

PREVENTIVE MEDICINE

Med 665

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Introduction

The primary objective of Preventive Medicine is to reduce the burden of suffering for the major preventable diseases. For the purpose of our discussion here, we will not specifically address many important factors affecting health such as safe housing, poverty and access to health care, but will focus on clinic-oriented interventions. This includes risk modification (e.g. tobacco cessation, diet, and exercise), vaccinations, and screening of diseases. One of the goals for this module is not only to know the current recommendations for preventive health services, but also to understand the risks and benefits of screening, the inherent limitations of the available tests, and the controversies surrounding many screening studies.

Learning goals:

- To know the major preventable diseases affecting different demographic populations.
- To understand the principles of screening.
- To know the current immunization recommendations for adults.
- To understand the theories of behavioral change and to begin to develop an effective approach.
- To know where to look up the latest evidence and recommendations for preventive measures.

Reading material:

The articles provided on the website are not meant to be comprehensive by any means; you will need to consult other sources such as the following:

- Dr. Paauw's Internal Medicine Clerkship Guide
- The Guide to Clinical Preventive Services by the US Preventative Services Task Force.
 - <http://www.ahrq.gov/> Then click on the link to 'Preventive Services.'
- Screening and Testing to Detect Cancer. National Cancer Institute.
 - <http://www.cancer.gov/cancertopics/screening>
- Up-To-Date Online. Access from the Healthlinks Care Provider Toolkit.
 - <http://healthlinks.washington.edu>
- CDC Immunization Guidelines. <http://www.cdc.gov.offcampus.lib.washington.edu/vaccines/>

Screening Principles / Prostate Cancer

A 52-year-old man comes to clinic for routine follow-up. He has heard a lot about PSA testing and wonders whether he should have the test. His father was diagnosed with prostate cancer at age 75.

1. What characteristics of a disease make it suitable for population-based screening interventions? What would ideal conditions for screening be in terms of:
 - disease prevalence and severity?
 - screening test performance?
 - treatment?
2. How does prostate cancer screening with PSA measure up to these ideals?
3. According to best estimates, men of what age are most likely to benefit from screening?
4. What are the risks of screening for prostate cancer?
5. How do we measure the accuracy of a screening test? What are the definitions of sensitivity, specificity, positive and negative predictive values?
6. Define lead-time and length biases

Breast Cancer

A 44-year old woman returns for follow-up. In the last year, her 48-year-old sister was diagnosed with breast cancer, and she is concerned about her own risk. Her menarche occurred at age 13, and she has never been pregnant. At age 40, she underwent a breast biopsy that found benign fibrocystic changes. She performs breast self-examination monthly. Her exam in the office is normal.

1. Review the risk factors that your patient has for developing breast cancer
2. How reassuring are her negative breast self-exams and your own exam in the office?
3. How do the risks and benefits of mammography in women aged 40-49 compare with those in women aged 50-69?

Your patient's 71-year-old mother is also concerned about breast cancer.

4. What are the potential benefits of mammography in women older than 69?
5. Who should **not** be screened with mammography?

Young Woman at College Entry

An 18-year old woman comes to clinic prior to entering college. From prior visits, you know that she smokes one pack of cigarettes daily, exercises infrequently, and is sexually active with men; her contraceptive of choice is condoms. She has had annual Pap smears for two years, and both have been normal. She requests that you complete a physical examination form, perform her annual Pap smear and bimanual exam, and document completion of required immunizations.

1. Which aspects of her health care would you discuss and what counseling would you offer?
2. Which immunizations are required for college entry?
3. At what age should women initiate cervical cancer screening? How often should Pap tests be performed?
4. Would you perform any additional tests?

Older Woman Establishes Primary Care

A 65-year old nun is referred to establish primary care. She has not seen a physician since her appendix was removed at age 12. She walks briskly for 30 minutes on most days, is a non-smoker and non-drinker, and takes no medications. Her parents and a younger brother are alive and well. Her blood pressure is normal, she has no lymphadenopathy or goiter, and her cardiovascular, chest, and abdominal exams are also normal.

1. Would you perform a Pap smear? Who does **not** require Pap testing? When is it OK to stop screening?
2. Which immunizations would you recommend?
3. Which lab tests would you order?

Middle-Aged Man with Hyperlipidemia

An asymptomatic 42-year old man has the following fasting lipid panel: total cholesterol 256, HDL 28, LDL 168, triglyceride 300.

1. What additional coronary risk factors should be reviewed?
2. Which aspects of the physical examination deserve special attention?
3. Which additional lab tests would you order?
4. What would your target LDL be under the following circumstances?:
 - no additional risk factors
 - diabetes
 - smoker with SBP 160 (on no antihypertensive treatment)
 - patient is a woman
 - angina
5. What counseling would you provide regarding exercise and diet?
6. You decide to treat his hyperlipidemia. Which drug would you choose?

