular disease was the only one that did not appear to diminish overtime in the largest lupus cohort ever assembled [1]. Since the initial description of the bimodal pattern of mortality in SLE by Urowitz et al [2], several large epidemiological studies have demonstrated that atherosclerotic CAD affects a significant proportion of these patients [3, 4]. It is noteworthy that the relative risk for myocardial infarction in young, pre-menopausal, female patients was estimated to exceed 50-fold that of age-matched healthy controls [5]. More recent studies confirmed these findings, as lupus patients aged 20-39 years had a 16-fold increase risk of death from CAD in a population-wide study from Sweden [6]. Increased morbidity for CAD has been confirmed even during the first year after disease diagnosis (relative risk for myocardial infarction of approximately 5) [7], as well as two years preceding disease diagnosis [8].

The pathophysiology of premature atherosclerosis in SLE is still incompletely understood and involves a complex interplay between both traditional and disease-related risk factors [9, 10]. Among the latter, SLE itself has been demonstrated to confer the greater risk for premature cardiovascular disease, as disease activity, cumulative damage, autoantibodies, soluble inflammatory factors and medications seem to play a significant role [11]. Nevertheless, the importance of traditional risk factors should not be underestimated, as early detection and management may improve long-term prognosis.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes	Atherosclerotic cardiovascular events (CVEs) occur in 6 to 11% of SLE patients whereas the first event is more likely to develop between the age of 48 and 50 years [1-5]. Furthermore, premenopausal women have an excess risk for developing clinical premature CAD (i.e. myocardial infarction) [5, 6]. Recent research has demonstrated an increased risk for CVEs in the first year after	

	● Yes ○ Varies ○ Don't know	disease diagnosis or, even, in the two years preceding diagnosis [7, 8].	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	See Table 1. Based on our meta-analysis [5, 12-29], renal impairment, as a result of lupus nephritis, was an independent predictor of CVEs [HR=2.89, 95%CI=2.78-2.99]. Neuropsychiatric involvement was associated with CVEs [HR=1.68, 95%CI=1.65-1.70]. A different low quality meta-analysis provided a higher HR=5.2 [95%CI=2.0-13.9], [30]. **Subgroup considerations**: Patients with renal and/or neuropsychiatric involvement. **Subclinical disease considerations:** Impaired renal function due to lupus nephritis was associated with increased aortic stiffness (HR=7.5) [31] and increased carotid IMT and plaque [32, 33], even in pediatric lupus patients [34]. Creatinine levels>110mmol/L were associated with a 16.4-fold increase of coronary calcification [35, 36]. Proteinuria was related to increased carotid IMT and plaque [33, 37, 38]. Leukopenia was related to increased aortic stiffness [31], while lymphopenia was related to the presence and progression of carotid IMT [39]. Co-morbidities, such as low bone mineral density and depression (HR=3.85), conferred increased risk for coronary artery calcification [40, 41].	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies		The panel agreed that the evidence for the association of renal and central nervous system involvement with CV risk is high and would remain high after considering the link with potential treatment for these risks factors.
VALUES	**Is there important uncertainty about or variability in how much**	The relative importance or values of the main outcomes of interest: **Outcome** **Relative Importance**	

	people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Coronary Artery Disease (angina, myocardial infarction, acute coronary syndrome, percutaneous transluminal coronary angioplasty, coronary artery by[pass graft, congestive heart failure) CRITICAL	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	No research evidence was identified.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	It was recently shown that the direct cost of acute MI in elderly patients in Ontario, Canada is approximately 30.000CAD for a 6-year period (3 years before and 3 years after the event). Overall, heart disease and stroke cost the Canadian economy approximately 21 billion CAD per year (Conference Board of Canada, 2010).	Additional costs due to need for assessment of renal and/or neuropsychiatric involvement. The panel felt that while there might be potential for increased costs to confirm the diagnosis of renal and/or neuropsychiatric lupus, the resource requirements would be part of standard of care and infrequently required.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence was identified.	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	No direct evidence.	The panel acknowledged that the benefit of recognizing renal and/or neuropsychiatric lupus phenotypes due to associated cardiovascular risk outweighed the small possible resource requirements.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No direct evidence.	Diagnostic modalities required to facilitate diagnosis of neuropsychiatric SLE (eg. MRI, SPECT scans) may not be available everywhere in Canada. The panel felt this might reduce equity.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No direct evidence for this.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		The panel acknowledged this would be part of standard patient assessment with a clinical history and physical examination as well as ongoing disease activity/damage assessments.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability				

	JUDGEMENT							IMPLICATIONS
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should documentation of renal and central nervous system involvement vs. no screening be used for assessing CV risk in SLE patients?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

RECOMMENDATION	***Best practice dictates that a cardiovascular (CV) risk assessment be performed in adult patients upon diagnosis of systemic lupus erythematosus*.** *Remarks:* This ETD supports Recommendations #2 and #3 as well as Best Clinical Practice Statements for "General Assessment" and "Cardiovascular Risk".
JUSTIFICATION	This ETD acknowledges the importance of particular phenotypes in SLE that have been shown to be independent predictors of atherosclerotic CVEs in several SLE cohorts. While resource requirements (eg. renal biopsy CNS imaging) might be increased in a subset of patients requiring this evaluation, the overall resource burden would be small to moderate at most and rely on clinical judgement. Specific documentation of renal and/or neuropsychiatric phenotypes when present was not felt to place a significant burden on equity, acceptability or feasibility.
SUBGROUP CONSIDERATIONS	Patients with renal and/or neuropsychiatric involvement.
IMPLEMENTATION CONSIDERATIONS	Diagnostic modalities for the assessment of renal involvement (renal biopsy) and neuropsychiatric disease (brain MRI, SPECT) may not be available in remote settings.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	

Table 1. Renal and neuropsychiatric SLE involvement and cardiovascular risk in SLE patients

Author(s): Tselios, Sheane, Gladman, Urowitz
Question: What is the association of renal and central nervous system involvement with CV risk in SLE patients?
Setting: outpatient

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients	Follow up	Relative (95% CI)		
Lupus Nephritis (abnormal serum creatinine) (follow up: mean 9,4 years)											
4	observational studies	not serious	not serious	not serious	not serious	none	131/1421 (9.2%)	9.4±7.6 years	**RR 2.89** (2.78 to 2.99)	⊕⊕⊕⊕ HIGH	CRITICAL
NPSLE (follow up: mean 9,4 years)											
3	observational studies	not serious	not serious	not serious	not serious	none	518/5164 (10.0%)	9.4±7.6 years	**RR 1.68** (1.65 to 1.70)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

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Question

Should **hsCRP monitoring** vs. **no monitoring** be used for **assessing CV risk in SLE patients**?

POPULATION:	SLE patients in Canada
INTERVENTION:	hsCRP monitoring
COMPARISON:	no monitoring
MAIN OUTCOMES:	CV outcomes and subclinical outcomes
SETTING:	outpatient
PERSPECTIVE:	population

BACKGROUND: Accelerated atherosclerosis leading to premature coronary artery disease (CAD) represents one of the major causes of death in patients with systemic lupus erythematosus (SLE); in particular, the standardized mortality ratio due to cardiovascular disease was the only one that did not appear to diminish overtime in the largest lupus cohort ever assembled [1]. Since the initial description of the bimodal pattern of mortality in SLE by Urowitz et al [2], several large epidemiological studies have demonstrated that atherosclerotic CAD affects a significant proportion of these patients [3, 4]. It is noteworthy that the relative risk for myocardial infarction in young, pre-menopausal, female patients was estimated to exceed 50-fold that of age-matched healthy controls [5]. More recent studies confirmed these findings, as lupus patients aged 20-39 years had a 16-fold increase risk of death from CAD in a population-wide study from Sweden [6]. Increased morbidity for CAD has been confirmed even during the first year after disease diagnosis (relative risk for myocardial infarction of approximately 5) [7], as well as two years preceding disease diagnosis [8]. The pathophysiology of premature atherosclerosis in SLE is still incompletely understood and involves a complex interplay between both traditional and disease-related risk factors [9, 10]. Among the latter, SLE itself has been demonstrated to confer the greater risk for premature cardiovascular disease, as disease activity, cumulative damage, autoantibodies, soluble inflammatory factors and medications seem to play a significant role [11]. Nevertheless, the importance of traditional risk factors should not be underestimated, as early detection and management may improve long-term prognosis.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Atherosclerotic cardiovascular events (CVEs) occur in 6 to 11% of SLE patients whereas the first event is more likely to develop between the age of 48 and 50 years [1-5]. Furthermore, premenopausal women have an excess risk for developing clinical premature CAD (i.e. myocardial infarction) [5, 6]. Recent research has demonstrated an increased risk for CVEs in the first year after disease diagnosis or, even, in the two years preceding diagnosis [7, 8].	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large	Table 1. Impact of hsCRP on cardiovascular events in SLE. Based on our meta-analysis [5, 12-29], high-sensitivity CRP confers an increased risk for CVEs [HR=2.8, 95%CI=2.7-2.9]. **Subclinical disease considerations:** HsCRP was an independent predictor of endothelial dysfunction [30] and increased arterial stiffness [31], carotid	

	○ Varies ○ Don't know	IMT and plaque (HR=3) [32-36] and coronary calcification presence and severity (HR = 1.65 - 4.15) [37-39]. Complement fragment C3 was associated with increased risk for arterial stiffness [35], increased carotid IMT [32, 40] and coronary artery calcification [41]. Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) increased risk for carotid IMT and plaque by 29-fold (levels>373pg/ml) [42], IL-6 was related to coronary artery calcification (HR=1.07) [43], VEGF to increased carotid IMT [44] and coronary calcification [39], TNFa, VCAM and E-selectin were associated with coronary calcification [39], as well as ICAM-1 [37, 39]. Low TGFb1 was related to increased IMT [45]. Type I interferons were independently associated with increased carotid IMT and severity of coronary calcification [46]. Adipocytokines were recently introduced as potential atherosclerosis risk factors; leptin (particularly >34ng/dl) conferred an increased risk for carotid IMT and plaque [42, 47]. Uric acid was an independent predictor of coronary calcification [48].	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies		The panel agreed that the evidence for the association of hsCRP with CV risk is high and would remain high after considering the link with potential treatment to prevent cardiovascular outcomes.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	**Outcomes and their relative importance:** **Outcome(s)** — **Relative Importance** Coronary Artery Disease (angina, myocardial infarction, acute coronary syndrome, percutaneous transluminal coronary angioplasty, coronary artery by-pass graft, congestive heart failure) — CRITICAL	

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Small increased cost to assess hsCRP in some centers in Canada. (eg. Province of Ontario, $6.71 CAD).	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies		

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	It was recently shown that the direct cost of acute MI in elderly patients in Ontario, Canada is approximately 30.000CAD for a 6-year period (3 years before and 3 years after the event). Overall, heart disease and stroke cost the Canadian economy approximately 21 billion CAD per year (Conference Board of Canada, 2010).	While additional costs for assessing hsCRP might be incurred in certain health regions across Canada, the panel felt that the benefit of the screening test for CV risk outweighed the potential increased cost.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	The panel felt that performance of this test may vary from region to region which might increase health inequity across Canada.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No direct evidence.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes	No research evidence was identified.	

	○ Yes ○ Varies ○ Don't know		

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	

	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should hsCRP monitoring vs. no monitoring be used for assessing CV risk in SLE patients?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	See Best Practice Statements for General Assessment and Cardiovascular Risk as well as Recommendations #2 and #3.				
JUSTIFICATION	The evidence for evaluating CRP specifically for cardiovascular risk assessment is high quality; there is also evidence of an increase in CVEs in the general population with abnormal CRPs. The unavailability of the test across health regions might increase inequity and resource requirements that contribute to the conditional status of this recommendation.				
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS	High sensitivity CRP may be not available in remote settings.				
MONITORING AND EVALUATION					
RESEARCH PRIORITIES					

Table 1. Association of high sensitivity CRP with cardiovascular events in SLE patients

Author(s): Tselios, Sheane, Gladman, Urowitz
Question: What is the association of HsCRP with CV risk in SLE patients?
Setting: outpatient

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SLE patients**	**Follow-Up**	**Relative Risk (95% CI)**		
High sensitivity C-reactive protein (follow up: mean 9,4 years)											
3	observational studies	not serious	not serious	not serious	not serious	none	1573	9.4±7.6 years	HR=2.8 95%CI=2.7-2.9	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval

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Question

Should **screening for antiphospholipid antibodies** vs. **no screening** be used for **assessing CV risk in SLE patients**?

POPULATION:	SLE patients in Canada	**BACKGROUND:**	Accelerated atherosclerosis leading to premature coronary artery disease (CAD) represents one of the major causes of death in patients with systemic lupus erythematosus (SLE); in particular, the standardized mortality ratio due to cardiovascular disease was the only one that did not appear to diminish overtime in the largest lupus cohort ever assembled [1]. Since the initial description of the bimodal pattern of mortality in SLE by
INTERVENTION:	screening for antiphospholipid antibodies		
COMPARISON:	no screening		

MAIN OUTCOMES:	IgG anticardiolipin antibody; IgM anticardiolipin antibody; IgG anti-b2 glycoprotein I antibody; Lupus anticoagulant; CV and subclinical CV outcomes	Urowitz et al [2], several large epidemiological studies have demonstrated that atherosclerotic CAD affects a significant proportion of these patients [3, 4]. It is noteworthy that the relative risk for myocardial infarction in young, pre-menopausal, female patients was estimated to exceed 50-fold that of age-matched healthy controls [5]. More recent studies confirmed these findings, as lupus patients aged 20-39 years had a 16-fold increase risk of death from CAD in a population-wide study from Sweden [6]. Increased morbidity for CAD has been confirmed even during the first year after disease diagnosis (relative risk for myocardial infarction of approximately 5) [7], as well as two years preceding disease diagnosis [8]. The pathophysiology of premature atherosclerosis in SLE is still incompletely understood and involves a complex interplay between both traditional and disease-related risk factors [9, 10]. Among the latter, SLE itself has been demonstrated to confer the greater risk for premature cardiovascular disease, as disease activity, cumulative damage, autoantibodies, soluble inflammatory factors and medications seem to play a significant role [11]. Nevertheless, the importance of traditional risk factors should not be underestimated, as early detection and management may improve long-term prognosis.
SETTING:	outpatient	
PERSPECTIVE:	population	

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Atherosclerotic cardiovascular events (CVEs) occur in 6 to 11% of SLE patients whereas the first event is more likely to develop between the age of 48 and 50 years [1-5]. Furthermore, premenopausal women have an excess risk for developing clinical premature CAD (i.e. myocardial infarction) [5, 6].	Recent research has demonstrated an increased risk for CVEs in the first year after disease diagnosis or, even, in the two years preceding diagnosis [7, 8].

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Based on our meta-analysis [5, 12-29]: Anticardiolipin antibodies (aCL) were independent predictors of CVEs IgG aCL [HR=2.31, 95%CI=2.25-2.37] IgM aCL [HR=2.17, 95%CI=2.12-2.22] IgG anti-β2GPI antibodies were associated with CVEs [HR=2.87, 95%CI=2.68-3.01]. Lupus anticoagulant (LA) was related to CVEs [HR=2.92, 95%CI=2.84-2.99]. A different meta-analysis [30] provided higher HRs for aCL [5.8, 95%CI=3.28-7.78] and LA [3.5, 95%CI=1.29-9.36].	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Subclinical disease considerations:** Anticardiolipin antibodies were associated with myocardial perfusion defects (HR=4.1) [31], carotid plaques (HR=5.2) [32] and coronary calcification [31]. Anti-b2GPI antibodies were related to coronary calcification [31]. Lupus anticoagulant was associated with carotid plaque (HR=5.2) [32] and coronary calcification (HR=4.4) [31]. Other antiphospholipid epitopes, such as anti-oxPAPC (oxidised palmitoyl arachinodoyl phosphocholine), were identified as risk factors for carotid IMT and plaque formation (HR=1.06) [33]. Low levels of natural IgM anti-phosphorylcholine antibodies were related to increased carotid IMT and plaque formation [34, 35]. Anti-dsDNA autoantibodies were associated with CVEs (HR=1.56) [31] and non-calcified coronary plaques [36].	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies		The panel agreed that the evidence for the association of antiphospholipid antibodies with CV risk is high and would remain high after considering the link with potential treatment to prevent cardiovascular outcomes.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability	The relative importance or values of the main outcomes of interest: **Outcome** — **Relative Importance** Coronary Artery Disease (angina, myocardial infarction, — CRITICAL	

	○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	acute coronary syndrome, percutaneous transluminal coronary angioplasty, coronary artery by-pass graft, congestive heart failure).	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	See above.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Additional costs due to need for antiphospholipid antibody assessment. It was recently shown that the direct cost of acute MI in elderly patients in Ontario, Canada is approximately 30.000CAD for a 6-year period (3 years before and 3 years after the event). Overall, heart disease and stroke cost the Canadian economy approximately 21 billion CAD per year (Conference Board of Canada, 2010).	

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	No direct studies	
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence was identified.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No anticipated impact however accessibility to these lab tests could vary from site to site thereby impacting equity amongst SLE patients in Canada.	

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No direct evidence for this criterion	Assessment of antiphospholipid antibodies particularly anticardiolipin (aCL) and anti-b2GPI antibodies, as well as lupus anticoagulant (LA) is currently recommended in the 14th International Congress on Antiphospholipid Antibodies Task Force [37]. Monitoring and follow-up is also recommended in the context of a new thrombotic event in the APA Task Force recommendations.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Availability of antiphospholipid antibodies across different health regions across Canada may vary.	

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the	Probably favors	Does not favor	Probably favors	**Favors the**	Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
	comparison	the comparison	either the intervention or the comparison	the intervention	**intervention**			
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**	

Conclusions

Should screening for antiphospholipid antibodies vs. no screening be used for assessing CV risk in SLE patients?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	See Best Practice Statements for General Assessments and Cardiovascular Risk.				

JUSTIFICATION	The evidence confirms a significant effect of antiphospholipid antibodies on cardiovascular outcomes in SLE patients. The panel agreed with the recommendations of the 14th International Congress on Antiphospholipid Antibodies Task Force [37]. The panel acknowledged the potential inequity across health regions for the performance of antiphospholipid antibodies, specifically available subtypes including anti-beta2 GP1 and lupus anticoagulant.
SUBGROUP CONSIDERATIONS	Patients with antiphospholipid syndrome.
IMPLEMENTATION CONSIDERATIONS	The aforementioned autoantibodies may be not available in remote settings.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	

Table 1. Impact of antiphospholipid antibodies on cardiovascular events in SLE

Author(s): Tselios, Sheane, Gladman, Urowitz
Question: What is the association of antiphospholipid antibodies with CV risk in SLE patients?
Setting: outpatient

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE Patients	Follow-Upo	Relative (95% CI)		
IgG anticardiolipin antibody (follow up: mean 9,4 years)											
5	observational studies	not serious	not serious	not serious	not serious	none	507/6195 (8.2%)	9.4±7.6 years	**RR 2.31** (2.25 to 2.37)	⊕⊕⊕⊕ HIGH	CRITICAL
IgM anticardiolipin antibody (follow up: mean 9,4 years)											
5	observational studies	not serious	not serious	not serious	not serious	none	507/6195 (8.2%)	9.4±7.6 years	**RR 2.17** (2.12 to 2.22)	⊕⊕⊕⊕ HIGH	CRITICAL
IgG anti-b2 glycoprotein I antibody (follow up: mean 9,4 years)											
2	observational studies	not serious	not serious	not serious	serious [1]	none	44/390 (11.3%)	8-12 years	**RR 2.87** (2.68 to 3.01)	⊕⊕⊕◯ MODERATE	CRITICAL
Lupus anticoagulant (follow up: mean 9,4 years)											
4	observational studies	not serious	not serious	not serious	not serious	none	364/4585 (7.9%)	9.4±7.6 years	**RR 2.92** (2.84 to 2.99)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. Few cardiovascular events

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Question

Should **carotid artery doppler ultrasound** be used for **assessing CV risk in SLE patients**?

POPULATION:	SLE patients in Canada
INTERVENTION:	carotid artery doppler ultrasound
COMPARISON:	no ultrasound
MAIN OUTCOMES:	Carotid artery intima-media thickness; Total plaque area of the carotid artery; CV events
SETTING:	SLE patients in Canada
PERSPECTIVE:	

BACKGROUND:

Accelerated atherosclerosis leading to premature coronary artery disease (CAD) represents one of the major causes of death in patients with systemic lupus erythematosus (SLE); in particular, the standardized mortality ratio due to cardiovascular disease was the only one that did not appear to diminish overtime in the largest lupus cohort ever assembled [1]. Since the initial description of the bimodal pattern of mortality in SLE by Urowitz et al [2], several large epidemiological studies have demonstrated that atherosclerotic CAD affects a significant proportion of these patients [3, 4]. It is noteworthy that the relative risk for myocardial infarction in young, pre-menopausal, female patients was estimated to exceed 50-fold that of age-matched healthy controls [5]. More recent studies confirmed these findings, as lupus patients aged 20-39 years had a 16-fold increase risk of death from CAD in a population-wide study from Sweden [6]. Increased morbidity for CAD has been confirmed even during the first year after disease diagnosis (relative risk for myocardial infarction of approximately 5) [7], as well as two years preceding disease diagnosis [8].

The pathophysiology of premature atherosclerosis in SLE is still incompletely understood and involves a complex interplay between both traditional and disease-related risk factors [9, 10]. Among the latter, SLE itself has been demonstrated to confer the greater risk for premature cardiovascular disease, as disease activity, cumulative damage, autoantibodies, soluble inflammatory factors and medications seem to play a significant role [11]. Nevertheless, the importance of traditional risk factors should not be underestimated, as early detection and management may improve long-term prognosis.

Certain atherosclerosis imaging techniques have been associated with cardiovascular events (CVEs) in SLE.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Atherosclerotic cardiovascular events (CVEs) occur in 6 to 11% of SLE patients whereas the first event is more likely to develop between the age of 48 and 50 years [1-5]. Furthermore, premenopausal women have an excess risk for developing clinical premature CAD (i.e. myocardial infarction) [5, 6]. Recent research has demonstrated an increased risk for CVEs in the first year after disease diagnosis or, even, in the two years preceding diagnosis [7, 8].	

<table>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know</td><td rowspan="2">Carotid Intima-media Thickness and Carotid Plaque
Increased carotid IMT and plaque formation occur at a later stage of the atherosclerotic process and are characterized by restricted reversibility potential. Carotid IMT was strongly associated with traditional as well as disease-related risk factors in SLE [21, 22, 29-56]. In longitudinal studies, IMT progressed in 28-40% of the patients in 20-34 months [36, 49-51]. Furthermore, increased carotid IMT was an independent predictor of future CVEs [HR 1.35 after 8 years of follow-up] [45].
In SLE patients, plaque detection rate ranged from 7% to 50% [22, 29, 31, 32, 34-37, 49, 50, 54, 56]. In one longitudinal study, carotid plaque frequency was increased from 20% to 24% of the patients in 2 years [50]. Regarding its predictive ability, Eder et al showed that total plaque area was more strongly associated with clinical CAD than carotid IMT (HR 9.55 vs. 2.02, respectively) in 103 patients [38]. Furthermore, Kao et al demonstrated a 4.26-fold increased risk for CVEs in 392 lupus patients with carotid plaque [45]. In addition, the concurrent presence of carotid and femoral plaques was a better predictor for CVEs than carotid plaque alone (HR=5.92) [39].</td><td></td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know</td><td></td></tr>
<tr><td>CERTAINTY OF EVIDENCE</td><td>What is the overall certainty of the evidence of effects?
○ Very low
○ Low
● Moderate
○ High

○ No included studies</td><td></td><td></td></tr>
<tr><td>VALUES</td><td>Is there important uncertainty about or variability in how much people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty</td><td>The relative importance or values of the main outcomes of interest:
<u>Outcome</u> <u>Relative importance</u>
Coronary Artery Disease (angina, myocardial infarction, acute coronary syndrome, percutaneous transluminal coronary angioplasty, coronary</td><td></td></tr>
</table>

	or variability ○ No important uncertainty or variability	artery by-pass graft, congestive heart failure).	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No research evidence was identified.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	These interventions for screening are beyond current standard of care in most cases and incur significant costs (~ $200 CAD per procedure)	

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence was identified.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know		
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	May depend on site and what test is available	

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or	Possibly important uncertainty or	**Probably no important**	No important uncertainty or				

	JUDGEMENT							IMPLICATIONS
	variability	variability	**uncertainty or variability**	variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**	
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

Conclusions

Should carotid artery doppler ultrasound vs. no screening be used for assessing CV risk in SLE patients?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

RECOMMENDATION	***For adults with SLE, we suggest that carotid ultrasonography not be part of the cardiovascular risk assessment, except in highly selected cases where expertise is available. [conditional recommendation; moderate quality evidence]*** *Remarks*: The test may provide additional information to risk stratify patients, particularly in the context of cerebrovascular events (secondary prevention) and those with one or more traditional cardiovascular risk factors. This test is characterized by a high rate of false positive results hence requiring special expertise.
JUSTIFICATION	There is no evidence comparing the risk of cardiovascular outcomes in patients with SLE when results from a carotid ultrasonography are used or not used in the cardiovascular risk assessment. Two studies show that carotid artery intima-media thickness is likely associated with a small increased risk of cardiovascular events, and total plaque area of the carotid artery is likely associated with a large increased risk (84). Carotid ultrasonography requires substantial resources, is not feasible in some institutions, and will probably reduce equity. Therefore, it is suggested that carotid ultrasonography be reserved only for selected cases and not all adults with SLE.
SUBGROUP CONSIDERATIONS	Patients with >1 traditional risk factors.
IMPLEMENTATION CONSIDERATIONS	Required expertise may not be available in remote settings.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	

Table 1. Association of increased carotid artery intima-media thickness and total plaque area of the carotid artery with increased cardiovascular events

Author(s): Tselios, Sheane, Urowitz, Gladman
Question: Should carotid artery doppler ultrasound be used for screening for CV risk in SLE patients?
Setting: outpatient

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SLE Patients**	**Follow Up**	**Relative (95% CI)**		
Carotid artery intima-media thickness (follow up: median 8 years)											
2	observational studies	not serious	not serious	not serious	serious [1]	none	495	8 years	**1.35 [95%CI=1.12-1.64]** **2.87 [95%CI=1.65-5.02]**	⊕⊕⊕◯ MODERATE	CRITICAL
Total plaque area of the carotid artery (follow up: median 8 years)											
2	observational studies	not serious	not serious	not serious	serious [1]	none	495	8 years	**4.26 [95%CI=1.23-14.83]** **9.55 [95%CI=3.46-26.39]**	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval

1. Few participants.

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Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

DATA SUPPLEMENT #5 OSTEOPOROSIS

Evidence to decision framework

What are the minimal investigations necessary to optimally monitor the risk of osteoporosis in SLE patients? OR

(Rephrased) - What are the minimal investigations necessary to optimally monitor the risk of fracture in SLE patients?

Problem: Risk of osteoporosis and fracture
Option: To perform more rigorous investigations (questionnaire, physical examination and/or paraclinical tests) to determine the risk for osteoporosis and fracture in SLE patients compared to general population.
Comparison: To perform equal investigations (as recommended in the Canadian Guidelines). See **[Annex 1]**
Setting: SLE patients in Canada
Perspective: Caregivers of SLE (rheumatologist, internal medicine) and SLE patients.

Background

The improved survival of patients with systemic lupus erythematous (SLE) (1) has focused attention on the morbidity related to long-term complications from the disease and its treatment. In particular, studies on bone health in patients with SLE demonstrated an increased incidence of bone loss, osteoporosis and fragility fractures in this population (2-7).

Osteoporosis (OP), a metabolic bone disease characterized by decreased bone mineralization, increased bone fragility and risk of fragility fracture. OP fracture can lead to increased morbidity and mortality (8, 9).

A clinical diagnosis of OP may be made in the presence of a fragility fracture, a fracture occurring from a fall from a standing height or less, without major trauma. In the absence of fragility fracture, bone mineral density (BMD) assessment by dual-energy x-ray absorptiometry (DAX) is the standard test to diagnose OP. According to the classification of the World Health Organization (WHO), OP is present when BMD falls more than 2.5 SD below that of a healthy young adult population, whereas osteopenia is present when BMD falls between 1.0 and 2.5 DS below that of a healthy young adult population(10).

Several diagnosis methods could detect vertebral fractures on lateral radiographs of thoracic and lumbar spine, but only few have been standardized for trials. The standardized semiquantitative method described by Genant et al (11) is the most used. In this method, vertebral fracture is defined as a reduction of at least 20% of the vertebral body height.

Subgroup considerations:

- SLE post menopausal women
- SLE patients with current or past use of glucocorticoids (GC).
    - Prolonged use of GC is defined, in Canadian Guidelines 2010 (12), as three months therapy at a prednisone-equivalent dose ≥ 7.5 mg daily.
- This document focuses on adults with SLE and recommendations for juvenile SLE (jSLE) could be part of future work.

NB: Sentences in italic refer to the general population and are used either to compare data from the SLE population, or to allow extrapolation in the absence of evidence in SLE patients.

X	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ ***Detailed judgements***	PREVALENCE OF OP 1) Canada: • Pineau and colleagues (2004): A study of 516 women with SLE seen between 1995 and 2000 found that 205 (mean age 45.2 ± 18.8) had a determination of BMD (2). Among the women whose BMDs were measured, 18% had osteoporosis and 49% had osteopenia. • *In general population, the Canadian Multicenter Osteoporosis Study (CaMos), a prospective cohort study of 9 423 noninstitutionalized individuals aged 25 years and older, found that **16%** of Canadian **women aged 50 years** and older and **6.6%** of Canadian **men** have OP based on WHO criteria (13).* 2) Mexico: • Cross-sectional study on 100 SLE pre-menopausal patients (mean age 32.8 ± 8.7), prevalence of OP was **5%** (3). • *In general premenopausal Mexican women (mean age 38.6 ± 6.4), **0.9%** (14).* 3) Sweden • In a cohort of SLE women (mean age 47), the prevalence of OP was **23%** and the BMD values at the lumbar spine and proximal femur are significantly lower compared to healthy controls (4). 4) Bulgaria • Cohort of SLE women, **68%** of women treated with GC have OP (n= 32, mean age 43.2 ± 12.0, SLE duration 13.4 ± 6.2 years, mean cumulative prednisone dose 34.4 g), compared to **19%** of SLE women never treated with GC (n=16, mean age 36.1 ± 9.0, SLE duration 3.2 ± 2.0) (5). FRACTURES 1) US population • There was nearly **a 5-fold increase in fracture** occurrence in women with SLE compared with women of similar age from the US population, with nearly half the fractures occurring before menopause (6). There were 86 symptomatic fractures compare to 18.1, the expected number of fracture. 2) Mexico • A cross-sectional Mexican study on 210 women with SLE (mean age 43): prevalence of **radiographic vertebral fractures was 26%**. 1 in 3 of these patients had normal bone mass density (BMD) at lumbar spine and hip (7).	

