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Utilization of genetic tests: analysis of gene-specific billing in Medicare claims data

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Purpose: We examined the utilization of precision medicine tests among Medicare beneficiaries through analysis of gene-specific tier 1 and 2 billing codes developed by the American Medical Association in 2012.

Methods: We conducted a retrospective cross-sectional study. The primary source of data was 2013 Medicare 100% fee-for-service claims. We identified claims billed for each laboratory test, the number of patients tested, expenditures, and the diagnostic codes indicated for testing. We analyzed variations in testing by patient demographics and region of the country.

Results: Pharmacogenetic tests were billed most frequently, accounting for 48% of the expenditures for new codes. The most common indications for testing were breast cancer, long-term use of medications, and disorders of lipid metabolism. There was underutilization of guideline-recommended tumor mutation tests (e.g., epidermal growth factor receptor) and substantial overutilization of a test discouraged by guidelines (methylenetetrahydrofolate reductase). Methodology-based tier 2 codes represented 15% of all claims billed with the new codes. The highest rate of testing per beneficiary was in Mississippi and the lowest rate was in Alaska.

Conclusions: Gene-specific billing codes significantly improved our ability to conduct population-level research of precision medicine. Analysis of these data in conjunction with clinical records should be conducted to validate findings.

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Key Words: billing code; genomic testing; hospital referral region; Medicare; pharmacogenetics

INTRODUCTION

In January 2015, the Obama administration launched the Precision Medicine Initiative to accelerate translation of scientific discoveries into individual treatments.[1,2] Precision medicine relies on the use of complex laboratory tests to identify specific chromosomal, DNA, RNA, protein, or metabolite abnormalities in patients' blood or tissue. Hundreds of precision medicine tests are listed in clinical practice guidelines and used in clinical care.[3,4] However, very little information exists regarding whether these tests are used appropriately or impact treatment decisions. There are concerns that precision medicine will benefit only a small segment of the population while increasing the cost of health care, with commercial interests benefiting at the expense of vulnerable patients and taxpayers.[5–8] Several researchers and policy makers have commented that successful translation of precision medicine requires population-level research that illustrates clinical utility and improved health outcomes.[9]

Health-services research in precision medicine has been impeded by poor documentation of tests in claims data and electronic health records. Until recently, payers were billed for molecular tests with methodology-based codes rather than analyte- or gene-specific codes. Methodology-based codes make it impossible to identify utilization of specific tests in claims data[10] and allow laboratories to bill for tests that lack clinical utility and are not covered by payers.[11] Furthermore, test results are frequently not translated into diagnostic codes, even when specific codes exist for molecular disease subtypes.[10]

To improve documentation of precision medicine, the American Medical Association (AMA) developed new, gene-specific billing codes (Current Procedural Terminology) for complex laboratory tests.[12] Two categories of codes were established. Tier 1 codes identify single-biomarker molecular tests. Tier 2 codes identify less common tests that are grouped by level of resources required for performance and interpretation. Both groups include genetic tests that measure hereditary or tumor-specific genes. Additional codes, described as multianalyte assays with algorithmic analyses (MAAA), were developed for tests that measure the expression of multiple genes and use proprietary algorithms to generate risk scores. Medicare adopted these new codes on 1 January 2013. It delayed adoption of MAAA codes until the end of 2013. Methodology codes were discontinued and laboratories were required to bill for precision medicine tests using the tier 1 and 2 codes.

The primary objectives of this study were to analyze implementation of gene-specific Current Procedural Terminology

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codes among Medicare beneficiaries, identify conditions for which these tests were ordered, describe characteristics of patients tested, and assess regional variations in testing. The second objective was to illustrate a method using claims data to estimate the total patient population eligible for specific tests. We analyzed claims of lung cancer patients to accomplish this objective.

MATERIALS AND METHODS

We conducted a retrospective cross-sectional study of all Medicare beneficiaries who underwent precision medicine tests billed with tier 1 or 2 codes. Data sources included 2012 and 2013 100% fee-for-service (FFS) Medicare claims data, specifically Part B, Outpatient, and the Denominator enrollment files. These files contain information for 100% of Medicare beneficiaries covered by the FFS program, which was the prevailing model of reimbursement within Medicare. Between 2010 and 2013, the FFS program reimbursed nearly 95% of physician office visits.[13] The majority of Medicare beneficiaries are 65 years or older. However, 16% of beneficiaries are younger than age 65 and are entitled to benefits due to disabling conditions such as end-stage renal disease or other medical conditions.[14] The Part B file contains claims for physician services and diagnostic tests suppliers. The Outpatient file contains claims submitted by other institutional and outpatient providers. The Denominator file contains administrative enrollment records, including patient demographics and Medicaid status, for beneficiaries enrolled in a given year. We restricted analysis to FFS beneficiaries who sought care in a physician office, inpatient or outpatient hospital, or ambulatory surgical center. We retained variables indicating the clinical reason for testing. The clinical reason was the principal diagnosis code in outpatient claims and the line-item diagnosis code in Part B. Both were based on the International Classification of Diseases, 9th revision (ICD-9). We summarized claims to identify the total number of claims billed with specific codes, number of beneficiaries tested, demographics of beneficiaries tested, and diagnosis codes for each claim. Diagnosis codes were aggregated using the Healthcare Cost and Utilization Project Clinical Classification software.[15] Using the patient's health insurance claim number, we obtained demographic data and zip code of residence.

