Risk Based Management of Abnormal Cervical Cancer Screening Results - The Next Guidelines Process

Richard Guido, MD

University of Pittsburgh

Magee-Womens Hospital of the PMC System

Disclosure

- ASCCP Board Member
- Inovio Pharmaceutical- DSMB consultant

Why Revise the Management Guidelines?

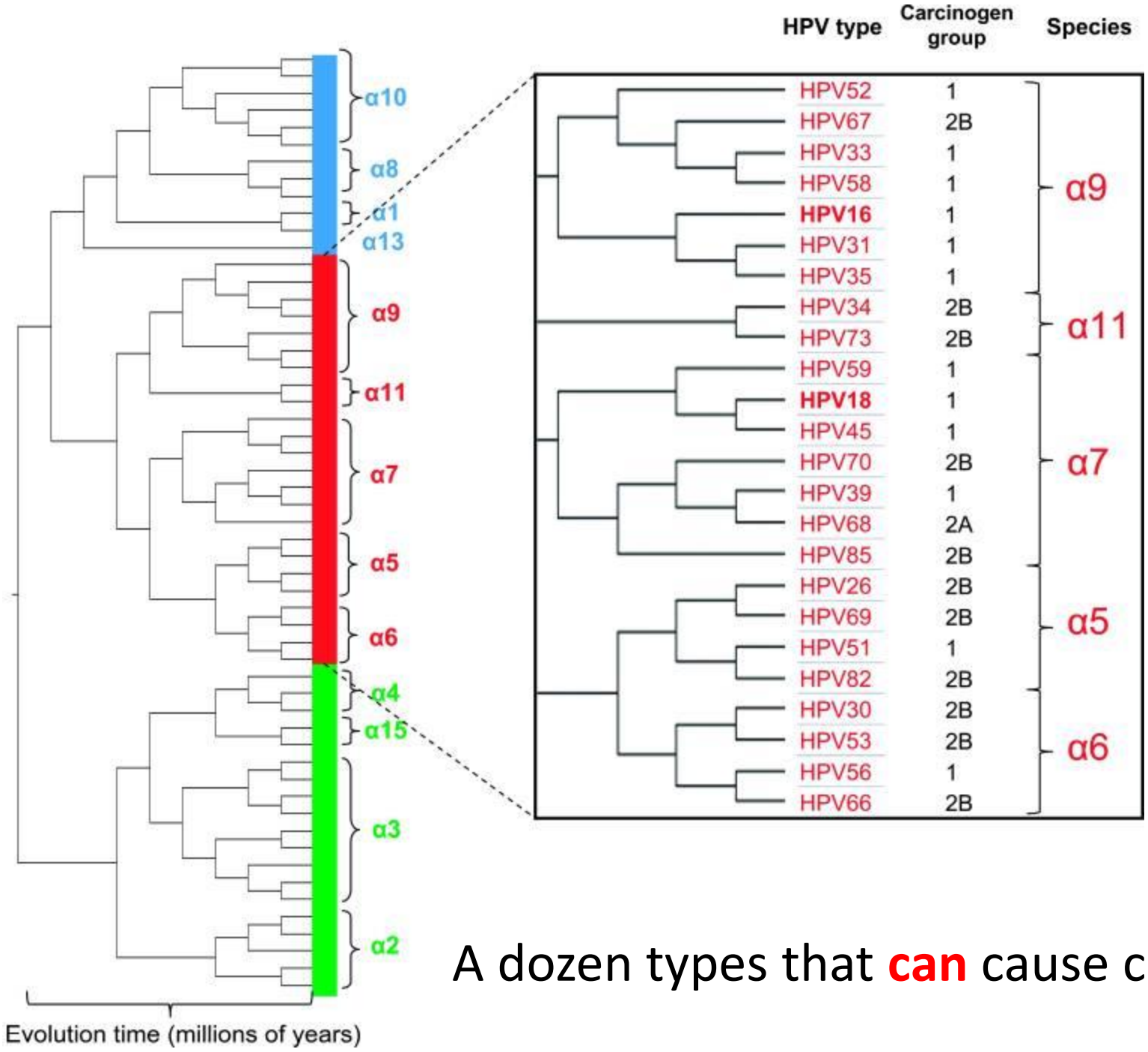
- Current guidelines are complex and difficult to follow
- A woman's past history of HPV infection, treatment, and HPV vaccination can dramatically affect her future risk of CIN3 and cancer
- Guiding principle of 2012 guidelines
  - Equal management of equal risks
- Guiding principle of 2019 guidelines
  - *Simplicity and precision*
  - *Clinical Actions based on individual risk*

Goals of the Project

- Develop clinical tools for the management of abnormal cervical cancer screening results
  - Widely available
  - Simple to use
  - Risk-Based
  - Developed via a consensus process
  - Adaptable to new technologies and data
  - Simplifies our existing guidelines
  - Incorporates key clinical and laboratory data
  - Adjust for population characteristics

