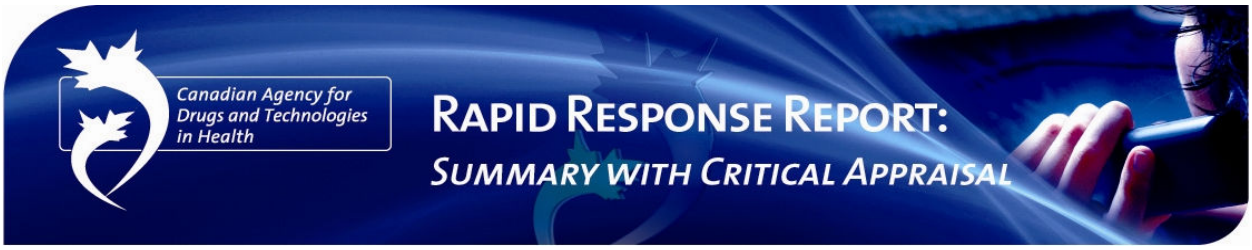

TITLE: Vitamin D Testing in the General Population: A Review of the Clinical and Cost-Effectiveness and Guidelines

DATE: 16 January 2015

CONTEXT AND POLICY ISSUES

Vitamin D is an essential nutrient required for bone homeostasis. Recently, supportive roles in the immune system and preventive roles in several disease states including diabetes, cancer, and cardiovascular disease have been proposed.[1] Serum 25-hydroxyvitamin D (25[OH]D) is the preferred mode of vitamin D status assessment due to its long half-life.[2] There are multiple assays used to measure this metabolite that lack concordance due to substantial intra- and inter-assay variability.[3] The optimal 25(OH)D concentration is in dispute. The Institute of Medicine[4] and the Endocrine Society[5] define deficiency as 25(OH)D less than 50 nmol/L, and the latter has defined insufficiency (or subclinical deficiency) as 50 to less than 75 nmol/L. Deficiency is characterized by low blood calcium and phosphate concentrations, and bone disease (rickets in children, and osteomalacia in adults).[6] Insufficiency is defined as lower than normal serum 25(OH)D concentrations without apparent clinical symptoms. However, insufficiency is a concern due to associations with disease outomes.[6] The variability among assays and cut-offs has led to inconsistencies in vitamin D status assessment, and complicates discernment of clinical effectiveness of vitamin D supplementation and testing. The rate of vitamin D deficiency in the general Canadian population was 32% (25[OH]D less than 50 nmol/L) based on the latest Canadian Health Measures Survey (2009-2011).[7] Deficiency has been associated with age,[8] sex,[8] season,[8] geographic region,[9] obesity,[10] dietary intake,[11] skin pigmentation,[1] education,[8] immigrant[12] and first nation status,[8,13] and income.[8]

Rising awareness about the potential link between vitamin D deficiency and adverse health outcomes has seen an increase in the rate of vitamin D testing in developed countries.[14] The cost of a single vitamin D test is moderate (e.g., $61.32 in British Colombia)[15] but the elevated testing rate contributes to substantial healthcare costs. Concern over rising costs led to reform in testing coverage in 2010 in Ontario,[16] followed by other provinces.[15,17,18] The changes in Ontario were based on a 2010 report by the Ontario Health Technology Advisory Committee (OHTAC) on the clinical utility of vitamin D testing (reviewed in this report).[19] Despite a lack of direct evidence on testing, a recommendation was made against providing testing for the general population.[19] Tests are now indicated only for individuals with specific conditions[20] (i.e.,

osteoporosis, rickets, osteomalacia, malabsorption syndromes, renal disease, and individuals taking medications that may affect vitamin D status). The Endocrine Society[5] and Osteoporosis Canada[21] also recommend against screening for low risk individuals. There is a lack of evidence to suggest that the rise in test frequency has translated into improved healthcare practices. For example, the temporal increase in testing in Australia has not resulted in improved osteoporosis detection in women aged 45 to 74.[22] There is also a lack of evidence on the cost-effectiveness of testing. In light of the rise in test frequency, assay and cut-off inconsistency, and the lack of evidence for the utility of testing, this report will investigate the clinical and cost-effectiveness of testing in the general population.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of vitamin D testing in the general population?

2. What is the cost-effectiveness of vitamin D testing in the general population?

3. What are the evidence-based guidelines associated with vitamin D testing in the general population?

KEY FINDINGS

There is limited evidence of varying quality suggesting that vitamin D testing is not warranted in the general population. Based on indirect evidence from studies investigating the effectiveness of vitamin D supplementation, two guidelines[23,24] and a systematic review concluded that vitamin D screening may be beneficial for populations at increased risk for vitamin D deficiency but not normal risk populations. These views were supported by results from one retrospective study, which suggested that vitamin D testing does not translate into improvements in vitamin D status. The majority of studies failed to identify direct evidence on the clinical utility of vitamin D testing. Conflicting economic evidence suggests that vitamin D testing may be cost-effective for reducing falls in older adults in the US, but not for reducing treatment costs in older adults or other at-risk groups in the UK.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused internet search. Methodological filters were applied to limit retrieval to systematic reviews and guidelines. The results of a second focused search (with main concepts appearing in the title or subject heading) were also included. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and November 26, 2014.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults (healthy or with any disease)
Intervention	Vitamin D testing
Comparator	None No testing with no vitamin D supplementation Supplementation with vitamin D without test results to support
Outcomes	Q1: Clinical effectiveness Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, or were published prior to 2010. Health technology assessment (HTA) reports, meta-analyses, systematic reviews, and evidence-based guidelines were excluded if there was incomplete reporting of methods or if they were superseded by a more recent, rigorous, or updated review or guideline. Randomized controlled trials (RCTs) and non-randomized studies were excluded if they were described in an included systematic review. Economic evaluations that reported costs and were not cost-effectiveness or cost-utility analyses were also excluded. Guidelines were excluded if there was no conduct of a systematic review of relevant literature or if methodology was unclear.

Critical Appraisal of Individual Studies

Key methodological aspects relevant to each study design were appraised. Systematic reviews were critically appraised using the AMSTAR checklist,[25] and the methods used when conducting the literature search, study selection, quality assessment, data extraction, and for summarizing the data were assessed. The Downs and Black checklist was used to appraise non-randomized studies.[26] Appropriateness and external validity of cohorts, blinding, recruitment time-frames, losses to follow-up, consideration of confounders, and completeness of reporting were assessed. Economic studies were appraised using the Drummond checklist.[27] Study design, data collection, analysis, and interpretation of results were evaluated. Evidence-based guidelines were appraised using the AGREE II instrument.[28] The scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence were assessed. For all study types, summary scores were not calculated; rather, a narrative review of the strengths and limitations of each included study was included.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 250 citations were identified in the literature search. Following screening of titles and abstracts, 246 citations were excluded and four potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these eight potentially relevant articles, two publications[22,29] were excluded for irrelevant outcomes or inappropriate methodology, while six publications met the inclusion criteria and were included in this report.[23,24,30-33] The study selection process is detailed in the PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

Two systematic reviews,[24,32] one non-randomized study,[31] one economic evaluation,[30] and two evidence-based guidelines[23,24] were identified regarding the clinical and cost-effectiveness of vitamin D testing. Detailed study characteristics are described in Tables A1 to A4 of Appendix 2.

