Report of the Screening Test Review Committee

ACADEMY OF MEDICINE, SINGAPORE

PATRON: PRESIDENT OF REPUBLIC OF SINGAPORE

March 2019

Executive Summary

Health screening is conducted to facilitate early diagnosis of diseases that have yet to manifest, so that treatment and intervention can be instituted promptly to achieve good health outcomes. Hence, it is conducted on individuals who have not sought medical attention on account of symptoms of that disorder, and individuals who considered themselves to be healthy may, after screening, be identified as potentially ill. In view of this, screening needs to be applied with much care, taking into consideration the potential benefits and harms to the individual. The World Health Organization (WHO) recommends that screening should follow specific principles, including:

a. Screening should be done only for an important heath problem of serious consequence, so that it could potentially have clear benefits to people's health.
b. The screening test must be reliable enough, and not cause harm to the person being screened.
c. There must be an acceptable and effective treatment for the disease when detected at an early stage, and scientific evidence that treatment of the disease at the early stage would yield better health outcomes.

While there are tests like the Pap smear and Faecal Immunochemical Test (FIT) that are suitable to be applied population-wide because of the scientific evidence supporting them, there are tests which are not evidence-based, and when conducted, can lead to significant physical and psychological harms to those screened. Given the wide range of medical conditions for which screening is being offered, and the tests available for screening, a framework to categorise screening tests is necessary.

The Screening Test Review Committee has reviewed the appropriateness of specific screening tests based on scientific evidence of their effectiveness and the potential benefits and harms. This report presents the recommendations on the various screening tests with respect to the disease being screened for, and serves as a guide to medical professionals who provide screening, and to individuals who wish to undergo screening. The report tiers its recommendations by placing the screening tests into 3 categories (more info at Table 1):

Category 1 – Suitable for population-level screening
There is good and robust evidence that the screening test is both clinically effective and cost effective for use to screen the population.
E.g. Pap smear to screen for cervical cancer, and FIT to screen for colorectal cancer.

Category 2 – Suitable for individual-level decision
The net benefit does not outweigh the risk in general populations, but the screening may be useful for high-risk populations, or there is some evidence that the screening test is effective but cost-effectiveness has not been evaluated or not favourable.
E.g. Kidney function test is useful for screening for impairment of kidney function in persons with diabetes, but not for screening the general population.

Category 3 – Not recommended
There is insufficient evidence to make a decision regarding the usefulness of the test, or there is good evidence that the screening test is not cost-effective, or that the net harm outweigh benefits.
E.g. CA125

Table of Contents

Screening Test Review Committee

Screening tests are widely available in Singapore, and are provided by both public and private healthcare institutions. In view of the general interest in health screening, a review of the situation would be useful.

A Screening Test Review Committee, comprising representatives from the Academy of Medicine, Singapore (AMS) was set up to provide expert opinion on the appropriate use of specific screening tests.

The composition of the Committee and its Terms of Reference are as follows:

<u>Terms of Reference</u>

The Screening Test Review Committee will:

a) Make recommendations on the categorisation of commercially-available screening tests within the Screening Test Framework, based on:

1. Careful review of published scientific evidence; and

2. Consideration of the overall strength of evidence and the likely benefits and harms that will accrue to the person undergoing such screening

b) Provide expert opinion on the appropriateness of use of specific screening tests for the early detection of disease, as and when such opinion is needed by Ministry of Health (MOH).

c) To review the current categorisation of screening tests within the Screening Test Framework to ensure continued relevance and appropriateness of the categorisation.

Screening Test Review Committee

COMMITTEE MEMBERS

Chairman	Prof Chia Kee Seng	Fellow
		College of Public Health and Occupational Physicians
Members	Dr Lim Yon Kuei Bernard	Chairman
		Chapter of General Surgeons, College of Surgeons, Singapore
	Dr Lester Leong	Chairman
		Chapter of Diagnostic Radiologists, College of Radiologists, Singapore
	Prof Lee Soo Chin	Fellow
		Chapter of Medical Oncologists, College of Physicians, Singapore
	Prof Lau Tang Ching	Fellow
		Chapter of Rheumatologists, College of Physicians, Singapore
	Dr Catherine Ong	Fellow
		Chapter of Infectious Disease Physicians, College of Physicians, Singapore
	Prof Lee Bee Wah	Fellow
		College of Paediatrics and Child Health, Singapore
	Dr Derrick Heng	Fellow
		College of Public Health & Occupational Physicians
	Dr Ong Hean Yee	Fellow
		Chapter of Cardiologists, College of Physicians, Singapore

Secretariat

	Ms Syairah Samsudin	Executive, Professional Affairs
		Academy of Medicine, Singapore

With the assistance of

	Ms Vivienne Ling &	Senior Manager & Manager
	Ms Ranjani Rajenthiran	Epidemiology & Disease Control Division
		Ministry of Health

Definition and Principles of Screening

Definition of Screening

The application of tests or procedures to detect disease early in asymptomatic people

Principles of Screening

Screening persons who are apparently well in order to pick up asymptomatic disease can be beneficial if early treatment is available to improve the prognosis. It is beneficial to society at large if identification leads to primary and secondary prevention. Wilson and Jungner cited the following principles of screening for early disease detection as a public health programme:

a)   The condition sought should be an important health problem
b)   The natural history of the disease should be adequately understood
c)   There should be a recognisable latent or early preclinical stage
d)   There should be a suitable and acceptable screening test or examination
e)   There should be an accepted treatment or useful intervention for patients with the disease
f)   Facilities for diagnosis and treatment should be available
g)   There should be an agreed policy on whom to treat as patients
h)   The cost of case-finding (including diagnosis and treatment of patients detected) should be economically balanced in relation to possible expenditure on medical care as a whole
i)   Case finding should be a continuing process and not a one-off project

Whether or not a screening policy results in improved health outcomes depends on a number of factors viz. the characteristics of the disease, the screening test, and the target population.

Screening may be considered where there is a high prevalence of the disease with potentially serious consequences, the disease condition has a natural history with a latent stage during which symptoms of disease are either not present or early; and when detected and managed, is beneficial in improving the likelihood of favourable health outcomes (viz. reduced disease-specific morbidity or mortality). The screening test should be acceptable to the public, simple, fairly readily applied, and valid. With regard to diagnosis, the condition must be treatable with treatment and care available for those who need it. Early treatment should improve the outcome compared to treating patients when they present with signs and symptoms of the disease.

There is also a need for screening on a continuing basis rather than single-occasion screening. One-off screening is of limited value because only a small proportion, often those at least risk, is likely to be screened, and screening picks up those persons in the population who just happen at that particular time to have that condition being checked for. It therefore does not affect the future incidence of disease. Continuing examinations at stipulated intervals have greater advantage as they cover more of the population at risk including, by re-examination, persons presenting with new disease.

Background

Given the wide range of medical conditions for which screening is being offered, and the tests available for screening, a framework to categorise screening tests is necessary.

The aim of the screening test framework is to provide clear guidance to doctors, other healthcare professionals and members of the public about the value of specific screening tests and clinical indications. The categorisation is based on a thorough and impartial review of the scientific evidence currently available.

The Screening Test Review Committee has met and decided upon the categorisation of the screening tests based on current clinical evidence, MOH clinical practice guidelines, established overseas clinical guidelines and after taking into account the inputs of the various Chapters and Colleges under the AMS. It will undertake the review on a periodic basis as and when new evidence and perspectives are available.

Categorisation of Screening Tests

A three-category framework for screening tests, with categories of "Not recommended", "Suitable for individual-level decision" and "Suitable for population-level screening" was used. The criteria for categorisation are detailed in Annex A. Annex B compares the recommendation categories used by the United States Preventive Services Task Force vis-à-vis the proposed policy framework. Table 1 summarises the definition and possible policy response for each category of screening tests within the framework.

Table 1: Three-Category Framework for Screening Tests

	Category	Definition	Possible policy responses
1	Suitable for population-level screening	There is good robust evidence that the screening test is both clinically effective and cost effective for use to screen the population	Broaden screening coverage as far as possible, by: a) Promoting public education b) Permitting Medisave use c) Providing means-tested subsidies d) Implementing national screening programmes e) Encouraging incorporation of such tests in community and workplace-organised screening
2	Suitable for individual-level decision	The net benefit does not outweigh the risk in general populations, but the screening may be useful for high-risk populations	Medisave use and means-tested subsidies may be considered for some tests where certain high-risk groups of individuals may benefit from the use of the tests.

			Clear criteria would need to be set, and screening providers monitored to prevent abuse
		OR There is some evidence that the screening test is effective but cost-effectiveness has not been evaluated or the cost effectiveness ratio is unfavourable	Continuing educational programmes for relevant healthcare providers to highlight need to tailor use of tests to individual circumstances
3	Not recommended	a) There is insufficient evidence to make a decision regarding the usefulness of the test	Patient education programmes to highlight lack of evidence and possible harm of screening using these tests.
		b) There is good evidence that the screening test is not effective, or that the net harm outweighs benefits	Continuing educational programmes to inform healthcare providers on the lack of evidence underlying these tests, and emphasise that onus is on the provider to justify the use of these tests in their patients
			Define standards of care under the National Standards of Care that recommend against use of these tests; physicians will need to justify use of these tests in their patients

This framework is not meant to replace the clinical judgment of physicians as doctors would still need to assess the suitability of specific screening tests for their patients.

For tests listed as Category 1 – 'suitable for population-level screening', the categorisation is only applicable for the specified age range. The report describes some circumstances in which specific Category 1 tests could be used outside the specified age range and/or for individuals who are at higher risk for the disease in question. In these situations, the decision should be made on an individual-level basis, based on consultations with a physician [i.e. similar to a Category 2 test "suitable for individual-level decision" (see below)].

High-risk groups may benefit from screening tests listed as "suitable for individual-level decision". In such cases, screening, including the age at which to start screening and the frequency of screening (if not specified), should be tailored to the individual profile of the patient in such high-risk groups, and based on consultations with a physician.

Report Structure

The report is presented via two axes:

1. By Disease

2. By Type of Tests (e.g. blood test, urine test)

This is to facilitate cross referencing and for the ease of those who would like to check for tests which are available for specific diseases.

In addition, a list of Category 1 and Category 2 screening tests are tabled as <u>Annex C</u> and <u>Annex D</u> respectively for easy reference.

Part I of Report: Categorisation of the screening tests by disease grouping

A) *Cancer*
B) *Heart and Vascular Diseases*
C) *Infectious Diseases*
D) *Metabolic, Nutritional, Endocrine and Rheumatology Conditions*
E) *Musculoskeletal Disorders*
F) *Obstetric and Gynaecological Conditions*
G) *Vision and Hearing Disorders*
H) *Congenital and Paediatric Conditions*
I) *Miscellaneous*

A) Cancer

1) **Breast Cancer** [1-11]

    1.1 Category 1 *Screening Tests (Suitable for population-level screening)*

    i) Mammogram for women 50 to 69 years of age

    > ***Recommendation:*** *All normal risk, asymptomatic women 50 to 69 years of age should be screened with mammography only, every 2 years.*

    Additional Information
    The underlying premise for breast cancer screening is that it allows for the detection of breast cancers before they become palpable. Small tumours are more likely to be early stage disease, having better prognosis, and are more successfully treated.

    Mammography-based screening is widely accepted as appropriate and beneficial for women above the age of 50. Combined analysis of eight prospective randomized clinical trials suggest that screening mammography produced a mortality benefit of approximately 22%[6] for women aged 50 to 69 years old in populations invited to screening. For women aged 40 to 49, there is great variation on recommendations for mammographic screening[7]. The additional mortality benefit is small for initiating screening at 40 instead of 50 years old, although it saves more life-years at a population level. The peak incidence of breast cancer in Singapore also continues to shift towards 60 years old. The recommendations for the 40 to 49 years old age group in Singapore are based on a balance between international guidelines and practice, the low incidence, higher costs and higher false positive rate of mammographic detection in this age group.

    Clinicians should discuss with women at normal risk aged 40 to 49 years old about the potential benefits, limitations and harms associated with screening mammography so that an informed choice can be made about attending breast cancer screening. They should base screening mammography decisions on the benefits and harms of screening, as well as on the woman's preferences

and breast cancer risk profile. If screening is to be performed, it should be done annually.

Potential risks of mammography include false-positive results, diagnosis and treatment for cancer that would not have become clinically evident during the patient's lifetime (over diagnosis), radiation exposure, false reassurance, and procedure-associated problems[8,9]. False-positive mammography can lead to increased anxiety and to feelings of increased susceptibility to breast cancer, as well as unnecessary diagnostic tests. Women with false negative mammograms may be given false assurance. Up to one-fourth of all invasive breast cancers are not detected by mammography in 40 to 49 years old, compared with one-tenth of breast cancers in 50 to 69 years old[10]. The diagnosis and treatment of breast cancer may be delayed because of a "normal" mammogram.

1.2 Category 2 *Screening Tests (Suitable for individual-level decision)*

i)   Magnetic Resonance Imaging (MRI) Breast

High Risk Groups: Women at more than 20% lifetime risk of breast cancer, carriers of BRCA or other high risk gene mutations (characteristics of women at risk for hereditary breast cancer predisposition syndromes are detailed in Annex E), and women with previous history of chest radiation therapy [11].

Others: Women with cosmetic injection augmentation.

Additional Information

In women with high genetic risk for breast cancer, MRI breast screening is performed annually as an adjunct to mammography as studies have shown that MRI detects more cancers (with a sensitivity of 71% to 100%) compared to mammography (sensitivity 25% to 40%). Mammogram screening should still be performed with MRI as some cancers which manifest as micro-calcifications on mammography may not be detected on MRI. MRI cannot replace mammographic screening in these women as some cancers may manifest as micro-calcifications which may not be shown on MRI.

Screening should start at age 25 to 30 years for women with gene mutations conferring high risk of developing breast cancer and their untested first degree relatives. In those with strong family history of breast cancer but no proven mutation, screening is recommended to commence as early as 5 to 10 years prior to the age of onset in the youngest family member to contract breast cancer, but not earlier than age 25 to 30.

Women who received radiation treatment to the chest, such as for Hodgkin disease[12], are also at high risk for developing breast cancer[13-16].

Diagnosis of breast cancer occurred at a mean of 18 years after diagnosis of Hodgkin disease with a range of 7 to 30 years. Although there is a lack of evidence with regards to MRI screening in this group, there is consensus opinion that MRI screening commencing 8 years after radiotherapy to the chest may offer similar benefit as for women with a strong family history.

There is not enough data demonstrating clinical benefit for MRI screening in women with moderate risk of breast cancer (15 to 20% lifetime risk), e.g. personal history of breast cancer, prior biopsy with atypical ductal hyperplasia or lobular neoplasia. Hence, no specific MRI screening recommendation is made for these women.

Breast MRI is not suitable for routine breast screening of women who are at normal risk of developing breast cancer. However, in women with diffuse breast injection augmentation, particularly of the free silicone type, the injected material may significantly obscure mammographic and sonographic visibility of the underlying breast tissue. This renders mammogram and ultrasound assessments ineffective for breast cancer screening. Hence MRI should replace mammogram screening in these cases. The recommended age and frequency of screening are similar to the mammogram screening guidelines for normal risk women[17-20].

1.3 Category 3 *Screening Tests (Not recommended)*

i) Ultrasound Breast

In women with dense breasts, adjunct ultrasound screening increases the breast cancer detection yield compared to mammogram screening alone[21,22]. However, this will be associated with a significant rise in false positives and in the use of additional healthcare resources for the work-up of added breast findings, most of which will be benign and not clinically significant. Moreover, there is no survival data available. In view of its doubtful overall benefit, the routine use adjunct ultrasound screening is not recommended.

ii) Tumour Marker for Breast Cancer (e.g. CEA and CA 15-3)

2) __Bladder Cancer__ [23]

2.1 Category 3 *Screening Tests (Not recommended)*

i) Urine dipstick or microscopic urinalysis, urine cytology and tests for urine biomarkers

3) __Cervical Dysplasia/ Cervical Intraepithelial Lesion /Cervical Cancer__ [24-44]

3.1 Category 1 *Screening Tests (Suitable for population-level screening)*

i) Pap Smear

ii) Human Papilloma Virus (HPV) testing

> **Recommendation:** *All women who have ever had sexual intercourse should undergo screening for cervical cancer from the age of 25. Women aged 25 to 29 years should be screened with the Pap smear, at least once every 3 years. Primary HPV testing is not recommended for women from the age of 25 to 29.*
>
> *Women aged 30 years and above should be screened with HPV testing. This should be performed at least once every 5 years.*

<u>Additional Information</u>

Women from age 30 years and above should be screened with HPV testing. In the event that they are screened positive for non 16 or 18 HPV strains, a Pap smear should be performed.

HPV testing using the Cobas HPV Test (Roche Molecular Systems, Inc) was approved by the US Food and Drug Administration (FDA) in April 2014 for primary cervical cancer screening. HPV Testing for primary cervical screening allows for less frequent screening and helps to identify women who need increased surveillance.

Studies have shown that compared with cytology, HPV DNA testing is more sensitive for identifying women who have CIN2+ (95% versus 55%). According to Ronco et al., a screening interval of at least 5 years for hrHPV screening is safer than cytology every 3 years.

However, HPV testing has lower specificity compared with cytology (94% versus 97%). Current screening guidelines recommend initiation of HPV testing at 30 years of age. Primary HPV screening at age 25 years may lead to increased colposcopies and unnecessary intervention; progression of dysplasia to cancer is uncommon in this age group; detection of most of the disease found in this age group can be safely deferred until age 30 and older; and it is unclear that identification of these women with CIN3+ would translate into a meaningful reduction of cervical cancer. Hence HPV testing in women younger than 30 years would have even lower specificity and not be useful in these women where there is a higher incidence of high risk HPV infection which is often regressive in nature.

HPV testing should **not** be used:
a. For screening before deciding on HPV vaccination
b. For routine Sexually Transmitted Infection (STI) screening
c. To screen women < 30 years old.

The overall effect of HPV vaccination on high grade lesions and cervical cancer is not yet established. It is presumed that vaccination would reduce the need for screening. However, current trials do not provide data on long term efficacy and the effects of vaccination would only be seen in 10 to 20 years' time. Hence, women who have been vaccinated should continue to be screened according to the proposed protocol.

3.2 Category 3 Screening Tests (Not recommended)

i) Ultrasound Pelvis

ii) Computed Tomography (CT) Pelvis

4) Colorectal Cancer [45-48]

4.1 Category 1 Screening Tests (Suitable for population-level screening)

i) Faecal Immunochemical Test (FIT) (stool analysis for faecal occult blood)

> **Recommendation:** *For average-risk individuals, screening for colorectal cancer should begin at age 50 years. FIT is one of the recommended screening*

tests and should be performed annually. Average-risk individuals refer to asymptomatic individuals and individuals who do not have a family history of colorectal cancer, as well as those with family history confined to non-first degree relatives or relatives older than 60 years old.

OR

ii) Colonoscopy

Recommendation: *Colonoscopy is one of the recommended screening tests for the average risk asymptomatic population, from age 50 years. For screening the general population at average risk, colonoscopy should be performed at an interval of no more than 5 to 10 years.*

For individuals at increased risk or high risk, screening by colonoscopy is also indicated. Please refer to the table below.

