

# Philippine Clinical Practice Guidelines for Periodic Health Examination: Screening for Renal, Metabolic, Nutritional, and Endocrine Disorders

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Screening for Renal, Metabolic, Nutrition, and Endocrine Disorders

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## ABSTRACT

**Background and Objective.** Renal, metabolic, nutritional, and endocrine disorders significantly affect Filipinos due to the resulting mortality, cardiovascular outcomes, and negative impact on quality of life. Screening for these disorders may lead to earlier detection and management of the disease, with subsequent improvement of clinical outcomes if early therapeutic options are available. This must be balanced with potential harms resulting from mislabeling and the adverse effects of treatment. The objective of this clinical practice guideline (CPG) is to provide recommendations to optimize patient care on screening for renal, metabolic, nutritional, and endocrine disorders among asymptomatic, apparently healthy Filipinos.

**Methods.** We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to CPG development recommended in the Department of Health Manual. The process included 1) generation of critical questions and critical outcomes, 2) retrieval of current evidence, 3) synthesis and assessment of the evidence base for these critical questions, 4) formulation of draft recommendations, 5) convening of a multisectoral stakeholder panel that evaluated the evidence base and considered feasibility, values, and preferences in formulating recommendations, and 6) planning for dissemination, implementation, impact evaluation, and updating. We performed a systematic synthesis of evidence to address screening for high climacteric syndrome, hypocalcemia or hypercalcemia, prediabetes, chronic kidney disease, hyperuricemia, malnutrition, nutritional anemia, among asymptomatic, apparently healthy adult Filipinos, and sexual maturity among asymptomatic, apparently healthy adolescent Filipinos.

**Results.** After the presentation of the evidence synthesis and deliberation of the consensus panelists, this CPG provides 18 recommendation statements for the eight conditions. These statement recommendations serve as guides for the primary care physicians in their screening



A full copy of the Philippine Clinical Practice Guidelines for Periodic Health Examination: Screening for Renal, Metabolic, Nutritional, and Endocrine Disorders can be found at this link:  
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for the identified renal, metabolic, nutritional, and endocrine disorders. The CPG recommends AGAINST screening for high climacteric syndrome among asymptomatic, apparently healthy women aged 45–55 years using hormonal tests. Moreover, the guideline DOES NOT recommend the use of serum calcium, electrocardiogram, or bone mineral density in screening for hypocalcemia or hypercalcemia; estimated glomerular filtration rate, urine albumin concentration, urine albumin-creatinine ratio, and kidney ultrasonography in screening for chronic kidney disease; mid-upper arm circumference in screening for malnutrition; and, serum uric acid in screening for hyperuricemia for apparently healthy, asymptomatic adults. Routine assessment for sexual maturity among asymptomatic adolescents is also NOT recommended. However, the guideline recommends using fasting plasma glucose and hemoglobin A1C in screening for prediabetes and type 2 diabetes mellitus; waist circumference, waist-hip ratio, and body mass index in screening for malnutrition; and hemoglobin and red blood cell parameters in screening for nutritional anemia.

**Conclusion.** The CPG for the Periodic Health Examination, a joint project of the Department of Health and the National Institutes of Health, addressed selected renal, metabolic, nutritional, and endocrine conditions and provided recommendations for their screening. The statements are made to guide the primary care physicians in the screening of identified renal, metabolic, nutritional, and endocrine disorders. These recommendations will be updated after three years or until new evidence arises.

*Keywords: guidelines, climacteric, menopause, hypocalcemia, hypercalcemia, prediabetes, chronic kidney diseases, hyperuricemia, malnutrition, obesity, anemia, sexual maturation*

## INTRODUCTION

The Philippine Guidelines on Periodic Health Examination (PHEX), initially published in 2004, is a comprehensive appraisal and synthesis of evidence on screening interventions committed to providing early prevention services among apparently healthy Filipinos. It was a long-awaited publication, and the first to offer evidence-based recommendations for screening tests made possible through the concerted effort of various medical and paramedical organizations composed of more than a hundred experts, researchers, and stakeholders.<sup>1</sup> It was inspired by the Canadian and the US Preventive Services Task Forces, but it was tailored to the Philippine setting.

Renal, metabolic, nutritional, and endocrine disorders pose a significant burden among Filipinos. High climacteric syndrome is associated with metabolic changes in women and decreased quality of life.<sup>2,3</sup> Disorders of calcium levels,

hypocalcemia and hypercalcemia, when severe, can lead to cardiovascular (CV) dysfunction.<sup>4,5</sup> Prediabetes, an intermediate state of hyperglycemia above normal but below diabetes threshold, is a risk factor for developing diabetes, which in turn is associated with the development of nephropathy, retinopathy, neuropathy, and macrovascular disease.<sup>6–9</sup> Chronic kidney disease is one of the leading causes of death and disability worldwide.<sup>10,11</sup> Hyperuricemia is a feature of gout and is also associated with nephrolithiasis and metabolic syndrome.<sup>12,13</sup> The proportion of overweight and obese individuals is increasing in the Philippines, while the burden of chronic energy deficiency remains.<sup>14</sup> Screening for nutritional anemias may be beneficial since replacement of micronutrient deficiencies will correct the anemia.<sup>15</sup> Differences in timing of sexual maturity may have a profound impact on the well-being of a growing adolescent, and screening for these disorders may allow early intervention and support for psychosocial development.<sup>16,17</sup>

This clinical practice guideline (CPG) is a systematic synthesis of evidence regarding screening for high climacteric syndrome, hypocalcemia or hypercalcemia, prediabetes, chronic kidney disease, hyperuricemia, malnutrition, and nutritional anemia among asymptomatic, apparently healthy adult Filipinos, and screening for sexual maturity among asymptomatic, apparently healthy adolescent Filipinos. This is defined as someone who does not have any symptoms of disease and is devoid of modifiable risk factors such as diabetes, hypertension, and smoking.

## METHODS

Following the recommended CPG process in the Department of Health (DOH) Manual on Practice Guideline Development, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used.<sup>18</sup> The GRADE Adolopment and Evidence-to-decision (EtD) framework was utilized in finalizing the recommendations.<sup>19,20</sup> This guideline was funded jointly by the DOH and the National Institutes of Health.

### Preparation

The Task Force Steering Committee (SC) set the CPG objectives, scope, target audience, and clinical questions. The SC convened the technical working group involved in creating the evidence base and the consensus panel (CP) involved in finalizing the recommendations for each included clinical question. Questions were prioritized using the criteria set by DOH.

