Philippine Clinical Practice Guidelines for Periodic Health Examination: Screening for Congenital and Developmental Disorders

Mary Ann R. Abacan, MD, MSc, MHPEd,[1] Kathryn R. Baltazar-Braganza, MD,[2,3]
Ian Theodore G. Cabaluna, MD, Gdip (Epi) MSc[4,5] and Isabella S. Ocampo, MD[6] for the
Philippine Periodic Health Examination Task Force on Screening for Congenital and Developmental Disorders

[1]*Division of Clinical and Metabolic Genetics, Department of Pediatrics, College of Medicine and Philippine General Hospital, University of the Philippines Manila, Manila, Philippines*
[2]*Department of Pediatrics, Faculty of Medicine and Surgery, University of Santo Tomas, Manila, Philippines*
[3]*Section of Neurodevelopmental Pediatrics, Child Neuroscience Division, Philippine Children's Medical Center, Quezon City, Philippines*
[4]*Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines Manila, Manila, Philippines*
[5]*Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila, Manila, Philippines*
[6]*Philippine General Hospital, University of the Philippines Manila, Manila, Philippines*

ABSTRACT

Background and Objective. Congenital and developmental disorders should be detected early to avoid complications such as disability and death. The Philippine clinical practice guidelines (CPG) were developed to guide healthcare professionals on screening for congenital and developmental disorders among apparently healthy neonates and children.

Methods. Following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to CPG development recommended by the Department of Health (DOH), the steering committee, composed of clinical geneticists, developmental pediatricians, family and community medicine physicians, and ambulatory and community pediatricians, set the objectives of the CPG and formulated clinical questions in consultation with stakeholders. There were 15 priority guideline questions that covered various disorders including inborn errors of metabolism, critical congenital heart disease, developmental delay, learning disabilities, and autism. Evidence review experts systematically reviewed existing clinical practice guidelines, appraised, and summarized the evidence. A multisectoral panel formulated recommendations through a formal consensus based on the evidence summaries. The CPG was externally reviewed prior to publication.

Results. The CPG provides twenty (20) recommendations on fifteen (15) prioritized questions in the screening for certain congenital and developmental disorders. This CPG contains recommendations for the screening for critical congenital heart disease, thalassemia, Glucose-6-phosphate dehydrogenase (G6PD) deficiency, developmental delay, and autism spectrum disorder. Recommendations against routine screening of cystic fibrosis, sickle cell disease, methionine adenosyltransferase deficiency, tyrosinemia, long chain 3-hydroxy acyl CoA dehydrogenase deficiency

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Corresponding author: Mary Ann R. Abacan, MD, MSc, MHPEd
Division of Clinical and Metabolic Genetics
Department of Pediatrics
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: mrabacan@up.edu.ph
ORCiD: https://orcid.org/0000-0002-6502-9096

(LCHADD) and mitochondrial trifunctional protein deficiency (MTPD), carnitine palmitoyl transferase types 1 and 2 (CPT1, CPT2) and glutaric aciduria type 2 (GA2), biotidinase deficiency, beta-ketothiolase deficiency, holocarboxylase synthetase deficiency, and isovaleric acidemia were made.

Conclusion. The consensus panel recommended the screening of certain conditions, based on the available evidence, the burden of disease, the cost of the confirmatory testing, and its applicability to the population. 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.

Keywords: congenital disorders, developmental disorders, newborn screening

INTRODUCTION

Inborn errors of metabolism (IEM) are rare. When considered collectively, the estimated global birth prevalence is 50.9 per 100,000 live births.[1] Some treatable IEM disorders can be detected through newborn screening. Congenital heart disease occurs in approximately 1% of newborns.[2] Developmental delays occur in 10-15% of preschool children, while autism spectrum disorders affect 0.6% of children worldwide.[3,4] Early detection of these conditions may lead to early intervention strategies which can improve the quality of life of affected children.

For this clinical practice guideline (CPG), the Task Force on the Screening for Congenital and Developmental Disorders prioritized key questions that involve screening asymptomatic, apparently healthy newborns and children for certain metabolic disorders included in the Expanded Newborn Screening panel, critical congenital heart diseases, and developmental disorders. There are currently no Philippine guidelines on the screening of these disorders.

METHODS

The Grading of Recommendations Assessment, Deve-lopment and Evaluation (GRADE) approach to CPG development recommended in the Department of Health (DOH) Manual on Practice Guideline Development was followed.[5] The GRADE Adolopment and Evidence-to-decision (EtD) framework was utilized in finalizing the recommendations (Figure 1).

Preparation

The Task Force Steering Committee set the CPG objectives, scope, target audience, and guideline questions. The steering committee comprised of pediatricians from different subspecialties (clinical genetics/metabolic specialists, developmental and behavioral pediatrics, ambulatory, and community pediatrics) and a family and community medicine specialist.