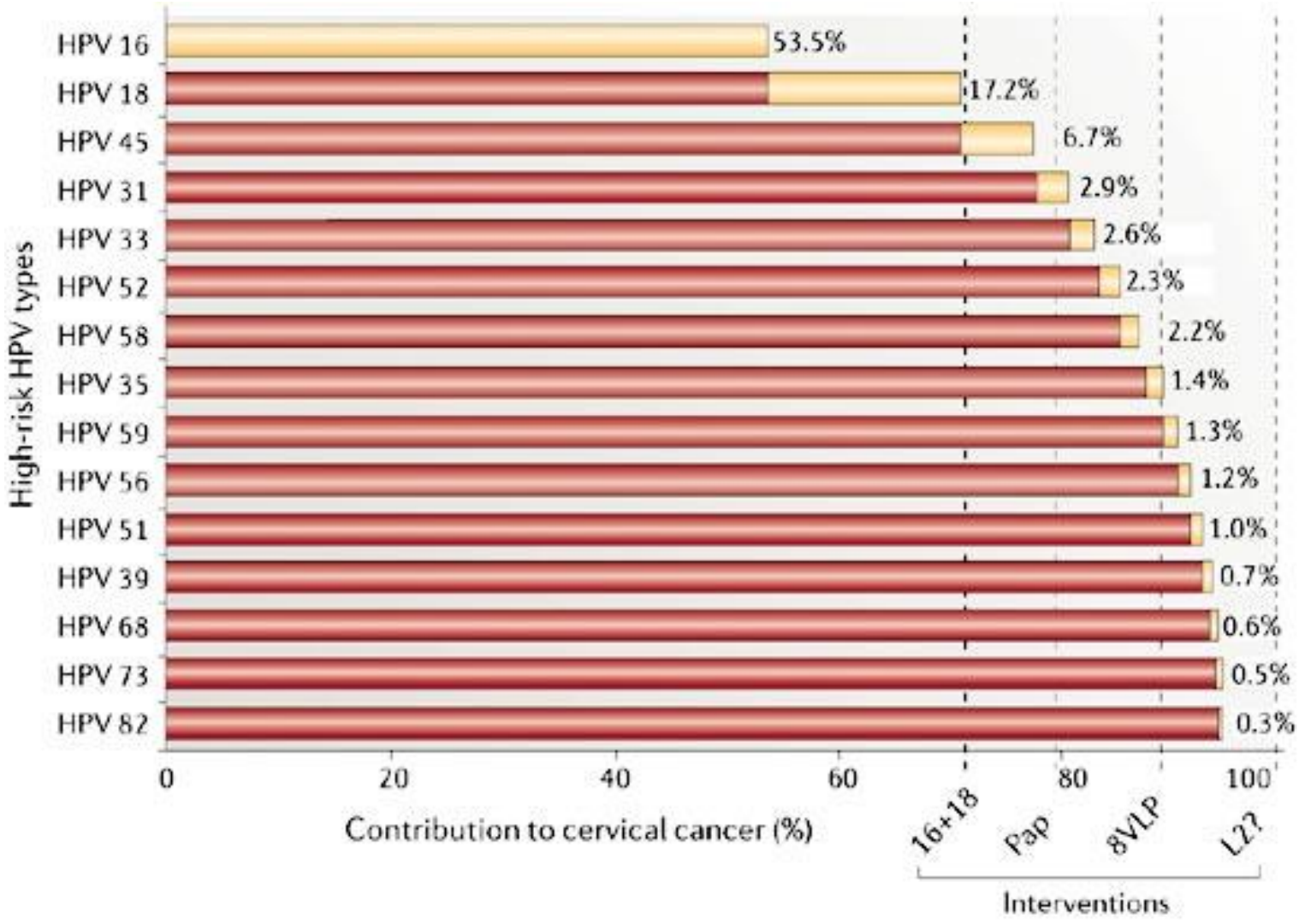
SCIENTIFIC BACKGROUND UNDERLYING RISK-BASED PARADIGM

*Understanding **how** HPV causes cervical cancer can revolutionize prevention*



A dozen types that **can** cause cancer

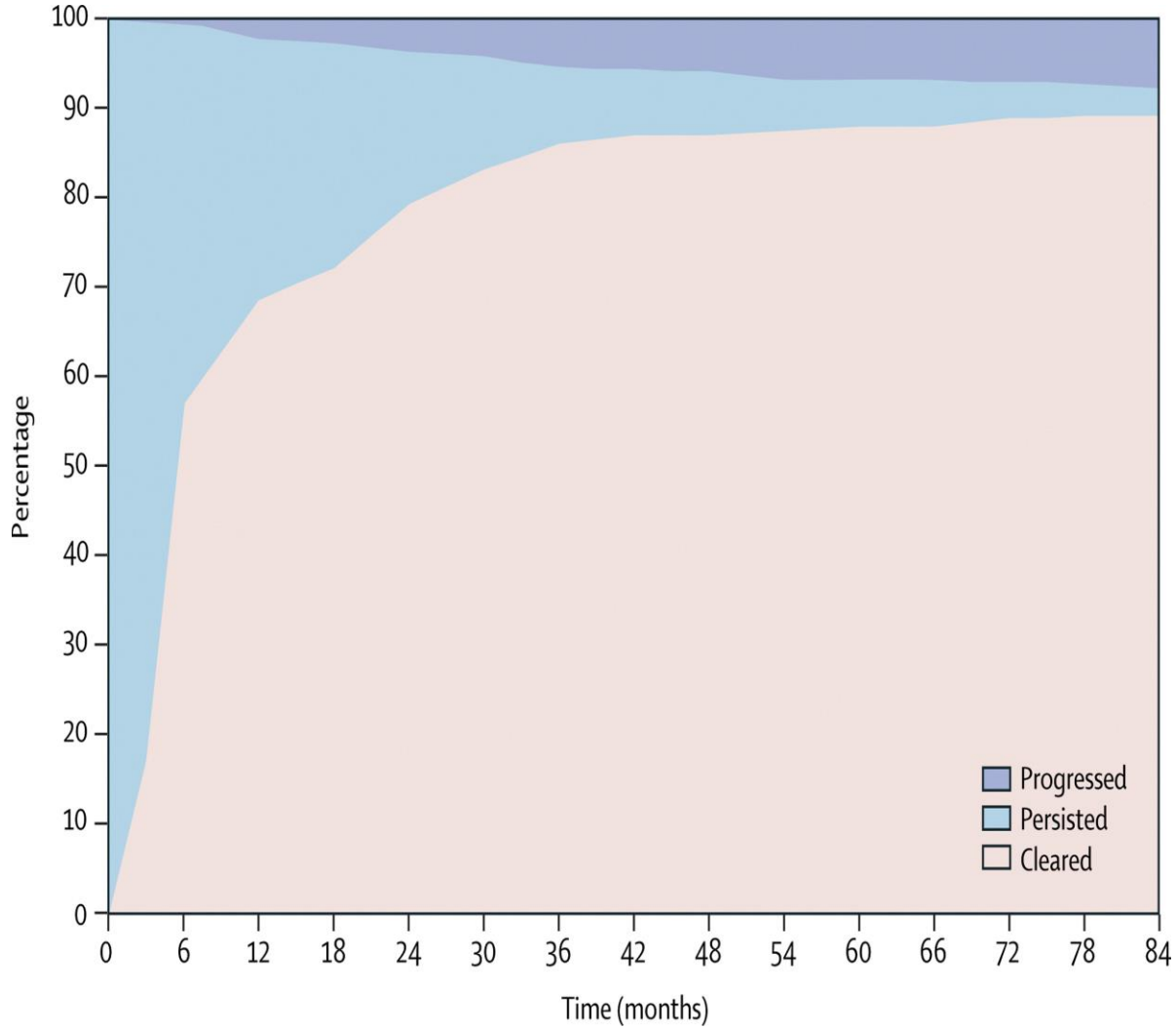
Worldwide Distribution of HPV Types in Cervical Cancer



Roden and Wu *Nature Reviews Cancer* **6**, 753–763 (October 2006) | doi:10.1038/nrc1973

nature REVIEWS CANCER

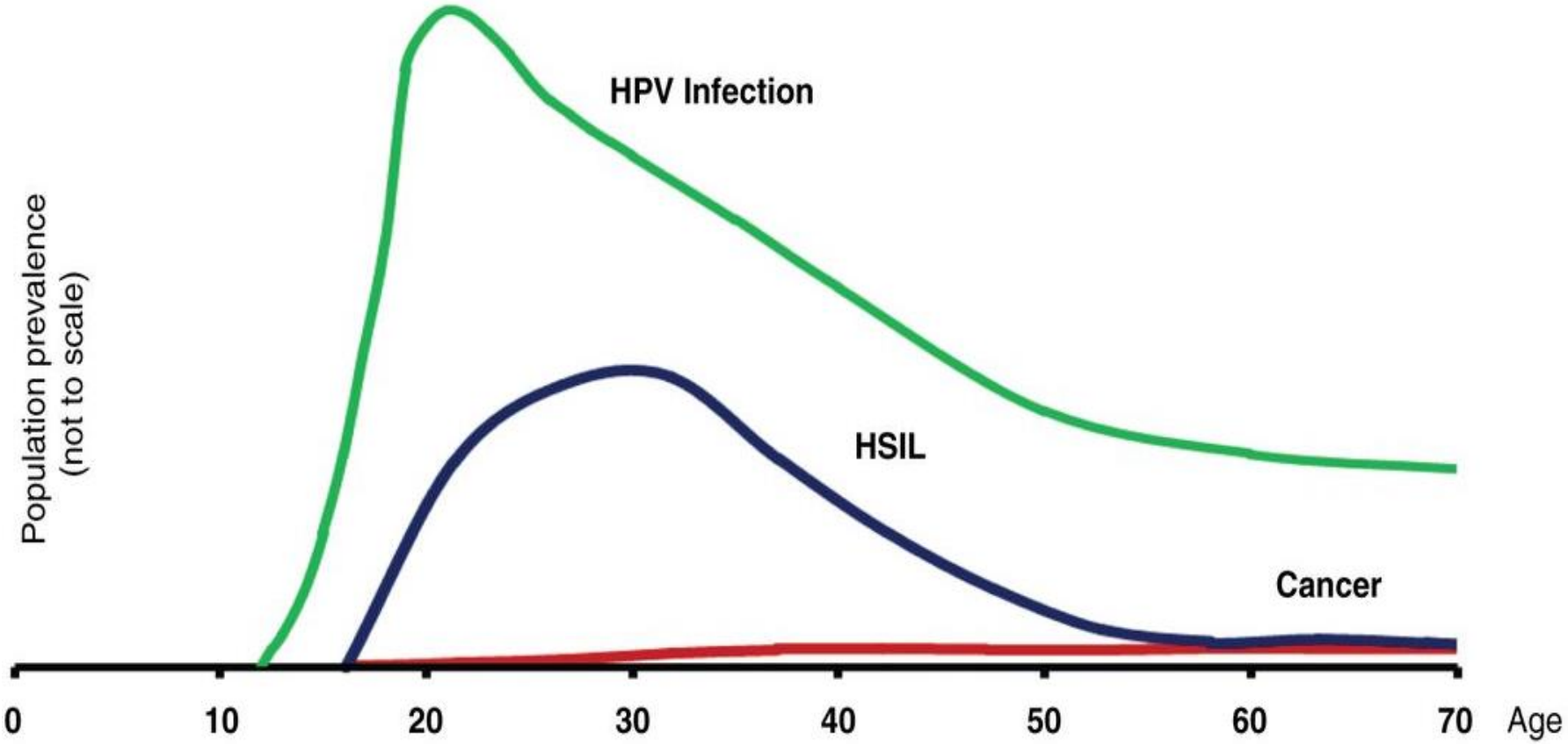
Most HPV infections clear…
those that persist cause disease over time
… knowing HPV history can predict current and future risks



How does the timeline of HPV acquisition and persistence fit into prevention?

