

Examples of Funded Grants in Implementation Science

Overview

The National Cancer Institute (NCI) frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let Implementation Science (IS) post excerpts of their dissemination and implementation (D&I) grant applications online.

About

We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application), where applicable. In addition, we only include a copy of 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).

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424 R&R and PHS-398 Specific

Table Of Contents

Table of Contents

Examples of Funded Grants in Implementation Science	1
Table Of Contents.....	2
SF 424 R&R Face Page.....	3
Project Summary	4
Project Narrative	5
Specific Aims	6
Research Strategy	7
References.....	19

SF 424 R&R Face Page

PI: ELLIOTT, THOMAS EDWARD

Grant Number: 1 R01 CA193396-01A1

Title: Implementing Cancer Prevention Using Patient - Provider Clinical Decision Support

FOA: PAR13-055

FOA Title: DISSEMINATION AND IMPLEMENTATION RESEARCH IN HEALTH (R01)

Organization: HEALTHPARTNERS INSTITUTE

Department: HealthPartners Institute

Senior/Key Personnel: Thomas Elliott

Organization: HealthPartners Institute

Role Category: PD/PI

Project Summary

Millions of U.S. adults and adolescents do not receive key evidence-based preventive care services. Rural populations are especially disadvantaged with multiple healthcare disparities, resulting in lower rates of primary and secondary cancer prevention interventions.

The objective of this project is to implement and evaluate the effectiveness of a sophisticated Web-based, electronic health record (EHR)-linked clinical decision support (CDS) system designed to improve primary and secondary cancer preventive care. To achieve this objective, we link EHR data to evidence-based cancer prevention algorithms in a secure Web site to: (a) identify at the point of care all eligible patients not up to date on their cancer prevention interventions; and (b) present to both patient and primary care provider (PCP) and/or a key member of the primary care team, certified medical assistant (CMA), appropriate evidence-based primary cancer prevention interventions and cancer screening options at the point of care. The Cancer Prevention-CDS will focus on breast cancer screening in women aged 50-74, colorectal cancer screening for both sexes aged 50-75, cervical cancer screening for women aged 21-65, human papilloma virus (HPV) vaccination for both sexes aged 11-26, and referrals for weight management and smoking cessation in all adults aged 18 and older. Effectiveness is assessed by cluster-randomizing 30 primary care clinics with roughly 285 PCPs and 153,000 study-eligible patients into one of three experimental conditions: Group 1: PCP-focused CDS intervention in which the PCP triggers use of the CDS system and engages patients in appropriate cancer prevention strategies. Group 2: CMA-focused CDS intervention in which the CMA triggers use of the CDS system and interacts with the patient to engage them in appropriate cancer prevention strategies before seeing their PCP, who will approve or discuss the plan with their patient. Group 3 clinics provide usual care with no intervention-related activity related to cancer prevention. With 10 clinics, 95 PCPs, and 51,000 potentially eligible patients per study arm, this study will formally test the hypothesis that Groups 1 and 2 are superior to Group 3 over an 18-month follow-up period with respect to: (a) significantly higher rates of appropriate screening for breast, cervix, and colorectal cancer, as defined by the United States Preventive Services Task Force; and (b) significantly higher rates of human papillomavirus (HPV) vaccination in males and females aged 11-26 years. We further posit that Groups 1 and 2 will have higher short-term health care costs but better long-term cost-effectiveness than Group 3. The Consolidated Framework for Implementation Research (CFIR) and RE-AIM conceptual frameworks will be used to guide implementation planning, organization, conduct, and impact evaluation of the intervention in a large rural healthcare system.

This project will engage a rural population with substantial healthcare disparities and gaps in the receipt of primary and secondary cancer prevention. Results will advance dissemination and implementation research methods that can reduce health disparities and improve healthcare for millions in medically underserved areas.

Project Narrative

If primary and secondary prevention practices for breast, colorectal, and cervical cancer were improved, more than 100,000 cancer deaths a year could be delayed or averted in the United States and the burden of these diseases on quality of life reduced. In this project, we will adapt, implement, and evaluate a proven electronic health record-linked, Web-based, personalized clinical decision support system to identify patients needing primary and/or secondary cancer prevention care. The objectives of this project are to improve the quality and consistency of primary and secondary prevention of common cancers in rural areas by providing patient-centered and evidence-based treatment recommendations to both primary care provider teams and patients at the point of care and provide an efficient and effective model for implementation and dissemination of cancer prevention in rural settings.

Specific Aims

The objective of this project is to close the gap in implementation of evidence-based, personalized cancer prevention in rural populations, thus accelerating progress towards Healthy People 2020 goals, with potential to prevent or delay as many as 100,000 cases of cancer annually.^{7,8} To achieve this objective, we aim to develop and implement a sophisticated electronic health record (EHR)-linked clinical decision support (CDS) system in rural primary care clinics to improve the quality of primary and secondary cancer prevention services in those at risk for common types of cancer. Rural primary care providers (PCPs) especially need effective and efficient tools due to suboptimal application of cancer prevention in their practices. Limited patient access, constrained time, and patients who are older, poorer, and less healthy than patients in urban areas characterize rural healthcare.⁹ To achieve this objective, the Cancer Prevention CDS (CP-CDS) links EHR data to evidence-based cancer prevention algorithms to deliver point-of-care, personalized, patient-centered cancer prevention recommendations to the patient through either the patient's PCP and/or the patient's certified medical assistant (CMA). The Consolidated Framework for Implementation Research (CFIR)¹⁰ will be used to guide how implementation is planned, organized, and conducted. The RE-AIM framework¹¹ will be used to evaluate impact and the optimum processes for implementing and disseminating a CP-CDS in rural primary care practices, which has not previously been done. This intervention builds on a decade of work by our research team, is specifically designed for widespread use in primary care settings that use EHR systems, and could improve quality of cancer preventive care and quality of life, decrease morbidity and mortality, advance implementation science as it pertains to rural primary care, and help achieve Healthy People 2020 goals.^{7,8} To accomplish these ambitious objectives, the project addresses these specific aims and hypotheses:

Specific Aim 1. Conduct a cluster-randomized trial that includes 30 primary care clinics with 285 PCPs and more than 153,000 patients to one of three study arms: (a) PCP-focused or (b) CMA-focused intervention using an EHR-linked, Web-based CP-CDS system, or (c) usual care (UC) to assess whether this intervention can improve the delivery of evidence-based, personalized primary and secondary cancer preventive care in rural primary care settings.

Hypothesis 1 (H1). Eligible study subjects will have significantly different rates of appropriate screening tests for breast, colorectal, and cervical cancer as defined by the U.S. Preventive Services Task Force (USPSTF) during the 18 months after the index visit by study arm, with PCP-focused higher than UC and CMA-focused higher than UC.

Hypothesis 2 (H2). Eligible study subjects will have significantly different rates of human papilloma virus (HPV) vaccination in appropriate cases, as defined by the Advisory Committee on Immunization Practices/Centers for Disease Control and Prevention during the 18 months after the index visit by study arm, with PCP-focused higher than UC and CMA-focused higher than UC.

Specific Aim 2. Assess the cost and cost-effectiveness of the Cancer Prevention CDS intervention from the health system perspective through empirical analysis and microsimulation modeling of patient use and outcomes.

Hypothesis 3 (H3). After controlling for demographics and baseline clinical risk factors, eligible study subjects will have significantly different overall healthcare costs during the 18 months after the index visit by study arm, with PCP-focused higher than UC and CMA-focused higher than UC.

Hypothesis 4 (H4). Using cost-effectiveness microsimulation modeling methods, eligible study subjects will have significantly different overall costs and cancer burden in a 30-year post-intervention simulated analysis by study arm, with PCP-focused lower than UC and CMA-focused lower than UC.

Specific Aim 3. Describe critical facilitators and barriers for the Cancer Prevention CDS implementation process, outcomes, and future dissemination strategies using a mixed-methods approach supported by the CFIR and RE-AIM conceptual frameworks.