The questions were prioritized using the criteria set by the DOH. The Task Force Steering Committee convened the technical working group involved in creating the evidence base and the consensus panel involved in formulating the recommendations.

The consensus panel (CP) comprised of multisectoral representatives from the Institute of Human Genetics – National Institutes of Health, the Philippine Academy of Family Medicine, the Philippine Pediatric Society, the Catholic Educational Association of the Philippines, the Association of Municipal Health Officers of the Philippines, the Philippine Society for Developmental and Behavioral Pediatrics, the Homeschool Association of the Philippine Islands, the Philippine Ambulatory Pediatrics Association, the DOH, and a social scientist representative. These representatives are aware that as part of the CPG dissemination, their affiliations will be part of the manuscript for publication.

COI Management

The steering committee, technical working group, and CP members submitted their declaration of conflict of interest (COI) and curriculum vitae. The declaration included a 4-year period of personal potential intellectual and/or financial conflicts of interest. A COI committee reviewed and evaluated the potential COI and gave their recommendation on how to manage them. In general, those with financial COI were not allowed to vote for questions related to the COI. Those with non-financial COIs (such as authorship related to the CPG topic) were allowed to participate. COIs were declared during the panel meeting and the final manuscript.

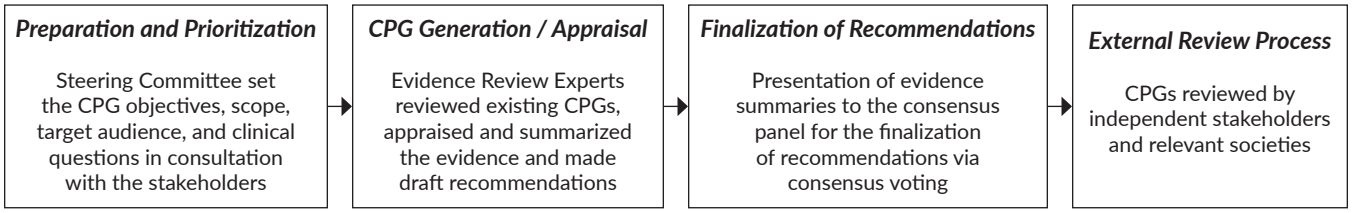

Figure 1. Summary of methodology.

Evidence Synthesis

The evidence review questions were developed using the PICO (population, intervention, comparator, and outcome) format.

The evidence review experts 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, the U.S. Preventive Services Task Force, and the National Institute for Health and Care Excellence. If there was a CPG of good quality and done within five years, the evidence summaries of the CPG were adopted.

If no CPG was found, a systematic medical literature search of the MEDLINE (via PubMed), The Cochrane Library, Google Scholar, JSTOR, and Herdin was performed. Systematic reviews that met the inclusion criteria to answer the clinical questions were used directly to identify relevant articles and to present the summary of findings. If no related reviews were found, *de novo* systematic reviews were conducted. The included studies were critically appraised for the methodological quality using 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. The GRADE approach was used to rate the certainty of evidence and the strength of recommendations (Table 1).

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 voted on the critical outcomes to be considered in the CPG (Appendix).

For each guideline question, the CP was provided with the evidence base 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 was 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 through formal consensus method. A consensus was reached when 75% or more of the voting CP members agreed on the proposed recommendation. If consensus was not reached initially, two further rounds of voting were allowed. A modified Delphi methodology was planned in case no consensus was reached after three rounds of voting. In case no consensus would be reached despite the modified Delphi technique, no recommendation would be indicated in the final CPG manuscript.

In general, a strong recommendation means that the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects. A weak recommendation means that the desirable effects of adherence to a recommendation probably outweigh the undesirable effect (Table 1).

Planning for Dissemination, Implementation and Update

The CPG was sent to the DOH for transmittal and publication. The Disease Prevention and Control Bureau will transmit copies of this CPG to the Philippine Health Insurance Corporation (PHIC), health maintenance organizations (HMOs), and NGOs involved in periodic health examination. The recommendations and the evidence summaries were posted in a web-based application (https://phex.ph). These recommendations and evidence summaries were also disseminated by the Task Force to their specific organizations.

The DOH planned to develop a simplified version of this CPG and to make this available in a format that will be ready for reproduction and dissemination to patients in different healthcare settings. The full manuscript is available at the

Table 1. GRADE Table of Strength of Recommendation and Certainty of Evidence*

Certainty of Evidence	Description
High	We are very confident that the true effect lies close to that of the estimated 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 maybe 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 intervention significantly outweigh disadvantages or disadvantages of the intervention significantly outweigh advantages
Weak	Advantages of the intervention may outweigh disadvantages, disadvantages of the intervention may outweigh advantages, or the relationship between advantages and disadvantages is not clear

**According to the GRADE Working Group*

DOH website (https://doh.gov.ph/dpcb/doh-approved-cpg/) under the Philippine Guidelines on Periodic Health Examination: Screening for Congenital and Developmental Disorders (https://drive.google.com/file/d/1NKYlwznjKCncNzqiPB9z66tLSnP5PX8T/view_). The CPGs will be updated every 3-5 years or earlier if new significant evidence becomes available.

