Examples of Funded Grants in Healthcare Delivery Research

Overview

The National Cancer institute (NCI) frequently receives requests for samples of funded grant applications. Several investigators and their organizations agreed to let the Healthcare Delivery Research Program (HDRP) post excerpts of their healthcare delivery research grant applications online.

About

We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. We only include a copy of the SF 424 R&R Face Page, Project Summary/Abstract (Description), Project Narrative, Specific Aims, and Research Strategy; we do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., performance sites, key personnel, biographical sketches). To maintain confidentiality, we have redated some information from these documents (e.g., budgets, social security numbers, home address, introduction to revised application).

Copyright Information

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424 R&R and PHS-398 Specific
Table of Contents

SF 424 R&R Face Page

PI: PASKETT, ELECTRA D

Grant Number: 1 P01 CA229143-01A1

Title: Improving Uptake of Cervical Cancer Prevention Services in Appalachia

FOA: PAR-18-290

FOA Title: National Cancer Institute Program Project Applications (P01 Clinical Trial Optional)

Organization: OHIO STATE UNIVERSITY

Senior/Key Personnel: Roger Anderson, Mark Dignan, Stephanie Kennedy

Role Category: MPI

Project Summary: Overall

The goal of this Program Project is to address the burden of cervical cancer incidence and mortality in Appalachia through the delivery of a clinic-based integrated prevention program that focuses on the major causes of cervical cancer (tobacco smoking, Human Papillomavirus (HPV) infection, and lack of cervical cancer screening) designed to target individual, social and community, health system and broader contextual-level barriers related to the burden of cervical cancer. Building upon our long history of collaborative research and community partnerships, the Program will test the effectiveness of health system-based interventions focused on tobacco use, HPV vaccination and cervical cancer screening (Pap test and/or self-testing with follow-up of positive tests), as part of an integrated clinic-based cervical cancer prevention program. The multi-level interventions (directed to three levels of influence – clinic, provider and patient) will be offered to eligible female patients and age-eligible children and young adults in four Appalachian states (Ohio, Kentucky, West Virginia and Virginia). Our research process is guided by a socio-ecological model based on the Social Determinants of Health, the Proctor Model for Implementation Science and a Community-Based Participatory Research (CBPR) framework. The aims of this Program Project are to: 1) Test the effectiveness of an integrated cervical cancer prevention program, consisting of three established interventions, designed to address three causes of cervical cancer in a region with one of the highest cervical cancer incidence and mortality rates in the United States; and 2) Evaluate the impact of the cervical cancer prevention program, including implementation, and acceptability, with attention to both short- and long-term impact and sustainability at the clinics. Four cores – Intervention and Consortium, Survey and Data Collection, Biostatistics and Evaluation, and Administrative – will facilitate the smooth and integrated operation of all projects. Integration and interaction of the projects in this Program is evident in several ways: 1) all projects focus on one health disparity; 2) participants will be recruited from the same health systems; 3) a core set of measures is being used by all projects; 4) all projects include transdisciplinary teams; 5) all projects build upon and extend findings from our long history of collaborative research and community partnerships; 6) all projects focus on multi-level assessment and/or interventions using the Warnecke model as a framework and utilize the Proctor et al. Implementation Science Framework; 7) all projects involve interaction with the community in some way, thus enhancing the CBPR nature of the Program; and 8) evaluation will assess implementation, service and client outcomes at the project and overall Program levels including: cost, satisfaction, effectiveness, sustainability, and safety, to name a few outcomes. If successful, this Program Project will provide evidence for a novel and innovative approach to address disparities in underserved communities with plans for sustainability and dissemination, as well as cost-effectiveness data.

Project Narrative: Overall

Building upon our long history of collaborative research and community partnerships, this Program Project will test the effectiveness of health system-based interventions focused on tobacco use, HPV vaccination and cervical cancer screening (Pap test and/or self-testing with follow-up of positive tests), as part of an integrated clinic-based cervical cancer prevention program in health systems in four Appalachian states. If successful, this Program Project will provide evidence for a novel and innovative approach to address disparities in underserved communities with plans for sustainability and dissemination, as well as cost-effectiveness data.

PHS 398 Research Plan:
SPECIFIC AIMS

The Appalachian region is a 205,000 square mile, mainly **rural**, region of the U.S. that includes one of the most medically underserved, and economically disadvantaged areas in the U.S (**Figure 1**). The National Cancer Institute has designated Appalachia as a special population based upon its significant cancer health disparities: overall cancer incidence and mortality rates in Appalachia are higher than the national average[1]. Cervical cancer, a preventable cancer in most of the developed world, is 23% more prevalent in Appalachian regions and women are 25% more likely to die from cervical cancer in this region compared to non-Appalachian areas[2-3]. **The goal of this Program Project is to address the burden of cervical cancer incidence and mortality in Appalachia through the delivery of a clinic-based integrated prevention program that focuses on the major causes of cervical cancer** (tobacco smoking, Human Papillomavirus (HPV) infection, and lack of cervical cancer screening) **designed to target individual, social and community, health system and broader contextual-level barriers related to the burden of cervical cancer**. Building upon our long history of collaborative research and community partnerships, the Program will test the ability of an integrated cervical cancer prevention program that delivers interventions on tobacco use, Human Papillomavirus (HPV) vaccination, and cervical cancer screening (Pap test and/or self-testing with follow-up of positive tests) at the clinic level to eligible female patients and age-eligible children and young adults to be effective as well as implemented by the clinic and acceptable to patients and clinics in four Appalachian states (OH, KY, WV, VA).

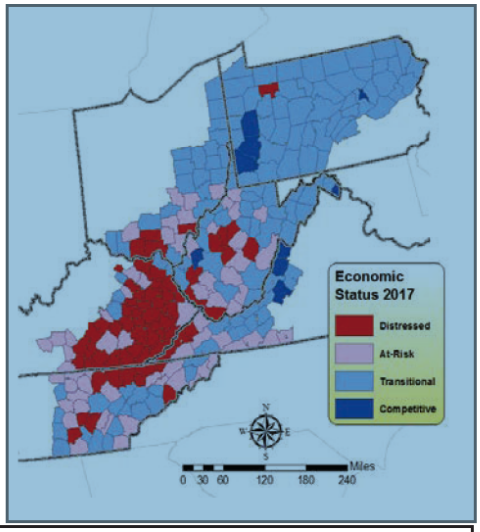


Figure 1. Appalachian Region of the US

Our research process is guided by a *socio-ecological model based on the Social Determinants of Health[1], the Proctor Model for Implementation Science[4] and* a *Community-Based Participatory Research[5]* framework. Each project is based on prior preliminary work of the Program team and will test the interventions, which will be bundled at the clinic level as an integrated cervical cancer prevention program using a theory-driven and community-engaged process with shared measures, an implementation science framework and an overall program evaluation. The aims of this Program Project are to:

Aim 1. Test the effectiveness of an integrated cervical cancer prevention program, consisting of three established intervention components, designed to address three causes of cervical cancer in a region with one of the highest cervical cancer incidence and mortality rates in the US; and

Aim 2. Evaluate the impact of the cervical cancer prevention program including implementation, and acceptability, with attention to both short and long-term impact and sustainability at the clinics.

The strategy utilized in this Program Project represents an innovative approach to reducing health disparities. Each project will test a culturally appropriate intervention for effectiveness using an implementation science design, with clinics in health systems randomized to early or delayed introduction to the prevention program. The **Intervention and Consortium Core** will facilitate community input in the refinement of the interventions, implementation of the interventions, as well as sustainability, and clinic-level dissemination strategies. The **Survey and Data Collection Core** will develop and implement common measures across projects to collect project-specific and program-level process and outcome data as conceptualized by our theoretical frameworks, and the **Biostatistics and Evaluation Core** will analyze data at both the project and overall Program level, including cost-effectiveness. The **Administrative Core** will facilitate the smooth operation of the integrated program, all projects and cores, maintain the oversight boards of the Program Project – the Steering Committee, the External Scientific Advisory Board, the Community Advisory Board and a Data and Safety Monitoring Board, and engage the services of two consultants in clinical and implementation science.

OVERALL IMPACT: If successful, this Program Project will provide evidence for a novel and innovative approach to address cervical cancer disparities in underserved communities with evidence for sustainability and dissemination, as well as cost –effectiveness, with the ultimate goal of reducing cervical cancer incidence and mortality in Appalachia.

RESEARCH STRATEGY

A. Program Background and Statement of Objectives

A.1.Overall Significance. Appalachia has a higher burden of cancer than other regions of the U.S. reflected by higher incidence and mortality rates [6-9]. Cervical cancer is an ideal example of a modifiable disparity – the causes of this cancer are largely known and if addressed, reductions in incidence and mortality are realized. While cervical cancer incidence and mortality rates have decreased over the last 6 decades, as efforts to address the known risk factors, e.g. smoking, HPV infection, lack of screening, have increased, pockets of the US, such as Appalachia, still have high incidence and mortality rates (**Table 1**).

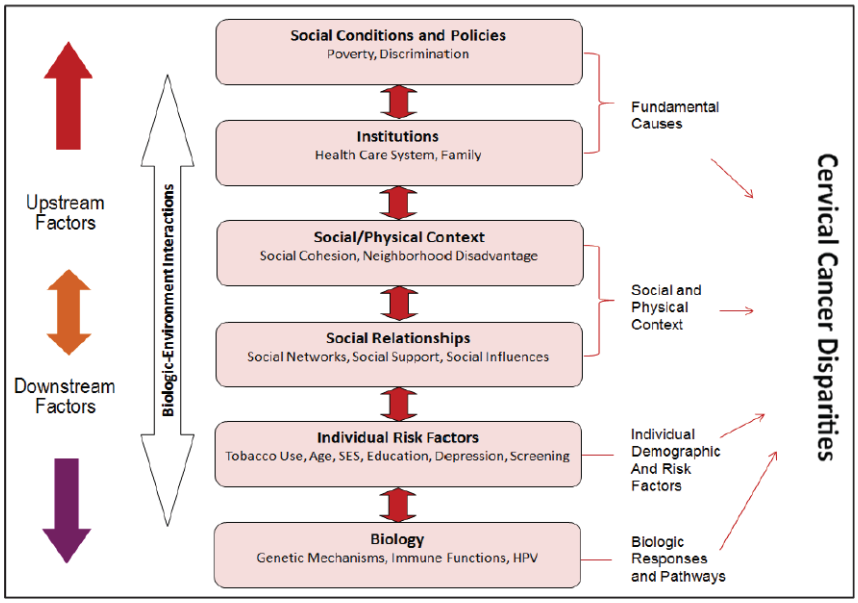


Figure 2. Multi-level Model of Cervical Cancer Disparities in Appalachia

Through our prior research in Appalachia (P50 CA105632, PI: **Paskett**), we have identified the high prevalence of risk factors for cervical cancer (smoking, lack of cervical screening, high rates of high-risk HPV infection, and low HPV vaccination rates) which combined account for the high cervical cancer incidence and mortality seen in Appalachia. Specifically since 2003, our research has found 1) Genetic alterations contribute to elevated risk of cervical cancer in non-smokers[10]; 2) smoking rates among women are higher in the region than the rest of the US[11]; 3) a high prevalence of high-risk HPV strains in women[12]; 4) low uptake of HPV vaccination[13]; 5) low rates of Pap smear screening[14]; and 6) poor follow-up after an abnormal Pap test[15]. We have also identified factors related to each of these behaviors and have tested interventions for Pap smear utilization, HPV vaccination, and smoking cessation. The result of our work can be described in a multi-level model for cervical cancer disparities in Appalachia (**Figure 2**). At the same time, we have developed strong and broad community relationships across several Appalachian states under the NCI-funded ACCN (CA153604, PI: **Dignan**) which has been used to facilitate our research[16-17]. Thus, implementation of effective interventions is the next step in this line of research in order to facilitate dissemination and ensure sustainability of effective interventions. The results from our previous research positions us well to move to the next level to test the implementation of a clinic-based integrated cervical cancer prevention program consisting of three interventions addressing three important factors related to cervical cancer in Appalachia – smoking cessation, HPV vaccination, and cervical cancer screening (with follow-up for positive results) – using the vast community partnerships across the four Appalachian states that the academic partners of this Program Project (The Ohio State University (OSU), West Virginia University (WVU), University of Kentucky (UK), and the University of Virginia (UVA)) have developed.

Table 1. Avg Annual Age-adjusted Cervical Cancer Incidence and Mortality, Appalachia vs Non-Appalachia* [3]

	Incidence			Mortality		
	Appalachia	Non-App	% Difference	Appalachia	Non-App	% Difference
Kentucky	10.4	8.5	22.4	3.4	2.7	25.9
Ohio	9.2	7.5	22.7	3.0	2.4	25.0
Virginia	6.9	6.5	6.2	2.5	2.0	25.0
West Virginia	9.8	**	**	3.2	**	**
US	8.3	7.9	5.0	2.6	2.4	8.0

**Average annual rate per 100,000, age-adjusted to the 2000 US standard population; most data were reported for 2002–2013,although, there are slight variations among states. ** West Virginia is entirely Appalachian.*

A.2. The Appalachian Region. The National Cancer Institute has designated Appalachia as a priority region with significant cancer health disparities. There are many general features of the Appalachia region that pose barriers in access to health care including average incomes lower than the rest of the U.S. and higher poverty rates, lower mean educational attainment, lack of health insurance, low penetration of managed care health systems (< 10% most counties), greater geographic isolation, less public transportation, and fewer physicians, clinics, hospitals and cancer centers per capita than the rest of the U.S.[18] Moreover, shortages of health care

providers are pervasive in this area, limiting the time providers have to discuss preventive services such as vaccination and cancer screening in regular clinic visits (See **Figure 1**). Even more concerning, access to state-of-the-art and quality care, such as smoking cessation services, is often lacking in medical facilities in many counties in Appalachia[6].

Our multi-state study region includes the areas of eastern Kentucky, southeastern Ohio, all of West Virginia, and southwestern Virginia, which are most disadvantaged by poverty, short supply of providers, hospitals, and medical centers, and greater travel distances. The study region includes 166 counties (70%) defined as 'low population' density (less than 50 persons per square mile), with 56% of residents in rural counties compared to 20% of the U.S. population. The Appalachian Regional Commission has designated 57 of these counties (34%) as 'economically distressed, and 40 as 'at-risk' (24%) (http://www.arc.gov/index.jsp) based upon unemployment and personal income rankings. For health care, 142 of the 166 counties (76%) are designated as whole or partial county health professional shortage areas by Medicare.[19] All of the above may be among the most important obstacles to reducing cervical cancer health disparities in Appalachia. Thus, a prevention program that includes interventions to assist clinics to provide state of the art quality services to patients in a non-disruptive manner, including outreach to patients who do not come in regularly, may be an innovative and cost-effective way to overcome the barriers to providing quality care in this area and reduce cervical cancer disparities.

A.3. Overall Program Aims. The aims of this Program Project are to:

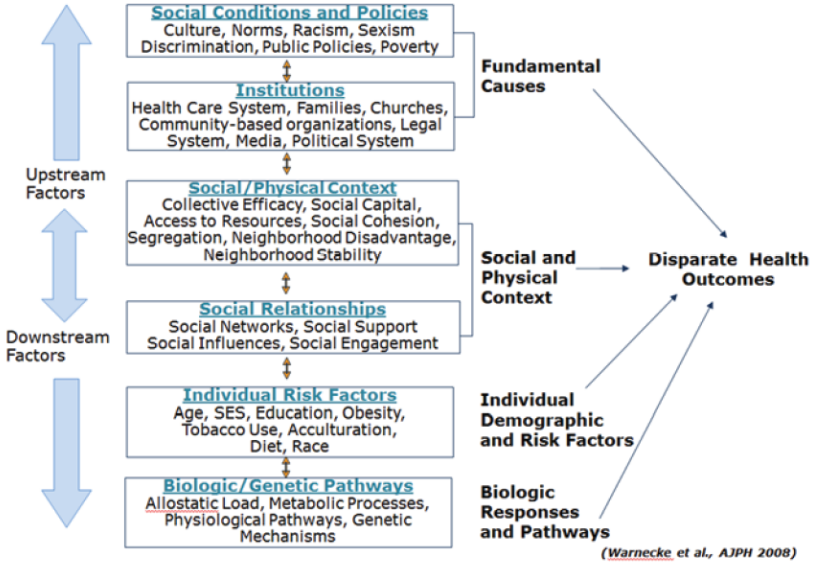
Aim 1. Test the effectiveness of an integrated cervical cancer prevention program, consisting of three established intervention components, designed to address three causes of cervical cancer in a region with one of the highest cervical cancer incidence and mortality rates in the US.

Aim 2. Evaluate the impact of the cervical cancer prevention program including implementation, and acceptability, with attention to both short and long-term impact and sustainability at the clinic.

B. Overall Approach

Research conducted under this Program Project will refine and test three practice-based multi-level interventions, packaged as an integrated cervical cancer prevention program, in group-randomized trials focused on smoking cessation, HPV vaccination, and cervical cancer screening and follow-up of positive results in Appalachia. A central theme of this Program Project is that the barriers to cervical cancer prevention in Appalachia are a function of pervasive individual-level and community characteristics (e.g., social and economic characteristics of communities, local supply of health care providers and facilities, and local providers' attitudes and practice patterns) as described by the ***Multi-Level Model of Population Health*** (**Figure 3**)[20]. We have identified the multi-level factors contributing to cervical cancer disparities in Appalachia in **Figure 2**. Using the Multi-Level Model to help understand individual and clinic-level barriers to the uptake of cervical cancer prevention strategies, the overall goal of this Program is to provide an **integrated approach** to reducing cervical cancer risk among patients/families in participating clinics/health systems. This approach represents a strategy that encourages efficient implementation of prevention interventions that can be introduced by the practitioner in a bundled manner to appropriate family members. We will also test whether such an integrated approach is sustainable and cost-effectiveness, as well as acceptable to patients and providers. Through the shared Cores, the interventions will be coordinated in both theory and approach including: 1) a multi-level clinic and community assessment to refine and customize the intervention components and obtain baseline rates of tobacco use/cessation, HPV vaccination, and cervical cancer screening; 2) pragmatic group randomized clinical trial designs 3) an implementation science framework; 4) shared measures across projects; and 5) a unified dissemination and evaluation plan, including cost-effectiveness. Our transdisciplinary research

Figure 3. Model for Analysis of Population Health and Health Disparities

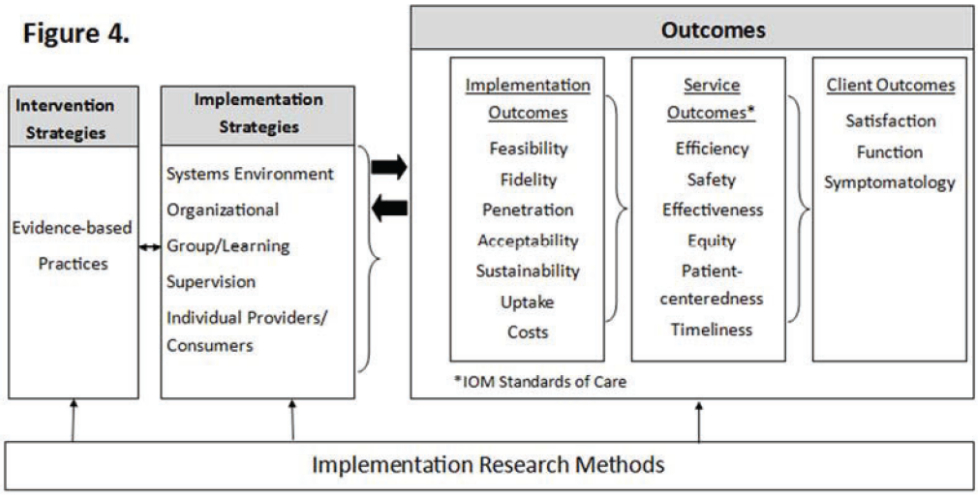


team includes cancer control and public health experts, social and behavioral interventionists, medical and community advisors, health care delivery system partners, and resources of our partnering academic institutions and community clinic partners serving Appalachia. The following principles and frameworks underlie our approach:

Community-Based Participatory Research (CBPR)[21] is utilized in this P01 to develop solutions to individual barriers to care, to refine the interventions to be tested, and plans for implementation in the clinics. CBPR emphasizes equitable engagement of community members, community-based health systems, governmental and service-providing agencies, and academic institutions in the process of designing and implementing all efforts related to changing the factors illustrated in the multi-level model. It also promotes learning and empowerment, equal power among participants, integrating knowledge and change for mutual benefit, and disseminating findings and knowledge gained to all partners. Key is the identification and mobilization of the strengths and resources within each of the communities, to allow interventions to tap into and mobilize social networks or social support systems that influence health and the unique strengths of each community. **Practice-Based Group Randomized Trials (GRTs).** In GRTs, identifiable groups of eligible participants are randomized to treatment condition with measurements taken on members from those groups to assess the impact of the intervention. The GRT is considered the gold standard for evaluating interventions that manipulate the physical or social environment, involve social processes, or cannot be delivered to individuals without the risk of contamination[22-23]. We have chosen to intervene in clinics within health systems as our prior research has consistently shown that Appalachian community members identify a health care providers' recommendation as the main motivator for engaging in prevention behaviors[14, 24]. While there is a shortage of providers in this region, established clinics are extremely interested in finding ways to streamline the provision of preventive services as we are proposing in this Program Project. Thus, we are capitalizing on the reputation of health care providers in the community while helping clinics to conduct these activities in a manner that does not compromise their ability to deliver quality care. Our randomization will be at the health system level allowing us to limit contamination likely in multi-level interventions.

Common Assessments and Measures. Projects in this Program Project will share a set of core variables and measures in multi-level analyses using our multi-level framework from Warneke et al[20] as well as an extensive collection of data descriptors pertinent to Appalachia, harmonized along key concepts, processes and outcomes in the health disparities framework as well as the Proctor implementation science framework. This will promote the ability for top-level comparison of results across projects, allows each project to share comprehensive analytic models efficiently, and assists with unified dissemination of the findings to community stakeholders and policymakers.

Figure 4.



Implementation Science Framework for Design and Assessment. The underlying framework for the design of evaluating our interventions is found in implementation science, meaning that we will test interventions for efficacy and then implementation and sustainability (**Projects 1** and **3**) or test the implementation of effective interventions and sustainability (**Project 2**). All projects will utilize a delayed intervention design (half of the clinics receive the intervention early while the others receive the interventions in a delayed fashion) and outcomes will include cessation of tobacco use, HPV vaccination, and cervical cancer screening and follow-up for positive results. In addition, we will adapt the Implementation Conceptual Framework of Proctor et al[4] (**Figure 4**) to assess the integrated cervical cancer prevention program outcomes, at the individual project level as well as for the overall Program Project. Our outcomes will focus on implementation, service and client assessments. **Figure 4** provides an overview of these outcomes and each project has specified their outcomes in relation to this framework in their respective section.

B.1. Preliminary Studies. The three projects included in this Program Project were selected for inclusion based on prior studies by the project teams. Preliminary work for each study is detailed below and each project and prior collaborations across the universities are highlighted in **Section C6**:

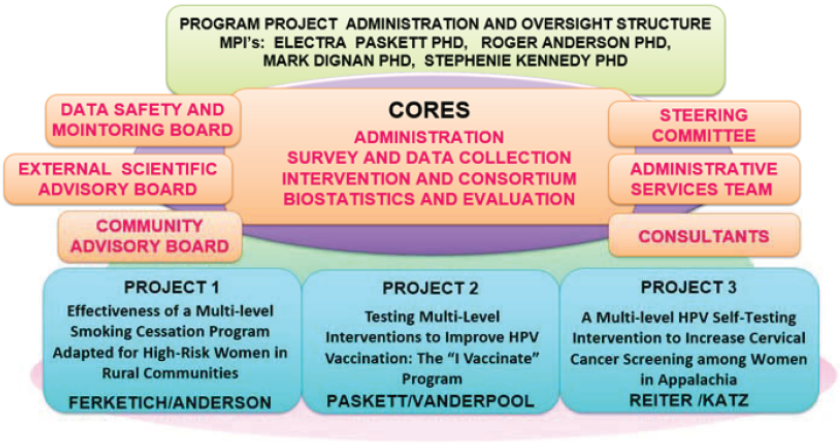
a. Tobacco Dependence Treatment to Medicaid-Enrolled Smokers (Ferketich and **Anderson).** Our prior work demonstrates our ability to modify smoking cessation programs to respond to community needs and improve cessation outcomes. A tobacco dependence treatment program for Medicaid-enrolled smokers from Appalachian Ohio was developed and implemented in 8 primary care clinics[25] and a modified version was subsequently tested in Appalachian Virginia by Drs. **Anderson** and **Ferketich**. The Ohio study used a group-randomized trial design, 214 smokers were enrolled from the clinics on a day they were visiting a provider. Over half had self-rated fair or poor health and the average Beck Depression Inventory score was 13 (10 or higher = elevated depressive symptoms). Intervention clinics (n=4) received systems-level changes that included identifying an office champion, provider training on delivering brief cessation counseling and prescribing pharmacotherapy, provider feedback, and educational materials for the clinic rooms. Smokers from these clinics who self-identified as ready to quit were offered 12 weeks of telephone cessation counseling. Control clinics (n=4) were given the Clinical Practice Guideline counseling, information on pharmacotherapy covered by Medicaid, and were directed to the Ohio quit line, and given a 1-week reminder contact. Over half (59.5%) of intervention smokers enrolled in weekly counseling and received an average of 6.5 phone calls. During these calls, the nurse tracked adverse events, withdrawal, and use of pharmacotherapy. At 3 months, smoking-related behaviors between the two conditions, 11.3% vs 3.5% confirmed quit rate suggested that a more intensive intervention with broader use of nicotine replacement therapy (NRT) and flexibility in readiness to quit date could be beneficial. The Virginia study piloted an 8-session trained navigator-led in-person and telephone based cessation program that allowed flexible quit dates and issued free NRT supplies to all participants (N=12) in a Federally Qualified Health Center (FQHC) and obtained a 25% quit rate at 3-months.

b. HPV Vaccination Uptake (P50CA105632, PI: Paskett) Supplement. The PARENT Project demonstrated effectiveness of a Multi-level Intervention (MLI) to improve physician knowledge about HPV and HPV vaccine and uptake of the HPV vaccine in intervention vs comparison counties[26]. Results also showed that the odds of vaccination among parents in the intervention counties who visited a healthcare provider and talked about the HPV vaccine were 3.4 times the odds of vaccination among those who did not talk to their healthcare provider. Thus, the aim of this supplement was to take what we know worked (i.e., MLI to promote HPV vaccine uptake) and assess the ability of implementation of the MLI in two clinics, as well as determine if we could obtain vaccination rates before, during and after implementation of the intervention in those clinics. The primary outcome was the rate of HPV vaccine initiation among 11-17 years olds within the health system assessed at baseline, 6 and 9-month intervals. Secondary outcomes included completion of the series of HPV vaccine shots. We also assessed the effect of the interventions on provider knowledge and attitudes about HPV vaccination and explored clinic-level factors that might impact vaccination rates (e.g., role responsibility and clinic characteristics). To date each of the two clinic sites have held the initial provider educational sessions as well as a follow up refresher session six months after implementation. Over 23 providers attended the education sessions. Baseline vaccination rates were obtained and educational materials (posters, brochures flyers) were revised with input from the clinic representatives. These materials were placed in the clinic exam rooms and waiting areas. The intervention was well received in both facilities with great interest and enthusiasm by providers and patients. Over 700 brochures were distributed to clinics and throughout the community at health related events. Rates in one clinic increased in 13-year-old females from 44% at baseline to 58% at 12 months and in 18-year-old females from 0% at baseline to 54% at 12 months. Follow-up data were not collected at the other clinic due to changes to their electronic health record system, resulting in reporting challenges that could not be successfully navigated within the timeframe of this supplement.

c. Health Outcomes through Motivation and Education (HOME) Project Pilot Study (**Reiter, Katz and Shoben**). This pilot study established the feasibility of mail-based HPV self-testing among Appalachian women [27]. We recruited a random sample of 103 unscreened and underscreened women from health clinics in Appalachian Ohio and mailed them an HPV self-test (the Evalyn® Brush). About 70% of women used their self-test at home and returned it by mail, of whom 26% had a high-risk HPV infection. About 25% of women attended a follow-up visit following completion of their self-test. All women who used their HPV self-test collected an adequate sample for HPV testing (i.e., 100% sample adequacy), and these women reported very high levels of satisfaction with the HPV self-test process.

B.2. Overview of Projects and Cores. Essential to the success of this Program Project is the basic tenant that all projects and cores are both inter-related and inter-dependent (**Figure 5**). Interactions and synergies among the Projects and Cores are described in the section below.

Figure 5. Program Project Organization and Leadership



Overview of Projects. Each project interacts with and collaborates with other projects through the use of a shared theoretical model, implementation framework, and common data measures. Moreover, the projects will be introduced and implemented in the clinics as *one integrated cervical cancer prevention program.* Each Project and Leader is listed in **Table 2**. The projects also coalesce along the *social determinants of health model,* each developing and testing an intervention targeting individual, social and physical contexts to address disparities in access to cervical cancer preventive services.

TABLE 2. List of Projects and Shared Cores

Component	Project and Core Leads
Project 1 – Smoking cessation	A Ferketich (OSU)/ R Anderson (UVA)
Project 2 – HPV vaccination	E Paskett (OSU)/ R Vanderpool (UK)
Project 3 – Cervical cancer screening	P Reiter(OSU)/ M Katz(OSU)
Administration Core (AC)	E Paskett(OSU)/R Anderson/ M Dignan (UK)/S Kennedy (WVU)
Core 1– Intervention and Consortium Core (ICC)	E Paskett (OSU)/ S Kennedy (WVU)
Core 2 – Survey and Data Collection Core (SDCC)	M Naughton(OSU)/ T Guterbock (UVA)
Core 3 – Biostatistics and Evaluation (BEC)	M Pennell (OSU)/ M Dignan (UK) / M Conaway (UVA)

Project 1. Break Free: Effectiveness of a multi-level smoking cessation program adapted for high-risk women in rural communities The "Break Free" Program is designed to deliver a locally based smoking cessation program developed in conjunction with community partners and delivered through health systems. The goal of the study is to test the effectiveness of our health-system-based intervention involving the clinic, provider, and patient levels, and will be one of the first to focus on sustainability outcomes, which has been a barrier in previous studies targeting healthcare clinics. Smoking is the leading cause of preventable death, and a major risk factor for cervical cancer, with studies indicating a two-fold increase in risk[28]among smokers. Despite the reduction in the smoking prevalence in the US, the rate of smoking in Appalachia is far above the national average with a high of 28 to 35 percent in many counties in the region. This high rate of smoking is one of the multiple significant pathways for higher cervical cancer in the region. Reducing the smoking prevalence in cervical cancer hot spots is a high priority that will confer additional health benefits, as smoking has been linked to numerous health conditions. Healthcare providers have been identified as being able to play a vital role in helping smokers quit. While previous studies have looked at the effects of clinic-level interventions on smoking outcomes, many have not been as intensive as the one we are proposing with uniform provision of Nicotine Replacement Therapy (NRT), they have not been tested in rural settings, and have not focused on implementation in an integrated cervical cancer prevention program and sustainability of the program after the research team leaves. Moreover, most have been "one size fits all" programs and have not adapted the quit protocol based on when a smoker wants to quit. Our program is designed to train and mentor clinic providers to initially deliver the Ask, Advise and Connect (AAC) model, which will connect female smokers who are interested in quitting with one session of counseling in the clinic. Follow-up counseling will be performed via telephone with a trained tobacco treatment specialist. During the clinic implementation period, we will train the clinic staff to deliver all of the counseling sessions and slowly transfer the counseling to the clinic. At the same time, we will assist clinics with the billing for such services, and training staff to conduct the program to facilitate sustainability.

Project 2. Testing Multi-Level Interventions to Improve HPV Vaccination: The "I Vaccinate" Program is designed to test a multi-level intervention in a delayed intervention design to improve HPV vaccination among girls and boys. The goal of the study is to test the effectiveness of a health system-based intervention that is directed to three levels of influence – clinic, provider, and patient (parent and child, or young adult) – to improve the uptake of the HPV vaccine among 11-12 year olds. We will also test whether age-appropriate interventions

increase catch up vaccination among 13-26 year olds. The interventions to be tested have been developed in conjunction with community partners and have been piloted in Appalachian populations; however, delivering this MLI as part of an integrated cervical cancer prevention program in an implementation science design is innovative. In addition to the primary outcome, uptake of HPV vaccination by age group, we will also assess the effectiveness of the intervention program among subgroups (e.g., females vs males); examine more successful components of the program; compare changes in knowledge and attitudes of providers via educational session pre-post surveys; and Identify changes in clinic practices that occur as a result of the program in terms of role responsibilities for vaccinations. Effective and highly utilized interventions will be disseminated to our clinical and community partners, as well as other health systems/clinics throughout Appalachia at the end of the study. This will facilitate uptake of effective interventions throughout health systems and clinics in Appalachia to reduce the burden of HPV-preventable diseases.

Project 3. A Multi-level HPV Self-Testing Intervention to Increase Cervical Cancer Screening among Women in Appalachia is designed to evaluate a cervical cancer screening intervention for unscreened and underscreened (not within guidelines) women. Cervical cancer is largely preventable through regular screening, yet many women are not within screening guidelines. Strategies to increase screening among these unscreened and underscreened women, including the use of HPV self-tests, have been identified as the most important cervical cancer screening research priority. HPV self-testing involves women using a device to collect their own cervicovaginal sample for HPV testing**.** Mail-based HPV self-testing programs have been used extensively in international settings, and the feasibility of implementing such programs in the United States (US) has been established by recent studies. An important next step in this field of research is to examine the effectiveness and implementation of a large mail-based HPV self-testing program in the US. The proposed study will take this next step by using an effectiveness-implementation hybrid approach to evaluate a multi-level cervical cancer screening intervention centered around HPV self-testing via a delayed intervention trial. The intervention will include mail-based HPV self-testing (patient-level), healthcare provider education sessions about HPV self-testing (provider-level), and PN for women who do not initially return their HPV self-test or who test positive for a high-risk (i.e., oncogenic) HPV infection (system-level).

Overview of Cores. As depicted in **Figure 5**, this P01 hosts four shared cores to facilitate overall Program and project specific aims and fulfill the following functions: a) efficiently manage program administrative activities and oversight to promote exchange and synergies of Program components (**AC**); b) construct, organize, and provide oversight of the clinic and community based interventions (**ICC**); c) provide a uniform approach to survey sampling, response rate generation, and to be responsible for an inter-related set of contextual measures and definitions (**SDCC**) and d) provide all analytic services for multi-level modeling, and interpretation; and conduct the program-level evaluation and analyses that integrate data collected in each project (**BEC**). **Table 3** below lists the Core services shared across projects. Each Core is briefly described below.

Table 3. Core Services Across Projects

Service	Core	Project 1	Project 2	Project 3
Administrative Services	AC	X	X	X
Study design and analysis, including sample size	BEC	X	X	X
Survey design and implementation	SDCC	X	X	X
Intervention materials – design, refinement, production	ICC	X	X	X
Patient Navigation –training and supervision	ICC	X		X
Cost effectiveness	BEC	X	X	X
Program evaluation	BEC	X	X	X
Clinic and community interactions	ICC	X	X	X

Administrative Core (AC). Core Directors: E Paskett (Contact PI), R Anderson, M Dignan, S Kennedy. The overarching objective of the **Administrative Core** (**AC**) is to provide Program leadership and coordination of all scientific, regulatory, administrative, and analytic responsibilities of this Program Project grant; to provide financial management support for all projects; and to coordinate interactions among projects, including facilitating meetings. We have designed an organizational and administrative structure that defines and preserves clear responsibilities and facilitates interactive dependence among Projects and Cores. The Principal Investigators of the Core are MPIs, responsible for day-to-day oversight of the important milestones, and integration among all Program components, will meet by phone weekly. A **Steering Committee** will be comprised of all Project and Core Leaders, as well as representatives from the health systems/clinics and community who will meet monthly by telephone conference. An **External Scientific Advisory Board** comprised of 4 external members from outside institutions will meet in person annually with the Program Project team. Two Consultants, Drs. Mack

Ruffin and Jamie Ostroff, will assist the team in clinical and implementation science aspects of the Program Project, respectively.

1. Intervention and Consortium Core (IC). Core Leads: E Paskett, S Kennedy. The purpose of the **ICC** is twofold: 1) to develop and deliver the interventions (including hiring, training, and monitoring the patient navigators and training of clinic staff) that are tested in the three research projects and 2) to serve as a focal point to organize, develop, and foster relationships between academic and community partners using Community-Based Participatory Research (CBPR) and the Science of Team Science (SciTS) principles/methodologies to address the goals of this Program Project. These two functions are intertwined in this Core as community input into the design of the interventions is essential to success of the projects. Longstanding partnerships between the four academic institutions (OSU, WVU, UK, and UVA), along with respective clinical and community partners, will serve as the cornerstone of this program project and this core.

2. Survey and Data Collection Core (SDCC). Core Leads: M Naughton, T Guterbock.

The **SDCC** provides expertise, services, and research collaboration necessary to create a database of indicators and measures that can be applied across all three Projects and the integrated cervical cancer prevention program to enhance research on cervical cancer prevention; and conduct data collection. The **SDCC** will ensure timely delivery of both multi-scaled contextual data sets and project specific datasets, provide support for pre-testing and instrument selection and conduct data collection. The Core will also provide consultation as needed to Program investigators with formative, qualitative research as a method to inform the development and pilot testing of survey instruments. Collaboration between each Project and the Core optimizes the collection of valid, reliable data, that the survey instrument meets the technical requirements and professional standards of survey research, and that the privacy and confidentiality of human subjects are protected during data collection. Core staff will monitor data collection and conduct verification checks of the final data file prior to delivery to the **Biostatistics and Evaluation Core** (**BEC**) for analysis.

3. Biostatistics and Evaluation Core (BEC). Core Leads: M Pennell, M Dignan, M Conaway.

The primary objective of the **BEC** is to provide the project investigators with a centralized resource for study design, statistical services, cost effectiveness analysis, and program evaluation. To achieve this goal, the core will collaborate with project investigators throughout the proposed Project to assist in study design and data analysis and evaluation of each project and the overall Program Project. This Core will also integrate the conceptual framework of the Program Project into relevant analyses, as appropriate. Evaluation will focus not only on project and overall program aims but also our goals of integration and reaching at risk women, families and communities with our interventions. The members of this core have extensive experience in collaborating with team members at the participating institutions.

B.3. Overall Innovation

The work proposed in this Program Project will contribute new understanding of multi-level determinants of disparities in relation to cervical cancer prevention in Appalachia, as well as a focus on addressing "high risk" individuals in the context of primary care practices and communities at risk. Novel approaches include:

1) A focus on a population with high incidence and mortality rates of cervical cancer with significant barriers to accessing traditionally provided cancer preventive services.

2) Advances in health disparities research by testing true multi-level interventions that are implemented into clinics as an integrated cervical cancer prevention program designed to link individuals with available providers in health care systems within communities, and facilitate access to state of the art cervical cancer prevention services in health care professional shortage areas.

3) Transcending state lines to create an Appalachian regional focus on the determinants of the cervical cancer burden using an implementation science framework and study designs not usually tested in this population.

4) An embedded cultural sensitivity to Appalachia from the participating institutions and investigators that focuses on acceptability of the Program within clinics.

5) Prioritization of sustainability of our interventions through input from community partners, both clinical and community, as well as continuous refinement of the Program in each clinic to foster sustainability and retention.

B.4. Justification of Costs of Program Project. With the Program Project structured as described above, rather than three independent R01's, the projects are able to use the shared cores more efficiently to conduct intervention, assessment and analytical tasks. Shared use of clinics, study personnel (at each University and at the Project Lead's site), as well as interventionists and analytical staff also make this Program Project cost efficient. The researchers have been working with communities in these four states for many years and have developed strong working relationships and trust which will enable this large clinic-based program to be conducted across 4 states and to run more smoothly than if we had to start from scratch with three independent R01 projects. Moreover, the Program Project will conduct both effectiveness and implementation science

research in one project period, thus, assuring that the integrated cervical cancer prevention program can be disseminated, if results are positive.

C. Synergy and Integration of the Program Project

C.1. Overview. The three projects and four shared cores in this proposal form an integrated research program both *scientifically* and *operationally*. As a common denominator, during active intervention clinics will deliver to their eligible patients intervention components on cervical cancer prevention that incorporate key recommendations from each of the three Project themes (smoking cessation; HPV self-testing and Pap tests; and HPV vaccinations). **Projects 2** and **3** have a reciprocal focus on HPV as a major risk exposure for cervical cancer by intervening in adults to promote cervical cancer screening and follow-up and in their children who are unvaccinated. **Project 1** focuses on the systematic inclusion of smoking cessation as a major risk factor for cervical cancer in an area with high smoking rates that if left unabated would continue to add to cancer risk in patients and in their families. To facilitate this integration, we will create a unified set of patient/family education materials that discuss our 'integrated cervical cancer program, listing all three components and messaging that encourages adherence and participation in each relevant intervention component. This will also allow for information about smoking cessation/prevention, for example, to be received by adolescents targeted in the HPV vaccination project and to women in the cervical cancer screening study and vice versa.

Scientifically, the projects are integrated at three distinct levels: **a**) at a **conceptual level**, the Program advances cervical cancer risk reduction **as a partnership, between patients, families and healthcare providers**; **b**) At the **structural level**, the Program introduces an intervention program to the clinic that addresses multiple interventions to cervical cancer reduction in a high risk environment targeting women and their families is appealing; **c**) At an **analytical level**, with the included three projects, we will have measures to assess the effectiveness of the separate interventions as well as the acceptability of the three interventions bundled at the health system level; **d**) At a level of **transdisciplinary science**, the projects are integrated through innovative use of conceptual models for intervention, design and outcome, reflecting the different disciplines of our team but integrated into one program with shared terminology. *Operationally,* the projects are integrated through an organizational structure and management oversight through the **AC** to ensure the cores support the projects and to allow investigators to work efficiently together across institutions. Our research cores are dedicated to research coordination/collaboration, sharing and adopting advanced research methods, standardization of variable definitions and interpretation, hosting integrated data libraries to address contextual-level variables, and expert data collection practices and shared sampling designs. This strength is complemented by a transdisciplinary team of investigators who share previous working relationships.

C.2. Theoretical Framework. Several theories have been used to explain and understand the pathways that are associated with cancer health disparities. These theories have examined many of the following factors: socioeconomic status, social discrimination (by using gender or race/ ethnicity), environment (living conditions, distribution of income), political and policy context (extent of primary care services, geographic location of health services, fairness of health financing, social policies), and political, social and economic relationships. These theories suggest that multiple levels of factors (i.e. determinants of health) beyond the characteristics of the individual, play a role, directly or individually, in determining individual risk and ultimately, and provide guidance to investigators toward *implementing strategies* designed with consideration of the social and physical environment of Appalachia. Our theoretical model of the Multi-level Model to Address Disparities[20] will facilitate the intervention design and application of the interventions into practice (**Figure 3**). This model is based on the Social Determinants of Health (SDH) framework[1] and will serve as the basis for identifying and addressing barriers and facilitators to implementation, adoption, and sustainability of our MLI's to increase the use of cervical cancer prevention interventions. In the model, the SDHs influence disparities independently and directly or through interactions across three levels: distal (i.e., population), intermediate (i.e., area), and proximal (i.e., individual)[1, 4]. The Proctor Model for Implementation Science[4] will facilitate study design and evaluation. All projects have operationalized each model (see Figures in each Project) and all cores will facilitate the use of these models, specific to their roles in the Program Project.

In this context, the focus will be on implementing an integrated cervical cancer intervention program to change health behaviors in the rural health care delivery environment. This environment was selected because our needs assessments showed that it is a fundamental part of the *social structure* in Appalachia and, as such it is a basic component of the *social environment*. The characteristics of the *implementation climate* will be addressed by having the local university personnel interact closely with clinics/health systems, providers and patients, as well as our community partners with assistance from the **ICC** to promote and support social conditions that shape health. To integrate the design and methodologies of the projects and conduct this research, and the teams of

investigators we have created four Core facilities, which are indispensable for the three research Projects in this Program Project.

C.3. Program Integration. The research projects will collect data from each level (with the help of the **SDCC**), enabling us to examine influences of the SDH on project outcomes. Additionally, the **BEC**, under the direction of Dr. **Dignan**, will use data from the research projects and will collect data from healthcare and community partners (with assistance from the **ICC**) to identify distal and intermediate factors to inform implementation and dissemination plans. The projects and their supporting cores are focused on a common theme: **developing and disseminating effective interventions that can be implemented in Appalachia to reduce cervical cancer**. Through the CAB (facilitated by the **ICC**), community partners will assist in conducting needs assessment to support CBPR[5], and health system partners will serve as recruitment sites. Integration is also evident in the projects through several shared study design features: 1) focus on prevention related to cervical cancer with national guidelines recommending prevention through smoking cessation, HPV vaccination and screening; 2) shared set of measures for implementation analysis; 3) technology-based approaches to data collection from electronic health records; 4) participation by investigators from several academic partners and research at multiple locations across Appalachia; 5) leveraged partnerships with community healthcare organizations; 6) addressing barriers to prevention through an integrated cervical cancer prevention program at the clinic level focusing on smoking cessation, HPV vaccination and cervical cancer screening; 7) data collected by each study will be used by the **AC** to develop a plan for disseminating effective interventions from the three projects; and 8) interaction with the community, enhancing the Program's CBPR.

