Designing & testing the future of home-based cervical cancer screening: results from a collaborative academic-embedded delivery system pragmatic randomized trial
Diana Buist  
Chris Thayer  
Kilian Kimbel  
Margie Wilcox  
Ellen Schartz  
Vina Graham  
Zoe Bermet  
Jane Dimer  
Kim Riddell  
KPWA Microbiology lab  
KPWA clinicians 
EAGLES

Tara Beatty  
Hongyuan Gao  
Lisa Shulman  
Mary Shea  
Ann Kelley  
Nora van Doren  
Scott Caparelli  
Janet Chestnut  
Sarah Levy  
Lin Thach  
Shaun Auld  
Jenna Leonardo  
Donna Luce  
Jennie Barrett  
Jessica Brandlin  
Tonika Davis-Arrington  
Margaret Shephard  
Vickie Taylor  
Tiffany Gaines  
Nora Wheat  
Joetta Mattson  
Dottie Oliver  
Jared Lopes  
Camilo Estrada  
Kevin Filocamo

Rachel Winer  
John Lin  
Colin Malone  
Constance Mao

UC Davis  
University of California

Jasmin Tiro  
Andrea Betts

Funding: National Cancer Institute - R01CA168598, PI Winer  
ClinicalTrials.gov: NCT02005510
Disclosure

None of the coauthors have any conflicts of interest to disclose
HPV and Cervical Cancer

• Human papillomavirus (HPV) is a common sexually transmitted infection.

• Most infections resolve spontaneously – a minority persist and cause pre-cancerous changes to cells of the cervix.

• Almost all cervical cancers are caused by human papillomavirus
Cervical Cancer Screening

• Two screening tests are used for prevention or early detection of cervical cancer:
  • **Pap tests** identify abnormal cells on the cervix
  • **HPV tests** detect the virus that causes these abnormal cells

• Pap and HPV tests are used individually or in combination (co-testing)
2018 USPSTF Guidelines

21-29 years: Pap every 3 years

30-65 years: 3 options:
   1) Pap every 3 years
   2) HPV alone (i.e. “primary HPV”) every 5 years
   3) Co-test every 5 years
US population of women aged 30-64

73,180,000
US population of women aged 30-64

73,180,000
18,295,000
US population of women aged 30-64

73,180,000
18,295,000
13,000
US population of women aged 30-64

73,180,000
18,295,000
13,000
50%
Future state
In-Clinic

In-Home

Colposcopy needed

In-clinic testing

Home test negative, screening complete
**Pragmatic randomized trial**

Compare the effectiveness of two programmatic approaches to increasing cervical cancer screening among women aged 30-64 years who are overdue for cervical cancer screening.

**Primary**
- Early detection and treatment of cervical neoplasia

**Secondary**
- Cervical cancer screening uptake
- Predictors of screening
- Patient experiences: knowledge, attitudes and barriers towards self-collect and follow-up
- Impact on health system & clinical teams

Over 30 months (February 2014- August 2016) we randomized 20,284 (16,590 individual women)
Main Findings

Benefits
✓ Increased screening uptake by 50% compared to usual care
✓ Patient-centered: convenient & easy to use
✓ No significant difference in CIN2+ detection or treatment

Areas for improvement
✓ Improving patient education to address concerns about ability to use kits correctly & distrust in test results
✓ Closing systems gaps and improving patient and provider education to increase adherence to diagnostic follow-up after an HPV positive kit result
Cervical Cancer Screening (CCS)

Assesses women 21–64 years of age who were screened for cervical cancer using either of the following criteria:

- Women age 21–64 who had cervical cytology performed every 3 years.
- Women age 30–64 who had cervical cytology/human papillomavirus (HPV) co-testing performed every 5 years.
Rationale and design of the HOME trial: A pragmatic randomized controlled trial of home-based human papillomavirus (HPV) self-sampling for increasing cervical cancer screening uptake and effectiveness in a U.S. healthcare system

Rachel L. Winer\textsuperscript{a,b,*}, Jasmin A. Tiro\textsuperscript{c}, Diana L. Miglioretti\textsuperscript{b,d}, Chris Thayer\textsuperscript{e}, Tara Beatty\textsuperscript{b}, John Lin\textsuperscript{f}, Hongyuan Gao\textsuperscript{b}, Kilian Kimbel\textsuperscript{b}, Diana S.M. Buist\textsuperscript{b}

