Addressing a ‘Last Mile’ Problem in Cervical Cancer Screening

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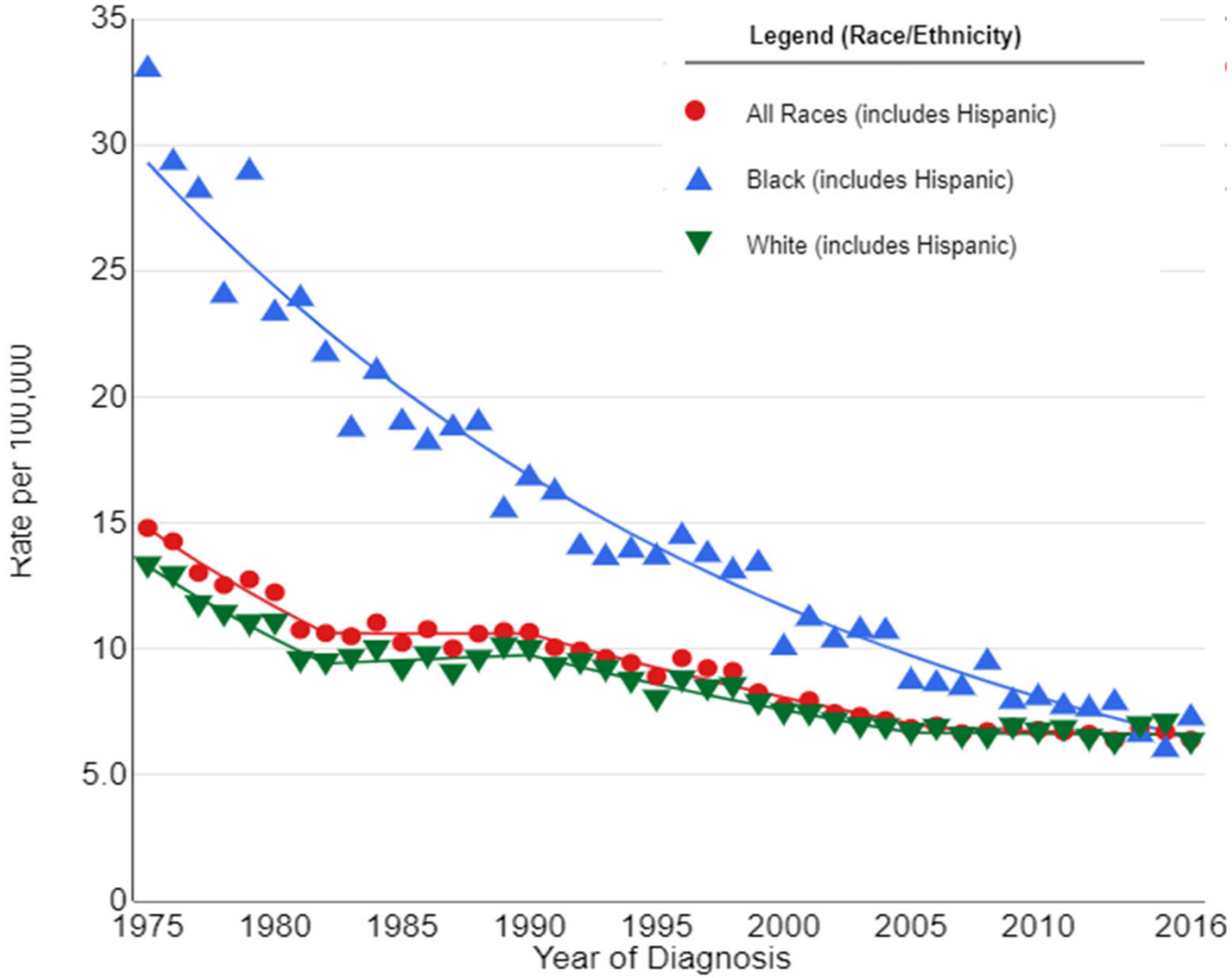
Cervical Cancer is Highly Preventable But is Still Not Fully Prevented!



