High-Quality Risk-based Cervical Cancer Screening for the U.S. and the World:

A Realistic Example of Precision Prevention

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Nicolas Wentzensen, MD, PhD, MS
Main Message

• Cervical cancer has a uniform etiology and pathogenesis worldwide: Persistent HPV is the necessary cause
• Cervical cancer prevention already a success in some high-resource countries
  – But “precision prevention” now possible
• Worldwide burden still increasing
• New strategies can greatly increase the reach of prevention efforts
Most Of HPV-Attributable Cancer Burden in LMIC*

* Low and middle income countries
Age-Adjusted Cervical Cancer Incidence
UN Human Development Index

Different settings merit separate strategies, all based on same underlying science
|------------------|--------------------------|-------------------------------|---------------------------------------------------------------|-----------------|-----------------------|

NCI Cervical Cancer Prevention Research: From Discovery to Impact
Some Basic Facts about Human Papillomaviruses
HPV Has a Relatively Small, Simple Genome
Which HPVs Cause Cervical Cancer?
A dozen types that \textit{can} cause cancer
Progression by HPV Type

Demarco et al., in preparation
HPV16 lineages/sublineages

Burk et al., Virology 2013.
E7 is hypovariable in cancers around the world

- HPV16+ women in our large cohorts, and
- 1,609 cancers around the world from IARC:

In cancers, E7 was significantly less variable than all other viral regions

<table>
<thead>
<tr>
<th>Viral region</th>
<th>% IARC cancers</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>E7</td>
<td>0.8%</td>
<td>reference</td>
</tr>
<tr>
<td>E5</td>
<td>6.3%</td>
<td>8.0E-11</td>
</tr>
<tr>
<td>E4</td>
<td>8.3%</td>
<td>1.9E-09</td>
</tr>
<tr>
<td>E6</td>
<td>8.4%</td>
<td>6.1E-05</td>
</tr>
<tr>
<td>L1</td>
<td>9.1%</td>
<td>7.0E-05</td>
</tr>
<tr>
<td>E1</td>
<td>22.0%</td>
<td>2.2E-04</td>
</tr>
<tr>
<td>E2</td>
<td>26.4%</td>
<td>5.1E-15</td>
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<tr>
<td>L2</td>
<td>43.6%</td>
<td>1.0E-14</td>
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<tr>
<td>URR</td>
<td>44.8%</td>
<td>2.2E-16</td>
</tr>
</tbody>
</table>

Mirabello et al., Cell 2017 Sep 7;170(6):1164-1174.
Where Do Cervical Cancers Originate?
The Cervical Squamo-Columnar Junction

Uniquely prone to HPV-induced carcinogenesis
HPV Natural History and Steps to Cervical Cancer
Here is What We Learned

Precancer = CIN3

Approximately 10 years

Persistence

Clearance

Invasion

CIN3 persistence or regression
Cervical Carcinogenesis

**True state**
- Normal cervix
- Infection
- Clearance
- Progression
- Regression
- Invasion
- Cancer

**Management**
- Routine screening
- Repeat testing
- Outpatient treatment
- Inpatient treatment

**CIN histology**
- Normal
- CIN1
- CIN2
- CIN3
- Cancer

**LAST histology**
- Normal
- LSIL
- HSIL
- Cancer

**Cytology**
- NILM
- ASC-US
- LSIL
- HSIL
- Cancer

**HPV test**
- Negative
- Positive
Prevention Methods
Preventing cervical cancer, possible interventions at each step of HPV natural history

Adapted from Cancer Epidemiol. Biomarkers Prev., 2013, 22, 553–560, Schiffman, M. & Wentzensen, N., Human papillomavirus infection and the multistage carcinogenesis of cervical cancer, with permission from AACR

Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.86
A scientific evaluation of one or two doses of the HPV vaccines
Objectives