External Review

Three independent stakeholders (representatives from the Philippine Academy of Physicians in School Health, Inc., the Autism Society of the Philippines, and the Philippine Society of Public Health Physicians) 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 prior to finalizing the CPG.

RESULTS

A total of 20 recommendations were made by the consensus panel. A summary can be found in Table 2.

Recommendation 1: Among asymptomatic, apparently healthy newborns, we recommend the screening of critical congenital heart disease using pulse oximetry. *(Moderate certainty of evidence, strong recommendation)*

Key findings: In the Philippines, it is estimated that congenital heart disease (CHD) accounts for 0.79% of all deaths to around 4.49 in 100,000- deaths across all age groups.[6] There were no recent direct RCT studies on screening for critical congenital heart disease (CCHD) versus no screening in apparently healthy newborns. Pooled sensitivity and specificity from a Cochrane review and an additional 11 studies showed that pulse oximetry screening had an overall sensitivity of 71% (95% CI 53-85) with a low certainty of evidence and a specificity of 100% (95% CI 100-100) with moderate certainty of evidence.[7-17]

Justification: The consensus panel agreed on the importance of screening, however, they considered that there could be inequity in management of the critical congenital heart disease due to the inaccessibility of corrective surgery in all provinces.

Recommendation 2: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of cystic fibrosis. *(Very low certainty of evidence, strong recommendation)*

Key findings: Cystic fibrosis is a life-long condition that affects 1/3,000-1/6,000 livebirths among those with European descent but is rare among those of Asian descent. There were two observational studies that showed benefit in survival, but the overall certainty of data was very low.[18,19] The most effective confirmatory testing combines immunoreactive trypsinogen testing (IRT) and DNA sequencing with a sensitivity of 100% (95% CI 80-100%) and a specificity of 99.99% (95% CI 99.98-99.99).[20-22]

Justification: The consensus panel agreed to recommend against screening due to the rarity of the disease coupled with the high cost of confirmatory testing and treatment of the disease.

Recommendation 3: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of sickle cell disease. *(Very low certainty of evidence, strong recommendation)*

Key findings: Sickle cell disease (SCD) has an estimated annual incidence of 20-40 in every 2,000,000 births in the Philippines with only eight registered cases in the Philippine Pediatric Society (PPS) from 2006-2021.[23,24] Primary studies reported favorable short and long-term outcomes for newborn screening programs for SCD.[25-28] Both high performance liquid chromatography (HPLC) and isoelectric focusing (IEF) are valid tests for screening of SCD with a reported positive predictive value of 99.81-100% and negative predictive value of 99.99-100%.[29] Tandem mass spectrometry (MS/MS) may have potential for newborn screening for SCD but it can only detect certain variants of hemoglobin and has not been fully validated.

Justification: The low burden of disease of this condition among the Filipino population and the very low certainty of evidence were the bases for the consensus panel to recommend against the screening of sickle cell disease.

Recommendation 4: Among asymptomatic, apparently healthy newborns, we recommend for the screening of thalassemia using HPLC (BIORAD KIT). *(Very low certainty of evidence, strong recommendation)*

Key findings: Thalassemia is the most common single gene disorder with a high prevalence among Mediterranean, Middle East, and Asian countries.[30-32] In the Philippines, the estimated prevalence is 1 in 1020 live births.[24] Treatment for thalassemia depends on the phenotype and ranges from no treatment for asymptomatic phenotypes or carriers to transfusion for severe phenotypes. The newborn screening program in the Philippines uses HPLC to screen neonates.[23] As of press time, there were no systematic reviews comparing different modalities of newborn screening for thalassemias. Uaprasert et al. reported the sensitivity and specificity of HPLC as 74.6% and 89.5%, respectively.[33]

Justification: Despite the very low certainty of evidence, the panel agreed that the benefit of early recognition and treatment for those who test positive outweighs the risks. Further, it was noted that there is a high burden of illness among Filipinos which makes it a good condition to screen for.