\textsuperscript{a} Department of Epidemiology, University of Washington, Box 359933, 325 9th Ave, Seattle, WA 98104, USA
\textsuperscript{b} Kaiser Permanente Washington Health Research Institute, 1730 Minor Ave, Suite 1600, Seattle, WA 98101, USA
\textsuperscript{c} Department of Clinical Sciences, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA
\textsuperscript{d} Division of Biostatistics, University of California Davis, Med Sci 1C, Room 145, One Shields Avenue, Davis, CA 95616, USA
\textsuperscript{e} Kaiser Permanente Washington, 2715 Naches Ave SW, PO Box 9010, Renton, WA 98057, USA
\textsuperscript{f} Department of Pathology, University of Washington, Box 359933, 325 9th Ave, Seattle, WA 98104, USA
Pragmatic RCT Design

Assessed for eligibility via electronic medical record

Inclusion criteria:
• Received “birthday letter” with Pap reminder 5 months prior
• Aged 30-64 years with an intact uterus
• Have PCP within integrated delivery system
• Continuously enrolled for ≥3.4 years
• No Pap within prior 3.4 years

All eligible women randomized 1:1 (round 1) (n=16,590)

Intervention arm (n=8,283)
• Usual care outreach for Pap screening
• Study team mails HPV self-sampling kit with research information sheet
• After 3 weeks, study team makes up to 3 kit reminder calls

Control arm (n=8,307)
• Usual care outreach for Pap screening
• No contact with study team
Your kit includes:

- Gloves
- 2 cotton swabs in separate wrappers
- A tube to hold the cotton swabs after you collect your sample
- A biohazard bag and a small, padded envelope for mailing your sample to us

Things to know before you collect your sample:

- Do not use the screening kit if you are pregnant.
- For best results, do not have sexual intercourse, douche, or use vaginal medications for 48 hours before collecting your sample.

1. Wash and dry your hands, then put on the gloves. Next, open the tube and take the first cotton swab out of the wrapper.
2. Spread apart the skin outside your vagina. With the other hand, gently push the cotton swab into your vagina as far as it will go without hurting—like you would with a tampon.
3. Hold the cotton swab at the middle with your fingers and break it in half. Try not to touch the cotton tip.
4. Put the cotton swab into the tube, then set the tube within easy reach. Throw away the broken end.
5. Rotate the cotton swab inside your vagina three full turns, keeping it as far inside as you can.
6. Take the cotton swab out of your vagina while spreading apart the outside skin.
7. Take the second swab out of the wrapper, then repeat steps 2-6. When you’re done, both swabs will be in the tube.
8. Close the tube, throw away the gloves, and wash your hands.
Assessed for eligibility via electronic medical record

**Inclusion criteria:**
- Received "birthday letter" with Pap reminder 5 months prior
- Aged 30-64 years with an intact uterus
- Have PCP within integrated delivery system
- Continuously enrolled for ≥3.4 years
- No Pap within prior 3.4 years

All eligible women randomized 1:1 (round 1) (n=16,590)

**Intervention arm** (n=8,283)
- Usual care outreach for Pap screening
- Study team mails HPV self-sampling kit with research information sheet
- After 3 weeks, study team makes up to 3 kit reminder calls

**Control arm** (n=8,307)
- Usual care outreach for Pap screening
- No contact with study team

Kit returned
- Woman mails kit directly to KPWA lab for testing
- Electronic results & recommended follow-up released to woman and woman’s own PCP
- Woman’s own PCP manages follow-up of HPV results

**Safety monitoring**
- HPV positive: Study team sends staff message to provider if HPV undermanaged

Cervical cancer screening follow-up tracking (Screening, diagnosis, and treatment)

No kit returned

Exclusion criteria:
- On “do not contact list” for research
- Pregnant
- Language interpreter needed

Re-assessed for eligibility & re-randomization (1 yr post-randomization)
- Re-randomized 1:1 (round 2) (n=3,231)
- Re-randomized 1:1 (round 3) (n=409)