			• *In Latin American countries, radiographic vertebral fractures in a random sample of 1922 women aged 50 years and older (mean age 68) are **11,2%** (15).* *3) Glucocorticoid (GC) users* • *Van Staa and colleagues (2003), evaluate predictors of vertebral fx, including a threshold for BMD in patients receiving oral GC (16). The study population comprised 306 patients with baseline and 1-year follow-up data on vertebral fx (111 receiving placebo and 195 receiving risedronate). In the placebo group, the statistically significant predictors of incident fx were the baseline lumbar spine BMD (for each 1-point decrease in T score, relative risk [RR] 1.85, 95% confidence interval [95% CI] 1.06–3.21) and the daily GC dose (for each 10 mg dose increase, RR 1.62, 95% CI 1.11–2.36). In the BMD threshold analysis, compared with nonusers of GC, patients receiving GC were younger, had a higher BMD at baseline, and had fewer prevalent fx; nevertheless, the risk of fx was higher in the GC users compared with nonusers (adjusted RR 5.67, 95% CI 2.57–12.54). **The increased risk of fx was observed in GC users regardless of whether OP was present**.* *4) Morbidity* • *A study on 4820 women and 1783 men from CaMos compared health utilities index (HUI) scores after 5 years of follow-up among participants with or without incident clinical fractures. Men and women with hip fractures, compared to those without, **have lower quality of life.** Men and women with hip fractures have significantly more pain. In women, self-care, mobility and ambulation are also negatively impacted (8).* *5) Mortality:* • *In Canada, a 5-year observational cohort study on 7753 randomly selected people (5566 women and 2187 men) aged 50 years and older, evaluated the relation between fractures and mortality. Compared with participants who had no fracture during follow-up, those who had a **vertebral fracture** in the second year were at increased risk of death (adjusted HR 2.7, 95% CI 1.1-6.6). Those who had a **hip fracture** during the first year were also at risk (adjusted HR 3.2, 95% CI 1.4-7.4) (9).* <u>FALL RISK IN SLE PATIENTS:</u> • Studies on fall risk in SLE have not been published yet. • Fall risk might be increased in SLE patients due to fatigue, muscle weakness (du	

			to GC induced myopathy and/ or vitamin D deficiency), arthritis, neuropathy, epilepsy or visual impairment (17).
			<u>OSTEOPOROSIS RISK FACTORS IN SLE:</u>
			• The etiology of bone loss in SLE is supposed to be multifactorial, including traditional OP risk factors, inflammation, metabolic factors, hormonal factors, serologic factors, and medication-induced adverse effects (17). See **[Figure 1]** adapted from Bultink's article.
			• Some data show that SLE is an independent predictor of OP beyond the association of GC use.
			  ○ Pineau and colleagues (2004): On 205 SLE women, 18% had OP and 49% had osteopenia. Low bone density was associated with increasing age and a higher amount of lupus-related end-organ damage but was not associated with disease activity or GC use (2).
			  ○ Lee and colleagues (2006): A cross-sectional study on 307 women with SLE evaluates the relationship between disease damage and BMD (18). Women were stratified by the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology cumulative disease damage index (SDI) and prior use of GC. Mean age was 32.7 ± 11.8yr, 24.4% were African American, 65% were premenopausal and mean SDI 1.3 ± 1.8. Women with SLE having disease damage and no GC use had BMD T-score at the hip and lumbar spine similar to those of women with disease damage and prior GC use. These finding suggest an association between disease damage and lower BMD T-scores in women with SLE.
			• See **[Tables]** Risk factors for low BMD and fractures in SLE patients.	

VALUES

Is there important uncertainty or variability about how much people value the main outcomes?

Important uncertainty or variability	*Possibly important uncertainty or variability*	*Probably no important uncertainty or variability*	*No important uncertainty or variability*	*No known undesirable outcomes*
☐	☐	☐	☒	☐

Detailed judgements

1) In SLE:
   - No studies on SLE patients.
   - No evidence that SLE may differ from non-SLE patients. – Except the fact that osteoporosis/fractures is another hit, adding to the burden of this mutisystemic disease

2) *In general pupulation:: Systematic review and meta-analysis of utility-base quality of life for OP related conditions in non-SLE patients (19).*

Outcome	Relative importance	Certainty of evidence (GRADE)
HSUV pre-Fx	0.76 (95% CI 0.75, 0.77)	☑☑☑☐ Moderate HSUV influenced by patient age
HSUV post-hip Fx	0.57 (95% CI 0.52, 0.63)	☑☑☑☐ Moderate HSUV influenced by time after Fx
HSUV post-vertebral Fx	0.59 (95% CI 0.55, 0.62)	☑☑☑☐ Moderate HSUV influenced by time after Fx, patient age and patient's sex
HSUV post-wrist Fx	0.72 (95% CI 0.67, 0.78)	☑☑☑☐ Moderate HSUV inflenced by time after Fx, patient's sex and Fx history

- HSUV: Health State Utility Values
  - Cardinal values to measure patient's Health preferences
  - Ranging between 0 and 1, where 1 represents perfect health, 0 represents death.
  - In this meta-analysis (n=62) most of the studies used EQ-5D HSUV. The EQ-5D evaluates the heath status through 243 distinct health states across five dimension (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).
- Fx: Fracture
- Pre-fracture HSUVs referred to HSUVs from OP patients without a fracture or retrospectively from patients with fractures evaluating the HSUV for the condition prior to the fracture event.

From our point of view, the relative importance or values of the main outcomes of interest (perform a BMD and assess fracture risk to prevent fracture):

		Moderate/ High fracture risk	
		(+)	**(-)**
Fracture Risk Assessment Tool (FRAX)	**(+)**	Real positive • Consequences: Earlier fracture prevention; prevent possible fracture, side effects of drugs, cost to system of treatment. • Relative importance: Important	False positive • Consequences: Unnecessary worry and treatment with drugs, side effects of drugs • Relative importance: Important
	(-)	False negative • Consequences: False reinsurance, no fracture prevention, eventual fracture (possible) • Relative importance: important	Real negative • Consequences: No repercussion • Relative importance: Low

GRADE DECIDE

Problem: Osteoporosis and fracturein SLE patients

Option: To perform more rigorous investigations to determine the risk for OP and fracture in SLE patients compared to general population.

Comparison: To perform equal investigations (as recommended in the Canadian Guidelines)

Setting: SLE patients in Canada

Perspective: Caregivers of SLE (rheumatologist, internal medicine) in SLE patients

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of the evidence of effects?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	SHOULD WE PERFORM **MORE RIGOROUS INVESTIGATIONS** IN SLE PATIENTS COMPARED TO GENERAL POPULATION? 1) In SLE patients: • No studies • EULAR recommendations (evidence 2b, C): Assess for adequate calcium and vit D intake, regular exercise and smoking habit + screen for OP according to existing guidelines (20). **[Annex 2]** 2) In population with similarities to SLE: • American Gastroenterological Association (AGA) technical review on OP in Gastrointestinal Diseases (21). **[Annex 3]** • ACR 2010 recommendations for GC (22). **[Annex 4]** *3) In general population:* • *Including patients with risk factors that may apply to SLE, investigations already suggested by Canadian guidelines 2010 (12).* **[Annex 1]** • *Even in general population, OP screening remains controversial because there is no definitive data. The gold standard that would support screening for OP is the demonstration in a well-designed randomized trial that screening reduces fractures risk. The only published randomized trial did not find a significant fracture benefit from screening but had some design limitations.* ○ *4800* ***postmenopausal women*** *from Scotland (aged 45 to 54 years) were randomly assigned to OP screening (BMD measurement with DXA) or no screening. Nine years later, the effect of screening on the uptake of treatment and the incidence of fractures were assessed by postal questionnaire. A greater proportion of women reported current or past use of hormone therapy in the screened vs control group (52.4% vs 44.5%) ($p < 0.001$). In addition, 36.6% of the screened vs 21.6% of the control groups ($p < 0.001$) reported use of vitamin D, calcium, alendronate, etidronale or raloxifene. In an intention-to-treat analysis, there was a no statistically significant reduction in the incidence of fracture in the screened group (8.8% vs 9,4%, HR 0.79, 95% CI o.60-1.04). Limitations of trial include a low response rate (60%) and self-report of HT or other OP medications* (23).	Background materials for 2010 Clinical Practice Guidelines for the Diagnosis and Management of OP in Canada, available at: http://www.cmaj.ca/content/suppl/2010/10/12/cmaj.100771.DC1 • The development of these guidelines followed the Appraisal of Guidelines, Research and Evaluation (AGREE) framework. • For the systematic review of Risk Assessment Models, they performed literature searches in seven electronic databases, adapted search strategies from systematic reviews performed by Cochrane Musculoskeletal Group and followed the PRISMA flow diagram for selection of studies, the PRESS (Peer Reviewed Electronic Search Strategy) checklist and Cochrane Collaboration Handbook. • They used the systematic review of OP therapies of MacLean and colleagues (who included 76 randomized trials and 24 meta-analyses) supplemented with data from 30 randomized controlled trials published since 2008. • They abstracted all papers, graded them for quality of evidence and assigned a level of evidence using established criteria. • They developed and graded initial recommendations. Then, an expert panel met to discuss recommendations. The group used a modified RAND/University of California, Los Angeles Delphi method for developing consensus to ensure clinical relevance and applicability. • They used a rigorous methodology and we agree with the recommendations.
How substantial are the desirable anticipated effects?	*Don't know* ☐ | *Not important* ☐ | *Somewhat important* ☐ | *Moderately important* ☒ | *Very important* ☐ | ***Varies*** ☐ **Detailed judgements**		
How substantial are the undesirable anticipated effects?	*Don't know* ☐ | *Very important* ☐ | *Moderately important* ☐ | *Somewhat important* ☐ | *Not important* ☒ | ***Varies*** ☐ **Detailed judgements**		
Do the desirable effects outweigh the undesirable effects?	*No* ☐ | *Probably No* ☐ | *Don't know* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐ ***Detailed judgements***		

			ARE THE **TESTS AS ACCURATE** IN SLE VS NON-SLE PATIENTS? A. BONE MINERAL DENSITY (BMD) MEASUREMENT • In SLE patients: o No study has specifically evaluated the accuracy of DXA in SLE o No evidence that SLE may differ from non-SLE patients • *In GC users: BMD may not be the sole reliable diagnostic approach for patients receiving GC, since fracture in patients on GC occur independently of the decline in bone mass (24).* • *In general population:* o *The WHO classification should not be used in healthy premenopausal women and men younger than age 50, because the relationship between BMD and fracture risk is not well established in this population. Z-scores, not T-scores, are preferred. A Z-score of -2.0 or lower is defined as "below the expected range for age", and a Z-score above -2.0 is "within the expected range for age" (The International Society for Densitometry). http://www.iscd.org/official-positions/2013-iscd-official-positions-adult/ (Accessed on June 2016)* o *BMD are used in conjunction with 10-year fracture risk assessment for OP screening (FRAX, CAROC).* o *FRAX is not validated under 40 years old.* o *DXA is recognized as the reference method to measure BMD with acceptable accuracy errors, good precision and reproducibility (25).* o *DXA disadvantages are that the machine is large and expensive, and uses ionizing radiation. Studies of **radiation dose** to patient from DXA confirm that patient dose is small (0.001 mSv) compared to chest radiograph PA (0.02 mSv), CT chest (8mSv) (26).* B. 10-YEAR FRACTURE RISK • Fracture Risk Assessment Tool (FRAX) of the World Health Organization (WHO): In Canada, a cross-sectional study on 271 women with SLE (mean age 43.8 (13.1), SLE duration 11.6 (10.4)), evaluated FRAX-Major ≥ 20% in 9 patients (5.3%), of whom 6 were taking OP medications. FRAX-Hip ≥ 3% occurred in 16 patients (9.4%), of whom 9 were taking OP medications(27). Because it is unclear whether SLE should be considered as a cause of	

			secondary OP or whether it is interchangeable with Rheumatoid Arthritis (RA), they also calculated FRAX scores by substituting SLE for RA. This did not make any difference in the number of patients who had FRAX-Hip ≥ 3%, and two more patients were identified as having FRAX-Hip ≥ 20%. So, FRAX is accurate in SLE patients because it **may identify patients at higher risk of fracture**. • Canadian Association of Radiologists and Osteoporosis Canada (CAROC): No study evaluated CAROC tool in SLE patients. <u>SHOULD WE **MONITOR BMD MORE OFTEN** IN SLE PATIENTS?</u> 1) In SLE: No studies *2) In general population:* • *Canadian Guidelines 2010 (12):* ○ *For patients who are undergoing treatment, repeat measurement of BMD should initially be **performed after one to three years**; the testing interval can be increased once therapy is shown to be effective.* ○ *If BMD has improved or remains unchanged, the patient is considered to have had a good response to therapy.* ○ *Continued loss of BMD or a new fx may reflect poor adherence with therapy, failure to respond to therapy or previously unrecognized secondary causes of OP.* • *The International Society for Densitometry (2013 ISCD official position):* ○ *Serial BMD testing can be used to determine whether treatment should be started on untreated patients, because significant loss may be an indication for treatment.* ○ *Serial BMD testing can monitor response to therapy by finding an increase or stability of bone density.* ○ *Serial BMD testing can evaluate individuals for non-response by finding loss of bone density, suggesting the need for reevaluation of treatment and evaluation for secondary causes of osteoporosis.* ○ *Follow-up BMD testing should be done when the expected change in BMD equals or exceeds the least significant change (LSC).* ○ *Intervals between BMD testing should be determined according to each patient's clinical status**: typically one year after initiation or change of therapy is appropriate**, with longer intervals once therapeutic effect is*	

			established. *3) In GC users:* • *A **rapid decline in bone mineral density** begins in the first 3 months of GC use and peak at 6 months (28).* • *GC decreases intestinal absorption of calcium and phosphate and increase urinary excretion of calcium. In addition, long-term exposure to GC inhibits osteoblast proliferation and reduces sex hormone production. The combined result is a loss of BMD reported as high as 8% in the trabecular bone and 2% in the cortical bone of the lumbar spine over a 20-week period at a mean dose of 7.5 mg/day prednisone (29).* • *Canadian Guidelines 2010 (12): No comments on frequency of BMD on GC patients.* • *International Society for Densitometry (2013 ISCD official position): In conditions associated with rapid bone loss, such as **glucocorticoid** therapy, testing **more frequently** is appropriate.* <u>SHOULD WE MONITOR SLE PATIENTS WITH **25-OH-D** DIFFERENTLY FROM WHAT IS SUGGESTED FOR GENERAL POPULATION?</u> 1) In SLE • Studies in different geographic regions show an increased prevalence of vitamin D deficiency among SLE patients (30-32). Moreover, low 25-hydroxyvitamin D (25[OH] D) levels were associated with low BMD in the lumbar spine in Dutch SLE patients (33). • In Toronto (2010), Toloza and colleagues studied vitamin D status and its relationship with disease, therapy features and BMD in women with SLE. 124 patients with SLE were assessed and levels of 25(OH) D were lower than 32ng/ml in **66.7 %** of patients and below 16 ng/ml in **17.9 %** patients (32). • Several factors might negatively influence vitamin D status in SLE: (17) o **Photosensitivity**: Ultraviolet light intolerance is highly frequent in SLE patients and leads to avoidance of sun exposure and subsequent reduced de novo vitamin D synthesis in the skin. o **Dark skin pigment:** Patients with darker skin pigment might be at an increased risk for the development of vitamin D deficiency, since melanin	

			blocks vitamin D synthesis in the skin. Kamen and colleagues demonstrated that African American patients indeed had significantly lower vitamin D levels than whites (31). ○ **Use of sunscreen:** Patients with SLE are strongly advised to use sunscreen continuously, which can lead to decreased and sometimes completely stopped de novo vitamin D synthesis in the skin(34). ○ **Renal failure**: Renal failure induces low 1,25$(OH)_2$D levels by loss of the renal enzyme hydroxylase α1. Association between high serum creatinine and low 1,25$(OH)_2$D levels in SLE patients was reported (32). ○ **GC treatment** might reduce vitamin D levels by suppressing the intestinal calcium absorption. Toloza and colleagues found an association between cumulative GC exposure and low serum levels of both 25(OH) D and 1,25$(OH)_2$D (32). ○ **Disease activity**: A cross-sectional study demonstrates a negative association between vitamin D levels and disease activity via Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (30). ○ **Anti–vitamin D antibodies:** The role of anti-vitamin D antibodies in SLE is unclear. These antibodies were detected in 4% of SLE patients, but were not related to vitamin D serum levels (35). • No evidence that the accuracy of the test is less in SLE patients. 2) *In general population: Canadian Guidelines 2010 (12)* ***[Annex 1]*** <u>SHOULD WE USE **BONE TURNOVER MARKERS (BTM)** IN SLE PATIENTS?</u> 1) In SLE patients: • Borba and colleagues (Brazil, 2009) investigated the effects of SLE disease activity on bone metabolism, their relation to inflammatory cytokines and vitamin D levels(30). They performed a cross-sectional analysis of 36 SLE patients (mean age 30.0) and compared them to 26 normal controls (mean age 32.8). In multiple regression analysis, the 25OHD level was associated with SLEDAI, **osteocalcin** and **bone-specific alkaline phosphatase.** • Seguro and colleagues (Brazil, 2015) enrolled 63 premenopausal SLE patients (mean age 31.1±6.8, disease duration 5.25±3.8 years) to determine 1-year incidence of BMD loss (by dual X-ray absorptiometry) and the value of bone turnover markers (P1NP, CTX, OPG, RANKL). 36.5 % of patients presented	

			BMD loss and for those, baseline P1NP levels were significantly lower (36.95±23.37, p=0.031). This study provides evidence that **N-terminal propeptide of type 1 collagen (P1NP**), the most specific bone formation marker, is a **predictor of BMD loss over 12 months in pre-menopausal SLE patients** (36). 2) *In general population:* • *International Osteoporosis Foundation (IOF) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommends one bone formation marker (serum procollagen type I N propeptide, s-PINP) and one bone resorption marker (serum C-terminal cross-linking telopeptide of type I collagen, s-CTX) to be used as reference markers and measured by standardised assays in observational and intervention **studies** (37).* • *However, their clinical value for monitoring is limited by inadequate appreciation of the sources of variability, by limited data for comparison of treatments using the same BTM and by inadequate quality control (38). So, committees typically recommend against their routine use.* <u>ARE **TREATMENTS AS EFFECTIVE** IN SLE VS NON-SLE PATIENTS? IS THE POTENTAIL OF SIDE EFFECTS SIMILAR?</u> 1) In SLE: • Panopalis et al (2009) published an article on recent epidemiologic data concerning bone health in SLE and discusses preventive and therapeutic strategies. Bisphosphonates (etidronale, alendronate, risedronate) are effective in the prevention and treatment of **glucocorticoid-induced OP** in major randomized, controlled trials. Hormone replacement therapy (HRT) also improves BMD, but the use of these agents in SLE has been limited due to concerns regarding their potential to cause SLE disease exacerbations and increased cardiovascular events. Few studies have been performed in SLE (39). • No evidence that bisphosphonates cause more adverse effects in SLE vs non-SLE patients 2) *In general population a review from the U.S. Preventive Services Task Force shows that, for postmenopausal women, bisphosphonates reduce primary vertebral and nonvertebral fractures. Bisphosphonates are not associated with serious adverse events (40).*	

			<u>SHOULD WE CONSIDER ANY DATA ON CERTAIN MEDICATIONS THAT WOULD HAVE EFFECT ON THE RISK OF FRACTURES AND BMD?</u> 1) Hydroxychloroquine (HCQ): • In our review, patients taking HCQ seems to be less likely to develop OP and osteopenia than patients not taking HCQ (41, 42). The protective effects may be due to their action of reducing the production or the effect of cytokines that by them have a deleterious effect on bone. • However, in another study, the use of HCQ was associated with BMD loss at the hip(43). This association might be explained by the potential negative effect of HCQ on calcitriol serum levels and BMD by inhibiting conversion of 25(OH)D to the active calcitriol(44). 2) Anticoagulation therapy: A study shows a negative relation with fractures, but we only have the abstract and they do not specify if patients used heparin or warfarin(45).	

RESOURCE USE	**How large are the resource requirements?**	*Large costs* ☐ *Moderate costs* ☐ *Small* ☒ *Moderate savings* ☐ *Large savings* ☐ ***Varies*** ☐ **Detailed judgeXments**	1) In SLE patients: No studies on cost effectiveness of osteoporosis investigations in SLE patients, but no evidence that SLE may differ from non-SLE patients 2) *In general population* • *Published in 2006, a systematic reviews and analyses of administrative data were performed to determine the appropriate use of BMD assessments using DXA, and the associated trends in wrist and hip fractures in Ontario. Total cost of a BMD was $106. The average annual cost of treatment for low BMD with bisphosphonates was $391. This estimate was based on weekly doses of 70mgs of alendronate ($6.195/tablet) and 35mgs of risedronate ($8.85/tablet) (46).* • *Price of some medical laboratories: osteocalcin (8.40$), C Telopeptide (8.00$)* • *A review article on the cost-effectiveness of bisphosphonates for prevention and treatment of OP identified: (47)* ○ *11 studies investigating bisphosphonates in **women with low BMD and prior fractures** (four were performed in the UK, one in the US, two in Canada, two in Scandinavia and two in Spain). Overall, bisphosphonates therapy was **most cost effective in population aged ≥70 years** and was unlikely to be cost effective in population aged ≤50 years.* ○ *Five studies investigating the cost effectiveness of **screening for low BMD before treatment.** Overall, screening for low BMD before treatment with alendronate or etidronate appeared to be cost effective both in **postmenopausal women in general** and in **women with rheumatoid arthritis** who were initiating corticosteroid therapy. Effectively, in women with rheumatoid arthritis who were initiating corticosteroid therapy, it was cost effective to screen those who were aged ≥55 years, and then treat with alendronate or etidronate (48).*	
	How large is the incre-mental cost relative to the net benefit?	*Very large ICER* ☐ *Large ICER* ☐ *Moderate ICER* ☐ *Small ICER* ☐ *Savings* ☒ ***Varies*** ☐	1) In SLE: • No studies in SLE patients. • No studies on more rigorous screening than suggested by the guidelines. 2) *In general population:*	

		Detailed judgements	• *Ontario-Based economic analysis (46): In 2006, the economic analysis focused on analyzing the economic impact of decreasing future hip fractures by increasing the rate of BMD testing in* ***men and women age greater than or equal to 65 years following a hip or wrist fracture****. A decision analysis showed the above strategy, especially when enhanced by improved reporting of BMD tests, to be cost-effective, resulting in a* ***cost-effectiveness ratio ranging from $2,285 (Cdn****) per fracture avoided (worst-case scenario) to $1,981 (Cdn) per fracture avoided (best-case scenario). A budget impact analysis estimated that shifting utilization of BMD testing from the low risk population to high risk populations within Ontario would result in a saving of $0.85 million to $1.5 million (Cdn) to the health system. The potential net saving was estimated at $1.2 million to $5 million (Cdn) when the downstream cost-avoidance due to prevention of future hip fractures was factored into the analysis.*	

GRADE DECIDE

Problem: Osteoporosis and fracturein SLE patients

Option: To perform more rigorous investigations to determine the risk for OP and fracture in SLE patients compared to general population.

Comparison: To perform equal investigations (as recommended in the Canadian Guidelines)

Setting: SLE patients in Canada

Perspective: Caregivers of SLE (rheumatologist, internal medicine) in SLE patients

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ☒ *Uncertain* ☐ *Probably reduced* ☐ *Reduced* ☐ ***Varies*** ☐ **Detailed judgementsX**	1) In SLE: • No studies on SLE patients, but no evidence that SLE may differ from non-SLE patients. • No studies on more rigorous screening than suggested by guidelines 2) *In general population:* • *Access to a BMD facility may be a factor in northern or rural communities (49).* • *Access to 25-OHD and turnover markers dosage may be a factor in northern or rural communities*	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ **Detailed judgements**	1) In SLE: • No studies on SLE patients. • No studies on more rigorous screening than suggested by guidelines 2) *In general population: 457 family **physicians** in Ontario were asked to fill in a self-administered questionnaire to examine the use of BMD in the primary care setting. Few Ontario physicians were limited in their use of BMD. The only significant limitations identified by more than 10% of respondents were travel distance to a densitometer, and concerns regarding the cost of the test. Results also suggest a positive correlation between the frequency of BMD and the physicians' reported confidence in the use of the test (50).*	There are no studies examining the acceptability to **SLE patients** to perform screening of OP with BMD. Since this test is not invasive, we believe that they may be acceptable to them. However, we should consider: • Burden of taking the tests? • Feelings about radiation exposure? • Another appointment? • Would not take the treatment anyway?
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ **Detailed judgements**	• No studies on SLE patients. • No studies on more rigorous screening than suggested by the guidelines	

	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
Type of recommendation	☐	☐	☐	☒	☐

Recommendation

For all adult patients with SLE, we suggest assessing for risk of osteoporosis and fractures every 1 to 3 years using a detailed history and focused physical examination, and measuring bone mineral density (BMD) in patients with other risk factors according to recommendations in the general population. [conditional recommendation; low quality evidence].

Remarks: The assessment can be based on the FRAX (Fracture Risk Assessment Tool) (in individuals older than 50) which includes factors such as age, sex, weight, previous history of fracture, smoking and alcohol habits, use of high-risk medications including glucocorticoids, and height measurement (https://www.sheffield.ac.uk/FRAX). Bone mineral density is especially measured in patients with a history of fragility fractures, who have long term glucocorticoid therapy (greater than 3 months), who use other high-risk medications, or who have hypogonadism or premature menopause. This recommendation does not apply to the pediatric SLE population where osteoporosis is defined by fractures and not BMD (https://www.iscd.org/official-positions/2013-iscd-official-positions-pediatric).

For all adults with SLE, we suggest screening 25-hydroxyvitamin D as part of the assessment for risk of osteoporosis and fractures. [conditional recommendation; low quality evidence]

Remarks: This recommendation excludes pediatric SLE patients as the evidence for 25-hydroxyvitamin D screening was limited to adult SLE patients.

Justification

Current guidelines in Canada recommend assessing risk of osteoporosis in indviduals over age 50 every 1 to 3 years (12). There is no evidence comparing outcomes related to osteoporosis in patients with SLE who had or did not have an assessment before age 50. However, studies show that the prevalence of osteoporosis or osteopenia, and incidence of fractures may be higher in adult women with SLE (mean age 45). [2-7]]. The panel agreed that the FRAX tool is likely applicable to patients with SLE, and that measuring bone mineral density can be consistent with recommendations for the general population [8]. There was some concern that facilities to measure bone mineral density may not be available in northern or rural communities, and there may be additional burden to individuals if there is not a nearby bone densitometer.

There is no evidence comparing assessment of vitamin D to no assessment and the effects on bone outcomes. However, studies show that vitamin D deficiency may be more prevalent in patients with SLE, in particular, patients with renal failure, glucocorticoid treatment, or photosensitivity (43-46). The panel agreed that there would be negligible costs when screening for vitamin D, and it would be acceptable, equitable and feasible. Follow up on the status of vitamin D levels might be considered after a period of treatment.

Subgroup considerations

These guidelines apply to

- SLE post menopausal women
- SLE patients with current or past use of glucocorticoids (GC).
    - Prolonged use of GC is defined, in Canadian Guidelines 2010 (12), as three months therapy at a prednisone-equivalent dose ≥ 7.5 mg daily.
- This document focuses on adults with SLE and recommendations for juvenile SLE (jSLE) could be part of future work.

Implementation considerations

Monitoring and evaluation considerations

Research priorities

Formal randomized studies or large observational cohort studies with longer term follow up evaluating outcomes secondary to rigorous investigations to determine the risk of osteoporosis and fracture in SLE patients compared to general population are needed to provide more specific recommendations regarding OP investigations in SLE.

Clinical recommendations

Who should I assess for osteoporosis and fracture risk?

Women and men over age 50 should be assessed for risk factors for osteoporosis and fracture to identify those at high risk for fractures.

1. Individuals over age 50 who have experienced a fragility fracture should be assessed [grade A].

How do I assess for osteoporosis and fracture risk?

A detailed history and a focused physical examination are recommended to identify risk factors for low bone mineral density, falls and fractures, as well as undiagnosed vertebral fractures (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.100771/DC1). In selected individuals, bone mineral density should be measured with dual-energy x-ray absorptiometry (Table 1).

1. Measure height annually, and assess for the presence of vertebral fractures [grade A].
2. Assess history of falls in the past year. If there has been such a fall, a multifactorial risk assessment should be conducted, including the ability to get out of a chair without using arms [grade A].

Table 1: Indications for measuring bone mineral density

Older adults (age ≥ 50 yr)	Younger adults (age < 50 yr)
Age ≥ 65 yr (both women and men)	Fragility fracture
Clinical risk factors for fracture (menopausal women, men age 50–64 yr)	Prolonged use of glucocorticoids*
Fragility fracture after age 40 yr	Use of other high-risk medications†
Prolonged use of glucocorticoids*	Hypogonadism or premature menopause (age < 45 yr)
Use of other high-risk medications†	Malabsorption syndrome
Parental hip fracture	Primary hyperparathyroidism
Vertebral fracture or osteopenia identified on radiography	Other disorders strongly associated with rapid bone loss and/or fracture
Current smoking	
High alcohol intake	
Low body weight (< 60 kg) or major weight loss (> 10% of body weight at age 25 yr)	
Rheumatoid arthritis	
Other disorders strongly associated with osteoporosis	

*At least three months cumulative therapy in the previous year at a prednisone-equivalent dose ≥ 7.5 mg daily.
†For example, aromatase inhibitors or androgen deprivation therapy.

