Self-Collection Devices for Pap Test
FDA Public Workshop
White Oak, MD
January 11, 2018
9:00 am – 4:00 pm (EST)
Welcome!

Donald St. Pierre
Acting Director

Office of In Vitro Diagnostics and Radiological Health
CDRH/FDA
General Announcements

• Please set phones, computers and blackberries to silent mode

• Wifi can be accessed in the Great Room area using the code publicaccess

• Food and beverage are available for purchase at the kiosk in the registration lobby during breaks and lunch

• Links to the archived webcast will be available on the workshop registration website shortly after the workshop

• The transcript will be available approximately 45 days following the workshop
General Announcements

• Meeting Agenda broken up into 2 main topics:
  - Clinical considerations (morning session)
  - Performance/validations considerations (afternoon session)

• Each session will have presentations and panel discussion

• Audience is encouraged to participate and ask questions

• Timekeepers: There will be a timekeeper at the front of the room if you are speaking. During each presentation, they will hold up little note cards for 5 minutes, 2 minutes, 1 minute and 30 seconds remaining.
Self-Collection Devices for Pap Test: Introduction & Background

FDA Public Workshop
January 11, 2018

Shyam Kalavar, MPH, CT(ASCP)
Division of Molecular Genetics and Pathology
OIR/CDRH/FDA
Outline

• Meeting Purpose/Objectives
• Scope of the Workshop
• Cervical cancer screening devices: Regulatory landscape
Meeting Purpose/Objectives

Purpose:
Provide a forum to discuss the topic of self-collection of specimens from the uterine cervix for the purposes of liquid-based Pap testing

Discuss clinical, scientific, technical, and programmatic aspects of the above topic
Meeting Purpose/Objectives

This meeting aims to:

1. Discuss the feasibility and benefits/risks of self-collection of specimens for Pap testing

2. Problems and current attitudes toward self-collection of specimens for Pap test

3. Discuss impact on current standard of care

4. Discuss potential general intended use

5. Discuss regulatory environment that will support self-collection for Pap test
Outline

• Meeting Purpose/Objectives
• Scope of the Workshop
• Cervical cancer screening devices: Regulatory landscape
Scope of Workshop

Self-collection of specimens from cervix for liquid-based Pap testing

*Out of Scope:*

- Self-collection of vaginal specimens
- Self-collection for HPV testing
- Self-collection for other STD testing such as CT/NG
Outline

• Meeting Purpose/Objectives
• Scope of the Workshop
• Cervical cancer screening devices: Regulatory landscape
Cervical Cancer Screening Devices: Current Regulatory Landscape

FDA approved cervical cancer screening devices

- Pap test system
- HPV test system

- Class III devices
- Regulated as a test system
- Liquid-based specimen collection
- Single specimen collection for Pap and HPV tests
- Conventional Pap smear is a pre-amendment device
Liquid-Based Pap Test

**ThinPrep Pap Test**

*ThinPrep Processor* (slide preparation)

*ThinPrep Imaging System* (semi-automated review of slides)

**BD SurePath Pap Test**

*BD PrepStain System* (slide preparation)

*BD FocalPoint GS Imaging System* (semi-automated review of slides)
General Intended Use of Liquid-based Pap Test

• Is a replacement for the conventional method of Pap smear

• Used in screening for the presence of atypical cells, cervical cancer, or its precursor lesions (Low-grade Squamous Intraepithelial Lesions, High-grade Squamous Intraepithelial Lesions), as well as all other cytologic categories as defined by The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses
Liquid-Based Pap Test System

Collection device
- Spatula/brush
  or
- Broom-type device

Professional collection!

Transfer to collection media
- PreservCyt
  or
- BD SurePath preservative fluid

Pre-quot (aliquot) specimen
for microbiology testing

Test report
Issued by testing lab to authorized clinician

Manual review or semi-automated review of slides
- ThinPrep Imaging System
  or
- BD FocalPoint Imaging System

Pap slide preparation
- ThinPrep Processor
  or
- BD PrepStain System
HPV Test

• Approved for primary screening – ages 25 years & older

• Co-testing: Pap test +HPV test – ages 30 years & older

• ASCUS Triage: 21 years and older with ASC-US (atypical squamous cells of undetermined significance) cervical cytology test results to determine the need for referral to colposcopy

• Several HPV approved devices
Examples of Self-Collection Devices

Self-Collected at Home:

- Fecal occult blood test (FOBT) kits for identification of occult blood in feces

Self-Collected at doctor’s office:

- Vaginal swabs for CT/NG testing
- Urine for CT/NG
References

FDA website for Premarket Approval (PMA)
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm
Thank you!
Cervical Cancer Screening

Mona Saraiya MD, MPH
Medical Officer
FDA Public Workshop
Silver Spring, Maryland
January 11, 2018
Conflicts of Interest: None
Cervical Cancer is Preventable

- 12,000 women develop and 4,000 women die of cervical cancer each year.
- As many as 93% of cervical cancers could be prevented by screening and HPV vaccination.
- In 2012, 8 million US women ages 21 to 65 were not screened for cervical cancer in the last 5 years.


What is Cervical Cancer?

Cervical cancer occurs when abnormal cells develop and spread in the cervix.
Natural History Model

Source: Cancer Epidemiol Biomarkers Prev; 2013, 22(4); 553–60.
Cervical pre-cancer in U.S. females

- 1.4 million new cases of low grade cervical dysplasia
- 330,000 new cases of high grade cervical dysplasia

Burden of Cervical Cancer in US, 2014

Rates of New Cancer Cases in the United States
Cervix, All Ages, All Races/Ethnicities, Female

In 2014, the latest year for which incidence data are available, 12,578 new cases of cervical cancer were diagnosed, and 4,115 women died of cervical cancer in the United States.

Cancer is the second leading cause of death in the United States, exceeded only by heart disease. One of every four deaths in the United States is due to cancer.

Cervical Cancer Rate by Demographics, 2014

Interventions

HPV Vaccine at 11-12 year old
Screening at age 21-65 year olds
Screening Guidelines
What is Cancer Screening?

• Looks for cancer before a person has symptoms
  • Diagnosis before symptoms may mean earlier stage of cancer and easier to treat
  • Appearance of symptoms may mean that cancer has grown or spread
• Abnormal screening results need follow-up to confirm cancer
  • Diagnostic tests

Source: National Cancer Institute Physician Data Query (PDQ®)
History of the Conventional Pap Smear

- Developed by Dr. George N. Papanicolaou in 1940's
- Most common cancer screening test
- Key part of annual gynecologic examination
- Has greatly reduced cervical cancer mortality in U.S.

Pap Test –
looks for changes in cells on cervix that could turn into cancer

Normal cervical cells

Cervical cancer cells
HPV test – looks for the virus that causes cell changes

CO-TEST: PAP + HPV
National Organizations Recommending Guidelines

- U.S. Preventive Services Task Force (USPSTF)
  - Federally appointed panel of independent experts
- American Cancer Society (ACS)
  - ACS, ASCCP and ASCP convened expert panel
- American College of Obstetrics & Gynecology (ACOG)
  - ACOG Committee on Practice Bulletins-Gynecology
<table>
<thead>
<tr>
<th>Age to start</th>
<th>ACS, ACOG 2012</th>
<th>USPSTF 2012</th>
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</thead>
<tbody>
<tr>
<td>Age to start</td>
<td>Age 21</td>
<td>Age 21</td>
</tr>
<tr>
<td>Women ages 21-29</td>
<td>Cytology every 3 years</td>
<td>Cytology every 3 years</td>
</tr>
<tr>
<td>Women ages 30-65</td>
<td>Cotesting every 5 years <em>(preferred)</em></td>
<td>Cotesting every 5 years or Every 3 years with Pap alone</td>
</tr>
<tr>
<td>Women ages &gt;65</td>
<td>Discontinue after age 65 years with adequate negative screening</td>
<td>Discontinue after age 65 years with adequate negative screening</td>
</tr>
<tr>
<td>Post-Hysterectomy</td>
<td>Discontinue if for benign reason</td>
<td>Discontinue if for benign reason</td>
</tr>
</tbody>
</table>
Interim Guidance Primary HPV testing, 2014 (ASCCP/ACOG/ACS)

• Primary HPV test can be considered for women starting at age 25 (one of many options).

