AWARD NUMBER: W81XWH-15-1-0273

TITLE: The Association between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk

PRINCIPAL INVESTIGATOR: Andrea Burnett-Hartman, PhD, MPH

CONTRACTING ORGANIZATION: Kaiser Foundation Research Institute

REPORT DATE: Oct 2019

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
Oct 2019	Final	1 Aug 2015- 31 July 2019

4. TITLE AND SUBTITLE

The Association Between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0273

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Andrea Burnett-Hartman

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Kaiser Foundation Research Institute

1800 Harrison St. 16th Floor

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The objective of this study is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with sessile serrated colorectal polyps (SSPs). The project's specific aims are as follows: 1) Estimate the risk of colorectal cancer or advanced polyps in patients who have SSPs with cytological dysplasia compared to patients with SSPs that lack cytological dysplasia; and 2) Evaluate if the risk of incident colorectal cancer or advanced polyps varies according to methylation markers in SSPs. The following tasks were completed during the project.: Human Subjects approval was obtained from all institutions, SSPs with subsequent colorectal neoplasia and interval cancers were identified, the pathology review form and protocol were finalized, assays for methylation markers were optimized, tissue slide and block pulling and the standard pathology reviews were completed, data cleaning of the pathology review data was finished and analyses of the pathology data was completed, tissue sectioning and DNA extraction was completed on all samples, molecular marker methylation testing was conducted on all samples, and data cleaning and analysis of molecular marker methylation testing was completed. Dr. Burnett-Hartman prepared a manuscript summarizing the results of this project; the target journal for this manuscript is *Cancer Causes and Control*; however, the manuscript has not yet been accepted for publication. Dr. Burnett-Hartman also participated in regular career development opportunities, including attending clinical research seminars, presenting at national and local research meetings, and continued to connect with new clinical partners at Kaiser Permanente Colorado and the University of Colorado and developed new research grant applications focused on colorectal cancer with these collaborators. Dr. Burnett-Hartman also maintained regular meetings with mentors and collaborators at the Fred Hutchinson Cancer Research Center, the University of Washington, and Kaiser's Institute for Health Research.

15. SUBJECT TERMS
Colorectal Cancer, Colorectal Polyps, Sessile Serrated Polyps, Methylation

16. SECURITY CLASSIFICATION OF: Unclassified			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified		USAMRMC

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. INTRODUCTION:

Recent research suggests that in addition to advanced conventional adenomas, some other polyp pathologies, such as sessile serrated polyps (SSPs), may be important precursors for colorectal cancer. Previously, SSPs were thought to have no malignant potential, but cross-sectional studies of molecular markers have linked SSPs to a subset of colorectal cancers characterized by a CpG Island methylator phenotype (CIMP) and methylation of key DNA repair genes, such as *MLH1* and *MGMT*. However, it is not clear which SSP features are associated with an increased risk of colorectal cancer. Thus, the primary objective of this study is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with SSPs. We hypothesize that patients with SSPs that exhibit cytological dysplasia, *MLH1* or *MGMT* methylation, or patients that have CIMP-high SSPs will have an increased risk of incident colorectal cancer and metachronous advanced colorectal polyps compared to patients with SSPs that lack these characteristics.

To test this hypothesis, we identified a cohort of patients who were diagnosed with SSPs at the University of Washington Medical Center during an index colonoscopy between 2003 and 2013. Within this cohort, we identified 265 patients with either an incident colorectal cancer diagnosis or a follow-up colonoscopy at least 6 months after the index colonoscopy at which we assessed the presence or absence of colorectal neoplasia. For these 265 study participants, we were able to locate clinical tissue blocks from the index colonoscopy of on 248 individuals. A standardized pathology review was completed on all biopsies from the index colonoscopy to confirm the SSP diagnosis, assess the presence of cytological dysplasia in the index SSPs, and assess the presence of other types of polyps or colorectal cancer at index colonoscopy.

We excluded 34 individuals who the study pathologist determined did not have an SSP at index colonoscopy and 10 people that had a synchronous or prior colorectal cancer. Thus, 204 individuals (9 with SSPs harboring nuclear dysplasia and 195 with SSPs without nuclear dysplasia) were included in our analyses of the association between index SSP nuclear dysplasia and subsequent colorectal neoplasia. We conducted a standard pathology review of biopsies and pathology reports from subsequent colonoscopies on these 204 individuals and determined that: 12 had incident colorectal cancer diagnoses and 7 had advanced polyps, for a total of 19 with subsequent advanced colorectal neoplasia and 185 with had no subsequent advanced colorectal neoplasia. We used logistic regression to estimate Odds Ratios (ORs) and 95% confidence intervals (Cis) comparing the risk of advanced colorectal neoplasia between individuals harboring SSP with nuclear dysplasia to those with SSP without nuclear dysplasia.