C.4. Interactions between Projects. Each project in this application will benefit from our multidisciplinary scientific cores, and a managerial hub that will allow maximum and efficient use of resources and features more cost effectively than could be attained by any one stand-alone study. The projects are interlinked and cohesive such that when taken together they form one prevention program that will be implemented in each clinic, the combined results and interventions will test a well-informed model for cervical cancer risk reduction in Appalachia. Moreover, evaluation will assess implementation, service and client outcomes at the project and overall Program level including: cost, satisfaction, effectiveness, sustainability, and safety to name a few outcomes (see **Table 4**).

Table 4. Overall Program Level Outcomes

Implementation	Services	Clients
Fidelity of the bundled program	Efficiency in delivery	Satisfaction with the program at the clinic level
Penetration of the interventions	Effectiveness of the interventions	Knowledge improvement
Acceptability of the program	Equity in delivery	
Sustainability of the program	Patient Centeredness & Timeliness of care	
Cost-Effectiveness	Safety of interventions	

C.5. Interactions between Cores. The four shared cores will interact through: monthly meetings held via conference call; Core leadership committee meetings designed to share progress and problem solving strategies; and annual retreats. Shared activities of planning, data collection, and dissemination activities will be fostered at all levels of the committee structure. In addition, each core has pre-planned integration activities with other cores which require sharing of data, processes and analyses, and reports. Thus, each Core Director will actively engage related cores for their shared and mutual benefit.

C.6. Prior Interactions and Collaborations.

The Project and Core investigator teams in this Program Project span four academic institutions and locations, and have previously worked together on various scientific projects including those in Appalachia. Below we highlight a few important interactions. In addition, each project write-up has relevant preliminary studies.

a. Appalachia Community Cancer Network. Drs. **Paskett**, **Dignan** and **Kenned**y co-led the NCI-funded Appalachian Community Cancer Network from 2004-2017 (U54CA153604). This Community Network Program was a collaboration of investigators from The Ohio State University, Penn State, West Virginia University, Virginia Tech, and the University of Kentucky and included components focused on community outreach, training and research. The community outreach component developed successful cancer education products tailored for the Appalachian population including '*Understanding Cancer: A Study Guide for Appalachian Community Members*.' This resource continues to be used as a resource for community presentations on cancer throughout central Appalachia. ACCN research included a 5-state RCT testing the effectiveness of an energy balance intervention[16]. The intervention was tested in partnership with the faith community in 28 churches across the 5 states and included baseline, 12 and 24-month evaluations, as well as delivery of interventions. **Over the grant period, this team has authored 27 publications, demonstrating the ability to work across state and university boundaries to conduct intervention and community-based research in community settings.**

b. Center for Population Health and Health Disparities. Investigators at the OSU (PI: **Paskett**; Co-Investigators: **Ferketich**, **Pennell**, **Katz**, **Reiter**) received funding for two rounds of the Centers for Population Health and Health Disparities (CPHHD – P50CA105632). The focus of the center was on the goal of understanding and reducing cervical cancer (CC) incidence and mortality rates in Appalachia. This goal was accomplished using 4 core principles: 1) the Social Determinants of Health Framework; 2) community-based participatory research; 3) multi-level framework ("from cells to society"); and 4) transdisciplinary team of researchers and community members. In the first cycle of funding, three projects focused on: tobacco cessation in women who smoked, uptake of Pap testing and correlates of HPV infection in women with and without cervical abnormalities. Results led to four projects in the second round of funding: **Project 1** conducted a case-control study to investigate multi-level (genetic, behavioral, and environmental) correlates of invasive CC. **Project 2** interviewed women to examine smoking behaviors among their social networks. **Project 3** conducted a cohort study where women received the HPV vaccine and followed for 12 months to assess the effect of stress (self-reported and biological) on the ability of the host immune system to mount an immunological response to HPV. In **Project 4**, a multi-level intervention (parents, providers, system-level) was tested in a group-randomized trial in 12 counties to see if HPV vaccine rates increased among females aged 9-17. Results indicated that genetic alterations were responsible for CC in non-smokers; women who smoked were more likely to have smokers in their social networks; HPV immune response was not altered by stress levels; and a multi-level intervention was effective in increasing uptake of the HPV vaccine. The CPHHD also worked closely with several community-based cancer coalitions to conduct this work. These coalitions will facilitate the work of this Program Project in Ohio. *Moreover, the principles utilized in the CPHHD underlie the function of this Program Project.*

c. GMAP. Investigators at UK (**Dignan**, Cromo) and UVA (**Anderson**) collaborate in the NCI supported Geographic Management of Cancer Health Disparities Program (GMaP): Region 1 Partnership. The GMaP regional site is based at the University of Kentucky Markey Cancer Center (UK MCC) and was funded for a three-year period, as a supplement to the UK MCC Cancer Center Support Grant to further its overall goal is to contribute to the reduction of cancer health disparities in Appalachia. Efforts to reach this goal include enhancing the capacity of regional cancer centers, associated academic partners, community partners, and early stage investigators to increase research on disparities by fostering collaborative research applications and facilitating the career development of the next generation of underrepresented cancer and cancer health disparities investigators.

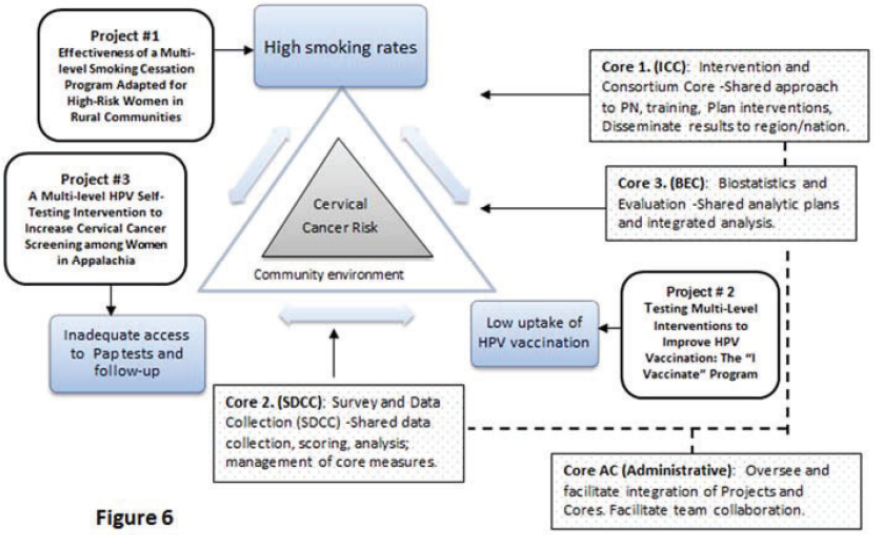


Figure 6

d. Behavioral Intervention Studies. Investigators at OSU (**Paskett**, **Naughton**, **Ferketich**) and UVA (**Anderson**) have numerous past and current collaborations in behavioral and health outcomes studies focused on disease prevention and cancer control. **Naughton** and **Anderson** have collaborated on a DOD funded Center for Breast Cancer Research that included one of the first center-to-home based exercise and lymphedema prevention interventions for women completing breast cancer treatment[29], as well as the assessment of quality of life and symptoms over time. Drs. **Naughton** and **Anderson** have also collaborated on several publications regarding the assessment of health-related quality of life and patient-reported outcomes in select populations[30-31].

C.7. Evaluation

a. Program-Level analyses. At the Program level, we will use **multi-level modeling** to examine the relative contributions of individual, community, primary care practice, and intervention effects on uptake of recommended cervical cancer prevention services in the participating clinics. This will be the first comprehensive modeling of how multi-level inputs contribute to cervical cancer reduction in Appalachia. We will validate our premise shown in **Figure 6** that cervical cancer risk in a community can be reduced by a concerted effort placed on the three main risk factors – smoking cessation, HPV vaccination and cervical cancer screening.

b. Individual-level variables. These variables will be collected directly, through surveys, and indirectly through ecological level data. Each project will collect or obtain a common 'core' set of variables including demographic characteristics, residence location, and provider(s) seen but will also create unique variables needed to address the project-specific objectives. A design involving one-study region and a uniform sampling frame among projects allow these unique individual-level data to be aggregated as contextual level data and shared across projects.

c. Contextual variables. Using an array of indicators of population characteristics, health care supply, and location of health care resources as shown in **Table 5**. Typically, contextual variables are measured at the county level, but because this project employs geocoding based on the individual's residence, we have the ability to consider units that may be more relevant to health-related behaviors than the county, such as minor civil divisions or named places. **Table 5** below displays several of the key contextual variables shared across projects (please see SDCC for full details); **Table 5** lists the Project-derived shared variables to be utilized in Program-level analyses. This will be facilitated by the **BEC**.

Table 5. Contextual Variables Shared Across Projects

Race/ethnic/family structure	U.S. Census, American Community Survey
Concentrated Economic Disadvantage	Percent individuals below poverty line; Percent individuals on public assistance; Percent female-headed households; Percent unemployed; Percent less than age 18; Percent African American (US Census)
Economic classification	Appalachia Regional Commission designations
Immigrant Concentration	Percent Latino; Percent foreign-born (US Census and American Community Survey)
Residential Stability	Percent in same house; Percent owner-occupied (US Census and American Community Survey)
Education level	Proportion adults with high school diploma (American Community Survey)
Population density	American Community Survey: county-level
Economic classification	ARC county-level economic classification
Primary care and specialists per population	ARF: county-level
Health care facilities/types	American Hospital Directory, Medicare claims, cancer registry data
Managed care market penetration	ARF: county-level

d. Cost-Effectiveness. The three projects will be implemented in the clinics as one integrated cervical cancer prevention program. Thus, we will conduct cost-effectiveness analyses for each project, as well as an analysis for the entire program as a whole. We hypothesize that each intervention program will be more cost-effective than the existing program. Cost-effectiveness analyses will be conducted in three broad steps by Dr. **Wendy Xu** (see **BEC**). We will first conduct a cost identification analysis. Second, the results of the cost analysis will be combined with the outcome measures to establish the cost per desirable outcome. To assess the sustainability of the intervention, we will also conduct exploratory cost-benefit or cost-effectiveness analyses. The potential savings or quality adjusted life-years extended as a result of the successful outcome will be obtained from the literature.

D. Overall Program Structure and Management

As described above, our leadership plan is based upon a strategic and leadership role of the Steering Committee within the **AC**, which will facilitate clear lines of communication and coordination among projects and cores, and includes sufficient time of experienced personnel to insure smooth operations, assistance with resolving scientific and operational issues, and maintaining a collaborative harmony among project and core priorities and interests while adhering to timelines and milestones. This will be accomplished, as described in the **AC** by holding regular meetings and communications, having agreed upon policies, centralized access to documents and tracking reports, and facilitating core-project and project-project exchanges. The MPIs of the overall Program Project will be responsible for leading and directing all management activities and will have an active role in advising on intellectual and logistic issues and aims of each project. Project Leaders and Core Directors will have the primary responsibility for directing the work needed to meet their specific aims.

D.1.Communication Plan. Although the PLs of the 3 Projects and 4 Cores reside at 3 different institutions, they have had a history of highly successful collaborations. In order to provide effective and interactive communication between all members of the Program Project, we will build a web-based interactive resource that allows for sharing of research findings as well as other relevant data to the Program Project. Monthly or bi-monthly teleconference will be conducted where each project and core will provide updates on progress, project interactions will be discussed to ensure program integration. Additional communication and coordination of the events pertinent to the Program Project will come through the contact PI and the **AC**. Finally, quarterly, semiannual and annual meetings provide an effective forum for monitoring and assessing progress of the research projects and effective use of the cores. Our consultants will interact through a combination of calls, teleconferences and in-person meetings with the entire team, projects and cores specifically and even clinics, as needed over the course of the Project.

D.2. Institutional Relationships. This Program Project is housed within the OSUCCC (contact MPI), part of the OSU, in collaboration with UK, UVA and WVU. Within OSU there are many intra-institutional relationships with colleges, schools, and programs that will be utilized to accomplish the goals of the proposed Program Project. These include: the OSUCCC/James Cancer Hospital, the OSU Wexner Medical Center, the College of Public Health and the Office of Minority Affairs. Within UK, the Markey Cancer Center, Department of Internal Medicine, College of Public Health and Department of Psychology are partners on the Program Project. At UVA partners include: the School of Medicine, the School of Nursing, and the UVA Cancer Center. WVU partners include the WVU Cancer Institute and School of Public Health, Office of Health Services Research.

D.3 Lines of Authority to OSUCCC. The Program Project leadership directly reports to the OSUCCC. To coordinate and manage the OSUCCC organization, the University supports the position of an OSUCCC Director, who reports to the second in command of the University, the Executive Vice President and Provost, Dr. Bruce McPheron. The OSUCCC Director, Dr. Pollock, meets regularly with an Executive Committee composed of University senior management to ensure oversight planning, and evaluation are in place. The Executive Committee, that meets monthly, is the major decision making body of the OSUCCC. It is chaired by the Director, and is composed of the Associate Directors for Clinical Research, Basic Research, Administration, Education, Translational Research, Biospecimen Research, and Population Sciences and Community Outreach (Dr. **Paskett**), and the Assistant Directors for Administration. It is responsible for the evaluation of the quality of the science, and the effectiveness of the Cancer Center's clinical, basic and population sciences cancer research. **Dr. Paskett**, as Contact MPI of this Program Project reports directly to Dr. Pollock. This Committee will review the progress of the Program Project annually.

D.4. Research Oversight. In addition to the ESAB and SC oversight on research matters, The OSU Office of Responsible Research Practices (ORRP) has oversight for the conduct of all studies and trials involving humans. The projects will be reviewed by the OSUCCC Clinical Scientific Review Committee and the OSU Cancer Institutional Review Board (IRB). The operation of these entities provides for rigorous checks and balances on data, safety monitoring, participant monitoring, and insurance on the validity of all research programs.

D.5. Authority of the MPIs. The MPIs, Drs. **Paskett**, **Anderson**, **Dignan** and **Kennedy**, will have overall scientific, administrative and financial responsibility for all of the elements of the Program Project. They will be advised by the ESAB. Dr. **Paskett** is the contact PI. The MPIs will make every effort to engage the CAB in all matters of Program Project operation, scientific and other matters. This will be facilitated by working closely with the **ICC**. Based on the recommendations of the SC, the MPIs will make final decisions on any issues that involve the timely progression of the research. As a policy, they will avoid micro-management and interference with individual projects unless serious problems develop. In addition, they will disburse project funds through the **AC**, and will have a clear accounting of the financial status of each project. Through these mechanisms, they will insure high quality, team-oriented and productive investigations.

D.6. Succession Plan For the successful implementation of this Program Project, the leader should have credibility in both population sciences as well as a cogent understanding of disparities research. Dr. **Paskett** exceedingly fulfills these criteria, as do all the MPIs. Should Dr. **Paskett** be unable to lead as Contact PI, either temporarily or permanently, Dr. **Anderson**, one of the MPIs, would assume this leadership. All MPIs have an impressive number of funded research efforts either completed or in progress at both the local and national level with experience in working on research projects in Appalachia to conduct large, multi-site research projects. Each has outstanding organizational skills and all are senior faculty members at their respective institutions.

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PROJECT SUMMARY – ADMINISTRATIVE CORE

The overall goal of the **Administrative Core** (**AC**) is to provide a structure to facilitate effective interactions toward accomplishment of the aims of this Program Project. To accomplish this goal, the **AC** will be structured into a Steering Committee and a Project Management Team. These groups will work together to accomplish the following specific aims: 1) Provide research direction by setting the research agenda focused on addressing cervical cancer disparities in Appalachia and promoting transdisciplinary research; 2) Ensure operational efficiency for all components of the Program by providing centralized grant administration, information dissemination, budget data processing, and seamless exchange of information and services; and 3) Promote integration of the Projects and Cores (**Survey and Data Collection, Intervention and Consortium**, and **Biostatistics and Evaluation**) to promote interaction among the four Universities, the investigators, the Appalachian communities, the participating community clinics/health systems; and relevant external entities. The proposed **AC** builds upon the successful experience of the structure of the Appalachian Community Cancer Network (P30 CA016058), in which the Multiple Principal Investigators (MPIs) worked together for over 10 years. The proposed structure will be led by a Headquarters unit located at The Ohio State University and be directed by MPIs, Drs. **Paskett**, **Anderson**, **Dignan** and **Kennedy**. The members of this team are well acquainted and have a track record of conducting research projects together, as well as each has substantial experience with conducting community based research in Appalachia. We have designed an organizational and administrative structure that defines and preserves clear responsibilities and facilitates interactive dependence among projects and cores. The MPIs will be responsible for day-to-day oversight of the important milestones, and integration among all Program components. The **AC** will also oversee the operation of the Steering Committee, an External Scientific Advisory Committee, comprised of four scientists from outside institutions, and will also work with the Intervention and Consortium Core to facilitate input from and meetings with members of the Community Advisory Board and the Clinical Partners, assuring Community-Based Participatory Research in all the aspects of the Program, and be responsible for regular meetings of the Data and Safety Monitoring Board, in conjunction with the **Biostatistics and Evaluation Core**. The Program also has two consultants – Drs. Mack Ruffin and Jaimie Ostroff – to advise on clinical issues and Implementation Science, respectively. Lastly, the **AC** will ensure that all components of the Program work seamlessly together to accomplish the Overall and specific project goals of the Program Project and that the two conceptual models which underlie the research – the Multi-Level Model for Addressing Health Disparities (for intervention and assessment) and the Proctor Implementation Framework (for implementation and evaluation of the interventions) are fully embraced and integrated.

SPECIFIC AIMS

The overall goal of the **Administrative Core** (**AC**) is to provide a structure to facilitate effective interactions toward accomplishment of the aims of this Program Project and specifically will foster and promote the goals of the Program Project and each component (cores and projects) by providing scientific direction, administrative support, oversight, integration of program activities and partners, and ensuring operational efficiency. The members of this Core will work together to accomplish the following specific aims:

Aim 1: Provide research direction by setting the research agenda focused on addressing cervical cancer disparities in Appalachia and promoting transdisciplinary research;

Aim 2: Ensure operational efficiency for all components of the Program by providing centralized grant administration, information dissemination, budget data processing, and seamless exchange of information and services; and

Aim 3: Promote integration of the Projects and Cores (Survey and Data Collection, Intervention and Consortium, and Biostatistics and Evaluation) to promote interaction among the four universities the investigators, the Appalachian communities, the participating community clinics/health systems; and relevant external entities.

The proposed **AC** builds upon the successful experience of the structure of the Appalachian Community Cancer Network (P30 CA016058), in which the Multiple Principal Investigators (MPIs) worked together for over 10 years. The proposed structure will be led by a Headquarters unit located at The Ohio State University (OSU) and be directed by Drs. **Paskett**, **Anderson**, **Dignan** and **Kennedy**, all MPIs. The members of this team are well acquainted and have a track record of conducting research projects together, as well as each has substantial experience with conducting community based research in Appalachia.

The overarching objective of the **AC** is to provide Program direction and leadership as well as coordination of all scientific, regulatory, administrative, and analytic responsibilities of this Program Project; to provide financial management support for all projects; and to coordinate interactions among projects, including facilitating meetings, milestone tracking, regulatory, community and other stakeholder engagement. We have designed an organizational and administrative structure that defines and preserves clear responsibilities and facilitates interactive dependence among Projects and Cores. The MPIs will be responsible for day-to-day oversight of the important milestones, and integration among all Program components. A Steering Committee whose purpose is to oversee the scientific integrity and operation of the Program Project, setting priorities, allocating resources and settling disputes for authorship or data distribution will be comprised of the MPIs, all Project, Core Leaders and Key Collaborators. They will meet monthly by telephone conference. The **AC** will communicate with the Program partners through email, monthly conference calls and quarterly calls regarding the intervention projects. We will also hold face-to-face meetings semi-annually, with the location rotating among the partner institutions. Face-to-face meetings will include all project staff, community advisors and partners. These 2-day meetings will provide opportunities for presentations and discussion, problem solving and an opportunity for informal networking with the local community. An External Scientific Advisory Board, comprised of four scientists from outside institutions, will meet in person annually to provide review and guidance for Program activities. The **AC** will also work with the **Intervention and Consortium Core** to facilitate input from and meetings with members of the Community Advisory Board and the Clinical Partners, assuring Community-Based Participatory Research in all the aspects of the Program. The **AC** will also be responsible for regular meetings of the **Data and Safety Monitoring Board**, in conjunction with the **Biostatistics and Evaluation Core**. We also have two consultants for the Program, Drs. Mack Ruffin and Jamie Ostroff, who will assist us with clinical and implementation science aspects, respectively. Lastly, the **AC** will ensure that all components of the Program work seamlessly together to accomplish the Overall and specific project goals of the Program Project and that the two conceptual models which underlie the research – the Multi-Level Model for Addressing Health Disparities (for intervention and assessment) and the Proctor Implementation Framework (for implementation and evaluation of the interventions) are fully embraced and integrated.

IMPACT: The **AC** is responsible for maintaining the research and administrative function of the projects, cores and oversight committees of the proposed Program Project. With seasoned MPIs and staff at all participating universities and strong community ties, this Program is poised to impact cervical cancer rates in Appalachia in a manner that will assure sustainability of the proposed interventions in a comprehensive, integrated fashion in primary care clinics.

RESEARCH STRATEGY

This Program includes faculty from The Ohio State University (OSU) The University of Virginia (UVA), The University of Kentucky (UK) and West Virginia University (WVU), building on the history of collaboration of these 4 institutions and community stakeholders. All partners are committed to reducing disparities from cervical cancer (CC) among women in Appalachia and beyond and have conducted prior studies that form the rationale for the proposed Program Project. This Program Project consists of the **AC**, three integrated research projects, three additional cores **Survey and Data Collection** (**SDCC**); **Intervention and Consortium** (**ICC**) and **Biostatistics and Evaluation** (**BEC**) cores; a Steering Committee, and three advisory boards – a Community Advisory Board (CAB) and an External Scientific Advisory Board (ESAB) as well as a Data and Safety Monitoring Board (DSMB). We also have two consultants for the program, Drs. Mack Ruffin and Jamie Ostroff. The structure of the Program is depicted in **Figure 1**. The description of the **AC** follows, by specific aim.

Aim 1: Provide research direction by setting the research agenda focused on addressing cervical cancer disparities in Appalachia and promoting transdisciplinary research.

A. LEADERSHIP and OVERSIGHT OF THE ADMINISTRATIVE CORE

Multiple Principal Investigators (MPIs). MPIs from each academic site in the consortium are responsible for specific tasks (as detailed below) in the **AC** as well as all Program activities at their site including providing budget oversight, identifying investigators to participate in the research projects and cores, identifying and fostering relationships with healthcare and community partners. MPIs include **Electra Paskett** at OSU; **Roger Anderson** at UVA; **Mark Dignan** at UK; and **Stephenie Kennedy** at WVU. The MPIs will meet by phone weekly in Year 1 as well as face-to-face meetings, described below. Phone meetings will taper to every two weeks in Years 2-5 or as needed. Specific roles in the **AC** are described below.

Electra D. Paskett, PhD, contact PI, will assume responsibility for management of the **AC**. She will be joined in this task by Drs. **Anderson**, **Dignan** and **Kennedy**, all Multiple PI/PDs of the Program Project. Dr. **Paskett** has directed the Center for Population Health and Health Disparities (CPHHD) at OSU (P50CA015632) for the last 12 years and served as director of its **AC** and Steering Committee. She also chaired the national CPHHD Steering Committee from 2005 – 2006. She is Associate Director for Population Sciences and Leader of the Cancer Control Program for the OSU Comprehensive Cancer Center (OSUCCC) and leads its Center for Cancer Health Equity. She is past President of the American Society for Preventive Oncology and chair of the Health Disparities Committee of the Alliance for Cooperative Trials in Oncology. Dr. **Paskett** is recognized for her work in addressing cancer health disparities among minority and rural populations and for her national leadership roles in the area of cancer disparities. Dr. **Paskett**, the contact PI, will share responsibility for the overall internal administration of the Program with the other MPIs and will supervise activities of the OSU site and community partners. She will also oversee the ESAB and the DSMB as well as the integration of the projects and Cores.

Roger Anderson, PhD is the Associate Director of Population Sciences and Co-lead of the Cancer Prevention and Control Program at the UVA Cancer Center (an NCI-designated Cancer Center). Dr. **Anderson** is also a site PI for the P50 Tobacco Centers for Regulatory Sciences (TCORS) and for the NCI supplement supported National Outreach Network (NON). Dr. **Anderson** will have responsibility for the activities of the VA clinics, staff and community partners and will, as part of his role in the **AC**, oversee the activities related to clinic-based assessments of the Program Project.

Mark Dignan, PhD is the PI of the Appalachia Community Cancer Center (ACCN), a NIH-funded community network program. He is also Director of the Prevention Research Center at UK and Co-lead of the Cancer Prevention and Control Program of the Markey Cancer Center (UKs NCI-designated Cancer Center). Dr. **Dignan** will have responsibility for the activities of the KY clinics, staff and community partners and will, as part of his role in the **AC**, oversee the Evaluation activities of the Program Project.

Stephenie Kennedy, EdD serves as an Associate Center Director at the West Virginia University Cancer Institute (WVUCI) and directs the office of Cancer Prevention and Control, which is responsible for education, outreach, and population-based research for the WVUCI. In this capacity she has served as the WVU PI for the ACCN, WV Breast and Cervical Cancer Screening Program (education and collaboration components), and WV Program to Increase Colorectal Cancer Screening. She represents the WVUCI on the Steering Committee of the statewide Comprehensive Cancer Coalition and serves as a key stakeholder for the WV Immunization Network. Dr. **Kennedy** will supervise the activities of the WV staff, clinics and community partners and will, as part of her role in the **AC**, oversee the CAB.

The Steering Committee (SC) will consist of the MPIs, the Project and Core Leads, two community members; and two members from the participating health systems, TBD every 2 years on a rotating basis. The Steering Committee (SC) will be responsible for providing research direction and priorities for the program. This goal will be accomplished through 1) oversight of the progress of program components; 2) evaluation of program

progress; 3) integration of program theme; and 4) review of manuscripts and presentations. The SC along with input from the Administrative Services (AS) Team will be responsible for approving budgets, reviewing the program project evaluations to ensure research projects and cores meet goals and objectives, recommending appropriate action if deficiencies are identified, and approving the annual progress report for submission to NCI. The SC will meet monthly with at least one in-person meeting (others via teleconference or Skype), and they will be available as needed to address urgent issues that cannot wait until the next scheduled meeting. The in-person meeting will occur during the annual Program meeting.

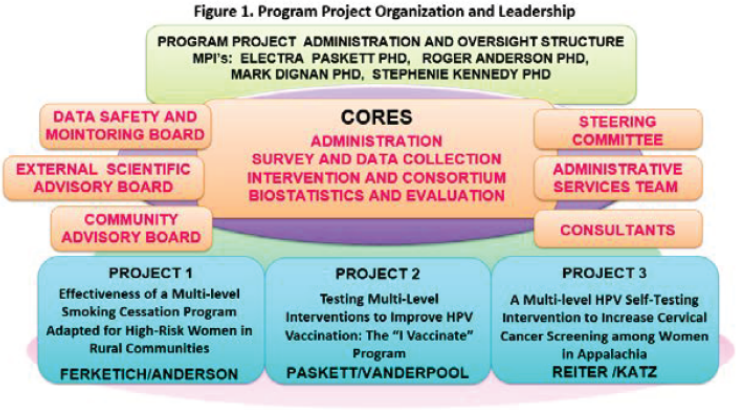
The Administrative Services (AS) Team (Sarah Wilkins and Cathy Tatum, OSU; Mark Cromo, UK; Lindsay Hauser, UVA, and Mary Ellen Conn, WVU) will support day-to-day operations of the Program Project as outlined below. Cathy Tatum will serve as the leader of the AS Team. Ms. Tatum has over 20 years of experience managing various aspects of multiple research projects, including both the OSU CPHHD and the Ohio ACCN office. This group will have monthly conference call meetings and will also communicate through, email and annual face-to-face meetings.

B. ORGANIZATIONAL AND GOVERNANCE STRUCTURE OF THE PROGRAM PROJECT

This **Program Project** is comprised of the **AC**, three research projects, three additional cores, and three advisory committees. Program components are described below. PIs at each partnering academic institution will oversee all Program activities at that site. The organizational structure is shown in **Figure 1**.

B.1 Advisory Boards

Figure 1. Program Project Organization and Leadership



B.1.a. External Scientific Advisory Board (ESAB). A group of four highly qualified individuals with expertise in cancer health disparities, rural health care delivery and tobacco/HPV vaccination research as well as implementation science have been recruited to comprise an External Scientific Advisory Board (ESAB). We have invited Dr. **Beti Thompson** (Fred Hutchinson Cancer Research Center) for her expertise in rural cancer health disparities research, Dr. **Greg Zimet** (Indiana University) for HPV vaccination research expertise, Dr. Anna McDaniel (University of Florida) for her expertise in tobacco cessation research, and Dr. Maria Fernandez (University of Texas) for expertise in cervical cancer screening and implementation science research. This group will meet in conjunction with one of the semi-annual Program Steering Committee meetings. The ESAB will observe and participate in the SC meeting. The next day, the ESAB will meet with investigators to assess progress of the cores and research projects. These meetings will be scientific exchanges as well as administrative reviews, and we anticipate that the members of the ESAB will provide significant scientific input into ongoing projects and strategic planning. Prior to all ESAB meetings, members will be provided with NIH style progress reports and copies of manuscripts and abstracts by the Program cores and projects. The ESAB will produce a brief written report of the annual meeting to provide their assessment of the Program and recommendations for addressing barriers and increasing efficiency.

B.1.b.Community Advisory Board (CAB). The CAB will provide critical input on community needs, interests and values. The CAB will consist of at least two representatives from each Program region, along with the **ICC** leads, Drs. **Paskett** and **Kennedy**. This group, composed of lay community members, including cancer survivors, health care delivery system representatives, will ensure that all projects are developed and implemented with community participation (see **Intervention and Consortium Core**). The CAB will meet on a quarterly basis during each year of the project. They will meet twice by teleconference, and twice face-to-face. The face-to-face meetings will be in conjunction with scheduled Program meetings, so as to reduce travel burden on CAB members and to reduce costs. CAB members will be invited to provide input on factors relating to issues of access and barriers, designs of the research projects and programs, and methods of assuring acceptance in the community. At subsequent meetings, the CAB will review aspects of the projects and programs as they are implemented in the community and provide feedback to the study investigators and staff.

B.1.c. Data Safety Monitoring Board (DSMB). The DSMB will review the progress and safety of the Program projects. Members will include at least five individuals, including clinicians and researchers experienced in cervical cancer, a clinical biostatistician, an individual with expertise in the regulatory aspects of clinical trials, and a layperson patient advocate. We have invited Dr. **Susan Flocke** (Case Western Reserve University) for her expertise in implementation science research design, Dr. Vickie Champion (University of Indiana) for her expertise in

intervention research, Dr. **Catherine Crespi** (UCLA) for her expertise in biostatistics and Dr. **Karen Freund** (Tufts University) for her clinical expertise, especially in testing interventions in underserved populations. No members of the DSMB will be associated with this research project.

B.1.d. Research Oversight. In addition to the EAB and SC oversight on research matters, The OSU of Responsible Research Practices (ORRP) has oversight for the conduct of all studies and trials involving humans. The projects in this program will be reviewed by the OSUCCC Clinical Scientific Review Committee (CSRC) and the OSU Cancer Institutional Review Board (IRB). The operation of these entities provides for rigorous checks and balances on data, safety monitoring, participant monitoring, and insurance on the validity of all research programs. Progress of the Program will be assessed including milestones reached, any challenges faced and how to address or resolve any barriers encountered through regular meetings with the Project and Core Leaders.

B.1.e. Consultants. Dr. Mack Ruffin is a consultant for the entire Program Project, serving as our clinical expert for all projects based on his training as a primary care physician and his expertise with cervical cancer screening, HPV vaccination and referring his patients for smoking cessation/counseling. Moreover, his research in cervical cancer and HPV, as well as HPV vaccination in primary care and underserved populations, including rural and Appalachian populations, make him uniquely qualified for this role. Lastly, he has experience working with the Ohio team in relation to cervical cancer prevention. Dr. Jamie Ostroff will also serve as a consultant for the entire program to provide her expertise in Implementation Science, especially as it relates to implementing and sustaining prevention interventions in clinical settings, including billing for prevention services. Drs. Ruffin and Ostroff will be onsite for project start-up and all advisory board meetings, and will participate in monthly teleconference calls during all active research phases.

AIM 2: Ensure operational efficiency for all components of the Program by providing centralized grant administration, information dissemination, budget data processing, and seamless exchange of information and services.

C. DUTIES OF THE ADMINISTRATIVE CORE

Business Management. Financial and fiscal oversight includes budgetary matters, purchasing, human resources, and arrangement of meetings and travel. The Business Manager at OSU, Ms. Sarah Wilkins and Ms. Cathy Tatum, will provide leadership in planning AC management functions. A proposed plan for shared tasks is described below.

C.1. Allocate and Oversight of Resources.

The AC will provide financial and fiscal oversight of the program components through several mechanisms. This includes budgetary matters, purchasing, human resources, travel, computer hardware and software. These activities will be the responsibility of the AS Team, who will coordinate with the OSUCCC Administrative Division. Budgetary allocations, decisions on how to allocate these monies are made at the program level by the MPIs and the project and core leaders who are responsible for the management of the approved fiscal resources. Ms. Wilkins will provide real time budget reporting to the MPIs (**Paskett**, **Anderson**, **Kennedy** and **Dignan**), and she and the AS Team, will oversee all financial transactions for the Program, including purchasing supplies and equipment, and processing participant incentives and other project costs. They will closely monitor expenditures to ensure that all funding agency regulations are followed. All budget management will be conducted in accordance with all regulations and generally accepted accounting practices. The budget serves as the vehicle for planning and resource allocation decisions as well as a method for maintaining integration of the Program, and provides the basis for fiscal management for administering and controlling expenditures.

C.2. Transactions and Purchases. The Administrative Division of the OSUCCC will provide real time budget tracking and reporting to Ms. Wilkins for the Program. Budgetary allocations, decisions on how to allocate these monies are made at the program level by the MPIs and the Project and Core Leaders. Project and Core Leaders are responsible for the management of fiscal resources approved for their respective cost center. The OSU grants manager, Tyler Fogal (OSUCCC), will oversee all financial transactions for the Program, including purchasing supplies and equipment, and processing participant incentives and other project costs.

Budget Planning and Management. Budget administration and management is the process of regulating expenditures during the fiscal year to ensure that they do not exceed authorized amounts and that they are used for program purposes. The budgeting systems and services for the program support the investigators across all of the components of the program, from planning to completion. Expenditures for investigators will be closely monitored by Mr. Fogal throughout the active research period making sure that all funding agency regulations are followed. The management of the budget is accomplished in a variety of ways: reconciling budget transactions, controlling expenditures, tracking receipts, monitoring projected financial status, reconciling expense accounts, and reporting to Dr. **Paskett** and the other MPIs on fiscal operations. The budget serves as the vehicle for planning and resource allocation decisions as well as a method for maintaining integration of the

program, and provides the basis for fiscal management for administering and controlling expenditures.

C.3. Human Resources. Each institutional partner will have control over their own personnel management including recruitment and hiring. Personnel evaluations will include input from Program leadership. The AS Team will coordinate and facilitate personnel management including recruitment, hiring, performance, planning and evaluation for the projects and cores. The AS Team will work with the Human Resources department to create new positions through the University's hiring system. They will advertise, establish interview criteria and procedures, and assist with making hiring and compensation in conjunction with project and core management. Ms. Tatum will work with OSUCCC Administration to coordinate these activities.

C.4 Travel. The AS Team will facilitate travel for all program investigators and research staff to attend any Program related meetings. These activities include making reservations with airlines and hotels, and arranging per diem for travelers. Program-related travel includes any required local or national meeting, meetings with communities, project sites, CAB and ESAB, meetings to present program results, to recruit trainees, professional development or training, or travel to develop or conduct interdisciplinary research and collaboration. Ms. Wilkins will be responsible for these activities in coordination with the respective counterparts at the other universities.

C.5. Meetings. The AS Team will be responsible for scheduling, planning, sending electronic reminders, preparing program meetings, meeting materials, recording and reporting minutes and making all other arrangements for all program-related conference calls and meetings. Ms. Wilkins and Ms. Tatum will conduct these activities for all program components including the DSMB, ESAB and the CAB. The multi-PIs will plan a yearly in person meeting for the entire Project team along with the AS team As mentioned above the MPIs will have weekly meetings by phone with AS Team members present, as appropriate. With their overlap in many professional organizations, committees and activities, the multi-PIs have numerous opportunities for unscheduled discussions to facilitate the work of the Program Project.

As Director of the **Administrative Core**, Dr. **Paskett** will meet with the Program's AS Team lead and Business Manager on a weekly basis. The AS Team lead, Cathy Tatum, M.A. has extensive expertise in program management and administration. The **AC** Director and the AS Team lead will schedule, organize and chair the monthly Steering Committee meetings. They will organize the agenda and meetings of the External Scientific Advisory Board, and coordinate with the ICC for joint meetings of the Steering Committee and CAB members, as well as facilitate integration of the consultants with each project and other components as relevant.

C.6. Review of Manuscript and Presentation Proposals. An important role of the SC is the review of manuscript/presentation proposals and requests to utilize data collected by Program Project investigators/trainees. This process will be facilitated by the AS Team. Currently, we have a formal mechanism for investigators and trainees to apply to analyze data for manuscript, presentation, and thesis/dissertation work that is very successful in the CPHHD. Analyses can be done by program statisticians or the proposer. The final product will also be reviewed by the SC to assure appropriate methodology, interpretation of the findings, citation of grant number, and investigators.

C.7. Human Subjects Assurance. Members of the AS Team from each institution will ensure that all core and project team members complete the appropriate human subjects training. All projects will also seek, obtain, and maintain OSUCCC Scientific Review Committee (CSRC) and Institutional Review Board (IRB) approval, and appropriate approvals will be obtained at each institution, as necessary. Ms. Tatum will assist the projects in coordinating CSRC and IRB applications, amendments, and reports. Staff from individual projects may prepare the materials, but the AC will review and coordinate submissions to ensure standardized procedures, facilitate information sharing, and provide administrative support. The **AC** will monitor to ensure that annual IRB reviews are done in a timely manner and in accordance with institutional requirements. (Note – if we are able to cede review to one IRB of record, we will and that will be the OSU IRB.) The DSMB will review the progress and safety of the projects.

C.8. Reporting to NIH. The **AC** leaders, with assistance from the AS and Core Leads, will generate an annual Program Progress report for NCI. The SC will review the report prior to submission. The AS team will prepare a timeline of due dates for required reporting and will communicate the reporting requirements to each project and core leader, as well as project managers. Mr. Fogal will submit reports directly to the sponsor. The AS will obtain updated biographical sketches for investigators for annual progress report submissions. The AS Team will also maintain tabular information on Program research project participants (race and/or ethnicity) for annual NIMHD reports. The AS team from each institution, with the assistance of Ms. Tatum, will maintain a central file of research papers, presentations, and other reports originating from or directly relevant to the Program Project to document the accomplishments of investigators and ensure publications are entered into PubMed Central as required by NIH.

AIM 3: ***Promote integration of the Projects and Cores to promote interaction among the four universities the investigators, the Appalachian communities, the participating community clinics; and relevant external entities.***

D. RESEARCH PROJECTS

The SC will ensure the Program's theme is carried throughout each component and that the Program's two conceptual models which underlie the research – the Multi-Level Model for Addressing Health Disparities (**Figure 2**)[1] (for intervention and assessment) and an adapted Proctor Implementation Framework (**Figure 3**)[2] (for implementation and evaluation of the interventions are used, operationalized, and evaluated in each component and the overall Program. Specifically, the Proctor Model will be adapted for use in a prevention program. The SC will ensure that Community Based Participatory Research (CBPR) is fostered in all components and will facilitate the use of transdisciplinary teams to accomplish project and core goals. Three research projects are included in the Program Project. The research projects build on prior research conducted by investigators focused on the Program Project theme of developing and disseminating effective interventions for cervical cancer prevention in Appalachia. These projects are designed to be implemented in health systems as a comprehensive cervical cancer risk-reducing prevention program designed to be culturally appropriate multilevel interventions with input from community partners. **Project 1** addresses smoking cessation in women in rural communities; **Project 2** addresses primary prevention of cervical cancer through HPV vaccination of girls and boys, and **Project 3** focuses on getting women who have delayed cervical cancer screening to be adherent using HPV self-testing as an emerging screening approach. We will work with community partners using principles of CBPR to test these community-based approaches to implementing interventions in the health care delivery systems partnering with the Program Project.

Figure 2.
Model for Analysis of Population Health and Health Disparities

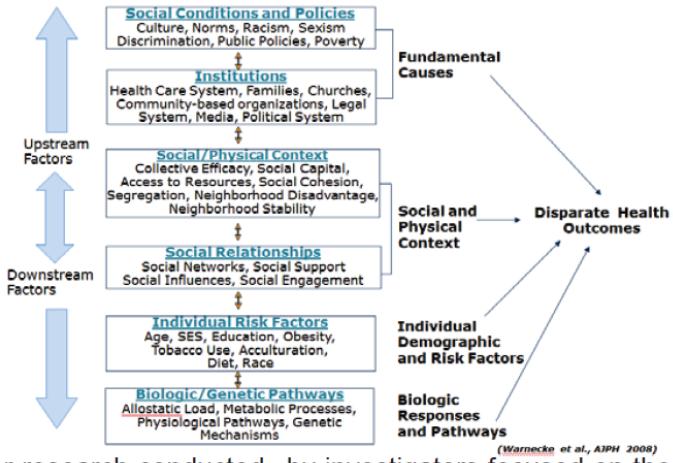
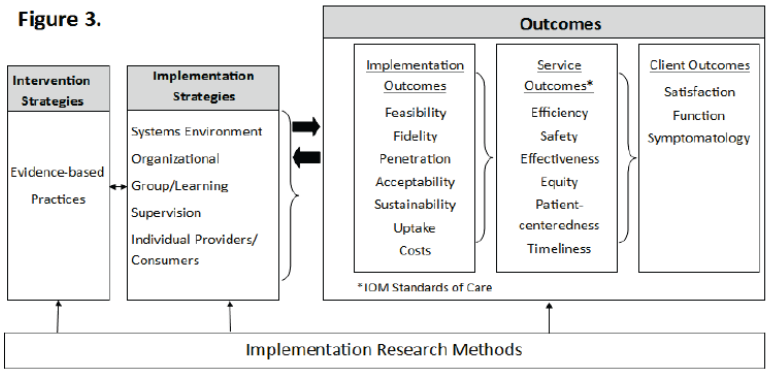


Figure 3.



D.1 Project 1 (Ferketich & Anderson). Effectiveness of a multi-level smoking cessation program adapted for high-risk women in rural communities. Currently, smoking prevalence is extremely high in many of the underserved communities in largely rural Appalachia and has not experienced the long-term declining trends in smoking evidenced elsewhere in the country. The goal of this project is to implement and test the effectiveness of a healthcare provider office-delivered smoking cessation intervention designed to reduce cervical cancer risk in rural Appalachian female smokers, and delivered as part of a broader, synergistic risk reduction program. The smoking cessation intervention will involve training physicians and nurses to institutionalize the Clinical Practice Guideline and referring smokers who are willing to quit, to a tailored, 8-session phone intervention (i.e., the Break Free program).

D.2. Project 2 (Paskett & Vanderpool). Testing Multi-Level Interventions to Improve HPV Vaccination: The "I Vaccinate" Program. The Appalachian region of the US has higher prevalence of hi-risk HPV infection among women, and thus, the need to reduce this disease burden in this underserved region is great. To address this need, a multi-disciplinary research team will test the effectiveness of a health system-based intervention that is directed to three levels of influence – clinic, provider, and patient – to improve the uptake of the HPV vaccine among 11-12 year olds. The interventions to be tested have been developed in conjunction with community partners and have been piloted in Appalachian populations.

D.3. Project 3 (Reiter, Katz). A Multilevel HPV Self-Testing Intervention to Increase Cervical Cancer Screening among Women in Appalachia. Despite current screening guidelines and recommendations, nearly 20% of age-eligible US women are not within screening guidelines [3-4]. Strategies to increase screening among

these women, including the use of HPV self-tests, have therefore been identified as the most important cervical cancer screening research priority by several US organizations [4]. The overall goal of this proposed study is to determine how a multilevel intervention that features HPV self-testing can increase cervical cancer screening among unscreened and underscreened women from Appalachia.

E. SERVICE CORES

The Program Project will include cores for Administrative, Survey/Data Collection, Intervention/Consortium interactions and Biostatistics and Evaluation. The **Administrative Core (AC)** (Co-Leads: **Paskett**, **Anderson**, **Dignan**, and **Kennedy**) and will support the Program Project by providing leadership in program planning and development and implementing effective communication channels. The **AC** will also implement an efficient organizational structure that will facilitate integration of the Program cores and projects. Finally, the **AC** will identify opportunities to disseminate effective interventions and lessons learned from the Program. The **Survey and Data Collection Core** (**SDCC**) (Co-Leads: **Naughton** and **Guterbock**) will lead efforts related to the creation of a database of indicators and measures that can be applied across all three Projects to enhance research on cervical cancer prevention. The **SDCC** will also provide support for interactions with electronic health systems and data capture for the Program Project. The **Intervention and Consortium Core (ICC)** (Leads: **Kennedy** and **Paskett**) will lead efforts to develop and deliver the interventions (including hiring, training, and monitoring the patient navigators) that are tested in the research projects and engage and maintain communications among all community partners. **The Biostatistics and Evaluation Core** (**BEC**) (Leads: **Pennell**, **Conaway** and **Dignan**) will focus on providing the project investigators with a centralized resource for study design and statistical services, as well as program evaluation. They will help to plan, implement, monitor and the analysis of results from the research projects and the overall Program Project, including cost-effectiveness. They will lead evaluation of the Program Project and provide feedback to overcome barriers and improve efficiency.