### COI Management

All task force members submitted their declaration of conflict of interest (COI) and curriculum vitae. A COI committee reviewed and evaluated potential conflicts of interest and provided a recommendation on how to manage them. In general, those with financial COI were not allowed to vote

**Table 1.** Grading of Severity and Strength of Recommendations

| Certainty of Evidence      | Description  |
|----------------------------|--|
| <b>High</b>                | We are very confident that the true effect lies close to that of the estimate of the effect.   |
| <b>Moderate</b>            | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.      |
| <b>Low</b>                 | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.  |
| <b>Very low</b>            | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.  |
| Strength of Recommendation | Description  |
| <b>Strong</b>              | Advantages of the intervention significantly outweigh disadvantages or disadvantages of the intervention significantly outweigh advantages.  |
| <b>Weak</b>                | Advantages of the intervention may outweigh disadvantages, disadvantages of the intervention may outweigh advantages, or the relationship between advantages and disadvantages is not clear. |

on questions related to the COI. Those with non-financial COIs (such as authorship related to the CPG topic) were allowed to participate, but COIs were declared during the CP meeting and the final manuscript. Since the chair of the SC was an industry speaker, this constituted a financial COI. As such, a co-chair without a financial COI was assigned. An evidence review expert (ERE) with COI was paired with another expert without COI as a secondary reviewer.

**Evidence Synthesis**

The clinical questions were developed using the PICO (population, intervention, comparator, and outcome) format. The ERE searched and appraised international practice guidelines related to periodic health screening, including but not limited to those of the Canadian Task Force on Preventive Health Care, U.S. Preventive Services Task Force, and National Institute for Health and Care Excellence. If the CPG were of good quality and done within five years, the evidence summaries of the CPG were adopted.

If no updated, relevant, and trustworthy CPG was found, a systematic medical literature search of the Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar was performed. Relevant local databases and websites of medical societies were also utilized in the search. The ERE also contacted authors of related articles to verify details and identify other research studies for appraisal, if needed. Systematic reviews that met our inclusion criteria to answer our clinical questions were used directly to identify relevant articles and a summary of findings. If no related systematic reviews were found, we conducted *de novo* systematic reviews. We critically appraised the methodological quality of the included studies using the standard tools, such as the Cochrane Risk of Bias tool (ROB 1.0) for randomized controlled trials (RCTs), Painless EBM appraisal criteria, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic accuracy studies, and the Newcastle–Ottawa Scale (NOS) for observational studies. We used the GRADE

approach to rate the certainty of evidence and the strength of recommendations (Table 1).<sup>21</sup>

**Evidence to Decision Consensus Approach**

The multisectoral CP was tasked to review the evidence summaries and develop recommendations during the *en banc* meeting. Prior to the meeting, the CP prioritized critical and important outcomes (Appendix).

The CP was provided with the evidence base for all the clinical questions and a draft recommendation solely based on the trade-offs between benefit and harm and the certainty of evidence. Each CP member was then asked to complete an EtD questionnaire. The purpose of this questionnaire survey is for each CP member to explicitly incorporate other important factors, such as cost-effectiveness, patient values and preferences, applicability, feasibility, appropriateness, equity, and resources in their decision-making.

The direction and strength of each recommendation were determined by a formal consensus method. Recommendations were taken to reach a consensus when 75% or more of the voters agreed on the proposed recommendation. If a consensus was not reached initially, two further rounds of voting were allowed. A modified Delphi methodology was planned in case no consensus was reached during the *en banc* meetings. On the rare occasion that no consensus is reached, no recommendation would be indicated in the final CPG manuscript. After the *en banc*, the full paper was submitted to the central committee for review.

In general, a strong recommendation means that the CP is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, while a weak recommendation means that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the CP is not confident (Table 1).

**Dissemination and Implementation**

All recommendations and evidence summaries were posted in a web-based application (<https://phex.ph>). The SC discussed with relevant stakeholders, such as DOH and

PhilHealth, to prepare a dissemination plan that will actively promote the adoption of this guideline with strategies for copyrights.

A full copy of this document was sent to the DOH for transmittal and publication. The Disease Prevention and Control Bureau will transmit copies of this CPG to PHIC, health maintenance organizations, and nongovernment organizations involved in periodic health examination. The recommendations and the evidence summaries will also be posted in the different medical societies involved in the CP, such as the Philippine Academy of Family Physicians, Philippine College of Physicians, Philippine College of Endocrinology, Diabetes, and Metabolism, and Philippine Society of Nephrology. The recommendations in this CPG will be updated after three years or until new evidence arises.

### External Review

Three independent stakeholders (a nephrologist, an endocrinologist, and a medical nutritionist) reviewed the draft guidelines on the content, clarity, acceptability, applicability, and feasibility of the recommendations. Their feedback was taken into consideration by the steering committee before finalizing the CPG.

## RESULTS

A total of 18 recommendations were made by the CP, as enumerated in Table 2.

**Recommendation 1.1. Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest AGAINST routine screening for high climacteric syndrome using follicle-stimulating hormone (FSH).** (*Low certainty of evidence, weak recommendation*)

**Recommendation 1.2. Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest AGAINST routine screening for high climacteric syndrome using luteinizing hormone (LH).** (*Low certainty of evidence, weak recommendation*)

**Recommendation 1.3. Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest AGAINST routine screening for high climacteric syndrome using estradiol.** (*Low certainty of evidence, weak recommendation*)

**Key findings:** There were no studies that evaluated screening using symptoms and hormonal tests such as LH, FSH, and estradiol for climacteric syndrome versus no screening among apparently healthy, asymptomatic women. Instead, the evidence summary consisted of one randomized controlled study that evaluated the effect of treatment of menopause, and four cross-sectional studies on the diagnostic accuracy of hormonal tests (FSH, LH, estradiol).

