

# Philippine Clinical Practice Guidelines for Periodic Health Examination: Screening for Neoplastic Diseases

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## ABSTRACT

**Background and Objective.** Cancer is among the leading causes of death in the Philippines, with an age-standardized mortality rate of 100 deaths per 100,000 persons. Despite the high incidence and mortality in the country, the Philippines has yet to implement a national early detection or screening program for cancers. The goal of these clinical practice guidelines (CPGs) is to provide evidence-based recommendations on screening for specific types of cancer: retinoblastoma, nasopharyngeal cancer, liver cancer, cervical cancer, oral cancer, colorectal cancer, breast cancer, prostate cancer, lung cancer, and gastric cancer.

**Methods.** The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to CPG development recommended in the Department of Health Manual was followed. There were 10 clinical questions covered in this CPG, of which 9 questions involved asymptomatic or apparently healthy adults, while 1 question involved early detection of retinoblastoma among children. The evidence of net benefit or harm of cancer screening was obtained through a systematic literature search from database inception up to August 2021. Additional information on cost-effectiveness, patient values and preferences, acceptability, feasibility of screening, and its impact on equity was also obtained. The final recommendations were made through consensus by a panel of representatives from multiple stakeholder groups.

**Results.** There were 20 recommendations formulated. Strong recommendations were given to screen the following: patients at risk for hepatocellular carcinoma using ultrasound with alpha-fetoprotein (AFP); women aged 30 to 65 years for cervical cancer with cervical cytology alone, or high-risk Human papillomavirus (HPV)



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testing alone, or visual inspection with acetic acid as alternative to Pap smear; adults aged 35 and older who are smokers or alcohol drinkers for oral cancer using visual examination, and women 50 to 69 years for breast cancer using mammography and biennial clinical breast examination. However, strong recommendations were made AGAINST screening for cervical cancer among women aged 21 to 29 years, and AGAINST screening for cervical cancer with high-risk HPV testing in combination with cytology (co-testing).

**Conclusion.** Through a comprehensive and systematic search of the best available evidence, the Neoplastic Diseases Task Force developed 20 recommendations on screening and risk factor assessment for 10 specific questions on neoplastic diseases. These recommendations serve as guidance on screening neoplastic diseases at the primary care level.

*Keywords: periodic health examination, neoplastic diseases, screening*

## INTRODUCTION

The Philippine Guidelines on Periodic Health Examination (PHEX) 2004 was a comprehensive guide on screening interventions for apparently healthy Filipinos.<sup>1</sup> This guideline is being updated to support the Universal Health Care Act, which aims to provide all Filipinos access to quality and affordable medical services.<sup>2</sup> This manuscript details the recommendations on screening for neoplastic diseases.

Cancer is among the leading causes of death in the Philippines, with an age-standardized mortality rate of 100 deaths per 100,000 persons.<sup>3</sup> The incidence of cancer in the Philippines is estimated to be 162 cases per 100,000 persons. The most frequently detected cancer types are breast cancer, lung cancer, colorectal cancer, liver cancer, and prostate cancer.<sup>3</sup> Despite the high incidence and mortality in the Philippines, the country has yet to implement a national early detection or screening program for cancers.<sup>4</sup>

This clinical practice guideline (CPG) provides evidence-based recommendations on the screening of neoplastic diseases and their risk factors among asymptomatic, apparently healthy adults and/or children. The recommendations were formulated following a comprehensive evaluation of the benefits, harms, costs, acceptability, feasibility, people's values and preferences, and the impact of screening on equity.

The clinical questions in this CPG involved the following types of cancer: retinoblastoma, nasopharyngeal cancer, liver cancer, cervical cancer, oral cancer, colorectal cancer, breast cancer, prostate cancer, lung cancer, and gastric cancer. Most clinical questions involved asymptomatic or apparently healthy adults, except for the question on retinoblastoma, which involved children. For breast cancer, the population of interest was women. The following general outcomes were

considered: all-cause mortality, cancer-related mortality, adverse effects due to screening or to treatment, diagnostic accuracy of screening, and cost-effectiveness of the screening tool.

## 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 followed. The GRADE Adolopment and Evidence-to-decision (EtD) framework was utilized in finalizing the recommendations.<sup>5,6</sup> The detailed methodology can be viewed in the full guideline manuscript through the PHEX website (<https://phex.ph>).

### Preparation

The Task Force Steering Committee set the CPG objectives, scope, target audience, and clinical questions. The Task Force Steering Committee convened the technical working group involved in creating the evidence base and the consensus panel (CP) involved in formulating the recommendations for each clinical question included.

Questions were prioritized using the criteria set by DOH. Ten clinical questions (Table 1) were prioritized for this CPG based on burden of illness, availability of screening tests and early treatment, applicability to the general population from

**Table 1.** Clinical Questions

No.	Clinical Question
1	Among children, should we do an annual ophthalmologic examination compared to no screening?
2	Among asymptomatic populations at risk for nasopharyngeal cancer, should we use the EBV blood test and/or nasopharyngoscopy compared with no screening?
3	Among otherwise healthy adults, should we do semi-annual or annual performance of the following tests alone or in combination (liver ultrasound and/or AFP)?
4	Among women, should we use HPV testing alone, cytology alone, or co-testing (i.e., cytology with HPV testing)?
5	Among otherwise healthy adults, should we do an annual ENT screening exam and dental check-up compared to no screening?
6	Among otherwise healthy adults, should the fecal immunochemical test be used instead of the fecal occult blood, or no screening?
7	Among apparently healthy asymptomatic adults, should we do a mammogram, breast ultrasound, or clinical breast examination?
8	Among asymptomatic men aged 40 to 80 years old, should we do annual PSA determination with or without digital rectal exam, or digital rectal exam alone, compared to no screening?
9	Among asymptomatic apparently healthy adults, should low-dose CT be used compared to chest X-ray?
10	Among asymptomatic populations at risk for gastric cancer, should we do screening (i.e., upper gastrointestinal series, upper endoscopy) compared with no screening?

childhood to old age, and perceived controversies, uncertainty, and variability in screening practices.

**Management of Conflicts of Interest**

All task force members, including the steering committee, technical working group, and CP, 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 conflicts of interest and gave its recommendation on how to manage them. In general, those with 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 the final manuscript.

**Evidence Synthesis**

The evidence review questions were developed using the PICO (population, intervention, comparator, and outcome) format. The evidence review experts (EREs) systematically 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, US Preventive Services Task Force, and National Institute for Health and Care Excellence. If the CPGs were of good quality and done within 5 years, the evidence summaries of the CPG were appraised using the AGREE II tool, and the evidence summary was adopted if the questions were relevant to the pre-specified review question.

If no recent and trustworthy CPG was found, a systematic search in electronic databases (MEDLINE via PubMed, CENTRAL, Google Scholar) was performed. Systematic reviews that answered the clinical questions were used to identify relevant articles and to formulate the summary of findings table. If no systematic reviews were found, *de novo* systematic reviews were conducted. Relevant local databases and websites of medical societies were also searched. Keywords were based on the PICO (MeSH and

free text) set for each question. The EREs also contacted authors of related articles to verify details and identify other research studies for appraisal, if needed.

At least two (2) reviewers worked on each PICO question. The ERE appraised the directness, methodological validity, results, and applicability of each relevant article included. We critically appraised the methodological quality of the included studies using the standard tools, such as the Cochrane Risk of Bias tool (ROB 1.0) for randomized controlled trials (RCTs), Painless EBM appraisal criteria, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic accuracy studies, and the Newcastle–Ottawa Scale (NOS) for observational studies.