There was no association between the presence of nuclear dysplasia in SSPs and advanced colorectal neoplasia risk (adjusted OR = 1.55; 95% CI: 0.16-14.86) (Table 1 – Appendix II). This suggests that nuclear dysplasia in SSPs may not be a good predictor of advanced colorectal neoplasia risk for individuals with SSPs that have been removed at endoscopy.

For our second aim, we assessed if molecular testing of index SSPs for CIMP and methylation of specific candidate genes can help predict which individuals with SSPs removed at endoscopy are at the highest risk for subsequent colorectal cancer or other colorectal neoplasia. We used logistic regression models to compare the risk of colorectal cancer and advanced colorectal polyps in those with each biomarker to those without each biomarker.

There was no association between CIMP-high SSPs and advanced colorectal neoplasia risk (adjusted OR =0.42; 95% CI: 0.03-5.74); however, individuals harboring SSPs with methylated *MLH1* had an increased risk of subsequent advanced colorectal neoplasia (adjusted OR = 13.79 (1.44-132.45) (Table 1 – Appendix II). Thus, methylated *MLH1* is a strong candidate biomarker associated with high-risk SSPs. Given that *MLH1* methylation was rare in this sample (2.5% of SSPs were *MLH1*-methylated), additional research is needed to determine if our results are replicated in a larger sample to validate *MLH1* methylation as a biomarker for high-risk in SSPs.

2. **KEYWORDS:**

Colorectal cancer, colorectal polyps, molecular markers, DNA methylation, sessile serrated polyps, screening

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?
Below is a table displaying the major goals and milestones for this project in accordance with the approved scope of work. Target completion dates, actual completion dates, and percent complete are also listed. Note, the table below shows goals and milestones for the entire project period.

Table. Major Goals and Milestones

	Target Completion Date	Actual Completion Date	Percent Complete	Notes
Study Set up				
Update local IRB and obtain approval	11/1/15	10/23/2015	100%	IRB approval was obtained through UW, Fred Hutch and KPCO.
Complete IACUC/ HRPO/ACURO applications and obtain approvals	1/1/16	2/12/16	100%	
Complete study protocol for tissue pulling/sectioning and pathology review	12/1/15	9/1/15	100%	We completed the protocol/form quickly, so that we could include the form in our human subjects applications.
Specific Aim 1: Estimate the risk of incident colorectal cancer or metachronous advanced polyps in patients who have SSPs with cytological dysplasia compared to patients with SSPs that lack cytological dysplasia.				
Pulling clinical polyp tissue slides and tissue blocks on 300 patients	4/1/16	2/1/17	100%	We originally planned to pull all slides and blocks at once. However, Northwest Biotrust worked with Dr. Upton to pull batches as Dr. Upton reviews them.
Standard Pathology review of 300 patients	7/1/16	4/1/17	100%	Dr. Upton begun pathology review later than expected due to changes in her office space; she has now completed path review.
Data cleaning of pathology data	9/1/16	6/1/17	100%	

Complete data analysis of pathology data using STATA and summarize data in tables, figures, and graphs	2/1/17	12/1/17	100%	This is complere
Preparation, submission, and presentation of abstract on pathology data for national meeting	8/1/17		0%	Dr. Burnett-Hartman presented results from 3 other projects at national meetings during the study period but did not have an abstract accepted for this analysis.
Manuscript preparation, co-author review, submission of manuscript for publication, and responding to journal reviewer comments	7/31/18	Publication date expected by 6/30/2020	80%	Dr. Burnett-Hartman prepared a manuscript that includes both the pathology and molecular marker test results; the target journal for this manuscript Cancer Causes and Control. The manuscript has not yet been accepted. Publication date expected in 2020.
Specific Aim 2: Evaluate whether the risk of incident colorectal cancer or advanced neoplasia varies according to certain methylation markers in SSPs, including the presence of CIMP, methylated *MLH1*, *MGMT* or *BMP3*.				
Tissue sectioning	9/1/16	12/1/18	100%	This activity was delayed, because path review needed to be complete before tissue sectioning, but this is now complete.
Polyp tissue DNA extraction and quantification for 300 samples	12/1/16	3/1/18	100%	DNA from samples were extracted after sectioning was complete.
Methylite PCR Assay for 300 Samples, including quality control procedures (i.e. *ALU* control and 5% blind replication sample)	8/1/17	5/31/18	100%	Testing was complete and included 296 unique samples.
Data cleaning of CIMP and candidate gene methylation data	9/1/17	1/1/19	100%	Cleaning was completed with some clarification from the lab.
Complete data analysis of methylation data using STATA and summarize data in tables, figures, and graphs	12/1/17	4/30/19	100%	Data analyses for molecular markers is now complete.