One randomized controlled trial (RCT) evaluated the effects of hormone therapy (HT) compared to placebo in postmenopausal women.<sup>23</sup> The study included 27,347 postmenopausal women aged 50–79 years. There was no significant difference in overall mortality (hazards ratio [HR] 0.99, 95% confidence interval [CI] [0.99, 1.08]) and CV mortality (HR 0.97, 95% CI [0.82, 1.14]). However, there was a trend towards harm for the risk of coronary heart disease (HR 1.04, 95% CI [0.89, 1.23]) and stroke (HR 1.16, 95% CI [1.00, 1.35]) with low certainty of evidence due to its indirectness.<sup>23,24</sup>

Based on four studies, the sensitivity of the FSH test to diagnose menopause ranged from 67.4% to 99.1%, while its specificity ranged from 70.6% to 97%.<sup>25–28</sup> In one study, FSH had high intraclass correlation coefficient (ICC; 0.70, 95% CI [0.55, 0.82]) in postmenopausal women but low ICC for premenopausal women (0.09, 95% CI [0, 0.54]), suggesting that a single measurement is sufficient to characterize serum FSH level in postmenopausal women but not in premenopausal women.<sup>25</sup> Based on one study, LH had a sensitivity of 98.2% and specificity of 97% in diagnosing menopause, while estradiol had a sensitivity of 83.8% and specificity of 97%.<sup>26</sup>

There are no available studies on the cost-effectiveness of screening for high-risk climacteric syndrome versus no screening in healthy, asymptomatic women. A cost-effectiveness model was developed to evaluate outcomes associated with hormone therapy in younger and older postmenopausal women aged 50–65 years old. HT for 5–30 years in younger postmenopausal women was found to be cost-effective compared with no treatment (incremental cost of \$2,438 per QALY gained). However, hormone therapy in later years results in a loss of QALY for several years before a net gain can be achieved (a net gain of 0.11 QALYs with a cost of \$27,953 per QALY gained with a loss of QALYs in the first 9 years).<sup>29</sup>

**Justification:** The CP considered that there were no studies that evaluated the effect of screening using serum FSH, LH, and estradiol for high climacteric syndrome. Routine use of hormonal tests for high climacteric syndrome was deemed by the CP to not significantly alter the management of the disease. Treatment of high climacteric syndrome did not result in significant benefit in overall and CV mortality, with possible harm for coronary heart disease and stroke.

**Recommendation 2.1. Among apparently healthy, asymptomatic adults, we recommend AGAINST routine screening for hypocalcemia or hypercalcemia using serum calcium.** (*Low certainty of evidence, strong recommendation*)

**Recommendation 2.2. Among apparently healthy, asymptomatic adults, we recommend AGAINST routine screening for hypocalcemia or hypercalcemia using an electrocardiogram (ECG).** (*Low certainty of evidence, strong recommendation*)

**Table 2.** Summary of Recommendations for Renal, Metabolic, Nutritional, and Endocrine Disorders

| Recommendation  | Certainty of Evidence | Strength of Panel Recommendation |
|---|-----------------------|----------------------------------|
| <b>Question 1. Should screening for high-risk climacteric syndrome be done among apparently healthy, asymptomatic women?</b>  |                       |                                  |
| 1.1. Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest AGAINST routine screening for high climacteric syndrome using follicle-stimulating hormone (FSH).   | Low                   | Weak                             |
| 1.2. Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest AGAINST routine screening for high climacteric syndrome using luteinizing hormone (LH).   | Low                   | Weak                             |
| 1.3. Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest AGAINST routine screening for high climacteric syndrome using estradiol.  | Low                   | Weak                             |
| <b>Question 2. Should screening for hypocalcemia or hypercalcemia be done among apparently healthy, asymptomatic adults?</b>  |                       |                                  |
| 2.1. Among apparently healthy, asymptomatic adults, we recommend AGAINST routine screening for hypocalcemia or hypercalcemia using serum calcium.   | Low                   | Strong                           |
| 2.2. Among apparently healthy, asymptomatic adults, we recommend AGAINST routine screening for hypocalcemia or hypercalcemia using an electrocardiogram (ECG).  | Low                   | Strong                           |
| 2.3. Among apparently healthy, asymptomatic adults, we recommend AGAINST routine screening for hypocalcemia or hypercalcemia using bone mineral density (BMD).  | Low                   | Strong                           |
| <b>Question 3. Should screening for prediabetes be done among apparently healthy, asymptomatic individuals?</b>   |                       |                                  |
| 3.1. Among apparently healthy, asymptomatic adults aged 40 years above, or younger if with risk factors*, we recommend screening for prediabetes and type 2 diabetes mellitus using fasting plasma glucose.   | Moderate              | Strong                           |
| 3.2. Among apparently healthy, asymptomatic adults aged 40 years above, or younger if with risk factors*, we suggest screening for prediabetes and type 2 diabetes mellitus using hemoglobin A <sub>1c</sub> .  | Moderate              | Weak                             |
| <b>Question 4. Should screening for chronic kidney disease be done among apparently healthy, asymptomatic adults?</b>   |                       |                                  |
| 4.1. Among apparently healthy, asymptomatic adults, we suggest AGAINST routine screening for chronic kidney disease (CKD) using estimated glomerular filtration rate (eGFR) computed with CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation. | Low                   | Weak                             |
| 4.2. Among apparently healthy, asymptomatic adults, we suggest AGAINST routine screening for CKD using urine albumin creatinine ratio (UACR) or urine albumin concentration (UAC).  | Low                   | Weak                             |
| 4.3. Among apparently healthy, asymptomatic adults, we suggest AGAINST routine screening for CKD using kidney ultrasonography.  | Low                   | Weak                             |
| <b>Question 5. Should screening for hyperuricemia be done among apparently healthy, asymptomatic individuals?</b>   |                       |                                  |
| 5. Among apparently healthy, asymptomatic adults, we recommend AGAINST routine screening for hyperuricemia using serum uric acid.   | Low                   | Strong                           |
| <b>Question 6. Should screening for malnutrition be done among apparently healthy, asymptomatic adults?</b>   |                       |                                  |
| 6.1. Among apparently healthy, asymptomatic adults, we suggest screening for central obesity using waist circumference (WC).  | Low                   | Weak                             |
| 6.2. Among apparently healthy, asymptomatic adults, we suggest screening for central obesity using the waist-hip ratio (WHR).   | Low                   | Weak                             |
| 6.3. Among apparently healthy, asymptomatic adults, we suggest AGAINST screening for malnutrition using mid-upper arm circumference.  | Low                   | Weak                             |
| 6.4. Among apparently healthy, asymptomatic adults, we recommend routine screening for obesity using body mass index (BMI).   | Low                   | Strong                           |
| <b>Question 7. Should screening for nutritional anemia be done among apparently healthy, asymptomatic adults?</b>   |                       |                                  |
| 7. Among apparently healthy, asymptomatic adults, we recommend screening for nutritional anemia using hemoglobin and red blood cell (RBC) parameters.   | Low                   | Strong                           |
| <b>Question 8. Should screening for sexual maturity be done among apparently healthy, asymptomatic adolescents?</b>   |                       |                                  |
| 8. Among asymptomatic adolescents, we suggest AGAINST routine assessment of sexual maturity using Tanner Staging.   | Low                   | Weak                             |