Box 1: Recommended biochemical tests for patients being assessed for osteoporosis

- Calcium, corrected for albumin
- Complete blood count
- Creatinine
- Alkaline phosphatase
- Thyroid-stimulating hormone
- Serum protein electrophoresis (for patients with vertebral fractures)
- 25-Hydroxyvitamin D*

*Should be measured after three to four months of adequate supplementation and should not be repeated if an optimal level (at least 75 nmol/L) is achieved.

1. The total daily intake of elemental calcium (through diet and supplements) for individuals over age 50 should be 1200 mg [grade B].
2. For healthy adults at low risk of vitamin D deficiency, routine supplementation with 400–1000 IU (10–25 μg) vitamin D_3 daily is recommended [grade D].
3. For adults over age 50 at moderate risk of vitamin D deficiency, supplementation with 800–1000 IU (20–25 μg) vitamin D_3 daily is recommended. To achieve optimal vitamin D status, daily supplementation with more than 1000 IU (25 μg) may be required. Daily doses up to 2000 IU (50 μg) are safe and do not necessitate monitoring [grade C].
4. For individuals receiving pharmacologic therapy for osteoporosis, measurement of serum 25-hydroxyvitamin D should follow three to four months of adequate supplementation and should not be repeated if an optimal level (≥ 75 nmol/L) is achieved [grade D].

Reference: Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010;182(17):1864-73.

Annex 1: Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada (continuation)

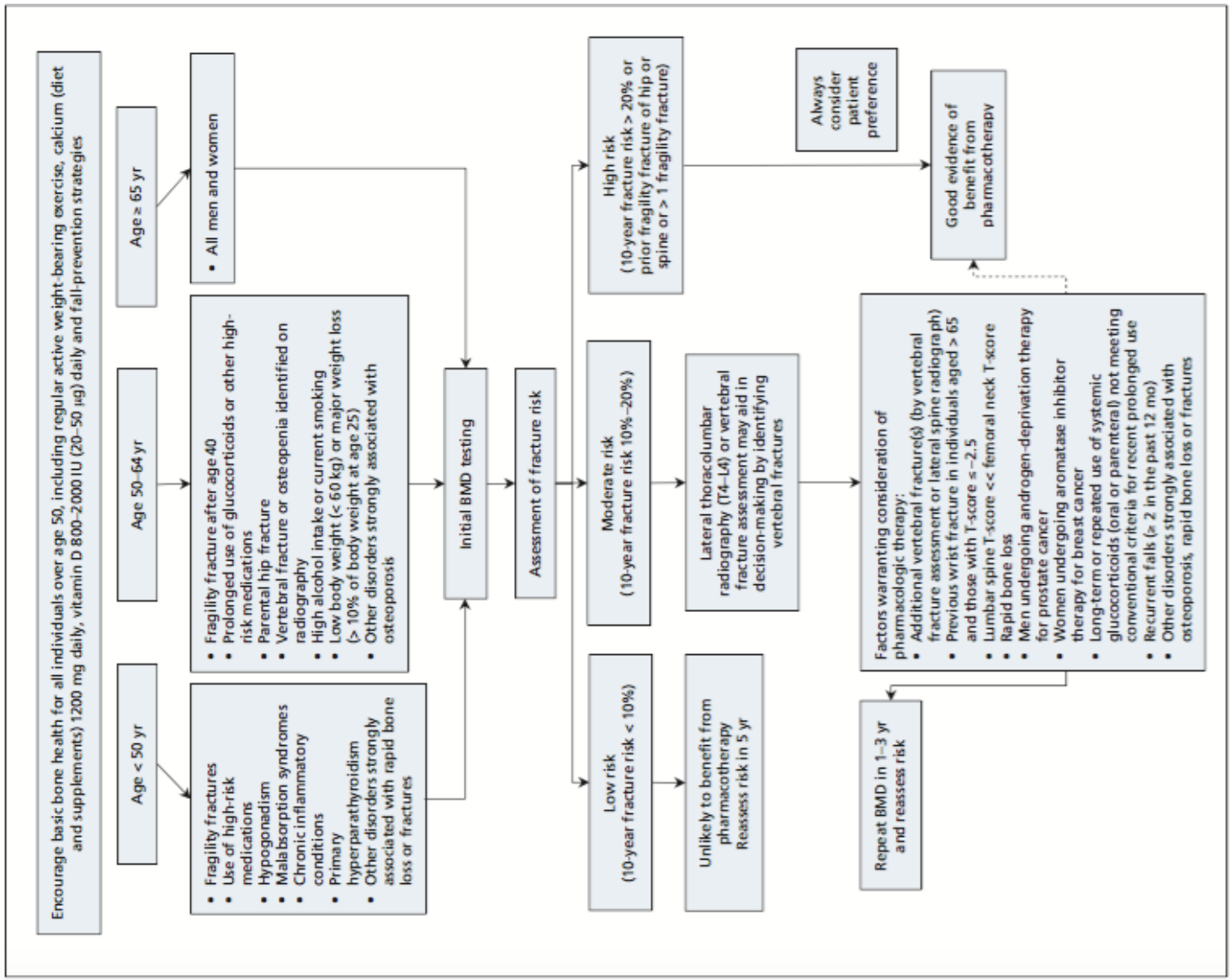


Figure 2: Integrated approach to management of patients who are at risk for fracture. BMD = bone mineral density. Dashed arrow indicates that evidence for benefit from pharmacotherapy is not as strong in this instance as for other recommendations.

Reference: Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010;182(17):1864-73.

Annex 2: EULAR Recommendations for Monitoring Patients with SLE in Clinical Practice and in Observational Studies

Table 1 List of recommendations with level of evidence and grade of recommendation, agreement, cost/risk ratio

Recommendation	Level of evidence and grade of recommendation	Agreement	Cost/risk
1. Patient assessment.			
In addition to the standard care of patients without lupus of the same age and sex, the assessment of patients with SLE must include the evaluation of:			
disease activity by a validated index at each visit			
organ damage annually			
general quality of life by patient history and/or by a 0–10 VAS (patient global score) at each visit	5, D	97.6	L/VL
comorbidities			
drug toxicity			
2. Cardiovascular risk factors			
At baseline and during follow-up at least once a year:			
assess smoking, vascular events (cerebral/cardiovascular), physical activity, oral contraceptives, hormonal therapies and family history of cardiovascular disease			
perform blood tests: blood cholesterol, glucose	1b, B	98.1	L/VL
examine for blood pressure, body mass index (and/or waist circumference)			
NB: some patients may need more frequent follow-up (ie, patients on glucocorticoids)			
3. Other comorbidities			
Osteoporosis. All patients with SLE:			
should be assessed for adequate calcium and vitamin D intake, regular exercise and smoking habits			
should be screened and followed for osteoporosis according to existing guidelines (a) for postmenopausal women; (b) for patients on steroids, or on any other medication that may reduce BMD	2b, C	93.8	M/VL
Cancer. Cancer screening is recommended according to the guidelines for the general population, including cervical smear tests	2b, C	92.3	M/L

Reference: Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Brey R, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis. 2010;69(7):1269-74.

Annex 3: American Gastroenterological Association Technical Review on Osteoporosis in Gastrointestinal Diseases

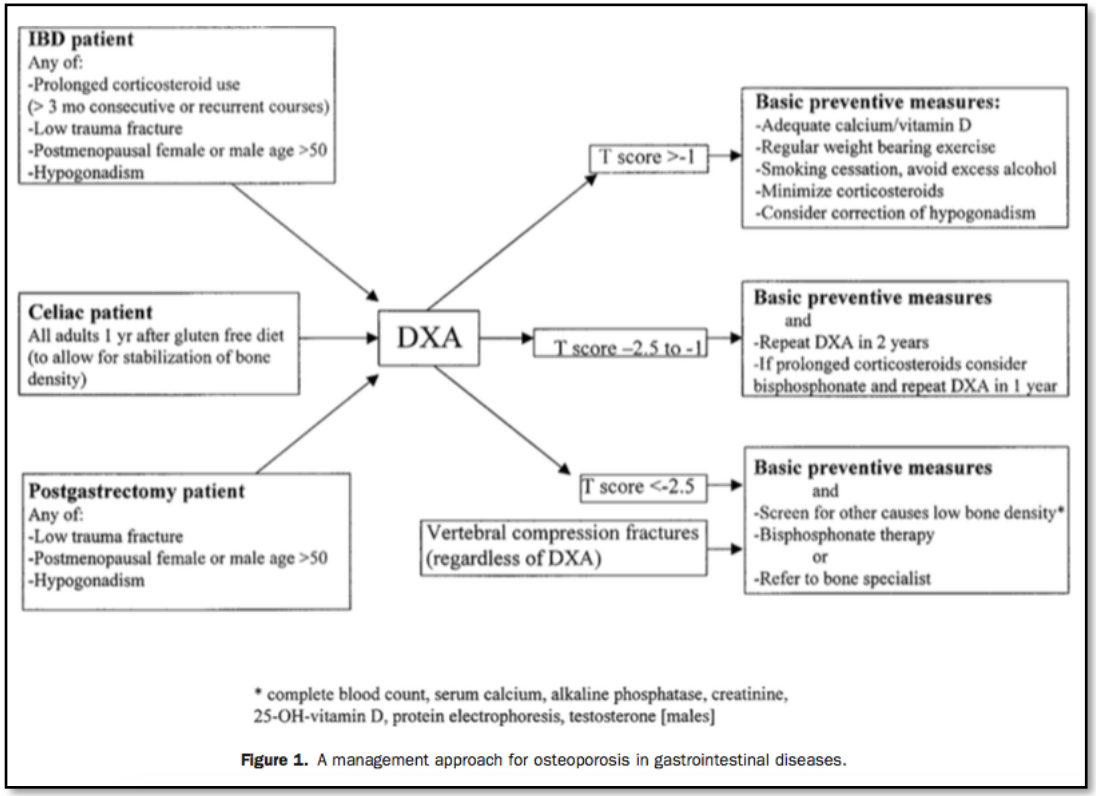


Figure 1. A management approach for osteoporosis in gastrointestinal diseases.

Reference: Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology. 2003;124(3):795-841.

Annex 4: ACR 2010 Recommendation for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Table 2. Recommendations on counseling for lifestyle modification and assessment of patients starting glucocorticoids at any dose with an anticipated duration ≥3 months

Recommendation	Level of evidence
Weight-bearing activities	C
Smoking cessation	C
Avoidance of excessive alcohol intake (>2 drinks per day)	C
Nutritional counseling on calcium and vitamin D intake	C
Fall risk assessment	C
Baseline dual x-ray absorptiometry	C
Serum 25-hydroxyvitamin D level	C
Baseline height	C
Assessment of prevalent fragility fractures	C
Consider radiographic imaging of the spine or vertebral fracture assessment for those initiating or currently receiving prednisone ≥5 mg/day or its equivalent	C
Calcium intake (supplement plus oral intake) 1,200–1,500 mg/day*	A
Vitamin D supplementation*	A

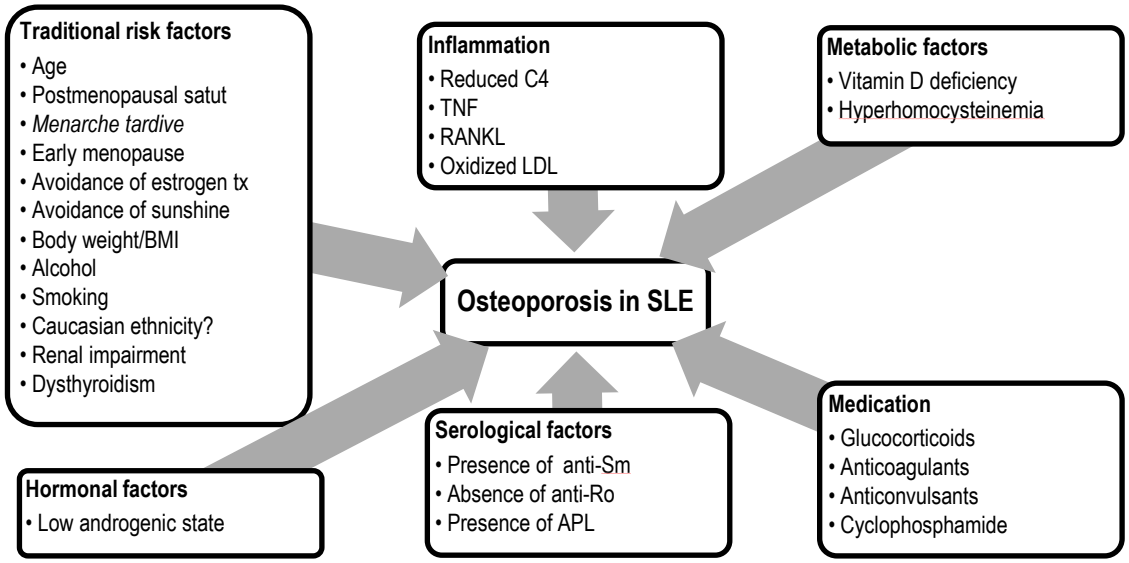
* Recommendations for calcium and vitamin D supplementation are for any dose or duration of glucocorticoids, rather than a duration of >3 months.

Table 3. Recommended monitoring for patients receiving prevalent glucocorticoid therapy for a duration of ≥3 months

Recommendation	Level of evidence
Consider serial bone mineral density testing	C
Consider annual serum 25-hydroxyvitamin D measurement	C
Annual height measurement	C
Assessment of incident fragility fracture	C
Assessment of osteoporosis medication compliance	C

Reference: Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken). 2010;62(11):1515-26.

Figure 1 Osteoporosis Risk Factors in SLE



Reference: Bultink IEM. Osteoporosis and fractures in systemic lupus erythematosus. Arthritis Care Res. 2012;64(1):2-8.

GRADE DECIDE

Tables: Risk Factors for Low Bone Mineral Density and Fractures in SLE Patients

Risk Factors for Low Bone Mineral Density (osteopenia and osteoporosis) at the Spine in SLE patients

Quality assessment							Summary of findings				Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ SLE patients	Effect/OR (95% CI)	NOS	Quality	
Postmenopausal status											
2 Furukawa, 2011(51) Lakshminarayanan, 2001(41)	Observational studies	Serious[1]	Not serious	Not Serious	Serious[2]	None	 58 92	 2.13 (0.31-14.61) **3.96 (1.59-9.85)**	 7 8	⊕⊕◯◯ Low	Important
Body mass index (kg/m²)											
1 Lee, 2007(52)	Observational studies	Serious[1]	Not serious	Not Serious	Serious[2]	None	 298	 **0.93 (0.89-0.98)**	 7	⊕⊕◯◯ Low	Important
History of smoking											
1 Furukawa, 2011(51)	Observational studies	Serious[1, 3]	Serious[4]	Not Serious	Serious[2]	None	 58	 0.41 (0.09-1.90)	 7	⊕◯◯◯ Very low	Important
Use of black tea or coffee											
2 Furukawa, 2011(51) Lee, 2007(52)	Observational studies	Serious[1, 3]	Serious[4]	Not Serious	Serious[2]	None	 58 298	 0.86 (0.23-3.21) **0.34 (0.17-0.72)**	 7 7	⊕◯◯◯ Very low	Important
Ethnicity (African American)											
1 Lee, 2007(52)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[2]	None	 298	 **4.42 (2.19-8.91)**[5]	 7	⊕◯◯◯ Very low	Not important
History of previous bone fracture											
1 Furukawa, 2011(51)	Observational studies	Serious[1, 3]	Serious[4]	Not Serious	Serious[2]	None	 58	 2.83 (0.75-10.65)	 7	⊕◯◯◯ Very low	Important
Ever pregnant (yes vs no)											
1 Lakshminarayanan, 2001(41)	Observational studies	Serious[1]	Not serious [6]	Not Serious	Serious[2]	None	 92	 **0.15 (0.04-0.62)**	 8	⊕⊕◯◯ Low	Important
Number of pregnancies, more than one											
2 Furukawa, 2011(51) Lakshminarayanan, 2001(41)	Observational studies	Serious[1]	Not serious[6]	Not Serious	Serious[2]	None	 58 92	 **5.85 (1.31-26.06)** **1.44 (1.07-1.94)**	 7 8	⊕⊕◯◯ Low	Important
Age at SLE diagnosis											
1 Lee, 2007(52)	Observational studies	Serious[1]	Not serious	Not Serious	Serious[2]	None	 298	 **0.96 (0.93-0.99)**	 7	⊕⊕◯◯ Low	Important
SLICC/ACR damage index (SDI)											
1 Lee, 2007(52)	Observational studies	Serious[1]	Not serious	Not Serious	Serious[2]	None	 298	 1.06 (0.89-1.26)	 7	⊕⊕◯◯ Low	Important
Renal involvement (proteinuria >0.5 m/ 24h, cellular casts or positive renal biopsy)											
2 Furukawa, 2011(51) Lee, 2007(52)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[2]	None	 58 298	 0.31 (0.09-1.05) 1.50 (0.71-3.16)	 7 7	⊕◯◯◯ Very low	Important
Current use of prednisone											
1 Lee, 2007(52)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[2]	None	 298	 1.54 (0.81-2.92)	 7	⊕◯◯◯ Very low	Important
Highest dose of prednisone, more than 50 mg / day											
1 Furukawa, 2011(51)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[2]	None	 58	 **0.25 (0.07-0.91)**[7]	 7	⊕◯◯◯ Very low	Important
History of IV methylprednisolone											
1 Furukawa, 2011(51)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[2]	None	 58	 0.30 (0.08-1.08)	 7	⊕◯◯◯ Very low	Important
Hydroxychloroquine duration, mo											
1 Lakshminarayanan, 2001(41)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[2]	None	 92	 **0.46 (0.25-0.84)**	 8	⊕◯◯◯ Very low	Important

[1] Under-matching in case-control studies, failure to match for prognostic factors and/or adjustment in statistical analysis

[2] Relatively few patients and few studies

[3] Differences in measurement of exposure (data collected by questionnaire survey)

[4] Unexplained heterogeneity of results and/or unexplained heterogeneity with studies in general population

[5] Most published studies examining bone health in SLE patients predominantly included withe individuals, and there is evidence that Caucasian and Asian ethnicity are associated with low BMD in SLE (Lakshminarayanan (2001), Li EK (1998)). In this study including 77 AA and 221 whites women, AA ethnicity was significantly associated with low BMD at the lumbar spine in women with SLE. Although AA ethnicity was not associated with low BMD at the hip, the finding of comparable mean hip BMD values and the significantly lower mean hip BMD Z score in AA compared to whites suggest that bone health in AA women may be at least similarly reduced as that of whites in the setting of SLE.

[6] Generally, the effect of ''any pregnancy'' and ''the number of pregnancies'' is a reduction of the risk of osteoporosis/osteopenia, but the magnitude of the effect became smaller as the number of pregnancies increases.

[7] Exposure to GC is generally considered to be a major factor contributing to the development of osteoporosis, although the net effect is still a matter of debate. In this study, they identified intake history of more than 50 mg oral steroids as a preventive factor of low BMD at lumbar spine. They used preventive continuous treatment of calcium and/or vitamin D and bisphosphonates for patients who have ever taken high-dose oral GC. These treatments could have played a protective role in minimizing the effect of steroids on bone density particularly at the LS; however, this cannot explain the increased protection from low BMD in patients who have taken a maximal dosage of > 50 mg/day of prednisolone. High-dose oral GC intake in the acute phase may protect bone mass at the LS by reducing inflammation due to proinflammatory cytokines in SLE patients.

GRADE DECIDE

Risk Factors for Low Bone Mineral Density (osteopenia and osteoporosis) at the Hip in SLE patients

Quality assessment							Summary of findings				Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ SLE patients	Effect/ OR (95% CI)	NOS	Quality	
Postmenopausal status											
1 Furukawa, 2011(51)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious[3]	None	58	2.17 (0.33-14.17)	7	⊕◯◯◯ Very low	Important
Body mass index (kg/m²)											
1 Lee, 2007(52)	Observational studies	Serious[1]	Not serious	Not Serious	Serious[3]	None	298	**0.90 (0.84-0.96)**	7	⊕⊕◯◯ Low	Important
History of smoking											
1 Furukawa, 2011(51)	Observational studies	Serious[1,4]	Serious[2]	Not Serious	Serious[3]	None	58	0.32 (0.05-1.86)	7	⊕◯◯◯ Very low	Important
Use of black tea or coffee											
2 Furukawa, 2011(51) Lee, 2007(52)	Observational studies	Serious[1, 4]	Serious[2]	Not Serious	Serious[3]	None	58 298	0.33 (0.07-1.53) 1.33 (0.53-3.36)	7 7	⊕◯◯◯ Very low	Important
Ethnicity											
2 Lakshminarayanan, 2001(41) Lee, 2007(52)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious[3]	None	92 298	**4.68 (1.44-15.20) Caucasian** 1.54 (0.69-3.46) African American	8 7	⊕◯◯◯ Very low	Not important
History of previous bone fracture											
1 Furukawa, 2011(51)	Observational studies	Serious[1, 4]	Serious[2]	Not Serious	Serious[3]	None	58	0.65 (0.16-2.67)	7	⊕◯◯◯ Very low	Important
Number of pregnancies, more than one											
1 Furukawa, 2011(51)	Observational studies	Serious[1]	Not Serious	Not Serious	Serious[3]	None	58	0.84 (0.21-3.36)	7	⊕⊕◯◯ Low	Important
Age at SLE diagnosis											
2 Lakshminarayanan, 2001(41) Lee, 2007(52)	Observational studies	Serious[1]	Not Serious	Not Serious	Serious[3]	None	92 298	**1.06 (1.02-1.10)** 0.98 (0.95-1.01)	8 7	⊕⊕◯◯ Low	Important
SLICC/ACR damage index (SDI)											
2 Lakshminarayanan, 2001(41) Lee, 2007(52)	Observational studies	Serious[1]	Not serious	Not Serious	Serious[3]	None	92 298	**1.32 (1.02-1.71)** **1.30 (1.08-1.57)**	8 7	⊕⊕◯◯ Low	Important
Renal involvement (proteinuria >0.5 m/ 24h, cellular casts or positive renal biopsy)											
2 Furukawa, 2011(51) Lee, 2007(52)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious[3]	None	58 298	0.58 (0.16-2.08) 0.79 (0.33-1.87)	7 7	⊕◯◯◯ Very low	Important
Current use of prednisone											
1 Lee, 2007(52)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious[3]	None	298	1.48 (0.71-3.09)	7	⊕◯◯◯ Very low	Important
Prednisone, average daily dose, mg											
1 Lakshminarayanan, 2001(41)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious[3]	None	92	**1.93 (1.17-3.17)**	8	⊕◯◯◯ Very low	Important
Highest dose of prednisone, more than 50 mg / day											
1 Furukawa, 2011(51)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious[3]	None	58	1.14 (0.29-4.46)	7	⊕◯◯◯ Very low	Important
History of IV methylprednisolone											
1 Furukawa, 2011(51)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious[3]	None	58	0.53 (0.13-2.15)	7	⊕◯◯◯ Very low	Important

[1] Under-matching in case-control studies, failure to match for prognostic factors and/or adjustment in statistical analysis

[2] Unexplained heterogeneity of results and/or unexplained heterogeneity with studies in general population

[3] Relatively few patients and few studies

[4] Differences in measurement of exposure (data collected by questionnaire survey)

Risk Factors for Low Bone Mineral Density (osteopenia and osteoporosis) at any Sites in SLE patients

Quality assessment							Summary of findings				Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ SLE patients	Effect/ OR (95% CI)	NOS	Quality	
Age											
1 Yee, 2005(53)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious[3]	None	242	1.0 (1.0-1.1)	7	⊕◯◯◯ Very low	Important
Postmenopausal status											
2 Furukawa, 2011(51) Yee, 2005(53)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious	None	58 242	1.62 (0.20-13.1) **13.3 (1.6-111.1)**	7 7	⊕◯◯◯ Very low	Important
History of smoking											
1 Furukawa, 2011(51)	Observational studies	Serious[1, 4]	Serious[2]	Not Serious	Serious	None	58	0.27 (0.06-1.28)	7	⊕◯◯◯ Very low	Important
Use of black tea or coffee											
1 Furukawa, 2011(51)	Observational studies	Serious[1, 4]	Serious[2]	Not Serious	Serious	None	58	0.28 (0.05-1.52)	7	⊕◯◯◯ Very low	Important
Ethnicity											
1 Yee, 2005(53)	Observational studies	Serious[1]	Not serious	Not Serious	Serious	None	242	**2.5 (1.2-5.4)** Non-Afro-Caribbean	7	⊕⊕◯◯ Low	Not Important
History of previous bone fracture											
1 Furukawa, 2011(51)	Observational studies	Serious[1, 4]	Serious[2]	Not Serious	Serious	None	58	1.50 (0.39-5.81)	7	⊕◯◯◯ Very low	Important
Number of pregnancies, more than one											
1 Furukawa, 2011(51)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious	None	58	4.45 (0.93-21.34)	7	⊕◯◯◯ Very low	Important
Disease duration											
1 Sinigaglia, 1999(54)	Observational studies	Serious[1]	Not serious	Not Serious	Serious	None	84	**1.2 (1.07-1.33)** for each year of disease	4	⊕⊕◯◯ Low	Important
Renal involvement (proteinuria >0.5 m/ 24h, cellular casts or positive renal biopsy)											
1 Furukawa, 2011(51)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious	None	58	0.27 (0.07-1.03)	7	⊕◯◯◯ Very low	Important
Highest dose of prednisone, more than 50 mg / day											
1 Furukawa, 2011(51)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious	None	58	0.30 (0.08-1.06)	7	⊕◯◯◯ Very low	Important
Prednisone > 10 mg / day											
1 Yee, 2005(53)	Observational studies	Serious[1,]	Serious[2]	Not Serious	Serious	None	242	**2.1 (1.1-4.2)**	7	⊕◯◯◯ Very low	Important
History of IV methylprednisolone											
1 Furukawa, 2011(51)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious	None	58	0.36 (0.10-1.30)	7	⊕◯◯◯ Very low	Important
Duration of prednisone therapy											
1 Sinigaglia, 1999 (15)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious	None	84	**1.16 (1.05-1.29)** for each year of therapy	4	⊕◯◯◯ Very low	Important

[1] Under-matching in case-control studies, failure to match for prognostic factors and/or adjustment in statistical analysis

[2] Unexplained heterogeneity of results and/or unexplained heterogeneity with studies in general population

[3] Relatively few patients and few studies

[4] Differences in measurement of exposure (data collected by questionnaire survey)

GRADE DECIDE

Risk Factors for Vertebral Fracture in SLE patients

Quality assessment							Summary of findings				Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ SLE patients	Effect/ OR (95% CI)	NOS	Quality	
Age											
2 Li, 2009(55) Mendoza-Pinto, 2009(7)	Observational studies	Serious[1]	Not Serious	Not Serious	Serious[2]	None	 152 210	 **1.068 (1.01-1.13)** **1.04 (1.01-1.06)**	 8 6	⊕⊕◯◯ Low	Important
Postmenopausal status											
2 Furukawa, 2013(56) Mendoza-Pinto, 2009(7)	Observational studies	Serious[1]	Serious[3]	Not Serious	Serious[2]	None	 52 210	 0.85 (0.02-38.0) 2.18 (0.71-6.70)	 7 6	⊕◯◯◯ Very low	Important
Body mass index (kg/m²)											
1 Li, 2009(55)	Observational studies	Serious[1]	Serious[3]	Not Serious	Serious[2]	None	 152	 **1.166 (1.02-1.33)**	 8	⊕◯◯◯ Very low	Important
Use of black tea or coffee											
1 Furukawa, 2013(56)	Observational studies	Serious[1, 4]	Serious[3]	Not Serious	Serious[2]	None	 52	 0.11 (0.01-1.01)	 7	⊕◯◯◯ Very low	Important
History of previous bone fracture											
2 Furukawa, 2013(56) Mendoza-Pinto, 2009(7)	Observational studies	Serious[1, 4]	Serious[3]	Not Serious	Serious[2]	None	 52 210	 **14.8 (1.62-134)** 0.42 (0.09-1.85)	 7 6	⊕◯◯◯ Very low	Important
Bone mineral density at L1-L4											
1 Li, 2009(55)	Observational studies	Serious[1]	Not Serious	Not Serious	Serious[2]	None	 152	 **0.005 (0.00-0.12)**	 8	⊕⊕◯◯ Low	Important
Low bone mineral density at total hip											
1 Mendoza-Pinto, 2009(7)	Observational studies	Serious[1]	Not Serious	Not Serious	Serious[2]	None	 210	 **1.09 (1.002-1.035)**	 6	⊕⊕◯◯ Low	Important
Bisphosphonates use											
1 Mendoza-Pinto, 2009(7)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious[2]	None	 210	 0.658 (0.25-1.72)	 6	⊕◯◯◯ Very low	Important
Cumulative glucocorticoids dose											
1 Mendoza-Pinto, 2009(7)	Observational studies	Serious[1]	Serious[2]	Not Serious	Serious[2]	None	 210	 1.01 (1.00-1.03)	 6	⊕◯◯◯ Very low	Important

[1] Under-matching in case-control studies, failure to match for prognostic factors and/or adjustment in statistical analysis

[2] Relatively few patients and few studies

[3] Unexplained heterogeneity of results and/or unexplained heterogeneity with studies in general population

[4] Differences in measurement of exposure (data collected by questionnaire survey)

Risk Factors for Fracture at any Sites in SLE patients

Quality assessment							Summary of findings				Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ SLE patients	Effect/ OR (95% CI)	NOS	Quality	
Age											
1 Yee, 2005(53)	Observational studies	Serious[1, 2]	Not serious	Not Serious	Serious[3]	None	242	**1.2 (1.1-1.3)**	7	⊕⊕◯◯ Low	Important
Premenopausal status											
1 Lee, 2007(57)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[3]	None	38	0.47 (0.19-1.17)	7	⊕◯◯◯ Very low	Important
Body mass index (kg/m²)											
1 Lee, 2007(57)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[3]	None	38	1.01 (0.95-1.07)	7	⊕◯◯◯ Very low	Important
Bone mineral density at total hip											
1 Lee, 2007(57)	Observational studies	Serious[1,]	Serious[4]	Not Serious	Serious[3]	None	38	0.97 (0.66-1.43)	7	⊕◯◯◯ Very low	Important
Reduced bone mineral density											
1 Yee, 2005(53)	Observational studies	Serious[1, 2]	Not serious	Not Serious	Serious[3]	None	242	**8.1 (1.7-40.0)**	7	⊕⊕◯◯ Low	Important
Calcium use											
1 Lee, 2007(57)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[3]	None	38	2.31 (0.93-5.75)	7	⊕◯◯◯ Very low	Important
Osteoporosis medications use (etidronate, alendronate, calcitonin)											
1 Lee, 2007(57)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[3]	None	38	**4.75 (1.62-13.94)[5]**	7	⊕◯◯◯ Very low	Important
Disease duration, years											
1 Lee, 2007(57)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[3]	None	38	**1.11 (1.05-1.17)**	7	⊕◯◯◯ Very low	Important
SLICC/ACR damage index (SDI)											
1 Lee, 2007(57)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[3]	None	38	1.24 (0.98-1.58)	7	⊕◯◯◯ Very low	Important
Renal involvement (proteinuria >0.5 m/ 24h, cellular casts or positive renal biopsy)											
1 Lee, 2007(57)	Observational studies	Serious[1]	Serious[4]	Not Serious	Serious[3]	None	38	0.89 (0.31-2.52)	7	⊕◯◯◯ Very low	Important

[1] Under-matching in case-control studies, failure to match for prognostic factors and/or adjustment in statistical analysis

[2] Self-reported fractures, not verified with medical records (clinics notes and radiographic reports)

[3] Relatively few patients and few studies

[4] Unexplained heterogeneity of results and/or unexplained heterogeneity with studies in general population

[5] The association between use of osteoporosis medications and fractures observed in this study likely represents women at higher fracture risk having been placed on such medications to minimize their risk for future fractures.

