INSTRUCTIONS:

- Complete this Data Only Protocol Template only when there is **no** existing authored protocol provided for this study.
- This Data Only Protocol Template is to be used ONLY for studies that involve the analysis of existing data.
- If your study includes intervention activities and is only utilizing existing data for screening purposes, use the Protocol Template.
- This Data Only Protocol Template is to be used in conjunction with the SMART KP IRB Core Data Form.
- Enter your responses to each question directly below the BLUE text in the fillable field.
- When completing this Data Only Protocol Template, if a section does not apply to your study then enter "N/A."

1. Protocol

Protocol Title

Appropriateness of Pharmacogenomic Testing in Patients with Metastatic Colorectal Cancer

Principal Investigator
Jared M. Freml, PharmD

Version Date
06/0214/2018

Form Author
Thomas Delate

2. Objectives

Describe the purpose, specific aims, or objectives and indicate the primary goal(s) of the study. State the hypotheses to be tested.

Primary: In patients with metastatic colorectal cancer, calculate the extent of pharmacogenomic testing for *KRAS*, *NRAS*, and *BRAF*.

Secondary 1: In patients with metastatic colorectal cancer who were treated with cetuximab or panitumumab, calculate the extent of pharmacogenomic testing for *KRAS*, *NRAS*, and *BRAF*.

Secondary 2: In patients with metastatic colorectal cancer who were treated with cetuximab or panitumumab and had pharmacogenomic testing for *KRAS*, *NRAS*, and/or *BRAF*, determine the appropriateness of the use of cetuximab or panitumumab based on the test results.

Secondary 3: In patients with metastatic colorectal cancer, compare the characteristics of patients who did and did not have pharmacogenomic testing for *KRAS*, *NRAS*, or *BRAF*.

3. Background

a. Scientific Background

Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge. A list of references or bibliography must be included as part of this document or uploaded separately.

Hematology/oncology pharmacotherapy is a rapidly progressing field with 21 and 47 newly-approved medications and treatment indications in 2016 and 2017, respectively.[1] Not only has there been expansion in new medications and indications, but there appears to be an ongoing evolution in pharmacogenomic testing that provides predictive or prognostic information about oncology therapies. This rapid growth has created challenges for physicians, pharmacists, and other healthcare staff to stay abreast of the new medications/indications and their associated clinical evidence.

Maintaining up-to-date knowledge on oncology-related pharmacogenomic and companion tests allows a practitioner to select the most effective therapies for patients. This in turn helps to protect patients from unnecessary side effects and financial toxicity associated with high-cost novel medications. In some cases, treating patients with a medication when pharmacogenomic testing suggests not to can increase mortality and tumor progression (e.g., in patients with *RAS* mutations who are treated with cetuximab or panitumumab).[6,7]

Cetuximab, approved in 2004, and panitumumab, approved in 2006, are monoclonal antibodies that target and block the tumor growth and progression signaling cascade via epidermal growth factor receptor (*EGFR-directed therapy*) in the setting of metastatic colorectal cancer. [6,7] Since approval of these medications, various mutations within the signaling cascade have been discovered. These mutations can render cetuximab and panitumumab ineffective.[6-8] Pharmacogenomic testing to identify patients who possess these mutations allows practitioners to target treatments more accurately.

In early 2009, the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion stating that patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations.[2] According to the clinical opinion, patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment if they have a *KRAS* mutation in codon 12 or 13.[2] Consequently, the prescribing information for both cetuximab and panitumumab were updated to recommend the mutation testing in July 2009.[3]

In 2015, the prescribing information for these medications and ASCO guidelines were expanded to include *NRAS* testing for mutations in codons 59 and 61 and codons 117 and 146.[4,5] Current prescribing information for both cetuximab and panitumumab state that these medications are not indicated for *RAS* (encompassing both *KRAS* and *NRAS*) mutant colorectal cancer or when the *RAS* mutation status is unknown.[6,7] The current NCCN guidelines for Colon Cancer, V2.2017, goes further recommending that patients should be tested for *BRAF* V600E mutations also due to growing evidence that this mutation predicts a lack of response to EGFR-directed therapies.[8]

