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A Suggested Approach To Simplify and Improve Cervical Screening in the United States

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Abstract

Cervical cancer prevention strategies in the United States have become complicated and even controversial, despite advanced understanding of carcinogenic human papillomavirus (HPV) infection as the necessary causal agent. Twenty years ago, etiologic and methodologic studies had already yielded two powerful preventive approaches. There are excellent vaccines to prevent the most carcinogenic types of HPV infection; reduced HPV endemicity will ultimately prevent a large fraction of cervical precancer and cancers. For prevention of cervical cancer in the interim, sensitive HPV tests that target women at risk of cancer, by detection of the DNA/RNA of approximately a dozen carcinogenic HPV types, permit early diagnosis and treatment of precancers.

While HPV vaccines and tests have continued to improve, implementation of these new HPV-based prevention methods has been relatively slow in the United States and in most places worldwide. Increasing vaccination rates is the clearest and most vital long-term priority. But, for decades to come, screening will also be important. To promote useful discussion, this commentary will raise some current critical issues in simplifying and speeding the rational introduction of HPV molecular methods into U.S. cervical screening.

Introduction to the currently confusing state of U.S. cervical screening

There is widespread and growing confusion and controversy (1–3) about cervical screening in the United States. Women and their providers face an expanding number of competing screening and triage approaches (4). Although a wealth of testing options can now provide unprecedented, “precision” prediction of cervical precancer risk as a surrogate endpoint for cancer risk (5, 6), the loss of simplicity and uniformity of our public health message (“Get your annual Pap”) is hindering movement to improved testing technology and strategies.

In the current state of flux, national guidelines and less formal guidance offer an overabundance of options and rather complex algorithms, based on cytology alone, cytology combined with HPV testing (cotesting) or, most recently, stand-alone HPV testing (7–10).

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The opinions expressed here are the personal views of the authors and do not necessarily represent the views of the U.S. National Cancer Institute. Some off-label and unapproved uses of diagnostic tests are discussed.

Stand-alone HPV testing is only approved for one specific HPV test (10), but more FDA approvals for this indication are very likely to follow.

There is debate regarding both negative and positive screening results, complicated by the co-existence of the several different test options. Most prominently, there is considerable resistance to the 5-year screening interval recommended for a negative cotest (both cytology and HPV negative) (1). The management of positive screening results is equally unresolved. While it is widely acknowledged that positive HPV tests require triage rather than universal, immediate colposcopic referral, the optimal triage methods are undecided and quite varied. Possible triage methods include cytology (3, 9–13) and related methods (e.g., p16/Ki67 dual staining)(14), HPV genotyping in various configurations (8, 10, 15), and other promising novel technologies including redesigned automated cytology (as presented by Schiffman et al. at the 30th International Papillomavirus Conference in 2015) and biomarkers like methylation (16–18). The multiple screening/triage combinations need to be better validated in large prospective studies and, in the absence of sufficient information, they have not been addressed in formal guidelines.

Moreover, cervical screening is a lifelong process rather than a single testing visit, further raising the level of complexity (5). For the subset of women needing management of positive findings, repeated testing with varying test methods makes interpretation of results more challenging. Most clinicians likely will find it increasingly difficult to integrate in “real-time” the full detail of available different kinds of test results, over multiple rounds of testing. In short, the effectiveness of cervical screening in the United States could be threatened by excessive and increasing complexity.

Although the current state of confusion is widely recognized, achieving more unified and widely accepted approaches to cervical screening in the U.S. will take considerable, concerted effort. Many important practical factors (e.g., cost, societal emphasis on safety, established laboratory and clinical practice patterns, and outdated quality metrics based on annual cytology) influence how U.S. women are screened. Scientifically demonstrated effectiveness is only one consideration in choosing between available strategies. Nonetheless, a discussion of relevant scientific evidence is a good place to begin; accordingly, the following discussion offers some research-backed suggestions for simplification as HPV testing enters U.S. screening programs.

Societal acceptance of a low but non-zero level of cancer risk

Screening simply cannot provide complete safety against cervical cancer, even if we were to adopt frequently repeated HPV-cytology cotesting starting in adolescence, at the cost of massive overtreatment (7, 8). For example, there are rare rapidly progressive cancers in very young women (19), uncommon cotest-negative cancers (20), and deep canal lesions that escape detection and progress, despite careful protocols. In deciding on screening strategies, we must explicitly accept low, non-zero risk levels. No group holds the sole expertise in setting the acceptable level. To re-iterate a fundamental point: societal understanding that a small number of cancers will unfortunately still occur in the presence of good cervical

screening is a precondition to devising rational screening and management guidelines that balance safety and overtreatment.