Review Manager, STATA, and GRADEPro were used for the quantitative synthesis of important clinical outcomes for each question. The ERE generated evidence summaries for each of the 10 questions. Each evidence summary included evidence on the burden of the problem, diagnostic performance, benefits, harm, and social and economic impact of the screening test/intervention. Evidence related to the Etd framework (i.e., cost of screening test, cost-effectiveness studies, qualitative studies) was also included in the evidence summaries. The certainty of evidence was assessed using the GRADE approach (Table 2).

**Formulation of the Recommendations**

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.

**Table 2.** Grading of Certainty of Evidence and Strength of Recommendations\*

Certainty of Evidence	Description
<i>High</i>	We are very confident that the true effect lies close to that of the estimate of the effect
<i>Moderate</i>	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
<i>Low</i>	Our confidence in the effect estimate is limited: The true effect maybe substantially different from the estimate of the effect
<i>Very low</i>	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
<i>Strong</i>	Advantages of the intervention significantly outweigh the disadvantages, or vice versa
<i>Weak</i>	Advantages of the intervention may outweigh disadvantages, disadvantages of the intervention may outweigh advantages, or the relationship between advantages and disadvantages is not clear

\*Adapted from GRADE Working Group

The evidence summaries were presented during their respective *en banc* meetings. The direction and strength of each recommendation were determined through a formal consensus method. A consensus was achieved if 75% of all CP members agreed. If initial voting did not yield a consensus, deliberations and discussions were encouraged. 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, while a weak recommendation means that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is not confident.

**Dissemination, Implementation, Monitoring, and Updating**

The guideline is currently being disseminated through the web-based application (<https://phex.ph>), which contains the evidence summaries and recommendations. It is also accessible online via the websites of the Philippine DOH and the participating organizations. Journal publications and/or panel presentations in medical education forums attended by physicians, allied health professionals, and the public are other ways of planned dissemination.

The CPG manuscript was approved by the Evidence Generation and Management Division of the Disease Prevention and Control Bureau of the DOH, and is for endorsement to the DOH Secretary as a DOH-approved

CPG. Monitoring of the uptake of the guideline can be done yearly through the Philippine Health Insurance Corporation reimbursement process. User access to the CPG through the websites can also be monitored annually. 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. Subject to funding availability, this guideline will be reviewed and updated three years after publication to incorporate end-user feedback and literature published since 2021. Additionally, the CPG questions that have strong strength of recommendations can be used as quality-of-care indicators to evaluate and monitor the uptake of the CPG.

**External Review**

External review was done independently by three (3) independent stakeholders, including clinical content and technical experts. The CPG manuscript was reviewed for rigor of development, editorial independence, completeness of the review, relevance of the evidence to the CPG questions, comprehensiveness of the output (i.e., the recommendation statements and the manuscript), and the planned methods of dissemination of the CPG. The feedback from the external review was considered and incorporated into the final CPG manuscript.

**RESULTS**

The guideline has twenty (20) recommendations, which are summarized in Table 3.

**Table 3.** Summary of Recommendations on Screening for Neoplastic Disorders and their Risk

Recommendation	Certainty of Evidence	Strength of Recommendation
<b>Question 1: Among children, should we do annual ophthalmologic examination compared to no screening?</b>		
1.1. Among all children less than 5 years, we suggest screening for retinoblastoma from the newborn period through serial ophthalmologic examinations using the red reflex test.	Very low	Weak
1.2. Among infants and children with a high risk* of developing retinoblastoma (i.e., positive family history), there is insufficient evidence to suggest for or against screening for retinoblastoma using the red reflex test.	Very low	None
* High risk refers to infants and children with suspicious findings in the red reflex test or with a positive family history of retinoblastoma. High-risk infants and children should be referred directly to an ophthalmologist.		
<b>Question 2: Among asymptomatic populations at risk for nasopharyngeal cancer, should we use the EBV blood test and/or nasopharyngoscopy compared with no screening?</b>		
2.1. Among asymptomatic apparently healthy adults, we suggest AGAINST screening for nasopharyngeal cancer using an EBV DNA test and/or nasopharyngoscopy.	Low	Weak
2.2. Among asymptomatic apparently healthy adults with a first-degree relative with known nasopharyngeal cancer, we suggest screening for nasopharyngeal cancer using EBV DNA test and/or nasopharyngoscopy.	Very low	Weak

**Table 3.** Summary of Recommendations on Screening for Neoplastic Disorders and their Risk (*continued*)

Recommendation	Certainty of Evidence	Strength of Recommendation
<b>Question 3: Among otherwise healthy adults, should we do semi-annual or annual performance of the following tests alone or in combination (liver ultrasound and/or AFP)?</b>		
3.1. Among asymptomatic, apparently healthy adults, we suggest AGAINST the use of ultrasound with AFP every 6 months to screen for hepatocellular carcinoma.	Low	Weak
3.2. Among patients at risk* to develop hepatocellular carcinoma who have or have not progressed to cirrhosis, we recommend the use of ultrasound with AFP every 6 months to screen for hepatocellular carcinoma.  <i>* Risk factors: Hepatitis B and/or C infection, Metabolic diseases, non-alcoholic/alcoholic liver diseases, Family history of liver cancer, Prolonged heavy alcohol consumption, Men &gt;40 years old</i>	Moderate	Strong
<b>Question 4: Among women, should we use HPV testing alone, cytology alone, or co-testing (i.e., cytology with HPV testing)?</b>		
4.1. Among women aged 21 to 29 years, we recommend AGAINST screening for cervical cancer with cervical cytology or visual inspection with acetic acid.	Low	Strong
4.2. Among women aged 30 to 65 years, we recommend screening for cervical cancer every 3 years with cervical cytology alone, or every 5 years with high-risk HPV testing alone.	Low	Strong
4.3. Among women aged 30 to 65 years, we recommend AGAINST screening for cervical cancer every 5 years with high-risk HPV testing in combination with cytology (co-testing).	Very low	Strong
4.4. Among asymptomatic women aged 30 to 65 years old, we recommend screening for cervical cancer every 3 years using visual inspection with acetic acid, as an alternative to the Pap smear.	Moderate	Strong
<b>Question 5: Among otherwise healthy adults, should we do an annual ENT screening exam and dental check-up compared to no screening?</b>		
5.1. Among asymptomatic apparently healthy adults aged 35 years and older, we suggest AGAINST screening for oral cancer once every 3 years by trained health workers.	Low	Weak
5.2. Among adults aged 35 years and older who are smokers and/or alcohol drinkers, we recommend screening for oral cancer using visual examination once every 3 years by trained health workers.	Moderate	Strong
<b>Question 6: Among otherwise healthy adults, should the fecal immunochemical test be used instead of the fecal occult blood test, or no screening?</b>		
6.1. Among average-risk and apparently healthy adults, there is insufficient evidence to recommend for or against screening for colorectal cancer using the fecal immunochemical test over the fecal occult blood test.	Very low	N/A
<b>Question 7: Among apparently healthy, asymptomatic adults, should we do a mammogram, breast ultrasound, or clinical breast examination?</b>		
7.1. Among apparently healthy asymptomatic women aged 50 to 69 years, we recommend screening for breast cancer every one to two years using mammography.	Low	Strong
7.2. Among apparently healthy asymptomatic women aged 50 years and older, we recommend performing clinical breast examination every 2 years to screen for breast cancer.	Moderate	Strong
<b>Question 8: Among asymptomatic men aged 40 to 80 years old, should we do annual PSA determination with or without digital rectal exam, or digital rectal exam alone, compared to no screening?</b>		
8.1. Among asymptomatic males aged 50 to 64 years old, we suggest screening every 2 years with PSA and digital rectal exam for prostate cancer.	Low	Weak
<b>Question 9: Among asymptomatic, apparently healthy adults, should low-dose CT compared to chest X-ray be used?</b>		
9.1. Among asymptomatic apparently healthy adults with low risk for lung cancer, we suggest AGAINST annual low-dose CT scan to screen for lung cancer.	Very low	Weak
9.2. Among asymptomatic apparently healthy adults with high risk* for lung cancer, we suggest an annual low-dose CT scan to screen for lung cancer.  <i>* Risk factors: Age &gt;50 years with a history of smoking, Family history of lung cancer</i>	Very low	Weak
<b>Question 10: Among asymptomatic populations at risk for gastric cancer, should we do screening (i.e., upper gastrointestinal series, upper endoscopy) compared with no screening?</b>		
10.1. Among apparently healthy adults aged 40 to 70 years without risk factors, we suggest AGAINST routine screening for gastric cancer using either upper endoscopy or upper gastrointestinal series.	Very low	Weak
10.2. Among apparently healthy adults with high risk* for gastric cancer, we suggest doing active screening for gastric cancer using upper gastrointestinal series or upper endoscopy.  <i>* Risk factors: Age ≥40 years, Family history of gastric cancer, Documented history of precancerous lesions for gastric cancer (i.e., atrophic gastritis, intestinal metaplasia), History of H. pylori infection, Obesity, History of smoking, History of high consumption of salted food</i>	Very low	Weak