To obtain the most frequent indications for testing, we included the preexisting molecular pathology codes and not otherwise classified (NOC) codes that remained in effect in 2013. These NOC codes were used by laboratories instead of MAAA codes. To identify specific algorithm-based proprietary tests, we used the Clinical Laboratory Improvement Amendments (CLIA) number of the laboratory combined with NOC codes used to bill for tests and the ICD-9 diagnosis code. This strategy was developed in our previous analysis of testing for lung cancer.[16] To identify patients potentially eligible for lung cancer tests, we selected patients who had a new diagnosis code for lung cancer and underwent surgical pathology analysis (codes 88305, 88307, and 88309) in 2013.

RESULTS

Analysis of tests billed to Medicare in 2013

Table 1 illustrates utilization and expenditures for both new and preexisting codes. Altogether, 1,455,162 beneficiaries were tested using these codes. There were 527,404 beneficiaries who underwent tests billed with new codes and 982,492 beneficiaries who underwent tests billed with pre-existing codes. Total payments for tier 1 and 2 codes were $256,242,345. The most frequently ordered tests were in two categories: (i) pharmacogenetic tests and (ii) tests for genes implicated in vascular disease. Cancer biomarkers and human leukocyte antigens tests were also frequently ordered. Tier 2 codes, which are not gene-specific, represented 15% of claims billed with new codes.

Each genetic test and its intended use is listed in **Supplementary Appendix 1** online.[17] **Table 2** illustrates the most commonly used tests with the three most frequently submitted diagnosis codes. Owing to space restrictions, we limited the discussion of results to categories with the highest frequency of testing. All tests, including demographics of beneficiaries tested, are listed in **Supplementary Appendix 2** online.

Pharmacogenetic tests

Tests in this category are billed using codes 81225–81227 and include genetic polymorphisms in three genes of the cytochrome p450 (CYP) family, *CYP2D6*, *CYP2C19*, and *CYP2C9*. The CYP2D6 protein metabolizes approximately 25% of commonly prescribed drugs, including antidepressants, antipsychotics, opioids, antiarrhythmics, and the breast cancer drug tamoxifen.[18] *CYP2C19* is involved in bioactivation of the antiplatelet drug clopidogrel.[19] Products of *CYP2C9* and *VKORC1* metabolize the anticoagulation drug warfarin.[20] A total of 519,340 tests were billed for the three CYP genes, which comprised 28% of total tests, and 91,859 *VKORC1* gene tests (code 81355), comprising 5% of tests. Medicare payments for these four markers amounted to $117,845,531, which represented 48% of total expenditures for tier 1 and 2 codes. Diagnosis codes most often submitted for CYP and *VKORC1* tests were those for long-term use of medications (V58.69), hypertension (401.0), and hypercholesterolemia (272.0). There were also 1,454 claims for the *UGT1A1* gene test (code 81350). The product of *UGT1A1* is needed for clearance of the drug irinotecan, which is used for colon cancer.[21] *UGT1A1* has also been implicated in coronary heart disease.[22] Patients diagnosed with colon cancer accounted for 12% of *UGT1A1* test utilization. Patients diagnosed with coronary atherosclerosis and hypertension accounted for 30% of *UGT1A1* tests.

Coagulation-related tests

This group includes two coagulation factors: factor V and factor II (codes 81240 and 81241), implicated in deep vein thrombosis and venous thromboembolism (VTE). These proteins are often tested together and were billed at similar frequencies (205,082 factor V tests and 193,436 factor II tests), accounting for 22% of tests billed and 8% of expenditures. The

Table 1 Utilization of new and preexisting billing codes among Medicare beneficiaries in 2013