• Women with a negative primary HPV test result should not be retested again for at least three years.

• An HPV test positive for HPV 16 or 18, two types associated with a higher risk of future disease, should be followed with colposcopy.

• A test that is positive for HPV types other than 16 or 18 should be followed with cytology testing.
ACOG 2016 Guidelines

- Supported Primary HPV testing
- Low-Risk groups: No screening for women who have total hysterectomy, no prior CIN2+
- High-risk groups
  - HIV-infected women
    - Screen when sexually active no later than 21 years
    - 21-29, cytology every year until 3 normal tests (then every 3 yrs)
    - 30-65, cytology every year until 3 normal tests (then q 3 years) or HPV + cytology every 3 years
  - Age to end: none
- Immunocompromised (non-HIV): screen start at age 21; similar to HIV for all else
- DES exposure: annual cytology screening
Draft USPSTF recommendations (2017)

• 21-29 y
  • Cytology every 3 years

• 30-65 y
  • Cytology every 3 years
  • HPV every 5 years
  • Co-testing no longer recommended

• > 65 y
  • Adequate screening history can stop
What Test Will be on the Menu and What Test Will You have?

I prefer the HPV and the Pap test every 5 years

I prefer the HPV test alone every 5 years

every 3 years
The 35,000 foot view: cervical cancer incidence and mortality in the US

What impacts cervical cancer incidence and mortality

- Coverage
- Coverage
- Coverage
- & Follow-up of abnormal tests
National Screening Prevalence

- 83% of women screened in past 3 years with a Pap test

White A, Cancer Screening Test Use, MMWR 2017
Who are the women who don’t get screened at all or get screened regularly?

- Lower Educated
- Underinsured
- Racial/Ethnic groups
  - Asian (Chinese)
  - American Indian/Alaskan Native
  - Hispanic (Mexican, Mexican-American, Central/South American)
- Foreign-born (in country less than 10 years)
- Sexual Orientation (Gay, Bisexual)
- Religion (Muslim)
- Rural/Geographic (Appalachia, US-Texas border, Pacific Islands)
Unequal Burden of Disease (1990s)

Cervical Cancer Burden

Source: Shingleton et al., 1995
Factors Contributing to Cervical Cancer Cases

- Never or rarely screened: 50%-60%
- Cytology test abnormal, patient lost to follow-up: 10%-15%
- Cytology test abnormal, mismanaged medically: 10%-15%
- Rarely screened: 5%-10%
- Uncommon cancers difficult to detect by cytology test: 5%-10%
- Rapidly progressive cervical cancer: 9%-12%
- False negative cytology test: 5%-10%

Sources:
NIH Consensus Conference
Janerich, Connecticut
Sung, California
Contributing Factors

Difficult to prevent

- 9%-12% Uncommon cancers difficult to detect by cytology test
- 5%-10% Rapidly progressive cervical cancer
Factors Contributing to 623 Cervical Cancer Cases among women who had a co-test
Kaiser Permanente, 2003-2015

Sources:
Castle et al, Gynecology Oncology 2017
Self-collection

- Can it increase acceptability?
  - Removes the need for a speculum examination
  - Removes need for clinician for initial screening (services can be focused on followup) - home, community centers, places of gathering
  - Can be combined with other self-collection tests done at the same time (Chlamydia/Gonorrhea)
- Much work has been done in low-resource settings
  - Pilot studies show high acceptability to women in North America
    - Appalachia-Kentucky
    - Somalian immigrants Minnesota
    - Black women-Mississippi
    - Hispanic women-North Carolina
- Unanswered questions
  - Does it lead to increased screening rates (at population level?)
  - Is followup increasing?
HPV Vaccine Impact on Screening?

• HPV vaccine will decrease HPV infection, pre-cancers, and cancer
  • NHANES study 64% decrease in HPV infection pre- and post- HPV vaccine in youngest age group
  • Studies have shown decrease precancers
  • One recent cohort followup showed decreased cancers

• Screening will need to be more HPV-based
  • Screening can be later and less frequent
What are other countries doing?

• Argentina - HPV-based screening, uptake increase from 20% to 86%

• Guatemala and Nicaragua introducing HPV/self-collection—

• Netherlands - HPV-based screening and self-collection to non-responders

• Australia - HPV-based screening, less frequent screening for entire population, and self-collection

• Uganda - uptake rates of greater than 95% (compared to 48.4% VIA)
Summary

Cervical Cancer is decreasing but its preventable

Coverage has been stagnant for several years

Screening guidelines are moving towards
  • HPV-based screening
  • Screening at later ages and less frequently
  • HPV vaccination has potential to change this even more

Self-collection can improve coverage
Go to the official federal source of cancer prevention information:  
www.cdc.gov/cancer

Follow DCPC Online!  
@CDC_Cancer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Will self-collection of cervical samples improve cervical cancer screening?

Paul N. Staats, MD
University of Maryland School of Medicine
Conflict of interest

• None to disclose
The Pap test and cervical cancer prevention

- 80% reduction in cervical cancer in US since 1955
  - #1 to #14 cause of cancer death in US
  - 2014: 12,500 cases, 4100 deaths in US
- HPV vaccine and HPV DNA testing have important roles, but Pap test remains a cornerstone of prevention

The Pap test and cervical cancer prevention

- Cervical cancer remains a significant killer
  - Worldwide: 500,000 cases, 250,000 deaths per year
  - US: 12,500 cases, 4100 deaths
  - Majority of cases in women with insufficient screening
- Access issues in developed and especially developing world
  - Lack of insurance/access to care
  - Health information
  - Practical barriers
  - Personal beliefs
  - Fear

- Is self-collection part of the answer in the US?

Estimated Cervical Cancer Incidence Worldwide in 2012

Estimated age-standardised rates (World) per 100,000
Literature basis for self-collection devices

- Many studies
- Variety of methods/devices
  - Swabs/brushes
  - Lavage
  - Tampon
- Most show decent sensitivity for HPV DNA testing compared to provider-collected tests
- Most show poor sensitivity for cytology compared to provider-collected tests
  - Mostly vaginal cells collected, not cervical

Women potentially affected by self collection
-US

Cervical cancer screening within last 5 years (~85%)

Switch to self (10%)

Inadequate screening – reported causes
- Lack of insurance
- No primary physician
- Health information
- Practical barriers
- Personal beliefs
- Fear
Specific issue areas for self-collection
-Laboratory perspective

• Specimen collection and transport
• Choice of laboratory
• Laboratory interpretation
• Reporting results
• Follow-up of results
Specimen collection and transport

- Patient must be able to collect dysplastic/neoplastic cells
Specimen collection and transport

• Materials must be safe for patient use
• If liquid-based cell preservation, specimen must be transportable
  • flammability, heat/cold tolerance, etc.
• Criteria for and handling of compromised specimens
Choice of laboratory

• Patient choice of laboratory versus designated partner laboratory arrangement
  • Quality
  • Turnaround time
  • Pricing
Laboratory interpretation

• How similar would self-collected specimens be to provider-collected Paps?
  • Would modified diagnostic and adequacy criteria be necessary?
  • Would additional training be necessary?

