Philippine Clinical Practice Guidelines for Periodic Health Examination: Screening for Prenatal Disorders

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A full copy of the Philippine Clinical Practice Guidelines for Periodic Health Examination: Screening for Prenatal Disorders can be found at this link: https://drive.google.com/file/d/1h2O1Tt5HKZeC7KVGY4wviBZbkzHi4uiD/view

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ABSTRACT

Background. The Philippine Guidelines on Periodic Health Examination (PHEX) support the Universal Health Care Act by providing guidance on quality, accessible, and affordable screening services for Filipinos. Conditions that develop in the prenatal period are a major cause of neonatal deaths in the Philippines and account for 14% of deaths in children under five.

Objectives. This guideline aims to provide evidence-based recommendations for screening prenatal disorders among asymptomatic, pregnant Filipino women. It also aims to equip general practitioners, obstetrics-gynecology specialists, allied health professionals, patients, policymakers, regulatory agencies, and healthcare institutions with tools and guidance that

facilitate informed, evidence-based healthcare decisions for pregnant women.

Methods. The development of this CPG followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to CPG development recommended in the Department of Health (DOH) Manual. Recommendations were finalized using the Evidence-to-Decision (EtD) framework. Evidence Review Experts conducted a systematic literature search and critically appraised recent local and international clinical guidelines. When necessary, they conducted *de novo* systematic reviews. Information on the benefits and harms of screening, cost-effectiveness, patient values and preferences, acceptability, feasibility, and its impact on equity was obtained. A multisectoral consensus panel reviewed the evidence and developed recommendations. A user-friendly web application and engagement with stakeholders for promotion and implementation were among the dissemination strategies. Experts conducted an external review to provide feedback on the methodology and recommendations.

Results. Eleven recommendations for different screening strategies to improve the health outcomes of pregnant women and neonates were developed. This CPG contains recommendations for the screening for maternal thyroid disease, gestational diabetes mellitus, group B Streptococcus infection, fetal aneuploidy, risk for pre-eclampsia, iron deficiency anemia, and undernutrition, and conducting cervical length measurements, first-trimester ultrasound, and second-trimester ultrasound.

Conclusion. This CPG provides 11 evidence-based recommendations. Applicability in the local setting was carefully considered through the involvement of different stakeholders. The recommendations herein shall hold until new evidence on screening, diagnosing, or managing various risk factors and diseases emerges, or contingencies dictate updating this CPG. This guideline will be updated after three (3) years.

Keywords:prenatal clinical practice guidelines, screening, antenatal care, maternal health, neonatal health

INTRODUCTION

The Philippine Guidelines on Periodic Health Examination (PHEX), first published in 2004, provided evidence-based recommendations for screening and early prevention services among apparently healthy Filipinos.[1] This 2023 CPG provides an update of the previous PHEX guidelines and supports the objectives of the Universal Health Care Act to ensure that all Filipinos have access to quality and affordable medical services.[2]

According to the World Health Organization (WHO), conditions that develop prenatally, which may be identified before birth, at birth, or later in life, contribute significantly to the global burden of disease. These conditions disproportionately affect low and middle-income countries.[3] In the Philippines, they are among the top 5 causes of neonatal deaths and account for 14% of deaths among children under 5 years old.[4]

Early detection of these conditions may reduce the burden of disease caused by prenatal disorders among Filipino mothers, their infants, and their families. This guideline aims to provide evidence-based recommendations for the asymptomatic, pregnant Filipino woman without modifiable risk factors for the disease condition.

METHODS

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to CPG development recommended in the Department of Health (DOH) Manual on Practice Guideline Development was used. The Evidence-to-Decision (EtD) framework was utilized in finalizing the recommendations.[5]

Preparation

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

Management of Conflicts of Interest

All task force members submitted their declaration of conflict of interest (COI) and curriculum vitae. A COI committee reviewed and evaluated the potential COIs and gave its recommendations on how to manage them. In general, those with a financial COI were not allowed to vote 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 panel meeting and in the final manuscript.

Evidence Synthesis

The evidence review questions were developed using the PICO (population, intervention, comparator, and outcome) format. The questions were related to prenatal disorders, namely, thyroid disease, gestational diabetes mellitus, group B streptococcus infection, fetal aneuploidy, pre-eclampsia, iron deficiency anemia, and undernutrition among pregnant women. The CP rated the importance of all the outcomes for each clinical question on a scale of 1 to 9. Only outcomes that were rated important to critical (average scores of 4 to 9) were included in the evidence reviews.

For each question, two EREs independently conducted a systematic search of various electronic databases, such as MEDLINE via PubMed, CENTRAL, and Google Scholar. Relevant local databases and websites of local and international medical societies were also included in the search. Keywords were based on the PICO for each question, using Medical Subject Headings and free text search.

Using the AGREE-II tool, two EREs independently appraised recent local and international clinical practice guidelines.[6] The international guidelines appraised included guidelines from the U.S. Preventive Services Task Force, the National Institute for Health and Care Excellence (NICE), the WHO, the American College of Obstetricians and Gynecologists (ACOG), the Royal College of Obstetricians and Gynecologists, and the Society of Obstetricians and Gynecologists of Canada. The appraisal results of existing CPGs and their evidence summaries determined the need for conducting *de novo* systematic reviews and meta-analyses. The evidence summaries of good quality CPGs (i.e., completed in the past 5 years, with at least a 75% overall rating, and at least an 80% rating in the Rigor of Development domain) were adapted using the GRADE Adolopment approach and updated.[5]

If the search did not yield a CPG that fulfilled the eligibility criteria, *de novo* systematic reviews were conducted. Two EREs appraised the methodological quality of included studies using the AMSTAR 2 tool for systematic reviews, the Cochrane Risk of Bias tool (ROB 1.0) for randomized controlled trials (RCTs), the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic accuracy studies, and the Newcastle-Ottawa Scale (NOS) for observational studies. Disagreements were discussed and resolved by consensus or consultation with a third reviewer. Quantitative synthesis was done using RevMan or R Studio, as appropriate.

The GRADE approach was used to rate the certainty of evidence and the strength of recommendations (Table 1).