		Tests	Beneficiaries[a]	Payments
HCPCS	**Gene/test**	**Number (%)**	**Number (%)**	**Dollars (%)**
Total preexisting codes	Preexisting codes	2,523,288 (100.0)	982,492 (100.0)	76,903,528 (100.0)
Total new codes	Tiers 1 and 2	1,832,279 (100.0)	527,404 (100.0)	256,242,345 (100.0)
81225–81227	CYP	519,340 (28.3)	454,575 (86.2)	117,845,531 (46.0)
81400–81408	Tier 2 (level 1-9)	274,208 (15.0)	183,744 (34.8)	6,716,666 (2.6)
81241	Factor V	205,082 (11.2)	185,084 (35.1)	13,187,524 (5.1)
81240	Factor II	193,436 (10.6)	174,076 (33.0)	7,633,652 (3.0)
81291	*MTHFR*	182,358 (10.0)	164,887 (31.3)	12,414,445 (4.8)
81355	*VKORC1*	91,859 (5.0)	81,345 (15.4)	4,188,876 (1.6)
81206–81208	*BCR-ABL1*	62,647 (3.4)	35,493 (6.7)	5,039,299 (2.0)
81370–81383	Histocompatibility antigens (HLA)	47,082 (2.6)	38,912 (7.4)	7,591,724 (3.0)
81211–81217	*BRCA*	44,762 (2.4)	42,036 (8.0)	56,763,760 (22.2)
81270	*JAK2*	40,225 (2.2)	35,044 (6.6)	2,625,106 (1.0)
81235	*EGFR*	22,581 (1.2)	20,437 (3.9)	3,820,761 (1.5)
81292–81301; 81317–81319	MMR (*MLH1, MSH2, MSH6, PMS2*)	20,118 (1.1)	18,272 (3.5)	5,225,342 (2.0)
81275	*KRAS*	19,909 (1.1)	17,453 (3.3)	2,920,758 (1.1)
81256	*HFE*	18,633 (1.0)	17,012 (3.2)	882,451 (0.3)
81210	*BRAF*	12,650 (0.7)	11,063 (2.1)	966,070 (0.4)
81267–81268	Chimerism analysis	10,449 (0.6)	4,139 (0.8)	1,661,200 (0.6)
81265–81266	STR analysis	8,277 (0.5)	7,546 (1.4)	1,296,089 (0.5)
81342	*TRG@*, gene rearrangement analysis	7,513 (0.4)	5,966 (1.1)	979,225 (0.4)
81220–81224	*CFTR*	6,647 (0.4)	5,637 (1.1)	195,855 (0.1)
81261–81262	*IGH@*, gene rearrangement analysis	6,388 (0.3)	5,194 (1.0)	794,359 (0.3)
81245	*FLT3*	4,033 (0.2)	3,371 (0.6)	434,060 (0.2)
81332	*SERPINA1*	3,830 (0.2)	3,657 (0.7)	177,549 (0.1)
81263	*IGH@*, somatic mutation analysis	3,457 (0.2)	3,128 (0.6)	687,368 (0.3)
81340-81341	*TRB@*, gene rearrangement analysis	3,433 (0.2)	2,791 (0.5)	430,122 (0.2)
81201–81203	*APC*	3,423 (0.2)	2,802 (0.5)	658,797 (0.3)
81310	*NPM1*	2,955 (0.2)	2,549 (0.5)	224,394 (0.1)
81228–81229	Cytogenetic analysis	2,805 (0.2)	2,260 (0.4)	55,487 (0.0)
81321–81323	*PTEN*	2,387 (0.1)	2,063 (0.4)	193,503 (0.1)
81315–81316	*PML/RARalpha*	2,208 (0.1)	1,201 (0.2)	214,130 (0.1)
81264	*IGK@,* gene rearrangement analysis	1,874 (0.1)	1,490 (0.3)	243,746 (0.1)
81257	*HBA1/HBA2*	1,708 (0.1)	1,535 (0.3)	98,295 (0.0)
81243–81244	*FMR1*	1,595 (0.1)	1,314 (0.2)	4,106 (0.0)
81350	*UGT1A1*	1,454 (0.1)	1,218 (0.2)	4,309 (0.0)
81324–81326	*PMP22*	639 (0.0)	568 (0.1)	19,391 (0.0)
81260	*IKBKAP*	273 (0.0)	215 (0.0)	12,139 (0.0)
81200	*ASPA*	258 (0.0)	181 (0.0)	1,915 (0.0)
81251	*GBA*	218 (0.0)	169 (0.0)	5,337 (0.0)
81280–81282	Long QT	209 (0.0)	188 (0.0)	246 (0.0)
81242	*FANCC*	207 (0.0)	185 (0.0)	7,516 (0.0)
81209	*BLM*	182 (0.0)	123 (0.0)	213 (0.0)
81330	*SMPD1*	178 (0.0)	122 (0.0)	213 (0.0)
81255	*HEXA*	175 (0.0)	148 (0.0)	6,128 (0.0)
81205	*BCKDHB*	157 (0.0)	115 (0.0)	245 (0.0)
81250	*G6PC*	124 (0.0)	106 (0.0)	4,797 (0.0)
81290	*MCOLN1*	118 (0.0)	100 (0.0)	5,097 (0.0)
81331	*SNRPN*	83 (0.0)	71 (0.0)	493 (0.0)
81302–81304	*MECP2* (Rett syndrome)	67 (0.0)	62 (0.0)	3,133 (0.0)
81252–81254	*GJB2/GJB6*	41 (0.0)	40 (0.0)	924 (0.0)
81161	*DMD*	24 (0.0)	23 (0.0)	- (0.0)

Preexisting codes are 83950, 83951, 86215, 86225, 86226, 86235, 86294, 86300, 86301, 86304, 86305, 86316, 87149, 88371, and 88372.

HCPCS,Healthcare Common Procedure Coding System.

[a]Total represents the number of beneficiaries who had at least one claim for a test billed with one of the new codes. The individual percentages of beneficiaries with claims for each test are calculated using that number as the denominator. These percentages add up to >100% because many beneficiaries received more than one test.

Source: Analysis by RTI International of 2013 Medicare claims.

