Alignment of Inhaled Chronic Obstructive Pulmonary Disease Therapies with Published Strategies

Analysis of the Global Initiative for Chronic Obstructive Lung Disease Recommendations in SPIROMICS

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Abstract

Rationale: Despite awareness of chronic obstructive pulmonary disease (COPD) treatment recommendations, uptake is poor. The Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) spans 2010–2016, providing an opportunity to assess integration of 2011 Global Initiative for Obstructive Lung Disease (GOLD) treatment strategies over time in a large observational cohort study.

Objectives: To evaluate how COPD treatment aligns with 2011 GOLD strategies and determine factors associated with failure to align with recommendations.

Methods: Information on inhaled medication use collected via questionnaire annually for 4 years was compiled into therapeutic classes (long-acting antimuscarinic agent, long-acting β -agonist, inhaled corticosteroids [ICS], and combinations thereof). Medications were not modified by SPIROMICS investigators. 2011 GOLD COPD categories A, B, C, and D were assigned. Alignment of inhaler regimen with first-/second-line GOLD recommendations was determined, stratifying into recommendation aligned or

nonaligned. Recommendation-nonaligned participants were further stratified into overuse and underuse categories.

Results: Of 1,721 participants with COPD, at baseline, 52% of regimens aligned with GOLD recommendations. Among participants with nonaligned regimens, 46% reported underuse, predominately owing to lack of long-acting inhalers in GOLD category D. Of the 54% reporting overuse, 95% were treated with nonindicated ICS-containing regimens. Among 431 participants with 4 years of follow-up data, recommendation alignment did not change over time. When we compared 2011 and 2017 recommendations, we found that 47% did not align with either set of recommendations, whereas 35% were in alignment with both recommendations.

Conclusions: Among SPIROMICS participants with COPD, nearly 50% reported inhaler regimens that did not align with GOLD recommendations. Nonalignment was driven largely by overuse of ICS regimens in milder disease and lack of long-acting inhalers in severe disease.

Keywords: chronic obstructive pulmonary disease; inhaled therapy; treatment

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Table 1. Alignment of inhaler therapies with Global Initiative for Chronic Obstructive Lung Disease recommendations

GOLD Category	First-/Second-Line Therapy	Underuse	Overuse
A	SAMA as needed or SABA as needed or <i>LAMA</i> or <i>LABA</i> or <i>SABA + SAMA</i>	N/A	ICS monotherapy or ICS + LABA or ICS + or LAMA + LABA or ICS + LAMA + LABA
B	LAMA or LABA or <i>LAMA + LABA</i>	No inhaler or ICS monotherapy	ICS + LABA or ICS + LAMA or ICS + LAMA + LABA
C	ICS + LABA or LAMA or <i>LAMA + LABA</i>	No inhaler or LABA monotherapy or ICS monotherapy	LAMA + ICS or ICS + LAMA + LABA
D	ICS + LABA or LAMA or <i>ICS + LAMA</i> or <i>ICS + LABA + LAMA</i> or <i>LAMA + LABA</i>	No inhaler or LABA monotherapy or ICS monotherapy	N/A

Definition of abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; LAMA = long-acting antimuscarinic agent; N/A = not applicable; SABA = short-acting β -agonist; SAMA = short-acting muscarinic antagonist. Bold regimens are first-choice inhaler regimens. Italicized regimens are second-choice inhaler regimens.

Chronic obstructive pulmonary disease (COPD) treatment recommendations are available to assist clinicians with selection of pharmacological therapy in COPD, but overall adherence to guideline recommendations remains limited (1, 2). The most widely used therapeutic strategy is proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). This treatment strategy was initially published in 2001, with updates in 2011 and most recently in 2018 (3–5). Despite the ubiquity of the GOLD treatment strategy, small observational studies report poor uptake of GOLD recommendations worldwide, with some studies demonstrating more than 50% of patients with COPD reporting treatments not consistent with guideline recommendations (1, 6–12). There is little information on how alignment with treatment recommendations changes over time or on factors associated with overuse and underuse. Identifying and describing patient populations who are receiving suboptimal medication regimens

can improve uptake of published treatment recommendations and overall COPD care.

The Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) is a large, multicenter, observational cohort study of current and former smokers with extensive data regarding physiologic status, clinical parameters, and medication use (13). SPIROMICS collected data from 2010 through 2016, permitting a unique opportunity to analyze associations between demographic factors and alignment with treatment recommendations, as well as how this alignment changed over time. Given 2011 GOLD treatment strategies (5) were used as the standard for diagnosis and management of COPD at the time of SPIROMICS data collection, the present analysis examines the alignment of medication use in SPIROMICS with 2011 GOLD recommendations. Some of the results of these studies were previously presented in the form of an abstract (14).