Risk Group	Onset (Age)	Frequency of colonoscopy screening
i) Average risk		
1. Asymptomatic or family history limited to non-first degree relatives	50 yrs	Every 5 to 10 yrs
ii) Increased risk		
1. Colorectal cancer in first degree relative (parent, sibling) age 60 yrs or younger or two or more first degree relatives	10 yrs prior to youngest case in the family or age 40 yrs, whichever is earlier	Every 5 yrs
2. Colorectal cancer in first degree relative over the age of 60 yrs	50 yrs	Every 5 to 10 yrs
3. Personal history of colorectal polyps	1 to 3 yrs after polypectomy in the presence of high risk features (>1cm, multiple, villous architecture); otherwise, 3 to 5 yrs after polypectomy for low risk polyps	-
4. Personal history of colorectal malignancy	One year after resection	Every 1 to 3 yrs
5. Personal history of ovarian or endometrial cancer	After resection	-
iii) High risk		
1. Family history of familial adenomatous polyposis^	10 to 12 yrs (from puberty)	Annually*
2. Family history of hereditary non-polyposis	20 to 25 yrs	Every 1 to 2 yrs

colorectal cancer (Lynch Syndrome)^		

3. Inflammatory Bowel Disease
   a. Left-sided colitis
   b. Pan-colitis
	From 15th yr of diagnosis
	From 8th yr of diagnosis
		Every 1 to 2 yrs
		Every 1 to 2 yrs

*Flexible sigmoidoscopy from age 10 to 12 years (puberty) until adenomas are identified, upon which screening is switched to colonoscopy

^ Refer to Annex E for guidelines to refer suspected individuals for cancer genetic risk assessment.

4.2 Category 2 Screening Tests (Suitable for individual-level decision)

i) Computed Tomography (CT) Colonography

As an alternative screening test to colonoscopy for average-risk individuals aged 50 years and above. The recommended frequency for individuals who opt for CT colonography is once every 5 years if initial screening is negative.

Additional Information

CT colonography, also known as virtual colonoscopy, is a minimally invasive imaging examination of the colon and rectum, using CT scan to acquire images and computer software to process the data for interpretation. It is the best available imaging test if optical colonoscopy is contraindicated or incomplete. When performed with bowel preparation and tagging agents it has been shown to be effective in detecting neoplasms ≥6 mm albeit with a slightly higher false positive rate compared with lesions ≥10 mm[49].

ii)   Faecal immunochemical test (FIT)-DNA test

As an alternative screening test to FIT stool analysis for average-risk individuals aged 50 years and above. The recommended frequency for individuals who opt for FIT-DNA test is once every 3 years if initial screening is negative.

4.3 Category 3 Screening Tests (Not recommended)

i) Carcinoembryonic Antigen (CEA)

ii) Abdominal X-ray (AXR)

iii) CT Abdomen

iv) Methylated SEPT9 DNA Test

5) Endometrial Cancer [50,51, 52-57]

5.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Ultrasound Pelvis

High risk groups: Women with Hereditary Non-Polyposis Colon Cancer (HNPCC) or Lynch Syndrome, who are at higher risk for endometrial cancer, may consider annual screening with regular pelvic examination and endometrial sampling, starting between the ages of 30 and 35[39]. Trans-vaginal ultrasound screening for endometrial cancer has good sensitivity before symptoms appear. However, there is limited evidence on mortality benefit. More than 75% of women with Lynch Syndrome who develop endometrial cancer present with stage 1 disease, similar to sporadic endometrial cancer, and are associated with a high survival rate. The potential benefits and limitations should be discussed with the patient to enable informed decision-making. Criteria regarding referral for cancer genetic risk assessment for women suspected Lynch Syndrome are detailed in Annex E.

5.2 Category 3 Screening Tests (Not recommended)

i) CT Pelvis

6) <u>Gastric Cancer</u> [58,50]

6.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Oesophago-Gastro Duodenoscopy (OGD)

High risk groups: Individuals with Hereditary Non-Polyposis Colon Cancer (HNPCC) or Lynch Syndrome, who are at higher risk for gastric cancer, may benefit from screening with oesophago-gastro duodenoscopy (OGD), starting from age 30 to 35 years. A frequency of 2 to 3 years is recommended, based on the individual's risk factors[42]. Criteria regarding referral for cancer genetic risk assessment for women suspected HNPCC (Lynch Syndrome) are detailed in Annex E.

7) <u>Liver Cancer (Hepatocellular Carcinoma)</u> [59-64]

7.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Alpha-Fetoprotein (AFP)

High Risk Groups: Hepatitis B carrier or individuals with liver cirrhosis

The test should be performed on a six monthly basis. There is no definite recommended age to start surveillance although local statistics show that Hepatocellular Carcinoma incidence starts to increase from the 40 to 49 age group.

<u>Additional Information</u>

Patients with chronic Hepatitis B infection or liver cirrhosis from other aetiologies are at increased risk of developing hepatocellular carcinoma, and surveillance should be offered to these at-risk individuals with the aim of detecting hepatocellular carcinoma that could be more amenable to therapy, and hence potentially leading to better outcomes.

A rise in AFP level (>20 ng/ml) in the absence of significant liver inflammation suggests hepatocellular carcinoma with a negative predictive value of 99% and a positive predictive value of up to 30% in non-cirrhotics and 60% in cirrhotics[56]. A rising trend strongly suggests the presence of hepatocellular carcinoma, although AFP should never be used alone to diagnose hepatocellular carcinoma.

ii) Ultrasound Hepatobiliary System (US HBS)

High Risk Groups: Hepatitis B carrier or individuals with liver cirrhosis

The test should be performed on a six monthly basis. There is no definite recommended age to start surveillance although local statistics show that hepatocellular carcinoma incidence starts to increase from the 40 to 49 age group.

<u>Additional Information</u>

The sensitivity of ultrasonography of the liver ranges from 58% to 87% in cirrhotics to 71% to 90% in non-cirrhotics, with a false positive rate of 28% to 82%. Regenerating and/or dysplastic nodules in cirrhosis are the leading cause of false-positive ultrasonography of the liver. A new finding of focal liver abnormality at ultrasound should prompt consideration of hepatocellular carcinoma, and this may be further evaluated by quadriphasic CT scan, MRI or where expertise is available, contrast-enhanced ultrasound.

7.2 Category 3 *Screening Tests (Not recommended)*

i) Liver Function Test (LFT)

8) **<u>Lung Cancer</u>** [65-69]

8.1 Category 2 *Screening Tests (Suitable for individual-level decision)*

i) Low-dose CT screening for Lung Cancer

High Risk Groups:

a) Individuals aged between 55 to 74 who have smoked $\geqslant$ 30 pack years and are continuing to smoke

b) Individuals aged between 55 to 74 who have smoked $\geqslant$ 30 pack years but quit <15 years ago

Low-dose CT screening should be done annually.

<u>Additional Information</u>

Low-dose computerized tomography (LDCT) refers to a non-contrast study obtained with a multidetector CT scanner during a single maximal inspiratory breath-hold. Radiation dose exposure is less than a third of a standard-dose

diagnostic chest CT scan. Several cohort studies and randomized control trials have demonstrated that screening was significantly more sensitive than chest radiograph in identifying early stage, asymptomatic lung cancers. The National Lung Screening Trial (NLST), a large randomized trial of screening LDCT in high-risk individuals, demonstrated a lung cancer mortality benefit of 20%, with all-cause mortality reduced by 6.7%. Many expert screening groups have incorporated results from the NLST in their recommendations[65,66], and generally suggested annual screening until high-risk individuals are no longer eligible for definitive treatments.

However, this has to be balanced with the unnecessary exposure to radiation, financial costs of CT screening, and a high rate of false positive findings. These may further lead to implications of further evaluation, such as the potential for morbidity and mortality from invasive procedures like a lung biopsy.

There is also an increasing incidence of lung adenocarcinoma in the Singapore population. The rate of lung carcinoma is also higher compared to United States and other western countries where the largest lung cancer screening trials were conducted. This reflects the Asia-pacific trend of higher rates of adenocarcinoma, particularly in women and also in non-smokers[70-75]. This may be due to a fundamental difference in genetic predisposition amongst Chinese non-smokers to lung adenocarcinoma, as well as the effects from exposure to environmental risk factors[76-96]. Further evidence is required from local population research so that any causative link between lung adenocarcinoma and the East Asian female and/or never-smoker phenotype can be established in the local context so that future screening guidelines can include these as risk factor targets for lung cancer screening.

8.2 Category 3 Screening Tests (Not recommended)

i)   Tumour Marker for Lung Cancer

ii) Chest X-ray (CXR)

9) Nasopharyngeal Carcinoma (NPC) [97-102]

9.1 Category 2 Screening Tests (Suitable for individual-level decision)

i)   Tumour Marker for NPC (EBV-EA-EBNA-1)

High Risk Groups: Individuals with a first degree relative (parent, sibling) with NPC

Additional Information

Familial aggregation of NPC is well documented in many epidemiological studies. Between 6.0% to 15.5% of newly diagnosed NPC patients will have a family history of NPC. In many studies and follow-up reports, first degree relatives have increased risk compared to the general population in the same age groups. This magnitude of familial risk in endemic regions is one of the highest among cancers.

Tumour markers for NPC (EBV IgA serology) should be combined with nasopharyngoscopy in the screening of high risk individuals. Serological tests alone, without endoscopy, are not recommended as a means of screening or monitoring of high risk individuals. As such, screening of high-risk individuals should be performed by a qualified specialist and include an appropriate history and examination, including nasopharyngoscopy.

ii) Nasopharyngoscopy

High Risk Groups: Individuals with a first degree relative (parent, sibling) with NPC

10) Oesophageal Cancer

10.1 Category 3 *Screening Tests (Not recommended)*

i) Oesophago-Gastro-Duodenoscopy (OGD)

11) Ovarian Cancer [103,104]

11.1 Category 2 *Screening Tests (Suitable for individual-level decision)*

i) Transvaginal Ultrasound

High Risk Group: BRCA-Carrier

Transvaginal pelvic ultrasound as screening for ovarian cancer may be considered. However, it can result in unnecessary surgeries with no clear mortality benefit[52,57]. The potential benefits and limitations should be discussed with the patient for informed decision-making.

11.2 Category 3 *Screening Tests (Not recommended)*

i) Cancer Antigen (CA) 125

ii) CT Pelvis

12) Pancreatic Cancer

12.1 Category 3 *Screening Tests (Not recommended)*

i) CA 19-9

ii) CT scan

13) Prostate Cancer [105-111]

13.1 Category 2 *Screening Tests (Suitable for individual-level decision)*

i) Prostate-Specific Antigen (PSA)

Men who are between 50 to 70 years of age, with an estimated life expectancy of more than 10 years, may be offered screening for prostate cancer after a discussion of both the potential benefits and harms associated with prostate cancer screening.

High Risk Groups: High-risk men, such as men with a strong family history of prostate cancer, i.e. one or more first-degree relatives (father, brother) diagnosed before age 65 years, may be offered screening 5 to 10 years younger than the youngest prostate cancer in the family.

Additional Information

Due to the uncertainty that PSA testing results in more benefit than harm, a thoughtful and broad approach to PSA is critical. The decision to use PSA for the early detection of prostate cancer should be individualised. Patients need to be informed of the risks and benefits of testing before it is undertaken.

Prostate cancer survival is related to many factors, especially the extent of tumour at the time of diagnosis. The 5-year relative survival among men with cancer confined to the prostate (localised) or with just regional spread is 100%, compared with 31.9% among those diagnosed with distant metastases. While men with advanced stage disease may benefit from palliative treatment, their tumours are generally not curable.

Although prostate biopsies rarely cause complications serious enough to require hospitalisation, screening is not an entirely benign process and may be associated with discomfort and possible complications of biopsy. In addition, false-positive results have a psychological cost. Chronic anxiety can also follow a negative prostate biopsy because this apparently favourable result cannot completely rule out prostate cancer given the relatively high false-negative biopsy rate.

13.2 Category 3 *Screening Tests (Not recommended)*

i) MRI Prostate

14) **Testicular Cancer** [112]

14.1 Category 3 *Screening Tests (Not recommended)*

i) Testicular Cancer Test (e.g. AFP and beta-HCG)

B) Heart and Vascular Diseases

1) **Abdominal Aortic Aneurysm (AAA)** [113, 114]

1.1 Category 2 *Screening Tests (Suitable for individual-level decision)*

i) Abdominal Ultrasonography

High Risk Groups: Men aged 65 to 75 years who have ever smoked

Additional Information

The United States Preventive Services Task Force (USPSTF) found good evidence that screening for AAA and surgical repair of large AAAs (5.5 cm or more) in men aged 65 to 75 years who have ever smoked (current and former smokers) leads to decreased AAA-specific mortality. There is good evidence that abdominal ultrasonography, performed in a setting with adequate quality assurance (i.e. in an accredited facility with credentialed technologists), is an accurate screening test for AAA. There is also good evidence of important harms of screening and early treatment, including an increased number of surgeries with associated clinically-significant morbidity and mortality, and short-term psychological harms. Based on the moderate magnitude of net benefit, the USPSTF concluded that the benefits of screening for AAA in men aged 65 to 75 years who have ever smoked outweigh the harms.

2) **Cerebral Aneurysm** [115, 116]

2.1 Category 2 Screening Tests (Suitable for individual-level decision)

i)   MRI/ Magnetic Resonance Angiography (MRA) brain

High Risk Groups:

a)   Individuals with a history of aneurysmal subarachnoid haemorrhage

b)   Individuals with autosomal dominant polycystic kidney disease

c)   Individuals who have two or more first-degree relatives (parent, sibling) with documented intracranial aneurysms.

Additional Information

Unruptured intracranial aneurysms occur in up to 6% of the general population. Most persons with these aneurysms remain asymptomatic and are usually unaware of their presence.

Subarachnoid haemorrhage associated with aneurysmal rupture is a potentially lethal event with a mortality rate as high as 50%. Many patients who survive the initial haemorrhage have permanent disability. In patients with a history of aneurysmal subarachnoid haemorrhage, the annual rate of new aneurysm formation is between 1 and 2%, and the risk of aneurysmal rupture appears to have increased. Therefore, surveillance of these patients with magnetic resonance angiography may be justified. Patients with a prior history of cerebral aneurysms have a higher rate of future de novo aneurysm formation and should be screened at 5-year intervals.

Screening should also be considered in patients with some rare conditions (e.g., autosomal dominant polycystic kidney disease) that are associated with an increased risk of aneurysms.

Patients with one affected first-degree relative should be differentiated from those with more than one such relative. Based on literature review, the Stroke Council of the American Heart Association does not recommend screening for aneurysms in patients who have only one first-degree relative with aneurysmal subarachnoid haemorrhage. The decision on whether or not to screen for intracranial aneurysms in patients who have two or more first-degree relatives with documented subarachnoid haemorrhage is best decided on a case-by-case basis.

3) **Cerebrovascular Disease (Stroke)** [114]

   3.1 Category 3 *Screening Tests (Not recommended)*

   i)   MRI/ MRA Brain

4) **Carotid artery stenosis** [117]

   4.1 Category 3 Screening Tests (Not recommended)

   i)   Duplex Ultrasonography

5) **Coronary Heart Disease (CHD)** [114,118-124]

   5.1 Category 2 *Screening Tests (Suitable for individual-level decision)*

   i)   Electrocardiography (ECG)

   The resting 12-lead ECG provides valuable information in the evaluation of symptoms such as, but not limited to, chest pain, syncope or breathlessness. However, there is presently no evidence that the routine ambulatory ECG provides additional information on cardiovascular risk or events in low asymptomatic subjects.

   Inter-observer variability, false positives and negatives are areas of concern in the widespread use of ECG in low risk populations.

   ECG may be performed[125, 126]:

   a) In asymptomatic hypertensive patients to evaluate for target end organ damage (Ventricular Hypertrophy)

   b) During and after initiation of medication that might alter QT intervals or has pro-arrhythmic effect.

   c) Pre-Participation in competitive sporting activity for all age groups or in age defined individuals who are previously sedentary as per local/international guidelines.

   d) Subjects in high risk occupation (such as but not exclusive to; airline pilots, firemen, commercial drivers)

Current data neither supports nor contradicts the use of routine screening ECG in patients with moderate to high cardiovascular risk.

<u>Additional Information</u>

A local study of asymptomatic patients referred to a tertiary cardiac centre for the suspicion of Coronary Artery Disease (CAD) based solely on ECG findings found a prevalence of 0.8% CAD in this population, suggesting that using the ECG as a screen for CAD is not helpful.

ii) High-Sensitivity C-Reactive Protein (hsCRP) [127-129]

hsCRP is a marker of inflammation, and may potentially reclassify risk for future cardiovascular events to identify asymptomatic individuals in addition to traditional clinical risk calculators. at risk for acute coronary events. Restricted and judicious use of hsCRP measurement is suggested for health screening.

hsCRP may be performed after a global risk assessment of coronary heart disease. Use of hsCRP measurement may be performed for health screening in those with an intermediate risk of 10 to 20% 10-year risk[94] (it may also be performed if there are unusual cardiovascular risk factors or if the result will change the decision to initiate lipid lowering therapy)[130]

hsCRP should not be routinely offered to those at either very low or very high cardiovascular risk [131].

hsCRP using standardised assays categorises patients as follows[132]

    a. Low risk <1.0 mg/L;

    b. Moderate risk 1.0 to 3.0 mg/L'

    c. High risk >3.0 mg/L;

iii) Apolipoprotein A [133] and B[134]

Apolipoprotein A and B determination is not recommended for routine cardiovascular disease screening.

Its advantage in prediction of events over non-HDL; which is technically easier to measure; has not been shown and their values correlates with treatment and effect of treatment.

Apolipoprotein measurements may be considered in patients with a strong family history or unusual manifestation of premature cardiovascular disease.

iv) CT Coronary Calcium Score [135-137]

Use of Coronary Artery Calcium Score (CACS), may be considered if the information provided by the CACS will help to guide the patient's management (e.g. initiation of lipid therapy), and after a global clinical risk score has been performed.

It may help to reclassify clinical risk score in asymptomatic patients with intermediate (10% and 20%) 10-year CHD risk or unusual risk factors and family history.

These recommendations do not apply to symptomatic patients regardless of risk.

<u>Additional Information</u>

Based on median dose of 2.3 mSv (range, 0.8 to 10.5 mSv) of exposure, a single scan at the age of 40 years old is estimated to result in a lifetime excess cancer risk of 9 (range, 3 to 42) and 28 (range, 9 to 130) cancers per 100 000 persons for men and women, respectively. Hence, unselected screening of individuals without prior consideration of the global risk score, or whether the CACS will alter management is not encouraged by all major international guidelines.

There is also currently no evidence to recommend repeat testing of CACS to assess progression of atherosclerosis and treatment may paradoxically increase calcium score.

v) Treadmill Stress Test [138,139]

In selected individuals, screening for CAD with treadmill stress test may be undertaken on an individualised basis in the evaluation of asymptomatic subjects such as:

a. Men older than 45 years of age and women older than 55 years of age who plan to start an exercise program.

b. Moderate to high CAD risk or subjects with diabetes who plan to start an exercise programme.

c. Subjects involved in high risk occupations with public safety implications.

This list is not meant to be exhaustive and contemporary recommendations from national/international societies apply.

Exercise testing is meant to assess exercise capacity, cardiovascular fitness, cardiovascular risk and flow limiting coronary lesions in major coronary branches. It was never intended to detect non-flow limiting vulnerable plagues which rupture and lead to Acute Coronary Syndrome (ACS). Non-flow limiting vulnerable plagues are the primary cause of ACS and the best predictors of the risk of plaque rupture are clinical risk scores and biomarkers such as lipids.

No test has 100% specificity and that includes exercise stress testing, where there is a high likelihood of false positive results when treadmill testing is carried out in an asymptomatic low risk population. In the past, this has led to further testing with stress imaging or invasive coronary angiography to allay concerns. This should be explained to the patient prior to testing.