## Red Reflex Test in Screening for Retinoblastoma

**Recommendation 1.1:** Among all children less than 5 years, we suggest screening for retinoblastoma from the newborn period through serial ophthalmologic examinations using the red reflex test. (*Very low certainty of evidence, weak recommendation*)

**Recommendation 1.2:** Among infants and children with a high risk\* of developing retinoblastoma (i.e., positive family history), there is insufficient evidence to suggest for or against screening for retinoblastoma using the red reflex test. (*very low certainty of evidence*)

\* High risk refers to infants and children with suspicious findings in the red reflex test or with a positive family history of retinoblastoma. High-risk infants and children should be referred directly to an ophthalmologist.

**Key findings:** There was no randomized clinical trial that directly compared screening versus no screening for retinoblastoma, since there is currently no screening test that could detect retinoblastoma at the preclinical stage. Early detection, rather than screening, is performed. Indirect evidence (two retrospective studies, n=487; very low certainty of evidence) showed a statistically significant improvement (87.7%, 95% CI 59.9% to 80.3%; 91.0% vs 78.0% 5-yr survival, p<0.001) in the 5-year overall survival rate with early diagnosis of retinoblastoma.<sup>7,8</sup> Other observational studies (2 retrospective studies, n=105) demonstrated that early diagnosis through systematic screening according to an “intensive” schedule resulted in significantly improved ocular outcomes (e.g., enucleation rate, loss of vision or eye salvage rate) versus no systematic screening according to an ‘intensive’ schedule among retinoblastoma patients with a positive family history.<sup>9,10</sup> In the study by Rothschild et al., the enucleation rate was only 5.0% in the screening group versus 65% in the non-screened subjects (RR = 0.08, 95% CI 0.03 TO 0.24).<sup>9</sup> Another study by Yousef et al. showed that out of 77 affected eyes (of 46 patients), the eye salvage rate was 100.0% among screened eyes versus only 52.0% in the non-screened eyes (RR = 0.013, 95% CI 0.0008 TO 0.21).<sup>10</sup>

No cost-effectiveness studies were found on screening with the red reflex test. Implementing a nationwide vision screening program necessitates a strong commitment in terms of planning and budget allocation. Eye screening among infants may require professional care and appropriate facilities, which might involve higher costs. Hence, despite the importance of more comprehensive vision screening procedures, their implementation can be difficult in Low- to Middle-Income Countries (LMICs) due to a lack of financial and human resources.

**Justification:** The consensus panel considered that retinoblastoma is a priority health problem and screening with the red reflex test (RRT) was deemed equitable, acceptable, and feasible. Evidence was lacking on the use of the RRT as a screening tool for retinoblastoma among

high-risk children. Children with suspicious findings in the RRT or who have risk factors (e.g., positive family history) are referred directly to ophthalmologists. Early detection was favorable with small harm, although the panelists deemed that there was uncertain diagnostic accuracy, and that the certainty of evidence is very low.

## EBV DNA and/or Nasopharyngoscopy in Screening for Nasopharyngeal Cancer

**Recommendation 2.1:** Among asymptomatic, apparently healthy adults, we suggest AGAINST screening for nasopharyngeal cancer using an EBV DNA test and/or nasopharyngoscopy. (*Very low certainty of evidence, weak recommendation*)

**Recommendation 2.2:** Among asymptomatic, apparently healthy adults with a first-degree relative with a known nasopharyngeal cancer, we suggest screening for nasopharyngeal cancer using EBV DNA test and/or nasopharyngoscopy. (*Very low certainty of evidence, weak recommendation*)

**Key findings:** There was no direct evidence on the impact of screening versus no screening for nasopharyngeal cancer using Epstein-Barr Virus (EBV) DNA and/or nasopharyngoscopy. EBV DNA and EBV serology [i.e., IgA against Early Antigen antibody (EA-IgA), IgA against Viral Capsid Antigen antibody (VCA-IgA), IgA against Epstein Barr Nuclear Antigen1 antibody (EBNA1-IgA), and IgG against Replication and transcription activator antibody (Rta-IgG)] have mainly been used for screening nasopharyngeal cancer (NPCA) in endemic areas.<sup>11-13</sup> There is currently no gold standard and consensus on which EBV blood test is best to screen for NPCA. However, most studies used EBV DNA, EBNA1-IgA, and VCA-IgA. Many studies also combined these blood tests in screening.<sup>14</sup> Nasopharyngoscopy has been traditionally used together with or after a positive EBV blood test as part of a two- or a three-stage screening protocol and not as a sole screening tool.

There have been a few NPCA screening programs conducted independently by oncology centers in Southeast Asia. However, the results of these programs cannot be pooled as they differed in the screening modality used and the frequency of screening.

A retrospective study in Hong Kong on NPCA screening among family members of NPCA patients (n=1,199) was carried out between 1994 and 2005. The participants underwent annual physical examination, focused history taking, nasopharyngoscopy, and EBV serology tests (VCA-IgA and EBNA1-IgA) at the same time. Eighteen participants developed NPCA in the screening program. The sensitivity and specificity of EBV serology for the program were 89% and 87%, respectively. The NPCA patients who underwent screening had a significantly higher proportion of

Stage I disease (41.2% vs. 0.7%;  $p < 0.001$ ; Risk Difference 40.5%, 95% CI 17.1%, 63.9%) compared with patients with symptomatic NPCA referred during the same period. Additionally, the hazard ratio (HR) for cancer recurrence or death in patients from group 1 is 0.319 (95% CI: 0.103 to 0.994) when compared to patients in group 2. However, there was no long-term follow-up to determine overall survival.<sup>15</sup>

No cost-effectiveness analysis or studies were found looking into screening with EBV DNA and/or nasopharyngoscopy for nasopharyngeal carcinoma. The unit cost of screening can be as low as PhP 17,549.00 (EBV-DNA, nasopharyngoscopy, histopathology, and neck CT scan) in a government hospital, and as high as PhP 48,049.00 (EBV-DNA, nasopharyngoscopy, histopathology, neck MRI) in the private setting (e.g., cost data collected by the PHEX Neoplastic Disease Task Force from a survey of Philippine Hospitals including UP-PGH, Jose Reyes Memorial Medical Center, East Avenue Medical Center, Chong Hua Hospital, Southern Philippines Medical Center, Hi-Precision Diagnostics, and private hospitals in Metro Manila, 2021). These costs do not include IV sedation fees by an anesthesiologist (if warranted), additional immunohistochemical stains, and additional scans to look for distant metastases if diagnosed with NPCA. These also do not include the cost for a re-test for EBV using EBV-DNA or EBV serology to exclude a transient EBV infection, as some screening studies have implemented. Some will repeat the EBV blood test 4–12 weeks after, while others will go straight to nasopharyngoscopy and imaging after a positive blood test.