Practitioner uptake and accurate application of the changing recommendations for pharmacogenomic testing prior to treating patients with cetuximab or panitumumab is likely to vary. Two recent European studies suggest that there are gaps in knowledge and application of *RAS* testing among oncologists.[11-12]

Anecdotal evidence at KPCO suggests that uptake and implementation of pharmacogenomic testing results by oncology practitioners varies. For example, patients may have been treated with cetuximab or panitumumab when pharmacogenomic testing results indicated that these patients should not have received these medications. Unfortunately, no formal evaluations of guideline-recommended oncology pharmacogenomic testing have been identified in the literature.

The purpose of the proposed study is to describe the uptake and implementation of guideline recommendations for *KRAS*, *NRAS* and *BRAF* pharmacogenomic testing among patients with metastatic colorectal cancer who are candidates for cetuximab or panitumumab therapy at KPCO and KPMA. Results from this study will provide information on if pharmacogenomic testing has been applied accurately in the oncology setting and identify if additional processes are needed to ensure appropriate use of such testing and its results.

References:

1. US FDA website. Viewed at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Viewed on Dec 18, 2017.
2. Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology Provisional Clinical Opinion: Testing for *KRAS* Gene Mutations in Patients with Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy. J Clin Oncol. 2009;27:2091-2096.
3. US FDA website. Viewed at: http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm172905.htm. Viewed on Dec. 5, 2016.
4. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended *RAS* Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monocolonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J Clin Oncol.2016; 34:179-185.
5. US FDA website. Viewed at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm289979.htm. Viewed on Dec. 5, 2016.
6. Erbitux Prescribing information. Viewed at: http://uspl.lilly.com/erbitux/erbitux.html. Viewed on Dec. 1, 2016
7. Vectibix Prescribing information. Viewed at: http://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/vectibix/vectibix_pi.ashx. Viewed on December 1, 2016.
8. Benson AB et al. NCCN Colon Cancer guidelines Version 2.2017. Viewed at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Viewed on December 18, 2017.
9. Brule SY et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and predictor of benefit from cetuximab in NCIC CO.17. Eur J Cancer. 2015;51(11):1405-14.
10. Lu HJ et al. Primary tumor location is an important predictive factor for wild-type *KRAS* metastatic colon cancer treated with cetuximab as front-line bio-therapy. Asia Pac J Clin Oncol.2016;12(3):207-15.

11. Trojan J et al. Panitumumab use in metastatic colorectal cancer and patterns of *KRAS* testing:results from a Europe-wide physician survey and medical records review. PLOS One. 2015;10(10):e0140717
12. Han van Krieken et al. Panitumumab use in metastatic colorectal cancer and patterns of *RAS* testing: results from a Europe-wide physician survey and medical records review. BMC Cancer. 2017;17:798.

b. Preliminary Data

Describe any relevant preliminary data.

Based on PTR work, approximately 110 patients will be eligible for inclusion

4. Study Design

Describe the overall approach of the study. If your study includes more than one group, arm, or subject population, describe that here.

Study Design

- Data-only, cross-sectional study
- Conducted at KP Colorado (KPCO) with KPCO patients' data
- Patients diagnosed with metastatic (Stage 4) colorectal cancer will be included
- Data will be collected from administrative databases and manual chart reviews
    - Data will be analyzed at KPCO
- Patients diagnosed between 1/1/2014 through 06/30/2018 will be included
- Patient characteristics will be collected during the six months prior to cancer diagnosis date (index date)
- Patients will be assessed for pharmacogenomic testing and chemotherapy initiation during the 180 days prior and 180 days after the index date
- Appropriateness of use will be based on American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines and prescribing information recommendations