5.2 Category 3 Screening Tests (Not recommended)

   i)   CT Coronary Angiogram

   ii) Homocysteine

   iii) Serum Uric Acid

6) Peripheral Vascular Disease (PVD) [114,140-143]

6.1 Category 2 Screening Tests (Suitable for individual-level decision)

   i)   Ankle Brachial Index (ABI)

High Risk Groups:

a) Asymptomatic individuals with diabetes mellitus

b) Individual aged 50 to 70 years who smoke

c) Individuals aged 50 to 70 years with both hypertension and hyperlipidaemia

<u>Additional Information</u>

ABI is a test for peripheral vascular disease which has been shown to be associated with CAD. The attraction of ABI screening as a biomarker of cardiovascular risk is that this test is relatively easy to do in the primary care setting and is non-invasive. As with any screening test, it should be considered after global risk scoring and when the result of testing is likely to alter management. Despite the potential value of ABI, a recent randomised trial of the use of aspirin in patients with abnormal ABI did not show any benefit.

C) Infectious Diseases

1) Chlamydia and Gonorrhoea [144,145]

1.1 Category 2 Screening Tests (Suitable for individual-level decision)

   i)   Urine or Cervical (for women)/Urethral (for men) swab for PCR

High risk group: Persons with at-risk sexual behaviour (e.g. having unprotected sex with multiple sexual partners, previous or co-existing STIs)

<u>Additional Information</u>

Chlamydia and Gonorrhoea are causes of urethritis in men and cervicitis and Pelvic Inflammatory Disease (PID) in women. In females, the primary benefit of screening and treatment is in the reduction of personal risk of reproductive sequelae, such as ectopic pregnancy and infertility. In males, who frequently have asymptomatic disease, screening and treatment reduces overall transmission of infection.

The same specimen can be used to test for both chlamydia and gonorrhoea.

2) Human Immunodeficiency Virus Infection (HIV) [146-147]

2.1 Category 2 *Screening Tests (Suitable for individual-level decision)*

i)   HIV Screen

a) Pregnant women:

Pregnant women should be offered the test during early antenatal visit. A repeat of the test may be necessary during the third trimester for pregnant women or those with a partner who engage in at-risk activities.

b) Individuals with active Tuberculosis (TB) infection:

HIV screening should be offered to those with recent diagnosis of active TB.

c) Healthcare workers:

All healthcare workers with direct patient contact are encouraged to know their status with regards to HIV infection, besides Hepatitis B and C infection by going for appropriate and regular testing. Healthcare workers who are practising in specialities or areas involving exposure-prone procedures should know their status.

Exposure-prone procedures refer to those invasive procedures where there is a risk that injury to the worker may result in exposure of the patient's open tissues to the blood of the worker. These procedures include those where the worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues (e.g. spicules of bone or teeth) inside a patient's confined anatomical space where the hands or fingertips may not be completely visible at all times, open body cavity, or wound. Refer to MOH Directive 2/2014 for details.

d) Individuals with at risk behaviours:

1.   Men and women (heterosexuals and men who have sex with men) having unprotected sex with multiple partners

2.   Past or present injection drug users

3.   Commercial sex workers

4.   Individuals whose past or present sex partner(s) are HIV-infected or injection drug users

5.   Individuals whose past or present sex partner(s) have at-risk behaviours

6.   Individuals diagnosed with Sexually Transmitted Infections (STIs) (i.e., Chlamydia, Gonorrhoea, Genital Herpes Simplex, Syphilis and HPV) or with Genital ulceration

Individuals with recent high-risk exposure should be screened at 1 month and repeated at 3 months after the last high-risk exposure to rule out a possible initial false negative result.

Individuals who continue to engage in high-risk behaviour should have screening tests on a regular basis. For these individuals, screening should be performed 6-monthly or more often, decided on a case-by-case basis.

Additional Information

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians should screen for HIV in all adolescents, adults at increased risk for HIV infection and all pregnant women.

The USPSTF found good evidence that appropriately timed interventions, particularly Highly Active Antiretroviral Therapy (HAART), lead to improved health outcomes for many of those screened, including reduced risk for clinical progression and reduced mortality. Since false-positive test results are rare, harms associated with HIV screening are minimal. Potential harms of true-positive test results include increased anxiety, labeling, and effects on close relationships. Most adverse events associated with HAART, including metabolic disturbances associated with an increased risk for cardiovascular events, may be ameliorated by changes in regimen or appropriate treatment.

The USPSTF concluded that the benefits of screening individuals at increased risk substantially outweigh potential harms.

The USPSTF also found good evidence that introduction of universal prenatal counselling and voluntary testing increases the proportion of HIV-infected women who are diagnosed and are treated before delivery. There is good evidence that recommended regimens of HAART are acceptable to pregnant women and lead to significantly reduced rates of mother-to-child transmission.

Early detection of maternal HIV infection also allows for discussion of elective caesarean section if viral load cannot be suppressed before delivery and avoidance of breastfeeding, both of which are associated with lower HIV transmission rates.

There is no evidence of an increase in foetal anomalies or other foetal harm associated with currently recommended antiretroviral regimens (with the exception of efavirenz). Serious or fatal maternal events are rare using currently recommended combination therapies. The USPSTF concluded that the benefits of screening all pregnant women substantially outweigh potential harms.

HIV infection is a known risk factor for progression from latent TB infection to TB disease. Progression to TB disease is often rapid among people infected with HIV and can be deadly. In addition, TB outbreaks can rapidly expand in patient groups infected with HIV. When HIV is diagnosed early, appropriately timed interventions can lead to improved health outcomes, including slower progression and reduced mortality.

3) Hepatitis A Infection

3.1 Category 3 Screening Tests (Not recommended)

i)   Hepatitis A Screen

4) **Hepatitis B Infection/Hepatitis B Carrier** [146-155]

4.1 Category 2 *Screening Tests (Suitable for population-level decision)*

i) Hepatitis B Screen

a) Asymptomatic Singapore residents with no known hepatitis B carrier status born before 1987 and did not undergo the local catch-up immunisation programmes from 2001 to 2004 (which were conducted for secondary schools, colleges and tertiary institutions) should be screened for Hepatitis B.

Additional Information

A national Hepatitis B seroprevalence study was conducted in 2010 to assess the seroprevalence of Hepatitis B Virus (HBV) markers in our adult population in Singapore and a comparison was made with the seroprevalence in 1998 and 2004.

The overall Hepatitis B Surface Antigen (HBsAg) prevalence among Singapore residents aged 18 to 69 years has remained stable, from 4.0% (1998) to 2.7% (2004) and 3.6% (2010), and was within the range of intermediate HBV endemicity; the overall population immunity to HBV was 43.9%.

While the national childhood HBV immunisation and catch-up programmes implemented in 1987 and 2001 to 2004 respectively, had a significant impact in reducing HBV infection and in raising the immunity of the local adult population 18 to 29 years of age, the prevalence of HBV infection in age groups 30 and above have increased from 2004 to 2010. Hence, it is recommended for all normal risk, asymptomatic adults with no known Hepatitis B carrier status born before 1987 and did not undergo the catch-up immunisation programmes from 2001 to 2004 to be screened for Hepatitis B.

b) Pregnant women:

All pregnant women, regardless of their age, should be tested for HBsAg during early antenatal visit, preferably during the first visit.

Additional information

The USPSTF found good evidence that universal prenatal screening for HBV infection using HBsAg substantially reduces prenatal transmission of HBV and the subsequent development of chronic HBV infection. The current practice of vaccinating all infants against HBV infection and post exposure prophylaxis with Hepatitis B immune globulin administered at birth (within 12 hours) to infants of HBV-infected mothers substantially reduces the risk for acquiring HBV infection.

c) Healthcare workers:

All healthcare workers with direct patient contact are encouraged to know their status with regards to Hepatitis B infection, besides HIV and Hepatitis C infection, by going for appropriate and regular testing. Healthcare workers who

are practising in specialities or areas involving exposure-prone procedures should know their status.

Additional information

Exposure-prone procedures refer to those invasive procedures where there is a risk that injury to the worker may result in exposure of the patient's open tissues to the blood of the worker. These procedures include those where the worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues (e.g. spicules of bone or teeth) inside a patient's confined anatomical space where the hands or fingertips may not be completely visible at all times, open body cavity, or wound. Refer to MOH Directive 2/2014 for details.

d) Other groups include foreigners and immigrants from countries where HBV are endemic should also be considered for screening.

Where appropriate, those who are found to have not been infected and have no antibody levels on screening should also be offered Hepatitis B vaccination to prevent future infections.

e) At Risk Groups:

1. Chronic haemodialysis patients

2. Past or present injection drug users

3. Individuals who underwent invasive procedures in health-care facilities with inadequate infection control practices

4. Individuals with known exposures to HBV, e.g. healthcare workers following needle stick injury involving HBV-positive blood, or recipients of blood or organs from a donor who tested HBV-positive

5. Individuals whose past or present sex partners were/are HBV-infected or injection drug users

6. HIV patients

5) **Hepatitis C Infection** [156-158]

5.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Hepatitis C Screen

a) At Risk Groups:

1. Children born to Hepatitis C Virus (HCV)-positive mothers

2. Chronic haemodialysis patients

3. Past or present intravenous drug abusers

4. Individuals who underwent invasive procedures in health-care facilities with inadequate infection control practices

5. Individuals with known exposures to HCV, e.g. healthcare workers following needle stick injury involving HCV-positive blood, or recipients of blood or organs from a donor who tested HCV-positive

6. Individuals whose past or present sex partners were/are HCV-infected or intravenous drug abusers

7. HIV patients

b) Healthcare workers:

All healthcare workers with direct patient contact are encouraged to know their status with regards to Hepatitis C infection, besides HIV and Hepatitis B infection by going for appropriate and regular testing. Healthcare workers who are practising in specialities or areas involving exposure-prone procedures should know their status.

Exposure-prone procedures refer to those invasive procedures where there is a risk that injury to the worker may result in exposure of the patient's open tissues to the blood of the worker. These procedures include those where the worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues (e.g. spicules of bone or teeth) inside a patient's confined anatomical space where the hands or fingertips may not be completely visible at all times, open body cavity, or wound. Refer to MOH Directive 2/2014 for details.

6) Intestinal Parasitic Infection [159]

6.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Stool for ova, cyst and parasites

Special consideration: New immigrants from countries with high prevalence of such diseases should be considered for screening.

Asymptomatic international travellers, who have been abroad for many months or longer, particularly in resource limited settings, could be screened for certain diseases, including stool examination for ova and parasites.

7) Rubella

7.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Rubella Serology

All pregnant women should be screened for rubella susceptibility during their first clinical encounter as a preventive measure.

The American Academy of Pediatrics (AAP), American College of Obstetricians and Gynaecologists (ACOG) and Advisory Committee on Immunization Practices (ACIP) recommend routine prenatal or antepartum serologic screening of all pregnant women and postpartum vaccination of those found to be susceptible.

8) **Syphilis** [160-163]

8.1 Category 2 *Screening Tests (Suitable for individual-level decision)*

i) Treponema Pallidum Particle Agglutination (TPPA)/ Treponema Pallidum Haemagglutination (TPHA),

OR;

ii) Syphilis Enzyme Immunoassay (EIA)

a) All pregnant women

Pregnant women should be screened for Syphilis (regardless of perceived risk) at the first antenatal visit in order to prevent in utero transmission of asymptomatic infection, which can lead to congenital Syphilis.

b) Individuals with at-risk behaviours:

1. Men and women (heterosexuals and men who have sex with men) having unprotected sex with multiple partners

2. Commercial sex workers

3. Persons who exchange sex for drugs

4. Persons diagnosed with other Sexually Transmitted Infections (STIs) (i.e., Chlamydia/Non-gonococcal Urethritis, Gonorrhoea, Genital Herpes, HPV, and HIV) or with Genital ulceration

The optimal frequency of screening is a matter of clinical discretion. Screening for syphilis should be performed 1 month after exposure, and repeated again after 3 months for at-risk groups as defined by above.

Additional information

Routine screening for all pregnant women is justified in view of the severe neonatal morbidity and mortality associated with congenital syphilis, as well as its potential preventability. There is evidence from several studies which demonstrate that prenatal screening for syphilis is cost-effective.

Although the USPSTF found no new direct evidence that screening for syphilis infection leads to improved health outcomes in persons at increased risk, there is adequate evidence that screening tests can accurately detect syphilis infection and that antibiotics can cure syphilis. Screening may result in potential harms (such as clinical evaluation of false-positive results, unnecessary anxiety to the patient, and harms of antibiotic use). The USPSTF concludes that the benefits of screening persons at increased risk for syphilis infection substantially outweigh the potential harms.

According to the US CDC, treponemal tests such as EIA detect antibodies specific for syphilis, and are detectable for life even after successful treatment. If a treponemal test is used for screening and the results are positive, a

nontreponemal test with titre should be performed to confirm diagnosis and guide patient management decisions.

Nontreponemal tests such as VDRL and RPR are simple, and are often used for screening. However, they are not specific for syphilis, can produce false-positive results, and by themselves, are insufficient for diagnosis. VDRL and RPR should each have their antibody titre results reported quantitatively. Persons with a reactive nontreponemal test should receive a treponemal test to confirm a syphilis diagnosis.

9) <u>Tuberculosis (TB)</u> [164-170]

9.1 Category 2 Screening Tests (Suitable for individual-level decision)

i)   Interferon-Gamma Release Assay (IGRA)

ii) Tuberculin Skin Test (TST)

High risk group: Screening for Latent Tuberculosis Infection (LTBI) in asymptomatic individuals with IGRA or TST is recommended for close contacts of infectious TB cases (i.e. bacteriologically positive cases of pulmonary tuberculosis, especially if acid-fast bacilli smear is positive), in particular, family members who live together or co-workers in workplace, HIV patients, transplant patients (Solid organ and Haem), dialysis, patients receiving anti-TNF agents.

<u>Additional information</u>

Either the TST or the IGRA may be used for the diagnosis of LTBI in adults and children 5 years or older. IGRA is the preferred test for adolescents and adults who have received Bacillus Calmette-Guerin (BCG) vaccination, while the TST is the preferred test for the diagnosis of latent tuberculosis in children <5 years of age.

iii) Chest X-ray (CXR)

High risk group: Screening for active pulmonary TB with CXR is recommended for close contacts of infectious TB patients (i.e. bacteriologically positive cases of pulmonary TB, especially if acid-fast bacilli smear is positive), specifically family members who live together, who have symptoms of TB (e.g. prolonged cough of more than three weeks), and/or are positive on IGRA / Mantoux tests suggesting possible LTBI.

Special consideration: Foreigners and employees from countries where the disease is highly prevalent.

D) Metabolic, Nutritional, Endocrine and Rheumatology Conditions

1) **Anaemia (Iron-deficiency Anaemia)** [171-174]

   1.1 Category 2 *Screening Tests (Suitable for individual-level decision)*

   i) Full Blood Count (FBC)

   High Risk Groups:

   a) Pregnant women and women planning to conceive

   b) Preterm infants and low birth weight infants

   c) Infants who are fed a diet of non-iron-fortified infant formula for >2 months

   d) Breast-fed infants who do not consume a diet adequate in iron after age 6 months (i.e. who receive insufficient iron from supplementary foods)

   e) Children who have special health-care needs (e.g. children who use medications that interfere with iron absorption and those who have chronic infection, inflammatory disorders, restricted diets, or extensive blood loss from a wound, an accident, or surgery).

   All pregnant women should be screened at the first prenatal visit; for women planning to conceive, they should be screened once before pregnancy. For infants and children at high risk as defined from (c) to (e), the frequency is once a year until 5 years old.

2) **Diabetes Mellitus** [175-178]

   2.1 Category 1 *Screening Tests (Suitable for population-level screening)*

   i) Fasting Blood Glucose

   ii) Glycosylated Haemoglobin (HbA1c)

   > **Recommendation:** *Screening should begin at age 40 years, and be considered in adults of any age if any of the risk factors for diabetes is present. Subsequently, screening should be carried out every three years for those with normal glucose tolerance and annually for those with Impaired Fasting Glycaemia (IFG) or Impaired Glucose Tolerance (IGT).*

   Risk factors for Diabetes Mellitus include (any one of the following):

   a) Overweight/obesity (body mass index ≥25.0 kg/m2)

   b) Hypertension ≥140/90 mmHg) or on therapy for hypertension

   c) First degree relative with diabetes mellitus

d) Women who have delivered a baby 4 kg or more; or previously diagnosed with gestational diabetes mellitus

e) History of cardiovascular disease

f) Women with polycystic ovary disease

g) Patients who are diagnosed to have TB

h) HDL cholesterol level <1.0 mmol/L (male), <1.3 mmol/L (female) and/or triglyceride level ≥2.2 mmol/L

i) IFG or IGT on previous testing

j) High risk race/ethnicity

Additional information on HbA1c[179,180-183]

HbA1c has been adopted as a diagnostic test for DM by the World Health Organization (WHO), the International Expert Committee of the American Diabetes Association (ADA), as well as other countries such as UK, Australia, New Zealand, Japan and Malaysia.

Based on analysis of local data from the National Health Survey (2010), both fasting blood glucose and HbA1c were found to be able to discriminate effectively between those with and without diabetes mellitus.

Hba1c is not suitable for use in individuals with the following medical conditions and/or physiological states: Haemoglobinopathies including thalassemia, iron deficiency anemia, vitamin B12/ folate deficiency, recent blood loss, haemolytic anemia, recent blood transfusion, chronic renal failure, chronic liver disease and pregnancy.

3) **Diabetic Microalbuminuria/Albuminuria/Nephropathy** [177,184]

   5.3 Category 2 Screening Tests (Suitable for individual-level decision)

   i) Urine Microalbumin/Creatinine Ratio

   Recommendation: Screening for albuminuria should begin 5 years after the diagnosis of Type 1 Diabetes. It should, however, begin immediately with the diagnosis of Type 2 Diabetes. Thereafter, screening for albuminuria should be done annually.

   Additional information

   Kidney disease develops in a similar, though not identical fashion in Type 1 and Type 2 Diabetes, with progressive proteinuria heralding the development of nephropathy. Less commonly, however, renal dysfunction may occur in the absence of the classic progressive albuminuria.

   Microalbuminuria (defined as low levels of urine albumin from 30 to 299 mg/day) develops in 40% of Type 1 diabetic patients about 5 years after initial presentation. When microalbuminuria is due to diabetic nephropathy, it is persistent. Without specific interventions, 80% will progress to a stage of

clinical proteinuria over a period of 10 to 15 years, where the urine albumin levels are >300 mg/l. End Stage Renal Disease (ESRD) usually occurs in 50% of Type 1 Diabetes with overt nephropathy within 10 years, and in more than 75% by 20 years.

A higher proportion of Type 2 diabetic patients may have proteinuria at the time of diagnosis of hyperglycaemia, as the onset of development of hyperglycaemia is usually not distinct like it is with Type 1 Diabetes. Without specific interventions, a smaller proportion (20 to 40%) with microalbuminuria will progress to overt nephropathy, but only about 20% of these patients would have progressed to ESRD within 20 years.

4) Gout [185-187]

4.1 Category 3 *Screening Tests (Not recommended)*

i)   Serum Uric Acid

5) Hyperlipidaemia [114,177,188,189]

5.1 Category 1 *Screening Tests (Suitable for population-level screening)*

i)   Fasting Lipids

ii) Non-Fasting Lipids

> **Recommendation:** *Screening should be carried out in all individuals aged 40 years and above. It is recommended that clinicians routinely screen younger adults (men and women aged 18 and older) for lipid disorders including hyperlipidaemia if they have other risk factors for coronary artery disease (CAD). If the results are within optimal range, screening should be repeated at 3 yearly intervals. For those assessed to be at very high risk or high risk of CAD in accordance to the Ministry of Health Clinical Practice Guidelines 2/2016, lipid screening should be repeated annually.*

In summary, the following groups are to be screened:

a) All individuals aged 40 years and above

b) All first degree relatives of familial hypercholesterolemia patients.