Program Interaction. The Program will promote and foster integration by promoting the interaction of Program investigators and staff. The MPIs and respective **AC** staff will meet centrally at the initiation of the Program and then talk weekly in the first year and semi-monthly in Years 2-5 unless more frequent calls are needed. A monthly teleconference meeting will be held with all Program leaders, (Core Leads, Project Leads and Co-Investigators, and MPIs) and additional investigators as needed, to review/monitor the scientific progress, discuss timelines, address any barriers and resolve any challenges. Each project and core will give updates and report progress including and relevant scientific updates. Cores and projects will also have teleconference meetings at least monthly that will involve all core/project investigators, staff, and trainees. The MPIs will hold a teleconference at least monthly to discuss Program management, budgets, and other leadership issues. Additional meetings with investigators and staff will be at the discretion of the MPIs. An annual meeting (rotating among university sites) will be an important forum for investigators, SC and ESAB members and all consortium partners (community and healthcare) to foster relationships, receive updates on Program Project activities at all sites, provide input and feedback on research projects and dissemination strategies, address issues affecting the Program Project, and increase exposure to health disparities research at the host site. It will also provide opportunities to develop proposals for additional transdisciplinary research projects.

F. Relevance to the Program

Program components are focused on a common theme – address the burden of cervical cancer incidence and mortality in Appalachia through testing an integrated cervical cancer prevention program implemented in clinics across 4 Appalachian states**.** Integration and interaction of the projects in this Program is evident in several ways (**Figure 1**): 1) all projects focus on one health disparity (CC); 2) participants will be recruited from the same local health systems; 3) a core set of measures is being used by all projects; 4) all projects include transdisciplinary teams; 5) all projects build upon and extend findings from our long history of collaborative research and community partnerships; 6) projects focus on multi-level assessment and/or interventions and utilize the Proctor et al Implementation Science Framework[2]; 7) all projects involve interaction with the community in some way, thus enhancing the CBPR nature of the Program; 8) through regular overall Program, project, core, and SC meetings review of the progress and any issues of the Program components is ongoing.

Interaction with Program Theme. The **AC** is an integral component of all the components of the proposed Program, due to the nature and goals of the **AC**. Thus, the **AC** is crucial to the success of the program, and the components of the Program Project would not be able to function smoothly without the services of the **AC**.

Integration of Program Theme. AC activities are integrated across the projects and cores. The **AC** will assure that the theme of the Program is carried throughout each component of the program project. In addition, the **AC** will ensure that the theoretical frameworks are utilized, operationalized, and evaluated in each component and the overall program. The **AC** will work with the projects and cores to ensure that CBPR is fostered in all components and will facilitate the use of transdisciplinary teams to accomplish project and core goals. Thus, the **AC** is crucial to the establishment and fostering of the mission of this proposed Program Project.

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PROJECT SUMMARY – PROJECT 1

The prevalence of smoking (25 – 35%) in many underserved Appalachia communities is nearly double the national rate and is a major contributor to the high-risk for cervical cancer in the region. **Project 1** – 'Break Free' (BF) will implement and test the effectiveness of a healthcare provider- and trained patient navigator-delivered smoking cessation intervention designed to reduce cervical cancer risk within an integrated cervical cancer prevention program. BF is the result of previous work of the team in adapting an evidence-based smoking cessation program to rural populations and will be tested, refined and implemented to achieve high impact and sustainability through billable cost-recovery. BF utilizes a standard format of clinical delivery of Ask, Advise and Connect (AAC) followed by 4 sessions of proactive telephone-based counseling with Nicotine Replacement Therapy support delivered to 600 adult female smokers in primary care practices of 10 non-overlapping health systems in the Appalachian region of four states (KY, OH, VA, WV). BF will be extended to all eligible smokers in the sustainability phase. Delayed versus early intervention health system groups will be compared. **Project 1** is closely coordinated with the overall Program Project by providing a key component of an integrated cervical cancer risk reduction/prevention program and its overall outcome and will rely on its shared Cores for harmonization in its implementation, measurement, evaluation and dissemination processes. **Project 1** aims are organized along three distinct levels of outcomes: 1) Service outcomes: Determine the effectiveness of a core component of an integrated cervical cancer prevention program designed to help female smokers quit by standardizing clinical practice supports and protocols; 2) Client outcomes: Determine satisfaction with the multilevel intervention; and 3) Implementation outcomes: Test the sustainability of the multi-level intervention via training of providers and staff on counseling and billing for evidence-based smoking cessation services. Successful implementation of BF in the diverse set of rural Appalachian clinics in participating health systems proposed, across 4 states, has the potential for a substantial and sustained impact by improving rural patients' access to high quality, culturally sensitive, and local evidence-based smoking cessation treatment. If successfully shown to be sustainable at the clinic level, BF could be disseminated widely within rural Appalachia, as well as to healthcare systems in other underserved geographic settings.

PROJECT NARRATIVE – PROJECT 1

Project 1 will test the Break Free intervention in rural Appalachia and is designed to lower cervical cancer risk by intervening on smoking, a major risk factor. Break Free will be offered to female smokers in the primary care setting though provider counseling and a proactive telephone-based intervention with Nicotine Replacement Therapy support. As one of three Projects in this Program Project, Break Free is an essential component of an integrated cervical cancer prevention program that will also offer HPV vaccination and cervical cancer screening to patients.

SPECIFIC AIMS

Because tobacco use is a major risk factor for cervical cancer, smoking assessment and cessation should be an essential component of any cervical cancer risk reduction program for females. Although the U.S. Public Health Service Clinical Practice Guideline *Treating Tobacco Use and Dependence*[1] recommends that health systems and providers systematically assess tobacco use, and facilitate smoking cessation in all patients, this can be a steep challenge for rural primary care practices and providers who often need electronic health record support to pre-identify smokers for services, as well as training in efficient and effective patient counseling, and access to comprehensive cessation programs that offer sustained assistance generally necessary for moderate impact. To assist clinics with the goal of cervical cancer prevention, we have embedded an evidence-based smoking cessation program within a larger, multifaceted, integrated clinical program designed to lower risk for cervical cancer among rural Appalachian women accessing care in clinics serving women in the region. This intervention stems from our previous work in Appalachia where we have adapted and tested a two-component system of Ask, Advise and Connect (AAC) + a multi-session smoking cessation program known as 'Break Free' for healthcare settings with input from regional and local health systems in rural Appalachia. Briefly, female smokers will be systematically identified and counseled by providers, and referred to a 4-6 week telephone intervention program with nicotine replacement therapy (NRT) delivered by trained local tobacco interventionists. An innovative feature of our approach is that Break Free treats both smokers who are ready to commit to quitting and those who plan to quit but not yet ready to initiate a cessation process, which makes it tailored to the readiness to quit of each smoker. The overall significance of Break Free is that it can offer clinics in rural Appalachia an integrated process for supporting goals of reducing smoking prevalence among patients. It includes office system strategies to identify smokers, provider delivery of AAC, pharmacotherapy at little or no cost to patients, and tutorials for preparing insurance claims for recoverable fees for counseling to support sustainability.

This Program Project application has an implementation science research focus, with three evidence-based cervical cancer prevention projects integrated within one clinic-based program. **Project 1** (smoking cessation) is designed as an 'effectiveness-implementation hybrid' study.[2] We will first test the efficacy of Break Free and then focus on examining implementation and sustainability outcomes in both Early and Delayed Arm Appalachian health systems. Service, client, and implementation outcomes will be examined as part of the implementation science framework.[3]

Aim 1 Service outcomes: Determine the effectiveness of a core component of an integrated cervical cancer prevention program designed to help female smokers quit by standardizing clinical practice supports and protocols. *Hypothesis 1a*: The Early Arm health system providers will perform the evidence-based AAC at a higher rate than the delayed intervention health system providers. *Hypothesis 1b*: The 6-month and 12-month abstinence rates among smokers receiving the program in Early Arm health systems will be higher than the quit rates among smokers in Delayed Arm health systems. *Hypothesis 1c*: Provider-delivered AAC rates will be similar across smoker characteristics (e.g., age, income, etc.).

Aim 2 Client outcomes: Determine satisfaction with the multilevel intervention. *Hypothesis 2a*: Female smokers, providers, and other clinic staff will report high levels of satisfaction with the Break Free program. *Hypothesis 2b*: Providers will improve knowledge and attitudes towards counseling.

Aim 3 Implementation outcomes: Test the sustainability of the multilevel intervention via training of providers and staff on counseling and billing for evidence-based smoking cessation services. *Hypothesis 3*: Health systems will increase the rate at which counseling sessions are provided to smokers and will increase the rate at which they seek reimbursement for this service.

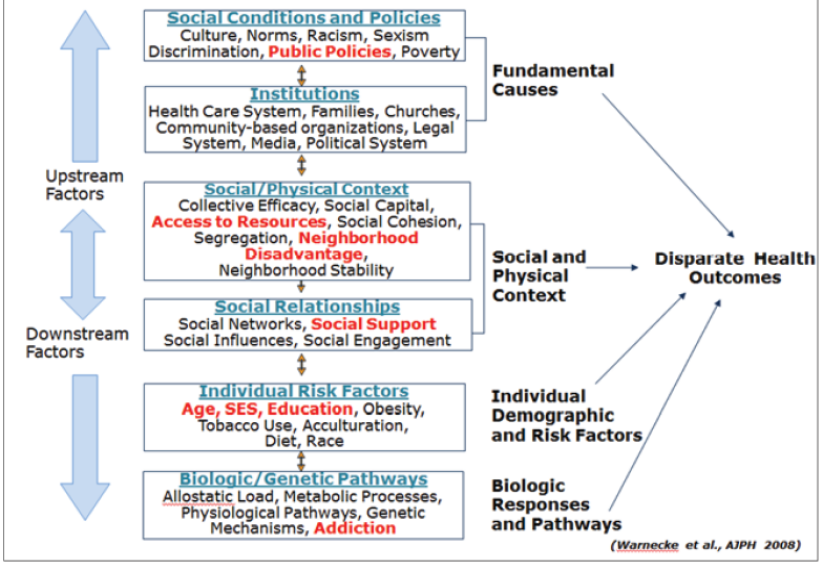
IMPACT: Successful implementation of Break Free in the diverse set of rural Appalachian clinics in participating health systems proposed, across 4 states, has the potential for a substantial and sustained impact by improving rural patient's access to high quality, culturally sensitive, and local evidence-based smoking cessation treatment. Because smoking is a major risk factor for cervical cancer and highly prevalent in rural populations, smoking cessation is an essential component of our integrated cervical prevention program. There are currently no integrated systems for patient smoking cessation that have been adapted to rural health systems and other low resource practice settings. If successfully shown to be sustainable at the clinic level, Break Free could be disseminated widely within rural Appalachia, as well as to healthcare systems in other underserved geographic settings.

RESEARCH STRATEGY

A. BACKGROUND AND SIGNIFICANCE

A1. Overview. A central theme of **Project 1** is focused on *implementing a sustainable provider- and smoker-level program that is tailored for rural health systems. The multilevel factors highlighted in red in the shared* ***Multi-Level Model of Population Health*** *(**Figure 1**)*[4] *are important for smoking cessation, including public policies (e.g., tobacco control policies, insurance policies), access to resources such as cessation pharmacotherapy and counseling, social support, age, socioeconomic status, and level of addiction.* Research conducted under **Project 1** will refine and test a practice-based multi-level intervention as a component of an integrated clinic-based prevention program for cervical cancer at the Program level to reduce cervical cancer risk among patients/families in participating clinics in needy rural counties. Through the shared Cores, the interventions will be coordinated in both theory and approach. Through the **Intervention and Consortium Core** (**ICC**), **Project 1** will include interventionist training, have support for tracking milestones and design refinement, and participate in the multi-Level community and clinic assessments. Through the **Biostatistics and Evaluation Core** (**BEC**), **Project 1** will access statistical design, analysis, and evaluation services in common with other Projects, guided by the shared Proctor model of implementation science[3] to study outcomes that fall into three categories: 1) service; 2) client; and, 3) implementation. Finally, support for data collection and measurement planned under **Project 1** will be provided by the centralized resources of the **Survey and Data Collection Core** (**SDCC**).

Figure 1. Model for Analysis of Population Health and Health Disparities



A2. Scientific Premise. Smoking rates in Appalachian regions are among the highest in the U.S. and because smoking continues to decline in urban regions, rural-to-urban disparities are widening.[5] Since 1996, the Clinical Practice Guideline *Treating Tobacco Use and Dependence* has recommended that healthcare systems adopt institution-wide changes to promote abstinence among patients.[1] While free quit lines exist and can be accessed from all rural geographies, they are often brief (i.e., single session), patient-initiated, and fail to offer NRT support. The latter barriers have limited the practicality and promise of these programs as a substitute for more formal and impactful evidence based programs. For example, the state tobacco quit line of Virginia is the only opportunity for tobacco cessation service available to rural regions and it does not routinely provide NRT and follow-up sessions to participants.

The three Clinical Practice Guideline recommendations that are the focus of this research are: 1) implement a tobacco user identification system at the clinic level (ask about, and document, smoking); 2) advise smokers to quit, assess for readiness to quit, assist with a quit attempt by connecting to services, and arrange for follow-up with counseling; and 3) encourage smokers to use both pharmacotherapy and counseling during quit attempts.[1] In the 21 years since the first publication of the Guideline, barriers such as knowledge, attitude, time, and cost interfere with healthcare systems' ability to fully implement the recommendations. These barriers are perhaps heightened in rural Appalachian regions given the normalization of smoking in the community, the reluctance of individual smokers to attempt to quit, and the widespread poverty that makes it difficult for practices to serve large Medicaid and uninsured populations and for patients to engage in intensive, high cost treatment programs. The research proposed in this application will address several of these barriers by training providers and staff on how to: 1) implement a tobacco user identification system if it does not already exist (i.e., ask); 2) deliver brief counseling (Ask, Advise, and Connect (AAC) to those who are ready to quit); 3) treat smokers who are not ready to quit in the next 30 days, but envision quitting in the next 6 months, with a validated rate reduction intervention; and 4) bill for any recoverable fees for cessation counseling services provided during an encounter. Currently, large public and private insurers cover tobacco cessation counseling;[6] however, many practices are not equipped to deliver or bill for it due to poor knowledge of the process and time constraints. Our proposed project will address this problem by partnering with healthcare practices to provide expertise in tobacco dependence

treatment delivery that will reflect healthcare reimbursement policies as they emerge. Importantly, we will train them on how to work within the reimbursement rules and procedures of their state.

A3. Smoking in Appalachia continues to be one of its largest public health burdens. As indicated in **Table 1**, the smoking prevalence in most of our Appalachian communities is extremely high, much greater than the national median of 15.1%,[7] with many individual counties in the Appalachia region above 30%.[8] Rural Americans have not experienced the significant decline in smoking that urban and suburban regions have since the all-time high of 43% in 1965.[9]

Table 1. Smoking Prevalence in the U.S. and Appalachian Region of Target States

	Overall	*Female*
National	15.1%	13.6%
Kentucky	26.0%	25.5%
Ohio	27.4%	26.6%
Virginia	28.0%	--
West Virginia	25.7%	25.7%

The high smoking rates in Appalachia may be driven by the economic disadvantage in the region,[10] tobacco production which families historically relied on for income, low population density which makes it less attractive for market penetration by wellness organizations, lack of community access to effective cessation programs, and underinvestment in smoking prevention.[11,12]

In addition to adult smoking, adolescent tobacco use is high in Appalachia. In West Virginia, past 30-day tobacco use among high school students is 18.4% among females and 19.2% among males.[13] Interestingly, in Kentucky, past 30-day tobacco use is higher among high school females (18.0%) than males (15.7%).[13] Rural adolescents also appear to have higher annual incidence rates of tobacco use. In the Buckeye Teen Health Study, a prospective cohort study of young adolescent males age 11-16 years in Ohio (led by **Amy Ferketich**, **Project 1** Leader), the one-year incidence rate of any tobacco product, among non-users at baseline, is 9.4% among Appalachian males compared to 6.3% among urban males (unpublished preliminary data). *Because of these high rates of Adolescent tobacco use, we will integrate smoking prevention material into* ***Project 2*** *so that adolescents can learn about tobacco use (and cessation) as they receive HPV vaccine information*.

A4. Women who smoke are at elevated risk of cervical cancer. Results from studies in the U.S., Europe, and China indicate that female smokers are at increased risk of cervical cancer and/or pre-cancerous lesions. Smokers in the European Prospective Investigation into Cancer and Nutrition cohort had a 2-fold increased risk of cervical cancer incidence over a median of 9 years of follow-up compared to non-smokers.[14] Additionally, smoking duration and intensity demonstrated a positive, and time since quitting smoking a negative, dose-response relationship with cervical cancer incidence. Feng and colleagues pooled data from 12 cross-sectional studies in China and reported that current smokers had significantly increased odds of cervical intraepithelial neoplasia grade 2 or worse and HPV compared to never smokers.[15]

One hypothesis is that smoking-related carcinogens disrupt the DNA in cervical cells[1617,18] Two tobacco-associated carcinogens have been detected in the cervix.[19] Benzo[*a*]pyrene (BaP), a polycyclic aromatic hydrocarbon, has been shown to cause cervical cancer in animal studies (24).[18] In a study with human cervical mucus samples, Melikan and co-authors found detectable levels of BaP.[18] The second carcinogen examined in relation to cervical cancer is nitrosamine 4-(methylnitrosamino)-l-(3-pyridyl)-l-butanone (NNK). Prokopczyk et al. found significantly higher levels of NNK in the cervical mucus of smokers compared to nonsmokers.[17] A second possible mechanism linking tobacco exposure to cervical cancer relates to the length of a human papillomavirus (HPV) infection, which is prolonged with tobacco use.[20]

A5. Healthcare providers are important, and effective, advocates for smoking cessation. The Clinical Practice Guideline provides a set of recommendations for healthcare systems, providers, insurers, and smokers.[1] The recommendations call on clinicians to document tobacco use, provide assistance for smokers trying to quit, and use motivational treatments when necessary. The Guideline has been around since 1996, but widespread adoption has not occurred. The prevalence of regularly asking patients about tobacco use ranges between 50% and 75%[21-25] and between 55% and 60% of smokers report that their providers advised them to quit smoking in the previous year.[24-27] However, provider-delivered advice to quit smoking has been consistently shown to increase abstinence rates among smokers. Stead and colleagues pooled data from 41 trials conducted between 1972 and 2012 that were designed to examine the effect of provider advice on cessation.[28] The results suggest that brief advice was associated with an increased odds of quitting at 6 months. The authors suggest that future research should focus on developing interventions to increase the rate at which smokers are identified in healthcare settings, advised to quit, and offered support.

There are many known barriers providers face to routinely providing brief cessation counseling, including lack of training on how to do so, low awareness of the Guideline, a belief that advising smokers to quit may harm the doctor-patient relationship, time constraints, and reimbursement issues.[24] Rural providers may face additional

barriers to helping smokers quit. First, transportation is a challenge in Appalachian regions, which makes it difficult to access healthcare.[29] Despite an increased need for medical care, rural individuals report fewer medical visits in the past year than individuals in large metropolitan areas,[30] which implies there are more health-related issues to address at each visit and thus tobacco cessation discussions may not be a priority. Rural regions also have fewer healthcare resources, such as health insurance and providers.[31]

Provider-targeted interventions appear to improve provider behavior. Results from systematic reviews suggest that training providers will increase the rate at which smokers are counseled during a clinical encounter. In a meta-analysis of 17 studies on the effectiveness of provider training on smoker and provider outcomes, tobacco dependence treatment training resulted in significant increases in all of the following: asking about tobacco, helping smokers to set a quit date, distributing cessation material, providing brief counseling, and arranging a follow-up appointment.[32] Importantly, provider training was also shown to result in a significant increase in point prevalence and continuous abstinence from smoking among smokers in the intervention practices. *This suggests that our model of training providers, with continued mentoring into the sustainability phase, will result in changes in clinically significant provider and smoker behavior.*

A6. Telephone counseling and nicotine replacement therapy (NRT) are proven methods to help smokers quit. Break Free counseling starts with one in-clinic/person session and then moves on to 4 phone counseling sessions for those ready to quit in the next 30 days. For those who plan to quit outside the 30-day time frame, Break Free offers an extended program that begins with smoking reduction to build self-efficacy toward quitting. As demonstrated by the most recent meta-analysis that was based on 51 published trials through 2013, phone counseling is an efficacious treatment for smoking cessation.[33] In addition, less than 4% of households in the U.S. have no phone service at all.[34] While web-based counseling could be an alternative, rural households are less likely to have reliable internet access such as broadband (63% in rural regions of the U.S. vs. about 75% in urban/suburban regions[35]). The situation is even worse in rural Appalachian regions. For example, only 55% of Ohio Appalachian households have broadband access.[36] *Not only is phone counseling an effective mode of tobacco dependence treatment, it is feasible for rural residents who would otherwise be faced with travel and technology barriers to receiving a cessation program*.

In addition to counseling, the Break Free program includes NRT in the form of patch and ad lib gum. For several reasons, this is the chosen course of pharmacotherapy. First, NRT is efficacious compared to control conditions. The most recent meta-analysis focused on NRT is based on data from over 50,000 participants in 117 trials.[37] NRT in patch form was associated with a significant increase in the odds of cessation at 6 or more months compared to control (OR 1.64, 95% CI 1.52-1.78). Similarly, NRT gum was found to increase the odds of cessation over control (OR 1.49, 95% CI 1.40-1.60). Combined patch and gum is effective because the patch will allow for a sustained level of nicotine in a smoker's system and gum will help with immediate cravings. Second, NRT is covered by Medicaid, Medicare, and many private insurance companies. Third, because it is available over the counter, and it has a proven safety record, it is a better choice for a cessation program that is delivered in a rural setting, as participants will not need to come back to the health clinic for a follow-up appointment. Moreover, a counselor with less medical training can monitor the treatment.

***A7. In summary, Project 1 is significant for the following reasons*:**

- Smoking rates are elevated in Appalachian regions of the U.S. and rural residents, in general, have not benefited from strong tobacco control efforts or programs designed to help smokers quit.
- Cervical cancer rates are high in Appalachia and smoking is a risk factor for both invasive cancer and abnormal lesions. Importantly, smoking cessation has also been related to decreased risk of cervical cancer. Thus, promoting cessation is a critical component of cervical cancer prevention and control.
- Provider-delivered interventions, and tobacco dependence treatment with NRT and phone counseling, are effective means to help smokers quit. However, sustainability has not been the focus of most studies.
- Most smokers are not ready to set a quit date in the next 30 days and more programs need to be developed and tested for these smokers.

A8. Innovation: This Program Project application is an innovative approach to cervical cancer prevention in the Appalachian region of the U.S. As indicated in the **Overview** to the application, cervical cancer is an important public health burden in Appalachia compared to other parts of the U.S. Although there are known methods for reducing risk and preventing cervical cancer, incidence and mortality rates continue to be elevated among Appalachian women. **Project 1** is part of a novel integrated clinic-based cervical cancer prevention program that is tailored to women who seek care in Appalachian health clinics. The particularly innovative aspects of this application are the following:

- The Program Project application is focused on implementation science, and includes important service, client, and implementation outcomes, all of which are important for reducing the burden of cervical cancer.
- Break Free is adapted to rural Appalachian smokers because providers where women seek care initiate it. Previous research demonstrates that Appalachians in general are less trusting of "outsiders"[38] and thus initiating a program from their provider's clinic will help to build trust and acceptability of the intervention. Furthermore, during the sustainability phase, Break Free will be fully delivered by clinic staff.
- Because Break Free starts in the clinic when women are already there for an encounter, and continues through phone counseling, it reduces the burden of travel to the clinic.
- Break Free has a separate protocol for smokers who are not ready to quit in the next 30 days, which could be even more important for adults in Appalachia who may face greater barriers to cessation given the culture and social norms surrounding smokers. In our own research, described in preliminary study #1 below, 75% of Appalachian clinic patients indicated an interest in quitting smoking in the next 6 months, yet only 46% expressed a desire to quit in the next 30 days.
- **Project 1**, in general, focuses on sustainability by training clinics on how to deliver and bill for counseling.

B. PRELIMINARY STUDIES

Our preliminary studies illustrate our experience in delivering clinic-level programs to underserved individuals in the Appalachian region of the U.S. Moreover, our previous work demonstrates expertise in clinic-level smoking cessation research. The first two pilot projects taught us the need to have more contact with clinics and greater oversight if we are to implement a sustainable smoking cessation program.

B1. Tobacco Dependence Treatment to Medicaid-Enrolled Smokers. A tobacco dependence treatment program for Medicaid-enrolled smokers from Appalachian Ohio was developed and implemented in 8 primary care clinics.[22] Using a group-randomized trial design, 214 smokers were enrolled from the clinics on a day they were visiting a provider. Over half had self-rated fair or poor health or elevated symptoms of depression. Intervention clinics (n=4) received health system level changes that included identifying a Clinic Champion, provider training on delivering brief cessation counseling and prescribing pharmacotherapy, provider feedback, and educational materials for the clinic rooms. Smokers from these clinics were offered 12 weeks of telephone cessation counseling. Control clinics (n=4) were given the Clinical Practice Guideline and smokers were directed to the Ohio quit line. An important finding is that 60% of smokers from intervention clinics enrolled in weekly phone counseling. This is notable because these smokers came into the clinic for a routine or medical visit, and yet a large percentage of them engaged in cessation counseling. At 3 months, there were no significant differences between intervention and control, but 24.2% in the intervention group self-reported abstinence vs. 15.7% in the control group, over half had a serious attempt to quit, and over one-third used pharmacotherapy. With respect to provider behavior reported by smokers, nearly 70% of intervention providers asked about tobacco use and advised smokers to quit. Less than one-third helped smokers quit but it should be noted that providers were encouraged to only help smokers quit if they were ready to quit. *From this study, we gained experience working with primary care clinics in Appalachia to implement a tobacco dependence treatment program. While providers indicated the program was useful, it was clear during the post-program evaluation that there was not enough support from our research team for the providers or clinic champions to sustain the program, and this will be addressed in the current proposal.*

B2. Pilot Test of Break Free in Appalachian Virginia. This one-arm pilot study was conducted by UVA and OSU investigators in rural Appalachian Virginia, and was adapted from a previous test in Ohio Appalachia by OSU investigators.[22,39] For this pilot test, a smoking cessation program was implemented in a Federally Qualified Health Clinic (FQHC) and in a retail pharmacy setting. The multi-component tobacco cessation model combined provider-based AAC, a CHW-led 8-session smoking cessation program, and free NRT. The primary goal of the project was to assess the feasibility and opportunities for a comprehensive smoking cessation model in a rural setting in different types of healthcare settings. The abstinence rate at the end of the eight session program among participants was 25%. Additionally, we found a statistically significant difference in pre- vs. post tobacco dependence scores. Early NRT use significantly predicted the reduction in average cigarettes per day, suggesting that concurrent NRT use contributed to increased success in cigarettes decreased usage and ultimately cessation. *Both the Ohio study on which Break Free was based, and Break Free in Virginia, achieved a moderate-sized quit rate at 3 months (~ 25%).*

B3. Behavioral Rate Reduction (RR) Studies. We have had a long history of conducting behavioral RR (BRR) studies in tobacco users not ready to quit. Dr. **Klesges** and colleagues conducted what we believe was the first RR research for smokers who were currently unable or unwilling to quit smoking (not ready to quit in the next 30 days). We initially called the approach "controlled smoking" instead of BRR.[40] We developed and validated

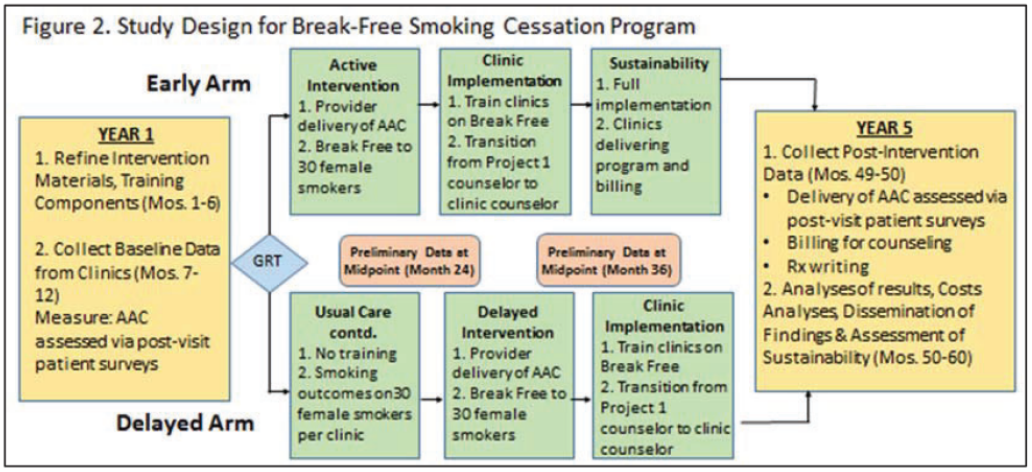
an intervention program, most of which is still in use, to increase biochemically confirmed abstinence. We intervened on three behavioral targets with a goal of 50% reduction in each behavior—the tar and nicotine content of the cigarette, the number of cigarettes per day, and the amount of each cigarette smoked. Over the next several years, we demonstrated that participants assigned to controlled smoking were significantly more likely to quit smoking, even out to a 2.5 year follow-up[41] and documented the validity of this approach in both clinical and public health settings.[40-42]

B4. Meta-Analysis of RR Studies. Several rate reduction reviews have concluded, based on dozens of studies, that Behavioral + Pharmacologic RR as a springboard for cessation promotes long-term cessation.[43,44] However, studies typically include a mix of smokers who are ready to quit smoking as well as smokers not ready to quit. In our meta-analysis,[45] we evaluated randomized clinical trials recruiting smokers that exclusively were not currently willing to quit smoking. Results indicated that RR more than doubled the odds of cessation (ORs 2.14-2.33, n = 3370) in these smokers. Thus, there is strong evidence that RR enhances cessation.

C. RESEARCH DESIGN AND METHODS

C1.Overview. Our multilevel intervention will be developed through **ICC** resources and activities to refine, train and launch provider-level and smoker-level programs for participating clinics from 10 rural Appalachian health systems (**Fig 2**). The clinic setting allows us to reach many smokers, as nearly 90% of smokers in Appalachian Ohio visited a healthcare provider in the past year (unpublished data from the Ohio Medicaid Assessment Survey). During the active intervention (13-24 mos.), health care providers (physicians, physician assistants, nurse practitioners, and nurses) will be trained on how to deliver AAC. Female smokers who are interested in quitting in the next 6 months will be referred to an in-person counseling session at the clinic, which will be led by a clinic staff member trained to be a tobacco treatment specialist (TTS). Clinic staff will deliver the baseline session and determine if the individual is ready to quit in the next month or between 1 and 6 months after enrollment. Smokers will then be directed to phone counseling. Because there is so much variability across state quit lines in their ability to proactively provide multiple-session counseling with NRT, we will offer a standardized, moderate intensity, phone counseling program with NRT. Between the single in-clinic session and telephone counseling, a total of 5 sessions will be provided in addition to NRT patch and gum. Smoking-related outcomes will be assessed 3, 6, and 12 months post-enrollment and compared to usual care clinics during months 13-24. During months 25-36, the active intervention clinics will move into a clinic implementation phase, where we will be assisted by the **ICC** to train the clinics to deliver the program and bill for it themselves. At the same time, the delayed arm clinics will be implementing the intervention. During months 37-48, the active intervention clinics will move into the sustainability phase and the delayed arm clinics will move into the implementation phase. Final data collection will be conducted during months 49 and 50. Provider-level outcomes will include delivery of AAC as reported by patients in post-visit surveys and smoker-level outcomes will include confirmed 7-day point prevalence abstinence, 7-day "floating" abstinence, and serious quit attempts. Smoker-level outcomes will be compared between the two arms. Sustainability measures will include clinic-level billing for cessation counseling and clinic-reported delivery of Break Free.

Figure 2. Study Design for Break-Free Smoking Cessation Program



C2. Research Design & Randomization. The effectiveness of the intervention will be evaluated using a Group Randomized Trial (GRT). In GRTs, identifiable social groups are randomized to a treatment condition with measurements taken on members from those groups to assess the impact of the intervention. In this project, health systems will be randomized to one of two study arms (Early vs. Delayed), and outcome measures (smoking-related, provider, sustainability) will be obtained from patient surveys (in clinic and phone surveys) and electronic health record reviews. To reduce contamination, the health system is the unit of randomization

because the interventions will be delivered at this level. All clinics within one health system will be randomized to the same condition. Randomization will be stratified by state.

C3. Project Population. There are 3 levels of intervention in **Project 1**. Level 1 is the health system/clinic and a location is eligible if it: 1) is based in one of the Appalachian regions included in this Program Project; 2) provides care to female smokers; and 3) does not currently offer an intensive cessation program. Level 2 includes the providers at these participating clinics. Eligible providers are: 1) practicing in one of the participating health systems and 2) involved in patient care. Level 3 includes females who are: 1) age 18 to 64; 2) smokers who consume at least 5 cigarettes per day (less than the minimum in most cessation studies, yet still enough to show signs of nicotine dependence); 3) ready to quit smoking in the next 6 months; 4) English-speaking; 5) able to participate in counseling; and 6) not pregnant. The rationale for the upper age limit is that we can focus on the Medicaid-eligible or enrolled population, which is large in Appalachia.

C3.1 Health systems, clinics, patients by State. We have established relationships with all 10 health systems (Level 1) participating in this Program Project and each has provided the research team with letters of support (see Letters of Support in the **Overall** Section from participating health systems). **Table 2** shows the **Project 1** numbers planned for each level of health systems, clinics, and patients.

Table 2. Clinics by Health System and State

	# systems	# clinics	Females by age		Providers
			18-29	30-64	
Ohio	*4*	*9*	*2,568*	*10,084*	*158*
Kentucky	*2*	*9*	*2,890*	*7,342*	*89*
WV	*2*	*9*	*8,044*	*21,902*	*280*
Virginia	*2*	*5*	*1,978*	*8,634*	*102*

C4. Baseline Assessment. During the first year a needs assessment will be conducted in collaboration with our health system/clinic and community partners. The **ICC** will spearhead this effort with **Project 1** investigators. In Phase 1, we will assess the extent to which smoking cessation services and adolescent prevention programs are offered in the counties and health systems using qualitative interviews with key informants plus environmental scans. Because we have already developed and piloted our proposed interventions, Phase 2 will use the information gathered from the first phase to tailor the intervention. Focus group participants will then be asked to comment on the intervention components. Phase 3 will consist of reviewing edited versions of the intervention materials by the same focus groups for final input prior to production of tailored intervention materials. One final set of materials will be used in all health systems. A benefit of the intervention design is that we will have the opportunity to further modify the intervention based on feedback from the real-world implementation in the Early Arm clinics.

The needs assessment will also include baseline data collection within each clinic. An administrator from each clinic will complete a short survey about the characteristics of each clinic (e.g., patient volume, provider size, # smokers), as well as describe the roles and responsibilities staff have for delivering tobacco cessation treatment. We will conduct environmental scans of each clinic to identify cessation and prevention materials and places to display intervention materials. In addition, consistent with one of the recommendations in the Clinical Practice Guideline,[1] a "Clinic Champion" will be identified at each clinic who will champion the implementation of all efforts of this integrated cervical cancer prevention program. This person will be a clinic employee and will be included as a co-author on manuscripts.

C5. Smoking Cessation Intervention Components. The Break Free intervention components come from our two pilot studies conducted with health systems in Appalachia. Materials were developed with input from community members and providers from the Appalachian Ohio and Virginia regions. Additionally, the provider-level training materials come from Rx for Change®, which is an organization that has developed public use smoking cessation educational materials and videos for providers. Materials will be tailored during the first six months and implemented in each arm according the timeline depicted in **Figure 2**.

Clinics within health systems will be asked to implement a tobacco user identification system, typically an electronic health record (EHR) system, if they do not have this functionality, and providers will be trained to deliver AAC to smokers during clinic encounters. Eligible female smokers who indicate an intention to quit smoking in the next 6 months will be referred to counseling, which will start in the clinic with an in-person session and then finish with telephone counseling sessions. **Project 1** needs for EHR support and provider training will be coordinated through the **ICC**, assisted by Dr. **Vandeusen**'s expert role in clinical systems support. To promote sustainability of the program, clinic staff will be trained on how to deliver the Break Free counseling sessions on their own and how to and bill for recoverable fees associated with the program.

C5.1. Level 1 – Clinics. The first component of the intervention, **implementation of a tobacco-user identification system**, is one of the key recommendations outlined in the Clinical Practice Guideline.[1] Each clinic will be assessed to determine how tobacco use status is documented, if at all. In some offices, tobacco use may be documented at every office visit, whereas in others, tobacco use may be asked but not documented consistently. We will work with each clinic/system to develop and implement the minimum required capability of electronically tracking and reporting tobacco use in their existing EHR systems at each visit. Through resources provided by the **ICC** and **SDCC** our goal is to institute an acceptable EHR identification of smokers in each clinic. Technical expertise on each electronic health records system will be provided by Dr. **Adam Baus** at West Virginia University (see **SDCC**) who will visit each health system, as needed, to identify the specific programming changes necessary to successfully meet the Clinical Practice Guideline. The **Project 1** team will work with the **ICC** will create smoking cessation materials for each clinic. We will start with the publicly available handouts created by Rx for Change© and adapt them to increase their readability and relevance for a rural Appalachian culture. This will be performed through the **ICC** during the first year of the study and focus group participants will be asked to provide feedback on these materials (see **C4**).

In addition to the cessation materials, smoking prevention educational brochures will be created and used with the **Project 2** intervention. Parents and teenagers will receive tobacco prevention information. Since most smokers start before the age of 18 years, it is critical to reach teenagers before they start using tobacco.

C5.2. Level 2 – Providers. For this part of the tobacco dependence treatment program, all providers (i.e., those who are directly involved in patient care) will be required to complete the training. The study team will work closely with each health system and clinic to hold training sessions at a convenient time. The following recommendations from the Guideline will be included in the intervention: 1) implementation of a tobacco-user identification system (see **section C5.1**); 2) education and training of providers and staff; and 3) recruitment and training of a "Clinic Champion" to promote compliance with the intervention (see **section C4**). As indicated in the **ICC** write-up, Clinic Champions will be selected by the clinic at the start of the Program Project is completed. Clinic champions will be integral members of the research team.

The ***Theory of Planned Behavior (TBP)*** is the theoretical framework for the provider level intervention, as it has been found to predict provider-delivered cessation counseling. The TPB predicts behavioral intentions, which, according to the model, ultimately lead to behavior.[46] The three components that affect behavioral intentions are: 1) attitudes, which are influenced by perceptions of the behavior (behavioral beliefs) and the perceived outcomes; 2) subjective norms, which are influenced by normative beliefs and motivation to comply with them; and 3) perceived behavioral control, which is the self-efficacy to carry out the behavior.

As indicated in **section A5**, provider training has been found to improve counseling behaviors and outcomes among smokers in the clinic. Therefore, a **provider education** session will be a key part of our intervention. This session will be designed to last no more than 60 minutes and it will take place at a convenient time (e.g., lunch-time meetings with a meal provided). The educational component will be delivered using a presentation format. The TPB[46] will be used as a theoretical framework for the session. First, attitude towards smoking cessation counseling will be targeted by addressing behavioral beliefs and evaluations of the behavioral outcomes. We will provide information about how the AAC may result in positive outcomes such as quit attempts, cessation, use of pharmacotherapy, an improved provider-patient relationship, and improved patient satisfaction. Normative beliefs will also be addressed. While most providers should believe that important referent individuals approve of cessation counseling, it will nonetheless be reinforced by summarizing the recommendations in the Guideline and reminding providers about professional organizations that recommend helping smokers quit during a clinical encounter. Additionally, we will address normative beliefs of the Appalachian region, which are more supportive of tobacco use (see **section A3**). Finally, perceived behavioral control will be addressed by demonstrating how the intervention can be incorporated into their standard practice by addressing standard barriers to counseling.

The following topics will be included in the educational session: 1) smoking in Appalachia and introduction to the Guideline (normative beliefs); 2) how to implement the AAC model (perceived behavioral control); 3) efficacy of pharmacotherapy and counseling (behavioral beliefs); and 4) details about how to bill Medicaid and insurance companies for counseling (perceived behavioral control). The last part of the session will include role play that will help providers become more comfortable with counseling, which should increase their level of perceived behavioral control. Standard scripts will be used for the role play session.

C5.3. Level 3 – Smokers. This part of the intervention is designed as a moderate-intensity intervention that will begin in the clinic with EHR system support, brief provider counseling, and effort of a TTS from the clinic staff to administer session 1 (described below). The latter staff role will be customized to each clinic based on staffing

availability, and will be supported by a stipend payment to the health systems. Beginning with session 2, the intervention transitions to a phone counselor.

Smokers will be advised to quit and assessed for their readiness to quit by the provider during a medical visit. Those who are interested in quitting in the next 6 months will be referred to the in-person counseling session in the clinic. It is important to note that the Break Free program includes the Guideline's recommendations for counseling and pharmacotherapy, which have been found to increase the rate at which smokers quit.

A clinic staff member who completes TTS training ("clinic counselor") will meet with the smoker before she leaves the clinic to discuss the benefits of quitting smoking, preparing to quit, and strategies to increase success, including pharmacotherapy (NRT patch and gum for this study) and counseling. This session will last 15-20 minutes. All participants will then be "connected" (the C in AAC) to Break Free phone counseling, which will be provided by our project team during the active intervention phase.

The Break Free phone counseling sessions will begin within a week of the clinic referral. During the active intervention phase in the Early Arm clinics, a **Project 1** research staff person will deliver phone counseling. At the same time, **Project 1** investigators will train the TTS clinic staff on the phone counseling protocol and eventually transition all of the counseling to the clinic, after which they can bill for the service. Phone counselors will use motivational interviewing techniques to guide individuals to a successful quit during their four calls. The phone counselor will complete a call sheet with each participant that tracks current NRT use, quit date, length of call and a brief overview of what was covered during the session. **Table 3** summarizes the content of the calls by type of program (standard or rate reduction). In the next two sections, detail about each Break Free delivery model is provided. Each delivery model starts with smoking rate reduction (RR) during Session 1. RR occurs by using strategies such as breaking brand loyalty, self-monitoring, and disrupting automatic triggers to smoke. During Session 2, when participants are deciding whether to set a quit date, some will be willing to quit and some will want to continue to reduce their smoking frequency. Break Free will offer strategies that are efficacious regardless of participants' immediate willingness/readiness to quit. Because cell phone minutes may be a concern among some participants, the budget includes money for pre-paid minutes for participants who need them.

Table 3. Break Free Protocols for Smokers Ready to Quit Immediately and within 6 Months

Session	***Standard – Quit within 30 days***	***Rate Reduction – Quit within 1-6 Months***
1	Rate reduction + NRT	Rate reduction + NRT
2	Set quit date Prepare to quit	Rate reduction Discuss future quit
3	Develop short-term relapse prevention plan	Rate reduction Discuss relapse prevention for future quit
4	Develop long-term relapse prevention plan	Rate reduction Discuss long-term relapse prevention for future quit Encourage targeted quit date

Standard Break Free program for smokers ready to quit in the next 30 days: The remaining three phone sessions of the standard program will include: Session 2: set a quit date and prepare to quit; Session 3: evaluate the quit date and develop a short term relapse prevention plan; Session 4: develop a long term relapse prevention plan. Participants who fail to quit on their quit date repeat Sessions 1 and 2 after Session 3.

RR Break Free program for smokers ready to quit in the next 6 months, but not in 30 days: The remaining three phone sessions of the tailored program are designed to move a smoker to a point where she is ready to set a quit date. Session 2 includes further rate reduction strategies, such as situational control (smoke in only certain situations or never smoke in others), temporal control (a time based strategy), and access (keep cigarettes in an inconvenient spot to avoid "automatic cigarettes") with a goal to reduce intake another 25%. Also included is a discussion about plans for a quit date "in the future. Session 3 will be focused on reducing smoking another 25% (75% reduction total). Counselors and participants will also discuss plans for short term relapse prevention during a future cessation attempt. Session 4 will include additional rate reduction by working with participants to reduce the amount of each cigarette smoked. One method to achieve this goal involves marking the cigarette with a non-toxic felt pen and participants will be encouraged to smoke 50% of each cigarette. A future quit date and a longer term relapse prevention strategy will also be encouraged.

Pharmacotherapy: All women who enroll in Break Free will receive a prescription for 8 weeks of NRT in the form of patch + gum. As most of the women at these clinics are insured, they should not have to pay for NRT beyond a minimal co-pay. For women who are uninsured, we will work with a local pharmacy during the active phase of the intervention to provide free NRT for study participants. Women will take the prescription to the pharmacy and we will provide the NRT for free during the active implementation phase. The dose of patch will be 21 mg and

participants will be instructed to apply a new patch each morning. If a participant experiences light-headedness with the 21 mg patch, the dose will be decreased to 14 mg daily. Participants will be told that they may chew up to 20 pieces of 4 mg NRT gum daily to reduce cravings. Side effects will be monitored during the counseling calls. Participants whose side effects are not managed with the usual recommendations (e.g., do not wear a patch at night, rotate the patch daily) will be referred to their provider at the clinic. The trained tobacco interventionist will be in regular contact with the clinics to discuss issues and successes.