Cervical cancer screening follow-up tracking (Screening, diagnosis, and treatment)
<table>
<thead>
<tr>
<th></th>
<th>Mailed HPV Kit</th>
<th>Usual Care</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening initiation</td>
<td>2646 (26.6%)</td>
<td>1917 (17.4%)</td>
<td>1.53 (1.45-1.61)</td>
</tr>
</tbody>
</table>
Randomized women

Randomized to in-home HPV screening arm

N=9,960

Randomized to usual care arm

N=9,891

Return HPV kit

N=1,206

HPV16+ or HPV18+

Other hrHPV+ only

Unsat hrHPV-

N=34

N=102

N=6

N=1,064

Pap or co-test

N=72

N=3

N=6

No Screening

Pap or co-test

N=1,440

N=7,314

N=1,719

N=8,172

Screening uptake captured up to 6 months after randomization

Colposcopy

N=1,206

Mailed HPV Kit

Usual Care

RR (95% CI)

Screening completed

2618 (26.3%)

1917 (17.4%)

1.51 (1.43-1.60)

Non-guideline recommended management
Randomized women

- N=9,960
- N=9,891

Randomized to in-home HPV screening arm

- N=1,206
  - Return HPV kit
    - N=34
      - HPV16+ or HPV18+
      - Other hrHPV+ only
      - Unsat
      - hrHPV-
    - Pap or co-test
      - N=102
        - Colposcopy referral*
          - N=31
            - CIN 2+
              - N=2
    - Pap or co-test
      - N=6
        - Surveillanc screen follow-up*
          - N=33
            - N=38
        - Return to routine screening
          - N=34

Randomized to usual care arm

- N=1,440
  - Pap or co-test
    - N=1,440
  - No Screening
    - N=7,314
      - Colposcopy referral*
        - N=42
          - Surveillance screen follow-up*
            - N=42
          - Return to routine screening
            - N=72
    - Pap or co-test
      - N=1,719
        - No Screening
          - N=8,172
      - Colposcopy referral*
        - N=35
          - Surveillance screen follow-up*
            - N=35
          - Return to routine screening
            - N=4

Diagnosis

- CIN 2+ captured up to 6 months after screening results
- Screening uptake captured up to 6 months after randomization

--- Non-guideline recommended management

<table>
<thead>
<tr>
<th>Mailed HPV Kit</th>
<th>Usual Care</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN2+</td>
<td>12 (0.1%)</td>
<td>8 (0.1%)</td>
</tr>
</tbody>
</table>
Randomized to in-home HPV screening arm

- N=1,206
- Return HPV kit
  - HPV16+ or HPV18+
  - Other hrHPV+ only
  - Unsat hrHPV-
  - Pap or co-test
    - N=20
      - Colposcopy referral*
        - N=31
          - CIN 2+
            - N=2
              - Treatment
                - N=2
      - Surveillance screen follow-up*
        - N=38
          - Return to routine screening
  - N=34
  - N=102
  - N=6
  - N=1,064

Randomized to usual care arm

- N=1,440
- Pap or co-test
  - N=72
    - Pap or co-test
    - N=1,440
  - No Screening
  - N=7,314

N=9,960

<table>
<thead>
<tr>
<th>Treatment Received</th>
<th>Mailed HPV Kit</th>
<th>Usual Care</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 (0.1%)</td>
<td>7 (0.1%)</td>
<td>1.70 (0.67-4.32)</td>
<td></td>
</tr>
</tbody>
</table>
Time to screening uptake

<table>
<thead>
<tr>
<th>Time since randomization, d</th>
<th>Control</th>
<th>Intervention</th>
<th>Intervention Arm</th>
<th>Intervention Arm, Kit</th>
<th>Intervention Arm, Pap</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9891</td>
<td>9960</td>
<td>9960</td>
<td>9960</td>
<td>9960</td>
</tr>
<tr>
<td>5</td>
<td>9612</td>
<td>9265</td>
<td>9542</td>
<td>9683</td>
<td>9683</td>
</tr>
<tr>
<td>10</td>
<td>9267</td>
<td>8370</td>
<td>8954</td>
<td>9376</td>
<td>9376</td>
</tr>
<tr>
<td>15</td>
<td>8952</td>
<td>8032</td>
<td>8954</td>
<td>9376</td>
<td>9376</td>
</tr>
<tr>
<td>20</td>
<td>8708</td>
<td>7775</td>
<td>8850</td>
<td>9142</td>
<td>9142</td>
</tr>
<tr>
<td>25</td>
<td>8418</td>
<td>7545</td>
<td>8817</td>
<td>8918</td>
<td>8918</td>
</tr>
<tr>
<td>30</td>
<td>8185</td>
<td>7351</td>
<td>8797</td>
<td>8783</td>
<td>8783</td>
</tr>
</tbody>
</table>

