WOMEN'S HEALTH

Recommendations for lab-based screening tests for adult women

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EDITOR'S NOTE

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

Health screening tests have a great impact on the public's health because they involve testing asymptomatic populations for specific diseases or health conditions for secondary prevention when interventions may halt or diminish disease progression before appearance of clinical signs and symptoms. The U.S. Preventive Services Task Force (USPSTF),[1] supported by the Agency for Healthcare Research and Quality, is widely considered to be the leading independent panel of experts in recommendations about disease prevention and in primary and secondary interventions. This organization conducts rigorous and impartial assessments of the scientific evidence for effectiveness of a broad range of clinical preventive services, including health screening.

According to the World Health Organization, all of the following criteria must be met in an effective screening program: significant societal burden; detectable asymptomatic phase; screening test accuracy; acceptability, availability, and feasibility; effective prognostication and intervention for those who screen positive; cost-effectiveness; assurance of informed consent and patient confidentiality.[2] In providing recommendations, the USPSTF considers these criteria but does not strictly use them when evaluating screening tests.

For example, if a screening test has been evaluated in a randomized control trial and has been shown to result in better outcomes for those in the screening group, the USPSTF does not consider cost-effectiveness. All screening recommendations are rated by the USPSTF into one of five grades:[3]

- **'A'** for strong recommendation with high certainty that net benefit is substantial,
- **'B'** for recommendation with high certainty that net benefit is moderate or moderate certainty that net benefit is moderate to substantial,
- **'C'** for individualized decision making with at least moderate evidence that net benefit is small,
- **'D'** against screening with moderate to high certainty that net benefit is close to zero or harms outweigh benefits, and
- **'I'** is a statement that no recommendation can be made due to available evidence that is insufficient, of poor quality, or conflicting, making it not feasible to objectively evaluate the net balance between health benefits and harms of screening.

Health screening should be offered or provided for A and B recommendations. C recommendation implies that screening should

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Table: Recommendations of the US Preventive Services Task Force for Laboratory-Based Health Screening of Adult women

Disease/Condition (Specific target population)	Laboratory screening test(s)	Grade
Cardiovascular Diseases		
Risk of coronary heart disease (≥45 years of age and at increased risk)	Total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides	A
Risk of coronary heart disease (20-44 years of age and at increased risk)	Total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides	B
Risk of coronary heart disease (≥20 years of age and not at increased risk)	Total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides	C
Risk of coronary heart disease	High-sensitivity C-reactive protein, leukocyte count, fasting blood glucose, homocysteine, and lipoprotein(a)	I

be offered or provided for selected patients depending on individual circumstances.[3] For D recommendation, screening should be discouraged. For I recommendation, if screening is offered, patients should understand the uncertainty about the balance of health benefits and harms.[4]

In this article, the recommendations of the USPSTF for all laboratory-based screening tests for or relevant to adult women are presented, along with a brief rationale based on evaluation of the balance of health benefits and harms. Some of these recommendations apply to both men and women, and they are also included. When applicable, specific CDC recommendations are also described. A previous article had described selected laboratory-based screening tests for aging males.[5] Laboratory screening tests described are those used for the risk of coronary heart disease; endocrine and metabolic disorders (chronic kidney disease, diabetes mellitus, hereditary hemochromatosis, and thyroid disease); infectious diseases caused by chlamydia, genital herpes, gonorrhea, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis; cancer of the bladder, cervix, colon and rectum, lung, ovaries, and pancreas; and substance abuse. This article is meant to provide the reader with an understanding and appreciation of whether and why specific laboratory screening tests should or should not be used for the evaluated diseases or conditions, sometimes using different target populations. Table 1 lists the USPSTF recommendations for screening of the diseases or conditions relating to adult women, along with the recommendation grade for each. Recommendations for laboratory screening tests for risk of coronary heart disease; endocrine and metabolic disorders, and during pregnancy; infectious diseases; neoplastic diseases; and substance abuse are presented and discussed.