Methods

Study Cohort

SPIROMICS is a multicenter cohort study with recruitment from 12 clinical centers and including former and current smokers (>20 pack-years) with and without COPD and nonsmoking control subjects (13). Participant recruitment occurred through referrals from physicians at each clinical center, community-based recruitment in locations where individuals were seeking medical care (i.e., doctors' offices, pulmonary rehabilitation clinics), or self-referrals. The analytical cohort for this study is limited to SPIROMICS participants with spirometry-defined COPD at the time of SPIROMICS visit (defined as post-bronchodilator ratio of forced expiratory volume in 1 s [FEV₁] to forced vital capacity [FVC] <0.70) with complete 2011 GOLD categorization (5) and medication use data at the baseline visit. All participants provided written informed consent, and institutional review boards at each

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SPIROMICS clinical center approved the study.

Data Collection

SPIROMICS participants were followed for up to 3 years with annual visits (baseline plus up to three annual follow-up visits). All SPIROMICS baseline and follow-up questionnaires are publicly available from www.spiromics.org. Data on demographics, smoking status and history, inhaler medication use, and COPD exacerbation occurrence were obtained via self-report at each visit. COPD exacerbations included any respiratory flare-up requiring healthcare use involving the use of antibiotics or systemic corticosteroids or both in the prior 12 months (15). History of emphysema, asthma, chronic bronchitis, and COPD was

defined at baseline via self-report of ever having received a physician diagnosis. Measurements collected at each visit included pre- and post-bronchodilator spirometry as well as respiratory assessments, including the modified Medical Research Council dyspnea scale (mMRC) (16) and the COPD Assessment Tool (CAT) (17). Analyses were completed using spirometry from the baseline visit. Medication use was assessed via a questionnaire asking, "[I]n the past 3 months, have you used..." a class of medication including inhaled steroids, inhaled bronchodilators, nebulized bronchodilators, and other oral medications. Medications were not modified by SPIROMICS investigators. Each category of inhaled drug was then followed by specific

brand names and dosages for participants to select. At each visit, participants were assigned GOLD categorizations of A, B, C, or D based on 2011 guidelines using exacerbations, airflow obstruction, and symptom burden. Symptom scores using the CAT were used for categorization as recommended by guidelines (5).

For the purpose of analysis, alignment with treatment recommendations at each visit was defined as alignment of the participant's prescribed regimen to either first- or second-line GOLD recommendations of inhaled medications only (Table 1). For GOLD-A, first-line therapy was as-needed use of short-acting anticholinergic agents (SAMA) or short-acting β -agonists (SABA). First-line pharmacologic therapy for GOLD-B

Table 2. Baseline demographics

	Full Cohort	GOLD A	GOLD B	GOLD C	GOLD D
No. of subjects	1,721	383 (22)	665 (39)	75 (4)	598 (35)
Age, yr	65.2 (8.0)	67.7 (7.3)	64.8 (8.2)	67.3 (7.4)	63.8 (7.9)
Male sex, <i>n</i> (%)	995 (58)	125 (33)	297 (45)	44 (59)	325 (54)
Race, <i>n</i> (%)					
White	1,401 (81)	324 (85)	547 (82)	61 (81)	469 (78)
Black	259 (15)	44 (11)	94 (14)	13 (17)	108 (18)
Other/missing	61 (4)	15 (4)	24 (4)	1 (1)	21 (3)
Current smoker, <i>n</i> (%)	579 (34)	99 (26)	297 (45)	14 (19)	169 (29)
Pack-years, median (Q1–Q3)	46 (35–62)	45 (33–59)	47 (38–66)	43 (35–60)	49 (35–63)
FEV ₁ /FVC, post-BD	0.51 (0.13)	0.59 (0.08)	0.57 (0.09)	0.43 (0.11)	0.40 (0.12)
FEV ₁ , post-BD					
Absolute, L	1.73 (0.77)	2.30 (0.69)	2.03 (0.61)	1.22 (0.48)	1.10 (0.47)
Percent predicted	60.6 (23)	78.8 (16)	71.3 (15)	44.6 (16)	39.0 (15)
FVC, post-BD					
Absolute, L	3.34 (1.05)	3.88 (0.99)	3.55 (0.98)	2.91 (1.03)	2.81 (0.91)
Percent predicted	88.4 (20)	100 (16)	94.7 (16)	78.7 (20)	75.1 (18)
GOLD FEV ₁ stratum, <i>n</i> (%)					
I	364 (21)	176 (46)	170 (26)	4 (5)	14 (2)
II	772 (45)	207 (54)	495 (75)	7 (9)	63 (11)
III	413 (24)	0 (0)	0 (0)	55 (73)	358 (60)
IV	172 (10)	0 (0)	0 (0)	9 (12)	163 (27)
Exacerbations in prior year, <i>n</i> (%)					
None	1,192 (70)	340 (90)	526 (80)	45 (61)	281 (47)
One	304 (18)	37 (10)	131 (20)	11 (15)	125 (21)
Two or more	206 (12)	0 (0)	0 (0)	18 (24)	188 (32)
CAT score					
Median (Q1–Q3)	15 (9–21)	6 (4–8)	17 (13–22)	7 (5–8)	20 (15–24)
≥10, <i>n</i> (%)	1,263 (73)	0 (0)	665 (100)	0 (0)	598 (100)
mMRC score					
Median (Q1–Q3)	1 (1–2)	0 (0–1)	1 (1–2)	1 (1–1)	2 (1–3)
≥2, <i>n</i> (%)	559 (32)	17 (4)	195 (29)	13 (17)	334 (56)
Self-reported, <i>n</i> (%)					
COPD	1,283 (77)	180 (51)	494 (77)	62 (85)	547 (95)
CB	438 (27)	49 (13)	156 (25)	17 (24)	216 (39)
Emphysema	814 (50)	104 (29)	276 (45)	43 (59)	391 (69)
COPD, CB, or emphysema	1,402 (81)	220 (57)	544 (82)	68 (91)	570 (95)
Asthma	388 (23)	52 (14)	158 (24)	18 (24)	160 (27)

Definition of abbreviations: BD = bronchodilator; CAT = COPD Assessment Test; CB = chronic bronchitis; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council dyspnea scale.

