



## Clinical Practice



### Predictive Values: What Do They Tell Us?

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Tests. More tests. And repeated tests. In our healthy patients who desire preventive health care, what kind of information do screening tests really provide? Most patients assume they are healthy, and want confirmation that they are healthy by having normal screening tests. An abnormal screening test generates reactions of surprise, guilt, anxiety, and worry both for the patient and for those in the patient's societal network.

A screening test offers neither confirmation of being healthy nor confirmation of illness. A screening test provides an "odds"; it gives "chances," "likelihoods," and "probabilities" of being normal or having disease. An abnormal screening test must be followed up with diagnostic tests whose results also offer only odds, chances, likelihoods, and probabilities of being normal or having disease.

Our job as physicians is to determine how close to zero or 100% the chances are of a patient having disease, and to pick a threshold probability of having disease at which we act, intervene, and treat.

In the case of cervical cancer, two tests are used in the process of screening. The tests offer different pieces of information that contribute to the chances of having cervical cancer. Cytology is the morphological identification of the most superficial cells desquamating from the cervical epithelium. Cytology testing is reported as normal, ASCUS, LSIL, HSIL, ASC-H, AIS, or SCC. The diseases that cytology testing attempts to identify are normal, virally infected epithelium (HPV, CIN 1), precancerous (CIN 2/3), and cancer (squamous, adenosquamous, or adenocarcinoma).

### HPV Testing

HPV testing in its current form is a DNA test of the mucous material sampled from the desquamated superficial cells of the cervical epithelium. The presence or absence of at least one, but not all, oncogenic HPV types that are known to cause cancer indicates whether there is an oncogenic actively replicating episomal HPV infection in the genital tract. HPV is incapable of replicating if already integrated into the human genome as it is in CIN 2/3 or cancer. Persistent oncogenic HPV infection can lead to genital cancers if not treated.

The test sensitivity and specificity give a certain "likelihood" or "probability" that the woman has cervical cancer. Or, that the woman has an HPV infection; or that she has a CIN 2/3 lesion. Likewise, these "post-test probabilities" also differ by individual women because each woman brings her own set of risk factors, past history, and current symptoms that determine the chances of her having cancer (or HPV infection, or CIN 2/3) before she is even tested ("pre-test probability").

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### Pap Testing

When our clinical question is “Does this woman have cervical cancer?” as she presents to our office, we immediately start to assess her risk of cervical cancer. We decide what her pre-test probability of having cancer is. We do this by assessing her risk factors (e.g., oral contraceptive use, number of lifetime sexual partners, past history of other sexually transmitted infection), her past screening history (e.g., any past abnormal Pap tests or positive HPV tests), and whether she has symptoms currently (e.g., discharge, postcoital bleeding). Often our assessment is that her chances of having cervical cancer are low; a pre-test probability under 5%. Once we have the results of the screening test, we revise our thoughts about how likely it is that she has cervical cancer. If the Pap test indicates squamous cell carcinoma, the sensitivity and specificity of the Pap test are such that the post-test probability that she has cancer soars to over 90%, well above a threshold for suspicion at which we, as physicians, would intervene (calculations use Bayes Theorem; see reference for more details). If, on the other hand, her Pap test was reported as normal, the post-test probability that she has cancer drops even lower than her pre-test probability to about 2%, leading us to counsel the woman that she does not have cervical cancer.

For the same woman, if our question is instead, “Does she have a CIN 2/3 lesion?” her pre-test probability does not change; it is the same: under 5%. If her Pap test indicates HSIL, then her post-test probability that she has CIN 2/3 exceeds 30%, again above a threshold probability at which we as physicians would act to intervene. Table 1 lists an example of post-test probabilities of being normal, having CIN 1, CIN 2/3, or cancer based on the corresponding conventional cytology diagnosis, or cutoff of diagnoses.