**Justification:** The consensus panel considered nasopharyngeal cancer as a priority health problem. Other guidelines did not specify an age range for screening, but ages 30 to 60 years were considered as an appropriate age range based on the available evidence and the panelists' experience with the disease. EBV blood test and/or nasopharyngoscopy were considered accurate tests, but EBV blood tests have limited accessibility. Among the EBV blood tests, EBV DNA is specified in the recommendation due to its higher diagnostic accuracy relative to the other tests, and its availability in the laboratories that offer EBV testing. Routine screening using EBV DNA test and/or nasopharyngoscopy was not deemed cost-effective, acceptable, or feasible, with uncertain evidence on patient values and preferences.

### Liver Ultrasound and/or AFP in Screening for Hepatocellular Carcinoma

**Recommendation 3.1: Among asymptomatic, apparently healthy adults, we suggest AGAINST the use of ultrasound with AFP every 6 months to screen for hepatocellular carcinoma.** (*Low certainty of evidence, weak recommendation*)

**Recommendation 3.2: Among patients at risk\* to develop hepatocellular carcinoma who have or have not progressed to cirrhosis, we recommend the use of ultrasound with AFP every 6 months to screen for hepatocellular carcinoma.** (*Moderate certainty of evidence, strong recommendation*)

\*Risk factors: Hepatitis B and/or C infection, Metabolic diseases, non-alcoholic/alcoholic liver diseases, A family history of liver cancer, Prolonged heavy alcohol consumption, Men >40 years old

**Key findings:** Based on one RCT, screening every six months using ultrasound (US) and alpha-fetoprotein (AFP) among patients predisposed to develop hepatocellular carcinoma (HCC) was associated with a 40% lower risk of HCC-related mortality compared to unscreened individuals (95% CI 8% to 61%).<sup>16</sup> There was no significant difference (Rate ratio 1.37, 95% CI 0.99 to 1.89) between the screened group and the unscreened group in terms of the number of cancers detected, but there was a significantly higher proportion of early stage HCC (subclinical stage; stage 1 60.5% screening group vs 0.0% control group, ( $p < 0.01$ ; RR 82.07 95% CI 4.92 to 1370.09) detected in the screened group. Although early detection can lead to longer survival, the magnitude of the benefit is unclear since longer survival may also be due to earlier diagnosis (lead time bias). Almost two-thirds of HCC patients are expected to survive for at least 1 year with screening.<sup>16</sup>

In terms of harm, screening using US and AFP causes minimal discomfort but no serious physical harm. However, there are risks associated with the performance of confirmatory tests for patients with positive screening results.<sup>17</sup> Confirmatory US and contrast-enhanced CT scan carry a 10% risk of mild adverse events, but the specific adverse events were not reported.<sup>18</sup>

No cost-effectiveness analysis or studies were found on screening with liver US and/or AFP for hepatocellular carcinoma. In the context of a health system with finite resources, opportunity costs of programs must be considered. It is not enough to evaluate the program's efficacy, benefits, harms, and costs. It is also necessary to assess the other programs that will be displaced and their attendant benefit, harms, and costs that will be foregone.<sup>19</sup>

**Justification:** The consensus panel considered that HCC is a priority health problem. Despite the low certainty of evidence, the benefits of screening with US and AFP and the tests' diagnostic accuracy were considered to outweigh potential harms. However, routine screening with US and AFP entailed moderate costs, and the panel deemed that

screening with US and AFP had poor acceptability and feasibility with uncertain effects on equity. With screening, the number of transplant-eligible patients is expected to increase. However, there are limited facilities that could perform a liver transplant. There are other treatment modalities for HCC aside from liver transplantation, such as surgical resection, ablation, embolization, and systemic treatments. Patients with cirrhosis may be asymptomatic, and the diagnosis of cirrhosis would entail the same tests (US and AFP).

### HPV Testing, Cytology, Co-testing, or Visual Inspection with Acetic Acid in Screening for Cervical Cancer

**Recommendation 4.1: Among women aged 21 to 29 years, we recommend AGAINST screening for cervical cancer with cervical cytology or visual inspection with acetic acid.** (*Low certainty of evidence, strong recommendation*)

**Recommendation 4.2: Among women aged 30 to 65 years, we recommend screening for cervical cancer every 3 years with cervical cytology alone, or every 5 years with high-risk HPV testing alone.** (*Low certainty of evidence, strong recommendation*)

**Recommendation 4.3: Among women aged 30 to 65 years, we recommend AGAINST screening for cervical cancer every 5 years with high-risk HPV testing in combination with cytology (co-testing).** (*Very low certainty of evidence, strong recommendation*)

**Recommendation 4.4: Among women aged 30 to 65 years, we recommend screening for cervical cancer every 3 years using visual inspection with acetic acid, as an alternative to the Pap smear.** (*Moderate certainty of evidence, strong recommendation*)

**Key findings:** A cluster RCT conducted in India investigated the effect of HPV testing using the Hybrid Capture II assay, cytology, and visual inspection with acetic acid (VIA) among women 30–59 years old (n=131,476).<sup>20</sup> Participants were randomized into four groups [HPV testing (n=34,126), cytology (n=32,058), VIA (n=34,074), and standard care control group (n=31,488)] with an 8-year follow-up.

There were more cases of CIN2+ detected with cytology or HPV testing compared to no screening. There was a 53% reduction (HR 0.47, 95% CI 0.32 to 0.69) in the detection of cervical cancer (Stage II and above) in the HPV testing group compared to no screening. Moreover, there was a decreased risk of cervical cancer-related mortality in the HPV testing group compared to no screening (HR 0.52 (95% CI 0.33, 0.83)). The age-standardized rate of invasive cancer among those with negative results on cytologic testing or VIA was >4x compared with HPV-negative women, highlighting the high negative predictive value (NPV) with HPV testing.

There were no randomized studies on the effect of HPV co-testing on mortality and detection of CIN and invasive cancer compared to a no-screening approach.

HPV testing and co-testing are more costly compared to cytology-based testing. In addition, false positives from HPV testing may result in more referrals for colposcopy.<sup>21</sup> A local cost-utility analysis evaluated screening (VIA and Pap smear) alone or in combination with vaccination against HPV infection using various coverage implementations. Pap smear was NOT deemed to be cost-effective due to its high cost.<sup>22</sup>

**Justification:** The consensus panel considered cervical cancer as a priority health problem. Despite the low certainty of evidence, the panelists strongly recommended screening using HPV testing or cytology since these tests were deemed to have moderate benefit with small harm. Screening using HPV testing, cytology, or co-testing was deemed to have high diagnostic accuracy. However, co-testing was deemed to entail high costs with a low to moderate certainty of evidence on the required resources. Screening using HPV testing, cytology, or visual inspection with acetic acid was deemed to be equitable, acceptable, and feasible with possibly important uncertainty or variability in terms of patient values and preferences.