(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

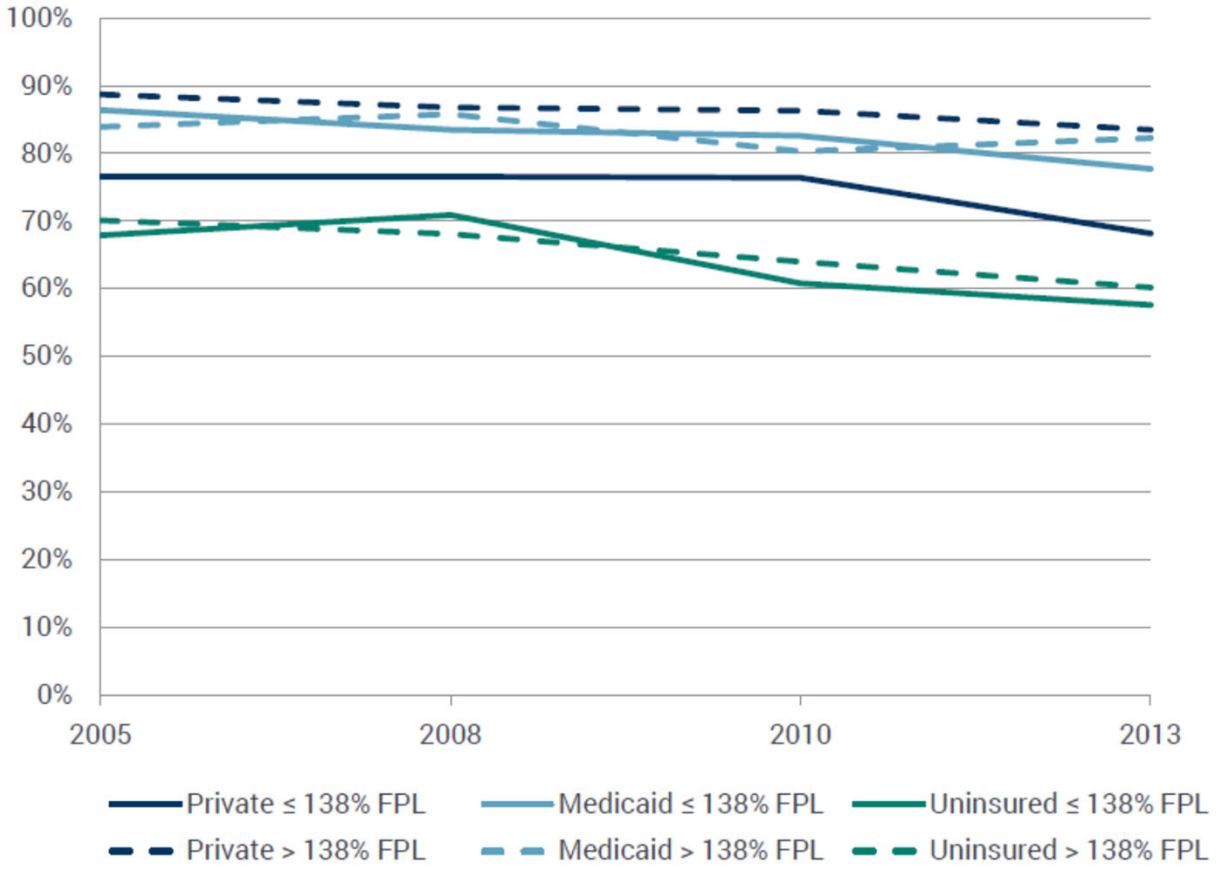
  OR Every 5 years with co-testing (Pap testing + HPV testing)