- 75% of HPV infections that lead to cancer are acquired before age 30
  - *Vaccination can prevent 85% of infections*
- Majority of precancer (CIN3) develops ages 25-35
  - *Goal of screening is to detect precancer*
- Cancer rates begin to rise at age 40 and continue to increase with age in an unscreened population
  - *Screening should end when a woman's lifetime risk falls below agreed upon thresholds*

Current US Prevention Strategy



HPV Vaccination

Cytology (Pap) Screening with HPV triage

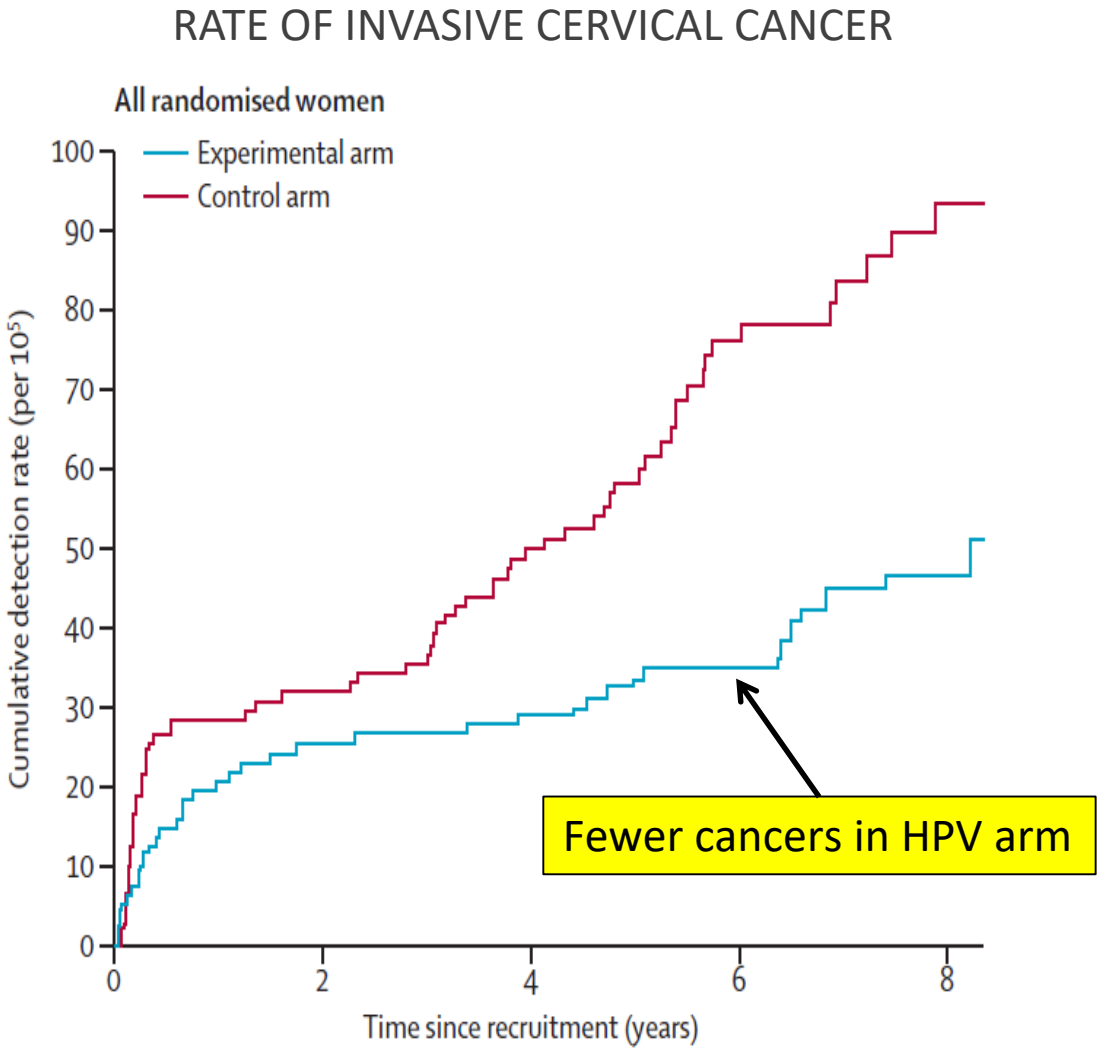
Primary HPV Screening

HPV and cytology co-testing

HPV testing prevents more cancer than cytology

because a negative HPV test is predictive of a woman's future cancer risk

- Pooled analysis of 4 European randomized trials
- 176,000 women 20 – 64 years old
- Followed for at least 2 rounds of screening, median follow-up 6.5 years



Ronco G. et al. Lancet 2014

CURRENT RESULTS AND PRIOR HISTORY PREDICT FUTURE RISK OF PRECANCER

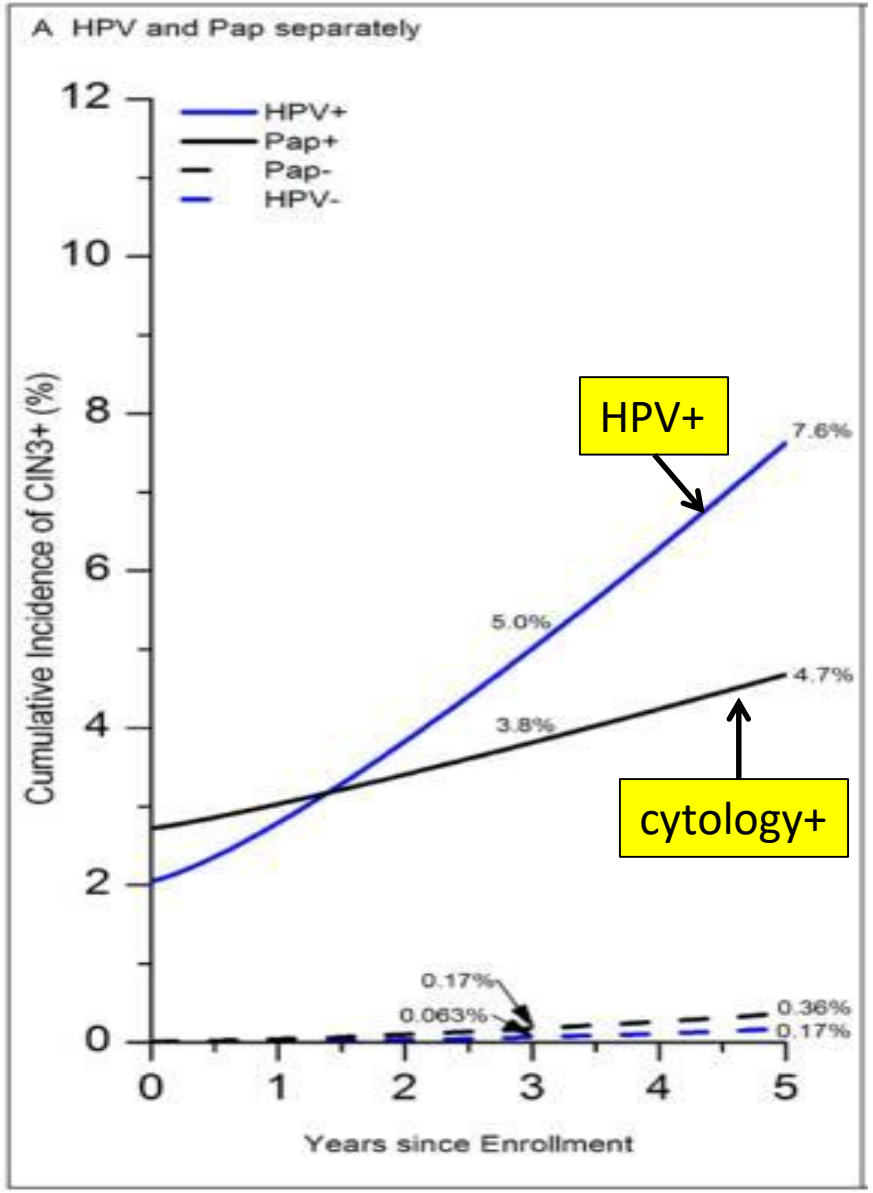
Current Cytology results predict future CIN3+ risks