### ENT Screening and Dental Check-Up for Screening for Oral Cancer

**Recommendation 5.1: Among asymptomatic, apparently healthy adults aged 35 years and older, we suggest AGAINST screening for oral cancer once every 3 years by trained health workers.** (*Low certainty of evidence, weak recommendation*)

**Recommendation 5.2: Among adults aged 35 years and older who are smokers and/or alcohol drinkers, we recommend screening for oral cancer using visual examination once every 3 years by trained health workers.** (*Moderate certainty of evidence, strong recommendation*)

**Key findings:** There was no evidence found on oral cancer screening using toluidine blue and fluorescent light compared to no screening. A Cochrane review that included one RCT was used to examine the evidence on the benefits and harms of a screening program for oral cancer over a 15-year follow-up period.<sup>23</sup> There were 279 individuals in the screening group and 244 in the control group who were diagnosed with oral cancer from 1996 to 2010. The screening arm had a 12% lower death rate than the no-screening arm, although this difference was not statistically significant (Rate ratio 0.88 (95% CI 0.69 to 1.12)).<sup>24</sup> However, among high-risk individuals (tobacco and/or alcohol users), there was significant reduction in mortality among those who were screened compared to no screening (RR 0.80, 95% CI 0.69 to 0.94).<sup>24</sup>

There were no available data on the quality of life and psychological effects among screened participants. There were no cases of severe adverse events such as mortality, vasovagal

attack, anaphylactic response, hemorrhage, hospitalization, infection, severe pain, or other adverse reactions (cosmetic or functional disabilities) as a result of screening, biopsies, or removal of lesions.<sup>24</sup>

In a low-resource country like India, the benefit of the screening program using visual examination was 269.31 life-years saved per 100,000 for all individuals and 1,437.64 life-years saved per 100,000 for those at high risk.<sup>19</sup> The incremental cost per life-year saved was USD 835.00 for all individuals, which decreased to USD 156.00 for individuals with high risk for oral cancer.<sup>25</sup> Visual examination for oral cancer screening was found to be cost-effective.<sup>25</sup> Visual examination may be performed for less than USD 6.00 per individual, considering the cost of diagnostic tests, treatment required, and the associated patients' time (based on the daily minimum wage of USD 5.00).<sup>25</sup>

**Justification:** The consensus panel considered oral cancer as a priority health problem. The majority of panelists favored annual ear, nose, and throat (ENT) screening and dental check-up due to the large benefit and good diagnostic accuracy despite the moderate costs and low certainty of evidence.

### Fecal Immunochemical Test in Screening for Colorectal Cancer

**Recommendation 6:** Among average-risk and apparently healthy adults, there is insufficient evidence to recommend for or against screening for colorectal cancer using the fecal immunochemical test over the fecal occult blood test. (*Very low certainty of evidence*)

**Key findings:** There was no direct evidence found on screening versus no screening for colorectal cancer using the Fecal Immunochemical Test (FIT). Biennial screening with FIT using either OC-Sensor or HM Jack, done 1–3 times, was associated with lower colorectal cancer (CRC)-specific mortality after a 6-year follow-up compared to no screening (adjusted RR 0.90, 95% CI 0.84 to 0.95).<sup>26,27</sup>

There were no studies that examined serious harms related to stool testing using FIT or fecal occult blood test (FOBT) since these are considered non-invasive tests, although diagnostic inaccuracy or harm from follow-up confirmatory tests, such as scoping procedures, are possible. One of the adverse events from colonoscopy following an abnormal stool test (FIT or FOBT) is serious bleeding. The pooled estimate was 17.5 events per 10,000 procedures (95% CI 7.6 to 27.5).<sup>26</sup>

CRC is considered preventable with early screening. However, screening for CRC was not included in the Z package established by PhilHealth in 2016, which aimed to fully subsidize the treatment cost of enrolled cancer patients.<sup>28</sup> In 2018, a cost-utility analysis (CUA) and budget impact analysis (BIA) determined the feasibility of a screening benefit package in the Philippines.<sup>29</sup> Four different screening modalities were evaluated: (a) FOBT

confirmed by colonoscopy every 10 years; (b) FIT confirmed by colonoscopy every 10 years; (c) FIT confirmed by flexible sigmoidoscopy and colonoscopy screening every 10 years; and (d) no screening. All screening modalities were noted to be cost-effective, considering that the ICERs fell below the 1 GDP per capita threshold. The most cost-effective strategy was FIT, followed by colonoscopy every 10 years. The findings of this CUA also showed that either FOBT or FIT followed by colonoscopy were reasonable screening strategies for CRC. The budget impact of both interventions was Php 9 billion with moderate adherence, or Php 1 billion assuming low adherence in the first year of national program implementation.<sup>29</sup>

**Justification:** The consensus panel considered CRC as a priority health problem. During the discussions, a select few panelists favored screening using FIT due to the large benefit, small harm, and diagnostic accuracy of the test. Screening using FIT was perceived as acceptable and feasible, would probably increase equity, and is associated with possible important uncertainty or variability in terms of patient values and preferences. Other Asian populations use FIT for screening CRC. However, despite these discussions, the consensus panel ultimately decided to make no recommendations for CRC screening using FIT over FOBT for CRC screening.

### Mammogram, Breast Ultrasound, or Clinical Breast Examination in Screening for Breast Cancer

**Recommendation 7.1:** Among apparently healthy, asymptomatic women aged 50 to 69 years, we recommend screening for breast cancer every one to two years using mammography. (*Low certainty of evidence, strong recommendation*)

**Recommendation 7.2:** Among apparently healthy, asymptomatic women aged 50 years and older, we recommend performing clinical breast examination every 2 years to screen for breast cancer. (*Moderate certainty of evidence, strong recommendation*)

**Key findings:** Based on data from eight RCTs (n=615,023), screening with mammography and/or CBE was shown to decrease the risk of breast cancer mortality compared to no screening (median follow-up 23 years) (RR 0.85, 95% CI 0.78 to 0.93).<sup>30-34</sup> Significant reduction in breast cancer mortality was also observed among those screened with mammography and/or CBE compared to those who were not screened (RR 0.81, 95% CI 0.70 to 0.92), with a long-term median follow-up of 18 years.<sup>5,6,10-12</sup> No significant difference was observed between mammography and/or CBE compared to no screening for all-cause mortality (RR 0.99, 95% CI 0.98 to 1.01) for a median follow-up of 16 years.

A prospective cluster RCT on CBE conducted by trained female primary health workers every 2 years for a total of four screening CBEs compared to no screening showed no significant reduction in breast cancer mortality in the overall

study population (RR 0.85, 95% CI 0.71 to 1.01).<sup>35</sup> Post hoc subgroup analysis showed a significant reduction in breast cancer mortality in women aged  $\geq 50$  years (RR 0.71, 95% CI 0.54 to 0.94), but no significant reduction in women  $< 50$  years old (RR 0.93, 95% CI 0.79 to 1.09).<sup>35</sup> There was no significant reduction in all-cause mortality among all ages (RR 0.95, 95% CI 0.81 to 1.10).