Preparation and submission, and presentation of abstract for national meeting	5/1/18		0%	Dr. Burnett-Hartman presented results from 3 other projects at national meetings during the study period but did not have an abstract accepted for this analysis.
Manuscript preparation, co-author review, submission of manuscript for publication, and responding to journal reviewer comments	7/31/18	Publication date expected by 6/30/2020	80%	Dr. Burnett-Hartman prepared a manuscript that includes both the pathology and molecular marker test results; the target journal for this manuscript Cancer Causes and Control. The manuscript has not yet been accepted. Publication date expected in 2020.
Additional Career Development Activities				
One-on-one meetings with mentors and collaborators	Throughout project period		N/A	Dr. Burnett-Hartman has had mentor meetings throughout the project period (see additional information under career development activities).
Attend and present at University of Washington Medical Center, Fred Hutchinson Cancer Research Center, and Kaiser Permanente clinical research seminars	Throughout project period		N/A	Dr. Burnett-Hartman has attended and presented at clinical research meetings (See additional information under career development activities).
Attend the American Society for Clinical Oncology GI Symposium and workshops	3/1/17	2/1/18	100%	The ASCO GI meeting was January 2018; Dr. Burnett-Hartman attended this meeting and presented findings from her research.
Attend and present study findings at Digestive Disease Week (The annual meeting of the American Gastroenterological Association, American Society for Gastrointestinal Endoscopy, Society of the Surgeons of the Alimentary Tract, and American Association for the Study of Liver Diseases)	7/1/18	6/15/18	100%	The DDW was June 2018, Dr. Burnett-Hartman attended this meeting and presented findings from her research.

What was accomplished under these goals?

As detailed in the table above, we accomplished the following goals/objectives:

1. Institutional Review Board Human Subjects review and approval through the University of Washington, Fred Hutchinson Cancer Research Center, and Kaiser Permanente Colorado.
2. Completed IACUC/ HRPO/ACURO applications and obtain approvals
3. Developed the standard pathology review form (see attached appendix)
4. Selected the final list of methylation markers to analyze in our colorectal polyp samples
5. Optimized the methylation assay for DNA methylation markers
6. Completed tissue slide and block pulling
7. Completed standard pathology review
8. Completed data cleaning for path review data and analysis of path review data
9. Completed DNA tissue sectioning and DNA extraction
10. Completed molecular marker DNA methylation assays and began cleaning the molecular marker data
11. Completing cleaning and analysis of polyp molecular marker data
12. A manuscript summarizing studying findings was completed for the target journal, *Cancer Causes and Contro*l. The manuscript is not yet accepted for publication, but we anticipate publication during the first half of 2020.

What opportunities for training and professional development has the project provided?

1. **Training in clinical cancer research through seminars** – During this award period, I attended multiple clinical research seminars, including: Translational Research in Oncology Seminars (quarterly through Kaiser Permanente), Center for Effectiveness and Safety Research Seminars (monthly through Kaiser Permanente), Genomics Workgroup Seminars (monthly through Kaiser Permanente), and Translational Research in Cancer Seminars (monthly through the Fred Hutchinson Cancer Research Center).

2. **Meetings with mentorship team** – I have maintained a strong mentorship team and meet with one or more of my mentors via phone, video conference, or in-person on a weekly basis. In these meetings, we discuss ongoing projects, future grant applications, study design, and analyses methods. My mentors include Drs. Grady, Newcomb, and Zheng from the Fred Hutchinson Cancer Research Center, Dr. Inadomi from the University of Washington, and Dr. Feigelson from Kaiser Permanente Colorado's Institute for Health Research.

3. **Protected time for clinical research and developing new collaborations with clinical researchers** – As planned, I have maintained 30% protected time for this award and over 60% time devoted to other successfully funded clinical research projects (see attached Research Support Document). Kaiser also provides institutional support to allow for future project development and grant proposal development. I also collaborated on 5 new successfully funded grant applications or contracts during this award. These include an NIH-funded project on Lynch Syndrome and a Garfield foundation-funded project on precision medicine, and 2 NIH-funded projects on cancer screening, and 1 collaborative project with NIH to build a national cohort aimed at studying cancer prevention. I also worked on 4 additional grant applications that have not yet been funded; 2 of these applications build on and expands the work completed under this application. I have maintained connections with new potential collaborators in clinical cancer research, including Dr. Mark Powis in Kaiser Gastroenterology and Dr. Alex Mentor in Kaiser Oncology, and Dr. Scott Kono in Kaiser Oncology. I made new collaborations with clinical researchers at the University of Colorado, including: Dr. Adriaan Van Bokhoven, a pathologist, and Dr. Greg Austin, a gastroenterologist. I also continue to serve on the KP Colorado Colorectal Cancer Quality Council.

