Disclaimer

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request cder_mpl1r_wp022_nsdp_v02

Request ID: cder_mpl1r_wp022_nsdp_v02

Query Description: This report contains estimated distribution of baseline covariates among members receiving various genetic tests: KRAS, BRAF, EGFR, BCR-ABL, and BRCA.

Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis (CIDA) tool, version 2.2.1

Data Source: The query was run against the Sentinel Distributed Database (SDD) for the time period of January 1, 2013 to December 31, 2015. The request was distributed to 14 Data Partners on June 17, 2016. See Appendix A for a list of the latest dates of available data for each Data Partner.

Study Design: This request was designed to assess baseline covariates for each cohort of interest.

Exposure of Interest: The exposures of interest were five different genetic tests of the respective genes V-Ki-ras2 Kirsten rat sarcoma viral oncogene (KRAS), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), epidermal growth factor receptor (EGFR), breakpoint cluster region-abelson (BCR-ABL), and the breast cancer susceptibility gene (BRCA). These tests were defined using Healthcare Common Procedure Coding System (HCPCS) Level II procedure codes and Current Procedural Terminology (CPT), 4th Edition procedure codes. Please refer to Appendix B for specific codes.

Cohort Eligibility Criteria: Those included in the cohort were required to be continuously enrolled in plans with both medical and drug coverage for at least 6 months (183 days) prior to their genetic test date, during which gaps in coverage of up to 45 days were allowed. The first valid incident genetic test in the query period to occur was examined.

Baseline Covariates: The following covariates were assessed during the baseline period: age, sex, comorbidity score, and health service utilization. Occurrence of these covariates was evaluated in the 6 months (183 days) prior to the date of genetic test.

Limitations: Algorithms to define exposures are imperfect and, therefore, may be misclassified.

Please see the *Appendix C* for the specifications of parameters used in the analyses for this request.

Notes: Please contact the Sentinel Operations Center Query Fulfillment Team (production@mini-sentinel.org) for questions and to provide comments/suggestions for future enhancements to this document.

Sentinel

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Glossary of Terms for Analyses Using Cohort Identification and Descriptive Analysis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the MSCDM.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). Along with the Principal Diagnosis Indicator, forms the Care Setting/PDX parameter.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: 1: Cohort includes only the first valid incident treatment episode during the query period; 2: Cohort includes all valid incident treatment episodes during the query period; 3: Cohort includes all valid incident treatment episodes during the query period until an event occurs.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a “continuously enrolled”

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.

Event Deduplication - specifies how events are counted by the MP algorithm: 0: Counts all occurrences of an HOI during an exposure episode; 1: de-duplicates occurrences of the same HOI code and code type on the same day; 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode.

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

Member-Years - sum of all days of enrollment with medical and drug coverage** in the query period preceded by an exposure washout

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure(s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

Washout Period (drug/exposure) -** number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) -** number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Table 1. Baseline Characteristics of Cohort of Patients Receiving the KRAS Genetic Test[1] from January 1, 2013 to December 31, 2015		
Characteristic	**KRAS**	
	N	**%/Std Dev[2]**
Patients	5210	100.0%
Patient Characteristics		
Mean age (std dev)	57.5	13.8
Age: 0-21 years	90	1.7%
Age: 22-44 years	674	12.9%
Age: 45-64 years	3161	60.7%
Age: 65+ years	1285	24.7%
Gender (Female)	2926	56.2%
Gender (Male)	2284	43.8%
Recorded History of:		
Combined Comorbidity Score	4.3	3.3
Health Service Utilization Intensity:		
Mean number of generic drugs	20.6	16.2
Mean number of unique drug classes	0.7	1.5
Mean number of filled prescriptions	14.9	14
Mean number of inpatient hospital encounters (IP)	7	5.5
Mean number of non-acute institutional encounters (IS)	0.5	0.9
Mean number of emergency room encounters (ED)	0	0.2
Mean number of ambulatory encounters (AV)	2.7	7.1
Mean number of other ambulatory encounters (OA)	6.6	5

[1]See Appendix B for the list of codes used to define exposures

[2]Value represents standard deviation where no % follows the value

Table 2. Baseline Characteristics of Cohort of Patients Receiving the BRAF Genetic Test[1] from January 1, 2013 to December 31, 2015

