Addressing a ‘Last Mile’ Problem in Cervical Cancer Screening

Vikrant Sahasrabuddhe, MBBS, MPH, DrPH
Program Director
Division of Cancer Prevention
Cervical Cancer is Highly Preventable But is Still Not Fully Prevented!

(1975-2016, SEER data)
Background

- >13,000 women continue to be newly diagnosed and >4,000 women continue to die due to cervical cancer every year in the United States

- The full public health impact of prophylactic HPV vaccination on reducing cervical cancer rates will not be realized for at least another generation

- *Over half of the incident cervical cancer* cases in the US are among women who have been *never screened* or *infrequently screened, and who do not participate in routine screening*

- *This ‘last mile’ problem represents a significant cancer health disparity* and needs to be addressed via concerted efforts to reduce and eventually eliminate cervical cancer as a public health problem in the United States
Background

Current US Guidelines for Cervical Cancer Screening Methods for Average-Risk Asymptomatic Women

- **Age 21 to 29:** Every 3 years with Pap testing
- **Age 30 to 65:**
  - Every 5 years with HPV testing
  - **OR** Every 3 years with Pap testing
  - **OR** Every 5 years with co-testing (Pap testing + HPV testing)

(The U.S. Preventive Services Task Force states that HPV testing or Pap testing alone are preferred options compared with co-testing)
Background

Utilization of Cervical Cancer Screening remains suboptimal for ~3 out of 10 women

Percentage of Eligible Women Undergoing Screening in the Past Three Years, by Insurance Status

Medicaid and CHIP Payment and Access Commission, 2016; www.macpac.gov
Background

Missed opportunities for cervical cancer screening

In 2012, 8 million women were not screened in the last 5 years.

7 out of 10 women who were not screened had a regular doctor and health insurance.

Women less likely to be screened:

- lower socioeconomic status and lower educational attainment
- racial/ethnic minorities and foreign-born
- residents of rural counties or areas with geographic inaccessibility to adequate screening services (e.g., Appalachia, Deep South, US-Mexico border region, Native American Reservations, Pacific/Outlying Islands)

Self Sampling for HPV testing

- Ease of collection
- When women choose (time, place)
- By themselves/in privacy
- No need for appointment or speculum examination
- Kits can be mailed back and forth, or can be brought back during other clinic visits

Pictures: adapted from presentation by Dr. Anita Lim, KCL, UK
Self Sampling for HPV testing

Not a new concept – already offered to non-attenders of organized cervical cancer screening programs in Europe

Several studies have shown high patient acceptability for self-sampling-based cervical cancer screening

Other advantages of self-sampling-based cervical cancer screening

- HPV self-sampling increases uptake in nonattenders of regular screening
- Attendance to follow-up care after testing HPV positive by self-sampling is high
- Majority of women who actively declined screening indicated interest in self-sampling
- Direct offer of self-sampling devices to women in communities that were under-screened generated high participation rates

Self Sampling for HPV testing

- Meta-analyses of several observational studies and screening trials shows self-sampling-based HPV testing has
  - higher sensitivity compared to cytology
  - comparable sensitivity vs. clinician-collected sampling for PCR-based HPV testing

- Yet no clinical guideline in the US has incorporated a self-sampling strategy for HPV testing, primarily due to lack of an FDA-approval of self-sampling for HPV testing as a standard of care or an alternative screening approach for women who do not/cannot access clinic-based/speculum-exam-based cervical cancer screening

Goals of this Initiative

**Overall Goal:** To improve cervical cancer screening coverage to underserved and never-screened/under-screened women by expanding the current FDA-approved indication of use for HPV tests to include prescription-based self-collection of cervicovaginal specimens for HPV testing

Specifically:

1. This concept envisions a **public-private partnership** between federal/HHS-partners (NCI, CDC), industry stakeholders (HPV assay manufacturers), academic partners, professional societies/clinical practice guidelines organizations (e.g., ASCCP, ACS, ACOG)

2. The focus of this partnership will be to **plan, design, and conduct a FDA-registrational screening trial**
   - to validate self-collected cervicovaginal specimen-based HPV testing as a comparable (non-inferior) alternative to provider-collected cervical specimen for HPV testing in cervical cancer screening
   - to permit premarket approval (PMA) applications to the FDA by HPV assay manufacturers for expanded indication of use for prescription-based self-collection of cervicovaginal specimens
General Contour of the Screening Trial (based on FDA input)

- Participants: n≈ 5,000 women from diverse clinical settings with varying underlying HPV detection rates
- Ages: 25-64 years
- **Primary endpoint: HPV test concordance** between paired collection of self-collected cervicovaginal specimens vs. provider-collected cervical specimens
- Non-inferiority design: Expected concordance: >=0.98; lower bound of 95%CI: >=0.95
- Secondary endpoints: Clinical sensitivity for CIN2+/CIN3+ detection
General Contour of the Screening Trial (based on FDA input)

- Participant enrollment; informed consent; provider collected specimen for HPV testing and liquid-based cytology

- Mailing of HPV self-collection kits at home 2-3 days after clinic visit; to be returned in 2 weeks

- Provider and self-collected specimen labeled with different/masked IDs sent to central laboratory for aliquoting

- Aliquot order-balanced batches randomly assigned and sent to each participating company for HPV testing.