Outcomes

- Primary: The proportion of patients with colorectal cancer who had pharmacogenomic testing for *KRAS*, *NRAS*, and *BRAF*.
-
- Secondary 1: The proportions of patients with colorectal cancer who had pharmacogenomic testing for *KRAS*, *NRAS*, and *BRAF* and were treated subsequently with cetuximab or panitumumab.
-
- Secondary 2: The proportions of patients with colorectal cancer who had pharmacogenomic testing for *KRAS*, *NRAS*, and *BRAF*, were treated subsequently with cetuximab or panitumumab, and were treated according to guidelines.
-
- Secondary 3: Contrasts of the characteristics of patients who did and did not have pharmacogenomic testing for *KRAS*, *NRAS*, and/or *BRAF*.

5. Study Population

a. Data Collection

Describe the type of data will you be accessing, including:

- How many records will be accessed?
- What is the date range for the data you will be working with?

Element	Timeframe	Data Source
Medical Record Number	1/1/2014 through 06/30/2018	Virtual Tumor Registry (VTR)
Date and Type of Cancer Diagnosis		VTR
Date of Birth		VTR
KP Membership	During the six months prior to index date	Virtual Data Warehouse (VDW)/Manual Chart Review (MCR)
Sex		VTR
Race		VTR
Hispanic Ethnicity		VTR
Dates, Types, and Results of Pharmacogenomic Testing	During the six months prior to and after index date	MCR
Dates and Types of Chemotherapy Dispensed/Infused	During the six months prior to and after index date	VDW
Comorbidities	180 days prior to index date	VDW
Prescription Medication Dispensings	180 days prior to index date	VDW
Chemotherapy Prescriber Clinic		VDW

b. Inclusion and exclusion Criteria

Describe

- How subjects will be identified?
- The criteria that defines who will be included in your final study sample.

Inclusion

1. Member of KP Colorado
2. Diagnosed with Stages 4 (metastatic) colorectal cancer between 1/1/2014 and 06/30/2018
3. Aged >= 18 years as of index date
4. Continuous KP membership during the six months prior to index date

Exclusion

1. Treatment with cetuximab or panitumumab for non-colorectal cancer

c. Vulnerable Populations

Indicate whether you will include or exclude each of the following special populations. This refers to subjects who are known members of these populations upon enrollment or at any time during the study.

- Children
- Pregnant women
- Neonates of uncertain viability or nonviable neonates (up to 28 days post birth)
- Prisoners (NOTE: The KP IRB does not have the appropriate membership to review research involving prisoners. Consultation with KFRI will be required.)

Children are excluded. Adults >= 90 years of age will be included (since this is a patient population with exposure to colorectal cancer) but not targeted. Pregnant women will be included but not targeted. Neonates will be excluded. Prisoners will be excluded.

IMPORTANT NOTE: Consider whether subjects will be in a vulnerable category at the time of data collection or during analysis. For instance, if you collect data about children who were ages 12 – 15 from years 2000 – 2002, you know that now those individuals are no longer children.

6. Data Analysis

Describe the data to be collected, including: (Upload data collection forms or a list of variables, or include a list here.)

- If the study involves collection of genetic information, describe this.
- Describe the data analysis plan, including any statistical procedures.
- When applicable, provide a power analysis.
- Describe any procedures that will be used for quality control of collected data.

Analysis

- Patients with colorectal cancer will be identified from the Virtual Tumor Registry
- Age will be calculated as of the index date
- KPCO membership will be assessed
- Patients meeting inclusion criteria will be assessed for pharmacogenomic testing
- Charlson comorbidity index (CCI) using comorbidity diagnoses and chronic disease score (CDS) using prescription medication dispensing will be calculated
- Proportion of testing will be calculated by dividing the count of patients who had testing by all patients included
- Patients will be assessed for types of chemotherapy dispensed/infused
    - Among patients who were treated with cetuximab or panitumumab, the proportion of testing will be calculated by dividing the count of patients who had testing by all patients included
    - Among the patients who were treated and tested, appropriateness of treatment will be assessed by the study oncologist and oncology pharmacist
        - The proportions of testing appropriateness will be calculated for each guideline
- Patient characteristics will be tabulated
    - Patient characteristics will be reported as means, medians, and standard deviations for interval-level and proportions for nominal- and ordinal-level data

