

# Understanding Chronic Obstructive Pulmonary Disease Management and Treatment Patterns in General Medicine: Results From the ASTER Study in Italy

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**Purpose:** The ASTER study described the management of chronic obstructive pulmonary disease (COPD) by general practitioners (GPs) in Italy, focusing on the treatment patterns and clinical outcomes of patients over 6 months.

**Patients and Methods:** This multicenter prospective cohort study included patients aged 40–80 years with spirometry-confirmed COPD, post-bronchodilator FEV<sub>1</sub> ≥50% of predicted value, and ≤1 exacerbation in the previous year. Eligible patients had a COPD assessment test (CAT) score of ≥10 and, according to the prescription limits for GPs before Note 99, they could have been treated in the last 3 months before enrollment exclusively with a short or long acting bronchodilator or an corticosteroid/long-acting beta<sub>2</sub>-agonist ICS/LABA. Patients were evaluated at enrollment, 3 months, and 6 months, with data collected on treatment, exacerbations, patient-reported outcomes (CAT and mMRC scores), and lung function.

**Results:** Overall, 385 patients were enrolled, and 344 (89.4%) met the study criteria, of which 332 (96.5%) completed the study. The cohort included patients with mild to moderate COPD, predominantly males (61.9%), and current/former smokers (91%). At baseline, ongoing treatments included LAMA (20.9%), ICS/LABA (13.7%), and LABA (2.9%). However, 62.5% of patients were not treated. By 6 months, only 10.2% of patients were not receiving any treatment and 55.4% were treated with a LABA/LAMA combination. FEV<sub>1</sub> showed a mean increase of 140 mL, mMRC ≥ 2 decreased from 54.9% to 23.5%, CAT exhibited a 3.6 point mean decrease, and only 13 patients (3.9%) experienced mild/moderate exacerbations in the last 6 months.

**Conclusion:** ASTER study highlights the effectiveness of COPD treatment by GPs in Italy. Early detection and proactive management, along with a regular treatment prescription was associated with improved lung function, dyspnea, quality of life, and a reduction in the incidence of exacerbations. Empowering GPs with diagnostic and therapeutic responsibilities, improves care and outcomes of COPD.

**Keywords:** long-acting beta<sub>2</sub>-agonist/muscarinic antagonist, lung function, quality of life, real-world evidence, treatment

## Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating condition that is characterized by poorly reversible airflow limitation, difficulty breathing during physical activities<sup>1–4</sup> decreased exercise capacity,<sup>5</sup> and limitations in daily activities.<sup>6–9</sup> According to the Italian National Statistics Institute (ISTAT) and the Global Burden of Diseases initiative,<sup>10–12</sup> in Italy, approximately 3.5 million adults are affected by COPD and 2.5% of all Disease Adjusted Life Years lost were attributable to COPD in 2021.<sup>13</sup> However, these figures may underestimate the actual prevalence of COPD because the disease is often diagnosed only in its advanced stages.<sup>11,14</sup> According to the Medicines Utilization Monitoring Center report recently published by the Italian Medicines Agency, some patients discontinue treatment early after initiating maintenance therapy,<sup>11</sup> emphasizing the need for improved COPD management in terms of appropriate diagnosis,

pharmacological treatment, and treatment adherence.<sup>15</sup> The management of COPD presents several challenges, including misdiagnosis, delayed diagnosis, failure to implement fundamental measures to slow disease progression (eg, tobacco cessation, vaccinations, and lifestyle changes), uncertainty in selecting the most appropriate drug for treatment, and poor adherence to therapy.<sup>16,17</sup> The Global Initiative for Chronic Obstructive Lung Disease (GOLD 2023–2025) recommend a comprehensive approach to COPD management, including accurate diagnosis and severity assessment, smoking cessation, and individualized pharmacological and non-pharmacological interventions, with a focus on managing exacerbations.<sup>15,18</sup> An e-Delphi study of 600 general practitioners (GPs) in Italy reported that although most GPs were familiar with the GOLD 2023 report and COPD reimbursement requirements, only 34% had access to spirometry. There was no consensus on the initial treatment options, and re-evaluation of triple therapy necessitated a specialist referral.<sup>19</sup>

Effective COPD management cannot be limited to expert care alone, especially when prevention and long-term monitoring are essential for optimal outcomes. To address the challenges in COPD management, the Italian Medicines Agency (AIFA) introduced Nota 99, which conforms to the GOLD report 2022 and confers GPs the responsibility of diagnosing and prescribing appropriate medication for mild to moderate COPD. Given the considerable prevalence of COPD, this act recognizes the critical role of GPs in managing COPD. Nota 99 allows GPs to prescribe any inhaled therapy, except for the single-device inhaler triple therapies, while maintaining specialist care for individuals with severe pulmonary obstruction or recurrent exacerbations.<sup>11</sup>

Given this new scenario, ASTER, an Italian observational prospective multicenter trial, was designed to provide the first meaningful insights into COPD management by GPs following the Nota 99, describing the characteristics of patients, treatment patterns (primary outcome), and clinical outcomes (secondary outcome) over a 6-month observation period.