Results of this pioneering project will: (a) lead to improved delivery of personalized, evidence-based primary and secondary cancer preventive services, helping achieve Healthy People 2020 goals;^{7,8} (b) advance our understanding of how best to integrate effective personalized cancer preventive CDS into primary care workflows; and (c) guide effective dissemination and implementation of similar EHR-linked, Web-based, personalized CDS systems to other rural primary care clinics and delivery systems.

Research Strategy

1. Significance

1.1 Gaps in Cancer Prevention Care: cancer remains a major cause of death and disability, despite significant advances in cancer treatment and improved understanding of cancer mechanisms of disease over the last 50 years.^{12,13} Although the U.S. age-adjusted cancer death rates have decreased very slightly over the last 20 years, the absolute number of people who will be diagnosed and die of cancer will continue to increase for the foreseeable future.¹³ Cancer is the second leading cause of death in the United States, but in several states, such as Minnesota, it is No. 1.¹⁴ Furthermore, the counties in Minnesota, Wisconsin, and North Dakota served by the healthcare system that this project will engage have the highest cancer death rates in their respective states.¹⁵ Since the sentinel article by Doll and Peto in 1981, massive evidence has accumulated confirming that nearly two-thirds of cancer deaths can be linked to tobacco use (30%), unhealthy diet/obesity (30%), and physical inactivity (5%).¹⁶⁻²¹ Unfortunately, the U.S. smoking rate remains a persistent problem (42 million adults still smoke),²² adult obesity and overweight rates have doubled over the last 40 years (to 35% and 34%, respectively),²³⁻²⁷ and fewer than 48% of adults meet the CDC's 2008 Physical Activity Guidelines.²⁸ Moreover, less than 10% of adults regularly engage in all four lifestyle practices known to reduce cancer risk: physical activity, healthy eating, no tobacco use, and effective weight management.¹⁷⁻²⁸ Innovative approaches to address primary as well as secondary prevention of cancer are urgently needed.

Most U.S. healthcare is delivered in clinics by primary care providers (PCPs), but cancer prevention often receives insufficient attention due to time constraints, competing priorities, lack of clinical decision support (CDS), PCP skepticism about patient adherence to recommendations, patient and PCP knowledge deficits related to cancer prevention, and complicated clinical guidelines based on an ever-evolving set of demographic, genetic, and behavioral risk factors.²⁷ In this scenario, electronic health record (EHR)-linked CDS systems would seem to have great potential to improve care, especially if it is addressed to both patients and PCPs. As early as 1992, the Institute of Medicine anticipated that EHR systems and linked CDS would rapidly improve chronic disease care and preventive care services.²⁹ However, this potential has been only slowly fulfilled.³⁰ With respect to cancer, the full impact of EHR-linked CDS for primary and secondary cancer prevention has yet to be actualized. In a recent review article evaluating CDS for cancer screening, only 10 articles met criteria for adequate study design and analysis.³⁰ None of the 10 studies combined two or more cancer screening tests, and most (8/10) implemented only simple reminder systems that were not very sophisticated. Furthermore, evidence demonstrating positive effects of CDS on cancer prevention clinical and economic outcomes is sparse, and studies that evaluate the relationship of Cancer Prevention (CP-CDS) systems to clinic and PCP workflow and efficiency, configuration of office teams, and interactions with patients and shared decision-making are nonexistent. To the best of our knowledge, no CP-CDS system that combines multiple current evidence-based cancer screening tests (secondary prevention) with primary cancer prevention interventions (smoking, obesity, human papilloma virus [HPV] vaccination) has been formally evaluated in primary care settings. Furthermore, we are aware of no dissemination and implementation research that has studied CP-CDS in primary care and determined effective processes and their outcomes.

1.2 Healthcare Disparities in Rural Populations: About 20% of Americans (60 million) live in rural areas characterized by older age, lower per capita income, transportation barriers, less education, poorer access to healthcare, lower use of cancer prevention care, and fewer physicians per capita than most urban areas, resulting in substantial health disparities.⁹ Rural PCPs need effective and efficient EHR-linked CDS systems to automate personalized data to reduce these disparities.

1.3 Implementing EHR-linked CDS Systems to Improve Cancer Prevention: Our project implements and evaluates a comprehensive CP-CDS system that embraces multiple components of primary and secondary prevention for common cancers. It is based on previous NIH-funded projects conducted by our team (DK068314, HL102144) demonstrating that a specific approach to EHR-linked CDS, providing evidence-based CDS to both the PCP and the patient at the point of care: (a) significantly improved important chronic disease outcomes (blood pressure [BP] and glucose control), (b) was consistently used by clinic teams at 75%-80% of targeted visits, and (c) received a 95% satisfaction rating from PCPs who used it. This EHR-linked CDS system is designed to incorporate evidence-based factors shown in meta-analyses to be linked to success, including (a) providing advice automatically within the clinic workflow, (b) providing CDS advice to both patients and providers, (c) providing monitoring and feedback on use rates, and (d) including healthcare team members other than physicians.³¹⁻³³

Based on the recent expansion of the roles of medical assistants in primary care reported by Bodenheimer and others, we believe they can improve the performance of cancer prevention services by further involving Certified Medical Assistants (CMAs), as discussed below.³¹⁻³³

Several recent developments make EHR-linked Web-based point-of-care CDS for cancer preventive services feasible on a large scale for the first time: (a) over 80% of PCPs now use EHR systems, (b) we have shown in a randomized controlled trial that our EHR-linked, Web-based approach to CDS significantly improves chronic disease care in high-risk adults,^{34,35} (c) this CDS system requires only minor adjustments in clinic workflow and does not slow PCPs down, (d) Web-based algorithms can be easily updated and are highly scalable to both large and small healthcare delivery systems, and (e) previous cost-effectiveness analysis indicates that this approach to CDS is highly cost-effective and may be cost-saving at scale.³⁴ After adapting previous work to the needs of our new clinical target, we will randomly assign 30 primary care clinics to 3 groups (10 intervention clinics in the PCP-focused group, 10 intervention clinics in the CMA-focused group, and 10 usual care clinics) with 285 PCP/CMA care teams and about 153,000 primary care patients. A particular focus in our project is to compare the impact of a PCP-focused CDS workflow with a CMA-focused CDS workflow.

2. Innovation: Innovative features of this project include: (a) extension of existing CDS technology to identify adults and adolescents at risk for common cancers and provide evidence-based personalized cancer preventive care recommendations at the point of care (multiple times, if necessary), (b) integration of both primary and secondary cancer prevention interventions in a single EHR-linked, Web-based algorithmic CDS tool has never been done before, (c) presentation of CDS recommendations to the patient and also to providers (either PCP or CMA), (d) inclusion of a cost, cost effectiveness, and provider satisfaction assessments to guide future use of the technology, and (e) acquisition of valuable qualitative and quantitative information needed to optimize dissemination and implementation of CDS systems in rural healthcare settings.

The degree of patient involvement in the development of the tool is also innovative. We work with a panel of patients and consultant experts to develop, pilot test, and optimize the patient and provider interfaces. Once finalized, interfaces are given to the patient and PCP or CMA care team just before the clinical encounter and enable visit planning by the PCP/CMA care team and expression of evidence-informed and personalized treatment preferences by the patient. This promotes evidence-informed patient decision-making and is an exciting advance in patient-centered care. The 3-arm research design allows testing of the comparative effectiveness of PCP-focused vs. CMA-focused CDS at the point-of-care. Other innovative aspects of the project include: (i) using the patient interface to efficiently elicit personalized cancer prevention preferences of each patient before the PCP visit, (ii) establishing clinic workflows that support timely provision of personalized, evidence-based CDS at the point of care, (iii) incorporating all treatment algorithms in a Web site rather than the EHR to enable efficient maintenance, quality assurance, and updates as guidelines evolve over time, and (iv) finally, this project creates a Web-based EHR-linked CDS template that is very scalable and can be rapidly disseminated to the 80% of primary care practices that now use EHRs, enabling consistent and reliable application of evidence-based CP-CDS to large populations of patients.