\* Risk factors for diabetes include history of impaired fasting glucose or impaired glucose tolerance (IGT); history of gestational diabetes mellitus or delivery of a baby weighing 8 lbs or above; polycystic ovary syndrome; overweight or obesity (BMI ≥23 kg/m<sup>2</sup>); WC ≥80 cm for women or ≥90 cm for men; WHR ≥0.85 for women or ≥1 for men; first-degree relative with type 2 diabetes mellitus; physical inactivity; hypertension (blood pressure ≥130/80 mmHg or on therapy for hypertension); diagnosis or history of any CV disease including stroke, peripheral arterial occlusive disease, or coronary artery disease; acanthosis nigricans; schizophrenia; serum high-density lipoprotein <35 mg/dL (0.9 mmol/L); and serum triglycerides >250 mg/dL (2.82 mmol/L).<sup>6,22</sup>

**Recommendation 2.3. Among apparently healthy, asymptomatic adults, we recommend AGAINST routine screening for hypocalcemia or hypercalcemia using bone mineral density (BMD).** (*Low certainty of evidence, strong recommendation*)

**Key findings:** There are no studies that evaluated the effect of screening for hypercalcemia and hypocalcemia among healthy asymptomatic adults.

A 2020 systematic review of four RCTs compared the effect of parathyroidectomy versus active surveillance in patients with mild asymptomatic hyperparathyroidism on skeletal outcomes, risk of nephrolithiasis, and quality of life. The parathyroidectomy group had higher bone mineral density (BMD) values in the lumbar spine (mean difference [MD] 3.55%, 95% CI 1.81, 5.29) and total hip (MD 3.44%, 95% CI 1.39, 5.49), but not in the femoral neck (MD 2.89%, 95% CI 0.06, 5.71) and forearm (MD 1.06%, 95% CI -1.30, 3.40). There was no significant benefit in reducing the risk of total fractures (relative risk [RR] 0.31, 95% CI 0.11, 1.10). There was an inconclusive effect on the risk of nephrolithiasis (RR 0.53, 95% CI 0.10, 2.87), and quality of life indices as measured by the Short Form (36) Health Survey (SF-36) score, except for general health (MD 0.40%, 95% CI 0.03, 0.76).<sup>30</sup> An RCT that compared parathyroidectomy with observation among patients with mild primary hyperparathyroidism showed that parathyroidectomy had inconclusive effect on mortality rate (HR 1.23, 95% CI 0.68, 2.23), time to first CV event (HR 0.81, 95% CI 0.33, 1.99), peripheral fractures (HR 0.75, 95% CI 0.37, 1.50), cerebrovascular disease (HR 0.73, 95% CI 0.20, 2.65), cancer (HR 1.78, 95% CI 0.71, 4.48) and nephrolithiasis (HR 0.34, 95% CI 0.06, 1.82) compared with observation alone.<sup>31</sup>

An RCT among 44 patients with primary hyperparathyroidism showed a significant increase in lumbar spine BMD (mean difference [MD] 0.04 g/cm<sup>2</sup>, 95% CI 0.02, 0.06) and total hip BMD (MD 0.03 g/cm<sup>2</sup>, 95% CI 0.01, 0.05) after 12 months among those given alendronate compared to placebo. No significant difference was found in the distal third of radius BMD (MD 0.004 g/cm<sup>2</sup>, 95% CI -0.02, 0.03) and femoral neck BMD (MD 0.014 g/cm<sup>2</sup>, 95% CI -0.01, 0.04) at 12 months. Among patients given alendronate, there was a significant reduction in bone turnover markers such as urinary N-telopeptide excretion (NTX) at 3 months (MD -60.27 nmol BCE/mmol Cr, *p* <0.001) and bone-specific alkaline phosphatase (BSAP) at six months (MD -15.98 µg/L, *p* <0.001), compared to baseline. NTX and BSAP remained elevated up to 12 months in the placebo group compared with baseline. No fracture was observed in the two groups.<sup>32</sup>

There were no diagnostic accuracy studies on the use of serum calcium among healthy, asymptomatic adults. One study evaluated the validity of unadjusted serum calcium and serum calcium adjusted for albumin (Payne equation) among hospitalized adult patients using ionized calcium as a reference standard. Unadjusted calcium was specific for both

hypocalcemia (specificity [Sp] 91.6%, 95% CI 88.0, 94.3%) and hypercalcemia (Sp 95.4%, 95% CI 93.4, 97.0%) but was not sensitive for either hypocalcemia (sensitivity [Sn] 60.7%, 95% CI 55.3, 65.9%) or hypercalcemia (Sn 68.6%, 95% CI 57.7, 78.2%). Payne corrected calcium was sensitive (Sn 95.4%, 95% CI 88.5, 98.7%) but not specific (Sp 75.5%, 95% CI 71.8, 78.9%) for hypercalcemia. Payne corrected calcium was specific (Sp 99.4%, 95% CI 97.8, 99.9%) but not sensitive (Sn 19.9%, 95% CI 15.9, 24.6%) for hypocalcemia.<sup>33</sup>

A study evaluated the use of a 24-hour ECG as screening for primary hyperparathyroidism. The authors reported no significant differences in average QT interval between patients with primary hyperparathyroidism compared with healthy controls (based on a scatterplot). The authors concluded that a 24-hour outpatient ECG is not suitable for primary hyperparathyroidism screening.<sup>34</sup>

There were no studies on the use of bone mineral density for screening for hypocalcemia or hypercalcemia. There are no studies on the cost-effectiveness of screening for hypercalcemia or hypocalcemia among healthy, asymptomatic adults.

**Justification:** The CP made a strong recommendation AGAINST the use of serum calcium, electrocardiogram, and bone mineral density in screening for hypocalcemia or hypercalcemia due to the absence of evidence. The prevalence of hypercalcemia in the emergency department is 0.6%, and its overall prevalence is 1/1000 in the general population.<sup>4</sup> There is a paucity of data on the prevalence of hypocalcemia in the general population, but it is commonly observed in institutionalized patients.<sup>35</sup> There were no studies that involved the use of serum calcium, electrocardiogram, or bone mineral density testing as routine screening tests for asymptomatic adults.