4. **Attendance at national meetings** –I attended the following National Clinical Research Meetings during the project period: Center for Safety and Effectiveness Research (Denver, CO, October 2015), American Society of Preventive Oncology (Columbus, OH, March 2016), Health

Care Systems Research Network (Atlanta, GA, April 2016), the American Association for Cancer Research Colorectal Cancer Symposium (Tampa, FL, September 2016), American Society for Preventive Oncology (Seattle, WA, March 2017), Health Care Systems Research Network (San Diego, CA, March 2017), ASCO Gastrointestinal Cancer Symposium (San Francisco, CA, January 2018), Digestive Disease Week (The annual meeting of the American Gastroenterological Association, American Society for Gastrointestinal Endoscopy, Society of the Surgeons of the Alimentary Tract, and American Association for the Study of Liver Diseases) (Washington DC, June 2018), and Health Care Systems Research Network (Portland, OR, April 2019)

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to report; we anticipate the publication of our manuscript summarizing these results during the first half of 2020.

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?

SSPs are newly identified precursors for CRC; however recent research suggests that many individuals with SSPs do not go on to develop CRC, and the dwell time (time that it takes for a precursor to progress to cancer) for SSPs is likely longer than the dwell time for other CRC precursors. Thus, it is important to identify biomarkers for increased CRC risk in SSPs. Our research suggesting that methylated-*MLH1* is biomarker for increased risk in SSPs may lead to future stool-based DNA CRC screening tests that include *MLH1* methylation testing. Our results may also lead to studies to assess the utility of *MLH1* methylation testing in SSP tissue to provide tailored colonoscopy surveillance recommendations among individuals with SSPs.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?
As noted above, our results may impact the DNA markers that are used in stool-based DNA testing for CRC screening. They may also provide an impetus for assessing the utility of *MLH1* testing in SSPs.

What was the impact on society beyond science and technology?
Our results may inform the surveillance for CRC in patients with specific types of SSPs and ultimately improve the effectiveness of CRC screening.

5. **CHANGES/PROBLEMS:**

Nothing to report.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

Publications, conference papers, and presentations

Burnett-Hartman AN, Newcomb PA, Zheng Y, Upton MP, Wurscher MA, Thomas S, Inadomi JM, Grady WM. Biomarkers in sessile serrated polyps associated with advanced colorectal neoplasia risk, formatted for *Cancer Causes Control.*

Books or other non-periodical, one-time publications

Nothing to report.

Other publications, conference papers and presentations
With protected time for research and career development, I was able establish or continue research collaborations that allowed me to participate in and lead additional research funded under other funding mechanisms. Below I have listed my other publications and conference presentations during the project period:

1. **Burnett-Hartman AN**. Improving colorectal cancer prevention through the identification of new precursors. Invited Speaker at the University of Washington Frontiers in Gastroenterology Seminar, 2015.

2. Chubak J, Garcia MP, **Burnett-Hartman AN**, Zheng Y, Corley DA, Halm EA, Singal AG, Klabunde CN, Doubeni CA, Kamineni A, Levin TR, Schottinger JE, Green BB, Quinn VP, Rutter CR. Time to colonoscopy after positive fecal blood test in four U.S. healthcare systems. *Cancer Epidemiol Biomarkers Prev* 2016; 25(2):344-50.

3. Adams SV, **Burnett-Hartman AN**, Karnopp A, Bansal A, Cohen SA, Warren-Mears V, Ramsey SD. Cancer Stage in American Indians and Alaska Natives Enrolled in Medicaid. *Am J Prev Med* 2016; 51(3):368-72.

4. **Burnett-Hartman AN**, Mehta SJ, Zheng Y, Ghai NR, McLerran DF, Chubak J, Quinn VP, Skinner CS, Corley DA, Inadomi JM, Doubeni CA; PROSPR Consortium. Racial/Ethnic disparities in colorectal cancer screening across healthcare systems. *Am J Prev Med* 2016; 51(4):e107-15.

5. McCarthy AM, Kim JJ, Beaber EF, Zheng Y, **Burnett-Hartman A**, Chubak J, Ghai NR, McLerran D, Breen N, Conant EF, Geller BM, Green BB, Klabunde CN, Inrig S, Skinner CS, Quinn VP, Haas JS, Schnall M, Rutter CM, Barlow WE, Corley DA, Armstrong K, Doubeni CA; PROSPR consortium. Follow-Up of abnormal breast and colorectal cancer screening by race/ethnicity. *Am J Prev Med* 2016; 51(4):507-12.