- Patients will be categorized into groups based on the reception of pharmacogenomic testing (yes/no)
- Characteristics will be compared between groups with chi-square tests of association and t-tests or non-parametric equivalents (depending on data distributions) for nominal- and ordinal-level and interval-level data, respectively
- A logistic regression model will be constructed with reception of the pharmacogenomic test as the dependent variable and patient characteristics as the independent variable

7. Risks and Benefits

a. Risks to Subjects

In addition to potential loss of confidentiality, list any other reasonably foreseeable risks to the subjects or to Kaiser Permanente as an institution related to the research. Consider whether the study should have a Certificate of Confidentiality from NIH.

Physical Risks: N/A

Psychological, social, economic, and legal risks: N/A
Vulnerable subjects: No vulnerable subjects will be targeted for inclusion
Risks to patient privacy and confidentiality: No human subjects will be contacted or receive any intervention as part of this study. The greatest risk, therefore, will be a breech of confidentiality of personal or health information. A password-protected database will be used in which a limited data set for analyses will be stored. Patient identifiers from this evaluation will not be revealed in any professional presentation or publication ensuring patient confidentiality. Upon completion of the study and data analysis, all study materials that do not need to be retained for compliance reasons will be promptly destroyed.
Risks to Investigators or Kaiser Permanente: There are no known risks to KP investigators or staff. No KP proprietary information or publication rights will be compromised. KP and the PI and co-investigators have no conflicts of interest with the study. Given the retrospective nature of this study, KP facilities, departments, other investigators and staff will not be affected.

b. Potential Benefits to Subjects

Describe any potential benefits that may result from this research.

Benefits of the Study This data-only analysis will provide important information regarding the return on investment for preemptive pharmacogenomic testing at KPCO. Research targeted at this issue is needed as information on the value of routine, pre-emptive PGx testing in large healthcare organizations (e.g., Kaiser Permanente) remains nexplored. Information from this study can be used to guide relevant and cost-effective PGx services at KPCO, and may support appropriate PGx testing on a broader scale nationally.

Risk-Benefit Justification As this is a data-only analysis with minimal risk to its subjects, any potential risks, discomforts, or inconveniences to subjects are reasonable in relation to the potential benefits. No human subjects will be contacted or receive any intervention as part of this study. The greatest risk, therefore, will be a breech of confidentiality of PHI. Patient profiles will only be assessed for the minimum set of variables required for study activity and analysis; therefore, limiting the amount of PHI used. Only the identified study team will have access to the study data.
Study Alternatives: N/A

8. Waiver of Informed Consent

NOTE: If you are obtaining signed Informed Consent, complete the Protocol Template.

Provide rationale and justification for the Waiver of Informed Consent for this study, including:

- Does the proposed research present no more than minimal risk to the study participants?
- How the waiver of informed consent will not adversely affect the rights and welfare of the participants.
- Why this research cannot practically be carried out without a waiver of informed consent.
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

This study involves no more than minimal risk. The potential benefits are high and were described in the risks and benefits section. It is in the opinion of the PI that the minimal risks that this study poses are far outweighed by the potential benefits. Individual patient information will not be disclosed or shared.

Files will be stored on the investigators' KPCO P: drive with password protection. Records will be stored in a secure KPCO password-protected computer server. Access to the files and dataset will be limited to those directly involved in the design, implementation, and analysis of the data. PHI that will be utilized for the conduct of this study will not be reused or disclosed to any other entity except as required by law. All data will be analyzed and reported in aggregate form only. Data will only be on a KPCO server and accessed with a password by the study team as described.