Prior Pap result	5 year risk CIN3+
NILM or ASCUS HPV negative	<1%
ASCUS (unknown HPV)	3-4%
ASCUS HPV +	7-8%
LSIL	5-6%
HSIL	50%

Gage J, et al. Obstet Gynecol 2016 December; 128 (6)

HPV predicts future risk better than cytology

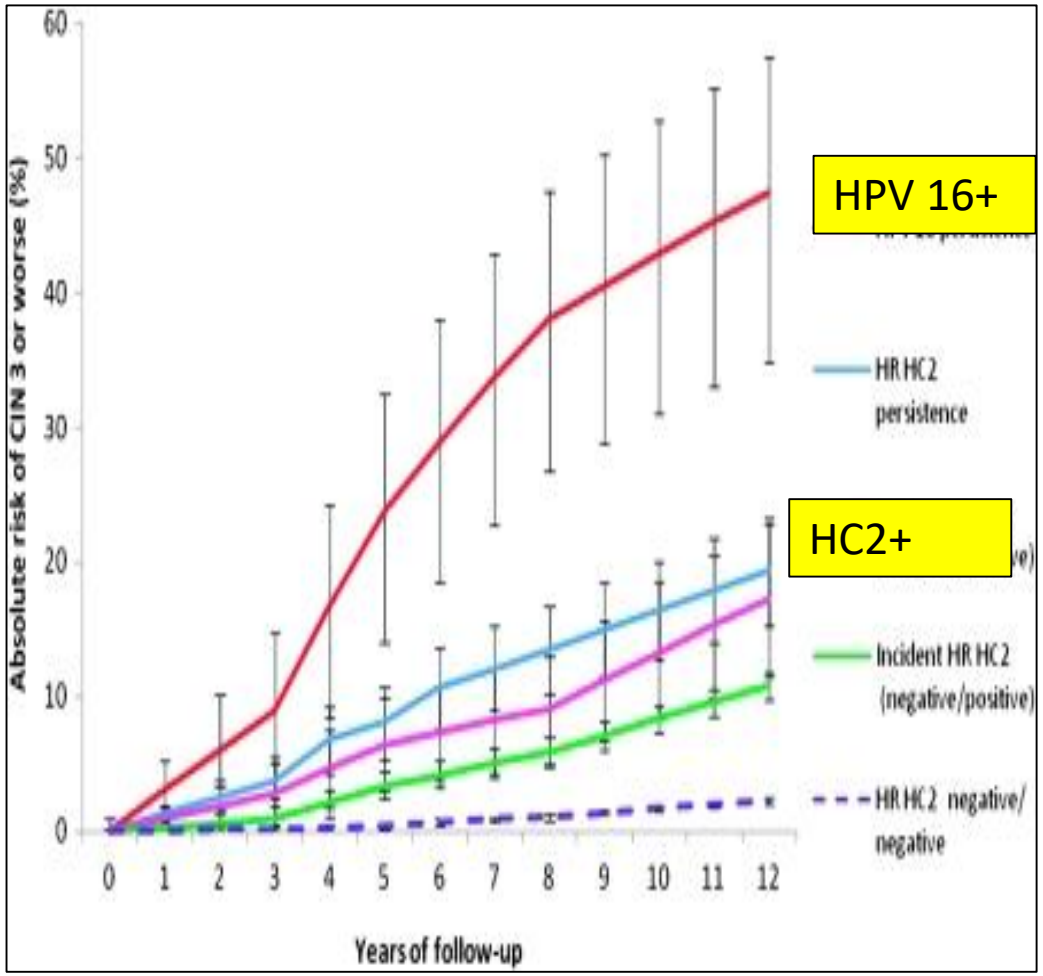
- 331,818 women over 2003-2009
- Followed for 5 years for CIN3+
- Both HPV and cytology predicted risk on the date of screening
- *HPV predicted future risk of CIN3 and cancer over 5 years*



Katki et al J Low Genit Tract Dis. 2013 Apr;17(5 Suppl 1):S28-35.

Persistent HPV is especially high risk

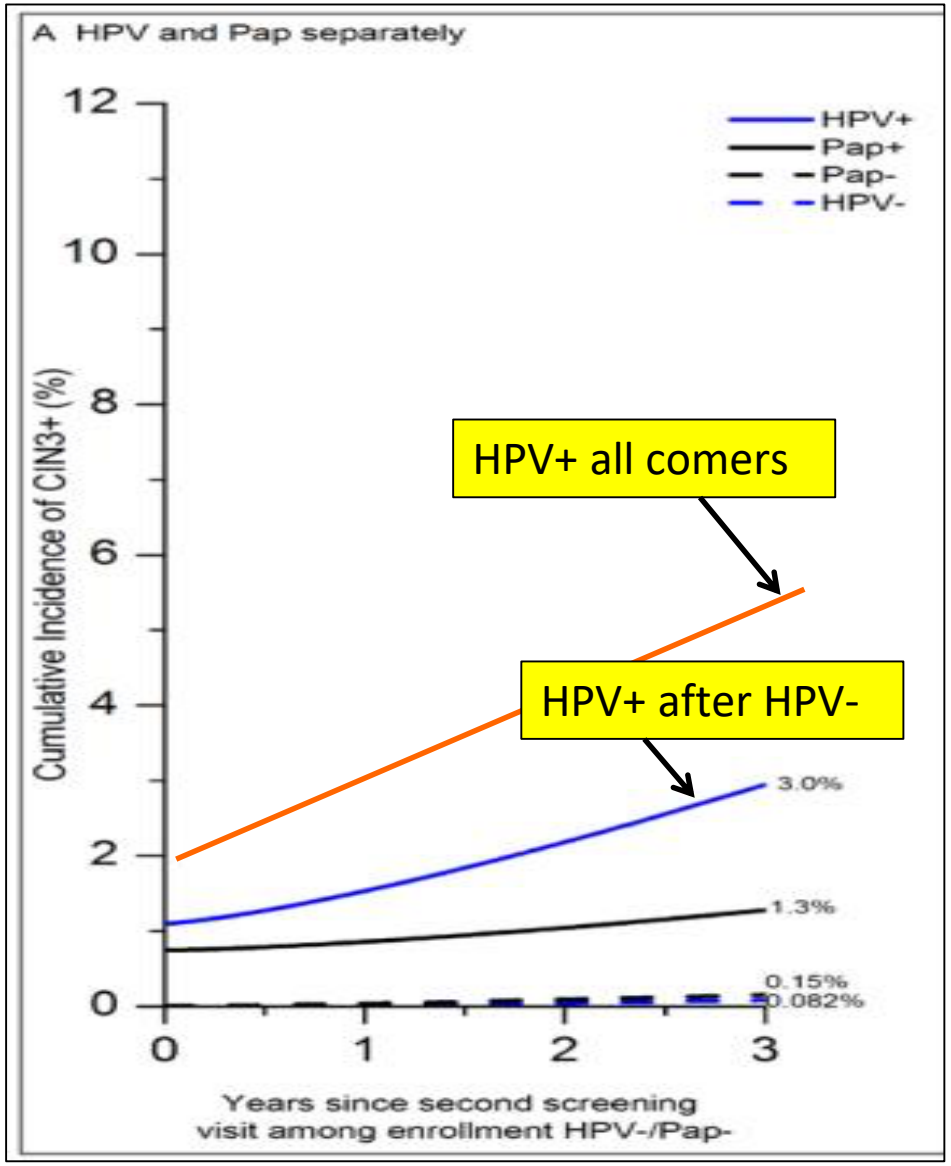
- 8656 women age 20-29 underwent co-testing 2 years apart
- Followed for 12 years for CIN3+
- Risk of CIN3+
  - 47% persistent HPV16+
  - 19% persistent HC2
  - HPV neg 2%
- *HPV history is an important risk modifier*



Kjaer, et al. J Natl Cancer Inst 2010 Oct 6; 102(19):1451-3

A new HPV infection is lower risk

- 331,818 women over 2003-2009
- Risk of CIN3+ at 3 years
  - 5% with unknown prior HPV result
  - 3% with negative prior HPV result
- *Prior negative HPV test reduced risk of CIN3 with a new HPV+ result*



Katki et al J Low Genit Tract Dis. 2013 Apr;17(5 Suppl 1):S28-35.