(Special consideration: Routine screening is generally not recommended in children. However, screening can be carried out from age of 2 years in children who have a first degree relative diagnosed with familial hypercholesterolemia, as this gives the opportunity to teach good eating practices)

c) All adults with pre-existing CAD, cerebrovascular or peripheral artery disease irrespective of age

d) All adults with diabetes mellitus irrespective of age

e) All adults with IFG or IGT irrespective of age

f) All adults aged 18 years and above who have other risk factors for CAD, which include:

   1. Multiple CAD risk factors (e.g. tobacco use, hypertension)

   2. A family history of cardiovascular disease before age 50 years in male relatives or before age 60 years in female relatives

   3. A family history suggestive of familial hyperlipidaemia

Additional information on non-fasting lipids

In the non-fasting state, triglyceride (TG) levels may be slightly higher than the corresponding levels in the fasting state. For Low Density Lipoprotein – Cholesterol (LDL-C), the levels may be slightly lower in the non-fasting state as compared to the corresponding levels in the fasting state. Population-based studies suggest that the variation in TG levels ranges from +0.1mmol/L to +0.3mmol/L while that the LDL-C ranges from -0.3mmol/L to -0.1mmol/L. A repeat fasting lipid panel may be considered in cases where there is uncertainty surrounding non-fasting lipid panel results.

6) <u>Hypertension</u> [118,189,190]

6.1 Category 1 Screening Tests (Suitable for population-level screening)

i) Blood Pressure Measurement

> **Recommendation:** *Periodic screening for hypertension is recommended for all adults aged 18 years or older. Blood pressure should be measured at least once every 2 years for individuals with diastolic pressure below 85 mmHg and a systolic pressure below 130 mmHg (i.e. normal BP). Measurements are recommended annually for persons with a diastolic blood pressure of 85 to 89 mmHg or systolic blood pressure of 130 to 139 mmHg (i.e. high normal BP). Persons with higher blood pressures or a major coronary risk factor such as diabetes mellitus require more frequent measurement.*

7) <u>Kidney Disorder (Kidney Dysfunction)</u> [191-193]

7.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Kidney Function Test/Renal Panel

Recommendation: Individuals at increased risk of developing chronic renal disease should undergo testing of serum creatinine in order to estimate the glomerular filtration rate.

High Risk Groups (Any one of the following risk factors):

a) Individuals with diabetes mellitus

b) Individuals with hypertension

c) Individuals with cardiovascular disease

d) Individuals aged 50 years and above and who is a smoker

e) Individuals with a family history of ESRD

The test is performed annually.

ii) Urine Analysis

Screening using dipstick analysis should be performed for the following individuals at risk for kidney disease:

High Risk Groups (Any one of the following risk factors):

a) Individuals with Diabetes Mellitus (DM)

b) Individuals with Hypertension (HTN)

c) Individuals with cardiovascular disease

d) Individuals aged 50 years and above and who is a smoker

e) Individuals with a family history of ESRD

Screening to detect microscopic haematuria and proteinuria in asymptomatic population is not recommended.

<u>Additional information</u>

The US Multiple Risk Factor Intervention Trial had shown that older age, smoking, hypertension and diabetes were significant risk factors for ESRD. Familial aggregation of renal disease, in excess of that predicted by clustering of diabetes and hypertension, had also been reported in a population-based case-control study. In view of this, individuals with any one of the mentioned risk factors should be considered for screening.

The National Kidney Foundation has more than 10 years of field experience with the Kidney Early Evaluation Programme (KEEP), a targeted screening programme directed at the general population with diabetes, hypertension or family history of kidney diseases. The criteria for high-risk groups were developed in the mid-1990s based on diabetes and hypertension being the leading cause of ESRD, accounting for 71% of all cases, and on increased ESRD rates in family members of dialysis patients.

8) Obesity [194]

8.1 Category 1 *Screening Tests (Suitable for population-level screening)*

i) Body Mass Index (BMI)

> **Recommendation:** *All individuals 18 years of age or older should be screened annually*

ii) Waist Circumference

> **Recommendation:** *All individuals 18 years of age or older should be screened annually.*

8.2 Category 3 *Screening Tests (Not recommended)*

i) Body Fat Measurement

9) Osteoporosis/ Osteopenia [195-200]

9.1 Category 2 *Screening Tests (Suitable for individual-level decision)*

i) Bone Mineral Density (BMD) Scan

High Risk Group: Postmenopausal Asian women with high Osteoporosis Self-assessment Tool for Asians (OSTA) score.

Additional information

It is not advisable to screen BMD in the whole population though the definition of osteoporosis is based on BMD, as the measurements are costly and the cost-benefit or cost-effectiveness of such a strategy has not been demonstrated.

For females, the Osteoporosis Self-Assessment Tool (OSTA) for postmenopausal Asian women should be used as a risk assessment tool first before deciding on whether BMD should be offered. The Osteoporosis Self-assessment Tool for Asians (OSTA), which is based on *age* and *weight*, categorises *postmenopausal* Asian women into high, moderate and low risk of having osteoporosis on subsequent BMD measurement.

A case-finding approach should be employed for women falling into the moderate risk category and they should be evaluated for clinical risk factors, and have BMD measured if these factors are present. The prevalence of osteoporosis is low enough in the low risk category for BMD to be deferred, unless the woman has other identified clinical risk factors.

Women with osteoporosis, who are being monitored for progression or who are being treated, should have a follow-up BMD, usually at an interval of at least one year. In women with osteopenia (BMD between 1 and 2.5 S.D. below the

mean peak bone mass of young adults) a reasonable interval might be 1 to 2 years, while in those with normal BMD (more than -1 S.D. below the mean peak bone mass of young adults) a more reasonable interval may be 2 to 5 years.

OSTA formula (for females): Applicable for Asian females who are postmenopausal

Age (years) – weight (kg) =

> 20 high risk (should screen with BMD)

0-20 moderate risk (screen with BMD if other risk factors for osteoporosis present)

< 0 low risk

Risk factors for low bone mass for which BMD measurement might be considered are as follows:

Non-modifiable risk factors

a) Personal history of previous fracture as an adult

b) History of fracture in a first degree relative (especially maternal)

c) Low body weight

d) Older age

Potentially modifiable risk factors

a) Current cigarette smoking

b) Alcohol abuse

c) Early natural or surgical menopause before the age of 45 years, or prolonged premenopausal amenorrhea lasting > 1 year

d) Drugs e.g. corticosteroids (equivalent to prednisolone > 7.5 mg/day for more than 6 months), excess thyroxine, anticonvulsants

e) Ongoing disease conditions e.g. hypogonadism, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, chronic obstructive airways disease, liver disease, malabsorption, chronic renal failure, rheumatoid arthritis, organ transplantation and anorexia nervosa

f) Prolonged immobilisation, poor health or fragility

g) Lifelong low calcium intake (< 500 mg/day among Asians)

h) Lack of regular physical activity

For Asian males, there is no validated osteoporosis self-assessment screening tool available as yet. Clinical risk factors should be assessed and the BMD measured if indicated based on medical assessment.

9.2 Category 3 Screening Tests (Not recommended)

i) Serum Calcium

ii) Erythrocyte Sedimentation Rate (ESR)

iii) Serum Phosphate

iv) Quantitative Ultrasound Scan (QUS) of the Calcaneum [201, 202]

Additional information

Quantitative ultrasound measures ultrasound velocity and ultrasound broadband attenuation in bone for assessing bone density compared to the more commonly used Dual-energy X-ray Absorptiometry (DXA) scan. The benefits of QUS include portability, not exposing patients to radiation, and being less expensive.

However, there is limited application for QUS in screening due to its low sensitivity for detecting osteoporosis. Also, T-scores on different QUS machines are not directly translatable to DXA T-scores based on WHO classification. Since DXA T-scores are well validated for diagnosis and prognosis, a low T-score on QUS heel would still require subsequent DXA scanning to confirm the diagnosis. Locally, the normative databases for Singaporeans for QUS machines have not been established and there are no agreed upon criteria. In addition, there is good access to DXA scanning in Singapore.

10) Rheumatoid Arthritis

10.1 Category 3 Screening Tests (Not recommended)

i) Rheumatoid Factor

11) Systemic Lupus Erythematosus (SLE) [203, 204]

11.1 Category 3 Screening Tests (Not recommended)

i) Anti-Double Stranded DNA Antibody (Anti-DS DNA Ab)

ii) Anti-Nuclear Antibody (ANA)

12) Thyroid Disorder (Thyroid Abnormality/ Thyroid Dysfunction)

12.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Thyroid Function Test (TFT)

High Risk Groups:

a) Obese people as defined conventionally by individuals in high-risk weight categories; hypothyroidism may be asymptomatic and yet, obesity accounts for excessive morbidity and mortality (Diabetes Mellitus, Hyperlipidaemia, Metabolic Syndrome, Polycystic Ovarian Syndrome, Ischaemic Heart Disease, Cancers and Obstructive Sleep Apnoea). Testing can be done just *once* in the workup for a secondary cause of obesity.

b) Any individual with autoimmune disease as this will predispose to thyroid disorders such as Grave's Disease or Hashimoto's Thyroiditis. The Thyroid-Stimulating Hormone (TSH) level in the individual should be assessed annually.

c) Pregnant women who have diabetes mellitus or adrenal disease as they tend to develop goitre during pregnancy and the consequences of mental retardation in the offspring are severe. Thyroid function test (TFT) should be performed once early on during pregnancy.

E) Musculoskeletal Disorders

1) Back Pain (Back disorder) [205]

1.1 Category 3 Screening Tests (Not recommended)

i) MRI Lumbar Spine

2) Neck Pain (Neck disorder) [206-208]

2.1 Category 3 Screening Tests (Not recommended)

i) MRI Cervical Spine

F) Obstetric and Gynaecological Conditions

1) Menopause [209-211]

1.1 Category 3 Screening Tests (Not recommended)

i) Serum 5-Dehydroepiandrosterone (DHEA)

ii) Serum Estradiol (E2)

iii) Serum Follicle-Stimulating Hormone (FSH)

iv) Serum Insulin-Growth Factor-1 (IGF1)

v) Serum Progesterone

vi) Serum Testosterone

2) <u>Maternal Colonisation with Group B Streptococcus (GBS) during pregnancy</u>[212-216]

2.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Vaginal and Rectal swab

High Risk Group: All pregnant women between 35 and 37 weeks gestation.

The Centres for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) recommend universal prenatal screening at 35-37 weeks of gestation. This contradicts the Royal College of Obstetricians and Gynaecologists (RCOG) guideline which does not recommend universal prenatal screening for GBS carrier. Though universal screening is not recommended by the RCOG, the indications for intrapartum antimicrobial prophylaxis (IAP) as stated in the RCOG guideline are similar to that of the CDC guideline.

G) Vision and Hearing Disorders

1) <u>Age-related Macular Degeneration (AMD)</u>[217]

1.1 Category 3 Screening Tests (Not recommended)

i) AMD screen (Amsler Grid Chart)

2) <u>Diabetic Retinopathy</u> [177]

2.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Retinal Fundal Photography

Recommendation: All patients diagnosed with diabetes require regular visual acuity assessment and eye examinations by trained personnel to screen for diabetic retinopathy. Type 1 diabetic patients should be examined 3 to 5 years after diagnosis of diabetes, and at least once yearly subsequently. Type 2 diabetic patients should have an ocular assessment at the time of diagnosis and at least once yearly subsequently.

3) <u>Glaucoma</u>

3.1 Category 3 Screening Tests (Not recommended)

i) Tonometry

4) <u>Hearing Loss in adults (Deafness in adults)</u> [218]

4.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Audiometry

High Risk Group: All persons exposed to excessive noise must undergo pre-employment and annual medical examinations which include audiometry under the Workplace Safety and Health (Medical Examinations) Regulations by Ministry of Manpower.

5) Hypertensive Retinopathy

5.1 Category 3 Screening Tests (Not recommended)

i) Retinal Fundal Photography

6) Vision Disorder in adults[219]

6.1 Category 3 Screening Tests (Not recommended)

i) Visual Acuity

H) Congenital and Paediatric Conditions

1) Antenatal and Foetal Abnormalities (Congenital) [220, 221]

1.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Screening tests done in pregnancy or antenatal screening tests (e.g. FBC, VDRL, HIV, Hepatitis B, urine microscopy as well as obstetric ultrasound foetal anomaly screening)

Recommendation: The above blood tests and urine test are recommended in early pregnancy (preferably during the first antenatal visit) as a once-off test. All women should be offered an obstetric ultrasound before 22 weeks gestation. This will include an ultrasound for foetal morphology and placenta localisation usually at 18 to 22 weeks gestation.

2) Down Syndrome [222]

2.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Down Syndrome Screening Test

Recommendation: All pregnant women, regardless of age, should be considered to be at risk for foetal aneuploidy and should be offered screening for Down Syndrome. All women should be made aware of the availability of screening tests for Down Syndrome and other chromosomal abnormalities.

This should include Nuchal Translucency Screening (NTS) combined with first trimester maternal serum screening (also known as the first trimester combined screening) or NTS combined with second trimester maternal serum testing (also known as step-wise sequential screening).

3) Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency in neonates

3.1 Category 1 *Screening Tests (Suitable for population-level screening)*

i) Cord Blood G6PD Screening

> **Recommendation:** *All newborns in Singapore are screened for G6PD deficiency using umbilical cord blood.*

4) Hearing Loss in neonates (Deafness in neonates) [226-228]

4.1 Category 1 *Screening Tests (Suitable for population-level screening)*

i) Audiometry

> **Recommendation:** *All newborns in Singapore are screened for congenital hearing impairment under the "Universal Newborn Hearing Screening" programme.*

Additional information

Screening is carried out using automated Auditory Brain-stem Response (AABR), Transient Evoked Oto-acoustic Emission (TEOAE) or Distortion Product Oto-Acoustic Emission (DPOAE). It should be completed preferably before hospital discharge, so that diagnosis of congenital hearing impairment can be confirmed before the infant is 3 months old and intervention can begin before the infant is 6 months old. This is in line with recommendations of the Joint Committee on Infant Hearing (JCIH) 2007 of the American Academy of Paediatrics (AAP).

In high-risk groups who have normal hearing screens at birth but remain at risk of progressive or delayed-onset hearing loss, repeat hearing screen is recommended, at up to 6-monthly intervals.

High-risk conditions for progressive or delayed-onset hearing loss

a) Parental or caregiver concern over hearing or delayed language, speech or development
b) Family history of permanent childhood hearing loss
c) Clinical findings associated with syndromes that are known to include sensori-neural or conductive hearing loss
d) Postnatal infections associated with sensori-neural hearing loss, including bacterial meningitis
e) *In utero* infection with toxoplasmosis, rubella, cytomegalovirus, herpes or syphilis
f) Neonatal conditions, specifically hyper-bilirubinaemia requiring exchange transfusion or persistent pulmonary hypertension requiring mechanical ventilation
g) Syndromes associated with progressive hearing loss, such as neurofibromatosis
h) Neuro-degenerative conditions (e.g. Hunter syndrome)

i) Head trauma

j) Recurrent or persistent otitis media with effusion for at least 3 months

5) Inborn Errors of Metabolism in neonates[226]

5.1 Category 1 Screening Tests (Suitable for population-level screening)

i) Metabolic Screen (Tandem Mass Spectrometry (TMS))

> **Recommendation:** *Under the National Expanded Newborn Screening Programme, all neonates would undergo an additional newborn screening test called the Metabolic Screen. The metabolic screen tests newborn babies for a group of disorders called Inborn Errors of Metabolism (IEM). About 25 to 30 IEMs can be screened for from a blood spot using a novel technology called TMS.*

Additional information

The metabolic screen test using TMS has a high predictive value with a sensitivity of 96%, specificity 99.8% and recall rate 1.5 to 2%. Patients with grossly abnormal screening tests are referred to metabolic specialists for further management. Those with borderline abnormal results are recalled for a repeat screening test.

6) Primary Hypothyroidism in neonates

6.1 Category 1 Screening Tests (Suitable for population-level screening)

i) Thyroid Function Test (TFT)

> **Recommendation:** *All new-borns in Singapore will get their cord blood tested once for primary hypothyroidism with Thyroid-Stimulating Hormone (TSH). If TSH is abnormal, then free thyroxine (T4) is tested.*

7) Retinopathy Of Prematurity (ROP) [227]

7.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Indirect Ophthalmoscope, Eye Speculum or Scleral Indentor

Recommendation: Screening should be carried out for infants with **any one** of the following:

a. Birth weight less than 1500 g **or**
b. Gestational age less than 32 weeks **or**
c. Prolonged oxygen therapy use

Additional information

Screening Protocol

a. Babies born before 27 weeks gestational age (i.e. up to 26 weeks and 6 days) - the first ROP screening examination should be undertaken at 30 to 31 week

b. Babies born between 27 and 32 weeks gestational age (i.e. up to 31 weeks and 6 days) - the first ROP screening examination should be undertaken between 4 to 5 weeks (i.e. 28 to 35 days) postnatal age

c. Babies >32 weeks gestational age but with birth weight <1500 grams – the first ROP screening examination should be undertaken between 4 to 5 weeks (i.e. 28 to 35 days) postnatal age

d. Minimum frequencies of screening should be weekly when:

   1. the vessels end in zone I or posterior zone II; **or**

   2. there is any plus or pre-plus disease **or**

   3. there is any stage 3 disease in any zone

e. Minimum frequencies of screening should be every 2 weeks:

f. In all other circumstances until the criteria for termination have been reached

g. All babies <32 weeks gestational age or birth weight <1500g or have undergone prolonged oxygen therapy should have their first ROP screening examination prior to discharge

Termination of ROP screening

Screening can be stopped when a baby is no longer at risk of sight-threatening ROP. In babies who never develop any ROP, the risk of sight-threatening ROP developing is minimal once the retinal vessels have entered zone III and eye examinations may be stopped when this happens, usually after 36 completed week's postmenstrual age.

In babies developing ROP which does not meet the criteria for treatment, screening can be safely stopped when any of the following characteristics of regression are seen on at least 2 successive examinations:

a. Lack of increase in severity

b. Partial resolution progressing towards complete resolution

c. Change in colour in the ridge from salmon pink to white

d. Transgression of vessels through the demarcation line

e. Commencement of the process of replacement of active ROP lesions by scar tissue

8) Developmental Vision Disorder [219,229]

8.1 Category 1 *Screening Tests (Suitable for population-level screening)*

i) Visual Acuity Test

Recommendation: For children aged 3 years and above.

Additional information

The USPSTF recommends vision screening for all children at least once between the ages of 3 and 5 years, to detect the presence of amblyopia or its risk factors. The most common causes of vision impairment in children are amblyopia and associated risk factors (strabismus, anisometropia, astigmatism, and hyperopia) and refractive errors not associated with amblyopia.

In its assessment, the USPSTF found adequate evidence that treatment for amblyopia or unilateral refractive errors is associated with moderate improvements in visual acuity for children 3 to 5 years of age and, in theory, permanent improvements throughout life. Although the average improvement in visual acuity resulting from treatment for amblyopia was ~1 line on a Snellen eye chart, the USPSTF concluded that the benefits are moderate because untreated amblyopia results in permanent, uncorrectable vision loss and the potential benefits are experienced over the individual's life span. Harms from treatment seem to be minimal. Therefore, the USPSTF concluded with moderate certainty that the overall net benefit is moderate.

Under the National Myopia Prevention Programme under the auspices of the Health Promotion Board, yearly vision screening is conducted for Kindergarten 1 and Kindergarten 2 students in all pre-schools. For the primary and secondary students, visual acuity screening is conducted as part of the annual health screening by the School Health Service. Additionally, three-dimensional (3D) vision screening and colour vision screening are performed on all Primary 1 children.