1. For each vaccine, evaluate the non-inferiority of 1 vs 2 doses in the prevention of new cervical HPV16/18 infections that persist 6+ months*

2. For each vaccine, evaluate 1 dose of HPV vaccination compared to 0 vaccination doses (virologic endpoint)

3. Compare sustained immune titers via measurement of serum antibodies between girls who received 1 and 2 doses of the HPV vaccines

*Lowy DR et al, Lancet Oncol 2015
Preventing cervical cancer, possible interventions at each step of HPV natural history

Adapted from Cancer Epidemiol. Biomarkers Prev., 2013, 22, 553–560, Schiffman, M. & Wentzensen, N., Human papillomavirus infection and the multistage carcinogenesis of cervical cancer, with permission from AACR

Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.86
The screening program

• Precision prevention: Goal to detect and treat true precancer while minimizing over-treatment
• Parts
  – Population screening (presumed normal)
  – Triage of positives
  – Treatment to prevent cancer
  – Post-treatment follow-up
• Lifetime strategy
• Must be concordant with HPV vaccination
• Cytology vs. HPV Testing vs. Cotesting
HPV as primary screen everywhere

• USPSTF draft recommendation
• Permits self sampling
• Type restriction
• High-throughput central tests vs Point-of-Care
• Existing US FDA-approved tests fundamentally similar, except for types individually identified
• Tests adapted to low-resource regions are nearly ready
Pooled analysis of 4 European randomized trials of HPV testing vs cytology

- 176,000 women 20 – 64 years old

RATE OF CERVICAL CANCER FOLLOWING NEGATIVE HPV TEST VS. NEGATIVE CYTOLOGY

Ronco G. et al. Lancet 2014
Why not cotesting with HPV testing and cytology?

- Kaiser Permanente Northern California (KPNC)
- 1,000,000+ women age 30-64
- HPV testing allows for extended screening intervals
- Very little additional reassurance of co-testing vs. HPV alone

Gage et al., JNCI, 2014
The screening program

• Precision prevention: Goal to detect and treat true precancer while minimizing over-treatment

• Parts
  – Population screening (presumed normal)
    • PRIMARY HPV TESTING AT EXTENDED INTERVAL
  – Triage of positives
  – Treatment to prevent cancer
  – Post-treatment follow-up
Cervical cancer screening programs in different settings

**High-resource settings**
- Primary screening: Cytology, HPV, Cotesting (Cytology and HPV)
- Triage test: Equivocal cytology, All positives, HPV-positive, cytology-negative
- Diagnosis: Colposcopic biopsy
- Treatment: Excision

**Low-resource settings**
- Primary screening: HPV, VIA
- Triage test: Visual or molecular triage
- Diagnosis: Colposcopic biopsy
- Treatment: Ablation

• Triage and diagnosis to decide who among the screen-positives needs treatment

References:
- Wentzensen Lancet Oncol 2014
- Schiffman Nat Rev Dis Primers 2016
Risk-based approach to screening and management

High risk:
- Treatment

Medium risk:
- Colposcopy

Low risk:
- Triage or repeat testing

Minimal risk:
- Regular screening interval

High / middle resource setting

0% 100%

Absolute risk of precancer

Treat

Do not treat

High risk:
- Treatment outweighs no treatment

Intermediate risk:
- Triage or surveillance?

Low risk:
- No treatment outweighs treatment

Low resource setting

Wentzensen JCV 2016
## Triage strategies

<table>
<thead>
<tr>
<th>Cytology-based</th>
<th>Molecular</th>
<th>Visual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology / Automation</td>
<td>HPV genotyping</td>
<td>VIA / Automation</td>
</tr>
<tr>
<td>p16/Ki-67 / Automation</td>
<td>Methylation</td>
<td>Colposcopy</td>
</tr>
</tbody>
</table>

**High / middle resource setting**

**Both settings**

**Low resource setting**
Cytology-based triage

Cytology / Automation

p16/Ki-67 / Automation
A new approach to automated cytology

• Scanning of cytology slides (FocalPoint)