## Materials and Methods

### Trial Design and Oversight

ASTER was an observational, multicenter, prospective cohort study conducted in Italy that focused on patients with COPD who were managed by GPs following standard protocols of clinical practice. Consecutive patients at each participation center who provided the written informed consent and privacy form and met the eligibility criteria were enrolled in the study. The study was conducted in 30 centres distributed throughout Italy in order to obtain results reasonably albeit not formally representative of the management of COPD in general medicine in Italy according to the Nota 99. This study was conducted in compliance with the Guidelines for Good Pharmacoepidemiology Practice (GPP)<sup>20</sup> and the regulatory elements of observational research in Italy.<sup>21</sup>

Eligible patients were aged 40–80 years and had spirometry-confirmed COPD (post-bronchodilator Forced Expiratory Volume in one second (FEV<sub>1</sub>) to Forced Vital Capacity (FVC) ratio <0.70) with an FEV<sub>1</sub> of ≥50% of the predicted value. Patients were enrolled if they had ≤1 exacerbation requiring antibiotics and/or oral corticosteroids; had no emergency room (ER) visits or hospitalizations for COPD in the past year; and, according to the prescription limits for GPs before Nota 99, they could have been treated in the last 3 months before enrollment exclusively with a short or long-acting bronchodilator or an ICS/LABA; and had a COPD Assessment Test (CAT) score ≥10 at the enrollment appointment. Patients were excluded if they were unable to undergo spirometry according to Nota 99, had received LABA/LAMA combinations within the previous 3 months, had low treatment adherence as judged by the clinician, inability to properly use an inhaler, were pregnant or breastfeeding, had a current asthma diagnosis, could not read or write in Italian, or were already enrolled in another clinical trial.

Each patient was assessed during the enrollment visit, which coincided with the reconfirmation of diagnosis and therapy prescription. Patients were then followed up with specific visits at 3 and 6 months, as outlined by standard clinical practice. During the enrollment visit, the GP collected the patient's history of respiratory disease and symptoms including those within the previous year, occupational and tobacco smoke exposure, COPD anamnesis, and previously prescribed COPD therapies as well as comorbidities and related therapies. The GPs provided the COPD Assessment Test (CAT)<sup>22</sup> to the patients and completed the modified Medical Research Council Dyspnea Scale (mMRC)<sup>23</sup> questionnaires. At the 3- and 6-month follow-up visits, the GP collected data on the incidence, severity, and treatment of exacerbations

and adjusted the treatment as needed. Additionally, at the 6-month visit, the GP collected information on functional parameters if spirometry was performed according to clinical practice, provided the CAT questionnaire to the patient, and completed the mMRC questionnaire.

## Primary and Secondary Effectiveness Analyses

The primary endpoint of the study was to describe treatment patterns during the 6-month observation period, including the proportion of patients taking different COPD medications and any changes in treatment patterns. The secondary endpoints were demographic and clinical features, FEV<sub>1</sub> at enrollment and after 6 months, patient-reported outcomes (CAT and mMRC scores) at enrollment and after 6 months, and the number of COPD exacerbations and exacerbations per patient during the observation period.

## Statistical Consideration

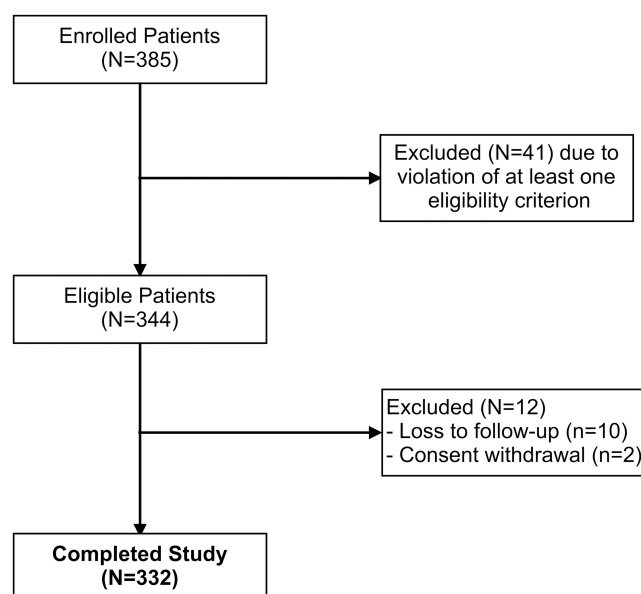
The sample size was determined based on feasibility considerations, including the duration of the enrollment period and the number of participating centers. It was estimated that approximately 400 patients can be enrolled over an 8-month period from 40 Italian study centers. Given an expected drop-out rate of approximately 20% over the 6-month observation period, 320 patients were expected to be available for the primary analysis; accordingly, simulations were performed to estimate the achievable precision of the 95% confidence interval (95% CI) of the expected proportions for 320 evaluable patients. This descriptive study had no defined formal hypotheses and no statistical significance testing was performed; data was analyzed using epidemiological methods. Descriptive statistics were provided for all variables and endpoints. All analyses were performed using the SAS software (SAS Institute, Cary, North Carolina, USA).