Table 2. Summary of Recommendations

	Recommendation Statement	Certainty of Evidence	Strength of Recommendation
1.	Among asymptomatic, apparently healthy newborns, we recommend for the screening of critical congenital heart disease using pulse oximetry.	Moderate	STRONG
2.	Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of cystic fibrosis.	Very Low	STRONG
3.	Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of sickle cell disease.	Very Low	STRONG
4.	Among asymptomatic, apparently healthy newborns, we recommend the screening of thalassemia using HPLC (BIORAD KIT).	Very Low	STRONG
5.	Among asymptomatic, apparently healthy newborns, we recommend for the screening of G6PD deficiency using fluorescence assay (PE neonatal kit).	Very Low	STRONG
6.	Among asymptomatic apparently healthy newborns, we recommend AGAINST the routine screening of homocystinuria.	Very Low	STRONG
7.	Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of methionine adenosyltransferase deficiency.	Very Low	STRONG
8.	Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of tyrosinemia I/II.	Very Low	STRONG
9.	Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of long chain 3-hydroxy acyl CoA dehydrogenase deficiency (LCHADD) and mitochondrial trifunctional protein deficiency (MTPD).	Very Low	STRONG
10.	Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of carnitine palmitoyl transferase types 1 and 2 (CPT1, CPT2) and glutaric aciduria type 2 (GA2).	Very Low	STRONG
11.	Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of biotidinase deficiency.	Very Low	STRONG
12.	Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of beta-ketothiolase deficiency.	Very Low	STRONG
13.	Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of holocarboxylase synthetase deficiency.	Very Low	STRONG
14.	Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of isovaleric acidemia.	Very Low	STRONG
15.	Among asymptomatic, apparently healthy children born preterm, we recommend the screening of developmental delay at 3-5 months, 12 months, 24 months corrected age, and at 36-48 months of age.	Low	STRONG
16.	Among asymptomatic, apparently healthy children who have any of the following risk factors: maternal alcohol use during pregnancy, gestational diabetes, gestational hypertension or maternal obesity, we recommend the screening of developmental delay at 9-, 18-, and 24-30 months using the ASQ (Ages and Stages Questionnaires.	Low	STRONG
17.	Among asymptomatic, apparently healthy children who were exposed to maternal cigarette smoking during pregnancy, there is insufficient evidence to recommend for or against the screening of developmental delay.	Low	N/A
18.	Among asymptomatic, apparently healthy children whose mothers were anemic, there is insufficient evidence to recommend for or against the screening of developmental delay.	Low	N/A
19.	Among asymptomatic, apparently healthy children, we recommend the screening of autism spectrum disorder between the ages 18 to 24 months using the M-CHAT R/F.	Moderate	STRONG
20.	Among asymptomatic, apparently healthy children, there is insufficient evidence to recommend for or against the screening of specific learning disorders (particularly reading disability) in the primary health care setting.	Very Low	N/A

Recommendation 5: Among asymptomatic, apparently healthy newborns, we recommend the screening of G6PD deficiency using fluorescence assay (PE neonatal kit). *(Very low certainty of evidence, strong recommendation)*

Key findings: G6PD deficiency is the most common X-linked enzyme deficiency and is estimated to affect 400 million people worldwide with a prevalence rate of 1:60 live births in 2020.[34,35] Three observational studies were identified that displayed the benefit of screening for G6PD deficiency in decreasing the number of hospitalized infants due to a hemolytic crisis, with some requiring exchange transfusion.[36-38] A study reported that fluorescence assay had a sensitivity of 100% and a specificity of 99% for detecting G6PD deficiency.[39]

Justification: Because of the high burden of the disease, the panel agreed that the management is cost-effective and preventative against the development of kernicterus, which would greatly benefit those patients that screen positive.

Recommendation 6: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of homocystinuria. *(Very low certainty of evidence, strong recommendation)*

Recommendation 7: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of methionine adenosyltransferase deficiency. *(Very low certainty of evidence, strong recommendation)*

Key findings: As of June 2021, the Philippines has detected two cases of homocystinuria since 1996 and no new case has been reported since 2019 after the implementation of compulsory expanded NBS program.[33,40] There has only been one reported case of hypermethioninemia detected out of 3,209,001 screened babies.[33] No randomized controlled trials (RCTs) comparing outcomes of patients with treatment versus no treatment were available both for homocystinuria and methionine adenosyltransferase (MAT) deficiency. Pooling of estimates could not be done for the accuracy of screening tests for homocystinuria and MAT deficiency due to a very low number of studies, incomplete follow up of patients, and differences in reference standard used.

Recommendation 8: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of tyrosinemia I/II. *(Very low certainty of evidence, strong recommendation)*

Key findings: In the Philippines, 10 patients have been diagnosed with Tyr I (1 in 267,416), and no cases of Tyr II and Tyr III have been detected since the introduction of expanded newborn screening in 2014.[33] No randomized controlled trial was available for review of evidence of outcomes between screening and non-screening for Tyr. However, a systematic review by Geppert et al. reviewed observational studies on the comparison of clinical outcomes of Tyr I patients receiving earlier versus later nitisinone treatment.[41] No association was also found between early treatment (p = 0.49) and late treatment (p = 0.07) and mortality. It was not possible to pool the results for screening due to the difference in confirmatory tests and incomplete follow-ups of the negative screens. Tyr 1 has been found to be one of the least cost-effective diseases for screening.[42]