The evidence reviewers generated evidence summaries for each of the eleven (11) questions. Apart from a systematic search of evidence on the benefits and harms of particular screening strategies, the TWG searched electronic databases for studies on patients' values, preferences, and health-seeking behavior, and economic evaluation studies for the interventions of interest, and the PhilHealth website to determine existing coverage rates and policies, and availability of resources. The evidence summary contained the screening pathway for the condition of interest, evidence on the burden of the problem, benefits and harms of screening, the diagnostic performance of screening tests, and the social and economic impact of the screening test. This information was presented to the CP before and during the *en banc* meeting.

Evidence to Decision Consensus Approach

The multisectoral CP reviewed the evidence summaries and developed recommendations during the *en banc* meeting. Before the meeting, the CP finalized the list of critical and important outcomes. The critical outcomes include preterm birth, perinatal or neonatal mortality, infant mortality, maternal mortality, and other pregnancy outcomes. (https://drive.google.com/file/d/1h2O1Tt5HKZeC7KVGY4wviBZbkzHi4uiD/view)

Each CP member was also asked to complete an EtD questionnaire to explicitly incorporate important factors such as cost-effectiveness, patient values and preferences, applicability, feasibility, appropriateness, equity, and availability of resources in their decision-making.

The direction and strength of each recommendation statement were determined by a formal consensus method, with consensus achieved when 75% or more of all eligible CP voters agreed on the proposed recommendation. Should the panel fail to achieve consensus, two additional rounds of discussion and voting were held. If the *en banc* meetings failed to yield a consensus, a modified Delphi methodology was planned.

Table 1. GRADE Approach to Assessing the Certainty of Evidence and Strength of Recommendations

Certainty of Evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	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.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	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**
Strong	Advantages of the screening significantly outweigh disadvantages or disadvantages of the screening significantly outweigh advantages
Weak	Advantages of the intervention may outweigh disadvantages, disadvantages of the intervention may outweigh advantages, or the relationship between advantages is not clear

Note: Factors that lower the certainty of evidence are 1) risk of bias, 2) inconsistency, 3) indirectness relative to the PICO question, 4) high probability of reporting bias, 5) sparse data or imprecision, and 6) publication bias. Factors that may increase certainty of evidence are: 1) plausible residual confounding, if present, would reduce the observed effect, 2) dose-response gradient, and 3) large effect.

In general, a strong recommendation for the use of an intervention means the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, whereas a strong recommendation against the use of an intervention means the panel is confident that the undesirable effects outweigh the desirable effects. A weak recommendation means the panel is less confident that the beneficial effects of adhering to a recommendation are likely to outweigh the undesirable effects.

External Review

Two independent reviewers examined the CPG manuscript. Two specialists in prenatal disorders from the University of the Philippines College of Medicine evaluated the completeness and relevance of the evidence, the clarity of the whole manuscript, and the acceptability, applicability, and feasibility of the recommendations using the AGREE II tool. In response to their feedback and comments, the SC revised portions of the methodology, including the description of the GRADE methodology, certainty of evidence, strength of recommendation, and consensus discussions.

Dissemination, Implementation, Monitoring, and Updating

All recommendations and evidence summaries were posted in an accessible and user-friendly web-based and mobile application (https://phex.ph). The SC discussed a dissemination plan with strategies for copyrights with relevant stakeholders, such as DOH and PhilHealth, to actively promote the adoption of this guideline.

Aside from being published in this journal, the full-text CPG will also be published on the official websites of the participating organizations, such as the Philippine Obstetrical and Gynecological Society. The CPG will also be presented at conventions and continuing education meetings of professional societies and academic institutions. The CPG recommendations will also be discussed in health forums and disseminated through the radio, television, and social media.

The SC and DOH will develop a program of implementation and monitoring to determine the adherence and best practices of relevant stakeholders in screening for prenatal disorders. Surveys in different healthcare institutions and among healthcare workers may be given annually to monitor adherence to the recommendations and gather further information regarding the applicability and impact of the guidelines. This can also be used for implementation research.

The recommendations herein shall hold until such time that new evidence on screening, diagnosing, or managing various risk factors and diseases emerges, and contingencies dictate updating this Philippine Guidelines on Periodic Health Examination. This guideline will be updated after three (3) years.

RESULTS

Eleven (11) recommendation statements were developed in this CPG, as summarized in Table 2.

Recommendation 1. We recommend antenatal screening with TSH and/or FT4 among asymptomatic pregnant Filipino women with risk factors for thyroid disease to detect maternal hypo-/hyperthyroidism. (*Low certainty of evidence, strong recommendation*)

Risk factors for thyroid disease include family history of autoimmune thyroid disease, presence of goiter, personal history of type 1 diabetes mellitus or any autoimmune disease, history of neck irradiation, previous miscarriages or preterm deliveries, and/or signs or symptoms suggestive of thyroid dysfunction.

The timing of testing was not specified due to the possible inaccuracy of the biochemical assessment in the first trimester.

Key findings: Universal screening involves performing TSH and/or FT4 tests for all pregnant women, while risk-based screening targets those with specific high-risk features. Monitoring continues for the term, with usual care provided for those testing negative.

No studies investigated the impact of universal screening for maternal thyroid function on the occurrence of fetal congenital anomalies. Universal screening compared to risk-based screening resulted in increased detection and diagnosis of thyroid dysfunction (either hypothyroidism or hyperthyroidism) (RR 3.28, 95% CI 2.04 to 5.26).[7] Results were inconclusive when universal screening was compared with risk-based screening in reducing the risk of miscarriage (RR 0.90, 95% CI 0.48 to 1.31), neonatal respiratory distress syndrome (RR 0.79, 95% CI 0.48 to 1.31), and perinatal or neonatal death (RR 0.92, 95% CI 0.42 to 2.02).[7,8] Pregnant women in the included studies underwent blood extraction for testing TSH, FT4, and/or FT3, and TPO-Ab.[7,8]

Thyroid dysfunction during pregnancy is associated with adverse perinatal and neonatal outcomes, including spontaneous abortion, high risk for small for gestational age, and neurocognitive issues in offspring.[9-11] Treatment of maternal hypothyroidism with levothyroxine is considered safe, but the use of propylthiouracil or methimazole carries potential risks to the fetus.[12-14]

Justification: The CP considered the benefits and harms of universal screening compared to risk-based screening, as well as the timing of testing, burden of disease, and applicability issues in the current healthcare setting. The CP noted research gaps, including the prevalence of thyroid disease in pregnant women and the lack of local studies. Despite the low certainty of evidence, the CP strongly recommends screening for maternal hypothyroidism due to its significant impact on newborns and the importance of preventing and early treatment of neonatal thyroid disorders. The CP identified major issues with universal screening, including a) feasibility and resource requirements at the

primary level, and b) inaccurate thyroid function tests causing false positives or unnecessary referrals. Therefore, risk-based screening was recommended.