**Recommendation 3.1. Among apparently healthy adults aged 40 years above, or younger if with risk factors\*, we recommend screening for prediabetes and type 2 diabetes mellitus using fasting plasma glucose (FPG).** (*Moderate certainty of evidence, strong recommendation*)

**Recommendation 3.2. Among apparently healthy adults aged 40 years above, or younger if with risk factors\*, we suggest screening for prediabetes and type 2 diabetes mellitus using hemoglobin A<sub>1C</sub> (HbA<sub>1C</sub>).** (*Moderate certainty of evidence, weak recommendation*)

\* Risk factors for diabetes include history of impaired fasting glucose or impaired glucose tolerance (IGT); history of gestational diabetes mellitus or delivery of a baby weighing 8 lbs or above; polycystic ovary syndrome; overweight or obesity (BMI ≥23 kg/m<sup>2</sup>); WC ≥80 cm for women or ≥90 cm for men; WHR ≥0.85 for women or ≥1 for men; first-degree relative with type 2 diabetes mellitus (T2DM); physical inactivity; hypertension (blood pressure ≥130/80 mmHg or on therapy for hypertension); diagnosis or history of any cardiovascular disease including stroke, peripheral arterial occlusive disease, or coronary artery disease; acanthosis nigricans; schizophrenia; serum high-density lipoprotein <35 mg/dL (0.9 mmol/L); and serum triglycerides >250 mg/dL (2.82 mmol/L).<sup>6,22</sup>

**Key findings:** No direct studies investigated the effect of screening for prediabetes on all-cause mortality, CV mortality, and microvascular complications.

A meta-analysis of 38 RCTs assessed the effect of behavioral and pharmacologic interventions for prediabetes. Pooled results showed that lifestyle interventions decreased the incidence of diabetes compared to no intervention (RR 0.78, 95% CI 0.69, 0.88). Pharmacologic interventions, including metformin,  $\alpha$ -glucosidase inhibitors, and thiazolidinedione significantly reduced the progression to diabetes compared to usual care or no intervention (metformin: RR 0.73, 95% CI 0.64, 0.83;  $\alpha$ -glucosidase inhibitors: RR 0.64, 95% CI 0.43, 0.96; thiazolidinediones: RR 0.50, 95% CI 0.28, 0.92). The authors reported no significant difference in the risk of hypoglycemia with the use of pharmacologic interventions for prediabetes (no pooled estimates provided). There was an increased risk for adverse gastrointestinal symptoms among persons who took metformin (RR 2.56, 95% CI 2.24, 2.91). Higher rates of musculoskeletal symptoms were reported in the lifestyle intervention group compared to the no intervention group (RR 1.15, 95% CI 0.96, 1.15,  $p < 0.02$ ).<sup>36</sup>

One systematic review evaluated the diagnostic accuracy of FPG and HbA<sub>1c</sub> using the oral glucose tolerance test (OGTT) as a reference standard. HbA<sub>1c</sub> had a pooled sensitivity of 49% (95% CI 40, 58%) and specificity of 79% (95% CI 73, 84%). FPG had a pooled sensitivity of 25% (95% CI 19, 32%) and specificity of 94% (95% CI 92%, 96%). The study concluded that HbA<sub>1c</sub> is neither sensitive nor specific for detecting prediabetes, while FPG is specific but not sensitive.<sup>37</sup>

Screening for both IGT and diabetes is cost-effective. Targeted screening of high-risk groups is more cost-effective than universal screening.<sup>38</sup> A 2014 cost-effectiveness simulation study has postulated avoidance of about \$124,600 and \$91,200 in lifetime medical expenditures if a new case of diabetes is prevented at age 40 and age 50 years, respectively.<sup>39</sup>

**Justification:** Prediabetes is an intermediate state of hyperglycemia between normal glucose tolerance and diabetes and is present in 27.7% of Filipino adults.<sup>14,40</sup> Evidence has been linked already to prediabetes as a major risk factor for the early development of nephropathy, neuropathy, retinopathy, and macrovascular disease.<sup>6-8</sup> Prediabetes is a strong risk factor in the development of diabetes, and can be addressed by both pharmacologic and lifestyle interventions. The panel gave a strong recommendation for FPG for prediabetes and T2DM due to the high prevalence of prediabetes in the general population and greater availability of FPG compared to HbA<sub>1c</sub>. HbA<sub>1c</sub> should only be done in laboratories certified by the National Glycohemoglobin Standardization Program; thus, the CP provided a weak recommendation for HbA<sub>1c</sub> due to the lack of standardization in many laboratories. The use of the 2-hour 75 g OGTT may be useful in individuals with high CV risk or prior diagnosis of prediabetes, but it is cumbersome and is not appropriate for apparently healthy adults without risk factors. Targeted

screening for prediabetes and T2DM for people with risk factors is cost-effective.

**Recommendation 4.1. Among apparently healthy, asymptomatic adults, we suggest AGAINST routine screening for chronic kidney disease (CKD) using estimated glomerular filtration rate (eGFR) computed with CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation.** (*Low certainty of evidence, weak recommendation*)

**Recommendation 4.2. Among apparently healthy, asymptomatic adults, we suggest AGAINST routine screening for CKD using urine albumin-creatinine ratio (UACR) or urine albumin concentration (UAC).** (*Low certainty of evidence, weak recommendation*)

**Recommendation 4.3. Among apparently healthy, asymptomatic adults, we suggest AGAINST routine screening for CKD using kidney ultrasonography.** (*Low certainty of evidence, weak recommendation*)

**Key findings:** A systematic review evaluated the diagnostic accuracy of UAC and UACR on screening for microalbuminuria in the general population. Across six studies, UAC had sensitivity values ranging from 28% to 87% and specificity values ranging from 75% to 96%, whereas ACR had sensitivity values ranging from 73% to 90% and specificity values ranging from 77% to 96%. These results were not pooled due to differences in discriminant values of UAC and UACR. There were no harms reported in the studies.<sup>41</sup> Another systematic review of two observational studies showed that the pooled sensitivity of the UAC  $\geq 20$  mg/dL in diagnosing CKD was 49% (95% CI 45, 53%), and the pooled specificity was 96% (95% CI 95, 96%).<sup>42</sup> No diagnostic accuracy studies on renal ultrasonography as a screening test for CKD in asymptomatic, apparently healthy individuals were found.

