National Cancer Institute

Risk Estimation for the Next Generation of Cervical Cancer Prevention Strategies

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Outline

- The cervical cancer prevention revolution
  - Widespread use of HPV tests (+HPV type-specific tests)
  - HPV vaccine providing partial protection
  - Next-generation biomarkers: HPV RNA tests, p16 stains
- Current screening programs rely on algorithms
  - Thesis: These algorithms will no longer suffice
- Instead, use a risk estimate of cervical precancer
  - I discuss the many advantages of risk estimation
- We are building a personalized risk tool to guide the prevention of cervical cancer

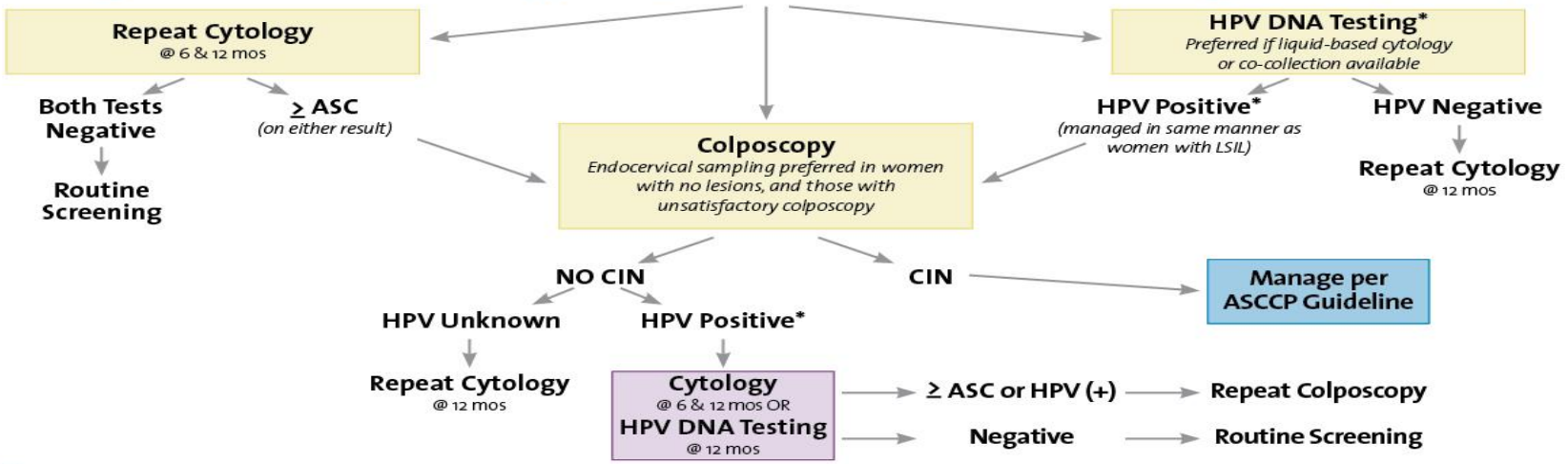
Katki et al, Lancet Oncol, 2009

Richness of Clinical Information

- Traditional
  - Repeated Cytology (Pap smear) and Histology (Colposcopically-directed biopsy)
  - HPV test triage in case of equivocal cytology
- New Biomarkers and Vaccine
  - HPV test as first-line screen (+HPV type-specific tests)
  - Next-generation biomarkers: HPV RNA tests, p16 stains
  - HPV vaccine providing partial prophylaxis
- Time-history of biomarkers is critical
  - Necessary cause: ***Persistent*** Carcinogenic HPV
  - Testing HPV+ at first visit more dangerous than testing HPV- followed by testing HPV+ in the next year
- Demographics
  - Age: HPV+ at 35 far more dangerous than HPV+ at age 25
  - Sexual behavior and Smoking

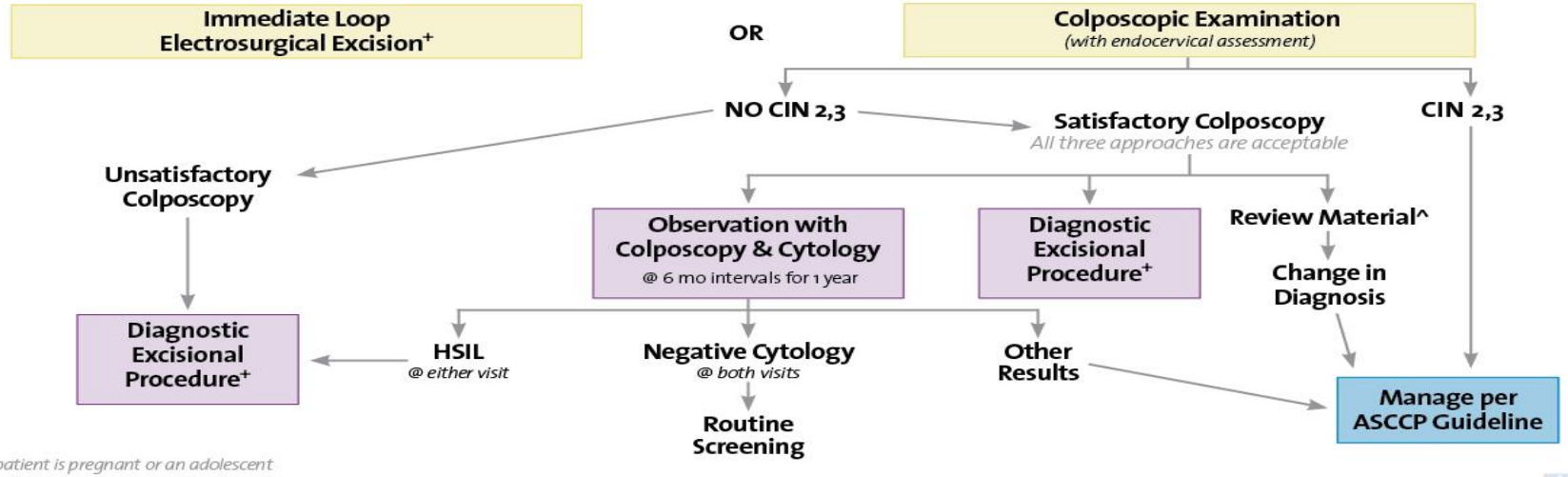
Consensus Algorithms for Decision Making

Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US)



*Test only for high-risk (oncogenic) types of HPV

Management of Women with High-grade Squamous Intraepithelial Lesion (HSIL) *



+ Not if patient is pregnant or an adolescent

^ Includes referral cytology, colposcopic findings, and all biopsies

* Management options may vary if the woman is pregnant, postmenopausal, or an adolescent

Drawbacks of Clinical Algorithms

- The # of branches escalates with # of new tests:
  - Multifold possible test results: Hard to come to consensus on appropriate clinical action
  - Hard to update: Need to revise algorithms for each new test
  - Hard to use: So complex that clinicians may be unable to comply
- Hard to incorporate continuous variables
  - Hard to incorporate HPV vaccines because the benefit of vaccination varies greatly with age
- Hides the level of evidence supporting each branch
- Cannot separate risk of cervical precancer with decisions to manage that risk to an acceptable level

Use Risk Estimate of Cervical Precancer

- Risk of developing cervical precancer (CIN3+ or CIN2+)
  - Currently, and also 1-, 3-, 5-years in the future
  - Can be computed easily in clinical practice by computer or PDA
- Information used
  - Current: age, test results, vaccination status
  - Past test results (if available) provide extra information
- Used to help decide
  - Whether to go for further diagnostic testing (especially colposcopy)
  - Whether to go for treatment by updating risk estimate with biopsy result
  - When the next screening visit should be scheduled
- Example 5-year risks of CIN3+
  - <1%: 33-years old, HPV-, cytology-
  - >80%: 33-years old, HPV+, persistent HPV16+, HSIL cytology, high-grade colposcopic impression

Castle et al, AJOG, 2007; Katki et al, Lancet Oncol, 2009

Advantages of using risk estimates

- Risk is the fundamental concept guiding clinical management
  - Risk is the basis for clinical decision-making
  - Risk boils down a complex battery of test results over time into one number
- Speeds the translation of research findings into clinical practice
  - New tests or updated evidence seamlessly added to a risk tool without requring an overhaul
- Separates risk from the subsequent decision to manage that risk
  - Simplifies and consistently applies that management
  - Ex: HPV- & ASC-US vs. NILM
- Uncertainty in risk estimate can be naturally presented
  - Risk estimates must be both powerful and accurate

Advantages of using risk estimates (2)

- Risk frees clinicians and members of Consensus Guideline committees to focus on the benefits, adverse events, and dollar costs of risk management strategies:
  - <1%: Return for screen in 5 years
  - 1%-10%: Additional diagnostic testing (e.g HPV RNA)
  - 10%-30%: Colposcopy
  - >30% & no desire for fertility: Immediate treatment
  - 30%-60% & desire fertility: Colposcopy & 6 month return
  - >60%: Immediate treatment

We are building a risk tool

- Data from HMOs, clinical trials, and observational studies
  - Kaiser-Permanente PaP Cohort: 400k women followed for 3-5 years with both HPV tests and cytology
  - ASCUS-LSIL Triage Study: Trial of 5k women followed every 6 months with all biomarkers for 2 years
  - Costa Rica Natural History Study: Longitudinal cohort of 10k women followed for 7+ years

- Each has advantages and disadvantages
  - Representativeness of real populations
  - Frequency and types of biomarker collection
  - Length of follow-up
  - Fixed follow-up times vs. risk-based follow-up times
  - Sample size

Three Components of the Risk Tool

- For estimating current risk of CIN3+ to decide whether to send to colposcopy
  - Probability of being diagnosed with CIN3+ given demographics (age) and current (and if available, past) test results (biomarker, cytology, histology)
- After colposcopy, update the risk
  - Probability of truly having CIN3+ given the histologic diagnosis and properties of the colposcopically-directed biopsy procedure
- To estimate future risk of CIN3+
  - Probability of acquiring each possible risk factor (HPV or cytologic abnormality) or current risk factors progressing/regressing in the future

Paradigm for Cancer Prevention

- Unlike other cancer risk prediction tools, why can we predict cervical precancer with sufficient power and accuracy to be used for screening?

  1. We can test for the necessary cause (HPV)
  2. We have a well-defined precancerous lesion (CIN3+)
  3. We can readily access the target organ for screening and effective treatment

- As we fulfill the above three criteria for other cancers, they will one day too be ready for large-scale prevention programs

- Cervical cancer prevention via risk estimation will be the paradigm for the rational, effective, and cost-effective way to prevent cancer