3. Preliminary Studies and Investigators

3.1 Preliminary Studies and Previous Experience: The core investigators (Drs. Elliott, O'Connor, Sperl-Hillen, Sherwood, and Flottemesch) form an experienced multidisciplinary team with expertise in oncology, primary care, CDS design and interfaces, health economics, biostatistics, health behavior change, and implementation science (HL102144, DK079861). The PI, Dr. Elliott, is an experienced oncologist and health services researcher with extensive experience in cancer prevention in rural settings.³⁶ His experience includes the Lake Superior Rural Cancer Care Project (CA056334), a cluster-randomized trial including 18 rural communities in Minnesota, Wisconsin, and Michigan that tested interventions to improve cancer treatment and patient outcomes, and the Minnesota Cancer Pain Project (CA057803), a cluster-randomized trial in 6 Minnesota cities of interventions to improve cancer pain management and patient outcomes. Drs. O'Connor and Sperl-Hillen are currently conducting a randomized trial evaluating CDS tools for adults with high 10-year reversible cardiovascular risk (HL102144), and our team previously completed a study showing that EHR-linked CDS improves glucose and BP control in adults with diabetes (DK068314). Dr. Sherwood has extensive experience as PI on multiple NIH studies focused on obesity prevention and/or treatment interventions in youth and adults (CA188892, HD068890, DK084475, DK078239, CA128211). Dr. Flottemesch is an economist nationally recognized for developing comparable and consistent microsimulation models evaluating the cost-effectiveness of various preventive health services recommended by the USPSTF³⁷⁻⁴⁰ and the Task Force on Community Preventive Services,⁴¹ as demonstrated by more than a decade of analytical support and technical advising to

the National Commission on Prevention Priorities. The team has published detailed, model-specific articles with respect to colorectal cancer and other conditions.⁴²⁻⁴⁶ Consultants Drs. Stange and Crabtree have extensive experience in primary care research, preventive services, patient outcomes, and qualitative methods, with special focus on dissemination and implementation research. In our many previous projects, we have developed effective project-management strategies, refined methods to access EHR data, developed effective provider and patient interfaces, addressed data privacy concerns, and developed an EHR-Web link that can generate sophisticated point-of-care CDS to more than 600 patients a minute. Our previous and ongoing work in cancer care and pain research (CA56334, CA57803, NS045361), comparative effectiveness research (HS019912), lifestyle interventions (AG023410, CA128211), cardiovascular care (HL102144, HL093345, HL090965, HL089451), and cardiometabolic care (HC95183, HS019859, DK06650, HS10639, DK068314), along with more than 400 publications on these and related topics, makes our team uniquely qualified to successfully conduct this ambitious project.⁴⁷⁻⁵⁸

3.2 Preliminary Assessment of the Study Population: Data collected 01/01/12 to 12/31/14 demonstrate that there will be a sufficient number of Essentia Health (EH) patients to power this cluster-randomized trial (Table 1). In addition, EH PCP primary cancer prevention activity at the study site, based on data collected 01/01/14 to 12/31/14 show: Referrals for smoking cessation services = 4.4% (1159 referrals/26,574 active smokers); Prescriptions for quit smoking drugs = 7.1% (1901 prescriptions/26,574 active smokers); Referrals to dietitians or weight management programs = 1.9% (1521 referrals /80,730 patients with BMI >25.0 kg/m²)

4. Approach

4.1 Theoretical Framework: This project will improve our understanding of how to implement and disseminate CDS systems in diverse primary care settings. The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM)¹¹ and the Consolidated Framework for Implementation Research (CFIR)¹⁰ provide conceptual frameworks to study the implementation and dissemination of the CP-CDS in primary care. We use RE-AIM

Cancer screening/prevention, ages	N patients eligible for screening*	% Up to date on screening or HPV vaccination ¹	% Current smoker	% Obese	Rural N (%)	Urban N (%)
Colorectal, 50-75	87,019	67.1	16.5	45.6	52,368 (60.2)	34,651 (39.8)
Breast, 50-74	44,542	65.9	16.0	43.5	26,940 (60.4)	17,602 (39.6)
Cervix, 21-65	75,420	53.9	21.8	41.1	40,028 (53.1)	35,392 (46.9)
Subjects eligible for HPV vaccine, 11-26 ¹	40,297	3 doses: 5.1 males, 19.5 females [#]	12.8	18.4	20,484 (50.8)	19,813 (49.2)

Patients with missing data are not included in denominator. Total patient population is significantly larger for all categories.
 **Data collection timeframe: Jan. 1, 2012 to Dec. 31, 2014
¹Patients who received cancer screening test or human papilloma virus vaccine
[#]1 or 2 doses of HPV vaccinations: 9.6% males, 30.1% females
²BMI>30.0

framework to quantify the reach and effectiveness of the CP-CDS and its potential for dissemination and scalability by evaluating CDS use rates, provider workflow, and patient/provider experience. The CFIR framework consists of 5 domains (the intervention, internal context [practice], external context [system], participants, and implementation process) that will be used to guide how implementation is planned, organized, and conducted. We will use key CFIR components to identify influences and adaptation of the implementation, direct observation of its fidelity, and evaluate its sustainability and prospects for wider dissemination (Specific Aim 3). This mixed-methods approach will greatly improve our understanding of how to successfully implement and disseminate CP-CDS and similar systems to other practice settings, clinical domains, and patient populations.

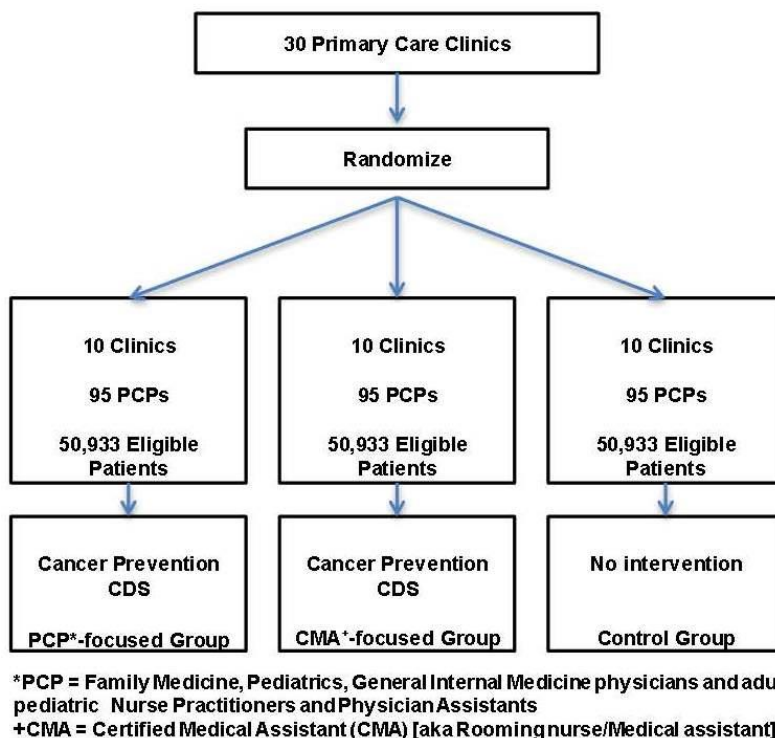
4.2 Study Design: Supported by CFIR and RE-AIM frameworks, the implementation process for CP-CDS has four phases: a) initial organizational engagement; b) adopting and piloting the CP-CDS with Essentia Health (EH) PCPs and patients; c) a cluster-randomized controlled trial with 3 arms in 30 EH primary care clinics, and d) evaluation of the implementation process and outcomes. For this 3-arm cluster-randomized controlled trial, 30 primary care clinics will be blocked on rural vs. urban location (using RUCA2-UR codes) and the proportion of patients at each clinic receiving Medicaid assistance and then randomly assigned to the PCP-focused intervention (PCP), CMA-focused intervention (CMA), or usual care (UC) (Figure 1) in a 1:1:1 allocation. Consenting provider teams at each clinic will be allocated to the same study arm as their clinic, and eligible patients of each PCP/CMA-care team will be allocated to the same study arm as their PCP.

4.3 Study Sites: This study will be conducted at 30 Essentia Health (EH) primary care clinics in North Dakota, Minnesota, and Wisconsin. Leaders at EH are fully committed to the project, as indicated in letters of support from

Drs. Nikceovich and Bianco. These 30 clinics have used the EpiCare® EHR since 2004 and have, on average, 12 PCP/CMA care teams and 6870 eligible patients per clinic (range, 805-20,334). Twenty participating EH clinics are classified as rural and 10 as urban by the RUCA2-UR coding system.