All values are mean (standard deviation) unless otherwise indicated.

participants was a long-acting antimuscarinic agents (LAMA) or a long-acting β -agonist (LABA). GOLD-C first-line therapy was either a LAMA or a combination of an inhaled corticosteroid (ICS) and a LABA. GOLD-D first-line therapy was either a LAMA or a combination of an ICS and a LABA. Second-line therapies are summarized in Table 1. Nonalignment with GOLD recommendations was defined as participants' inhaler regimens that did not fit within first- or second-line recommendations based on GOLD categorization.

Recommendation-nonaligned participants were further stratified into overuse and underuse on the basis of maintenance inhaler use as outlined in Table 1. Underuse was defined as use of less medication than allotted for a specific GOLD class. GOLD-B participants were defined as reporting underuse if they lacked long-acting maintenance therapy, such as LAMA or LABA, or lacked long-acting maintenance therapy, such as LAMA or LABA. For GOLD-B participants, use of ICS monotherapy was categorized as underuse. Both GOLD-C and GOLD-D underuse was defined by no maintenance therapy or use of LABA or ICS monotherapy. Overuse was defined as use of more medications than recommended for a specific GOLD classification. For GOLD-A, overuse included treatment with any ICS, combination ICS and LABA, combination of ICS and LAMA, combination of LAMA and LABA, or LAMA/LABA/ICS therapy. GOLD-B overuse included treatment with any ICS-containing regimen (excluding ICS monotherapy, because this was classified as underuse). For GOLD-C participants, overuse was defined as combination of LAMA and ICS or use of LAMA/LABA/ICS. Analyses were conducted to examine the impact of income, education, and prior history of physician-diagnosed asthma on alignment with GOLD recommendations. Secondary analysis of alignment with 2017 GOLD recommendations was also conducted.

Statistical Methods

Baseline differences in demographic and clinical factors between cohort participants, stratified by alignment with recommendations, were assessed using chi-square tests (categorical variables) or analysis of variance (ANOVA) (continuous variables). Differences in medication use patterns at baseline, stratified by alignment and by treatment, were assessed

via chi-square tests using Fisher's exact test to account for low frequency counts. Change in alignment over time was assessed among participants with complete follow-up data with the 'PTREND' STATA module, calculating chi-square test results for departure from the trend line of alignment over visits. To reduce the risk of type I error related to multiple comparisons, a Bonferroni-corrected *P* value less than 0.002 (derived from the largest set of simultaneous comparisons [$n = 22$]) was used to define statistical significance in all comparisons. All analyses were completed with Stata 15.0 software (StataCorp).

Results

Participant Characteristics

The total SPIROMICS cohort ($N = 2,974$) included 1,831 individuals with spirometry-confirmed COPD ($FEV_1/FVC, <0.7$). The analytical cohort in the present study included 1,721 participants with spirometry-confirmed COPD and complete baseline medication use and 2011 GOLD categorization data, representing 94% of participants with COPD in SPIROMICS (see Figure E1 in the online supplement). The average age was 65.2 years; 58% were male; 81% were white; and 34% were current smokers (Table 2). At baseline, 22% of participants were classified as GOLD-A, 39% as GOLD-B, 4% as GOLD-C, and 35% as GOLD-D. Distribution of race was similar among GOLD categories; however, all other

demographic and clinical characteristics were different among GOLD categories. GOLD-A participants were oldest (67.7 ± 7.3 yr), whereas GOLD-D participants were youngest (63.8 ± 7.9 yr). GOLD-A participants had the highest proportion of women (67%), whereas GOLD-C had the lowest proportion of women (41%). The GOLD-B cohort had the highest prevalence of current smokers (45%), whereas GOLD-C had the lowest prevalence of current smokers (19%). Lung function was lowest in GOLD-D (FEV_1 percent predicted, $39 \pm 15\%$) and highest in GOLD-A (FEV_1 percent predicted, $78.8 \pm 16\%$). Of the total cohort, 66% had mild to moderate airflow obstruction. As expected, higher proportions of GOLD-A and GOLD-B participants (90% and 80%, respectively) than GOLD-C and GOLD-D participants (61% and 47%, respectively) had no exacerbations. Of the total cohort, 81% reported having a physician diagnosis of either COPD, chronic bronchitis, or COPD, with GOLD-D participants being most likely to report any of these diagnoses. Only 57% of GOLD-A participants reported a diagnosis of either COPD, chronic bronchitis, or emphysema.