Recommendation 2: Among asymptomatic pregnant Filipino women, we suggest AGAINST routine measurement of cervical length during the second trimester. *(Very low certainty of evidence, weak recommendation)*

Key findings: Preterm birth, defined as delivery before 37 weeks of gestation, is a leading cause of perinatal and neonatal morbidity and mortality worldwide.[15-18] Risk factors include prior preterm birth, maternal age, multiple gestations, infections, and cervical insufficiency.[16]

Two RCTs compared screening through ultrasound cervical length measurement (low-risk singletons screened once in the second trimester using a 2.5 cm cut-off, and

Table 2. Summary of Clinical Questions and Recommendations on Prenatal Disorders

Recommendations	Certainty of Evidence	Strength of Recommendation
Question 1. Should screening for thyroid disease using biochemical tests be offered to all asymptomatic pregnant Filipino women to improve maternal and perinatal outcomes?		
1. We recommend antenatal screening with TSH and/or FT4 among asymptomatic pregnant Filipino women with risk factors[a] for thyroid disease to detect maternal hypo-/hyperthyroidism.	Low	Strong
Question 2. Should routine measurement of cervical length during the second trimester be offered to all asymptomatic pregnant Filipino women to prevent perinatal morbidity and mortality?		
2. Among asymptomatic pregnant Filipino women, we suggest AGAINST routine measurement of cervical length during the second trimester.	Very Low	Weak
Question 3. Should screening for gestational diabetes mellitus (GDM) using the oral glucose tolerance test (OGTT) be offered to all pregnant Filipino women to decrease perinatal mortality and morbidity?		
3. We suggest screening for gestational diabetes mellitus (GDM) among pregnant women using a 75-g OGTT in the second trimester (24-28 weeks).	Very Low	Weak
Question 4. Should screening for group B Streptococcus (GBS) using culture be offered to all pregnant Filipino women to improve perinatal outcomes?		
4. We suggest screening pregnant women with risk factors[b] for group B Streptococcus followed by intrapartum antibiotic prophylaxis for those who screen positive and have a planned vaginal delivery to prevent early onset neonatal GBS sepsis.	Very Low	Weak
Question 5. Should a first-trimester ultrasound be offered to all pregnant Filipino women to improve maternal and perinatal outcomes?		
5. We suggest a first-trimester ultrasound in all pregnant Filipino women.	Very Low	Weak
Question 6. Should screening for fetal aneuploidy using nuchal translucency be offered to all pregnant Filipino women in the first trimester?		
6. We suggest nuchal translucency measurement at 11-14 weeks age of gestation be offered to all pregnant Filipino women to screen for Down syndrome; and be offered to pregnant women at high risk for fetal anomaly to screen for major congenital heart disease.	Very Low	Weak
Question 7. Should a second-trimester ultrasound be offered to all pregnant Filipino women to improve maternal and perinatal outcomes?		
7. We suggest a routine second-trimester ultrasound for all pregnant Filipino women.	Low	Weak
Question 8. Should the risk for pre-eclampsia be assessed in the first trimester for all pregnant women?		
8. We suggest assessing the risk for preeclampsia in the first trimester in all pregnant women.	Very Low	Weak
Question 9. Should multimarker screening rather than maternal factors alone be used to screen for pre-eclampsia among pregnant women?		
9. We suggest using multimarker screening rather than screening for maternal risk factors alone to assess the risk for preeclampsia in the first trimester in all pregnant women.	Low	Weak
Question 10. Should screening for iron deficiency anemia using complete blood count be offered to all asymptomatic pregnant Filipino women to improve maternal and perinatal outcomes?		
10. We suggest AGAINST screening for iron deficiency anemia using complete blood count among all asymptomatic pregnant Filipino women.	Very Low	Weak
Question 11. Should screening for undernutrition via measurement of mid-upper arm circumference be offered to all pregnant Filipino women to improve maternal and perinatal outcomes?		
11. We suggest screening for undernutrition via measurement of mid-upper arm circumference in all pregnant Filipino (adolescent and adult) women.	Very Low	Weak

[a] *Risk factors for thyroid disease include family history of autoimmune thyroid disease, presence of goiter, personal history of type 1 diabetes mellitus or any autoimmune disease, history of neck irradiation, previous miscarriages or preterm deliveries, and/or signs or symptoms suggestive of thyroid dysfunction.*

[b] *Risk factors for GBS include the following: previous GBS infection, age younger than 20 years, increased parity, obesity, multiple sexual partners, and recent or frequent antibiotic use.*

high-risk twin pregnancies screened serially in the second trimester using a 3.5 cm cut-off) with no screening. There was an inconclusive effect of screening versus no screening on the risk of preterm birth (RR 1.04, 95% CI 0.67 to 1.63), neonatal deaths (RR 0.20, 95% CI 0.01 to 4.19) and neonatal respiratory distress syndrome (RR 2.03, 95% CI 0.38 to 10.90), maternal hospitalization for preterm labor (RR 1.29, 95% CI 0.75 to 2.23). There was no significant difference in gestational age in weeks between the screened and unscreened groups (MD 0.24 weeks, 95% CI -0.61 to 0.12).[19,20]

Justification: The CP considered the following in recommending AGAINST routine cervical length measurement: 1) there was an inconclusive effect of routine cervical length measurement on prevention of preterm birth, and 2) the moderate to large costs associated with routine cervical length measurement. Cervical length measurements are conducted primarily to prevent preterm birth, making preterm birth a critical outcome. There are no studies that evaluated the effect of routine screening of cervical length among pregnant women with a history of prior spontaneous preterm birth, which is currently a common practice in the Philippines. There was also an inconclusive effect of routine cervical length measurement among high-risk pregnant women, including women with twin pregnancies but without a history of prior preterm birth or cervical insufficiency. Due to the very low certainty of evidence, one CP member voted for a strong recommendation against routine cervical length measurement.

