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Cost of Biomarker Testing Among Patients with Metastatic Lung or Thyroid Cancer in the US: A Real-World Commercial Claims Database Study

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BACKGROUND

- Clinical biomarker testing practices vary widely in patients with lung and thyroid cancers despite guideline-recommended approaches.[1-4]
- The study of biomarker testing practices are confounded with practices such as 'code stacking'[5]
- There is a need to understand how codes are used and the ultimate cost to payers and patients based on these practices

OBJECTIVES

- This retrospective observational study was designed to evaluate the utilization of biomarker codes and to measure the costs of biomarker testing
- Specifically, this study evaluated:
  - Total lifetime costs to the payer and patient associated with biomarker testing
  - Costs to the patient and payer by insurance plan type
  - Costs by specific reimbursement code

METHODS

Data source

- IBM Marketscan commercial databases
  - A de-identified real-world administrative claims database collected from commercial, employer-based health care plans
  - Exempt from IRB review: de-identified data are not considered human subjects research in accordance with 45 CFR 46.102(f)

Eligibility criteria

- **Lung cancer cohort**
  - First of 2+ lung cancer diagnosis codes (C34-C34.92) observed January 1, 2015 - December 31, 2019; no prior cancer codes
  - Subgroup: patients with codes for metastatic disease
- **Thyroid cancer cohort**
  - First of 2+ thyroid cancer diagnosis codes (C73) observed January 1, 2015 - December 31, 2019; no prior cancer codes
  - Two Subgroups: patients with (1) codes for metastatic disease; (2) codes suggestive of medullary thyroid cancer (MTC) (MEN2 or calcitonin codes)
- Cohorts are mutually exclusive

RESULTS

- 23,633 eligible patients were included in the lung cancer cohort and 36,867 in the thyroid cancer cohort (Figure 1)
- The characteristics of these patients are summarized in Table 1
- Most patients in the lung cancer cohorts had claims for biomarker testing after diagnosis (Table 2)
- Comprehensive/NGS testing codes were infrequently observed in any cohort

Table 2. Biomarker testing frequency and lifetime costs of biomarker testing

	Lung cancer cohort (n=23,633)	Lung cancer-metastatic disease (n=13,320)	Thyroid cancer cohort (n=36,867)	Thyroid cancer-metastatic disease (n=2,241)	Medullary thyroid cancer cohort (n=164)
Single-gene or comprehensive/next-generation sequencing (NGS) biomarker test code, n (%)	16,100 (68.1)	10,052 (75.5)	6,679 (18.1)	936 (41.8)	74 (45.1)
Comprehensive/NGS test code, n (%)	1,221 (5.2)	897 (6.7)	122 (0.3)	49 (2.2)	0 (0.0)
Median (min-max) total lifetime costs of biomarker testing: payer*	$393.80 (0-34,468)	$461.50 (0-34,468)	$147.60 (0-25,118)	$231.80 (0-25,118)	$169.90 (0-1,759)
Median (min-max) total lifetime costs of biomarker testing: patient out-of-pocket*	$0.00 (0-17,202)	$0.00 (0-14,003)	$0.00 (0-5,204)	$0.00 (0-3,864)	$0.00 (0-407)

*Among patients with at least one single-gene or comprehensive/NGS biomarker test code, median total costs per patient for biomarker testing from diagnosis to end of follow-up; all other costs of care are excluded. Costs are adjusted to 2020 US dollars.

Table 3. Payer cost per biomarker test code*

Single- gene biomarker codes210		
Code	Number of claims with code observed	Median (min-max) payer cost
81235	3,048	$249.85 (0-7,218)
81288	7	$324.90 (61-439)
81311	805	$226.46 (0-1,944)
81301	246	$267.24 (0-13,023)
81210	1,701	$122.04 (0-8,850)
81275	1,517	$157.55 (0-5,519)
81278	622	$144.21 (0-1,232)
88342	31,138	$66.03 (0-4,291)
88341	27,019	$93.12 (0-6,308)
88344	920	$68.11 (0-2,875)
88364	122	$64.11 (0-520)
88365	288	$93.04 (0-725)
88360	6,339	$96.85 (0-4,154)
88377	3,697	$192.16 (0-7,286)
88374	1,127	$150.40 (0-4,341)
88367	58	$108.78 (0-847)
88368	306	$133.43 (0-2,103)
88373	21	$56.25 (0-1,213)
88369	116	$55.98 (0-1,523)
88366	69	$127.67 (0-1,475)
88365	288	$93.04 (0-725)
81402	949	$97.98 (0-$1,426)
81403	1,862	$93.90 (0-7,239)
81404	1,909	$181.62 (0-7,141)
81519	78	$4,008.94 (317-4,903)
81228	1	$1,016.70 (--)
81229	12	$1,727.58 (256-5,790)
0016U	2	$2,047 (1,807-2,288)