The goal of cervical screening programs: diagnosing and treating precancer to prevent cancer

Strictly speaking, “screening” applies to women at presumed low general population risk of disease, while “management” applies to the actions taken after a positive screen. An HPV or cytologic test can be done in either setting. Most discussions of screening *programs*, including this one, address both population screening and management of abnormal results.

The primary goal of cervical cancer screening programs in the U.S. is *not* to find invasive cancer. Rather, the goal is to prevent cervical cancer by detecting and treating true cancer precursors (which for this presentation will be called “precancer”). Precancer is the subset of high-grade intraepithelial lesions, or CIN3/AIS, or whatever terms are used in the prevailing classification scheme, which would progress to invasive cancer if left untreated. Treatment of a lesion not destined to progress to morbid cancer is overtreatment (21). Just as perfect safety is unachievable, overtreatment is unavoidable, although we hope to limit it while maintaining acceptable safety. Deciding on the right balance is critical to setting screening intervals (because overtesting can lead to overtreatment) and making management guidelines.

For example, one ongoing debate is how long to wait for the next routine visit after a negative screen (1, 7, 8), which is a non-scientific question of societal or personal tolerance of small risks, and the value assigned to avoiding such risks. An ideal cervical screening interval would lead to meaningfully large numbers of detected true precancers but virtually no cancers. Finding very few true precancers per screen implies that the screening interval may be too short. Finding too many invasive cancers implies that the interval may be too long. The exact balance must be discussed and decided.

Simplified view of HPV natural history and the stages in cervical cancer development

It is important to agree on how to view the disease process that cervical screening is designed to interrupt. Many diagnostic terms are used in various cervical screening programs; however, the key stages in cervical carcinogenesis can be conceived of simply as *normal cervix*, *high-risk HPV infection*, *precancer*, and *cancer* [Figure 1, top row] (22). Each stage of cervical carcinogenesis has a characteristic age distribution; the characteristic age curves can be viewed as proxies for time since cervical HPV acquisition, which occurs mainly in adolescence and early adulthood (22). Each stage logically links to a corresponding clinical action. In the absence of diagnostic error, the stages can be viewed conceptually as follows: (i) Women without current HPV infection of one or more of the dozen high-risk (also called carcinogenic or oncogenic) HPV types (23) are at virtually zero risk of having concurrent cervical cancer and are at ultra-low risk for the next several years (24–26). HPV negativity should lead to continued routine screening at extended intervals. (ii) Only women testing positive for current infection from carcinogenic HPV types

(HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) require intensified management. The high-risk types are genetically related and restricted to a few species groups within the alpha genus of HPV (27). These infections as a group are nonetheless extremely common and almost always “clear” within 1–2 years (28, 29). At any age, newly-appearing cervical HPV infections are most likely to clear, while the longer an HPV infection persists (remains detectable on one of the standard DNA/RNA assays), the more likely the infection will continue to persist, associated with a high long-term risk of precancer (25, 29, 30). The theoretically ideal response to HPV infection without precancer would be to retest at an interval that permits the major proportion of infections to clear, e.g., 2 years. In practice, it is difficult for woman and their providers to wait that long and prolonged follow-up intervals risk loss-to-followup; therefore, return testing at about 1 year is currently recommended (8).

Predicting the immediate risk and subsequent outcome of infections is currently the major challenge in cervical screening. Two principles are worth emphasizing: as part of minimizing overdiagnosis and overtreatment, the carcinogenic type group must be defined as those types causing invasive cancer, not precancer (which can be caused by a larger group of types) (31, 32). Second, within the high-risk group, the 13 carcinogenic HPV types vary greatly in carcinogenic strength, from the uniquely strong (HPV16) to the marginal (e.g., HPV51) (31, 33).

The task of defining which infections place a woman at risk, while most are benign, is made more challenging by our difficulty in defining true precancers. We presently do not have a way to distinguish a precancer that will invade from one that will not (34). Pragmatically, all currently used definitions of precancer represent some overdiagnosis, by including a majority that will not progress to cancer. Thus, cervical precancer remains a heterogeneous classification as defined by current colposcopic biopsy methods (35) and, while it is the best diagnostic method we currently have, it remains an imperfect surrogate endpoint for cancer.