• Example: Transformation zone sampling
  • Bethesda system does not require evidence of TZ sampling for an adequate specimen, but the studies on which this is based presume physician visualization and sampling of cervical os

• Example: Fixation and preparation artifacts
  • FDA requires specific training on reading liquid-based preparations due to differences from direct smears
Reporting results

• To whom does the lab report results?
  • Directly to the patient?
    • Potentially leaves patients holding an abnormal result but without a way to act on it
    • Report generated would need to be very clear on meaning of result and appropriate follow-up
      ; language and/or literacy issues for some patients
  • Patient designates a physician?
    • Those most in need of self-testing don’t have one

• What does the lab do if the patient/responsible physician cannot be reached?
  • Patient care and liability issue

• How are results reported
  • Mail: how to confirm receipt
  • Phone: no permanent record
  • Electronic: patients may not have access
  • Multiple methodologies: potential confusion
Follow-up of results

• How do patients without a doctor follow up abnormal results?
Conclusion

• Self-collected Pap tests are not identical to provider-collected Pap tests
  • Wide range of issues that are distinct
    • Collection and transport
    • Choice of laboratory
    • Laboratory interpretation
    • Reporting results
    • Follow-up of results

• Potential for patient harm if not thoroughly demonstrated to have identical performance to provider-collected Pap tests
Is Self-Collection of Cervical Samples Feasible and Will It Work?

Mark Schiffman, MD, MPH
COI Statement

- NCI has received HPV and cytology testing results, equipment and reagents at reduced or no cost from several commercial groups, including Qiagen, Roche, and BD, and Arbor Vita.
- The studies have been directed by NCI independently.
- I have no personal financial or other COI to report.
Essential Background
The Cervical Squamo-Columnar Junction

Uniquely prone to HPV-induced carcinogenesis
Purpose of Cervical Screening

• To reduce cervical cancer death and suffering by detection and treatment of cervical cancer precursors ("precancers") or early treatable cancers
• To avoid doing harm to women, especially those not truly needing treatment
Adenocarcinoma versus Squamous Cell CA

- An increasingly important fraction of cervical cancers in the United States are adenocarcinomas
- Both caused mainly by HPV
- Different causal pathways
- Cytology screening has been much more effective for squamous lesions
- We understand the pathogenesis of squamous lesions better
Here is What We’ve Learned: Squamous Pathway

- Precancer = CIN3
- Approximately 10 years
- Clearance
- Persistence
- Invasion
- CIN3 persistence or regression
HPV and Cervical Carcinogenesis

Population prevalence

Not to scale
Preventing cervical cancer, possible interventions at each step of HPV natural history

Carcinogenic human papillomavirus infection
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.86

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.
Two Alternative Prevention Strategies

Current approach in high-resource settings

- 2-Dose Vaccination
- HPV Screening and triage, followed by colposcopy and biopsy

Alternative approach

- 1-Dose Vaccination
- HPV Screening (with triage)

Multiple screening rounds with intervals varying by age

Single screen or few screening rounds
Age is the Other Important Modifier

- More difficult to screen post-menopausal women due to increasingly hidden position of squamo-columnar junction
The Screening Program

• Parts
  • Population screening (women presumed normal)
  • Triage of screen-positive women
  • Treatment to prevent cancer
  • Post-treatment follow-up

• Lifetime strategy
• Must be concordant with HPV vaccination
• Cytology vs. HPV Testing vs. Cotesting
# Cervical cancer screening programs in different settings

<table>
<thead>
<tr>
<th>Primary screening</th>
<th>Triage test</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>Equivocal cytology</td>
<td>All positives</td>
<td>Excision</td>
</tr>
<tr>
<td>HPV</td>
<td>All positives</td>
<td>HPV-positive, cytology-negative</td>
<td>Ablation</td>
</tr>
</tbody>
</table>

- **High-resource settings**
  - Primary screening: Cytology, HPV
  - Triage test: Equivocal cytology, All positives
  - Diagnosis: Colposcopic biopsy
  - Treatment: Excision

- **Low-resource settings**
  - Primary screening: HPV
  - Triage test: VIA
  - Diagnosis: Visual or molecular triage

**Will Self-Sampling Work for....?**

<table>
<thead>
<tr>
<th>Squamous</th>
<th>Adenocarcinoma</th>
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<tbody>
<tr>
<td><strong>Screening</strong></td>
<td><strong>Screening</strong></td>
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<tr>
<td>Cytology</td>
<td>HPV</td>
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<td>HPV</td>
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<td>Cytology-</td>
<td>HPV</td>
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<td>Based</td>
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<td>HPV</td>
<td>Based</td>
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<tr>
<td>HPV</td>
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</table>
Self-Sampling Methods Similar in Performance for HPV Testing
Squamous: Primary screening – Cytology

• Long-standing belief that direct cervical sampling is important for sensitivity of cervical cytology
• No recent studies found to prove this conclusion?
Squamous: Primary Screening - HPV

- Multiple studies showing that self-sampling nearly as sensitive as clinician-sampling
- Sensitive (e.g., target-amplification DNA) assay important for equivalence
- Specificity similar to clinician-sampling
Squamous - Triage

- For cytology screening, triage is HPV testing if ASC-US
- For primary HPV testing, HPV 16/18 positive goes to colposcopy (if typing), HPV 12 other positive gets cytology. If cytology is ASCUS+, then go to colposcopy. If cytology is negative, then 1 year follow up
- Several novel methods in development (N.B., these are research tools only at this point, see next slide)
- For most, we do not know whether they will work on self-sampled specimens
Ongoing Research: Triage Following HPV Screening (Besides Cytology)

<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 and Adjuncts</td>
</tr>
</tbody>
</table>

- High / middle resource setting
- All settings
- Depends on resource settings
A research approach to automated cytology

- Scanning of cytology slides
- Computer-based score indicating risk of precancer:
  - High
  - Moderate
  - Low

Schiffman IJC 2016
Research: 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

Wentzensen JNCI 2015
Molecular triage

HPV genotyping

Methylation

Also HPV RNA and oncoproteins among others
Absolute risk of progression (%)

Progression by HPV Type

Demarco et al., in preparation
Clinical Performance of Viral Methylation

- Research use integrated NG-based HPV detection, genotyping and methylation assay
- Applications in high- and low-resource settings (self-sampling)
Adenocarcinoma: Screening

- Cytology is not as sensitive a screen for adenocarcinoma in situ as for squamous precancer
- HPV16 subvariants, HPV18, and HPV45 cause most cases
- We lack evidence on relative sensitivity of self-sampling for these cases
Summary

• Worth examining combination of self-sampling with cytology or analogous methods, to know its accuracy especially for adeno.

• PERSONAL OPINION. Self-sampling strategy with most support is HPV testing
  • Triage with partial typing of highest-risk types

• PERSONAL OPINION. Methylation appears promising for self-sampling but in early research and development

• Will self-sampling work as a primary screen? I would personally suggest the answer to be yes, with some identified “holes” in data especially regarding roles of HPV testing versus cytology methods, and regarding increasingly common diagnoses of AIS and adenocarcinoma.
Panel Discussion Topic 1:
Clinical considerations – Self-collection devices for Pap test

• Moderator: Shyam Kalavar, MPH, CT(ASCP)
• Panelists:
  - Mona Sariaya, MD, MPH
  - Paul Staats, MD
  - Dorothy Rosenthal, MD, FIAC
  - Mark Schiffman, MD, MPH
  - Jacqueline Cunkelman, MD, MPH
  - Tamika Felder
Self-Collection Devices for Pap Test
FDA Public Workshop

Lunch Break
11:45 am – 1:00 pm (EST)
Self-Collection as an Outreach Approach to Increase Cervical Screening in Under-/Un-Screened U.S. Female Populations

Philip E. Castle, PhD, MPH
Professor, Epidemiology and Population Health, Albert Einstein College of Medicine
CEO, Global Coalition Against Cervical Cancer

castle.philip@gmail.com

January 11, 2018
Disclosures

- I have received HPV tests and assays at a reduced or no cost for research from Roche, Becton Dickinson, Cepheid, and Arbor Vita Corporation.
Systematic Review and Meta-Analyses of Participation in Self-Collection vs. Clinic-Based Screening.