Table 2 Categories of gene-specific tests by the three most frequently submitted ICD-9 diagnosis codes

Category/gene test	Tests	Diagnosis	%	Diagnosis	%	Diagnosis	%
Vascular disease							
Factor II	193,436	Disorders of lipid metabolism	25	Essential hypertension	15	Long-term use of medications	12
Factor V	205,082	Disorders of lipid metabolism	24	Essential hypertension	14	Long-term use of medications	11
MTHFR	182,358	Disorders of lipid metabolism	26	Essential hypertension	16	Long-term use of medications	12
Pharmacogenetic							
CYP2C19	233,745	Long-term use of medications	21	Disorders of lipid metabolism	20	Essential hypertension	13
CYP2D6	154,925	Long-term use of medications	33	Essential hypertension	10	Pain	5
CYP2C9	130,670	Long-term use of medications	28	Essential hypertension	12	Disorders of lipid metabolism	6
UGT1A1	1,454	Coronary atherosclerosis	24	Colon cancer	12	Essential hypertension	6
VKORC1	91,859	Long-term use of medications	30	Essential hypertension	15	Disorders of lipid metabolism	7
Genetic predisposition to cancer							
APC	3,423	History of colon polyps	29	Colon cancer	12	Lung cancer	7
BRCA1/2	44,762	Breast cancer	46	History of breast cancer	25	Ovarian cancer	9
MMR	20,118	Colon cancer	37	History of GI cancer	27	Family history of cancer	6
PTEN	2,387	Breast cancer	23	Prostate cancer	14	Lung cancer	11
Somatic cancer biomarkers (solid tumors)							
BRAF	12,650	Colon cancer	20	Lung cancer	15	Malignant melanoma	15
EGFR	22,581	Lung cancer	62	Secondary malignancy	7	Lymph node metastasis	3
KRAS	19,909	Colon cancer	31	Lung cancer	26	Secondary malignancy	8
Hematologic malignancy							
BCR-ABL1	62,647	Myeloid leukemia	53	Diseases of white blood cells	12	Neoplasm of uncertain behavior	6
FLT3	4,033	Myeloid leukemia	35	Neoplasm of uncertain behavior	13	Lung cancer	5
IGH@ (gene rearrangement)	6,388	Lymphoma	23	Lymphoid leukemia	9	Neoplasm of uncertain behavior	8
IGH@ (mutations)	3,457	Lymphoid leukemia	61	Diseases of white blood cells	13	Lymphoma	6
IGK@	1,874	Lymphoma	25	Multiple myeloma	10	Neoplasm of uncertain behavior	7
JAK2	40,225	Neoplasm of uncertain behavior	28	Diseases of white blood cells	15	Other diseases of blood	15
NPM1	2,955	Lymphoid leukemia	35	Neoplasm of uncertain behavior	13	Lung cancer	5
TRB@	3,433	Lymphoma	19	Neoplasm of uncertain behavior	12	Diseases of white blood cells	10
TRG@	7,513	Lymphoma	21	Neoplasm of uncertain behavior	12	Diseases of white blood cells	11
STR	8,277	Nonspecific findings in blood	51	Prostate cancer	24	Myeloid leukemia	5
Chimerism	10,449	Myeloid leukemia	34	Neoplasm of uncertain behavior	16	Lymphoid leukemia	10
Histocompatibility complex							
HLA	47,082	HIV disease	9	Joint disorder	7	Neoplasm of uncertain behavior	5
Hemochromatosis							
HFE	18,633	Nonspecific findings in blood	17	Disorders of iron metabolism	17	Unspecified anemia	7
Tier 2							
Levels 1–9	274,208	Disorders of lipid metabolism	14	Long-term use of medications	14	Essential hypertension	8
Other	21,746						

HLA, human leukocyte antigens; ICD-9, International Classification of Diseases, 9th revision; STR, short tandem repeat.

Source: Analysis by RTI International of 2013 Medicare claims.

methylenetetrahydrofolate reductase (*MTHFR*) gene is also involved in regulation of blood coagulation. A total of 182,358 *MTHFR* tests were billed, which represented 10% of new tests billed and 5% of expenditures. Diagnosis codes submitted with these tests had almost identical distributions: hypercholesterolemia (25%), malignant hypertension (15%), and long-term use of medications (12%).

Genetic predisposition to cancer

Genes that identify hereditary cancer risk (codes 81201–81203, 81211–81217, 81292–81301, 81321–81323) accounted for 4% of tests billed. These included *BRCA1/2* tests for breast and ovarian cancers; mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, involved in hereditary nonpolyposis colorectal cancer; the *APC* gene for familial adenomatous polyposis; and *PTEN* for hamartoma tumor syndrome. *PTEN* somatic mutations occur in many cancers and are usually associated with poor outcomes, so this test is also used as a prognostic tool. The highest expenditures were for *BRCA1/2*, which accounted for 2% of tests billed but 22% ($56,763,760) of total expenditures.

Somatic cancer biomarkers for solid tumors

Epidermal growth factor receptor (*EGFR*), *KRAS*, and *BRAF*, the three most common tests for somatic cancer mutations in solid tumors,[23] accounted for 3% (55,140) of tests billed and 3% of expenditures. These tests, which predict the therapeutic response to specific cancer treatments such as tyrosine kinase inhibitors (TKIs), were conducted in lung, colon, and melanoma cancer patients. We observed similarities in age- and gender-related distributions of these tests (**Supplementary Appendix 2** online). Patients older than age 75 underwent the most testing (39% of the 48,953 beneficiaries tested). Women underwent tests more frequently than men.