Baseline medication use is summarized in Figure E2 and Table E1. At baseline, 27% of the entire cohort reported not using any inhaler (short-acting or maintenance), whereas 37% reported no long-acting maintenance inhaler use. The most prevalent maintenance inhaler use among GOLD-A and GOLD-B participants was a combination of LABA/ICS (10% and 20%, respectively), whereas triple therapy with

Figure 1. Proportion of Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) participants aligning with Global Initiative for Chronic Obstructive Lung Disease (GOLD) first- or second-line treatment recommendations, stratified by baseline GOLD group.

LAMA/LABA/ICS was the most common in GOLD-C and GOLD-D participants (37% and 43%, respectively). Of the total cohort, 4% reported ICS monotherapy as their only maintenance inhaler. Oral glucocorticoid use was uncommon in the cohort (4%), with increasing use in GOLD-C and GOLD-D participants. Specifically, glucocorticoid use was reported in 0.5% of GOLD-A participants, 1% of GOLD-B participants, 5% of GOLD-C participants, and 8% of GOLD-D participants.

Overall Alignment with 2011 GOLD Recommendations

At baseline, only 52% of overall participants' regimens aligned with GOLD first-/second-line treatment recommendations (Figure 1), with lowest alignment in GOLD-B (14%) and GOLD-C (33%). Highest alignment with recommendations was among GOLD-A and GOLD-D (77% and 80%, respectively) in the overall cohort. As seen in Table 3, age, sex, and race did not differ between participants whose treatment aligned with GOLD recommendations compared with those whose treatment did not. Participants with regimens not aligning with recommendations had better lung function (FEV₁ percent predicted, 66% vs. 56%; FVC percent predicted 92% vs. 85%; $P < 0.01$ for both comparisons). These participants were also more likely to be current smokers (41% vs. 28%; $P < 0.001$) and to report no exacerbations in the prior 12 months (78% vs. 63%; $P < 0.001$). Participants with regimens not aligning with recommendations reported less severe dyspnea (mMRC score ≥ 2 ; 29% vs. 35%) but worse overall COPD control (CAT score ≥ 10 ; 83% vs. 64%). There was no difference in self-report of either COPD, chronic bronchitis, or emphysema. Baseline maintenance inhaler use among the 833 participants with regimens not aligning with GOLD recommendations is summarized in Figure E3 and Table E2. A total of 29% reported no short-acting or maintenance inhalers, and 45% reported no maintenance inhaler use. The most prevalent regimen of both GOLD-A and GOLD-B recommendation–nonaligned participants was LABA/ICS (45% and 23%, respectively). The most prevalent regimen of GOLD-C recommendation–nonaligned participants was LAMA/LABA/ICS (56%). Among nonaligned GOLD-D participants, 73% reported no maintenance inhaler use, with 19% reporting LABA monotherapy use.

Table 3. Demographics of cohort, stratified by alignment with recommendations at baseline

	Recommendation Aligned	Recommendation Nonaligned	P Value
No. of subjects	888	833	
Age, yr	65.5 (7.8)	64.9 (8.2)	0.11
Male sex, <i>n</i> (%)	524 (59)	471 (57)	0.30
Race, <i>n</i> (%)			0.22
White	736 (83)	665 (80)	
Black	125 (14)	134 (16)	
Other/missing	27 (3)	34 (4)	
Current smoker, <i>n</i> (%)	246 (28)	333 (41)	<0.001
Pack-years, median (Q1–Q3)	46 (35–62)	45 (36–63)	<0.001
FEV ₁ /FVC, post-BD	0.48 (0.14)	0.54 (0.11)	<0.001
FEV ₁ , post-BD			
Absolute, L	1.61 (0.82)	1.86 (0.69)	<0.001
Percent predicted	55.9 (25)	65.5 (19)	<0.001
FVC, post-BD			
Absolute, L	3.26 (1.09)	3.42 (1.01)	0.002
Percent predicted	85.4 (21)	91.5 (19)	<0.001
GOLD FEV ₁ stratum, <i>n</i> (%)			
I	182 (21)	182 (22)	
II	269 (30)	503 (60)	
III	298 (34)	115 (14)	
IV	139 (16)	33 (4)	<0.001
GOLD category, <i>n</i> (%)			
A	295 (33)	88 (11)	
B	90 (10)	575 (69)	
C	25 (3)	50 (6)	
D	478 (54)	120 (14)	<0.001
Exacerbations in prior year, <i>n</i> (%)			
None	553 (63)	639 (78)	
One	159 (18)	145 (18)	
Two or more	166 (19)	40 (5)	<0.001
CAT score			
Median (Q1–Q3)	14 (7–21)	16 (11–21)	<0.001
≥ 10 , <i>n</i> (%)	568 (64)	695 (83)	<0.001
mMRC score			
Median (Q1–Q3)	1 (0–2)	1 (1–2)	<0.001
≥ 2 , <i>n</i> (%)	315 (35)	244 (29)	0.006
Self-reported, <i>n</i> (%)			
COPD	662 (77)	621 (77)	0.96
CB	246 (30)	192 (25)	0.09
Emphysema	465 (55)	349 (45)	<0.001
COPD, CB, or emphysema	719 (81)	683 (82)	0.59
Asthma	184 (21)	204 (25)	0.03

Definition of abbreviations: BD = bronchodilator; CAT = COPD Assessment Test; CB = chronic bronchitis; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council dyspnea scale. All values are mean (standard deviation) unless otherwise indicated.