Colorectal Cancer Screening

The USPSTF recommends screening all adults age 50 and older for colorectal cancer. Fecal occult blood testing (FOBT), flexible sigmoidoscopy every 5 years (with or without FOBT), and colonoscopy every 10 years are all recommended strategies. There are insufficient data to determine which strategy is best.

FOBT reduced the risk of death due to colorectal cancer in a placebo-controlled trial. In a case-control study, flexible sigmoidoscopy reduced the risk of death from cancers within the reach of the scope by 59%. A study of one-time screening with FOBT and flexible sigmoidoscopy found that these methods missed 24% of cases of advanced neoplasia compared with colonoscopy.

1. Name 3 causes of false positive and false negative hemoccult tests.
2. What are the limitations and risks of flexible sigmoidoscopy?
3. What risk factors would make you more likely to recommend screening with colonoscopy?

In a randomized, placebo-controlled trial, screening for colorectal cancer with hemoccult cards in patients older than 50 was associated with a 33% reduction in 13-year mortality due to colorectal cancer. The 13-year mortality due to colorectal cancer in the population assigned to screening was 0.59% as compared with 0.88% in the unscreened population (absolute risk reduction 0.29%).

4. How many people need to be screened with hemoccult cards for 13 years in order to prevent one death from colorectal cancer?

Extra credit

In a separate study assessing the reliability of hemoccult testing among patients with a prior history of colorectal cancer, hemoccult testing had the following accuracy: sensitivity 33%, specificity 95%.

5. What is the positive predictive value (PPV) of the hemoccult test in the general population (estimated prevalence of disease = 0.5%)? What would the PPV if the prevalence was 5.0%?

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Updated by A Chun (2/2005), L Schellenberg Johnson (1/2006), G Terasaki (6/2007)

Screening Principles / Prostate Cancer

1. The purpose of screening is to detect disease at an asymptomatic and treatable stage to reduce morbidity and mortality. A common misconception is that the detection of disease itself is the endpoint measure. An effective screening program must demonstrate a reduction in mortality/ morbidity or an improvement in quality of life. Whether a particular screening intervention achieves this goal depends on the following characteristics of the disease, screening test, treatment, and population being screened.

Factor	Ideal Characteristics
Disease	Prevalent or high burden of suffering Detectable pre-symptomatic phase
Test	Accurate (sensitive, specific, good predictive values) Acceptable to patients (non-invasive, minimal discomfort) Cost-effective
Treatment	Reduces morbidity and mortality Acceptable risk/benefit ratio
Population	High disease prevalence Good life expectancy Willing to comply with test, follow-up, and therapy

“First, do no harm.” If a patient presents with a complaint, we try our best to diagnose the problem without any guarantees of success. In screening, however, we are subjecting an asymptomatic patient to a test. The onus is on us to ensure some reasonable level of benefit for the patient.

2. **Disease prevalence and severity:** There are approximately 230,000 new diagnoses of prostate cancer each year and 30,000 deaths due to prostate cancer yearly. Prostate cancer is the second leading cause of death from cancer among men in the United States. More than 75% of prostate cancer cases are in men >65yo, this group accounts for 90% of the deaths from prostate cancer. The incidence of prostate cancer is approximately 60% greater in black men compared to white men.

Prostate cancer is a heterogeneous disease; different cases of prostate cancer have varying growth rates and potential for causing death. Autopsy studies of men, who died from causes unrelated to prostate cancer, demonstrate that 1/3 of men <80 year old and 2/3 of men >80 year old had evidence for prostate cancer on prostate biopsies. An American male has a lifetime risk of developing prostate cancer of 16% and a risk of dying from prostate cancer of only 3%. This discrepancy between prostate cancer diagnoses and deaths suggests that some tumors that are detected by screening may be clinically unimportant. Research is lacking on what characteristics of the cancer will determine the clinical severity of disease. Thus it is difficult to identify the most clinically appropriate target for screening.

Screening Test: There have been controversies in determining the most useful cut off point of the PSA level. The use of a higher PSA cut off risks missing some cancers; whereas the use of a lower PSA may

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increase the numbers of false positives, unnecessary biopsies and proportion of biopsies that identify clinically insignificant disease. Published in 5/2004 NEJM (Thompson IM et al, N Engl J Med 2004;350:2239-46), 18,000 men underwent PSA testing and DRE yearly for seven years. At seven years, 2,950 men who had persistently normal PSA levels (<4ng/ml) underwent biopsies. Of these men, 6.6% had cancer with PSA < 0.5ng/ml, 10% had cancer with PSA 0.6-1.0 ng/ml, 17% had cancer with PSA 1.1-2.0 ng.ml, 24% had cancer with level of 2.1-3.0 ng/ml, and 27% had cancer with PSA 3.1-4.0 ng/ml.