- Women who are HPV positive on either specimen or have cytologic abnormalities will undergo colposcopy/biopsy and quality-assured histopathology
Partnership Development and Pre-Trial Launch Phase

- **Convening a forum of key stakeholders** to collaboratively develop a public-private-partnership to design and implement an independent regulatory-grade screening clinical trial

- **Surveying and identifying the range of potential clinical sites in diverse delivery settings** in the United States (e.g., federally-qualified health centers catering to screening of under-served women, general screening clinics and referral colposcopy clinics in both managed care organizations and safety net hospitals) for conducting this multicenter trial
Partnership Development and Pre-Trial Launch Phase

- **R&D Contract (RFP) Solicitation:**
  - Publish RFP and review offerors to fund two distinct components:
    - Data Management, Auditing, and Coordinating Center (DMACC)
    - Clinical Sites for Participant Enrollment

- **Partnership formalizations:**
  - Develop partnership agreements (CTAs/MTAs) with industry partners with current FDA approvals for PCR-based HPV testing assays (Roche, BD, Hologic)

- **Protocol development and study launch:**
  - Develop scientific protocol and standard operating procedures
  - Launch nation-wide, multicenter screening trial in diverse delivery settings to support premarket approval (PMA) application for cervicovaginal self-collection for HPV testing indication to the FDA by industry partners
Trial Conduct and Analysis Phase

- NCI will oversee the conduct, monitor, and analyze results of the clinical trial
  - Inform estimates of screening efficacy by key patient-level (e.g., age, cytology status) and facility/system-level (e.g., care delivery setting) factors

- NCI will maintain the data master file for this trial and will submit it to the FDA
  - All clinical and laboratory data will be linked to create a Master Data File, which will used for study analyses and FDA evaluation

- Companies will receive redacted datasets composed of only data related to their own test and will cross-reference this file in their PMA applications.
  - This will ensure independence of the data while allowing simultaneous evaluation of HPV assays by several manufacturers
Budget

<table>
<thead>
<tr>
<th>NCI funding (via R&amp;D Contract RFP)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Data Management, Auditing, and Coordinating Center (DMACC)</td>
<td>1.5 million</td>
</tr>
<tr>
<td>• Clinical sites (5-6 sites)</td>
<td>4.5 million</td>
</tr>
<tr>
<td><strong>Total Costs (Direct + F&amp;A) (over period of performance of 3 years)</strong></td>
<td><strong>6 million</strong></td>
</tr>
</tbody>
</table>

**Industry Co-funding:** contribute resources via HPV testing (on self-collected cervicovaginal specimens and provider-collected cervical specimens; to be done in a masked fashion) + costs for premarket approval (PMA) applications to the FDA

**Other federal funding:** CDC may provide technical assistance and/or co-fund this initiative through supplementing its National Breast and Cervical Cancer Early Detection Program (NBCCEDP) clinics
Key Features of this Initiative

- Coalesces nascent and disjointed efforts to formally lay out a pathway for **regulatory approval for self-sampling** approaches for HPV testing

- Public-private partnership model will collaboratively address a key barrier that **cannot be addressed via disparate efforts** from either the public sector or industry in isolation

- Maximize potential for **independent ‘honest broker’ role for the NCI** in a multi-stakeholder partnership between federal and industry partners

- Provide evidence to **change clinical care guidelines** (e.g., ASCCP/ACS/ACOG practice guidelines) and public health practice (e.g., USPSTF cervical cancer screening recommendations) via a new standard-of-care approach to screening

- Eventually provide a **convenient and speculum-exam-free screening approach for all women** and thereby strengthen adherence to current screening guidelines and likely reduce excess health care costs
Potential to build on and link with other NIH/NCI-initiatives

- Several years of discussions and deliberations between NCI scientists and partners
  - NCI-led and NCI-supported efforts for generation of scientific evidence base for FDA approvals and introduction for HPV testing in clinical practice in the US
- Several models for joint NIH-FDA-industry-academic initiatives for FDA regulatory approvals for self-sampling approaches for disease prevention
- NIH/NCI currently funds and supports several initiatives (intramural and extramural) focused on self-sampling approaches for HPV testing

States with ongoing NIH/NCI-funded studies* focused on evaluation of uptake and implementation of self-sampling-based HPV testing

NCI Cancer Moonshot℠ initiative: ‘Accelerated Control of Cervical Cancer’

*listing not exhaustive
Responses to review by BSA Subcommittee (Drs. Anderson, Lacey, and Willman)

- **Ensuring participation by HPV assay manufacturers**
  - Several discussions already underway, including pre-submission meetings with the FDA; manufacturers will have ‘skin in the game’ by bearing costs for HPV testing

- **Site selection critical for ensuring success in achieving sample size & quality**
  - Initial survey will maximize opportunity for selection of participating sites from a wide-range of centers across diverse care delivery settings across the US

- **Focus on sensitive ethical/cultural aspects related to research participation and follow-up of minority populations**
  - Trial will be nested within clinical care settings; careful site selection to ensure representation of sites with strong history of successful patient navigation

- **Long-term measurement of impact of the initiative**
  - Several NCI & CDC efforts to measure effectiveness of HPV prevention interventions (vaccination and screening); will need continued long-term impact assessments
This initiative will seek to address a key ‘Last Mile’ problem in Cervical Cancer Screening: the lack of availability of FDA-approved self-sampling-based HPV testing assays.
Concept Development Team

Vikrant Sahasrabuddhe (*lead*), Mark Schiffman, Nicolas Wentzensen, Brandy Heckman-Stoddard, Sarah Kobrin, Mona Saraiya, Megan Clarke, Asad Umar, LeeAnn Bailey, Elaine Knight, Gary Della Zanna, Jian Lou, Leshia Hansen, Li Cheung, Prajakta Adsul, Jeanne Murphy.