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

Background

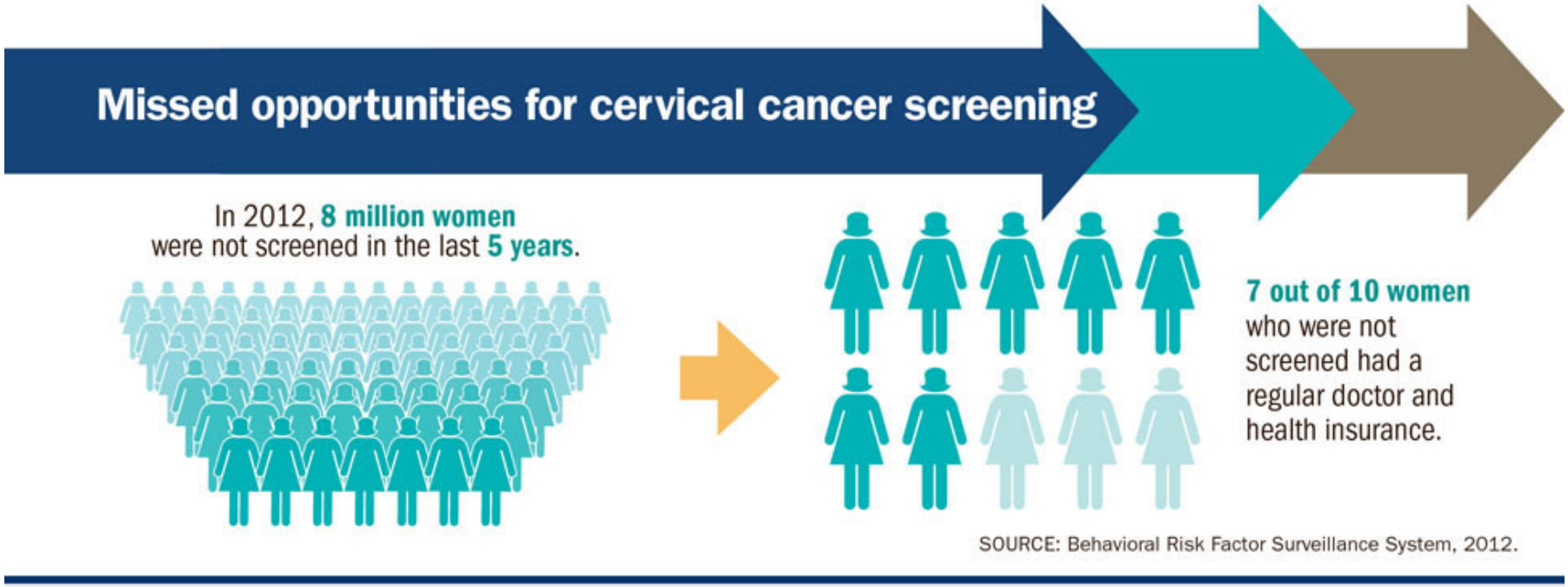
Utilization of Cervical Cancer Screening remains suboptimal for ~3 out of 10 women

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

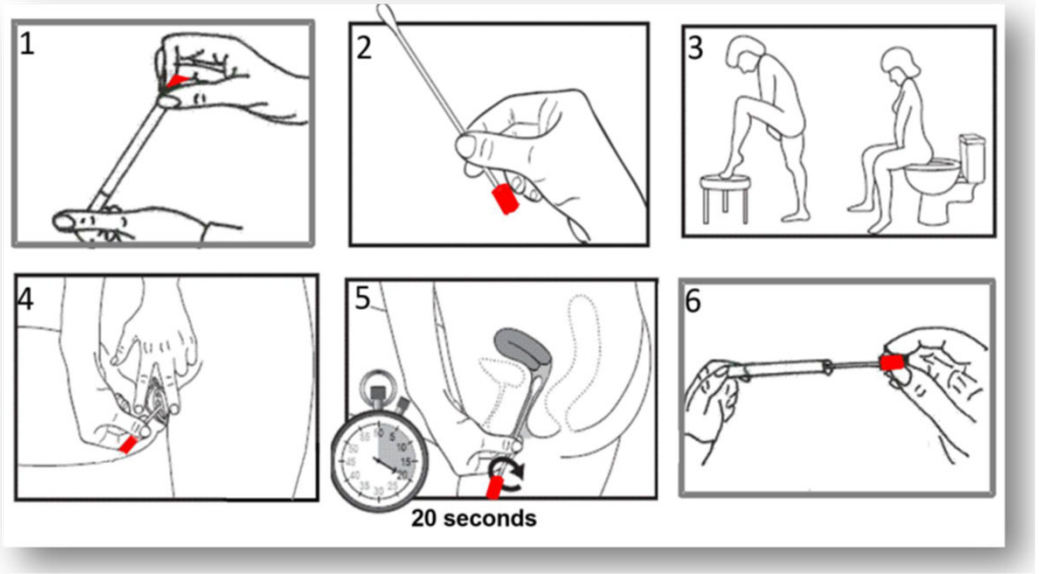


Women less likely to be screened:

- 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

Arbyn et al 2018, Snijders et al, 2012, Lim et al 2017, Nelson et al 2016, Duffy et al, 2017, Marlow et al, 2018