6. **Burnett-Hartman AN**, Newcomb PA, Inadomi JM, Upton MP, Grady WM. Interval colorectal cancer after colonoscopy: tumor characteristics, demographics, and polyp history. Poster presentation at the American Society for Preventive Oncology (ASPO) meeting, 2016.

7. **Burnett-Hartman AN**, Newcomb PA, Zeng CX, Zheng Y, Inadomi JM, Fong C, Upton MP, Grady WM. Using medical informatics to evaluate the risk of colorectal cancer in patients with clinically diagnosed sessile serrated polyps. Oral presentation at the American Association for Cancer Research Meeting Colorectal Cancer National Meeting, 2016.

8. Adams SV, **Burnett-Hartman AN**, Karnopp A, Bansal A, Cohen SA, Warren-Mears V, Ramsey

SD. Cancer treatment delays in American Indians and Alaska Natives enrolled in Medicare. *J Healthcare Poor Underserved* 2017; 28(1):350-361

9. Hardikar S, **Burnett-Hartman AN**, Chubak J, Upton MP, Zhu L, Potter JD, Newcomb PA. Reproductive factors and risk of colorectal polyps in a colonoscopy based study in western Washington state. *Cancer Causes Control* 2017; 28(3):241-46.

10. Xinwei H, Phipps AI, **Burnett-Hartman AN**, Adams SV, Cohen SA, Hardikar S, Kocarnik J, Ahnen D, Baron JA, Newcomb PA. Timing of aspirin and other NSAID use in relation to colorectal cancer survival, *J Clin Oncol* 2017; 35(24):2806-13.

11. **Burnett-Hartman AN**, Feigelson HS, Croen L, Harris JN, Honda S, Horberg M, Rowell S, Schaefer C, Somkin C, Tolsma DD, VanDenEeden S, Weinmann S, Young DR, Aziz N. The Kaiser Permanente Research Bank: A Collaborative Resource for Population Health and Cancer Research. Poster presentation at the American Society for Preventive Oncology (ASPO) Meeting, 2017.

12. **Burnett-Hartman AN,** Ritzwoller D, Feigelson HS. Low-dose CT Lung Cancer Screening Program 2014-2016 in Kaiser Permanente Colorado. Invited Speaker at the Health Care Systems Research Network National Meeting (HCSRN), 2017.

13. **Burnett-Hartman AN**, Adams SV, Bansal A, McDougall JA, Cohen SA, Karnopp A, Warren-Mears V, Ramsey SD. Indian Health Service Care System and cancer stage in American Indians and Alaska Natives. *J Healthcare Poor Underserved* 2018; 29(1):245-52.

14. Hardikar S, **Burnett-Hartman AN**, Phipps AI, Upton MP, Zhu L, Newcomb PA. Telomere length differences between colorectal polyp subtypes in a colonoscopy-based study, *BMC Cancer* 2018; 18(1):513.

15. Rahm AK, Cragun D, Hunter JE, Epstein MM, Lowery J, Lu CY, Pawloski PA, Sharaf RN, Liang SY, **Burnett-Hartman AN**, Gudgeon JM, Hao J, Snyder S, Gogoi R, Ladd I, Williams MS. Implementing universal Lynch syndrome screening (IMPULSS): protocol for a multi-site study to identify strategies to implement, adapt, and sustain genomic medicine programs in different organizational contexts. *BMC Health Serv Res* 2018; 18(1):824.

16. Chubak J, Yu O, Ziebell RA, Bowles EJA, Sterrett AT, Fujii MM, Boggs JM, **Burnett-Hartman AN**, Boudreau DM, Chen L, Floyd JS, Ritzwoller DP, Hubbard RA. Risk of colon cancer recurrence in relation to diabetes. *Cancer Causes Control* 2018; 29(11):1093-1103.

17. **Burnett-Hartman AN**, Powers JD, Chubak J, Corley DA, Ghai NR, McMullen CK, Pawloski PA, Feigelson HS. Tumor Characteristics and Treatment in Early-onset Colorectal Cancer. Poster presentation at the American Society of Clinical Oncology – Gastrointestinal Cancers Symposium (ASCO – GI) Meeting, 2018.

18. **Burnett-Hartman AN**, Chubak J, Hua X, Kamineni A, Ziebell R, Hardikar S. Newcomb PA. The association between sessile serrated adenomas/polyps and subsequent advanced colorectal neoplasia. Poster presentation at Digestive Diseases Week National Meeting, 2018.

