2006

The Science of Prevention Strategies

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From newborn screening for Phenylkentonurea (PKU) and the birth dose of Hepatitis B vaccine to prostate and breast cancer screening and pneumococcal immunization for older adults, the science of health maintenance is multi-tiered and spans the lifetime of an individual. Primary, secondary, and tertiary prevention strategies are used in concert with each other to enable healthcare professionals and their patients to sustain and improve the quality of life.

Primary Prevention

Primary prevention mainly involves interventions that are designed to reduce the occurrence of a particular disease. For example, immunizations are given year round to both adults and children to prevent infectious diseases. Folic acid is recommended to pregnant mothers to reduce the incidence of spinal cord defects in their newborns. In each of these strategies, the person does not yet have the disease we are trying to prevent and in most cases, may not even have any risk factors (e.g. polio vaccination of children). However, in some cases, vaccination may be used to prevent or mitigate comorbid conditions. For example, people with diabetes should be offered the pneumococcal vaccine as they are at increased risk of complications from pneumococcal pneumonia.

Secondary Prevention

Secondary prevention is targeted at detecting disease in individuals who may not yet be symptomatic. For example, osteoporosis, which is often referred to as the "silent disease," causes a progressive deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Since low bone mass has been shown to be highly predicative of future fracture risk, one preventative strategy includes using bone mineral density (BMD) scans to screen patients for decreased bone mass. While central dual-energy X-ray absorptiometry (DXA) of the femoral neck is currently the gold standard for diagnosis of osteoporosis, peripheral tests are useful preliminary screening tools that can help identify people who may have osteoporosis.[1,2] As such, pharmacists can play a critical role in identification and referral of patients at risk for osteoporosis through pharmacy based-BMD screening.

In recent years, many pharmacists have also launched point-of-care screening programs to detect other health conditions such as diabetes, high cholesterol and hypertension. The widespread use of blood glucose meters, for example, has identified millions of people with elevated fasting plasma blood glucose (FPG) indicative of diabetes, before they were ever detected by a physician. It is important to note that screening differs from diagnosis. A diagnosis can only be made by a clinician licensed to diagnose, which a pharmacist is not. The results of screening tests, however, often are the first step to establishing a medical diagnosis. A diagnosis is usually made during an examination when patients are symptomatic for the disease and/or more definitive tests support the diagnosis. For example, a skin test (purified protein derivative (PPD)) positive for tuberculosis (TB) would indicate a patient has been exposed to the disease, but a chest x-ray, sputum samples, and a physical exam would be needed to make the diagnosis of active TB.

The importance of disease screening programs has long been advocated by the public health sector. In recent years, as community pharmacies have been undergoing a transformation from product-orientated services to patient-orientated services, more pharmacists are beginning to

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Figure 1: Considerations in Planning a Screening Program

1. The disease or condition being screened should be a major medical problem.
2. Acceptable treatment should be available for individuals with the disease who are discovered through the screening process.
3. Access to health care facilities and services for follow-up should be available.
4. The disease should have a recognized course, with early and late stages of the disease being identifiable.
5. Tests and testing procedures should be acceptable to the general public.
6. The natural history of the disease should be adequately understood.
7. Policies and procedures should be determined to know who should be referred for further testing or treatment.
8. The process should be simple enough to encourage large groups of people to participate.
9. Screening should not be an occasional activity; it should be conducted on an ongoing basis

see the value of screening for disease in their practice sites. Since community pharmacists see a wide variety of people in varying states of health on a daily basis, they are in a good position to identify patients at risk for diseases such as diabetes, hyperlipidemia, and hypertension. While screening programs generally involve the application of relatively simple and inexpensive tests, it important to first recognize and appreciate some of the fundamental key elements that form the basis behind screening.

Screening Programs

A number of criteria must be considered before a decision is made to implement a screening program. To begin with, there are three different types of screening programs.

Multiphasic screening

Multiphasic screening is defined as the use of two or more screening tests together among large groups of people to screen for more than one disease. For example, health fairs that conduct blood glucose, cholesterol, and blood pressure screening could give a better point-in-time cardiovascular risk assessment for people.

Mass screening

Mass screening simply refers to a screening test applied to a large population without regard to risk factors. For example, setting up a blood glucose check in the mall and then screening everyone who inquires. This will likely yield less abnormal blood glucose values, but is relatively inexpensive and easy to set-up. In fact, the U.S. Preventive Services Task Force [3] and the American Diabetes Association (ADA)[4] do not recommend mass blood glucose screenings in asymptomatic individuals. This is because there are many false positives when the test is applied to the general population, which has about a 7% prevalence of diabetes, and there is insufficient evidence to support its cost effectiveness. The U.S. Preventative Task Force suggests that screening in high risk individuals (i.e. family history of diabetes, BMI ^{3}25 kg/m^2, etc) is more likely to identify individuals who would benefit from early detection and treatment.