Systematic Review of Community-Based Outreach using Self-Collection.
## Meta-Analysis: Participation Statistics

<table>
<thead>
<tr>
<th>Scenario of invitation</th>
<th>#</th>
<th>Absolute participation</th>
<th>Relative participation</th>
<th>Participation difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Self-sampling % (95% CI)</td>
<td>Control % (95% CI)</td>
<td></td>
</tr>
<tr>
<td><strong>Per-protocol</strong></td>
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<tr>
<td>Mail-to-all</td>
<td>17/19†</td>
<td>19.2 (15.3-23.5)</td>
<td>11.1 (7.5-15.5)</td>
<td>1.78 (1.29-2.45)</td>
</tr>
<tr>
<td>Opt-in</td>
<td>4/6†</td>
<td>7.0 (2.4-13.6)</td>
<td>13.1 (11.1-15.2)</td>
<td>0.51 (0.31-0.85)</td>
</tr>
<tr>
<td>Community campaign</td>
<td>1</td>
<td>15.6 (12.4-19.5)</td>
<td>6.0 (4.2-8.7)</td>
<td>2.58 (1.67-3.99)</td>
</tr>
<tr>
<td>Door-to-door</td>
<td>4</td>
<td>94.2 (80.2-100)</td>
<td>53.3 (10.5-93.2)</td>
<td>1.99 (0.68-5.85)</td>
</tr>
<tr>
<td><strong>Intention-to-treat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mail-to-all</td>
<td>17/19†</td>
<td>24.0 (20.6-27.5)</td>
<td>11.1 (7.5-15.5)</td>
<td>2.25 (1.73-2.94)</td>
</tr>
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<td>4/6†</td>
<td>14.5 (10.1-19.6)</td>
<td>13.1 (11.1-15.2)</td>
<td>0.98 (0.71-1.35)</td>
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</tr>
<tr>
<td>Door-to-door</td>
<td>4</td>
<td>94.6 (83.0-99.9)</td>
<td>53.3 (10.5-93.2)</td>
<td>2.01 (0.66-6.15)</td>
</tr>
</tbody>
</table>

Certain studies reported that certain women, allocated to the self-sampling, had a Pap smear taken. The sum of the number of self-samples taken + Pap smears taken, were counted in the ITT analyses. In studies, where no such cases were reported, the number of events in the PP and ITT analyses were considered as equal.

†Rossi, 2011 & Rossi, 2015 had 2 control groups (one where a Pap smear was taken by a clinician and another where a sample for HPV testing was taken by a clinician).
### Meta-Analysis: Absolute Participation by Study

#### Self-sampling arm (PP)

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mail-to-all</td>
<td>31.3 (29.5, 33.2)</td>
</tr>
<tr>
<td>Bais, 2007</td>
<td>27.5 (27.0, 28.1)</td>
</tr>
<tr>
<td>Gok, 2010</td>
<td>16.7 (14.0, 19.9)</td>
</tr>
<tr>
<td>Gok, 2012</td>
<td>34.0 (31.9, 36.1)</td>
</tr>
<tr>
<td>Gok, 2010</td>
<td>30.8 (30.2, 31.4)</td>
</tr>
<tr>
<td>Darlin, 2013</td>
<td>14.7 (12.6, 17.0)</td>
</tr>
<tr>
<td>Sancho-Garnier, 2013</td>
<td>8.9 (7.9, 10.0)</td>
</tr>
<tr>
<td>Gok, 2010</td>
<td>19.5 (18.4, 20.8)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td>21.1 (18.4, 24.1)</td>
</tr>
<tr>
<td>Cadman, 2015</td>
<td>20.9 (16.9, 25.6)</td>
</tr>
<tr>
<td>Sultana, 2016</td>
<td>11.5 (11.0, 12.1)</td>
</tr>
<tr>
<td>Kitchener, 2017</td>
<td>7.4 (6.1, 9.1)</td>
</tr>
<tr>
<td>Subtotal (I^2 = 99.6%, p = 0.0)</td>
<td>19.2 (15.3, 23.5)</td>
</tr>
</tbody>
</table>

#### Self-sampling arm (ITT)

<table>
<thead>
<tr>
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<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mail-to-all</td>
<td>34.3 (32.4, 36.2)</td>
</tr>
<tr>
<td>Bais, 2007</td>
<td>27.7 (27.2, 28.3)</td>
</tr>
<tr>
<td>Gok, 2010</td>
<td>19.6 (16.7, 23.0)</td>
</tr>
<tr>
<td>Gok, 2010</td>
<td>26.4 (25.0, 27.9)</td>
</tr>
<tr>
<td>Gok, 2010</td>
<td>30.0 (29.1, 31.1)</td>
</tr>
<tr>
<td>Darlin, 2013</td>
<td>14.7 (12.6, 17.0)</td>
</tr>
<tr>
<td>Bais, 2007</td>
<td>21.6 (20.4, 22.8)</td>
</tr>
<tr>
<td>Gok, 2010</td>
<td>24.6 (22.8, 26.5)</td>
</tr>
<tr>
<td>Gok, 2010</td>
<td>30.3 (30.0, 30.5)</td>
</tr>
<tr>
<td>Racey, 2016</td>
<td>31.9 (27.2, 37.1)</td>
</tr>
<tr>
<td>Sultana, 2016</td>
<td>15.9 (15.3, 16.5)</td>
</tr>
<tr>
<td>Kitchener, 2017</td>
<td>21.3 (19.0, 23.8)</td>
</tr>
<tr>
<td>Subtotal (I^2 = 99.3%, p = 0.0)</td>
<td>24.0 (20.6, 27.5)</td>
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</table>

#### Participation in control arm

<table>
<thead>
<tr>
<th>Study</th>
<th>testcontrol</th>
<th>ES (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Mail-to-all</td>
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<td>17.6 (13.6, 22.6)</td>
</tr>
<tr>
<td>Bais, 2007</td>
<td></td>
<td>16.6 (12.7, 21.4)</td>
</tr>
<tr>
<td>Gok, 2010</td>
<td></td>
<td>13.9 (11.4, 16.8)</td>
</tr>
<tr>
<td>Gok, 2010</td>
<td></td>
<td>7.2 (5.2, 9.2)</td>
</tr>
<tr>
<td>Piana, 2011</td>
<td></td>
<td>4.5 (3.6, 5.5)</td>
</tr>
<tr>
<td>Virtanen, 2011</td>
<td></td>
<td>25.9 (24.8, 27.0)</td>
</tr>
<tr>
<td>Gok, 2012</td>
<td></td>
<td>6.5 (4.1, 10.2)</td>
</tr>
<tr>
<td>Sancho-Garnier, 2013</td>
<td></td>
<td>2.0 (1.7, 2.3)</td>
</tr>
<tr>
<td>Haguenoer, 2014</td>
<td></td>
<td>13.8 (12.4, 15.4)</td>
</tr>
<tr>
<td>Casman, 2015</td>
<td></td>
<td>11.8 (10.4, 13.2)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td></td>
<td>23.2 (21.6, 24.8)</td>
</tr>
<tr>
<td>Enerly, 2016</td>
<td></td>
<td>15.4 (13.5, 17.7)</td>
</tr>
<tr>
<td>Sultana, 2016</td>
<td></td>
<td>6.2 (5.2, 7.3)</td>
</tr>
<tr>
<td>Kitchener, 2017</td>
<td></td>
<td>16.2 (15.0, 17.4)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td></td>
<td>14.9 (13.2, 18.0)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td></td>
<td>12.0 (10.9, 13.3)</td>
</tr>
<tr>
<td>Darlin, 2013</td>
<td></td>
<td>4.2 (3.8, 4.6)</td>
</tr>
<tr>
<td>Subtotal (I^2 = 99.4%, p = 0.0)</td>
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<td>11.1 (7.5, 15.5)</td>
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</table>