Additional support: All women who complete counseling and are using NRT, but want additional support, will be offered up to 3 additional months of NRT (with a prescription from the provider) and follow-up contacts in the form of monthly calls from a phone counselor (initially **Project 1** staff, transitioning to clinic staff). This additional support will be designed to help women sustain abstinence for longer than the initial 3 months, as previous research with Appalachian smokers suggests that abstinence drops after 3 months.[39]

C6. Clinic Implementation. The intervention components will be implemented in the Early Arm Clinics over 18 months starting in Year 2 (see **Figure 2**). During this phase, staff from the study and the **ICC** will work closely with the clinics to successfully implement the study components. Throughout this process, we will review our Project implementation plans and progress with Dr. Ruffin, who serves the Program as a clinical expert based on his training as a primary care physician and his research expertise with implementing protocols for risk factor reduction and screening uptake in primary care, including in rural and Appalachian populations. First, each clinic will have at least one trained TTS, recruited from existing staff or newly hired, depending on feasibility and preference of the clinic lead. The TTS will complete the onsite and phone counseling with women enrolled in the Break Free program. Second, study staff assigned to each clinic, who will be working with all **Projects 1-3** in this Program, will work with clinic staff to implement a tobacco user identification system that meets the functional requirements of this study within the constraints of each clinic's existing EHR environment (please see **aim 4** of **Survey and Data Collection Core** (**SDCC**) for general approach). Third, the Clinic Champion will be integral to assuring that the first two components are successful. TTS training will be performed with The University of Kentucky's accredited online training program designed for health professionals who wish to have a greater understanding of tobacco dependence treatment as well as provide science-based treatment tools needed to help smokers quit. The clinic-based TTS will deliver both the first session of the Break Free program (the "C" in the AAC model) in the clinic, and the subsequent phone calls. Because of the above required clinic preparation period, the Break Free program will begin enrollment between the 6 and 9 month period in Year 2. The remainder of Years 2 and 3 for the Early Arm Clinics will be spent trouble-shooting and collecting process measures to assess what works and what needs to be modified to inform the sustainability phase. Starting in Year 3, the same steps will be taken to implement the intervention components in the Delayed Arm Clinics.

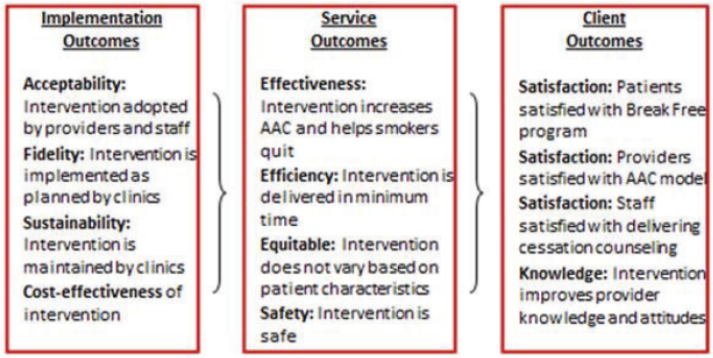
While the Early Arm Clinics are in the Active Intervention (**Figure 2**), the Delayed Arm Clinics will continue to deliver their usual care. Data will be collected from smokers to establish baseline/comparison smoking-related outcomes. The research team will assess how tobacco users are identified and if there is a formal within-clinic smoking cessation or a program affiliated within a larger health system (if the clinic is one of several in a system). To determine "usual care" tobacco-related outcomes in these clinics, clinics will enroll eligible female smokers who are interested in quitting in the next 6 months and call them at 3, 6, and 12 months to see if they have quit smoking (and confirm with cotinine, as described below).

C7. Sustainability Phase. Throughout the active and clinic implementation phases of the program, our research team will periodically meet with clinic managers and health system representatives in the **ICC** convened Clinical Consortium to develop practical solutions or options that reduce office and clinical burden, in collaboration with our clinical implementation sciences expert consultant, Dr. Jamie Ostroff. Project Leaders will also work with each clinic to identify discounts or low-cost NRT supplies for smokers without medication benefits. During Year 4, when the focus in the Early Arm Clinics is entirely on fidelity and sustainability, our research team will no longer provide the counseling. Rather, clinics will need to deliver and bill for the counseling to sustain the program. Our research team will track sustainability and fidelity during this period through process measurements supported by the **SDCC** conducted with key personnel in the health systems, such as providers, and medical and/or nursing directors to address matrix of outcomes planned by the **BEC** for overall program evaluation. An important component of clinic sustainability of Break Free will be recovering maximum allowable costs for smoking cessation counseling from health insurers. We will transfer knowledge and resources on reimbursement strategies in this regard gained from our participation in the currently funded NCI P30 Cancer Center Smoking Cessation Initiative (C3I), which includes UVA (**Anderson**) and UK (**Burris**) as member sites, and which has program sustainability as a major aim. In addition we will draw upon the experience of our external advisory board recruited for this purpose (please see the **ICC** for details on advisors and consultants and

oversight of sustainability across all Projects). Thus, in the sustainability phase we will document current billing and NRT procurement practices of each health system, potential barriers in optimizing reimbursement, and their potential solutions. This report will be presented to our **ICC** Clinic Consortium comprised of medical directors and leaders for feedback and refinement. In the final step we will prepare customized, prescriptive reports for each system based on each clinic's professional and administrative resources that reflect current reimbursement regulations.

C8. Outcome Assessment. The clinic-, provider- and smokers-level measures will be assessed throughout all phases of the program. These measures are summarized in **Figure 3** and described in greater detail below. We will work closely with the **SDCC** to develop and administer the questionnaires to assess the outcomes.

Figure 3. Project 1 Study Outcomes



C8.1. Implementation Outcomes: **Acceptability of the intervention** will be examined by examining whether it is adopted by providers and staff. These provider-level outcomes will include self-reported changes in the delivery of the AAC and the rate of referrals to the in-clinic smoking cessation counselor.

Fidelity to the intervention will be assessed two ways. First, a random sample of women will be called the day after the phone counseling and asked questions about the content of the call. Second, self-administered, anonymous, post-provider visit surveys will be conducted with patients. Every other month, a one week period (i.e., Mon-Sat) will be randomly selected and during that week all patients will be asked to answer questions about whether the provider: 1) asked about tobacco use; and if a smoker, 2) advised the individual to quit; 3) discussed cessation; and, 4) connected the smoker to counseling. These surveys will be anonymous, collected in a sealed envelope, and mailed to our project team.

Sustainability of the intervention will be tracked during the final phase of the study. To determine if clinics are able to maintain Break Free, we will track: 1) self-reported continuation of cessation counseling by TTS-trained staff; 2) number of counseling sessions billed for overall and for each individual smoker who has at least one session; and, 3) electronic health record documentation of tobacco use (with **SDCC**).

Cost-effectiveness of the intervention will be assessed by the **BEC** by considering costs of each component including NRT supplies, TTS time and training, smoking cessation counselor time and training, telephone and material costs, and other administrative costs. We will value the costs of each activity using standard costs.

C8.2. Service Outcomes: **Effectiveness of the intervention at increasing brief cessation counseling** will be assessed using the patient post-visit surveys, described above. We will examine survey responses to see if they increase over time, which is the goal following the implementation phase.

Effectiveness of the intervention at helping smokers quit will be assessed through follow-up with smokers that will be conducted by clinic staff. Smoker-level outcomes will include: 1) 7-day point prevalence abstinence; 2) 7-day floating abstinence; 3) prolonged abstinence; and 4) at least one 24-hour quit attempt. A 24 hour quit attempt is an important endpoint given that it is associated with a greater likelihood of future cessation.[43]

Seven day point prevalence abstinence will be measured using both self-report of any tobacco use and biochemical confirmation using expired salivary cotinine. Biochemical confirmation will be used because the participants will be enrolled in a study that involves their providers, which may influence their reporting of tobacco use. The Society for Research on Nicotine and Tobacco (SRNT) recommends that these "higher demand" interventions use biochemical confirmation to confirm self-reported data.[47] Women who self-report not smoking in the past 7 days will receive a saliva collection kit by mail and a $10 gift card. They will be asked to mail the kit back to OSU, where it will be processed and shipped to a lab we have used in other studies for cotinine assessment. Abstainers will be classified as those participants who self-report no use of tobacco during the past week and have a salivary cotinine concentration of 14 ng/mL or less. *Floating abstinence* will be assessed at each follow-up and will be defined as not smoking during any consecutive 7-day period since the last assessment. *Prolonged abstinence* will be assessed at each follow-up and will be defined as no smoking after a two-week grace period from the quit date.[48] Following conventions for smoking cessation trials,[49] participants will be

considered as not having experienced the outcomes if they do not complete a follow-up assessment or confirm abstinence with cotinine.

Whether the intervention is **equitable** will be assessed by exploring interactions between smoker-level characteristics and whether the provider delivers AAC. The post-visit surveys supported through the **SDCC** form part of the fidelity assessment described by the **BEC** will be further examined to determine if providers are delivering AAC to women of various ages, insurance status, and education levels in a similar way.

C8.3. Client Outcomes: **Satisfaction among providers, staff, and smokers** will be assessed at various time points during the study. Providers and staff will be assessed at the mid-points (see **Figure 2**) and smoker satisfaction will be assessed at the end of the Break Free counseling sessions and again at 6 months.

Effectiveness of the intervention at improving provider knowledge and attitudes will be assessed using surveys at baseline, 30 days post-training, and end of implementation phase. Physician behavior has been examined using the TBP framework. Puffer and Rashidian found that attitudes and perceived behavioral control explained 40% of the variance in intention to provide advice to quit smoking in the next 3 months.[50] Similarly, McCarty and colleagues found that attitudes and perceived behavioral control were significantly associated with delivering cessation advice.[51] TPB model constructs will be measured at the beginning of the study and at the end of the intervention phase in each clinic using a modification of the questions used in previous provider-level studies.[22,52] Each of the TBP constructs will be assessed: 1) attitudes (e.g. "My doing this can ultimately benefit the patient's health"); 2) normative beliefs (e.g. "My colleagues expect me to do this"); and 3) perceived behavioral control (e.g. "Doing this is difficult to achieve").

C9. Analysis Plan: Below is a summary of the planned analyses and statistical power for the primary outcome analysis. More details are provided in the **BEC**.

C9.1. Sample size justification: The sample size for **Project 1** is 51 women smokers per health system, for a total of 510 women enrolled. This is based on a two sample test of the 7-day point prevalence abstinence at 6 months with power calculated using a standard group randomized design formula, shown in section B1.a. in the **BEC**. Assuming a 10% quit rate in the delayed group, a 25% quit rate in the early intervention group, and a conservative estimate of the interclass correlation of 0.017, a total of 10 health systems, equally randomized to early and delayed intervention groups, and 43 smokers per health system will provide 80% power at a two-sided significance level of 5%. The power for other alternatives and other assumptions are given in section B1.a in the **BEC**. The sample size was inflated to 51 per health system (or 510 total) to allow for 20% dropout.

C9.2. Analysis plan: Hierarchical (mixed) models will be used to compare smoking cessation outcomes at 6- and 12-months between smokers in the Early and Delayed Arm health systems. Logistic models will be used for the binary outcomes, including the point prevalence, floating and prolonged abstinence, and at least one 24-hour quit attempt. Models for count data will be used for the number of quit attempts in the follow-up period. Subsequent analyses will adjust for patient-level characteristics in comparing smoking cessation at 6 and 12 months among patients in the Early and Delayed Arm health systems.

Rates of the use of evidence-based AAC will be collected at a randomly chosen month at each clinic. Mixed logistic regression models, with a random effects for provider and clinic, will be used to assess the proportion of patients receiving AAC over the time periods per-intervention, during intervention and in the post intervention periods. As with the smoking cessation outcomes, patient characteristics, both as main effects and in interactions with the time period, will be used to assess whether the AAC proportion differs by patient characteristics such as age or socioeconomic status.

Mixed models will be used to assess measures of staff and provider satisfaction with the program and to evaluate changes in provider knowledge and attitudes over time. Similar models will be used to evaluate patient satisfaction with the Break Free program, using random effects for health system and primary provider. Subsequent analyses will add patient characteristics in order to evaluate whether satisfaction with the Break Free program differs by these characteristics. ***Because only women will be enrolled in this cervical cancer risk reduction program, sex as a biological variable will not be explored.***

C.10. Data Management. The primary source of provider- and smoker-level data will be self-administered, post-visit, and phone surveys to assess outcomes. We will use REDCap as our data entry system for these data, as well as the needs assessment data and provider questionnaire data, as described in the **SDCC**. The folders will be stored in locked filing cabinets in a locked office.

C.11. Investigators and Management Plan. Amy Ferketich is a Professor in the Division of Epidemiology at OSU and has experience leading smoking cessation studies targeting low-income smokers in Appalachia using

clinic-based and population-based models to deliver programs. She was an investigator on both rounds of the Center for Population Health and Health Disparities at OSU (PI: **Paskett**). She will be the **Project 1** Leader (. **Roger Anderson** is a Professor of Public Health Sciences and Associate Director for Population Sciences and Co-leader for Cancer Control and Population Health Research at UVA. His research focuses on cancer disparities in Appalachia, health policy, and health systems interventions. He will be the Co-Leader of **Project 1**. Drs. **Ferketich** and **Anderson** have collaborated on a pilot smoking cessation study delivered to smokers in rural Appalachian Virginia, and are co-investigators in the national Tobacco Centers for Regulatory Sciences (TCORS) network. Dr. **Anderson** whose expertise is in health services research and cancer prevention will oversee the practice integration, policy- and dissemination-related aspects of **Project 1**. **Jessica Burris** is an Assistant Professor of Psychology at UK and has expertise in cancer prevention and control, with a specific focus on smoking cessation. She is currently the PI on a NCI K07 that examines cancer diagnosis as "teachable moment" for smoking cessation. She also leads a smoking cessation intervention for cervical cancer patients in rural, Appalachian Kentucky and the UK Markey Cancer Center's system-wide tobacco treatment program. **Mark Conaway** is a Professor of Public Health Sciences at UVA and has expertise in statistics and multicenter clinical trial designs. Drs. **Conaway** and **Anderson** collaborate at UVA in assisting faculty in Public Health Science to develop and test cancer screening and prevention research. **Bob Klesges** is a Professor of Public Health Sciences who was recently recruited to at UVA to lead tobacco control and addiction research. He brings three decades of expertise in delivering cessation interventions to high-need populations, including protocols that combine pharmacotherapy and behavioral therapy to reduce the rate at which individuals smoke before they attempt to quit, as well as interventions delivered in healthcare clinics.

C12. Scientific Rigor. Project 1 is designed to include a rigorous test of the efficacy of Break Free and sustainability of the intervention in later years of the funding. The following aspects of the design increase the scientific rigor: randomization of health system, fidelity assessment, biochemical verification of abstinence, blinded post-visit surveys, and statistical models that account for within-system correlations of outcomes.

C13. Study Timeline

Year 1 – Baseline needs assessment and baseline data collection
Year 2 – Active intervention in Early Arm health systems; usual care in delayed health systems
Year 3 – Clinic implementation in Early Arm (transitioning to sustainability) and intervention in Delayed Arm
Year 4 – Sustainability in Early Arm and clinic implementation in Delayed Arm
Year 5 – Post-intervention data collection, data analysis, cost analysis, dissemination of findings

C14. Diffusion and Dissemination of Efficacious Interventions. Project 1 leadership will work with the **ICC** to assist with the effective dissemination of the study results. This will be accomplished through rural primary care and health systems stakeholders, presentations to health system boards serving Appalachian regions of each of the 4 study States, and national presentations targeting health care professionals. Our presentation will be coordinated though the **Administrative Core** (**AC**) so that both the overall Program results and specific smoking cessation results are presented at the appropriate venues or forums. In addition, **Project 1** will develop a free Manual of Operations and toolkit for practices that want to implement Break Free.

C15. Program Relevance

C15.1. Relevance to Program Theme: Break Free is designed to eliminate use of combustible tobacco, a major risk factor for cervical cancer. Because smoking is endemic in Appalachia, Break Free can also help reduce the intergenerational transmission cervical cancer risk to adolescent girls through role modeling.

C15.2. Interaction with Program Components and Cores: Break Free was designed as a stand-alone clinic-based program for rural smokers to facilitate effective AAC and cessation. In this Program Project, it forms an essential component of a broader integrated cervical cancer prevention program for rural women presently at risk, and their children who will become at risk as they mature toward adulthood. Break Free utilizes the development, implementation, measurement and evaluation skills of the Program Project's shared cores to insure a level of full integration and synergy with **Projects 2** and **3**. Within our integrated cervical cancer prevention program, Break Free will be delivered by clinic staff to adult women alone or in combination with HPV self-sampling and Pap test access prompting (**Project 3**). For children who are identified for HPV vaccination (**Project 2**), Break Free will incorporate age-appropriate smoking prevention education provided in the clinic by trained staff using the American Academy of Family Physicians, prevention materials developed.

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PROJECT SUMMARY – PROJECT 2

Prior research has demonstrated that health care provider recommendation is the most influential factor affecting HPV vaccine uptake and completion among adolescents and young adults. However, many providers are not recommending the vaccine at opportunistic times such as the targeted ages of 11-12 when most children receive Tdap and meningococcal vaccines. To improve the uptake of the HPV vaccine among 11-12 year olds – the age group of focus for the Centers for Disease Control and Prevention (CDC) – a multi-disciplinary research team across four Appalachian states will test the effectiveness of a health system-based intervention, as part of an integrated clinic-based cervical cancer prevention program (with **Projects 1** and **3**), that is directed to three levels of influence – clinic, provider, and patient. Using a delayed intervention design in a group randomized implementation trial, we will examine outcomes of effectiveness, acceptability, and sustainability along the Implementation Science Framework. We will also test in a secondary aim whether interventions targeted to the 13-26 year olds increases catch-up vaccination. This study is part of the Program Project, "Improving Uptake of Cervical Cancer Prevention Services in Appalachia," and as such, is intricately integrated with the Cores of the Program. The interventions to be tested have been developed in conjunction with community partners, address multi-level factors within the Social Determinants of Health that impact disparities in HPV-related disease, and have been piloted in Appalachian populations. Specific aims are to: 1) Primary Outcome: Test the effectiveness of a multi-level intervention directed at clinics, providers, and patients (parents of children aged 11-12) to improve HPV vaccine initiation and completion in health systems in four Appalachian states (KY, OH, WV, and VA) among children aged 11-12, and assess the effectiveness of the intervention program among subgroups, e.g., females vs males; 2) Secondary Outcomes: Assess: a) sustainability of the intervention; b) cost impacts of the intervention; c) changes in clinic practices that occur as a result of the intervention in terms of staff responsibilities for the vaccination process and reducing missed opportunities for vaccination; and d) whether interventions directed to 13-26 year olds increases catch-up vaccination; and 3) Secondary Outcomes: Examine: a) changes in knowledge and attitudes of providers via educational session pre-post surveys and b) satisfaction with the intervention at the multiple levels. If effective, this multi-level intervention will be disseminated to our clinical and community partners as well as other partners throughout Appalachia to facilitate the uptake of effective interventions throughout health systems and clinics in Appalachia to help reduce the burden of HPV-preventable diseases.

PROJECT NARRATIVE – PROJECT 2

This project will test the implementation of a practice based intervention to improve uptake of the HPV vaccination among patients 11-12 and 13-26 years old in health centers in Appalachia, as part of an integrated cervical cancer prevention program.

SPECIFIC AIMS

As of 2017, approximately 79 million Americans are currently infected with the Human Papillomavirus (HPV) and 14 million people become newly infected each year. Each year in the United States (U.S.), there are about 19,400 women and 12,100 men affected by cancers caused by chronic infection with HPV[1,2] at the following sites: cervix, vagina, vulva, anus, penis, rectum, and oropharynx. Prior to the availability of the HPV vaccine, HPV-related disease cost the U.S. more than $8 billion in direct costs annually, with $1 billion allocated for HPV-related cancer treatment, $300 million for genital warts, and $200 million for the treatment of recurrent respiratory papillomatosis[3]. The largest proportion ($6.6 billion) was used for prevention and treatment of cervical cancer[4] Thus, HPV infection is a very serious and prevalent condition. Fortunately, there **is** a vaccine to prevent infection with the most common HPV types as well as those responsible for 90% of cervical cancer cases[5-6]. Unfortunately, completion rates for the vaccine series are low in the U.S. (49.5% in 2016) for females and very low among males (37.5% in 2016) aged 13-17[7]. Starting in December 2016, two shots are now recommended for those who initiate vaccination under age 15[8-9], therefore completion rates may improve. In certain populations where HPV-associated cancers are more prevalent, efforts to increase uptake of the vaccine should be a priority.

The Appalachian region of the U.S. has higher than average incidence and mortality rates for HPV-related cancers, including cervical cancer[10], higher rates of HPV infection[11-12], and lower rates of HPV vaccination[13]. Thus, the need to reduce the disease burden in this underserved region is great. Prior research has demonstrated that the most influential factor to the uptake of the HPV vaccine series is a health provider recommendation[14-16]. Providers are not strongly recommending the vaccine even at opportunistic times such as when 11-12 year olds receive Tdap and meningococcal vaccines[17-20]. The Centers for Disease Control and Prevention (CDC) has a campaign targeted to providers to improve this oversight "You Are the Key to Cancer Prevention", however, little gains in vaccination have been observed[21]. Catch-up vaccination is recommended for males (to age 21 with allowances to age 26) and females (up through age 26) and few organized efforts are being tested for this group of at-risk young adults.

To improve the uptake of the HPV vaccine among 11-12 year olds, the age group of focus for the CDC, a multi-disciplinary research team will test the effectiveness of a health system-based intervention, as part of an integrated clinic-based cervical cancer prevention program (with **Projects 1** and **3**), that is directed to three levels of influence – clinic, provider, and patient. Using a delayed intervention design in a group randomized implementation study, we will examine outcomes along the Implementation Science Framework proposed by Proctor[22]. We will also test in a secondary aim whether exposure to interventions for 13-26 year olds improves catch up vaccination. This study is part of the Program Project "Improving Uptake of Cervical Cancer Prevention Services in Appalachia," and as such, is intricately integrated with the Cores of the Program (See **Section C17.2**). The interventions to be tested have been: developed in conjunction with community partners, address multi-level factors within the Social Determinants of Health (SDH) that impact disparities in HPV-related disease, and have been piloted in Appalachian populations. Specific aims are to:

Aim 1 Primary Outcome: Test the effectiveness of a multi-level intervention (MLI) directed at clinics, providers, and patients (parents of children aged 11-12) to improve HPV vaccine initiation and completion in health systems in four Appalachian states (KY, OH, WV, and VA) among children aged 11-12 and assess the effectiveness of the intervention program among subgroups, e.g., females vs males.

Aim 2 Secondary Outcomes: Assess : a) sustainability of the intervention; b) cost impacts of the intervention; c) changes in clinic practices that occur as a result of the intervention in terms of staff responsibilities for the vaccination process and reducing missed opportunities for vaccination; and d) whether interventions focused on 13-26 year olds increases catch-up vaccination.

Aim 3 Secondary Outcomes: Examine a) changes in knowledge and attitudes of providers via educational session pre-post surveys; and b) satisfaction with the intervention at the multiple levels.
If effective, this intervention will be disseminated to our clinical and community partners as well as other partners throughout Appalachia. This will facilitate uptake of effective interventions throughout health systems and clinics in Appalachia to reduce the burden of HPV-preventable diseases.

IMPACT: Few MLIs to improve the uptake of HPV vaccination have been tested among health systems and clinics that mainly serve low-income populations in Appalachia. If an MLI delivered at the health system level targeting clinics, providers, and patients is effective, this intervention can be delivered by health systems to promote HPV vaccination among this underserved population, thus, saving lives and reducing unnecessary healthcare costs.

RESEARCH STRATEGY

A. BACKGROUND AND SIGNIFICANCE

A.1. Introduction

The Appalachian region of the U.S. has higher than average incidence and mortality rates for cervical cancer (see **Table 1**), and thus, the need to reduce this disease burden in this underserved region is great. Persistent HPV infection is responsible for nearly all cases of cervical cancer, 90% of anal cancers, 70% of oropharyngeal cancers, and 60%-75% of vaginal, vulvar, and penile cancers[1-2]. Fortunately, there is a vaccine to prevent infection with the most common HPV types as well as those responsible for 90% of cervical cancer cases[9]. Unfortunately, completion rates for the HPV vaccine are low in the U.S. females (49.5% in 2016) and lower among males (37.5% in 2016) aged 13-17[7, 23] and the rates in Appalachia are also low (<60% for both females and males)[7]. HPV vaccine uptake and completion rates are low for myriad reasons, including: lack of awareness of the need to be vaccinated, cost issues, lack of physician recommendation, and confusion about guidelines[17, 20, 24] as well as negative attitudes and beliefs about HPV vaccine, cervical cancer, and vaccines in general[19, 24]. Interventions targeted to underserved communities who represent an understudied population and who could benefit from such a *multi-level* approach to reducing risk for HPV-associated diseases are desperately needed.

A.2.Scientific Premise Cervical cancer is a public health problem in Appalachia. More than 25 million people live in Appalachia where almost half of the region is rural and most of the residents are White and non-Hispanic[25]. Appalachian residents are more likely to have lower incomes, higher poverty rates, lower levels of education, higher unemployment rates, and poorer health than non-Appalachians[26]. The Appalachian region has higher than average incidence and mortality rates for cervical cancer (**Table 1**), and two of the four states (KY, WV) participating in this project have some of the highest incidence and mortality rates for cervical cancer among white women in the nation[27], reinforcing the need to reduce the disease burden in this underserved region.

Table 1. Avg Annual Age-adjusted Cervical Cancer Incidence and Mortality, Appalachia vs Non-Appalachia*[28]

	Incidence			Mortality		
	Appalachia	Non-App	% Difference	Appalachia	Non-App	% Difference
Kentucky	10.4	8.5	22.4	3.4	2.7	25.9
Ohio	9.2	7.5	22.7	3.0	2.4	25.0
Virginia	6.9	6.5	6.2	2.5	2.0	25.0
West Virginia	9.8	**	**	3.2	**	**
US	8.3	7.9	5.0	2.6	2.4	8.0%

**Average annual rate per 100,000, age-adjusted to the 2000 US standard population; most data were reported for 2002–2013, although there are slight variations among states. ** West Virginia is entirely Appalachian.*

HPV infection is a chronic and prevalent disease. HPV is the most common sexually-transmitted infection nationally; it is usually asymptomatic and can lie dormant for years before symptoms appear[29]. From 2013-2014, prevalence of any genital HPV infection among adults 18-59 years of age was 42.5% in the total population, with 23% of those being a high-risk genital HPV infection[12]. Persistent HPV infection is responsible for virtually all cases of cervical cancer, 91% of anal cancers, 70% of oropharyngeal cancers, and 69% of vaginal, vulvar, and penile cancers[30]. Moreover, HPV is associated with other health conditions that take a toll on those infected as well as their loved ones, including genital warts[31], cervical abnormailities[32], complications with fertility and pregnancy[33], and poor birth outcomes[34]. Thus, HPV infection is a very serious and prevalent condition. Fortunately, there is a vaccine to prevent infection with the most common HPV types as well as those responsible for 90% of cervical cancer cases[5].

HPV vaccine uptake is low in Appalachia. In the U.S., the Advisory Committee on Immunization Practices (ACIP) currently recommends the 9-valent HPV vaccine for adolescents and young adults to prevent cervical, vaginal, and vulvar cancer among females and to prevent genital warts and anal cancer among females and males. The ACIP recommends a two-dose HPV vaccine series for those who initiate vaccination under age 15, with the second dose administered 6-12 months after the first dose. Those who initiate over age 14 should still receive the 3-dose series within 6 months. The ACIP recommends routine HPV vaccination for adolescents ages 11-12 years, but the vaccine is approved and may be administered as young as age 9, with catch-up vaccinations for ages 13-26 years[8, 35]. Unfortunately, completion rates for the vaccine series are low in the U.S. for females (49.5% in 2016) and very low among males (37.5% in 2016) aged 13-17[7, 36] Rates are even lower in Appalachia (**Table 2**). HPV vaccine uptake and completion are low for myriad reasons, including: lack of awareness of the need to be vaccinated, cost issues, lack of physician recommendation, and confusion about guidelines[15, 37-38] as well as negative attitudes and beliefs about HPV vaccine, cervical cancer, and vaccines in general[16, 39]. While interventions in the general population would be beneficial, populations that suffer from a higher burden of

Table 2. Estimated vaccination coverage (≥ 2 doses) adolescents aged 13-17 yrs., 2016[7, 23]

	% Females ≥ 2 HPV doses	% Males ≥ 2 HPV doses
Kentucky	39.7	28.5
Ohio	42.5	44.1
Virginia	41.1	37.4
West Virginia	49.7	33.0
U.S. (overall)	**49.5**	**37.5**

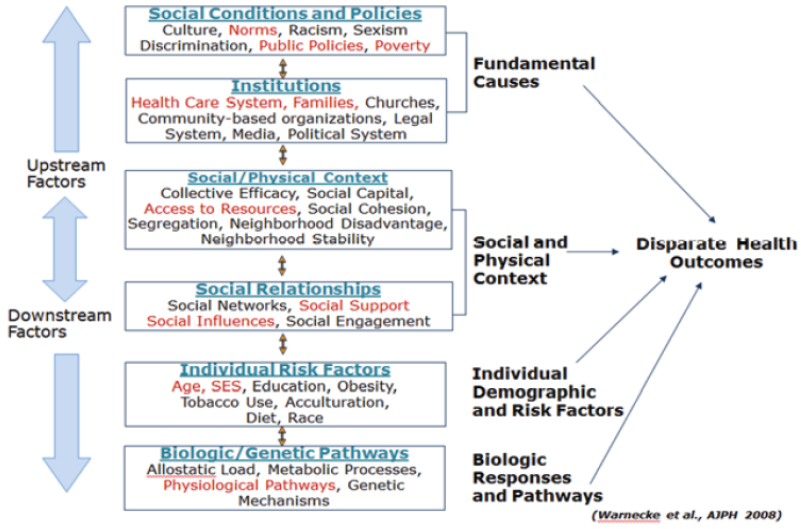
vaccine-preventable diseases and have a lower vaccine series completion rate, such as the Appalachian region, deserve special attention and efforts (**Table 2**). Thus, interventions targeted to underserved communities who represent an understudied population and who could benefit from such a *multi-level* approach to reducing risk for HPV-associated diseases are desperately needed.

Prior research has demonstrated that the most influential factor to the uptake of the HPV vaccine series is a health provider recommendation[14-16]. However, providers are not recommending the vaccine at opportunistic times, such as when 11-12 year old vaccines (i.e., Tdap and meningococcal) are given, due to lack of time, low knowledge about HPV and vaccination, weak or no recommendation, perceptions of parental hesitancy, and low self-efficacy in explaining the HPV vaccine to parents[17-20]. The CDC developed a campaign targeted to providers to improve this oversight; however, little gains in vaccination have been observed[21]. Moreover, catch-up vaccination is recommended for males and females up to age 26, and few organized efforts are being tested for this group of at-risk young adults.

Interventions to improve HPV vaccination are limited. Several studies have examined the efficacy of interventions to improve uptake of HPV vaccination among girls and boys; however, few educational interventions use HPV vaccine uptake as an outcome and validate findings with medical record review. Most educational intervention studies published to-date focus on literate populations with higher educational attainment, with limited effectiveness noted[40-42]. A study by Vanderpool et al. reported increased vaccine series completion among young adult women in Appalachian Kentucky who participated in an educational intervention using a theory-grounded, health communication DVD[43]. Two other studies directed at parents have also shown positive effects. Aragones used a using a nonequivalent group design to test an education session plus text-messaging intervention compared to an education session intervention among Mexican-American parents with a child who needed the HPV vaccine. Based on parental report, there was an 88% series completion rate among those receiving the 1st HPV vaccine dose in the education plus text messaging group compared to 40% in the education only group (p=0.004)[44]. Parra-Medina tested a *promotora* outreach, education, and navigation program for HPV vaccination among Hispanic women with a daughter who did not receive the HPV vaccine. Compared to the brochure-only parent participants, those parents who received the promotora navigation program were more likely to complete the vaccine series[45]. Practice and community-based interventions may offer more promise[42]. Perkins found that a provider-focused intervention at two federally qualified community health centers consisting of 6 to 8 education sessions, feedback about HPV vaccination rates, and quality improvement incentives (credits for maintaining board certification), significantly increased HPV vaccine initiation among females in the active intervention period compared to control clinics, however, differences did not remain significant in the post-intervention period[46]. This review demonstrates that more intensive, multi-component interventions directed at either clinicians and/or parents are effective in increasing vaccination rates, with sustainability still a problem. Thus, there is a need to identify feasible and scalable interventions.

Figure 1.

Model for Analysis of Population Health and Health Disparities



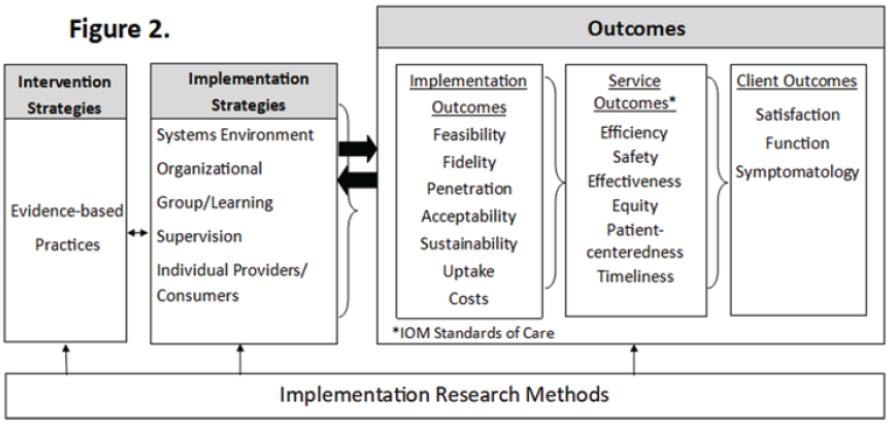
Multi-Level interventions (MLI) are promising solutions to address health disparities. Although there is some consensus among researchers that it is necessary to change the SDH to reduce health disparities[47], the majority of interventions targeting such disparities are focused on the individual, ignoring the social as well as physical environments within which individuals live and work[48]. MLIs are gaining more interest as a way to reduce disparities among underserved populations[49]. These interventions, however, are usually focused on few levels, mainly the individual and the provider. Some studies also include policy-level interventions (e.g., insurance coverage) and changes at the community-level (e.g., social marketing)[50-51]. While these interventions have been tested in areas such as smoking and diet, none have been directed at HPV vaccine uptake in Appalachian populations. The investigators assembled to conduct **Project 2** have vast experience in identifying and addressing multi-level barriers that contribute to cancer disparities (See **Section B**). The Model for the Analysis

of Population Health and Health Disparities developed by the P50 Centers for Population Health and Health Disparities (CPHHD) investigators (**Figure 1**)[52], including Project PI **Paskett**, will be utilized to understand not only the multi-level factors that hinder and facilitate adherence to HPV vaccination recommendations, but help understand the relationships between levels (see **Survey Core**). In addition, we will adapt the conceptual model of Proctor et al. (**Figure 2**) to assess the outcomes of the interventions in the clinic/health system setting[22].

Thus, there is the need to support the testing of our proposed interventions among health systems as well as to develop and validate simple, effective interventions that work among this population, to address multi-level factors within the SDH that impact disparities in HPV-related diseases.

A.3. Significance of the Expected Research Contribution. The proposed project focuses on HPV-related diseases, which are a great burden in the Appalachian area of the US. HPV infection is widespread, but rarely discussed in the general population, and infers a risk for a host of diseases that range from genital warts to poor birth outcomes and cancer, most notably among underserved populations. The goal of this project is to test a MLI, as part of an integrated cervical cancer prevention program (with **Projects 1** and **3** – see **Overview**), directed at health system levels of clinic, providers, parent and patient (parents, children aged 11-12) designed to increase adherence to recommendations for the HPV vaccine among males and females aged 11-12 in Appalachia, and to see if directed interventions affect catch-up rates among those aged 13-26. The aims reflect an effectiveness implementation hybrid type 2 design in which our outcomes include both HPV vaccine completion as well as implementation outcomes from the Proctor et al. framework[22]. Moreover, this intervention will be implemented in selected clinics of participating health systems (**hereafter referred to as "clinics"**) that primarily serve low-income residents, thus ensuring access to those who are at the highest risk for persistent HPV infection and the disease risks that accompany this chronic infection state. Working with the **Intervention and Consortium Core** (**ICC**), the results of **Project 2** will be disseminated to our community and clinical partners throughout the Appalachian region to reduce HPV-related disease disparities among underserved populations.

Figure 2.



A.4. Innovation. The proposed project is innovative for several reasons. It is one of the first MLI's tested using an implementation science design focusing on the uptake of the HPV vaccine in an Appalachian population. Since the rates of vaccination are still low across much of the country[21, 36], MLI's may show promise for changing these low rates, especially using an implementation science framework, which is appealing to clinics, as the intervention can be delivered to many more patients (Reach). Moreover, this type of an approach aligns with quality improvement initiatives, including efforts to reach HEDIS guidelines for vaccination[53], among health systems. In addition, we will be able to document relevant intermediate outcomes that are critical to understanding efforts to scale up and maintain the intervention in these clinics over time. The MLI to be included in this project features commonly used interventions such as educational presentations, patient brochures and videos, staff role-definition/training, electronic health record reminders, etc., however, these types of intervention components **have not been tested together in an implementation science format**, as proposed. Secondly, this intervention will be part of an **integrated cervical cancer prevention program** at each clinic. This type of approach has not been tested in the past. It, too, is appealing to clinics and has potential to be utilized for management of other diseases in busy clinics, such as diabetes management. Thirdly, using a delayed intervention group design will allow for refining of intervention components after the early implementation phase to ensure acceptance. Such a design is not novel on its own; however, when bundled and testing a MLI, it is novel. This will also increase buy-in from the practices, as their voice will be heard in terms of implementation and design modification. Fourth, we will be testing a program for implementation and sustainability in participating clinics, making adaptations, as necessary that will ensure the integrated cervical cancer prevention program can be sustained and disseminated. Lastly, we are including cost-effectiveness and user outcomes, such as satisfaction, which are also novel in these types of studies, especially for studies of HPV vaccination interventions. Moreover, we will work with clinics to help them implement our strategies in a time-efficient manner

and build capacity for conducting the aspects of this intervention, which will also help with sustainability. This design, intervention and the outcomes, as packaged, are all innovative in terms of HPV vaccination interventions.

B. PRELIMINARY STUDIES

Our preliminary studies showcase our experience with: a) confirming the efficacy in Appalachian populations of the MLI to be tested; b) preliminary evidence of our ability to implement the intervention components in clinics; and c) our experience with HPV vaccination interventions and statewide efforts.

B.1 PARENT Project (P50CA105632 PI: Paskett) The PARENT (Parents in Appalachia Receive Education Needed for Teens) Project developed and evaluated a multi-level intervention (MLI) to increase HPV vaccination rates among young girls and adolescent females (ages 9-17) that live in Ohio Appalachia. The intervention was culturally appropriate and directed at parents (Level 1) of young girls living in Ohio Appalachia, health care providers (Level 2) practicing at local health departments and provider offices, and health departments and provider offices (Level 3) in Ohio Appalachia [54]. The clinic-level intervention included study specific waiting room and examination room posters, brochures, and tabletop tent cards for the HPV vaccine intervention. The provider component included an educational session facilitated by a member of the research team, and included a 1-hour PowerPoint presentation and handouts on the HPV vaccine, focusing on current evidence-based HPV vaccine information and communication strategies, modified from an evidence-based tobacco cessation program[55] and was designed to assist physicians in discussing HPV vaccinations with parents. Providers completed surveys that assessed HPV vaccine knowledge and attitudes before and after the educational session. Lastly, for the parent level intervention, parents were mailed an educational brochure and DVD video about HPV and HPV vaccination, a magnet reminder to get the 2nd and 3rd HPV vaccine shot, and a CDC HPV vaccine information statement. Unfortunately, this study DID NOT implement all levels at the same clinics, e.g., parents were not from the participating clinics, although they were from the same counties.

From medical record review (MRR) data, 17 (13.1%) daughters of participants from the intervention counties received the first HPV vaccine shot within 6 months compared to eight (6.5%) daughters of participants from the comparison counties (p=0.002). Among the 155 participants in the HPV vaccine intervention counties who responded to questions about viewing the intervention materials, 139 (89.7%) reported that they watched the video and 146 (94.2%) reported that they read the brochure and vaccine informational statement. Parents in the intervention counties averaged 9.4 ± 1.0 correct answers to HPV and HPV vaccine knowledge questions (out of ten) on the post-educational survey, which was significantly higher than their knowledge score at baseline (7.4 ± 2.1, p<0.001) and the baseline score of parents in the comparison arm (7.3 ± 1.9, p=0.001)). Prior to the in-clinic educational session, providers averaged 4.4 correct answers to HPV and HPV vaccine questions out of five (N=57, SD=0.7) which significantly (p<0.001) increased to an average of 4.9 correct out of five following the education session (N=55, SD=0.3). *This study, while minimal in effect, provides evidence of the efficacy of the MLI components used in the proposed project, which will instead focus all levels of the MLI at the same clinic.*

B.2. HPV Vaccination Supplement (P50CA105632, PI: Paskett). The PARENT Project demonstrated effectiveness in improving physician knowledge about HPV and the HPV vaccine and uptake of the vaccine in intervention vs comparison counties, however, uptake of the vaccine was low[56]. Reasons for this finding stem from study design limitations in that we were not able to assess the effect of the intervention on rates of HPV vaccine in clinic patients. Moreover, our results clearly show that the odds of vaccination among parents in the intervention counties who visited a healthcare provider and talked about the HPV vaccine were 3.4 times the odds of vaccination among those who did not talk to their healthcare provider[56]. Thus, the aim of this supplement was to take what we know works (i.e., MLI to promote HPV vaccine uptake) and assess the ability of implementation of the MLI in two clinics as well as determine if we can obtain vaccination rates before during and after implementation of the intervention in those clinics. The primary outcome is the rate of HPV vaccine initiation among 11-17 years olds within the health system – assessed at baseline 6 and 9-month intervals. Secondary outcomes will include completion of the series of HPV vaccine shots. We will also assess the effect of the interventions on provider knowledge and attitudes about HPV vaccination and explore clinic-level factors that might impact vaccination rates (e.g., role responsibility and clinic characteristics). Each of the two clinic sites have held the initial provider educational sessions as well as a follow up refresher session six months after implementation. Over 23 providers attended the education sessions. Baseline vaccination rates were obtained and educational materials (posters, brochures flyers) were revised with input from the clinic representatives. These materials were placed in the clinic exam rooms and waiting areas. The intervention was well received in both facilities by providers and patients. Overall, 700 brochures were distributed and rates in one clinic increased in 13 year old females from 44% at baseline to 58% and in 18 year old females from 0% to 54%.