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

Arbyn et al 2018, Arbyn et al 2014, Cuzick et al 2006

Goals of this Initiative

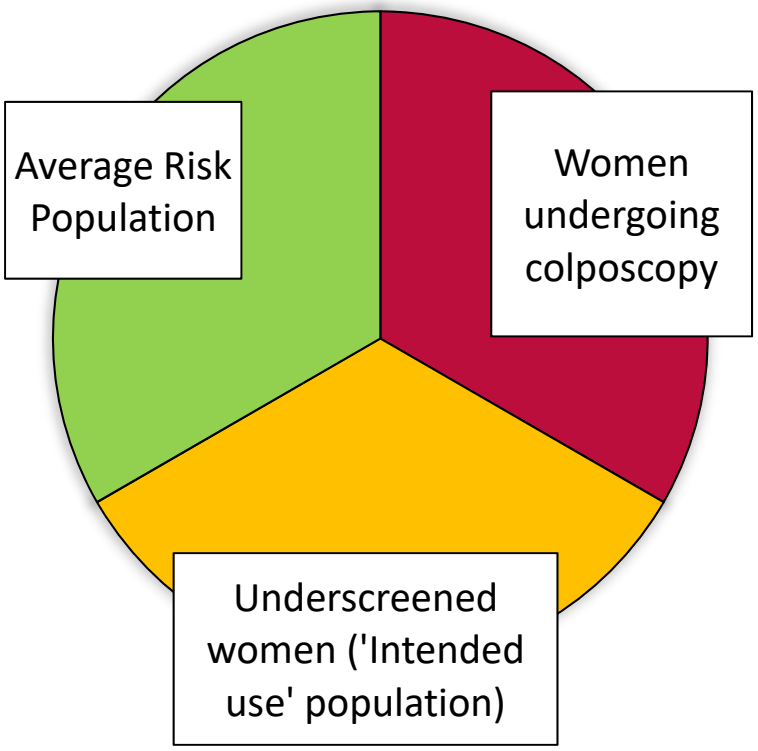
Overall Goal: To improve cervical cancer screening coverage to underserved and never-screened/under-screened women by **expanding the current FDA-approved indication of use** for HPV tests to include **prescription-based self-collection** of cervicovaginal specimens for HPV testing

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)

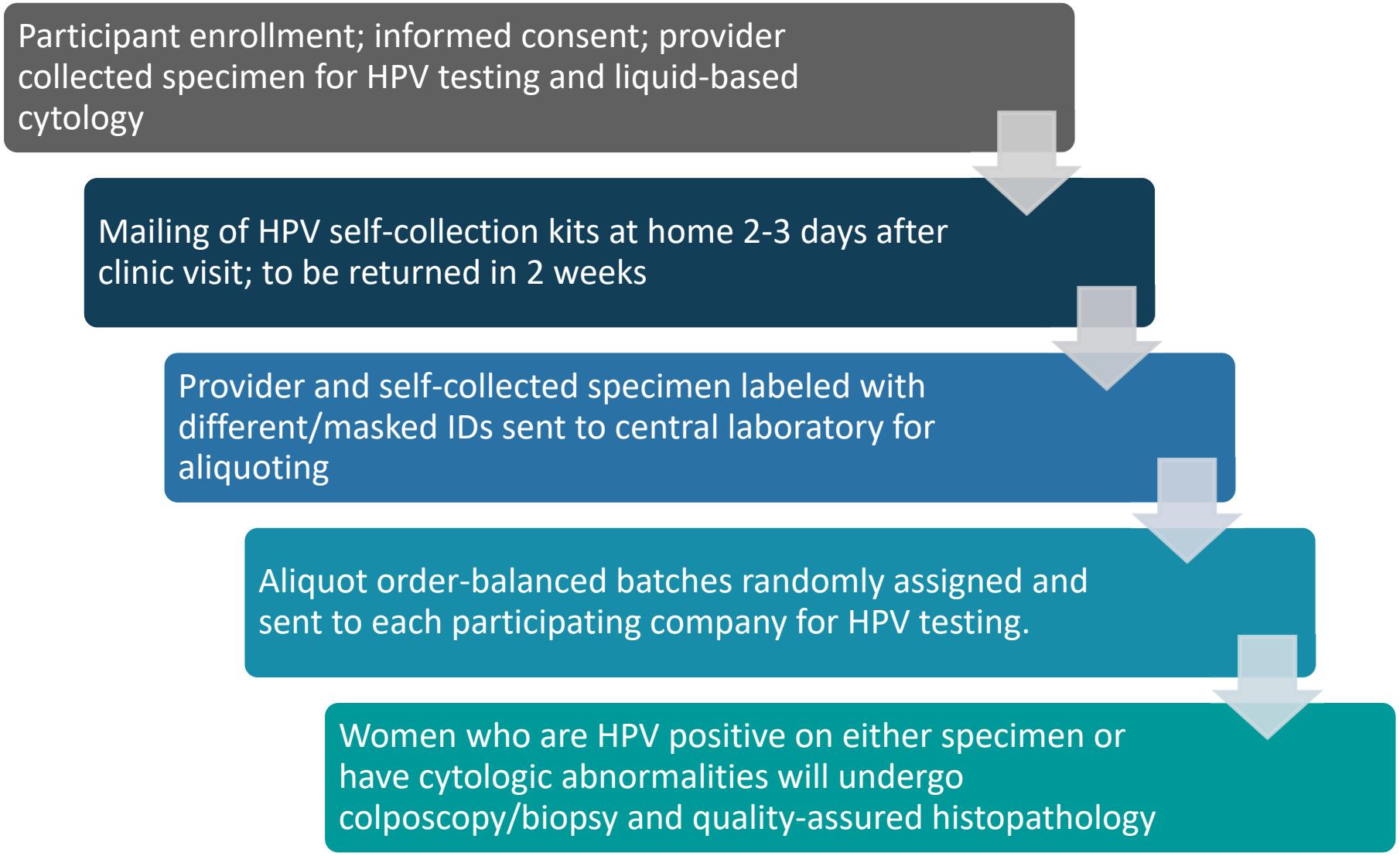
2. The focus of this partnership will be to **plan, design, and conduct a FDA-registrational screening trial**
   - to validate self-collected cervicovaginal specimen-based HPV testing as a comparable (non-inferior) alternative to provider-collected cervical specimen for HPV testing in cervical cancer 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)