Prior HPV+ or unknown history is higher risk

- 26,799 women with a current positive HPV+ test and no prior CIN2+
- Cumulative CIN3+ incidence rates over 4 years among women with current HPV+/Pap neg screen
  - Past HPV-positive: 4.36
  - Past HPV-negative: 1.32
  - Past HPV- unknown: 4.67
- *Note prior HPV+ or unknown screening history have higher CIN3+ risk with the SAME current screening result*
- ***KNOWLEDGE OF THE PAST SCREENING AND RESULT HISTORY MATTERS***

Castle, P. Obstet Gynecol 2011:117:650-6;

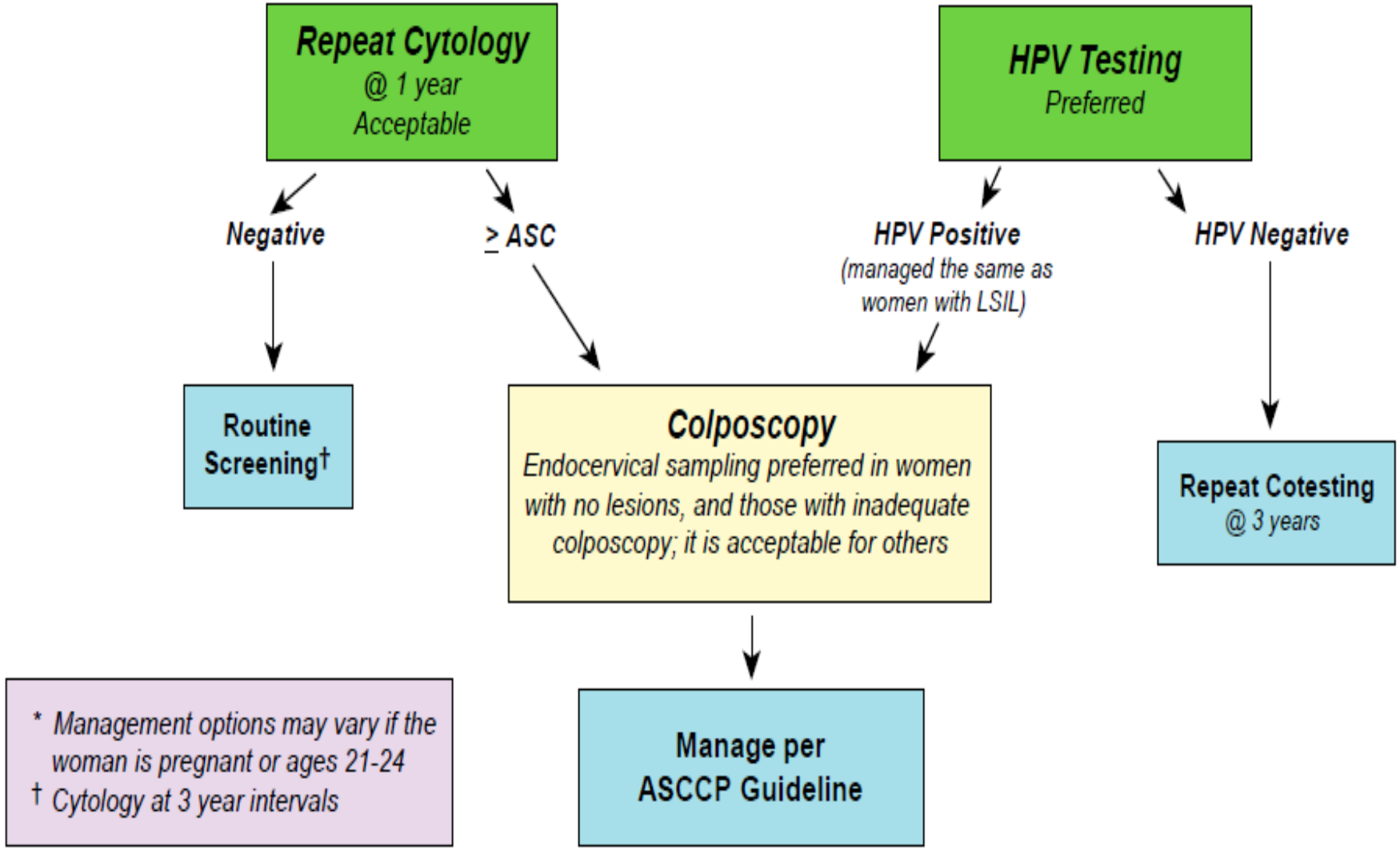
Objectives of cervical cancer screening

1) Prevent cervical cancer
2) Find cervical cancer early so it is curable
3) Decrease testing and treatment that won't prevent cancer and may cause reproductive harm

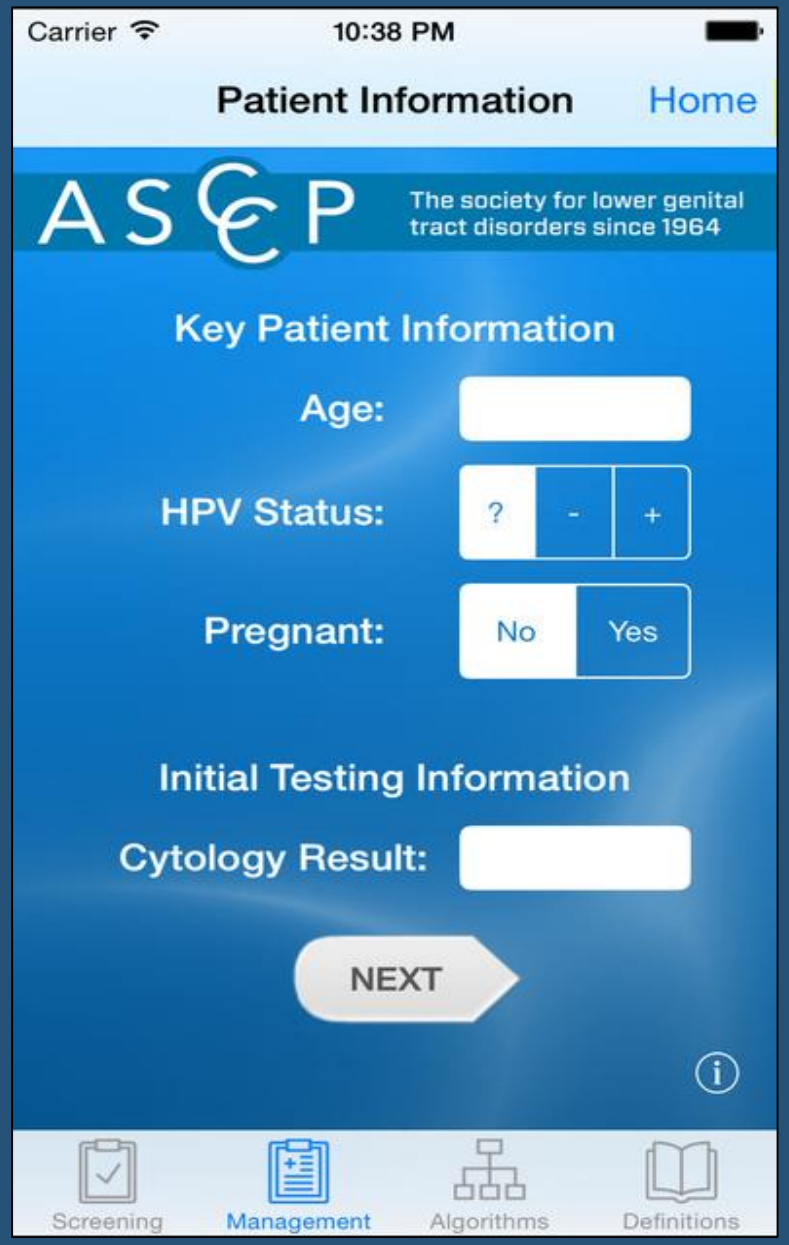
Risk based testing should allow better precancer detection in high risk women, and fewer procedures in low-risk women