9) Idiopathic Scoliosis in adolescents [230-233]

9.1 Category 1 *Screening Tests (Suitable for population-level screening)*

i) Scoliometer

Recommendation: Screening examination for scoliosis should be conducted for all females and males during the early adolescent years.

Additional information

Under the Health Promotion Board's School Health Screening Programme, all adolescents would receive spinal screening. Females are screened at Primary 5 and 6, Secondary 1 and 2 to check for abnormal curvature of the backbone. Males are screened at Secondary 2.

Scoliosis screening should be aimed at identification of suspect cases of scoliosis for referral for early diagnostic evaluation and confirmation to facilitate non-surgical therapy (i.e. bracing), preventing the need for surgery, or to rule out suspicion. The Scoliosis Research Society International Task Force, an expert panel, recommends scoliometer (alone with an Adams Forward bending test) as the best tool in terms of reliability and validity to measure truncal asymmetry, a proxy for spinal deformities.

10) Thalassaemia [228, 234-236]

10.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Thalassaemia Screen

High Risk Groups:

a) Pregnant women who are from racial and ethnic groups with a high incidence of haemoglobinopathies (e.g., individuals of African, Caribbean, Latin American, Mediterranean, Middle Eastern, or Southeast Asian descent) should be screened, preferably at the first prenatal visit.

b) Family history of Thalassaemia

The screening should be done once-off at the first prenatal visit for pregnant women.

Additional information

The USPSTF recommends screening for haemoglobinopathies like thalassaemia with haemoglobin electrophoresis or other tests of comparable accuracy in pregnant women at the first prenatal visit. This is especially for those who are members of racial and ethnic groups with a high incidence of haemoglobinopathies (e.g., individuals of African, Caribbean, Latin American, Mediterranean, Middle Eastern, or Southeast Asian descent).

11) Spastic Hip Displacement [237-239]

11.1 Category 2 Screening Tests (Suitable for individual-level decision)

i) Antero-Posterior Pelvis X-ray

Recommendations: For children with cerebral palsy

Additional information

Children with cerebral palsy are at risk of spastic hip displacement. Clinical examination alone is insufficient to evaluate hip displacement in this particular group. Decisions for treatment and surveillance must be made in conjunction with an antero-posterior radiograph of the pelvis and hip joint with the child in

the supine position. The most accepted and reproducible measurement for hip displacement is migration percentage (MP) which is the most valid, reliable, and useful measure of hip displacement in children with CP. However, radiological measures may be less accurate in the very young and will not be accurate below 12 months of age.

I) Miscellaneous

1) Benign Prostatic Hyperplasia (BPH)

1.1 Category 3 *Screening Tests (Not recommended)*

i)   Prostate-Specific Antigen (PSA)

ii) MRI Prostate

2) Chronic Obstructive Pulmonary Disease (COPD)[240]

2.1 Category 3 *Screening Tests (Not recommended)*

i)   Spirometry

3) Purpose of identification

The following tests are for the purposes of identification rather than for health reasons.

i)   Blood Group

ii) Rhesus Factor

Part II of Report: Categorisation of screening tests by type of tests

A) General
B) Blood (Non-tumour markers)
C) Blood (Tumour markers)
D) Urine
E) Stool
F) Imaging: X-Ray, Ultrasound, CT, MRI
G) Eye
H) Special

A) General

Category 1 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	1	Blood Pressure Measurement	Hypertension	D 6.1(i)
2	1	Body-Mass Index (BMI)	Obesity	D 8.1 (i)
3	1	Waist Circumference	Obesity	D 8.1 (ii)

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	Electrocardiography (ECG)	Coronary Heart Disease	B 5.1 (i)

Category 3 screening tests (NOT RECOMMENDED AS SCREENING TESTS)

No.	Category	Screening Test	Disease/Condition	Details (See)
1	3	Body Fat Measurement	Obesity	D 8.2 (i)

B) Blood (Non-tumour markers)

Category 1 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	1	Fasting Blood Glucose	Diabetes Mellitus	D 2.1 (i)
2	1	HbA1c	Diabetes Mellitus	D 2.1 (ii)

3	1	Fasting Lipid	Hyperlipidaemia	D 5.1 (i)
4	1	Non-Fasting Lipid	Hyperlipidaemia	D5.1 (ii)
5	1	Thyroid Function Test (TFT)	Primary Hypothyroidism in Neonates	H 6.1 (i)

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	Apolipoprotein A and B	Coronary Heart Disease	B 5.1 (iii)
2	2	Full Blood Count (FBC)	Anaemia (Iron Deficiency Anaemia)	D 1.1 (i)
3	2	Hepatitis B Screen	Hepatitis B Infection	C 4.1 (i)
4	2	Hepatitis C Screen	Hepatitis C Infection	C5.1(i)
5	2	hsCRP	Coronary Heart Disease	B 5.1 (ii)
6	2	Human Immunodeficiency Virus (HIV) screen	Human Immunodeficiency Virus Infection	C 2.1 (i)
7	2	Interferon-Gamma Release Assay (IGRA)	Tuberculosis (TB)	C9.1(i)
8	2	Kidney Function Test/ Renal Panel	Kidney Disorder/ Dysfunction	D 7.1 (i)
9	2	Rubella Serology	Rubella	C 7.1 (i)
10	2	Syphilis Enzyme Immunoassay (EIA)	Syphilis	C8.1(ii)
11	2	Thalassaemia Screen	Thalassemia	H 10.1 (i)
12	2	Thyroid Function Test (TFT)	Thyroid Disorder/ Dysfunction	D 12.1 (i)
13	2	Treponema Pallidium Particle Agglutination (TPPA)/ Treponema Pallidum Haemagglutination (TPHA)	Syphilis	C 8.1 (i)

Category 3 screening tests (NOT RECOMMENDED AS SCREENING TESTS)

No.	Category	Screening Test	Disease/Condition	Details (See)
1	3	Anti-Double Stranded DNA Antibody (Anti-DS DNA Ab)	Systemic Lupus Erythematosus (SLE)	D 11.1 (i)
2	3	Anti-Nuclear Antibody (ANA)	Systemic Lupus Erythematosus (SLE)	D 11.1 (ii)
3	3	Serum Calcium	Osteoporosis	D 9.2 (i)
4	3	Serum 5-Dehydroepiandrosterone (DHEA)	Menopause	F 1.1 (i)
5	3	Erythrocyte Sedimentation Rate (ESR)	Osteoporosis	D 9.2 (ii)
6	3	Serum Estradiol (E2)	Menopause	F 1.1 (ii)
7	3	Serum Follicle-Stimulating hormone (FSH)	Menopause	F 1.1 (iii)
8	3	Hepatitis A Screen	Hepatitis A Infection	C 3.1 (i)
9	3	Hepatitis C Screen	Hepatitis C	C 4.1 (i)
10	3	Homocysteine	Coronary Heart Disease	B 5.2 (ii)
11	3	Insulin-Growth Factor-1 (IGF1)	Menopause	F 1.1 (iv)
12	3	Serum Phosphate	Osteoporosis	D 9.2 (iii)
13	3	Serum Progesterone	Menopause	F 1.1 (v)
14	3	Rheumatoid Factor	Rheumatoid Arthritis	D 10.1 (i)
15	3	Serum Testosterone	Menopause	F 1.1 (vi)
16	3	Serum Uric Acid	Coronary Heart Disease	B 5.2 (iii)
			Gout	D 4.1 (i)

For identification purposes

No.	Category	Screening Test	Disease/Condition	Details (See)
1	Nil	Blood Group	Purpose of identification	I 3 (i)
2	Nil	Rhesus Factor	Purpose of identification	I 3 (ii)

C) Blood (Tumour markers)

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	Alpha-Fetoprotein (AFP)	Liver Cancer (HCC)	A 7.1 (i)
2	2	Prostate-Specific Antigen (PSA)	Prostate Cancer	A 13.1 (i)
3	2	Tumour marker for NPC (EBV-EA-EBNA-1)	Nasopharyngeal Carcinoma (NPC)	A 9.1 (i)

Category 3 screening tests (NOT RECOMMENDED AS SCREENING TESTS)

No.	Category	Screening Test	Disease/Condition	Details (See)
1	3	CA 125	Ovarian Cancer	A 11.2 (i)
2	3	CA 19-9	Pancreatic Cancer	A 12.1 (i)
3	3	Carcinoembryonic Antigen (CEA)	Colorectal Cancer	A 4.3 (i)
4	3	Liver Function Test (LFT)	Liver Cancer (HCC)	A 7.2 (i)
5	3	Methylated SEPT9 DNA Test	Colorectal Cancer	A 4.3 (iv)
6	3	Prostate-Specific Antigen (PSA)	Benign Prostate Hyperplasia (BPH)	I 1.1 (i)
7	3	Testicular Cancer Test (e.g. AFP and beta-HCG)	Testicular Cancer	A 14.1 (i)

No.	Category	Screening Test	Disease/Condition	Details (See)
8	3	Tumour Marker for Breast (e.g. CEA and CA15-3)	Breast Cancer	A 1.3 (ii)
9	3	Tumour Marker for lung	Lung Cancer	A 8.2 (i)

D) Urine

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	Urine Analysis	Kidney Disorder (Kidney dysfunction/abnormality)	D 7.1 (ii)
2	2	Urine Microalbumin/Creatinine Ratio	Diabetic Albuminuria/Microalbuminuria /Nephropathy	D 3.1 (i)
3	2	Urine PCR	Chlamydia infection and Gonorrhoea	C 1.1 (i)

Category 3 screening tests (NOT RECOMMENDED AS SCREENING TESTS)

No.	Category	Screening Test	Disease/Condition	Details (See)
1	3	Urine dipstick or microscopic urinalysis, urine cytology and tests for urine biomarkers	Bladder Cancer	A 2.1 (i)

E) Stool

Category 1 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	1	Faecal Immunochemical Test (FIT)	Colorectal Cancer	A 4.1 (i)

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	FIT – DNA test	Colorectal Cancer	A 4.2 (ii)
2	2	Stool for ova, cyst and parasites	Intestinal Parasitic Disease	C 6.1 (i)

F) Imaging

i) X-Ray:

Category 1 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	1	Mammogram	Breast Cancer	A 1.1 (i)

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	Bone Mineral Density (BMD) Scan	Osteoporosis	D 9.1 (i)
2	2	Chest X-Ray (CXR)	Tuberculosis (TB)	C 9.1 (iii)
3	2	Antero-Posterior Pelvis X-ray	Spastic Hip Displacement	H 11.1 (i)

Category 3 screening tests (NOT RECOMMENDED AS SCREENING TESTS)

No.	Category	Screening Test	Disease/Condition	Details (See)
1	3	Abdominal X-Ray (AXR)	Colorectal Cancer	A 4.3 (ii)
2	3	Chest X-Ray (CXR)	Lung Cancer	A 8.2 (ii)

ii) Ultrasound:

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	Abdominal Ultrasonography	Abdominal Aortic Aneurysm (AAA)	B 1.1 (i)

No.	Category	Screening Test	Disease/Condition	Details (See)
2	2	Ultrasound Hepatobiliary System (US HBS)	Liver Cancer (HCC)	A 7.1 (ii)
3	2	Transvaginal Ultrasound	Ovarian Cancer	A 11.1 (i)
4	2	Ultrasound Pelvis	Endometrial Cancer	A 5.1 (i)

Category 3 screening tests (NOT RECOMMENDED AS SCREENING TESTS)

No.	Category	Screening Test	Disease/Condition	Details (See)
1	3	Duplex Ultrasonography	Carotid Artery Stenosis	B 4.1 (i)
2	3	Quantitative Ultrasound Scan (QUS) of the Calcaneum	Osteoporosis	D 9.2 (iv)
3	3	Ultrasound Breasts	Breast Cancer	A 1.3 (i)
4	3	Ultrasound Pelvis	Cervical Dysplasia/ Cervical Intraepithelial Lesion /Cervical Cancer	A 3.2 (i)

iii) CT:

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	CT Colonography	Colorectal Cancer	A 4.2 (i)
2	2	CT Coronary Calcium Score	Coronary Heart Disease	B 5.1 (iv)
3	2	Low-dose CT Scan	Lung Cancer	A 8.1 (i)

Category 3 screening tests (NOT RECOMMENDED AS SCREENING TESTS)

No.	Category	Screening Test	Disease/Condition	Details (See)
1	3	CT Abdomen	Colorectal Cancer	A 4.3 (iii)
2	3	CT Coronary Angiogram	Coronary Heart Disease	B 5.2 (i)
3	3	CT Pelvis	Cervical Dyplasia/ Cervical Intraepithelial Lesion /Cervical Cancer	A 3.2 (ii)

			Endometrial Cancer	A 5.2 (i)
			Ovarian Cancer	A 11.2 (ii)
4	3	CT Scan	Pancreatic Cancer	A 12.2 (ii)

iv) MRI:

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	MRI Breast	Breast Cancer	A 1.2 (i)
2	2	MRI Brain/MRA	Cerebral Aneurysm	B 2.1 (i)

Category 3 screening tests (NOT RECOMMENDED AS SCREENING TESTS)

No.	Category	Screening Test	Disease/Condition	Details (See)
1	3	MRI Brain/MRA	Cerebrovascular Disease (Stroke)	B 3.1 (i)
2	3	MRI Cervical Spine	Neck Pain (neck disorder)	E 2.1 (i)
3	3	MRI Lumbar Spine	Back Pain (back disorder)	E 1.1 (i)
4	3	MRI Prostate	Benign Prostate Hyperplasia (BPH)	I 1.1 (ii)
			Prostate Cancer	A 13.2 (i)

G) Eye

Category 1 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	1	Visual Acuity Test	Developmental Vision Disorder (in children)	H 8.1 (i)

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	Indirect Ophthalmoscope, Eye Speculum or Scleral Indentor	Retinopathy of Prematurity (ROP)	H 7.1 (i)
2	2	Retinal Fundal Photography	Diabetic Retinopathy	G 2.1 (i)

Category 3 screening tests (NOT RECOMMENDED AS SCREENING TESTS)

No.	Category	Screening Test	Disease/Condition	Details (See)
1	3	Visual Acuity Test	Vision Disorder (in adults)	G 6.1 (i)
2	3	AMD screen (Amsler grid chart)	Age-related Macular Degeneration (AMD)	G 1.1 (i)
3	3	Retinal Fundal Photography	Hypertensive Retinopathy	G 5.1 (i)
4	3	Tonometry	Glaucoma	G 3.1 (i)

H) Special

Category 1 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	1	Audiometry	Hearing Loss in neonates (Deafness in neonates)	H 4.1 (i)
2	1	Colonoscopy	Colorectal Cancer	A 4.1 (ii)
3	1	Cord blood G6PD Screening	G6PD Deficiency	H 3.1 (i)
4	1	Human Papilloma Virus (HPV) test for women aged 30 years and above	Cervical Dysplasia/ Cervical Intraepithelial Lesion /Cervical Cancer	A 3.1 (ii)
5	1	Metabolic Screen (Tandem Mass Spectrometry (TMS))	Inborn Errors of Metabolism (IEM)	H 5.1 (i)

No.	Category	Screening Test	Disease/Condition	Details (See)
6	1	Pap Smear for women aged 25 to 29 years	Cervical Dysplasia/ Cervical Intraepithelial Lesion /Cervical Cancer	A 3.1 (i)
7	1	Spinal Screening (Scoliometer)	Scoliosis	H 9.1 (i)

Category 2 screening tests

No.	Category	Screening Test	Disease/Condition	Details (See)
1	2	Ankle Brachial Index (ABI)	Peripheral Vascular Disease	B 6.1 (i)
2	2	Antenatal screening tests or pregnancy screening tests (eg. FBC, VDRL, HIV, Hepatitis B, urine microscopy as well as Obstetric Ultrasound Foetal Anomaly screening)	Antenatal and Foetal abnormalities (Congenital)	H 1.1 (i)
3	2	Audiometry	Hearing Loss in adults (Deafness in adults)	G 4.1 (i)
4	2	Cervical and Urethral swab for PCR	Chlamydia Infection and Gonorrohea	C 1.1 (i)
5	2	Down Syndrome Screening Test	Down Syndrome	H 2.1 (i)
6	2	Nasopharyngoscopy	Nasopharyngeal Carcinoma (NPC)	A 9.1 (ii)
7	2	Oesophago-Gastro Duodenoscopy (OGD)	Gastric Cancer	A 6.1 (i)
8	2	Treadmill Stress Test	Coronary Heart Disease	B 5.1 (v)
9	2	Tuberculin Skin Test	Tuberculosis	C 9.1 (ii)
10	2	Vaginal and Rectal Swab	Maternal colonisation with GBS during pregnancy	F 2.1 (i)

Category 3 screening tests (NOT RECOMMENDED AS SCREENING TESTS)

No.	Category	Screening Test	Disease/Condition	Details (See)
1	3	Oesophago-Gastro-Duodenoscopy (OGD)	Oesophageal cancer	A 10.1 (i)
2	3	Spirometry	Chronic Obstructive Pulmonary Disease (COPD)	I 2.1 (i)

Criteria for Categorisation of Screening Tests

1	**Suitable for population-level screening**
	The disease condition is an important health problem; Its natural history is well understood; It is recognisable at an early stage; There is robust evidence (based on meta-analysis of randomised controlled trials, or high-quality randomised controlled trials (RCTs) available) that use of the screening test improves survival; The target population for the test is the general population at normal risk (although age can be used to stratify this population into risk groups) Recommendations made by trusted expert authorities (e.g. local clinical practice guidelines (CPGs), US Preventive Services Task Force) uniformly support use of screening test; Population-level screening programmes have been implemented successfully elsewhere; Cost-effectiveness data available, based on preferable local, or, if not, overseas data reporting cost effective analysis ratios within the acceptable threshold for Singapore.
2	**Suitable for individual-level decision**
	The disease is recognisable at an early stage; There is some evidence that use of the screening tests improves survival, though not necessarily at same level of robustness; The screening test is not suitable for general populations at normal risk (even after stratification by age into risk groups), although evidence suggests that some more narrowly-defined high-risk groups (defined by other factors such as personal and family history) may benefit; Risk-benefit ratio of benefit to harm is different for different individuals, and may exceed 1 in some groups; Cost-effectiveness data suggest cost effective analysis ratios are above acceptable threshold for Singapore, or there is no cost-effectiveness data.
3	**Not recommended**
	The current evidence is insufficient to assess the balance of benefits and harms of the service;

	Evidence is lacking, or of poor quality, or is conflicting so that no decision can be made based on the information available.
	Or:
	The natural history of the disease is not well understood;
	There is no easily recognisable early stage of disease;
	The performance characteristics of the screening test (in terms of sensitivity and specificity) are poor;
	There is evidence that even narrowly-defined high risk groups will not benefit from the test;
	The screening test, or follow-up tests arising from a positive screen, are associated with significant medical risks
	The risk-benefit ratio consistently exceeds 1 for all members of the population.
	Recommendations made by trusted expert authorities are uniformly against use of screening test

Executive health screening packages are advertised prevalently in Singapore. These packages bundle screening tests from Category 1 and 2 as well as Category 3, which include screening tests that are not recommended. Further details on executive health screening is at Appendix A-1.

Executive Health Screening Packages

Screening tests are performed to detect diseases at an early stage, while individuals are still asymptomatic. The foresight that comes with screening, allows for treatment of the diseases at a much earlier stage. However, every screening test can be harmful too[241]. For example, unwarranted x-rays examinations expose the individual to unnecessary radiation and endoscopy of the bowel can lead to bleeding or serious injuries (in rare cases). Hence, it is important that that the benefits and harms of screening tests is evaluated before it is introduced as a Category 1 test or Category 2 test which is suitable for population-level and individual-level screening, respectively.