The Physicians Health Study, using a PSA cut off of 4ng/ml, calculated a sensitivity of 73.2% and a specificity of 85.4%. A PSA value >4ng/ml has a positive predictive value of 20-30%. Men who undergo screening have a 15-40% risk of requiring a biopsy for further evaluation. Since the PPV of the PSA test is relatively low, many of these men will undergo a biopsy for a false positive screening test. The utility of monitoring PSA velocity (change over time) or the ratio of free to total PSA values is also not clear. Digital rectal exam (DRE) has been found to have a sensitivity of 59% and a positive predictive value of 10% to 30%.

Follow-up for an abnormal screening test: The diagnostic standard for prostate cancer, transrectal needle biopsy, is imperfect. It has the potential to miss 10-30% of cases of prostate cancer. A typical biopsy is actually 4-6 blind biopsies on normal appearing prostate tissue.

Treatment: There have been no trials to date that have demonstrated a clear mortality benefit from screening for prostate cancer. The goal of screening is to detect clinically localized (and thus treatable) prostate cancer. One RCT has demonstrated decreased mortality from prostate cancer but not a decreased overall mortality benefit comparing patients who had radical prostatectomy to those who underwent “watchful waiting” in men with clinically detected (i.e. not detected from screening) localized cancer. A clear mortality benefit for the treatment of cancers diagnosed from screening has not been shown for radical prostatectomy, external beam radiation, brachytherapy, androgen deprivation therapy.

3. A decision analysis performed by the American College of Physicians (Ann Intern Med 1997;126:480-4.) concluded that screening for localized prostate cancer followed by surgical treatment confers a potential for 3 more years of life gained for men in their 50s, 1.5 years of life gained for men in their 60's, and 0.4 more years of life gained for men in their 70's. Men with a positive family history for prostate cancer and black men have a greater risk for developing prostate cancer, but no studies have demonstrated that earlier or more aggressive screening is indicated in these groups of patients. The ACP and American Urological Society agree that men >70yo should probably not undergo screening. In addition, men who have a life expectancy of <10 years should probably not be tested.
4. First, abnormal test results create anxiety. Because PSA testing has a positive predictive value of only 22%, 4 out of 5 men with abnormal results are false-positives and will have worried unnecessarily. There are six different scenarios depending on the test outcome. See the table below (JAMA. 1999. 281: 2029). Some of the patients with a true positive result (a^0) will have significant disease and will benefit from early detection and treatment. However, other patients (a^1) with a true positive result may have underlying disease which is inconsequential and therefore be subjective to unnecessary labeling, evaluation and treatment for a condition that would not have affected their lives. An example of this is a patient found to have a low-grade prostate cancer but will probably die of his heart disease instead. This is, in essence, similar to a false positive result (b). There is also a risk of false negative results in a patient with significant disease (c^0) that may falsely reassure both patient and physician, leading to a

Table 2. Summary of Benefits and Harms of Screening by Underlying Disease State*

	Reference Standard Results			
	Disease or Risk Factor Present		Disease or Risk Factor Absent	
Screening test positive	a ⁰ =True positives (significant disease)	or	a ¹ ="True" positives (inconsequential disease)	b=False positives
Screening test negative	c ⁰ =False negatives (significant disease)	or	c ¹ ="False" negatives (inconsequential disease)	d=True negatives

*a⁰ indicates disease or risk factor that will cause symptoms in the future (significant disease); a¹, disease or risk factor asymptomatic until death (inconsequential disease); b, false positives; c⁰, missed disease that will be significant in the future; c¹, missed disease that will be inconsequential in the future; and d, true negatives. Sensitivity = a/a+c and specificity = d/b+d.

delay in diagnosis. On the other hand, patients with a false negative result and inconsequential disease are not harmed because they would not have suffered from the 'missed' disease in the end.

Second, approximately 25% of men who are screened with PSA will ultimately require transrectal ultrasound-guided biopsy. This is costly and causes short-term discomfort. Third, treatment of localized cancer has known risks but unproven benefit. Therefore, some men will be made aware of a cancer (very stressful) that may not have affected their survival and incur the risks of treatment, which are:

	<u>Impotence</u>	<u>Incontinence</u>	<u>Colitis</u>	<u>Death</u>
Radical prostatectomy	>50%	20-30%	N/A	0.5-1.0%
Radiation	40-67%	1-2%	10%	0.2-0.5%

5. The accuracy of screening tests is defined in terms of sensitivity, specificity, positive and negative predictive values.