Recommendation 3: We suggest screening for gestational diabetes mellitus (GDM) among pregnant women using a 75-g OGTT in the second trimester (24-28 weeks). *(Very low certainty of evidence, weak recommendation)*

Key findings: One case-control study showed that at-risk women (defined as women of South Asian or Black Caribbean ethnicity, body mass index >30 kg/m^2, or previous pregnancy affected by GDM or macrosomia (birth weight >4.5 kg) who underwent screening for GDM were less likely to deliver stillbirths compared to those who did not undergo screening (adjusted OR 0.68, 95% CI 0.47 to 0.97).[21,22]

One cohort study reported that neonates whose mothers were screened for GDM via OGTT were more likely to experience neonatal hypoglycemia (OR 2.00, 95% CI 1.42 to 2.82) and were more likely to be admitted to the neonatal ICU compared to those delivered by women who were not screened (OR 1.55, 95% CI 1.29 to 1.86). There was inconclusive evidence on the effect of screening for GDM compared to no screening on the likelihood of birth injuries (OR 0.94, 95% CI 0.49 to 1.80).[23] Pooled results from 3 cohort studies showed that women screened for GDM were more likely to deliver neonates that were large for gestational age (LGA) compared to those who were not screened (OR 1.93, 95% CI 1.02 to 3.64).[23-25]

Another cohort study reported that pregnant women screened for GDM using OGTT were more likely to have gestational hypertension or pregnancy-induced hypertension compared to those who were not screened for GDM (OR 3.39, 95% CI 1.65 to 6.97).[25] There was inconclusive evidence on the effect of screening for GDM compared to no screening on the likelihood of preterm delivery (OR 1.22, 95% CI 0.79 to 1.88).[25]

Justification: The CP considered the contrasting effect of screening. In terms of some critical outcomes, such as stillbirth, LGA, macrosomia, and neonatal ICU admissions, may be accounted for by the study designs of the available evidence. These were retrospective observational studies with unclear methods of event tracking and reporting. There were RCTs that provided indirect evidence on the effectiveness of treatment for GDM subsequent to screening, which reported better outcomes. The screening strategies used in these trials varied and included procedures such as risk-based evaluation and OGTT.

The CP suggested the use of a 75-gram OGTT as the preferred strategy to screen for GDM in the second trimester, despite the lack of RCTs directly comparing screening to no screening and the variability in dosage and approach to screening in the available studies. This recommendation aims to establish a standardized practice and provide guidance to healthcare practitioners regarding the recommended course of action. Furthermore, the strategy currently endorsed by most international guidelines is the 1-step 75-gram OGTT procedure.

Recommendation 4: We suggest screening pregnant women with risk factors* for group B Streptococcus (GBS) followed by intrapartum antibiotic prophylaxis for those who screen positive and have a planned vaginal delivery to prevent early onset neonatal GBS sepsis.** *(Very low certainty of evidence, weak recommendation)*

* *Risk factors for GBS include the following: previous GBS infection, age younger than 20 years, increased parity, obesity, multiple sexual partners, and recent or frequent antibiotic use.*

** *Intrapartum antibiotic prophylaxis is only indicated in women who will undergo vaginal delivery.*

Key findings: Limited epidemiological studies show that the prevalence of group B Streptococcus (GBS) infection in the country is low.[26-28] A single-center study reported 2.5% positivity for GBS, while a multicenter study estimated 0.3 per 1,000 live births.[26-28] However, GBS infection leads to significant morbidity and mortality, particularly early-onset neonatal GBS sepsis. Mortality rates from early-onset neonatal GBS sepsis ranged from 2-10% in term infants and 20-30% in preterm infants.[29,30]

Pooled results from 13 cohort studies showed that universal screening for GBS is associated with reduced odds of early-onset GBS sepsis compared to risk-based screening

(OR 0.51, 95% CI 0.29 to 0.89).[31-43] Universal screening is associated with 83 fewer cases of early onset GBS sepsis per 100,000 live births compared to risk-based screening (95% CI 120 fewer to 19 fewer).[24,31-35,37-43]

There was an inconclusive effect of universal screening compared to no screening on EON-GBS mortality (OR 0.28, 95% CI 0.01 to 11.60) and GBS pneumonia (OR 0.10, 95% CI 0.01 to 1.66).[38,40,41,43] There was also an inconclusive effect on the odds of antibiotic resistance to penicillin or ampicillin between the 2 groups (OR 3.52, 95% CI 0.41 to 30.18).[32,37] There was no significant difference in the odds of preterm birth from all causes among those with universal screening compared to no screening (OR 1.05, 95% CI 0.97 to 1.16).[40]

All the available studies performed GBS screening with rectovaginal swabs. The majority were collected at 35-37 weeks age of gestation (AOG) and were compared to a risk-based screening at the time of delivery.

Justification: The CP emphasized the high risk of neonatal mortality from GBS sepsis, despite the limited epidemiologic studies reporting low prevalence of GBS locally. Screening for GBS requires a rectovaginal swab culture, which is not widely available in many hospitals or health centers. It is also expensive and necessitates trained healthcare workers to perform it. Due to accessibility and equity issues, the panel suggested screening for GBS only among women with risk factors (such as preterm labor, prolonged rupture of membranes, and history of previous GBS infection).