Recommendation 9: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of long chain 3-hydroxy acyl CoA dehydrogenase deficiency (LCHADD) and mitochondrial trifunctional protein deficiency (MTPD). *(Very low certainty of evidence, strong recommendation)*

Recommendation 10: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of carnitine palmitoyl transferase types 1 and 2 (CPT1, CPT2) and glutaric aciduria type 2 (GA2). *(Very low certainty of evidence, strong recommendation)*

Key findings: According to the metabolic registry of the Clinical Genetics and Research Unit – Institute of Human Genetics, one case of CPT1D and three cases of GA2 were clinically detected and confirmed by mutational analysis. As of June 2021, no cases of CPT1D, CPT2D, LCHADD, MTPD and GA2 were identified by the expanded newborn screening since its implementation.[40] One systematic review on the pre-symptomatic management of LCHADD and MTPD found that there were statistically significant fewer deaths (OR 0.36, 95% CI 0.13 to 1.02, p=0.05), cardiomyopathy (OR 0.28, 95% CI 0.09 to 0.85, p=0.02), liver pathology (OR 0.06, 95% CI 0.01 to 0.60, p=0.02), retinopathy (OR 0.09, 95% CI 0.01 to 0.64, p=0.02), hypoglycemia (OR 0.10, 95% CI 0.02 to 0.50, p=0.005), and myopathy (40% vs 82.4%, p = 0.03) among those screened.[41] It was not possible to calculate sensitivity, specificity, or negative predictive value as there was no systematic follow-up of babies who had screened negative.[43]

The respective cohorts for CPT1D, CPT2D, and GA2 had very small sample sizes (two, five, and seven cases, respectively).[44-46] Due to very low number of sample size, no definitive conclusions can be drawn regarding the benefit of early screening and subsequent intervention for CPT1D, CPT2D, and GA2. The overall certainty of evidence across all outcomes is very low. There is a very low false positive rate of <0.001% for the BNS as a screening test for CPT1D and CPT2D.[47]

Recommendation 11: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of biotidinase deficiency. *(Very low certainty of evidence, strong recommendation)*

Key findings: According to the Metabolic Registry of the Institute of Human Genetics, there was only one case of biotinidase deficiency reported in the Philippines since screening started in 2014 resulting in an estimated prevalence of 1 in 1,748,857.[23] There were no systematic reviews, meta-analysis or randomized controlled trials found on complications or morbidity. There was one observational cohort comparing screened children to symptomatic children and the presence of hearing impairment, visual disorder, and developmental delay.[48] Among those screened asymptomatic newborns versus those not screened but clinically detected, there was decreased visual impairment (0% vs 33%, p<0.001), decreased hearing impairment (0% vs 33%, p=0.004), decreased speech delay (16% vs 50%, p=0.022), decreased delayed onset of walking (0% vs 42%, p=0.002), and decreased delayed onset of sitting (4% vs 25%). There was a pooled sensitivity of 0.93 for the NBS as a screening test.[49-53]

Recommendation 12: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of beta-ketothiolase deficiency. *(Very low certainty of evidence, strong recommendation)*

Key findings: Worldwide, a total of 250 confirmed cases of Beta-ketothiolase deficiency (BKTD) have been reported with varying ethnicity.[54] In the Philippines, no case of BKTD has been reported since the introduction of expanded newborn screening in 2014.[55] Only one study showed that those who underwent NBS had fewer cases of mortality compared to those previously diagnosed or selectively screened (0% vs 30%).[56] No randomized controlled trials, CPGs or systematic reviews were found comparing outcomes of patients with treatment versus no treatment among those with BKTD. The pooled sensitivity of expanded newborn screening (ENBS) is 0.52.[56]

Recommendation 13: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of holocarboxylase synthetase deficiency. *(Very low certainty of evidence, strong recommendation)*

Key findings: According to the 2020 Philippine Newborn Screening Report, the prevalence of holocarboxylase deficiency is 1/1,069,667 since the inception of routine testing in the country.[35] Only case reports were found which showed that prompt initiation of biotin supplementation with usual dose range of 5-20 mg/day significantly improved the dermatologic lesions and neurologic complications in most cases.[57-68] In an observational study by Lund et al., expanded newborn screening (ENBS) showed an overall false positive rate of 0.038%, positive predictive value of 37%, and specificity of 99.99%.[69]

Recommendation 14: Among asymptomatic, apparently healthy newborns, we recommend AGAINST the routine screening of isovaleric acidemia. *(Very low certainty of evidence, strong recommendation)*

Key findings: In the Philippines, there have been three confirmed cases of isovaleric acidemia since 2014, giving a prevalence of 1.1 in 1,000,000.[35] Data on the benefits of screening versus no screening from three longitudinal, observational studies were pooled.[69-71] There was net benefit seen in preventing long-term neurocognitive impairment and extending quality-adjusted life years. However, all studies had very low overall certainty of evidence. Newborn screening had 100% sensitivity and 99.99% specificity.[72,73]

Justification for recommendations 6-14: The very low burden of these diseases among Filipinos coupled with the high cost of confirmatory testing and treatment led the consensus panel to decide against the screenings for the discussed diseases.