However, various medical centres, bundle Category 1, 2 and 3 tests in their packages. While Category 2 tests may be carried out after a thorough evaluation of the individual's risk of specific disease conditions, Category 3 tests such as CA125 to screen for ovarian cancer, are not recommended due to insufficient evidence of effectiveness, good evidence that the screening test is not cost-effective, or that the net harm outweighs benefits.

Furthermore, there are too many false positives when multiple tests are performed such that is the case when an individual signs up for an executive health screening package. A false positive shows an abnormality that is not there and may warrant more invasive testing (which comes with its own costs and risks of severe complications) to be done only to find that individual does not have the disease he/she is being screened for. In addition, false positive outcomes can lead to significant psychology harms in the form of substantial anxiety while awaiting further confirmatory testing to be done. Furthermore, there are studies that show that even after further tests exclude the possibility of serious conditions, the psychological distress may persist to affect mood and daily functioning[242-244].

In view of this, medical professionals and individuals are strongly discouraged from providing and submitting themselves, respectively, to multiple screening tests that are neither indicated based on the individual's risk profiles, nor evidence-based.

US Preventive Services Taskforce Recommendation Categories Compared to the Proposed Framework

	USPSTF		MOH
	Definition	**Suggestions for Practice**	**MOH proposed framework**
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.	Equivalent to "Recommended for Population-level screening"
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.	Equivalent to "Recommended for Population-level screening"
C	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.	Offer or provide this service only if other considerations support the offering or providing the service in an individual patient.	Equivalent to "Recommended for Individual-level decision"
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.	Equivalent to "Not recommended"
I Statement (Inconclusive statement)	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Refer to the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.	Equivalent to "Not recommended"

LIST OF CATEGORY 1 SCREENING TESTS[1]

No.	Screening Test	Disease	Age Group
1	Audiometry	Hearing Loss in neonates	All neonates
2	Blood Pressure Measurement	Hypertension	Individuals aged 18 yrs and above
3	Body Mass Index (BMI)	Obesity	Individuals aged 18 yrs and above
4	Colonoscopy[2]	Colorectal Cancer	Individuals aged 50 yrs and above
5	Faecal Immunochemical Test[3] (FIT)	Colorectal Cancer	Individuals aged 50 yrs and above
6	Fasting Blood Glucose	Diabetes Mellitus	Individuals aged 40 yrs and above
7	Glycated Haemoglobin (HbA1c)	Diabetes Mellitus	Individuals aged 40 yrs and above
8	Fasting Lipids	Hyperlipidaemia	Individuals aged 40 yrs and above
9	Non-fasting Lipids	Hyperlipidaemia	Individuals aged 40 yrs and above
10	G6PD Screen with cord blood	G6PD Deficiency in neonates	All neonates
11	Human Papillomavirus (HPV) DNA test	Cervical Dysplasia/ Cervical Intraepithelial Lesion /Cervical Cancer	Women age of 30 years and above who ever had sexual intercourse
12	Mammogram	Breast Cancer	Women aged 50 to 69 yrs

---

[1] Category 1 screening tests are suitable for population-level screening; there is good and robust evidence that these tests are clinically effective and cost effective for use at the population level.
[2,10] Either an annual FIT or a 10-yearly colonoscopy is recommended for Colorectal Cancer screening in an average-risk individual aged 50 years and above.

13	Metabolic Screen (Tandem Mass Spectrometry (TMS))	Inborn Errors of Metabolism (IEM)	All neonates
14	Pap Smear	Cervical Dysplasia/ Cervical Intraepithelial Lesion /Cervical Cancer	Women aged 25 to 29 years who ever had sexual intercourse
15	Spinal screening (Scoliometer)	Scoliosis	All females and males during the early adolescent years
16	Thyroid Function Test (TFT)	Primary Hypothyroidism in neonates	All neonates
17	Vision Acuity Test	Developmental Vision Disorder (in children)	Children aged 3 years and above
18	Waist Circumference	Obesity	Individuals aged 18 yrs and above

LIST OF CATEGORY 2 SCREENING TESTS[4]

No.	Screening Test	Disease	High Risk Group
1.	Abdominal Ultrasonography	Abdominal Aortic Aneurysm	Men aged 65 to 75 who have ever smoked
2.	Alpha-Fetoprotein	Liver Cancer	Hepatitis B carrier or individuals with liver cirrhosis
3.	Ankle Brachial Index	Peripheral Vascular Disease	Individuals with diabetes mellitus; Individuals aged 50-70 yrs and are smokers or with both hypertension and hyperlipidaemia
4.	Antenatal and Pregnancy Screening Tests	Antenatal and Foetal abnormalities (Congenital)	All pregnant women
5.	Apolipoprotein A and B	Coronary Heart Disease	Individuals with intermediate Coronary Heart Disease risk
6.	Audiometry	Hearing Loss in adults	Individuals exposed to excessive noise
7.	Bone Mineral Density Scan	Osteoporosis	Individuals with high Osteoporosis risk e.g. high OSTA score
8.	Chest X-ray	Tuberculosis (TB)	Close Contacts; Foreigners from countries with high disease prevalence
9.	CT Colonography	Colorectal Cancer	Individuals above 50 yrs not going for screening colonoscopy or FIT
10.	CT Coronary Calcium Score	Coronary Heart Disease	Individuals with intermediate coronary heart disease risk
11.	Down Syndrome Screening	Down Syndrome	All pregnant women

---

[4] Category 2 screening tests are suitable for individual-level decisions; the screening tests may be useful for high-risk populations, or there is evidence that the screening tests are effective, but favourable cost-effectiveness has not been established.

No.	Screening Test	Disease	High Risk Group
12.	Electrocardiography	Coronary Heart Disease	Individuals with intermediate Coronary Heart Disease risk
13.	Faecal immunochemical test (FIT) – DNA test	Colorectal Cancer	Individuals aged 50 yrs and above
14.	Full Blood Count	Anaemia (Iron-deficiency)	All pregnant women, women of childbearing age, high risk infants, high risk children
15.	Hepatitis B Screen	Hepatitis B Infection	All pregnant women; Asymptomatic Singapore residents with no known hepatitis B carrier status and have not been previously vaccinated; Healthcare workers; Immigrants from countries where Hepatitis B is endemic; Persons with known exposure to HBV; Persons on chronic haemodialysis; Intravenous drug abusers; Persons who have undergone invasive procedures in healthcare facilities with inadequate infection control practices; Persons with HBV-positive or at-risk sex partners; HIV patients
16.	Hepatitis C Screen	Hepatitis C Infection	Children born to HCV-positive mothers; Persons with known exposure to HCV; Persons on chronic haemodialysis; Intravenous drug abusers; Persons who have undergone invasive procedures in healthcare facilities with inadequate infection control practices; Persons with HCV-positive or at-risk sex partners; Healthcare workers; HIV patients
17.	hsCRP	Coronary Heart Disease	Individuals with intermediate Coronary Heart Disease risk
18.	Human Immunodeficiency Virus (HIV) screen	Human Immunodeficiency Virus Infection	All pregnant women; Healthcare workers; Individuals with active TB infection; Individuals with at-risk sexual behaviour; Intravenous drug abusers, Persons with HIV-positive or at-risk sex partners; Persons with known HIV exposure
19.	Interferon-Gamma Release Assay	Tuberculosis (TB)	Close contacts of TB; High-risk individuals: HIV, patients receiving anti-TNF agents, dialysis, transplants (solid organ and haematological)
20.	Kidney Function Test	Kidney Disorder/ Dysfunction	Individuals with Diabetes Mellitus or Hypertension or Cardiovascular Disease; Individuals aged 50 yrs and above who are smokers; Individuals with a family history of End-Stage Renal Failure

No.	Screening Test	Disease	High Risk Group
21.	Low-dose CT Screening	Lung Cancer	Individuals aged between 55-74 who have smoked ≥ 30 pack years and are continuing to smoke; Individuals aged between 55 to 74 who have smoked ≥ 30 pack years but quit <15 years ago
22.	MRI/ MRA Brain	Cerebral Aneurysm	Individuals with a personal or family history of 2 or more first-degree relatives with subarachnoid haemorrhage; Individuals with Autosomal Dominant Polycystic Kidney Disease
23.	MRI Breast	Breast Cancer	Proven BRCA carriers; Women at high genetic risk for Breast Cancer; Women with Breast Injection augmentation that severely impairs evaluation of the breasts on mammography and sonography
24.	Nasopharyngoscopy	Nasopharyngeal Carcinoma	Individuals with a first degree relative with Nasopharyngeal Carcinoma
25.	Oesophago-Gastro Duodenoscopy	Gastric Cancer	Individuals with Hereditary Non-Polyposis Colon Cancer or Lynch Syndrome
26.	Pelvis X-ray (Antero-posterior)	Spastic Hip Displacement	Children with Cerebral Palsy
27.	Prostate-Specific Antigen (PSA)	Prostate Cancer	Men aged 50 to 70 yrs; High-risk men such as men with a strong family history of Prostate Cancer may be offered screening at an earlier age
28.	Retinal Fundal Photography	Diabetic Retinopathy	All individuals with Diabetes Mellitus
29.	ROP Screen	Retinopathy of Prematurity	Infants with birth weight <1500g; Gestational age < 32 wks; Prolonged oxygen use
30.	Rubella Serology	Rubella	All pregnant women
31.	Stool for ova, cyst and parasites	Intestinal Parasitic Infection	Immigrants from countries with high disease prevalence

No.	Screening Test	Disease	High Risk Group
32.	Syphilis Enzyme Immunoassay (EIA)	Syphilis	All pregnant women; Individuals with at-risk sexual behaviour; HIV patients
33.	Thalassemia Screen	Thalassemia	Pregnant women from ethnic groups with high disease prevalence; Individuals with a family history of Thalassemia
34.	Thyroid Function Test	Thyroid disorder	Obese individuals; Individuals with autoimmune disease; Pregnant women with Diabetes Mellitus or Adrenal Disease
35.	Transvaginal Ultrasound	Ovarian Cancer	BRCA carriers
36.	Treponema Pallidium Particle Agglutination / Treponema Pallidum Haemagglutination	Syphilis	All pregnant women; Individuals with at-risk sexual behaviour
37.	Treadmill Stress Test	Coronary Heart Disease	Individuals with an intermediate Coronary Heart Disease risk
38.	Tuberculin Skin Test	Tuberculosis (TB)	Close contacts of TB
39.	Tumour Marker for NPC (EBV-EA-EBNA-1)	Nasopharyngeal Carcinoma (NPC)	Individuals with a first degree relative with NPC
40.	Ultrasound Hepatobiliary System	Liver Cancer	Hepatitis B carriers; Individuals with liver cirrhosis
41.	Ultrasound Pelvis	Endometrial Cancer	Individuals with Hereditary non-polyposis colon cancer or Lynch syndrome
42.	Urine Analysis	Kidney Disorder/ Dysfunction	Individuals with Diabetes Mellitus or Hypertension or Cardiovascular Disease; Individuals aged 50 yrs and above who are smokers; Individuals with a family history of End-Stage Renal Failure
43.	Urine or Cervical/Urethral swab for PCR	Chlamydia and Gonorrohea	Individuals with at-risk sexual behaviour

No.	Screening Test	Disease	High Risk Group
44.	Urine Microalbumin/ Creatinine ratio	Diabetic Albuminuria/ Nephropathy	All individuals with Diabetes Mellitus
45.	Vaginal and Rectal swab	Maternal colonisation with GBS in pregnancy	All pregnant women between 35 and 37 weeks gestation.

Cancer Genetic Testing [245, 246]

Cancer genetic counselling is an important aspect of the care of individuals at increased risk of a hereditary cancer syndrome. It involves taking a thorough family history (immediate and extended family; usually first, second and third-degree relatives) to do a risk assessment by the cancer genetic specialists who will help to determine if the particular syndrome has a genetic component. This is only meant as a guideline for medical practitioners to facilitate identification and maximise appropriate referral of at-risk individuals to cancer genetic specialists for proper cancer genetic consultation. In general, common indications for hereditary cancer predisposition syndromes that may warrant evaluation include young age of onset for cancer, multiple primary cancers, bilateral cancers (e.g. bilateral breast or renal cancer) and strong family history i.e. involving multiple family members with similar or related cancers , although an absence of a family history does not exclude a hereditary cause as there is a possibility of de novo mutations, small family size, incomplete knowledge on family members' medical history etc. Genetic testing is advised for affected family members first, if alive, after which predictive testing can be offered to at risk family members.

Suspected Hereditary Cancer Syndrome	Who should be referred for cancer genetic risk assessment
Hereditary Breast and Ovarian Cancer Syndromes	1. Personal or family history of breast cancer diagnosed <40 years of age; 2. Family with two or more breast cancers, at least one aged < 50 years of age; 3. Family with both breast and epithelial ovarian cancers 4. One of more women diagnosed with breast cancer before age 50 with additional family history of cancer, such as prostate cancer and pancreatic cancer. 5. Personal or family history of male breast cancer, any age; 6. Personal history of epithelial ovarian cancer, any age; 7. Multiple tumours (bilateral breast cancer, multiple breast cancers or breast and ovarian cancer in same patient); 8. Known *BRCA* gene or other rare gene mutations such as TP53, PTEN in the family; 9. An a priori 10 to 20% probability of finding a mutation based on predictive models such as BRCAPRO, BOADICEA or Manchester Score[a] (***Special note***: *Family history would be in reference to first- and second-degree relatives. BRCA1/2 mutation carriers are also at risk for pancreatic and prostate cancer and clinicians*

	should additionally ask for these cancers in taking the family history)
Lynch Syndrome (LS)	**Tumour Microsatellite Instability (MSI) and/or Immunuhistochemical (IHC) staining for mismatch repair (MMR) proteins** should be considered in 1. Colorectal Cancer (CRC)[b] diagnosed <50; 2. Presence of synchronous or metachronous CRC or other LS-related tumours, regardless of age; 3. CRC in an individual <60 years of age with the MSI-H[c] histology (presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern); 4. CRC at any age, plus CRC or LS-related tumours diagnosed <50 years in at least one first-degree relative; 5. CRC at any age, plus CRC or LS-related tumours diagnosed <50 years in two or more first- or second-degree relatives (***Special note***: *If an MSI unstable tumour harbours the BRAF gene p.V600E mutation, it is most likely sporadic and germ line testing for mismatch repair genes is not necessary*) **Referral for clinical germline testing for mismatch repair genes** should be considered: 1. Meets Amsterdam criteria[d] or any of the above listed criteria for tumour MSI or IHC testing for MMR proteins 2. Endometrial Cancer <50 years; 3. Known LS mutation in family; (***Special note***: *Consider testing individuals with ≥10% risk of LS on any mutation model (e.g., MMRpro, PREMM, MMRpredict)*[a]

Familial Adenomatosis Polyposis (FAP)	1. Patients with classic FAP (>100 adenomas) should be advised to pursue genetic counselling and genetic testing, if they have siblings or children who could potentially benefit from this testing.
	2. Patients with classic FAP, in whom genetic testing is negative, should undergo genetic testing for bi-allelic MYH mutations.
	3. Patients with 10 to 100 adenomas can be considered for genetic testing for attenuated FAP and if negative, for MYH associated polyposis.
	(*Special note: It should be highlighted that the number of adenomas is the cumulative number of adenomas seen in a patient's lifetime*)

[a] This assessment should be made by a trained cancer genetics specialist; [b] CRC: colorectal cancer; [c] MSI-H: microsatellite instability (high); [d] Amsterdam criteria: At least 3 family members affected with cancer, spanning two generations, with at least one affected family member diagnosed below age 50 years; the 3 affected family members have to be first degree relatives of each other. In the Amsterdam I criteria, all 3 affected family members must have colorectal cancer; in Amsterdam II criteria, the affected family members may have colorectal, uterine, small bowel, ureteric or renal pelvis cancer.

References:

1) U.S Preventive Services Task Force. Breast Cancer: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/breast-cancer-screening1?ds=1&s=BREAST CANCER SCREENING

2) Jin J. Breast Cancer Screening Guidelines in the United States. JAMA. 2015;314(15):1658.

3) American Society of Clinical Oncology. Cancer.Net: Hereditary Breast and Ovarian Cancer. Available from: http://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer

4) American Congress of Obstericians and Gynecologists. Routine Screening for Hereditary Breast and Ovarian Cancer Recommended. Available from: http://www.acog.org/About-ACOG/News-Room/News-Releases/2009/Routine-Screening-for-Hereditary-Breast-and-Ovarian-Cancer-Recommended

5) BC Cancer Agency. Hereditary Breast and Ovarian Cancer. Available from: http://www.screeningbc.ca/Hereditary/ForHealthProfessionals/HereditaryBreastandOvarianCancer.htm

6) Nelson, H.D., Fu, R., Cantor, A., Pappas, M., Daeges, M. and Humphrey, L., 2016. Effectiveness of breast cancer screening: systematic review and meta-analysis to update the 2009 US Preventive Services Task Force recommendation. Annals of internal medicine, 164(4), pp.244-255.

7) Mandelblatt, J.S., Cronin, K.A., Bailey, S., Berry, D.A., De Koning, H.J., Draisma, G., Huang, H., Lee, S.J., Munsell, M., Plevritis, S.K. and Ravdin, P., 2009. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. Annals of internal medicine, 151(10), pp.738-747.

8) Jørgensen, K.J. and Gøtzsche, P.C., 2009. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. Bmj, 339, p.b2587.

9) Etzioni, R., Gulati, R., Mallinger, L. and Mandelblatt, J., 2013. Influence of study features and methods on overdiagnosis estimates in breast and prostate cancer screening. Annals of internal medicine, 158(11), pp.831-838.

10) Independent UK Panel on Breast Cancer Screening, 2012. The benefits and harms of breast cancer screening: an independent review. The Lancet, 380(9855), pp.1778-1786.

11) Saslow, D., Boetes, C., Burke, W., Harms, S., Leach, M.O., Lehman, C.D., Morris, E., Pisano, E., Schnall, M., Sener, S. and Smith, R.A., 2007. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA: a cancer journal for clinicians, 57(2), pp.75-89.

12) Travis L. B., Hill D. A., Dores G. M., et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA, 2003:290(4), 465–475

13) Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst. 1993;85:25-31

14) Travis LB, Curtis RE, Boice JD Jr. Late effects of treatment for childhood Hodgkin's disease. N Engl J Med. 2003;95:971-980.

15) Aisenberg AC. Problems in Hodgkin's disease management. Blood. 1999;93:761-779.

16) van Leeuwen FE, Klokman WJ, Van't Veer MB, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol. 2000;18:487-497.

17) Peng HL, Wu CC, Choi WM, Hui MS, Lu TN and Chen LK. Breast cancer detection using magnetic resonance imaging in breasts injected with liquid silicone. Plastic Reconstructive Surgery 1999 Dec, 104(7): 2116-2120.

18) Youk JH, Son EJ, Kim EK, Kim JA, Kim MJ, Kwak JY and Lee SM. Diagnosis of breast cancer at dynamic MRI in patients with breast augmentation by paraffin or silicon injection. Clinical Radiology 2009 Dec, 64(12):1175-1180.

19) Leibman AJ and Misra M. Spectrum of imaging findings in the silicone-injected breast. Plastic Reconstructive Surgery 2011 July, 128(1): 28e-9e.

20) American College of Radiology. Practice parameter for the performance of contrast-enhanced magnetic resonance imaging (MRI) of the breast.

21) Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, Shah K. Supplemental Screening for Breast Cancer in Women With Dense Breasts: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016 Feb 16;164(4):268-78. doi: 10.7326/M15-1789.