There was a wide range of alignment across the 13 study sites, ranging from 33% to 69%. This difference, when assessed by ANOVA, was not statistically different ($P = 0.91$).

Underuse versus Overuse

Among participants whose treatment did not align with recommendations, 449 (54%) were due to underuse and 384 (46%) were due to overuse (Figure 2). Among nonaligned participants, overuse was seen in 100% of GOLD-A participants, 46% of

GOLD-B participants, 60% of GOLD-C participants, and 0% of GOLD-D participants. Sex and race were similar between those reporting underuse versus those reporting overuse (Table 4).

Compared with the overuse group, members of the underuse group were more likely to be current smokers (49% vs. 31%; $P < 0.001$) and to have a greater proportion with severe obstruction as measured by FEV₁ (GOLD FEV₁ strata III/IV) (27% vs. 7%; $P < 0.001$). Participants with underuse also had worse

Figure 2. Distribution of overuse and underuse among Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) participants not aligning with Global Initiative for Chronic Obstructive Lung Disease (GOLD) first- or second-line treatment recommendations, stratified by baseline GOLD group.

overall symptom control, defined as CAT score greater than or equal to 10 (96% vs. 69%; $P < 0.001$), despite a similar proportion with mMRC score greater than or equal to 2 (30% vs. 29%; $P = 0.82$), and a higher proportion had two or more exacerbations in the year before baseline visit (7% vs. 2%; $P < 0.001$). Given the increased symptoms and exacerbations, participants with underuse were also more likely to be classified as GOLD-C or GOLD-D (30% vs. 8%; $P < 0.001$). The underuse group was less likely to report a diagnosis of either COPD, chronic bronchitis, or emphysema (72% vs. 93%; $P < 0.001$) as well as asthma (19% vs. 32%; $P < 0.001$).

Underuse was predominately driven by no long-acting inhaler (83%), followed by ICS monotherapy (14%) (Table E3). Inappropriate ICS-containing inhalers accounted for all of those classified with overuse in the recommendation-nonaligned participants, most commonly LAMA/LABA/ICS (48%). When we compared the distribution of overuse and underuse among the nonaligned group, we again found a wide range of overuse across sites (0–63%), with no statistical difference by site observed by ANOVA ($P = 0.26$).

Change in Alignment with GOLD Recommendations over Time

A total of 431 participants (25% of the analytical cohort) had complete follow-up data for GOLD categorization and medication use. There were no substantial

differences in baseline demographics and medication use between those with and without complete follow-up data (Tables E4 and E5). Average alignment with GOLD recommendations for GOLD-A and GOLD-D participants was 76% at the baseline visit, and it did not change with updated GOLD status in subsequent years ($P = 0.72$ and $P = 0.52$, respectively) (Figure 3 and Table E6). Both GOLD-B and GOLD-C participants had a statistically nonsignificant but numerical increase in alignment over time (GOLD-B, 10–17%; GOLD-C, 36–55%).

Sensitivity Analysis

Ever reporting physician-diagnosed asthma was associated with greater nonalignment to recommendations (53% vs. 46%; $P = 0.034$). History of asthma in this COPD cohort was associated with greater prevalence of overuse than among participants without asthma (58% vs. 41%; $P < 0.001$). Among participants with overuse reporting asthma, 51% reported LABA/ICS use, whereas 38% reported LAMA/LABA/ICS use. This contrasts with the participants with COPD without asthma, in whom the most common regimen was LAMA/LABA/ICS (53%), followed by LABA/ICS (41%). The overall use of an ICS-containing regimen did not differ between participants with COPD with or without asthma ($P = 0.47$).

Among participants whose treatment did not align with recommendations, lower income was associated with underuse. Specifically, 59% of participants with annual

income less than \$35,000 reported underuse compared with 51% of participants with annual income of \$35,000 or higher ($P = 0.027$). Similar trends were seen with an income threshold of \$50,000 ($P = 0.05$). There was no difference in alignment with recommendations when stratified by attained education level ($P = 0.316$). In addition, in the participants whose treatment did not align with recommendations, there was no difference of education level for overuse or underuse.

When we compared GOLD categorization between 2011 and 2017 publications, we observed that 72% of participants remained within the same GOLD category between the two definitions. The most substantial reclassification was among the 598 GOLD-D (2011) participants, with 406 (68%) reclassified as GOLD-B using 2017 criteria. When we compared alignment with GOLD 2011 and 2017 treatment recommendations, we observed that 47% did not align with either 2011 or 2017 treatment recommendations, whereas 35% aligned with both recommendations. Only 27 participants (2%) aligned with 2017 recommendations but not 2011 recommendations. A total of 289 participants (17%) had regimens aligned with 2011 recommendations but not 2017 recommendations. Of these 289 participants, 98% reported overuse per 2017 recommendations. This was due to reclassification from GOLD-C/D to GOLD-A/B owing to removal of FEV₁ criteria.