**Table 1.** Individual Post-test Probabilities of Having Cervical Disease Dependent on the Cytology Diagnosis and the Disease State of Interest

Pre-test Probability	Cytology Diagnosis	Disease State	Post-test Probability of Having the Disease State <sup>a</sup>	Post-test Probability of Being Normal <sup>a</sup>
5%	LSIL	CIN 1	12.3%	2.7%
5%	HSIL	CIN 2/3	30.9%	2.4%
5%	SCC	Squamous carcinoma of the cervix	90.4%	2.6%
5%	> ASCUS	Any CIN or cancer	49.0%	1.3%
5%	> LSIL	Any CIN or cancer	72.5%	1.6%

<sup>a</sup>Calculated with Bayes Theorem as presented in Sox HC, Glatt MA, Higgins MC, Marton KI. *Medical Decision Making*. Boston, MA: Butterworth-Heinemann; 1988.

Data source: Jones BA, Novis DA. Cervical biopsy-cytology correlation: a College of American Pathologists Q-Probes study of 22,412 correlations in 348 laboratories. *Arch Pathol Lab Med*. 1996;120:523-531.

The woman may have different questions to ask of you, though. She may ask, “Given that my Pap test is HSIL, what is my chance that I have a CIN 2/3 lesion?” Based on the well-screened populations used in the large CAP studies (the cervical acid phosphatase, or CAP, Pap test is a double-staining, single-slide microscopic method of correlating conventional Pap results with biopsy results), the chances that she has a CIN 2/3 lesion given her HSIL Pap result is about 75%. She is asking, “What is the positive predictive value of an HSIL result for the Pap test?”

### Positive Predictive Value

The positive predictive value (PPV) of a test changes as the prevalence of disease in the population increases or decreases, and as such is not a stable indicator of test performance in every population or for any particular woman. In one specific case where the pre-test probability of a woman having CIN

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2/3 is equivalent to a prevalence of CIN 2/3, then the post-test probability of her having CIN 2/3 is equivalent to the PPV.

For example, a study shows that for any conventional Pap test abnormality of ASCUS or worse in a population whose prevalence of CIN 2+ (CIN 2 disease or worse) is 30/100,000, the sensitivity is 76%, the specificity is 96%, and the PPV is 16% for CIN 2+. Your patient presents to you and you feel that based on your history and exam her probability of having CIN 2+ is also 30/100,000 before you do your Pap test. If she has any Pap abnormality of ASCUS or worse, then with an abnormal Pap test result the post-test probability of her having CIN 2 or worse is the PPV of 16%. Your decision now is whether this 16% is above your threshold to recommend further workup. Current professional society guidelines do consider 16% to be a sufficiently high post-test probability to warrant colposcopy and biopsy.

As seen in Table 2, the PPV of a conventional Pap test for detecting CIN 2/3 and cancer disease taken at the cytology result of atypical or worse is 16% in a well-screened population, but rises to 38% in an unscreened population. The PPV is dynamically variable as the prevalence of disease in the population changes.

**Table 2.** Positive Predictive Values of Screening Tests Vary by Population Screened, Cytology Diagnosis, and Disease State of Interest

Population Screened	Cytology Diagnosis	Disease State	Positive Predictive Value	Negative Predictive Value
Well screened <sup>a</sup>	LSIL	CIN 1	67.0%	71.4%
Well screened <sup>a</sup>	HSIL	CIN 2/3	75.0%	85.7%
Well screened <sup>a</sup>	SCC	Squamous carcinoma of the cervix	67.7%	99.4%
Well screened <sup>b</sup>	> ASCUS	CIN 2/3 or cancer	15.8%	97.5%
Unscreened <sup>c</sup>	> ASCUS	CIN 2/3 or cancer	37.9%	97.7%
Well screened <sup>b</sup>	> LSIL	CIN 2/3 or cancer	34.0%	97.3%
Well screened <sup>b</sup>	> LSIL	Any CIN or cancer	36.0%	92.2%

<sup>a</sup>Jones BA, Novis DA. Cervical biopsy-cytology correlation: a College of American Pathologists Q-Probes study of 22,412 correlations in 348 laboratories. Arch Pathol Lab Med. 1996;120:523-531.

<sup>b</sup>Cuzick J, Szarewski A, Cubie H, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet. December 6, 2003;362(9399):1871-1876.

<sup>c</sup>Almonte M, Ferreccio C, Winkler JL, et al. Cervical screening by visual inspection, HPV testing, liquid-based and conventional cytology in Amazonian Peru. Int J Cancer. August 15, 2007;121(4):796-802.