Recommendation 5. We suggest a first-trimester ultrasound for all pregnant Filipino women *(Very low certainty of evidence, weak recommendation)*

Key findings: One observational study among patients who underwent in vitro fertilization investigated the accuracy of ultrasound in fetal aging.[44] First-trimester ultrasound (11-14 weeks of gestation) was seen to slightly overestimate the gestational age by the following mean days: 1.3 ± 0.2 days for singletons, 1.4 ± 0.2 days for twins, and 0.8 ± 0.4 days for triplets.[44]

Evidence from RCTs showed an inconclusive effect of first-trimester ultrasound compared to no ultrasound on the detection of non-viable pregnancies (RR 0.97, 95% CI 0.52 to 1.80) and ectopic pregnancy (RR 2.74, 95% CI 0.11 to 66.51).[45,46]

Post-maturity labor induction was used as a surrogate outcome for post-term pregnancy outcomes. There was an inconclusive effect of first-trimester ultrasound compared to no ultrasound on the incidence of post-term labor induction or adverse perinatal outcomes (RR 1.13, 95% CI 0.16 to 8.08).[46,47] There was also an inconclusive effect of routine first-trimester ultrasound scan compared to selective scan on the incidence of post-term labor induction (RR 0.83, 95% CI 0.50 to 1.37).[45,47,48]

Routine first-trimester ultrasound compared to selective scan also had an inconclusive effect on fetal congenital anomaly detection (RR 3.06, 95% CI 0.12 to 74.74) and intrauterine growth restriction detection (RR 0.43, 95% CI 0.13 to 1.44).[45,48]

Justification: The CP had a thorough discussion on whether to formulate a strong or weak recommendation for a first-trimester ultrasound in all pregnant Filipino women. The main factors influencing this decision were the importance of fetal aging as a critical outcome, pragmatic considerations, resource requirements, and equity issues. The evidence suggests that ultrasound, unlike reports of the last menstrual period, is very accurate in determining fetal aging in the first trimester. Although there was no evidence that linked the knowledge of fetal aging in the first trimester to improved maternal and perinatal outcomes, the specialists' clinical experience and the accuracy of first-trimester ultrasound were considered. Accurate fetal aging guides clinicians to provide appropriate tests and interventions expected at certain gestational ages to improve important outcomes (i.e., post-maturity labor induction, fetal congenital anomaly detection, intrauterine growth restriction detection) at later stages of pregnancy.

However, there was inconclusive evidence on other critical outcomes such as the detection of non-viable pregnancy, ectopic pregnancy, and multiple pregnancy. Moreover, the CP considered the feasibility and resource requirements of this recommendation statement. Ultrasound machines are unavailable in rural health units, imposing a financial burden on patients who must travel to the nearest hospital with ultrasound capabilities. There is also a scarcity of skilled practitioners, specifically ultrasonographers, in various rural areas of the country. Inequity that may arise due to the accessibility issues and resource constraints, despite the possible coverage of ultrasound in future PhilHealth packages.

Recommendation 6. We suggest nuchal translucency measurement at 11-14 weeks AOG be offered to all pregnant Filipino women to screen for Down syndrome; and be offered to pregnant women at high risk for fetal anomaly, to screen for major CHD. (*Very low certainty of evidence, weak recommendation)*

Note: Risk factors for fetal anomaly include the following: 1) advanced maternal age (>35 years old), 2) positive serum screen (defined as an elevated result in any of the following serum tests: alpha-fetoprotein [AFP], human chorionic gonadotropin [hCG], unconjugated estriol [uE3], and inhibin-A), 3) other congenital anomalies on ultrasound, 4) history of prior fetus with birth defects or aneuploidy, 5) history of intrauterine fetal death, and 6) history of neonatal death.[49]

Key findings: All cohort studies recruited pregnant women at 10 to 14 weeks age of gestation who underwent nuchal translucency (NT) screening using various cut-off values for interpretation. Among participants with risk factors for fetal anomaly (such as advanced age, positive serum screen(Pregnancy associated plasma protein-A [PAPP-A] and B-HCG), presence of other ultrasound anomalies, and

history of previous fetus with anomaly), the pooled sensitivity of NT screening for detecting Down Syndrome was 62.2% (95% CI 54.1 to 69.7%) while the pooled specificity was 96.5% (95% CI 93.6 to 98.1%).[50-56] Among pregnant women at high risk for Edwards syndrome, the sensitivity was 71% (95% CI 29 to 96%) and the specificity was 97.0% (95% CI 96 to 98).[57] Among women at high risk for major congenital heart disease (CHD), the sensitivity was 90% (95% CI 55 to 100%) and the specificity was 91% (95% CI 89 to 93%).[58]

Among participants at low risk for fetal anomaly, the pooled sensitivity was 67.8% (95% CI 61.4 to 73.6%) and the pooled specificity was 96.3% (95% CI 95.5 to 96.9%) for detecting Down syndrome.[50,59-79] For detecting Edward Syndrome among participants at low risk for fetal anomaly, the pooled sensitivity was 63.0% (95% CI 43.5 to 79.1) and the pooled specificity was 97.4% (95% CI 94.9 to 98.6).[76,80-82]

Thirteen cohort studies conducted among pregnant women at low risk for major CHD (n = 197,270) revealed pooled sensitivity was 25.0% (95% CI: 17.0 to 35.1, I^2=76.8%), while specificity was 97.2% (95% CI: 95.3 to 98.4, I^2 = 99.6%) for detecting major CHD.[83-95]

Justification: The intervention specified in the clinical question was "nuchal translucency (NT) measurement alone," excluding biomarkers due to affordability and accessibility issues. Hence, the evidence presented focused on the effectiveness of using nuchal translucency measurement as a standalone method for screening chromosomal disorders and congenital disorders. However, the term "alone" was omitted by the Panel in order to avoid limiting the tests (e.g., biomarkers) that clinicians can offer to their patients.

The CP formulated a weak recommendation for NT screening due to the following: 1) there is no evidence directly evaluating the impact of NT screening. The available evidence focused on the diagnostic accuracy of using NT measurement as a standalone test; 2) the possibility of false positive results in NT screening for chromosomal and congenital disorders that can induce anxiety during pregnancy was regarded as an undesirable effect of the screening process. However, it was noted that the anxiety experienced after positive screening results is transient and typically not sustained beyond the first trimester.[96,97] Counseling services may also be provided by trained health workers; 3) feasibility, resource, and equity concerns due to the unavailability of confirmatory testing (invasive sampling) in most areas of the country.