Systematic Reviews and Meta-Analyses

The 2014 systematic review by LeBlanc et al., [32] reviewed the current evidence on overall as well as sub-group differences in clinical effectiveness of vitamin D screening and treatment in asymptomatic adults with vitamin D deficiency. The review was conducted for the United States (US) Preventive Services Task Force (USPSTF) in support of establishing recommendations for screening.[34] The review protocol was developed in consultation with experts and the public. Vitamin D deficient populations were defined as at least 90% of the population with 25(OH)D levels of 75 nmol/L or less. The systematic review did not identify any studies that fit the inclusion criteria for evidence on vitamin D screening. However, they did identify seven trials on the effectiveness of vitamin D supplemenation in deficient populations (25[OH]D less than 50 nmol/L), and 10 studies in insufficient populations (25[OH]D less than 75 nmol/L). In addition, 24 trials evaluating harms associated with vitamin D treatment were identified.

The 2014 systematic review by the Australian Government Department of Health (AGDH) contained clinical and economic evidence regarding vitamin D testing.[33] This review included multiple research questions. The focus was on patients with a risk of vitamin D deficiency (including but not limited to post-menopausal women and elderly men with bone disease, patients with chronic diseases, patients with multiple sclerosis, and children with rickets), but also included the general population. The review contained some components of a guideline as well as components of a HTA but no formal recommendations were made and a full economic evaluation was not conducted. The economic evidence was assessed by conducting a systematic review. The review presented a substantial amount of evidence from an HTA conducted by the Washington State Health Care Authority (WSHCA).[35] The systematic review for clinical evidence searched for studies regarding appropriate indications for medically necessary vitamin D testing, effectiveness of testing in each population, and safety and quality implications associated with vitamin D testing. The intervention was vitamin D testing compared to no testing and the endpoints of interest were health outcomes (morbidity, mortality, and quality of life), safety, patient behavior, and clinical decisions. The systematic review identified 61 studies (systematic reviews, meta-analyses, RCTs, and economic evaluations) published between 2003 and 2012 related to the various research questions. The majority of these studies

did not fit the inclusion criteria as the intervention was vitamin D testing, not vitamin D supplementation.

Non-Randomized Studies

One retrospective study[31] regarding the clinical effectiveness of vitamin D testing in an adult managed care population was retrieved. This study was conducted in the United States and retrospectively assessed individuals who had undergone multiple 25(OH)D tests. Enrolled patients had attended a large medical group and an independent physician association between 2011 and 2013. There were no health-related exclusion criteria and any patients with at least one 25(OH)D test were included. The study aimed to determine whether testing was associated with an improvement in vitamin D status as measured by a follow up test. The primary endpoint was change in 25(OH)D status (defined as sufficient [greater than or equal to 30 ng/mL] or insufficient [less than 30 ng/mL]). Based on the two tests, individuals were classified as sufficient-sufficient (two sufficient tests), sufficient-low (2nd test insufficient), low-sufficient (2nd test sufficient), and low-low (two insufficient tests). A managed care enrollment database, electronic medical records, and laboratory encounter databases were used as data sources and ICD-9 and CDT codes were used to collect information on comorbidities. Pharmacy claim databases were screened to determine dispensing of high dose (50000 International Units [IU]) vitamin D therapy.

Economic Evaluation

One economic evaluation[30] regarding the cost-effectiveness of vitamin D testing in community dwelling older adults was retrieved. A cost-effectiveness analysis from the societal perspective in the US was conducted. A Markov decision model was constructed to assess the cost-effectiveness of falls prevented with population vitamin D screening compared to universal supplementation without screening. The report focused on community-dwelling Caucasian adults 65 years and older. Population data was sourced from national surveys and cost, utility and probability data was sourced from published resources. The population was assumed to have no history of falls or baseline vitamin D screening or supplementation prior to entry into the model. Vitamin D status was classified as insufficient (25[OH]D less than 25 ng/mL), deficient (25[OH]D less than 15 ng/mL) or sufficient (25[OH]D greater than or equal to 25 ng/mL). Increased risk of falls was assumed for individuals with lower vitamin D status and the prevalence of insufficiency and deficiency was sourced from the US National Health and Nutrition Examination Survey (2003-2006). The dose of vitamin D supplement varied (0 to 4000 IU) based on the measured vitamin D status for individuals subjected to screening, and was equal (1000 IU) for all patients in the universal supplementation group. Adherence to treatment was assumed to be 80% (range, 50 to 90%), and effectiveness had an anticipated onset at 6 months (range, 3 to 9 months) for individuals who received supplements. It was assumed that the level of supplementation given would not result in toxicity and that efficacy was consistent across age and gender. Evaluation of the consistency of model inputs and assumptions with current costs, efficacy estimates, and risk of falls was not within the scope of this report. Subgroup analyses were conducted to investigate potential differences in cost-effectiveness for younger (65 to less than 80 years) and older (80 years and older) adults. Sensitivity analyses were conducted to investigate the influence of potential differences in fall risk reduction due to vitamin D supplementation, and cost of 25(OH)D testing.

Evidence-Based Guidelines

Two evidence based guidelines were identified.[23,24]

The National Institute for Health and Care Excellence (NICE) guideline,[24] published in 2014 in the United Kingdom (UK) had an evidence base comprised of a systematic review[36] and economic evaluation[37] designed to obtain evidence on the clinical and cost-effectiveness of interventions (including vitamin D screening) to increase awareness and uptake of existing guidance on vitamin D. The patient populations of interest were pregnant and breastfeeding women, infants and young children less than five years, adults 65 years and older, individuals with low or no exposure to sun, and individuals with darker complexions (i.e., "people of African, African-Caribbean or South Asian family origin").[24] This guideline was intended for viewing by individuals working within the National Health Service, local health authorities, manufacturers of vitamin D supplements, and the public, private, voluntary and community sectors. Recommendations made regarding testing were intended to be carried out by health and social care practitioners. Only the economic evaluation[37] contributed relevant evidence addressing the research question on utility of testing. A decision analytic model was developed and cost-consequence analysis was used to make a comparison of the cost-consequences of deficiency following universal provision of vitamin D supplements (assuming a 100% uptake) or targeted vitamin D supplementation of individuals who tested positive for vitamin D deficiency (defined as 25[OH]D less than 25 nmol/L). The main source of model input data for pregnant and breastfeeding women, and children less than five years, was a study conducted in Birmingham. Additional data sources for adults over 65 years and people with darker complexions included the Office of National Statistics, the Department of Health, 2011 census data, hospital data, and primary research. The sub-group of individuals with low or no exposure to sun was not assessed in the economic evaluation. It was assumed that the vitamin D test was 100% accurate. Both scenarios (universal supplementation and targeted supplementation of deficient individuals following screening) were assumed to result in a 50% reduction in symptomatic vitamin D deficiency.

The OHTAC guideline[19,23] was authored by the Medical Advisory Secretariat and published in 2010 in Canada. It included a systematic review[23] designed to obtain evidence on the clinical utility of vitamin D testing in average risk Canadians and patients with kidney disease. The guideline was intended for viewing by the Ontario Ministry of Health and Long Term Care. Recommendations and health promotion were indented to be carried out by healthcare providers and the Ministry of Health and Long Term Care. The systematic review did not identify any direct evidence on the utility of testing, as defined by the inclusion criteria of this CADTH report. The report defined clinical utility as "the ability to improve bone health outcomes with the focus on the average risk population".[23]

Summary of Critical Appraisal

Study strengths and limitations are presented in Tables A5 to A8 of Appendix 3.

Systematic Reviews and Meta-Analyses

Both systematic reviews[32,33] provided a priori objectives. They completed a comprehensive literature search for English language publications using multiple databases and searched reference lists. Both reviews provided a full list of included studies and formally assessed quality

of evidence. These quality assessments were used in the formulation of conclusions. Neither study used a formal tool to assess risk of bias but elements of other quality assessment reviewed potential biases.