Comprehensive/next-generation sequencing (NGS) codes		
Code	Number of claims with code observed	Median (min-max) payer cost
81445	255	$549.98 (0-14,487)
81450	9	$786.19 (463-9,357)
81455	138	$3,976.50 (0-13,217)
0022U	3	$1,097.21 (395-2,292)
0037U	186	$3,145.67 (0-6,007)
0013U	0	--
0012U	0	--
0026U	16	$2,928.10 (0-5,962)
0179U	0	--
0204U	0	--
0208U	0	--
0048U	0	--
0047U	1	$3,222.94 (--)

*Biomarker test codes used in the entire study population (both lung and thyroid cancer cohorts combined)

CONCLUSIONS

- Real-world data suggest that the lifetime cost of biomarker testing is low for patients with lung or thyroid cancers
  - In the context of other studies that have evaluated cancer costs, this suggests that biomarker testing represents a very small fraction of the total cost of care for patients receiving active treatment[6]
    - Estimated total lung cancer cost: $391,281-$1,515,997
    - Estimated total thyroid cancer cost: $112,641-$251,536
- Most patients with lung cancer undergo biomarker testing, consistent with what is shown in other database studies of electronic medical records; however, the actual number or types of tests conducted cannot be clearly elucidated from these data.
  - The low rates specifically of comprehensive/NGS biomarker testing codes are not consistent with these studies, suggesting that other coding schemes may be used. This should be investigated in future research
  - Future research is needed to compare the coding patterns observed in this study with electronic medical record or chart data to associate these findings with actual biomarker tests conducted.

Methods, continued

Codes for biomarker testing and MTC diagnosis

Single- gene biomarker codes	
81235	EGFR (EPIDERMAL GROWTH FACTOR RECEPTOR) (EG, NON-SMALL CELL LUNG CANCER) GENE ANALYSIS, COMMON VARIANTS (ES), EXON 19 LREA DELETION/INSERTION, AND EXON 21 L858R MUTATION
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis, promoter methylation analysis
81311	KRAS (NEUROBLASTOMA RAS VIRAL (V-RAS) ONCOGENE HOMOLOG) (EG, COLORECTAL CARCINOMA), GENE ANALYSIS, VARIANTS IN EXON 2 (EG, CODONS 12 AND 13) AND EXON 3 (EG, CODON 61)
81301	MSI-HI/dMMR
81210	BRAF gene analysis
81275	KRAS (KIRSTEN RAT SARCOMA VIRAL ONCOGENE HOMOLOG)(EG, CARCINOMA) GENE ANALYSIS; VARIANTS IN EXON 2 (EG, CODONS 12 AND 13)
81276	KRAS (KIRSTEN RAT SARCOMA VIRAL ONCOGENE HOMOLOG)(EG, CARCINOMA) GENE ANALYSIS; ADDITIONAL VARIANT(S) (EG, CODON 61, 117, 146)
88342	IMMUNOHISTOCHEMISTRY OR IMMUNOCYTOCHEMISTRY, PER SPECIMEN; INITIAL SINGLE ANTIBODY STAIN PROCEDURE
88341	immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
88344	immunohistochemistry or immunocytochemistry, per specimen; each multiplex antibody stain procedure
88364	in situ hybridization (eg, FISH), per specimen; each additional single probe stain procedure (List separately in addition to code for primary procedure)
88365	in situ hybridization (eg, FISH), per specimen; initial single probe stain procedure
88360	IHC, eg HER2; EIN/PI
88377	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe, (FISH)
88374	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each multiplex probe stain procedure (FISH)
88367	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe, (FISH)
88368	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe, (FISH)
88373	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each additional single probe stain procedure (List separately in addition to code for primary procedure). Should be used with 88368 (FISH)
88369	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; each additional single probe stain procedure (List separately in addition to code for primary procedure) Should be used with 88368 (FISH)
88366	in situ hybridization (eg, FISH), per specimen; each multiplex probe stain procedure
88365	in situ hybridization (eg, FISH), per specimen; initial single probe stain procedure
81402	Molecular pathology procedure, Level 9 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants, immunoglobulin and T-cell receptor gene rearrangements, chromosomal microdeletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 8 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
81228	Comparative genomic hybridization; Cytogenomic constitutional (genome-wide) microarray analysis, interrogation of genomic regions for copy number variants (e.g. bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	Cytogenomic (genome-wide) analysis for known abnormalities (e.g. oligonucleotide SNP) variants for chromosomal abnormalities
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma) gene analysis, V600 variant(s)
0016U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy

Comprehensive/next-generation sequencing (NGS) codes	
81445	TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN NEOPLASM, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 5-50 GENES (EG, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PIGFRB, POR, PIK3CA, PTEN, RET), INTERROGATION FOR SEQUENCE VARIANTS AND COPY NUMBER VARIANTS OR REARRANGEMENTS, IF PERFORMED
81450	TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, HEMATOLYMPHOID NEOPLASM OR DISORDER, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 51 OR GREATER GENES (EG, ABL1, BRAF, CDH20, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PIGFRB, POR, PIK3CA, PTEN, RET), INTERROGATION FOR SEQUENCE VARIANTS AND COPY NUMBER VARIANTS OR REARRANGEMENTS, IF PERFORMED
81455	TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN OR HEMATOLYMPHOID NEOPLASM, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 51 OR GREATER GENES (EG, ALK, BRAF, CDH20, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PIGFRB, POR, PIK3CA, PTEN, RET), INTERROGATION FOR SEQUENCE VARIANTS AND COPY NUMBER VARIANTS OR REARRANGEMENTS, IF PERFORMED
0022U	TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, NON-SMALL CELL LUNG NEOPLASM, DNA ANALYSIS OF 23 GENES, INTERROGATION FOR SEQUENCE VARIANTS AND REARRANGEMENTS, REPORTED AS PRESENCE/ABSENCE OF VARIANTS AND ASSOCIATED THERAPY(IES) TO CONSIDER
0037U	TARGETED GENOMIC SEQUENCE ANALYSIS, SOLID ORGAN NEOPLASM, DNA ANALYSIS OF 324 GENES, INTERROGATION FOR SEQUENCE VARIANTS, GENE COPY NUMBER AMPLIFICATIONS, GENE REARRANGEMENTS, MICROSATELLITE INSTABILITY AND TUMOR MUTATIONAL BURDEN
0013U	Oncology (solid organ neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, fresh or frozen tissue or cells, report of specific gene rearrangement(s)
0012U	Hereditary disorders, gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood, report of specific gene rearrangement(s)
0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy", or "Negative, low probability of malignancy")
0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of actionable mutation(s)
0204U	Oncology (thyroid), mRNA, gene expression analysis of 593 genes including BRAF, RAS, RET, PAX8, and NTRK) for sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected
0208U	Oncology (medullary thyroid carcinoma), mRNA, gene expression analysis of 106 genes, utilizing fine needle aspirate, algorithm reported as positive or negative for medullary thyroid carcinoma
0048U	PROPRIETARY LABORATORY ANALYSIS
0047U	RNA SEQUENCING : 61 GENE

MTC codes	
CPT: 258.02, 258.03	Multiple endocrine neoplasia [MEN] type IIA; Multiple endocrine neoplasia [MEN] type IIB
ICD10: E31.20, E31.22, E31.23	Multiple endocrine neoplasia [MEN] syndrome, unspecified; Multiple endocrine neoplasia [MEN] type IIA; Multiple endocrine neoplasia [MEN] type IIB
CPT: 82308	Calcitonin (hormone) level

Statistical analysis

- Descriptive statistics were conducted using SAS EG 7.1
- All costs were adjusted to US$ in 2020 using the medical component of the Consumer Price Index
- No statistical comparisons were made

Results, continued

Figure 1. Study cohorts

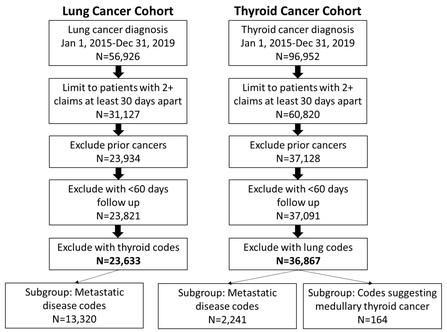

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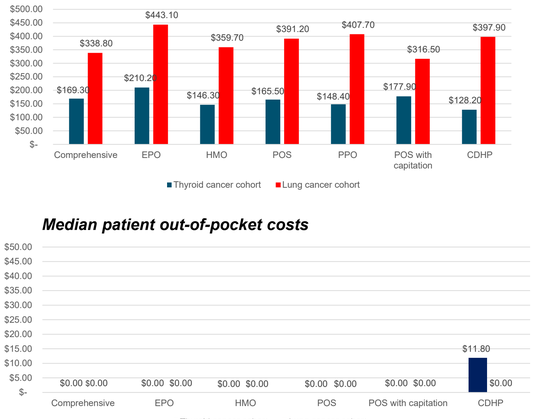
Table 1. Characteristics at diagnosis