#### Community participation

<table>
<thead>
<tr>
<th>Study</th>
<th>Participation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazzano-Ponce, 2011</td>
<td>98.2 (97.9, 98.4)</td>
</tr>
<tr>
<td>Arrossi, 2015</td>
<td>79.8 (78.4, 81.2)</td>
</tr>
<tr>
<td>Moses, 2016</td>
<td>99.2 (97.1, 99.8)</td>
</tr>
<tr>
<td>Modibbo, 2017</td>
<td>92.5 (88.0, 95.4)</td>
</tr>
<tr>
<td>Subtotal (I^2 = 99.7%, p = 0.0)</td>
<td>94.2 (80.2, 100.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Participation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazzano-Ponce, 2011</td>
<td>96.2 (97.9, 98.4)</td>
</tr>
<tr>
<td>Arrossi, 2015</td>
<td>83.0 (81.5, 84.2)</td>
</tr>
<tr>
<td>Moses, 2016</td>
<td>99.2 (97.1, 99.8)</td>
</tr>
<tr>
<td>Modibbo, 2017</td>
<td>92.5 (88.0, 95.4)</td>
</tr>
<tr>
<td>Subtotal (I^2 = 99.6%, p = 0.0)</td>
<td>94.8 (83.0, 99.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Participation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazzano-Ponce, 2011</td>
<td>96.2 (97.9, 98.4)</td>
</tr>
<tr>
<td>Arrossi, 2015</td>
<td>86.8 (86.2, 87.4)</td>
</tr>
<tr>
<td>Moses, 2016</td>
<td>91.9 (79.0, 102)</td>
</tr>
<tr>
<td>Modibbo, 2017</td>
<td>56.5 (48.3, 63.2)</td>
</tr>
<tr>
<td>Moses, 2016</td>
<td>48.4 (42.3, 54.6)</td>
</tr>
<tr>
<td>Subtotal (I^2 = 99.9%, p = 0.0)</td>
<td>53.3 (10.5, 93.2)</td>
</tr>
</tbody>
</table>
Meta-Analysis: Participation Difference by Study

### PP

<table>
<thead>
<tr>
<th>Study</th>
<th>testconstr</th>
<th>PD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mail-to-all</td>
<td>Cyto</td>
<td>0.14 (0.09, 0.19)</td>
</tr>
<tr>
<td>Bais, 2007</td>
<td>Cyto</td>
<td>0.11 (0.07, 0.15)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td>Cyto</td>
<td>0.03 (-0.01, 0.07)</td>
</tr>
<tr>
<td>Arrossi, 2015</td>
<td>Cyto</td>
<td>0.19 (0.18, 0.21)</td>
</tr>
<tr>
<td>Lazcano-Ponce, 2011</td>
<td>Cyto</td>
<td>0.02 (0.00, 0.03)</td>
</tr>
<tr>
<td>Door-to-door</td>
<td>Cyto</td>
<td>0.02 (-0.00, 0.04)</td>
</tr>
<tr>
<td>Zehbe, 2016</td>
<td>Cyto</td>
<td>0.25 (0.22, 0.27)</td>
</tr>
<tr>
<td>Gok, 2012</td>
<td>Cyto</td>
<td>0.24 (0.21, 0.27)</td>
</tr>
<tr>
<td>Haguenoer, 2014</td>
<td>Cyto</td>
<td>0.02 (0.00, 0.04)</td>
</tr>
<tr>
<td>Cadman, 2015</td>
<td>Cyto</td>
<td>0.03 (0.01, 0.04)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td>Cyto</td>
<td>0.08 (0.06, 0.10)</td>
</tr>
<tr>
<td>Enerly, 2016</td>
<td>Cyto</td>
<td>-0.02 (-0.05, 0.01)</td>
</tr>
<tr>
<td>Racey, 2016</td>
<td>Cyto</td>
<td>0.05 (-0.00, 0.11)</td>
</tr>
<tr>
<td>Sultana, 2016</td>
<td>Cyto</td>
<td>0.05 (0.04, 0.07)</td>
</tr>
<tr>
<td>Kitchener, 2017</td>
<td>Cyto</td>
<td>-0.09 (-0.11, -0.07)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td>HPV</td>
<td>0.02 (-0.02, 0.06)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td>HPV</td>
<td>0.08 (0.06, 0.09)</td>
</tr>
<tr>
<td>Darlin, 2013</td>
<td>Cyto/HPV</td>
<td>0.10 (0.08, 0.13)</td>
</tr>
<tr>
<td>Subtotal (I2 = 98.7%, p = 0.000)</td>
<td></td>
<td>0.08 (0.04, 0.12)</td>
</tr>
<tr>
<td><strong>Opt-in</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td>Cyto</td>
<td>-0.08 (-0.11, -0.05)</td>
</tr>
<tr>
<td>Broberg, 2014</td>
<td>Cyto</td>
<td>0.03 (0.00, 0.06)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td>Cyto</td>
<td>-0.01 (-0.03, 0.00)</td>
</tr>
<tr>
<td>Kitchener, 2017</td>
<td>Cyto</td>
<td>-0.15 (-0.16, -0.13)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td>HPV</td>
<td>-0.09 (-0.13, -0.06)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td>HPV</td>
<td>-0.02 (-0.03, -0.00)</td>
</tr>
<tr>
<td>Subtotal (I2 = 98.3%, p = 0.000)</td>
<td></td>
<td>-0.05 (-0.12, 0.01)</td>
</tr>
<tr>
<td><strong>Community campaign</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zehbe, 2016</td>
<td>Cyto</td>
<td>0.10 (0.05, 0.14)</td>
</tr>
<tr>
<td>Subtotal (I2 = %, p = .)</td>
<td></td>
<td>0.10 (0.05, 0.14)</td>
</tr>
<tr>
<td><strong>Door-to-door</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lazcano-Ponce, 2011</td>
<td>HPV</td>
<td>0.11 (0.11, 0.12)</td>
</tr>
<tr>
<td>Arrossi, 2015</td>
<td>HPV</td>
<td>0.61 (0.59, 0.63)</td>
</tr>
<tr>
<td>Modibo, 2017</td>
<td>HPV</td>
<td>0.36 (0.28, 0.44)</td>
</tr>
<tr>
<td>Moses, 2016</td>
<td></td>
<td>0.51 (0.45, 0.57)</td>
</tr>
<tr>
<td>Subtotal (I2 = 99.9%, p = 0.000)</td>
<td></td>
<td>0.40 (0.04, 0.75)</td>
</tr>
</tbody>
</table>