Based on the first PHEX, universal screening for asymptomatic, apparently healthy children was not recommended. Therefore, for recommendations 15-18, these high-risk populations were identified as possible risk factors for developmental delay.

Recommendation 15: Among asymptomatic, apparently healthy children born preterm, we recommend the screening of developmental delay at 3-5 months, 12 months, 24 months corrected age, and at 36-48 months of age. *(Low certainty of evidence, strong recommendation)*

Note: Preterm is defined as an infant born less than 37 weeks age of gestation.

Key findings: The 2017 National Institute for Health and Care Excellence (NICE) Guideline on Developmental Follow-up of Children and Young People Born Preterm reviewed 19 studies that looked into the association between gestational age and various developmental disorders.[74] Results of these studies could not be pooled due to differences in the inclusion/exclusion criteria for participants, ages of participants at the time of assessment, confounders adjusted for in multivariate analysis models, outcome definitions and measurement tools, and consistency of results. High quality evidence from one study showed a significant increase in the risk of neurodevelopmental disorder (developmental delay, cerebral palsy, blindness, or deafness) comparing children born at 22–26 weeks of gestation as compared to those born 27–28 weeks of gestation assessed at 2–3 years corrected age.[75,76]

Justification: The consensus panel agreed that along with the high prevalence of premature births, screening for developmental delay will lead to early intervention and therefore, improved outcomes. These benefits outweigh the risks of screening. The frequency of screening was based on the 2017 NICE Guidelines on Developmental Follow-up of Children and Young People Born Preterm.

Recommendation 16: Among asymptomatic, apparently healthy children who have any of the following risk factors: maternal alcohol use during pregnancy, gestational diabetes, gestational hypertension, or maternal obesity, we recommend the screening of developmental delay at 9-, 18-, and 24-30 months using the ASQ (Ages and Stages Questionnaires). *(Low certainty of evidence, strong recommendation)*

Key findings: Low quality evidence showed the following: a significantly increased risk of intellectual disability (OR 1.81, 95% CI 1.53 to 2.14) with prenatal alcohol use, significantly increased risk of developmental delay in infants of mothers with gestational diabetes (OR 2.33, 95% CI 1.08 to 5.05), significant increase in risk in delay in gross motor skills (OR 2.33, 95% CI 1.17 to 4.26), and non-significant increased risk for developmental delay among infants born to mothers with gestational hypertension (OR 3.58, 95% CI 0.93 to 13.78).[77-79] A systematic review of 41 studies (meta-analysis done on 32 of the 41 studies included six case-control and 26 cohort studies involving a total of 36 cohorts) showed that pre-pregnancy obesity significantly increased the risk of compromised neurodevelopmental outcomes (OR 1.51, 95% CI 1.35 to 1.69).[80]

Justification: The panel agreed that these risk factors are significant and that the recommendation of screening time was based on the American Academy of Pediatrics (AAP) Guidelines.

Recommendation 17: Among asymptomatic, apparently healthy children who were exposed to maternal cigarette smoking during pregnancy, there is insufficient evidence to recommend for or against the screening of developmental delay. *(Low certainty of evidence)*

Key findings: Low quality evidence from two studies showed conflicting results. One prospective cohort showed non-significant increased risk of gross motor delay (OR 1.4, 95% CI 0.10 to 20.9).[81] Low quality evidence from the other prospective study showed non-significant increased risk of suspected developmental delay (PR 1.29, 95% CI 0.86 to 1.92).[82]

Justification: Although the panel agreed that maternal cigarette smoking during pregnancy has been associated with poor outcomes for both mothers and their babies, the studies revealed insignificant results for screening for developmental delays. The panel decided that the evidence was not enough to make any recommendation.

Recommendation 18: Among asymptomatic, apparently healthy children whose mothers were anemic, there is insufficient evidence to recommend for or against the screening of developmental delay. *(Low certainty of evidence)*

Key findings: Low quality evidence from a prospective study showed non-significant increased risk of suspected developmental delay (PR 1.48, 95% CI 0.95 to 2.29).[82]

Justification: The panel decided that the lone study was not enough basis to make a recommendation.