• Machine learning score indicating risk of precancer:
  • High
  • Moderate
  • Low

Schiffman IJC 2016
p16/Ki-67 dual stain (DS) and HPV genotyping

- 13,000 HPV-positive women enrolled at Kaiser Permanente Northern California
- Automated dual stain analysis feasible
Molecular triage

HPV genotyping

Methylation
Molecular marker discovery: TCGA, SUCCEED

- Somatic mutations, copy number variation, methylation, HPV integration
- **TCGA**: Integrated characterization of cervical cancers
- **SUCCEED**: Integrated characterization of cervical precancers
Methylation of the HPV genome

Wentzensen JNCI 2012, Mirabello JNCI 2012, Clarke CEBP 2013
Clinical performance of viral methylation

- Now developing an integrated NG-based HPV detection, genotyping and methylation assay
- Applications in high- and low-resource settings (self-sampling)
Visual triage
Low resource settings: Automated image analysis

- NCI Colposcopy Image database (>100K)
  - Guanacaste Natural History Study
  - Costa Rica Vaccine Trial
  - ALTS Trial
  - Biopsy Study

- Machine Learning Challenge

- Evaluation sites
  - Rutgers University (Mark Einstein)
  - Nigeria
  - El Salvador

Extramural partners, non-profits, companies
High resource settings: Improving colposcopy

- First US colposcopy guidelines were developed by a joint intramural-extramural effort and published in 2017
- NCI Biopsy Study provided key evidence for these recommendations
**Large-scale evaluation of screening and triage strategies**

<table>
<thead>
<tr>
<th>Group</th>
<th>3-year risk of precancer</th>
<th>Sample</th>
<th>Expected precancers</th>
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</thead>
<tbody>
<tr>
<td>HPV+</td>
<td>5%</td>
<td>50,000</td>
<td>2,500</td>
</tr>
<tr>
<td>HPV-/Pap+</td>
<td>0.5%</td>
<td>10,000</td>
<td>50</td>
</tr>
<tr>
<td>HPV-/Pap-</td>
<td>0.05%</td>
<td>10,000</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>70,000</td>
<td>2,555</td>
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</table>

<table>
<thead>
<tr>
<th>2 years</th>
<th>3 years</th>
<th>5 years</th>
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<tr>
<td>Baseline enrollment</td>
<td>Repeat sample collection</td>
<td>Follow-up for endpoints</td>
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2015

**Improved Risk-Informed HPV Screening (IRIS):** A large prospective study to evaluate biomarkers for cervical cancer screening, triage, and management nested in a large integrated healthcare system (Kaiser Permanente Northern California)
New screening and management guidelines for the US

Collaboration between DCEG, ASCCP, CISNET, DCCPS

Risk matrix:

Calculating risk of precancer for screening and triage tests

Setting risk-action thresholds

Black box

Screening and triage tests

Routine Screening

Follow up in 12 months

Colposcopy

Recommendation

COLPOSCOPY REFERRAL

Show details

A 42 year old woman with LSIL cytology and HPV16 has a n% risk of CIN3+, which is above the colposcopy referral threshold of m%.
Integrating vaccination and screening: HPV-Faster

1-Dose Vaccination

HPV Screening and triage

Bosch 2015 Nat Rev Cancer
# A comprehensive program for every setting

## Vaccination
- **High-resource settings**: 2 Doses
- **Low-resource settings**: 1 Dose

## Primary screening
- **Cytology**
- **HPV**
- **Cotesting (Cytology and HPV)**
- **HPV**
- **VIA**

## Triage test
- **Equivocal cytology**
- **All positives**
- **HPV-positive, cytology-negative**
- **Visual or molecular triage**

## Diagnosis
- **Colposcopic biopsy**

## Treatment
- **Excision**
- **Ablation**