No RCTs involving breast US compared to no screening were identified. Available studies have suggested the use of US as a supplement to mammography in the evaluation of high-risk women or those with higher breast density.

Estimates of overdiagnosis varied widely.<sup>36-40</sup> Among women aged 40–49 years, 55% of identified invasive and in situ cancers were estimated to be over-diagnosed, and 48% of identified invasive cancers were estimated to be over-diagnosed 20 years after screening. Among women aged 50–59 years, 25% of identified invasive and in situ cancers were estimated to be over-diagnosed, and 16% of identified invasive cancers were estimated to be over-diagnosed in 5 years after screening.

Cost-effectiveness studies showed that screening with mammography was cost-effective compared to no screening.<sup>41-43</sup>

**Justification:** The panelists favored screening because of the diagnostic accuracy of screening, because the benefits were deemed to outweigh the harms, despite the low certainty of evidence and the moderate costs of screening. Screening using a mammogram, breast ultrasound, or a clinical breast examination was considered acceptable and feasible, although not equitable. It was emphasized that clinical breast examination (which is performed by a trained health worker) is different from a self-breast examination that could be done by a patient.

### PSA Determination and/or Digital Rectal Exam in Screening for Prostate Cancer

**Recommendation 8: Among asymptomatic males aged 50 to 64 years old, we suggest screening every 2 years with PSA and digital rectal exam for prostate cancer. (Low certainty of evidence, weak recommendation)**

**Key findings:** Three RCTs had different pre-biopsy thresholds for prostate-specific antigen (PSA) values and had different screening intervals. These RCTs showed no significant difference in prostate cancer-specific mortality (RR 0.92, 95% CI 0.8 to 1.07) and all-cause mortality (RR 0.99, 95% CI 0.97 to 1.02) for screening with PSA compared with no screening.<sup>44-46</sup> The highest reduction in prostate cancer-specific mortality was seen in patients in Sweden who were screened every 2 years for 20 years and had a PSA screening threshold of 2.5–3.0 ng/mL (RR 0.58, 95% CI 0.46 to 0.72).<sup>47</sup>

There is no available data from the above RCTs to analyze the effect of screening versus no screening of high-

risk patients on mortality. One RCT compared screening of *BRCA1/2* germline pathogenic mutation carriers with screening of participants who were negative for *BRCA1/2* mutation. Those with *BRCA2* mutations had a higher incidence of prostate cancer, a younger age at diagnosis, and clinically significant tumors.<sup>48</sup>

There is no evidence on the effectiveness of standalone digital rectal examination (DRE) compared to no screening for prostate cancer in improving clinical outcomes.<sup>49,50</sup>

Different PSA thresholds were used in the RCTs reviewed. Lower thresholds of PSA led to the diagnosis of more cases of prostate cancer, but false positive rates were 11.3% to 19.8% when cutoffs were 4 ng/ml and 3 ng/ml, respectively.<sup>51</sup> False positive results lead to unnecessary additional testing and possible biopsy. The most frequent complications with prostate biopsy were blood in semen (93%), blood in urine (66%), pain (44%), shivers (19%), and fever (18%). Of the patients who underwent biopsy, 1.4% (95% CI 0.8 to 2.4%) were admitted to the hospital due to sepsis.<sup>52</sup>

There are no local cost-effectiveness evaluations of prostate cancer screening. A study in Sweden showed that the most cost-effective approach was screening between ages 55–59 at 2-year intervals, which cost \$72,791.00 per Quality-Adjusted Life Years (QALY).<sup>53</sup>

**Justification:** The consensus panel considered the following when formulating this recommendation: Prostate cancer is a priority health problem. Screening with PSA and DRE was favored, with small-to-moderate benefit, small harm, and low-to-moderate costs. Screening with PSA and DRE was equitable, acceptable, and feasible, with possible important uncertainty or variability with patient values and preferences. However, there is a great risk for overtreatment, and the panelists emphasized the importance of informing the patient of this risk prior to screening.

### Low-Dose CT in Screening for Lung Cancer

**Recommendation 9.1: Among asymptomatic, apparently healthy adults with low risk for lung cancer, we suggest AGAINST annual low-dose CT scan to screen for lung cancer. (Very low certainty of evidence, weak recommendation)**

**Recommendation 9.2: Among asymptomatic, apparently healthy adults with high risk\* for lung cancer, we suggest an annual low-dose CT scan to screen for lung cancer. (Very low certainty of evidence, weak recommendation)**

\* Risk factors: Age  $> 50$  years with a history of smoking, Family history of lung cancer

**Key findings:** Evidence on the diagnostic accuracy, benefits, and harms of low-dose computed tomography (LDCT) for lung cancer screening was obtained from three systematic reviews.<sup>54-56</sup> All these reviews recruited participants at high risk for lung cancer based on age and smoking history.

Eight RCTs showed that LDCT significantly reduced lung cancer-related deaths compared to no screening or screening with chest radiograph (CXR) (RR 0.87, 95% CI 0.78 to 0.98). Subgroup analysis showed that the benefit in reducing lung cancer-related deaths was observed only when LDCT was compared to no screening (6 RCTs; RR 0.80, 95% CI 0.69 to 0.92).<sup>8</sup> The 2 RCTs that compared LDCT against chest X-ray (CXR) showed no difference in lung cancer-related deaths (RR 0.95, 95% CI 0.82 to 1.10). Eight RCTs showed no significant difference in LDCT in all-cause mortality compared to no screening or screening with CXR (RR 0.99, 95% CI 0.94 to 1.05).<sup>54</sup>

Nine RCTs showed that screening with LDCT resulted in significantly higher early-stage (Stage I–II) tumor detection rates compared to no screening or screening with CXR (RR 2.42, 95% CI 1.71–3.44).<sup>54</sup> Subgroup analysis showed significantly higher early-stage tumor detection rates when LDCT was compared with CXR (6 RCTs; RR 1.52, 95% CI 1.04 to 2.23%) and even higher early-stage tumor detection rates when compared to no screening (RR 2.73, 95% CI 1.91 to 3.90).

Five RCTs estimated that the percentage of over-diagnosed lung cancer cases was at 30% (95% CI 6% to 55%).<sup>56</sup> This figure is higher for LDCT versus no screening at 38% (95% CI 14% to 63%).

No cost-effectiveness studies were found on screening for lung cancer using LDCT. Based on a study in 2018, the mean combined out-of-pocket health expenditures of Filipino cancer patients were PhP 181,789.00.<sup>57</sup> Indirect costs, including transportation fees, meals, and outside caregiver salaries, amounted to PhP 70,510.20. Medication for symptomatic relief (non-chemotherapy) expenses amounted to PhP 51,138.42. Hospitalization costs ranged from no expenses to PhP 9,885.57.<sup>12</sup> Treatment for lung cancer was associated with a catastrophic financial burden. Chemotherapy alone costs PhP 50,000–120,000 per month. Medicines were estimated to cost as much as PhP 100,000 or more monthly.<sup>58</sup>

**Justification:** The consensus panel considered that for high-risk patients, screening with LDCT was associated with moderate-to-large clinical benefit, small harms, and had good diagnostic accuracy, although there may be high costs. Screening with LDCT was considered equitable and acceptable, with variable feasibility. There was not enough data for persons with low baseline risk for lung cancer, hence the panel formulated a weak recommendation AGAINST screening for this population group.