### ITT

<table>
<thead>
<tr>
<th>Study</th>
<th>testconstr</th>
<th>PD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mail-to-all</td>
<td>Cyto</td>
<td>0.17 (0.12, 0.22)</td>
</tr>
<tr>
<td>Bais, 2007</td>
<td>Cyto</td>
<td>0.11 (0.07, 0.16)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td>Cyto</td>
<td>0.06 (0.02, 0.10)</td>
</tr>
<tr>
<td>Arrossi, 2015</td>
<td>Cyto</td>
<td>0.19 (0.18, 0.21)</td>
</tr>
<tr>
<td>Lazcano-Ponce, 2011</td>
<td>Cyto</td>
<td>0.06 (0.04, 0.08)</td>
</tr>
<tr>
<td>Door-to-door</td>
<td>Cyto</td>
<td>0.06 (0.04, 0.08)</td>
</tr>
<tr>
<td>Zehbe, 2016</td>
<td>Cyto</td>
<td>0.30 (0.27, 0.32)</td>
</tr>
<tr>
<td>Gok, 2012</td>
<td>Cyto</td>
<td>0.24 (0.21, 0.27)</td>
</tr>
<tr>
<td>Haguenoer, 2014</td>
<td>Cyto</td>
<td>0.11 (0.08, 0.13)</td>
</tr>
<tr>
<td>Cadman, 2015</td>
<td>Cyto</td>
<td>0.09 (0.07, 0.10)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td>Cyto</td>
<td>0.10 (0.08, 0.12)</td>
</tr>
<tr>
<td>Enerly, 2016</td>
<td>Cyto</td>
<td>0.10 (0.07, 0.14)</td>
</tr>
<tr>
<td>Racey, 2016</td>
<td>Cyto</td>
<td>0.17 (0.10, 0.23)</td>
</tr>
<tr>
<td>Sultana, 2016</td>
<td>Cyto</td>
<td>0.10 (0.09, 0.11)</td>
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<tr>
<td>Kitchener, 2017</td>
<td>Cyto</td>
<td>0.05 (0.02, 0.08)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td>HPV</td>
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<td>Giorgi-Rossi, 2015</td>
<td>HPV</td>
<td>0.10 (0.08, 0.11)</td>
</tr>
<tr>
<td>Darlin, 2013</td>
<td>Cyto/HPV</td>
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</tr>
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<td>Subtotal (I2 = 97.0%, p = 0.000)</td>
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<td><strong>Opt-in</strong></td>
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<td>Broberg, 2014</td>
<td>Cyto</td>
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<td>Giorgi-Rossi, 2015</td>
<td>Cyto</td>
<td>0.00 (-0.01, 0.02)</td>
</tr>
<tr>
<td>Kitchener, 2017</td>
<td>Cyto</td>
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<td>Giorgi-Rossi, 2011</td>
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<td>Giorgi-Rossi, 2015</td>
<td>HPV</td>
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<td>Subtotal (I2 = 93.5%, p = 0.000)</td>
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<td><strong>Community campaign</strong></td>
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</tr>
<tr>
<td>Zehbe, 2016</td>
<td>Cyto</td>
<td>0.10 (0.05, 0.14)</td>
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<tr>
<td>Subtotal (I2 = %, p = .)</td>
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</tr>
<tr>
<td><strong>Door-to-door</strong></td>
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<tr>
<td>Lazcano-Ponce, 2011</td>
<td>HPV</td>
<td>0.11 (0.11, 0.12)</td>
</tr>
<tr>
<td>Arrossi, 2015</td>
<td>HPV</td>
<td>0.64 (0.62, 0.66)</td>
</tr>
<tr>
<td>Modibo, 2017</td>
<td>HPV</td>
<td>0.36 (0.28, 0.44)</td>
</tr>
<tr>
<td>Moses, 2016</td>
<td></td>
<td>0.51 (0.45, 0.57)</td>
</tr>
<tr>
<td>Subtotal (I2 = 99.9%, p = 0.000)</td>
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<td>0.40 (0.03, 0.78)</td>
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<td>Study</td>
<td>testcontrstr</td>
<td>RP (95% CI)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Mail-to-all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bas, 2007</td>
<td>Cyto</td>
<td>1.77 (1.36, 2.31)</td>
</tr>
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<td>Gok, 2010</td>
<td>Cyto</td>
<td>1.66 (1.27, 2.16)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td>Cyto</td>
<td>1.20 (0.92, 1.57)</td>
</tr>
<tr>
<td>Piana, 2011</td>
<td>Cyto</td>
<td>3.66 (2.34, 4.13)</td>
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<tr>
<td>Szarewski, 2011</td>
<td>Cyto</td>
<td>1.41 (1.04, 1.91)</td>
</tr>
<tr>
<td>Virtanen, 2011</td>
<td>Cyto</td>
<td>1.07 (0.99, 1.15)</td>
</tr>
<tr>
<td>Wikstrom, 2011</td>
<td>Cyto</td>
<td>3.72 (3.20, 4.32)</td>
</tr>
<tr>
<td>Gok, 2012</td>
<td>Cyto</td>
<td>4.73 (2.98, 7.49)</td>
</tr>
<tr>
<td>Haguenoer, 2014</td>
<td>Cyto</td>
<td>1.16 (1.00, 1.35)</td>
</tr>
<tr>
<td>Cadman, 2015</td>
<td>Cyto</td>
<td>1.45 (1.21, 1.75)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td>Cyto</td>
<td>1.66 (1.46, 1.90)</td>
</tr>
<tr>
<td>Enerly, 2016</td>
<td>Cyto</td>
<td>0.91 (0.78, 1.06)</td>
</tr>
<tr>
<td>Racey, 2016</td>
<td>Cyto</td>
<td>1.36 (0.98, 1.88)</td>
</tr>
<tr>
<td>Sultana, 2016</td>
<td>Cyto</td>
<td>1.87 (1.57, 2.23)</td>
</tr>
<tr>
<td>Kitchener, 2017</td>
<td>Cyto</td>
<td>0.46 (0.37, 0.57)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td>HPV</td>
<td>1.12 (0.86, 1.45)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td>HPV</td>
<td>1.63 (1.45, 1.82)</td>
</tr>
<tr>
<td>Darlin, 2013</td>
<td>Cyto/HPV</td>
<td>3.50 (2.24, 5.46)</td>
</tr>
<tr>
<td>Subtotal (I2 = 98.6%, p = 0.000)</td>
<td></td>
<td>1.78 (1.29, 2.45)</td>
</tr>
<tr>
<td>Opt-in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td>Cyto</td>
<td>0.42 (0.29, 0.60)</td>
</tr>
<tr>
<td>Broberg, 2014</td>
<td>Cyto</td>
<td>1.27 (1.03, 1.56)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td>Cyto</td>
<td>0.89 (0.77, 1.04)</td>
</tr>
<tr>
<td>Kitchener, 2017</td>
<td>Cyto</td>
<td>0.09 (0.06, 0.14)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2011</td>
<td>HPV</td>
<td>0.39 (0.27, 0.56)</td>
</tr>
<tr>
<td>Giorgi-Rossi, 2015</td>
<td>HPV</td>
<td>0.87 (0.77, 0.99)</td>
</tr>
<tr>
<td>Subtotal (I2 = 98.6%, p = 0.000)</td>
<td></td>
<td>0.51 (0.31, 0.85)</td>
</tr>
<tr>
<td>Community campaign</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zehbe, 2016</td>
<td>Cyto</td>
<td>2.58 (1.67, 3.99)</td>
</tr>
<tr>
<td>Subtotal (I2 = .%, p = .)</td>
<td></td>
<td>2.58 (1.67, 3.99)</td>
</tr>
<tr>
<td>Door-to-door</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lazcano-Ponce, 2011</td>
<td>Cyto</td>
<td>1.13 (1.12, 1.14)</td>
</tr>
<tr>
<td>Arrossi, 2015</td>
<td>HPV</td>
<td>4.15 (3.85, 4.47)</td>
</tr>
<tr>
<td>Modibbo, 2017</td>
<td>HPV</td>
<td>1.64 (1.44, 1.86)</td>
</tr>
<tr>
<td>Moses, 2016</td>
<td></td>
<td>2.05 (1.80, 2.33)</td>
</tr>
<tr>
<td>Subtotal (I2 = 99.9%, p = 0.000)</td>
<td></td>
<td>1.99 (0.68, 5.85)</td>
</tr>
</tbody>
</table>

Relative participation

<p>| Subtotal  (I2 = 99.9%, p = 0.000) |             | 1.99 (0.68, 5.85) | Subtotal (I2 = 99.9%, p = 0.000) |             | 2.01 (0.66, 6.15) |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>#</th>
<th>Absolute proportion</th>
<th>#</th>
<th>Relative Proportion</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Self-sampling</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Unsatisfactory sample</td>
<td>17</td>
<td>0.9% (0.5-1.4%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Test-positivity†</td>
<td>20</td>
<td>11.2% (9.8-12.7%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Compliance to F-U</td>
<td>19</td>
<td>80.0% (65.6-91.4%)</td>
<td>11</td>
<td>0.91 (0.80-1.05)</td>
</tr>
<tr>
<td>CIN2+/1000 invited</td>
<td>17</td>
<td>2.5% (1.3-4.0‰)</td>
<td>13</td>
<td>2.43 (1.48-4.00)</td>
</tr>
<tr>
<td>CIN2+/1000 screened</td>
<td>17</td>
<td>8.6% (6.3-11.3‰)</td>
<td>13</td>
<td>0.96 (0.48-1.90)</td>
</tr>
</tbody>
</table>

# number of studies; † test positivity of hrHPV-test in the self-sampling arm (per-protocol);
Conclusions:

• Opt-out (mail to everyone) increases absolute participation by ~12%.