4.4 Study Participants: PCPs and Patients: To participate, PCPs must practice at one of the randomly assigned EH clinics and meet all these additional eligibility criteria: (a) be a general internist, family physician, pediatrician, or adult or pediatric care nurse practitioner or physician assistant, (b) provide ongoing primary care for 25 or more patients who meet study criteria for cancer risk for each of the targeted cancers (pediatricians included and assessed only on HPV vaccinations), and (c) provide written informed consent to participate in the study. CMAs who serve as rooming nurses have central roles in clinic workflow and interact directly with patients before and after the visit with their PCP. CMAs also function as panel managers, health coaches, and team documenters/clinical scribes.³¹⁻³³ Each EH PCP has at least one CMA in their care team, and CMAs will be included as study participants if their PCP consents to participate. There are currently 380 eligible PCPs at the 30 clinics. We anticipate, based on experience in several studies, that we will successfully recruit 75% (N=285) PCPs (95/study group). Reviewers may be skeptical of this high recruitment rate, but power will be adequate even if as few as 81 PCPs (27 per study group) enroll. The larger sample enables subgroup analyses. To be included in Aim 1 analysis, patients must meet all the following eligibility criteria: (a) be 11-80 years old, inclusive, at an index clinical encounter with their consented PCP during the 18-month accrual period, (b) have no

Figure 1. Research Design for Cluster-Randomized Trial



current or past cancer diagnosis other than nonmelanoma skin cancer, (c) no hospice care, cancer chemotherapy, Alzheimer's disease codes, or major cardiovascular event for 12 months before the index visit, (d) have at least 2 subsequent primary care visits within 24 months of the index visit, with at least one visit 12 or more months after the index visit. For each eligible patient, the study period begins on the date of the first qualifying visit (index visit) and ends on the earlier of either the date of death or the date of the last clinic visit in the study period. Based on preliminary EH data in Table 1, we estimate that 152,800 patients will meet eligibility criteria. Less than 5% of patients per year switch from their EH primary care clinic to another EH or non-EH clinic, and losses due to death will be <1% per year. Validated algorithms accurately match over 98% of patients to a regular PCP. Ultimately, after accounting for all exclusions, we anticipate that about 525 eligible adults per consented PCP/CMA care team (149,625 total patients) will be available for analysis. Plans for dealing with missing data are detailed in Section 2.2.8.5. We will request a waiver of informed consent for patients from the Institutional Review Board (IRB) because the care recommendations in the CP-CDS intervention are limited to evidence-based care already recommended in current national and regional clinical guidelines. The IRB has waived patient consent in similar circumstances.

4.5 Description of Usual Care and Intervention Conditions

4.5.1 Usual Care Condition (Arm C): In the usual care group of the study, clinics and their consented PCPs will have no access to the CP-CDS intervention. Some existing Epic reminder systems in EH clinics do address cancer screening tests with reminders that are pop-up alerts, which are easily ignored. These alerts are marginally effective, resulting in current suboptimal rates of cancer screening tests and very low rates of referrals for weight management and smoking cessation and HPV vaccinations (section 3.2). There is no systematic CP-CDS system in EH clinics other than what will be implemented as part of this project in the 2 intervention arms. Simple alerts

have generally been ineffective due to many factors, such as alert fatigue, provider burden, and no patient engagement.^{30,32,59}

4.5.2 Intervention Condition: CP-CDS is rooted in a series of antecedent studies that have developed successful forms of outpatient CDS.⁴⁵⁻⁴⁷ Our project's intervention will have 2 experimental arms: **Arm A = PCP-focused group** and **Arm B = CMA-focused group**. Specific steps in design and implementation of the CP-CDS intervention are described next.

Step 1. Identify Eligible Patients. Extract Clinical Data from EHR, and Send to Web site: In HL102144, we created and validated programming to (i) extract pharmacy, laboratory, vital signs, demographic, comorbidity and other data from the EHR, and (ii) export these data to a secure Web site inside the HealthPartners Medical Group firewall. Web site algorithms will use these EHR-extracted data to identify eligible patients needing primary and/or secondary cancer prevention within 2 weeks of a routine, non-urgent primary care visit. Patients younger than 18 years will not be identified for smoking cessation or weight management treatment or referrals due to the need for different approaches required by adolescents, which is beyond the study scope. Patients 11 to 17 years old will be identified for HPV vaccination only if a parent is present during the clinical encounter. Patients aged 18 and older will be identified for cancer screening tests, HPV vaccinations, smoking cessation, and weight management, if eligible, according to national guidelines previously presented. To avoid firing the CDS too often and burdening the PCP/CMA care team, the CDS algorithms will identify eligible patients only once every 4 months (up to 6 times during the 24-month intervention period). A complete presentation of these primary and secondary cancer prevention needs criteria is in Appendix F.

Step 2. Create Primary & Secondary Cancer Prevention CDS Algorithms: The Web-based treatment algorithms used in this project are based on national guidelines, approved in advance by primary care clinical leaders at EH, and reflect current evidence and community standards of care.⁶⁰⁻⁷¹ Similar algorithms have been tested in 2 previous research projects (DK068314, HL102144). The algorithms for this project will include ICD- 10⁷² codes and will be updated (and revalidated) as required by changes in national guidelines.

Step 3. Collect Patient-Centered Data Using Personalized Tools: Within 2 weeks before their visit, patients will be contacted by email and/or text message to access MyHealth (aka MyChart) to complete needed data. Those not responding or without MyHealth accounts will be contacted by phone by the clinic care coordinator. Nonresponders to MyHealth or phone will be invited to provide these data by the CMA at clinic visit during rooming process. Patient-centered, personalized tools include: Breast cancer risk assessment tool⁵ (BCRAT, NCI), Colorectal cancer risk assessment tool⁶ (CRCRAT, NCI), and Patient Readiness to Change questions (for each cancer prevention need identified, patient will be asked to check/click/respond: Yes/No to "Ready to act" and "Want to discuss.") Only patients needing a cancer prevention intervention will be presented these tools and questions. The BRCAT and CRCAT will compute personalized risks for these cancers, which can be presented during the CP-CDS encounter. Details about these tools and questions are in Appendix G.

Step 4. Identify Available Treatment Options for Cancer Prevention Needs: Web-based algorithms (examples in Appendix F) identify evidence-based prevention options that address each unmet cancer prevention need. Specific CDS recommendations given to a patient are based on both (a) statements from USPSTF,^{60,62-63,66-70} NCI,⁶⁵ CDC,⁶⁴ and ACIP,⁶⁴ and (b) the specific patient's current clinical state, including age, sex, smoking status, BMI, HPV vaccine status, comorbid conditions, allergies, and past screening tests for the 3 target cancers. Cancer screening and treatment recommendations for smoking cessation, HPV vaccination, and obesity management are given as needed. The PCP and/or CMA use the CP-CDS Smart Form to refer the patient directly to appropriate internal or community resources for smoking cessation or obesity management and to order (PCP) or pend orders (CMA) for HPV vaccinations and appropriate cancer screenings. The Smart Form is an EHR form designed to fit into providers' workflow containing actionable functions such as order sets, goals of care, referrals, follow up, and monitoring patient adherence.⁷⁷