Discussion

In this analysis of a large cohort of individuals with COPD participating in an observational cohort study, nearly 50% reported inhaler regimens that do not align with first- or second-line recommendations present at the time of data collection. Regimens not aligning with GOLD recommendations were evenly split between overuse and underuse. Underuse was primarily due to lack of maintenance inhalers, whereas overuse was due to inappropriate use of ICS-containing regimens. Aside from GOLD-B participants, overall alignment with recommendations did not change during follow-up. These findings highlight the lack of substantial uptake of published recommendations and the relatively stable treatment patterns for COPD over time.

The GOLD recommendations are internationally recognized as the standards

Table 4. Aligned and nonaligned cohort, stratified by underuse versus overuse at baseline

	Underuse	Overuse	P Value
No. of subjects	449	384	
Age, yr	64.4 (8.3)	65.5 (8.0)	0.05
Male sex, n (%)	260 (58)	211 (55)	0.39
Race, n (%)			0.47
White	360 (80)	305 (79)	
Black	68 (15)	66 (17)	
Other/missing	21 (5)	13 (4)	
Current smoker, n (%)	216 (49)	117 (31)	<0.001
Pack-years, median (Q1–Q3)	49 (38–63)	45 (35–61)	0.09
FEV ₁ /FVC, post-BD	0.54 (0.12)	0.54 (0.10)	0.88
FEV ₁ , post-BD			
Absolute, L	1.87 (0.75)	1.84 (0.60)	0.53
Percent predicted	65.2 (22)	65.8 (15)	0.67
FVC, post-BD			
Absolute, L	3.43 (1.06)	3.42 (0.95)	0.85
Percent predicted	90.5 (20)	92.8 (17)	0.08
GOLD FEV ₁ stratum, n (%)			
I	118 (26)	64 (17)	
II	210 (47)	293 (76)	
III	93 (21)	22 (6)	
IV	28 (6)	5 (1)	<0.001
GOLD category, n (%)			
A	0 (0)	88 (23)	
B	309 (69)	266 (69)	
C	20 (4)	30 (8)	
D	120 (26)	0 (0)	<0.001
Exacerbations in prior year, n (%)			
None	353 (80)	286 (76)	
One	60 (13)	85 (22)	
Two or more	33 (7)	7 (2)	<0.001
CAT score			
Median (Q1–Q3)	17 (12–22)	14 (8–20)	<0.001
≥10, n (%)	429 (96)	266 (69)	<0.001
mMRC score			
Median (Q1–Q3)	1 (1–2)	1 (1–2)	0.94
≥2, n (%)	133 (30)	111 (29)	0.82
Self-reported, n (%)			
COPD	279 (65)	342 (92)	<0.001
CB	85 (20)	107 (30)	0.003
Emphysema	162 (39)	187 (52)	0.002
COPD, CB, or emphysema	324 (72)	359 (93)	<0.001
Asthma	85 (19)	119 (32)	<0.001

Definition of abbreviations: BD = bronchodilator; CAT = COPD Assessment Test; CB = chronic bronchitis; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council dyspnea scale.

All values are mean (standard deviation) unless otherwise indicated.

for COPD diagnosis and treatment. Despite this ubiquity, nonadherence to both diagnostic and treatment recommendations are prevalent (1, 6, 7, 9). Prior studies have identified some barriers to poor uptake, including provider familiarity and time constraints (8, 18). To our knowledge, this is one of the largest analyses examining factors associated with overuse and underuse in a well-characterized COPD population, as well as the largest to examine change in alignment with recommendations over

time. We found that alignment with recommendations was largely unchanged from reports examining 2007 GOLD guidelines (7), despite increased awareness and publications surrounding the GOLD recommendations over the last decade.

GOLD-B and GOLD-C participants had the highest rates of recommendation nonalignment. Prior studies have suggested that the complexity of GOLD assessments may impact alignment with recommendations (19). Using the 2011 GOLD guidelines,

classification into a group requires both spirometry and symptoms. Spirometry is frequently not obtained (8), which may lead to misclassification. Although all SPIROMICS participants underwent spirometry within the context of research visits, providers prescribing inhalers may not have obtained spirometry. In addition, the 2011 recommendations did not include guidance on stepping up or stepping down therapy, which may have led to persistent nonalignment with treatment strategies (20).