Risk of Coronary Heart Disease

For women aged 20 and older at increased risk for coronary heart disease, there is good evidence that lipid-lowering drug therapy substantially decreases incidence of coronary heart disease in those with abnormal lipids, and there is good evidence that harms from screening and treatment are small and include possible labeling and adverse effects associated with lipid-lowering therapy such as rhabdomyolysis (**A** recommendation for women 45 years of age or older and **B** recommendation for those between 20 and 44 years of age).[6] Good-quality evidence shows that total cholesterol, low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol are independent predictors of risk for coronary heart disease, and that total cholesterol/HDL-cholesterol ratio or LDL-cholesterol/HDL-cholesterol ratio classify risk better than total cholesterol alone.[6] Although triglycerides level is a strong univariate predictor of cardiovascular events, its association with these events is reduced substantially by adjustment for other risk factors. For women aged 20 and older who are not at increased risk for coronary heart disease, individualized decision making is recommended, given that there is at least moderate evidence that net benefit of screening is small (**C** recommendation). High-sensitivity C-reactive protein (CRP) has been the most rigorously studied nontraditional marker for risk of coronary heart disease. However, on the basis of the latest USPSTF review, there is inconclusive evidence that considering changes in CRP level lead to primary prevention of coronary heart disease events (**I** recommendation).[7] Analyses from four large cohorts were consistent in finding evidence that including CRP improves risk stratification among initially intermediate-risk persons, that CRP has desirable test characteristics, and that good data exist about the prevalence of elevated CRP levels in intermediate-risk persons.[8] However, limited evidence links changes in CRP levels to primary prevention of cardiovascular events. Other laboratory risk markers evaluated by the USPSTF were lipoprotein(a), homocysteine, leukocyte count and fasting blood glucose. Current evidence, however, does not support routine use of any of these markers for further risk stratification of intermediate-risk persons, and there is little evidence to determine harms of using nontraditional markers to screen for risk of coronary heart disease. Potential harms of screening include lifelong use of medications without proven benefit and psychological harms from being misclassified in a higher risk category.

Endocrine/Metabolic Disorders and Pregnancy

Endocrine and Metabolic Disorders

▸ **Chronic kidney disease:** No clinical trials have evaluated the screening or monitoring of chronic kidney disease; therefore,

Table: Recommendations of the US Preventive Services Task Force for Laboratory-Based Health Screening of Adult women ***continued...***

Disease/Condition (Specific target population)	Laboratory screening test(s)	Grade
Endocrine/Metabolic Disorders and Pregnancy		
Bacteriuria (Pregnant women)	Urine culture	A
HBV infection (Pregnant women)	Serologic hepatitis B surface antigen test	A
HIV infection (Pregnant women)	Anti-HIV antibody test followed by Western blot/immunofluorescent assay if positive	A
Rh (D) incompatibility (Pregnant women)	D blood typing and D antibody testing	A
Rh (D) incompatibility (Unsensitized D-negative women at 24-28 weeks' gestation)	D antibody testing	B
Syphilis infection (Pregnant women)	VDRL or RPR test, followed by FTA-ABS test	A
Chlamydial infection (Pregnant women who are ≤24 years of age or older at increased risk for infection)	Nucleic acid amplification test (urine or vaginal swabs)	B
Diabetes mellitus (Those with sustained blood pressure of >135/80 mm Hg)	Fasting plasma glucose and hemoglobin A1c	B
Diabetes mellitus (Those with sustained blood pressure of ≤135/80 mm Hg)	Fasting plasma glucose and hemoglobin A1c	I
Gestational diabetes mellitus	Oral glucose tolerance test	I
Gonorrhea infection (Pregnant women at increased risk of infection)	Culture/Nucleic acid amplification test	B
Gonorrhea infection (Pregnant women not at increased risk of infection)	Culture/Nucleic acid amplification test	I
Iron deficiency anemia (Pregnant women)	Serum hemoglobin and hematocrit	B
Bacterial vaginosis (Pregnant women at low risk for preterm delivery)	Gram stain	D
Bacterial vaginosis (Pregnant women at high risk for preterm delivery)	Gram stain	I
Hereditary hemochromatosis	Test for C282Y homozygosity	D
Lead poisoning (Pregnant women)	Blood lead test	D
Chronic kidney disease	Tests for urinary protein and serum creatinine	I
Thyroid disease	Thyroxine (T4), free T4, and thyroid-stimulating hormone	I

evidence that routine screening improves clinical outcomes for asymptomatic adults is inadequate (**I** recommendation).[9,10] Although potential harms of screening may include adverse effects from venipuncture and psychological effects of labeling a person with the disease, evidence on the harms of screening is inadequate.[9] Patients falsely identified as having the disease, by being tested for urinary protein and serum creatinine, may receive unnecessary treatment and diagnostic interventions resulting in harmful effects given that there is convincing evidence that medications used to treat early disease may have adverse effects.[9]