Test result	Condition	
	Present	Absent
Positive	a	b
Negative	c	d

Definitions

a = true positive **b** = false positive
c = false negative **d** = true negative

Sensitivity = a/a+c = proportion of persons with condition who test positive

Specificity = d/b+d = proportion of persons without condition who test negative

Positive Predictive Value (PPV) = a/a+b = proportion with positive tests who have the disease

Negative Predictive Value (NPV) = d/c+d = proportion with negative tests who are disease free

An important point: very sensitive tests can be useful for screening; highly specific tests are necessary for confirmation.

SpIN (specificity if positive, rules in disease)

SnOUT (sensitivity if negative, rules out disease)

6. Both of these forms of bias could make it appear that a screening intervention improves survival when, in fact, no such effect exists. Lead time is the time period from diagnosis at a pre-symptomatic stage to the time at which symptoms would have developed if no screening had occurred. Lead time bias can occur if a disease for which no effective treatment exists is diagnosed before the onset of symptoms. Patients whose disease is diagnosed "early" appear to live longer than those who are diagnosed at the onset of symptoms, but because treatment is ineffective, death occurs at the same time with or without

screening. Length time bias refers to a situation in which a disease is heterogeneous: some cases are aggressive whereas others are indolent. Cases that progress rapidly from onset to symptoms and diagnosis are less likely to be asymptomatic, so screening is more likely to detect the indolent form. This makes it appear that screening and early treatment are more effective than usual care.

For more information link to <http://www.acponline.org/journals/ecp/primers/marapr99.htm>.

Prostate cancer is a disease for which these considerations are relevant. Randomized trials of PSA screening are needed to determine whether screening actually improves survival.

Breast Cancer

1. See <http://bcra.nci.nih.gov/brc/> to find a computerized tool to identify a woman's risk for breast cancer. Known risks for breast cancer are a past history of DCIS or LCIS, older age, earlier age of menarche, older age at first live birth, family history of first degree relative with breast cancer, prior breast biopsies, prior history of atypical hyperplasia on a breast biopsy. Other risk factors such as age at menopause, dense breast tissue on a mammogram, use of birth control pills or hormone replacement therapy, high-fat diet, alcohol, physical activity, obesity, or environmental exposures are not included in this risk assessment tool for two reasons: evidence is either not conclusive or researchers cannot accurately determine how much these factors contribute to the calculation of risk for an individual woman.
2. Only one study has looked at the utility of clinical breast exam (CBE) alone compared to mammography screening with a clinical breast exam in the detection of breast cancer. This study did not find a mortality difference between the two groups. The CBE utilized in this study was standardized and took an average of 10 minutes (far different from clinical reality). The sensitivity of CBE is estimated to be 54% with a specificity of 94%. The American Cancer Society recommends CBE every 3 years for women age 20-39yo and yearly for women >40 year old. Although a mortality benefit has not been shown for CBE, experts feel that this examination is an important time for doctors and patients to discuss risks for breast cancer, changes in their breasts and early detection.

A complete clinical breast exam includes proper positioning (to allow examination of the breast tissue against the chest wall, having the patient lie on a vertically placed pillow allows for this in patients with large breasts), examining the breast tissue in vertical strips from the axilla to the bra line, using the pads of the three middle fingers in circular motion to examine superficial, deep and deeper tissue planes. It is recommended that a clinician spend 3 minutes per breast.

No trial has demonstrated a mortality benefit for women who routinely perform breast self-examination (BSE). Women who perform monthly self breast exam are more likely to seek medical attention for benign lesions. It is thought that women who perform breast self examination will become more familiar with their breasts and will be more likely to identify new lesions should they develop. The American Cancer Society recommends that beginning in their 20s women should be educated about the pros and cons of breast self examination and it is acceptable for women to decide to perform BSE occasionally or to not do so.

3. For women age 50-69 year old all reports of studies comparing screening with no screening as well as meta-analyses have demonstrated a 20-35% reduction in mortality from breast cancer with screening. The data in patients age 40 to 49 is controversial. Younger women have more dense breast tissue and thus a more difficult to interpret mammogram. Younger women also tend to have faster growing

cancers. Thus the effects of screening in younger women are slower to appear and are less dramatic than findings in women over the age of 50. Meta-analyses have shown that screening in women over the age of 40 results in a 20% decrease in 15 year mortality.

A woman has a 10.7% chance of a false positive result with each mammogram. Since women are screened annually, the risk of a false positive mammogram increases over time. It is estimated that after 10 mammograms, 49% of women will have a false positive result, 19% of these women will require a needle biopsy. See tables in Elmore article for visual presentation about risks and benefits of breast cancer screening.

The American Cancer Society recommends that women undergo yearly mammogram screening starting at the age of 40. The USPTF recommends that women begin mammogram screening at age 40 with a frequency of 1-2 years. The American College of Physicians, the largest internal medicine organization, recommends screening starting at age 50.