Diagnostic categories compared with the four underlying stages of carcinogenesis

We need to understand the strengths and weaknesses of each cervical testing method (histopathology from colposcopically-directed biopsy, cytology, and HPV testing) in determining whether the true state of the cervix is normal, HPV infection, precancer, or cancer.

Histopathologic diagnoses

Moving from top to bottom in Figure 1, we rely primarily on histopathologic diagnosis from colposcopically-directed biopsy to define whether precancer or cancer is present. Histopathology remains our reference diagnostic method but, nonetheless, it is misclassified on multiple levels. Histopathologic definition of precancer is especially prone to false-positive, “high-grade lesions” (CIN2 and even CIN3, noting that we know much less about AIS) that would never lead to clinically-diagnosed cancers even if untreated, as evidenced most compellingly by the very large ratios of CIN2 and CIN3 found in screening programs compared to observed lifetime risks of invasive cancer in previously unscreened populations

(36). Moreover, error in colposcopic targeting of biopsies leads to underdiagnosis and underestimates the prevalence of possibly precancerous lesions in a woman (37). At the low-grade end of the spectrum, the distinction between histopathologic diagnoses of HPV infection (CIN1 or LSIL) and non-infection (benign biopsy) is not reproducible, sensitive, or specific, severely limiting the usefulness of this category (38).

Cytologic results

Cytologic definition of the state of the cervix began in the original Papanicolaou classification as a probability of underlying cancer, but has become increasingly “diagnostic”. The Bethesda System has terms corresponding to normal (NILM), infection (LSIL), precancer (HSIL/AIS), and cancer (39); however, the accuracy of cytology at “the low end” for defining high-risk HPV infection is very low. Most high-risk infections have concurrent normal cytologic results (40), and many minor cytologic abnormalities are caused by low-risk HPV types or are unrelated to HPV (41). Moreover, a large proportion of histopathologic precancers are found among women with LSIL or equivocal LSIL (i.e., ASC-US) rather than HSIL (42).

HPV test results

High-risk type-specific or pooled HPV testing provides the reference definition of high-risk infections. However, HPV testing cannot distinguish infection from precancer or cancer. Even genotype-specific typing yields only risk associations, not unequivocal distinctions.

Phasing out unneeded and unhelpful tests, terms, and distinctions

In striving for simplified essential screening strategies, it might be time to retire some familiar but ultimately distracting details of current HPV tests, cervical cytology classifications, and histologic nomenclatures. Some might be viewed as holdovers from earlier classification schemes that predated our improved understanding of HPV natural history.

Simplifying HPV testing

First, there is no clinical reason to test for HPV infections other than the 13 high-risk types (13, 43). For the core group of proven carcinogenic types, the amount of detail given by the testing laboratory to the clinician and woman is worth careful consideration. Different HPV infections act independently and one might persist while another clears (44). There is no evidence at present that tracking them at the individual type level is clinically useful. There is some evidence for distinguishing the highest risk HPV types like HPV16. Defining the optimal amount of typing detail is an important and current research goal.

Simplifying cytologic results

There is strong evidence supporting the combination of LSIL and HPV-positive ASC-US into a diagnostic term indicating “cytologic evidence of HPV infection” (5). ASC-US represents the majority of non-normal cytologic results, but it is an unreliable characterization, has limited biological meaning (it expresses uncertainty between NILM and LSIL), and can be divided by HPV testing into normal cervix (uninfected with high-risk

HPV types, with risk similar to a negative cytology result) versus HPV infected (equivalent in risk of precancer to LSIL) (45, 46). Combining HPV-positive ASC-US and LSIL would create a relatively large category encompassing the great majority of all non-normal results, in accordance with the high prevalence of HPV infection compared with the uncommon occurrence of precancer. If HPV testing is used instead of cytology to define infection, the most useful cytologic distinctions are the severe ones that suggest underlying precancer: HSIL (with the corresponding equivocal result of ASC-H) indicates a high risk of underlying precancer, but less than 1% of women receive this result (47). According to current guidelines, women with HSIL can be treated immediately as an option (8). Of note, almost no women are classified in U.S. screening programs as having cytologic results of invasive cancer (5). Similarly, glandular results of AGC and AIS are useful when found but rare.