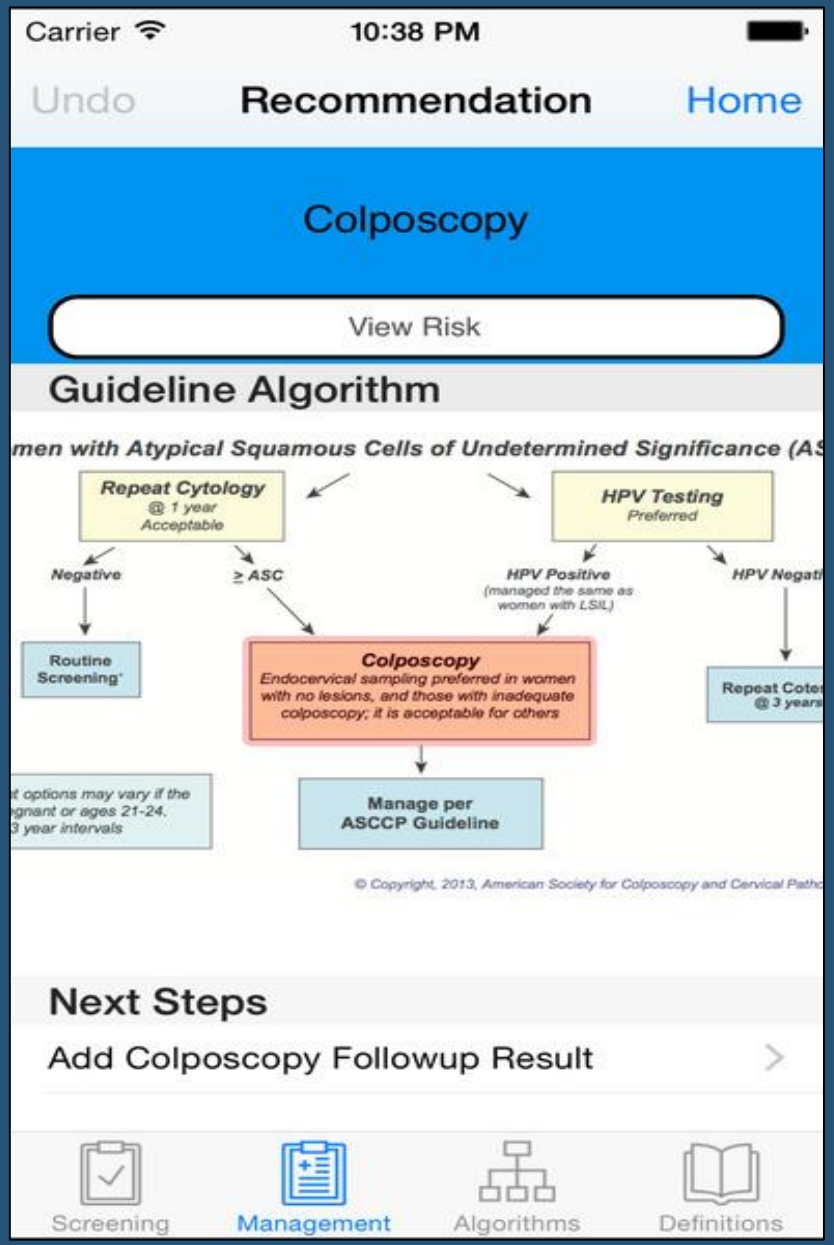
Current risk-Based management

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



Current ASCCP application

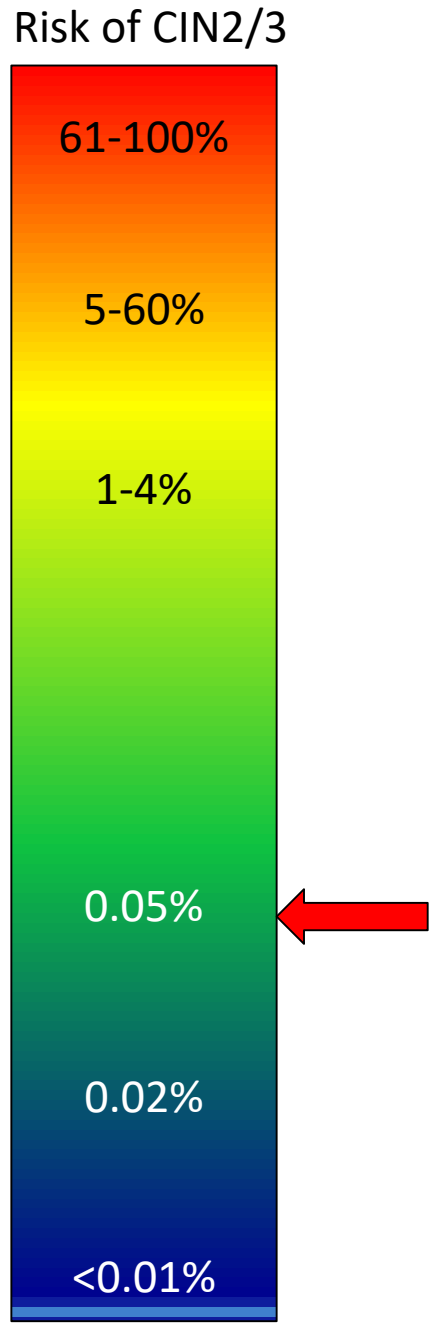


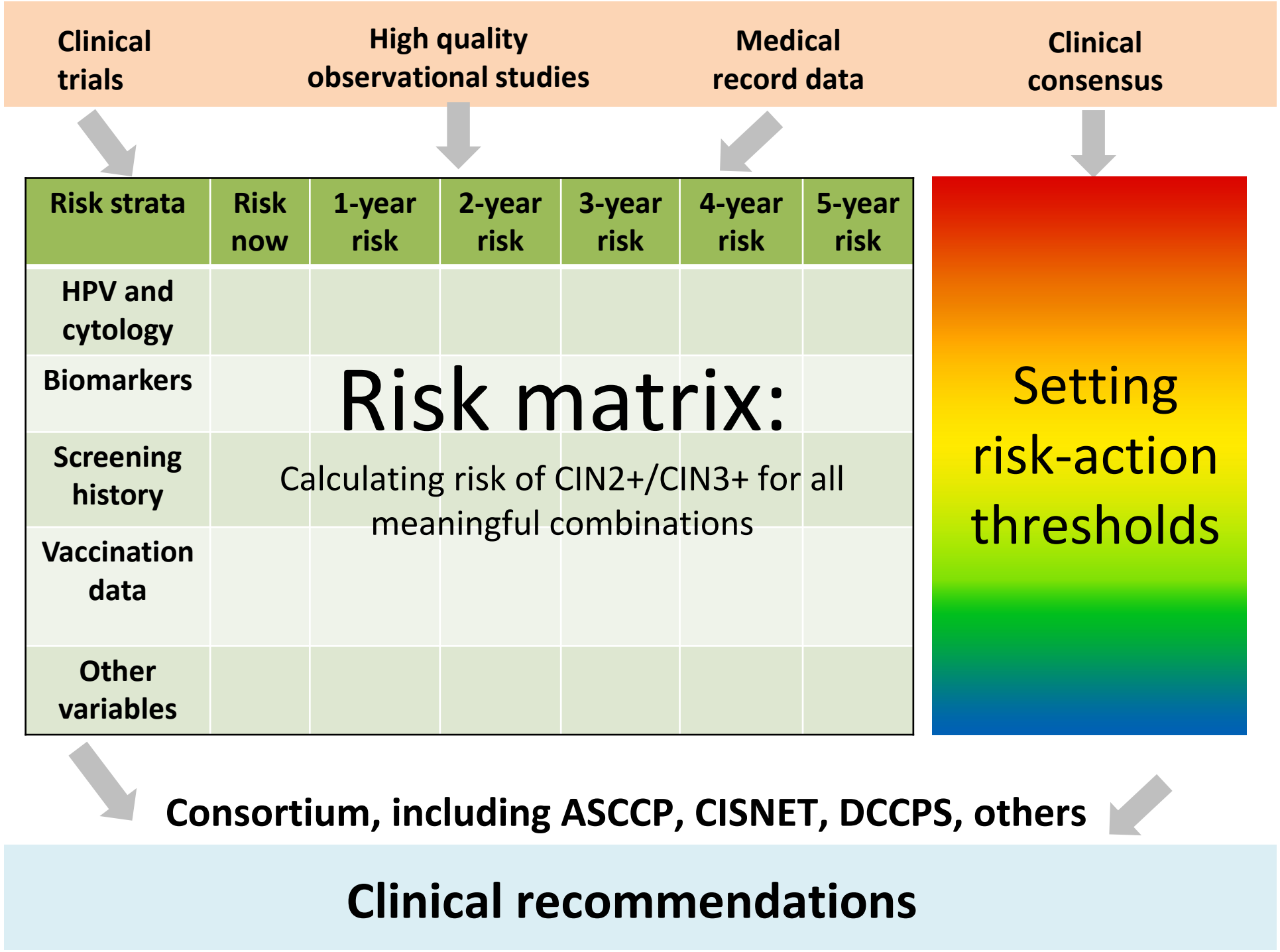


The next generation of risk-Based management

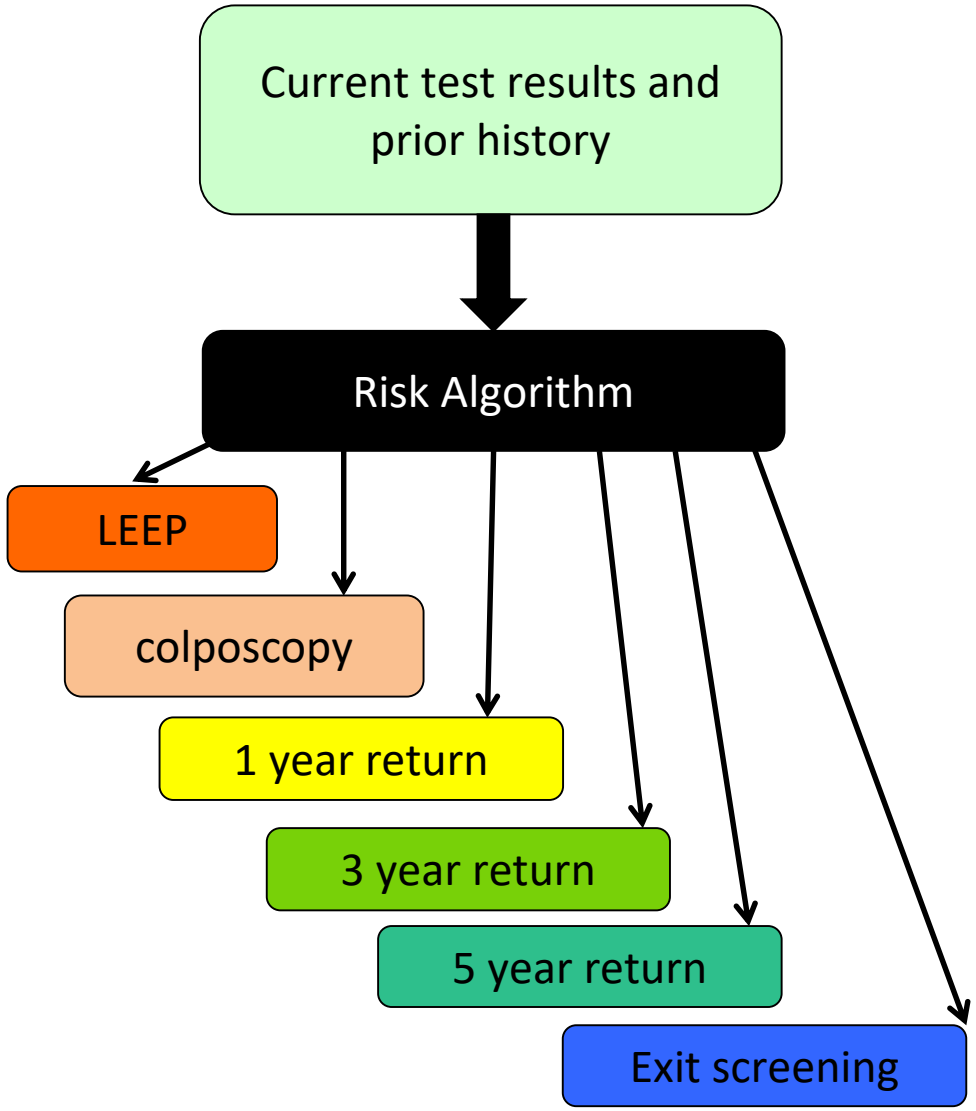
New Risk-based algorithm

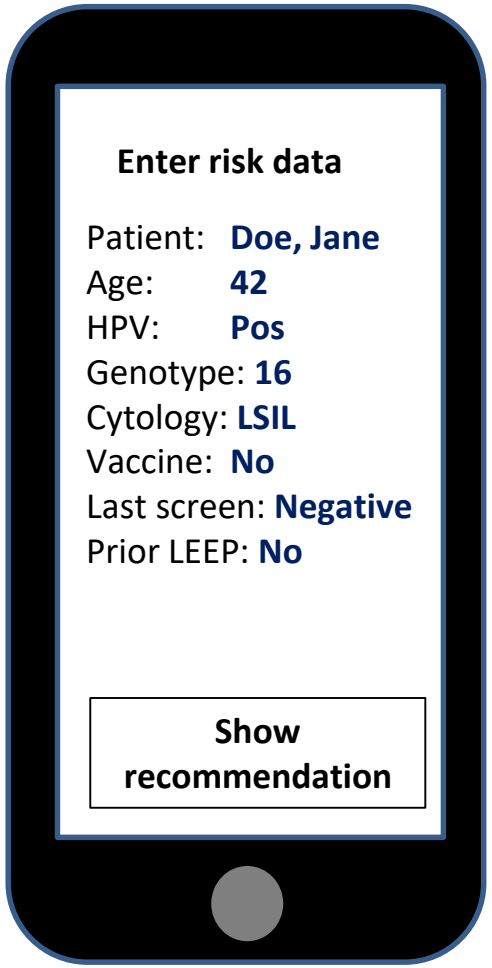
- Provider enters woman's current test results and past history
- Risk matrix is used to calculate her risk of CIN2/3