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

NCI funding (via R&D Contract RFP)	***Total***
• Data Management, Auditing, and Coordinating Center (DMACC)	1.5 million
• Clinical sites (5-6 sites)	4.5 million
Total Costs (Direct + F&A) (over period of performance of 3 years)	**6 million**

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

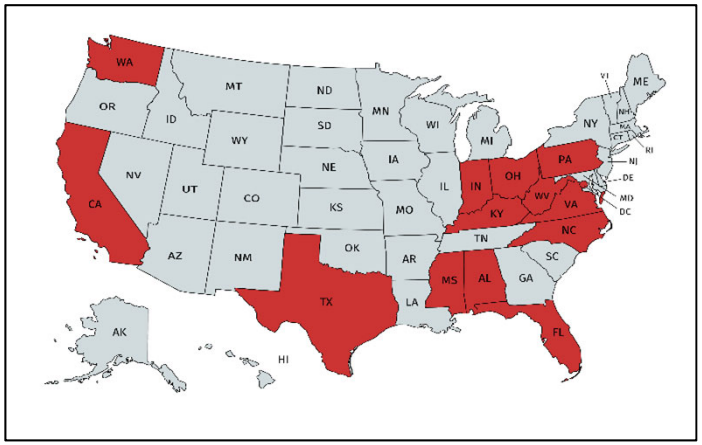
- Provide evidence to **change clinical care guidelines** (e.g., ASCCP/ACS/ACOG practice guidelines) and public health practice (e.g., USPSTF cervical cancer screening recommendations) via a new standard-of-care approach to screening

- 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

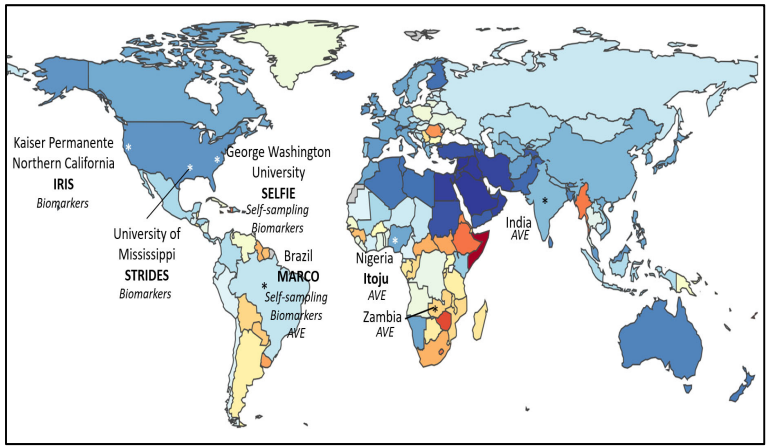
Potential to build on and link with other NIH/NCI-initiatives

