Predicting clinical outcome of type-specific HPV infections: Deciding what else clinicians need to know.

> Maria Demarco National Cancer Institute DCEG/CGB Rockville, MD, USA





Disclosures

The NCI has received HPV and cytology test results at no cost from Roche Molecular Systems and BD Diagnostics for independent evaluations of these technologies.





Background

- ASCCP is beginning the process of updating cervical screening and management guidelines.
- The guidelines will recommend clinical actions based on risk instead of complicated algorithms.
- NCI's role is to generate public, precise, and accurate risk estimates.
- To do so, we need data from large cohorts and trials.





Current ASCCP application

Carrier 🗢 10:3	8 PM	-	Car
Patient Ir	nformation Ho	me	Ur
ΑЅϾΡ	The society for lower gen tract disorders since 196	iital i4	
Key Patient	Information		(
Age:			G
HPV Status:	? - +		men v
Pregnant:	No Yes		Rou Scree
Initial Testin	g Information		t options ignant or 3 year int
Cytology Resu	ult:		
	EXT		N
	(Û	A
Screening Management	Algorithms Definition) pons	Sc

Source: http://www.asccp.org/store-detail2/asccp-mobile-app

Undo Recommendation Home Colposcopy View Risk Guideline Algorithm ner with Atypical Squamous Cells of Undetermined Significance Image of the state of t	Carrier ຈ	10:3	8 PM		
Colposcopy View Risk Diagona of the description o	Undo	Recomm	endatio	n	Home
View Risk Guideline Algorithm Interview of the stypical Squamous Cells of Undetermined Significance Import Cytology Import Colposcopy Import Colposcopy Import Colposcopy and Central All Import 2013, American Society for Colposcopy and Central All Import 2013, American Society for Colposcopy and Central All Import 2013, American Society for Colposcopy and Central All Import 2013, American Society for Colposcopy and Central All Import 2013, American Society for Colposcopy and Central All Import 2013, American Society for Colposcopy and Central All <		Colpo	scopy		
Guideline Algorithm nen with Atypical Squamous Cells of Undetermined Significance Image: Cyclogy Ima	\square	View	Risk		
regions may vary if the part or ages 21-24. year intervals Recet Steps Routine	Guidelin	e Algorithi	m		
Professing Profes	men with Atypica	I Squamous Cell	s of Undetern	nined Sig	nificance (A
Negative Routine Breening Protoconvictal scale and and the scenar Protoconvictal scale and the scenar and the scenar and the scenar and the scale and the scenar and th	@ 1 yea Acceptabl	bology k	*	HPV Te Prefer	red
Colposcopy Encounting Colposcopy Encounted Lastracting proferent in women with no testions, and those with invaluant options may vary if the Manage per ASCCP Guideline Copyright, 2013, American Society for Colposcopy and Cervice II Next Steps Add Colposcopy Followup Result	Negative	≥ ASC	HPV Po (managed th women wit	₩ esitive esame as th LSIL)	HPV Noga
aptions may vary if the paint or ages 21-24, year intervals Next Steps Add Colposcopy Followup Result	Routine Screening'	Colpe Endocervical sample	DSCOPY ng preferred in wome		Parasal Cat
opdions may vary if the manage per ASCCP Guideline • Copyright, 2013, American Society for Colposcopy and Central I Next Steps Add Colposcopy Followup Result		with no lesions, and colposcopy; it is a	those with inadequat icceptable for others	te	@ 3 yea
Copyright, 2013, American Society for Colposecepty and Centeral	options may vary if the mant or ages 21-24, year intervals	Mana	¥ age per Guideline		
Next Steps Add Colposcopy Followup Result		© Copyri	ight, 2013, American Sc	ciety for Colposi	copy and Cervical Pat
Next Steps Add Colposcopy Followup Result					
Add Colposcopy Followup Result	Next Ste	ps			
	Add Colpo	scopy Follo	wup Resu	ult	>
			Æ		\square



Achieving precision and simplicity



MOU

NCI's role:

• Generate risk estimates

ASCCP's role:

- Generate risk action thresholds
- Create guidelines
- Produce app





Preliminary methodological considerations

- Choice of endpoint (CIN2+ vs. CIN3+ vs. consideration of cancer)
- Level of detail for HPV genotyping and cytology
- Time to outcome (0, 1, 2, 3, 4, 5 years) used for decisions
- Threshold to consider a factor important vs. not





Objectives of this talk

- If we know HPV status, what other factors are important for guidelines?
- Example: co-factors like age, race, smoking, hormonal contraceptive.





Selection of datasets and variables

- Data from 27,224 HPV infected women in the NCI-KPNC PaP study.
- 3-year absolute risk of CIN3+.
- Variables:

HPV type group (LA, Onclarity, Cobas)	16, 18/45, 31/33/52/58, 35/39/51/59/66/68
Cervical cytology result	NILM, ASCUS/LSIL, ASC-H+
Age	30-44, 45 or older
Race/ethnicity	NH African American, all other race/ethnicity combinations
Smoking	never, former, current
Hormonal contraceptive use (DMPA, OCP)	0, 1 or more prescriptions





Relative risks of CIN3+ for most important factors

		Frequency	Estimated RR	95% CI
	16	3026	6.9	(6.0, 8.0)
	18/45	1515	3.4	(2.9, 4.1)
ΠΡν	31/33/52/58	3903	2.9	(2.9, 4.1)
	35/39/51/59/66/68	4440	1.0	-
	ASC-H+	11033	6.0	(5.4, 6.6)
Cytology	ASCUS/LSIL	1943	1.6	(1.4, 1.8)
	NILM	15679	1.0	-

In contrast, cofactors have lower RRs between 1.0 and 1.5: Age, race, smoking, OCP use





Absolute risks of CIN3+ for most important factors

		Frequency	Estimated RR	95% CI	Estimated AR	95% CI
HPV	16	3026	6.9	(6.0, 8.0)	27	(25, 28)
	18/45	1515	3.4	(2.9, 4.1)	10	(9, 11)
	31/33/52/58	3903	2.9	(2.9, 4.1)	12	(12, 13)
	35/39/51/59/66/68	4440	1.0	-	5	(4, 5)
Cytology	ASC-H+	11033	6.0	(5.4, 6.6)	43	(40, 45)
	ASCUS/LSIL	1943	1.6	(1.4, 1.8)	13	(12, 14)
	NILM	15679	1.0	-	4	(4, 5)







HC2+

11













Most behavioral cofactors studied did not change absolute 3-year risk of CIN3+ given HPV type and cytology.





Conclusions

- The fate of most infections is determined mainly by HPV test and cytology.
- ASCCP application questions could include:
 - 1. HPV status
 - 2. HPV type
 - 3. Cytology results
 - 4. Most cofactors are probably not worth adding to guidelines
- AR based models are the first step in the clinical decision making process.
- Other cofactors need to be studied: past medical history, vaccination status, HIV.
- We are considering statistical methods that take into account risk and prevalence.