Potential harms from screening include anxiety from a positive test, the loss of income from days spent undergoing further work-up and monitoring, delays in receiving treatment after a positive result, and false assurance about health status from false negative results.<sup>42</sup>

An RCT showed that screening the general population for microalbuminuria using UAC and treating albuminuric subjects with angiotensin-converting enzyme (ACE) inhibitors did not lead to a significant reduction in the risk of CV events (RR 0.61, 95% CI 0.34, 1.10).<sup>43</sup>

A systematic review reported that population-based screening for CKD was not cost-effective. Screening the general population using microalbuminuria was not cost-effective unless performed in high-risk groups or at infrequent intervals.<sup>44-47</sup> These high-risk groups include people with diabetes, hypertension, or advanced age. No cost-effectiveness studies that included kidney ultrasound to screen for CKD were found.

**Justification:** The CP recommended AGAINST the use of eGFR, UACR, UAC, and kidney ultrasonography in screening for kidney disease due to a lack of conclusive evidence on its benefit. Routine screening for CKD with eGFR computation, UACR or UAC, and kidney ultrasonography is not advised in the absence of risk factors.

The eGFR computed using the CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation has been validated in Filipinos. Other equations use creatinine in combination with cystatin C or creatinine alone, but cystatin C is not readily available in the Philippines. The equation is not meant to be used if acute kidney injury is suspected. Primary care providers are advised to compute the eGFR in the outpatient setting and not interpret creatinine results independently. UACR is more widely available than UAC and is more convenient for patients since only a spot sample is submitted.

**Recommendation 5. Among apparently healthy, asymptomatic adults, we recommend AGAINST routine screening for hyperuricemia using serum uric acid.** (*Low certainty of evidence, strong recommendation*)

**Key findings:** There were no direct studies that investigated the benefits of screening for hyperuricemia using serum uric acid.

An open-label trial evaluated the effect of allopurinol compared to placebo among asymptomatic participants with hyperuricemia and no known comorbidities. After 16 weeks, the allopurinol group had significantly decreased serum uric acid levels (MD  $-1.40$  mg/dL, 95% CI  $-2.01, -0.79$ ) compared to the control group. No significant differences were found in eGFR (MD  $5.20$  mL/min/1.73 m<sup>2</sup>, 95% CI  $-1.72, 12.2$ ), systolic blood pressure (MD  $0.10$  mmHg, 95% CI  $-5.16, 5.39$ ), and diastolic blood pressure (MD  $1.00$  mmHg, 95% CI  $-5.30, 7.30$ ) between the two groups.<sup>48</sup>

Twelve RCTs evaluated the safety of urate-lowering therapies (ULT) among individuals with asymptomatic hyperuricemia. The studies included a total of 2,448 patients. There was inconclusive effect on the risk of elevated liver function tests (RR  $1.29$ , 95% CI  $0.71, 2.33$ ), gastrointestinal symptoms (RR  $1.23$ , 95% CI  $0.97, 1.57$ ), worsening kidney function (RR  $0.74$ , 95% CI  $0.43, 1.29$ ), cardiovascular events (RR  $0.87$ , 95% CI  $0.68, 1.12$ ), stroke (RR  $0.51$ , 95% CI  $0.16, 1.68$ ), death (RR  $0.97$ , 95% CI  $0.64, 1.47$ ), and dermatologic symptoms (RR  $1.04$ , 95% CI  $0.66, 1.62$ ) among asymptomatic hyperuricemic patients given allopurinol or febuxostat compared to no intervention.<sup>49-60</sup>

There were no local cost-effectiveness studies in screening for hyperuricemia among asymptomatic healthy individuals.

**Justification:** The CP gave a strong recommendation AGAINST routine screening for hyperuricemia due to the absence of causality between serum uric acid levels and clinical outcomes.

**Recommendation 6.1. Among apparently healthy, asymptomatic adults, we suggest screening for central obesity using waist circumference (WC).** (*Low certainty of evidence, weak recommendation*)

**Recommendation 6.2. Among apparently healthy, asymptomatic adults, we suggest screening for central obesity using the waist-hip ratio (WHR).** (*Low certainty of evidence, weak recommendation*)

**Recommendation 6.3. Among apparently healthy, asymptomatic adults, we suggest AGAINST screening for malnutrition using mid-upper arm circumference (MUAC).** (*Low certainty of evidence, weak recommendation*)

**Recommendation 6.4. Among apparently healthy, asymptomatic adults, we recommend routine screening for obesity using body mass index (BMI).** (*Low certainty of evidence, strong recommendation*)

**Key findings:** There were no studies that evaluated the effect of screening with anthropometric measures compared to no screening on all-cause mortality, CV mortality, myocardial infarction, quality of life, diabetes, or hypertension.

The association of various anthropometric indices with clinical outcomes was evaluated in four studies.<sup>61-64</sup> All-cause mortality was significantly associated with WC and WHR (every 10-cm increase in WC: HR  $1.11$ , 95% CI  $1.08, 1.13$ ; every 0.1 increase in WHR: HR  $1.2$ , 95% CI  $1.15, 1.25$ ).<sup>61</sup> High WHR significantly increased CV mortality risk despite having a normal weight (men: HR  $1.78$ , 95% CI  $1.23, 2.57$ ; women: HR  $2.25$ , 95% CI  $1.66, 3.05$ ).<sup>62</sup>

High WC was also associated with the risk of developing T2DM, and is the most crucial anthropometric measure to predict T2DM.<sup>63,64</sup> Every 10-cm increase in WC was associated with 61.0% higher risk for diabetes (RR  $1.61$ , 95% CI  $1.52, 1.70$ ), and showed a strong and linear association between higher WC and diabetes. Meanwhile, each 0.1 unit increase in WHR was associated with 63.0% higher risk for T2DM (RR  $1.63$ , 95% CI  $1.50, 1.78$ ). High BMI was associated with a higher risk of developing T2DM. For every 5 kg/m<sup>2</sup> increase in the BMI, the risk of having diabetes was increased by 72% (RR  $1.72$ , 95% CI  $1.65, 1.81$ ).<sup>63</sup>

For MUAC, an individual participant data meta-analysis (IPDMA) of 20 datasets of 13,835 adults reported a pooled sensitivity of 84.1% (95% CI [74%, 91%]) and a pooled specificity of 83.2% (95% CI 72, 91%) in identifying underweight individuals. The population included in these studies was people living with human immunodeficiency virus or tuberculosis, low-resource and development settings, and individuals at risk of undernutrition.<sup>65</sup>

No evidence was available on the cost-effectiveness of malnutrition screening, although the impact of obesity in the Philippine economy was huge and costly.