Recommendation 19: Among asymptomatic, apparently healthy children, we recommend screening of autism spectrum disorder between the ages 18 to 24 months using the M-CHAT R/F. *(Moderate certainty of evidence, strong recommendation)*

Key findings: There were no direct studies found on universal autism spectrum disorder (ASD) screening versus no screening among apparently healthy children on adaptive functioning or impact on familial psychosocial dynamics. Instead, studies on the effectiveness of early intervention among children diagnosed with ASD were looked at. A Cochrane review evaluated the effects of early intensive behavioral intervention (EIBI) on children less than six years old and found that treatment with EIBI resulted in a net benefit, with a mean adaptive behavior score which was 9.58 points higher (95% CI 5.57 to 13.60, P< 0.001) on the Vineland Adaptive Behaviors Scale (VAB-S), compared to children who received treatment as usual.[83] Based on six cross-sectional (cohort type accuracy) studies, which used the DSM-IV and various additional behavior tests (VABS, CARS, ADOS, MSEL) as the reference standard, the pooled sensitivity of the M-CHAT-F was 0.83 (95% CI: 0.55 to 0.95) and the pooled specificity was 0.95 (95% CI: 0.84 to 0.99).[84-89] In 2014, the M-CHAT-F was revised into the M-CHAT R/F by dropping three items, reorganizing the remaining items, simplifying language, and adding examples. These changes were made in order to decrease false positives while maintaining a high sensitivity. Based on a 2014 study by Robins and others, the sensitivity of the M-CHAT R/F is estimated at 0.85 (95% CI 0.79 – 0.92), while the specificity is estimated at 0.99 (95% CI 0.99 – 0.99).[90]

Justification: Although the M-CHAT R/F has not been validated in Filipino as of press time, the very high burden of disease along with the benefit of early intervention for those who screen positive for ASD led the panel to vote for this recommendation. The panel agreed that the M-CHAT R/F needs to be validated in Filipino and possibly other dialects especially since this is a parent-reported tool. They also discussed the harm of over-labeling patients and emphasized the importance of proper training for the healthcare workers who will be administering, interpreting, and explaining these results to the parents of the patients.

Recommendation 20: Among asymptomatic, apparently healthy children, there is insufficient evidence to recommend for or against the screening of specific learning disorders (particularly reading disability) in the primary health care setting. *(Very low certainty of evidence)*

Key findings: Specific learning disability (SLD) is a neurodevelopmental disorder that impedes the ability to learn or use specific academic skills (e.g., reading, writing and arithmetic), which is the foundation of other academic learning.[91] The latest meta-analysis on different dyslexia treatments evaluating reading performances showed a modest effect (mean standard difference 0.38, 95% CI 0.31-0.46) compared to no intervention. However, this study was limited by the inclusion of mostly low-powered studies with small effect sizes and considerable heterogeneity.[92] There were no studies identified on the direct effect of screening for learning disability. There is also no standardized screening protocol being used specifically for reading disabilities.

Justification: The panel did not give any recommendation because based on the studies presented in this review, there was no unified standard tool identified to screen for learning disorders, specifically reading disabilities. They also considered whether it was more appropriate for the primary educators of these children rather than physicians to screen for reading disabilities.

DISCUSSION

A total of 20 recommendations (14 for congenital disorders and six for developmental disorders) were made to answer the 15 key questions prioritized in this CPG. In general, the consensus panel took into consideration the evidence presented, the burden of disease, the cost of the confirmatory testing, and its applicability to the population in formulating the recommendations. The consensus panel recommended the screening of critical congenital heart disease, thalassemia, G6PD deficiency, developmental screening for neonates with risk factors (prematurity, maternal alcohol use during pregnancy, gestational diabetes, gestational hypertension, or maternal obesity), and autism spectrum disorder.

Since the previous PHEX, there have been developments in the screening for congenital and developmental disorders. This CPG updated the previous recommendations made. Presently, the Philippines screens for 29 disorders through the expanded newborn screening program. For this CPG, only 15 of the disorders were prioritized to be included in the key questions. Thus, the recommendations were specific to the disorders that were stated.

Research Gaps

Many research questions from the identified guideline questions in this CPG remained unanswered in terms of the benefits and harms of screening, equity, applicability, and feasibility. Direct evidence was lacking to provide a definitive list of conditions to be recommended for inclusion in the NBS due to the rarity of the disorders and the lack of studies comparing outcomes among newborns who were screened and unscreened.

For congenital metabolic disorders, establishing direct evidence through clinical trials may be problematic. Because of this challenge, establishing the diagnostic performance of tests as indirect evidence may be adequate. However, the burden of these diseases is low worldwide, and studies on these disorders may not always be available.

For developmental disorders, there is still no specific screening tool identified for certain conditions such as learning disorders and developmental delay. Psychometric properties of some standardized tools used to detect developmental delays among apparently healthy children have not been established. These tests have also not been validated in the local vernacular as of press time.

Few cost-effectiveness studies are available to evaluate screening of diseases included in this CPG. Most of the available cost-effectiveness studies are conducted in Western countries. In fact, for congenital disorders, there are no cost-effective studies found. This is possibly due to the very small number of participants in the country who would qualify for these studies. For developmental disorders, specifically for reading disabilities and autism spectrum disorder, the burden of disease has been increasing but cost-effectiveness of screening is still not adequately investigated.