4. There have been few studies looking at the effects of mammogram screening in women >70 years old. Although mammography is more accurate in this age group and the incidence of breast cancer is greater, the incidence of DCIS of uncertain clinical significance also rises in women >70 years old. A decision analysis (JAMA, 1999) suggests that it is unlikely to be cost-effective to screen women older than 70. It is recommended that screening be continued in this age group unless the life expectancy is decreased due to another co-morbid condition.
5. Although it is unclear whether there should be an upper age limit for breast cancer screening, annual mammography should definitely be discontinued when an individual's life expectancy is less than the average life expectancy for breast cancer presenting as a palpable mass (about 3-4 years) or when an individual's health status precludes treatment for breast cancer.

Young Woman at College Entry

1. Please review the USPSTF Prevention Tables for a comprehensive list.

Smoking

- i. Smoking is accountable for one of every five deaths, lung cancer is the leading cause of cancer-related death in the US. It also contributes to low birth weight and fire-related injuries. Although smoking is less common among men in recent years, it has increased among women and especially younger women.
- ii. Physician intervention is effective. Smokers told to quit by a physician have higher one-year quit rates: 12% vs. 6%.
- iii. Setting a "quit date" is an important part of successful cessation counseling.
- iv. Discuss the benefits (health, economic, and social) to be gained as well as the obstacles to be overcome (reasons to smoke: social, personal, tension, etc.). The health benefits of cessation include: 50% reduction in 15-year mortality; 50% reduction in 1-year CAD mortality; reduced lung and or esophageal cancer rates after 10 years; normalization of FEV₁ decline.
- v. Bupropion and nicotine replacement are effective adjuncts to counseling and may be particularly useful for patients with signs of nicotine addiction (smoking first thing in am, smoke more than a pack a day, or report withdrawal symptoms with previous quit attempts).

- vi. Monitor progress at follow-up visits or with calls, assure the patient they can quit. Successful quitting often occurs only after several unsuccessful attempts.
- vii. Self-help materials and referral to community support programs may be considered.

Diet and Exercise

- i. Limit fat and cholesterol
- ii. Adequate calcium intake
- iii. Screen for problem eating (bingeing/purging, abnormal body self-image)
- iv. Brisk walking for 30 minutes on most days helps reduce the rate of cardiovascular disease events. Blood pressure, weight control, and blood sugar are all improved. Loss of 5-10 kg, even in a markedly obese person, can improve blood pressure and glycemic control. More vigorous aerobic activity is required to make a meaningful impact on cholesterol.

Safe sexual Practices

- i. Advise patients about using barrier contraception to avoid transmission of sexually transmitted diseases.
- ii. Avoidance of unwanted sexual encounters (i.e., date rape) and pregnancy.
- iii. Screening for domestic violence

Alcohol and Drug Use

- i. Patients should be advised to limit their alcohol use. Over 11 million Americans meet criteria for abuse or dependence of alcohol or other drugs. Alcohol is involved in over half of all motor vehicle crash, fire, drowning, homicide, and suicide deaths. There are over 560,000 hospitalizations per year for alcohol-related conditions. Use on most college campuses is very high.
- ii. USPSTF recommends asking all adults about the quantity and frequency of their use of wine, beer, liquor, and other drugs. If alcohol use is noted, ask the CAGE questions (a yes to at least 2 of 4 questions is positive).
 - C: Have you ever felt you ought to Cut down on drinking?
 - A: Have people Annoyed you by criticizing your drinking?
 - G: Have you ever felt bad or Guilty about your drinking?
 - E: Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (Eye-opener)?
- iii. Screen for recreational drug use, RAVE party attendance, etc.

2. Vaccinating your patients is one of the most effective forms of prevention. Please remember to inquire about primary vaccinations, a second dose of MMR for those who have not received one previously (or do not have documented immunity to measles and rubella), and hepatitis B (for higher risk adults without documented immunity). Women of childbearing age who receive MMR should be advised to avoid pregnancy for 4 weeks after the vaccination. College freshmen who will be living in dormitories are at slightly increased risk of meningococcal disease and influenza; more and more colleges are requiring the meningococcal vaccine. The ACIP recommends that providers advise patients of this risk and consider meningococcal vaccine and yearly influenza vaccine. Tetanus and diphtheria (Td) are recommended every ten years. For patients less than 65, a one time tetanus, diphtheria, and acellular pertussis vaccine (Tdap) is recommended in place of a Td booster, especially healthcare workers. The ACIP recently added a recommendation for the Human Papillomavirus (HPV) vaccine in a three shot

series for woman less than 26 years of age. Ideally, this should be administered prior to the onset of sexual activity. Finally, this year the ACIP is anticipated to release official recommendations for an attenuated varicella virus vaccine to patient 65 and older to reduce the risk of herpes zoster (shingles) and post-herpetic neuralgia.