## Results

### Participant Disposition and Characteristics

Initially, 385 patients were enrolled in the ASTER study, and 41 of these who did not meet the eligibility criteria were excluded (Figure 1), resulting in 344 (89.4%) eligible patients. Of these eligible patients, 332 (96.5%) completed the study, whereas 12 (3.5%) were lost to follow-up ( $n = 10$ ) or excluded due to consent withdrawal ( $n = 2$ ).

The majority of the eligible patients were men (61.9%) and predominantly Caucasian (98.8%) (Table 1). Most patients had either primary (18.9%) or secondary education (71.7%) and were unemployed or retired (73.6%). At



**Figure 1** Study flowchart.

**Note:** N, total number of patients.

**Table 1** Characteristics of the Patients at Enrollment

Characteristic	Subcategory	Number of Eligible Patients (N = 344)
Age at enrollment (years)	Mean (SD)	68.1 (8.1)
Sex	Male	213 (61.9%)
Race	Caucasian	340 (98.8%)
Highest level of education achieved by the patient at enrollment (n=318) <sup>†</sup>	Primary	60 (18.9%)
	Secondary*	228 (71.7%)
	Tertiary	28 (8.8%)
Occupational status at enrollment (n=337) <sup>†</sup>	Employed	74 (22.0%)
	Unemployed/Retired	248 (73.6%)
Body mass index (kg/m <sup>2</sup> )	Mean (SD)	26.1 (4.7)
	Range	16.5–45.5
Smoking status at enrollment (n=343) <sup>†</sup>	Never smoked	31 (9.0%)
	Used to smoke	143 (41.7%)
	Current smoker	169 (49.3%)
Estimated amount consumed on average (pack/year)	Mean (SD)	41.9 (23.3)
	Range	1.0–189.0
Comorbidities <sup>‡</sup>	Arterial hypertension	168 (58.3%)
	Diabetes	69 (24.0%)
	Cardiac ischemic disease	48 (16.7%)
	Depression	36 (12.5%)
	Neoplastic disease	25 (8.7%)
	Osteoporosis	23 (8.0%)
	Atrial fibrillation	16 (5.6%)
	Kidney insufficiency	15 (5.2%)
	Heart failure	14 (4.9%)
	Lung cancer	6 (2.1%)
	CAP	1 (0.3%)
Other current clinically relevant comorbidities	137 (47.6%)	
Occupational risk factors for COPD at enrollment (n=310) <sup>†</sup>	Previous exposure	42 (13.5%)
	Current exposure	10 (3.2%)
Number of concomitant medications	Median (Q1–Q3)	3.0 (2.0–5.0)
	Range	1.0–13.0

**Notes:** \*Includes middle school (Level I, n = 139) and high school (Level II, n = 89). <sup>†</sup>In the percentage calculation, the total population (denominator) excludes unknown patients. <sup>‡</sup>Percentages were calculated using the number of eligible patients with the presence of comorbidities at enrollment. Q1 (First Quartile): The first quartile is the value below which 25% of the data points in a dataset fall; Q3 (third quartile): the third quartile is the value below which 75% of the data points in a dataset fall.

**Abbreviations:** CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; N, total number of patients; SD, standard deviation.

enrollment, 49.3% of the patients were active smokers, 41.7% had previously smoked, and 9.0% had never smoked. The majority of patients (83.7%) had comorbidities at enrollment, with arterial hypertension (58.3%), diabetes (24.0%), and cardiac ischemic disease (16.7%) being the most common (Table 1). Moreover, 50% of patients were regularly treated with  $\geq 3$  medications for concomitant diseases. The most prevalent COPD symptoms were cough (82.6%), shortness of breath (66.3%), and phlegm (48.0%). More than half of the patients (54.1%) had mild to moderate dyspnea (mMRC grade  $\leq 2$ ) at enrollment (Table 2). Further, 77.6% of the patients reported experiencing the same COPD symptoms in the year before enrollment as they did at the time of diagnosis.