Social science research also plays a vital role in examining the impact of diseases. Although there are some local studies that examine the motivations of parents in entering their children into screening programs for these developmental disorders, these need to be updated. These studies can become determinants for government to push for or against the screening of these disorders. Qualitative studies may also provide more information on the probable harm of mislabeling.

There are three topics where no recommendations were made by the panel due to insufficient evidence. In such cases, it is prudent for clinicians to carefully weigh the benefits and harms of screening, and to discuss these with the patient's caregivers for a shared decision-making process.

Updating and Dissemination

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.

CONCLUSION

The consensus panel recommended the screening of the following conditions: critical congenital heart disease, thalassemia, G6PD deficiency, developmental delay, and autism spectrum disorder. These recommendations were

made based on the available evidence, the burden of disease, the cost of the confirmatory testing, and its applicability to the population. On the other hand, the consensus panel recommended against the screening of other congenital disorders due to the rarity of these disorders and the high cost of the testing. 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.

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 CPG, but this document should not be the sole basis for evaluating insurance claims. Recommendations from the PHEX app and the guidelines therein 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

At the time of CPG development, Dr. Mary Ann Abacan (chair) and Dr. Mary Anne Chiong (member) were members of the Panel of Experts Committee on Phenylketonuria, Galactosemia and Metabolic Diseases of the Newborn Screening Reference Center. They are also both members of the Philippine Pediatric Society. Dr. Kathryn Baltazar-Braganza declares no conflicts of interest but she is a member of the Philippine Pediatric Society and the Philippine Society for Developmental and Behavioral Pediatrics. Dr. Isabella Ocampo declares no conflicts of interest but she is a member of the Philippine Pediatric Society. Dr. Ian Theodore Cabaluna received payment as honoraria from the Philippine Heart Association, the Philippine College of Chest Physicians, and the Department of Health. All authors are also affiliated with the University of the Philippines Manila.

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TASK FORCE MEMBERS

Task Force Steering Committee

Chair: Mary Ann R. Abacan, MD, FPPS
Co-chair: Kathryn R. Baltazar-Braganza, MD, MSc (cand.)
Members: Mary Anne D. Chiong, MD, MSc
Anna Guia O. Limpoco, MD, MSc, DFM, FPAFP
Maria Isabel O. Quilendrino, MD, DPPS, FPSDBP
Angelica Cecilia V. Tomas, MD

Technical Working Group

Technical Coordinator: Kathryn R. Baltazar-Braganza, MD, MSc (cand.)

Evidence Review Experts:
Christine Mae S. Avila, MD, DPPS
Hazel S. Baconga, MD, DPPS
Reginald B. Balmeo, MD, DPPS, DPAPP
Liza Marie P. Bejemino, MD, DPPS
Fides Roxanne M. Castor, MD, DPPS
Ma. Theresa M. Collante, MD, FPPS, FPRA, CCD
Melissa A. Dator, MD, MBA, DPPS, DPSN
Ma. Margarita S. de Rivera, MD, DPPS
Vaneza Leah A. Espino, MD, DPPS, DPAPP
Natasha Ann R. Esteban-Ipac, MD, FPPS, DPSAMS
Erena S. Kasahara, MD, DPPS
Mark Andrew O. Perez, MD, DPPS, DPSN, DPNSP
Corinna Victoria M. Puyat, MD
Marie Julianne C. Racoma, MD, DPPS
Charlotte Averill Y. Tan, MD
Grazielle S. Verzosa, MD, DPPS

Consensus Panel

Maria Melanie Liberty B. Alcausin, MD, FPPS
Abigael C. Andal, MD, FPAFP
Martin Graciano Raymundo S. Baquiran, MD, MPH, FPPS, FAAP
Hairam R. Encendencia, MD, MCHM, DFM
Cindy C. Llego, MD, FPPS, FPSDBP
Janet Marriane Go-Nierva, MD, FPPS, FPSNbM
Florence B. Nitafan
Maria Socorro L. Romabiles, PhD
Benjamin P. Sablan Jr., MD, MDM
Maria Wilda T. Silva, MD, MBA in Health

Consensus Panel Meeting Facilitator: Carlo Irwin A. Panelo, MD, MA

Administrative Staff

Technical Writer: Isabella O. Santos, MD, DPPS
Administrative Officer: Claudette V. Silva

APPENDIX

Critical Outcomes

The consensus panel members considered the following outcomes for all the clinical questions:

Critical Outcomes	Important Outcomes
Morbidity	Diagnostic performance: true positive
Disease-related mortality	Diagnostic performance: false negative
Disease-related hospitalization	Diagnostic performance: true negative
All-cause mortality	Diagnostic performance: false positive
Survival	
All-cause hospitalization	