Go to the CDC vaccine page to download the latest Adult Immunization Schedule Recommendations. <http://www.cdc.gov/vaccines/>

3. There are no large randomized controlled trials that have demonstrated mortality benefit from cervical cancer screening, however large observational trials have provided significant amounts of evidence that this is true. Cervical cancer is related to infection with certain serotypes of HPV, a sexually transmitted virus. It is recommended by the American Cancer Society and USPSTF that women with a cervix undergo cervical cancer screening within 3 years of onset of sexual activity or age 21 yo, whichever occurs first. Screening is recommended yearly. Women >30 yo who have had 3 or more normal pap smears can switch to screening every 3 years. Women over the age of 65 who have had adequate screening and remain low risk for cervical cancer can stop screening. Women, who have had a hysterectomy for benign reasons, do not need to be screened further. Women with HIV, a history of DES exposure prior to birth, immunosuppression due to chemotherapy or steroid use, should continue to be screened yearly irregardless of age or prior normal screening. It is recommended that initial screening be every 6 months in women with HIV infection, this can be changed to yearly screening following 3 consecutive normal studies.
4. See USPSTF table for a complete list. Screening for and eradicating asymptomatic chlamydial infection in high-risk women reduced the incidence of pelvic inflammatory disease by 56% in a randomized trial. Risk factors include age < 25, multiple sex partners in the last 6 months, nulligravidity, and douching. Treatment was with azithromycin 1000 mg single dose. Ligase chain reaction (LCR) testing with cervical samples is more sensitive than with urine.

Older Woman Establishes Primary Care

1. This is a judgment call and would depend on her history. If she has been celibate her entire life, she does not require testing. Women who have never been sexually active, women status-post hysterectomy for benign disease, and women 65 years and older with repeatedly normal smears and stable sexual relationships are at extremely low risk and do not require testing. Therefore, if she reports no history of sexual relations, screening would be unnecessary. If not, annual screening would be recommended until 3 smears are negative.
2. All patients 65 years and older are recommended to have an annual influenza vaccination. The pneumovax is also recommended for patients >65 yo; a second booster for the pneumovax is only recommended if the first pneumovax was given prior to age of 65 yo. Patients with chronic renal failure, nephrotic syndrome, asplenia, immunosuppression due to HIV, chronic steroid use, or recent chemotherapy, should also receive a second booster of the pneumovax. A tetanus-diphtheria booster is indicated every 10 years. If someone has never received the primary series for tetanus, this should be given at 0 weeks, 4 weeks and 6-12 months. Although there are fewer than 65 cases of tetanus each year, many occur in older adults who never received the primary series or whose immunity has waned; the case-fatality rate in adults 50 years and older is 42%. Tdap (Td with acellular pertussis) is not recommended for patient older than 64 years of age. Adults born before 1957 are considered immune to measles, mumps and rubella. A second MMR immunization (if they do not have documentation of a

second shot in their lifetime) should be given for patients <50yo, women should not become pregnant within 4 weeks of MMR vaccine. A one time attenuated varicella virus vaccine is recommended for adults older than 64 to prevent herpes zoster and post-herpetic neuralgia. Hepatitis A, B, polio and meningococcal vaccinations are not recommended unless the patient is at higher risk for these infections due to behaviors: occupational exposure, men who have sex with men, IVDU, travel to endemic countries (The meningococcal vaccination is recommended for travel to sub-Saharan Africa and required for those going to Mecca, Saudi Arabia). There has not been a wild-type case of polio in the US since 1979; she would only require vaccination if she were to travel to a polio-endemic country such as Afghanistan, India, Pakistan, Nigeria, Niger, and Egypt.

3. Lipid profile, hemocult and/or flexible sigmoidoscopy, and mammography are recommended by the USPSTF. The National Osteoporosis Foundation and the USPSTF recommend screening all women over 65 with DEXA (age 60 if risk factors for osteoporosis). The ACP recommends screening women with TSH, and the American Geriatric Society recommends screening for vitamin B12 deficiency.