Selective Screening

Selective screening (also known as targeted screening) is applied to subsets of the population that are known to be at high risk for a disease or certain condition based on risk factors, such as family history, age, race, environmental exposures, etc. This form of screening would likely yield the greatest number of positive individuals, but requires that some people be turned away because they don't meet criteria. In fact, by increasing the prevalence of a disease (i.e. screening in individuals with risk factors), the positive predicative value (the proportion of people with a disease that screen positive for a disease) of a test will increase. Pharmacists who engage in screening programs should select patients based on risk factors (either patient identified or from prescriptions suggestive of comorbid risk factors). Some other factors that are important to consider when planning a screening program for a large population are listed in Figure 1.

Once a decision has been made to implement a screening program, the next important issue to consider is what measuring instrument is necessary for the screening. Ideally, a good screening test should be simple, rapid, safe and inexpensive. Some examples of commonly used instruments are questionnaires, point of care analyzers (e.g. blood glucose meter), and equipment such as a blood pressure cuff and sphygnomometer.

Screening Test Accuracy

Arguably the most important aspect of a screening test is its accuracy. Accuracy, also known as validity, measures how close the screening test result comes to the gold standard for that lab value. For example, the FDA allows up to a 20% deviation from the true value for blood glucose meters. Reliability, or precision, is defined as the degree to which a measure or a result can be replicated. It is usually measured by performing two or more independent measurements and then comparing the findings. Lack of reliability is often due to human error, such as performing manual blood pressure on an individual by different people or if the test value naturally fluctuates, such as blood pressure.

Any screening test can give you an incorrect result. The direction of the error is important. Screening tests are used to classify individuals as having or not having a specific disease. As such, true positives refer to those who test positive for a disease and who actually have the disease. On the other hand, people who test positive but do not have the disease are called false positive. True negatives refer to those who test negative and do not have the disease while people who test negative but have the disease are called false negatives. Figure 2 represents graphically this concept.

Sensitivity and Specificity of Tests

Once these four measures of validity are obtained, one can determine the sensitivity and specificity of the test. The sensitivity of a test is the proportion of correct results among people who actually have the disease. The specificity of a test is the proportion of correct results among people who do not actually have the disease. There is a relationship between sensitivity and specificity when considering the cutoff points for a given test. Unlike the predictive value of a test, sensitivity and specificity are not affected by the prevalence of a disease. A cutoff point is the level above which you would say the test result is positive. Unfortunately, most diseases do not have an absolute line where you can divide those with disease and those without 100% of the

Figure 2: Classification of a Test Result

	Disease	**No Disease**
Screen Positive	a True Positive	b False Positive
Screen Negative	c False Negative	d True Negative

Sensitivity + Specificity = Validity
Accuracy = (a+d)/(a+b+c+d)

Table 1. Pharmacist Provided Screenings in the Community Setting

Screening	Example of Screening Tools	Target Values				Reference
Blood Glucose	Any Glucometer	**Relationship to Food**	**Normal**	**Impaired Fasting Glucose**	**Diabetes[1]**	Diabetes Care 28:S37-S42, 2005
		Fasting Plasma Glucose[2]	<100 mg/dl	100–125 mg/dl	≥126 mg/dl	
		[1] Provisional diabetes diagnosis needs to be confirmed with history and physical [2] Fasting defined as no caloric intake in the last 8 hours				
Blood Pressure	Blood pressure cuff and sphygnomometer	**Systolic (mm Hg)**	**Diastolic (mm Hg)**	**Classification**		Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure JAMA 2003; 289: 2560-2572
		< 120	< 80	Normal		
		120-139	80-89	Pre-Hypertension		
		140-159	90-99	Stage 1 Hypertension		
		≥160	≥100	Stage 2 Hypertension		
Cholesterol	Cholestech LDX or any other point-of care screening machine	**Cholesterol Type**	**Result (mg/dl)**	**Classification**		Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110 (2):227-39.
		Total Cholesterol	< 200	Desirable		
			200-239	Borderline high		
			> 240	High		
		LDL	< 100	Optimal		
			100-129	Near optimal/Above optimal		
			130-159	Borderline high		
			160-189	High		
			> 190	Very High		
		HDL	< 40	Undesirable		
			³ 60	Desirable		
		Triglycerides	< 150	Normal		
			150-199	Borderline high		
			200-499	High		
			³ 500	Very high		
Bone Density	Achilles Express®, Achilles InSight®, QUS-2®	**BMD [(1)] T-score**		**Fracture risk**		T-score classified by World Health Organization, however, T-score breakdown may vary depending on ultrasound machine used.
		Normal T > -1.0		Low		
		Osteopenia T –1 to –2.5		Medium		
		Osteoporosis T <-2.5		High		
		[(1)] Bone Mineral Density				