Characteristics	Lung cancer cohort	Lung cancer-metastatic disease	Thyroid cancer cohort	Thyroid cancer – metastatic disease	Medullary thyroid cancer cohort
Number of patients (n)	23,633	13,320	36,867	2,241	164
Year of diagnosis, n (%)					
2015	5,559 (23.5)	3,373 (25.3)	8,362 (22.7)	593 (26.5)	35 (21.3)
2016	5,138 (21.7)	2,934 (22.0)	8,217 (22.3)	520 (23.2)	34 (20.7)
2017	4,923 (20.8)	2,734 (20.5)	8,272 (22.4)	442 (19.7)	39 (23.8)
2018	5,127 (21.7)	2,764 (20.8)	8,390 (22.8)	480 (21.4)	44 (26.8)
2019	2,886 (12.2)	1,515 (11.4)	3,626 (9.8)	206 (9.2)	12 (7.3)
Age, mean (SD) years	57.0 (6.6)	56.5 (6.7)	45.6 (11.5)	46.0 (12.8)	40.4 (15.2)
Gender, n (%)					
Female	12,781 (54.1)	6,949 (52.2)	28,827 (78.2)	1,458 (65.1)	103 (62.8)
Male	10,830 (45.8)	6,361 (47.8)	8,012 (21.7)	780 (34.8)	60 (36.6)
Unknown/missing	22 (0.1)	10 (0.1)	28 (0.1)	3 (0.1)	1 (0.6)
Region, n (%)					
North Central	5,389 (22.8)	3,086 (23.2)	6,879 (18.7)	427 (19.1)	28 (17.1)
Northeast	4,516 (19.1)	2,434 (18.3)	8,255 (22.4)	520 (23.2)	28 (17.1)
South	11,114 (47.0)	6,265 (47.0)	15,309 (41.5)	907 (40.5)	81 (49.4)
West	2,528 (10.7)	1,492 (11.2)	6,242 (16.9)	377 (16.8)	25 (15.2)
Unknown/missing	86 (0.4)	43 (0.3)	182 (0.5)	10 (0.5)	2 (1.2)
Health care plan type, n (%)					
Comprehensive	1,157 (4.9)	678 (5.1)	750 (2.0)	42 (1.9)	4 (2.4)
EPO	188 (0.8)	104 (0.8)	369 (1.0)	29 (1.3)	1 (0.6)
HMO	2,499 (10.6)	1,375 (10.3)	4,043 (11.0)	242 (10.8)	16 (9.8)
POS	2,059 (8.7)	1,119 (8.4)	3,723 (10.1)	208 (9.3)	12 (7.3)
PPO	13,211 (55.9)	7,474 (56.1)	19,935 (54.1)	1,223 (54.6)	90 (54.9)
POS with capitation	277 (1.2)	146 (1.1)	475 (1.3)	35 (1.6)	4 (2.44%)
CDHP	2,099 (8.9)	1,212 (9.1)	3,147 (8.5)	191 (8.5)	17 (10.4)
Other/missing	2,143 (9.1)	1,212 (9.1)	4,425 (12.0)	271 (12.1)	20 (12.2)
Duration of follow-up, mean (SD) months	14.2 (12.0)	12.6 (11.1)	22.8 (14.3)	22.2 (14.9)	24.7 (13.3)

Abbreviaions: SD, standard deviation; EPO, exclusive provider organization; HMO, health maintenance organization; POS, point-of-service; CDHP, consumer-driven health plan.

Figure 2. Median total lifetime costs of biomarker testing by insurance plan type



Abbreviations: EPO, exclusive provider organization; HMO, health maintenance organization; POS, point-of-service; CDHP, consumer-driven health plan.

Limitations

- Some of the specific biomarker codes identified for study are rarely used; costs associated with codes that have low frequency utilization should be interpreted with caution.
- The infrequent observation of comprehensive/NGS codes suggests that these tests may be submitted for reimbursement using combinations of other single-gene codes, and that the practice of code stacking may persist, but this cannot be directly evaluated in these data that lack information about the actual test performed.
- Data are recorded in this database for reimbursement of health care claims, not for patient care. The coding structures used for biomarker testing reimbursement may not accurately reflect the actual test conducted. Therefore, clinical interpretation of specific biomarker tests used in routine practice, particularly for comprehensive/NGS testing, should be avoided.

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