Hematologic malignancies

Tests in this category detect chromosomal rearrangements and mutations of specific malignancies and are used in bone marrow transplantations (*BCR-ABL1*, *FLT3*, *IGH*, *IGK*, *JAK2*, *NPM1*, *TRB*, and *TRG*). Tests for hematologic malignancies accounted for 7% of tests billed and 4% of expenditures. The most frequently used tests were *BCR-ABL1* and *JAK2*. The *BCR-ABL1* test is used to confirm or rule out diagnosis of chronic myelogenous leukemia or Philadelphia chromosome–positive acute lymphoblastic leukemia, to predict benefit of treatment with anti-*ABL1* TKIs (such as imatinib), and to monitor patients who have undergone transplantation for chronic myelogenous leukemia. The diagnosis code most frequently submitted with this test was myelogenous leukemia. A patient may undergo

Table 3 Most frequent diagnoses submitted for test orders

	Tier 1 and 2 codes	Preexisting codes	NOC	Total	Percent
Total	1,832,279	2,523,288	517,464	4,873,031	100.00
Breast cancer	41,931	605,956	22,275	670,162	13.75
Long-term use of medications	278,624	24,452	36,491	339,567	6.97
Disorders of lipoid metabolism	250,704	34,598	26,069	311,371	6.39
Cancer of ovary and other female genital organs	16,333	219,482	3,772	239,587	4.92
Hypertensive disease	186,862	31,978	8,039	226,879	4.66
Systemic lupus erythematosus and connective-tissue disorder	1,543	151,066	242	152,851	3.14
Rheumatoid arthritis and related disease	3,961	105,744	27,524	137,229	2.82
Diabetes	78,124	31,880	11,404	121,408	2.49
Joint/rheumatoid disorders	9,902	90,352	941	101,195	2.08
Abnormal cytological, histological, immunological, and DNA findings	817	92,511	328	93,656	1.92
Diseases of the musculoskeletal system and connective tissue	41,059	43,579	5,798	90,436	1.86
Pancreatic cancer	1,773	86,743	607	89,123	1.83
General symptoms	25,224	40,746	5,904	71,874	1.47
Leukemia	59,745	1,675	8,566	69,986	1.44
Coronary atherosclerosis	64,905	2,468	2,260	69,633	1.43
Antineoplastic chemotherapy	1,918	63,865	9	65,792	1.35
Other cardiovascular	36,651	10,201	1,319	48,171	0.99
Vitamin D deficiency	23,851	21,684	2,483	48,018	0.99
Central pain syndrome	33,987	9,759	3,003	46,749	0.96
Thyroid disorder	22,364	18,965	4,863	46,192	0.95
935 other diagnoses, each less than 1%	652,001	835,584	345,567	1,833,152	37.62

Tier 1 comprises gene-specific codes (81200–81383) and tier 2 comprises the molecular pathology procedure level codes (81400–81408). Preexisting codes are 83950, 83951, 86215, 86225, 86226, 86235, 86294, 86300, 86301, 86304, 86305, 86316, 87149, 88371, and 88372. NOC codes are 81479, 84999, 87799, 87999, and 88399.

NOC, not otherwise classified.

Source: Analysis by RTI International of 2013 Medicare claims.

BCR-ABL1 testing multiple times, as illustrated by the higher number of claims compared with beneficiaries tested. *JAK2* mutation analysis (V617F and exons 12–13 mutations) is used to confirm the diagnosis of myeloproliferative neoplasms other than chronic myelogenous leukemia, such as polycythemia vera, essential thrombocythemia, and primary myelofibrosis.

The chimerism and short tandem repeat analysis accounted for 1% of tests billed and 1% of expenditures. These are genetic identity tests used for recipient and donor testing during bone marrow transplantation and for evaluation of engraftment status after transplantation. Short tandem repeat profiling is also used for specimen identification and control of contamination, which can be applied in the context of any diagnosis.[24] Neoplasm of uncertain behavior was a common diagnosis billing code for these tests.

Molecular pathology level (tier 2) codes

Approximately 15% of tests, accounting for 3% of expenditures, were billed with tier 2 codes 81400–81408, which do not identify specific analytes measured. Approximately one-third of beneficiaries had claims with tier 2 codes. Disorders of lipid metabolism and malignant hypertension collectively accounted for 22% of these tests. Long-term use of medications accounted for 14%.

Most common conditions for genetic testing

Table 3 lists the top 20 diagnostic categories submitted as indications for testing. The most frequent diagnosis for testing was breast cancer, accounting for 670,162 (14%) of claims. There were 586,856 (88%) claims for CA 15-3 (code 86300), 31,781 (5%) claims for *BRCA1/2,* and 15,569 (2%) claims for oncotype DX breast cancer assay. The second and third most frequent diagnoses were long-term use of medications and disorders of lipid metabolism, which is consistent with our analysis of the gene-specific billing codes.