Step 5. Present Cancer Prevention Options to PCP/CMA Care Teams and Patients: Clinic Workflow: In this project, CP-CDS recommendations are presented to the patient directly and the PCP and/or CMA, depending on assigned intervention group, using a sequence of clinic staff steps successfully implemented in previous studies and pretested interface formats. Participating PCPs and CMAs in intervention clinics are trained to use the provider and patient interfaces of CP-CDS as follows: When a patient needing cancer prevention interventions has a clinical encounter with a consented PCP or CMA, the following protocol is automatically implemented: (i) after vital signs are entered into the EHR, CP-CDS assesses cancer prevention needs, identifies target patients, and provides a best practice alert (BPA). In response to a single click, CP- CDS displays the interface screen to the CMA within 1 second (with no additional prompts or triggers needed). The CMA prints the

patient and PCP versions of the CP-CDS sheet, (ii) if a patient's mental and physical status appears stable, the CMA hands the patient sheet (example in Appendix B) to the patient, saying "This sheet shows how you can reduce your risk of cancer later in your life. Are you interested in doing something about any of these things?" For patients in the PCP-focused group, the CMA also says, "Let your doctor know during your visit today about your questions or needs for cancer prevention." Alternatively, for patients in the CMA- focused group, the CMA also says, "I will be pleased to discuss these needs or help you to act on your decisions and, if desired, set up appropriate referrals or tests for you. Your doctor will want to know about your decisions, discuss your options, and confirm your plan." If the patient agrees to a plan, the CMA activates the plan via the EHR CP-CDS Smart Form with pended orders or referrals displayed on the EHR for the PCP to discuss with the patient and approve during the exam room visit, (iii) for both the PCP-focused and CMA- focused groups, a printed version of the provider CP-CDS (example in Appendix B) is either placed in the basket outside the exam room for rapid review by the PCP before entering the exam room or displayed on the EHR screen with one click on the EHR navigator bar, depending on the PCP preference, and (iv) in both the PCP- and CMA-focused groups, the PCP uses the CP-CDS PCP interface to guide changes in cancer prevention care and uses the CP-CDS patient interface to reinforce patient actions. The CP-CDS will embrace the 5 A's (Ask, Advise, Assess, Assist, Arrange) to promote patient activation by having these elements embedded in the provider interface.⁴ The patient version may be printed as part of the After Visit Summary. After discussion with the patient, the PCP can order screening tests, medications, or make referrals to internal programs or community resources to address smoking and/or obesity by using the CP-CDS Smart Form.

Provider Interface. CDS included on the provider interface is specific and based on whether the patient has significant cancer risk factors or is due for a cancer screening. Both PCP- and the CMA-focused groups use the provider interface. Prototype CDS algorithms are included in Appendix F and are based on the recommendations published by USPSTF, NCI, CDC, and ACIP.⁶⁰⁻⁷⁰ They will be updated over time to ensure ongoing congruence with national evidence-based guidelines. Information displayed on the CP-CDS provider interface are: smoking and obesity management options, medical interventions (HPV vaccine status, screening status for breast, colorectal, cervical cancer), 5 A's, BCRAT & CRCRAT results, patient's preferences, and suggested re-visit interval. All treatment recommendations are labeled as suggestions, and the interface sheets emphasize that this CDS does not take the place of clinical judgment or a PCP's detailed knowledge of a particular patient. The provider interface is a powerful visit-planning tool that most PCPs prefer to view in print just before entering the exam room.

Patient Interface. A simple visual approach is preferred, because patients may have low levels of numeracy and misinterpret probabilistic information. A visual display of recommended lifestyle modifications (smoking cessation, weight reduction/counseling), medical interventions (HPV vaccination, medications for tobacco cessation), and screening tests for the 3 target cancers are included, depending on the needs of the patient identified by the CDS algorithms. Similar visual patient interfaces we used in earlier studies have been well received by most adult and teen patients,⁷³⁻⁷⁴ accommodate low numeracy, and have been shown in studies by others to be a strong motivational strategy.⁷⁵⁻⁷⁹ However, the prototype interfaces shown in the Appendix B will be substantively modified to address key issues related to cancer prevention care, with extensive input from our adult and teen representatives from EH Patient Councils and extensive pilot testing before randomization.

Incorporating Patient Preference. A key design feature is efficient elicitation of evidence-informed patient treatment preferences. Because patient readiness to take health-related actions often varies across clinical domains, all domains (behavioral change, screening tests, medical interventions) with potential benefit for that patient at that visit are presented. The CP-CDS will determine patient's readiness to change with 2 questions described above to facilitate efficient use of PCP/CMA time. Patient readiness to act is a predictor of subsequent adherence and success of treatment, as we and others have shown.⁷⁸⁻⁸⁷ We will carefully assess adherence to both recommended screening tests and other medical interventions by following each patient's completion of cancer screening tests, HPV vaccinations, obesity management, and smoking cessation during the 24 months after the index visit. During this time, we expect patients to make at least 3 additional visits, which allows revisiting the treatment plan, and observing and recording patient outcomes in the EHR.

Step 6. PCP/CMA Team Activate CP-Smart Form: The Smart Form displays screening tests, HPV vaccinations, and options for managing smoking cessation and weight management as appropriate for each patient. Clicks on the Smart Form order tests and drugs, make referrals, set up follow-up and monitoring plans, and elicit patient's health goals by addressing questions: What will I do? How will I do it? By when? (Data provided by patient and entered in Smart Form). The CP-Smart Form includes monitoring patient's EHR for progress toward completion/working on tests, procedures, and referrals for cancer prevention activities.

Progress is reported to the provider and clinic care coordinator via the EHR in-basket. Patient contact is maintained by MyHealth or clinic care coordinator phone calls to determine progress and help complete care goals. This feedback and monitoring function creates opportunities for behavior change. The Smart Form can be printed and given to the patient with the After Visit Summary. Details of the Smart Form's automated follow-up and monitoring functions are in Appendix G. The CP-Smart Form will contain clinic- and community-based resources for smoking cessation and weight management services, counselors, and programs with locations, contact information, program type, delivery methods, and benefits and costs presented and updated annually.

Step 7. Iterative Use of Cancer Prevention CDS over Series of Visits: A key design feature of this intervention is its repeated use at all routine office visits of eligible patients in intervention study arms A & B. Pilot data indicate that nonpregnant eligible adults will average 3-6 primary care visits during the combined 33-month accrual and follow-up periods.⁸⁷⁻⁸⁸ After the CP-CDS is activated during the 18-month accrual period, subsequent activations are limited to once every 4 months to minimally disrupt clinic workflows. In a previous study (HL102144), rates of use of a cardiovascular CDS system by consented and nonconsented PCPs were 70%-80% of targeted care visits. CP-CDS gives updated treatment suggestions for patients and PCPs to consider at each visit, because CDS evolves as the patient's clinical status, lifestyle, and cancer prevention needs change over time.

4.6 Implementation of the Cancer Prevention CDS Intervention: Throughout the implementation of the CP-CDS, we will conduct key informant interviews, focus groups, surveys, usability testing, and continuous quantitative and qualitative feedback between researchers and participants to measure the implementation processes and outcomes as recommended by the CFIR and RE-AIM frameworks. **Organizational Engagement:** In **Phase 1**, we will engage EH clinic leadership and managers, informatics personnel, and PCPs through meetings to identify potential influences of implementation of this project. **Pilot Testing:** All CP-CDS algorithms and interfaces will be extensively pilot-tested among stakeholders in **Phase 2** to adapt the implementation. Representatives from EH Patient Councils will evaluate the patient interfaces to maximize patient-centeredness. We will then recruit 5 PCP-CMA teams from EH clinics not in the study and pilot test CP-CDS in eligible patients for 4 weeks. Pilot test PCPs and CMAs will be consented and offered compensation to complete online surveys and give feedback on their experience with the CDS tool, including the utility of prompts and effect on clinic workflow. After further modification of the CP-CDS, the project will enter Phase 3. **EH Patient Advisory Councils:** EH has 18 volunteer patient advisory councils that engage patients and families as advisors, mentors, and educators. The main goal of this program is to improve the patient and family experience and quality of healthcare. Drs. McCarty and Conway are involved in these patient councils and will help recruit representative members to regularly review and critique project pilot phase activities, CDS interfaces, survey tools, focus group objectives and results, and project deliverables. This existing infrastructure is ideal for introducing CDS technology to primary care, gaining the reaction and input of patients and families, and refining adaptation of the intervention.