▸ **Diabetes mellitus:** Direct evidence is lacking on the health benefits of detecting type 2 diabetes by either targeted or mass screening, and indirect evidence also fails to demonstrate health benefits for screening the general population.[11] However, individuals with hypertension probably benefit from screening because blood pressure targets for those with diabetes are lower than those without diabetes; and in those with hypertension and diabetes, lowering blood pressure below conventional target values reduces the incidence of cardiovascular events and mortality.[12] Intensive glycemic control in persons with clinically detected diabetes mellitus reduces progression of microvascular disease. Screening for type 2 diabetes every three years in asymptomatic adults with sustained blood pressure (either treated or untreated) of greater than 135/80 mm mercury is recommended (**B** recommendation).[13] In addition to criteria for plasma or blood glucose measurement, diabetes may also be diagnosed by demonstrating increased blood ▸▸

Table: Recommendations of the US Preventive Services Task Force for Laboratory-Based Health Screening of Adult women ***continued...***

Disease/Condition (Specific target population)	Laboratory screening test(s)	Grade
Infectious Diseases		
Chlamydial infection (Sexually active, nonpregnant women ≤24 years of age)	Nucleic acid amplification test (urine or vaginal swabs)	A
Chlamydial infection (≥25 years of age if not at high risk for infection)	Nucleic acid amplification test (urine or vaginal swabs)	C
HIV infection (15-65 years of age)	Anti-HIV antibody test followed by Western blot/immunofluorescent assay if positive	A
Syphilis infection (Those at high risk for infection)	VDRL or RPR test, followed by FTA-ABS test	A
Syphilis infection (Those not at high risk for infection)	VDRL or RPR test, followed by FTA-ABS test	D
Gonorrhea infection (Sexually active women at high risk for infection)	Culture/Nucleic acid amplification test	B
Gonorrhea infection (Nonpregnant women not at high risk for infection)	Culture/Nucleic acid amplification test	D
HCV infection (Those at high risk for infection and one-time screening of those born in 1945-1965)	Anti-HCV antibody testing followed by confirmatory PCR	B
Bacteriuria (Nonpregnant women)	Urine culture	D
Genital HSV infection	Anti-HSV-2 antibody test, PCR, HSV culture, and Western blot	D
HBV infection (Nonpregnant women)	Serologic Hepatitis B surface antigen test	D

hemoglobin A1c concentrations.[14] Observational studies report no serious long-term adverse psychological effects such as anxiety from receiving a new diagnosis of type 2 diabetes mellitus from screening.[12] However, longer-term effects of labeling a large proportion of the population as abnormal are unknown. For adults with blood pressure of 135/80 mm mercury or lower, there is inadequate evidence that early diabetes control as a result of screening provides an incremental benefit for microvascular clinical outcomes compared with initiation of treatment after clinical diagnosis given that the benefits of tight glycemic control on microvascular clinical outcomes, such as severe visual impairment or end-stage renal disease, take years to become apparent (**I** recommendation).[12]

▸ **Hereditary hemochromatosis:** Although available data suggest that 38%-50% of C282Y homozygotes develop iron overload and 10%-25% develop some type of hemochromatosis-associated morbidity, current research provides very limited numbers of observations and research designs are subject to bias.[15] There is fair evidence that clinically important disease due to hereditary hemochromatosis is rare in the general population, and that a low proportion of individuals with a high-risk genotype (C282Y homozygotes) manifest the disease.[16] Even among these individuals, it appears that only a small subset will develop symptoms of hemochromatosis, and an even smaller proportion of them will develop advanced stages of clinical disease. Also, the risk of iron overload is reduced further for pre-menopausal women due to the monthly menstrual blood loss. There is poor evidence that early therapeutic phlebotomy, the primary treatment for hemochromatosis, improves morbidity and mortality in screening-detected versus clinically detected individuals.[16] Screening could lead to identification of a large number of individuals who possess high-risk genotype but may never manifest clinical disease, and this may result in unnecessary surveillance, treatments and invasive work-up, labeling and anxiety. Potential harms of genetic screening for hereditary hemochromatosis appear to outweigh its potential benefits (**D** recommendation).[16]