Characteristic	BRAF	
	N	%/Std Dev[2]
Patients	4907	100.0%
Patient Characteristics		
Mean age (std dev)	55.6	14.5
Age: 0-21 years	121	2.5%
Age: 22-44 years	821	16.7%
Age: 45-64 years	2919	59.5%
Age: 65+ years	1046	21.3%
Gender (Female)	2789	56.8%
Gender (Male)	2118	43.2%
Recorded History of:		
Combined Comorbidity Score	3.9	3.3
Health Service Utilization Intensity:		
Mean number of generic drugs	20	15.8
Mean number of unique drug classes	0.7	1.3
Mean number of filled prescriptions	14.6	13.7
Mean number of inpatient hospital encounters (IP)	6.8	5.4
Mean number of non-acute institutional encounters (IS)	0.5	0.9
Mean number of emergency room encounters (ED)	0	0.2
Mean number of ambulatory encounters (AV)	2.4	7
Mean number of other ambulatory encounters (OA)	6.4	4.9

[1]See Appendix B for the list of codes used to define exposures

[2]Value represents standard deviation where no % follows the value

Table 3. Baseline Characteristics of Cohort of Patients Receiving the EGFR Genetic Test[1] from January 1, 2013 to December 31, 2015

Characteristic	EGFR	
	N	%/Std Dev[2]
Patients	4730	100.0%
Patient Characteristics		
Mean age (std dev)	60.4	12.9
Age: 0-21 years	40	0.8%
Age: 22-44 years	408	8.6%
Age: 45-64 years	2803	59.3%
Age: 65+ years	1479	31.3%
Gender (Female)	2641	55.8%
Gender (Male)	2089	44.2%
Recorded History of:		
Combined Comorbidity Score	4.4	3.3
Health Service Utilization Intensity:		
Mean number of generic drugs	20.5	15.6
Mean number of unique drug classes	0.8	1.4
Mean number of filled prescriptions	16	14.1
Mean number of inpatient hospital encounters (IP)	7.6	5.6
Mean number of non-acute institutional encounters (IS)	0.5	0.9
Mean number of emergency room encounters (ED)	0	0.2
Mean number of ambulatory encounters (AV)	2.5	7.1
Mean number of other ambulatory encounters (OA)	7.2	5.1

[1]See Appendix B for the list of codes used to define exposures

[2]Value represents standard deviation where no % follows the value

Table 4. Baseline Characteristics of Cohort of Patients Receiving the BCR-ABL Genetic Test[1] from January 1, 2013 to December 31, 2015

Characteristic	BCR-ABL	
	N	%/Std Dev[2]
Patients	5,360	100.0%
Patient Characteristics		
Mean age (std dev)	53.5	14.8
Age: 0-21 years	98	1.8%
Age: 22-44 years	1314	24.5%
Age: 45-64 years	2952	55.1%
Age: 65+ years	996	18.6%
Gender (Female)	2868	53.5%
Gender (Male)	2492	46.5%
Recorded History of:		
Combined Comorbidity Score	2.2	2.9
Health Service Utilization Intensity:		
Mean number of generic drugs	15.3	15.1
Mean number of unique drug classes	0.6	1.5
Mean number of filled prescriptions	15.5	14.7
Mean number of inpatient hospital encounters (IP)	6.5	5.4
Mean number of non-acute institutional encounters (IS)	0.3	0.8
Mean number of emergency room encounters (ED)	0	0.1
Mean number of ambulatory encounters (AV)	1.7	6.1
Mean number of other ambulatory encounters (OA)	6.2	5

[1]See Appendix B for the list of codes used to define exposures

[2]Value represents standard deviation where no % follows the value

Table 5. Baseline Characteristics of Cohort of Patients Receiving the BRCA Genetic Test[1] from January 1, 2013 to December 31, 2015

Characteristic	BRCA	
	N	%/Std Dev[2]
Patients	23,111	100.0%
Patient Characteristics		
Mean age (std dev)	48.4	11.8
Age: 0-21 years	247	1.1%
Age: 22-44 years	8527	36.9%
Age: 45-64 years	12992	56.2%
Age: 65+ years	1345	5.8%
Gender (Female)	21776	94.2%
Gender (Male)	1335	5.8%
Recorded History of:		
Combined Comorbidity Score	1.2	2.3
Health Service Utilization Intensity:		
Mean number of generic drugs	11.8	12
Mean number of unique drug classes	0.3	0.8
Mean number of filled prescriptions	9.7	11
Mean number of inpatient hospital encounters (IP)	4.5	4.3
Mean number of non-acute institutional encounters (IS)	0.1	0.5
Mean number of emergency room encounters (ED)	0	0.1
Mean number of ambulatory encounters (AV)	0.7	3.5
Mean number of other ambulatory encounters (OA)	4.3	4.1