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Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

Problem: What are the minimum investigations that should be obtained to diagnose asymptomatic osteonecrosis in a SLE patient?

Option: To diagnose osteonecrosis in SLE patients by performing:

- History (by physician)
- Laboratory tests
- Imaging studies

Comparison: To not perform the option

Setting: SLE patients in Canada

Perspective:

- Population
- Caregivers of SLE (rheumatologists, internal medicine) and SLE patients

DATA SUPPLEMENT #6 ASYMPTOMATIC OSTEONECROSIS

Evidence to decision framework

What are the minimum investigations that should be obtained to screen asymptomatic osteonecrosis in a SLE patient?

Problem: What are the minimum investigations that should be obtained to diagnose asymptomatic osteonecrosis in an SLE patient?	***Background*** Non-traumatic osteonecrosis (ON) is now a well-recognized complication in systemic lupus erythematosus (SLE), having first been described by Dubois and Cozen in 1960[1]. The risk of a completely healthy individual developing ON is estimated at less than one in 100,000[2], but there are specific populations, including SLE patients, who are more affected. Indeed, the reported prevalence in SLE is between 10–15% but can be up to 44% when asymptomatic patients are included[3, 4]. The femoral head is the most common site for ON in the general population and in SLE patients[5, 6]. ON may present clinically with gradual onset of pain that may progress to severe pain when bone collapse occurs, but may also be silent. The clinical implication when bones collapse is a severe joint damage requiring total joint arthroplasty (TJA) or total joint replacement (TJR). It is not clear how we should optimally monitor the risk and diagnose ON in an SLE patient. We aim here to address this question as part of developing clinical practice recommendations on ON in SLE patients.
Option: To diagnose asymptomatic osteonecrosis in SLE patients by performing: • Laboratory tests • Imaging studies	
Comparison: To not perform the option	
Setting: outpatients	
Perspective: • Population	

NB: Sentences in italic refer to the general population and are used either to compare data from the SLE population, or to allow extrapolation in the absence of evidence in SLE patients.

✕	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

PROBLEM	**Is the problem a priority?**	Yes	FREQUENCY AND IMPACT OF ASYMPTOMATIC ON IN SLE PATIENTS 1) The true natural history of asymptomatic ON remains unknown. It is possible that some of these cases may go on to repair spontaneously and never present clinically. So the therapeutic implications of the finding of radiographic or MRI evidence of asymptomatic ON are uncertain. Particularly keeping into account that effective treatment able to prevent the worsening of the disease is still lacking and that there is no consensus on the appropriate treatment of patients with asymptomatic ON of the femoral head. o Further research into the progression of MRI detected asymptomatic lesions is necessary to determine their significance and the true natural history of ON. 2) The true prevalence of ON, when asymptomatic lesions are included with more recent MRI studies, is higher than described for clinically apparent ON. o In a small study, by serial MRI screening of hips and knees in SLE patients on high doses of CS therapy (40 mg/day or more equivalent prednisolone per day), ON was observed in 44% (32/72 patients) of patients, with a multifocal distribution in the majority of the cases[4]. o In SLE children, the prevalence of ON (mostly asymptomatic) seems to be up to 40%[7] but in another study, ON was seen in 6% of pediatric patients, 49% of adolescent patients and 41% of adults patients[8]. 3) There is low to very low-quality evidence for the natural progression of asymptomatic ON from observational studies often with inconsistent results across studies. The likelihood of progression is therefore still difficult to predict. o Asymptomatic and small ON lesions may heal or remain stable without progression or development of significant damage to the joint[9]. o A systematic review about the natural history of untreated asymptomatic ON of the femoral head, showed that patients affected by SLE presented the most benign course. The authors noted that small, medial asymptomatic lesions that occupied <25 % of the femoral head or spared the lateral two-thirds of the weight-bearing portion had the best prognosis, with a collapse rate of <10 %. One point of interest is that SLE subgroups of patients had the best prognosis of all with an overall rate of bone collapse of 17% compared to 38% for the general population[10]. o Another study used MRI to document the long-term natural history of asymptomatic ON associated with CS therapy in SLE patients. This study was focused on the MRI evolution over 10 years in SLE patients who already suffered from a non-collapsed and asymptomatic ON at the hips or knees. At the end of follow up, 49% of the joints demonstrated spontaneous repair of the necrotic area. ON completely disappeared in 9% of the cases. Progression of the ON lesions occurred in 15% of the cases, invariably associated with an increase of CS dosage due to SLE recurrence[11]. o Of the subgroup of asymptomatic knee ON lesions treated with observation, 80 % were successful in avoiding TJA and had no signs of radiographic progression[12]. o ON of the shoulder has a slower progression to symptomatic disease and ultimate collapse then the hip and knee, probably because it is not a weight-bearing joint and may better tolerate collapse[13]. 4) There is low to very low-quality evidence for the effects of treatment on the progression of asymptomatic ON. There are no studies in the specific SLE population, but no evidence that it differs from non-SLE patients. o *A systematic review about the treatment of asymptomatic ON concluded that the decision to treat pre-collapse disease should be based on lesion size. They suggested that small and large lesion (<15% and >30% of femoral head) should be observed as they are unlikely to progress or to be successfully*	

VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Probably no uncertainty or variability	○ No studies on SLE patients. ○ No studies on performing investigations to screen asymptomatic ON.	
BENEFITS AND HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	Low	<u>PERFORMING INVESTIGATIONS TO SCREEN ASYMPTOMATIC ON</u> **1. Laboratory tests** ○ There are no laboratory tests that can reliably detect asymptomatic ON in SLE patients, nor in general population. **2. Imaging studies** ○ There is no evidence in the literature supporting a systematic screening of asymptomatic ON in SLE patients by imaging modality. ○ The radiologic screening of patients for asymptomatic ON is debated. Given the benefits of early diagnosis and treatment, some authors recommend MRI screening for patients receiving high dose CS[15, 16, 17], particularly if there is ON of another joint. • This may be local[18, 19] or whole body[20] investigation. • Traditionally bone scintigraphy has been used for whole body screening however whole body MRI (STIR sequence) has recently been described as a viable screening tool[20] and may offer greater sensitivity. ○ Some authors suggest that the detection of ON at one site in SLE patients should always suggest screening other joints for ON by radiographs or MRI[21].	The panel agreed that there was no evidence for screening of asymptomatic ON, and used evidence for screening for symptomatic ON as a comparator (i.e. the evidence at best for asymptomatic would be only as high as that for symptomatic).
	How substantial are the desirable anticipated effects?	Trivial		
	How substantial are the undesirable anticipated effects?	Trivial		
	Do the desirable effects outweigh the undesirable effects?	Does not favour either intervention or comparison		
RESSOURCE USE	**How large are the resource requirements?**	No studies	○ No studies in SLE patients. ○ No studies on performing investigations to screen asymptomatic ON.	The panel agreed that the costs of imaging with MRI or SPECT would be large, and small for radiographs.
	How large is the incremental cost relative to the net benefit?	No studies	○ No studies in SLE patients. ○ No studies on performing investigations to screen asymptomatic ON.	The panel agreed that the costs are large compared to net trivial benefit.

EQUITY	**What would be the impact on health inequities?**	Probably increased inequity	○ No studies in SLE patients. ○ No studies on performing investigations to screen asymptomatic ON.	However, one should also take into consideration that performing MRI or bone scan screening may increase the average wait time for obtaining these tests.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	Probably yes	○ No studies on SLE patients. ○ No studies on performing investigations to screen asymptomatic ON. ○ The worst case scenario in ON is TJA and/or TJR: no evidence that SLE may differ from non-SLE patients– except the fact that a surgery is another hit, adding to the burden of this multisystemic disease. ○ *A Canadian population-based survey examined patients' perceptions of TJA and how they relate to willingness to consider TJA. Their conclusions were that participants overestimated the pain and disability needed to warrant TJA. These misperceptions were strongly associated with unwillingness to consider TJA. Although participants had reasonably accurate views of the outcomes following TJA, and were accepting of the potential risks with this surgery, the majority felt that arthritis pain and disability should be extreme before TJA should be considered*[22]. ○ *The same group also found that, among appropriate candidates for TJA, only one-third were definitely or probably willing to consider TJA as a treatment option. Among those with severe arthritis, no more than 15% were definitely willing to undergo arthroplasty, emphasizing the importance of considering both patients' preferences and surgical indications when evaluating need and appropriateness of rates for surgery*[23].	<u>Performing imaging studies:</u> There are no studies examining the acceptability to physicians to perform screening of ON with imaging studies. Since these tests are not invasive, we believe that they may be acceptable to them. The operative treatment of patients with asymptomatic ON remains a controversial topic; patients may be reluctant to undergo a surgical procedure, and to accept the attendant risks, for a symptom free disease.
FEASABILITY	**Is the option feasible to implement?**	Probably yes	○ No studies on SLE patients. ○ No studies on performing investigations to screen asymptomatic ON.	<u>Performing imaging studies :</u> There is uncertainty about the feasibility of screening given the lack of direct evidence and expected resources needed to perform an ON screening program to either all asymptomatic SLE patients or to SLE patients with risk factors.

Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	x				
Recommendation	***For adult and pediatric patients with systemic lupus erythematosus who do not have clinical symptoms suggestive of osteonecrosis, we suggest not screening for or performing investigations for osteonecrosis [conditional recommendation; low quality evidence]***				
Justification	See Symptomatic Osteonecrosis.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation considerations					
Research priorities					

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Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

GRADE DECIDE

Problem: What are the minimum investigations that should be obtained to diagnose symptomatic osteonecrosis in a SLE patient?

Option: To diagnose osteonecrosis in SLE patients by performing:
- History (by physician)
- Laboratory tests
- Imaging studies

Comparison: To not perform the option

Setting: SLE patients in Canada

Perspective:
- Population
- Caregivers of SLE (rheumatologists, internal medicine) and SLE patients

DATA SUPPLEMENT #7 SYMPTOMATIC OSTEONECROSIS

Evidence to decision framework

What are the minimum investigations that should be obtained to diagnose symptomatic osteonecrosis in a SLE patient?

Problem:
What are the minimum investigations that should be obtained to diagnose symptomatic osteonecrosis in an SLE patient?

Option:
To diagnose symptomatic osteonecrosis in SLE patients by performing:
- History (by physician)
- Laboratory tests
- Imaging studies (radiography versus MRI or SPECT)

Comparison:
To not perform the option

Setting:
outpatient

Perspective:
- Population

Background

Non-traumatic osteonecrosis (ON) is now a well-recognized complication in systemic lupus erythematosus (SLE), having first been described by Dubois and Cozen in 1960[1].

The risk of a completely healthy individual developing ON is estimated at less than one in 100,000[2], but there are specific populations, including SLE patients, who are more affected. Indeed, the reported prevalence in SLE is between 10–15% but can be up to 44% when asymptomatic patients are included[3, 4]. The femoral head is the most common site for ON in the general population and in SLE patients[5, 6].

ON may present clinically with gradual onset of pain that may progress to severe pain when bone collapse occurs, but may also be silent. The clinical implication when bones collapse is a severe joint damage requiring total joint arthroplasty (TJA) or total joint replacement (TJR).

It is not clear how we should optimally monitor the risk and diagnose ON in an SLE patient. We aim here to address this question as part of developing clinical practice recommendations on ON in SLE patients.

Subgroup considerations:
- SLE patients with asymptomatic ON (see other table) and risk factors for ON

NB: Sentences in italic refer to the general population and are used either to compare data from the SLE population, or to allow extrapolation in the absence of evidence in SLE patients.

X	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	Yes	FREQUENCY AND IMPACT OF SYMPTOMATIC ON IN SLE PATIENTS ○ Symptomatic ON is a relatively frequent and disabling complication occurring in patients with SLE and often requiring major surgical procedures as treatment. ○ It has been reported to occur in approximately 15%[3, 7, 8, 9, 10, 11, 12, 13, 14, 15]. • The prevalence of symptomatic lesions in studies carried when magnetic resonance imaging (MRI) was not available varied from 2.1 to 30%[3, 13, 16]. In these studies, diagnosis of ON was proved by radiographs and/or computerized tomography (CT) scan and/or single-photon emission computed tomography (SPECT) and/or biopsy. ○ ON is often multifocal[17, 18], which further increases the extent of disability. • Of 95 patients with ON, 68 (71.6%) patients had ON of the femoral head and 52 (55%) of them had bilateral ON of the femoral head[18]. • Others have indicated that bilateral hip ON occurs in up to 100% of SLE patients with ON[19]. ○ ON most often affects the femoral head, followed by the knee, the shoulder and the ankle. Symptomatic multifocal disease affecting more than three of these joints is infrequent in SLE patients, occurring approximately 3 % of the time[20]. ○ ON has been recognized as a feature of the accumulated damage in SLE[21]. Symptomatic ON is one component of musculoskeletal damage in the SLICC/ACR Damage Index (SDI). • Previous studies of SLE patients have demonstrated that ON causes disability and affects quality of life (QoL)[22]. • Symptomatic ON does not increase mortality but heavily impacts on QoL and causes a significant physical disability as measured by the Health Assessment Questionnaire (HAQ). In SLE patients, patients with ON had higher HAQ scores compared to control (0,7 vs 0,4, p=0,012) and lower SF-20 scores of physical functioning (52,4 vs 72,1, p=0,0023), suggesting increased disability[18]. • Another study showed similar results on HAQ in SLE patients. Patients with ON had higher HAQ score compared to control (1,5 vs 1,0, p=0,001)[23]. ○ Symptomatic ON requires a medical or surgical treatment. In case of symptomatic lesions, surgical treatment is usually required[24], but it's a matter of controversy.	

<table>
<tr>
<td>VALUES</td>
<td>Is there important uncertainty or variability about how much people value the main outcomes?</td>
<td>Possibly</td>
<td>1) No evidence in the literature about how SLE patients value symptomatic ON.
2) From our point of view, the relative importance or values of the main outcome of interest:
<table>
<tr><th>Outcomes</th><th>Consequences</th><th>Relative importance</th></tr>
<tr><td>ON not identified (accurately) – Real negative</td><td>No repercussions</td><td>Very low</td></tr>
<tr><td>ON not identified (falsely) – False negative</td><td>False reassurance, disability, pain and lower quality of life, eventual possible joint collapse and need of extensive surgery (TJA and/or TJR)</td><td>Important</td></tr>
<tr><td>ON identified (accurately) – Real positive</td><td>Leading to subsequent evaluation for possible treatment before joint collapse</td><td>Important</td></tr>
<tr><td>ON identified (falsely) – False positive</td><td>False positive ON not reported in literature</td><td>Very low</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>BENEFITS AND HARMS OF THE OPTIONS</td>
<td>What is the overall certainty of the evidence of effects?</td>
<td>Low to Very Low for SLE</td>
<td rowspan="4"><u>PERFORMING INVESTIGATIONS TO DIAGNOSE SYMPTOMATIC ON</u>

1) Questionnaire and physical exam
○ In the literature, no specific questionnaire or physical exam has been described to reliably establish the diagnosis of symptomatic ON in SLE population, nor in general population.
○ The EULAR recommendations for the monitoring of adverse events of CS therapy suggest investigations to diagnose ON in case of complaints only[25, 26]. Therefore, physicians should pay attention to complaints.
○ In a study about the outcome of core decompression for ON, authors failed to identify SLE-related predictors associated with poor prognosis[27].
○ There are multiple risk factors associated with ON in the literature, but the major factor remains the use of CS.
• The use of CS is associated with a 19 fold increased risk of ON in SLE patients and ON is really rare in SLE patients who didn't received CS[11].
• The research evidence suggest that ON is closely associated with the use of high dose of CS early in the course of SLE and especially in patients who develop Cushingoid appearance[3, 11, 12, 28, 29, 30].
• In another study, no cases of ON were found in patients who received a low or medium CS dose, equivalent to <30 mg/day of prednisone[31].
• The treating physician should be aware of the possible occurrence of ON for patients with CS us [26].
• ON should be suspected when deep joint pain develops in SLE patients on high dose of CS, since synovitis are less common with high dose of CS.
○ ON is much more prevalent in SLE than in other systemic conditions requiring the use of CS, suggesting that the use of CS is not the only factor. There are multiple clinical variables who were associated with ON : Raynaud's phenomenon[32,</td>
<td rowspan="4">The panel agreed that the evidence was low to very low for the association of various SLE risk factors with symptomatic osteonecrosis, suggesting that questionnaires or physical exams are not adequate to diagnose symptomatic ON. However, corticosteroid use may be an indicator of greater risk of ON.

Evidence was reviewed for</td>
</tr>
<tr>
<td>How substantial are the desirable anticipated effects?</td>
<td>Moderate to high</td>
</tr>
<tr>
<td>How substantial are the undesirable anticipated effects?</td>
<td>Trivial</td>
</tr>
<tr>
<td>Do the desirable effects outweigh the undesirable effects?</td>
<td>Yes</td>
</tr>
</table>

			[33, 34], vasculitis[3, 32, 34], antiphospholipid syndrome[35], arthritis[11], pleural effusion and central nervous system disease[12, 36]. • But all these research evidences are weak and the association between these variables and the development of ON is not as strong as the one with CS. Therefore, the use of CS remains the only major factor strongly associated with ON in SLE patients. ○ There is a controversy association between ON and SLE activity. A study reported a positive correlation between the development of ON and the SLEDAI score ≥ 8 in the year preceding the clinical diagnosis of ON[37]. In this study, SLEDAI score remained an independent risk factor for ON, even when a logistic regression analysis was performed for CS use. • On the contrary, other studies did not find a correlation with disease activity[11, 12, 38] or severity[22]. **2) Laboratory tests** ○ There is no laboratory tests that can reliably establish the diagnosis of ON in SLE patients, nor in general population. ○ There is still some controversy about the role of antiphospholipids as a risk factor in ON. Some studies found a positive link between ON and anticardiolipin antibodies[3, 35] and lupus anticoagulant[12, 35]. However, others studies didn't find a correlation[11, 38, 39]. ON has been identified in patients with primary antiphospholipid syndrome (APS) without previous CS therapy, suggesting a role for lupus anticoagulant and anticardiolipin antibodies[40]. Not all data regarding the risk of ON in patients with primary APS are concordant, suggesting, at best, a weak association[41]. **The Summary of Findings are available in Table 1 (Risk factors for symptomatic osteonecrosis in SLE patients) and in Figures 1-3.** **3) Imaging studies** ○ *Clinically suspected ON can be confirmed only by diagnostic imaging or biopsy. Imaging methods used for the diagnosis include conventional radiography, CT scan, radionuclide bone scans (performed by using either planar bone scintigraphy or SPECT imaging), and MRI. However, these methods vary in their cost, diagnostic accuracy, and the information provided[42].* ○ *Evidences show that MRI has the best sensitivity and specificity (99% each) compared to radiography and should be used to diagnose clinically suspect ON with normal radiography in early disease[24].* ○ *Early diagnosis is important to stage ON and to assess the efficacy of treatment. Pre-collapse stage ON have better outcome than post-collapse stage ON and require less total joint replacement[27].* ○ *An expert Panel on Musculoskeletal Imaging from The American College of Radiology has developed evidence-based guidelines to diagnose ON in general population[42].* • *Their methodology and evidence table with the strength of evidence of each study of their literature review is available at :* • *https://www.acr.org/-/media/ACR/Files/Practice-Parameters/mr-hip-pelvis.pdf,* • *https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteri* Although they did not review for resource use, equity, acceptability nor feasibility. ○ *Considering that radiographs are the least expensive and most widely available imaging technology, the American College of Radiology suggests that this modality should be obtained as the initial study in every patient suspected to have*	recommendations for imaging in the general population, the panel agreed that these recommendation would apply to patients with SLE.

			ON. Both anteroposterior and frogleg lateral views should be obtained because a subchondral fracture or cortical depression may be seen only on one of the two projections[42]. ○ *If the radiograph findings are equivocal for ON or are normal on the symptomatic side, then MRI is indicated to confirm the diagnosis and to exclude other potential causes for the patient's hip pain. In patients in whom MRI cannot be performed, a bone scan with SPECT imaging is a reasonable alternative for diagnosing radiographically occult ON*[42]. ○ *Planar bone scintigraphy is less sensitive than MRI (56 versus near 100%). It is least sensitive for early-stage lesions where it might be most useful to diagnose the disease. This test is less sensitive for joints other than the hip and is also not useful as a screening tool. This is one of the reasons why planar bone scintigraphy are not used as a diagnostic or screening tool for ON*[43]. ○ *In one study*[44]*, SPECT was found to be more sensitive than MRI in identifying early femoral head osteonecrosis in renal transplantation patients (100% versus 66%). The disadvantage of bone scintigraphy in assessment of osteonecrosis is the lack of anatomic evaluation and specificity*[42]. ○ *CT, although less sensitive than MRI and bone scintigraphy for detection of early femoral head osteonecrosis, is more specific and has the advantage of allowing anatomic assessment*[42]. ○ Concerning the undesirable effects, all imaging modality do not have the same inconveniences or risks. • *One major concern is radiation. Patients may have concerns about radiation exposure. Patients are not exposed to radiation during an MRI, which may be more acceptable to some patients, especially for children or pregnant women.* • *In general, radionuclide bone scanning may be minimally less safe than MRI*[45]. • *Effective dose of radiation are described in millisievert (mSv)*[45]*:* ▪ *Radionuclide bone scans delivers 4,5-6,3 mSv* ▪ *X-ray delivers 0,01-0,7 mSv* ▪ *MRI has delivers mSv* • *Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as be bothered by the noise. This may be less of a problem with new MRI machines, if available. It has been reported that up to 30% of patients' experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia. Some patients may have difficulty remaining still during the scan*[46, 47]. • *MRI may be contraindicated in specific patients, e.g. patients with metallic implants, including pacemakers.* • *Patients may have concerns about the intravenous injection of radiopharmaceutical agent for bone scanning.* ○ *The EULAR recommendations for the monitoring of adverse events of CS therapy suggest an imaging to diagnose ON in case of complaints only*[25,26].	
RESSOURCE USE	**How large are the resource requirement?**	NO studies	○ No studies on cost effectiveness of symptomatic ON diagnosis in general population, nor in SLE patients. ○ *In general population:* ○ There are some evidences about the different prices of MRI vs bone scan from The Canadian Agency for Drugs and Technologies in Health[45]. Cost estimates based on the Ontario schedule of benefits for physicians services under the Health Insurance Act (September 2011) are shown below: • *A MRI costs 501,90$* • *A SPECT costs 344,01$* ○ *Based on the Ministry of Health and Long-Term Care of Ontario (in 2015):*	<u>Performing a questionnaire and physical exam:</u> Under lack of local evidence on costs for radiographs, we think that the resources needed to allocate are

			• *An unilateral hip X-Ray costs 25.58$* • *A femur X-Rays (including one joint) costs 16.05$* ○ *In April 2015, the report from the Canadian Institute for Health Information on waiting times for procedures showed that 5 out of 10 provinces continued to submit comparable wait time data for CT and MRI scans in 2014[48].* • *Among these 5 provinces, the typical wait (50th percentile) for an MRI scan in 2014 ranged from 29 to 82 days and was 2 to 5 times longer than the typical wait for a CT scan.* • *The 90th percentile ranged from 30 to 68 days for CT scans and from 73 to 214 days for MRI scans.* • *Overall, volumes for MRI and CT scans increased over the past 5 years, with ranges in wait times remaining fairly stable, especially for CT scans.* • *In general, the reporting of diagnostic imaging data has improved over time but continues to be a challenge, in that it is the area with the fewest provinces reporting.* ○ *Others data from the Wait Time Alliance[49] showed that the average waiting time for a MRI is 60 days compared to 30 days for a radionuclide bone scan (in 2014)* • *So radionuclide bone scan may be an alternative in event of lack of availability of MRI and could improve access to care.*	probably small.
	How large is the incremental cost relative to the net benefit?	No studies; unknown	○ No studies in SLE patients. ○ No studies on performing investigations to diagnose symptomatic ON.	
EQUITY	**What would be the impact on health inequities?**	Possibly increased inequity	○ No studies on SLE patients, but no evidence that SLE may differ from non-SLE patients. ○ No studies on performing investigations to diagnose symptomatic ON. ○ *In general population:* • *Some regions may not have access to MRI scanners. If available, a bone scan with SPECT imaging may be performed, Nevertheless, some regions may not have access to nuclear cameras and/or do not have the available personnel to perform and interpret tests to image ON[45].* ○ *Therefore, we believe that inequities might be experienced with imaging other than radiographs.*	
ACCEPTABILITY	**Is the option acceptable to key stakeholder?**	Uncertain – probably acceptable to both	○ No studies on SLE patients. ○ No studies on performing investigations to diagnose symptomatic ON.	
FEASABILITY	**Is the option feasible to implement?**	Probably	○ No studies on SLE patients. ○ No studies on performing investigations to diagnose symptomatic ON.	

Type of recommendation	**We recommend against the option or for the alternative**	**We suggest not to use the option or to use the alternative**	**We suggest using either the option or the alternative**	**We suggest using the option**	**We recommend the option**
Recommendation	***Best clinical practice dictates that adult and pediatric SLE patients, in particular patients who had a history of glucocorticoid exposure, receive information about the symptoms of osteonecrosis, including progressive or sudden deep joint pain which is worse with weight bearing.*** ***For patients who have suspected clinical symptoms of osteonecrosis, we suggest radiographs as the initial imaging modality rather than MRI or bone scan with SPECT according to recommendations in the general population. (conditional recommendation, low quality evidence)***				
Justification	There is no evidence comparing outcomes of patients with SLE with or without suspicion of osteonecrosis who are screened or not screened with radiographs. Studies show that the prevalence of osteonecrosis and asymptomatic osteonecrosis may be higher in patients with SLE [3,4]. The evidence is still unclear about the progression of asymptomatic osteonecrosis and small lesions; some may heal or others progress to cause significant damage to the joint [20,27,31,33,43,50]. There is also low to very low quality evidence about the effects of treatments on the progression of asymptomatic osteonecrosis. There is low to very low quality evidence for a small association of most risk factors with osteonecrosis[51]. In patients with a high suspicion of osteonecrosis due to clinical symptoms, it is unclear if laboratory tests could be used to evaluate the risk of osteonecrosis[52]. The panel agreed that the accuracy of different imaging modalities would be similar in the general population and in patients with SLE, that radiographs are less expensive than bone scan with SPECT or MRI, and some regions may not have access to the latter.				
Subgroup considerations	SLE patients with asymptomatic ON and risk factors for ON. • Please refer to the Evidence to Decision Table "What are the minimum investigations that should be obtained to screen asymptomatic osteonecrosis in a SLE patient?"				
Implementation considerations					
Monitoring and evaluation considerations					
Research priorities	Formal randomized studies or large observational cohort studies with longer term follow up evaluating outcomes secondary to rigorous monitoring of ON in SLE patients are needed to provide more specific recommendations regarding ON in SLE. • Large prospective observational studies in SLE patients to better determine the natural evolution of symptomatic ON in SLE patients. • Large prospective interventional studies in SLE patients to prevent or delay bone collapse and TJA/TJR in symptomatic ON.				

Table 1. What is the association of various risk factors with symptomatic osteonecrosis in SLE patients?