Simplifying histopathologic diagnoses

The recently proposed LAST nomenclature abandons altogether CIN and older nomenclatures (35), which have been shown not to reflect accurately the stages of cervical carcinogenesis. If only HPV-positive women were referred to colposcopy, pathologists could concentrate on whether the histology revealed precancer (or cancer, with such details as glandular versus squamous pathology). They would not need to focus on reporting histologic signs of HPV infection. Accordingly, the LAST proposal accepts CIN3 as true precancer (as a practical compromise until a more specific biomarker is found) and recommends p16 staining to adjudicate equivocal precancers (including CIN2). The LAST proposal will help if used as recommended to clarify CIN2 diagnoses. However, there is a risk of overusing p16 staining in CIN1 cases, with the result of upgrading and overtreating lesions that represent infections, since many CIN1 lesions are p16-positive. Consequently, judicious use of p16 staining will be necessary to bring histologic diagnosis of high-grade lesion into closest possible agreement with true underlying precancer.

Gradual replacement of cervical cytology by HPV-based strategies for primary screening

Simply put, HPV testing is the most sensitive method to distinguish the normal cervix from a high-risk HPV infection indicating appreciable risk of precancer/cancer. All major comparisons, except for studies with serious ascertainment biases (2, 3) have reported that HPV is more sensitive than cytology, predicting lower risks when negative, and holding prognostic value for longer subsequent periods (20, 48, 49).

The superior sensitivity and negative predictive value of HPV testing will likely lead to its adoption as the main primary screening method. As an interim strategy in the transition to HPV testing, cotesting might be used, but that is an expensive strategy not under consideration outside of the U.S. It has been shown quite convincingly that, among HPV-negative women, the marginal increase in reassurance achieved by adding cytology is small, approximately 0.003% lower risk of cancer over 5 years (20). While HPV-negative cancers do rarely occur, HPV test-negative, cytology-positive cotest results mainly represent HPV testing error or cytologic abnormalities (mainly ASC-US caused by low-risk HPV types or

as “look-alikes”) unrelated to cervical cancer risk (50). Eventually, the impact of HPV vaccination is likely to push screening away from cytology or cotesting to stand-alone HPV screening that includes partial typing (51, 52).

If we accept that the U.S. will eventually rely on HPV-based screening rather than cytology, then it is important to validate the best possible FDA-approved tests, and to understand how they compare in distinguishing infections from precancer. The available cross-sectional and the scant prospective comparative data indicate gross comparability of the approved tests when negative (53, 54). In other words, the most highly validated tests that have obtained or are seeking FDA approvals are roughly comparable in analytic sensitivity and prediction of low risk of underlying or subsequent precancer when negative. Thus, the similarities of the assays outweigh the differences at the first-cut level of determining whether the primary screening result should be classified as normal or abnormal (including HPV infected/precancer/cancer). This agreement across assays is much higher than the typically reported reproducibility of cervical cytology (38, 53–56). If the similar reassurance provided by approved tests is confirmed by large-scale prospective data, it will mean that it does not matter much to clinical management of negative results which validated test is used, and past medical histories will not need to distinguish which HPV test was negative.

The main uncertainties regarding HPV screening relate to the management of the less than 10% of women in the targeted age group that test positive. The high prevalence of HPV relative to the low risk that infection represents diagnosable precancer/cancer led the recent ASCCP-sponsored guidelines committee to recommend against sending all HPV-positive women to colposcopic biopsy (5, 8, 57). The results of worldwide testing of invasive cancers, including adenocarcinomas, suggest that genotyping for HPV16 and HPV18 (and perhaps HPV45) is worthwhile in guiding management (31, 33). The value of identifying more types, perhaps combined in groups according to risk of developing precancer, requires study. The newer test methods tend to include partial genotyping (58–60); in the U.S., women with the highest-risk genotypes (HPV16 and HPV18 in current guidelines) are sent immediately to colposcopy while the rest are retested in a year (8).

Even with partial genotyping, HPV screening demands a paired triage test if one wishes to avoid high rates of referral to colposcopy with low yield of precancer/cancer. The combinations include cytology (perhaps grouped in a few categories) and some promising, novel triage approaches, such as a immunocytochemical dual stain on a cytology preparation that is scored as positive or negative (14), and an automated cytologic method that be programmed to provide a severity score possibly useful for triage, (as presented by Schiffman et al. at the 30th International HPV Conference in 2015). Methylation methods would not require the preparation of a cytology slide, but are early in development (16).

The market place will not necessarily provide the optimal answer to which of the increasing number of available assays should be used for screening and triage. The required strictness and specificity of FDA approvals are creating competing “systems”, each approved with detailed specifications of collection device (swab, brush, broom), collection buffer, and testing technology. Each company with FDA-approved or pending tests has its own

approach, several of which do not include conventional cytologic screening and interpretation.