Implementation of the Cluster-Randomized Trial (Phase 3): We will train intervention clinics to use CP-CDS using strategies similar to those EH routinely uses to inform clinic teams of changes to the EHR. They include face-to-face group or individual meetings with all intervention clinic PCPs, CMAs, and clinic staff, plus email reminders with links to a short instructional video demonstrating CMA and PCP roles in CP-CDS use. Training will be completed and CP-CDS fully implemented at the 20 intervention clinics within 30 working days of the project "go-live" date. **Strategies to Ensure PCP and CMA/Care Team Use of the Intervention:** Following implementation, all intervention clinic staff will receive weekly email reports showing CP-CDS use rates. The project manager will meet either in person or remotely with each intervention clinic's nurse manager monthly throughout the 42-month intervention period to assess continued use of CP-CDS and to gather feedback ensuring real-time observation of implementation fidelity. The CP-CDS screen includes a **Visit Resolution Form (VRF)** inviting the PCP to click, before closing the encounter record, one of 3 boxes: (1) any action taken based on CP-CDS recommendations, (2) other cancer prevention-related actions taken, or (3) no cancer prevention-related action taken. If box (3) is clicked, another box must be clicked to indicate why no action was taken. This tool serves multiple purposes: it incentivizes the PCP to take action to avoid additional clicks, quantifies the percentage of visits at which each intervention group PCP is using CP-CDS, and enables us to give feedback to PCPs and clinic leaders on comparative use of CP-CDS. We anticipate that CP-CDS will usually display fewer than 3 times per day per PCP. Support from EH leaders and clinic PCP leaders, plus monitoring and feedback, will help maximize provider adherence to CP-CDS study protocols, as demonstrated by CDS use at 75%-80% of targeted visits in previous projects. The VRF is presented to both PCP-focused and CMA-focused intervention groups.

Evaluation of Implementation Process and Outcomes (Phase 4): During the cluster-randomized trial,

components of the RE-AIM and CFIR frameworks will be assessed to determine mediators of CP-CDS implementation, use, clinical outcomes, and future strategies for dissemination and implementation.

4.7 Definition and Measurement of Dependent Variables: We will use a mixed-methods approach to determine the facilitators and barriers for achieving the specific aims. Appendix A contains the definitions, sources, and metrics for study variables.

Cancer Screening Tests (Aim 1, H1): The dependent variable for H1 is a binary variable indicating that the patient is up to date on screening tests for breast, cervical, and colorectal cancer by 18 months after the index visit. Each patient will be classified as up to date or not (composite endpoint) on all appropriate screening tests, depending on sex, age, risk factors, and date of last needed screening tests according to active USPSTF recommendation statements. This variable will be based on EHR-captured procedure codes, and data will be obtained from the index visit date through the end of the study.

HPV Vaccination Rates (Aim 1, H2): The dependent variable for H2 is a binary variable indicating that the patient has had all 3 HPV vaccinations recommended by ACIP/CDC within 18 month of the index visit. This variable will be coded as “1” for patients having all 3 vaccinations and “0” for patients with 0-2 vaccinations. HPV vaccination data will be obtained from the EHR from the index visit date through the end of the study.

18-month Health Care Costs (Aim 2, H3): Costs for this analysis are defined as intervention costs as well as the incremental medical care costs associated with the intervention from the health system perspective. Intervention costs include CDS implementation and maintenance, training, and incentives but exclude intervention research and development costs. Medical care costs include costs of all medical services- including laboratory, physician services, and screening tests-incurred in the 18-month post-index date period by participants in each study group, as indicated by EH billing and clinical encounter data. Described in detail in the Section 4.9.3 below, we will use relative value units (RVUs) and diagnosis-related groups (DRG) to calculate inpatient and outpatient costs for patients randomly assigned to each study group and standard accounting methods to measure the cost of the CP-CDS intervention. Emergency visits and hospitalizations may be too infrequent in the study sample to accurately predict a population-wide impact of the study interventions. If there were no intervention impact on these utilization components during the study period, including their costs would substantially increase variance in the cost data without adding to the accuracy of the cost assessment. Therefore, we will first assess whether there is a differential impact between CP-CDS and usual care on use of these services and will include their costs only if a difference is observed. Reliance on EH billing records for measuring medical care use may miss costs incurred in other health systems; however, this opportunity is expected to be equal across randomized study arms, and cross-system medical utilization is expected to be relatively limited in the primarily rural study population.

Long-term Cost and Health Outcomes (Aim 2, H4): Microsimulation modeling will be used to predict long- term medical costs, health outcomes, and cost-effectiveness across study arms over a 30-year post- intervention period. Health outcomes will include incidence, morbidity, and mortality of breast, cervical, and colorectal cancers and the predicted medical costs corresponding to treatment of these conditions. Calculation and reporting of incremental CE ratios (ICERs) will follow the guidelines of the Panel on Cost-Effectiveness in Health and Medicine from the health system perspective.⁸⁹

Facilitators and Barriers of Implementation (Aim 3): For this analysis, we use the CFIR and RE-AIM frameworks to assess implementation process and outcomes.^{10,11} RE-AIM metrics are: a) percent and type of patients reached, b) for whom the intervention was effective, c) percent of clinics and providers adopted the intervention, d) consistency and cost of intervention implementation, and e) proportion of intervention components and effects maintained. CFIR metrics include PCP and CMA perceptions of CDS source, strength and quality of the evidence base, iterative adaptability and testing of the CDS and usability testing; external policies and incentives affecting implementation; implementation climate and readiness; PCP/CMA engagement; fidelity of implementation and modifications made; and PCP/CMA knowledge, attitudes, beliefs, and self-efficacy about the CDS. Detailed descriptions of these metrics are in Appendix A.

Our mixed-methods approach includes: a) semi-structured interviews conducted with 8-10 EH leaders and PCPs during Year 1 to understand organizational support and culture to guide CDS implementation and Year 4 to plan future dissemination; b) meeting minutes from organizational engagement and study implementation, c) patient focus groups during Years 2-4 (6 groups of 6-8 patients recruited from the CDS arms) to learn about their experiences with the CDS and perceived barriers and facilitators to act on the CDS personalized recommendations; d) PCP/CMA focus groups during Years 2-4 (6 groups of 6-8 subjects recruited from the CDS arms) to learn how to improve CDS use, effectiveness, and dissemination to other clinics; e) cross- sectional PCP

surveys conducted in Year 1 before randomization (pretest) and Year 4 (post-test) among 30 randomly selected PCPs in each study arm (total 90) to assess perceptions of primary practice systems using the 20-item Physician Practice Connections Readiness Survey (PPC-RS, Appendix G), including PCP demographics, experience, and use of CDS;⁹⁵ f) in Year 4, PCPs/CMAs in Arms A & B will complete the 10-item System User Scale (SUS, Appendix G) to assess their experience with the CDS;⁹⁶ and g) patient surveys in Years 2-4 on a cohort of 150 from each arm (total = 450) to assess their experience with cancer prevention care in their primary care clinics using the Clinic and Group Consumer Assessment of Healthcare Providers and Systems (CG-CAHPS, Appendix G).⁹⁷ After giving consent, patients will complete the survey and answer questions about their participation in clinic- or community-based education, counseling or programs about smoking cessation and weight management. Patient survey eligibility criteria include at least two PCP visits in 1 year before the index date and have MyHealth Internet access to be contacted and complete the consent and survey. Patients will be surveyed within 15 days of their index visit and after an 18-month visit. These visits will automatically trigger delivery of the survey via MyHealth. Drs. Crabtree and Conway, experts in primary care improvement, focus group technique, and qualitative research methods, will lead the work of this aim.

Dependent Variables for Secondary Analyses: In Appendix A, primary and secondary dependent variables are defined, some of which assess potential moderators of intervention effects. Secondary analyses include (a) rural-urban comparisons, (b) separate binary outcomes for the 3 screenings tested as a composite in H1: colorectal, breast, and cervical cancer, (c) a binary outcome of any HPV vaccinations vs. none within 18 months of the index date, and (d) binary indicators for referrals to internal or community programs for obesity management, smoking cessation, or medications prescribed for smoking cessation.

4.8 Measurement of Independent Variables Primary Predictor: The primary predictor is the treatment arm to which a clinic is randomized. This variable will be coded as a two degree of freedom contrast with the usual care (UC) arm as the reference category. Planned contrasts will examine pairwise differences in treatment arms.