Quality assessment							Summary of findings				Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SLE pts**	**Relative Effect**	**NOS score**	**Quality**	
Average/mean daily dose of corticosteroids											
3 Calvo-Alén (2006) Hamijoyo (2008) [1] Uea-areewongsa (2009)	OBS	Serious¶	Not serious	Not serious	Serious#	None	 91 136 40	 OR 1.033 (0.995 -1.072) OR 1.9 (0.89–4.51) OR 1.10 (0.95-1.33)	 6 6 7	⊕⊕◯◯ LOW	IMPORTANT BUT NOT CRITICAL
Highest dose of corticosteroids											
7 Griffiths (1979) [2] Aranow (1997) [3Δ] Gladman (2001) Calvo-Alén (2006) Lee (2014) [4] Fialho (2007) ~ Kunyakham (2012) [5]	OBS	Serious¶	Serious*	Not serious	Not serious	None	 68 64 140 91 128 46 736	 **OR 9.1538 (1.0592 - 79.1089)** **OR 4.2 (2.5-6.9)** **OR 1.02 (1.01-1.04)** **OR 1.025 (1.003-1.047)** **OR 2.9845 (1.2418 - 7.1731)** OR 1.02 (0.97-1.07) OR 1.07 (0.61-1.89)	 4 7 8 6 6 6 4	⊕⊕◯◯ LOW	IMPORTANT BUT NOT CRITICAL
Corticosteroids use											
2 Uea-areewongsa (2009) Gladman (2001)	OBS	Not serious	Not serious	Not serious	Very serious#	None	 40 140	 **OR 1.185 (1.011–1.390)** **OR 18.5 (3.2-359.6)**	 7 8	⊕⊕◯◯ LOW	IMPORTANT BUT NOT CRITICAL
Total cumulative corticosteroids dose [6]											
6 Mok (1998) [7] Mok (1998) [8] Gladman (2001) Hamijoyo (2008) [9] Zacarias (2014) ~ Hamijoyo (2008) [10]	OBS	Serious¶	Serious*	Not serious	Not serious	None	 181 181 140 136 243 136	 **OR 2.8348 (1.1644 - 6.9016)** **OR 8.0000 (3.6352 - 17.6057)** **OR 1.04 (1.01-1.07)** **OR 2.92 (1.3–6)** **OR 19.07 (2.7 – 133.7)** OR 2.09 (0.94–4.66)	 7 7 8 6 - 6	⊕⊕◯◯ LOW	IMPORTANT BUT NOT CRITICAL
Cushingoid appearance											
10 Zizic (1985) Massardo (1992) Mont (1997) Mok (1998) Gladman (2001) Lee (2014) Weiner (1989)	OBS	Serious¶	Serious*	Not serious	Not serious	None	 54 190 103 181 140 128 27	 **OR 33.0000 (7.3499 - 148.1662)** **OR 5.6838 (1.5765 - 20.4921)** **OR 4.0250 (1.5865 - 10.2115)** **OR 3.3059 (1.4183 - 7.7057)** **OR 3.8 (1.7-10.4)** **OR 21.792 (2.594–183.083)** OR 1.1250 (0.0600 - 21.0878)	 6 6 7 7 8 6 6	⊕⊕◯◯ LOW	NOT IMPORTANT

Fialho (2007) ˜ Prasad (2007) Hamiijoyo (2008)							46 130 136	OR 4.4754 (0.2317 - 86.4311) OR 1.7813 (0.6837 - 4.6409) OR 1.2736 (0.6063 - 2.6753)	6 6 6		
SLEDAI > 8 in the previous year											
1 Fialho (2007)˜	OBS	Serious¶	Serious*	Not serious	Very serious#	None	46	**OR 6.78 (1.05–43.55)**	6	⊕◯◯◯ VERY LOW	NOT IMPORTANT
Arthritis											
13 Gladman (2001) Smith (1976) Dimant (1978) Griffiths (1979) Zizic (1985) Weiner (1989) Massardo (1992) Watanabe (1997) Calvo-Alen (2006) Prasad (2007) Al Saleh (2010) Kunyakham (2012) Sayarlioglu (2012)	OBS	Serious¶	Serious*	Not serious	Not serious	None	140 14 234 68 54 27 190 113 91 130 126 736 203	**OR 4.2 (1.6-13.7)** OR 19.2857 (0.7977 - 466.2647) OR 2.8055(0.1606-48.9951) OR 1.6847 (0.0852- 33.2928) OR 0.3459 (0.0135 - 8.8752) OR 0.7857 (0.0440 - 14.0272) OR 7.1453 (0.4179 - 122.1671) OR 6.2583 (0.3468 - 112.9221) OR 0.9423 (0.2538 - 3.4979) OR 1.0000 (0.4573 - 2.1865) OR 1.5 (0.6-3.7) OR 1.42 (0.48-4.26) OR 2.3917 (0.7931 - 7.2123)	8 6 5 4 6 6 6 6 6 6 7 4 5	⊕⊕◯◯ LOW	NOT IMPORTANT
Neuropsychiatric SLE											
15 Mok (1998) Al Saleh (2010) Lee (2014) Smith (1976) Griffiths (1979) Zizic (1985) Nagasawa (1989) ˜ Weiner (1989) Massardo (1992) Watanabe (1997) Sheikh (1998) Gladman (2001) Uea-Areewongsa (2009) Kunyakham (2012) Sayarlioglu (2012)	OBS	Serious¶	Serious[3]	Not serious	Not serious	None	181 126 128 14 68 54 111 27 190 113 26 140 40 736 203	**OR 4.0109 (1.7950 - 8.9623)** **OR 3.5 (1.7-6.9)** **OR 3.1818 (1.2807 - 7.9050)** OR 3.4615 (0.1192 - 100.5161) OR 0.4286(0.0487 - 3.7734) OR 1.2000 (0.4041 - 3.5632) OR 1.2632 (0.4075 -3.9156) OR 4.6429 (0.7086 - 30.4191) OR 0.6108 (0.1328 - 2.8086) OR 3.4545 (0.5975 - 19.9722) OR 1.3333 (0.2419 - 7.3485) OR 1.0 (0.5-1.9) OR 0.1228 (0.0132 - 1.1384) OR 1.54 (0.67-3.23) OR 1.8077 (0.6775 - 4.8230)	7 7 6 6 4 6 5 6 6 6 6 8 7 4 5	⊕⊕◯◯ LOW	NOT IMPORTANT
Raynaud's phenomenon											
20 Aranow (1997) Δ Sayalioglu (2012)	OBS	Serious¶	Serious*	Not serious	Not serious	None	64 203	**OR 1.8 (1.1-2.8)** **OR 2.1038 (1.0950 - 4.0418)**	7 5	⊕◯◯◯ VERY LOW	NOT IMPORTANT

Smith (1976) Dimant (1978) Griffiths (1979) Zizic (1985) Nagasawa (1989) ˜ Weiner (1989) Massardo (1992) Watanabe (1997) Mok (1998) Sheikh (1998) Gladman (2001) Calvo-Alén (2006) Fialho (2007) ˜ Prasad (2007) Hamijoyo (2008) Al Saleh (2010) Castro (2011) ˜ Lee (2014)							14 234 68 54 111 27 190 113 181 26 140 91 46 130 136 126 40 128	OR 11.6667 (0.4826 - 282.0614) OR 0.7598 (0.3058 - 1.8881) OR 0.9355 (0.2139 - 4.0912) OR 1.5734 (0.5367 - 4.6130) OR 1.2308 (0.4980 - 3.0420) OR 0.3810 (0.0729 - 1.9920) OR 2.8247 (0.9651 - 8.2669) OR 1.2308 (0.2252 - 6.7271) OR 0.9576 (0.4137 - 2.2170) OR 0.9524 (0.1999 - 4.5380) OR 0.8 (0.4-1.6) OR 0.8810 (0.3580 - 2.1675) OR 0.3061 (0.0679 - 1.3804) OR 1.2048 (0.6035 - 2.4053) OR 1.4937 (0.5900 - 3.7816) OR 2.5 (1.0-6.1) OR 0.4800 (0.0812 - 2.8385) OR 2.0323 (0.9975 - 4.1403)	6 5 4 6 5 6 6 6 7 6 8 6 6 6 6 7 6 6		
Vasculitis											
12 Mont (1997) Hamijoyo (2008) Al Saleh (2010) Sayarlioglu (2012) Weiner (1989) Massardo (1992) Mok (1998) Sheikh (1998) Gladman (2001) Fialho (2007) ˜ Kunyakham (2012) Lee (2014)	OBS	Serious¶	Serious *	Not serious	Not serious	None	103 136 126 203 27 190 181 26 140 46 736 128	**OR 3.5024 (1.3321 - 9.2088)** **OR 4.45 (1.65–12.18)** **OR 2.7 (1.4-5.3)** **OR 2.6825 (1.1388 - 6.3187)** OR 0.9167 (0.1614 - 5.2067) OR 2.1833 (0.7822 - 6.0944) OR 0.4503 (0.1634-1.2409) OR 4.2593 (0.1850 - 98.0744) OR 1.9 (0.8-4.7) OR 1.5000 (0.3139 - 7.1683) OR 1.78 (0.19-16.31) OR 1.9159 (0.8592 - 4.2722)	7 6 7 5 6 6 7 6 8 6 4 6	⊕◯◯◯ VERY LOW	NOT IMPORTANT
Serositis[11]											
10 Al Saleh (2010) Sayarlioglu (2012) Smith (1976) Dimant (1978) Griffiths (1979) Zizic (1985) Massardo (1992) Mok (1998) Kunyakham (2012) Lee (2014)	OBS	Serious¶	Serious *	Not serious	Not serious	None	126 203 14 234 68 54 190 181 736 128	**OR 2.7 (1.4-5.3)** **OR 2.6708 (1.3593 - 5.2476)** OR 1.0000 (0.1204 - 8.3065) OR 1.8600 (0.6050 -5.7184) OR 1.0364 (0.2256 - 4.7606) OR 0.7778 (0.2403 - 2.5179) OR 1.5914 (0.5844 - 4.3337) OR 0.6250 (0.2406 -1.6239) OR 1.51 (0.28-5.30) OR 1.7442 (0.7919 - 3.8417)	7 5 6 5 4 6 6 7 4 6	⊕⊕◯◯ LOW	NOT IMPORTANT

Anticardiolipin antibodies IgM											
5 Al Saleh (2010) Mok (1998) Fialho (2007) ˜ Prasad (2007) Sayarlioglu (2012)	OBS	Serious¶	Serious *	Not serious	Serious#	None	126 181 46 130 203	**OR 3.6 (1.9-6.8)** OR 1.1429 (0.2271 - 5.7508) OR 3.8889 (0.2212 - 68.3843) OR 0.5075 (0.1729 - 1.4897) OR 1.0649 (0.3832 - 2.9594)	7 7 6 6 5	⊕◯◯◯ VERY LOW	NOT IMPORTANT
Anticardiolipin antibodies IgG											
6 Al Saleh (2010) Mok (1998) Fialho (2007)˜ Uea-Areewongsa (2009) Sayarlioglu (2012) Lee (2014)	OBS	Serious¶	Serious *	Not serious	Serious#	None	126 181 46 40 203 128	**OR 2.7 (1.4-5.3)** OR 0.6746 (0.3216 - 1.4152) OR 3.8889 (0.2212 - 68.3843) OR 1.8889 (0.3848 - 9.2709) OR 0.8509 (0.3103 - 2.3336) OR 0.2258 (0.0460 - 1.1085)	7 7 6 7 5 6	⊕◯◯◯ VERY LOW	NOT IMPORTANT
Lupus anticoagulant											
6 Mok (1998) Nagasawa (1989) ˜ Calvo-Alén (2006) Al Saleh (2010) Sayarlioglu (2012) Lee (2014)	OBS	Serious¶	Serious *	Not serious	Not serious	None	181 111 91 126 203 128	**OR 2.88 (1.14 - 7.18)** OR 2.9333 (0.7935 - 10.8433) OR 3.8667 (0.3368 - 44.3905) OR 0.5 (0.2-1.2) OR 0.4167 (0.0343 - 5.0577) OR 0.3212 (0.0965 - 1.0692)	7 5 6 7 5 6	⊕⊕◯◯ LOW	NOT IMPORTANT
Hypertension											
12 Smith (1976) Lee (2014) Zizic (1985) Nagasawa (1989) ˜ Mok (1998) Calvo-Alén (2006) Prasad (2007) Uea-Areewongsa (2009) Al Saleh (2010) Sekiya (2010) Δ Kunyakham (2012) Sayarlioglu (2012)	OBS	Serious¶	Serious *	Not serious	Not serious	None	14 128 54 111 181 91 130 40 126 17 736 203	**OR 0.0178 (0.0006 - 0.5215)** **OR 2.5802 (1.0643 - 6.2555)** OR 1.8333 (0.4676 - 7.1881) OR 1.3818 (0.3975 - 4.8033) OR 1.9571 (0.4661 - 8.2175) OR 1.5119 (0.6329 - 3.6116) OR 1.2038 (0.6040 - 2.3992) OR 1.5882 (0.2356 - 10.7048) OR 1.8 (0.99-3.1) OR 1.3333 (0.1546 - 11.4983) OR 1.35 (0.64-2.69) OR 1.8063 (0.8982 - 3.6323)	6 6 6 5 7 6 6 7 7 6 4 5	⊕⊕◯◯ LOW	NOT IMPORTANT
Oral ulcers											
8 Sayarlioglu (2012) Smith (1976) Dimant (1978)	OBS	Serious¶	Serious *	Not serious	Not serious	None	203 14 234	**OR 2.5212 (1.2943 - 4.9108)** OR 1.8750 (0.2036 - 17.2702) OR 0.5839 (0.1299 -2.6237)	5 6 5	⊕⊕◯◯ LOW	NOT IMPORTANT

Griffiths (1979) Weiner (1989) Mok (1998) Al Saleh (2010) Lee (2014)							68 27 181 126 128	OR 0.5714 (0.0640-5.0994) OR 1.0000 (0.1998 - 5.0043) OR 1.0039 (0.3128 - 3.2216) OR 1.6 (0.8-2.9) OR 1.3810 (0.6817 - 2.7974)	4 6 7 7 6		
Renal disease[12]											
15 Al Saleh (2010) Uea-Areewongsa (2009) Mok (1998) Smith (1976) Dimant (1978) Griffiths (1979) Zizic (1985) Zizic (1985) Zizic (1985) Weiner (1989) Massardo (1992) Massardo (1992) Watanabe (1997) Sheikh (1998) Prasad (2007) Kunyakham (2012) Sayarlioglu (2012) Lee (2014)	OBS	Serious¶	Serious*	Not serious	Not serious	None	 126 40 181 14 234 68 54 54 54 27 190 190 113 26 130 736 203 128	 **OR 3.0 (1.7-5.4)** **OR 7.80 (1.25-48.75)** **OR 2.2595 (1.0582 - 4.8245)** OR 1.7778 (0.2140 - 14.7672) OR 0.3711 (0.0836 -1.6473) OR 2.5294 (0.5670 - 11.2836) OR 0.7246 (0.1917 - 2.7386) OR 2.7176 (0.7900 - 9.3490) OR 4.3333 (0.8814 - 21.3053) OR 0.4000 (0.0623 - 2.5680) OR 1.5491 (0.5637 - 4.2569) OR 1.9569 (0.7114 - 5.3834) OR 0.7500 (0.1600 - 3.5147) OR 1.1667 (0.2344 - 5.8080) OR 1.2955 (0.4762 - 3.5242) OR 1.29 (0.73-2.25) OR 1.8947 (0.9828 - 3.6527) OR 1.4706 (0.7266 - 2.9765)	 7 7 7 6 5 4 6 6 6 6 6 6 6 6 6 4 5 6	⊕⊕◯◯ LOW	NOT IMPORTANT
Alopecia											
7 Mok (1998) Smith (1976) Dimant (1978) Griffiths (1979) Zizic (1985) Sayarlioglu (2012) Lee (2014)	OBS	Serious¶	Serious*	Not serious	Not serious	None	 181 14 234 68 54 203 128	 **OR 0.2861 (0.0968 - 0.8454)** OR 0.2889 (0.0099 - 8.3887) OR 0.7746 (0.3163- 1.8967) OR 1.6087 (0.3660 - 7.0699) OR 1.1429 (0.3902 - 3.3472) OR 1.6382 (0.8540 - 3.1424) OR 1.2197 (0.5973 - 2.4904)	 7 6 5 4 6 5 6	⊕⊕◯◯ LOW	NOT IMPORTANT
Antimalarial											
9 Mok (1998) Uea-Areewongsa (2009) Al Saleh (2010) Massardo (1992) Gladman (2001) Calvo-Alen (2006) Prasad (2007) Fialho (2007) ~ Kunyakham (2012)	OBS	Serious¶	Serious*	Not serious	Not serious	None	 181 40 126 190 140 91 130 46 736	 **OR 0.2311 (0.1082 - 0.4934)** **OR 0.09 (0.01-0.96)** **OR 0.45 (0.25-0.8)** OR 2.5576 (0.9272 -7.0549) OR 2.2 (0.998-8.1) OR 0.6844 (0.2625 - 1.7847) OR 0.8300 (0.4158 - 1.6570) OR 0.6452 (0.1051 - 3.9609) OR 0.58 (0.18-1.81)	 7 7 7 6 8 6 6 6 4	⊕⊕◯◯ LOW	NOT IMPORTANT

Immunosuppressive agents[13]											
15 Mok (1998) [14] Gladman (2001) Calvo-Alén (2006) Al Saleh (2010) [15] Al Saleh (2010) [16] Lee (2014) [17] Lee (2014) [18] Bergstein (1974) ~ Nagasawa (1989) ~ Mok (1998) [19] Prasad (2007) Fialho (2007) ~ Uea-Areewongsa (2009) [20] Uea-Areewongsa (2009) [21] Uea-Areewongsa (2009) [22] Al Saleh (2010) [23] Kunyakham (2012) Sayarlioglu (2012) Lee (2014) [24]	OBS	Serious[¶]	Serious[*]	Not serious	Not serious	None	181 140 91 126 126 128 128 35 111 181 130 46 40 40 40 126 736 203 128	**OR 4.0109 (1.7950 - 8.9623)** **OR 2.7 (1.02-8.8)** **OR 3.0769 (1.2608 - 7.5088)** **OR 9.6 (5.1-18.3)** **OR 3.5(1.7-6.9)** **OR 2.779 (1.106–6.981)** **OR 2.662 (1.143–6.200)** OR 1.4118 (0.2217 to 8.9902) OR 0.6908 (0.2319 - 2.0579) OR 1.4703 (0.7097 - 3.0463) OR 1.2796 (0.6424 - 2.5486) OR 1.1667 (0.2552 - 5.3327) OR 1.8571 (0.5216 - 6.6123) OR 0.5294 (0.1079 - 2.5984) OR 3.1538 (0.1211 - 82.1697) OR 1 (0.6-1.9) OR 1.30 (0.76-2.21) OR 1.8400 (0.9561 - 3.5410) OR 1.2918 (0.5737 - 2.9089)	7 8 6 7 7 6 6 3 5 7 6 6 7 7 7 7 4 5 6	⊕⊕◯◯ LOW	NOT IMPORTANT

[1] Mean daily dose prednisone-equivalent (≥ 10 mg)
[2] Prednisolone >10 mg/day
[3] Dose over the preceding 5 years of at least 30mg/day
[4] High-dose steroid therapy :> 30 mg, but<100 mg of prednisone equivalent per day
[5] High-dose steroid therapy was defined as a steroid dosage equivalent to prednisolone > 30 mg/day at any time during follow-up
[6] Practically, total cumulative CS dose may be hard to get (depends on patient charting…)
[7] Total cumulative prednisone dose in 1 month > 1.8g
[8] Total cumulative prednisone dose in 4 months > 4g
[9] Mean total cumulative prednisone-equivalent dose ≥ 23.4 g
[10] Mean cumulative prednisone-equivalent dose in first month ≥ 1.37 g
[11] Serositis includes pericarditis and/or pleuritic.
[12] Renal disease was defined as proteinuria of >0.5g/day and/or active urinary sediment and/or creatinine >1.4mg/dL and/or biopsy proven lupus nephritis.
[13] Immunosuppressive therapies includes methotrexate, azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil
[14]Cyclophosphamide
[15]Cyclophosphamide
[16] Mycophenalate mofetil
[17] Cyclophosphamide
[18] Azathioprine
[19] Azathioprine
[20]Cyclophosphamide
[21]Azathioprine
[22]Mycophenalate mofetil
[23]Azathioprine
[24] Mycophenalate mofetil
[¶]Under-matching in case-control studies, failure to match for prognostic factors and/or adjustment in statistical analysis

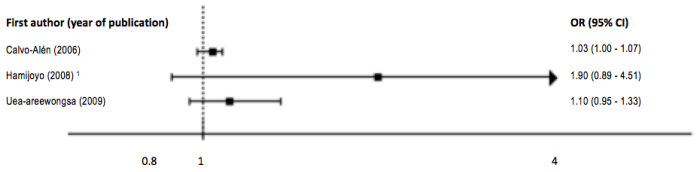
#There were few events across studies.
*There were statistically significant, unexplained heterogeneities of results for hazard ratio or odds ratio.
ΔStudies evaluating risk factors for asymptomatic ON in SLE patients
~Studies evaluating risk factors for both symptomatic and asymptomatic ON in SLE patients.

Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

Figure 1

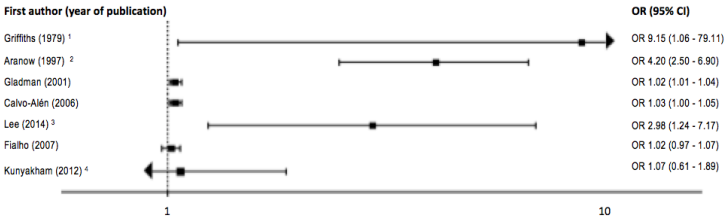
A. Corticosteroids

Mean daily dose of CS



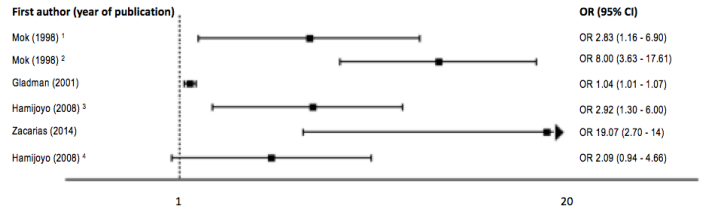
[1] Mean daily dose prednisone-equivalent (≥ 10 mg)

Highest dose of CS



[1] Prednisolone >10 mg/day
[2] Dose over the preceding 5 years of at least 30mg/day
[3] High-dose steroid therapy:>30 mg, but<100 mg of prednisone equivalent per day
[4] High-dose steroid therapy was defined as a steroid dosage equivalent to prednisolone > 30 mg/day at any time during follow-up

Total cumulative CS dose



[1]Total cumulative prednisone dose in 1 month > 1.8g
[2]Total cumulative prednisone dose in 4 months > 4g
[3] Mean total cumulative prednisone-equivalent dose ≥ 23.4 g
[4] Mean cumulative prednisone-equivalent dose in first month ≥ 1.37 g

Figure 2

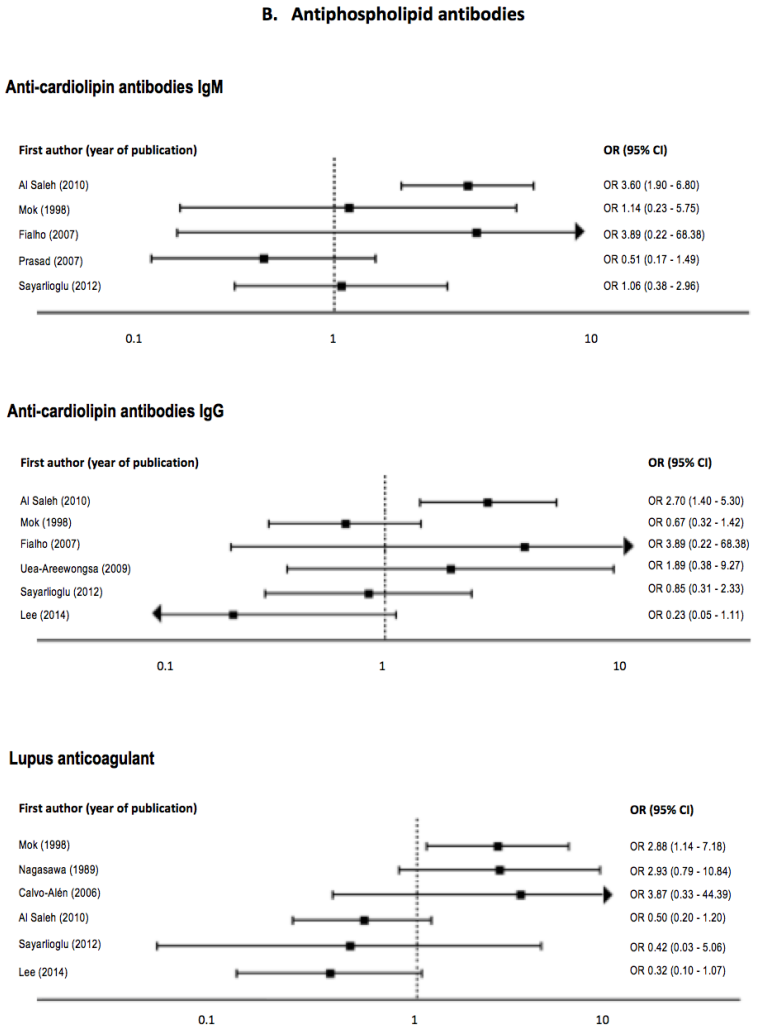
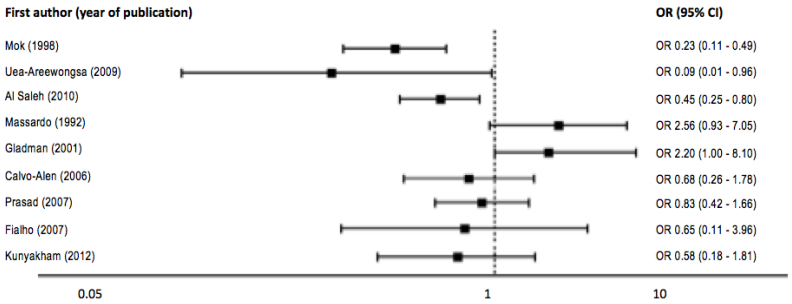


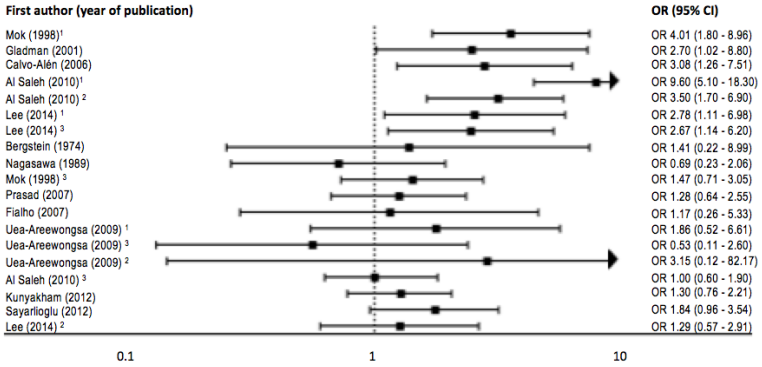
Figure 3

C. Medication

Antimalarials



Immunosuppressive agents



[1] Cyclophosphamide
[2] Mycophenalate Mofetil
[3] Aazathioprine

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Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

DATA SUPPLEMENT #8 PERIPARTUM ETDs

Evidence to Decision Framework: Monitoring in SLE Pregnancies

What are the minimal investigations to optimally monitor the risk of pregnancy complications in SLE women?

Patients: SLE women

Intervention: More baseline and follow-up clinical investigations and/or more frequent medical visits during pregnancy compared to the general population.

Comparison: Equal clinical investigations and medical visits during pregnancy as compared to the general population

Main outcomes: The main outcomes include preterm birth, placenta-mediated complications (Preeclampsia/eclampsia, small for gestational age (SGA), placenta abruption, and stillbirth), complete congenital heart block (CHB) and disease flare/active disease.

Setting: Pregnant SLE women in Canada

Perspective: Caregivers of SLE patients (internists, rheumatologists, obstetrician) and pregnant SLE women

Background:

SLE predominantly affects women, particularly during their childbearing years. In Canada, every year, there are approximately 400 SLE deliveries[51]. The following is a description of the Canadian guidelines for pregnancy monitoring (i.e. visits and investigations) in the general population[25,33]:

Routine visits

- Weeks 4 to 28: 1 prenatal visit a month
- Weeks 28 to 36: 1 prenatal visit every 2 weeks
- Weeks 36 to 40: 1 prenatal visit every week

Routine investigations:

- 0-14 weeks: prenatal genetic screening with ultrasound, blood group, rh D and red cell antibodies, Hb, MCV, Rubella ab, HIV, HBV (HCV if risk factors), Syphilis, chlamydia, gonorrhea, Midstream urine for C&S, Glucose tolerance test or fasting blood glucose, TSH, PAP test if indicated.

Routine investigations:

- 18-20 weeks: detailed fetal ultrasound
- 24-26 weeks: repeat Rh ab titer offered to negative women, Gestational diabetes screening
- 35-37 weeks: group B strep screening

Routine prenatal care at each visit:

- Blood pressure measurement
- Weight measurement
- Fetal movement and heart tones
- Symphysis-fundus height
- STI screening if indicated
- Urine dipstick testing for proteinuria
    - UPCR or 24-hour collection if suspicion of preeclampsia

	Criteria	Judgement	Research evidence	
Problem	**Is the problem a priority?**	○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	**Increased risk of pregnancy complications in women with SLE** The PROMISSE study[9] looked at 385 SLE women with inactive, mild or moderate disease • 1/5 (19%) experienced placenta-mediated pregnancy complications • Preterm delivery 9% • Disease flare 13% • CHB 1/154 anti-Ro-exposed fetuses • Uncomplicated pregnancies 61% **Maternal complications, such as preeclampsia/ eclampsia, are associated with substantial maternal morbidity (and fetal morbidity)** • Preeclampsia/eclampsia[45] • Placebta abruption 1-4% • Preterm birth 30-60% • IUGR 10-25% • Perinatal death 1% **Fetal complications, such as preterm birth, small for gestational age, and CHB are associated with substantial morbidity for the offspring**: Preterm birth: neonatal mortality RR 6.82 (95% CI 3·56–13·07)[24]) SGA: neonatal mortality RR 1.83 (95% CI 1·34–2·50)[24]) CHB: 17% stillbirths; 80% of live births will require pacemaker[5] See Table 1.	
Desirable effects	**How substantial are the desirable anticipated effects?**	○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ **Don't know**	No randomized or non-randomized studies comparing increased monitoring in pregnant SLE patients versus routine monitoring recommended for the general pregnant population Positive screening tests can produce anxiety for patients and their families, and financial costs to the individual and health care system as a result of additional diagnostic tests. In general population of pregnancies, screening for genetic anomalies in first trimester, repeated ultrasound, and group B strep are associated with transient increase in anxiety levels, but overall high acceptance and satisfaction by pregnant women[48]	

	Criteria	Judgement	Research evidence	
Undesirable effects	**How substantial are the undesirable anticipated effects?**	○ Large ○ Moderate ○ Small ○ **Trivial** ○ Varies ○ Don't know	A study assessed the experience of 14 women with anti-Ro regarding fetal monitoring Although women experienced increased stress related to each fetal echocardiogram, they expressed overall reassurance and satisfaction with monitoring, and would have another pregnancy only if same level of monitoring[40]. Summary of findings (see Tables below): Studies show that women with SLE likely have greater adverse pregnancy outcomes than women in the general population; and greater number of SLE flares which may lead to greater adverse pregnancy outcomes [9,53]. In addition, approximately 1-2% of anti-Ro exposed pregnancies in women with SLE have babies with congenital heart block compared to <0.01% in the general population[9,53]. There may be more SLE pregnancies with Doppler anomalies than without anomalies between 24-35 weeks of gestation[9,53]. Among pregnant women with prior or active renal disease, adverse pregnancy outcomes are greater than those without renal disease [9,53]. A 2013 Cochrane meta-analysis on fetal and umbilical Doppler ultrasound in high-risk pregnancies reviewed 18 completed studies including just over 10,000 women. The trials were generally of unclear quality with some evidence of possible publication bias. Associated with a reduction in perinatal deaths (RR 0.71, 95% CI 0.52 to 0.98, 16 studies, 10,225 babies, 1.2% versus 1.7 %, NNT = 203 (95% CI 103 to 4352).	