▸ **Thyroid disease:** Screening for occult thyroid dysfunction in adults using tests for thyroxine (T4) and thyroid-stimulating hormone (TSH) would be valuable if there were clinical benefits of early treatment, including relief of previously unrecognized symptoms.[17] Although there is fair evidence that TSH testing can detect subclinical thyroid disease in people without symptoms of thyroid dysfunction, there is poor evidence that treatment improves clinically important outcomes in adults with screen-detected thyroid disease (**I** recommendation).[18] Although yield of screening is greater in certain high-risk groups, such as postpartum women as well as those with Down syndrome and the elderly, there is poor evidence that screening these groups leads to clinically important benefits; and evidence regarding the efficacy of treatment in women found by screening to have subclinical thyroid dysfunction is inconclusive.[19] Data on adverse effects of the broader use of levothyroxine are sparse,[19] and there is potential for harm caused by false positive screening tests even though the magnitude of harm is unknown.[18] As an ini-

Table: Recommendations of the US Preventive Services Task Force for Laboratory-Based Health Screening of Adult women ***continued...***

Disease/Condition (Specific target population)	Laboratory screening test(s)	Grade
Neoplastic Diseases		
Cervical cancer (21-65 years of age)	Cervical cytology every 3 years	A
Cervical cancer (30-65 years of age)	Cervical cytology and HPV DNA every 5 years	A
Cervical cancer (<21 years of age)	Cervical cytology or combination of cervical cytology/HPV DNA	D
Cervical cancer (>65 years of age with adequate prior negative screening and not otherwise at high risk of cervical cancer)	Cervical cytology or combination of cervical cytology/HPV DNA	D
Cervical cancer (Those with hysterectomy involving removal of cervix and no history of high-grade lesion or cancer)	Cervical cytology or combination of cervical cytology/HPV DNA	D
Cervical cancer (<30 years of age)	HPV DNA with or without cervical cytology	D
Colorectal cancer (50-75 years of age)	Fecal occult blood test	A
Colorectal cancer (76-85 years of age)	Fecal occult blood test	C
Colorectal cancer (>85 years of age)	Fecal occult blood test	D
Colorectal cancer (≥50 years of age)	Fecal DNA test	I
Breast and ovarian cancer susceptibility (Women with family history associated with high risk cancer)	*BRCA1* and *BRCA2* mutation tests	B
Breast and ovarian cancer susceptibility (Women with family history not associated with high risk of cancer)	*BRCA1* and *BRCA2* mutation tests	D
Ovarian cancer	Serum CA-125 test	D
Pancreatic cancer	Serological cancer marker tests such as CA 19-9	D
Bladder cancer	Microscopic urinalysis for hematuria and urine cytology	I
Lung cancer	Sputum cytology	I
Substance Abuse		
Illicit drug use	Toxicological tests of blood or urine	I

** BRCA, breast cancer; CA, carbohydrate antigen; FTA-ABS, fluorescent treponemal antibody absorbed; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; Hg, mercury; HIV, human immunodeficiency virus; HPV, huamn papilloma virus; HSV, herpes simplex virus; LDL, low-density lipoprotein; PCR, polymerase chain reaction; RPR, Rapid Plasma Reagin; VDRL, Venereal Disease Research Laboratory*

tial screen for thyroid disease, sensitive TSH testing offers the greatest promise.[17]

Screening During Pregnancy

Bacterial vaginosis: For pregnant women at low risk for preterm delivery, there is moderate certainty that screening for bacterial vaginosis has no net benefit (**D** recommendation).[20] For pregnant women at high risk for preterm delivery, evidence is conflicting and the balance of benefits and harms cannot be determined (**I** recommendation).

Bacteriuria: In pregnant women, convincing evidence indicates that detection of and treatment for asymptomatic bacteriuria with antibiotics significantly reduces the incidence of symptomatic maternal urinary tract infections and low birth weight (A recommendation).[21] Potential harms associated with treatment for asymptomatic bacteriuria include adverse effects from antibiotics and development of bacterial resistance.