The LeBlanc et al., review[32] was generally well designed and conducted. The review was intended to include only individuals who were asymptomatic with vitamin D deficiency, however it was noted that clinical symptoms could not be definitively ruled out. Duplicate study selection was completed and abstraction was completed by a single author and reviewed by a second. Both non-English publications and conference abstracts were excluded. The list of studies described study quality, characteristics, interventions and outcomes. Quality was assessed both for single studies and aggregated sources using the USPSTF tool. Studies were graded as good, fair, or poor based on this assessment. Meta-analyses reported heterogeneity but publication bias could not be assessed. The reason given was the small number of studies identified for each outcome. Risk of bias was not assessed using a formal tool but randomization, intervention fidelity, and post-randomization exclusions were appraised using the USPSTF tool. The primary funding source and potential conflicts of interest were declared.

The AGDH review[33] was comprehensive but poorly organized and implemented inconsistent methodology. In the presentation of the results the objectives were altered due to the lack of direct evidence on vitamin D testing. The intervention of vitamin D testing was updated to include vitamin D supplementation trials to represent the 'potential utility of vitamin D testing'. The review included a wide-range of patient populations, increasing generalizability but introducing a range of health-related confounders. For the systematic reviews of clinical and economic evidence, information on the number of authors involved in study selection and data extraction was not provided. Searches of the HTA databases and the Cochrane library were longer in duration than MEDLINE and PUBMED searches. Reference lists of review articles were hand searched and consulting clinicians were asked for knowledge of any unpublished studies or relevant clinical guidelines during the consultation process. Risk of bias of individual trials was not assessed using a formal tool but the National Health and Medical Research Council Dimensions of Evidence tools were used to appraise the quality of all trial types and included assessment of blinding and allocation. The review stated that meta-analyses were conducted but, with the exception of one outcome (effect of vitamin D supplementation with or without calcium on risk of falls, three separate meta-analyses), forest plots and data were sourced from other systematic reviews. Heterogeneity was reported for all meta-analyses but risk of publication bias was reported inconsistently. Funding sources of all retrieved studies were declared but funding sources and potential conflicts of interest of the review authors were not disclosed beyond author affiliations. Overall, there was a general lack of evidence on vitamin D testing and consequently the majority of the evidence focused on the benefits of supplementation. The authors' justification for this change in scope was that vitamin D screening would not improve health outcomes without effective treatment.

Non-Randomized Studies

The non-randomized study[31] had good external validity but lacked the necessary design elements to rule out substantial confounding. An a priori objective was clearly stated and patient demographics, treatments, and potential confounders were clearly described. Main findings were presented clearly with variance and statistical significance reported where appropriate. A sample size calculation was not reported. Incidence of abnormal vitamin D screening was determined using lab databases. No adverse events or reports of side-effects were included. Although vitamin D supplementation is unlikely to result in adverse events, high dose (50000 IU)

supplements were utilized by the study population and this dose has been associated with undesirable outcomes such as hypercalcemia, and renal and skeletal outcomes.[38] Selection and measurement bias could not be controlled due to lack of blinding and randomization to high-dose vitamin D therapy. Recruitment was conducted retrospectively and no exclusion criteria were applied, increasing the external validity but reducing internal validity due to the presence of many potential health-related confounders. In addition, incomplete surveillance of non-osteoporosis medications was conducted, limiting the ability to assess potential drug-interactions, or reasons for limiting vitamin D therapy that may have contributed to persistent insufficiency. Compliance with vitamin D supplementation recommendations following testing, and vitamin D therapy with over-the-counter products was not discussed. No losses to follow up were reported although only a proportion of individuals had sufficient numbers of 25(OH)D tests to be eligible for analysis. Differences between these patients and those with one test or less were only discussed in terms of their vitamin D status. Multivariate analysis to assess differences between the four vitamin D status transition states was conducted. Patients were followed up at 400 days (the duration between first and second tests) so the long-term clinical utility of vitamin D testing, as well as the short-term influence of testing on vitamin D status could not be assessed. The duration of follow up would be sufficient to capture biochemical changes (i.e., 25(OH)D) given long-term compliance, but would miss short term changes in vitamin D status. In addition, the possibility of external factors that could contribute to changes in vitamin D status over the 400 day period was not assessed.

Economic Evaluation

The economic evaluation[30] was well designed but limited by the lack of evidence to support several model inputs. The research question and type of economic model were clearly stated. Sources for all model inputs and effectiveness estimates were provided, but the method of combining data from multiple sources, as well as the original study design (and limitations), was not provided in several cases. For most inputs, data from aggregated sources was used. The primary outcome of falls prevented was clearly stated and the incremental cost-effectiveness ratio equation was provided. It was stated that there was insufficient evidence to estimate the indirect cost of falls and productivity losses so the analysis was limited to direct costs only, effectively underestimating total societal costs. The currency and price data was recorded as US dollars and the base year of 2011. All costs were inflated to 2011 values and the discounting rate was 3% per year. Details of the model were presented visually and a data table of model inputs was provided. Ranges for probabilities, costs, and utilities were used in one-way sensitivity analyses and probabilistic sensitivity analyses. Justification for these ranges was referenced but not discussed. Potential confounders such as body weight and malabsorption syndromes were not considered as modifiers of response to supplementation. Outcomes were reported as disaggregated incremental cost effectiveness ratios and net monetary benefit. The authors provided a clear answer to the research question and the conclusions considered appropriate caveats such as vitamin D dose, cost of testing, and external validity. The time-horizon (36 months) was specified and attributed to the duration of RCTs contained within meta-analyses used to determine model-inputs. The study was conducted from the US perspective, covered only the older community-dwelling Caucasian population, and limited vitamin D doses to a maximum of 4000 IU. Therefore, generalizability to wider populations (e.g. other ethnic, age and disease state groups), the Canadian context, and individuals receiving higher dose supplements is limited. Moreover, responsiveness to vitamin D supplementation and vitamin D status is known to vary across demographics, further limiting the generalizability of this economic model. Lastly, healthcare and payer perspectives were not considered, so this analysis may be of limited relevance to certain audiences.

Evidence-Based Guidelines

Overall, the NICE guideline[24] was well designed and provided clear, actionable recommendations. The overall objectives of the guideline[24] were stated as were the specific research questions. The relevant population was defined and the intended users of the guideline were outlined for each component. Various stakeholders (including groups from the general public)[39] were consulted during the guideline development process and invited to submit evidence. Systematic review methods were used to search for clinical evidence and a cost-comparison analysis was completed to provide economic evidence. Inclusion criteria were clearly described as were the strengths and limitations of the identified evidence, as assessed by protocols from NICE Public Health Guidance. The quality of the evidence was considered in the formulation of conclusions and recommendations. Recommendations were listed along with the corresponding target audience and group tasked with implementing them. They were established through informal consensus, considering: the strength and applicability of the evidence (using Grading of Recommendations Assessment, Development and Evaluation [GRADE] criteria),[39] the potential impact on health and health inequalities, quality and diversity legislation, ethical issues and social value judgments, cost-effectiveness from the public sector perspective, harms, and ease of implementation and anticipated changes. Recommendations were not exclusively supported by evidence statements and this was indicated throughout. However, all recommendations relevant to this report were 'inferred' from the evidence. A draft of the recommendations was circulated for review amongst stakeholders before publication. The guideline is intended to be reviewed three years post-publication to determine the necessity of an update. A reference tool to support putting the guideline into practice was provided and recommendations were made regarding how to monitor and evaluate outcomes related to guideline implementation. Financial and other conflict of interest disclosure for involved stakeholders and authors were not explicitly stated beyond academic and professional affiliations.