	Criteria	Judgement	Research evidence	
Certainty of the evidence	**What is the overall certainty of the evidence of effects?**	○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	A 2010 Cochrane review on utero-placental Doppler ultrasound for improving pregnancy outcome reviewed 2 studies involving 4993 participants. Both studies included women at low risk for hypertensive disorders, with Doppler ultrasound of the uterine arteries performed in the second trimester of pregnancy. The methodological quality of the trials was good. No difference in short-term maternal and fetal clinical outcomes. No randomized studies assessing the utero-placental vessels in the first trimester or in women at high risk for hypertensive disorders. **See tables 2-6.** **Other considerations** The gold standard for proteinuria during pregnancy is total protein ≥300 mg in a 24 h urine sample[35]. Dipstick tests are unreliable owing to variations in protein excretion, activity, diet and posture. Dipstick ≥1+ has a positive predictive value of 82–92% for proteinuria of ≥300mg/day but low negative predictive value (34–60%). Use of protein/creatinine ratio is recommended in several guidelines (cut-off ≥30 mg/mmol). Sensitivity (89–96%) and specificity (75–78%). Reasonable 'rule out' test due to its high sensitivity and low negative likelihood ratio (0.12)	The panel agreed that the evidence for increased risks of poor maternal and fetal/neonatal outcomes from single arm SLE cohorts or studies comparing women with SLE to women in the general population informs this recommendation. This evidence is low to moderate quality.
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?**	○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ **No important uncertainty or variability** ○ No known undesirable outcomes	The relative importance of the main outcomes of interest – Preterm birth – Placenta-mediated complications – CHB – Disease activity/flare All critical, little variability – Even for autoimmune CHB -much rarer but high morbidity – estimated incidence of 1/20 000[5] In a study of 114 SLE women assessing the psychological impact of the disease, SLE was viewed as a barrier to childbearing by 27%[44] Most common concerns included worries that pregnancy might exacerbate the disease, that medications or the disease might harm the fetus.	

	Criteria	Judgement	Research evidence	
Balance of effects	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?**	○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ **Favors the intervention** ○ Varies ○ Don't know	The potential desirable effects are improved maternal and fetal outcomes. These likely outweigh the stress related to increase monitoring and potentially increased costs.	In reviewing the final manuscript revisions, there was a unanimous vote of YES to change the balance of effects to "favors the intervention" from "probably favors the intervention" given the significant morbidity that accompanies CHB and its sequelae as well as important management issues that arise upon detection of CHB, which virtually only occurs in anti-Ro/La positive mothers. (31 authors voted YES; 2 authors (JM/LB) are deceased, and 2 did not respond to the email voting round).
Resources required	**How large are the resource requirements (costs)?**	○ Large costs ○ Moderate costs ○ **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		Pregnant women already have routine prenatal investigations and visits. Some SLE-related investigations would be added to baseline and follow-up routine investigations. There are also few women in the overall population with SLE and pregnant.

	Criteria	Judgement	Research evidence	
Certainty of evidence of required costs	**What is the certainty of the evidence of resource requirements (costs)?**	○ Very low ○ **Low** ○ Moderate ○ High ○ No included studies	There are no direct cost data available for SLE patients and more frequent monitoring There would be increased cost of certain lab tests and more frequent physician visits. As cost examples lupus anticoagulant is at least 15$ in Quebec, follow-up visit to rheumatologist is between 80-150$ in Quebec, fetal ultrasound with Doppler is 75$	
Cost-effectiveness	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?**	○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ **Favors the intervention** ○ Varies ○ No included studies	Increased direct healthcare cost of SLE pregnancies versus general population – US study[48] – $20,665 [$20,709] versus $12,591 ($27,896) – Cost of medication was inferior in SLE pregnancies – Canadian study[50] – Multivariate analysis adjusting for age, race, hypertension, diabetes – 32% (95% CI 29, 36) increment in costs, or alternatively a 3 690$ (95% CI 2 814, 4 567) The increased cost of pregnancy complications – Example in a large US database hypertensive disorders of pregnancy were associated with mean increase in cost of $6152 (SD = $5312) compared to unaffected pregnancies.	
Equity	**What would be the impact on health equity?**	○ Reduced ○ Probably reduced ○ Probably no impact ○ **Probably increased** ○ Increased ○ Varies ○ Don't know	There is no direct evidence. A recent study specifically assessed the effect of race/ethnicity on SLE pregnancy outcomes in a large US sample[51]. Black and Hispanic SLE women had increased risk of preeclampsia, preterm births, and IUGR versus White SLE women. So, increased monitoring of SLE pregnancies might lead to better outcomes in this vulnerable population	

	Criteria	Judgement	Research evidence	
Acceptability	**Is the intervention acceptable to key stakeholders?**	○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	As alluded to earlier, pregnant women in general favor more rigorous monitoring even if at the expense of increased stress	
Feasibility	**Is the intervention feasible to implement?**	○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	There is no direct evidence. While feasible there are manpower issues in rheumatology and obstetrics in Canada to overcome. Benchmark wait time set by SOGC in 2008 regarding routine prenatal care and assessment of high-risk pregnancies	

Conclusions

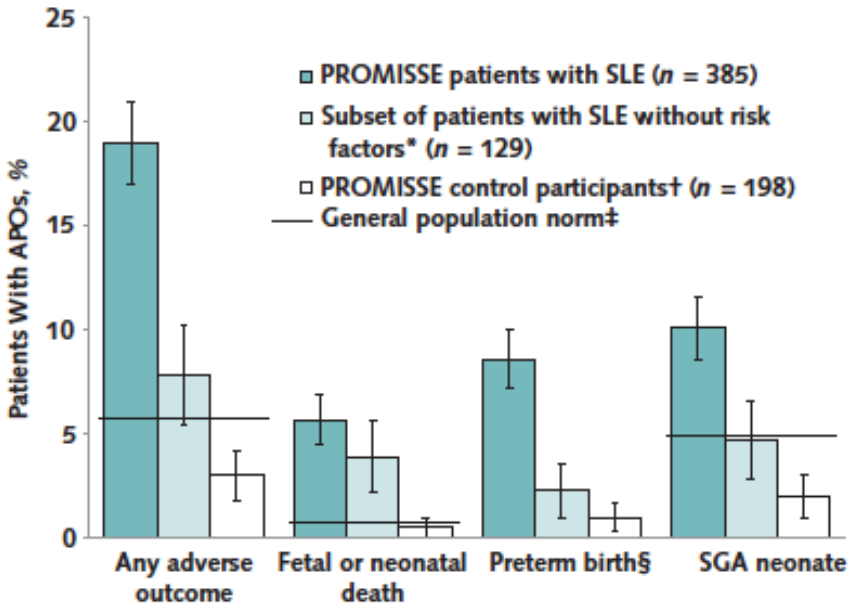
What are the minimal investigations to optimally monitor the risk of pregnancy complications in SLE pregnancies?

Type of recommendation	We recommend against the intervention or for the comparison	We suggest against the intervention or for the comparison	We suggest either the intervention or the comparison	We suggest the intervention	We recommend the intervention
	○	○	○	○	X
	Best practice dictates that all women living with SLE who are planning a pregnancy or who become pregnant should have their individual situations discussed with experts in the area, with referral to an SLE care provider and obstetrical care providers, and an overall plan should be made for their pregnancy care. *Best practice dictates that for women with SLE, a complete history, physical and lab evaluation be provided immediately prior to pregnancy and each trimester of pregnancy, and when flare is suspected during pregnancy. Lab evaluation should include antiphospholipid antibodies (see Best Clinical Practice General Assessments) with further testing depending on results.* *Remarks: These laboratory and clinical measurements should be performed to assess whether the patients have active lupus nephritis, pre-eclampsia and/or increased proteinuria due to pre-existing renal disease and increased cardiac output in the setting of pregnancy. Multidisciplinary care approaches with relevant caregivers including obstetrics and gynecology, maternal-fetal medicine and nephrologists is often necessary to facilitate the evaluation and management of these complex patients. Of note, the*				

Recommendation	*renal assessments cannot be interpreted in isolation of other clinical and laboratory parameters. The 14th International Congress on Antiphospholipid Antibodies Task Force provide recommendations regarding the evaluation of antiphospholipid antibodies and treatment of antiphospholipid antibody syndrome*[52] . *1) For women with SLE, we recommend that anti-Ro and anti-La antibodies be measured prior to pregnancy or during the first trimester. (strong recommendation, low quality evidence).* Remarks: CHB only occurs in 1-2% of anti-Ro/La antibodies-positive pregnancies, but the vast majority of CHB cases arise from anti-Ro/La positive mothers. Although screening for anti-Ro/La antibodies prior to pregnancy and/or performing fetal echocardiography in anti-Ro/La antibodies positive pregnant mothers have not been shown to improve outcomes, early detection of CHB in anti-Ro/La positive mothers is likely to influence management. Management of positive lab results is beyond the scope of these recommendations. *2) For pregnant women with SLE, we suggest that uterine and umbilical Doppler studies be performed in the second or third trimester, or at the time of a suspected flare. (conditional recommendation; low quality evidence).* Remarks: Timing is at the discretion of the maternal-fetal medicine or obstetrical specialist who is involved in the care (eg. when placental insufficiency is suspected). *3) For women with prior or active lupus nephritis who are pregnant, we suggest measuring serum creatinine and urine protein to creatinine ratio every 4-6 weeks, or more frequently if clinically indicated. We suggest blood pressure and urinalysis be measured prior to pregnancy and every 4-6 weeks until 28 weeks, every 1-2 weeks until 36 weeks and then weekly until delivery. [conditional recommendation; low quality evidence]*
Justification	There is no evidence assessing the effect of providing or not providing additional screening tests on outcomes of pregnant women who have SLE. Studies show that women with SLE likely have greater adverse pregnancy outcomes than women in the general population; and greater number of SLE flares which may lead to greater adverse pregnancy outcomes. In addition, approximately 1-2% of anti-Ro exposed pregnancies in women with SLE have babies with congenital heart block compared to <0.01% in the general population [9, 53] which the panel agreed was associated with significant management implications and morbidity in the peripartum period. There may be more SLE pregnancies with Doppler anomalies than without anomalies between 24-35 weeks of gestation[9,18,27,53].. Among pregnant women with prior or active renal disease, adverse pregnancy outcomes are greater than those without renal disease[9,53]. The panel agreed that additional follow-up visits and testing would be acceptable, feasible, and would not increase resources and costs due to the overall small numbers of pregnant women with SLE, and probably increase equity by ensuring standard monitoring. Management of antiphospholipid antibodies was not in the scope of these recommendations. Management of antiphospholipid antibodies was not in the scope of these recommendations but is considered important in peripartum assessments of SLE patients.
Subgroup considerations	

Implementation considerations	All women living with SLE who are planning a pregnancy or who become pregnant should have their individual situations discussed with experts in the area, with referral to an SLE care provider and obstetrical care providers, and an overall plan should be made for their pregnancy care.
Monitoring and evaluation	
Research priorities	

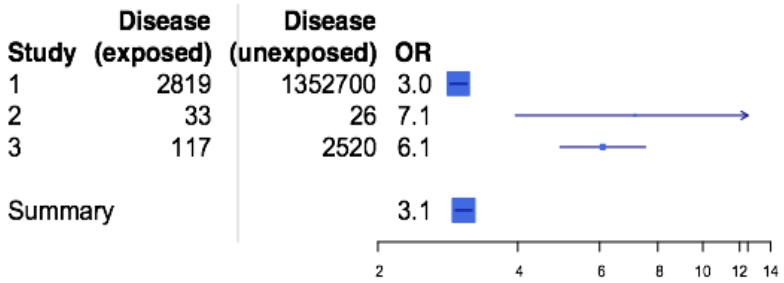
Figure. Frequency of APOs in patients and healthy control participants.



Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

Appendix 1: APOs in patients and healthy control participants

Appendix 2: Preterm births (SLE deliveries versus general population deliveries[3,14,43])



QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE deliveries	General population deliveries	Relative (95% CI)		
3	Observational studies	Not serious	Not serious	Not serious	Not serious	None	2969/14205 (20.9%)	1355246/ 16760375 (8.1%)	cf forest plot	Moderate	CRITICAL

Appendix 3: Placenta-mediated pregnancy complications (SLE pregnancies versus unaffected pregnancies[9])

QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of	Study design	Risk of	Inconsistency	Indirectness	Imprecision	Other	SLE	Unaffected	Relative		

studies		bias				considerations	pregnancies	control pregnancies	Risk(95% CI)		
1	Observational study	Not serious	Not serious	Not serious	Serious	None	73/385 19% (15, 23)	6/198 3% (1,6)		Moderate	CRITICAL

**APO defined as: fetal or neonatal death, preterm birth <36 weeks due to placental insufficiency, hypertension, or preeclampsia, SGA*

Appendix 4: Congenital heart block (Anti-Ro-exposed pregnancies versus deliveries from general population[7,8,11,17, 19, 46])

QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-Ro – exposed pregnancies	95% CI (range)			
5	Observational studies	Not serious	Not serious	Not serious	Not serious		9/486 (1.85%)	0.14, 8.7%	N/A	Moderate	CRITICAL

QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General population (mean annual incidence)	Annual incidence range (1970-94)			
1	Observational study	Not serious	Not serious	Not serious	Not serious		1/17 000	1/6 500, 1/64 000	N/A	Moderate	CRITICAL

Appendix 5: SLE Flares (Incidence of flare in SLE pregnancies[35])

QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flare in SLE pregnancies	95% CI			

36	Observational studies	Not serious	Serious	Not serious	Possible		747/2509 (29.7%)	27.3, 31.0%	N/A	Moderate	CRITICAL

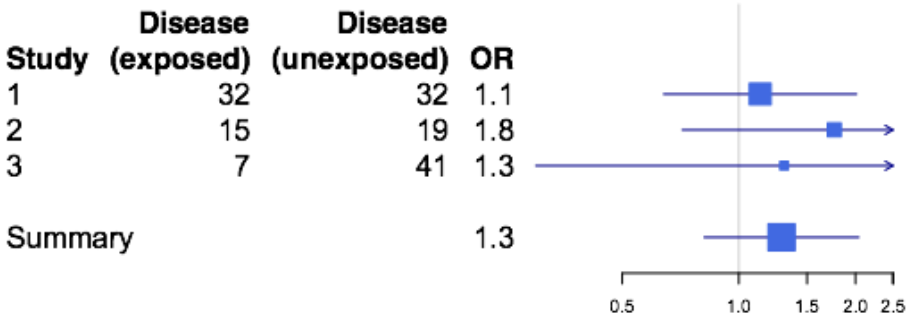
Appendix 6: SLE Flare (Pregnant SLE patients versus non-pregnant SLE patients) All flares[47]

QUALITY ASSESSMENT							**Rate of flare per patient/month**			**QUALITY**	**IMPORTANCE**
# of studies	Study design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregnant SLE patients (n=68)	Postpartum SLE patients (n=43)	Matched non-pregnant SLE patients (n=50)		
1	Observational studies	Not serious	Not Serious	Not serious	Not serious	None	0.082 +/- 0.004	0.049 +/- 0.004	0.039 +/- 0.003	Moderate	CRITICAL

Appendix 7 : SLE Flare (Pregnant SLE patients versus non-pregnant SLE patients) Lupus nephritis flare[39]

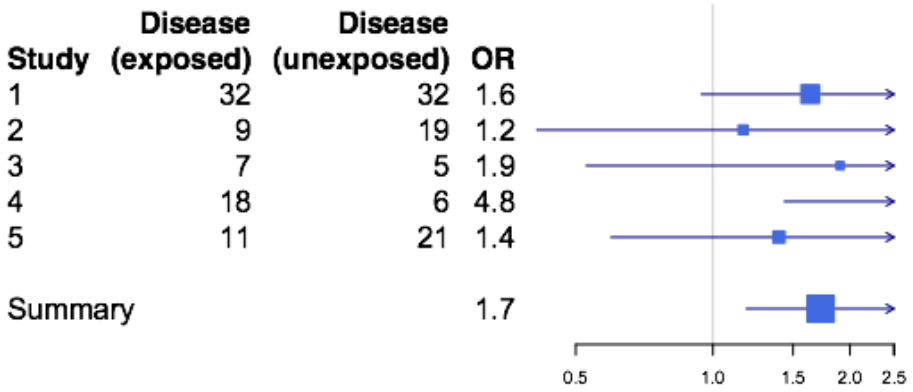
QUALITY ASSESSMENT							**# OF PATIENTS**		**EFFECT**	**QUALITY**	**IMPORTANCE**
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregnant SLE patients	Matched non-pregnant SLE patients	Relative (95% CI)		
1	Observational studies	Not serious	Not serious	Not Serious	Not serious	None	33/74 (44.6%)	31/74 (41.9%)	N/A	Moderate	CRITICAL

Appendix 8: Preterm births among live births (Antiphospholipid antibodies[1,12,27])



QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	aPL-exposed SLE live births	aPL-unexposed SLE live births	Relative (95% CI)		
3	Observational studies	Not serious	Not serious	Not serious	Not serious		54/152 (35.5%)	92/262 (35.1%)	cf forest plot	Moderate	CRITICAL

Appendix 9: Preterm births among live births (Prior/active LN[1,12,26,35,38])



QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Renal involvement	No involvement	Relative (95% CI)		
5	Observational studies	Not serious	Not serious	Not serious	Possible		77/281 (27.4%)	83/454 (18.3%)	Not estimable	Moderate	CRITICAL

Appendix 10: Preterm births among live births (Prior lupus nephritis[35])

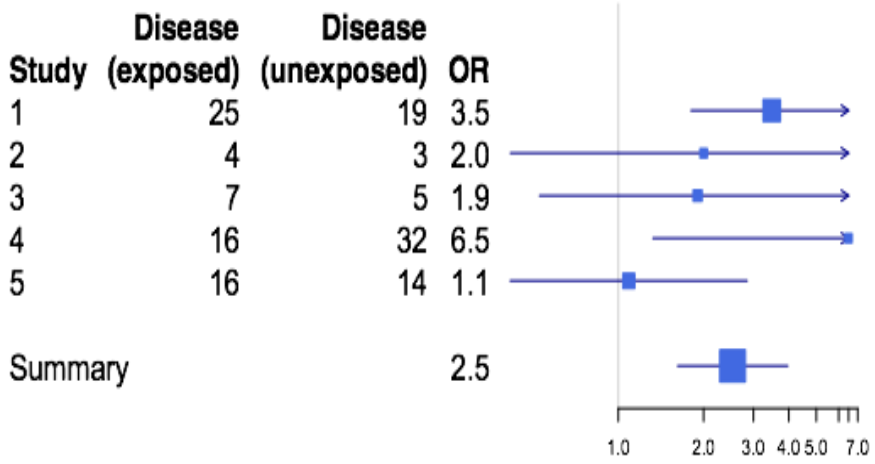
QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Renal involvement	No involvement	Relative (95% CI)		
34	Observational studies	Not serious	Not serious	Not serious	Possible		----	-----	1.2 (0.9, 1.5)	Moderate	CRITICAL

Appendix 11: Preterm births among live births (Active lupus nephritis[35])

QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Renal involvement	No involvement	Relative (95% CI)		
33	Observational studies	Not serious	Not serious	Not serious	Possible		----	----	1.5 (1.1, 2.6)	Moderate	CRITICAL

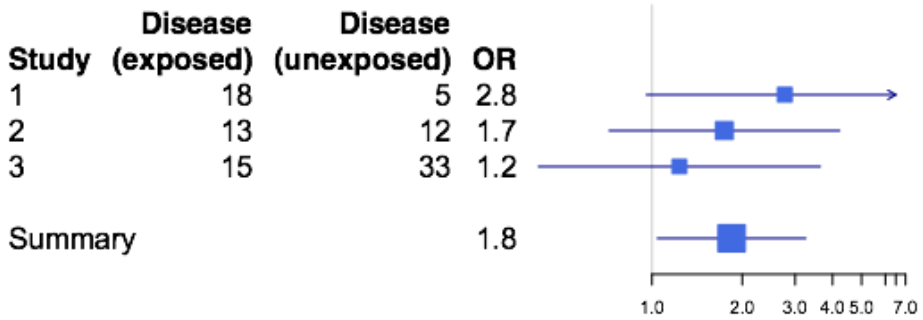
**Overall incidence of preterm birth in all included studies 37.1% (95% CI 34.8, 39.4)*

Appendix 12: Preterm births among live births (Flare/active disease[1,13,27,28,38])



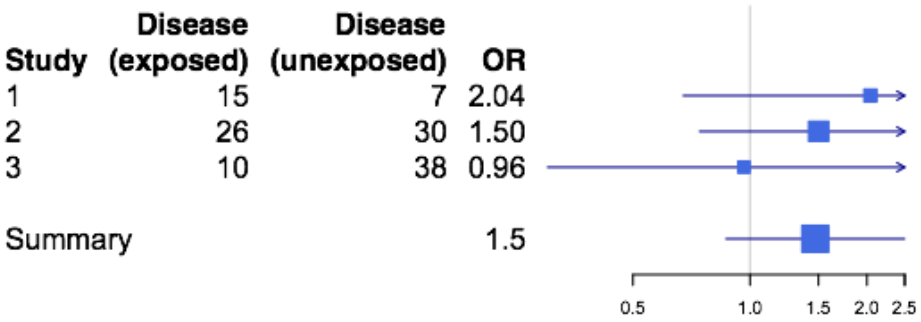
QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE pregnancies with flare	SLE pregnancies without flare	Relative (95% CI)		
2	Observational studies	Not serious	Not serious	Not serious	Not serious		68/261 (26.1%)	73/477 (15.3%)	cf forest plot	Moderate	CRITICAL

Appendix 13: Preterm births among live births (Anti-Ro antibodies[1,7,27])



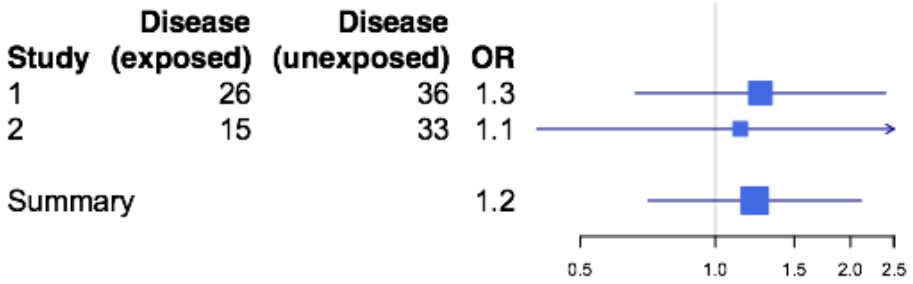
QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-Ro-exposed SLE pregnancies	Anti-Ro-unexposed SLE pregnancies	Relative (95% CI)		
3	Observational studies	Not serious	Not serious	Not serious	Not serious		38/186 (20.4%)	50/210 (23.8%)	cf forest plot	Moderate	CRITICAL

Appendix 14: Preterm births among live births (Anti-DNA antibodies[12,13,27])



QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-DNA-exposed SLE live births	Anti-DNA-unexposed SLE live births	Relative (95% CI)		
3	Observational studies	Not serious	Not serious	Not serious	Not serious		51/108 (47.2%)	75/169 (44.3%)	cf forest plot	Moderate	CRITICAL

Appendix 15: Preterm births among live births (Low C3/C4 levels[13,27])



QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE pregnancies with low C3/C4	SLE pregnancies without low C3/C4	Relative (95% CI)		
2	Observational studies	Not serious	Not serious	Not serious	Not serious		41/92 (44.6%)	69/164 (42.1%)	cf forest plot	Moderate	CRITICAL

Appendix 16: Preterm births among live births (Umbilical artery Doppler between 24 -35 weeks[18])

QUALITY ASSESSMENT							# OF PATIENTS		Difference in proportion (95% CI)	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE pregnancies with doppler anomalies	SLE pregnancies with no anomalies			
1	Observational study	Possible	Not serious	Not serious	Not serious		5/6 (83.3%)	12/50 (24.0%)	59.3% (17.4, 76.1%)	Low	CRITICAL

**Absent or reversed diastolic end-flow*

Appendix 17: Placenta mediated complications (PROMISSE study[9])

Question: Course of placenta mediated complications over pregnancy
Setting: Appendix 17: Placenta mediated complications (PROMISSE study) (9)
Bibliography: 9. Buyon JP, Kim MY, Guerra MM, Laskin CA, Petri M, Lockshin MD, et al. Predictors of pregnancy outcomes in patients with lupus: a cohort study. Ann Intern Med. 2015 Aug;163(3):153-63.
Author(s): Vinet, MacDonald, Bernatsky

№ of studies	Quality assessment						Effect			Quality	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
Placenta mediated complications											
1	observational studies	not serious	not serious	not serious	serious [a]	none	SLE pregnancies with APO: 73 out of 385 (19%) (see Table)			⊕⊕⊕◯ MODERATE	CRITICAL

a. Imprecision is possible therefore downgraded to serious

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Appendix 18: Placenta mediated complications

Table 4. Predictors of APOs From Logistic Regression Models*

Predictor Variable	Model 1: APO at Any Time During Pregnancy (n = 385 [73 events])		Model 2: APO After 23 wk (n = 370 [62 events])		Model 3: APO After 35 wk (n = 318 [30 events])	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Baseline						
Non-Hispanic white (yes vs. no)	0.45 (0.24–0.84)	0.013	0.44 (0.21–0.93)	0.032	0.40 (0.15–1.08)	0.071
Current antihypertensive use (yes vs. no)	7.05 (3.05–16.31)	<0.001	13.14 (4.79–36.04)	<0.001	7.69 (2.37–24.96)	<0.001
LAC status (positive vs. negative)	8.32 (3.59–19.26)	<0.001	7.80 (2.83–21.45)	<0.001	4.04 (1.05–15.61)	0.043
PGA score (>1 vs. ≤1)	4.02 (1.84–8.82)	<0.001	3.78 (1.47–9.73)	0.006	3.20 (0.93–10.96)	0.064
Platelet count (per decrease of 50 × 10^9 cells/L)	1.33 (1.09–1.63)	0.006	1.41 (1.12–1.78)	0.003	1.35 (1.01–1.82)	0.046
20–23 wk						
Flare						
Mild/moderate vs. none	–	–	3.14 (1.25–7.90)	0.015	–	–
Severe vs. none	–	–	5.87 (1.15–29.96)	0.033	–	–
Change in C3 level from baseline (per 0.10-g/L decrease)	–	–	1.24 (1.03–1.50)	0.025	–	–
SLEPDAI score (per 2-point increase)	–	–	1.43 (1.06–1.94)	0.020	–	–
32–35 wk						
Flare						
Mild/moderate vs. none	–	–	–	–	1.95 (0.55–7.00)	0.30
Severe vs. none	–	–	–	–	9.60 (1.95–47.35)	0.006
Change in C3 level from baseline (per 0.10-g/L decrease)	–	–	–	–	1.21 (0.97–1.50)	0.087

Appendix 19: Placenta mediated complications (Prior lupus nephritis[4(2011),35(2010)])
Question: Course of placenta mediated complications over pregnancy
Setting: Appendix 17: Placenta mediated complications (PROMISSE study) (9)
Bibliography: (9) Buyon JP, Kim MY, Guerra MM, Laskin CA, Petri M, Lockshin MD, et al. Predictors of pregnancy outcomes in patients with lupus: a cohort study. Ann Intern Med. 2015 Aug;163(3):153-63. (4). Bramham K, Hunt BJ, Bewley S, Germain S, Calatayud I, Khamashta MA, Nelson-Piercy C. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. J Rheumatol. 2011 Sep;38(9):1906-13. (35) Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol. 2010 Nov;5(11):2060-8.
Author(s): Vinet, MacDonald, Bernatsky

№ of studies	Quality assessment						Effect			Quality	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
Placenta mediated complications (Lupus Nephritis (4,35))											
1	observational studies	not serious	not serious	not serious	serious [a]	none	Pregnancies with Prior Lupus Nephritis: 12/43 (28%); SLE pregnancies without prior lupus nephritis 10/64 (16%); Difference in Proportion (95% CI 12% (-3,29)			⊕⊕⊕◯ MODERATE	CRITICAL

a. Imprecision is possible therefore downgraded to serious

QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregnancies with prior lupus nephritis	SLE pregnancies without prior lupus nephritis	Relative Risk(95% CI)		
1	Meta-analysis	Not serious	Not serious	Not serious	Not serious		?/1000	?/1751	1.14 (1.02, 1.29) Preeclampsia 9.1% (7.4, 10.8%)	Moderate	CRITICAL

Appendix 20: Congenital heart block (Anti-Ro/La-antibodies exposure in isolated CHB (in utero ad less than 28 days)[5])

QUALITY ASSESSMENT							# OF PATIENTS		EFFECT	QUALITY	IMPORTANCE
# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cases with anti-Ro/La exposure	Cases without anti-Ro/La exposure	Relative Risk(95% CI)		
39	Observational studies	Not serious	Not serious	Not serious	Not serious		1230/1416 (87%)	186/1416 (13%)	N/A	Moderate	CRITICAL

Appendix 21 : Pregnancy outcomes

Table 1. Pregnancy Outcomes in Patients With SLE*

Variable	Gestational Age		
	≤23 wk	>23-≤35 wk	>35 wk
Pregnancies with PROMISSE study-defined APOs	11	32	30
Mean gestational age at end of pregnancy, *wk*	18.2	29.6	37.7
Study-defined APOs			
Fetal death	11	5	2
Neonatal death	0	5	0
Delivery at <36 wk due to placental insufficiency, GHTN, or PE	4	27	2
SGA neonate†	3	9	27
Other pregnancy complications in patients with SGA neonates			
Premature preterm rupture of membranes and/or premature labor	0	0	4
Delivery at >35 wk with GHTN/PE or oligohydramnios	0	0	3‡

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Appendix 22: Pregnancy outcomes

Pregnancies with other APOs	4	20	52
Mean gestational age at end of pregnancy, *wk*	19.6	32.1	38.7
Outcomes			
Termination of pregnancy	1§	2‖	0
Incompetent cervix	2	0	0
Premature preterm rupture of membranes and/or premature labor	1	14	14
Delivery at >35 wk with GHTN/PE or oligohydramnios	0	0	28¶
Delivery for other obstetric indications	0	2**	5††
Delivery for maternal indications	0	2‡‡	6§§
Uncomplicated pregnancies	0	0	236

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Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

DATA SUPPLEMENT #9 Cervical Cancer Screening

Evidence to decision framework

Problem: What are the minimal investigations to optimally monitor the risk of malignancy in SLE patients? **Should we screen SLE patient 'more often' for cervical pre-cancerous lesions?**

Option: More rigorous screening in SLE patients compared to the general population, especially in particular malignancies – e.g. Cervical cancer

Comparison: Less or equal malignancy screening as compared to the general population

Setting: Systemic Lupus Erythematosus patients in Canada

Perspective: Caregivers of SLE (rheumatologists, internal medicine) and SLE patients

Background

Systemic lupus erythematosus (SLE), an autoimmune disorder with complex environmental and genetic interactions, affects approximately 1 in 1000 women in North America[1]. In the last five decades, advances in management have improved 5-year survival to over 90%[2]. The longer survival translates, in some cases, to considerable long-term morbidity, including distinct cancer profiles. In Canada, the incidence of and mortality from cervical cancer has decreased from 1.5% in 1972 to 0.7% in 2006, with risk of death reported at 0.2% (3). Cervical cancer accounts for up to 300 000 annual deaths and is the second most commonly occurring cancer in women. The number of cervical cancer cases increases in women aged 25 years and older and peaks in middle aged females (> 50 yo) (4,5). Causes for cervical cancer include early sexual activity, multiple sexual partners, HPV infection, genital warts, sexually transmitted diseases, genital tract abnormalities, age, smoking, passive smoke, poor nutrition, immunodeficiency and malnutrtion

Cervical cancer: The Papanicolaou test (sometimes called Pap test or Pap smear) is a method of screening (in women who have been sexually active) for potentially pre-cancerous and cancerous processes in the cervix. The goal of cervical screening is to decrease cervical cancer incidence and mortality through the early detection and treatment of pre-cancerous lesions and early-stage invasive cervical cancer (6,7). Abnormal findings are often followed up by more diagnostic procedures, and/or, interventions that aim to prevent progression to cervical cancer [8-10]]. Cervical cancer risk is linked to human papilloma virus, HPV. Infection with high-risk HPV types increases the chance or progression from milder lesions to more severe abnormalities and/or cervical cancer [11]. Cervical intraepithelial neoplasia (CIN, also known as cervical dysplasia), are potentially premalignant changes (dysplasia) of squamous cells on the surface of the cervix. Progression to cervical carcinoma in situ (CIS) occurs in approximately 11% of CIN1 and 22% of CIN2. Progression to invasive cancer occurs in about 1% of CIN1, 5% in CIN2 and 12% in CIN3.[6,12]

The Canadian Task Force on Preventative Health Care developed recommendations on cytology screening for cervical cancer utilizing the GRADE methodology in 2013 providing high-quality evidence for women aged 30-69 years leading to strong recommendation for routine screening (strong recommendation; high quality evidence) and 20-24 (weak recommendation, moderate-quality evidence) [6].