**Justification:** The CP considered that in the Philippines, the prevalence of overweight and obesity among adults increased more than two-fold since 1993.<sup>14</sup> BMI was deemed a simple screening tool, feasible in primary care settings, and accepted as a standard for assessing nutritional status among adults globally using only two simple metrics: weight and height. WC is measured to provide an indicator of intra-abdominal adipose tissue, whereas WHR is determined for fat distribution, both of which may not be captured with BMI alone. Increased WC, WHR, and BMI are associated with increased all-cause and cardiovascular mortality and the development of T2DM. Although the evidence presented shows the outcomes for BMI as a continuous variable, the CP adapts the recommendation in PHEX1 in using the Asia-Pacific classification as more appropriate for the local setting, with obesity being classified as a BMI of 25 kg/m<sup>2</sup> or higher.

**Recommendation 7. Among apparently healthy, asymptomatic adults, we recommend screening for nutritional anemia using hemoglobin and red blood cell (RBC) parameters.** (*Low certainty of evidence, strong recommendation*)

**Key findings:** Four observational cohort studies with a total of 1,779,861 participants, one small RCT with 45 participants in a repeated measures design, and one meta-analysis including 102 studies were retrieved.<sup>66–70</sup>

Two cohort studies showed that treatment of anemia reduced all-cause mortality compared to no treatment (young women: HR 0.81, 95% CI [0.69, 0.94]; men: adjusted HR 0.67, 95% CI [0.59, 0.77]). There was an inconclusive effect on the risk of mortality due to acute myocardial infarction (young women: HR 0.92, 95% CI [0.59, 1.44]; men: 0.71, 95% CI [0.35, 1.42]) and risk of CV mortality (adjusted HR 0.75, 95% CI [0.52, 1.07]).<sup>66,67</sup>

In terms of harm, one cohort study reported that the use of more than five blood collection tubes for phlebotomy was associated with a higher risk of vasovagal syncope compared to five tubes or less (odds ratio [OR] 8.10, 95% CI 3.76, 17.5).<sup>68</sup> After 8 weeks of treatment of iron deficiency anemia with parenteral iron, there is a decrease in white blood cell (WBC) count (MD  $-1.2 \times 10^9/L$ , 95% CI  $-1.24, -1.16$ ) compared with baseline.<sup>69</sup>

A meta-analysis of 102 studies reported that the M/H ratio, calculated as the percentage of microcytic RBCs divided by the percentage of hypochromic RBCs, had a sensitivity of 92% (95% CI 87, 98%) and a specificity of 86% (95% CI 81, 91%) in differentiating iron deficiency anemia (IDA) from thalassemia. This index showed the highest sensitivity and specificity among 11 other RBC indices in the meta-analysis.<sup>70</sup>

**Justification:** Although the certainty of evidence is low, the CP recommended screening for nutritional anemia because of the high prevalence of anemia, especially in women and in the elderly. The Expanded National Nutrition Survey 2019 results showed that the prevalence of anemia among

adults aged 20–59 years old in the Philippines has decreased (7.2%). However, anemia continues to be a burden for women and the elderly, with prevalence in the elderly at 16.9%, and in women (10.0%), being double that of men (4.3%).<sup>14</sup> A 2018 study conducted by the Food and Nutrition Research Institute found that iron-deficiency was still the most prevalent cause of anemia in the National Capital Region (NCR), affecting up to 37.6% of anemic individuals studied.<sup>15</sup>

The evidence included women 20–39 years old and men younger than 60 years, but the CP still recommended the use of hemoglobin and red blood cell (RBC) parameters, given the prevalence of anemia among Filipinos and the benefit of micronutrient supplementation. Only hemoglobin and RBC parameters are needed in screening for anemia. These tests are often part of a complete blood count (CBC) in most laboratories. Screening for nutritional anemia is cost-effective, equitable, feasible, and acceptable. The recommendation is applicable for screening for nutritional anemia only, and excludes other causes of anemia, such as anemia from blood loss, anemia of inflammation, hemoglobinopathies, and other genetic causes of anemia.

**Recommendation 8. Among apparently healthy, asymptomatic adolescents, we suggest AGAINST routine assessment of sexual maturity using Tanner staging.** (*Low certainty of evidence, weak recommendation*)

**Key findings:** There were no studies that compared routine assessment of sexual maturity to no assessment on relevant clinical outcomes. A cohort study in Japan investigated the association between pubertal timing or the timing of the development of secondary sexual characteristics and health outcomes. Male children who developed secondary sex characteristics early (age 9–10 years) are more likely to have poor quality of life (adjusted OR 5.96, 95% CI [1.89, 18.86]), poorer sleep quality (adjusted OR 3.76, 95% CI [1.31, 10.82]), and poorer over-all health (adjusted OR 2.85, 95% CI [1.05, 7.77]), compared to those who develop secondary sex characteristics at age 12–13 years. Female children who develop secondary sexual characteristics at a younger age were more likely to experience mental health difficulties (adjusted OR 1.54, 95% CI [1.02, 2.33] for 9–10 years; adjusted OR 1.55, 95% CI [1.22, 1.97] for 10–11 years; adjusted OR 1.31, 95% CI [1.06, 1.62] for 11–12 years), poorer overall health (adjusted OR 1.50, 95% CI [1.02, 2.19]), compared to those who develop secondary sex characteristics at age 12–13 years.<sup>16</sup>

A 2020 cross-sectional study in Brazil explored the association between body adiposity and stages of pubertal development. Children were grouped according to their pubertal development stage. A higher adjusted prevalence ratio (aPR) for central obesity or WC was observed in both males (aPR 2.21, 95% CI [1.12, 4.35]) and females (aPR 2.18, 95% CI [1.04, 4.57]) with early pubertal development stages compared to those with normal pubertal development stages.<sup>71</sup>

There were no studies that compared Tanner staging to other tests for sexual maturity. There were no cost-effectiveness studies on the use of Tanner staging for assessment of sexual maturity among asymptomatic adolescents found in this search.