The cost-comparison analysis[37] within the NICE guideline[24] was not a traditional cost-effectiveness analysis as it did not assess utility of testing. The primary outcome of cost per additional persons using vitamin D supplements was justified by the authors as a result of lacking evidence on the prevalence of vitamin D deficiency related health outcomes (e.g., bone disease) among populations of interest. Overall the analysis was simplified and did not account for many potential confounders (for example, differences in baseline vitamin D status and underlying disease risk), and indirect costs. Sub-group analysis was conducted for pregnant and breastfeeding women, children less than 5 years, adults 65 years and older, and people with darker complexions.[24] The assumption of 100% 25(OH)D test accuracy was inappropriate given substantial evidence of issues with sensitivity and specificity.[40] In addition, the assumption that both scenarios would result in a 50% reduction in symptomatic vitamin D deficiency does not account for the potential for more frequent identification and subsequent treatment of deficient individuals in the screening group. The risk of fractures for adults over 65 was taken from a study in elderly women. The appropriateness of this data source to represent all older adults is unclear. One-way sensitivity analyses were conducted for the subgroups of pregnant and breastfeeding women and children less than 5 years to assess the influence of prevalence of vitamin D deficiency, uptake of vitamin D supplementation, and cost of testing. Two-way sensitivity analyses were conducted to assess the influence of prevalence of deficiency (women and children) and percent benefiting from supplementation (only adults over 65 years). The perspective of the analysis was not stated. The generalizability of this data to broader populations (e.g., the general population) and other vulnerable subgroups (e.g., postmenopausal women) is limited, as it its applicability in the Canadian setting.

Overall, the OHTAC guideline[23] was adequately designed with a few methodological flaws. Objectives and individual health related questions were stated a priori. Expertise and designations of those involved in development was not declared but government, clinicians, external experts, and manufacturers were involved in the process. This does not necessarily capture the perspectives of all groups of interest, including the public. One author was involved in study selection up until full text review, at which point studies under debate were reviewed by a clinical epidemiologist or a panel of epidemiologists to reach consensus. A comprehensive systematic search was conducted on multiple databases for English language documents. A list of included studies was provided and the quality of each study was assessed using GRADE criteria and reported. No meta-analysis was conducted and heterogeneity and publication bias were not assessed. A formal tool was not used to assess risk of bias but methods of recruitment, sampling, selection, and generalizability were assessed. A list of conclusions generated in the systematic review was translated into specific and actionable recommendations. The link between these recommendations and the evidence is clear however, the recommendations suggest not testing based on a lack of evidence rather than evidence against the clinical effectiveness. The methods used for formulating recommendations was based on decision determinants considering: "clinical benefit, consistency with expected societal and ethical values, value for money, and feasibility of adoption into healthcare system".[19,23] Prior to publication, the report was reviewed by experts. No procedure or resources were provided for implementing recommendations and no protocol for updating the review or monitoring progress was provided. Options were given for providing the intervention (e.g., for different health conditions). Facilitators and barriers to implementation were not described beyond stating feasibility of adoption. No economic data was reviewed; therefore, resource implications were unclear. Potential conflicts of interest were stated but potential influence of government funding was not discussed. Due to the exclusion of individuals with conditions other than kidney disease, the generalizability of the findings to broader clinical populations is limited. However, this was taken into account in the formulation of recommendations.

Summary of Findings

What is the clinical effectiveness of vitamin D testing in the general population?

Detailed findings are presented in Tables A9 and A10 of Appendix 4.

The LeBlanc et al., review did not identify any direct evidence (up to August 2014) regarding the effectiveness of vitamin D screening versus no screening on clinical outcomes in persons with low vitamin D levels. Evidence was presented only regarding the utility of supplementation; therefore, no review of findings can be provided. Due to the lack of relevant data this study is not included in the summary in Appendix 4.

The AGDH review[33] was designed to retrieve evidence on the appropriate indications, clinical effectiveness, and safety and quality implications of vitamin D testing but did not uncover any studies or reviews with direct evidence related to these topics. Consequently, the review was revised to consider the effectiveness of vitamin D supplementation as a proxy intervention for the utility of testing. The identified studies exclusively assessed the clinical effectiveness of vitamin D supplementation but not testing. The review briefly discussed potential harms of testing as outlined in one HTA.[35] The potential for harms due to venipuncture and false-negative tests were noted as minimal and no studies were identified regarding adverse events of testing. Overall, the authors concluded that vitamin D screening may have some utility in identifying

individuals at risk for vitamin D deficiency who may benefit from supplementation, based on the evidence of effectiveness of supplementation in several sub-groups.

Overall, results of the non-randomized study[31] suggest that vitamin D testing does not translate into universal improvements in vitamin D status. Individuals included in the non-randomized study were older, had higher 25(OH)D levels and body mass index (BMI), more osteoporosis diagnoses and medications, had a higher rate of DEXA scanning, and were more likely to be dispensed high dose vitamin D therapy than individuals who were excluded for only having one test result. Based on these factors it is possible that those with a single-test who were excluded were at lower baseline risk for vitamin D deficiency and related health outcomes. The study reported that a small proportion (21%) of patients maintained sufficient vitamin D status. A total of 59% either maintained abnormal status or transitioned from sufficiency to abnormal status. Only 20% transitioned from abnormal status to sufficiency. Consequently, 8% of the patients benefited from testing with regards to improved vitamin D status. Comparing those who transitioned from sufficient to abnormal to those who maintained sufficiency, participants who became abnormal were younger, had higher BMI, had lower 25(OH)D status at first test, had fewer osteoporosis diagnoses, less DEXA scans, and a greater number of high dose vitamin D therapy prescriptions dispenses. Comparing those with persistent abnormal status to those with initially abnormal status who achieved sufficiency, participants with persistent abnormal status were younger, had higher BMI, had lower 25(OH)D status at first screening, were more likely to be African American, were more likely to be prescribed high dose vitamin D supplementation. Multivariate regression analysis of variables identified in univariate analysis showed that younger age was associated with transitioning from sufficient to low. Younger age was also a factor associated with persistent abnormal status, as was high BMI.

The systematic review within the NICE guideline[24] only identified evidence regarding the effectiveness of community education programs, universal vitamin D supplementation, and public awareness campaigns for “increasing uptake of existing guidance on vitamin D among at-risk groups” . The OHTAC guideline[23] did not uncover any direct evidence investigating the utility of vitamin D testing and used supplementation as a proxy for their recommendations. Guideline recommendations are discussed below.

What is the cost-effectiveness of vitamin D testing in the general population?

Detailed findings are presented in Tables A11 to A12 of Appendix 5.

The AGDH review[33] included a systematic review of economic evidence that only identified one low quality cost-analysis conducted from the US Veterans Administration Medical Centres perspective. This study compared in the inpatient and outpatient costs for individuals who had received at least one routine vitamin D test and subsequent screenings. They found that costs were lower for individuals with sufficient vitamin D status at the first screening compared to those who were deficient. In addition, they observed that costs were lower for those with two or more follow up screenings compared to those without follow up or only one follow up screening suggesting that subsequent monitoring could reduce medical costs. This analysis did not compare costs of screening versus not screening. As such, it demonstrated overall lower costs for individuals who were monitored repeatedly, but does not provide evidence to support screening in the place of universal supplementation. Moreover, as utilities and cost-effectiveness were not considered, allocative efficiency could not be assessed.