B.3. HPV Comic Book Project (R21 CA12803, PI: Katz). A comic book was used as one component of a multi-level intervention to improve HPV vaccination rates among adolescents. Parents suggested and provided input

into the development of the HPV vaccine comic book. Following the development of the comic book, a pilot study was conducted to obtain initial feedback about the comic book among parents (n=20) and their adolescents ages 9 to 14 (n=17) recruited from a community-based organization[57]. Parents completed a pre-posttest including items addressing HPV knowledge, HPV vaccine attitudes, and about the content of the comic book. Adolescents completed a brief interview after reading the comic book. After reading the comic book, HPV knowledge improved (2.7 to 4.6 correct answers on a 0–5 scale; $p<0.01$) and more positive attitudes toward HPV vaccination ($p<0.05$) were reported among parents. Parents confirmed that the comic book's content was acceptable and adolescents liked the story, found it easy to read, and thought the comic book was a good way to learn about being healthy. *The comic book will be used as one of the patient-directed interventions in this project.*

B.4. Partnerships to Improve HPV Vaccination. Three NCI-designated cancer centers (OH, VA, KY), which are part of the Improving Uptake of Cervical Cancer Prevention Services in Appalachia project, received an NCI Administrative Supplement focused on addressing HPV vaccine uptake in their respective catchment areas. The OSU supplement addressed the following goals: a) complete an environmental scan of the local/state issues and barriers, as well as research activities and linkages with regards to HPV vaccination; and b) develop/enhance linkages/partnerships with coalitions/immunization programs and relevant stakeholders to identify research priorities that will directly address the findings of the environmental scan and the challenges identified in the catchment area. As part of the environmental scan, a survey was administered to parents of adolescents 11 – 17 years of age. The survey assessed HPV vaccine knowledge, attitudes and behaviors among parents in Ohio. One hundred fifty six out of 200 planned parent surveys were administered. A majority of respondents had heard of the HPV vaccine prior to completing the survey (83.1%). The University of Virginia's (UVA) HPV vaccine supplement goals included conducting an environmental scan that allowed for continued engagement with key stakeholders on several levels. Assessments within UVA's healthcare system identified that bundling vaccinations may be a beneficial method to ensure vaccination completion[58]. The role of social marketing strategies to ensure proper public health dissemination related to the vaccine[59] and the role of state policy in vaccination initiation[60] were also important. The goal of the UK project was to conduct an assessment of the HPV vaccination environment in KY and specifically Appalachian KY[61]. Dr. **Vanderpool** and her team conducted key informant interviews with academic, clinical, community, and public health partners across the state; a 1-year media scan of news and TV programming[62]; a provider survey (n=182); and six in-depth interviews with Appalachian KY pediatricians with high HPV vaccination rates. One particular finding from the provider survey indicated that while the majority of providers (74%) present the HPV vaccine as "cancer prevention" to parents, 43% present it as "optional", and only 25% present it as a vaccine that is "due" or required[63]. *These studies will be used to design questions for the focus groups to be conducted in the Clinic and Community Assessment Phase of the proposed project and demonstrate the fact that providers in this area are not recommending the vaccine. We will also address skills to strongly recommend the vaccine in the provider education sessions.*

B.5. University of Kentucky HPV Vaccination Research Projects Dr. **Robin Vanderpool** (Co-Lead) is an Associate Professor in the UK College of Public Health, Department of Health, Behavior & Society and Director of Community Outreach and Engagement at the UK Markey Cancer Center (MCC). He is active in cancer prevention and control research in Appalachian KY communities, including serving as PI of the Appalachian Center for Cancer Education, Screening, and Support (ACCESS; 1U48DP005014-02) which is part of the CDC- and NCI-funded Cancer Prevention and Control Research Network (CPCRN); co-investigator with the UK Rural Cancer Prevention Center (RCPC), a CDC-funded Prevention Research Center (1U48DP005014-01); and Project Lead of three NCI supplements awarded to MCC focused on HPV vaccination (P30CA177558-02S2), community health education in Appalachian KY (P30CA177558-03S2), and assessing population health in Markey's catchment area (P30CA177558-04S5). Related specifically to barriers and facilitators to HPV vaccination among adolescents, young women, and healthcare providers, Dr. **Vanderpool** has published 16 articles on the topic, including the primary outcome paper in the *Journal of Communication* from the RCPC's efficacious health communication intervention, "1-2-3 Pap", which was selected as the first research-tested HPV vaccination intervention to be posted on NCI's Cancer Control P.L.A.N.E.T. website [43]. Dr. **Vanderpool** is also co-lead of the CPCRN HPV vaccination signature project focused on dissemination of effective HPV vaccination-related community-clinical linkages. Additionally, she is an active member of the American Cancer Society's (ACS) National HPV Vaccination Roundtable. *In combination with her HPV vaccination research, Dr.* ***Vanderpool*** *has experience working with clinical sites on cancer control projects[64] making her an ideal co-leader for this project.*

C. RESEARCH DESIGN AND METHODS

C.1. Overview. The overall goal **Project 2** is to test a MLI focused on clinics within 10 participating health systems, providers, and patients (parents and children) within these clinics from four Appalachian states to

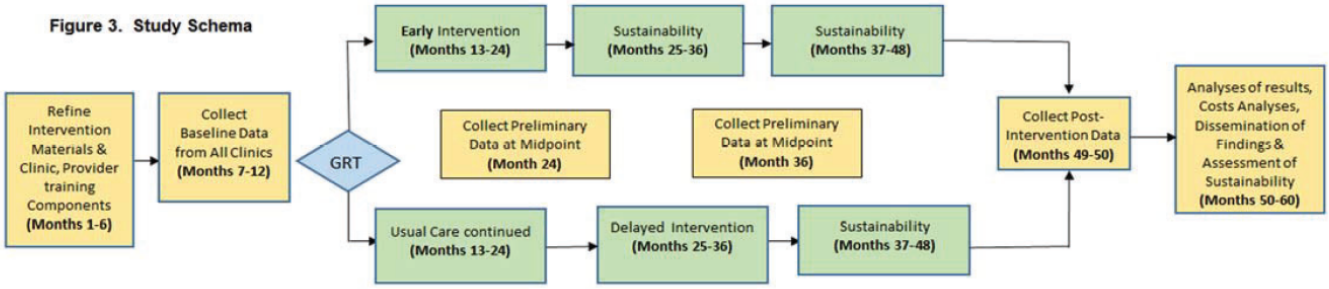
improve HPV vaccine uptake among 11-12 year olds who are patients of participating health systems. The intervention components are described in **Table 3**.This project is designed as a pragmatic trial where all participating clinics will get the intervention; however, half will receive the program early (immediately following the Baseline Assessment at the beginning of Year 2 and following the Needs Assessment phase) and the other half will be randomized to receive the program 12 months later (delayed group). The unit of randomization will be the health system to avoid any possible contamination amongst the three levels of intervention, and 5 health system will be randomized to each arm. The primary outcome will be the change in rate of HPV vaccine initiation among 11-12 years olds within the health system between 12 months (end of the Clinic and Community Assessment) and 24 months end of Implementation in the early intervention arm). In addition to 12 and 24 months, initiation rates will also be collected at baseline, 36 and 49 month time periods to assess trends. The theoretical framework of the SDH conceptualized in the Model of the Analysis of Population Health and Health Disparities developed by investigators within the CPHHD[52] will allow us to examine multi-level barriers from the individual to distal level and their effects on vaccine uptake, as well as barriers and facilitators to adherence to the intervention program and vaccination. Outcomes will focus on service (effectiveness – HPV rates), implementation (acceptability, fidelity, sustainability, penetration and cost-effectiveness), and client satisfaction in line with the Conceptual Model described by Proctor et al.[22] to guide the implementation process and outcomes of **Project 2**. The study schema is shown in **Figure 3**.

***Table 3**. I Vaccinate Took Kit*

CLINIC	PROVIDER	PATIENT
Posters and table tents	Educational Presentation	
Brochures		Invitation letter/call
EHR Reminder System	Feedback- HPV vaccination rates	11-12 well child visit
HPV vaccine for 11-12 year olds	Newsletter	Brochure
I Vaccinate logo	Reminders in visit	Magnet
EHR clinic-level vaccination rates	Catch up campaign ages 13-26	18-26 Reminder letter

C.2. Research Design and Randomization. Outcomes will be evaluated using a Group Randomized Trial (GRT). In GRTs, identifiable social groups are randomized to a treatment condition with measurements taken on members from those groups to assess the impact of the intervention. The GRT is considered the gold standard for evaluating interventions that manipulate the physical or social environment, involve social processes, or cannot be delivered to individuals without the risk of contamination[65-67]. In this project, 10 health systems will be randomized to one of two study arms (early vs delayed), and outcome measures (rate of HPV vaccination initiation and completion of the series) will be obtained from Medical Record Review (MRR) using clinics' Electronic Health Records (EHR). The county was chosen as the unit of randomization because the interventions are being delivered at the health system level and this will reduce contamination as patients and providers may visit/practice in more than one clinic within a health system. Randomization will be stratified by state (OH, KY, WV, and VA).

Figure 3. Study Schema



C.3. Project Population. There are three levels of intervention and thus, three levels of participants. Level 1 is the health systems/clinics. A clinics are eligible if they: 1) are located in one of the counties that are part of this Program; 2) provide care to patients aged 11-26; and 3) provide immunizations (see Letters of Support from the 10 health systems). Level 2 includes the providers at these participating clinics. Health care providers (physicians, nurses) and office staff will be: 1) practicing in a clinic in one of the participating health systems; 2) personnel involved in the vaccine process (determined by individual clinics); and 3) able to speak, read, and write English. Patients (Level 3) will include all patients age 11-12 (primary) and 13-26 (secondary) as well as their legal guardians (if appropriate) who: 1) are able to speak, read, and write English, as there are very few Spanish-speaking residents in these communities; 2) are a resident of one of the participating counties; and 3) receives care at a participating clinic (See **Table 4**). Project Leaders and staff have met and established relationships with all health systems (Level 1) participating in this multicenter trial and each has provided the research team with letters of support (see Letters of support from participating health systems). Details on selection of the health systems are in the **ICC**. Level 2 focuses on health care providers (physicians, nurses) and

office staff practicing at the participating clinics. **Table 4** shows the number of providers eligible for **Project 2** by state and health system. **Table 4** also shows the number of patients (Level 3) who are eligible for this project by age, gender, and state.

C.4. Theoretical Framework. Well-established behavioral and communication theories have guided the development of the proposed interventions, including the Health Belief Model (e.g., perceived benefit)[68 69], PACE Communication System (e.g., patient activation)[70-71], and Social Support (e.g., emotional support for vaccination by the navigator)[72-73]. These theories have demonstrated efficacy in improving adherence to preventive services and will be used for the proposed project. Providing individually-tailored content about HPV vaccination is important, as these approaches increase information relevance and have been shown to improve health

TABLE 4. Healthcare Partners by State	# of Clinics	# of Providers	Patients by Age Group							
			Girls			Boys			Men	Women
			11-12	13	14-17	11-12	13	14-17	18-26	18-26
Kentucky	9	89	564	240	1072	612	296	932	1393	2890
Ohio	9	158	492	222	919	540	246	932	884	2568
Virginia	5	102	291	200	529	315	115	382	920	1978
West Virginia	9	280	1460	748	3144	1356	759	2692	2206	8044

outcomes[74]. The Warnecke Model[52] (see **Overview**) will serve as the basis for identifying and addressing multi-level barriers and facilitators to adherence to HPV vaccination recommendations as well as how the levels interact with one another, and the influence of proximal level factors on adherence[52]. We will also utilize the Implementation Framework described by Proctor et al.[22] for study design and outcome assessment.

C.5. Baseline Assessment. During the Program's first year, we will focus on a multi-level assessment including focus groups in conjunction with the **ICC**. This will be done closely with our health system/clinic and community partners and will focus on intervention refinement and clinic inventory. For the **intervention refinement**, first, we will conduct an assessment of the counties and health systems in regards to HPV, HPV vaccination, and cervical cancer. This Phase will include qualitative research with providers and community members as well as environmental scans, obtaining baseline information about the clinics, and gathering baseline rates of HPV vaccination, by age group and gender, at the clinic level. These activities will be led by the **ICC**. As we have developed and piloted our proposed interventions (**Section B.2** and **B.3**), the second phase will use the information gathered from the first phase to refine and customize (to clinics) the proposed interventions to be tested in the clinics using focus groups. Phase 3 will consist of reviewing edited versions of the intervention materials by the same focus groups for final input prior to production of tailored intervention materials for the clinics. This methodology has been successfully utilized in our prior studies[75]. The design of the intervention projects, i.e., early vs delayed intervention, will also allow for further editing based on feedback from the real-world implementation for the intervention in the early intervention groups before implementation in the delayed intervention groups.

For **clinic inventories**, a comprehensive assessment will be conducted within each participating health system. While this will be done for the entire Program Project, for **Project 2**, rates of HPV vaccine initiation and completion for patients aged 11-12, 13-17, and 18-26, by gender, will be obtained for each clinic from reviews of medical records. A complete inventory of any HPV vaccination promotional items will also be obtained from each clinic and the systems used to facilitate ordering the HPV vaccine shots will be assessed. We will also have an administrator from each clinic complete a short survey about the characteristics of each clinic (e.g., patient volume, provider size), as well as describe the roles and responsibilities staff have for ordering and completing HPV vaccinations (e.g. responsibilities for asking, providing and follow-up on shots). We will review the EHR each clinic utilizes in conjunction with the **Survey and Data Collection Core** (**SDCC**) and conduct environmental scans of each clinic to identify HPV-related material and places to post/place intervention materials. This assessment will allow us to target the intervention components to the specific environment of each clinic. In addition, a "Clinic Champion" will be identified who will champion the implementation of all efforts of this project and the integrated cervical cancer prevention program in each clinic (see **ICC** Section B.1.a.3). This person will be a member of the Clinic Consortium (see **ICC**) and will be a co-author on papers from this project. Many clinics have not named this person as yet, but this role is noted in the Letters of Support.

C.6. Intervention Components. The intervention components included in the program (see **Table 3**) that will be tested in this project come from: 1) the PARENT study[56 75] described in **Section B.1**; 2) the CDC website for providers[76]; and 3) two additional studies (See **Section B.2** and **B.3**). Moreover, an age-appropriate strategy will

be utilized across all of the levels of intervention to address differences in vaccination messaging and age considerations, as shown in **Table 5**[77-78], to address our primary and secondary aims. The PARENT study materials have been developed with input from the Appalachian communities and have been found to be effective in increasing HPV vaccination in age group 11-12. Additional messaging and materials will be implemented at all levels for patients age 13-17 and 18-26. We are, thus, assessing the effectiveness of these interventions when combined in a MLI program as part of an integrated cervical cancer prevention program and delivered to clinics. These interventions will be customized (e.g., logo, phone numbers, clinic champion picture) to each clinic in Year One, during the Assessment Phase, and then implemented within the early intervention clinics within the first 12 months following the Assessment Phase with assistance from the project personnel from each respective university. After this implementation phase, the clinics will utilize the program in without project personnel assistance for 24 additional months. The delayed group will then get the intervention components during at Month 24 and staff will help implement the components over the next 12 months. Following this phase, all clinics will remain in the real world implementation phase and periodic assessments of HPV vaccination rates will occur, as described above. The intervention components are described by level below and are shown in **Table 4**. The overall program will be called "I Vaccinate" to carry a positive message about vaccination throughout the clinic and with clinic staff. The other components of the integrated cervical cancer prevention program (smoking and screening) will be available and offered to mothers when they bring their children into the clinic, as appropriate. Women aged 18-26 will also be given information on the smoking cessation component as well when they are being informed about HPV vaccination.

C.6.1. Level 1 – Clinics. The clinics will receive customized posters, brochures, and table tents from the PARENT project (see **Section B**). These feature children and will also feature a local health care provider and his/her family and match the characteristics and messaging in the provider and patient components from the PARENT project[56], but will include the "I VACCINATE" logo (**Figure 4**), and be customized to the clinic. The **SDCC** will work closely with clinics to utilize the EHR so that HPV vaccine rates will be easily downloadable (See **SDCC** expertise). Reminder systems will also be built within the EHR that can be sent to both providers and patients for vaccine initiation and follow-up (for shots 2 and/or 3). As part of the clinic level intervention will also define and implement roles and responsibilities for staff and providers in the clinic regarding the HPV vaccination process so that the message of vaccination is consistent. For example – the initiator will be the check-in staff, the enforcer will be the medical assistant, the nurse will be the reinforcer, the physician/provider will be the closer, the check-out staff will conduct follow-up to schedule the follow-up shot, and the person who does reminder calls/letters will be the reviewer. **Table 5** details the age-specific interventions at this level.

Figure 4. "I Vaccinate" Logo

Table 5. Age - Appropriate Interventions				
EMR	**Age Group**	**Key Level**	**Secondary Level**	**Message**
Standing orders	11-12	Provider	Parent	*Provider:* Strong Screening Recommendation *Parent:* Increase Knowledge & Awareness *Use:* I Vaccinate (3 levels)
Recalls • Refusals • Shot Reminders[77]	13-17	Parent	Provider	*Parent:* Address Vaccine Hesitancy[78] *Provider:* Persistence in Recommendation *Use:* CDC Materials (3 levels)
Audit with Feedback • Invited • Refused • Accepted	18-26	Patient	Provider	*Patient:* Address Cancer Prevention & Reproductive Health *Provider:* Reinforce Cancer Prevention & Reproductive Health *Use:* ACS Materials

C.6.2. Level 2 – Providers. Health care providers and staff will complete a self-administered questionnaire that focuses on HPV vaccine knowledge, beliefs, attitudes, and practices. The survey will ask about state and national cervical cancer incidence and mortality rates, their knowledge about parental concerns regarding the HPV vaccine, and what they know about patient-level predictors of HPV vaccination. Provider knowledge will be measured by five true/false statements with correct answers representing higher levels of knowledge. Providers will also provide information about their age, gender, race, ethnicity, education, and job title. Providers will then receive an educational presentation, tested in the PARENT Project, during one of their regularly scheduled staff meetings. The educational session will be facilitated by a member of the research team, and will include a 1-hour PowerPoint presentation and handouts on the HPV vaccine, focusing on current evidence-based HPV vaccine information and communication strategies designed to assist providers in discussing HPV vaccinations with parents/patients, and age-appropriate strategies (**Table 5**). The communication strategies for the HPV vaccine education session will focus on teaching providers to offer a strong recommendation for the vaccine when bundling with the other vaccines for 11-12 year olds. We have edited the material from the PARENT project to include vaccination for boys. We will also teach them to use the strategies used in the PARENT Project (adapted 5A's and 5R's[56]) for vaccine hesitant parents – especially important for parents of youth aged 13-17. We will also focus on assuring completion of the HPV vaccine series within 6-12 months after the first shot is given. In addition, we will review

the roles and responsibilities for staff at the clinic for HPV vaccination (see **C.5**) and provide role-playing for staff to clearly see their roles in assuring active presentation of the components of the "I Vaccinate" Program and completion of vaccination. Staff will complete a second survey after the educational session. Intervention components targeting the providers include: in-visit reminders from the EHR (discussed above), audit with feedback on HPV vaccination rates on a quarterly basis delivered to providers by the clinic champion, and a newsletter. A booster session will also be held at 6 months to reinforce the intervention and receive feedback from the providers, review the audit with feedback process, and increase compliance with HEDIS measures to vaccinate adolescents by age 13.

C.6.3. Level 3 – Patients. Parents of children aged 11-12 and 13-17 as well as patients aged 18-26 will receive information about the HPV vaccine via mailed information and during in-person visits. For the 11-12 year olds, a reminder letter, generated by the EHR, will be mailed to their parents 1 month before the child turns 11 or to all 11-12 year olds who have not had this visit to inform them about the 11-12 year old well child visit. The "I Vaccinate" program will be explained and will be accompanied by the brochure. A phone number will be included so that the parent can schedule the appointment. Clinic staff will be able to talk with parents (with information learned at the Provider Training Session) at the visit and address any concerns about the vaccines. For those aged 13-26 who have not received the HPV vaccine, the EHR will send reminder letters to each along with targeted educational information before the next visit (see **Table 5**). Those who receive the first HPV vaccine shot will be given a follow-up appointment as they leave the initial visit and then a phone call reminder when the second (and third shots for those over age 15) are due. For the children aged 11-14, we will have copies of the targeted (i.e., clinic and gender of child) comic book (see **B.3**.) available in the clinics to provide information on the HPV vaccine. Providers will be trained to ask about and review key messages in the comic book at the visit.

C.7. Clinic Training/Implementation. Using the Implementation Strategies described by Proctor et al.[22], the intervention components will be implemented in the Early Intervention Clinics over 12 months starting in Year 2 as part of an integrated cervical cancer prevention program at the clinic level – including smoking cessation (**Project 1**) and cervical cancer screening (**Project 3**) for women (including mothers of children eligible for HPV vaccination). The project staff will work closely with the clinics and clinic champions to successfully implement the components of this project and coordinate the implementation of the components of the other 2 projects. For **Project 2**, clinic staff (providers and staff) will be trained in their respective roles by project and respective university staff. Concurrently, staff from the SDCC will work with the clinics to implement the EHR "I Vaccinate" Tracking System which will facilitate tracking and reporting of HPV vaccinations (including audit with feedback), in-visit reminders for providers, and letters/reminders to patients/parents (see section above). Once these two components are in place, clinic staff/provider training will begin. Then, patient-directed components will then be implemented. We envision this taking 6-9 months to implement fully and the remainder of the implementation phase for the Early Intervention Clinics will be spent trouble-shooting and collecting process measures to assess what works and what needs to be modified. After this 12-month phase, the same steps will be taken to implement the intervention components in the Delayed Intervention Clinics over the subsequent 12 months.

C.8. Sustainability Phase. After the Implementation Phase is concluded, the clinics will enter the Sustainability Phase. This Phase will last up to 24 months for the Early Intervention Clinics and at least 12 months for the Delayed Intervention Clinics. During this phase in each group of clinics, researchers will step back and allow the clinics to manage the intervention components with the assistance of the field staff ("I Vaccinate" program staff). Audit with feedback will continue. Staff at the respective universities will be available for consultation and trouble-shooting, but the goal of this phase is to determine how the "I Vaccinate" program works in real world settings. Any "I Vaccinate" materials that need to be replenished or modified will be done by the project staff. The clinic champions will have responsibility at the clinics for this phase. Clinics will be provided with a stipend in each year of the project to help defray the administrative costs of implementing and sustaining this program.

C.9. Outcome Assessment. To assess **Aim 1** – Service Outcome, the primary outcome for **Project 2**, we will assess the change in rate of HPV vaccination initiation among 11-12 year olds and secondarily among those 13-26 from baseline to the end of the Implementation Phase. The effectiveness of the intervention will be assessed by comparing Early vs Delayed Intervention Clinics at the end of the first Implementation Phase adjusting for baseline rates and Pre- vs Post Implementation rates in the Delayed Implementation Clinics. Secondary outcomes include completion of the HPV vaccination series, missed opportunities for vaccination (i.e. not vaccinating when receiving 11-12 year old vaccines or for other visits) and vaccination rates at the end of the Sustainability Phase, which will be compared to Post Implementation rates to assess the sustainability of the intervention. All data will be obtained from the EHR.

C.9.1. Baseline HPV Vaccination Rates. Rates of HPV vaccine initiation and completion will be assessed in Year 1 by examining medical records for patients aged 11-12, 13-17, and 18-26 within each clinic. These rates

will be examined by gender, pay or status, provider, time since last visit, and rates of other childhood vaccination. (See below for review of EHR abstraction process.)

C.9.2. Annual HPV Vaccination Rates. With the implementation of the "I Vaccinate" program, we will be able to assess HPV vaccination rates (initiation and completion) by the EHR system. The rates will be obtained annually in all clinics and the same assessments described for baseline rates will be obtained annually.

C.9.3. Electronic Medical Health (EHR) Abstraction. Information about HPV vaccination rates will be obtained from EHR for clinic patients aged 11-12 and 13-26. We will collect data on HPV vaccination as well as the characteristics described above to assess factors associated with adherence. The EHR will provide project-related data from individual patients' medical records. Data including age, gender, race and ethnicity, county of residence and insurance status will be pulled from the EHR system by the SDCC to conduct the analyses for this project. This eliminates the need to obtain written medical record release from participants and is consistent with the pragmatic approach described previously.

C.10. Statistical Analysis. Below is a summary of the planned analyses and statistical power for the primary outcome analysis (Service Outcomes) as well as the Implementation and Client Outcomes (secondary outcomes) (see **Figure 5**). **More details are provided in the Biostatistics and Evaluation Core (BEC).**

C.10.1. Analysis Plan. The primary outcome (Service Outcome) is the change in HPV vaccine initiation rates among 11-12 year old patients from 12 months (end of the Assessment) to 24 months (end of early intervention). Following an approach described by Pennell et al.[79] and implemented in one of our previous GRTs[80], rates will be computed at the health system level and an ANCOVA model will be used to compare the change in vaccination rate between the early and delayed intervention arms adjusting for the 12 month rate of the health system (i.e., health system will be the unit of analysis). The same analysis plan will be used to compare change in Implementation Outcomes and to compare change in uptake of the second and third shots.

C.10.2. Sample Size and Power. Our sample size justification is based on our primary outcome analysis: an ANCOVA model comparing the two intervention arms with respect to change (between months 12 and 24) in the HPV vaccine initiation rate among 11-12 year-old patients adjusting for the 12-month rate. Based on preliminary data obtained from our HPV vaccination supplement, we expect an initiation rate of 30% among 11-12 year-olds in both arms at 12 months and in the delayed intervention arm at 24 months. Assuming an intra-class correlation coefficient (icc) of 0.01 and a two-sided type-I error rate of 5%, a sample size of five health systems/arm and 150 11-12 year olds per health system provides over 90% power to detect an increase in initiation rate to 43% or greater in the intervention arm at 24 months at varying levels of correlation between the 12 month and 24 month rates within a system (**Table 5**). In the PARENT study, the icc was slightly negative[56]; thus icc = 0.01 is a conservative assumption that follows the recommendation of Hade et al. for sample size calculations[81].

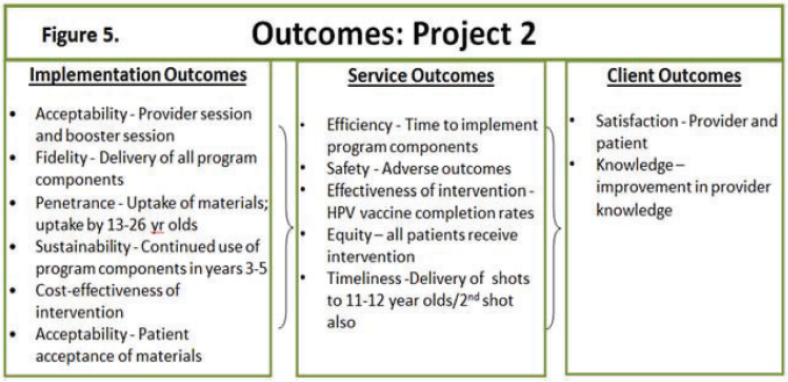
***Table 6**. Power Analysis for Primary Outcome*

	Intervention Effect*		
R†	11%	12%	13%
0.5	80%	**87%**	**91%**
0.6	86%	**91%**	**94%**
0.7	**92%**	**95%**	**96%**

**Change in vaccination rate for early intervention – change for delayed intervention.*
†Correlation between pre- and post-intervention vaccination rates of the health systems.

C.10.3. Secondary Outcomes

C.10.3.a. Service Outcomes. Secondary outcomes in this category include: 1) efficiency; 2) safety; 3) equity; and 4) timeliness of the intervention. These outcomes will be assessed as follows: 1) **Efficiency** will be determined by assessing the time required to implement the program overall and by component at each clinic. We will compare the early to delayed clinics in this respect as well as type of clinic. 2) While the HPV vaccine has been studied for over 10 years and its safety profile established, we will assess **safety** by keeping track of any adverse reactions reported from the HPV vaccine shots. These rates will be calculated and compared to the rates published by the CDC. 3) **Equity** will be assessed by examining the rates of vaccination by gender and race, as applicable, as well as age. 4) **Project Timelines** will be assessed in two ways – first, those who receive the shot by age 13 vs receive the shot by age 26 and secondly, among those who receive the first shot, what proportion receive the second shot within 12 months (of those age 11-12).



C.10.3.b. Aim 2: Implementation Outcomes. Process evaluation will be used to assess other Implementation as well as Client Outcomes (also IOM Standards of Care) of the Proctor Conceptual Model[22] as shown in **Figure 5**. We will also examine the degree of adaptations made in the interventions at each clinic to assess the impact

on effectiveness. This evaluation will be done by a combination of methods including provider/staff surveys, observations at the clinic and examination of medical record data as follows: 1). To assess **sustainability**, we will use logistic regression models with random health systems effects to compare odds of vaccination at the end of sustainability period to odds of vaccination at the end of the implementation period. The data for these analyses will come from the health systems' EHRs and thus will be comprised of all patients within the specified age ranges seen at the clinics over that time period. The sustainability analysis will be stratified by intervention arm with primary interest being in the comparison within the early intervention arm; 2). We will conduct the **cost-effectiveness analyses** of using the MLI intervention to promote HPV vaccination in three broad steps. The first step will consist of a cost analysis of the intervention. With the goal of MLI delivered at the health system level targeting clinics, providers and patients, the cost analysis underlying the cost-effectiveness calculations will be based on the payer perspective to exclude costs purely attributable to the research and costs incurred by the parents participating in the intervention. The study design will allow straightforward calculation of the intervention's cost. Fixed costs for training physicians and staff in the clinic and producing educational materials will be calculated from the project's direct expenditures since an insurer adopting the intervention will incur equivalent expenditures. Providers in the clinics will be asked to assess the average time required to implement the intervention. Since reimbursement rates for Medicaid and private insurance vary across states and payers, physician time will be values at Medicare fee-for-service rates. Staff time will be valued based on average salaries at their position. HPV vaccine costs will be approximated by the national average Medicaid reimbursement rates since price and rebate information for most insurance carriers is not publicly available. Next, the results of the cost analysis will be combined with the outcome measures to establish the incremental cost-effectiveness ratios (ICER). The ICER measures the cost at which an added unit of outcome can be achieved by the intervention instead of the control. Specifically, this will be the cost per positive outcome as a result of the MLI. The primary cost-effectiveness measure will be the MLI intervention's cost per vaccination initiation among 11-12 year olds after the Assessment phase. To assess the sustainability of the intervention, an exploratory cost-effectiveness analysis will be conducted to assess the cost-benefit or return on investment for the MLI. With the age distribution of the intervention sample, the average savings per vaccination initiation will be calculated from the literature; 3). For **changes in role responsibilities for vaccination in the clinics**, environmental scans will be done quarterly in each clinic to assess the use of HPV vaccination promotional materials, use of EHR to produce reminder and vaccine rates, and the use of audit and feedback of rates. A random sample of physicians will be asked to assess the provider-directed "I Vaccinate" materials at 6 months into the Implementation Phase in each group of clinics; and 4). The same analysis strategy used to compare change in initiation rates among 11-12 year olds by intervention arm will be used to compare **changes in initiation rates among 13-17 and 18-26 year olds.**

C.10.3.c. Aim 3 - Client Outcomes. Outcomes include: a) compare changes in knowledge and attitudes of providers via educational session pre-post surveys; and b) determining satisfaction with the multi-level intervention at the provider and clinic–level. a). **Changes in Knowledge** following the educational session will be assessed using linear mixed models containing random health system effects. b). For **satisfaction with the program**, providers and staff will be asked about the "I Vaccinate" program at 6 month intervals in terms of how they use it on a daily basis, as well as any recommendations for modifications. Project staff will monitor on a monthly basis the use of the various "I Vaccinate" program components to assess use over time. Patients will also be asked about the materials and the program. Staff from the SDCC will conduct the evaluations.

C.11. Data Management. The primary source of patient-level data will be the EHRs used by collaborating health systems, who will manage all EHR data (see **SDCC**). We will use REDCap as our data entry system for the assessment data and provider questionnaire data, as described in the **SDCC**. The folders will be stored in locked filing cabinets in a locked office. No information about a project participant will be given to third parties, including family members, unless that participant has given written or witnessed verbal consent.

C.12. Project Management Plan. Overall responsibility for the proposed project will belong to Dr. **Paskett**, Project Lead. She will oversee the implementation and evaluation of the intervention with Dr. **Katz** (OSU). Dr. **Vanderpool** (UK), Co-Lead of the project, will assist Dr. **Paskett** in the refinement and management of the interventions and in the interpretation of the data, as will Dr. **Pamela Murray** (WVU) and Dr. **Jessica Malpass** (VA). Dr. **Pennell** (**BEC**) will coordinate the statistical evaluation. Our consultants, Drs. Mack Ruffin and Jamie Ostroff, will assist the team with implementing HPV vaccination in primary care and implementation science methodology, respectively. Ms. Tatum will provide management of daily activities, supervise field operations, and be the liaison to the SDCC. She will coordinate the Community and clinic assessment phase data collection, as well as the process evaluation. Data management will be under the direction of the **SDCC**.

C.13. Scientific Rigor/Reproducibility. Strategies to maximize rigor will include: input from an External

Scientific Advisory Board (ESAB) and Community Advisory Board (CAB); provider education sessions; use of a delayed intervention design; use of previously tested measures on provider surveys; use of a MLI that has been previously tested for effectivess[56] and will be refined for each participating clinic; use of logistics patterned heavily after those from our previous pilot study; and confirmation of our main outcomes through medical records. Strategies to promote reproducibility will include: data sharing via request (as appropriate); publication of results; and presentation at conferences (see Resource Sharing Plans).

C.14. Relevant Biological Variables. The patient-level component will target females and males (since the focus is HPV vaccination) who are ages 11-12 and 13-26 (since HPV vaccination is recommended at ages 11-12 with catch up for those 13-26[35]). Provider education sessions will include males and females of all ages, provided they are healthcare providers or staff at a participating health system.

C.15. Project Timeline

Year 1	Q1	Q2	Q3	Q4
Start-up activities/Hire and train staff	•	•		
Protocol Development and Approval	•	•	•	•
Baseline Needs Assessment	•	•	•	•
MRR Data Collection – Baseline HPV Rates (Groups EI and DI)	•	•	•	•
Refinement of Intervention materials	•	•	•	•
Monthly team meetings	•	•	•	•
Year 2				
MRR Data Collection – HPV Rates	•			
Implement Early Intervention -Group EI	•	•	•	•
Data cleaning and management	•			
Monthly team meetings	•	•	•	•
Year 3				
MRR Data Collection – HPV Rates				
Implement Early Intervention -Group EI	•	•	•	•
Sustainability Phase Group EI (thru Year 5)			•	•
Implement Late Intervention -Group DI(thru Year 4)			•	•
Data cleaning and management			•	
Monthly team meetings	•	•	•	•
Year 4				
MRR Data Collection – HPV Rates				•
Late Intervention -Group DI	•	•	•	•
Sustainability Phase -Group EI (thru Year 5)	•	•	•	•
Monthly team meetings	•	•	•	•
Year 5				
MRR Data Collection – HPV Rates	•	•		
Sustainability Phase Group EI (thru Year 5)	•	•		
Sustainability Phase Group DI (thru Year 5)	•	•	•	•
Report writing/ project shut down			•	•
Monthly team meetings	•	•	•	•
**EI = Early Intervention DI=Delayed Intervention				

C.16.Limitations/Problems

C.16.1. Outcome Ascertainment. Project 2 will use EHRs to obtain HPV vaccination outcomes. In our vast experience obtaining outcome data from clinics, we will be able to obtain the needed data.

C.16.2. Implementation of Interventions. Implementation of the planned interventions is a common problem in all implementation and dissemination studies. We are confident that we will be able to implement the core interventions proposed in all clinics by using the following: 1) community-based participation through the **ICC**; 2) what we have learned from prior experience working with health systems in Appalachia; 3) offering a payment to clinics to offset any expenses, hire staff, and create goodwill (see **ICC**); 4) providing the opportunity to use effective materials after the project; 5) culturally competent and sensitive, well-trained staff; and 6) having easily integrated interventions that have been tested in prior studies and adapted from each clinic.

C.16.3. Contamination. In behavioral research, contamination is a threat to intervention integrity. We have chosen a group randomized design, with the health system as the unit of randomization. Thus, the most obvious sources of contamination will be eliminated, as all providers and clinics within one health system are more likely to talk amongst themselves about new innovations at the clinic.

C.16.4. Inability to Assess Individual Effects of the Intervention Components. Since this intervention is bundling many components and is being introduced as one program, we will not be able to tease out which components were successful. This is a noted limitation of MLI's however; we will have some process evaluation measures to gauge satisfaction and use of individual components.

C.17. Relevance to Program Project

C.17.1. Relevance to Program Project Theme. The theme of this PPG is to develop and disseminate effective interventions that can be implemented in Appalachia to reduce cervical cancer using an integrated approach. **Project 2** focuses on testing a health system-based intervention that is directed to three levels of influence – clinic, provider, and patient – to improve the uptake of the HPV vaccine among 11-12 year olds. **Project 2** is central to this theme and will contribute important information on the implementation and dissemination of clinic-based interventions and how an integrated cervical cancer prevention program can be implemented in clinics.

C.17.2. Interaction with Program Project Components. This project is one of three components of an integrated cervical cancer prevention program introduced to clinics. This project interacts with all the Cores of the P01. The **SDCC** will assist with development and implementation of the surveys and methods to obtain data and will oversee data management as well as utilization of the EHRs at the clinics. The **BEC** will provide biostatistics support as well as guidance in process evaluation and cost-effectiveness. The **Administrative Core** will oversee the project operations (including budget and hiring of staff) and facilitate the ESAB Board and the DSMB review of project progress. The **ICC** will facilitate the input of the community and clinical partners in all aspects of the project, including diffusion and dissemination, as well as the CAB and the Clinical Consortium and will assist with implementing effective interventions to our partners as well as others within Appalachia.

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PROJECT SUMMARY – PROJECT 3

Most cases of cervical cancer occur among unscreened and under screened women. Strategies to increase screening among these women, including HPV self-testing, have therefore been identified as the most important cervical cancer screening research priority. HPV self-testing involves women using a device to collect their own cervicovaginal sample for HPV testing. International studies have repeatedly shown that many unscreened and under screened women will use an HPV self-test at home and return it by mail, and recent efforts in the United States (US), including our own work, have established the feasibility of implementing such mail-based programs. An important next step in this field of research is to examine the effectiveness and implementation of a large, mail-based HPV self-testing program in the US.

The overall goal of the proposed project is to determine the effectiveness and implementation of a multi-level cervical cancer screening intervention that features HPV self-testing for unscreened and under screened women from Appalachia, a region with longstanding cervical cancer disparities. The intervention will include mail-based HPV self-testing (patient-level), healthcare provider education sessions about HPV self-testing (provider-level), and patient navigation for women who do not initially return their HPV self-test or who subsequently test positive for a high-risk (i.e., oncogenic) HPV infection (system-level). The proposed study will include 1180 unscreened and under screened Appalachian women who are ages 30-64 and be implemented as part of the integrated health system-based cervical cancer prevention program “Improving Uptake of Cervical Cancer Prevention Services in Appalachia.”

Importantly, the proposed project will take an effectiveness-implementation hybrid approach that will allow for the assessment of both intervention effectiveness and implementation. Specific aims will address each outcome type (service, implementation, and client outcomes) recommended for implementation research: Aim 1 (service outcomes) will determine the effectiveness of the multi-level intervention in increasing cervical cancer screening (primary outcome); Aim 2 (implementation outcomes) will assess the acceptability, fidelity, sustainability, and cost-effectiveness of the intervention; and Aim 3 (client outcomes) will determine satisfaction with the intervention at the patient-, provider-, and system-level. Each aim will make a significant research contribution and, taken together, will be one of the most innovative and comprehensive HPV self-testing efforts to date in the US. As HPV self-testing continues to emerge as a cervical cancer screening strategy in the US, these findings will provide an evidence base on both intervention effectiveness and implementation that will be highly valuable in guiding future HPV self-testing programs and cervical cancer screening policies.

PROJECT NARRATIVE – PROJECT 3

This project will evaluate a multilevel cervical cancer screening intervention centered around HPV self-testing. This project is responsive to the mission statement of NCI by improving women's health and advancing scientific knowledge on HPV self-testing as a cervical cancer screening strategy. This project is relevant to public health by directly addressing: a) Healthy People 2020 objectives to reduce cervical cancer rates and increase cervical cancer screening; and b) a high-priority research area identified by several national health organizations.

SPECIFIC AIMS

Most cases of cervical cancer occur among unscreened and underscreened women.[1,2] Current screening guidelines from the United States (US) Preventive Services Task Force and other organizations recommend women ages 30-65 receive a combination of cytology (i.e., Pap test) and human papillomavirus (HPV) testing (on samples collected by healthcare providers) every 5 years.[3,4] However, nearly 20% of age-eligible women in the US are not within guidelines.[5] Strategies to increase screening among these women, including HPV self-testing, have therefore been identified as the most important cervical cancer screening research priority.[4]

HPV self-testing involves women using a device to collect their own cervicovaginal sample for HPV testing. International work has shown that up to about 40% of unscreened and underscreened women who are sent an HPV self-test in the mail will use the test at home and return it by mail (i.e., mail-based HPV self-testing).[6-17] As a result, multiple countries (the Netherlands and Australia) recently integrated mail-based HPV self-testing into their national screening programs.[18,19] In the US, focus group and survey studies have shown that most women would be willing to use an HPV self-test (i.e., high acceptability), and recent pilot studies, including our own work, have established the feasibility of mail-based HPV self-testing programs.[20-28]

Given the emergence of HPV self-testing, there is a need to examine the effectiveness and implementation of large mail-based HPV self-testing programs in the US. In doing so, it is critical to identify strategies that may increase women's return of a mailed HPV self-test and receipt of follow-up care, if needed. One promising strategy is patient navigation (PN). PN is a patient-centered healthcare delivery model that provides education and support to help people overcome concerns and barriers to care.[29] Many concerns and barriers to HPV self-testing (e.g., worry about doing the test incorrectly, etc.[10,23,30,31]) and receipt of follow-up care[32-34] are modifiable and can be addressed by PN. However, very little is known about PN in the context of HPV self-testing.

The proposed project will evaluate a multilevel cervical cancer screening intervention centered around HPV self-testing via a delayed intervention trial. The intervention will include mail-based HPV self-testing (patient-level), healthcare provider education sessions about HPV self-testing (provider-level), and PN for women who do not initially return their HPV self-test or who subsequently test positive for a high-risk (i.e., oncogenic) HPV infection (system-level). The intervention will be part of an integrated cervical cancer prevention program implemented in clinics within health systems in Appalachia, a geographic region with cervical cancer disparities.[35-39] We will use an effectiveness-implementation hybrid approach[40] for this project, which will allow us to assess both the effectiveness and implementation of the intervention. Specific aims will address each outcome type (service, implementation, and client outcomes) recommended for implementation research:[41]

Aim 1 (service outcomes): Determine the effectiveness of the intervention in increasing cervical cancer screening (primary outcome). Hypothesis 1a: The intervention will increase screening among unscreened and underscreened Appalachian women who are ages 30-64. Further, PN will increase HPV self-test return among women who are initially non-returners. Screening will be defined as: a) return of an HPV self-test and negative for a high-risk HPV infection; b) return of an HPV self-test, positive for a high-risk HPV infection, and attendance at a follow-up appointment; or c) receipt of a clinic-based test (e.g., Pap test). Hypothesis 1b: The increase in screening will be similar across patient characteristics (e.g., age, rurality, etc.).

Aim 2 (implementation outcomes): Assess the acceptability, fidelity, sustainability, and cost-effectiveness of the intervention. Hypothesis 2a: Health systems will report high levels of intervention acceptability, and the intervention will be implemented with high levels of fidelity and sustainability. Hypothesis 2b: The intervention will be a cost-effective strategy for increasing cervical cancer screening.

Aim 3 (client outcomes): Determine satisfaction with the intervention at the patient-, provider-, and system-level. Hypothesis 3a: Women will report high levels of satisfaction with HPV self-testing (if HPV self-test is returned) and PN (if received). Hypothesis 3b: Healthcare providers will report high levels of satisfaction with the provider education sessions and have improved knowledge, attitudes, and beliefs about HPV self-testing. Hypothesis 3c: Patient navigators will report high levels of satisfaction with providing PN to women.

IMPACT: The overall goal of the proposed project is to determine the effectiveness and implementation of a multilevel cervical cancer screening intervention that features HPV self-testing for unscreened and underscreened women from Appalachia. The project is innovative because it will evaluate the first large mail-based HPV self-testing program for women from Appalachia. **Project 3** is significant because it will not only provide an evidence base on intervention effectiveness but also provide valuable insight into its implementation (including sustainability) in health systems. As HPV self-testing continues to emerge as a screening strategy in the US, findings will be highly valuable in guiding both future HPV self-testing programs and screening policies.

RESEARCH STRATEGY

A. BACKGROUND AND SIGNIFICANCE

A.1 Introduction. Cervical cancer causes a significant disease and economic burden in the United States (US). Over 13,000 new cases and 4,000 deaths from cervical cancer occur annually in the US.[42] Persistent infection with high-risk (i.e., oncogenic) human papillomavirus (HPV) types, mainly types 16 and 18, cause almost all cervical cancers.[43] HPV is the most common sexually transmitted infection (STI) in the US,[44] with over 40% of women infected with at least one type of HPV and 29% infected with a high-risk HPV type.[45]

Cervical cancer screening is cost-effective and has greatly reduced cervical cancer incidence.[46,47] Current guidelines recommend women ages 30-65 receive a combination of cytology (i.e., Pap test) and HPV testing on provider-collected samples every 5 years (preferred) or cytology alone every 3 years (acceptable).[3,4] Recommendations still include cytology, though interest in HPV testing as a lone screening test is growing. Indeed, the Food and Drug Administration has approved an HPV test as a first-line screening test,[48] and the US Preventive Services Task Force (USPSTF) released draft guidelines recommending HPV testing alone every 5 years as an option for women ages 30-65.[49] Cervical cancer screening remains suboptimal in the US, with nearly 20% of age-eligible women not within guidelines[5] and screening rates decreasing over the last decade.[5,50] This is concerning since most cervical cancer cases occur among unscreened and underscreened women.[1,2] Strategies to increase screening among these women, including the use of HPV self-tests, have been identified as the most important cervical cancer screening research priority by several US organizations.[4]

A.2. Scientific Premise. HPV self-testing has increased cervical cancer screening in international studies. HPV self-testing involves women using a device to collect their own cervicovaginal sample for HPV testing. The sensitivity and specificity of HPV self-tests are high and comparable to provider-collected samples.[51,52] Many unscreened and underscreened women who are sent an HPV self-test in the mail will use the test at home and return it by mail (i.e., mail-based HPV self-testing), with up to 40% return in large international studies.[6-17] These studies repeatedly showed that HPV self-testing increases cervical cancer screening compared to usual care (e.g., a reminder letter about screening)[6-17] and is cost-effective.[53] As a result, multiple countries (the Netherlands and Australia[18,19]) recently integrated mail-based HPV self-testing for unscreened/underscreened women into their national screening programs. In these countries, HPV testing serves as a first-line primary screening test, with follow-up care (triage cytology, colposcopy, etc.) for women who test positive for a high-risk HPV infection.[18,19]

HPV self-testing is an emerging cervical cancer screening approach in the US. HPV self-testing is not yet an approved or recommended screening approach in the US, but research has produced encouraging results. Focus group and survey studies have shown that most US women would be willing to use a self-test at home (i.e., high acceptability).[21-24,27] Recent US studies, including our own work, implemented small pilot mail-based HPV self-testing programs and established the feasibility such programs.[20,25,28] These pilot studies were very successful, with at least 64% of women returning the self-test mailed to them. Current NIH-funded studies are further examining such programs.[54,55] Critical next steps in this field are to: a) examine the effectiveness and implementation of a large mail-based HPV self-testing program; and b) identify strategies to increase women's return of a self-test that is mailed to their home and receipt of follow-up care, if needed. Such information will be critical to informing both future HPV self-testing programs and cervical cancer screening policies.

PN is a promising but underexplored strategy for increasing HPV self-test return and receipt of follow-up care. PN is a patient-centered health-care service delivery model that that provides education, support, and assists individuals in overcoming concerns and barriers to care.[29] PN has repeatedly increased cancer screening behaviors, including Pap testing, and receipt of follow-up care.[56-60] Thus, it is important that PN be examined for helping women use/return an HPV self-test and receive follow-up care, if needed. Many of the most common concerns and barriers reported by women about using an HPV self-test are modifiable and include: concerns about using the test incorrectly; uncertainty about test accuracy; and worry about returning a test by mail.[10,23,30,31] This suggests that PN may be an effective strategy for increasing HPV self-test return, but no published studies could be found that examine how PN increases this outcome.