Among the participants not aligning with recommendations, those who reported underuse were more likely to have more severe obstruction (GOLD III/IV), be more symptomatic, and have a higher proportion of COPD exacerbations. The association between underuse and more severe disease burden has several potential explanations. Those with underuse were less likely to report a diagnosis of obstructive lung disease, raising the possibility that these patients either were not being diagnosed or were not aware of their diagnoses. Alternatively, the higher burden of symptoms and exacerbations among these participants may be underrecognized by providers, therefore leading to underuse. Without use of objective scales, physicians are frequently unable to properly identify symptoms most affecting their patients (21). Participants reporting underuse were more likely to be current smokers, so providers may have attributed symptoms to smoking rather than to COPD. Similarly to other studies (7, 10), the majority of participants with underuse lacked maintenance inhalers. Moreover, nearly one-third of these participants did not report any inhaler use (either short or long acting). The lowest income group was associated with underuse, suggesting that medication cost may contribute to nonalignment with published treatment strategies. These findings differ from those of Nishi and colleagues, who observed that patients with COPD with dual eligibility for Medicare and Medicaid are more likely to use maintenance inhalers, likely owing to a reduced copay burden (22). SPIROMICS did not capture insurance status, limiting the ability to determine how this factor may be impacting alignment with guidelines. These symptomatic participants reporting underuse highlight a group that, if appropriately treated, could have improvement of symptom burden.

Participants reporting overuse were more likely to have mild obstruction

Figure 3. Change in alignment with first- or second-line Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations over follow-up visits among 431 SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) participants with complete follow-up data.

(GOLD I/II), and all were on an ICS-containing regimen. ICS-containing regimens in COPD are indicated for GOLD-C or GOLD-D COPD (4, 5). A recent analysis has shown that more than one-third of those classified as GOLD-A and over half of those classified as GOLD-B for inhaler therapy are inappropriately prescribed ICS regimens (23). In that analysis, ICS/LABA therapy was the initial treatment choice for over 50% of patients. Similarly, we found that over 50% of all participants were prescribed ICS-containing regimens, and 92% of overuse participants were in GOLD-A or GOLD-B. Given the prevalence of asthma in this group with overuse, the ICS inhaler regimens may reflect treatment for asthma or asthma-COPD overlap. The treatment paradigm for asthma-COPD overlap has yet to be elucidated (24). The overall use of ICS did not differ between the overusing participants with and without asthma, and it remains unclear if ICS could be an appropriate treatment for these participants. Another reason for overuse with ICS may be related to combination medication availability. For the first two years of this study, ICS/LABA combined inhalers were the only long-acting combination inhalers available (25). Nevertheless, although overuse may provide symptomatic benefits, therapies are not risk free, because there are many known side effects of ICS, including thrush and increased risk of pneumonia (26).

Among the 25% of the analytical cohort with complete follow-up data, failure to align with recommendations was largely stable over the duration of follow-up in SPIROMICS. Given that there were no guidelines for stepping down therapy in 2011, many overuse participants may have been stepped up to achieve disease control and, once adequately controlled on ICS, may have been recategorized as GOLD-A or GOLD-B with overuse due to ICS therapy. In our analysis, patients with overuse were less symptomatic, which may dissuade practitioners from stepping down therapy once symptoms are controlled. Prior studies have described inertia among healthcare providers regarding changing current practices (27). A recent audit evaluating treatment of COPD in outpatient settings showed that at follow-up visits, providers are most likely to keep the current regimen (64.8%) or step-up therapy (17.5%), whereas only 9.7% of visits involved stepped-down therapy (20). A smaller study in Hong Kong showed that over three visits, less than one-third of patients had changes in pharmacologic therapy, and the primary reason for change was insufficient disease control (10).

This study has several limitations. Data collection for exacerbations, smoking history, and medication use were obtained via self-report, increasing the chance for information and recall bias. Medication

prescriptions were not verified with pharmacy records. Participants' accuracy of reporting medications may have increased over serial study visits (Hawthorne effect). In addition, there are no data on the type of providers, difference in prescribing practices among pulmonologists and primary care physicians, appropriate inhaler technique, and influence of pharmaceutical marketing forces, all of which may impact alignment with treatment recommendations. The GOLD recommendations, although widely cited and used to inform treatment, are limited in the strength of evidence supporting some treatment recommendations (5). Although our analysis was not designed to assess the validity of GOLD recommendations, the degree of uncertainty in some GOLD recommendations is a limitation impacting our analysis. This analysis was done using a cohort of patients self-selected to participate in SPIROMICS and therefore may bias toward more severe and symptomatic groups, decreasing generalizability to the COPD population as a whole. Despite these limitations, the robust and standardized data collection within a large COPD cohort representing the full spectrum of COPD provides a unique opportunity to assess integration of published COPD treatment strategies over time and explore factors related to failure to align with those recommendations. These findings highlight the possibility of implementation sciences to improve guideline adherence in COPD treatment.

In conclusion, this analysis demonstrates that nearly half of individuals with COPD participating in an observational cohort study reported inhaler regimens not aligning with available treatment recommendations. Overuse and underuse of COPD treatment were equally prevalent and persisted over time, highlighting the need to reassess patient-tailored treatment strategies regularly. Given the changing landscape of classifying and treating patients with COPD, improvement of dissemination and uptake of published recommendations have the potential to improve care for patients with COPD. ■