The economic evaluation[30] reported that, from the societal perspective, screening had a greater net monetary benefit at a threshold of $50000 per quality adjusted life year compared to universal supplementation. This was assuming a cost of $0.077 per vitamin D capsule; $41.66 per test; a probability of: falls from 13.6 to 20.1% (female) or 13.2 to 21% (male), injurious falls from 34.9 to 33.6% (female) or 20.8 to 26.8% (male), death from 1.07 to 4.86% (female) or 1.66 to 6.78% (male); and a health utility loss of 0.044 for a fall and 0.161 for a fall with fear of falling. Subgroup analysis of adults age 65 to less than 80 and adults 80 years and older suggested a greater net monetary benefit of population screening for adults 80 years and older and a greater net monetary benefit of universal supplementation for adults 65 to less than 80 years of both genders. In one-way sensitivity analysis of female data, the risk reduction of falls due to supplementation and cost of serum 25(OH)D testing had the largest impact on net monetary benefit.[30] For women, at greater than 11% fall risk reduction, both interventions were cost-effective, but at greater than 27% risk reduction screening was more cost effective. Both strategies were cost-effective across the range, but for tests costing less than $51 screening was more cost-effective. In probabilistic sensitivity analysis, 52.8% of simulations indicated screening was most cost-effective versus 36.3% for universal supplementation. This general pattern occurred for all age subgroups suggesting a benefit of screening across female age groups. In one-way sensitivity analysis of male data screening was more cost-effective at greater than 25% fall risk reduction, and for tests less than $53. Both interventions were cost-effective across all ranges used in sensitivity analysis. In probabilistic sensitivity analysis, 54.3% of simulations indicated that screening was most cost effective versus 38.2% for universal supplementation. This trend occurred for men over 80 years old but for men aged 65 to less than 80 the two interventions were more cost-effective in a similar percentage of simulations, suggesting no advantage.

The results of the cost-comparison analysis embedded within the evidence-based guideline[24] did not support population screening for vitamin D deficiency in most scenarios. The incremental cost effectiveness ratio for the various population sub-groups ranged from 9 million to 160 million dollars per additional person using vitamin D supplements. This analysis assumed a cost of £20.70 for a year of vitamin D supplementation (1000 IU), £2505 to treat each case of symptomatic vitamin D deficiency, £16.50 per test, and a 50% probability of uptake of supplementation and of benefit from supplementation. For pregnant and breastfeeding women, and children less than 5 years, even if symptomatic deficiency was eradicated in the screening group - in order to be cost saving, the outstanding rate of deficiency in the universal supplementation groups would need to be at least 1.5% and 7%, respectively. In the adults 65 years and older group, at least 20% greater benefit from testing (for risk reduction of falls) over universal supplementation was needed to be cost saving. Univariate sensitivity analysis showed that as the prevalence of vitamin D deficiency increased, the incremental cost of testing versus supplementation increased. Specific thresholds were not reported for this analysis. As the cost of supplements increased, the incremental cost of testing decreased. For cost saving, supplements would need to exceed £25 in pregnant and breastfeeding women, £15 in children less than 5 years, and £23 in adults 65 years and older. As the cost of testing increased the incremental cost of testing increased but specific thresholds were not reported for this analysis.

What are the evidence-based guidelines associated with vitamin D testing in the general population?

Detailed results are available in Table A13 of Appendix 6.

The NICE report[24] recommends that vitamin D tests be completed only for patients with apparent symptoms of vitamin D deficiency, high risk of deficiency (e.g., due to low exposure to sunlight), or underlying health conditions (e.g., osteomalacia or history of falls). Recommendations were made against routine screening for individuals without any of the above criteria. Lastly, the guideline recommended further research into the comparative cost-effectiveness of preventive approaches to vitamin D deficiency compared to the cost of testing and treatment.

The OHTAC guideline[19,23] provides recommendations against routine vitamin D testing. This recommendation does not apply to high risk individuals (i.e., osteoporosis, rickets, osteopenia, malabsorption, renal disease, use of drugs affecting absorption or metabolism of vitamin D). This was based on conclusions from the systematic review[23] that high risk individuals should follow physician guidance for testing and supplementation, and the limitations due to ambiguities in target serum levels and vitamin D measurement, and availability of clear guidelines on vitamin D supplementation. These recommendations were made on the basis of the lack of evidence on the clinical effectiveness of vitamin D testing, limited evidence of clinical benefits of adequate serum vitamin D levels on bone health outcomes, and a lack of evidence on benefits of adequate serum levels on other health outcomes (i.e., cancer, CVD, all-cause mortality, chronic kidney disease). Furthermore, there was no evidence that vitamin D measurements encourage adherence to Health Canada guideline for vitamin D intake.

Limitations

Clinical Evidence

The relevance of the LeBlanc review,[32] the AGDH review,[33] the NICE guideline,[24] and the OHTAC guideline[19,23] is limited by the scarcity of direct evidence regarding the clinical effectiveness of vitamin D testing. While several publications had some methodological flaws,[23,33] two well-designed evidence searches[24,32] were unable to identify any studies relevant to the research question. This lack of evidence meant that these studies could not contribute meaningfully to the clinical component of this report. The decision to include studies assessing the clinical and cost-effectiveness of vitamin D supplementation clouded the presentation of results. Although this was the only potentially useful evidence available, it relies on the utility of supplementation as a proxy for effectiveness of testing. In the case of both systematic reviews[32,33] the exact involvement of funding sources was not completely clear. A more detailed explanation of the influence of affiliations and funding would have aided in interpretation of the results.

The results of the single non-randomized study[31] should be interpreted in light of the following limitations. There was an overall lack of consideration of potential confounders (e.g., use of over the counter vitamin D, treatment compliance, medication use), which limits the interpretation of results. The study was conducted in a population that had at least two 25(OH)D tests performed, so the effectiveness of testing in individuals who only underwent one test is unclear. Repeat testing may not be indicated or feasible for the general population. Lastly, follow up monitoring was performed at one year, so the investigators did not have the ability to assess any shorter term changes in status.

Economic Evidence

The economic evaluations[24,30] were not conducted in the Canadian context. They were limited to older community dwelling adults receiving a maximum of 4000 IU,[30] and populations at risk of deficiency.[24] Resource implications for the general population could not be assessed in either case. The US study[30] only considered direct costs due to the lack of evidence resulting in potentially underestimated societal costs. The model[30] assumed a uniform response to treatment for both strategies, which is unlikely given that the targeted supplementation of tested individuals would probably result in fewer non-deficient individuals being treated. As a result, the benefit of universal supplementation may be overestimated and that of screening and targeted supplementation underestimated. Confounders such as malabsorption syndromes and BMI, with the potential to influence vitamin D status and response to supplementation were not considered by either study.[24,30] Lastly, not all perspectives were considered, which greatly limits the relevance of this study to payers and policy makers who may be tasked with making decisions about vitamin D testing.

Guidelines

The majority of evidence presented in the NICE guideline[24] was based on studies in the UK population and recommendations reflected the intended UK audience. Funding and other conflict of interest of the guideline authors and stakeholders was not declared beyond academic and professional affiliations. The Canadian OHTAC guideline[19,23] was based on a systematic review of older studies (up until 2009) that had several methodological deficiencies (e.g., lack of duplicate screening) and may require updating. It made recommendations without providing support for implementation and monitoring. In addition, it did not consider at-risk populations (other than kidney disease patients), [19,23] whereas the NICE guideline[24] only considered at-risk populations so the recommendations must be interpreted accordingly. The final recommendations made by both guidelines[19,23,24] regarding testing indications were based on a lack of evidence rather than direct evidence regarding the clinical effectiveness of testing.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The clinical effectiveness of vitamin D testing was evaluated by two systematic reviews,[32,33] two evidence-based guidelines[19,23,24] and one non-randomized study.[31] Overall, there was a paucity of evidence directly evaluating the clinical utility of testing, highlighting the need for further research.