22) Wendie A. Berg et al. Combined Screening with Ultrasound and Mammography Compared to Mammography Alone in Women at Elevated Risk of Breast Cancer: Results of the First-Year Screen in ACRIN 6666. JAMA. 2008 May 14; 299(18): 2151–2163.

23) U.S Preventive Services Task Force. Bladder Cancer in Adults: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/bladder-cancer-in-adults-screening

24) World Health Organization International Agency for Research on Cancer (IARC). IARC confirms efficacy of cervix cancer screening for women 25-65 in reducing mortality. Press release No.151. IARC 97 Cervix Cancer Screening Meeting 2004 Apr 20-27. Available from: http://www.iarc.fr/en/media-centre/pr/2004/pr151.html

25) American College of Radiology (ACR). ACR–Society for Pediatric Radiology Practice Parameter for the Performance of Computed Tomography (CT) of the Pelvis. Available from:http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/CT_Abdomen_Pelvis.pdf

26) U.S Preventive Services Task Force. Cervical Cancer: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/cervical-cancer-screening

27) Katki HA, Kinney WK, Fetterman B, et al, Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol 12 (7):663-72, 2011.

28) Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin 52 (6): 342-62, 2002 Nov-Dec.

29) Goldie SJ, Kim JJ, Wright TC. Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. Obstet Gynecol 103 (4): 619-31, 2004.

30) Cox T, Cuzick J. HPV DNA testing in cervical cancer screening: From evidence to policies. Gynecol Oncol 103: 8-11, 2006.

31) Moyer VA. Screening for cervical cancer: U.S. Preventive services task force recommendation statement. Ann Intern Med E 424, March 14, 2012.

32) Rijkaart DC, Berkhof J, Rozendaal L, et al. Human papillomavirus testing for the detection of high grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomized controlled trial. Lancet Oncol 13(1):78-88, 2012.

33) Kitchener HC, Almonte M, Thomson C, et al. HPV testing in combination with liquid based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol 10(7): 672-682, 2009.

34) Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human pappiloma virus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol 11 (3): 249-57, 2010.

35) Wright T, Schiffman M, Solomon D, et al. Interim guidance for the use of papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol 2: 304-9, 2004.

36) Ronco et al. (2013). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. The Lancet 383 (9916): 524-532

37) Thomas C. Wright, Mark H. Stoler, Catherine M. Behrens, et al. Primary cervical cancer screening with human papillomavirus: End of study results from ATHENA study using HPV as the first –line screening test. Gynecologic Oncology 136,2015:189-19

38) Leinonen M, Nieminen P, Kotaniemi-Talonen L,et al. Age –specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. J Natl Cancer Inst 2009; 101:1612-23

39) Ronco G,Giorgi-Rossi P, Carozzi F et al. Human Papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years:results at recruitment for a randomized controlled trial. Lancet Oncol 2006;7:547-55

40) Dilner J, Rebolj M, Birembaut P, et al. Long term predictive value of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. BMJ 2009;337:a1754

41) Progress with Cervical Cancer Screening in UK; Scientific Impact Paper No.7 March 2017; Royal College of Obstetricians & Gynaecologists

42) Screening Adolescents and Young Women; Boardman et.al; Obstet Gynecol Clin North Am. 2013 June ; 40(2): 257–268

43) Screening for Cervical Cancer With High-Risk Human Papillomavirus Testing: A Systematic Evidence Review for the U.S. Preventive Services Task Force; Agency for Healthcare Research and Quality; U.S. Department of Health and Human Services; AHRQ Publication No. 17-05231-EF-1 September 2017

44) Natural History of Cervicovaginal Papillomavirus Infection in Young Women; Ho et.al; The New England Journal of Medicine 1998;338:423-8

45) U.S Preventive Services Task Force. Colorectal Cancer Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/colorectal-cancer-screening

46) U.S Preventive Services Task Force. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(23):2564-2575.

47) Cabebe EC. Medscape: Colorectal Cancer Guidelines. Available from: http://emedicine.medscape.com/article/2500006-overview

48) U.S Multi-Society Task Force: Genetic Testing of Tumour is Recommended for Colorectal Cancer Patients. Available from: http://www.asge.org/assets/0/73730/0e79daf5-c1c1-41ba-bb21-5afc768a82a4.pdf

49) Lin JS, Piper MA, Perdue LA, Rutter C, Webber EM, O'Connor E, Smith N, Whitlock EP. Screening for Colorectal Cancer: A systematic review for the U.S Preventive Services Task Force. Evidence Synthesis 2015, 135.

50) National Registry of Diseases Office. Singapore Cancer Registry: Annual Registry Report - Trends in Cancer Incidence in Singapore, 2010 – 2014. Available from: https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/cancer-trends-report-2010---2014_web.pdf?sfvrsn=0

51) National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

52) Crispens (2012) Endometrial and Ovarian Cancer in Lynch Syndrome. Clin Colon Rectal Surg, 25(2): 97-102.

53) Vasen et al (2013). Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts, Gut, 62(6):812-23.

54) Lindor et al. (2006). Recommendations for the Care of Individuals With an Inherited Predisposition to Lynch Syndrome, JAMA, 296 (12): 1507-17.

55) Renkonen-Sinisalo et al (2007). Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. International Journal of Cancer, 120 (4).

56) Lu et al. (2005). Gynecologic Cancers in Lynch Syndrome/HNPCC. Familial Cancer, 4 (3):249-254.

57) Jacobs et al (2011). Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol, 12(1): 38-48.

58) U.S. American Society of Clinical Oncology. Cancer.Net. Lynch syndrome. Available from: http://www.cancer.net/cancer-types/lynch-syndrome

59) El-Serag HB, Davila JA. Surveillance for hepatocellular carcinoma: in whom and how? Therap Adv Gastroenterol. 2011 Jan; 4(1): 5–10.

60) Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53:1020-1022.

61) National Registry of Diseases Office. Cancer Incidence and Mortality 2003 – 2012 and Selected Trends 1973 – 2012 in Singapore. Singapore Cancer Registry, Report No. 8, 2015.

62) McMahon BJ, Bulkow L, Harpster A, et al. Screening for hepatocellular carcinoma in Alaska Natives infected with chronic hepatitis B: a 16-year population-based study. Hepatology 2000;32:842-6.

63) Masi et al. Digestive and Liver Disease 2005;37:260-268.

64) Lok, A.S., Sterling, R.K., Everhart, J.E., Wright, E.C., Hoefs, J.C., Di Bisceglie, A.M., Morgan, T.R., Kim, H.Y., Lee, W.M., Bonkovsky, H.L. and Dienstag, J.L., 2010. Des-γ-carboxy prothrombin and α-fetoprotein as biomarkers for the early detection of hepatocellular

65) U.S CDC. Lung Cancer. Available from: http://www.cdc.gov/cancer/lung/basic_info/screening.htm

66) The National Lung Screening Trial Research Team. Reduced Lung-cancer mortality with low-dose computed tomographic screening, N Engl J Med 2011; 365:395-409

67) Bach PB, Mirkin JN, Oliver TK et al. Benefits and harms of CT screening for lung cancer: a systematic review, JAMA 2012, 13; 307(22):2418-242

68) Wood, D.E., 2015. National Comprehensive Cancer Network (NCCN) clinical practice guidelines for lung cancer screening. Thoracic surgery clinics, 25(2), pp.185-197.

69) Canadian Task Force on Preventive Health Care, 2016. Recommendations on screening for lung cancer. Canadian Medical Association Journal,188(6), pp.425-432.

70) Devesa SS, Bray F, Vizcaino AP, and Parkin DM. (2005). International lung cancer trends by histologic type: Male:Female differences diminishing and adenocarcinoma rates rising. Int. J. Cancer, 117(2) :294–299.

71) Wu-Williams et al. (1990). Lung cancer among women in north-east China. Br. J. Cancer, 62 (6), 982–7.

72) Seow et al. (2000) from Meat Cooking and Lung Cancer Risk in Chinese Women. Cancer Epidemiol. Prev. Biomarkers, 9(11).

73) Charloux A, Quoix E, Wolkove W, Small D, Pauli G, and Kreisman H (1997). The increasing incidence of lung adenocarcinoma: reality or artefact? A review of the epidemiology of lung adenocarcinoma.. Int. J. Epidemiol, 26(1):14-23.

74) Zhou W and Christiani DC. (2011). East meets West: ethnic differences in epidemiology and clinical behaviors of lung cancer between East Asians and Caucasians. Chin. J. Cancer, 30(5):287–92.

75) Bai et al. (2016). Evaluation of Pulmonary Nodules: Clinical Practice Consensus Guidelines for Asia, J Thorac, 8(9): 2319-2323

76) Wakelee at al. (2007). Lung cancer incidence in never smokers. J. Clin. Oncol, 25 (5): 472–8.

77) Rudin et al. (2009). Lung cancer in never smokers: molecular profiles and therapeutic implications. Clin. Cancer Res, 15 (18): 5646–61.

78) Planchard D and Besse B. (2015). Lung cancer in never-smokers. Eur. Respir. J, 45(5).

79) Wu YL and Zhou Q. (2007). Lung Cancer Management in the Asia-Pacific Region: What's the Difference Compared with the United States and Europe? Results of the Second Asia Pacific Lung Cancer Conference. J Thorac Oncol, 2: 574–576.

80) Donington JS et al. (2006). Lung Cancer in Women: Exploring Sex Differences in Susceptibility, Biology, and Therapeutic Response. Clin. Lung Cancer, 8(1): 22–29.

81) Subramanian J and Govindan R. (2010). Lung cancer in 'Never-smokers': a unique entity. Oncology (Williston Park), 24 (1) :29–35.

82) Yano et al. (2008). Never-smoking nonsmall cell lung cancer as a separate entity. Cancer, 113 (95); 1012–1018.

83) Devesa SS, Bray F, Vizcaino AP and Parkin DM. (2005). International lung cancer trends by histologic type: Male:Female differences diminishing and adenocarcinoma rates rising. Int. J. Cancer, 117(2) :294–299.

84) Gao et al. (1987). Lung cancer among Chinese women, Int. J. cancer, 40 (5): 604–9.

85) Toh CK and Lim WT. (2007). Lung cancer in never-smokers. J. Clin. Pathol, 60(4): 337–40.

86) Hoover RN and Lim WT. (2000). Cancer--nature, nurture, or both. N. Engl. J. Med., 343 (2): 135–6.

87) Toh et al. (2010). Correlation between epidermal growth factor receptor mutations and expression of female hormone receptors in East-Asian lung adenocarcinomas, J. Thorac. Oncol., 5 (1): 17–22.

88) Sun S, Schiller JH, and Gazdar AF. (2007). Lung cancer in never smokers — a different disease. Nat. Rev. Cancer, 7 (10): 778–790.

89) Cheng et al. (2016). The International Epidemiology of Lung Cancer: Latest Trends, Disparities, and Tumour Characteristics. J. Thorac. Oncol, 11 (10) : 1653–1671.

90) Funatogawa I, Funatogawa T, and Yano E. (2012). Trends in smoking and lung cancer mortality in Japan , by birth cohort, Bulletin of the World Health Organisation, 91(5): 332–340.

91) Mitsudomi T, Kosaka T, and Yatabe Y. (2006). Biological and clinical implications of EGFR mutations in lung cancer. Int. J. Clin. Oncol, 11 (3): 190–198.

92) Bell et al. (2008). Increased prevalence of EGFR-mutant lung cancer in women and in East Asian populations: Analysis of estrogen-related polymorphisms. Clin. Cancer Res, 14(13): 4079–4084.

93) Shi et al. (2015). Molecular epidemiology of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology - Mainland China subset analysis of the PIONEER study. PLoS One, 10 (11): e0143515.

94) C- Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction (2012), The New England Journal of Medicine, 367: 1310:1320.

95) Shigematsu et al. (2005). Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. Cancer Res, 65 (5):1642–1646.

96) Shi et al. (2014). A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol, 9 (2): 154–162.

97) Centre for Health Protection, Hong Kong. Health advice on prevention and screening of cancer for the healthcare professionals. Available from: http://www.chp.gov.hk/files/pdf/Advice_on_Cancer_Prevention_professionals.pdf

98) Ji MF, Wang DK, Yu YL, et al. Sustained elevation of Epstein-Barr virus antibody levels preceding clinical onset of nasopharyngeal carcinoma. British J of Cancer. 2007 Feb;96(4):623-630.

99) Jia WH, Feng BJ, Xu ZL, et al. Familial risk and clustering of nasopharyngeal carcinoma in Guangdong China. Cancer 101(2): 363–369.

100) Loh KS, Goh BC, Lu J, et al. Familial Nasopharyngeal Carcinoma in a Cohort of 200 Patients. Arch Otolaryngol Head Neck Surg. 2006;132(1):82-85.

101) Hemminki K, Sundquist J, Bermejo JL. How common is familial cancer? Ann Oncol 2008;19:163-167.

102) Ng WT, Choi CW, Lee MC, et al. Familial nasopharyngeal carcinoma in Hong Kong: epidemiology and implication in screening. Familial Cancer 2009; 8:103.

103) U.S Preventive Services Task Force. Ovarian Cancer: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/ovarian-cancer-screening

104)   American College of Radiology (ACR). ACR–Society for Pediatric Radiology Practice Parameter for the Performance of Computed Tomography (CT) of the Pelvis. Available from:http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/CT_Abdomen_Pelvis .pdf

105)   U.S Preventive Services Task Force. Prostate Cancer: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/pro state-cancer-screening

106)   American Cancer Society. Prostate Cancer Prevention and Early Detection. Available from: http://www.cancer.org/acs/groups/cid/documents/webcontent/003182-pdf.pdf

107)   Hoeks CM1, Fütterer JJ, Somford DM, et al. Multiparametric MRI for prostate cancer screening. Ned Tijdschr Geneeskd. 2009; 13:B487.

108)   Hugosson J, Carlsson S, Aug G et al. Mortality results from the Goteburg randomised population-based prostate-cancer screening trial. Lancet Oncol. 2010;11:725-732.

109)   Ries LAG, Melbert D, Krapcho M, et al (Eds). SEER Cancer Statistics Review, 1975-2004, National Cancer Institute, Bethesda, MD 2007.

110)   Rietbergen JB, Kruger AE, Kranse R, et al. Complications of transrectal ultrasound-guided systematic sextant biopsies of the prostate: evaluation of complication rates and risk factors within a population-based screening program. Urology 1997;49:875.

111)   Fowler FJ Jr, Barry MJ, Walker-Corkery B, et al. The impact of a suspicious prostate biopsy on patients' psychological, socio-behavioral, and medical care outcomes. J Gen Intern Med 2006;21:715.

112)   U.S Preventive Services Task Force. Testicular Cancer: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/test icular-cancer-screening

113)   U.S Preventive Services Task Force. Abdominal Aortic Aneurysm: Screening. Available from:http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationSt atementFinal/abdominal-aortic-aneurysm-screening

114)   Ministry of Health. Clinical Practice Guidelines: Screening of cardiovascular disease and risk factors. Singapore: Ministry of Health 2011.

115)   Vega C, Kwoon J.V and Lavine S.D. Intracranial Aneurysms: Current Evidence and Clinical Practice. Am Fam Physician. 2002 Aug 15;66(4):601-609.

116)   Cerebral aneurysm - Screening - BMJ Best Practice. Available from: http://bestpractice.bmj.com/topics/en-us/490

117)   U.S Preventive Services Task Force. Carotid Artery Stenosis: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStateme ntFinal/carotid-artery-stenosis-screening

118) Ministry of Health. Clinical Practice Guidelines: Hypertension. Singapore: Ministry of Health; 2016 (draft).

119) U.S Preventive Services Task Force. Coronary Heart Disease: Screening with Electrocardiography. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/coronary-heart-disease-screening-with-electrocardiography

120) Waring WS, Webb DJ, Maxwell SRJ. Uric acid as a risk factor for cardiovascular disease. QJM Nov 2000, 93(11) 707-713. doi: 10.1093/qjmed/93.11.707.

121) Wheeler JG, Juzwishin KDM, Eurujsdittur G, et al. Serum Uric Acid and Coronary Heart Disease in 9,458 Incident Cases and 155,084 Controls: Prospective Study and Meta-Analysis. Keech A, ed. PLoS Medicine. 2005;2(3):e76. doi:10.1371/journal.pmed.0020076.

122) Culleton BF, Larson MG, Kannel WB, Levy D. Serum Uric Acid and Risk for Cardiovascular Disease and Death: The Framingham Heart Study. Ann Intern Med. 1999;131:7-13. doi:10.7326/0003-4819-131-1-199907060-00003.

123) Kwok BWK, Tang HC, Wee SL, et al. Pattern and Outcome of Subsidised Referrals to Cardiology Specialist Outpatient Clinics. Ann Acad Med Singapore 2008;37:103-108.

124) Fowkes FR, Price JF, Stewart MW, et al. Aspirin for Prevention of Cardiovascular Events in a General Population Screened for a Low Ankle Brachial Index: A Randomized Controlled Trial. JAMA. 2010;303(9):841-848. doi:10.1001/jama.2010.221.

125) Sharma et al. (2017). International Recommendations for ECG Interpretation in Athletes. J Am Coll Cardiol, 69:1057–75

126) USPSTF. (2014). Screening for CHD with ECG statement, Am Family Phy, 89 (20): 136A-B

127) Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003; 107:363.

128) Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107:499.

129) Calonge, N., Petitti, D.B., DeWitt, T.G., Gregory, K.D., Harris, R., Isham, G., LeFevre, M.L., Loveland-Cherry, C., Marion, L.N., Moyer, V.A. and Ockene, J.K., 2009. Using nontraditional risk factors in coronary heart disease risk assessment. Annals of Internal Medicine, 151(7), pp.474-482.

130) Yousuf et al. (2013). High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? J Am Coll Cardiol, 62(5): 397-408.

131) Piepoli et al. (2016). 2016 European Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal, 37(29): 2315-2381.

132) Ridker et al. (2016). A Test in Context: High-Sensitivity C-Reactive Protein. J Am Coll Cardiol 67(6):712–23).

133) Stein, J.H. and Rosenson, R.S., 1997. Lipoprotein Lp (a) excess and coronary heart disease.Archives of internal medicine, 157(11), pp.1170-1176.

134) Di Angelantonio et al. (2009). Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 302(18): 1993-2000.

135) Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. Arch Intern Med 2004; 164:1285.

136) Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010; 56:e50.1

137) Okwuosa TM, Greenland P, Ning H, et al. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. J Am Coll Cardiol 2011; 57:1838.

138) Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002; 106:1883.

139) Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. Circulation 1989; 80:87.

140) U.S Preventive Services Task Force. Peripheral Arterial Disease (PAD) and CVD in Adults: Risk Assessment with ABI. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/peripheral-arterial-disease-pad-and-cvd-in-adults-risk-assessment-with-ankle-brachial-index

141) United States Preventive Services Task Force. Recommendation Statement: Screening for Peripheral Arterial Disease. Agency for Healthcare Research and Quality, Washington, DC 2005.

142) Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. Arterioscler Thromb Vasc Biol 2005; 25:1463.

143) Lin JS, Olson CM, Johnson ES, Whitlock EP. The ankle-brachial index for peripheral artery disease screening and cardiovascular disease prediction among asymptomatic adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2013; 159:333.

144) U.S Preventive Services Task Force. Chlamydia and Gonorrhea: Screening. Available from:http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/chlamydia-and-gonorrhea-screening?ds=1&s=CHLAMYDIA

145) U.S Department of Health & Human Services. Agency for Healthcare Research and Quality Archive: Screening for Chlamydial Infection. Available from: http://archive.ahrq.gov/clinic/ajpmsuppl/chlarr.htm

146) U.S Preventive Services Task Force. Human Immunodeficiency Virus (HIV) Infection: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/human-immunodeficiency-virus-hiv-infection-screening#consider

147) U.S Preventive Services Task Force. Screening for HIV: Recommendation Statement. Am Fam Physician. 2005 Dec 1;72(11):2287-2292.