Chlamydial infection: There are no studies evaluating effectiveness of screening for chlamydial infection in pregnant women who are at increased risk of infection. However, screening identifies infection in asymptomatic pregnant women, there is a high prevalence of infection among pregnant women at increased risk of infection, and fair evidence of improved pregnancy and birth outcomes for women treated for chlamydial infection (**B** recommendation).[22] Potential harms of screening include anxiety and various problems arising from positive results and overtreatment. Screening with nucleic acid amplification testing of urine or vaginal swabs is recommended at the first prenatal visit, and for patients with continuing or new risk

of infection, screening is also recommended during the third trimester.[22]

Online

▶ This article continues online at **www.advanceweb.com/laboratory** with a discussion of infectious diseases, neoplastic diseases and substance abuse. You'll also find the references for this article under our "Magazine" tab.

▶ **Genital herpes simplex virus (HSV) infection:** Screening asymptomatic pregnant women using serological screening tests for HSV antibody does not reduce transmission of genital HSV to newborn infants, and there is no evidence that treating seronegative women decreases risk for neonatal infection.[23] There is limited evidence that performance of Caesarean section in women with active HSV lesions at the time of delivery decreases neonatal HSV infection. There is limited evidence of safety of antiviral therapy in pregnant women and neonates.[23] Potential harms of screening include false-positive test results, labeling, and anxiety, as well as false negative tests resulting in false reassurance. The potential harms of screening for genital HSV infection outweigh potential benefits (**D** recommendation).[23]

▶ **Gestational diabetes mellitus:** There is adequate evidence that treatment of screen-detected gestational diabetes mellitus with dietary modifications, glucose monitoring and insulin if needed can significantly reduce the risk of preeclampsia, fetal macrosomia and shoulder dystocia.[24] When these outcomes are considered collectively, there is a moderate net benefit for both mother and infant. However, the benefit of treatment on long-term metabolic outcomes in women who are treated for gestational diabetes mellitus compared with those who are not treated is uncertain (**I** recommendation).[24]

▶ **Gonorrhea infection:** Pregnant women with gonorrhea infection are at higher risk for premature rupture of membranes, preterm labor, chorioamnionitis, and perinatal transmission to infants can cause severe conjunctivitis resulting in blindness if untreated.[25] There is fair evidence that screening tests (culture and nucleic acid amplification tests of endocervical swabs, or nucleic acid amplification tests of urine or vaginal swabs) can accurately detect gonorrhea infection, good evidence that antibiotics can cure the infection, and fair evidence that screening pregnant women at high risk for gonorrhea may prevent the complications associated with gonococcal infection during pregnancy (**B** recommendation).[25] Although no study has directly examined harms of screening or treatment for gonorrhea infection, potential harms may include opportunity costs to the clinician and patient (time and other resources); stress, labeling and further testing due to positive or false-positive test results; and harms resulting from adverse drug reactions. At-risk pregnant women should be screened at first prenatal visit, and for those at continued risk or with a new risk factor, a second screening should be conducted during the third trimester.[25] In women, gonorrhea is a major cause of cervicitis and pelvic inflammatory disease, which can lead to ectopic pregnancy, infertility and chronic pelvic pain. However, prevalence of gonorrhea infection in pregnant women not at increased risk of infection is low, and the balance between benefits and harms of screening in pregnant women not at increased risk of infection cannot be determined (**I** recommendation).

▶ **Hepatitis B virus (HBV) infection:** Screening for HBV infection in pregnant women to identify newborns who will require prophylaxis against perinatal infection is a well-established, evidence-based standard of current medical practice (A recommendation).[26] A 2006 systematic review of randomized, controlled trials found that newborn prophylaxis reduced perinatal transmission of HBV infection. There is good evidence that universal prenatal screening for HBV infection using hepatitis B surface antigen (HBsAg) test substantially reduces prenatal transmission of HBV and subsequent development of chronic HBV infection.[27] Current practice of providing post-exposure prophylaxis with hepatitis B immune globulin administered at birth to infants of mothers infected with HBV substantially reduced risk for acquiring HBV infection.[26] HBsAg test should be ordered at first prenatal visit, and pregnant women with unknown HBsAg test status or with new or continuing risk factors at admission to hospital, birth center or other delivery setting should be (re-)screened.[26] Although potential harms of screening are no greater than small, there are no published studies that describe harms of screening for HBV infection in pregnant women.[26]