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References

- Overington JD, Huang YC, Abramson MJ, Brown JL, Goddard JR, Bowman RV, *et al*. Implementing clinical guidelines for chronic obstructive pulmonary disease: barriers and solutions. *J Thorac Dis* 2014;6:1586–1596.
- Grimshaw JM, Schünemann HJ, Burgers J, Cruz AA, Heffner J, Metersky M, *et al*. ATS/ERS Ad Hoc Committee on Integrating and Coordinating Efforts in COPD Guideline Development. Disseminating and implementing guidelines: article 13 in integrating and coordinating efforts in COPD guideline development: an official ATS/ERS workshop report. *Proc Am Thorac Soc* 2012;9:298–303.
- Global Initiative for Chronic Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease 2018 report [accessed 2018 Jul 30]. Available from: www.goldcopd.org.
- Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Am J Respir Crit Care Med* 2001;163:1256–1276.
- Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187:347–365.
- López-Campos JL, Abad Arranz M, Calero-Acuña C, Romero-Valero F, Ayerbe-García R, Hidalgo-Molina A, *et al*. Guideline adherence in outpatient clinics for chronic obstructive pulmonary disease: results from a clinical audit. *PLoS One* 2016;11:e0151896.
- Sharif R, Cuevas CR, Wang Y, Arora M, Sharma G. Guideline adherence in management of stable chronic obstructive pulmonary disease. *Respir Med* 2013;107:1046–1052.
- Perez X, Wisnivesky JP, Lurslurchachai L, Kleinman LC, Kronish IM. Barriers to adherence to COPD guidelines among primary care providers. *Respir Med* 2012;106:374–381.
- Sehl J, O'Doherty J, O'Connor R, O'Sullivan B, O'Regan A. Adherence to COPD management guidelines in general practice? A review of the literature. *Ir J Med Sci* 2018;187:403–407.
- Chan KP, Ko FW, Chan HS, Wong ML, Mok TY, Choo KL, *et al*. Adherence to a COPD treatment guideline among patients in Hong Kong. *Int J Chron Obstruct Pulmon Dis* 2017;12:3371–3379.
- Papala M, Kerenidi N, Gourgoulanis KI. Everyday clinical practice and its relationship to 2010 and 2011 GOLD guideline recommendations for the management of COPD. *Prim Care Respir J* 2013;22:362–364.
- Maio S, Baldacci S, Martini F, Cerrai S, Sarno G, Borbotti M, *et al*. COMODHES study group. COPD management according to old and new GOLD guidelines: an observational study with Italian general practitioners. *Curr Med Res Opin* 2014;30:1033–1042.
- Couper D, LaVange LM, Han M, Barr RG, Bleecker E, Hoffman EA, *et al*. SPIROMICS Research Group. Design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). *Thorax* 2014; 69:491–494.
- Ghosh S, Anderson WH, Putcha N, Han MK, Curtis JL, Criner GJ, *et al*. Alignment of COPD medication use patterns with GOLD guidelines: analysis of the SPIROMICS cohort [abstract]. *Am J Respir Crit Care Med* 2018;197:A4246.
- Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, *et al*. SPIROMICS investigators. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2017;5:619–626.
- Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581–586.
- Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34:648–654.
- Salinas GD, Williamson JC, Kalhan R, Thomashow B, Scheckermann JL, Walsh J, *et al*. Barriers to adherence to chronic obstructive pulmonary disease guidelines by primary care physicians. *Int J Chron Obstruct Pulmon Dis* 2011;6:171–179.
- Cabrera C, Casanova C, Martín Y, Mirabal V, del Carmen Sánchez M, Álvarez F, *et al*. Agreement between a simple dyspnea-guided treatment algorithm for stable COPD and the GOLD guidelines: a pilot study. *Int J Chron Obstruct Pulmon Dis* 2016;11:1217–1222.
- López-Campos JL, Abad Arranz M, Calero Acuña C, Romero Valero F, Ayerbe García R, Hidalgo Molina A, *et al*. Determinants for changing the treatment of COPD: a regression analysis from a clinical audit. *Int J Chron Obstruct Pulmon Dis* 2016;11:1171–1178.
- Miravittles M, Ferrer J, Baró E, Lleónart M, Galera J. Differences between physician and patient in the perception of symptoms and their severity in COPD. *Respir Med* 2013;107:1977–1985.
- Nishi SPE, Maslonka M, Zhang W, Kuo YF, Sharma G. Pattern and adherence to maintenance medication use in Medicare beneficiaries with chronic obstructive pulmonary disease: 2008–2013. *Chronic Obstr Pulm Dis (Miami)* 2018;5:16–26.
- Contoli M, Corsico AG, Santus P, Di Marco F, Braido F, Rogliani P, *et al*. Use of ICS in COPD: from blockbuster medicine to precision medicine. *COPD* 2017;14:641–647.
- Diagnosis of diseases of chronic airflow limitation: asthma, COPD, and asthma–COPD overlap syndrome (ACOS). Based on the Global Strategy for Asthma Management and Prevention and the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease 2015 [accessed 2018 Jul 30]. Available from: www.goldcopd.org/asthma-copd-asthma-copd-overlap-syndrome.
- CenterWatch. FDA approved drugs for pulmonary/respiratory diseases. February 28, 2018 [accessed 2018 Jul 30]. Available from: <https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/18/pulmonary-respiratory-diseases>.
- Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014;(3):CD010115.
- Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, *et al*. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458–1465.