These recommendations did not apply to several subgroups including immunosuppressed patients such as those on chemotherapy and those on chronic corticosteroid treatment. HPV screening was not addressed either alone or in combination with cytology testing due to the observation that evidence is still evolving.

These recommendations will be used as a basis for the decision about screening for pre-cancerous lesions in women with SLE. (The recommendations do not address screening with human papilloma virus (HPV) testing (alone or in combination with Pap testing). In our judgment, such a recommendation would be premature until the

evidence in this area is further developed. *Cytology (conventional or liquid-based, manual or computer-assisted)*
• For women aged less than 20 years, we recommend not routinely screening for cervical cancer. (Strong recommendation; high-quality evidence)
• For women aged 20–24 years, we recommend not routinely screening for cervical cancer. (Weak recommendation; moderate-quality evidence)
• For women aged 25–29 years, we recommend routine screening for cervical cancer every 3 years. (Weak recommendation; moderatequality evidence)
• For women aged 30–69 years, we recommend routine screening for cervical cancer every 3 years. (Strong recommendation; high-quality evidence)
• For women 70 years of age or older who have undergone adequate screening (i.e., 3 successive negative Pap test results in the last 10 yr), we recommend that routine screening may stop. For all other women 70 years of age or older, we recommend continued screening until 3 negative test results have been obtained. (Weak recommendation; low-quality evidence)

Subgroup considerations: Pediatric or juvenile SLE; Immunosuppression

X	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ ***Detailed judgements***	The overall cancer incidence risk in SLE is approximately 15-20% more than in the general population (13,14). Several studies have shown a link between SLE and cervical cancer, possibly associated with higher HPV infection rates in SLE and high risk abnormal Pap tests in SLE patients [15-19]. No data on mortality from cervical cancer in SLE patients. While data fairly consistently show an increase of pre-cancerous cervical changes in SLE, this does not necessarily translate into an over-all increase in death due to cancer.	Not an increase risk of invasive cervical cancer
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☒ *No known undesirable outcomes* ☐ **Detailed judgements**	***The relative importance or values of the main outcomes of interest:*** **Outcome** — **Relative importance** — **Variability** Prevalence of pre- & cervical cancer — Critical — Little variability Prevance of pre- and cervical cancer with immunosuppression	HPV vaccination- future consideration

			Critical Prevalence of HPV in SLE Critical Mortality	

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BENEFITS & HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	*No included studies* ☐ | *Very low* ☒ | *Low* ☐ | *Moderate* ☐ | *High* ☐	No randomised or non-randomised studies were found which compared more rigorous screening in SLE patients versus screening recommended for the general population [29] <u>Evidence for increased risk of cervical cancer:</u> See table below. <u>Evidence for sensitivity and specificity of cytology and HPV tests in people with SLE</u> Accuracy of tests not reportedly different than general population although HPV genotypes and # of types might vary <u>Evidence for benefits and harms of screening in SLE</u> Positive screening tests can produce worry for patients and their families, and financial costs to the individual and health care system as a result of additional diagnostic tests [6]. While treatment of CIN reduces incidence of later stage disease, not all untreated CIN progresses to cancer which means many women undergo unnecessary treatment procedures. However, similar to Canadian data for general population, this does not likely outweigh the benefits (see Canadian recommendations for cervical cytology screening).	Refer to quality of evidence of original Candian Task Force Guidelines; Very low evidence whether immunosuppression confers greater risk of cervical dysplasia in SLE patients; low quality evidence in prev/HPV in SLE; evidence is used indirectly for the SLE population. No data availalble in different age groups; there is data in general population and panel felt there was no reason to think it would be "at least the same" The panel was split regarding the undesirable effects beings "somewhat": versus "moderately" important; → Annals of Internal Medicine article on harms of screening; some women recommended for coloposcopy immediately ; (10% vs 2 % incidence) TP 14; FP 49/1000/TN 931/FN 6; concern about it leading to increased LEEP procedures with higher false positivity (21,22) False positive fate – Cancer Care Ontario; More value placed on false positives (eg. SLE pt with multiple investigations, with false + testing implies increased further testing) If false positive occurred, may impact management of SLE – eg. may not choose certain therapies; Patient perspective – false positive can increase anxiety, future health
	How substantial are the desirable anticipated effects?	*Don't know* ☐ | *Not important* ☐ | *Somewhat important* ☐ | *Moderately important* ☐ | *Very important* ☒ | ***Varies*** ☐ **Detailed judgements**		
	How substantial are the undesirable anticipated effects?	*Don't know* ☐ | *Very important* ☐ | *Moderately important* ☐ | *Somewhat important* ☒ | *Not important* ☐ | ***Varies*** ☐ **Detailed judgements**		
	Do the desirable effects outweigh the undesirable effects?	*No* ☐ | *Probably No* ☐ | *Don't know* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Moderatel*** ☐ ***Detailed judgements***		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				care use Value placed on false positivity (eg. Canadian Task Force placed on value on this as well); SUBGROUP considerations: - Immunocompromised (definition of immunosuppression discussed; consider SLE immunosuppressed)

Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

Author(s): Stephanie Keeling, Basile Tessier-Cloutier, Ann Clarke, Sasha Bernatsky
Date: September 12, 2015
Question: Prevalence and association of risk factors with cervical cancer and pre-cancerous lesions for systemic lupus erythematosus patients
Setting: Rheumatology and primary care clinics in Canada, Caregivers of Systemic Lupus Erythematosus patients
Bibliography: Esmaeili H, Ghahremanzadeh K. Association of Pap smear abnormalities with autoimmune disorders. Pak J Biol Sci 2011; 14: 600–604. Tam L-SS, Chan AY, Chan PK, et al. Increased prevalence of squamous intraepithelial lesions in systemic lupus erythematosus: association with human papillomavirus infection. Arthritis Rheum 2004; 50: 3619–3625. Klumb EM, Araºjo ML, Jesus GR, et al. Is higher prevalence of cervical intraepithelial neoplasia in women with lupus due to immunosuppression? J Clin Rheumatol 2010; 16: 153–157. Dhar JP, Essenmacher L, Ager J, Sokol RJ. Ominous cervical cytopathology in women with lupus. International Journal of Gynecology and OBstetrics 2005; 89:295-296. Nath R, Mant C, Luxton J, Hughes G et al. High risk of human papillomavirus Type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. Arthritis Rheum 2007; 57(4):619-625. Bateman H, Yazivi Y, Leff L, Peterson M, Paget SA. Increased cervical dysplasia in intravenous cyclophosphamide patients with SLE: a preliminary study. Lupus 2000; 9:542. Ognenovski VM, Marder W, Somers EC, Johnston CM et al. Increased incidence of cervical intraepithelial neoplasia in women with systemic lupus erythematosus treated with intravenous cyclophosphamide. J Rheum 2004; 31:1763-1767. Kim SC, Glynn RJ, Giovannucci E, Hernandez-Diaz S, et al. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases: a population-based cohort study. Ann Rheum Dis 2015;7:1360-1367. Dugue P, Lynge E, Rebolj M Increased risk of high-grade squamous intraepithelial lesions in systemic lupus erythematosus: Additional data from Denmark. Autoimmunity Revieiws 2014; 13:1241-1242.

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SLE with cervical cancer screening**	**Control Population with cervical cancer screening**	**Relative (95% CI)**	**Absolute (95% CI)**	
Prevalence of pre- and cervical cancer (assessed with: Cervical cytology (abnormal Pap Smears - all types including ASCUS, low to high grade intraepithelial neoplasia))											
3 [1,2] (Studies 23-25)	observational studies	not serious [3]	not serious	not serious	not serious	none	95/577 (16.5%)	241/3049 (7.9%)	**RR 2.08** (1.67 to 2.60)	85 more per 1000 (from 53 more to 126 more) [3]	⊕⊕⊕◯ MODERATE [3]
Risk of high-grade cervical dysplasia and cervical cancer (assessed with: claims-based algorithm with 2 ICD-9 & current procedural terminology codes for revelant gynecological procedures or treatment with the diagnosis date using billing data in an electronic records database)											
1 (Study 28)	Observational study	Not serious	Not serious	serious	Not serious	None	40 cases/14,513 SLE patients	818 cases/533,332 non-SLE (non autoimmune patients)	**HR (fully adjusted) 1.53** (1.07, 2.19)	---	⊕⊕◯◯ LOW
Prevalence of pre- and cervical cancer (assessed with: Cervical cytology (high-grade squamous intraepithelial lesions (HSIL))											

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE with cervical cancer screening	Control Population with cervical cancer screening	Relative (95% CI)	Absolute (95% CI)	
7 (Study 29)	observational studies	serious[4] ?quality	not serious	not serious	serious	none	24/416 (5.8%)	54/11408 (0.47%)	**OR 8.66** (3.75 to 20.00)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW [4]
1 (Study 30)	Observational study	Not serious	Not serious	Not serious	Not serious	None	25 HSIL cases/2497 SLE patients	14,286 HSIL/1567,911 General population	**OR 1.7** (1.1 to 2.5)		⊕⊕⊕◯ MODERATE CR
Prevalence of HPV (Human Papilloma Virus) in SLE patients (assessed with: HPV genotyping)											
3 [5]	observational studies	not serious [6]	not serious	not serious	serious	none	61/288 (21.2%)	169/2312 (7.3%)	**RR 2.90** (2.22 to 3.78)	139 more per 1000 (from 89 more to 203 more)	⊕⊕◯◯ LOW [6]
Association of immunosuppression (cyclophosphamide) with pre- and cervical Cancer in SLE (follow up: range 3 years to 7 years; assessed with: Cervical cytology)											
2 [7]	observational studies	not serious [8]	not serious	serious [9]	serious	none	16/99 (16.2%)	2/52 (3.8%)	**RR 5.82** (1.38 to 24.50)	185 more per 1000 (from 15 more to 904 more)	⊕⊕◯◯ LOW [8 9]

MD – mean difference, RR – relative risk

1. The prevalence of atypical cervical smears in SLE patients varies from 24% to 36% versus 5% to 15% in controls (23-25). Risk factors in SLE associated with cervical intraepithelial neoplasia (CIN) include increased prevalence of high-risk HPV (15,26), multiple HPV infections versus controls (15), especially HPV-16 (26), with higher HPV-16 loads seen more frequently in SIL (squamous intraepithelial lesion) (26). The contribution of chronic immunosuppression (eg. prednisone, cyclophosphamide) to development of cervical intraepithelial neoplasia (CIN)/SIL is conflicting in studies (27).
2. A case control study in 2011 confirmed that the frequency of abnormal Pap smear testing was higher in SLE patients (8.1%) versus controls but was marginally nonsignificant OR 4.78 (95% CI 0.94-24.3) (p=0.006)
3. Newcastle-Ottawa Scale for cross-sectional studies was completed ranging from 7 to 8.
4. Meta-analysis of 7 studies in 2014; 3 cross-sectional, 2 case control, 1 retrospective cohort and 1 with unclear study design; quality not assessed in meta-analysis; no significant heterogeneity (Ref 29). The high effect estimate in this meta-analysis was discussed in Dugue et al (Ref 30); concern regarding the controls, country of study origin and small sample sizes were pointed out as possible concerns.

5. SLE itself may lead to defective clearance mechanisms toward HPV or HPV infected epithelial cells (31); Immunosuppression in SLE patients decreases immune response to viruses such as HPV (32-34); One study found independent risk factors associated with persistent HPV included pre-existing HPV infection (p=0.04), multiple HPV infection during incident infection (p=0.02); cumulative prevalence of HPV infection increased significantly (12.5% baseline to 25% after 3 years; p=0.006); 18.8% pts had 68 incident infections; cumulative prevalence of high-risk HPV infection (11.1% at baseline to 20.8% after 3 years, p=0.02); and multiple HPV infection also increased significantly (6.9% at baseline to 16.7% after 3 years; p=0.009) ; 33/68, (48.5%) of incident infections persisted for > or equal to 6 months; overall 29/32 (90.6%) pre-existing infection and 10/68 (14.7%) of incident infections cleared (35)
6. Newcastle-Ottawa Scale for cross-sectional studies were 8 out of 9 stars
7. Immunsuppressants (eg. azathioprine, prednisone, cyclophosphamide, cyclosporine A, hydroxychloroquine) similar in SLE patients with normal Pap smears, abnormal Pap smears and those with SIL in cross-sectional study in Hong Kong evaluating prevalence of abnormal Pap smears and HPV in SLE patients (15). Multivariate analysis showed that SLE women with long-term use of immunosuppression (including cyclophosphamide, azathioprine or mycophenolate mofetil (besides corticosteroids) had higher prevalence of low-grade and high-grade intraepithelial lesions compared to those without long-term use (68.7% vs 31.1%, P=0.03) in a cross-sectional study of 171 SLE patients (87 receiving immunosuppression for at least 1 year compared to 222 age- and sociocultural-paired women) with routine cervical cytology (36). **Uncertainty in evidence so low quality**
8. Retrospective study with variability in reporting of cyclophosphamide group; variability in reporting of Pap smears (ie. "wherever possible, cases discussed with pathologist" suggests it was not standard for all cases
9. Contribution of other immunosuppression (eg. prednisone, azathioprine) may impact directness

RESOURCE USE	**How large are the resource requirements?**	*Large costs* ☐ *Moderate costs* ☐ *Small* ☒ *Moderate* ☐ *Large* ☐ ***Varies*** ☐ h**Detailed judgements**	Cervical cytology is widely available in all Canadian provinces. Tests for HPV are not offered in all provinces and are more costly. No data on morbidity/mortality with addition of HPV testing in SLE. HPV testing may be more sensitive than cytology (36-38), and may provide additional benefit in reducing cervical cancer in the SLE patient with higher prevalence of HPV (39). Cost implications of more frequent screening in SLE patients (eg. every 3 years according to Canadian Task Force recommendations for women aged 30-69) or annually) are unavailable. The prevalence of SLE in Canada (estimated to be 0.1-0.5%) (40). Availability of cervical cytology +/- HPV screening across Canada. In Canada, age-standardized participation rates for Pap testing (percentage of eligible women in the target population who had at least one Pap test in a three-year period) reported across provinces are similar, ranging from 64.9% to 70.1%. Cytology turnaround time is a measure of the system's capacity to process Pap tests in a timely manner and is influenced by human resources and information systems. In Canada the median cytology turnaround time ranged from 13 to 44 days in 2009, 11 to 51 days in 2010 and 13 to 57 days in 2011. Cytology turnaround time was between 13 and 17 days in most provinces (41).	NEGLIGIBLE COSTS: No data on SLE and cervical screening cost effectiveness; Resource requirements would be greater with 1 year than 3 years – involves staffing/laboratory tests/test cost; this is additional screening per year for ~ 15000 women (age > 20 yo) in Canada; this change is from every 3 years to every 1 year; not quite trivial due to some resource use therefore weighted as small

	How large is the incre-mental cost relative to the net benefit?	*Very large* ☐ *Large ICER* ☐ *Moderate ICER* ☐ *Small ICER* ☐ *Savings* ☐ ***Varies*** ☐ **Detailed judgements**	No direct cost data available for SLE patients and more frequent cervical cytology +/- HPV screening.	Do not know

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ☒ *Uncertain* ☐ *Probably reduced* ☐ *Reduced* ☐ ***Varies*** ☐ **Detailed judgements**	According to the Canadian Task Force on Preventative Health Care, certain subgroups of women may receive less adequate cervical screening: immigrant groups, Aboriginal women, women with low socioeconomic status (42-45). Albertan First Nations over 45 years of age have twice the prevalence of systemic lupus erythematosus than non-First Nationals females. An American study comparing preventative services reported by insured women with SLE enrolled in the University of California, San Francisco Lupus Outcomes Study (n=685) were compared to two representative samples from a statewide health interview survey (general population sample, n=18,013) and a sample with non-rheumatic chronic conditions (n=4,515). While 70% of eligible respondents reported cervical cancer screening and mammography, multivariate regression analysis showed that individuals with SLE who were younger and with less education were significantly less likely to receive preventative services. Enrollment in HMO's did not improve cancer screening rates. Individuals with higher number of physician visits were more likely to receive cancer screening services (46).	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ **Detailed judgements**	No evidence in SLE patients on patient preferences for screening more frequently; limited data from Canadian Task Force on Preventative Health Care which supports frequent screening intervals to provide a feeling of security compared to longer intervals (6,47). A survey of 146 Canadian SLE patients for cancer surveillance rates found that screening rates were below the general population cancer screening rates (48).	Regarding the survey, the SLE population with lower rates of screening have lower rates of primary care age/gender appropriate screening (eg. highly medicalized) and therefore are not receiving standard of care screening Future Considerations: increased dialogue with providers of cancer screening (eg. GP/OB GYN) Adherence strategies to these more frequent

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ **Detailed judgements**	No gold standard for frequency of evaluation of SLE patients currently exists. As of 2008, there were 350 rheumatologists in Canada, or about 1.2 rheumatologists per 100,000 Canadians, about half the number of rheumatologists needed to provide adequate care. As many as 1/3 of Canada's rheumatologists will retire before 2018 (51,52). The care gap to include co-morbidity management (eg. increased cervical cancer screening) in lupus patients may widen as access to subspecialist care itself for optimal lupus care is currently threatened due to man power issues.	Recruitment of primary care and obstetrics and gynecology to perform more frequent cervical screening and consider implementation (if available) of HPV screening is feasible but requires future discussions with these caregivers. Existing issues with access to care for lupus care may influence the intent of implementing more regular cervical cancer screening for SLE patients in Canada. Future considerations: dialogue with providers of PAP to adopt these recommendations; increased awareness that SLE is immunosuppressed

SUMMARY OF JUDGMENTS

Criteria	Favours the alternative	Probably favours the alternative	Choose either option or alternative	Probably favours the option	Favours the option
Problem	☐	☐	☐	☐	X☐
Values	☐	☐	☐	☐	X☐
Certainty of the evidence of effects	☐	☐	☐	X☐	☐
Desirable effects	☐	☐	☐	☐	X☐
Undesirable effects	☐	☐	☐	☐	X☐
Balance of effects	☐	☐	☐	☐	X☐
Resource use	☐	☐	☐	☐	X☐
Cost-effectiveness	☐	☐	☐	☐	X☐
Equity	☐	☐	☐	☐	X☐
Acceptability	☐	☐	☐	☐	X☐
Feasibility	☐	☐	☐	X☐	☐

Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☒	☐

Recommendation [Recommendation]

For all female adult patients with SLE who are, or have been sexually active, regardless of sexual orientation, we suggest annual cervical cancer screening rather than screening every 3 years at least up to the age of 69. [conditional recommendation; low quality evidence].

Remarks: Recommendations for the general population are based on age and should also apply to women with SLE (6). The Canadian general population screening interval is every 1-3 years depending on age, risk and jurisdiction. However, women with SLE, in particular those who receive immunosuppressive medications, are recognized to be a high-risk group. The decision to stop screening after the age of 69 is individualized and based on a lifetime history of normal Pap test results.

Justification

There is no evidence in women with SLE comparing different intervals between screening for cervical cancer lesions and the effects on outcomes. There is high quality evidence for screening every 3 years in the general population with cytology(60) . However, studies show that the prevalence of cervical lesions, human papilloma virus (HPV) infection, and cancer are likely higher in women with SLE, and may be greater in women treated with immunosuppression. The panel agreed that providing more frequent screening would be acceptable and feasible, and results in negligible costs given current practice.

Subgroup considerations

Juvenile SLE
HPV positive patients
Immunosuppresion – moderate to strong

Implementation considerations

Monitoring and evaluation considerations

Research priorities

Formal randomized studies or large observational cohort studies with longer term follow up evaluating outcomes secondary to rigorous monitoring of specific malignancies in SLE patients are needed to provide more specific recommendations regarding malignancy monitoring in SLE. As it pertains to cervical cancer, these studies require longer follow-up with performance of both cervical cytology and HPV screening to evaluate the relative contribution of performing both or either measures to outcomes including mortality specific to cervical malignancy. Clarification of optimal frequency of performing these tests is needed. Contribution of immunosuppression broken down by specific agent (eg. corticosteroids, antimalarials, cyclophosphamide, mycophenolate mofetil and newer agents (eg rituximab, belimumab) would be useful to clarify whether there is a dose-response with different immunosuppressants and risk of cervical dyspasia and associated HPV status. Economic analyses from these studies is recommended given the data supporting less monitoring for the general population in recent years.

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Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

DATA SUPPLEMENT #10 INFLUENZA

Question

Should **annual inactivated influenza vaccination** vs. **no vaccination** be used for **adults and children with systemic lupus erythematosus**?

POPULATION:	adults and children with systemic lupus erythematosus
INTERVENTION:	annual inactivated influenza vaccination
COMPARISON:	no vaccination
MAIN OUTCOMES:	Number of influenza associated infections and/or influenza-like illness; serious infections secondary to influenza; hospitalisations; rates of sero-conversion; disease flares; adverse events of vaccination (serious and mild);
SETTING:	single centres, outpatient clinics
PERSPECTIVE:	Population level

BACKGROUND: Infectious complications are among the most common causes of morbidity and mortality in people with SLE. People with SLE represent an immune compromised population (due to underlying disease, therapy or both) that Health Canada (http://www.phac-aspc.gc.ca/naci-ccni/flu-2015-grippe-eng.php#iii1), the Centre for Disease Control (http://www.cdc.gov/flu/about/disease/high_risk.htm), and the World Health Organization (http://www.who.int/influenza/ vaccines/use/en/), consider a vulnerable population at risk for complications secondary to influenza infection. Hence, they recommend that immunocompromised individuals received annual influenza vaccination.

This study will complete a systematic review of the literature identifying studies of the efficacy of influenza vaccinations among people with SLE, as well as any potential adverse events specific to this population. There is also a question of whether two annual influenza vaccinations or one are required.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are 12,200 influenza related hospitalizations and 3500 deaths per year in Canada (http://www.statcan.gc.ca/pub/82-624-x/2015001/article/14218-eng.htm). People with SLE are immunocompromised by their disease and therapies which puts them at risk for serious complications secondary to influenza infection. As such, regulatory bodies recommend that immunocompromised individuals receive annual influenza vaccination. Canadians with selected chronic conditions (excluding SLE) had a higher vaccination rate in 2013-2014 (32%) compared to those without a chronic condition (22%), both of which were below the National Advisory Committee on Immunization (NACI) target of 80%(http://www.statcan.gc.ca/pub/82-624-x/2015001/article/14218-eng.htm). Prior studies have raised concerns that influenza vaccination may increase autoantibody production and/or disease activity in people with	

		SLE, which appeared to be associated with a low antibody response to vaccination (Crowe et al. A&R, 2011). There is also some question about whether one or two annual vaccinations are required.	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	**PREVENTION OF INFLUENZA OR INFLUENZA-LIKE ILLNESS** People with SLE: In our review, we did not find any prior studies examining the proportion of infection reduction in people with SLE. People who are immunocompromised: Meta-analysis of 209 studies (including people with HIV, cancer, transplants, autoimmune diseases or respiratory diseases treated with immunosuppressants) showed a reduction in influenza-like illness (OR=0.23; 95% CI 0.16, 0.34) as well as in laboratory confirmed influenza infection (OR 0.15; 95% 0.03, 0.63) (Beck, et al. PlosOne, 2011). [NOS meta-analysis of papers not <5 stars. However many of the studies included in the meta-analysis are moderate to high bias by QUIPS.] In the five studies of people with autoimmune diseases (Beck et al JIID 2012), the authors reported that the low rates of influenza-like illness was possibly comparable to the rates in immunocompetent controls. **PROTECTIVE IMMUNITY** People with SLE: The majority of studies reviewed reported on the proportion of patients with SLE who gained protective immunity following influenza vaccination, often contrasting these rates with those in non-SLE populations. Cross-sectional studies reported proportions of those with sero-protection. The proportion who gained influenza antibodies/protective immunity varied (range 32% (Williams, 1978) to 93%(Del Porto, 2006)) both within and between studies and is likely due to between subject differences such as age, medications (including steroid dose and additional immunosuppressives) and duration of follow-up (1week to 5 years). A number of studies concluded that the average proportion of SLE patients with protective immunity was lower than that observed in healthy controls (65% SLE vs. 84% healthy controls, Borba 2012; 81% SLE vs. 96% controls, Aikawa, 2012; 74% SLE vs. 95% controls, Campos, 2013; 87% SLE vs. 90% controls, Brodman, 1978). Older studies did not show significant differences in seroconversion rates (Pons, 1979; Loui, 1978; Herron, 1979; Brodman, 1978). This could be due to differences in the immunosuppression strategies in the different eras.	The guideline group agreed that the number of people with SLE with sero-conversion after influenza vaccination may be lower than in people without SLE, but it appears that there is still a large reduction in influenza and influenza-like illnesses. In addition, the guideline group agreed that there is a risk of having minimal protection from vaccination and someone presuming that they are protected when they are not. The guideline group agreed that there may be little to no difference in protective immunity when providing 2 doses of influenza vaccine or 1 dose annually. The guideline group agreed with the role for Live Attenuated Influenza Vaccine (LAIV) in those with SLE as proposed by the National Advisory Committee on Immunization (NACI) of Health Canada: "Live vaccines are generally contraindicated in people

		The majority of studies administered a single influenza vaccine. However 3 studies administered 2 doses (1 month apart) of influenza vaccine and the resultant rates of seroconversion fell within the range observed for those receiving only a single dose (Mathian, 2011; Ogimi, 2011; Aikawa, 2013). Of note, a single study (Muller, 2013) specifically addressed this question of antibody production following one and two doses of influenza vaccines, in a small population (n=16) patients previously treated with Rituximab (only 5/16 with SLE). They did not observe a significant benefit of a second influenza vaccine (within 3-4 weeks apart), (38% antibody response after single, 44% (an additional 1 patient) after 2nd booster). **SERIOUS INFECTIONS SECONDARY TO INFLUENZA** People with SLE: We identified a single study (Stojanovich, 2006) that reported rate reductions in serious infection rates secondary to influenza. **SERIOUS ADVERSE EVENTS** People with SLE: The majority of studies sought to report adverse reactions, few studies reporting serious adverse events following influenza vaccination. These included a case of a febrile seizure (Akiawa, 2013); one with blurred vision (Lu, 2010); 1 patient hospitalized for a respiratory illness and a death secondary to AMI with a history of coronary disease (Ristow, 1978). **MILD ADVERSE EVENTS** People with SLE: Mild adverse event frequency varied by the amount of detail sought by each investigator, yet most studies made some report of mild adverse events. The evidence showed little difference in mild adverse events between those with and without SLE. **FLARES** People with SLE: The proportion of patients who experienced an SLE flare following vaccination ranged from 2-5% (Wiesik-Szewcyk 2010; Ritterhouse, 2011) with a severe flare. Most studies did not distinguish mild from severe flares and some reported flare rates of 12% (Abu-Shakra, 2000) to 43% (Vista, 2012). Most concluding that the flares were not different from those who did not receive the vaccine (Abu-Shakra, 2000) or stating flare rates over the period of observation did not significantly differ from the expected flare rate (Herron, 1979).	with immune compromising conditions, with some exceptions." The trivalent formulation of LAIV has been administered to approximately 170 children and adults with mild to moderate immune suppression due to HIV infections and 10 children with mild to moderate immune suppression due to cancer demonstrating a similar safety profile to healthy individuals. (http://www.phac-aspc.gc.ca/naci-ccni/flu-2015-grippe-eng.php#iii1)
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	There are large effects from non-randomised studies providing moderate quality evidence. The evidence for adverse events or flares was low to very low quality due to the few participants and events in the reports. The evidence suggested that there may be little to no difference in adverse events or flares.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Considering these outcomes: influenza infection, serious complications of influenza infection, serious or minor adverse effects from vaccination, and the risk of disease flare following immunization, there are no reports of patients' values.	The guideline group agreed that people with SLE would value the risks of influenza and consequences greater than a disease flare.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	The large reductions in influenza and influenza like illness and related serious adverse that likely occur with one annual vaccination outweighed the small number of adverse outcomes and flares related to SLE that may occur.	