▶ **Human immunodeficiency virus (HIV) infection:** There is convincing evidence that identification and treatment of HIV-positive pregnant women dramatically reduces rates of mother-to-child transmission.[28] However, no study has directly evaluated the effects on clinical outcomes of screening versus no screening for HIV infection.[29] Antiretroviral therapy in combination with avoidance of breastfeeding and elective Caesarean section in women with viremia reduces risk for mother-to-child transmission.[30] There is convincing evidence that individual antiretroviral drugs, drug classes, and combinations are all associated with increased risk for cardiovascular and some short-term adverse events such as increased risk of preterm delivery during pregnancy, but the magnitude of such risks appears to be small.[28] Evidence is insufficient to determine optimum time intervals for HIV screening; however, a reasonable approach is one-time screening of all pregnant women to identify women who are already HIV-positive, with repeated screening of those known to be at increased risk of HIV infection (**A** recommendation).[28]

▶ **Iron deficiency anemia:** There is fair evidence that treating asymptomatic pregnant women who have iron deficiency anemia results in moderate benefits in health outcomes (**B** recommendation).[31] However, there is no evidence addressing harms of screening pregnant women for iron deficiency anemia. Potential harms include false-positive results,

anxiety, cost, gastrointestinal symptoms, and unintentional overdose.[31]

Lead poisoning: Given the significant potential harms of treatment and residential lead hazard abatement and no evidence of treatment benefit, the USPSTF concluded that harms of screening for elevated blood lead levels in asymptomatic pregnant women outweigh potential benefits (**D** recommendation).[32]

Rh (D) incompatibility: The USPSTF found good evidence that D blood typing, anti-D antibody testing and intervention with Rh(D) immunoglobulin, as appropriate, prevents maternal sensitization and improves outcomes for newborns, and these benefits substantially outweigh any potential harm.[33] Therefore, it is strongly recommended that all pregnant women undergo D blood typing and antibody testing during their first prenatal visit (A recommendation). There is fair evidence that repeated antibody testing for unsensitized D-negative women (unless the father is also known to be D-negative) and intervention with D immunoglobulin, as appropriate, provides additional benefit over a single test at the first prenatal visit in preventing maternal sensitization and improving outcomes for newborns.[33] The benefits of repeated testing substantially outweigh any potential harm; therefore, the USPSTF recommends repeated D antibody testing for all unsensitized D-negative women at 24-28 weeks' gestation, unless the biological father is known to be D-negative (**B** recommendation).

Syphilis infection: Untreated syphilis during pregnancy is associated with stillbirth, neonatal death, bone deformities, and neurologic impairment; and there is adequate evidence that screening tests can accurately detect syphilis infection, and convincing observational evidence that universal screening of pregnant women decreases proportion of infants with clinical manifestations of syphilis infection.[34] Nontreponemal tests commonly used for initial screening are Venereal Disease Research Laboratory (VDRL) or Rapid Plasma Reagin (RPR), followed by confirmatory fluorescent treponemal antibody absorbed (FTA-ABS) or *T. pallidum* particle agglutination (TP-PA).[35] All pregnant women should be tested at their first prenatal visit. Current recommendations for women in high risk groups call for screening at first prenatal visit, and again during third trimester (at 28 weeks of gestation) and at delivery.[36] Although there is no new direct evidence that screening for syphilis infection leads to improved health outcomes in persons at increased risk for infection, there is adequate evidence that screening tests can accurately detect syphilis infection and that antibiotics can cure syphilis.[35] Screening and treatment may result in potential harms, including false-positive results that require clinical evaluation, unnecessary anxiety to the patient and harms of antibiotic use.[34,35] Drug-related harms include anaphylaxis from penicillin allergy, and Jarisch-Herxheimer reaction occurring within first 24 hours after treatment.[36] Screening of pregnant women is strongly recommended with high certainty that net benefit is substantial (**A** recommendation). ■

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