Estimating the population potentially eligible for *EGFR* testing

Each year, approximately 228,190 individuals are newly diagnosed with lung cancer in the United States.[25] Most of these patients are eligible for Medicare. We identified 229,954 Medicare beneficiaries who had a lung cancer diagnosis in 2013 and no previous claims with a lung cancer diagnosis. Many of these patients may have been too frail or had comorbid medical conditions that precluded an invasive biopsy. These patients would have been diagnosed via fine-needle aspiration rather than core needle biopsy, and there would not be enough tumor tissue available for *EGFR* testing. Therefore, we considered the eligible patient population to be patients who had a claim for lung tissue surgical pathology analysis (codes 88305, 88307, and 88309). A total of 142,469 newly diagnosed patients had lung tissue available for *EGFR* testing. Cancer registry data suggest that approximately half of these patients (71,235) had clinical characteristics that made them eligible for *EGFR* testing.[26]

In 2013, 18,906 patients had claims for *EGFR* testing. Only 12,440 of these tests were conducted in patients identified in 2013 claims data. There were 6,466 patients who had received a diagnosis of lung cancer before 2013, which suggests that *EGFR* testing was conducted on archived tissue. There were 887 patients identified and tested in 2013 who had no claims for surgical pathology analysis. These patients probably were either newly eligible for Medicare in 2013 or underwent a biopsy and surgical pathology analysis late in the calendar year of 2012 and received the lung cancer diagnosis and *EGFR* testing in 2013. These data suggest that 17.5% of patients eligible for *EGFR* testing were tested.

Demographic and regional variation in testing

In 2013, the Medicare population was 56% female, 77% white, 10% black, 8% Hispanic, and 5% of other ethnicity.[14] Demographic characteristics of patients tested varied widely by individual tests. The age category, gender, race, and vital status of patients separated by test are summarized in **Supplementary Appendix 2** online. Disease prevalence may explain variations in testing between patient groups. Therefore, analysis of variations in testing should be performed according to a specific disease or test.

A higher proportion of females were tested to identify hereditary risk for cancers (*BRCA1/2* and MMR) and for factor II and factor V mutations. Gender variation was expected for *BRCA1/2* testing but may warrant investigation for MMR. The higher proportion of females tested for factor II and factor V mutations corresponds to the overall gender distribution within the Medicare population.[14]

Across most test groups, minorities represented a smaller proportion of those tested than in the population. However, a higher proportion of blacks underwent pharmacogenetic, histocompatibility, factor II, and factor V testing than are represented in the Medicare population. Analysis of ethnic/racial variations in access to testing needs to be factored into the prevalence of disease within specific populations. With existing knowledge about the incidence of breast, colon, and lung cancer among minority patients, it is clear that the lower proportion of blacks undergoing hereditary and somatic cancer genetic tests warrants investigation.

Patient-level variations in access to testing are partially explained by regional variations in practice patterns. Analysis of the zip code of residence for beneficiaries tested revealed substantial regional variation in testing. The number of beneficiaries per state and rate of testing (beneficiaries tested/all fee-for-service beneficiaries) per hospital referral region (HRR) for gene-specific tests are illustrated in **Figure 1**. Huntsville, Alabama, had the highest rate of testing (25.19%); Great Falls, Montana, had the lowest (0.6%). Among the HRRs in the highest quintile of testing, the rate of CYP tests ranged from 23% of tests in Panama City, Florida, to 57% in Baton Rouge, Louisiana.

DISCUSSION

In 2013, 527,404 (1.5%) of the 34 million fee-for-service Medicare beneficiaries underwent precision medicine tests billed with the AMA's new tier 1 and 2 codes. This study illustrates that gene-specific billing codes, developed by the AMA