As new assays are introduced in the market, these combinations may change, but the companies are naturally inclined to seek increased market share with their proprietary combinations. Understanding the best approaches will require unbiased, publicly financed, and rigorous comparisons of HPV screening and paired triage methods. The needed head-to-head comparisons will require very large, prospective cohorts with biospecimen collections and long-term follow-up. The ability to 1) test for multiple assays from the same specimens, and 2) obtain excellent disease ascertainment in long-term follow-up permits us to address important questions about screening and management in observational studies, without requiring randomized controlled trials for every decision. Linking the performance data to costs will enable decision makers to choose between alternatives.

As one such effort, the U.S. National Cancer Institute (NCI) is conducting a trial to provide the “big data” needed to compare HPV screening and triage tests. In collaboration with Kaiser Permanente Northern California (KPNC), NCI is collecting residual cervical biospecimens from approximately 70,000 women (including 50,000 HPV-positive) cotested over the next few years. This random sample of the KPNC population will be followed actively with repeat collections for 5 years, and then passively by linkage to the KPNC electronic medical records for another 5 years. The NCI expects to compare all FDA-approved screening and triage assays using the stored aliquots. The sampling and testing schemes are beyond the scope of this discussion but the aim is simple: to provide the comparative effectiveness data needed for the next set of cervical screening guidelines. The youngest members of the cohort will include many vaccinated women, permitting consideration of that increasingly important risk modifier. A major cost-effectiveness component is incorporated. Collaboration with many other, similar projects underway throughout the world will be a priority, to achieve the sample sizes and data/specimen exchanges needed for international comparisons.

Adoption of a risk-based approach to cervical screening and management

Early cervical screening and management guidelines were based in large part on expert opinion, which invariably relied on the experts’ implicit sense of risk. In other words, the experts’ cumulative experiences led them to internal risk estimates that they used to argue for more or less intensive interventions. As a step forward, later guidelines have incorporated more transparent and explicit principles of “equal management of equal risk”, “risk thresholds”, and “benchmarking” (61). Equal management of equal risk implies that regardless of the test results leading to a particular risk, management should be the same. A good example is HPV-positive ASC-US and LSIL, which have equivalent risks and should be managed the same (or, as we propose, should be combined).

Thresholds of risk of precancer, or preferably cancer, are set for each level of management. Decisions based on estimates of immediate versus 3-year or 5-year risk tend to agree, with a few important exceptions; HPV-positive NILM tends to have low immediate risk of detecting precancer, but the risk rises sharply with follow-up as lesions grow to the level of

colposcopic detectability). The current options in the U.S. could be limited to four risk bands. Recognition that any screening result will inevitably place a woman into one of these four bands is another part of simplifying cervical screening. The bands are, in order of descending risk/intensity of management: treatment of precancer/cancer, colposcopic biopsy, enhanced (shorter interval) screening, and routine screening. When a new screening or triage test is introduced, the risks following combinations of positive and negative result can be computed, and the proper management (assignment of one of the four risk/action bands) for each combination can be benchmarked against other test combinations yielding similar risk.

Here, we are not addressing the remaining fifth action band, exiting (when risk of cervical cancer morbidity and mortality approaches zero, e.g., following benign hysterectomy or among older women after a lifetime of normal screening). We still require more prospective evidence to determine how best to exit screening in the HPV testing era; at present, enough follow-up time has not yet passed.

As another simplifying point, in the context of new screening and management guidelines, it is unclear whether any of the known etiologic cofactors for the development of cervical cancer among HPV-infected women (22) are clinically important enough to influence management. Ongoing studies are designed to address whether details of smoking status, hormonal contraceptive use, multiparity, or coinfection with other STIs (note that we are not discussing HIV-infected women) warrant altering clinical management of cervical screening results.

Impact of HPV vaccination

Although the first cohort of vaccinated young women is just now entering the age of screening, it is already evident that vaccination will speed the transition from cytology to HPV testing, specifically to testing with partial typing (62). Vaccination decreases the incidence of subsequent precancer, but only modestly reduces the total number of abnormal cytologic results (or pooled HPV typing results). Vaccine-targeted types represent the minority of the total pool of infections, including the pool of types that cause ASC-US or LSIL, which are much more common than HSIL/AIS (the specific cytologic signs of precancer). With “fewer needles in the haystack”, the positive predictive value of cytology or pooled HPV testing suffers in a vaccinated cohort (22, 63). As vaccine penetration increases and time passes, future populations will require adjustments to whatever screening is done. Screening below age 25 among vaccinated cohorts might not be needed given extremely low risk of cancer in early ages. For future public health monitoring of vaccine effectiveness and durability of protection in the U.S., using HPV tests that distinguish between vaccine-targeted and non-targeted high-risk types would be useful.