The CP deemed that the benefit of NT outweighed the risks. Pregnant women who have positive screening results may be offered other screening tests, such as a noninvasive prenatal test (NIPT) of cell-free DNA or a congenital anomaly scan. Confirmatory tests, such as amniocentesis at 16-18 weeks with biomarkers, or amniocentesis at any time for fetal karyotyping, may be done in select areas in the country. Early detection of aneuploidy or congenital anomalies will allow counseling and appropriate planning, such as referral to other services for early intervention for correctable anomalies. Failure of early identification of the condition may lead to detrimental consequences in later stages (e.g., the formation of excess amniotic fluid that may lead to preterm labor, or the birth of the baby with a condition that will have health, economic, and social implications).

Recommendation 7. We suggest a routine second-trimester ultrasound for all pregnant Filipino women. *(Low certainty of evidence, weak recommendation)*

Key findings: Routine second trimester ultrasound was associated with increased detection of fetal anomalies before 24 weeks age of gestation compared to selective or no ultrasound (RR 3.39, 95% CI 1.76 to 6.54).[98-100] Routine second trimester ultrasound was also associated with increased detection of multiple pregnancies by 24-26 weeks age of gestation (RR 1.89, 95% CI 1.17 to 3.04) and decreased induction of labor for post-term pregnancy (RR 0.48, 95% CI 0.32 to 0.73).[98,99,101-104]

Second-trimester ultrasound underestimated the true gestational age by a mean of -0.1 ± 0.4 days for singletons, -0.6 ± 0.3 days for twins, and -0.6 ± 0.5 days for triplets. When compared to first-trimester ultrasound estimates, second-trimester estimates had larger variability and were less accurate than in the first trimester. There was an inconclusive effect of routine ultrasound in the second trimester compared to selective or no ultrasound on the risk for placenta previa (RR 1.32, 95% CI 0.09 to 18.95) and small for gestational age (RR 1.49, 95% CI 0.93 to 2.38).[98,101]

Justification: The CP deemed that the desirable effects of routine second trimester ultrasound were large (i.e., detection of 3 more fetal congenital anomalies per 1,000 pregnancies before 24 weeks AOG, 4 more multiple pregnancies per 1,000 pregnancies by 24 to 26 weeks AOG, 15 fewer inductions of labor for post term pregnancy per 1,000 pregnancies), with trivial harm (i.e., feeling worried about their pregnancy). The CP also considered that a routine second-trimester ultrasound is acceptable to key stakeholders and feasible to implement. In the absence of ultrasound, other approaches, such as performing Leopold's maneuver, checking the fundal height, and detecting two heart rates, are currently being done to detect multifetal pregnancy. The portable Doppler monitor, which is now widely available and mostly provided by local government units, is used to identify fetal heart tones. The CP also raised concerns about resource requirements, since district and provincial hospitals in remote areas experience deficiencies in equipment and human resources needed to perform an ultrasound.

Recommendation 8. We suggest assessing the risk for pre-eclampsia in the first trimester in all pregnant women. (*Very low certainty of evidence, weak recommendation)*

Key findings: Preeclampsia is commonly defined as new-onset hypertension with proteinuria or end-organ dysfunction after 20 weeks age of gestation.[105] No studies that evaluated

the effect of screening for preeclampsia compared to no screening were found.

One RCT compared the effects of more frequent prenatal visits compared to less frequent visits (14 versus 9 visits) in the first trimester. There was no significant difference in the risk of preterm labor between the 2 groups (RR 1.01, 95% CI 0.86 to 1.18).[106] There was an inconclusive effect on the risk of stillbirth (RR 1.00, 95% CI 0.54 to 1.86).[106]

Five RCTs examined the effect of low-dose aspirin (≤150 mg/day) treatment among pregnant women <16 weeks AOG at risk for pre-eclampsia (with or without preeclampsia) compared to no treatment.[107] There was a lower risk of perinatal death among women given low-dose aspirin (RR 0.47, 95% CI 0.25 to 0.88). Meta-regression analysis showed a reduction in prenatal death even in pregnancies without preeclampsia (RR 0.40, 95% CI 0.19 to 0.78).[107] In these studies, maternal risk factors alone (4 RCTs) and multimarker screening comprising maternal risk factors, biomarkers, and uterine artery pulsatility index evaluated via ultrasound (1 RCT) were used to identify women at risk for preeclampsia.[107]

Justification: This guideline question involved screening for preeclampsia using any strategy (either through screening for maternal factors alone or through multimarker screening). The paucity of trials that evaluated the effect of screening for preeclampsia contributed to the very low level of evidence. The CP considered the benefit of the treatment (i.e., low-dose aspirin from 5 RCTs) among women identified to be at risk for preeclampsia in reducing perinatal death.

Recommendations from ACOG and NICE can be used to guide healthcare providers in identifying maternal risk factors for preeclampsia and, consequently, to provide prophylactic or linked treatment (i.e., low-dose aspirin). These risk factors include any of the following: previous pregnancy with preeclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus, chronic hypertension, and those with more than one of the following moderate risk factors (first pregnancy, maternal age of 35 years or older, a body mass index of more than 30, family history of preeclampsia, sociodemographic characteristics (African-American, low socioeconomic status), and personal history factors(low birth weight, adverse pregnancy outcomes, more than 10-year pregnancy interval).

The subsequent recommendation (recommendation 9) for pre-eclampsia specifies the suggested screening test to be used.

Recommendation 9. We suggest using multimarker screening rather than maternal risk factors alone to assess the risk for pre-eclampsia in the first trimester in all pregnant women. *(Low certainty of evidence, weak recommendation)*

Key findings: Multimarker screening includes using prediction models or risk calculators that include variables such as maternal risk factors, biomarkers (i.e., placental-like growth factor [PLGF] and pregnancy-associated plasma protein-A [PAPP-A]), and/or uterine artery pulsatility index determined through ultrasound.