- Computer algorithm generates risk score



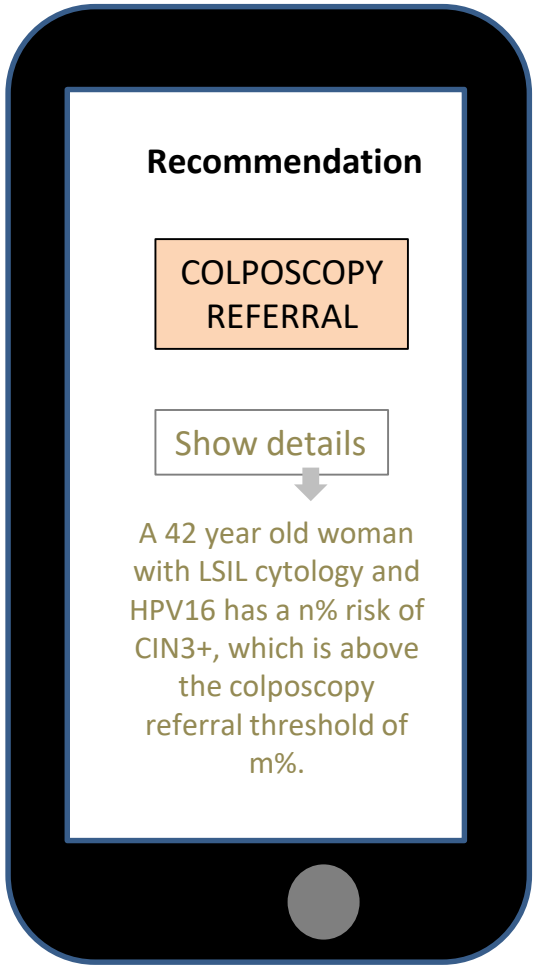

Clinical trials
High quality observational studies
Medical record data
Clinical consensus
Risk strata
Risk now
1-year risk
2-year risk
3-year risk
4-year risk
5-year risk
HPV and cytology
Biomarkers
Screening history
Vaccination data
Other variables
Risk matrix:
Calculating risk of CIN2+/CIN3+ for all meaningful combinations
Setting risk-action thresholds
Consortium, including ASCCP, CISNET, DCCPS, others
Clinical recommendations