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence. Resources required include manufacturing and production of vaccine, cost to pharmacies to carry vaccine, and cost of administration by pharmacist, nurse, etc. No additional cost to individuals to vaccinate all patients with SLE as the vaccine is freely available to all Canadian residents who seek immunization.	The guideline agreed that the cost to society would be minimally increased if overall numbers of vaccinated increased.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No direct studies of cost-effectiveness in SLE, but many studies in healthy populations, children, adults <65 years and in adults >65. A cost-utility analysis of universal influenza vaccination in Ontario (Sander 2010) demonstrated an incremental cost-effectiveness ratio of $10,797 per QALY (quality-adjusted life year) gained. There was significant reduction in cases of influenza and mortalities, and reduction in health care services costs.	The guideline group agreed that the impact of influenza is significant and overall cost-effectiveness of vaccine in Canada for healthy populations is evident, so extrapolating to immunosuppressed population we would propose that cost-benefit is positive.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced	No research evidence.	The guideline group agreed that for SLE patients, this represents most likely an

	○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	Except for BC, Quebec and New Brunswick, all provinces and territories in Canada offer universal vaccination. For immunocompromised patients (potentially most of the SLE population, all provinces except PEI cover costs of vaccination.	opportunity for increased equity due to universal access to the vaccines (with the exception of PEI).
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence.	The guideline group agreed that for people with SLE, this is an annual single-dose vaccination easily available (as simple as going to a local pharmacy for this shot) and would be acceptable to individual patients. They agreed that most rheumatologists would recommend this to their patients; and the healthcare payer has already endorsed this by providing funding to pay for most high-risk populations (including SLE).
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		As influenza vaccination is universally available and free of charge to almost all Canadians and most immunocompromised patients (including SLE), this intervention is definitely feasible at the disease population level. As adults and older children (>9 years old) only require a single dose per season, this is not burdensome,

			therefore this is feasible at an individual level.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	

	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should annual inactivated influenza vaccination vs. no vaccination be used in adults and children with systemic lupus erythematosus?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●
RECOMMENDATION	*We recommend that adults and children with SLE receive an annual inactivated influenza vaccination in a single dose. (Strong recommendation, Moderate quality evidence).* Remarks: It is important that clinicians ascertain influenza vaccination status by asking adults and children with SLE during the clinic visit. Education about the benefits of the influenza vaccination is an important part of the consultation. See also the National Advisory Committee on Immunization (NACI) recommendations to avoid the use of Live Attenuated Influenza Vaccine in immunocompromised populations [http://www.phac-aspc.gc.ca/naci-ccni/flu-2015-grippe-eng.php].				
JUSTIFICATION	In people with SLE, there is moderate quality evidence that there are likely large reductions in influenza and influenza like illness and related serious adverse events, and a trivial number of adverse outcomes and flares related to SLE with annual influenza vaccination in a single dose (6,7,11,19). There is likely no difference in benefits when providing two doses. The costs to society would likely be minimally increased if the overall numbers of people vaccinated increased, and it would still be cost-effective, although less than in the general population. Influenza vaccinations are acceptable to people with SLE, healthcare providers, and is funded by healthcare payers. The influenza vaccination is presently feasible to implement and providing universal access to the vaccine would probably increase equity.				

SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Availability of the influenza vaccination varies between rheumatology practises. Other options for the SLE patient to receive their influenza vaccination include: family physician office, walk-in medical clinic, public health unit, public health flu vaccination campaigns and local pharmacies.
MONITORING AND EVALUATION	Future considerations might include quality assurance projects to evaluate the extent of vaccination for SLE patients in primary care and rheumatology clinics.
RESEARCH PRIORITIES	Acceptability of the influenza vaccine the adult and pediatric SLE populations in Canada may warrant future qualitative research

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DATA SUPPLEMENT #11 HEPATITIS B

Question

Should **screening for HBV infection** vs. **no screening** be used for **people with SLE**?

POPULATION:	people with SLE	**BACKGROUND:**	Hepatitis B virus (HBV) primary infection can manifest as acute hepatitis with or without hepatic dysfunction and resultant chronic liver disease, with resultant diagnosis at that time. More often the disease is not clinically overt initially, existing in a dormant state, with patients referred to as "chronic carriers". A relatively rare but potentially devastating manifestation of hepatitis reactivation in the setting of intrinsic (e.g. hematologic malignancy/ immunodeficiency/ coinfection) or extrinsic (e.g. immunosuppression, corticosteroids, chemotherapy) immunosuppression is "de novo" hepatitis – an acute, severe and potentially deadly reactivation of the disease. Active HBV is diagnosed through the detection of Hepatitis B Surface Antigen (HBSAg) or in rare cases of "occult" HBV infection (OBI), through the detection of Hepatitis B DNA (via PCR) in the absence of HBSAg. Most of these patients are positive for anti-Hepatitis B Surface Antibody (anti-HBsAb) and/or anti-Hepatitis B Core Antibody (anti-HBcAb). Important in the detection of chronic carriers of HBV are anti-HBsAb and/or anti-HBcAb in anti-HBSAg negative individuals. An important note is that HBV vaccination results in anti-HBsAb positivity (but no alteration in the other relevant diagnostic markers) and thus clear documentation of HBV vaccination status and timing are critical in the evaluation of possible HBV chronic carrier status. In Canada, HBV vaccination is routine for those traveling to endemic areas, and is also recommended in high risk individuals (1).
INTERVENTION:	screening for HBV infection		
COMPARISON:	no screening		
MAIN OUTCOMES:	hepatitis B activation evidence of hepatic injury death SLE disease activity		
SETTING:	outpatient or inpatient		
PERSPECTIVE:	population		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Up 350 million individuals may be chronic carriers of HBV, with 75% of cases clustered in Asia and the Western Pacific countries (2) but with a global distribution. Chronic carriers are at risk of reactivation of hepatitis - a state that could lead to hepatic failure, that in rare circumstances can be fulminant and fatal. With regards to immunomodulatory therapies, corticosteroids may directly stimulate HBV replication whereas all immunosuppressives may disinhibit intrinsic anti-viral mechanisms and thus trigger HBV reactivation. Furthermore, immunosuppressive agents may suppress serologic markers of disease (eg anti-HBsAb and anti-HBcAb) necessitating screening prior to the initiation of immunomodulatory therapies. Concern has been raised that HBV infection might initiate or exacerbate SLE (3).	

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?
○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know

Screening versus no screening
No studies were identified that compared outcomes of SLE patients screened for HBV with outcomes of SLE patients who were not screened for HBV.

Prevalence in the general population in Canada The Canadian Health Measures Survey (CHMS) found the seroprevalence of current HBV infection, inclusive of both acute and chronic infection, to be 0.4% over a period of data collection spanning 2007 to 2011. Serological evidence of a previous HBV infection was identified among 4.2% of participants (4).

Prevalence of HBV positivity in SLE patients: The prevalence of HbsAg positivity ranged from 0%-8.7% globally (5-17). In all studies, the prevalence of HbsAg+ was either not significantly different than the general population, or significantly lower than the general population.

Outcomes of patients HBsAg positive or HBV carrier

	No. of Participants; no. of studies (ref)	HBV reactivation	Hepatic injury	Death
HBsAg positive SLE patients	89;6 (10,15,16,18-20)	24.7%	19.1%	9.0%
HBsAg positive rheumatological patients (including SLE)	80;4 (21-24)	20%	-	0%
HBV carrier (HBsAb+ and/or HBcAb+) SLE patients	41;1 (15)	2.4%	0%	2.4%
HBV carrier (HBsAb+ and/or HBcAb+) rheumatological patients (including SLE)	247;3 (21,25,26)	4.4%	0%	1.2%

*Note some patients were receiving immunomodulatory agents.

Immunomodulatory regimens associated with outcomes:
HbsAg+ SLE patients: Reactivation of HBV has been associated with hydroxychloroquine, prednisone+cyclophosphamide, anti-TNF, rituximab+cyclophosphamide, and azathioprine; but not associated with pulses of IV methylprednisone (18, 23). Hepatic failure due to HBV associated with prednisone+azathioprine, prednisone+cyclophosphamide (16).
HBV carrier (HbsAb+ and/or HbcAb+) SLE patients: Reactivation of HBV associated with high dose pred+cyclophosphamide, tacrolimus+mizoribine+pred 5mg/d, tacrolimus+pred 5mg/d, sulfasalazine, bucillamine (25).

While the prevalence of HBV may be similar to the general population, the guideline panel agreed that patients with SLE may be at risk of HBV reactivation (with or without immunomodulatory agents) and the benefits of screening and then providing prophylactic treatment in SLE patients with HBV to prevent reactivation may be large. There may be a reduction in death and hepatic injury. The panel did not make a distinction between patients at high or low risk of HBV infection.

The panel also agreed that there may be trivial undesirable effects of screening (e.g. trivial consequences if falsely screened positive and treated unnecessarily).

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Outcomes when prophylactic anti-virals provided to prevent HBV reactivation:** 25 SLE patients and 8 unselected rheumatologic HBV+ patients or carriers at high risk to develop HBV reactivation were treated in 4 studies, in nearly all cases with the nucleoside analog lamivudine (26,20,22,24). No patient experienced clinical reactivation of HBV. **Outcomes when anti-virals provided for treatment of HBV reactivation:** 23 SLE patients were treated in 4 studies (16,18,19,24). 3 patients died, 20/23 had clinical improvement **Screening tests available for HBV:** Serology for HBV is performed using chemiluminescent microparticle immunoassay testing. The Hamilton Regional Medical Laboratory Program uses the ARCHITECT assay, and validation studies using blood donors and patients who are known HBV carriers have shown sensitivity of 99.8% and specificity of 99.5% (27). Likelihood of HBV positivity: 4.4% (mid-range of HBV positivity in studies) or 0.4% (in Canada). If not screened, the number of people that are HBV+ = 40/10,000 or 440/10,000. Using 99.8% sensitivity and 99.5% specificity means in 10000 patients (0.4% risk), 0 would be missed (and risk reactivation and consequences) and 50 would be falsely told they were positive and receive treatment unnecessarily. Using 99.8% sensitivity and 99.5% specificity means in 10000 patients (4.4% risk), 1 would be missed (and risk reactivation and consequences) and 48 would be falsely told they were positive and receive treatment unnecessarily.	
CERTAINTY OF EVIDEN	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	The quality of the evidence is low to very low due to risk of bias of the non-randomised studies for prevalence and prognosis and very few participants.	

CE			
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No preference data specific to SLE patients was found comparing screening to no screening. In the general HBV population, a cohort of patients surveyed about their preferences for anti-viral therapy for HBV revealed that most patients preferred oral therapy with once-daily dosing and a fixed duration of treatment (28). Drug efficacy was considered the most important factor in drug selection.	The guideline panel agreed that patients would probably value the outcomes of preventing activation, hepatic injury and death greater than any inconvenience of screening tests and taking prophylactic anti-virals.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	No research evidence was identified.	The guideline panel agreed that the large benefits of screening and trivial harms outweighed the potential harms of not screening.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Costs of screening as per Hamilton Regional Laboratory Medicine Program is $24.50 each for HbsAg, HbsAb, and HbcAb. In 2012, the cost per day of anti-virals used as prophylaxis/treatment for HBV was - lamivudine 100mg - Can $4.56 - telbivudine 600mg - Can $18.30 - tenofovir 300mg - Can $16.74 - entecavir 0.5mg - Can $22.00 - adefovir 10mg - Can $22.62 Lamivudine, entecavir, and adefovir are covered by the Ontario Drug Benefit program. Cost analysis for treatment of the following health states for HBV were - CHB: Can $2,191 (antiviral drug costs not included) - Compensated cirrhosis: Can $2,987 - Decompensated cirrhosis: Can $11,228 - HCC: Can $13,350 - Liver transplant (first year): Can $99,066 - Transplant care (subsequent years): Can $38,242 (29)	The guideline panel agreed that the costs of screening are negligible. Patients do not typically assume the cost for the test.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies	Costs based on costs from programmes and 1 study which summarised the costs.	

COSTEFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	No cost-benefit analysis of HBV testing in the SLE patient was found.	The guideline panel agreed that the costs of the consequences of reactivation (including liver injury and death) if screening was not done would outweigh the costs of the screening tests and prophylactic treatment.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No studies were found that assessed effects on health equity.	The panel agreed that Hepatitis B may be more prevalent in populations who are less likely to access medical care. If health behaviours were sought as risk factors for HBV, this may create health disparities between high risk groups and the general population.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No studies measured acceptability to patients and health care providers.	The guideline panel agreed that screening is likely to be acceptable to patients and healthcare providers as obtaining serology is minimally invasive and there is an appropriate intervention (i.e. vaccination or prophylaxis).

FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No studies measured implementation.	The guideline panel agreed that serological testing for HBV is generally available through Canadian outpatient laboratories and hospital laboratories. There may be some difficulty in implementing intervention if there is concern regarding a delay initiating immunomodulatory therapies.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should screening for HBV infection vs. no screening be used for people with SLE?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention Conditional recommendation against the intervention Conditional recommendation for either the intervention or the comparison Conditional recommendation for the intervention Strong recommendation for the intervention ○ ○ ○ ● ○
RECOMMENDATION	*For adult and pediatric patients with a diagnosis of SLE and high- risk behaviours for HBV acquisition, we suggest screening for Hepatitis B surface antigen and repeating according to recommendations for the general population. For patients being considered for immunomodulatory therapy, we suggest screening before starting treatment. (conditional recommendation, low quality evidence)*
JUSTIFICATION	The panel agreed that the evidence for screening in the general population with high-risk behaviours for HBV would apply to people with SLE. In addition, people with SLE receiving immunomodulatory agents and positive for HbsAg may have a high risk of HBV reactivation. HBV reactivation may increase the risk of hepatic injury and death in these patients (16,18,19,20,21,26,30). However, prophylaxis with anti-viral agents prior to or concomitantly with immunomodulatory therapy may reduce the risk of reactivation (20). The applicability of these recommendations to SLE patients solely on an antimalarial remains uncertain, given that previous studies have shown that antimalarials reduce the risk of infection in SLE patients (31).In contrast, some studies identified cases of reactivation in SLE patients on hydroxychloroquine; however, these occurred in combination with other medications (32) and the likelihood of reactivation in patients taking hydroxychloroquine could not be statistically determined. Reactivation of hepatitis B can also occur in patients not on immunomodulatory therapy (33). Overall the likelihood of reactivation in patients on antimalarials is probably low, though this cannot be determined to a high degree of certainty based on the level of evidence. The costs of not screening and the consequences of hepatic injury and death outweigh the negligible costs of screening (34). Screening is probably feasible and acceptable to both patients and health care providers as it is a minimally invasive test, and providing screening probably has no impact on health equity (28).
SUBGROUP CONSIDERATIONS	Because asking about high risk health behaviours may increase inequity between high risk and low risk groups, this recommendation was not limited to high risk groups only. However, repeat screening for patients with known high risk behaviours is suggested.
IMPLEMENTATION CONSIDERATIONS	Screening for hepatitis B is widely available in laboratories across Canada. Health care workers must provide a lab requisition to the patient.
MONITORING AND EVALUATION	Hepatitis B screening should be completed at baseline for SLE patients, and repeated if there are risk factors for acquisition of hepatitis B.
RESEARCH PRIORITIES	Registries should be developed and maintained that collect data about the outcomes of people who have systemic lupus erythematosus and have hepatitis B infection, including reactivation.

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Online supplement to Canadian Rheumatology Association Recommendations for the Assessment and Monitoring of Systemic Lupus Erythematosus, *The Journal of Rheumatology*, doi:10.3899/jrheum.171459

DATA SUPPLEMENT #12 HEPATITIS C SCREENING

Question

Should **screeening for HCV** vs. **no screening** be used for **people with SLE**?

POPULATION:	people with SLE	**BACKGROUND:**	Hepatitis C (HCV) is a major cause of liver cirrhosis and hepatocellular carcinoma, particularly in developing countries. HCV is primarily transmitted through percutaneous exposure to blood. The World Health Organization (WHO) estimates that 3% of the world population has been infected with HCV with approximately 170 million chronic carriers of the virus (1). It is estimated that 50% of all infected are unaware that they are infected.
INTERVENTION:	screeening for HCV		
COMPARISON:	no screening		
MAIN OUTCOMES:	hepatitis C sustained virological response, hepatitis C activation, hepatic injury, death, SLE disease activity		
SETTING:	outpatient or inpatient		

PERSPECTIVE: population	The *Canadian Health Measures Survey (*CHMS) estimated the seroprevalence of HCV antibody (anti-HCV), a marker of lifetime exposure to the virus, to be 0.5% of the household-dwelling population in Canada from 2007 to 2011 (2). However, modelled prevalence estimates, taking into account vulnerable populations not surveyed by the CHMS (such as the homeless, prison inmates, and foreign-born populations who do not speak English or French) indicate that the rate of anti-HCV in the Canadian population may be closer to 1% with approximately 42-45% of those being unaware of their status. The prevalence of chronic HCV infection was estimated to be 0.6%. The American Association for the Study of Liver disease (AASLD) and Infectious Disease Society of America (IDSA) current guidelines recommend one time HCV testing in persons born between 1945-1965 (without prior ascertainment of risk) and testing in all persons with behaviours, exposures and conditions associated with increased risk of HCV infection (injection drug use, long term hemodialysis, percutaneous/parenteral exposures in an unregulated setting, healthcare works after needle stick, sharps or mucosal exposure to HCV infected blood, children born to HCV infected women, prior recipients of transfusions or organ transplants (particularly prior to July 1992), HIV infection, unexplained chronic liver disease (3). New therapies called direct acting antivirals (DAAs) act on the virus itself to eradicate it from the body, unlike older medicines like interferon injections that work by stimulating an immune response. These new treatments are very effective and can achieve cure rates of over 90% (4). In most situations now, there is no need for interferon, which was responsible for many of the side effects previously associated with HCV treatment. The new treatment combinations require shorter treatment durations (between 8 to 24 weeks), have reduced side effects and appear to be effective at all stages of the disease.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Infections are a leading cause of mortality in SLE patients, up to 25% in some cohorts (5). HCV infection prevalence may be higher in SLE populations compared to the general population in some risk groups (6). Management of patients who are anti-HCV+ could be tailored to include greater monitoring of liver function, or providing treatments with less impact on liver function. Furthermore, it is questioned whether HCV could be reactivated in the setting of immunosuppressive treatments, commonly used in treatment of SLE (7). HCV reactivation could lead to worse outcomes, but treatment could result in improved outcomes for SLE patients.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Screening versus no screening of HCV** A systematic review of the literature found no studies comparing outcomes of SLE patients screened for HCV to SLE patients not screened for HCV. Instead data from 17 studies reporting HCV activation, hepatic injury, disease activity and death related to HCV and SLE are provided (6-22). **Prevalence of anti-HCV antibodies in people with SLE** The prevalence of anti-HCV positivity in people with SLE across many countries ranged from 0.9%-18.5% (8-11,13-17,20,21). In some cohorts, the prevalence of anti-HCV antibodies was higher than the general population (11,20). In 2011, the prevalence of hepatitis C infection in the general population in Canada was approximately 0.7% (23). People in the general population at high risk of HCV include people born or having lived in regions of high prevalence, people exposed to HCV infected bodily fluids, and babies born to infected mothers. **Outcomes of SLE patients with Hepatitis C antibodies (anti-HCV positive)** **HCV Reactivation:** Varying definitions used in studies. In one study, 10/26 patients had reactivation (7). In another study of 19 patients with Hepatitis C antibodies 13 had detectable HCV RNA (6). **Liver enzyme elevations:** One study (119 people with lupus nephritis; 15 HCV+, 104 HCV-) showed elevated liver enzymes in HCV+ compared to HCV- patients (19). Another study (61 people) showed no difference between HCV+ and HCV- patients (6). In an HCV+/autoimmune disease cohort (180 people), 79% had liver enzyme elevations (22). **Abnormalities on liver biopsy:** One study of HCV+ SLE patients studied 19 patients, 11 of whom had a liver biopsy - 8 patients had portal fibrosis, and 2 had cirrhosis (6). In one study of 180 patients with autoimmune diseases and HCV+ (43 SLE patients), 51 had liver biopsy, with chronic active hepatitis seen in 39, and cirrhosis in 8 (22). **SLE Disease Activity:** One study evaluated SLEDAI in 75 SLE patients with and without HCV and there were no significant	The guideline panel agreed that - the prevalence of anti-HCV antibodies may be higher in patients with SLE than in the general population - the prevalence in SLE patients in Canada is likely slightly higher than the general population and approximately 1% (other populations may be at higher risk, e.g. people exposed to HCV infected bodily fluids) - reactivation may occur in close to 1/2 of SLE patients with anti-HCV antibodies (but it is unclear if it is associated with specific drugs or other factors) - most SLE patients, in particular with lupus nephritis, who are HCV+ may have elevated liver enzymes, and hepatic injury (such as chronic hepatitis and cirrhosis) - there appears to be no difference in SLEDAI disease activity in SLE patients who are anti-HCV+ or anti-HCV-

		differences in disease activity (16). Another study evaluated SLEDAI in 98 patients with SLE who were anti-HCV+ or anti-HCV-, there was no difference in SLEDAI scores between these groups (15). **Mortality:** One study (119 lupus nephritis patients) showed increased mortality in HCV+ SLE patients compared to HCV- patients, while another study (158 SLE patients) did not find differences in the survival curves in their cohort over 10 years (7,19). **Immunomodulatory therapies in HCV+ SLE patients** One study found no difference in the use of steroid, hydroxychloroquine, or azathioprine in 10/26 patients with HCV who experienced reactivation compared to those who did not experience reactivation (7). One study found no relation between dose of steroid used and viral load or liver function score in 19 SLE patients with HCV (6). One study showed late relapse in 2/6 patients who had achieved a sustained virological response post-HCV therapy, and both were receiving chronic steroid (7.5-10mg/day) (7). **HCV treatment in HCV+ SLE patients** In one study of SLE patients with HCV who experienced reactivation, 9/10 patients received pegylated interferon and ribavirin (7). 3 patients achieved rapid virological response, and 7 achieved early virological response. 6 patients achieved sustained virological response though 2 experienced late relapse. In another study, 4 patients were treated for HCV, with amantadine (12 months), ribavirin (12 months), ribavirin+interferon (6 months), and ribavirin (6 months) respectively (6). Only the latter patient had a sustained virological response, while the others showed no response. **Screening tests for HCV** Serology for HCV is performed using enzyme immunoassay (EIA) testing. Sensitivity for third-generation HCV EIA is 98% and specificity is 99%. Sensitivity of HCV RNA by quantitative PCR is 99% and specificity is 98%. Likelihood of HCV positivity: 1% (estimated in Canada) or 10% (mid-range of HCV positivity in studies).	- mortality may be increased in lupus patients who are anti-HCV+, in particular lupus nephritis (but the evidence is uncertain) - in SLE patients who are HCV+ outcomes may not be related to specific immunomodulatory therapies - it is unclear but response may be rapid to HCV treatment though it may not be sustained in SLE patients with HCV reactivation - if 10 000 SLE patients were screened (1% prevalence), 98 would be correctly identified, but 90 would go for further unnecessary testing and 20 would be missed. If the prevalence is higher than more are identified correctly, with only slightly more false positives.

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**If not screened,** the number of people who would be HCV+ is 100/10,000 or 1000/10,000. These people may be at increased risk of consequences of HCV+ (e.g. elevated liver enzymes, hepatic injury) **If 10 000 screened and 1% prevalence:** 98 would be correctly identified and go for further testing, 2 would be missed (and risk consequences) and 99 would be falsely told they were positive and have further testing, risk greater monitoring or restriction of different therapies. **If 10 000 screened and 10% prevalence:** 980 would be correctly identified and go for further testing, 20 would be missed (and risk consequences) and 90 would be falsely told they were positive and have further testing, risk greater monitoring or restriction of different therapies.	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	There was no direct evidence. Instead evidence from small non-randomised studies for prevalence for HCV and the consequences of screening and HCV+ in SLE patients was used.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Cotler et al described patients values and preferences regarding hepatitis C infection and compared these to physician estimates of preference (24). On average, patients believed that hepatitis C without symptoms was associated with an 11% reduction in preference value from that of life without infection, and the most serious condition (severe symptoms, cirrhosis) was believed to carry a 73% decrement. Physicians' estimates were not significantly associated with patients' preference values for hepatitis C health states, treatment side effects, or with patients' thresholds for accepting treatment. Given this discrepancy, there may be some uncertainty regarding the main outcomes. Similar preference ratings for cirrhosis related to hepatitis C has been shown in other cohorts, however, and amongst patients there may not be large variability.	The guideline panel agreed that patients would place a high value on avoiding severe symptoms of hepatitis C.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The desirable effects of screening SLE patients (identification, reduction of hepatic consequences, mortality) were greater than the undesirable effects (false positives).
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No cost-benefit analysis of HCV testing in the SLE patient was found. Costs of screening as per Hamilton Regional Laboratory Medicine Program is $24.50 for hepatitis C antibody. Costs of anti-HCV and HCV RNA tests are typically not incurred by the patient. As examples: During the initial and late disease phases, BC spent an estimated $1,850/person/year and $6,000/person/year, respectively, on direct HCV-related health care (25). Costs increase with disease progression and hospitalization was the largest cost component across all disease phases, followed by medical services and publicly funded drugs. Total health care costs associated with HCV (excluding treatment) are expected to increase by 60% from 2013 until the peak in 2032, with the majority attributable to cirrhosis and its complications (81% in 2032 versus 56% in 2013) (26). The lifetime cost for an individual with HCV infection in 2013 was estimated to be $64,694.	The panel agreed that - Increased cost may be incurred with the more sensitive HCV RNA testing upon finding positive anti-HCV antibody (and false positives with anti-HCV antibody would receive the HCV RNA test unnecessarily) - If increased number of infections found, increased cost with current treatment for cure, although this may be offset by lower cost due to morbidity and medical management of cirrhosis, HCC where diagnosis is not made.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		The guideline panel agreed that screening may be cost effective for SLE patients since screening would identify people who are anti-HCV+ who could be managed and treated to avoid consequences of hepatitis C.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was found.	Hepatitis C is prevalent in at risk populations who are less likely to access medical care (e.g. incarcerated, drug abuse). Standard screening would allow for equal surveillance of all populations and potentially serve as access point for these populations to access treatment and screening for complications of chronic liver disease
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Rates of HCV screening in SLE patients:** One study assessed the rates of screening prior to initiation of immunomodulatory agents in SLE in a cohort of 100 patients in Chicago (12). They found that the rate of screening was 33%. One patient tested positive for anti-HCV.	Likely to be acceptable to patients and healthcare providers as obtaining serology is minimally invasive. However, current screening rate is low.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Serological testing for HCV is generally available through Canadian outpatient laboratories and hospital laboratories. Funding agencies may require more cost-effectiveness data prior to consider coverage.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should screeening for HCV vs. no screening be used for people with SLE?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○ Conditional recommendation against the intervention ○ Conditional recommendation for either the intervention or the comparison ○ Conditional recommendation for the intervention ● Strong recommendation for the intervention ○
RECOMMENDATION	***For adults and pediatric patients with a diagnosis of SLE and high risk behaviours for hepatitis C virus (HCV) acquisition, we recommend screening for HCV and repeating according to recommendations in the general population. For all other adult and pediatric patients with a diagnosis of SLE, we suggest screening for HCV and repeating according to recommendations in the general population. (conditional recommendation, low quality evidence)***
JUSTIFICATION	The prevalence of hepatitis C in people diagnosed with systemic lupus erythematosus is approximately 1%. The prevalence is likely higher in people exposed to infected bodily fluids, who were born or living in high prevalence regions, or who have lupus nephritis. The panel agreed that the evidence for screening in the general population with high risk behaviours for HCV would apply to people with SLE (3). The prevalence of HCV in people diagnosed with SLE ranges from 1%-20.4% in studies; however, in many of these studies the baseline prevalence of HCV infection is higher than that in the general Canadian population (8,9,10,11,13,15,16,17,20). No studies have reported the prevalence of HCV infection amongst Canadian patients with SLE. The prevalence of HCV infection in the general Canadian population is 0.7% (Government of Canada, 2016). The prevalence is likely higher in people exposed to infected bodily fluids, who were born or living in high prevalence regions (3). Serious adverse events may occur in those who experience reactivation of hepatitis C in the setting of SLE, such as cirrhosis and hepatic failure (6,19,22). Screening for hepatitis C infection can identify patients who may be candidates for highly effective direct-acting antiviral (DAA) therapies to treat HCV, and would allow the clinician in the meantime to avoid therapies for SLE that may have hepatotoxic effects and increase the potential for hepatic injury (27). False positives may occur on screening for HCV antibody; however, in such situations, confirmatory testing with HCV RNA would typically be negative and would reveal these cases to be false positives (18).

SUBGROUP CONSIDERATIONS	see above.
IMPLEMENTATION CONSIDERATIONS	Screening for hepatitis C is currently low and efforts to increase screening may be needed. It is essential that screening programmes also include and provide access to hepatitis C anti-viral therapies.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Registries should be developed and maintained that collect data about the outcomes of people who have systemic lupus erythematosus and hepatitis C infection, including reactivation.

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