The overall trend was conclusions[33] and recommendations[24] supporting testing for populations at risk of deficiency (e.g., patients at risk of osteoporosis) but not for the general population. The non-randomized study supported these guidance statements by reporting that vitamin D testing does not translate into universally improved status and in some cases can lead to worsened status. In general, the recommendations against universal testing appeared to be made based on indirect evidence (i.e., the clinical and cost-effectiveness of supplementation). Similarly, a number of current guidelines[15,18,19,29,34,35,41] on vitamin D testing have relied on evidence linking vitamin D supplementation to cost-savings or improved clinical outcomes as a proxy for the utility of testing. To reduce uncertainty and support the evidence base for decision-making on vitamin D testing, future trials may benefit from investigating the direct clinical utility of vitamin D testing, rather than the association between vitamin D status and clinical outcomes. However, resolution for the lack of standardization among vitamin D assays and methods of classifying deficiency is needed before this type of study can be conducted rigorously.

Cost-effectiveness of vitamin D testing was evaluated by one systematic review,[33] one economic evaluation[30] and one evidence-based guideline.[24] Population screening appears to be more cost-effective than universal supplementation for preventing falls in community dwelling older adults from the US societal perspective.[30] There is also evidence of greater cost-effectiveness with increasing age.[30] From the UK perspective,[24] it is more cost-effective to universally supplement at-risk groups than it is to institute vitamin D testing and targeted supplementation. The generalizability of these findings to the Canadian context, other populations, and individuals receiving higher dose therapy is limited. In addition, the relevance of these conclusions to other perspectives and current costs is unknown.

Overall, the current available evidence does not support vitamin D testing in the general population. However, it suggests that testing may provide some clinical and cost-benefits over universal supplementation for vulnerable sub-groups (e.g., elderly individuals). Differences in methods of testing and classifying vitamin D deficiency between studies, and outstanding disagreement about appropriate assays and cut-offs should be taken into account in interpretation of this report. Further research is needed to orient the evidence base to the Canadian context, and to determine the utility of testing in other relevant subgroups (e.g. post-menopausal women).

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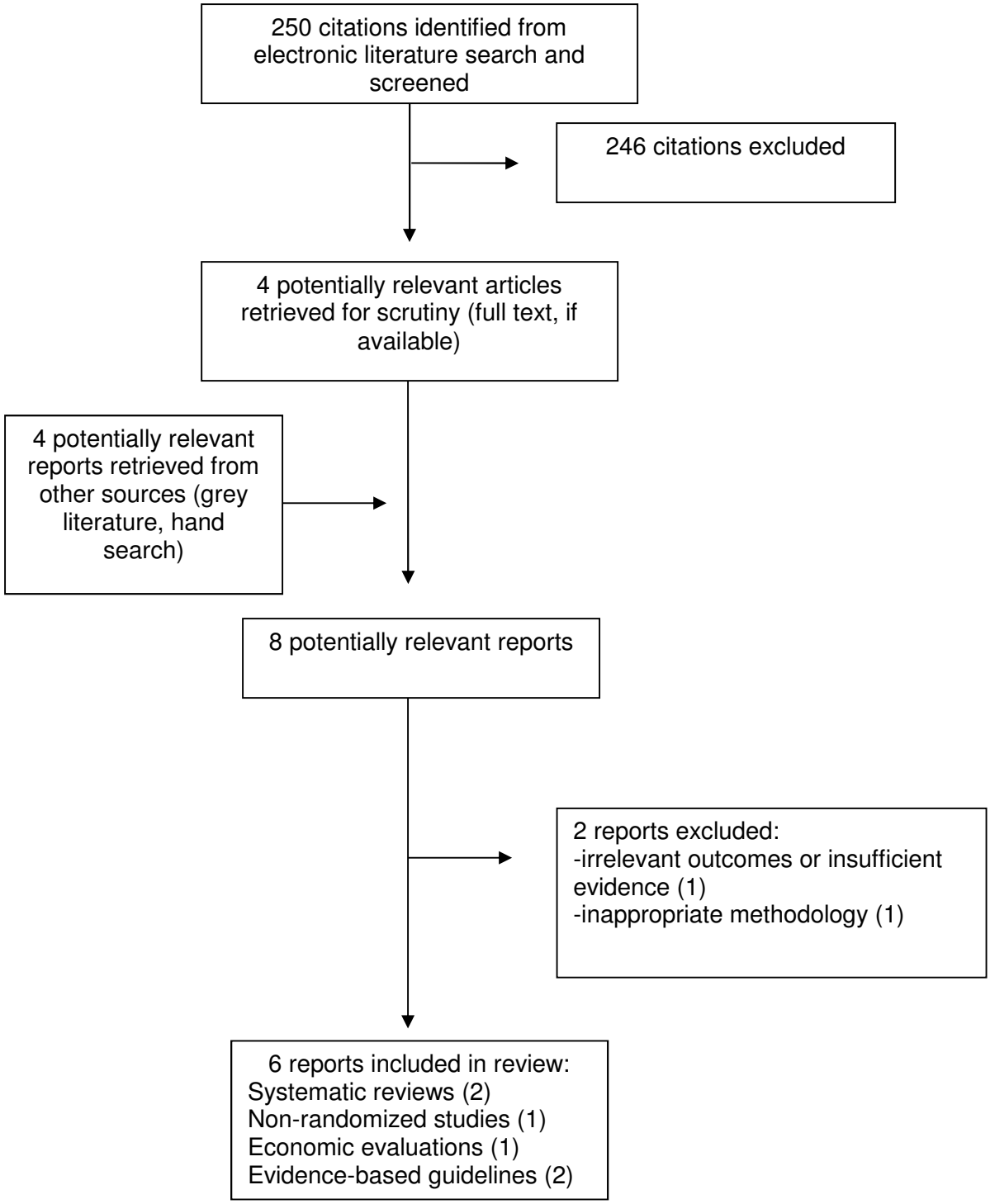
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes
LeBlanc, 2014,[32] United States	Vitamin D supplementation as intervention, n = 41 (n = 17, clinical benefits, n = 24, harms) Vitamin D testing as intervention, n = 0	Vitamin D deficient individuals (populations with at least 90% 25(OH)D levels below 50 or 75 nmol/L0	• Vitamin D screening • Vitamin D supplementation	• No testing • No supplementation	• Health outcomes (falls, fractures, mortality) • Harms
Australian Government Department of Health[33], 2014, Australia	*Clinical* n = 61 overall n = 0 for vitamin D as intervention *Economic* n = 1 cost analysis	Patients at risk of vitamin D deficiency: • Post-menopausal women and elderly men with bone disease • Patients with chronic diseases • Patients with multiple sclerosis • Children with rickets • General population	Single or multiple vitamin D tests **No clinical literature identified so vitamin D supplementation was assessed as an intervention*	• No testing • Single or multiple vitamin D tests **No clinical literature was identified so vitamin D supplementation and no supplementation were used as comparators*	• Change in patient management • Health outcomes (morbidity, mortality, quality of life) • Safety • Cost of testing • Cost-effectiveness of testing

Table A2: Characteristics of Included Non-Randomized Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Wei, 2014,[31] Australia, US	Retrospective cohort study	Managed care patients enrolled at a large medical group over 3 years	Vitamin D test and follow up test	None	Change in vitamin D status* measured by 25(OH)D • Sufficient to sufficient • Sufficient to insufficient • Deficient to deficient • Deficient to sufficient

*Vitamin D status classified as: insufficient = < 30 ng/mL, or sufficient ≥30 ng/mL.