Summary of a new cervical screening paradigm: simple causal model, complex risk estimation, simplified public health and clinical practices

The major premise of this commentary is that, to escape the increasing state of confusion over cervical screening, the prevention community should use the new HPV-based test

methods to define simple risk categories that correspond to the stages of cervical carcinogenesis. In moving to a simple, biologically accurate classification scheme linked to clinical actions, the radical part might be the elimination of some current cytologic and even some histologic distinctions and terms that are no longer helpful.

An important goal of guidelines groups, in active dialogue with advocates representing those affected, should be to decide something non-scientific: the thresholds of acceptable risk linked to each of the management options. It will be necessary to address difficult issues of equipoise when risk estimates from test results are close to established risk thresholds, when there is no obviously correct choice between alternative choices (HPV-positive NILM with certain non-HPV16 types provides an example of a difficult “judgment call” as to whether colposcopy is warranted.) Once societal norms are established, regardless of tests used, the clinicians can note into which risk band a woman falls, suggesting which of the four actions (or five actions if exiting is included) they will take. As always, they can modify actions based on special circumstances, recognizing that guidelines function as suggestions not fixed policy.

Extension to women following colposcopy

Though beyond the scope of this commentary, similar issues pertain to women following colposcopy if, as is usually the case, a treatable precancer is not found. Colposcopy that does not find precancer will be an increasing occurrence as women are referred for persistent HPV positivity; such women as a group are at risk of precancer that, even if truly present, might be too early and small for visual detection. To avoid creating an even larger group of women attending colposcopy clinic, one important answer will be to increase the reassurance of negative colposcopy by increasing colposcopic sensitivity, e.g., by multiple biopsies targeting even faintly aceto white lesions (37). At the same time, although there is no existing or (to our knowledge) pending FDA-approved indication for HPV testing of women post-colposcopy, clinical guidelines will likely recommend relying on the reassurance of sequential negative stand-alone HPV testing or some form of cotesting to return women to general screening (64).

Finally, it is noteworthy that the next generations of HPV-based tests are already in sight. If we adapt to the principles of equal management of equal risk, risk thresholds, and benchmarking, we will be ready to adjust to the inevitability of further technical change in the spirit of “continuous improvement”.

Abbreviations and Acronyms

AGC	Atypical glandular cells
AIS	Adenocarcinoma in situ
ASC-H	Atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance

CIN	Cervical intraepithelial neoplasia
DNA	Deoxyribonucleic acid
FDA	U.S. Food and Drug Administration
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
KPNC	Kaiser Permanente Northern California
LAST	Lower Anogenital Squamous Terminology
LSIL	Low-grade squamous intraepithelial neoplasia
NCI	U.S. National Cancer Institute
NILM	Negative for intra-epithelial lesion or malignancy
RNA	Ribonucleic acid

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Figure 1. Comparison of Common Test Results and Categories in Cervical Screening Programs To the Stages of Cervical Cancer Development

Cervical screening programs generate a large number of terms and categories that only imperfectly correspond to the now-established stages in cervical carcinogenesis (top row). A focus on diagnosis of each stage, with simplification of terms could usefully organize available test methods and maximize concordant clinical action (rescreening at an extended interval when screening indicates a normal cervix, accelerated retesting for high-risk HPV infection, colposcopic biopsy to diagnose precancer treatable by outpatient procedures, and curative or palliative treatment of invasive cancer.) The figure indicates that no screening or diagnostic test is perfect. For example, histology, our current diagnostic reference standard, tends to overcall precancer because we cannot yet determine which severe intraepithelial microscopic abnormalities indicate that the lesion would invade if untreated (rather than regress or persist). The impact of replacing the CIN scale with LAST criteria incorporating p16 testing to clarify precancer are not yet known. In any case, histology cannot accurately distinguish HPV infection from the normal cervix. Similarly, cytologic categories are prone to misclassification of HPV status and whether infection has progressed to precancer/cancer.

HPV testing is most effective at establishing normalcy (i.e., lack of infection implying extremely low risk of precancer/cancer) but it cannot distinguish between benign infection and precancer/cancer; secondary triage tests and extended testing intervals are needed to prevent substantial overtreatment.

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