Two previous studies[22,61] examined whether PN increased women's receipt of a Pap test after completing an HPV self-test. Neither showed a positive effect of PN, but both studies had several key limitations. Mainly, neither used mail-based HPV self-testing. Women instead completed an HPV self-test on site (e.g., at a health department). This is a key limitation since mail-based HPV self-testing maximizes the potential reach and convenience of self-testing, thus making it the most appealing approach for large self-testing programs. Thus, there is a need to examine if PN can help ensure receipt of follow-up care, if needed, in the context of a mail-based HPV self-testing program in healthcare professional shortage areas like Appalachia.

Women in Appalachia can benefit greatly from HPV self-testing. Areas within Appalachia have among the highest cervical cancer incidence and mortality rates in the US, with many Appalachian counties having mortality rates that exceed the national rate by 20-40% or more.[38,62-66] The disparities in Appalachia may be due to several factors, including lower cervical cancer screening rates and increased prevalence of high-risk HPV infection.[36,37,67] In fact, our past work has shown that up to 30% of Appalachian women are not within cervical cancer screening guidelines.[37] Key barriers to screening reported by Appalachian women include lack of time and/or transportation, embarrassment, and forgetting to make an appointment.[68-71] Mail-based HPV self-testing and PN may help overcome these barriers and increase screening among Appalachian women.

A.3. Significance of the Expected Research Contribution. Healthy People 2020 set objectives to reduce cervical cancer rates and increase cervical cancer screening.[72] A promising new approach for helping achieve these objectives is HPV self-testing. Multiple countries recently integrated mail-based HPV self-testing into national cervical cancer screening programs,[18,19] and it is an emerging approach in the US that was cited as a high-priority research area by several organizations.[4] The acceptability and feasibility of HPV self-testing in the US has been established by recent studies, including our own work.[21-26,73] A critical next step in moving this field of research forward is to examine the effectiveness and implementation of a large mail-based HPV self-testing program in areas with cervical cancer disparities.

The proposed **Project 3** will take this next step by determining the effectiveness and implementation of a large, health system-based multilevel intervention that is centered around mail-based HPV self-testing. Each aim will make a significant research contribution and address each outcome type (service, implementation, and client outcomes) recommended for implementation research.[41] **Aim 1** (service outcomes) will determine the effectiveness of the multilevel intervention. **Aim 2** (implementation outcomes) will assess the acceptability, fidelity, sustainability, and cost-effectiveness of the intervention. **Aim 3** (client outcomes) will determine satisfaction with the intervention among patients, providers, and patient navigators. Moreover, **Project 3** will be part of an integrated cervical cancer prevention program implemented in clinics within health systems.

A.4. Innovation

The proposed study is innovative because it will:

- **Implement one of the first large mail-based HPV self-testing programs in the US.** Small pilot studies have established the feasibility of such programs,[20,25,28] but only a couple of NIH-funded studies are underway to examine larger programs.[54,55] Our study will be the first to focus on women from Appalachia.
- **Assess the added benefit of PN on HPV self-test return and receipt of follow-up care, if needed.** To our knowledge, no published studies have examined how PN increases HPV self-test return, and only a few studies (which had several key limitations, as described in **Section A.2.**) have examined PN in the context of receipt of follow-up care after HPV self-testing.
- **Use an effectiveness-implementation hybrid approach.** This novel approach will provide an evidence base on both intervention effectiveness and implementation, including sustainability, in health systems.[41] In using this approach, we will assess each outcome type (service, implementation, and client outcomes) recommended for implementation research.[41]
- **Utilize a delayed intervention trial design**. This design will allow us to address all study aims in a manner that ensures all participating health systems will receive the multilevel intervention.
- **Be part of an integrated cervical cancer prevention program**. The program will be implemented in clinics within health systems in Appalachia, a geographic region with longstanding cervical cancer disparities.[35-39]

B. PRELIMINARY STUDIES

Our preliminary work shows: a) our expertise in HPV self-testing and mail-based self-testing programs; b) data suggesting PN may improve HPV self-testing outcomes; and c) our ability to implement effective PN programs.

B.1. Acceptability of HPV Self-Testing and Devices (2014-2015). We conducted focus groups with Appalachian women and healthcare providers to gather feedback about HPV self-testing (PIs: **Reiter**, **Katz**).[24,74] Both women and providers were very positive about HPV self-testing, and many women indicated they would be willing to use an HPV self-test mailed to them. Women thought HPV self-testing would address many of the barriers to Pap testing. Potential barriers to HPV self-testing included concerns about not using the self-test correctly, test accuracy, and returning a test in the mail. We showed women several self-test devices and the instructions for each device and asked for feedback. Women most preferred the Evalyn® Brush and thought the instructions for this device were easy to read and understand, which guided our decision to use this device in the below pilot study and the proposed project. *Results show the high acceptability of HPV self-testing among Appalachian residents, identify potential barriers/concerns about self-testing, and indicate the Evalyn® Brush as the most preferred self-test device with easy-to-understand instructions.*

B.2. Health Outcomes through Motivation and Education (HOME) Project Pilot Study (2015-2017). This pilot study established the feasibility of mail-based HPV self-testing among Appalachian women (PIs: **Reiter**, **Katz**; Co-I: **Shoben**).[25] We recruited a random sample of 103 unscreened/underscreened women (i.e., no Pap test in at least 3 years) from health clinics in Appalachian Ohio and mailed them an HPV self-test (the Evalyn® Brush). Over 70% of women used and returned their self-test, of which 26% had a high-risk HPV infection. About 33% of women with a high-risk HPV infection attended a follow-up appointment. All women who used their HPV self-test collected an adequate sample for HPV testing (i.e., 100% sample adequacy).

This study did not include PN, but survey data from this study suggest PN will be beneficial to HPV self-test return and follow-up care. On study surveys, nearly 60% of women indicated it would have been helpful if study staff had contacted them to help (i.e., PN) with the self-test and/or follow-up visits. Nearly 70% of these women preferred that the help be provided by telephone. Further, women indicated concerns about self-testing similar to those from the above focus groups (e.g., concerns about using the test incorrectly, etc.), as well as concerns about receiving follow-up care (lack of transportation, cost/insurance, etc.). These findings reiterate that many concerns about HPV self-testing and follow-up care are modifiable and can be addressed by PN.

For this pilot study, we also conducted education sessions with providers and staff (n=33) from participating clinics to ensure they were knowledgeable about HPV self-testing.[75] Pre-/post- comparisons showed that the sessions improved providers' knowledge and attitudes/beliefs about self-testing (all $p<0.05$). *Overall, our pilot study shows our ability to implement a mail-based HPV self-testing program and conduct effective HPV self-testing provider education sessions. It also suggests that PN may increase HPV self-test return and receipt of follow-up care. The proposed project will draw heavily upon the methodology and successes of this pilot study.*

B.3. Ohio Patient Navigation Research Program (2005-2011). This group randomized trial tested the effects of PN on time to diagnostic resolution among persons with abnormal cancer screening tests (cervical, breast, or colorectal)(PI: **Paskett**; Co-I: **Katz**).[59] We recruited 862 participants, trained patient navigators, and provided telephone-based PN. Navigators successfully contacted almost 90% of participants randomized to PN. The resolution rate at 15 months was 65% higher in the PN arm compared to the control arm ($p=0.012$). *This study shows the positive effects of PN on health outcomes and our ability to implement an effective telephone-based PN program, including the training of navigators and contacting participants assigned to PN.*

C. APPROACH

C.1. Project Team and Management Plan. We have a history of collaboration and expertise in cervical cancer prevention,[23,24,77-86] behavioral interventions,[87-100] PN,[29,34,57,59,101-106] and health disparities research in Appalachia.[35-37,107-113] Dr. **Reiter** (Project Co-Leader; The Ohio State University [OSU]) is an epidemiologist with expertise in cervical cancer prevention, interventions, and data collection. He will lead implementation of the trial and data collection activities. Dr. **Katz** (Co-Leader; OSU) is a behavioral researcher with expertise in health communication, interventions (including PN), and qualitative research. She will lead provider education sessions and PN activities. Each Co-Leader will lead different parts of the project using their complementary expertise but will collaborate on decisions. Dr. **Vanderpool** (Co-I; University of Kentucky) is a behavioral researcher with expertise in Appalachian health and cervical cancer prevention. Dr. **Mitchell** (Co-I; University of Virginia) is a women's health nurse scholar whose work focuses on cervical cancer screening among rural women. Dr. **Ashcraft** (Co-I; West Virginia University) is a social scientist with expertise in sexual health and interventions (including mail-based STI testing). Dr. **Shoben** (Co-I; OSU) is a biostatistician with expertise in randomized trials and will lead quantitative data analyses through the **Biostatistics and Evaluation Core** (**BEC**). Dr. **Xu** (Co-I; OSU) is a health services researcher who will lead cost-effectiveness analyses through the **BEC**. Dr. Ruffin (consultant; Penn State University) is a physician and clinical researcher who will ensure study materials are medically accurate and help with study implementation. Dr. Ostroff (consultant; Memorial Sloan Kettering Cancer Center) is an expert in implementation science, which is key given the effectiveness-implementation hybrid approach[40] for **Project 3**. See the **Overall** for letters of support for Drs. Ruffin and Ostroff. The PLs will meet with project staff weekly and the entire project team on a monthly basis. The project team will also work in close collaboration with the Community Advisory Board and Clinic Consortium throughout the entire project, as fully described in the **Intervention and Consortium Core** (**ICC**) section.

Table 1. Health Systems/Clinics by State

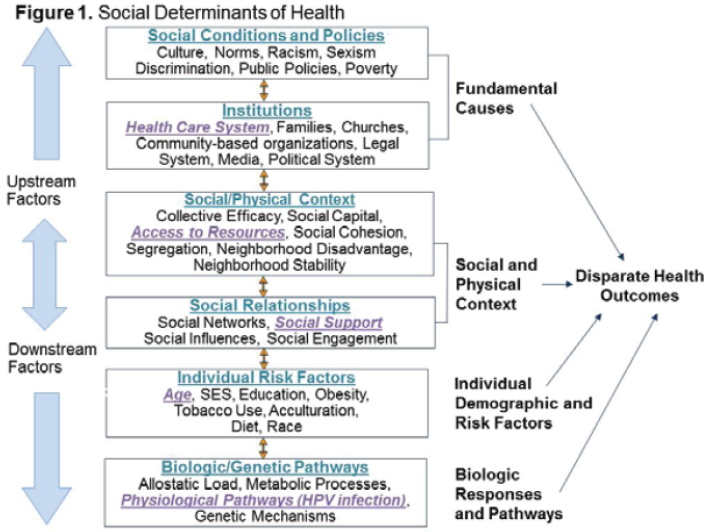
	# Health Systems/Clinics	Patients (Women Ages 30-64)	Healthcare Providers	% Women Screened*
Ohio	4/9	10,084	158	45%-69%
Kentucky	2/9	7,342	89	55%-58%
West Virginia	2/9	21,902	280	32%-33%
Virginia	2/5	8,634	102	23%-24%

*Range across participating health systems of the percent of women ages 21-64 with a Pap test in the last 2 years (data by the US Dept of Health and Human Services[76])

C.2. Health Systems. Program leadership through the **ICC** has established relationships with all participating health systems. **Table 1** shows the number of providers, women in the target age range, and current screening rates in the clinics of the health systems by state.

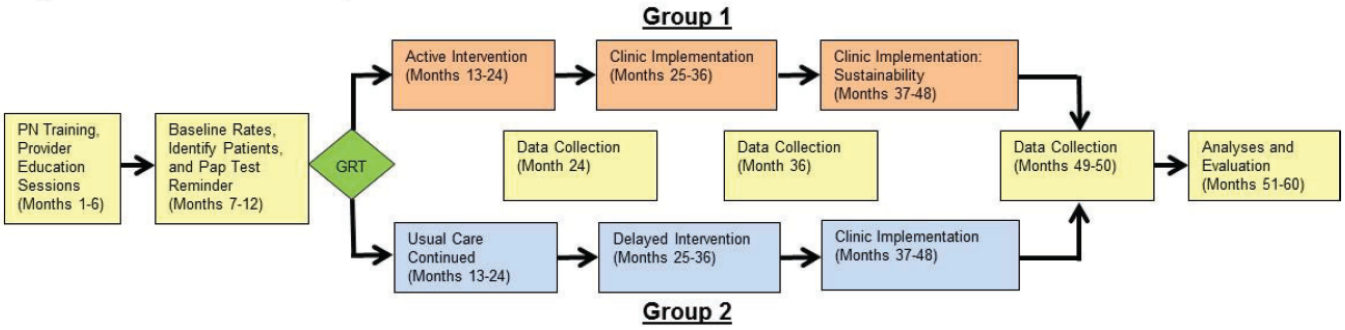
C.3. Conceptual Model. Project 3 will include social determinants of health from several levels of the model by Warnecke et al. for population health and health disparities (**Figure 1**).[114] This project will examine Physiological Pathways (HPV infection), Individual Demographics (age), Social and Physical Context (social support via PN and access to resources), and Fundamental Causes (health care systems).

Figure 1. Social Determinants of Health



C.4. Project Overview/Considerations. We will examine the effectiveness and implementation of the multilevel intervention using a delayed intervention trial (**Figure 2**), as part of an integrated cervical cancer prevention program in clinics from health systems. We considered three key issues in designing the trial. First, we will treat HPV self-testing as a first-line primary cervical cancer-screening test instead of a "co-test" with Pap testing. This means that women who test negative for high-risk HPV on their self-test will be considered "screened" without further care (described further in **Section C.9.c.**). This will allow us to mirror the national screening programs in other countries[18,19] and emphasize the positive attributes of mail-based HPV self-testing (reach, convenience, etc.). Second, we will send all women identified as potentially eligible in participating clinics (see **Section C.5.d.**) a standard reminder letter to get a Pap test and allow several months for them to do so before sending HPV self-test devices. This will ensure that all unscreened/underscreened women will receive at least a reminder letter. Third, PN will be telephone-based. We believe telephone-based PN is an efficient and sustainable approach, while in-person PN is not, given the large geographic size the clinics serve. Further, data from our past work showed that women most preferred telephone-based PN (see **Section B.2.**).

Figure 2. Overview of Delayed Intervention Trial



C.5. Year 1 Activities

C.5.a. Training of Patient Navigators (Months 1-6). As described further in **Section C.6.a.,** PN will be provided to help women both: a) use/return their HPV self-test (if they do not initially return their device); and b) attend an in-clinic follow-up visit if their returned self-test is positive for high-risk HPV infection. To improve these outcomes, patient navigators (PNs) will perform the following activities: a) provide information about HPV, cervical cancer, and screening; b) address patients' concerns/barriers about HPV self-testing and attending a follow-up visit (if needed); c) help set goals and plans for achieving these outcomes; and d) provide social support. These activities are key components of behavior change technique[115] and were used in our past PN work.[59] All PN will be provided via telephone. Except during the Sustainability Phase (see **Section C.8.a.**), the PNs will be two OSU employees who are current navigators for other research projects. Both PNs are female, in the same age range as the targeted age range for this project, have PN experience for cancer-related studies, and are long-term residents of Appalachia. This is important since the success of PN is dependent upon the PN's ability to communicate with the target population in a culturally accepted way.

PN training will involve a one week training session led by the **ICC**, with guidance from Dr. **Katz** (who has

expertise training PNs[59,116]). Modeled after our past PN work,[59] training will include both a review of general PN principles and project-specific training. General PN principles will include training on keeping relationships professional with patients, potential ethical issues (e.g., confidentiality), and how to work as a link between patients and the clinic (see the **ICC** for more details). Project-specific training will include detailed information about the project and how to: a) provide information in an understandable format about HPV, cervical cancer, and screening (including self-testing); b) interpret HPV testing results and discuss the results; c) address patients' likely concerns, barriers, and questions; d) help patients set goals and plans for screening; e) provide social support; f) compile a list of potential local resources (e.g., transportation systems); and g) complete project forms. Training will also introduce the PNs to the clinics/health systems and key personnel at each clinic. These training topics map directly onto the functions of the PNs described above.

Training activities will include case studies, content reading, role-playing, and mock interactions with patients. During training, we will stress how to: provide information about HPV, cervical cancer, and screening, with a focus on Appalachian disparities; describe the effectiveness of HPV self-testing; and address women's concerns/barriers. For social support, PNs will be trained to provide support that is informational (i.e. trusted source of information), emotional (e.g., supportive listening, expressing concern, etc.), and instrumental (e.g., help with transportation, etc.). PNs will apply these skills when interacting with patients (see Section C.6.a.).

C.5.b. Provider Education Sessions (Months 1-6). To ensure providers and staff at clinics are knowledgeable about HPV self-testing, we will conduct education sessions as the provider-level component of the multilevel intervention. Eligibility criteria will include: a) employee at a clinic of a participating health system; b) age 18 or older; and c) involved with the cervical cancer screening process, including physicians, nurses, physician assistants, staff that assist with scheduling screening tests, etc. Providers and staff will attend one session each (about 60 minutes long). We will conduct a session at each clinic within a health system, with Dr. **Katz** leading the sessions. All sessions will be completed prior to HPV self-tests being sent to patients. Attendees will view a standardized automated PowerPoint presentation from our previous pilot study.[75] The presentation will provide information about HPV and cervical cancer, screening recommendations, HPV self-testing and how to talk with patients about testing results, **Project 3**, and how this project fits into the integrated cervical cancer prevention program. It will discuss how our project will treat HPV self-testing as a first-line primary screening test. The presentation will instruct clinics to follow their policies (follow-up care, etc.) when patients are seen during the project. Education session content will be the same for all clinics.

Based on our pilot study,[75] we estimate about 80% attendance at the sessions (about 503 attendees total). To maximize attendance, we will work with clinics to find a convenient session time (e.g., at an existing meeting). Each attendee will complete a brief written pre- and post-test survey. Using items from our pilot study,[117] surveys will assess: demographics (pre- survey only); knowledge, attitudes, and beliefs about HPV self-testing (pre- and post-surveys); and satisfaction with the session (post- survey only). The resulting survey data will be used in evaluation (see **Section C.9.e.**). Attendees will provide written consent prior to the start of the session.

C.5.c. Material Refinement and Clinic Assessment (Months 1-6). We will refine materials and conduct a clinic assessment during Months 1-6. For the former, we will refine materials (e.g., letters to participants, surveys, etc.) developed previously for our pilot study[25] via vigorous community-engaged processes (focus groups, in-depth interviews, etc.) so that the materials are adapted to the participating clinics and for the project. Refinement will be guided by input from our Community Advisory Board in the **ICC**.

The clinic assessment will help us better understand each clinic/health system so our intervention can be effectively and efficiently implemented. For the assessment, we will work closely with the "champion" at each clinic/health system (see **ICC** section). This person will champion project implementation at their clinic/health system. The clinic "champion" will provide us with insight about the roles and responsibilities that each provider and staff person has in screening patients for cervical cancer (and any associated follow-up care) and any potential barriers/concerns with implementing the project as part of the integrated cervical cancer prevention program. The Survey and Data Collection Core (**SDCC**) will work with the "champion" to obtain information about the electronic health record (EHR) system utilized by each health system, as the EHR will be used to identify potentially eligible women (during Month 7) and provide data on project outcomes (during Years 2-5).

C.5.d. Baseline Rates and Patient Identification (Month 7). We will use EHR systems at each health system to obtain baseline cervical cancer screening rates and identify potentially eligible women. Eligibility criteria will include: a) female; b) ages 30-64 (64 will be the upper age limit instead of 65 so women do not age out of the screening guidelines); c) not within screening guidelines (i.e., no Pap test in last 3 years or no Pap test plus clinic-based HPV test in last 5 years); d) resident of an Appalachian county; e) not currently pregnant; f) intact cervix; g) no history of invasive cervical cancer; h) seen in a participating clinic/health system in last 2 years

(i.e., active patient); and i) have a working telephone. We will require a working telephone (landline or cell) since PN will be telephone-based. All women in our past pilot study had a working telephone, and over 96% of Appalachian households have telephone access.[118] Participation will be limited to one woman per household.

C.5.e. Pap Test Reminder Letter (Months 7-12). We will next mail all identified potentially eligible women a standard reminder letter to get a Pap test. The letter will indicate that, according to EHR, they are due for a Pap test and encourage them to contact their clinic to schedule a Pap test (contact information will be provided). All letters will appear on clinic/health system letterhead and be signed by a clinic representative. Many health systems have utilized this type of reminder letter for Pap testing,[119] so it can be considered "usual care." We think it is important that all potentially eligible women receive this letter that encourages Pap testing before any HPV self-tests are sent. The letter will also ask women to confirm their eligibility criteria (as defined above). If any of the criteria are incorrect, women will indicate correct information and return the letter in a provided postage-paid return envelope. Women who return their letter and are found to be ineligible will not continue in the project. Return of a letter will be considered consent for providing this information.

We will then allow five months for women who are sent a reminder letter (and are not found to be ineligible) to receive a Pap test. At the end of the five-month period, we will work with the clinics/health systems and use EHR to identify women who received a Pap test since the reminder letters. Any woman who has received a Pap test will not continue in the project, as they are no longer unscreened/underscreened. Based on the mean effect size of past studies of mailed cervical cancer screening reminder letters, we anticipate that only about 5% of women who are sent a reminder letter will receive a Pap test during the five-month period.[119]

C.5.f. Randomization (Month 12). The **BEC** will randomize health systems to one of two treatment groups for the cervical cancer prevention program (**Figure 2**). A 1:1 allocation scheme stratified by state will be used (i.e., five systems per treatment group). Health system will be the unit of randomization since the intervention will include a system-level component and to reduce the potential for contamination. All clinics in a health system will be in the same treatment group. Group 1 will receive active intervention in Months 13-24, clinic implementation in Months 25-36, and sustainability in Months 37-48. Group 2 will receive usual care continued in Months 13-24, delayed intervention in Months 25-36, and clinic implementation in Months 37-48. The randomization scheme will ensure that at least one health system per state will be in Group 1 and Group 2.

C.6. Year 2 Activities

C.6.a. Group 1: Active Intervention (Months 13-24). Group 1 clinics/health systems will receive Active Intervention in Months 13-24, including HPV self-test devices sent to women (patient-level component) and PN (system-level component). **Figure 3** provides an overview of these components. During the Active Intervention phase, the project team will conduct all logistics/tasks (described below). The clinics/health systems will become more involved in the logistics/tasks during the subsequent phases (as described in later sections).

HPV Self-Test Distribution and Return. Women in Group 1 clinics/health systems who did not get a Pap test in the five months after the reminder letter will be on a sampling frame to receive an HPV self-test. We will randomly sample from this list, stratified by clinic. We will sample a total of 390 women (78 per Group 1 health system) and mail each sampled woman an HPV self-test. Self-tests will be sent by first class mail. Women will be sent the HPV self-test and subsequent HPV testing free of charge.

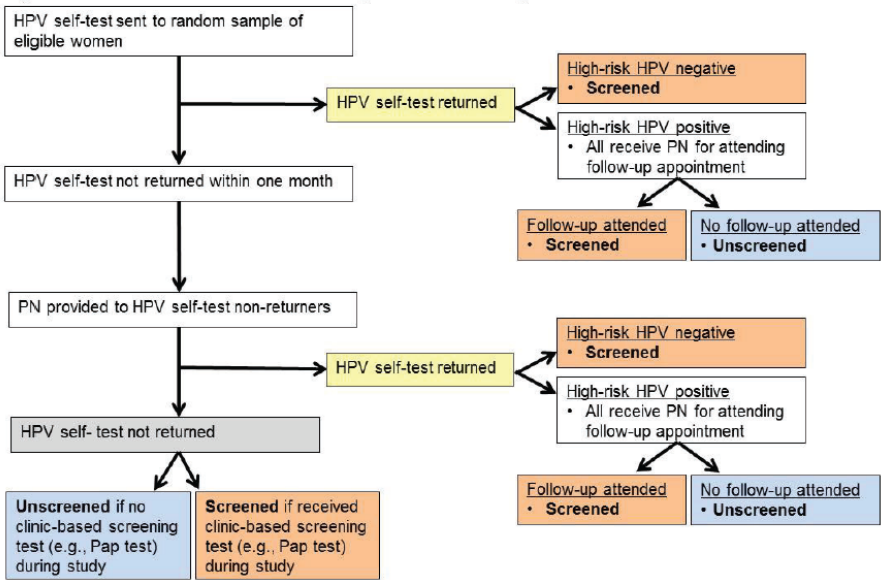
The Evalyn® Brush will be the HPV self-test device used for this project. Appalachian women reported the highest acceptability for this device in focus groups,[24] and we used this device in our pilot study (see Preliminary Studies).[25] The Evalyn® Brush is made by Rovers Medical Devices.® It has fine bristles to collect the sample and several desirable features (e.g., wings to standardize insertion depth). It has been used in several research studies[25,120-122] and has strong agreement with provider-collected samples.[120]

We will send several materials with the self-test: an introductory letter, instructions for the self-test, an information sheet about cervical cancer, a plastic sample bag, and a postage-paid return box. The introductory letter will explain the self-test's purpose and tell women they can request a replacement device if one is needed for any reason. Device instructions will have step-by-step instructions created by the manufacturer for using/returning the self-test. To ensure women are knowledgeable about cervical cancer, we will include an information sheet created by the Centers for Disease Control and Prevention (CDC).[123] To return the self-test, women will place a used self-test in the plastic sample bag and then place the sample bag in the return box. Return of an HPV self-test will be considered consent for the self-test. The Evalyn® Brush can have dry transport (i.e., no transport medium) and maintain sample integrity for several weeks prior to HPV testing.[120]

Patient Navigation for HPV Self-Test Device Return. Women who have not returned their HPV self-test

within one month of the device being sent will receive telephone-based PN (from an OSU-based navigator) for self-test return. We chose a one-month period because nearly all self-tests were returned within one month in our pilot study. PNs will attempt to contact these initial non-returners by telephone, making at least 10 attempts at different times and on different days, including weekends. If no contact is made after 10 attempts, PNs will send women a letter asking them to contact the PNs. Using a similar approach, PNs contacted almost 90% of participants in our past work.[59] During the call, PNs will apply their training (see **Section C.5.a.**) to provide information about HPV and self-testing, address women's concerns and barriers to using/returning their self-test, help women set goals and plans for using/returning their self-test, and provide social support. PNs will also ask women if they need a replacement device sent. To ensure consistency in the process, PNs will use developed guides during calls. If a woman has already returned her self-test by the time of contact, the PN will ask if she had any questions.

Figure 3. Overview of the HPV Self-Testing and Patient Navigation Processes



PNs will contact each of these initial non-returners at least once about using/returning their self-test, with additional contacts as needed (e.g., if PNs need to locate further information after the first contact). This will allow PNs flexibility that is tailored to each woman's needs. During the contact process, PNs will complete electronic encounter forms that include: a) day/time and outcome of each call attempt; b) PN activities performed; c) barriers, concerns, and questions raised by women; d) actions taken by PNs in response and if issues have been resolved; and e) total call time. Following completion of PN (or 10 contact attempts without success), we will give women one additional month to return their HPV self-test. All women who do not return their self-test following this additional month will be classified as having not returned their HPV self-test.

HPV Testing. All returned HPV self-tests will be sent to a laboratory at the CDC for HPV testing (see letter of support). The laboratory has expertise in HPV testing and done this testing for our past work.[25,36] Testing will use a modified cobas® HPV test,[124] which produces one of the following outcomes for each sample: (a) positive for high-risk HPV type 16 or 18; (b) positive for a high-risk HPV type other than type 16 or 18 (i.e., type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 or 68); (c) negative for high-risk HPV types; or (d) inadequate sample. The detectable high-risk HPV types cause almost all cervical cancers.[125] We do not expect "inadequate sample" to occur often since all women in our pilot study collected adequate samples, but will send a replacement device for resampling if it does occur. The CDC will send HPV testing results to the study team via secure email and using only participant ID numbers. Results will be available about one month after a sample is sent to the CDC.

Notification of Results. Upon receipt of HPV testing results, we will send notifications to both the women (for those who return their HPV self-test) and their providers. Similar notifications were used in our pilot study.

Notification to Healthcare Provider. Working with the project "champion" at each clinic/health system, we will first provide a hardcopy notification to the appropriate healthcare provider for each woman. The notification will indicate a woman's HPV testing results and include an interpretation of the results. Contact information for the project team will be provided in case the healthcare provider has any questions.

Notification to Women. A notification letter will be mailed to the woman and include HPV testing results and an interpretation of the results. The letter will indicate appropriate next steps based on the HPV testing results. For women who test negative for high-risk HPV types, the letter will indicate that no follow-up care is needed (since HPV self-testing will be treated as a first-line primary screen test) and state when their next cervical cancer screening test should occur. For women who test positive for high-risk HPV types, the letter will indicate that they should contact their clinic to schedule a follow-up appointment and that a PN will contact them to help with this process. Contact information for the project team will be provided if the woman has any questions.

Patient Navigation for Follow-Up Appointment. All women who test positive for a high-risk HPV type will receive PN (from an OSU navigator) for scheduling/attending a follow-up appointment (i.e., a Pap test or other follow-up care [e.g., colposcopy] as deemed appropriate by the health system). We think it is important to provide PN to all of these women given their HPV infection and lack of screening prior to this project. PNs will attempt to contact women by telephone starting one week after women's notification letters are mailed (to allow time for letter delivery). PNs will make at least 10 attempts at different times and on different days, including weekends. PN activities will be similar to those described above for HPV self-test use/return. Using developed guides, these calls will focus on women's HPV testing results and the importance of scheduling/attending a follow-up appointment. PNs will be aware of HPV testing results prior to the calls. PNs will contact these women at least once about scheduling/attending a follow-up appointment, with additional contacts as needed. PNs will again complete electronic encounter forms during the contact process (as described previously).

C.6.b. Group 2: Usual Care Continued (Months 13-24). Women in Group 2 clinics/health systems who did not get a Pap test in the five-month period following the reminder letter being sent will be on a sampling frame to continue with usual care. We will randomly sample from this list, stratified by clinic. We will sample a total of 390 women (78 per Group 2 health system) and mail each sampled woman an additional reminder letter to get a Pap test (i.e., usual care continued).

C.6.c. Groups 1 and 2: Data Collection (Month 24). There will be two data collection activities at Month 24: a medical record review and a patient satisfaction survey.

Medical Record Review. The SDCC will work with the project "champion" at each health system to gather data from EHR. For women in Groups 1 and 2, we will confirm whether any received a Pap test during months 13-24. For women in Group 1 who tested positive for a high-risk HPV type based on their self-test, we will also confirm: a) any follow-up appointment attended; b) any follow-up care received (e.g., Pap test, colposcopy, etc.); and c) any cervical abnormalities (precancerous and cancerous) found during this follow-up.

Patient Satisfaction Survey. We will send all women who were sent an HPV self-test during Months 13-24 (i.e., Group 1) a patient satisfaction survey about HPV self-testing. We will send the survey to both self-test returners and non-returners. The survey will examine women's decisions/experiences with their self-test and PN (if applicable), as this information will be valuable in evaluating the intervention. The survey will assess reasons for returning or not returning the self-test, satisfaction with the self-test (appearance, usability, etc.) and its instructions (appearance, readability, etc.). For women who received PN, we will assess their satisfaction with PN. We will provide women with a postage-paid return envelope, and survey return will be considered consent. A replacement survey will be sent two and four weeks later if no survey has been received. Women will be sent a $25 gift card for returning the survey. We anticipate about 80% of women will return their satisfaction survey based on the return of mailed surveys in our past HPV self-test pilot study.[25]

C.7. Year 3 Activities.

C.7.a. Group 1: Clinic Implementation (Months 25-36). The Clinic Implementation phase will occur in Group 1 clinics/health systems during Months 25-36. This phase will involve the project team and ICC training the clinics on project logistics/tasks, and the clinics then implementing the intervention. Implementation will mirror the Active Intervention phase (see Section C.6.a.), but the clinics will conduct project logistics/tasks (minus PN), with oversight and assistance from the project team (if needed). All PN during the Clinic Implementation phase will still be provided by the OSU-based navigators. However, during this phase, the project team and ICC will identify and train a staff person at each clinic who will assume PN duties during the Sustainability Phase (see **Section C.8.a.**). PN training for these individuals will follow the approach from **Section C.5.a.**

The project team and **ICC** will train clinic staff on: a) using EHR to identify eligible women in their health system; b) distribution and return processes for HPV self-tests and subsequent HPV testing; c) notification of HPV testing results; and d) communication with PNs. The clinics will then apply this training to implement the intervention as part of the integrated cervical cancer prevention program. During implementation, the project team will provide oversight and assistance via weekly calls with clinics. In this phase, 100 eligible women (20 per Group 1 health system) who are unscreened/underscreened will be randomly sampled from the sampling frame and sent an HPV self-test. This could include both women not previously sent a self-test and those who were sent a self-test previously but did not return it (if randomly sampled again).

C.7.b. Group 2: Delayed Intervention (Months 25-36). Group 2 clinics/health systems will receive delayed intervention in Months 25-36. This will be identical to the Group 1 Active Intervention (see **Section C.6.a.**), with the project team doing all logistics/tasks. In this phase, 100 eligible women (20 per Group 2 health system) who are unscreened/underscreened will be randomly sampled from the sampling frame and sent a self-test.

C.7.c. Groups 1 and 2: Data Collection (Month 36). Similar to data collection at Month 24 (see **Section C.6.c.**), data collection at Month 36 will include a medical record review and a patient satisfaction survey.

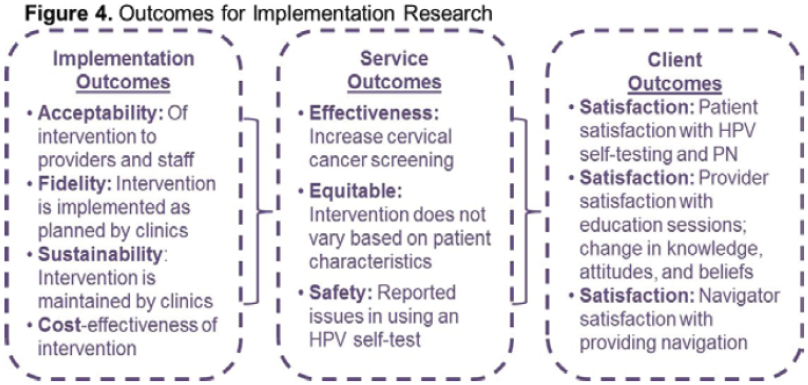
Medical Record Review. For all women in Groups 1 and 2, we will confirm whether women received a Pap test during Months 25-36. For women in Groups 1 and 2 who tested positive for a high-risk HPV type based on their self-test, we will confirm: a) any follow-up appointment attended; b) any follow-up care received; and c) any cervical abnormalities (precancerous and cancerous) found during this follow-up care.

Patient Satisfaction Survey. The survey and methodology will be identical to those described in **Section C.6.c.** We will send a survey to all women in Groups 1 and 2 who were sent an HPV self-test in Months 25-36.

C.8. Year 4 Activities

C.8.a. Group 1: Sustainability Phase (Months 37-48). Group 1 clinics/health systems will move to the Sustainability Phase in Months 37-48. During this phase, the project team will step back and allow the clinics/health systems to fully lead intervention implementation, including all PN activities. The project team will only be consulted if issues arise that the clinics/health systems cannot resolve. This phase will allow us to examine intervention sustainability in real world settings. In this phase, 100 eligible women (20 per Group 1 health system) who remain unscreened/underscreened will be randomly sampled from the sampling frame and sent an HPV self-test.

Figure 4. Outcomes for Implementation Research



C.8.b. Group 2: Clinic Implementation (Months 37-48). The Clinic Implementation Phase will occur in Group 2 health systems in Months 37-48. This phase will be identical to the Clinic Implementation Phase for Group 1 (see **Section C.7.a.**). In this phase, 100 eligible women (20 per Group 2 health system) who remain unscreened/underscreened will be randomly sampled from the sampling frame and sent an HPV self-test.

C.9. Year 5 Activities.

C.9.a. Groups 1 and 2: Data Collection (Months 49-50). Data collection at Months 49-50 will include: a medical record review and a patient satisfaction survey. The methodology for these activities will be similar to data collection at Month 36 (see **Section C.7.c.**). The **SDCC** will also conduct in-depth interviews with the PNs (both OSU-based and health system-based) to assess their experiences/satisfaction with the PN process.

C.9.b. Analyses and Evaluation (Months 51-60). We will conduct analyses/evaluation of each outcome type recommended for implementation research:[41] implementation, service, and client outcomes (**Figure 4**).

C.9.c. Aim 1 (Service Outcomes). Service outcomes will include intervention effectiveness, equitableness, and safety (**Table 2**). We hypothesize the multilevel intervention will increase cervical cancer screening and that PN will increase HPV self-test return among women who do not initially return their self-test (Hypothesis 1a). We think PN will increase HPV self-test return among these initial non-returners given PN's positive effect on health outcomes in past studies.[56-60] Lastly, we hypothesize the increase in screening will be similar across patient characteristics (i.e., equitableness)(Hypothesis 1b).

Table 2. Service Outcomes and Data Sources

Outcome	Measure	Level	Data Source
Effectiveness	Cervical cancer screening	Patient-level	HPV self-test data and medical records
Equitableness	Demographic and health-related characteristics	Patient-level	Medical records
Safety	Reported issues in using an HPV self-test	Patient-level	Patient satisfaction surveys

Measures. The patient-level effectiveness outcome and primary outcome for **Project 3** will be whether or not women get "screened" during the project. There are three ways a woman can be considered "screened." The first is to return their HPV self-test and test negative for high-risk HPV types. The second is to return their HPV self-test, test positive for high-risk HPV types, and then attend a follow-up appointment at their health system. We are requiring these women to attend a follow-up appointment to be considered "screened" given their HPV infection. The third way is to receive a clinic-based screening test (e.g., Pap test), regardless of HPV self-test return status. This will most likely apply to women in Group 2 health systems during the Usual Care Continued phase (see **Section C.6.b.**), but past studies have shown that some women will get a Pap test after receiving an HPV self-test in the mail (without using the self-test).[15] All women not meeting one of these three criteria will

be considered "unscreened." To determine this outcome, we will examine HPV self-test return status, HPV testing results, and EHR data (follow-up appointment attendance, Pap testing, etc.) for each sampled woman.

Among women who return their HPV self-test, we will examine the timing of device return and categorize each as returned within one month of distribution (i.e., prior to any PN) or after one month of distribution (i.e., following PN). We will also examine HPV testing results (positive or negative for high-risk HPV types) and collect data from EHR on the number of normal and abnormal Pap tests received by each woman and any cervical abnormalities found (i.e., low-grade squamous intraepithelial lesion, etc.).

To assess if the intervention is equitable (**Figure 4**), we will examine patient characteristics via data from EHR (collected by the **SDCC**). This will include age, rurality (based on women's home address and rural-urban commuting area [RUCA] codes[126]), and when their most recent cervical cancer screening test prior to project entry occurred (if ever). Lastly, to assess safety, we will examine data from the patient satisfaction survey to see if women report any issues about using their HPV self-test. We do not anticipate such reports to be common, as the Evalyn® Brush has been used safely and easily by women in several research studies.[25,120-122]

Sample Size. The project's total sample size will be 1180 women across Years 2-4 (590 women from Group 1 clinics/health systems and 590 from Group 2 clinics/health systems). This includes 780 women from Year 2 (390 women from Group 1 clinics/health systems and 390 from Group 2 clinics/health systems) who will be examined in primary analyses for **Aim 1**. These sample sizes are feasible given the expected sampling frame size (see **Table 1**) and will give us at least 90% power for the below analyses.[127] The power calculation assumed a two-sided alpha=0.05, an intraclass correlation coefficient<0.017 (based on our pilot study), and the below outcome occurrences. Dr. **Shoben** will lead all quantitative analyses.

Primary Analyses. Primary analyses will examine the proportion of women from Year 2 screened, as defined above, at 24 months and use an intent-to-treat approach. To compare treatment groups (Group 1 vs. Group 2), we will use generalized linear mixed models (GLMMs) to account for the correlation between women from the same clinic,[128] though we expect cluster effects to be low (i.e., intraclass correlation coefficient<0.017 based on our pilot study). Since our outcome is binary, we will use a logit link to estimate odds ratios for the GLMMs. We expect that 30% of women from Group 1 clinics/health systems and 10% of women in Group 2 clinics/health systems will be categorized as screened (based on large, international HPV self-testing studies[6,7,11,12,129]). The primary model will be unadjusted, but we will conduct sensitivity analysis that include potential confounders due to imbalance from randomization (p<0.10 when comparing groups). Results will determine the effectiveness of the multilevel intervention in increasing cervical cancer screening compared to usual care.

Secondary Analyses. We will conduct several secondary analyses for **Aim 1**. First, we will examine the proportion of HPV self-test returners who returned their self-test following receipt of PN. Results will provide valuable data on the added benefit of PN on HPV self-test return. Second, we will use GLMMs with a logit link to examine potential differences in the proportion of women screened across project years within each treatment group (i.e., comparing Years 2, 3, and 4 for Group 1). These analyses will include all 1180 women. Results will determine how screening rates changed over time, which will be key in assessing whether the intervention maintained its initial success during the Clinic Implementation and Sustainability Phases. Third, to assess if the intervention was equitable, we will use GLMMs with a logit link to examine if patient characteristics (as described above) are associated with women being categorized as "screened". Fourth, to assess safety, we will descriptively examine women's reports of any issues experienced when using their HPV self-test. Lastly, we will descriptively examine the prevalence of high-risk HPV infection, abnormal Pap tests, and cervical abnormalities among women (as described above).

C.9.d. Aim 2 (Implementation Outcomes). Implementation outcomes will examine the acceptability, fidelity, sustainability, and cost-effectiveness of the intervention. We hypothesize that participating clinics/health systems will report high levels of intervention acceptability, and the intervention will be implemented with high fidelity and sustained by the clinics/health systems (Hypothesis 2a). We also hypothesize that the intervention will be a cost-effective strategy for increasing cervical cancer screening (Hypothesis 2b).

Acceptability. Acceptability will examine whether clinic personnel, including the project "champions", find the intervention to be acceptable. This will be assessed via semi-structured interviews (led by the **SDCC**) and end-of-project surveys with health system personnel (as described in the Program Evaluation section for the **BEC**). We will descriptively examine the resulting data to determine acceptability.

Fidelity. We will use several strategies to ensure and examine fidelity (i.e., the degree to which the multilevel intervention is conducted according to protocol). At the patient-level, we will work with the **SDCC** to develop an electronic tracking system to track all mailings (e.g., self-test distribution) and other data collection activities. At

the provider level, we will conduct the provider education sessions using a standardized PowerPoint presentation. Data during the sessions will be collected using a checklist that includes key observations related to fidelity (e.g. the presence of participants during entire session). At the system-level, we will examine the fidelity of the PN calls by descriptively examining data from the PN encounter forms (see **Section C.6.a.**) and through quality assurance of PN calls. PN calls will be recorded for quality assurance, and 10% of calls will be randomly selected and evaluated on an ongoing basis. During PN evaluation, we will use a checklist of topics and PN activities that should have occurred during the call. Issues that emerge during evaluation will be discussed with the PNs. We will descriptively examine PN encounter form data regarding PN activities performed, concerns/questions raised by women, and actions taken by PNs in response to these issues.

Sustainability. We will examine the screening rate among Group 1 clinics/health systems in Months 37-48 (Sustainability Phase), as well as fidelity outcomes (see previous paragraph) during this time. As a reminder, Group 1 clinics/health systems will fully lead intervention implementation, including PN, during this phase.

Cost-effectiveness. Dr. **Xu** (**BEC**) will lead the cost-effectiveness analyses, which will be from a payer perspective. We will first conduct a cost identification analysis. We will carefully consider all costs of the intervention, including those for HPV self-test devices, PN training/implementation, staff, mailing costs, and administrative costs. PN implementation data will be based heavily on information collected on the PN encounter forms (see **Section C.6.a.**). We will value the costs of each item using standard costs, and we will carefully distinguish costs related to scientific research from those of the interventions themselves. We will only include the intervention costs in our cost-effectiveness analyses. We will then aggregate the measures of costs and intervention effectiveness and calculate incremental cost-effectiveness ratios (ICER). The ICER measures the cost at which an added unit of outcome can be achieved by the intervention. Thus, the ICER will represent the marginal cost of an additional patient screened for cervical cancer due to the intervention. We will also conduct sensitivity analyses. For example, we will perform analyses using 10-year age intervals since women from different age groups may have varied probabilities of the outcome. We will use the bootstrap method to estimate standard errors and CIs for cost-effectiveness measures (i.e., ICERs) using TreeAge Pro software.

C.9.e. Aim 3 (Client Outcomes). For client outcomes, we will determine the satisfaction with the multilevel intervention at the patient-, provider-, and system-levels (**Table 3**).

Table 3. Client Outcomes and Data Sources

Outcome	Measure	Level	Data Source
Satisfaction	Satisfaction with HPV self-testing and PN	Patient-level	Patient satisfaction survey
Satisfaction	Satisfaction with provider education sessions and change in knowledge, attitudes, and beliefs	Provider-level	Surveys from provider education sessions
Satisfaction	Satisfaction with providing PN to women	System-level	In-depth interviews with patient navigators

Patient-Level. We hypothesize that women will report high levels of satisfaction with HPV self-testing (if HPV self-test is returned) and PN (if received) (Hypothesis 3a). Patient-level satisfaction data will come from the patient satisfaction surveys sent to women. We will examine satisfaction with both the HPV self-test device (appearance, usability, return process, etc.) and its instructions (appearance, readability, etc.). We will use items from our past HPV self-test work to assess these constructs.[24,25] For women who received PN, we will also assess their satisfaction with PN using items from our past PN research.[130] All satisfaction items will use 5-point Likert response scales. We will consider means of 4.0 and greater to indicate high levels of satisfaction. We expect about 80% of women who were sent an HPV self-test to return a completed patient satisfaction survey (based on mailed survey return in our pilot study[25]), resulting in a total of 632 returned surveys. This sample size will allow us to characterize means +/-0.08 standard deviation units in descriptive analyses.