Table A3: Characteristics of Included Cost Studies

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Lee, 2014,[30] US	Cost effectiveness analysis, Societal perspective	Population screening (25[OH]D), Universal Supplementation (0 to 4000 IU, depending on scenario) OR No testing or supplementation	Caucasian community dwelling older adults (65 to 80 years)	36 months (one month cycles)	• No previous history of falls, screening, or supplementation • Increased risk of falls for those with insufficient and deficient vitamin D status • Uniform dose for all given universal supplementation • Varied dose for those subjected to population screening • Maximum dose of 4000 IU in the deficient group and no toxicity • 80% supplementation compliance • Efficacy onset at six months • Consistent efficacy across age and gender

25(OH)D = serum 25-hydroxyvitamin D; IU = international units; US = United States.

Table A4: Characteristics of Included Guidelines

Objectives			Methodology		
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations Development and Evaluation**
NICE, 2014[24]					
Health and social care practitioners	Interventions (including vitamin D screening) to increase awareness and uptake of existing guidance on vitamin D among at-risk groups	Clinical and cost-effectiveness	Two systematic reviews, and one economic evaluation	NICE Public Health Guidance Protocols Used	Established through informal consensus that took into account: • Strength and applicability of evidence • Potential impact on health and health inequalities • Quality and diversity legislation • Ethical issues and social value judgments • Cost-effectiveness (public sector perspective) • Harms • Ease of implementation and anticipated changed Reviewed by stakeholders prior to publication
OHTAC, 2014[19,23]					
Ministry of Health and Long Term Care	Vitamin D screening Vitamin D supplementation	Clinical effectiveness	One systematic review[23]	GRADE criteria	Based on evidence compiled within the systematic review and conclusions stated. Decision determinants criteria used to establish recommendations considered: • Overall clinical benefit • Consistency with expected societal and ethical values • Value for money • Feasibility of adoption into the health system

NICE = National Institute for Health and Care Excellence; OHTAC = Ontario Health Technology Advisory Committee

APPENDIX 3: Critical Appraisal of Included Publications

Table A5: Strengths and Limitations of Systematic reviews Assessments using AMSTAR[25]

Strengths	Limitations
AGDH, 2014[33]	
• Objectives clearly stated • Multiple databases searched • Grey literature, reference lists and experts were consulted for additional evidence • List of included studies provided • Trials were assessed for quality using the National Health and Medical research Council Dimensions of Evidence Tool • Quality was considered in formulation of conclusions • Funding sources of original studies declared • Heterogeneity and risk of publication bias was reported	• Intervention of a priori objectives revised to accommodate lack of relevant evidence • Information on the number of authors involved in study selection and data extraction was not disclosed • Search duration was extended only for HTA databases and Cochrane library • Quality assessment of systematic reviews deferred to original publication • Most meta-analyses conducted by original review authors; full results not presented • Funding and conflict of interest of review authors not listed
LeBlanc, 2014[32]	
• Objectives clearly stated • Multiple databases searched • Grey literature, reference lists consulted for additional evidence • List of included studies provided • Trials were assessed for quality using the US Preventive Services Task Force tool • Quality was considered in formulation of conclusions • Funding sources and conflict of interest of review authors declared • Heterogeneity reported for meta-analyses	• Risk of bias not assessed using formal tool • Potential clinical symptoms contributing to underlying deficiency in the population could not be rules out • Abstraction was only conducted by a single author • Funding sources of original studies not declared • Publication bias not assessed

AGDH = Australian Government Department of Health; HTA = Health Technology Assessment; US = United States

Table A6: Strengths and Limitations of Non-Randomized Studies using Downs and Black[26]

Strengths	Limitations
Wei, 2014[31]	
• Objective clearly stated • Patient demographics, treatments and confounders were described. • Main study findings were presented with variability statistics and p-values where appropriate • Good external validity (limited exclusion criteria) • Multivariate analysis conducted	• No data collected on adverse events • No data on use of OTC vitamin D supplements • No compliance data for high dose vitamin D therapy or OTC supplements • No data collected on sun exposure • Many disease related confounders due to lack of health related exclusion criteria • Incomplete monitoring of non-osteoporosis medications • Sample size calculation not reported • Only a subset of the total population has sufficient vitamin D tests to be eligible; differences between eligible and ineligible individuals were not discussed • Follow up limited to 400 days

OTC = over the counter

Table A7: Strengths and Limitations of Economic Studies using the Drummond Checklist[27]	
Strengths	**Limitations**
Lee, 2014[30]	
• Objective and type of analysis clearly stated • Intervention and primary outcome clearly defined • Data from aggregated sources was used for model inputs in most cases • Incremental cost-effectiveness ratios were stated and presented disaggregated • Country of currency and base year (2011) were stated • Model structure presented visually • Details of model inputs presented • Time horizon (36 months) stated • Discounting (3%) was applied • Sensitivity analysis conducted • Conclusions consider appropriate caveats • Adjustments for currency and inflation were made	• Original study design and limitations for sources of model inputs were not provided • Only direct costs were considered due to insufficient evidence • Doses limited to 4000 IU • Limited external validity; conducted from the US societal perspective for community dwelling older adults • Assumption of a uniform response to treatment is inaccurate • Confounding demographic factors such as body weight, malabsorption syndromes not considered in model

IU = International Units

Table A8: Strengths and Limitations of Guidelines using AGREE II[28]	
Strengths	**Limitations**
NICE, 2014[24]	
• Objectives clearly stated in the context of intended users and target population • Systematic reviews and an economic evaluation were used as supportive evidence • Stakeholders (including general public) consulted throughout guideline development process • Inclusion criteria clearly described • Strengths and limitations of the identified evidence stated and assessed using NICE Public Health guidance • Quality of evidence used in the formulation of conclusion and recommendations • Recommendations were clear and actionable; target audience and implementers were clear • Strength and quality of evidence considered in recommendations • All recommendations relevant to this report were supported by evidence • Guideline was reviewed by stakeholders prior to publication • A guideline update protocol was listed • A tool for implementation of the guideline and subsequent monitoring is available • Subgroup analysis and sensitivity analysis was conducted for the cost-comparison analysis	• Conducted from the UK perspective using primarily UK data • Funding and other conflict of interest was not declared beyond academic and professional affiliations • Cost-comparison analysis was simplified and did not consider many potential inputs and confounders • Many model inputs were derived from non-aggregated data sources, or from studies conducted in inappropriate subject populations

Table A8: Strengths and Limitations of Guidelines using AGREE II[28]	
Strengths	**Limitations**
OHTAC, 2010[23]	
• Objectives clearly stated • Comprehensive literature search completed • Quality of evidence assessed using GRADE criteria • Full list of included studies provided • Conflict of interest declared • Recommendations clear and actionable • Method of formulating recommendations described • Reviewed by experts prior to publication • Relevant to the Canadian setting	• Expertise and affiliations of groups involved with guideline not specifically described • Public opinion not considered • Only a single author involved in study selection • Number of authors involved in abstraction unclear • No pooled results presented; therefore, no heterogeneity or publication bias risk reported • No formal tool used for risk of bias assessment • Recommendations rely on lack of evidence • No procedure for implementing/monitoring recommendations or updating the review presented • No economic data reviewed; resource implications unclear • Limited generalizability to at risk populations

GRADE = Grading of Recommendations Assessment, Development and Evaluation; NICE = National Institute for Health and Care Excellence; OHTAC = Ontario Health Technology Advisory Committee.