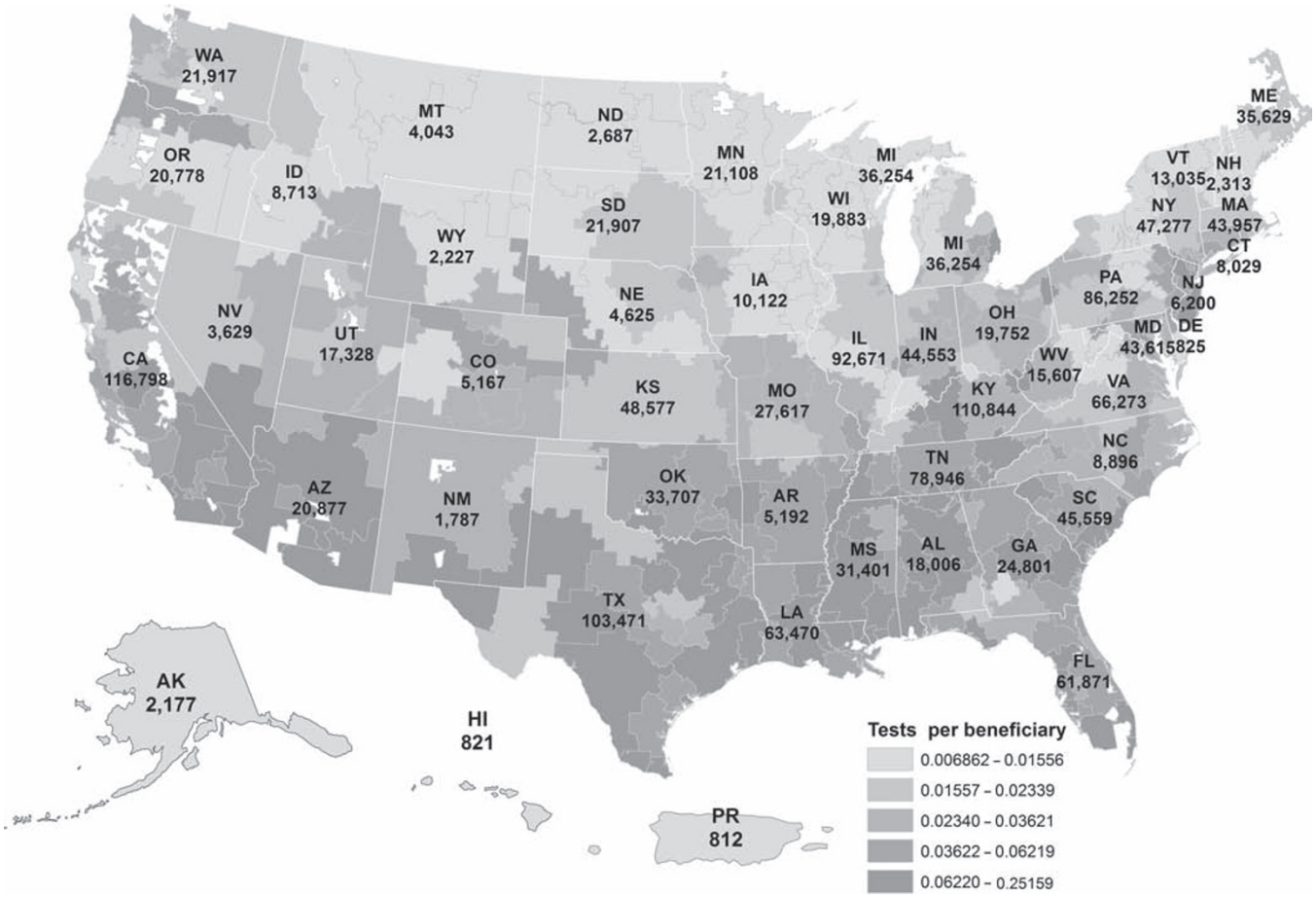

Figure 1 Frequency and rate of testing by state and hospital referral region. Numbers indicate the number of tests conducted in each state; color intensity corresponds to the rate of testing (beneficiaries tested/all fee-for-service beneficiaries).

and adopted by Medicare in 2013, improved documentation of precision medicine and facilitated population-level research.

In 2013, there were both underutilization of certain guideline-recommended tests and overutilization of tests that lack clinical utility. We expected to see frequent testing associated with high-prevalence conditions typical for an older population, such as cardiovascular disease and cancer. Given that 80% of drugs used today are metabolized by the CYP proteins,[27] the high volume of pharmacogenetic testing for CYP variants was not a surprise. However, as of July 2015, Medicare limited the coverage for pharmacogenetic tests.[28]

It was surprising to see a high level of utilization of *MTHFR* testing because it is not supported by guidelines. The *MTHFR* gene is involved in homocysteine metabolism, which is related to unfavorable cardiovascular events,[29] and *MTHFR* polymorphisms are suspected to affect susceptibility to coronary heart disease.[30] However, the clinical utility of *MTHFR* testing has been questioned by the American College of Medical Genetics and Genomics (ACMG), which discourages its use as part of its Choosing Wisely campaign.[31] In addition, the 2012 Endocrine Society hypertriglyceridemia guidelines exclude *MTHFR* testing,[32] and the 2011 American Congress of Obstetricians and Gynecologists recommend against screening for *MTHFR* polymorphisms in pregnancy.[33] Centers for Medicare & Medicaid Services cover *MTHFR* testing if it is necessary for the diagnosis of a specific genetic disorder (e.g., homocystinuria), but not for the assessment of thrombosis risk in asymptomatic patients (screening for inherited thrombophilia). Furthermore, local coverage determinations for biomarkers during the time of the study specifically stated that coverage was dependent on the result of the test directly impacting the treatment being delivered to the beneficiary.[34] Nevertheless, with 182,358 tests ordered, *MTHFR* was one of the most frequently ordered and represented 10% of tests billed using gene-specific codes. A recent paper pointed out that commonly practiced inpatient testing for inherited thrombophilia, which includes *MTHFR* testing, does not influence VTE management and is not clinically useful.[35] However, these authors substantially overestimate Medicare reimbursements for these tests.

By contrast, there appears to be underutilization of some tests that have strong evidence for use. During the time of the study, *EGFR* testing was indicated and covered by Medicare for all patients who had newly diagnosed or recurrent metastatic lung cancer with adenocarcinoma histology and who were considered for first-line therapy with an EGFR TKI.[36,37] The College of American Pathologists, the International Association for the

Study of Lung Cancer, the Association for Molecular Pathology, and the American Society of Clinical Oncology jointly issued a clinical practice guideline recommending *EGFR* testing for lung cancer patients.[36] However, it appears that only 17.5% of newly diagnosed patients were tested. It is important to develop methodologies for identifying the appropriate patient population eligible for testing. Claims data have limited clinical characteristics, such as the histologic subtype, to identify at the patient level who is eligible for testing. However, population-level statistics can be applied to conduct a high-level analysis of whether large groups of patients are appropriately accessing testing. Our analysis indicated persistent underutilization of *EGFR* testing in lung cancer. Gene-specific billing codes now allow payers to identify whether patients are being prescribed TKIs prior to undergoing *EGFR* testing. This could lead to more cost-effective use of those drugs.