19. Huyghe JR, Bien SA, Harrison TA…..**Burnett-Hartman A**……Peters U. Discovery of common and rare genetic risk variants for colorectal cancer. *Nat Genet* 2019; 51(1):76-87.

20. **Burnett-Hartman AN**, Hua X, Rue T, Golchin N, Kessler L, Rowhani-Rahbar, A. Risk Interval Analysis of Emergency Room Visits Following Colonoscopy in Patients with Inflammatory Bowel Disease. *PLoS One* 2019; 14(1):e0210262.

21. Clarke CL, Kushi LH, Chubak J, Pawloski PA, Bulkley JE, Epstein MM, **Burnett-Hartman AN**, Powell B, Pearce CL, Feigelson HS. Predictors of long-term survival among high-grade serous ovarian cancer patients. *Cancer Epidemiol Biomarkers Prev* 2019; 28(5):996-999.Apr 9.

22. Rahm AK, **Burnett-Hartman A**, Lu C, Sharaf R, Lowery J, Epstein M, Pawlowski P, Liang S, Ladd I, Hunter JE. The Healthcare System Research Network (HCSRN) as a unique environment for Dissemination and Implementation Research: A Case Study of a Multi-Site Research study in Precision Medicine. *eGEMS* 2019;7(1):16. DOI: http://doi.org/10.5334/egems.283

23. Bowles EJA, Yu O, Ziebell R, Chen L, Boudreau DM, Ritzwoller DP, Hubbard RA, Boggs JM, **Burnett-Hartman AN**, Sterrett A, Fujii M, Chubak J. Cardiovascular medication use and risks of colon cancer recurrence and second cancer events. *BMC Cancer* 2019; 19(1):270.

24. **Burnett-Hartman AN**, Powers JD, Chubak J, Corley DA, Ghai NR, McMullen CK, Pawloski PA, Feigelson HS. Tumor Characteristics, Treatment, and Survival in Early-onset Colorectal Cancer. *Cancer Causes Control* 2019; 30(7):747-755.

25. Blum-Barnett E, Madrid S, **Burnett-Hartman AN**, Mueller S, McMullen C, Dwyer A, Feigelson HS. Financial Burden and Quality of Life among Early-onset Colorectal Cancer Survivors: A Qualitative Analysis. *Health Expect* 2019; 22(5):1050-1057.

26. **Burnett-Hartman, AN,** Kamineni, A, Corley, DA, Singal, AG, Halm, EA, Rutter, CM, Chubak, J, Lee, JK, Doubeni, CA, Inadomi, JM, Doria-Rose, VP and Zheng, Y 2019 Colonoscopy Indication Algorithm Performance Across Diverse Health Care Systems in the PROSPR Consortium. *eGEMs (Generating Evidence & Methods to improve patient outcomes)*, 7(1): 37, doi: https://doi.org/10.5334/egems.296

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Andrea Burnett-Hartman*
Project Role:	*Principle Investigator*
Researcher Identifier	ANDREABH
Nearest person month worked:	*3.60*
Contribution to Project:	*Dr. Burnett-Hartman is the PI of this project and is responsible for the overall scientific and administrative management for this project, including: compliance with human subjects policies, study design, protocol development, analysis, interpretation, and dissemination of research results.*
Funding Support:	No additional funding was provided

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report

What other organizations were involved as partners?
We had two subcontracts under this award. Our partners are Fred Hutchinson Cancer Center and the University of Washington.

Organization 1 Name: Fred Hutchinson Cancer Research Center

- **Location of Organization:** 1100 Fairview Ave. N., Seattle, WA 98109
- **Partner's contribution to the project**: Development and optimization of the methylation specific PCR assays used to assess the polyp DNA was conducted at Fred Hutch, as was the. DNA and methylation analyses that were completed in Year 3. Also, Dr. Grady is serving as a mentor to Dr. Burnett-Hartman under this award, and they meet regularly to discuss project progress and career development opportunities. Dr. Burnett-Hartman also attends Dr. Grady's monthly seminars in Translational Research in Colorectal Cancer.
- **Financial support**: Years 1-3 total funds committed $100,378; $100,378 spent; $0 balance remaining**.**
- **In-kind support**: N/A
- **Facilities**: The Fred Hutchinson Cancer Research Center has state-of-the-art laboratories for conducting medical research. The labs encompass a total of 35,000 square feet and include, private lab space, common shared equipment rooms, shared resource space (for genotyping and other molecular work, pathology/histology, and specimen processing), and offices and conference facilities for faculty and staff. The molecular testing for this project was completed under the direction of the Grady Lab at the Fred Hutchinson Cancer Research Center.
- **Collaboration:** Dr. Burnett-Hartman worked closely with Dr. William Grady on study design, selection of the relevant methylation markers, and assay development in Years 1 and 2 and completion of methylation testing in Year 3. Dr. Grady also actively mentors Dr. Burnett-Hartman.
- **Personnel exchanges**: N/A