Provider-Level. We hypothesize that healthcare providers and staff will report high levels of satisfaction with the provider education sessions and have improved knowledge, attitudes, and beliefs about HPV self-testing (Hypothesis 3b). Provider-level satisfaction data will come from the post-test surveys from provider education sessions (see **Section C.5.b.**). We will assess provider satisfaction using items from our past work evaluating provider-level interventions.[75,87] All satisfaction items will use 5-point Likert response scales. We will consider means of 4.0 and greater to indicate high satisfaction. With an expected 503 attendees at provider education sessions, we will be able to characterize means +/-0.11 standard deviation units in descriptive analyses.

To examine changes in knowledge, attitudes, and beliefs about HPV self-testing, we will analyze pre- and post-test survey data from provider education sessions. Knowledge will be assessed with six true/false items. Attitude/belief items will assess constructs (perceived benefits of self-testing, self-efficacy to talk with patients about self-testing, etc.) using 5-point Likert response scales. Survey items will be based on items from our pilot study.[75] We will compare pre- and post- data using GLMMs with an identity link (i.e., a linear mixed model) to

account for the correlation between providers at the same clinic,[128] though we expect an intraclass correlation coefficient<0.017 based on our pilot study. Based on pilot study results,[75] we expect the mean number of correct knowledge items will increase by about 1.2 items from pre- to post-test. Similarly, we expect means for attitude/belief items to increase by about 0.4 units (on a 5-point scale) from pre- to post-test. With an expected 503 attendees total at provider education sessions, we will have at least 80% power to detect such differences.

System-Level. At the system-level, we hypothesize that PNs will report high levels of satisfaction with providing PN to women. Data will come from the in-depth interviews with the PNs (both OSU-based and health system-based) about their experiences and satisfaction with the PN process. These interviews will be led by the **SDCC**. Digital recordings from the interviews will be transcribed verbatim, reviewed for accuracy, and entered into qualitative software. To examine satisfaction, two coders will independently code the qualitative data using thematic content analysis. Inter-coder reliability will be assessed.

C.10. Scientific Rigor/Reproducibility. Rigor will be maximized through: input from an External Scientific Advisory Board (ESAB) and Community Advisory Board; provider education sessions; use of a delayed intervention trial design; random sampling of patients from the sampling frame; training and use of experienced PNs; use of existing measures on study surveys; use of an HPV self-test device that has been used extensively;[25,120-122] use of logistics patterned heavily after those from our previous pilot study; and confirmation of several project outcomes through medical records. Strategies to promote reproducibility will include: data sharing via request (as appropriate); publication of results; and presentation at conferences (see Resource Sharing Plans).

C.11. Relevant Biological Variables. The patient-level component will target only females (since the focus is cervical cancer screening) who are ages 30-64 (since draft guidelines from the USPSTF recommend HPV testing alone every 5 years for women in this age range[49]). Provider education sessions will include males and females of all ages, provided they are healthcare providers or staff at a participating health system.

C.12. Potential Challenges/Strategies. Recruitment: We will have a large sampling frame of women to help ensure we reach our desired sample size. Outcome Ascertainment: We should have complete outcome data for all women on HPV self-test return status and HPV testing results, and we will confirm additional outcomes (e.g., attendance at follow-up appointments) through medical records. Some women may seek care at an outside health system, though all women will be active patients at a participating clinic/health system. Contamination: We do not expect contamination given that randomization will occur at the health system level and that all clinics will receive the same multilevel intervention. Analyses will also account for any correlations among patients and providers. Generalizability: We will recruit from health systems that serve women in the Appalachian region of four states. Future efforts will expand to other geographic areas.

C.13. Project Timeline (Table 4). The timeline is based on our past intervention work.[59,90,92,93,97,98,112]

Table 4. Project Timeline

Year 1	Q1	Q2	Q3	Q4
PN training / Provider Education	●	●		
Baseline Rates / Identify Patients			●	●
Pap Test Reminders / Randomize			●	●
Monthly Team Meetings	●	●	●	●
Year 2				
Group 1: Active Intervention	●	●	●	●
Group 2: Usual Care Continued	●	●	●	●
Data Collection and Management				●
Monthly Team Meetings	●	●	●	●
Year 3				
Group 1: Clinic Implementation	●	●	●	●
Group 2: Delayed Intervention	●	●	●	●
Data Collection and Management				●
Monthly Team Meetings	●	●	●	●
Year 4				
Group 1: Clinic Sustainability	●	●	●	●
Group 2: Clinic Implementation	●	●	●	●
Monthly Team Meetings	●	●	●	●
Year 5				
Data Collection and Management	●			
Analyses and Evaluation	●	●	●	●
Monthly Team Meetings	●	●	●	●

C.14. Relevance to Program Theme. The Program's theme is to test effective interventions that can be implemented in health systems in Appalachia to reduce cervical cancer. Our project will test a multilevel intervention to improve cervical cancer screening among unscreened/underscreened women. This is central to the Program's theme since most cervical cancers occur among such women.[1,2] Our intervention will have the potential for wide dissemination, and it can guide future HPV self-testing programs and screening policies.

C.15. Interaction with Program Components. Our project will be part of an integrated cervical cancer prevention program and interact with all project cores. We will work with the **SDCC** for the development and implementation of surveys and to ensure the use of common data measures. The **BEC** will lead data analyses and evaluation of the intervention. The **ICC** will help facilitate the implementation of this project through PN training and gather the input of the community and clinical partners for all aspects of the project. The **Administrative Core** will oversee the project operations (including budget) and facilitate the ESAB and the Data and Safety Monitoring Board.

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PROJECT SUMMARY– INTERVENTION AND CONSORTIUM CORE (ICC)

The purpose of the Intervention and Consortium Core (ICC) is to serve as the central hub to provide expertise on: 1) implementation of the research interventions; and 2) organization, development, and fostering of relationships using Community-Based Participatory Research (CBPR) and the Science of Team Science (SciTS) principles/methodologies, ultimately bringing together a transdisciplinary team of community members and health disparities researchers from a number of disciplines to address the goals of this Program Project. Longstanding partnerships between The Ohio State University, West Virginia University, University of Kentucky, and the University of Virginia will serve as the cornerstone of the Program Project, along with their respective clinical and community partners. In addition, the interventions to be tested in the three research projects have been developed and piloted with community partners and, thus, are designed to be culturally appropriate. Building upon the successful relationships established among the Appalachian community, provider networks, public health entities, community groups, and the Appalachia Community Cancer Network (ACCN) during previous projects, this Core proposes the following specific aims: **1)** Engage community based organizations, stakeholders, regional health care providers, public health entities, and policy makers across the lifespan of the Program Project from planning through evaluation; **2)** Participate in the conduct of Multi-Level Community and Clinic Assessments, engaging community, clinic, and academic partners in the process to inform and develop plans for the implementation of the comprehensive cervical cancer prevention program in the participating clinics; **3**) Collaborate with research project investigators and community members to review, pilot test, refine and implement the multi-level interventions targeting the clinic, provider and patients to be utilized in the three research projects at clinic sites; and **4**) Train relevant clinic and project staff on the implementation of the interventions for all three research projects, including the Patient Navigators, and provide ongoing technical assistance and quality assurance to maintain consistency and fidelity of protocol delivery. Drs. **Stephenie Kennedy** and **Electra Paskett** will lead this Core, with support of Drs. Vandeusen and Ostrof (proposed consultant). This Core will lead community engagement (through the Community Advisory Board), clinic interactions (through a Clinic Consortium), and intervention refinement, implementation and sustainability for this Program Project. The ICC will include the Program's two conceptual models which underlie the research – the Multi-Level Model for Addressing Health Disparities (for intervention and assessment) and the Proctor Implementation Framework (for implementation and evaluation of the interventions) in all activities. Evaluation of the Core activities, specifically related to implementation and community engagement, will be conducted by the Biostatistics and Evaluation Core (BEC).

PROJECT NARRATIVE – CORE 1 (ICC)

This core will help refine the interventions to be tested in the integrated cervical cancer prevention program and also facilitate input from the community and help implement the program into participating health systems.

SPECIFIC AIMS

The purpose of the **Intervention and Consortium Core** (**ICC**) is to serve as the central hub to provide expertise on: 1) implementation of the research interventions; and 2) organization, development, and fostering of relationships using Community-Based Participatory Research (CBPR) and the Science of Team Science (SciTS) principles/methodologies, ultimately bringing together a transdisciplinary team of community members and health disparities researchers from a number of disciplines to address the goals of this Program Project. Longstanding partnerships between The Ohio State University (OSU), West Virginia University (WVU), University of Kentucky (UK), and the University of Virginia UVA) will serve as the cornerstone of the Project, along with their respective clinical and community partners. In addition, the interventions to be tested in the three research projects have been developed and piloted with community partners and, thus, are designed to be culturally appropriate. Building upon the successful relationships established among the Appalachian community, provider networks, public health entities, community groups, and the Appalachia Community Cancer Network (ACCN) during previous projects, this Core proposes the following specific aims:

Aim 1. Engage community based organizations, stakeholders, regional health care providers, public health entities, and policy makers across the lifespan of the Program Project from planning through evaluation.
Aim 2. Participate in the conduct of Multi-Level Community and Clinic Assessments, engaging community, clinic, and academic partners in the process to inform and develop plans for the implementation of the comprehensive cervical cancer prevention program in the clinics of the participating health systems.
Aim 3. Collaborate with research project investigators and community members to review, pilot test, refine and implement the multi-level interventions targeting the clinic, provider and patients to be utilized in the three research projects at clinic sites.
Aim 4. Train relevant clinic and project staff on the implementation of the interventions for all three research projects, including the Patient Navigators (PN), and provide ongoing technical assistance and quality assurance to maintain consistency and fidelity of protocol delivery.

Drs. **Stephenie Kennedy** and **Electra Paskett** will lead this Core, with support of Drs. **Vandeusen** and Ostroff (Consultant). They both have extensive experience conducting CBPR in Appalachian communities to address disparities in cancer incidence and mortality. This Core will lead community engagement (through the Community Advisory Board [CAB]), clinic interactions (through a Clinic Consortium), and intervention design for this Program Project. Housing these three tasks in a Core allows for standardization in our approach to engagement and intervention delivery across diverse regions and clinical sites. The **ICC** will include the Program's two conceptual models which underlie the research – the Multi-Level Model for Addressing Health Disparities (for intervention and assessment) and the Proctor Implementation Framework (for implementation and evaluation of the interventions) in all activities. Evaluation of the Core activities, specifically related to implementation and community engagement, will be conducted by the **Biostatistics and Evaluation Core** (**BEC**).

IMPACT: The **ICC** will foster the link between the researchers and the community to refine, implement and evaluate the components of this Program Project. Moreover, because of the use of CBPR, the interventions will be of high quality and external validity, and are feasible and readily incorporated into routine practice. Sustainability of the integrated comprehensive cervical cancer program relies on the accomplishments of this Core.

RESEARCH STRATEGY

3. CORE SERVICE STRATEGY

A. Core Leadership and Membership.

This Core will be co-lead by Drs. **Kennedy** and **Paskett**, thus facilitating mentoring, with support from Dr. **Vandeusen**, who has experience as Medical Director of an Appalachian health system.

Stephenie K. Kennedy, EdD serves as an Associate Center Director at the WVU Cancer Institute (WVUCI) and directs the office of Cancer Prevention and Control, which is responsible for education, outreach, and population-based research for the Cancer Institute. In this capacity she has served as the WVU Principal Investigator for the ACCN, WV Breast and Cervical Cancer Screening Program (education and collaboration components), and WV Program to Increase Colorectal Cancer Screening. She is a co-lead of the Community Engagement Core for WV Clinical and Translational Science Institute. She represents the WVUCI on the Steering Committee of the statewide Comprehensive Cancer Coalition and serves as a key stakeholder for the WV Immunization Network. Dr. **Kennedy** is a native Appalachian who understands the culture and the importance of building relationships. Through these experiences building and managing consortia of academic, clinical, and community-based partners across the state and region, she has developed the skills and expertise needed to lead the first two aims of this Core.

Electra D. Paskett, PhD has directed the Center for Population Health and Health Disparities (CPHHD) at OSU (P50CA015632) for the last 12 years, which focused on understanding the reasons for cervical cancer disparities in Appalachian Ohio. She also chaired the national CPHHD Steering Committee from 2005 – 2006. She is Associate Director for Population Sciences and Leader of the Cancer Control Program for the OSU Comprehensive Cancer Center (OSUCCC) and leads its Center for Cancer Health Equity. Dr. **Paskett** has conducted several intervention studies in Appalachia, testing behavioral interventions developed with CBPR principles in conjunction with community partners[1-4]. She is also well known for her research testing the effectiveness of PNs to assist underserved populations in complying with recommended tests[5]. Thus, Dr. **Paskett** is well qualified to lead Aims 3 and 4 of this Core.

Jeff Vandeusen, MD, formerly Medical Director of Adena Cancer Center in Appalachian Ohio, and now Associate Director of Education in the OSUCCC and faculty in the College of Medicine at OSU, will be the Core Medical Director and assist with engaging and implementing the integrated cervical cancer prevention program in the clinics, as well as help to ensure sustainability and dissemination of the prevention program. Dr. **Vandeusen** will foster relationships with clinic partners, as well as navigate specific nuances in the integrated cervical cancer prevention program, such as billing for cessation services. He will be an integral part of the Clinic Consortium.

Jamie Ostroff, PhD, will serve as a consultant for the entire Program Project, including the **ICC**, to provide her expertise in Implementation Science, especially as it relates to implementing and sustaining prevention interventions in clinical settings, including billing for prevention services and clinic retention. Her research focuses on developing and evaluating innovative methods for treating tobacco dependence in medical settings. She currently is the PI of a large study using Implementation Science methods to test a clinic-based smoking cessation program in dental practices in New York City. This experience will be invaluable to her role in this Program Project. (See Budget Justification of the **Administrative Core** (**AC**) for more details).

Jessica Burris, PhD is a clinical psychologist who has expertise in cancer prevention and control science, with a focus on tobacco use. Drs. **Burris** (UK) and **Roger Anderson** (UVA) will be their respective state's liaison with the clinics and community members participating in this Program.

Regional staff with expertise in collaboration, partnering, and CBPR, as well as knowledge of the Appalachian population and key chronic disease partners, will also be part of the **ICC**. Darla Fickle, MA, Program Director for the **ICC**, has more than 20 years of experience establishing collaborative partnerships in the Appalachian Ohio region with a special emphasis on planning, implementing, and evaluating cancer control programs and conducting CBPR projects. Ms. Fickle was born and raised in Appalachia Ohio. Mary Ellen Conn, MS, has over 20 years of experience working with community-based and clinical partners on cancer prevention and control programs. She currently serves as the Program Director for the WV Program to Increase Colorectal Cancer Screening and leads a quality improvement initiative with 34 primary care clinics to implement evidence-based interventions to increase screening. Ms. Conn is a native West Virginian with an understanding of the culture and health issues specific to Appalachian residents. Shawna Deems, LSW, will oversee the PN intervention piece. Ms. Deems, Program Manager of OSU's Wayfinder – Patient Navigation Program, is a member of the Academy of Oncology Nurse & Patient Navigators (AONN) and has collaborated with AONN to develop a Patient Navigation Certification Exam and a Patient Navigation Code of Ethics. Through integrated clinic and professional collaboration, she has developed a comprehensive Wayfinder – Patient Navigation Training which has been adapted to train PNs at affiliate and regional health centers, as well as multiple OSU sites.

B. ACTIVITIES AND FUNCTIONS OF CORE

B.1. ***Aim 1:*** *Engage community based organizations, stakeholders, regional health care providers, public health entities, and policy makers across the lifespan of the Program Project from planning through evaluation.*

B.1.a. Community Partners in Research

B.1a.1. Community-Based Participatory Research (CBPR). The members of community-based organizations, coalitions, medical practices, and the public health community are uniquely positioned to understand the culture and health needs in their local communities. Over the past 12 years, the leaders of this Core have led outreach/educational activities and research projects with over 50 community-based coalitions, clinics, and organizations[6-7] to address disparities in Appalachia (**See Section C1.b.**). Using the vast experience the team has in engaging and working with Appalachian communities, the **ICC** will work closely with community coalitions, the CAB and Clinic Consortium to conduct a thorough community and clinic assessment and then test, evaluate, and disseminate the proposed interventions that are expected to reduce cervical cancer disparities. The transdisciplinary team of researchers will use an integrated approach to conduct three prevention-based research projects in partnership with the community to address health disparities in cervical cancer risks in rural Appalachia: smoking cessation, HPV vaccination, and cervical cancer screening. This collaboration will be guided by the following CBPR principles: 1) acknowledging the community as a unit of identity; 2) building on strengths and resources within the community; 3) facilitating a collaborative, equitable partnership in all phases of research; 4) co-learning and capacity building among all partners; 5) integrating and achieving a balance between knowledge generation and intervention for the mutual benefit of all partners; 6) focusing on local relevance of public health problems; 7) involving systems development using a cyclical and iterative process; 8) disseminating results to partners and involving them in the dissemination of results; and 9) establishing a long-term process and commitment to sustainability[8].

B.1.a.2. Community Advisory Board (CAB). We will utilize a CAB to ensure that all assessment, research, and translation activities, as well as priorities, reflect community-identified needs, interests, and values. Each participating academic institution will send two representatives to comprise the CAB, which will guide the prioritization and development of consortium-wide efforts in relation to the goals of this Program Project. CAB members will provide input on factors relating to issues of access and barriers, designs of the research projects and programs, and methods of assuring acceptance in the community. The CAB will review aspects of the projects and programs as they are implemented in the community and provide feedback to the study investigators and staff. The members will represent community-based cancer coalitions, local clinics/health departments, cancer survivors, health care providers, and local community agencies. We also include one policy maker and one representative from the payer perspective (see Letters of Support from Rep David Leland and Todd White from Aetna). Three CAB members will serve on the Program Project Steering Committee (SC) (see **AC**) as key advisory members. These individuals volunteered to participate in this role during the planning of the Program Project application. James Harris serves as the Executive Director of Health Access, a free clinic in WV reaching the medically underserved. He has a unique perspective as a clinic administrator, coalition member/leader, and a life-long Appalachian. Deanna Tribe, Associate Professor Emerita, is a retired Community Development Specialist with OSU Extension. She conducted training sessions on Appalachian culture, as well as worked with families and communities in the region. A native of Vinton County in Appalachia Ohio, she has resided most of her life in her home county and served on the OSU CAB. Fran Feltner, DNP, is Director of the Center of Excellence in Rural Health in Hazard, KY. Dr. Feltner is a native of Appalachian Kentucky and has a long history of community service and advocacy. She has experience with clinic administration and has served on UK CAB.

B.1.a.3. Healthcare Partners listed in **Table 1** below will form the **Clinic Consortium**, responsible for implementation of the program, trouble shooting, sharing best practices, and sustainability of the program. These clinics were recruited based on previous experience and the advice of community advisors. We will maintain them through active engagement in the consortium and provision of adequate technical assistance and support. If a clinic withdraws, then the CAB and the PI from the affected state will work together to identity a suitable replacement. Alternate clinics have been identified in each state in case this occurs. Each clinic will also select a clinic champion upon the start of the project. We did not select this person now as clinics: 1) need to be assured that program will indeed start; 2) be able to select their own champion; and 3) select someone who is currently on staff and willing. All clinics agreed to name a clinic champion and this process of selection. The **ICC** will serve as an intermediary to facilitate interactions and foster productive relationships with healthcare partners participating in the research projects and assist study investigators in implementing principles of CBPR[9]. The Consortium will be led by Drs. **Kennedy** and **Vandeusen** and a representative from each health system/clinic (this person could be the clinic champion). Two Consortium members (on an annual rotating basis) will serve on the Program SC (see the **AC**) to provide input to the overall management of the Program. The Consortium

members will meet quarterly by phone and discuss aspects of the projects and implementation of the Program at the clinics. Sharing of best practices and solutions to challenges will be encouraged. Health systems/clinics

Table 1. Healthcare Partners	# of Clinics	# of Providers	Patients by Age Group									County
			Girls			Boys			Men	Women		
			11-12	13	14-17	11-12	13	14-17	18-26	18-26	30-65	
Kentucky												
Big Sandy	5	57	353	144	697	373	178	546	927	1746	5575	Johnson, Martin, Pike, Floyd, Magoffin
Juniper Health	4	32	211	96	375	239	118	386	466	422	1767	Morgan, Lee, Wolf, Breathitt
Ohio												
Muskingum Valley Health Centers	2	85	180	69	347	173	72	295	377	1117	5999	Muskingum, Morgan
CAO Family Medical Centers	2	24	149	67	209	158	73	238	204	387	1691	Lawrence
Ohio Hills Health Services	4	35	36	20	111	49	24	100	86	210	1177	Belmont, Harrison, Monroe
HealthSource of Ohio	1	14	127	66	252	160	77	299	217	212	1217	Brown
Virginia												
Southwest VA Community Health System & Stone Mountain Health Services	4	87	141	70	399	185	102	252	703	794	4824	Wise, Russell, Smyth, Washington
The Health Wagon	1	15	150	130	130	150	13	130	217	689	3810	Lee, Scott, Wise, Dickenson, Buchanan, Russell
West Virginia												
Family Care Health Centers	5	119	695	379	1627	686	392	1338	1085	3609	11897	Putnam, Boone, Kanawha
Community Care Health Centers	4	161	765	369	1517	670	367	1354	1121	2424	10005	Upshur, Harrison, Pocahontas

will receive an annual stipend to defray some the administrative costs associated with participating in this Program (see Budget Justification of **ICC).** Core Leads will communicate regularly to the SC regarding aspects of the Consortium's meetings and issues clinics report.

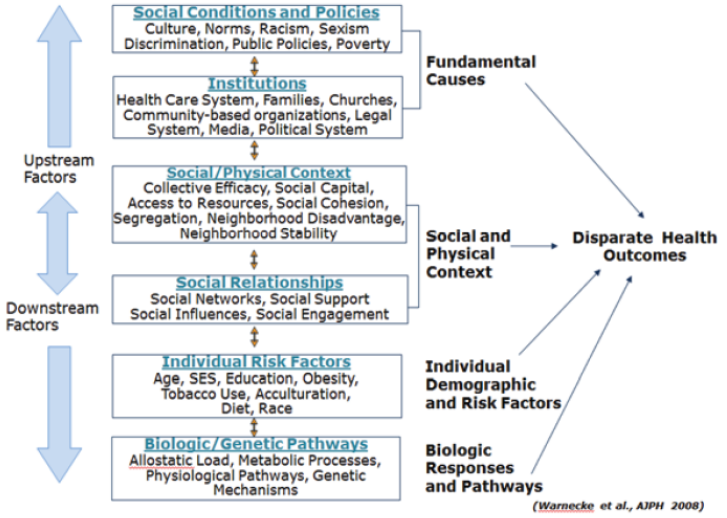
B.1.b. Relevant Expertise and Participation with Community Members. There are currently over 50 coalitions and key partners in the 4 Appalachian states participating in this Program. These partnerships and coalitions represent a mature network built on trust, the result of many years of careful assessment, sharing of time and resources, identification of lay leaders and local resources, and capacity building through training and education. In preparation for this application, Core and Project Leaders conducted numerous meetings with existing and new potential community partners. Community coalitions have provided letters of support for this Program Project. Interactions with the coalitions will continue during the upcoming project period, i.e., support of local coalition meetings and activities, and community interactions and technical assistance will be coordinated by regional members of the **ICC.**

B.1.c. Implementation of Prevention Interventions in Appalachian Clinics. The West Virginia Program to Increase Colorectal Cancer Screening (WV PICCS) **(Kennedy-**Pl) aims to increase colorectal cancer screening to the national goal of 80% or at least 10% over a clinic baseline rate. The Program focus is changing protocols within primary care practices to increase referral and completion of screening. Clinic sites complete assessments and a systematic review of their current use of electronic health records and identification of improvements, participate in provider assessment/feedback activities, and implement evidence-based interventions (EBls) such as client reminders, provider reminder/recall systems, or reduction of structural barriers. Supportive activities of patient navigation and small media are used to enhance the EBls. The implementation phase is followed by a sustainability phase with reduced technical support. This experience will guide the activities of the **ICC** in implementation of interventions and sustainability.

B.1.d. Theoretical Framework of the Program Project. The **ICC** will address the theme of the Program Project, reducing cervical cancer disparities in Appalachia, by testing the implementation of a practice-based prevention program consisting of three interventions addressing three important factors related to cervical cancer in Appalachia -smoking cessation, HPV vaccination, and HPV self-testing/Pap testing-by using a collaborative participatory approach, including key stakeholders that will link the researchers with the community-both clinics and lay members. Integral to the approach of the **ICC** is that the barriers to cervical cancer prevention in Appalachia are a function of pervasive individual-level and community characteristics related to cervical cancer (e.g., poor social and economic characteristics of communities, low supply of health care providers and facilities for preventive services, and local providers' attitudes and practice patterns) as described by the Multi_Level.Model.of.Population.Health.**(Figure 1**)1, which will guide the development and assessment of the interventions (see **Overview** Figure 2 for multilevel model related to cervical cancer in Appalachia). In addition, the **ICC** is guided by the Implementation Conceptual Framework of Proctor et al.10 **(Figure 2)** to assess program outcomes, at the individual project level as well as for the overall Program Project.

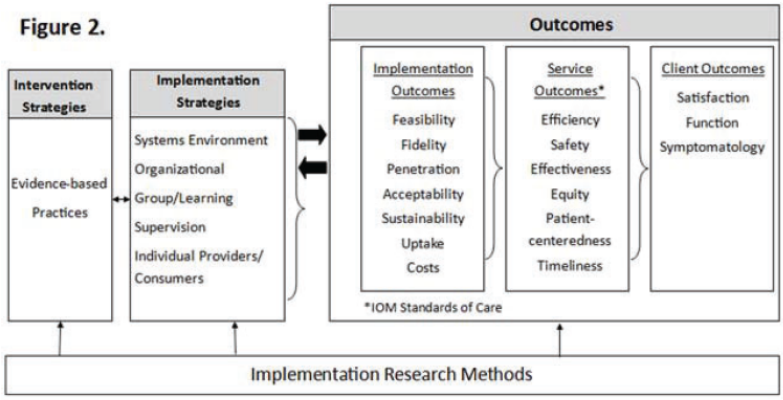
B.2. *Aim 2.* *Participate in the conduct of Multi-Level Community and Clinic Assessments, engaging community, clinic, and academic partners in the process to inform and develop plans for the implementation of the comprehensive cervical cancer prevention program in the implementation of the comprehensive cervical cancer prevention program in the participating health systems (referred to as clinics).*

Figure 1. Model for Analysis of Population Health and Health Disparities



In Year 1, the **ICC** will lead a Community and Clinic Assessment in all counties and clinics participating in the Program Project. All efforts in each clinic will be done in conjunction with the clinic champion (see **Section B.1.a.3**). The purpose of this Community and Clinic Assessment is two-fold: 1) to obtain information about the clinics that is needed to implement the proposed integrated cervical cancer prevention program and 2) identify county and other local resources that can assist in ensuring that the intervention is successfully implemented and patients are adherent to the intervention programs. The **Clinic Assessment** will gather information on: clinic hours and personnel (staff and providers, including roles), patient population (description as well as patient flow, and proportion of patients needing screening, vaccination, and smoking cessation), physical structure of the clinic building (e.g. number of exam rooms, waiting rooms, etc.), Electronic Health Record (EHR) system (type and capabilities as well as staff utilization), educational materials and posters, referral patterns for patients (other providers and assistance programs), billing systems and quality assurance activities. The usual schedule for in-service and clinic meetings will also be obtained. We will assess the organizational level constructs that influence implementation outcomes as described by Damschroder in the Consolidated Framework for Implementation Research[11], such as contextual factors that influence implementation (e.g., leadership engagement, organizational readiness, implementation climate, culture, patient needs and resources, etc.). The assessment will also include qualitative interviews with ten patients and two providers per clinic. The **Community Assessment** will be facilitated by working with the Clinic Consortium partners, clinic champions, as well as the CAB and local coalition partners. To identify community resources, staff will compile a complete list of community organizations and services that offer tobacco cessation resources, the cervical cancer screening process, and services that can facilitate HPV vaccination. Information collected during the Assessment phase will facilitate the development of materials to implement the integrated cervical cancer prevention program (see **Section B.3.c**).

Figure 2.



B.3. *Aim 3.* *Collaborate with research project investigators and community members to review, pilot test, refine, and implement the multi-level interventions targeting the clinic, provider and patients to be utilized.*

B.3.a. Intervention Refinement. The **ICC** will work with the investigators of each of project to provide input during intervention refinement. All intervention materials will be reviewed through the use of focus groups with up to 24 community members (contacted by the CAB and our coalition partners) and reviewed by content experts to ensure acceptability and health literacy needs of the target population. Additionally, the **ICC** will also conduct formative, qualitative research to inform the refinement and pilot testing of survey instruments (see the **Survey and Data Collection Core** (**SDCC**)), written instructions, and/or patient education materials and assist with modification of program materials to better meet the needs of the populations.

B.3.b. Project-Specific Interventions. Project 1: Implement and test the effectiveness of the "Break Free" healthcare provider office-delivered smoking cessation intervention designed to reduce cervical cancer risk in rural, Appalachian female smokers. **Project 2:** Test the effectiveness of a multi-level intervention directed at

clinics, provider, and patients (parents of children aged 11-12) to improve HPV vaccine initiation and completion in children aged 11-12 and to determine whether attention to the younger age group increases catch up vaccination among 13-26 year olds. **Project 3:** Determine how a multi-level intervention that features HPV self-testing can increase cervical cancer screening among unscreened and under-screened women.

B.3.c. Comprehensive Program Information. To explain the comprehensive prevention program to all patients of participating clinics, the **ICC** will work with clinics to develop tailored, customized informational materials, thus integrating all projects in to a comprehensive prevention program delivered at the clinic level. To facilitate this integration, we will create a unified set of clinician/patient/family education materials that discuss our integrated cervical cancer program, listing all three components and messaging that encourages adherence and participation in each relevant intervention component. We will include staff training, posters, reminders, etc. to keep staff aware of the intervention components. This will also allow for information about smoking cessation/prevention, for example, to be received by adolescents targeted in the HPV vaccination project and to women in the cervical cancer screening study and vice versa. The **ICC** will facilitate input from the clinic partners as well as the CAB in developing these materials.

B.4. ***Aim 4****. Train relevant clinic and project staff on the implementation of the interventions for all 3 research projects, including the PNs, and provide ongoing technical assistance and quality assurance to maintain consistency and fidelity of protocol delivery.*

B.4.a. Intervention Implementation. We will use the health system organizational to assure orderly and non-disruptive implementation of the program and each intervention component. Importantly, the **ICC** will roll out each project one at a time in each health system within the first 6 months of the early implementation phase so as not to burden any one health system. We will coordinate this process such that project is implemented every 2 months in varying order, where some health systems will begin with **Project 1** and then **Project 2** and finally **Project 3**, while others will begin with **Project 2** etc., This insures that the structure of the roll out does not become imbalanced by state/health system. We will monitor this roll out plan closely and adjust it as needed. Moreover, we will utilize a monitoring system as each project intervention is implemented and evaluate implementation through "Plan, Do, Study, Act" evaluation cycles, as was done in the WVU colorectal cancer screening implementation project (See **B.1.c**). In all phases of program implementation, we will involve our Implementation Science consultant, Dr. **Jamie Ostroff**, who will review our plans and progress and make recommendations to the **ICC** on executing these activities.

Training is an important step in building the foundation for implementation delivery. We will lead training on each of the intervention projects, both internally and externally. The first priority is internal training with program coordinators and other staff from each state to have a full understanding of each project in order to consistently implement the program with health system/clinic partners. The second phase of training will be with each health system/clinic partner. Training at this level will be multi-focal and cover provider and staff education on the intervention protocols, screening guidelines, vaccination recommendations, and smoking cessation tools. Ongoing technical assistance and monitoring of implementation, including use of checklists, will be utilized to ensure protocol maintenance at each site across states. Barriers to implementation will be identified by individual meetings with clinic staff and providers, as well as at these educational sessions. Staff will work with each clinic/provider, as needed, to address and eliminate barriers to implementation. This process will be ongoing. Whenever Project Coordinators identify protocol drift, or at least every six months, protocols will be reviewed with clinic staff to ensure fidelity or to make needed changes to ensure implementation. This process will be done in close collaboration with each of the project teams.

B.4.b. Patient Navigator Training and Implementation. Project 3 will utilize PNs (Lyons and Walunis) to deliver components of the intervention. As such, the **ICC** (in collaboration with the Project team) will train and oversee the implementation of this intervention component. Navigators will be housed at OSU and will conduct navigation via phone, as this has been highly successful in other studies utilizing navigation[5] at OSU. The selection of PNs was based on relevant experience, education and ability to consummate the 8-domains and competencies of patient navigation established by Strusowski[12] with supplementary training. Ms. Lyons and Ms. Walunis both are from Appalachia and have extensive experience as PNs in other research projects. The **ICC** will conduct PN training, and will include a comprehensive explanation of the patient navigator role within each project. Training will include case studies, content reading, discussion, and role-play on issues such as cancer risk factors, diagnosis and treatment modalities, motivational interviewing skills, communicating with healthcare providers, and an introduction to the American Cancer Society (ACS) and National Cancer Institute (NCI). We will assess domains and competencies prior to authorizing the patient navigator to begin. During the implementation of the study protocols, Ms. Deems will generate weekly reports on navigation that include the number of patients reached and the content of the encounter (e.g., scheduling of medical visits). She will hold

regular meetings with the PNs to discuss and share cases for the purpose of the enhancement of communication among fellow PNs, address questions or concerns, and generate solutions. The research project team will design a standardized checklist/data/metric collection form to document each "encounter" with a participant, and collect the potential barriers and PN actions in checklist format so that all PNs can easily document each barrier and the associated intervention. The PNs will complete the form for each encounter with a patient. In addition, we will collect descriptive and modifiable characteristics of the participant and their interaction.

B.4.c. Sustainability Planning and Training in Clinics. As clinics complete active interventions, sustainability plans will be developed with each clinic/health system that include training topics and timelines that achieve training and benchmarks for additional staff. We will utilize strategies successful at WVU to sustain colorectal cancer screening interventions in primary care practices in this Program Project in relation to tobacco, HPV vaccination and cervical cancer screening. These sustainability plans will be developed by having clinic sites complete assessments: throughout the active and clinic implementation phases of the program, each Project research team will periodically meet with clinic managers to identify efficiencies and practices that encourage sustainability. These analyses will be presented to our health system representatives on the Clinical Consortium to develop and prioritize strategies and opportunities to support long-term sustainability. Examples include synergies such as including key program enhancements in future EHR upgrades, updating office policies and practices to continue routine identification and reach of needy patients and their families, and reviewing strategic opportunities in the clinic that can lower implementation costs such as by optimizing how health insurance is billed for covered screening and counseling. Moreover, the recent movement by insurers to link reimbursement levels to population health metrics and bundled services will only add impetus, from the health systems perspective, to sustain delivery of these three important preventive health services: HPV vaccination, screening, and smoking cessation. I**CC** staff will complete a systematic review of each clinics/health systems report to identify areas of improvements. Our consultant, Dr. **Jamie Ostroff** will assist us in developing these plans for sustainability at each clinic.

B.4.d. Evaluation of the Intervention Component. The evaluation of the integrated cervical cancer prevention program will use a mixed-method approach and will be conducted by the **BEC** under the direction of Dr. **Dignan**. Evaluation will be focused not only on the interventions of each specific project, but also the overall integrated cervical cancer prevention program. The aims of the **ICC** will structure the evaluation and will focus on assessing the extent to which each aim is reached in the anticipated amount of time. For **Aim 1**, the evaluation will include review of records of stakeholder engagement, while for **Aim 2**, the evaluation will assess completion of the community and clinic assessments and their utility in intervention planning. For **Aims 3** and **4,** the evaluation will assess interactions among the **ICC** and project investigators in intervention development, staff training, and monitoring implementation fidelity. Quantitative and qualitative data will be needed for evaluation of all four aims, and collection will be led by the **SDCC** with evaluation by the **BEC**. Our evaluation will utilize outcomes from the Proctor Implementation framework[10] (**Figure 2**) to assess this intervention component – specifically: implementation (e.g., penetration - did everyone who needed a navigator receive navigation), service (e.g., timeliness – did the navigator contact patients in a timely manner) and client (e.g., satisfaction – were patients satisfied with navigation) outcomes.

C. RELEVANCE TO PROGRAM

C.1. Interactions with Program Components. The **ICC** is central to the execution of each of the research projects, as well as the **AC**, **SDCC**, and **BEC**. The **ICC** will develop and foster participation of the community, and is responsible for developing and implementing the overall training and materials related to the integrated cervical cancer prevention program. The **ICC** will work with the AC to form and conduct meetings of the CAB and the Consortium Core, and will assist the **SDCC** in recruitment and data collection activities as necessary, focusing on issues related to cultural acceptance. The **ICC** will lead the Community Assessment Phase with input from all components of the Program Project, as well as coalition partners and the Clinic Consortium, and be responsible for dissemination activities.

C.2. Integration of Program Theme. The Program Project will leverage the strengths within the partnering networks to enhance knowledge of, access to, and use of primary prevention and secondary measures to reduce health disparities by targeting cervical cancer risk factors. The **ICC** is integral to this theme, as well as implementing the two conceptual models of the Program. The **ICC** will support community involvement in this transdisciplinary work in health disparities by providing CBPR to the projects comprising this Program, and will assist in the design and implementation of the multi-level interventions intended to improve preventive behaviors among residents of the five states, including integrating aspects of the social determinants of health that influence the uptake and sustainability of the prevention program. **C.3. Overlap with Existing Shared Resources.** This Core does not overlap with any existing shared resources at the member institutions.

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PROJECT SUMMARY - SURVEY AND DATA COLLECTION CORE (SDCC)

The primary objective of the **Survey and Data Collection Core** (SDCC) is to provide all Program Project investigators and staff with a centralized resource for measurement and data collection. To achieve this goal, our **SDCC** team will collaborate with the investigators and health system partners and the other cores.

The specific aims for the **SDCC** are to:
1. Collaborate with the project investigators in the selection, development and design of individual project and overall measures and data collection procedures;
2. Identify and implement common measures across all projects to examine the influence of the Social Determinants of Health as specified by the Multilevel Model of Population Health;
3. Train intervention and clinic staff across the three projects and the health care systems, as needed, in the study instruments and data collections procedures;
4. Utilize the electronic health record systems (EHRs) for participant identification, intervention delivery, and data collection for all three projects; and
5. Monitor data tracking systems for the individual projects and the overall program and work with staff to minimize missing data and missed patient assessments.

The Core will be led by Drs. **Michelle Naughton** (The Ohio State University) and **Thomas Guterbock** (University of Virginia). The coordination and data collection from electronic health records will be under the direction of Dr. Adam Baus at the West Virginia University, in partnership with the staff at the participating health systems. The team of investigators and staff is highly qualified to complete the specific aims of the **SDCC** and support the overall program project and three integrated projects. The Core will work in close cooperation with the **Intervention and Consortium Core** (ICC) to develop data collection approaches and procedures that are integrated into community structures and culture throughout Kentucky, Ohio, West Virginia and Virginia. The **SDCC** will also work closely with the **Biostatistics and Evaluation Core** (BEC) to ensure the collection of quality data for the planned analyses. The **Administrative Core** (AC) will then utilize the project results produced by the **SDCC** and **BEC** to facilitate the dissemination of the study results and effective interventions to reduce disparities in cervical cancer incidence and treatment.

PROJECT NARRATIVE – CORE 2 (SDCC)

The SDCC is integral to the proposed Program Project by providing outcomes measurement and data collection services across all three projects. This core will assist in advancing our scientific knowledge of HPV prevention strategies through interventions designed to promote HPV vaccination rates, increase HPV self-testing, and decrease smoking rates in Appalachia. These outcomes directly coincide with the NCI stated goals of improving women's health and cancer prevention strategies. This project also has public health relevance by targeting the Appalachian region of the U.S., which has high rates of tobacco use and cervical cancer, in order to decrease cancer incidence, as well as morbidity and mortality, in line with the Health People 2020 objectives.

SPECIFIC AIMS

The primary objective of the **Survey and Data Collection Core** (**SDCC**) is to provide all Program Project investigators and staff with a centralized resource for measurement and data collection. To achieve this goal, our SDCC team will collaborate with the investigators and health system partners, and the other cores.

The specific aims for the **SDCC** are to:

1. Collaborate with the project investigators in the selection, development and design of individual project and overall measures and data collection procedures;
2. Identify and implement common measures across all projects to examine the influence of the Social Determinants of Health as specified by the Multilevel Model of Population Health;
3. Train intervention and clinic staff across the three projects and the health care systems in data collection instruments and procedures, as needed;
4. Utilize the electronic health record systems (EHRs) for participant identification, intervention delivery, and data collection for all three projects; and
5. Monitor data tracking systems for the individual projects and the overall program and work with staff to minimize missing data and missed patient assessments.

The Core will be led by Dr. **Michelle Naughton** (The Ohio State University) and Dr. **Thomas Guterbock** (University of Virginia). The coordination and data collection from electronic health records will be under the direction of Dr. **Adam Baus** at West Virginia University, in partnership with the staff at the participating health systems. The team of investigators and staff is highly qualified to complete the specific aims of the **SDCC** and support the overall Program Project and three integrated projects. The Core will work in close cooperation with the **Intervention and Consortium Core** (**ICC**) to develop data collection approaches and procedures that are integrated into community structures and culture throughout Kentucky, Ohio, West Virginia and Virginia. The **SDCC** will also work closely with the **Biostatistics and Evaluation Core** (**BEC**) to ensure the collection of quality data for the planned analyses. The **Administrative Core** (**AC**) will then utilize the project results produced by the **SDCC** and **BEC** to facilitate the dissemination of the study results and effective interventions to reduce disparities in cervical cancer incidence and treatment.

IMPACT: The P01 will leverage the strengths within the participating academic institutions and health care systems to enhance knowledge of, access to, and use of approaches to reduce health disparities in cervical cancer in Appalachia. The **SDCC** is integral to this mission in its measurement functions, data collection, and data quality activities.

RESEARCH STRATEGY

3. CORE SERVICES STRATEGY

A. CORE LEADERSHIP AND MEMBERSHIP

A.1. Members of Core

Michelle Naughton, PhD, MPH, will serve as Co-Lead of the **SDCC**. She is a Professor of Internal Medicine, Division of Cancer Prevention & Control, at The Ohio State University (OSU). She has extensive experience in survey design, measurement and patient-reported outcomes, as well as data collection and tracking, project implementation and staff supervision in both observational and clinical trials.[2-18] As an example, she oversaw the collection of cardiovascular and cancer medical record outcomes for the Southeast Region of the Women's Health Initiative (WHI), which spans 9 states, from 2010-2014. She currently has funded studies in ascertaining treatment toxicities in metastatic lung cancer patients, using the PRO-CTCAE, and a smart phone text-based intervention that assesses gynecologic, breast, and GI cancer patients' physical and psychological symptoms and needs during adjuvant therapy. She is also the co-chair of the Health Outcomes Committee for the Alliance for Clinical Trials in Oncology. She has worked with Drs. **Paskett**, **Anderson**, and **Dignan** for many years on both intervention and observational studies.

Thomas M. Guterbock, PhD, will serve as Co-Lead of the Core. Dr. **Guterbock** is Director of the Center for Survey Research, Professor of Sociology, and Research Professor of Public Health Sciences at the University of Virginia. He is a nationally known survey methodologist and researcher with experience across a wide range of issues in health, health care, and health services research. He has wide experience working with interdisciplinary teams and is known for his skill in survey design and in devising smoothly flowing questionnaires. He is a frequent presenter of research papers at the annual meetings of the American Association for Public Opinion Research (AAPOR) and served on the AAPOR Executive Council as the elected 2006-2007 Standards Chair. He served as 2010-11 President of the Association of Academic Survey Research Organizations, an association which he helped to found. Dr. **Guterbock**'s training includes both qualitative field methods and advanced multivariate statistical methods. In his capacity as founding director of Center for Survey Research at UVA, he has been involved in over 400 funded survey projects, covering telephone, mail-out, in-person, and Internet modes as well as multi-mode projects. Projects related to health include population surveys of health behaviors and health needs,[19] surveys of practitioners and patients on HPV vaccine uptake,[20] surveys of consumer health information preferences and communication,[21-22] use of social media to communicate about health,[23-24] health issues affecting African-Americans,[25] unmet surgical need in Rwanda,[26-28] and studies of technological and ethical issues confronting health professionals.[29]

Adam Baus, PhD, MA, MPH, will serve as the health informaticist for all projects. Dr. **Baus** has 14 years of experience working with the West Virginia University Office of Health Services Research on electronic health records (EHR)-based quality of care improvement and practice-based research initiatives in safety-net primary care clinics. Dr. **Baus**' experience and expertise will help the projects effectively access and leverage EHR data for evaluation and research. His public health research focuses on empowering primary care partners to fully use routinely collected clinical data for the purposes of improved patient care, population health, and ultimately decreased health care costs. His publications[30-37] concern ensuring data quality in EHR, facilitating use of EHR data for prevention and control of chronic disease and injury, and working collaboratively with primary care partners to address local-level health concerns. He has worked with Dr**. Mark Dignan** in the initial phases of a West Virginia/Kentucky health analytics learning network.

Cecil Pollard, MA, will serve as a liaison for creating and sustaining partnerships across our participating primary care and academic partners. His three-plus decades of experience in working in this capacity in West Virginia and the region uniquely positions him as an agent for spurring action-oriented research effecting practice and policy change. He has worked with Dr. **Dignan** in the initial phases of a West Virginia/Kentucky health analytics learning network.