- **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'

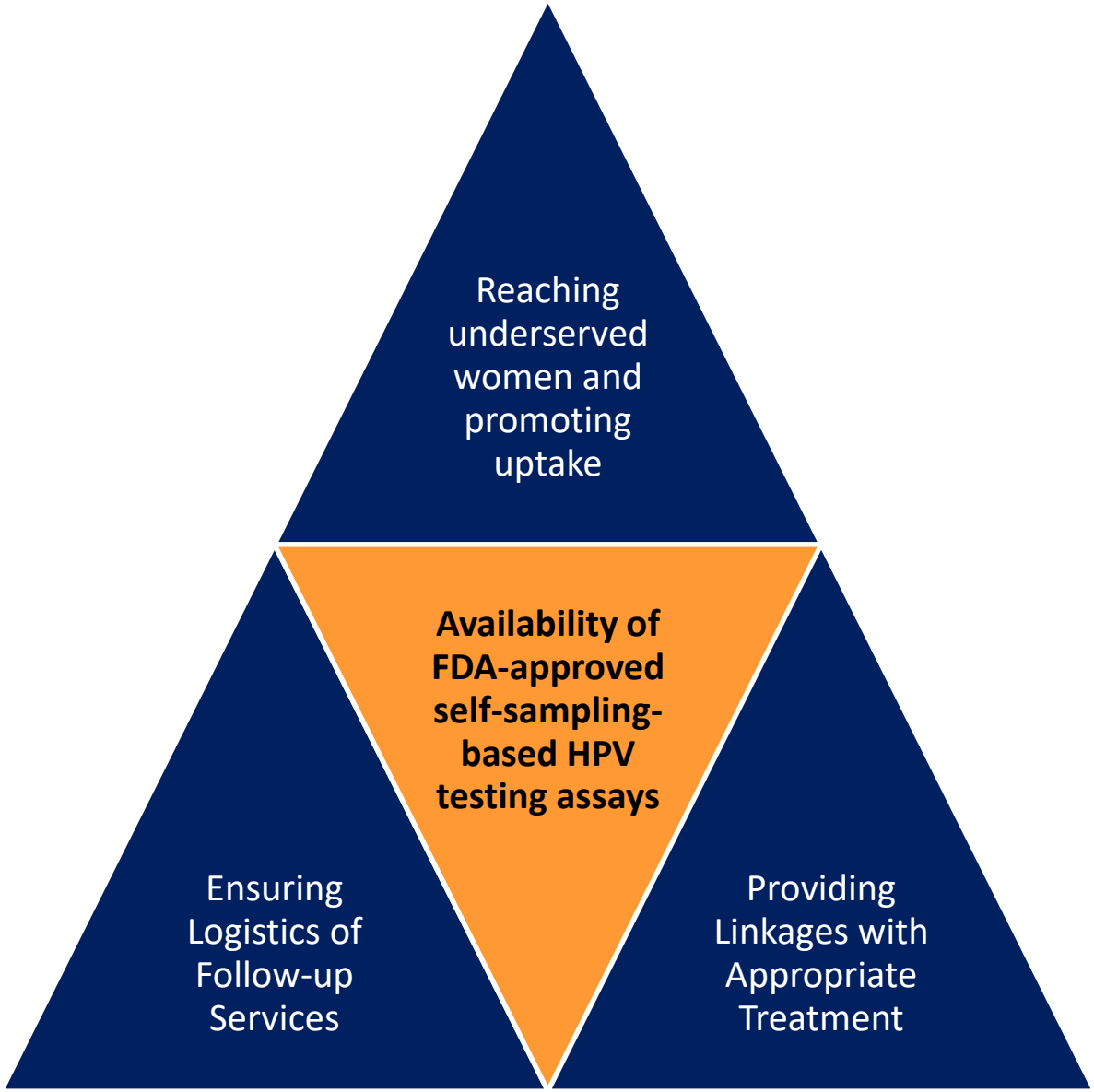


*listing not exhaustive

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.