Organization 2 Name: University of Washington

- **Location of Organization:** 1959 NE Pacific St., Box 357470, Seattle, Washington
- **Partner's contribution to the projec**t: Dr. Upton served as Co-Investigator on this project and worked on the pathology-related aspects of the project, including a standard pathology review for people with clinically diagnosed sessile serrated polyps.

- **Financial support:** Years 1-3 total funds committed $53,757; $53,757 spent; $0 remaining balance**.**
- **In-kind support:** *N/A*
- Pathology stores and keeps inventory of H&E slides and associated formalin-fixed paraffin-embedded tumor blocks on patients who had biopsies and/or resections performed at the University of Washington Medical Center and Harborview Medical Center. Northwest Biotrust at the University of Washington has the infrastructure to efficiently pull H&E slides and tumor blocks for clinical and research purposes. This project used Northwest Biotrust to pull relevant tissues slides and blocks; Dr. Upton, anatomic pathologists at the University of Washington reviewed these slides and blocks in a designated office equipped with a high-powered digital microscope.
- **Collaboration** Dr. Burnett-Hartman worked closely with Dr. Melissa Upton to develop the pathology review form and Dr. Upton used that form to of review index H&E slides to confirm the sessile serrated polyp diagnosis and characterize nuclear dysplasia within the polyp tissue samples. She also reviewed biopsies and pathology report data from subsequent endoscopies.
- **Personnel exchanges** *N/A*

8. SPECIAL REPORTING REQUIREMENTS

N/A

9. APPENDICES:

Appendix I: Pathology Review Form

Appendix II: Table 1. Odds ratios of the association between sessile serrated polyp biomarkers and advanced colorectal neoplasia.

Appendix III: Final Report of Inventions and Subcontracts

APPENDIX I - STANDARD PATHOLOGY REVIEW FORM

Date of Pathologist Review ____ / ____ / ____	**STUDY ID:**
DATA ENTRY **Date: ___ / ___ / ___ Initials: ____**	**DATA QC** **Date: ___ / ___ / ___ Initials: ____**

	Comments:
Materials for Review: Slides (#) Box #	

10=polyp(s) NOS	16=villous adenoma	22=traditional serrated adenoma (TSA)	30=Carcinoma in situ
11=hp1=goblet cell hp	17=P-J polyp	23=mixed polyp HP/AD	40=Invasive CRC
12=hp2=microvesicular hp	18=juvenile/inflammatory polyp	24=mixed polyp SSP/AD	90=normal
13=adenoma NOS	19=other polyp	25=mixed polyp SSP/TSA	91=inconclusive (cannot tell if normal or lesional)
14=tubular adenoma	20=sessile serrated polyp	26=mixed polyp TSA/AD	93=benign
15=tubulovillous adenoma	21=indeterminate for HP vs SSP	27=prolapse polyp	99=other

Slide	**Code (see above) & Confidence (0-100)**		**Comments**	**% Lesional**	**Tangential Orientation**	**Nuclear Dysplasia**	**Abnormal Crypts**	
							#	**%**
	___ ___				☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	___ ___				☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	___ ___				☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	___ ___				☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	___ ___				☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	___ ___				☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	___ ___				☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	___ ___				☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		

APPENDIX II:

Table 1. Odds ratios of the association between sessile serrated polyp biomarkers and advanced colorectal neoplasia.

	Cases N= 19 N (%)	Controls N = 185 N (%)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Age (years)				
<65	9 (6)	144 (94)	ref	ref
≥65	10 (20)	41 (80)	3.90 (1.49-10.24)	3.98 (1.16-13.59)
Sex				
Female	9 (8)	100 (92)	ref	ref
Male	10 (11)	85 (89)	1.31 (0.51-3.37)	0.78 (0.22-2.74)
Nuclear Dysplasia				
Absent	18 (9)	177 (91)	ref	ref
Present	1 (11)	8 (89)	1.23 (0.15-10.39)	1.55 (0.16-14.86)
CIMP-status[b]				
Low/No	12 (7)	138 (93)	ref	ref
High	1 (8)	11 (92)	1.05 (0.12-8.80)	0.42 (0.03-5.74)
***MLH1*-methylated[b]**				
No	11 (7)	147 (93)	ref	
Yes	2 (50)	2 (50)	13.36 (1.71-104.17)	13.79 (1.44-132.45)

[a]Mutually adjusted for all factors in Table 1

[b]CIMP-status and *MLH1* methylation testing results available for 13 cases and 149 controls

REPORT OF INVENTIONS AND SUBCONTRACTS

(Pursuant to "Patent Rights" Contract Clause) (See Instructions on back)

Form Approved
OMB No. 9000-0095
Expires Jan 31, 2008

PLEASE DO NOT RETURN YOUR COMPLETED FORM TO THE ABOVE ORGANIZATION. RETURN COMPLETED FORM TO THE CONTRACTING OFFICER.