An important finding was that, contrary to AMA predictions, tier 2 codes were used extensively, representing 15% of tests billed. Like older methodology-based codes, tier 2 codes do not identify the gene/protein analyzed. Therefore, some gene-specific tests are included in tier 2 claims. Two of the three most clinically relevant variants of the *KRAS* gene, mutations in codons 12 and 13, are reported with gene-specific code 81275. However, testing for *KRAS* codon 61 is included in the level 4 code 81403 and full-gene sequencing of *KRAS* is included in the level 6 code 81405. The latter two codes do not identify specific genes. Because this code is shared with numerous biomarkers, it is not possible to determine how many claims for 81403 were for *KRAS* codon 61. Tier 2 codes introduce inaccuracy into our study and return us to the lack of transparency that existed with methodology code stacking. This problem is further complicated by laboratories moving toward multigene panels[38] that can be billed with tier 2 codes, which requires researchers to verify whether a gene of interest is included in the panel. Since 2013, the AMA has been expanding the list of analytes covered by tier 2 codes, which presents a challenge for researchers trying to evaluate implementation and health outcomes of precision medicine.

Even with gene-specific coding, there are limitations inherent in claims data analysis. Diagnosis and procedure codes help researchers infer clinical scenarios. However, claims data often lack sufficient detail to conclusively state whether testing was concordant with specific guidelines. In many cases, medical record data are required to determine the appropriateness of testing and to measure the impact of test results on treatment decisions. For example, a thorough evaluation of pharmacogenetics testing would require researchers to link prescription data to test results. There are many reasons that this analysis would be difficult using Medicare claims data. Data from the Medicare Part D prescription drug program include claims from only two-thirds of Medicare beneficiaries.[14]

Claims data do not readily identify the relationship between a coverage decision and test utilization. The Centers for Medicare & Medicaid Services make coverage decisions or sponsor administrative programs that may impact whether providers order specific tests. For example, the National Coverage Determination for Pharmacogenomic Testing for Warfarin Response implemented in 2010 provided coverage with evidence development for pharmacogenetic testing of CYP2C9 and/or VKORC1 alleles to predict warfarin response. Testing was limited to once in a lifetime per beneficiary and reimbursed only for candidates for anticoagulation therapy with warfarin who were enrolled in a clinical trial. This coverage decision probably impacted utilization of these tests.

There are several other examples of the limitations of using claims data to analyze appropriateness of testing. The US Preventive Services Task Force statement on *BRCA1/2* testing includes a recommendation to use family history to refer patients to genetic counseling and it discourages population screening.[39] Claims data do not provide sufficient detail to capture family history and patient preferences are not captured. Another example relates to factor V and factor II, which were among the most frequently billed tests in our analysis. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group recommended against factor V and factor II testing in two very specific scenarios involving adults with a personal or family history of idiopathic VTE. Nevertheless, EGAPP was careful to mention that "recommendations do not extend to patients with other risk factors for thrombosis, such as contraceptive use" and that "testing might have clinical utility in some circumstances, such as for identifying factor V Leiden homozygosity among asymptomatic family members of adults with idiopathic VTE or counseling patients about the risks and benefits of antithrombotic therapy."[40] These relevant clinical data are not captured in claims data.

Our analysis represents the necessary first step for evaluating guideline-concordant utilization of precision medicine tests in Medicare data. Linking test utilization to zip code and prevalence of disease in that geographic region enables policy makers to quickly identify and develop targeted interventions to further assess concordance with guidelines. The next step would be to validate what is reported in claims data by linking these data to disease registries or electronic health records. Information from those sources (test results, drug data, and specific clinical information, e.g., disease subtype and stage) is needed to assess appropriateness of testing and to define the denominator for calculating utilization. In addition, it would be valuable to conduct a longitudinal analysis to analyze the impact of testing on subsequent health-care utilization.

Another aspect of precision medicine implementation that was beyond the scope of the current study relates to inconsistent reimbursement policies. Although Medicare contractors are supposed to accept other local coverage determination policies, these policies can contribute to regional variation in the utilization of similar items and services. Variations in coverage are currently being addressed by the proposed legislation (the Local Coverage Determination Clarification Act of 2016). Regional differences in testing demonstrated in our analysis may be partially explained by actual differences in local coverage determinations as well as by the clinicians' perception of

coverage. There may have also been uncertainty among providers about whether presymptomatic or predictive testing was covered by Medicare during this time period.

The Precision Medicine and Cancer Moonshot Initiatives emphasize the importance of improving documentation of gene-specific testing and molecular disease subtypes within claims data. Successful translation of precision medicine requires population-level research to determine whether tests are used appropriately, impact treatment decisions, and improve health outcomes, as well as to measure whether patients from different racial or ethnic backgrounds benefit equally. Claims data for 55 million Medicare beneficiaries, when linked to electronic health records and disease registries, are a valuable resource with which to conduct population-level analysis of precision medicine.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

The authors declare no conflict of interest.

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