Reducing complexity for providers





Data entry



Recommendation

INTRODUCTION TO GUIDELINES PROCESS

Professional organizations and guidelines

- **USPSTF**: Has introduced new proposal for screening
  - Does not deal directly with management guidelines
- **ACS**: next cycle just starting
  - Also does not typically deal with positive results
- **ACOG**: has aligned closely with ACS and ASCCP in past rounds

- American Society for Colposcopy and Cervical Pathology (**ASCCP**-sponsored): **management of abnormal screening results**
- ASCCP-NCI collaborating on next round of management guidelines
  - NCI generates risk estimates for a risk-based approach

Guidelines Start With Facts, But End With Values

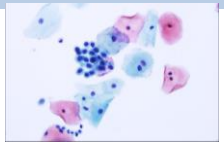
- We can compute risks of test results, but…
- How much do health decision analyses reflect facts versus values?
- What is the standard of cancer protection that you consider to be acceptable?
  - The protection associated with annual cytology or the protection associated with q3 year cytology?

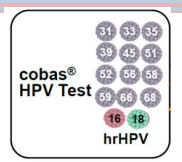
Why is risk based management better?

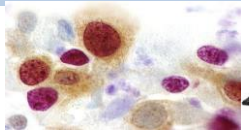
- The amount of testing matches the woman's risk of CIN3
- Should improve cancer prevention AND decrease unnecessary testing
- Risk matrix can be easily updated with new data and new testing technologies to give more precise estimates without changing the user interface

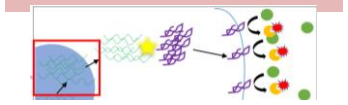
Colposcopy adjuncts in development

Cytology-based	Molecular	Visual
Cytology / Automation	HPV genotyping	VIA / Automation
p16/Ki-67 / Automation	Methylation	In-vivo imaging









Examples of Clinical Situations Where Risk is Presently Used

- Risk of Fracture due to Osteoporosis
  - Medical Treatment
- Risk of Heart Disease Based on History/Lab Data
  - Modification of behavior
  - Drug Therapy
- Risk of Cardiovascular Event following Major Surgery
  - Alteration is surgery, anesthesia, post op care
- Gail Model for Breast Cancer Risk
  - Chemoprevention with SERM
- Equal Management of Equal Risk
  - Abnormal Cervical Cancer Screening Test
  - ASCCP 2012 Katki H et al
- Bayesian Risk Estimates of Cervical Cancer
  - Austin M

How do we see risk?

- Medical Practice
  - Risk can be viewed as the probability of getting a disease over a certain period of time
- Philosophically
  - Risk is defined as the product of probability and the consequence of the adverse event
  - This is one area that we have failed at identifying the key issues of the adverse events

Nguyen T, Eisman J Fracture Risk Assessment: From Population to Individual Clin Densitom 2017,20(3)

Population Medicine vs Individual Care

- Population risks are derived from data from a group of individuals
- A group based estimate is used to define the intrinsic risk of an individual
- Population risk are continuous
- Individual Risk are Binary (yes/no)
  - I will either get the condition (cervical cancer) or I will not
  - Despite these limitation risk assessments can be meaningful.

Nguyen T, Eisman J Fracture Risk Assessment: From Population to Individual Clin Densitom 2017,20(3)

Risk Factors Included in the FRAX and GARVAN Fracture Risk Calculator

FRAX

- Age
- Gender
- Femoral Neck BMD
- Body Weight
- Height
- History of prior Fracture
- Parental History of hip Fracture
- Current Smoking
- Chronic glucocorticoid use
- RA
- Secondary Osteoporosis
- Alcohol Use

GARVAN

- Age
- Gender
- Femoral neck BMD
- Number of prior Fractures
- Number of falls during the last 12 months

Cervical Cancer/Precancer Risk

Simplified Tool

- Age
- Cytology
- HPV status
- Vaccine History
- Treatment History

Complex Tool

- Age
- Cytology
- HPV status
- HPV subtype
- Treatment History
- Vaccine History
- Smoking History
- Duel Stain
- Colposcopy Impression
- Immunosuppression Status
- Prior Screening History

Individual vs Population

- Individual risk change with time
- Models must be able to account for this
- This is important for our development of a risk calculation that depends on events
  - Prior Screen History
  - Previous treatment
  - Change from healthy to Immunosuppressed

4 “R” of predictive model

- Reliability
  - Good sensitivity and specificity
- Reproducibility
  - Risk factors included in the model/tool should be highly reproducible and found in independent populations
- Relevance
  - Clinical relevance: Treating high risk women makes a difference
- Real-world value
  - Easy to use and inexpensive

Goals of Planning Meeting
Feb 2, 2018

- Consensus endorsement of the risk base paradigm
- Develop list of additional experts/organizations to involve
- Clinical Action Thresholds (CATs)
- Risk level that will result in a clinical action.
  - Example (perform colpo, Immediate LEEP, Return for co-test in 1 year)
- Identify the critical information we need determine CATs and areas of missing information
- Plan how we will incorporate public input
- Plan for subsequent meetings

Participants

Leadership

• Dick Guido, MD	ASCCP
• Rebecca Perkins, MD	ASCCP
• Mark Schiffman, MD, MPH	NCI

Steering Committee

• Phil Castle, PhD, MPH	
• Dave Chelmow, MD*	ACOG
• Paul Han, MD	
• Warner Huh, MD*	SGO
• George Sawaya, MD	
• Barbara Moscicki, MD	
• Teresa Darragh, MD	
• Nico Wentzensen, MD	
• Amy Wiser, MD	

Organizations

Jeffery Quinlan, MD	American Academy of Family Physicians
Debbie Saslow, PhD	American Cancer Society
David Chelmow, MD*	ACOG
E J Mayeaux, MD	IFCPC
Barbara Crothers, DO	College of American Pathologist
Aimee Holland, DNP	Nurse Practitioners in Women's Health
Warner Huh, MD*	Society of Gynecologic Oncology
Mona Saraiya, MD	CDC
Deborah Arrindell	American Sexual Health Association
Ysabel Duron	Latino Cancer Institute
Tamika Felder	Cervivor
Ritu Nayar, Md**	Cytopathology Education and Technology Consortium

RESULTS OF PLANNING MEETING

WORKING GROUPS

- TREATMENT
- COLPOSCOPY
- SURVEILLANCE
- RISK MODIFICATION
- COST ANALYSIS
- NEW TECHNOLOGIES
- COMMUNICATIOIN AND IMPLEMENTATION

Goals for consensus process Meeting 2

- Discuss the determinations made by the Working Groups
- Review the input from the open discussion period
- Have final voting on the CATs and their associated risk thresholds
- Finalize publication plans
- Finalize the educational plans for the lay public.

Engagement of Patients Advocates

- Previous Guidelines have only involved the scientific community
- Previous consensus meeting have been based on
  - ASCCP System for describing recommendation
  - GRADE System
- Goal is to involve patient advocates in setting Clinical Action Thresholds

Conclusion

- Management Guidelines are widely used
- New technology and testing can improve the precision of care for women with abnormal screening tests
- New guideline process will be
  - Based on Consensus Clinical Action Thresholds
  - Provide better precision
  - Simplify the management process