• Opt-in does not increase participation.

• Door-to-Door increases absolute participation by 40% and requires greater resources.
Methods:

• Systematic review included:
  • Studies using a community approach to increase screening participation
  • Studies including cervico-vaginal self-collection for HPV testing
  • Published in PubMed through Feb 16, 2017

• Selection:
  • Two reviewers reviewed list independently
  • Selected studies meeting criteria
  • Reviewed lists together to reach consensus on included studies
Results:

• A total of 10 studies included.
• Methods and local screening contexts differed such that a quantitative meta-analysis was not possible.
• Recruitment methods for included studies:
  • Door-to-door recruitment (N=3)
  • Enrollment followed by randomization (N=2)
  • Choice (N=3)
  • Other community approach (N=2)
Choice: Winer, 2016

- **Population**
  - Hopi women, 21–65 y.o.

- **Location**
  - Hopi Reservation, Arizona, United States

- **Intervention**
  - Enrollment sites: community events, door-to-door, Hopi Office of Prevention and Intervention Cancer Support Services (HCSS) office.
  - Choice: self-collection at home vs. HCSS

- **Participation**
  - 329 (93.2%) of women completed self-collection
    - Most (79%) collected at home, compared to 21% who self-collected at HCSS.

Choice: Ilangovan, 2016

- **Population**
  - Haitian and Latina women, 30–65 y.o., no cytology in the previous 3y.

- **Location**
  - Miami, Florida, United States

- **Intervention**
  - CHW recruited from two safety net clinics: one primarily serving Latinas, one primarily serving Haitians. Participants recruited by a CHW who spoke their native language.
  - Choice of self-collection or discussion about Pap with provider.

- **Participation**
  - 121 (100%) who chose self-collection collected samples @ clinics.
  - 46 (78%) of women choosing a cytology discussion had cytology < 5 months.

Choice: Castle, 2011

- **Population**
  - Women 26–65 y.o., unscreened in ≥3 years

- **Location**
  - Mississippi Delta, Mississippi, United States

- **Intervention**
  - CHW recruited door-to-door
  - Women offered choice of Pap voucher or self-collection at home
  - Women not completing cytology within 30 days were re-contacted

- **Participation**
  - 62 (80.5%) of women who choose self-collection returned samples
  - 17 (40.5%) of women who choose Pap attended a cytology visit

Other: Vanderpool, 2014

- **Population**
  - Women 30–64 y.o., no cytology in the past 4 years

- **Location**
  - Southeastern Kentucky, United States

- **Intervention**
  - Study nurse recruited and enrolled women at a free primary clinic

- **Participation**
  - All 31 recruited participants enrolled and completed self-collection

Cluster-randomization: Zebhe, 2016

- **Population**
  - 25-69 y.o., First Nations Community, Living on a Reservation

- **Location**
  - Thunder Bay District, Northwest Ontario, Canada

- **Intervention**
  - Community-based research assistants recruited participants through: community events, door-to-door, social media, mail, and Health office networks
  - Recruitment methods varied by community cluster

- **Participation:**
  - 54 (13.4%) of eligible women recruited for self-collection
  - 35 (5.9%) of eligible women offered cytology

Conclusions:

• In general, a community approach using self-collected samples increases participation.

• Approach is more labor intensive and expensive
Final Comments:

• More, direct engagement = greater participation

• Major questions:
  ➢ Is the “Juice Worth the Squeeze” i.e., is it more cost-effective to use active (door-to-door) or passive (mail to all) delivery of self-collection?
  ➢ How can passive approaches be improved to increase participation (e.g., social media)?
Self-Collection Devices for Pap Test:

Study Design Issues with Validation of Pap tests with Samples Self-Collected at Home

FDA Public Workshop
January 11, 2018

Marina Kondratovich, Ph.D.
OIR/CDRH/FDA
Outline

• Intended use population
• Reported Pap results for self-collected cervical cytology specimens
• Clinical performance study
  - Issue with agreement evaluation
  - Comparison using gold standard
• Discussion points
1) Intended Use Population

- Women (intended users of the Self-Collection (SC) device for the Pap test) in the clinical study: representative of the US population with regard to age, race, levels of education;

- Instructions for use should be “simple”, in plain language with pictorial explanations “How to use”;

- Cytology specimens should be self-collected at home using ONLY instructions for use (women should not have any verbal instructions before using the device). Once the specimen is collected, users ship the samples to a designated laboratory for processing.

- Immediately following self-collection, women should answer questions about whether women were comfortable with use of the device and whether they understood how to use the self-collection device.
1) Intended Use Population (cont.)

Hypothetical study:
The subjects who are enrolled in the clinical study are women with self-scheduled appointments to cervical cancer screening clinics. Women who are non-responders to the cervical cancer screening program are not included in the study (but these women are a part of the intended use population).

Please discuss:

1. Possible biases of the study which includes ONLY subjects who participate in the cervical cancer screening;

2. Whether clinical study should include also women who are non-responders to their regular cervical cancer screening program. How these women can be enrolled in the clinical study?
2) Reported Pap results for self-collected cervical cytology specimens

Study size and values of clinical performance measures depend on how Pap results are reported. Pap results with Physician- Collected (PC) specimens are reported according to The 2001 Bethesda System.

<table>
<thead>
<tr>
<th>The 2001 Bethesda System for PC specimens</th>
<th>SC specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scenario 1</td>
</tr>
<tr>
<td>NILM</td>
<td>NILM</td>
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<tr>
<td>ASC-US/AGUS</td>
<td>ASC-US/AGUS</td>
</tr>
<tr>
<td>LSIL</td>
<td>LSIL</td>
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<tr>
<td>ASC-H</td>
<td>ASC-H</td>
</tr>
<tr>
<td>HSIL</td>
<td>HSIL</td>
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<tr>
<td>Cancer</td>
<td>Cancer</td>
</tr>
<tr>
<td>UNSAT</td>
<td>UNSAT</td>
</tr>
</tbody>
</table>
2) Reported Pap results for self-collected cervical cytology specimens

Study size and values of clinical performance measures depends on how Pap results are reported.

- The more categories are reported, the larger study size should be (Result “Abnormal” is ≈10%; Results “HSIL” is ≈0.6%-1%)

Please discuss

1. How Pap results can be reported i) to physicians (if the device is by prescription), ii) to women (if device is OTC).
2. What will be next steps for women with “Normal” results by SC Pap test?
3. What will be next steps for women with UNSAT results by SC Pap test? (published literature suggest that percent of UNSAT results can be as high as 10%).
3) Clinical Performance Study

Study design:

- N representative subjects from the intended use population
- Each subject has
  - Self-Collected Pap result obtained in laboratory using approved imaging device (Lab SC) and
  - Physician-Collected Pap result obtained in laboratory using approved imaging device (Lab PC).