## Upper Gastrointestinal Series or Upper Endoscopy in Screening for Gastric Cancer

**Recommendation 10.1:** Among apparently healthy adults aged 40 to 70 years without risk factors, we suggest AGAINST routine screening for gastric cancer using either upper endoscopy or upper gastrointestinal series. (*Very low certainty of evidence, weak recommendation*)

**Recommendation 10.2:** Among apparently healthy adults with high risk\* for gastric cancer, we suggest doing active screening for gastric cancer using upper gastrointestinal series or upper endoscopy. (*Very low certainty of evidence, weak recommendation*)

\*Risk factors: Age  $\geq$ 40 years, Family history of gastric cancer, Documented history of precancerous lesions for gastric cancer (i.e., atrophic gastritis, intestinal metaplasia), History of *H. pylori* infection, Obesity, History of smoking, History of high consumption of salted food

**Key findings:** There were no RCTs that compared active screening using either upper endoscopy or upper gastrointestinal series with no screening among apparently healthy or asymptomatic adults on mortality and other patient-important outcomes. It was noted in the literature search that RCTs were difficult to implement, particularly in countries like Korea and Japan, where gastric cancer screening has been introduced in their national programs.<sup>59</sup>

A systematic review and meta-analysis that included observational studies evaluated the effect of at least one endoscopic screening (including mass screening or opportunistic screening) followed by entry or no entry into a surveillance program among adults aged  $>$ 18 years without a diagnosis of gastric cancer in the general population. These studies compared screening with no screening, other screening methods (radiographic screening), or expected numbers in the general population.<sup>59</sup> Based on 10 studies (n=342,013), screening was associated with a significant reduction in gastric cancer-specific mortality compared to no screening (RR 0.60, 95% CI 0.49 to 0.73).<sup>59</sup>

A large case-control study reported significantly reduced odds of all-cause mortality among those screened using upper endoscopy compared to no screening (OR 0.83, 95% CI 0.81 to 0.85), with the odds ratios increasing directly with age but not with economic status.<sup>60</sup> Similarly, a cohort study reported significant reduction in all-cause mortality rates among those screened using upper endoscopy compared to no screening (HR of 0.80, 95% CI 0.72 to 0.89, for  $<$ 2 years follow up; HR 0.83, 95% CI 0.76 to 0.91, for 2–5 years follow up).<sup>61</sup>

Among the cohort studies that evaluated the effect of gastric cancer screening by photofluorography on mortality, we pooled the results from four individual studies regarding gastric cancer-related mortality. The overall pooled relative risk estimates for gastric cancer-related mortality among screened individuals compared to unscreened individuals were RR 0.63 (95% CI 0.54 to 0.73), indicating a significant 37% reduction in mortality associated with screening.

Cost-effectiveness studies among Filipino Americans in the U.S. (patients aged 50 years, with subsequent endoscopy only when indicated) showed that one-time endoscopic screening bundled with colonoscopy for colorectal cancer screening was the most cost-effective. Among Asian Americans, Filipino Americans had the highest ICER, but these were still cost-effective at the predetermined willingness-to-pay threshold. The ICER for males was higher (USD 88,190) than for females (USD 83,732). Biennial endoscopic surveillance was less effective, caused more harm, and was more costly.<sup>62</sup> Overall among Asian Americans, one-time endoscopic screening bundled with colonoscopy was also found to be cost-effective at the predetermined willingness-to-pay threshold of USD 100,000/QALY, with an ICER of USD 71,451/QALY.<sup>63</sup>

*Justification:* The consensus panel considered the following when formulating this recommendation: Gastric cancer is a priority health problem. Screening with upper GI series or upper endoscopy is favored as there is perceived tradeoff between the large benefit and the good diagnostic accuracy of the tests, with the moderate harm and moderate cost of the tests. The certainty of evidence of benefits and harms was judged to be very low, while the certainty of the evidence for resource requirements was deemed moderate. Screening with upper GI series or upper endoscopy is feasible with reduced equity, variable acceptability, and possibly important uncertainty or variability with patient values and preferences. Data used as the basis for the recommendations came from countries with a high incidence of gastric cancer.

## DISCUSSION

The PHEX Neoplastic Disease Task Force formulated 20 recommendations regarding screening for ten neoplastic diseases and their risk factors. This CPG is a systematic synthesis of evidence to address screening for the following neoplastic diseases: retinoblastoma among children; nasopharyngeal carcinoma among asymptomatic, at-risk adults; liver cancer among asymptomatic, apparently healthy individuals; cervical cancer among asymptomatic, apparently healthy women; oral cancer among asymptomatic apparently healthy adults; colorectal cancer among apparently healthy, average-risk adults; breast cancer among asymptomatic, apparently healthy women; prostate cancer among asymptomatic, 40–80-year old men; lung cancer among asymptomatic, apparently healthy adults; and gastric cancer among asymptomatic apparently healthy adults.

The PHEX Task Force accentuates some caveats of this CPG using equity and applicability lenses. The 11-member consensus panel was composed of a patient representative, 2 representatives from the DOH, and 8 clinicians from specialty oncology societies. The 10 evidence review experts were clinical epidemiologists and/or medical oncologists.

## Research Gaps

Many neoplastic diseases covered in this CPG lacked direct evidence on the screening methods specified in the clinical question: EBV blood test versus nasopharyngoscopy among the general population and high-risk persons (NPCA); US and AFP in the general population (HCC); HPV co-testing and primary HPV testing (cervical cancer); toluidine blue or fluorescent light versus no screening (oral cancer); FIT versus FOBT (CRC); breast US versus no screening (breast cancer); DRE versus no screening (prostate cancer); LDCT versus no screening for the low-risk population (lung cancer); and active screening using either upper endoscopy or upper gastrointestinal series versus no screening (gastric cancer). There is no screening test capable of detecting retinoblastoma in the preclinical phase, and the evidence for the RRT was only for the diagnosis of ocular abnormalities in general. It was suggested during the CP meeting that future CPGs on retinoblastoma could investigate the use of indirect funduscopy as a tool for early diagnosis. In terms of benefits and harms, there were no studies that covered overall survival and NPCA-specific mortality for NPCA, and all-cause mortality for oral cancer and CRC. Studies on psychological distress were also lacking for HCC and oral cancer.

Conducting trials on some cases, such as for gastric cancer, presents a challenge as high-incidence countries have long-established screening programs for these cancers, making it difficult to recruit participants. The non-invasiveness of FIT and FOBT as stool exams also deters the conduct of further large-scale trials to directly compare the two screening tests. Additionally, while there have been cost-effectiveness studies and acceptability studies done for many of the neoplasms covered above, many of these studies were conducted in Western settings or in countries with incomparable disease burden. Hence, these may not apply to the Philippine setting.

The clinical question on CRC had no recommendation by the panel regarding screening. The previous PHEX guidelines had already asked the question “Among otherwise healthy adults should screening for colorectal cancer using a fecal occult blood test compared to no screening be done?”, and the recommendation of the consensus panel then was “Among asymptomatic apparently healthy adults aged at least 50, we recommend screening for colorectal cancer using annual FOBT or FIT, followed by colonoscopy, when indicated (strong recommendation, high certainty evidence)”. The clinical question on screening for colorectal cancer in this set of clinical guidelines now asks whether a fecal immunohistochemical test is a more accurate screening test than a fecal occult blood test. For this question, the recommendation is “Among average risk and apparently healthy adults, there is insufficient evidence to recommend for or against screening for colorectal cancer using the fecal immunochemical test over the fecal occult blood test.”