Middle-Aged Man with Hyperlipidemia

1. The NCEP Adult Treatment Panel III guidelines consider the following to be major coronary risk factors: smoking, hypertension (BP \geq 140/90 or on medication), diabetes, family history of premature coronary disease (male family members before age 55, female before age 65), HDL cholesterol < 40, and age (men >45, women > 55). Additional risk factors, not considered in the NCEP guidelines, include: left ventricular hypertrophy, elevated lipoprotein (a), elevated clotting factors (e.g., fibrinogen), and markers of chronic inflammation (e.g., C-reactive protein).
2. This patient is at elevated risk of atherosclerotic vascular disease (stroke, MI, and PVD). The exam should focus on blood pressure, cutaneous stigmata of familial hyperlipidemia, pulses (volume and bruits), cardiac exam, and neurologic exam.
3. Secondary causes of hypercholesterolemia should be excluded: TSH; BUN, creatinine, urinalysis (screen for nephrotic syndrome); hepatic function tests (screen for cholestatic liver disease). The USPSTF does recommend screening for diabetes with a fasting glucose in patients with known hypertension or hyperlipidemia. If drug therapy is considered, baseline liver function and muscle enzymes (AST) should be ordered.
4. NCEP treatment recommendations are based on fasting LDL levels. Three target LDL levels are designated:
 - 1) coronary disease or coronary disease risk equivalents (other clinical forms of atherosclerotic disease, including PVD, abdominal aortic aneurysm, symptomatic carotid disease; diabetes; or multiple risk factors that confer a 10-year risk for coronary disease >20%)
 - 2) multiple risk factors that confer a 10-year risk of coronary disease <20%
 - 3) 0-1 risk factor

Projections of 10-year risk of coronary disease are based on Framingham risk scoring.

LDL Cholesterol Goals and Thresholds for Initiating Lifestyle and Drug Therapy

<u>Risk Category</u>	<u>LDL Goal</u>	<u>Lifestyle changes</u>	<u>Drug Therapy</u>
CAD or risk equivalents (10-year risk >20%)	< 100	\geq 100	\geq 130 (100-129: drug optional)

2+ Risk factors (10-year risk <20%)	< 130	≥ 130	10-yr risk 10-20%: ≥ 130 10-yr risk <10%: ≥ 160
0-1 Risk factor	< 160	≥160	≥ 190 (160-189: drug optional)

According to NCEP recommendations, LDL goals for the individuals listed are:

- No additional risk factors: 1 risk factor is present (HDL <40). LDL goal is <160
- Diabetes is a CAD risk equivalent. LDL goal is <100
- Multiple risk factors present. Framingham risk score is 15 conferring a 10-yr CAD risk of 20%. LDL goal is <130.
- The Framingham risk scoring differs for men and women. This is the only difference in ATP III guidelines. 1 Risk factor present. LDL goal is <160.
- Criteria for the diagnosis of CAD include (but are not limited to) angina, known MI, or q-waves on ECG. LDL goal is <100.

A paper published in 2004 demonstrated a benefit for intensive lipid lowering in patients hospitalized for an acute coronary syndrome. 4,162 patients with an acute coronary syndrome were randomized to pravastatin 40mg versus high dose atorvastatin 80mg po qd. The mean LDL was 95 in the pravastatin group and 62 in the atorvastatin group. The high dose atorvastatin group had a 16% decrease in cardiovascular outcomes at 2 years. (Cannon CP et al, Intensive Versus Moderate Lipid Lowering with Statins After Acute Coronary Syndrome, N Engl J Med 2004;350(15): 1495-504).

6. Key elements of therapeutic lifestyle changes include:

- Reduced intake of saturated fat (<7% of total calories) and cholesterol (<200 mg per day)
- Increase intake of plant stanols/sterols (2 g/d) and soluble fiber (10-25 g/d)
- Weight reduction
- Increased physical activity

Referral to a dietician and regular follow-up to assess compliance and effect on lipid levels are essential. Figure 1 in the reference outlines recommended steps in therapeutic lifestyle changes.

7. This 42-year-old man has 1 CAD risk factor, so the LDL goal is <160 and the threshold for drug initiation is 190. NCEP guidelines state that drug therapy is “optional” for patients whose LDL is 160-189. Additional reasons to treat such a patient would include the presence of other (non-NCEP) risk factors such as elevated C-reactive protein or lipoprotein a. Options for drug therapy include: bile acid sequestrants (cholestyramine and colestipol), niacin, HMG CoA reductase inhibitors (or “statins”: lovastatin, pravastatin, simvastatin, atorvastatin, etc.), and fibrates (gemfibrozil and fenofibrate). The effectiveness of statins to reduce morbidity and mortality has been repeatedly demonstrated. Their proven benefit, potent impact on cholesterol levels, easy tolerability, and once-daily (bedtime) dosing make them the drugs of first choice for most patients in spite of their cost. Niacin was also shown to reduce 15-year all-cause mortality in the Coronary Drug Project trial, and it is cheap. However, several daily doses and careful dose escalation are needed to reach the 2-3 gram/d required. Patients with primary elevations of triglyceride (diabetics, metabolic syndrome) are often treated with a fibrate as a first line agent.