Patient and Provider Characteristics: Patient and provider characteristics listed in Appendix A will be documented so we can assess the extent to which results apply to subgroups of patients or whether patient or PCP characteristics modify intervention efficacy. Patient sex will be an important covariate and stratifying factor in the analysis because screening rates for H1 are likely to be different by sex. Clinic randomization may introduce random or selection-induced patient or PCP covariate imbalance, necessitating adjustment. Patient characteristics obtained from the EHR, include demographics, pre-intervention comorbidities (derived from dated ICD-10 diagnosis codes), Charlson score, insurance status, vital signs, height, weight, smoking status, HPV vaccine status, family history of breast or colorectal cancer, and previous cancer screening test dates and results, among others. Furthermore, primary care visit dates will link patients and PCPs. We will have complete data for PCP characteristics, including age, years since graduation, sex, full-time or part-time status, physician or allied provider (ie, nurse practitioner), specialty board certification status, years with EH, and proportion of linked patients up to date on cancer prevention at baseline. CMA demographic data will also be available.

4.9 Analysis Plan

4.9.1 Aim 1 Analytic Approach

Hypotheses 1 & 2 in Aim 1 posit that patients seen at clinics with the CMA-focused or PCP-focused cancer screening CDS will be more likely than patients seen at UC clinics without the CDS to have appropriate screening for breast, cervical, and colon cancer (H1), and a full course of three HPV vaccinations (H2) within 18 months of an index visit. Because clinics are the unit of randomization and the outcome varies at the level of the patient, generalized linear mixed-model regression with a logit link and binomial error distribution will be used to test the effect of the interventions. The general form of the analytic model for H1 & H2 is:

$$\text{DependentVariable}_{kji} = \psi_{000} + \psi_{100}\text{CMA_CDS}_k + \psi_{200}\text{PCP_CDS}_k + \psi_{001}\text{SEX}_i + [\nu_{k00} + u_{kjo} + e_{kji}]$$

The dependent variable in each model is a binary indicator of appropriate screening (H1) or complete course of HPV vaccination (H2). The dependent variable is predicted by the two fixed-effect terms representing the study arm contrast (CMA_CDS and PCP_CDS). Patient sex is included as a fixed effect because screening rates for H1 and vaccination rates for H2 are likely to be different. We will screen patient characteristics to determine whether they differ across study arm and include patient covariates in the model when they are unbalanced by treatment arm. Interaction terms between patient sex and study arm are included to allow for differential effect of the intervention by patient sex. Random terms are included for clinic (ν_{k00}), provider (u_{kjo}), and patient (e_{kji}).

A significant treatment group effect ($P < 0.05$) and positive and significant parameters for the treatment group terms ψ_{100} and ψ_{200} for each hypothesis will support the H1 & H2 predictions that clinics with CDS interventions are

more effective than clinics without them for increasing cancer screening and HPV vaccination rates. This model will include patient sex and patient variables unbalanced by study arm as well as the indicated random effects. Treatment group heterogeneity by sex will be assessed by including interaction terms between patient sex and the two study arm indicators. A likelihood ratio test will be used to evaluate the necessity of retaining the interaction terms of patient sex by study arm.

4.9.2 Aim 1 Sample Size Justification

Hypothesis 1: Using a preliminary data pull of patient visits from 2011-2013, we estimate there are 9390 male patients (3133 per study arm) aged 50-75 with clinic visits over 18 months who are not up to date on colon cancer screening and are associated with the estimated 75% of providers who will consent to study participation. We estimate there are 33,264 female patients (11,088 per study arm) with clinic visits over 18 months who are not up to date on all three screens for colorectal cancer (ages 50-75), breast cancer (ages 50-74), and cervical cancer (ages 21-65) and are associated with the estimated 75% of providers who will consent to study participation. The proportion of men up to date with colorectal cancer screening is 60%, and the proportion of women up to date on all three cancer screens is 34%, yielding a weighted pooled average of 40%. Among those not up to date on screening and thus study eligible, the anticipated pattern of effects for up-to-date screening rates is shown in Table 2 (11% UC, 18% PCP CDS, 24% CMA CDS). The effective sample size for the analysis is reduced to 484-1754 per arm due

Table 2. Anticipated pattern of effects for H1 (composite of appropriate screening)	
UC	11% (12% F, 7% M)
PCP CDS	18% (19% F, 14% M)
CMA CDS	24% (25% F, 20% M)

to anticipated ICCs of 0.005 to 0.02, reflecting the clustering of patients within clinics. With this range of effective sample sizes and 10 clinics per arm, we will have 80% power ($\alpha_2=0.05$, R square of screening with other covariates from 0 to 0.1) to detect a minimum detectable difference of being up to date on screening 18 months after patient index visits of 11% in patients seen in UC clinics and 14%–18% for patients seen in clinics assigned to the PCP CDS study arm. This minimum detectable difference is for the 1 df contrast comparing UC and PCP CDS arm clinics. A larger difference in proportion of patients screened is expected between UC and CMA CDS arm clinics, so these detectable differences are adequate for this comparison.

Hypothesis 2: From the preliminary data pull, we estimate that 21,277 patients (7092 per study arm) aged 11- 26 with clinic visits over 18 months have not received all 3 HPV vaccinations and associated with the estimated 75% of providers who will consent to study participation. The proportion of patients with all 3 HPV vaccinations is currently 19.5% for females and 5.1% for males (12% pooled). Among those without all 3 HPV vaccinations and thus study eligible, the anticipated pattern of effects for receipt of all 3 HPV vaccinations is shown in Table 3 (20% UC, 33% PCP CDS, 40% CMA CDS). The effective sample size for the analysis is reduced to 468- 1562 per arm due to anticipated ICCs of 0.005 to 0.02, reflecting the clustering of patients within clinics. With this range of

effective sample sizes and 10 clinics per arm, we will have 80% power ($\alpha_2=0.05$, R square of HPV vaccination with other covariates from 0 to 0.1) to detect a minimum detectable difference of completion of all 3 HPV vaccinations at 18 months following patient index visits of 20% (pooled female and male) in patients seen in UC clinics and 26.0%–31.3%

Table 3. Anticipated pattern of effects for H2 (receipt of 3 HPV vaccinations)	
UC	20% (30% F, 10% M)
PCP CDS	33% (45% F, 20% M)
CMA CDS	40% (55% F, 25% M)

for patients seen in clinics assigned to the PCP CDS study arm. Therefore, we anticipate adequately powered minimum detectable effect sizes in the anticipated pattern of effects for a range of ICCs and contributions of other variables such as patient sex to the prediction of the study endpoint.

4.9.3 Aim 2 Analytic Approach

18-Month Utilization (H3): Incremental medical costs will be estimated using standard health econometric methods. A generalized estimating equation (typically assuming a gamma distribution and log link function) will be used to estimate costs by study arm while allowing clustering by clinic and controlling for demographics and baseline clinical risk factors.⁹⁰⁻⁹⁴ The marginal effect of being assigned to an intervention clinic will provide an estimate of the incremental medical cost associated with the CP-CDS intervention. Urban and rural clinic- based eligible subjects receiving care from consented PCPs will also be compared. The estimates assume that the CP-CDS is implemented in a large health plan with an EHR capable of exporting data to Web-based clinical algorithms. Implementation in settings without this capability would likely incur additional costs. While market prices generally are a good estimate of the costs for medical services, the charged amount in this billing system is specific to EH at a particular time and may provide a biased view of costs between pre- and post-intervention periods due to

variation in billing practices in provider contracts. To address this, we will use previously developed standard algorithms that use RVUs to calculate costs specific to professional/laboratory services and DRGs for inpatient utilization.⁹²⁻⁹⁴ Professional (inpatient and outpatient) and other outpatient claims (eg, laboratory, radiology) are assigned RVUs using procedure codes. Each encounter with a standard CPT4 code is matched to the Medicare Resource Based RVUs. For procedures not reimbursed by Medicare, we use a national standard DRG fee schedule from McGraw-Hill. For procedure codes specific to EH, we calculate the average paid for that procedure and convert these amounts into RVUs. RVUs are multiplied by the national conversion factor (eg, \$34 in 2012).