## CONCLUSION

Through a comprehensive and systematic search of the best available evidence, the Neoplastic Diseases Task Force developed 20 recommendations on screening and risk factor assessment for 10 specific questions on neoplastic diseases. These recommendations serve as guidance on screening neoplastic diseases at the primary care level.

### Disclaimer

This guideline is intended to be used by general practitioners, specialists, and health professionals who are primary care providers. Although adherence to this guideline is encouraged, it should not restrict the primary care providers from using their sound clinical judgment in handling individual cases. Payors and policymakers, including hospital administrators and employers, can also utilize this 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.

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.

The content of this CPG is the intellectual property of the DOH. Kindly provide the proper citations when using any part of this document in lectures, research papers, and any other format presented to the public. The electronic version of this material can be accessed online on the DOH website.

Queries, suggestions, and other concerns regarding this CPG may be directed to the DOH office by email.

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All authors certified fulfillment of ICMJE authorship criteria.

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## APPENDIX

### Summary of Questions

Question	Critical Outcomes	Question	Critical Outcomes
<i>Should we do annual ophthalmologic examination compared to no screening among children?</i>	<ul style="list-style-type: none"> <li>Retinoblastoma-related mortality</li> <li>Five-year overall survival (OS) rate</li> <li>Loss of vision (ocular outcomes):</li> <li>Adverse events:                             <ul style="list-style-type: none"> <li>Toxicity related to pupillary dilation</li> <li>Pain, discomfort, bradycardia, respiratory depression, and hypertension</li> <li>False-positive findings leading to parental anxiety and over-referral</li> </ul> </li> <li>Diagnostic performance of screening tests:                             <ul style="list-style-type: none"> <li>Sensitivity and specificity</li> <li>Positive likelihood ratio (PLR); Negative likelihood ratio (NLR)</li> <li>Diagnostic odds ratio</li> </ul> </li> </ul>	<p><i>Should the fecal immunochemical test (FIT) be used instead of the fecal occult blood test (FOBT), or should there be no screening among otherwise healthy adults?</i></p> <ul style="list-style-type: none"> <li>CRC-Specific Mortality</li> <li>All-cause mortality</li> <li>Adverse Events</li> <li>Diagnostic Performance of FIT in Diagnosing CRC</li> <li>Diagnostic Performance of FOBT in Diagnosing CRC</li> </ul>	
<i>Among asymptomatic populations at risk for nasopharyngeal carcinoma (NPCA), should we use the EBV blood test and/or nasopharyngoscopy compared with no screening to decrease mortality?</i>	<ul style="list-style-type: none"> <li>NPCA Incidence</li> <li>NPCA-Specific Mortality</li> <li>All-Cause Mortality</li> <li>Progression-Free Survival</li> <li>Sensitivity and Specificity of EBV Serology; Plasma EBV DNA Testing; EBV Blood Tests</li> <li>Disease-Free Survival (DFS)</li> <li>Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) for EBV Blood Tests</li> </ul>	<p><i>Should a mammogram, breast ultrasound, or clinical breast examination be done among asymptomatic, apparently healthy women?</i></p> <ul style="list-style-type: none"> <li>Breast Cancer Mortality</li> <li>All-Cause Mortality</li> <li>Overdiagnosis from Mammography Screening</li> <li>False-Positive Mammography Rates</li> <li>Biopsies on False-Positive Results</li> <li>Sensitivity and Specificity; diagnostic performance of testing</li> <li>Adverse events</li> </ul>	
<i>Should we perform semi-annual or annual liver ultrasound and/or AFP among asymptomatic, healthy adults to detect hepatocellular carcinoma?</i>	<ul style="list-style-type: none"> <li>HCC Mortality</li> <li>Survival Rates (1-year, 2-year, 3-year, 4-year, 5-year survival)</li> <li>Proportion of Cancers Detected</li> <li>Harms Associated with HCC Screening</li> <li>Adverse Events from Confirmatory Tests</li> <li>False Negative Results and Delayed Diagnosis</li> <li>Sensitivity and Specificity of Screening Tests (US and AFP)</li> </ul>	<p><i>Among asymptomatic men aged 40–80 years old, should we perform annual PSA determination with DRE, PSA alone, or DRE alone compared to no screening to decrease prostate cancer mortality?</i></p> <ul style="list-style-type: none"> <li>Prostate Cancer-Specific Mortality</li> <li>All-Cause Mortality</li> <li>False Positive Results from PSA Screening</li> <li>Complications and Adverse Effects of Prostate Biopsy</li> <li>Diagnostic Performance e.g., (PSA Alone in; PSA + DRE)</li> <li>Sensitivity and Specificity</li> <li>Positive and Negative likelihood ratios</li> </ul>	
<i>Should we perform semi-annual or annual liver ultrasound and/or AFP among asymptomatic, healthy adults to detect hepatocellular carcinoma?</i>	<ul style="list-style-type: none"> <li>HCC Mortality</li> <li>Survival Rates (1-year, 2-year, 3-year, 4-year, 5-year survival)</li> <li>Proportion of Cancers Detected</li> <li>Harms Associated with HCC Screening</li> <li>Adverse Events from Confirmatory Tests</li> <li>False Negative Results and Delayed Diagnosis</li> <li>Sensitivity and Specificity of Screening Tests (US and AFP)</li> </ul>	<p><i>Should low-dose CT compared to chest X-ray be used for early detection of lung cancer among asymptomatic, apparently healthy adults?</i></p> <ul style="list-style-type: none"> <li>Lung Cancer-Related Mortality</li> <li>All-Cause Mortality</li> <li>Overdiagnosis Rates</li> <li>False-Positive Rates (Baseline and Subsequent Screening Rounds)</li> <li>Complications Following False-Positive Results</li> <li>Sensitivity and Specificity of LDCT for Lung Cancer Detection</li> <li>Diagnostic Accuracy of LDCT</li> </ul>	
<i>Among asymptomatic, apparently healthy women, should we do screening for cervical cancer using HPV testing alone, cytology alone, or co-testing (cytology + HPV testing)?</i>	<ul style="list-style-type: none"> <li>Incidence of CIN2+, all Cervical Cancer</li> <li>Cervical Cancer-Related Mortality</li> <li>Incidence of Cervical Cancer with Co-Testing</li> <li>Adverse Events of Screening and Treatment Procedures</li> <li>False Positive Rates for CIN2+ Detection in Co-Testing</li> <li>Diagnostic Accuracy of HPV Testing, Cytology, and Co-Testing</li> <li>Diagnostic Performance of Pap Smear, HPV DNA Test, and Co-Testing</li> </ul>	<p><i>Among asymptomatic populations at risk for gastric cancer, should we do active screening (i.e., upper GI series, serum pepsinogen, H. pylori serology, upper endoscopy)?</i></p> <ul style="list-style-type: none"> <li>Gastric Cancer-Specific Mortality</li> <li>All-Cause Mortality</li> <li>Adverse Events of Upper Endoscopy Screening</li> <li>Sensitivity and Specificity</li> <li>Diagnostic Accuracy</li> <li>False-Negative Cases</li> </ul>	
<i>Should we do annual ENT screening exams and dental check-ups compared to no screening among otherwise healthy adults?</i>	<ul style="list-style-type: none"> <li>Oral Cancer Mortality</li> <li>Five-Year Survival Rate</li> <li>Oral Cancer Incidence</li> <li>Harms of Screening and Diagnostic Procedures</li> <li>Sensitivity of Visual Examination for Detecting Oral Cancer</li> <li>Specificity and Positive Predictive Value of Screening Programs</li> </ul>		