The specificity of the NICE method of maternal factors only and the mini-combined test with biomarkers (Mini combined test is a multimarker screening: risk factors plus MAP plus uterine pulsatility index plus serum markers PLGF or PAPP-A) compared to a reference standard of clinical diagnosis of pre-eclampsia were similar (Sp 90%, 95% CI 90 to 91% for the NICE method; Sp 91%, 95% CI 90 to 91% for mini-combined test).[108] However, the combination of PAPP-A, mean arterial pressure (MAP), and maternal risk factors (multimarker screening) had higher sensitivity (Sn 43%, 95% CI 38 to 47%) compared to screening for maternal risk factors only (Sn 30%, 95% CI 26 to 35%).[108] The odds of detecting preeclampsia are increased by around four times with a positive multimarker screen (positive likelihood ratio 4.56) and about three times with a positive result by the NICE method (positive likelihood ratio of 3.13) compared to a clinical diagnosis of pre-eclampsia.[108]

One RCT done in Ireland reported no significant difference in the risk of eclampsia with the addition of placental growth factor to usual care compared to usual care (includes clinical assessment, biochemical, and hematologic tests) (0% vs 0.2%, p = 0.27).[105] Among pregnant women with suspected preeclampsia, the addition of serum placental growth factor to usual care compared to usual care alone had inconclusive effect on the risk of preterm delivery (RR 0.92, 95% CI 0.60 to 1.42), risk of developing HELLP syndrome (hemolysis, elevated liver enzymes and low platelet) (RR 1.18, 95% CI 0.17 to 8.38) and risk of maternal mortality (RR 3.50, 95% CI 0.14 to 86.80).[105]

Justification: Based on the evidence, the CP deemed that multimarker screening is more accurate than screening using maternal risk factors alone. Concerns about feasibility and resource constraints were raised, particularly considering the high cost associated with multimarker screening. The CP considered that patients in low-resource settings may undergo contingent screening that includes evaluation of maternal risk factors and arterial pressure, without the uterine artery pulsatility index or serum biomarkers. Risk calculators used in multimarker screening allow risk assessment even with incomplete data.

Recommendation 10. We suggest AGAINST screening for iron deficiency anemia using complete blood count among all asymptomatic pregnant Filipino women. *(Very low certainty of evidence, weak recommendation)*

Key findings: No evidence was found on the effect of screening versus no screening for iron deficiency anemia (IDA) in pregnancy.

A diagnostic accuracy study involving 170 Filipino women of reproductive age from Manila found that complete blood count (CBC) parameters could satisfactorily discriminate iron deficiency anemia.[109] A hematocrit cutoff

value of 35.5% had a 100% sensitivity and 93% specificity to detect iron deficiency anemia. Other CBC parameters, such as mean corpuscular hemoglobin (Sn 89%, Sp 73% at cut-off value 29.15 pg) and mean corpuscular hemoglobin concentration (Sn 78%, Sp 83% at cut-off value 337.50 g/L) were also found to have satisfactory diagnostic accuracy.[109]

Pregnant women with anemia have significantly increased odds of preterm birth compared to those without anemia (OR 1.69, 95% CI 1.45 to 1.96).[110-136] Maternal anemia is significantly associated with increased odds of perinatal or neonatal death (OR 1.26, 95% CI 1.05 to 1.52), infant death (OR 4.18, 95% CI 1.57 to 11.12), and maternal death (OR 1.50, 95% CI 1.02 to 2.21).[112,113,117,118,123,125,127,129,131,134,137-146,139] Maternal anemia is also associated with increased odds of attention-deficit/hyperactivity disorder (ADHD) in the offspring (adjusted OR 1.37, 95% CI 1.14 to 1.64) and low birthweight in the offspring (OR 1.54, 95% CI 1.32 to 1.81).[110,112,114,115,118,120,125-128,130,131,134,136,147-153] Maternal anemia was not significantly associated with NICU admission (OR 1.14, 95% CI 0.96 to 1.37).[109,117,119,121,122,139]

Iron supplementation during pregnancy significantly decreased the risk of low birthweight in the offspring compared to no iron supplementation (RR 0.82, 95% CI 0.72 to 0.94).[154] There was no significant difference in the risk of preterm birth (RR 0.96, 95% CI 0.81 to 1.14), and no significant benefit in reducing neonatal death (RR 0.81, 95% CI 0.56 to 1.19) among pregnant women who received oral iron supplementation compared to those without iron supplementation.[154] The risk of maternal anemia (Hgb less than 110 g/L) at term was lower in women who received oral iron supplementation during pregnancy compared to those without iron supplementation, regardless of anemia status at baseline (RR 0.30, 95% CI 0.19 to 0.46).[154]

Justification: No studies were found that directly assessed screening compared to no screening for IDA using CBC in pregnancy. The CP considered that, based on WHO guidelines, CBC is not recommended to determine the need for iron supplementation. Instead, the prevalence of anemia in a certain population should be considered as the determining factor for the dosage of iron supplementation in patients. In the Philippines, the prevalence of anemia is at 25.5%. For settings where the IDA prevalence ranges from 20-40%, 30 mg of elemental iron in the first trimester and doubled in the second trimester is recommended.

Practice variation with regard to iron supplementation among obstetrician-gynecologists (OB-GYNs)/private practitioners, and midwives was also considered. In the rural setting, midwives give iron supplements on the first visit of the patient. Among OB-GYNs/private practitioners, iron supplements are not prescribed in the first visit, especially in the first trimester. During the first trimester, the iron requirement among pregnant women is not high, and iron supplementation could aggravate nausea and vomiting. Only folic acid is then prescribed, while iron supplementation is started in the second trimester or when IDA is detected. This timing, followed by OB-GYNs, is based on textbooks on prenatal care and the POGS CPG on maternal nutrition, stating that iron stores are still sufficient in the first trimester of pregnancy.

Recommendation 11. We suggest screening for undernutrition via measurement of mid-upper arm circumference (MUAC) in all pregnant Filipino (adolescent and adult) women. *(Very low certainty of evidence, weak recommendation)*

Note: The suggested screening cut-off value in MUAC is ≤23.5 to detect underweight in the general adult population.

Key findings: No studies were found that evaluated the effects of screening compared to no screening using MUAC among pregnant women. There were also no studies evaluating the diagnostic accuracy of MUAC among pregnant women.