Jill Oliveri, DrPH, will serve as the overall **SDCC** manager under Dr. **Naughton**'s and **Guterbock**'s supervision. She has served as the Project Manager on several NIH funded cancer control, community-based research projects in the Appalachia area with Dr. **Paskett**, and is currently a Program Director for the OSU Comprehensive Cancer Center (OSUCCC). Dr. Oliveri has experience in survey design and implementation, as well as data tracking.

Heather Aker, MPH. Ms. Aker is the Program Director for the Behavioral Measurement Shared Resource (BMSR) at the OSUCCC. The BMSR consists of a team of behavioral scientists with expertise in research design, measurement and data collection methods. For this Program Project, Ms. Aker will design data collection instruments and data entry systems using software programs (e.g., REDCap), provide training and support for

research data collectors, and assist in monitoring data collection and quality. Ms. Aker has extensive experience in providing instrument design and quantitative and qualitative data collection services for Drs. **Paskett**, **Reiter**, **Pennell** and **Katz**, as well as Drs. **Dignan** and **Kennedy** (through ACCN).

A.2. Plans for Leadership and Distribution of Core Resources. The key personnel of the **SDCC** (Drs. **Naughton**, **Guterbock**, **Baus**, Oliveri; and Ms. Heather Aker) will have regularly scheduled monthly calls to review progress toward measure selection, forms development, data collection, missing and/or incomplete forms, quality control and EHR data abstraction. **SDCC** personnel will also communicate directly with other **SDCC** members via email and phone between monthly calls, as needed. Communication with individual project investigators, staff and other core directors will be facilitated by proximity, (for example, Drs. **Ferketich**, **Paskett**, **Reiter** and **Katz** are all at OSU), and long standing relationships between the investigators across the four state sites. In addition, all investigators have experience in working in large, multi-center projects and coordinating across research and clinic sites. First priority for Core resources will be activities associated with the specific aims of each project and the overall Program goals. All investigators will have equal access to Core resources.

B. ACTIVITIES AND FUNCTIONS OF CORE

B.1. Overview of the Core Functions of the SDC Core. The **SDCC** will provide expertise, services, and research collaboration necessary to create a database of valid measures to enhance research on cervical cancer prevention and early detection in Appalachia. The Program Project is comprised of three projects that will be implemented as an integrated program in 10 health systems across four states (Ohio, Virginia, West Virginia, and Kentucky). Randomization will be stratified by state, with clinics assigned to the same intervention arm (early vs delayed intervention) in each project (e.g., health systems assigned to early intervention in **Project 1** will also be assigned the early intervention arm in **Projects 2** and **3**). The decision to keep the arms consistent within a health system was based on providing a bundled prevention program at each clinic site.

The **SDCC** will assist with instrument selection, provide support for pre-testing and instrument development, as well as the conduct of data collection (e.g., paper and electronic survery; semi-structured interviews). Collaboration between each project team and the **SDCC** will optimize the collection of valid, reliable data, ensuring that survey instruments meet the technical requirements and professional standards of survey research, while also satisfying the need for usability and cultural competence, and protecting the privacy and confidentiality of human subjects during data collection. **SDCC** staff will monitor and assist project staff with data collection, and will deliver raw data sets to the **BEC** for data cleaning, reformatting, and analysis. The conduct of each specific aim of the **SDCC** is described below.

B.2 Aim 1: Selection of overall Program and project measures and data collection procedures.

The **SDCC** will be responsible for the identification and production of all data collection instruments and forms, as well as pretesting data collection instruments (in-person, focus groups, clinic-level in-depth interviews and forms), as needed. The **SDCC** will also assist investigators and staff in refining data collection procedures, training staff on data collection, and will provide technical support for the coordination of data collection across each project component. Both manual data collection forms and direct electronic entry using computers, iPads or cell phones will be used, depending on the project and the capabilities for internet and phone service in each region. Some instruments, such as those intended for providers, will be self-administered, while others will be designed for either self- or interviewer-administration, as indicated by literacy levels and needs of project participants. **Table 1** provides an overview of the currently identified assessment tools for each component, as well as each project. Primary data collection will be managed using REDCap (Research Electronic Data Capture). REDCap is a secure web-based electronic data capture software package developed by Vanderbilt University and institutional partners (including OSU). The BMSR at OSU will assist in the collection and management of these data. The abstraction of data from electronic health records is described in **Aim 4**.

Table 1. Program Measures

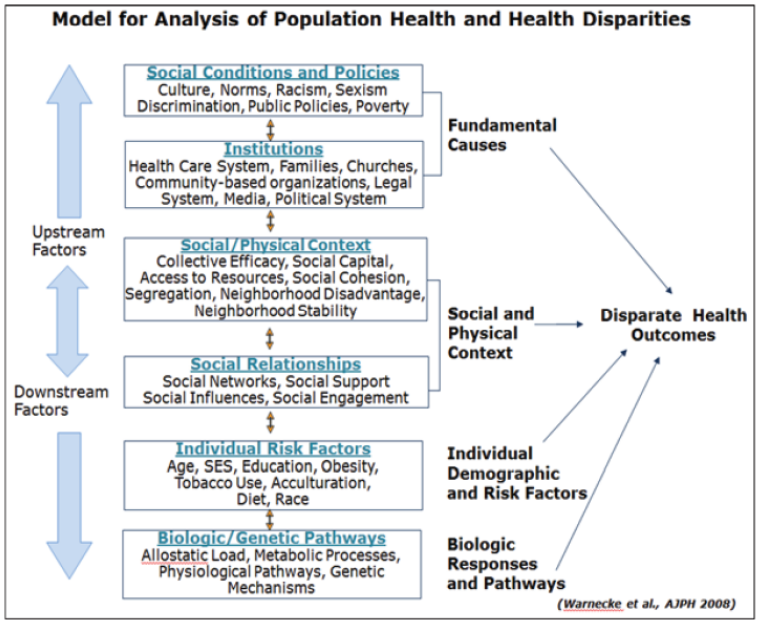
Metric	Data Source	Project 1	Project 2	Project 3
Practice Characteristics: (Surveys entered into REDCap) • practice specialization (e.g., pediatrics; internal medicine; family medicine) • # of M.D. practice providers • # of staff persons and their positions within the practice (i.e., LPN) • # of patients served by the practice • Address, zip code and county of practice location	- Practice and Provider Characteristics' Surveys -Forms to be developed and tested during the first 5 months of year 1.	X	X	X

• Catchment area served by practice • EHR system used at the site • Internet capabilities of practice location **Provider Characteristics:** (Surveys entered into REDCap) • Age and gender of all M.D. providers and staff • Board certifications of M.D. providers • Length of time in practice of M.D.s • length of time all M.D. providers and staff have been at this practice	-Data will be completed by the office manager at each practice to save physician and staff time. Data will be directly entered into REDCap via office computers. -Practice and provider information will be used for all 3 projects.			
Patient Demographic Information: • age • gender • race/ethnicity • provider name • county of residence • zip code • insurance status/payer • education (if in the EHR and/or asked in the project specific measures) • home address	Electronic Health Record	X X	X X X X X X X X X	X X X X X X X X X
Health Record Chart Abstraction: • Patient's smoking status at baseline **Project 1:** • Billing codes for tobacco dependence/treatment (e.g., counseling; pharmacotherapy) **Project 2:** • Baseline HPV Vaccination Rates by age groups (11-12, 13-17, 18-26) • Baseline rates of other vaccination rates by age groups • Annual HPV Vaccination Rates (I Vaccinate Program) **Project 3:** • Dates of pap tests within project period • Follow-up appointments for pap test results • Any follow-up care received (e.g., Pap test, colposcopy) • Cervical abnormalities (precancerous and cancerous)	Electronic Health Record	X X	X X X X	X X X X X
Project-Specific Measures: **Project 1:** **Provider Measures:** • Theory of Planned Behavior (TPB) Constructs (baseline and end of intervention using paper or electronic surveys): 1) attitudes; 2) normative; 3) perceived behavioral control; 4) anticipatory regret; and 5) moral imperative. • Office staff (interviewed at baseline): tobacco use status, attitudes toward cessation, and level of comfort in promoting a comprehensive cessation program. Provider-level outcomes: Self-reported changes in the delivery of the 3A's (ask, advise, assess), and rate of referrals to smoking cessation counseling in the clinic. • Feedback to providers (monthly): Proportion of patients referred to in-clinic counseling, set a quit date for the next 30 days, enrolled in the "reduce-to-quit" protocol, started telephone counseling, and if billed for cessation counseling. **Smoker/Participant Measures: (self-administered paper or electronic surveys)** a. Baseline Measures: • Perceived Stress Scale • Centers for Epidemiologic Studies Depression Scale (CES-D) • Presence of chronic conditions • Fagerström Test of Nicotine Dependence (FTND) • Age at smoking initiation • Current tobacco consumption (all products) • Previous quit attempts • Use of pharmacotherapy or cessation counseling in the past b. Outcome Measures: • 7-day point prevalence abstinence (self-report and salivary cotinine) • floating abstinence • prolonged abstinence • at least one 24-hour quit attempt c. Sustainability Measures:				

• self-reported continuation of cessation counseling by staff members trained as TTSs • number of counseling sessions billed overall and for each individual smoker who has at least one session (EHR) **Project 2** a. Outcome Measure: • Rates of HPV Vaccination (Year 1) (EHR) b. Provider Measures (self-administered survey at baseline using either paper forms or an electronic device): • HPV vaccine knowledge • HPV vaccine beliefs • HPV vaccine attitudes • HPV vaccine practices **Project 3** a. Provider Measures (self-administered baseline survey, completed via mail or using a link to the form online via REDCap): • HPV self-testing knowledge • HPV self-testing beliefs • HPV self-testing attitudes • HPV self-testing practices			
Patient and Provider Satisfaction with Program Interventions: • Participant satisfaction with intervention (online or mailed survey) • Provider & staff satisfaction with intervention (online or paper survey and interview) • Parent satisfaction with intervention (online or mailed survey) • Provider satisfaction with patient navigation (online or paper survey and interview) • Patient satisfaction with patient navigation (online or mailed survey)	**Project 1** X X -- -- X	**Project 2** X X X -- X	**Project 3** X X -- X X
6) Overall Program Level Evaluation (See section B.4., Aim 4 in the BEC; Forms will be developed and pre-tested in Years 4-5) • Implementation of the program in the health care system • Services provided to patients (efficiency, effectiveness, equity, patient-centered, timeliness of care, safety) • Patient Outcomes	• Semi-structured interviews with providers, program staff and a random subset of patients • Qualitative and quantitative data collection		

B.3 Aim 2: Identify and implement common measures across all projects to examine the influence of Social Determinants of Health (SDH), as specified by the Multilevel Model of Population Health.

In collaboration with the investigators and lead staff from each of the projects and cores, a common module of measures will be developed and collected from participants across all projects to examine the influence of Social Determinants of Health (SDH), using the Multi-level Model of Population Health.[1] (See figure below, and the description of the model in the **Program Overview**, Section B). The final set of common measures will be discussed and finalized by members of the Steering Committee (SC), which includes representation from all projects and cores. Several theories have been used to explain and understand the pathways that are associated with cancer health disparities. These theories have examined the following factors: socioeconomic status, social discrimination (by using gender or race/ ethnicity), environment (living conditions, distribution of income), political and policy context (extent of primary care services, geographic location of health services, fairness of health financing, social policies), and political, social and economic relationships. These theories suggest that multiple levels of factors (i.e. determinants of health) beyond the characteristics of the individual, play a role, directly or indirectly, in determining individual risk, and illustrate the utility of the SDH model addressing disparities by *implementing strategies* designed for the social and physical environment of Appalachia. In this context, the focus will be on implementing interventions to change health behaviors in the rural health care delivery



environment. This environment was selected because our needs assessments showed that health care clinics are a fundamental part of the *social structure* in Appalachia and, as such, are basic components of the *social environment*. The **SDCC** will be integral to the development of appropriate measures and data collection methods best suited to the health care systems and communities in the study areas. These measures will contain variables for program-level analyses, individual-level variables, and contextual variables.

Program-Level analyses. **Multi-level modeling**, (see Section B.2.c. of the **BEC**), will examine the relative contributions of individual, community, primary care practice, and patient navigation effects on the uptake of recommended cervical cancer prevention services in the clinics and communities. This will be the first major modeling of how multi-level inputs contribute to cervical cancer reduction in Appalachia.

Individual - level variables. Individual-level variables will be collected directly through paper or electronic surveys, and electronic health records. In addition to data specific to each proposed project, each project will collect a common core set of variables, including patient demographics, provider characteristics, practice location and catchment area serviced. The overall Program design involving one study region (Appalachia), and a uniform sampling frame among projects, allows these unique individual-level data to be aggregated as contextual level data and shared across projects.

Contextual variables. Indicators of population characteristics, health care supply, and location of health care resources will be collected. Typically, contextual variables are measured at the county level, but because this project employs geocoding based on the individual's residence, we have the ability to consider additional units that may be more relevant to health-related behaviors, such as minor civil divisions or named places. A description of the contextual variables to be measured is in Section C.7.c. of the **Program Overview**.

B.4 Aim 3: Train staff in data collection instruments and procedures across the 3 projects.

SDCC staff will train the intervention and clinic staff of each project, as needed, on project outcome and evaluation measures and proper procedures for data collection. This training will include the time table of data collection instruments across the three projects and the Program as a whole; the mode(s) of data collection (e.g., pen and paper; computer-based; iPads); procedures for interviewer-administration and self-administration of forms; how to answer patients' questions regarding data collection instruments; data entry procedures; data error checks; and quality control and regulatory requirements. Training for the *implementation* of the multi-level intervention materials and procedures for each of the three projects will be completed by the **Intervention and Consortium Core** (**ICC**). Similar methods for training and supervising staff will be used in this Program as have been used in the OSU Center for Population Health and Health Disparities (CPHHD).

B.5. Aim 4: Utilize the electronic health records systems (EHRs) for participant identification, intervention delivery and data collection for all three projects.

B.5.a. Using the electronic health records systems for project needs. In order to best support health systems in using their EHRs for identifying patients in need of screening and follow-up care, as well to deliver interventions, such as patient appointment reminders, we will conduct health information technology assessments at all sites. These assessments will be conducted with key personnel in the health systems, such as chief information officers, medical and/or nursing directors, and quality improvement leaders. Based on findings from these assessments, we will know how to best direct our support and resources for either building new or bolstering existing efforts in using EHR data for the three projects and the integrated cervical cancer prevention program. We have confirmed that all participating health systems use EHRs, including Allscripts Pro, Athena, Compugroup Medical, eClinicalWorks, EPIC, Meditab-IMS, and NextGen. The proposed work is of direct benefit to participating health systems not only for enhancing their ability to use EHR data for patient care and population health, but also for responding to national efforts in meeting Meaningful Use criteria and in becoming recognized Patient-Centered Medical Homes. Both of these national efforts are data-intensive, and mandate that EHRs be well integrated into primary care and have data that are of sound quality and actualized to support improved patient care and population health.

B.5.b. The EHR for data collection. Data to be collected from the EHRs (**Table 1**) will include demographic information on all project participants (age, gender, race/ethnicity, type of health insurance, provider name, zip code, county of residence), smoking status (**Project 1**), vaccination history for **Project 2** (date of each HPV shot; recommendation; other vaccines), and Pap Test screening information for **Project 3** (date of most recent; follow-up recommendations and treatments). Leveraging EHR data in identifying priority patient populations, offers a clear advantage[33, 38-41] in conducting practice-based research and quality of care improvement efforts.

B.5.c. The Office of Health Services Research (OHSR) at West Virginia University. The OHSR at West Virginia

University has extensive experience integrating data from disparate EHRs, and re-purposing these data for population health initiatives and practice-based research. OHSR, under the direction of Dr. **Baus** and Mr. Pollard, will manage all data collected from the EHR systems. OHSR has a three-decade history of working with health care systems, state and local health and academic partners in quality of care improvement and, more recently, practice-based research initiatives. In a partnership among the West Virginia Clinical and Translational Science Institute and the University of Kentucky Center for Clinical and Translational Science, OHSR has been part of an interdisciplinary team leveraging i2b2 and the Shared Health Research Informatics Network (SHRINE) for the purpose of starting a regional data sharing and learning network.[42-43] This effort, started in mid-2014, brought together disparate EHR data from West Virginia and Kentucky primary care centers, and under guidance from a data governance committee, has identified priority uses for these data. Data management efforts have advanced from employing i2b2 to using SAS as a means of data harmonization across disparate EHR systems, and Tableau as a companion software for the creation of data visualizations and information dissemination to partners. These procedures will be used in the current Program Project to standardize data gathered across the health systems. These data will then be securely transmitted to the **BEC** at OSU for data set construction and analysis, ensuring appropriate regulatory and privacy requirements for these data. The proposed Program Project will be a natural extension of the regional health data collaborative already underway.

B.6. Aim 5: Monitor data tracking systems and work with staff to minimize missing data.
The role of the **SDCC** will be to select and/or develop project-specific data collection measures, train and assist staff in data collection procedures, monitor the data for quality control, and securely disseminate the data to the **BEC** (**Figure 2**). The BMSR will develop tracking systems for all forms entered into REDCap, (either through direct data entry using an electronic device or forms completed on paper and later data entered into REDCap). **SDCC** staff will monitor all forms for completeness and missed assessments, and ensure that data collection procedures work smoothly for each project. **SDCC** staff will be responsible for the implementation of quality assurance measures and will work with individual project staff and investigators to troubleshoot data collection problems. Raw data collected by the **SDCC** will be exported to the **BEC** for the preparation of datasets for analyses.

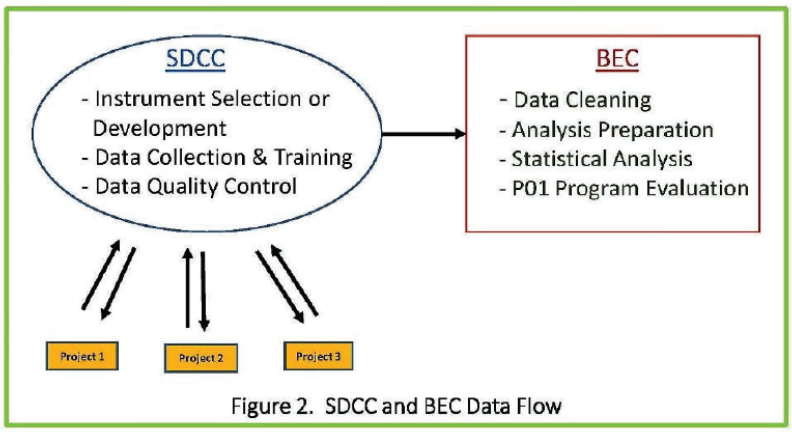


Figure 2. SDCC and BEC Data Flow

C. RELEVANCE TO PROGRAM

C.1. Interaction with Program Components. The **SDCC**, given its roles in measurement, instrument selection, data collection, monitoring, and quality control, is central to the execution of each of the three projects and the overall Program objectives. Core members will conduct crucial tasks for each project and the integrated prevention program, as described above. The **SDCC** will also work closely with the **BEC** to ensure the collection of quality data for the planned analyses. The Core will work in close cooperation with the **ICC** to develop data collection approaches and procedures that are integrated into community structures and culture throughout Kentucky, Ohio, West Virginia and Virginia. The **Administrative Core** (**AC**) will then utilize the project results produced by the **SDCC** and **BEC** to facilitate the dissemination of the study results and effective interventions to reduce disparities in cervical cancer incidence and treatment.

C.2. Integration of Program Theme. The P01 will leverage the strengths within the partnering health systems to enhance knowledge of, access to, and use of primary prevention and secondary measures to reduce health disparities by preventing cervical cancer. The **SDCC** is integral to this theme in its measurement, data collection, and data quality activities. The Core will play a crucial role in measuring factors related to the social determinants of health, and in identifying ways to decrease smoking, increase HPV vaccine uptake, and increase the rate of cervical cancer screening.

C.3. Overlap with Existing Shared Resources. The activities of this core do not overlap with any existing shared resources at the member institutions. Instead, the **SDCC** is complementary to the available resources of the Program Project member institutions.

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PROJECT SUMMARY – BIOSTATISTICS AND EVALUATION CORE (BEC)

The primary objective of the Biostatistics and Evaluation Core (BEC) is to provide the project investigators with a centralized resource for comprehensive statistical services as well as cost effectiveness analysis and program evaluation. To achieve this goal, the Core will collaborate with project investigators throughout the proposed Program Project to design the proposed studies, perform data analysis, and evaluate each project and the overall program project. The Core consists of statisticians with an extensive track record in health disparities research and behavioral intervention studies, a health services researcher with expertise in cost effectiveness analysis, and a nationally recognized cancer prevention researcher with expertise in evaluating health behavior interventions. The members of this Core have built strong collaborative relationships with one another and with project investigators, having worked together on previous grants and publications. The Core will leverage their expertise and relationships with investigators to conduct the following specific aims: a) collaborate with the project investigators in the formulation of hypotheses and the design of experimental studies; b) conduct the analysis of data generated by the project investigators including summary statistics, hypothesis testing of the primary outcome data, and sensitivity and exploratory analyses leading to hypothesis discovery; c) conduct cost effectiveness analyses of each component of the intervention program and the overall program; and d) build on a foundation of program evaluation established in previous collaborations, and, using the Proctor Model for Implementation Research, track and assess implementation of project plans and core activities, and provide feedback to leadership. The BEC will have extensive interactions with the Survey and Data Collection Core (SDCC) to ensure that the data are collected and distributed in a manner that allows effective analysis of data from the projects. The BEC will also collaborate with the other cores to prepare for Data and Safety Monitoring Board meetings and perform needs assessments of the different health systems. The statistical analyses performed by the Core will also play a crucial role in the dissemination of effective interventions.

PROJECT NARRATIVE – CORE 3 (BEC)

The BEC is integral to the proposed Program Project due to its role in statistical design, analysis, and evaluation. This core will assist in advancing our scientific knowledge of HPV prevention strategies through interventions designed to promote HPV vaccination rates, increase HPV self-testing, and decrease smoking rates in Appalachia. These outcomes directly coincide with the NCI stated goals of improving women's health and cancer prevention strategies. This project also has public health relevance by targeting the Appalachian region of the U.S., which has high rates of tobacco use and cervical cancer, in order to decrease cancer incidence, as well as morbidity and mortality, in line with the Health People 2020 objectives.

SPECIFIC AIMS

The primary objective of the **Biostatistics and Evaluation Core** (**BEC**) is to provide the project investigators with a centralized resource for comprehensive statistical services as well as cost effectiveness analysis and program evaluation. To achieve this goal, the Core will collaborate with project investigators throughout the proposed Program Project to design the proposed studies, perform data analysis, and evaluate each project and the overall Program Project.

The specific aims for this Core are:

Aim 1: Collaborate with the project investigators in the formulation of hypotheses and the design of experimental studies.

Aim 2: Conduct the analysis of data generated by the project investigators including summary statistics, hypothesis testing of the primary outcome data, and sensitivity and exploratory analyses leading to hypothesis discovery.

Aim 3: Conduct cost effectiveness analyses of each component of the intervention program and the overall Program.

Aim 4: Build on a foundation of program evaluation established in previous collaborations, and, using the Proctor Model for Implementation Research[1], track and assess implementation of project plans and Core activities, and provide feedback to leadership.

This Core will integrate the conceptual framework of the Center (see **Overview**) into relevant analyses, as appropriate. The members of this core have extensive experience working with the project investigators and in evaluating multilevel interventions. Key personnel were also members of the Biostatistics and Data Management cores of Dr. **Paskett**'s NCI-funded P50 (CARE I) and subsequent renewal (CARE II). The specific aims listed above are reflective of the activities that were required to efficiently and effectively run these previous cores as well as activities that are required to satisfy the specific needs of these projects. The Core members are also active in methodological research related to the proposed project and hence are versed in the latest analytical techniques for the data they will be working with. While data collection and quality control will be the primary responsibility of the **Survey and Data Collection Core** (**SDCC**), the **BEC** will work closely with members of the **SDCC** to ensure that we receive high quality data that can be used to answer the research questions of the various projects.

RESEARCH STRATEGY

3. CORE SERVICES STRATEGY

A. CORE LEADERSHIP AND MEMBERSHIP

A.1. Members of Core

Michael L. Pennell, PhD, will lead the Core and serve as lead Biostatistician for **Project 2**. Dr. **Pennell** is an Associate Professor in the Division of Biostatistics in the College of Public Health (CPH) at The Ohio State University (OSU). Dr. **Pennell** was an investigator on Dr. **Paskett**'s (**Project 2** Co-Lead) P50 supplement to investigate design and analysis alternatives for multilevel intervention studies. He was also an investigator on Dr. **Paskett**'s NIH-funded Group Randomized Trials (GRTs) examining community[2], clinic-based[3], and multilevel[4] interventions to increase practice of preventive behaviors. Dr. **Pennell** has extensive experience in multi-level modeling in his methodological[5] and collaboration work[3,4,6] and applies cutting-edge methodology to analyze GRTs[2]. His research focuses on Bayesian methodologies which allow one to use information from previous studies in analysis[7] and in nonparametric modeling of random effect distributions[8].

Mark Dignan, PhD, MPH, will lead the evaluation component of the Core. Dr. **Dignan** is a Professor in the Department of Internal Medicine and Director of the Prevention Research Center at the University of Kentucky. His research has focused on community-based cancer prevention and control for most of his career and has included projects that developed and evaluated mass media programs, lay health advisor and navigator interventions for patients and the public, and health care provider programs designed to increase screening and adherence to follow-up recommendations among medically underserved rural and minority populations. Dr. **Dignan**'s current research includes ongoing collaborations with Drs. **Paskett**, **Kennedy** and **Anderson** focusing on reducing health disparities among Appalachian populations. These projects include a multi-site community-based intervention trial to reduce obesity and a training program to prepare patient navigators working with the Appalachian population. Dr. **Dignan** also has extensive experience developing and implementing evaluation for cancer-related projects. Recently he led evaluation of programs providing cancer education for community health aids in Alaska[9,10] and an intervention to meet information needs of low income cancer survivors[11].

Mark R. Conaway, PhD, will co-lead the Biostatistics component of the Core and serve as the lead statistician for **Project 1**. Dr. **Conaway** is a Professor in the Division of Translational Research and Applied Statistics in the Department of Public Health Sciences at the University of Virginia (UVA). Dr. **Conaway** has collaborated with Dr. **Andersen** on several smoking cessation protocols at UVA and prior to coming to UVA, he was a member of the Cancer Control Committee of the CALGB which was led by Dr. **Paskett**. Dr. **Conaway** has considerable experience in the design and analysis of clinical trials[12–14].

Abigail B. Shoben, PhD, Associate Professor in the Division of Biostatistics in the CPH at OSU, will be the lead Biostatistician for **Project 3**. Dr. **Shoben** has collaborated with Dr. **Reiter** (**Project 3** Co-Lead) on past interventions, including multiple NIH-funded projects. She has extensive experience in clinical trials with correlated data in both her applied[15] and methodological work[16]. Her research focuses on methods for improving efficiency of group randomized and longitudinal trials[17] and impacts of assumption violations in these trials[18].

Wendy Xu, PhD, will perform the cost effectiveness analysis for each project and the overall program. Dr. **Xu** is an Assistant Professor in the Division of Health Services Management and Policy in the CPH at OSU. She is a Co-Investigator on a project led by Dr. **Paskett** examining cost-effectiveness of various approaches to improve cancer screening among rural women in Ohio and Indiana. Dr. **Xu** is a health services researcher and health economist. She is teaching economic evaluation using cost-effectiveness analysis tools at OSU.

Fabian Camacho, MA, MS, will provide statistical support and data prep (e.g., data cleaning, reformatting data sets) for **Project 1**. Mr. Camacho has over 18 years of experience in data analysis/management of public health projects, with specific training and expertise in key research areas for this project, including statistical/causal analysis of observational data, geographical analysis, and programming with health claims and public access survey data sets. He has worked on several projects with Dr. **Anderson** (**Project** 1 Co-Lead) including the analysis of treatment patterns of breast cancer patients in North Carolina Registry linked Medicare/Medicaid data, investigation of recurrence algorithms in Medicare data, disparities and access to cancer care in Appalachia using registry linked claims data, effects of regular primary care on cancer stage, projects assessing quality of life in cancer, development of patient satisfaction scales, and effects of waiting time on satisfaction.

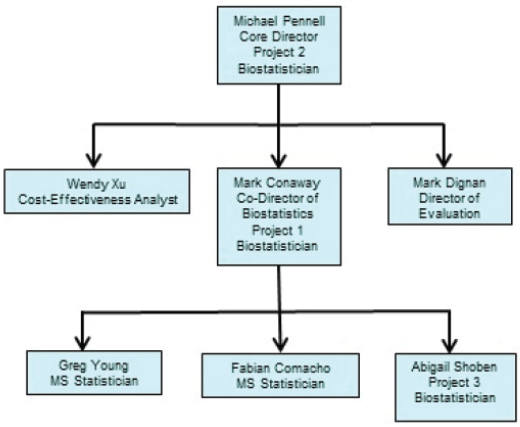


Figure 1. Administrative Structure of BEC

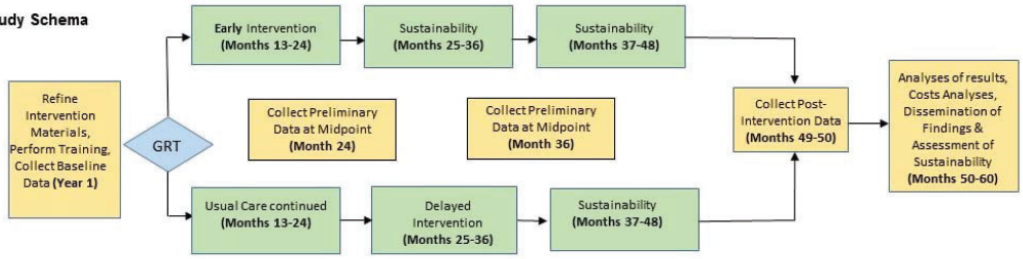
Gregory Young, MS, Senior Biostatistician in the Center for Biostatistics at OSU, will provide statistical support and data prep for **Projects 2** and **3**. He has worked with Dr. **Paskett** on a P50 and several R01s over the past ten years and has numerous publications with her team[3,19–21]. Mr. Young has worked on several GRTs including a recent multi-level CRC screening intervention and a church-based weight loss intervention with Drs. **Dignan** and **Kennedy**[20]. He has extensive experience in community-based studies and will be involved in both preparing data for analysis and running analyses under the direction of Drs. **Pennell** and **Shoben**.

A.2. Plans for Leadership and Distribution of Core Resources. **Figure 1** illustrates the administrative structure of the Core. Dr. **Pennell** will lead all Core meetings and preparation of Data Safety Monitoring Board reports. Dr. **Dignan** will lead all evaluation activities of the Core and Dr. **Conaway** will be Co-Director of the Core and lead the Biostatistics component under the supervision of Dr. **Pennell**. Drs. **Conaway**, **Pennell**, and **Shoben** will supervise the statistical analyses for **Projects 1**, **2**, and **3**, respectively. Core members will meet monthly to discuss project updates, data management issues, and proposed analyses. These meetings will support synergy in analysis across the projects by providing a forum for trouble shooting analysis problems, sharing analysis code, and developing new statistical methods, as necessary. First priority of resources will be given to the specific aims of the projects. To ensure that Core resources are utilized appropriately, analysis requests will require a manuscript proposal and review by the P01 Steering Committee (see the **Administrative Core**), which includes Dr. **Pennell**. All investigators will have equal access to Core resources through the manuscript proposal procedure and requests will be prioritized based on a first come first serve basis.

B. ACTIVITIES AND FUNCTIONS OF CORE

B.1. Aim 1: Formulation of hypotheses and the design of experimental studies. Members of this Core have worked closely with the Project Leads to ensure that the projects were properly designed and powered to test hypotheses proposed and achieve the specific aims. All three projects are Group Randomized Trials (GRTs) evaluating interventions targeting behaviors that reduce cervical cancer risk. In GRTs, identifiable social groups are randomized to treatment condition with measurements taken on group members to assess the impact of the intervention. The GRT is considered the gold standard for evaluating interventions that manipulate the physical or social environment, involve social processes, or cannot be delivered to individuals without the risk of contamination[22–24]. In all three projects, clinics within the same health system will be randomized to either an early or delayed intervention arm (**Figure 2**). The projects involve multilevel interventions (MLIs) targeting health systems, providers, and patients: the MLI in **Project 1** is intended to increase the 6-month quit rate among female smokers aged 18-64 years; the MLI in **Project 2** is intended to increase uptake of the HPV vaccine; and the MLI in **Project 3** is intended to improve completion rates of cervical cancer screening. Since providers will be exposed to the intervention in all three projects and providers often see patients at different clinics within the same health system, intervention arm will be assigned at the health system level to avoid contamination.

Figure 2. Study Schema



The three projects will be implemented as an integrated cervical cancer prevention program in clinics in ten health systems across four states. Randomization will be stratified by state, with clinics assigned to the same arm (early vs delayed intervention) in each project; e.g., health systems assigned the early intervention in **Project 1** will also be assigned the early intervention arm in **Projects 2** and **3**. The decision to keep intervention arm consistent within a health system was based on the desire to deliver a bundled prevention program to each clinic. The study design also avoids effect attenuation that could occur if a clinic's intervention arm differs by project;

since all three interventions target cervical cancer risk factors it is possible that one of the interventions could have a positive effect on the outcomes of the other projects (this is particularly relevant to **Projects 2** and **3**).

The Core statisticians assigned to each project will meet weekly with project investigators during the first 6 months of Year 1 and monthly thereafter to discuss the progress of data collection and any design-related issues that may occur. Core members will work with project personnel to resolve such issues to ensure that decisions are not made that compromise the integrity of the design and/or power of the proposed analyses. All manuscripts based on project data will undergo a rigorous review process in which a core statistician will carefully review the aims to determine if the hypotheses are testable using the project data. We will also help investigators differentiate between hypothesis testing and hypothesis generating scenarios and plan analyses appropriate for each (i.e., analyses which control type-I error rate versus analyses which control false discovery rate).

B.1.a Sample size determination. The sample size justification for each project was based on a comparison of proportions by treatment arm, accounting for clustering caused by the health system-level randomization. The sample size for **Project 1** was based on a comparison of smoking cessation rates at 6 months with power calculated using the following formula adapted from Donner and Klar[22]:

$$\textbf{Power} = \Pr\left(T \geq t_{2g-2,1-\alpha/2} - \frac{|\Delta|}{\sqrt{V}}\right) \quad (1)$$

where $t_{2g-2,1-\alpha/2}$ is the 100(1-α/2) percentile from the t distribution with 2g-2 degrees of freedom, Δ is the intervention effect (difference in quit rates), and V is the variance of estimated intervention effect:

$$V = \frac{[\pi_I(1-\pi_I)+\pi_C(1-\pi_C)]*[1+\rho(m-1)]}{mg}, \quad (2)$$

with π_I and π_C denoting the quit rates in the early and delayed intervention arms, respectively, ρ is the health system-level intraclass correlation coefficient (ICC), g is the number of health systems per arm, and m is the number of subjects per health system. Assuming the abstinence rates in the delayed and early intervention arms are 10% and 25%, respectively, and an ICC estimate of 0.017, 5 health systems per arm and 43 subjects per health system will provide 80% power for the primary outcome at a two-sided α of 0.05. If the actual ICC is as high as 0.027 (42% greater than the clinic-level ICC we observed in a previous smoking cessation study[25]) the power would be 80% for a comparison of 10% vs 27% abstinence rates; with an ICC of 0.014, there is 90% power for these abstinence rates. The sample size was inflated to 51 per health system (or 510 total) to allow for 20% dropout (a conservative estimate based on our previous studies). Inflating our sample size by this dropout rate, ensures the power values above under the conservative assumption of no power benefit from imputation.

The sample size for **Project 2** was based on an ANCOVA model applied to health system-level vaccination rates (i.e., health system is the unit of analysis); this analytical approach is described in Pennell et al.[26] and was implemented in Krok et al.[2] In the ANCOVA model for our primary outcome analysis, we will compare the two intervention arms with respect to change in health system-level rates of HPV vaccine initiation among 11-12 year old patients over the early intervention period, adjusting for the rate at 12 months (baseline). The power calculation for this project required two modifications to the formula used in Project 1: different degrees of freedom (2g-3) and a modified variance formula accounting for the adjustment for the 12-month rate:

$$V = \frac{[\pi_I(1-\pi_I)+\pi_C(1-\pi_C)]*[1+\rho(m-1)]*(1-R^2)}{mg}, \quad (3)$$

where R is the correlation between the health system-level rates at 12 and 24 months[26]. In a previous HPV intervention study[4], we observed a small negative county-level ICC; thus we invoked the conservative approach recommended by Hade et al.[27] and used a small positive ICC (0.01) for our power calculations. In addition, based on data from a pilot study of our intervention, we assumed a 30% vaccine initiation rate in the delayed intervention arm at 24 months. At a two-sided type-I error rate of 5% and varying correlation between the health system rates at 12 and 24 months ($0.5 \leq R \leq 0.7$), our sample size of g = 5 health systems/arm and m = 150 11-12 year olds per health system provides over 90% power to detect an intervention effect of 13% or greater.

The **Project 3** sample size calculation was similar to **Project 1**. In this study, we conservatively assume 10% of women in the delayed intervention health systems will come into adherence with cervical cancer guidelines and 25% in the early intervention group will come into adherence. Assuming a conservative ICC of 0.017 (ICC=0 in our pilot data), 78 women per health system will provide 90% power at a two-sided α of 0.05. We actually expect that 30% of women will come into adherence, which would give us greater than 90% power for ICC values ≤0.036.

B.2. Aim 2: To conduct and direct the statistical analysis of data

B.2.a Primary Outcome Analysis.

B.2.a.1 Project 1. Hierarchical (mixed) models will be used to compare patient-level smoking cessation outcomes at 6- and 12-months between patients within clinics in the early vs delayed intervention health systems.

Logistic models will be used for the binary outcomes, including the primary outcome of 7-day point prevalence. Similar analyses will be done for the secondary outcomes including floating and prolonged abstinence and at least one 24-hour quit attempt. Mixed effects logistic models will also be used to compare the proportion of patients receiving "Ask, Advise, and Connect" from their providers pre-intervention, during the intervention and post-intervention. Number of quit attempts following the intervention will be analyzed using models for count data. Mixed model estimates will be obtained using residual pseudo likelihood maximization[28] and Wald tests will be used for hypothesis tests with degrees of freedom calculated using the between-within method[29]. Mixed models will be fit using PROC GLIMMIX in SAS (SAS Inc., Cary, NC).

B.2.a.2 Project 2. In **Project 2**, our primary interest is in the change in HPV vaccination initiation rates among 11-12 year olds between 12 (end of baseline) and 24 (end of early intervention) months of the grant period. Vaccination rates will be aggregated at the health system level and analyzed using an ANCOVA model which regresses the change in rate for an individual health system on arm (early vs. delayed intervention) and baseline rate. To account for differences in number of patients across health systems, the ANCOVA models will be weighted using an approach described by Johnson et al.[30] Similar analyses will be used to compare intervention arms with respect to uptake of the first HPV shot by 13-26 year olds and series completion (all age groups).

B.2.a.3 Project 3. The statistical methods for the primary analyses are identical to **Project 1**: logistic mixed models will be used to compare binary patient-level outcomes (e.g., coming into adherence with screening guidelines) between intervention groups.

B.2.b. Common Statistical Procedures across Projects

B.2.b.1 Intent-to-Treat Principles. Data analyses for all three projects will employ intent-to-treat principles[31,32]. Randomization carries the expectation that known and unknown predictors are balanced out across treatment arms at baseline and any subsequent modification of treatment assignment would compromise this balance and bias results. To avoid this problem, we will analyze patient data based on treatment arm determined at baseline, regardless of the level of adherence of patients, providers, and health systems.

B.2.b.2 Confounding. Health systems will be randomized to study arm, stratified by state. However, since the number of health systems is small (N=10), patient factors (e.g., age, insurance status) may differ by arm due to chance. To avoid potential biases in intervention effect estimates caused by imbalance in baseline factors, we will perform comparisons of patient-level and health system-level characteristics by arm. Any factors that differ by a meaningful amount across study arms (e.g., a difference in proportions of 0.1 or greater) will be considered a potential confounder. In **Projects 1** and **3**, health system-level and patient-level confounders will be included as covariates in the primary outcome model. In **Project 2**, health system-level confounders will be included as covariates in the ANCOVA model used to analyze the primary outcome, but we will account for patient-level confounders using a two-stage approach described in Hayes and Moulton[23]: first, we will fit a logistic regression model to the patient-level outcomes containing an indicator of time point (12 vs. 24 months) and any confounders, but ignoring the intervention effect. These logistic regression models will be used to generate residuals and the average residual values within each health system at 12 and 24 months will be used in the ANCOVA model.

B.2.b.3 Missing Data. We recognize that despite our best efforts to minimize the amount of dropout and missing data, we expect some missing outcome data in **Project 1** (**Projects 2** and **3** will use Electronic Health Record data). To avoid biases due to relationships between dropout and patient characteristics, we will use multiple imputation methods appropriate for multilevel data[33] to impute missing outcome data. The imputation models will include health system, intervention group, and any patient factors that differ between those who dropped out and those that completed the study. The number of imputed data sets will equal the dropout percentage as recommended by White et al[34]. Results from the imputed data sets will be combined using Rubin's rules[35].

B.2.c. Additional Analyses. In all three projects, changes in provider knowledge and attitudes about smoking cessation/vaccination/screening following education sessions will be evaluated using mixed models, containing random provider and health-system level effects. We will extend these models in subsequent analyses to examine relationships between the pre-post changes and provider characteristics. Logistic regression models will also be built to identify patient-level and health-system level predictors of each primary outcome.

Each project will also examine sustainability of the proposed intervention. In **Project 1**, we will track the rate at which women are referred to counseling and the billing for cessation counseling. Hierarchical models for count data will be used to estimate the trends over time. In **Project 2**, each intervention arm will be followed after the

intervention period to assess sustainability of the intervention (24 additional months for the early intervention and 12 months for the delayed intervention). A logistic regression model containing random health system effects will be used to compare odds of HPV vaccination at the end of the sustainability period to the odds at the end of the intervention period. The analyses will be stratified by intervention arm with the focus being on the results from the early intervention arm - in this arm, an odds at the end of the sustainability period greater than or equal to the odds at the end of the intervention period will be evidence of sustainability. Sustainability in **Project 3** will be assessed via qualitative and quantitative measures of intervention fidelity such as tracking mailing of self-test kits and evaluating a subset of patient navigator calls.

B.3 Aim 3: Cost Effectiveness Analysis. We will conduct cost-effectiveness analyses for each project, as well as an analysis for the entire Program. The cost-effectiveness analyses will be conducted in three broad steps. We will first conduct a cost identification analysis from a payer perspective rather than the broader societal perspective. We will carefully consider all costs of each intervention (e.g., device type, patient navigator), including those for recruitment, screening tests, personnel training/implementation, staff, data, and administrative costs. We will value the costs of each activity using standard costs and distinguish costs related to our scientific research and those of the interventions themselves. We will only include the intervention costs for the cost analyses. Costs will be discounted and measured in 2019 dollars to ensure comparable estimates, given the differences in timing of the projects and their multi-year follow-up periods. Sensitivity analyses will be conducted by varying the costs of each input and measuring the corresponding variances in the overall costs. The projects will share resources, thus, a highly detailed database will be created across the interventions so that relative uses of a variety of health workforce personnel, health care resources, and other key inputs can be compared. Second, the results of the cost analysis will be combined with the outcome measures to establish the cost per desirable outcome. Specifically, we will characterize the overall incremental costs associated with the early intervention program, compared to no program or a delayed program. We will aggregate the measures of costs and intermediate effect measures of each intervention and calculate the incremental cost-effectiveness ratio, which measures the cost at which an added unit of outcome can be achieved by the early intervention instead of the delayed intervention. Lastly, we will conduct exploratory cost-benefit or cost-effectiveness analyses. We will use potential costs saved from the literature and construct Markov models to project Quality Adjusted Life Years (QALY) for each of the cohorts. The utility (quality) weights and the life years saved from the health outcomes used to calculate QALYs will be drawn from the published literature.

B.4 Aim 4: Program Evaluation. Program evaluation will include documentation and monitoring of implementation (process evaluation) and assessment of progress in reaching goals and objectives (outcome evaluation). Evaluation will focus on each project and core separately as well as the P01 overall and will utilize a mixed-method approach. Examples of process indicators at the project level include adherence to study timelines, communication and interaction between investigators and staff at the different sites, identification and resolution of challenges related to study execution, resolution of conflicts among the study team, and satisfaction of healthcare partners with study personnel and activities. Similar indicators will be developed for each project and core. We will also develop detailed measures for process metrics such as presentations at professional conferences and peer-reviewed publications and abstracts.

Outcome evaluation will focus on assessment of the extent to which project and core goals and objectives are met. Examples of outcome metrics include meeting enrollment and retention goals, fidelity of intervention implementation, and collection of evaluation data. We will provide regular feedback to project leadership and individual investigators on process and outcome metrics. The Core biostatisticians will analyze quantitative data and Dr. **Dignan** will lead analysis of qualitative data drawing on his experience from previous studies[36–38].

Assessment of dissemination and implementation will be guided by the Proctor et al[1] Implementation Research model. As shown below in **Table 1**, the model focuses evaluation on the broad categories of implementation, services, and patient outcomes and provides guidance for measures in each category. Using this model, we will develop metrics to quantify efficiency and through patient report, assess satisfaction with the intervention. To assess penetration, we will collaborate within our Core to analyze patient outcomes. Similarly, for acceptability, we will review enrollment data to quantify gender and racial/ethnic group representation in the study population. For sustainability, we will conduct interviews with health system leadership to assess the likelihood of intervention adoption. We will include in this assessment documentation of alterations to the interventions that health systems will make to facilitate integration.

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