It is not practical to obtain consent and authorization as some of the potential study patients may be deceased, terminated KPCO membership, and/or be may be inaccessible to provide consent and authorization.

Identification and screening for patient eligibility and assessing the specified study outcomes could not be down without the waiver and access to PHI.

Study investigators have no plans to provide study participants with information pertinent to the study at this time, however, if results are published, participants would have access to the results. Also, the results of this study may influence care some surviving patients receive. Results will be shared/discussed with stakeholders within KPCO in aggregate form.

9. Waiver of HIPAA Privacy Rule Authorization

NOTE: this only applies if the study involves the use or disclosure of PHI.

Provide rationale and justification for the Waiver of HIPAA Privacy Rule Authorization for this study, including.

- Why the research could not practicably be conducted without the waiver.
- Why access to and use of the PHI is necessary for the research.
- Why the use or disclosure of PHI for the research poses no more than minimal risk to the subjects' privacy (must have an adequate plan to protect the PHI from improper use or disclosure, a plan to destroy identifiers at the earliest opportunity

consistent with the purpose of the research, and when applicable, written assurances from collaborators that PHI will not be reused or re-disclosed to any other entity).

It is not practical to obtain consent and authorization as some of the potential study patients may be deceased, terminated KPCO membership, and/or be may be inaccessible to provide consent and authorization.

Identification and screening for patient eligibility and assessing the specified study outcomes could not be down without the waiver and access to PHI.

Files will be stored on the investigators' KPCO P: drive with password protection. Records will be stored in a secure KPCO password-protected computer server. Access to the files and dataset will be limited to those directly involved in the design, implementation, and analysis of the data. PHI that will be utilized for the conduct of this study will not be reused or disclosed to any other entity except as required by law. All data will be analyzed and reported in aggregate form only. Data will only be on a KPCO server and accessed with a password by the study team as described.

PHI that will be utilized for the conduct of this study will not be reused or disclosed to any other entity except as required by law. PHI will be destroyed at the earliest opportunity after publication of the findings is complete.

10. Privacy, Confidentiality, and Data Security

a. Describe the plan for storage of data.

- Who will have access and how.
- Where the data will be stored and for how long.
- What identifiers will be included.
- Any other steps that will be taken to ensure security (e.g., password protection, encryption, separation of identifiers from data and specimens, certificates of confidentiality).
- Describe the plan to destroy/archive or retain data at the end of the study.

Access to the study data will be limited to PI, Co-I, and research asst.

Files will be stored on the investigators' KPCO P: drive with password protection. Records will be stored in a secure KPCO password-protected computer server. Access to the files and dataset will be limited to those directly involved in the design, implementation, and analysis of the data. PHI that will be utilized for the conduct of this study will not be reused or disclosed to any other entity except as required by law. All data will be analyzed and reported in aggregate form only. Data will only be on a KPCO server and accessed with a password by the study team as described.

Patient MRN will be used to link databases and for manual chart review

PHI that will be utilized for the conduct of this study will not be reused or disclosed to any other entity except as required by law. PHI will be destroyed at the earliest opportunity after publication of the findings is complete.

Data will be encrypted for any internal KPCO data transfers between study team members

b. Does this study involve the disclosure of PHI to a collaborator?

If any data will be sent outside of this site, list each recipient (may list by role or category if the information is the same for several different entities). For each recipient, describe:

- What will be sent.
- Whether the information will be fully identifiable (PHI, if health information), a Limited Data Set, de-identified, or aggregate.
- How the information will be transferred securely (for instance, Secure File Transfer).

No

c. Will data be stored for future research?

If data will be stored for future research use after this study is complete, describe:

- Where the data will be stored and for how long.
- Who will have access and how.
- Procedures to release data to other researchers, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

No

11. Prior Approvals

Describe any approvals that will be obtained prior to commencing the research. (e.g., school, external site. funding agency, or other KP departments).

N/A