Low maternal MUAC is associated with increased odds for low-birth-weight infants (adjusted OR 1.93, 95% CI 1.07 to 3.49), preterm birth (OR 2.06, 95% CI 1.48 to 2.86), and adverse birth outcomes (OR 3.47, 95% CI 1.49 to 8.11).[155-163]

An individual participant data meta-analysis (of which 64.4% were from non-pregnant women) was conducted to determine appropriate MUAC cut-off values for accurate detection of low BMI (<18.5 kg/m2) among adults. The included studies were done in Africa, South Asia, Southeast Asia, North America, and South America. The pooled area under the receiver operating curve (AUROC) of MUAC was 0.91 (range 0.61 to 0.98), using BMI as the reference standard. Based on these results, the authors reported that MUAC can clearly discriminate between underweight and non-underweight populations.[164]

Justification: Although BMI is still regarded as the standard tool for evaluating nutritional status, MUAC was considered by the CP due to the following 1) it can be used among pregnant women across various ages of gestation; 2) practicality of use in local settings, particularly in humanitarian situations where tools such as weighing scales may be limited; and 3) MUAC can clearly discriminate between underweight and non-underweight general adult populations based on its AUROC.

Moreover, MUAC has already been included in existing protocols for assessing nutritional status among infants and children; thus, using it among pregnant women was considered viable. Cutoff values and their interpretation (i.e., ≤23.5 to ≤25 cm to detect undernutrition) must be provided to serve as guides for primary care health workers. There is a research gap on the suitable cut-off levels for Filipino pregnant adolescents and women. The CP also emphasized that MUAC should only be used to screen for undernutrition in the first trimester. In the second and third trimesters, weight monitoring is crucial among pregnant women to ensure healthy weight gain.

DISCUSSION

This CPG provides evidence-based recommendations for screening of selected prenatal disorders among pregnant Filipino women. These guideline questions and recommendations aim to improve health outcomes of all pregnant Filipino women and their newborns, such as improved detection of maternal disease, and reduction of stillbirth, preterm birth, maternal hospitalization, neonatal birth injuries and disorders, and admission to the NICU. The recommendations in this guideline may facilitate informed decision-making of various stakeholders, including general practitioners, obstetrician-gynecologists, family physicians, neonatologists, endocrinologists, midwives, allied healthcare students and professionals, trainees, patients, and policymakers. Academic medical institutions may use this CPG as a reference to educate doctors-in-training on the best practices in screening for prenatal disorders. In addition, the CPG may be used as a guide by policymakers, labor force administrators, regulatory agencies, and government and private financial and healthcare delivery institutions in the Philippines to promote quality healthcare services for pregnant women.

The recommendations on prenatal disorders in this guideline are aligned with some international guidelines. For instance, the Polish Guidelines 2021 recommend routine TSH testing for women at 4–8 weeks of pregnancy, but they do NOT recommend routine FT3/FT4 testing.[165] Similarly, the ACOG Practice Bulletin advises TSH testing for pregnant patients with risk factors such as personal or family history of thyroid disease, type 1 diabetes, clinical suspicion of thyroid disease, significant goiter, or distinct thyroid nodules.[166] The French College of Gynecologists and Obstetricians (FCGO) and NICE do not support routine or repeated cervical length measurements using transvaginal ultrasound.[167,168] The FCGO stated that cervical length screening may be considered by individual practitioners at 18–24 weeks AOG, particularly for women with a history of preterm birth.[167] Both ACOG and ADA recommend GDM screening at 24-28 weeks, with ADA also advising earlier screening for high-risk women.[166,169] The ACOG recommends antepartum screening for Group B streptococcus (GBS) for all pregnant women at 36 0/7 – 37 6/7 weeks of gestation, regardless of the planned mode of delivery, unless there is a need for intrapartum antibiotic prophylaxis due to GBS bacteriuria or a previously infected newborn. The international guidelines of NICE, Society of Obstetricians and Gynecologists of Canada (SOGC), ACOG, and International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommend first-trimester ultrasound scans for different reasons (i.e., to determine gestational age, detect multiple pregnancies, screen for anomalies, and screen for preterm preeclampsia).[170,171] The recommendation of NT screening aligns with other international guidelines except the SOGC, which advises AGAINST screening in the first trimester without biochemical markers in singleton pregnancies.

All international guidelines also offer a second-trimester ultrasound and favor preeclampsia screening. NICE 2021 and USPSTF 2017 recommend screening through BP measurement. Other guidelines (ISSHP 2022, SOGC 2022, FIGO 2019) suggest screening using a combination of risk markers, blood pressure, uterine artery pulsatility index, and PLGF, if available.[168,170-174] International guidelines differ in their recommendations for IDA screening using CBC. No international CPGs recommend screening for undernutrition among pregnant women using MUAC.

The recommendations of this CPG were formulated taking into consideration the applicability to the Filipino setting and the impact on equity. 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, and patients) values, settings, and circumstances.

Strengths and Limitations

This CPG underwent a rigorous process to generate evidence-based recommendations and ensure applicability in the local setting through the involvement of different stakeholders. The evidence reviews were conducted in 2022. This CPG will be updated as necessary to ensure that new evidence will be included and considered in formulating, if necessary, new recommendations.

Research Gaps

Even though prenatal disorders are one of the leading causes of neonatal mortality in the country, studies about their true burden and epidemiology in the population are still lacking. For instance, the prevalence of GBS and thyroid disease among pregnant women is yet to be determined. The effects of screening on some outcomes of interest are still unknown. For example, no studies have assessed the effect of thyroid function screening on fetal congenital abnormalities or compared different doses of OGTT and other tests in the screening for GDM.

Moreover, most of the evidence found, including cost-effectiveness studies, was done in high-income countries; hence, concerns about local applicability were raised by the CP. Information on patient preferences and the availability of technological resources in various areas of the country is also lacking. Research on maternal and neonatal health regarding thyroid dysfunction, thyroid function tests, and specific cut-off levels in MUAC determination to detect undernutrition in the Philippines should be included or reinforced in the national health research agenda.

CONCLUSION

This CPG provides 11 evidence-based recommendations. Applicability in the local setting was carefully considered

through the involvement of different stakeholders. The recommendations herein shall hold until new evidence on screening, diagnosing, or managing various risk factors and diseases emerges, and contingencies dictate updating this CPG. This guideline will be updated after three (3) years.

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 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. This document should also not be treated as strict rules on which to base legal action.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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