[1]See Appendix B for the list of codes used to define exposures

[2]Value represents standard deviation where no % follows the value

Appendix A: Latest Date of Available Data for Each Data Partner up to Request End Date (12/31/2015)

DP ID	End Date
DP0001	6/30/2015
DP0002	4/30/2015
DP0003	12/31/2014
DP0004	10/31/2014
DP0005	11/30/2015
DP0006	2/28/2015
DP0007	12/31/2015
DP0008	9/30/2015
DP0009	11/30/2015
DP0010	7/31/2015
DP0011	7/31/2014
DP0012	9/30/2015
DP0013	6/30/2015
DP0014	10/31/2015

Appendix B: List of Procedure Codes used to Define Exposures in this Request

Code	Description	Code Type
KRAS		
81275	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13	CPT-4 Procedure
S3713	Kras mutation analysis testing	HCPCS Procedure
BRAF		
81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant	CPT-4 Procedure
EGFR		
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)	CPT-4 Procedure
BCR-ABL		
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative	CPT-4 Procedure
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative	CPT-4 Procedure
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative	CPT-4 Procedure
BRCA		
81211	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)	CPT-4 Procedure
81212	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants	CPT-4 Procedure
81213	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants	CPT-4 Procedure
81214	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)	CPT-4 Procedure
81215	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant	CPT-4 Procedure
81216	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis	CPT-4 Procedure
81217	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant	CPT-4 Procedure
S3818	Complete gene sequence analysis; BRCA1 gene	HCPCS Procedure
S3819	Complete gene sequence analysis; BRCA2 gene	HCPCS Procedure
S3820	Complete BRCA1 and BRCA2 gene sequence analysis for susceptibility to breast and ovarian cancer	HCPCS Procedure
S3822	Single mutation analysis (in individual with a known BRCA1 or BRCA2 mutation in the family) for susceptibility to breast and ovarian cancer	HCPCS Procedure
S3823	Three-mutation BRCA1 and BRCA2 analysis for susceptibility to breast and ovarian cancer in Ashkenazi individuals	HCPCS Procedure

Appendix C: Modular Program Specifications for cder_mpl1r_wp022_nsdp_v02

Sentinel's Cohort Identification and Descriptive Analysis (CIDA) tool, version 2.2.1, will be used to investigate the characteristics of individuals receiving the tests of interest. Covariates will be calculated based on a 183 Day Look-Back Period. The query period was from January 1, 2013 - December 31, 2015, and the enrollment gap was set at 45 days. Age groups were split as follows: 0-21, 22-44, 45-64, 65+. In total, 5 scenarios were examined in this request.

Enrollment Gap: 45 Days
Age Groups: 0-21, 22-44, 45-64, 65+
Query Period: January 1, 2013 - December 31, 2015
Coverage Requirement: Medical and Drug
Covariate Evaluation Window: 183 Days

		Drug/Exposure				Covariates to Consider:
Scenario	Enrollment Requirement (days)	Incident exposure	Incident w/ respect to:	Washout (days)	Cohort Definition	Covariates
1	183	KRAS	KRAS	183	01	Age, Gender, Combined Comorbidity Index
2	183	BRAF	BRAF	183	01	Age, Gender, Combined Comorbidity Index
3	183	EGFR	EGFR	183	01	Age, Gender, Combined Comorbidity Index
4	183	BCR-ABL	BCR-ABL	183	01	Age, Gender, Combined Comorbidity Index
5	183	BRCA	BRCA	183	01	Age, Gender, Combined Comorbidity Index

ICD-9, ICD-10, HCPCS, and CPT codes are provided by Optum360. NDC codes are checked against First Data Bank's "National Drug Data File (NDDF®) Plus"

Cohort Definition of 01 will only consider the first incident episode for each user during the query period that satisfies the washout period.