Similarly, the cutoff used for the test result and the endpoint chosen for disease detection influence the PPV. Let's look at how the PPV changes when the cutoff used for the test result is changed.

Unlike cholesterol testing, where the results are scaled numbers, the Pap test results are categories of severity. A single Pap test diagnosis can be the test result of interest, or a combination of Pap test results grouped by severity can be the cutoff used for the test result. The most broad cutoff for Pap test reports is anything abnormal versus normal; in other words, a report of ASCUS, LSIL, HSIL, AIS, adenocarcinoma, or squamous cell carcinoma would be considered a cutoff of "ASCUS or worse." In the example in Table 2, the Pap test cutoff was ASCUS or worse, the disease endpoint was CIN 2/3 or cancer, the population was well screened, and the corresponding PPV was 16%. When the conventional cytology test cutoff is changed to LSIL or worse (instead of atypical or worse) for detection of a CIN 2/3 or cancer lesion in a well-screened population, the PPV increases to 34%.

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Likewise, when the endpoint chosen for the disease detection changes from CIN 2/3 or cancer to a more robust endpoint of any histologic CIN disease including cancer, and the Pap test cutoff remains at LSIL or worse in a well-screened population, the PPV rises to 36%. Table 2 shows how the PPV changes with different test results/cutoffs, different disease endpoints, and different prevalences of disease within the populations screened. Without noting these factors, the PPV is meaningless. Your next patient's Pap was normal, instead of HSIL. An educated patient might ask, "What is my chance of truly being normal, given that the Pap is normal?" She is looking for reassurance that her normal result means she does not have CIN 2/3. In this case, she is asking what is the "negative predictive value" (NPV). One data set from a well-screened population indicates the NPV is 86%. She has an 86% chance that she truly is normal, and does not have CIN 2/3, given her normal Pap test result.

### Negative Predictive Value

The bottom half of Table 2 shows that our current screening tests look for the combination of CIN 2/3 and cancer using any abnormal cytology reading (ASCUS or worse). Under this scenario the NPV is very high. The NPV, as the PPV, is not a discriminating indicator of how well cervical cancer screening tests perform due to their subjectivity to the populations and algorithms for follow-up embedded in the defining studies.

The sensitivity and specificity of the tests offer a more rigorous interpretation of how well the proposed tests will perform in a population for a particular disease state using particular cutoff levels for the screening test. The sensitivity and specificity of the tests allow you as the physician to revise your estimates from your initial assessment (pre-test probability) of her probability of having a CIN 2+ lesion with the results of the screening tests to arrive at a post-test probability of having CIN 2+ disease. It is then your medical decision whether this post-test probability exceeds your professional threshold to recommend further diagnostic workup. Most physicians recommend further diagnostic workup (e.g., colposcopy and biopsy) when the abnormal screening test bumps the woman's post-test probability above 15%.

The sensitivity and specificity of the tests are often combined into one number called the likelihood ratio (LR). This allows us to balance the two pieces of information that sensitivity and specificity provide. The greater the LR of a positive test and the smaller the LR of a negative test, the more discriminating the screening test is. Predictive values of screening tests offer less useful information for clinical decision making.

In summary, as new tests for cervical cancer screening are refined and developed, physicians may discern their usefulness to clinical decision making by the following characteristics:

- the population in which the study was performed (e.g., well screened, unscreened);
- the disease entity being identified by the gold standard of histology (e.g., any CIN, only cancer, CIN 2+);
- the different gradations of abnormality the screening test offers (e.g., cytology interpretations and cutoffs, relative light unit (RLU) cutoff values for Hybrid Capture II high-risk HPV testing (Digene, Gaithersburg, MD, USA), viral load cutoff values, other measures of HPV infectivity);
- the test characteristics of the screening test (e.g., sensitivity and specificity);
- the predictive values of the screening test for the defined population under study.

Almonte M, Ferreccio C, Winkler JL, et al. Cervical screening by visual inspection, HPV testing, liquid-based and conventional cytology in Amazonian Peru. *Int J Cancer*. August 15, 2007;121(4):796-802.

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