![Diagram showing the process of Pap slide collection and results from SC and PC vials leading to Lab SC and Lab PC results.](image)
Positive Percent Agreement (PPA) = $\frac{A}{A+C}$ with 95% CI
Negative Percent Agreement (NPA) = $\frac{D}{B+D}$ with 95% CI.

%UNSAT by Lab PC and %UNSAT by Lab SC

Published literature suggest that levels of PPA is not high (around 80%) => Gold Standard should be applied.
### Scheme A. Gold Standard is applied to ALL subjects

<table>
<thead>
<tr>
<th></th>
<th>Lab SC</th>
<th>Lab PC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pos</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Lab SC</td>
<td>40</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Neg</td>
<td>10</td>
<td>930</td>
<td>940</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>950</td>
<td>1,000</td>
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</table>

#### Gold Standard Positive

<table>
<thead>
<tr>
<th></th>
<th>Lab SC</th>
<th>Lab PC</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>Lab SC</td>
<td>40</td>
<td>20</td>
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<tr>
<td>Neg</td>
<td>10</td>
<td>930</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>950</td>
</tr>
</tbody>
</table>

\[
\text{Se}_{\text{Lab SC}} = \frac{38+9}{83} = 56.6\%
\]

\[
\text{Se}_{\text{Lab PC}} = \frac{38+6}{83} = 53.0\%
\]

\[
\text{Ratio} = \frac{\text{Se}_{\text{Lab SC}}}{\text{Se}_{\text{Lab PC}}} = \frac{38+9}{38+6} = 1.07 \text{ times}
\]

#### Gold Standard Negative

<table>
<thead>
<tr>
<th></th>
<th>Lab SC</th>
<th>Lab PC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>Lab SC</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Neg</td>
<td>4</td>
<td>900</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>911</td>
</tr>
</tbody>
</table>

\[
\text{Sp}_{\text{Lab SC}} = \frac{900+4}{917} = 98.6\%
\]

\[
\text{Sp}_{\text{Lab PC}} = \frac{900+11}{917} = 99.3\%
\]

\[
\text{Ratio} = \frac{\text{Sp}_{\text{Lab SC}}}{\text{Sp}_{\text{Lab PC}}} = \frac{900+4}{900+11} = 0.992 \text{ times}
\]
**Scheme B. Gold Standard is applied to all double positive and all discordant subjects**

<table>
<thead>
<tr>
<th>Lab SC</th>
<th>Pos</th>
<th>Neg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos</td>
<td>40</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Neg</td>
<td>10</td>
<td>930</td>
<td>940</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab PC</th>
<th>Pos</th>
<th>Neg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Gold Standard Positive**

- Gold Standard Positive
- Gold Standard Negative

- \( Se_{Lab SC} = \frac{(38+9)}{?} \)
- \( Se_{Lab PC} = \frac{(38+6)}{?} \)

> It is impossible to estimate sensitivities

**Ratio**

\[ \frac{Se_{Lab CS}}{Se_{Lab PC}} = \frac{(38+9)}{(38+6)} = 1.07 \text{ times with 95\% CI} \]

**Gold Standard Negative**

- \( Sp_{Lab SC} = \frac{(?+4)}{?} \)
- \( Sp_{Lab PC} = \frac{(?+11)}{?} \)

> It is impossible to estimate specificities

**Ratio**

\[ \frac{1-Sp_{Lab SC}}{1-Sp_{Lab PC}} = \frac{(2+11)}{(2+4)} = 2.2 \text{ times with 95\% CI} \]
Scheme B. *Gold Standard is applied to all double positive and all discordant subjects*

- It is impossible to estimate sensitivities and specificities

- Estimates of the ratio of sensitivities and the ratio of false positive rates are unbiased.

*Condition for scheme B:* Performance of Pap test with Physician-Collected specimens should be known in the intended use population.
Discuss:

1) What is a minimum and maximum time frames between two collections that can be adequate
   i) to allow the cervix to recover from the previous sampling and
   ii) to allow considering that both Pap results can be the same.

2) Designs of scheme A (all subjects have GS) and scheme B (all double positive and all discordant subjects have GS)

3) For scheme B, take into consideration that performance of Pap test with PC specimens is well established for the women participated in their regular cervical screening program (can be assumed that Pap test performance with PC specimens for the women who are non-responders is not worse).
3) Clinical Performance Study: Gold Standard

Approach I

Target condition = Cervical disease;
Gold Standard = Colposcopy and biopsy if needed
3) Clinical Performance Study: Gold Standard Approach I

Scheme B. All double positive and all discordant subjects should have colposcopy/biopsy results

<table>
<thead>
<tr>
<th></th>
<th>Lab PC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pos</td>
</tr>
<tr>
<td>Lab SC</td>
<td></td>
</tr>
<tr>
<td>Pos</td>
<td>40</td>
</tr>
<tr>
<td>Neg</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
</tr>
</tbody>
</table>

Notes:
- Subjects with Lab PC=Neg and Lab SC=Pos should be referred to colposcopy/biopsy;
- Consider prevalence of cervical disease (defined as CIN2+ or CIN3+) => large study for estimation of the ratio of sensitivities
3) Clinical Performance Study: Gold Standard

Approach II
Target condition = Patient Cytology Status

For example, Ad.Com. SC result=ASC-US, Ad.Com. PC result=HSIL => Patient Cytology Status=HSIL
3) Clinical Performance Study: Gold Standard

Approach II

Target condition = Patient Cytology Status

**Adjudication Committee**

- Three experts
- Pap result by Expert 1 (manual read)
- Pap result by Expert 2 (manual read)
- If results of Expert 1 and Expert 2 are the same then this result is a result of the Adjudication Committee
- If results of Expert 1 and Expert 2 are different then result of Expert 3 is needed.
- Adjudication Committee result is according to majority rule for three experts
- If all three results are different then Adjudication Committee result is a consensus result of three experts
3) Clinical Performance Study: Gold Standard

Discuss:

Advantages and disadvantages of both approaches for the Gold Standard (colposcopy/biopsy or Patient Cytology Status) taking into consideration

- Relevance of the target condition (Cervical disease determined by colposcopy/biopsy and Patient Cytology Status)
- Size of the study for estimation of the ratio of sensitivities
Panel Discussion Topic 2: Performance considerations for self-collection devices for Pap test

• Moderator: Cheng Cui, PhD
• Panelists:
  - Philip Castle, PhD, MPH
  - Marina Kondratovich, PhD
  - Christine Booth, MD, FCAP
  - Richard Conlen, MD, FACOG
## Public Comments

<table>
<thead>
<tr>
<th>Order</th>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jeff Andrews</td>
<td>BD</td>
</tr>
<tr>
<td>2</td>
<td>Charles Lucher</td>
<td>GyneConcepts, Inc.</td>
</tr>
<tr>
<td>3</td>
<td>Erwin Skibell</td>
<td>GyneConcepts, Inc.</td>
</tr>
<tr>
<td>4</td>
<td>Sean Boyle</td>
<td>Roche</td>
</tr>
<tr>
<td>5</td>
<td>Barbara Crothers</td>
<td>American Society of Cytopathology</td>
</tr>
<tr>
<td>6</td>
<td>Kainat Ishteyaque</td>
<td>NHSRC</td>
</tr>
<tr>
<td>7</td>
<td>Alex Rudolph</td>
<td>Personal Health Management, LLC</td>
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<tr>
<td>8</td>
<td>Arthur Furnier</td>
<td>University of Miami Miller School of Medicine</td>
</tr>
<tr>
<td>9</td>
<td>Jennifer Smith</td>
<td>University of North Carolina, Chapel Hill</td>
</tr>
<tr>
<td>10</td>
<td>Edward Evantash</td>
<td>Hologic, Inc.</td>
</tr>
</tbody>
</table>
Closing Remarks

Reena Philip
Division Director

Division of Molecular Genetics and Pathology
Office of In Vitro Diagnostics and Radiological Health
CDRH/FDA