**Justification:** The CP voted AGAINST routine assessment for sexual maturity using Tanner staging due to lack of evidence. A disadvantage of routine Tanner staging is the discomfort associated with undressing. There were no studies to make judgments upon for the certainty of evidence on cost and for the cost-effectiveness of Tanner staging.

## DISCUSSION

The recommendations in this CPG apply to patients who are asymptomatic and apparently healthy, which can be ascertained after a thorough clinical history and physical examination. The screening recommendations are not applicable to patients who have risk factors, are symptomatic, or have abnormal physical findings.

This CPG recommends AGAINST screening for high climacteric syndrome among asymptomatic, apparently healthy women aged 45–55 years using hormonal tests. Moreover, the guideline DOES NOT recommend the use of serum calcium, ECG, or bone mineral density in screening for hypocalcemia or hypercalcemia; eGFR, UAC, UACR, and kidney ultrasonography in screening for chronic kidney disease; MUAC in screening for malnutrition; and serum uric acid in screening for hyperuricemia in apparently healthy, asymptomatic adults. Routine assessment for sexual maturity among asymptomatic adolescents is also NOT recommended. However, the CPG recommends using FPG and HbA<sub>1C</sub> in screening for prediabetes and type 2 diabetes mellitus; WC, WHR, and BMI in screening for malnutrition; and hemoglobin and RBC parameters in screening for nutritional anemia.

In rural areas, tests for screening may not be readily available. The CP considered accessibility to and the costs of these tests. For example, FPG was strongly recommended for screening for prediabetes due to widespread availability in the country, in contrast to the weak recommendation using HbA<sub>1C</sub> due to the lack of standardization of this test in many laboratories. BMI was also given a strong recommendation despite low certainty of evidence due to the ease of measuring in the clinic setting. Other tests, such as the eGFR and serum uric acid, were not recommended due to a lack of benefit in the asymptomatic and apparently healthy population. The search for risk factors through a detailed history is more appropriate in these cases.

### Limitations

The PHEX Task weighed the available evidence using equity and applicability lenses. Comprehensive history taking, physical examination, and monitoring are essential parts of evaluating risk factors and the probability of developing

diseases. This CPG does not necessarily supersede the consumers' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances.

Although this CPG intends to influence the direction of health policies for the general population, it should not be the sole basis for recreating or abolishing practices that aim to improve the health conditions of many Filipinos, particularly those part of the workforce.

### Research Gaps

Many research questions from the identified clinical questions in this CPG were unanswered in terms of benefits and harms of screening, equity, applicability, and feasibility. Direct evidence was lacking to aid in providing definite recommendations for screening certain conditions using the tests. As recommended by the CP, most of the screening tools in this guideline deal with taking the appropriate history and physical examination, such as vasomotor symptoms in menopause, risk factors and physical findings for hypocalcemia or hypercalcemia, risk factors for chronic kidney disease, history of gout or nephrolithiasis for hyperuricemia, and evaluating for differences in timing of sexual maturity. There is limited data on these tests.

Generating direct evidence on the effect of screening versus no screening may be difficult. Because of this challenge, we considered the diagnostic performance of tests as indirect evidence. However, the accuracy of some tests in detecting early diseases and their role in preventing the development of chronic or more severe conditions is still not investigated.

There were some cost-effectiveness studies available for screening certain disease conditions in this CPG, but most of them were conducted in Western countries. In some conditions, such as in prediabetes and obesity, there is an abundance of international data that may be applied locally.

Social science research also plays a vital role in examining the impact of diseases. However, few qualitative studies were found to provide a holistic view of the impact of screening for some conditions. Qualitative studies can also provide information on motivators or determinants among the general population in participating in a screening program despite the probable harm of stigma and mislabeling afterward.

Examining needs and monitoring implementation of screening programs were also found to be not well-established, even if, in some conditions, guidelines and programs are already in place. Perspectives and experiences of clinical practitioners and other stakeholders directly involved in screening programs were rarely reported in studies.

Many research questions emerged from collating the evidence for this CPG and can be explored further. Filling in these gaps can provide a clearer picture of the impact of screening programs using the previously mentioned tests and may influence the recommendations in the update of this CPG.

## CONCLUSIONS

This CPG addressed selected renal, metabolic, nutritional, and endocrine conditions and provided recommendations for their screening. The statements guide the primary care physicians in the screening of identified renal, metabolic, nutritional, and endocrine disorders and influence the direction of health policies for the general population. However, this should not be the sole basis for recreating or abolishing practices to improve the health conditions of many Filipinos. Clinicians must always exercise sound clinical judgment, taking into consideration the individual patient's history and current physical examination in the management of the condition.

## Disclaimer

This guideline is intended to be used by general practitioners, specialists, and health professionals who are primary care providers. Although adherence to this guideline is encouraged, it should not restrict the primary care providers from using their sound clinical judgment in handling individual cases. Payors and policymakers, including hospital administrators and employers, can also utilize this clinical practice guideline (CPG), but this document should not be the sole basis for evaluating insurance claims. Recommendations from the Periodic Health Examination (PHEX) app and the guidelines therein should also not be treated as strict rules on which to base legal action.

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All authors certified fulfillment of ICMJE authorship criteria.

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## APPENDIX

### List of Critical and Important Outcomes

| Outcomes   | Score priority | Rank      |
|--|----------------|-----------|
| <i>All-cause mortality</i>   | 9              | Critical  |
| <i>Cardiovascular mortality</i>  | 9              | Critical  |
| <i>Fatal and non-fatal myocardial infarction</i>   | 9              | Critical  |
| <i>Stroke or cerebrovascular disease</i>   | 9              | Critical  |
| <i>Chronic stable angina</i>   | 7              | Important |
| <i>Coronary revascularization</i>  | 7              | Important |
| <i>End-stage renal disease</i>   | 7              | Important |
| <i>Major adverse cardiovascular event</i>  | 7              | Important |
| <i>Unstable angina</i>   | 7              | Important |
| <i>Carotid or cerebrovascular revascularization</i>  | 6              | Important |
| <i>Heart failure</i>   | 6              | Important |
| <i>Peripheral arterial revascularization</i>   | 6              | Important |
| <i>Proteinuria</i>   | 6              | Important |
| <i>Repair of aneurysm</i>  | 6              | Important |
| <i>Reduction of laboratory parameters (e.g., low-density lipoprotein, troponin, brain natriuretic peptide)</i> | 5              | Important |
| <i>Symptom reduction</i>   | 4              | Important |