1.a. NAME OF CONTRACTOR/SUBCONTRACTOR	c. CONTRACT NUMBER	2.a. NAME OF GOVERNMENT PRIME CONTRACTOR	c. CONTRACT NUMBER	3. TYPE OF REPORT *(X one)*
Kaiser Foundation Research Institute	W81XWH-15-0273	Same	W81XWH-15-0273	a. INTERIM [X] b. FINAL
b. ADDRESS *(Include ZIP Code)*	**d. AWARD DATE** *(YYYYMMDD)*	**b. ADDRESS** *(Include ZIP Code)*	**d. AWARD DATE** *(YYYYMMDD)*	**4. REPORTING PERIOD** *(YYYYMMDD)*
1800 Harrison St. 16th Floor Oakland, CA 94612-3433	20150815	Same	20190731	a. FROM 20150815 b. TO 20190731

SECTION I - SUBJECT INVENTIONS

5. "SUBJECT INVENTIONS" REQUIRED TO BE REPORTED BY CONTRACTOR/SUBCONTRACTOR *(If "None," so state)*

NAME(S) OF INVENTOR(S) *(Last, First, Middle Initial)* a.	TITLE OF INVENTION(S) b.	DISCLOSURE NUMBER, PATENT APPLICATION SERIAL NUMBER OR PATENT NUMBER c.	ELECTION TO FILE PATENT APPLICATIONS *(X)* d.				CONFIRMATORY INSTRUMENT OR ASSIGNMENT FORWARDED TO CONTRACTING OFFICER *(X)* e.	
			(1) UNITED STATES		(2) FOREIGN			
			(a) YES	(b) NO	(a) YES	(b) NO	(a) YES	(b) NO
NONE								

f. EMPLOYER OF INVENTOR(S) NOT EMPLOYED BY CONTRACTOR/SUBCONTRACTOR		g. ELECTED FOREIGN COUNTRIES IN WHICH A PATENT APPLICATION WILL BE FILED	
(1) (a) NAME OF INVENTOR *(Last, First, Middle Initial)*	(2) (a) NAME OF INVENTOR *(Last, First, Middle Initial)*	(1) TITLE OF INVENTION	(2) FOREIGN COUNTRIES OF PATENT APPLICATION
(b) NAME OF EMPLOYER	(b) NAME OF EMPLOYER		
(c) ADDRESS OF EMPLOYER *(Include ZIP Code)*	(c) ADDRESS OF EMPLOYER *(Include ZIP Code)*		

SECTION II - SUBCONTRACTS *(Containing a "Patent Rights" clause)*

6. SUBCONTRACTS AWARDED BY CONTRACTOR/SUBCONTRACTOR *(If "None," so state)*

NAME OF SUBCONTRACTOR(S) a.	ADDRESS *(Include ZIP Code)* b.	SUBCONTRACT NUMBER(S) c.	FAR "PATENT RIGHTS" d.		DESCRIPTION OF WORK TO BE PERFORMED UNDER SUBCONTRACT(S) e.	SUBCONTRACT DATES *(YYYYMMDD)* f.	
			(1) CLAUSE NUMBER	(2) DATE *(YYYYMM)*		(1) AWARD	(2) ESTIMATED COMPLETION
NONE							

SECTION III - CERTIFICATION

7. CERTIFICATION OF REPORT BY CONTRACTOR/SUBCONTRACTOR *(Not required if: (X as appropriate))* [ ] SMALL BUSINESS or [X] NONPROFIT ORGANIZATION

I certify that the reporting party has procedures for prompt identification and timely disclosure of "Subject Inventions," that such procedures have been followed and that all "Subject Inventions" have been reported.

a. NAME OF AUTHORIZED CONTRACTOR/SUBCONTRACTOR OFFICIAL *(Last, First, Middle Initial)*	b. TITLE	c. SIGNATURE	d. DATE SIGNED
Trecia J. Leung	Senior Director, Sponsored Programs Administration	Trecia J. Leung	10/28/19