Cumulative screening uptake (%)

0 30 60 90 120 150 180

Days since randomization

Control Arm

Intervention Arm

Intervention Arm, Kit

Intervention Arm, Pap
Main Findings

Benefits

✓ Increased screening uptake by 50% compared to usual care
✓ Patient-centered: convenient & easy to use
✓ No significant difference in CIN2+ detection or treatment

Areas for improvement

✓ Improving patient education to address concerns about ability to use kits correctly & distrust in test results
✓ Closing systems gaps and improving patient and provider education to increase adherence to diagnostic follow-up after an HPV positive kit result
Semi-structured interviews

Goal: Describe women’s attitudes, emotional responses, and informational needs after receiving a positive kit result and completing recommended follow-up.

Focused on 3 domains:

1) Reaction to mailed HPV kit
2) Reaction to positive test results
3) Understanding about different screening and follow-up strategies (Pap vs. HPV tests)
• 46 women interviewed (out of 75 invited) with HPV+ kit result
  • 38 completed all recommended follow-up
  • 8 did not complete all recommended follow-up
Likes

• Test convenience
• Private setting

Opportunities

• Improving access to information on interpreting HPV test results and next steps (will be true for primary HPV testing too)
• Education on HPV and role in cervical cancer
• Understanding discordant results
Survey of women’s experiences with unsolicited mailed kits

Goal:

• Identify HPV/cervical cancer knowledge, perceived risk, and Pap attitudes associated with returning a HPV self-screening kit

• Characterize HPV kit-user experiences, barriers, and future screening intentions and preferences

Compared 116 kit returners (272 invited) & 119 non-returners (1083 invited)
Likes

• Easy to follow instructions
• Swab easy to insert
• Easy to use kit correctly
• Convenient to mail back kit
• Felt in control of health after using kit

Opportunities

• 8% reported pain
• 12% felt physically uncomfortable when using the kit
• 6% using it was embarrassing
• 9% was not sure got a good sample from vagina
• 6% wasn’t sure if they could trust the screening kit
Main Findings

**Benefits**
- Increased screening uptake by 50% compared to usual care
- Patient-centered: convenient & easy to use
- No significant difference in CIN2+ detection or treatment

**Areas for improvement**
- Improving patient education to address concerns about ability to use kits correctly & distrust in test results
- Closing systems gaps and improving patient and provider education to increase adherence to diagnostic follow-up after an HPV positive kit result
Improving the promise of embedded pragmatic trials: Surmountable barriers encountered in an evaluation of home-based HPV self-sampling to increase cervical cancer screening in overdue women

D.S.M. Buist\textsuperscript{a,\ast}, J.A. Tiro\textsuperscript{b}, C. Thayer\textsuperscript{c}, T. Beatty\textsuperscript{a}, D.L. Miglioretti\textsuperscript{a,d}, J. Lin\textsuperscript{e}, R.L. Winer\textsuperscript{e}
What it took to get this off the ground

• A lot of meetings!
  • ~1.5 years of discussion and negotiation with: Lab; Primary care & OB/GYN; Prevention and Outreach teams

• Negotiating on target population

• Alignment with evolving guidelines

• Multiple clinical champions and clinical co-investigator

• Extensive back and forth with IRB for approval
Additional challenges & methodological opportunities

• Blinding research team
• Trial fidelity vs. rapid evaluation and correction during the course of the study
• Reviewing records to ensure providers have done correct follow-up for a test they did not order and are not (necessarily) familiar with – while avoiding potential performance bias
• Ensuring successful integration with the clinical delivery system and appropriate measurement of system impact
• Critical monitoring of system changes
Thank you & questions