Long-term Outcomes (H4): We will leverage four existing microsimulation models of breast cancer screening, colorectal cancer screening, HPV vaccination, and smoking cessation for the prediction of cancer incidence and medical costs among study arms over a 30-year post-intervention period. Observed differences between study groups in screening, smoking cessation, and HPV vaccination rates will be the primary inputs to the models for this prospective analysis. Contemporary cancer incidence and cancer stage-progression rates, disease-related costs, and other key model parameters will be reviewed and updated as necessary.

For breast cancer, we use a six-stage Markov microsimulation to identify three time points relevant to breast cancer: 1) age of detection, 2) the most likely age of incidence, and 3) the age(s) of subsequent disease progression. This is first done for the life of each simulated woman in the base case (ie, the scenario without the modeled CP-CDS intervention). Then, for each woman identified as developing breast cancer in this base case scenario, the impact of the intervention on screening rates, adherence, and disease morbidity and mortality is determined using the three time points. The natural progression of colorectal cancer is modeled using a 9-state discrete-time Markov model with key model parameters provided in Appendix D. Age-, race-, and sex-specific rates of polyp occurrence are contained within the model. All modeled colorectal cancer cases begin as adenomatous polyps that progress to local, regional, and distant cancer. Four screening modalities with polyp and cancer specificity and sensitivity abstracted from clinical trials are included: fecal occult blood testing (FOBT), flexible sigmoidoscopy, and colonoscopy. Costs associated with screening and treatment are abstracted from published studies.⁹⁸⁻¹⁶⁶ We evaluate HPV vaccination using a 19-state discrete-time Markov model of cervical cancer.¹⁶⁷⁻¹⁷⁴ Model characteristics are provided in Appendix D. HPV vaccine effectiveness is derived from published estimates.¹⁷⁴⁻¹⁸⁴ HPV and lesion progression/regression rates are derived from published estimates.¹⁸⁵⁻²⁰¹ Cervical cancer incidence and stage progression are estimated from the NCI's SEER program registries and published estimates.²⁰²⁻²⁰⁴ Lung cancer is a major outcome in our smoking prevention microsimulation model. Lung cancer incidence and stage-progression is estimated by the SEER program. Smoking-attributable disease costs are estimated from CDC's Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) system.

4.9.4 Aim 3 Analytic Approach: Measures of centrality will be computed for each of the RE-AIM metrics. Mixed models will access changes in patient- and provider-reported outcomes with distributional and model modifications made as needed for each outcome. For provider and patient experience survey metrics, we will describe the proportion of respondents indicating highest satisfaction for specific items at each time point and change over time for these items and composite scales. Spearman correlations will be used to examine relationships between items, scales, and other study outcomes. Dr. Conway will lead the qualitative analysis of interviews and focus groups with frequent consultation with Dr. Crabtree using a content analysis process of iterative data reduction. Information will be extracted and organized into categories, themes, and patterns that emerge using grounded theory methods.²⁰⁵ We will use an open coding scheme followed by axial coding, then selective coding to develop themes and concepts. After coding is complete, we will use descriptive data analysis to examine the weight and intensity of categories by their repetition within and across interviews, using counts and frequencies, using Nvivo10 to facilitate these analyses.²⁰⁶

4.9.5 Missing Data: All analytic variables will be derived from EHR or administrative databases in which it is rare for care delivery information to be incompletely recorded and in which CMAs update cancer screening tests and immunizations, even if done outside EH, at each visit. Thus, most missing data will be considered missing completely at random. Several additional factors will effectively minimize missing data. The patient study eligibility criteria for the analytic sample are restricted to patients having two subsequent primary care visits following an index visit. The rural setting of the study provides few care alternatives for patients for obtaining cancer screenings and HPV vaccinations beyond their primary care clinic. Finally, few patients switch from one EH primary care clinic to another. These factors all help to ensure that patients who will be coded in the analysis as lacking a cancer screening or HPV vaccinations are in fact lacking these events and have not obtained this care elsewhere. The planned likelihood-based analysis using all available data will ensure accurate parameter estimation, assuming the data are at least missing at random (MAR).

4.9.6 Secondary Analyses: CMA CDS will be tested against PCP CDS on the composite outcome of up to date on all three screenings for H1 and receipt of all 3 HPV vaccinations for H2 using the analytical approach described for Aim 1. In secondary analysis, the analytic model described for Aim 1 will also be used to examine each of the screening rates separately (colorectal, breast, cervix). The analysis for H2 will test a secondary binary outcome of any HPV vaccinations vs. none received within 18 months of the patient index date. Additional secondary outcomes will include binary indicators for referrals to internal or community weight management or smoking cessation programs and any medications prescribed for smoking cessation. To examine treatment heterogeneity, the analytic model for Aim 1 will be augmented with a clinic-level indicator of rural vs. urban clinic and study arm by rural/urban interaction terms to test the effect of clinic setting on endpoints used in H1 & H2 and to test for differences in treatment arm effects in different clinic settings. Patient-level covariates by study arm interaction terms will be included to test differences in treatment arm effects by number of patient encounters and insurance status. A process analysis will be conducted to test whether the number of CDS activations within the intervention arm clinics is related to endpoints for H1 & H2.

4.10 Data Sources, Data Quality, and Data Management for Hypothesis Tests and Analysis: We will follow established data management procedures developed and refined sequentially in previous projects (DK068314, HL102144, HL115082). A relational database to store patient-level data extracted from administrative and EHR (Clarity) databases has been developed, linking information across service settings to a specific individual on a specific date using a fixed patient identifier. More detail on data standardization, data validation, and data security is in Appendix C.

4.11 Organization of Project: Dr. Elliott will lead weekly meetings of the research team to ensure that tasks are completed according to study protocol, communicate with the IRB and DSMB, and oversee budgetary and administrative aspects of the project. Team members: Drs. Elliott, McCarty, Conway, O'Connor, Sperl-Hillen, Sherwood, Flottemesch, Asche, and project managers at EH and the Institute. Detailed descriptions of the role of each investigator and consultant, an organizational chart, and task timeline are in the Budget Justification.

4.12 Strengths and Limitations of the Study: Valid EHR data are key to this project, and some data may be missing or inaccurate. However, dates of all mammograms, colonoscopies, and PAP/HPV tests and smoking history are updated by CMAs at each office visit and are easily retrieved to inform both the CDS and for use in the analyses. In previous studies, others and we have validated EHR-derived data elements needed in the analysis,⁴⁷⁻⁵⁸ and our study endpoints use easily validated data. Budgetary constraints limit the primary cancer prevention intervention strategy to HPV vaccination, with secondary analysis of smoking cessation and obesity management. These potential limitations should be weighed against the strengths of this ambitious, timely, and innovative project. National and regional data show dramatic deficits in preventive cancer care, especially in rural areas; the counties in this study are ranked in the bottom half of the counties in Minnesota, North Dakota and Wisconsin in health status and outcomes.¹⁵ Unfortunately EHR systems have failed to deliver consistent clinical benefits in outpatient settings.^{30,59} However, over a series of NIH-funded projects, we developed a scalable EHR-linked, Web-based CDS system that significantly improved important chronic disease outcomes.⁴⁷⁻⁵⁸ We now adapt this CDS system to cancer preventive care and posit that directing provider and patient attention to cancer prevention at the point of care will improve delivery of cancer prevention services in rural primary care clinics. Our 3-arm design also compares the effectiveness of PCP-led to CMA-led workflows to engage patients in cancer preventive services; previous studies suggest better outcomes when clinic staff initiate discussion of preventive care services before the PCP encounter.^{31,56,59} Economic analysis and cost-effectiveness microsimulation modeling are additional study strengths. Other strengths include use of RE-AIM and CFIR conceptual frameworks, our expertise in CDS programming and evaluation, and the size of EH's rural population in 3 states.

4.13 Dissemination and Future Plans: Using the CFIR and RE-AIM frameworks for reporting, the results of this project will be presented at national scientific meetings and in peer-reviewed journals. However, our main dissemination goal is to spread CP-CDS use widely to other primary care practices and delivery systems based on our findings and further informed by the implementation conceptual frameworks. Drs. Elliott, O'Connor, Sperl-Hillen, Sherwood, Stange, and Crabtree are ideally positioned to do this, as they are national leaders in primary care and quality improvement.

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