APPENDIX 4: Summary of Clinical Findings

Table A9: Summary of Findings of Systematic Reviews	
Main Study Findings	**Author's Conclusions**
AGDH, 2014[33]	
• No direct evidence on the clinical effectiveness of vitamin D testing for health outcomes, patient behavior, or clinical decisions • No direct evidence on harms associated with vitamin D testing • No direct evidence on the cost-effectiveness of vitamin D testing • One poor quality cost analysis concluded that for individuals with at least one vitamin D test, repeated monitoring could reduce medical costs compared to a single follow up test or no follow up	• Vitamin D testing may have some utility in identifying individuals at risk for vitamin D deficiency (e.g. individuals with known poor bone health) who may benefit from supplementation

Note: LeBlanc et al.,[32] 2014 retrieved no direct evidence on vitamin D testing and is excluded from this summary tables.

Table A10: Summary of Findings of Non-Randomized Studies			
Wei, 2014[31]			
Vitamin D Status Transition Group	**n (%)**	**Significant Co-Variates (Univariate Analyses)‖**	**Significant Co-Variates (Multivariate Analyses)‖, ¶**
Sufficient-to-sufficient*	234 (20.8)	N/A	N/A
Sufficient-to-low†	132 (11.7)	• Younger age • Lower 25(OH)D concentration at first screening • Greater difference between first and second test • Fewer osteoporosis diagnoses • Fewer DEXA scans • Higher BMI • Greater rate of high dose vitamin D prescriptions	• Younger age
Low-to-sufficient‡	222 (19.7)	N/A	N/A
Low-to-low§	538 (47.8)	• Younger age • Greater proportion of African Americans • Lower 25(OH)D concentration at first screening • Lower difference between first and second test • Greater rate of obesity • Higher BMI • Greater rate of high dose vitamin D prescriptions	• Younger age • Higher BMI

25(OH)D = serum 25-hydroxyvitamin D; BMI = body mass index; DEXA = dual-energy x-ray absorptiometry
*Patients with sufficient vitamin D results from both tests[31]
†Patients with sufficient results from the first test but abnormally low results (insufficient or deficient) from the second
‡Patients with abnormally low results from the first test but sufficient results from the second
§Patients with abnormally low results from both tests
‖Statistically significant at $p < 0.05$ or lower
¶Multivariate logistic regression analysis of variables significant in univariate analysis

APPENDIX 5: Summary of Economic Findings

Table A11: Summary of Findings of Economic Evaluations

Main Study Findings	Author's Conclusions
Lee, 2014[30]	
Assuming: • Dose of 1000 IU for all in universal supplementation group • Dose of 0 to 4000 IU for all in population screening group, depending on measured vitamin D status • Cost of $0.077 per vitamin D capsule • $41.66 per vitamin D test • Probability of falls ranging from 13.2 to 21% and injurious falls ranging from 20.8 to 34.9, depending on gender • Probability of death ranging from 1.07 to 6.78, depending on gender • Health utility loss of 0.044 for a fall and 0.161 for a fall with fear of falling Screening had a greater net monetary benefit at a willingness to pay threshold of $50000/QALY compared to universal supplementation Females: Net monetary benefit* of $224 versus $189 for universal supplementation ($p < 0.001$) Males: Net monetary benefit of $298 versus $260 for universal supplementation ($p < 0.001$)	• Both population screening and universal supplementation are cost-effective strategies for reducing risk of falls in older Caucasian adults, though population screening has a greater net monetary benefit • At more advanced age (> 80 years) population screening is preferred to universal supplementation

Subgroup Analysis†

Group	Net Monetary Benefit of Population Screening	Net Monetary Benefit of Universal Supplementation
Women 65 to <80 years	$59	**$71**
Women ≥ 80 years	**$563**	$428
Men 65 to <80 years	$114	**$120**
Men ≥ 80 years	**$703**	$571

One-Way Sensitivity Analyses

Sex	Cost of testing	Fall risk reduction due to vitamin D supplementation
Female	Population screening more cost-effective for tests costing < $51, both interventions cost-effective across the range of testing costs	Population screening remained cost-effective for risk reduction values > 27%, both interventions were cost-effective above 11% risk reduction
Male	Population screening more cost-effective for tests costing <$53, both interventions cost-effective across range of test costs	Both interventions cost-effective across the range of falls risk reduction, population screening more cost-effective for risk reduction > 25%

Probabilistic Sensitivity Analyses

Sex	% of simulations for which population screening was most cost-effective	% of simulations for which universal supplementation was most cost-effective
All females	52.8%	36.3%
Females, 65 to < 80 years	42.6%	37.2%
Females, ≥ 80 years	73.4%	23.4%
All males	54.3%	38.2%
Males, 65 to < 80 years	42.5%	44.2%
Males, ≥ 80 years	71.5%	26.2%

IU = international units; QALY = quality adjusted life years
*Higher incremental net monetary benefit indicates a more cost-effective strategy[30]
†The strategy with greater cost effectiveness is bolded

Table A12: Summary of Economic Findings of Guidelines	
Main Study Findings and Recommendations	**Author's Conclusions**
NICE, 2014[24]	
Cost-comparison analysis • ICER = 9 million to 160 million per additional person using vitamin D supplements, depending on subgroup	• Testing and targeted supplementation is not a cost-effective strategy versus universal supplementation of pregnant and breastfeeding women, children < 5 years, and adults ≥ 65 years in the UK

Subgroup Results of Cost-comparison Analysis†	
Group	ICER for testing for deficiency rather than providing universal supplementation
All	£56,809,806
Pregnant and breastfeeding women	£9,177,737
Children < 5 years	£21,272,947
Adults ≥ 65 years	£25,359,122
People with darker skin*	£160,181,034

ICER = incremental cost-effectiveness ratio; UK = United Kingdom
*e.g., "people of African, African-Caribbean or South Asian family origin"[24]

APPENDIX 6: Summary of Guideline Findings

Table A13: Summary of Recommendations from Evidence-Based Guidelines

Main Study Findings	Author's Conclusions
NICE, 2014[24]	
Recommendations • Vitamin D testing should only be completed for patients with apparent symptoms of vitamin D deficiency, high risk of deficiency, or underlying health conditions • Individuals with low risk for deficiency should not be tested Findings Further research into the comparative cost-effectiveness of preventive approaches to vitamin D deficiency versus the cost of testing and targeted treatment	Vitamin D testing should only be conducted in high risk individuals; further research regarding cost-effectiveness of testing is needed
OHTAC, 2010[19,23]	
Recommendations • Vitamin D testing should not be routinely conducted (with the exception of at risk patient populations) • Health Canada guidelines for vitamin D intake and supplementation "should be followed and promoted through education of healthcare providers and the general population" Findings: There is a lack of evidence on the clinical effectiveness of testing, a lack of concordance on vitamin D status and measurement, and a lack of evidence to support adequate status and favorable health outcomes Decision determinants criteria suggest: • There is a "low/small overall clinical benefit of vitamin D testing in the healthy population, and feasibility of adoption into the health system" • The consistency of vitamin D testing in the healthy population with expected societal and ethical values and the value for money is unknown/not yet evaluated • Clinical benefit, consistency with expected societal and ethical values, and value for money of vitamin D testing for at risk populations is unknown • Feasibility of adoption of vitamin D testing for high risk populations is "high/large"	Vitamin D testing is not recommended for healthy populations and should only be conducted in high risk individuals due to the lack of evidence on the clinical utility of testing.

NICE = National Institute for Health and Care Excellence; OHTAC = Ontario Health Technology Advisory Committee