time. The establishment of such cutoff points is a critical part of planning an effective screening program. For example, the FPG for a given patient may be in the high range for a population even though that person may not be diabetic. Similarly, some diabetic individuals who are at the lower end of the curve for the diseased group may also have blood glucose values in the high normal range. This kind of a distribution creates an overlap such that some healthy individuals may have elevated blood glucose, and some diabetic patients may have glucose levels in the lower range for the abnormal group. The challenge now is to determine where to set the cut off points to maximize both specificity and sensitivity. If we were to improve sensitivity, the cut point used to classify individuals as diabetic should be moved farther in the range of those that are not diabetic (e.g. using 100 mg/dl instead of 126 mg/dl for FPG). Keep in mind, the higher you set the cutoff, the more false negatives you will get. With a very serious, rapidly progressive disease where a definitive test is available, you might be content to screen a lot of people positive who really don't have the disease (false positive) rather than miss a few who really have the disease (false negative). Diabetes doesn't have a different definitive second stage test (e.g. chest x-ray after a positive PPD) and is not a rapidly progressive disease. Thus, the cutoff for FPG screening is generally set at ³100 mg/dl which still errors on the side of low false negatives, but is not too low as to send an unacceptable number of people to their physicians for a diabetes work-up who don't have diabetes. The category of FPG at 100-125 mg/dl is also known as impaired fasting glucose (i.e. "pre-diabetes"). For diagnostic purposes, the level of 126 mg/dl on different days with an associated risk factor is used. Table 1 gives the ADA recommendations for screening cutoffs. However, if specificity was the focus, the cut point should be moved further in the range typically associated with the disease (i.e. a higher cutoff). Consider the traumatic emotional implications of a false positive for an HIV test. When considering blood-glucose meters, keep in mind the accuracy and precision listed on the package insert are the machine compared to a laboratory standard, not actually to the diagnosis of diabetes or non-diabetes. However, blood glucose is assumed to be an excellent proxy for diabetes.

Since point-of-care devices that measure analytes can become imprecise or inaccurate, quality control is important to maintain. The Clinical Laboratory Improvement Act (CLIA) was established in 1988 and regulates certain testing equipment and testing sites.[5] This law was established to help ensure that patients' lab test results are accurate, reliable, and timely regardless of where they are performed. The law defines a laboratory as "any facility that performs laboratory testing on specimens derived from humans for the purpose of providing information for the diagnosis, prevention, treatment of disease, or assessment of health". Three categories of tests have been established: waived complexity, moderate complexity (including the subcategory of provider-performed microscopy), and high complexity. Waived tests refer to tests that are generally "safe for home use" and are simple and accurate as to render likelihood of erroneous results negligible. Pharmacies and pharmacists will only perform waived

complexity tests. Examples of tests granted waived status under CLIA include blood glucose monitoring devices, ovulation tests, and home drug tests (e.g. marijuana). All waived laboratories must also enroll in CLIA and pay the applicable fee. Under the good laboratory practices, CLIA lab procedures must include the following: maintaining a proper physical environment, follow manufacturers' instructions, quality control (QC) procedures, documentation of test results, and proper disposal of biohazardous waste. California further defines the implementation of CLIA in Business and Professions Code Section 1244. Some of the more restrictive provisions require the pharmacist to establish a supervisory committee consisting of a physician and licensed laboratory technologist.

The quality control measures required under CLIA could reasonable include use of control solutions and using correct strip code numbers for blood glucose meters. If your strip and meter return a value outside the control solution range, discard the strips and try another batch before replacing the meter. Better means of ensuring quality control for blood glucose meters would be to use linearity solutions that verify your meter's results over a range of blood glucose values and parallel testing of clinical samples with laboratory values. Your laboratory technologist in your supervisory committee should be able to conduct the latter testing in their laboratory for you.

Tertiary Prevention

Unlike primary and secondary prevention, tertiary prevention includes activities designed to reduce the complications of chronic diseases. An example of this type of prevention is physical therapy after an injury or aspirin for post myocardial infarction patients. Figure 3 illustrates the full spectrum of prevention strategies using diabetes.

It is clear that from health to disease, we have many chances to intervene and prevent an individual from going to the next stage. With the recent focus on medication therapy management, we should remember the age old adage that "an ounce of prevention is worth a pound of cure."

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Figure 3. Stages of Disease and Prevention Strategies for Diabetes