148) Ang LW, Cutter J, James L, et al. Seroepidemiology of hepatitis B virus infection among adults in Singapore: A 12-year review. Vaccine 2013, 32(1):103-10.

149) Ministry of Health. Clinical Practice Guidelines: Chronic Hepatitis B Infection. Singapore: Ministry of Health; 2011.

150) U.S CDC. Testing and Public Health Management of Persons with Chronic Hepatitis B Virus Infection. Available from: http://www.cdc.gov/hepatitis/hbv/testingchronic.htm

151) U.S Preventive Services Task Force. Hepatitis B, Non Pregnant Adolescents and Adults: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-b-virus-infection-screening-2014#Pod6

152) U.S Preventive Services Task Force. Hepatitis B in Pregnant Women: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-b-in-pregnant-women-screening

153) Ang LW, Cutter J, James L, et al. Seroepidemiology of hepatitis B virus infection among adults in Singapore: A 12-year review. Vaccine 2013, 32(1):103-10.

154) MOH Directive 2/2014 – Addendum 'Management of healthcare workers (medical, dental, nursing and paramedic) with hepatitis B, hepatitis C and HIV'

155) A list of endemic countries for Hepatitis B can be found at the US CDC Website: Centers for Disease Control. Surveillance for viral hepatitis – United States, 2013 http://www.cdc.gov/hepatitis/statistics/2013surveillance/commentary.htm#hepatitisB

156) U.S Preventive Services Task Force. Hepatitis C: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/hepatitis-c-screening?ds=1&s=hepatitis C screening

157) World Health Organization. Hepatitis C. Available from: http://www.who.int/mediacentre/factsheets/fs164/en/

158) U.S CDC. Hepatitis C FAQs for Health Professionals. Available from: http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm

159) U.S CDC. Yellow Book: Chapter 45. Available from: http://wwwnc.cdc.gov/travel/yellowbook/2016/post-travel-evaluation/screening-asymptomatic-returned-travelers

160) U.S Preventive Services Task Force. Syphilis Infection in Nonpregnant Adults and Adolescents: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/syphilis-infection-in-nonpregnant-adults-and-adolescents

161) U.S CDC. Syphilis - CDC Fact Sheet (Detailed). Available from: http://www.cdc.gov/std/syphilis/stdfact-syphilis-detailed.htm

162) U.S Preventive Services Task Force. Syphilis Infection in Pregnancy: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/syphilis-infection-in-pregnancy-screening

163) Shahrook, S., Mori, R., Ochirbat, T. and Gomi, H., 2014. Strategies of testing for syphilis during pregnancy. The Cochrane Library.

164) U.S CDC. Tuberculosis. Factsheet. Recommendations for Human Immunodeficiency Virus (HIV) Screening in Tuberculosis (TB) Clinics. Available from: http://www.cdc.gov/tb/publications/factsheets/testing/hivscreening.htm

165) U.S Preventive Services Task Force. Draft recommendation statement: Screening for Latent Tuberculosis Infection. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/latent-tuberculosis-infection-screening?ds=1&s=TUBERCULOSIS SCREENING

166) Ministry of Health Singapore. Prevention, Diagnosis and Management of Tuberculosis. MOH Clinical Practice Guidelines 1/2016. https://www.moh.gov.sg/content/dam/moh_web/HPP/Doctors/cpg_medical/current/2016/tuberculosis/MOH%20TB%20CPG%20Full%20version%20for%20website.pdf

167) A list of countries can be found in this report by the World Health Organization. Global tuberculosis report 2016. Available at: http://www.who.int/tb/publications/global_report/en/ (Accessed on December 29, 2016).

168) U.S Preventive Services Task Force. Guide to Clinical Preventive Services: Report of the U.S. Preventive Services Task Force. 2nd edition. Baltimore (MD): Williams & Wilkins; 1996. 25, Screening for Tuberculous Infection-- Including Bacille Calmette-Guérin Immunization.

169) U.S CDC. TB Prevention. Available from: http://www.cdc.gov/tb/topic/basics/tbprevention.htm

170) Ministry of Health, Singapore. Tuberculosis. Available from: https://www.moh.gov.sg/content/moh_web/home/diseases_and_conditions/t/tuberculosis.htm

171) U.S CDC. Recommendations to Prevent and Control Iron. MMWR 1998;47 (No. RR-3).

172) U.S Preventive Services Task Force. Iron Deficiency Anemia in Pregnant Women: Screening and supplementation. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/iron-deficiency-anemia-in-pregnant-women-screening-and-supplementation

173) U.S Preventive Services Task Force. Iron Deficiency Anemia in Young Children: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/iron-deficiency-anemia-in-young-children-screening

174) National Institute for Health and Care Excellence, U.K. NICE guidelines [CG62]: Antenatal care for uncomplicated pregnancies. Available from: https://www.nice.org.uk/guidance/cg62/chapter/1-Guidance#screening-for-haematological-conditions

175) U.S Preventive Services Task Force. Abnormal Blood Glucose and Type 2 Diabetes Mellitus: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/screening-for-abnormal-blood-glucose-and-type-2-diabetes?ds=1&s=DIABETES

176) U.S Preventive Services Task Force. Gestational Diabetes Mellitus, Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/gestational-diabetes-mellitus-screening?ds=1&s=DIABETES

177) Diabetes Clinical Practice Guidelines 2014, Ministry of Health Singapore, Accessed at: https://www.moh.gov.sg/content/dam/moh_web/HPP/Doctors/cpg_medical/current/2014/diabetes_mellitus/cpg_Diabetes%20Mellitus%20Booklet%20-%20Jul%202014.pdf

178) American Diabetes Association. Standards of medical care in diabetes--2010. Diabetes Care 2010; 33 Suppl 1:S11.

179) Diagnostic Criteria for Diabetes, Diabetes UK at https://www.diabetes.org.uk/professionals/position-statements-reports/diagnosis-ongoing-management-monitoring/new_diagnostic_criteria_for_diabetes

180) The Australian Diabetes Society established an expert committee in 2011, included representatives from the Royal College of Pathologists of Australasia (RCPA) and the Australasian Association of [10]Clinical Biochemists (AACB) to provide a position statement concerning the role of HbA1c in the diagnostic pathway.

181) Nakagami T, Uchigata Y. Guidelines for Diabetes Mellitus: from the perspective of diagnosis and treatment. Assessed at https://www.jstage.jst.go.jp/article/jhep/41/4/41_533/_pdf/-char/ja

182) Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus (5thEdition), Ministry of Health (Malaysia), December 2015

183) HbA1c as a diagnostic test was formally endorsed by the New Zealand Society for the Study of Diabetes (NZSSD) in October 2011.

184) Molitch ME, DeFronzo RA, Franz MJ,e tal. Nephropathy in diabetes. Diabetes Care 2004;27(Suppl 1):S79-83.

185) Rothschild BM, Francis ML and Miller SV. Gout and Pseudogout. Available from: http://emedicine.medscape.com/article/329958-diagnosis

186) Eggebeen AT. Gout: An update. Am Fam Physician. 2007 Sep 15; 76(6):801-808.

187) Zhang W, Doherty M, Pascual E, et al. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the standing committee for international clinical studies including therapeutics (ESCISIT). Ann Rheum Dis. 2006 Oct; 65(10): 1301–1311.

188) MOH Clinical Practice Guidelines 2/2016. Lipids. November 2016. https://www.moh.gov.sg/content/moh_web/healthprofessionalsportal/doctors/guidelines/c pg_medical/2016/cpgmed_lipids.html [last accessed 15 June 2017].

189) U.S. Preventive Services Taskforce. Final Recommendation Statement. High Blood Pressure in Adults: Screening. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatem entFinal/high-blood-pressure-in-adults-screening#Pod1[last accessed 15 June 2017]

190) Patrice Lindsay, Sarah Connor Gorber, Michel Joffres, Richard Birtwhistle, Donald McKay, Lyne Cloutier, Recommendations on screening for high blood pressure in Canadian adults. Vol 59: september • septembre 2013. Canadian Family Physician. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3771717/pdf/0590927.pdf.[last accessed 15 June 2017]

191) Collins AJ, Gibertson DT, Synder JJ, et al. Chronic kidney disease awareness, screening and prevention: rationale for the design of a public education program. Nephrology (Carlton) 2010 Jun;15 Suppl 2:37-42.

192) National Kidney Foundation, U.S. Kidney Early Evaluation Program (KEEP). Available from: http://www.kidney.org/news/keep/index.cfm

193) Multiple Risk Factor Intervention TrialRisk Factor Changes and Mortality Results. JAMA. 1982;248(12):1465-1477. doi:10.1001/jama.1982.03330120023025

194) Health Promotion Board, Singapore. Clinical Practice Guidelines: Obesity. Singapore: Health Promotion Board-Ministry of Health; 2016.

195) International Osteoporosis Foundation. Osteoporosis. Available from: https://www.iofbonehealth.org/whos-risk

196) Qaseem A, Snow V, Shekelle P, et al. Screening for Osteoporosis in Men: A Clinical Practice Guideline from the American College of Physicians. Ann Intern Med. 2008;148:680-684. doi:10.7326/0003-4819-148-9-200805060-00008.

197) National Institute for Health and Clinical Excellence, U.K. NICE guidelines [CG79]: Rheumatoid arthritis in adults: management. NICE; 2009. Available from: https://www.nice.org.uk/guidance/CG79/chapter/1-Guidance

198) National Osteoporosis Guideline Group (NOGG). http://www.shef.ac.uk/NOGG/index.html (Accessed on December 29, 2016).

199) U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. preventive services task force recommendation statement. Ann Intern Med 2011; 154:356.

200) Koh L KH et al. A Simple Took to Identify Asian Women at Increased Risk of Osteoporosis. Osteo Intl 2001 12:699-705.

201) Bauer, D.C., Glüer, C.C., Genant, H.K. and Stone, K., 1995. Quantitative ultrasound and vertebral fracture in postmenopausal women. Journal of Bone and Mineral Research, 10(3), pp.353-358.

202) Marín, F., González-Macías, J., Díez-Pérez, A., Palma, S. and Delgado-Rodríguez, M., 2006. Relationship Between Bone Quantitative Ultrasound and Fractures: A Meta-Analysis. Journal of bone and mineral research, 21(7), pp.1126-1135.

203) Gill JM, Quisel AM, Rocca PV et al. Diagnosis of Systemic Lupus Erythematosus. Am Fam Physician. 2003 Dec 1; 68(11):2179-2187.

204) Kurien BT, Scofield RH. Autoantibody Determination in the Diagnosis of Systemic Lupus Erythematosus. Scand J Immunol. 2006 Sep;64(3):227-35.

205) Chou R, Qaseem A, Snow V, et al, Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007 Oct 2;147(7):478-91.

206) Eubanks JD. Cervical Radiculopathy: Nonoperative Management of Neck Pain and Radicular Symptoms. Am Fam Physician. 2010 Jan 1;81(1):33-40.

207) Young WF. Cervical Spondylotic Myelopathy: A Common Cause of Spinal Cord Dysfunction in Older Persons. Am Fam Physician. 2000 Sep 1;62(5):1064-1070.

208) Newman JS, Weissman BN, Angevine PD, et al, Expert Panel on Musculoskeletal Imaging. ACR Appropriateness Criteria® chronic neck pain. Reston (VA): American College of Radiology (ACR); 2013, 14p.

209) Kahwati LC, Haigler L, Rideout Stacey. Which is the best way to diagnose menopause? J Fam Pract. 2005 Nov; 54(11):1000–1002.

210) Australasian Menopause Society. Information sheet: Diagnosing Menopause. Available from: http://www.menopause.org.au/index2.php?option=com_content&task=emailform&id=420

211) Rasat R, Livesey JL, Espiner EA, et al. IGF-1 and IGFBP-3 screening for disorders of growth hormone secretion. N Z Med J. 1996 May 10;109(2021):156-159.

212)   Verani JR, Lesley M, Schrag S. Prevention of Perinatal Group B Streptococcal Disease: Revised Guidelines from CDC, 2010. CDC, MMWR, 59(RR10); 1-22. November 19, 2010.

213)   Royal College of Obstetricians and Gynaecologists. The Prevention of Early-onset Neonatal Group B Streptococcal Disease. Green-top Guideline No. 36, 2nd Edition. July 1, 2012.

214)   Niduvaje, K., Amutha, C., and Roy, J. (2006) Early Neonatal Streptococcal Infection. Indian Journal of Paediatrics, (73): 573-576.

215)   Tan, K.W. et al. (1998). Group B Streptococcal Septicaemia/Meningitis in Neonates in a Singapore teaching hospital. Australia and New Zealand Journal of Obstetrics and Gynaecology.38:4: 418-423

216)   American Academy of Paediatrics. Committee on Infectious Diseases and Committee on Fetus and Newborn. Policy Statement. Recommendations for the Prevention of Perinatal Group B Streptococcal (GBS) Disease. PEDIATRICS Volume 128, Number 3, September 2011

217)   U.S Preventive Services Task Force. Impaired Visual Acuity in Older Adults: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/impaired-visual-acuity-in-older-adults-screening

218)   Workplace Safety and Health Council. Workplace Safety and Health Guidelines. Singapore: Workplace Safety and Health Council; 2014.

219)   Health Promotion Board, Singapore. Management of Functional Decline for Primary Care Doctors Workgroup. Community Functional Screening Follow-up Resource for Primary Care Doctors. Available from: http://www.hpb.gov.sg/HOPPortal/content/conn/HOPUCM/path/Contribution%20Folders/uploadedFiles/HPB_Online/Programmes/HPB%20CFSP%20Follow-Up%20Resource%20PC%20Doctors.pdf

220)   The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Pre-Pregnancy Counselling. College Statement, C-Obs 3(a). Apr 2015. Available from: https://www.ranzcog.edu.au/college-statements-guidelines.html

221)   The International Society of Ultrasound in Obstetrics and Gynecology Prenatal Ultrasound Screening Task Force. Practice Guidelines for Performance of the Routine Mid-Trimester Foetal Ultrasound Scan. Jun 2010. Available from: http://www.isuog.org/NR/rdonlyres/66695A04-5937-4EAB-AA90-E01E7E9D9A33/0/

222)   Academy of Medicine, College of Obstetricians and Gynaecologists, Singapore. AMS Consensus Statement: Recommended 'Best Practice' Guidelines on Antenatal Screening for Trisomy 21 (Down Syndrome) and Other Fetal Aneuploidies. Jan 2008. Available from: http://ams.edu.sg/view-pdf.aspx?file=media%5c754_fi_329.pdf&ofile=Consensus_Statement_Downs_Syndrome.pdf

223) Low WK, Pang KY, Lim SB, Joseph R. Universal Newborn Hearing Screening: The need, implementation and challenges. Ann Acad Med Singapore 2005; 34:301-6.

224) Futures, B. and American Academy of Pediatrics, 2008. Recommendations for preventive pediatric health care. Retrieved from http://www.asha.org/.../Expert-Panel-Recommendations-on-Newborn-Hearing-Screening/

225) Bright Futures/American Academy of Pediatrics. Recommendations for Preventive Pediatric Health Care - Periodicity Schedule. www.aap.org/en-us/professional-resources/practice-support/Pages/PeriodicitySchedule.aspx

226) Rajadurai S. Expanded Newborn Screening Using Tandem Mass Spectrometry. Aescapulus, Issue 03 / 2007. 2007

227) Royal College of Ophthalmologists, Royal College of Paediatrics and Child Health, U.K. Guideline for the Screening and Treatment of Retinopathy of Prematurity. Available from: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2008-SCI-021-Guidelines-Retinopathy-of-Prematurity.pdf

228) U.S Preventive Services Task Force. Guide to Clinical Preventive Services: Report of the U.S. Preventive Services Task Force. 2nd edition. Baltimore (MD): Williams & Wilkins; 1996. 43, Screening for Haemoglobinopathies. Available from: http://www.ncbi.nlm.nih.gov/books/NBK15438/

229) U.S. Preventive Services Task Force. Recommendations: Visual impairment in children aged 1-5: Screening. January 2011.

230) Labelle H, Richards S B, De Kleuver M, et al. Screening for adolescent idiopathic scoliosis: an information statement by the scoliosis research society international task force. Scoliosis. 2013; 8: 17.

231) Health Promotion Board, Singapore. Primary School Health Screening. Available from: http://www.hpb.gov.sg/HOPPortal/health-article/632

232) Health Promotion Board, Singapore. Secondary School Health Screening. Available from: http://www.hpb.gov.sg/HOPPortal/health-article/690

233) Thilagaratnam S. School-based screening for scoliosis: is it cost-effective? Singapore Med J 2007; 48 (11) : 1013. http://smj.sma.org.sg/4811/4811a6.pdf (last accessed 1 July 2017)

234) U.S Preventive Services Task Force. Screening for Sickle Cell Disease in Newborns: Recommendation Statement. Am Fam Physician. 2008 May 1;77(9):1300-1302.

235) U.S Department of Health and Human Services, Advisory Committee on Heritable Disorders in Newborns and Children. Recommended Uniform Screening Panel. Mar 2015. Available from: http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommended panel/index.html

236) The Society of Obstetricians and Gynaecologists of Canada, Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada and the Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. Joint SOGC-CCMG Clinical

practice guideline no. 218: Carrier Screening for Thalassemia and Hemoglobinopathies in Canada. Oct 2008. Available from: http://sogc.org/guidelines/carrier-screening-for-thalassemia-and-hemoglobinopathies-in-canada/

237) Shore B, Spence D, Graham H. The role for hip surveillance in children with cerebral palsy. Current Reviews in Musculoskeletal Medicine. 2012;5(2):126-134.

238) Wynter M, Gibson N, Kentish M, et al. Australian Hip Surveillance Guidelines for Children with Cerebral Palsy 2014. Available from: https://ausacpdm.org.au/wp-content/uploads/sites/10/2015/06/140070-THOMASON-HipS-booklet-A5_web.pdf

239) American Academy for Cerebral Palsy and Developmental Medicine: Hip surveillance. Available from https://www.aacpdm.org/publications/care-pathways/hip-surveillance.

240) U.S Preventive Services Task Force. Chronic Obstructive Pulmonary Disease: Screening. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/chronic-obstructive-pulmonary-disease-screening

241) Informed Health Online [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006 – Benefits and risks of screening tests. 2013 Nov 7 [Updated 2016 Dec 27]

242) Leonila F. Dans, Maria Asuncion A. Silvestre, Antonio L. Dans. Trade-off between benefit and harm is crucial in health screening recommendations. Part I: General principles. Journal of Clinical Epidemiology 64 (2011) 231e239

243) van der Velde JL, Blanker MH1, Stegmann ME, de Bock GH2, Berger MY, Berendsen AJ.A systematic review of the psychological impact of false-positive colorectal cancer screening: What is the role of the general practitioner? Eur J Cancer Care (Engl). 2017 May;26(3). doi: 10.1111/ecc.12709. Epub 2017 May 11

244)   K.E. Rogstad. The psychological impact of abnormal cytology and colposcopy. BJOG: an International Journal of Obstetrics and Gynaecology April 2002, Vol. 109, pp. 364–368

245) Hampel H, Bennett RL, Buchanan Adam, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genetics in Medicine (2014) 17, 70-87.

246) The Singapore Cancer Network Cancer Genetics Workgroup. Singapore Cancer Network (SCAN) guidelines for Referral for Genetic Evaluation of Common Hereditary Cancer Syndromes. Ann Acad Med Singapore 2015; 44:492-510.

Acknowledgment