Colorectal Cancer Screening

1. False Positive Results. **Bleeding** from any GI source, even minor gastritis from aspirin or NSAIDs, other than adenomatous polyps or colorectal cancer and the ingestion of **peroxidase**-containing foods (horseradish, turnips, melons) are the most important causes of false-positive results. Patients are also advised to avoid eating red meat. **Rehydration** of hemocult slides prior to guaiac testing increases sensitivity and reduces specificity (more false positives).
False-negative results. **Intermittent bleeding** is the rule with cancers. Furthermore, blood is not distributed evenly throughout stool, so **sampling error** may occur. **Dietary antioxidants** (especially vitamin C) may interfere with the testing reaction, and samples that have been held an extended period prior to testing may not react. Note that iron does not cause false positive guaiac tests.

The sensitivity of FOBT is 30-40%. Four large high quality randomized controlled trials have found that biennial FOBT reduces the mortality from colorectal cancer by 15-21% over 8-13 years. There have only been case control studies that suggest that screening sigmoidoscopy and colonoscopy reduce colorectal cancer mortality.

The use of a single FOBT sample obtained from digital rectal exam in the office is a poor screening test (Collins et al, Ann Intern Med 2005;142:81-85). This single test has a sensitivity of 4.9%, a positive likelihood ratio of 1.68 and a negative likelihood ratio of 0.98 for detecting advanced neoplasia (i.e. a negative test does not change the likelihood at all of a patient having advanced neoplasia).

2. The principal limitations of flexible sigmoidoscopy are its cost and the fact that it can only view the distal 60cm of the colon, from which only 40-65% of cancers and 65-75% of polyps originate. A study by Lieberman et al (N Engl J Med 2001;345(8):555-60), 2885 patients underwent screening with a one time FOBT (x3) followed by a colonoscopy. Sigmoidoscopy was defined as findings in the distal 60cm of the colonoscopy exam in this study. The sigmoidoscopy exam would have identified 70% of cases of advanced neoplasia. Sigmoidoscopy plus FOBT identified 75.8% of advanced neoplasia and the combined strategy would result in fewer overall endoscopies (if FOBT was positive patients would go straight to colonoscopy, if sigmoidoscopy alone identified an adenomatous polyp then the patient had to have a follow up colonoscopy). Sigmoidoscopy + FOBT would miss about 25% of all advanced neoplasias. Potential complications of sigmoidoscopy include perforation and bleeding. Both are rare, occurring in approximately 1/10,000 sigmoidoscopies.
3. Colonoscopy is the most accurate screening method and should be recommended for any patient willing to accept the inconvenience and discomfort. Older age, a positive family history, and a history of adenomatous polyps of any size are associated with a higher risk of proximal neoplasia. Patients with these risk factors should be considered for screening with colonoscopy. The main drawbacks of colonoscopy are the cost, need for sedation, and a greater risk of serious bleeding and perforation requiring surgery, this is about 0.1%.
4. The “number needed to treat” (NNT) is the inverse of the absolute risk reduction between the treated and untreated groups. In this case, $1/(0.0029) = 345$ people. This means that the average primary care provider would have to screen their entire panel annually for 13 years to prevent one death from colon cancer.

Extra credit

5. Positive predictive value is defined as the proportion of patients with positive hemocult results who actually have colorectal cancer. To answer this question, set up a 2 x 2 box using the known prevalence of disease and sensitivity and specificity of the test in this population. Then solve for PPV.

For example, if the prevalence of colorectal cancer is 0.5%, 5 patients in 1000 would have the disease and 995 would not (**these numbers are placed in the lowest row**). Based on a sensitivity of 33%, testing would only detect 1.67 (0.33×5) true positives and 3.33 would be false negative (**left column**). Because the specificity is 95%, there would be 945 true negatives ($x/995 = 0.95$; solve for x; $x = 945$) and 50 false positives. Then solve for PPV: $TP / (TP + FP) = 3.2\%$.

		Colorectal Cancer (prevalence 0.5%)		
		+	-	
Hemocult	Positive	1.67	50	51.67
	Negative	3.33	945	948.33
		5	995	1000

$$\text{PPV} = 1.67 / (1.67 + 50) = 3.2\%$$

$$\text{NPV} = 945 / (945 + 3.33) = 99.6\%$$

Repeating the process in a screening population with a disease prevalence of 5% demonstrates the powerful influence on predictive values. As prevalence increases, PPV rises and NPV falls.

		Colorectal Cancer (prevalence 5.0%)		
		+	-	
Hemocult	Positive	16.7	47.5	64.2
	Negative	33.3	902.5	935.8
		50	950	1000

$$\text{PPV} = 16.7 / (16.7 + 47.5) = 26\%$$

$$\text{NPV} = 902.5 / (902.5 + 33.3) = 96.4\%$$

The actual PPV of hemocult testing in the general population is 2.2%. This means that only 1 person out of 50 with a positive result actually has cancer. Clearly, a more efficient and accurate screening method for colorectal cancer is needed.