Of the eligible patients, 196 (57%) were classified as incident patients—symptomatic individuals not previously diagnosed with COPD by spirometry but likely prescribed treatments such as LAMA, LABA, or ICS/LABA by their GP without a confirmed diagnosis—while 148 (43%) were classified as prevalent patients with a prior COPD diagnosis (Table S1). Incident patients had a higher FEV<sub>1</sub> (mean, 2.0 vs 1.7), were slightly younger (mean age, 67.2 vs 69.2 years), were more likely to be employed (25.4% vs 17.4%) and had fewer comorbidities (80.6% vs 87.8%) than prevalent patients. In addition, incident patients experienced severe dyspnea less frequently (mMRC grade  $\geq 2$ : 40.3% vs 53.4%) and had a lower incidence of poor quality of life (CAT score of 21–30: 14.3% vs 19.6%) than prevalent patients.

## Primary Endpoint results

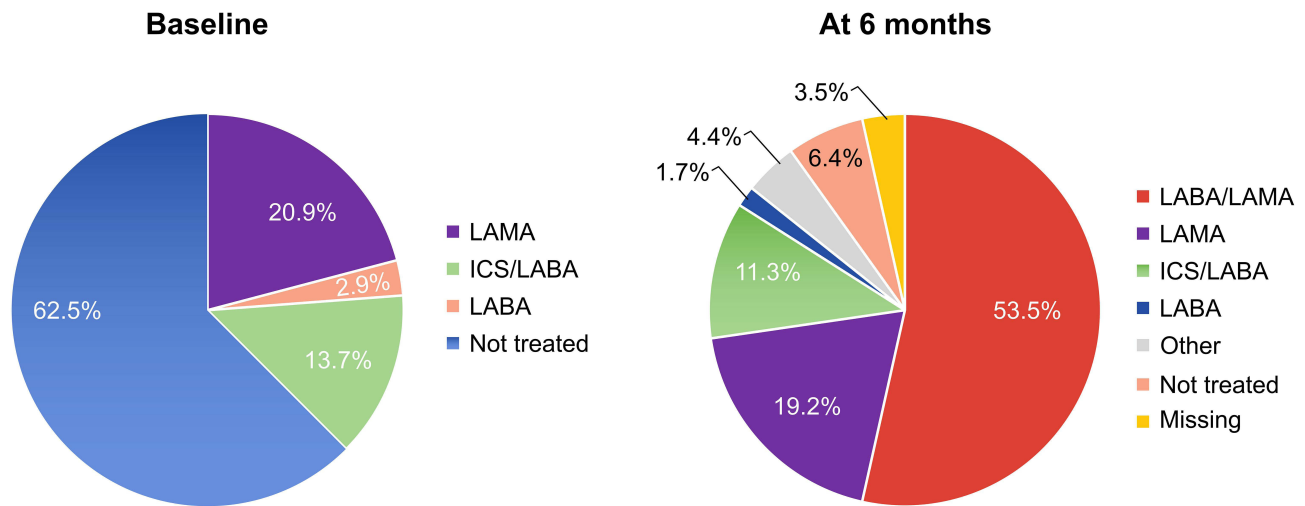
At enrollment, 20.9% of patients were treated with LAMA, 13.7% with an ICS/LABA combination, 2.9% with LABA, and 62.5% (30 prevalent and 185 incident patients) were not receiving any treatment (Figure 2). At the 3-month follow-up, 56.7% of patients were being treated with LABA/LAMA, 21.2% with LAMA, and 12.2% with ICS/LABA (Table S2). At the 6-month follow-up, 53.5% of the patients were being treated with a LABA/LAMA combination, 19.2% with LAMA, and

**Table 2** Disease Characteristics at Enrollment (Eligible Patients)

Characteristic	Subcategory	Number of Eligible Patients (N = 344)
Relevant medical history from the year prior to enrollment	None	264 (76.7%)
	Asthma-like bronchitis	20 (5.8%)
	Depression	14 (4.1%)
	Neoplastic disease	12 (3.5%)
	Heart failure	7 (2.0%)
	Atrial fibrillation	3 (0.9%)
	CAP	1 (0.3%)
	Other clinically relevant medical history*	32 (9.3%)
Number of COPD exacerbations in the last year	0	264 (76.7%)
	1	80 (23.3%)
mMRC grade at enrollment classes	<2	186 (54.1%)
	$\geq 2$	158 (45.9%)
CAT score categories at enrollment	Score 10–20 (medium impact)	282 (82.0%)
	Score 21–30 (high impact)	57 (16.6%)
	Score >30 (very high impact)	5 (1.5%)

**Notes:** \*Participants may have more than one medical history.

**Abbreviations:** CAP, community-acquired pneumonia; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council (Dyspnea Scale); N, total number of patients.



**Figure 2** Treatment pattern of COPD medications for eligible patients at enrollment (baseline) and at the 6-month follow-up.

**Abbreviations:** ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta-agonist; N, total number of patients at each visit; n = number of patients in each category.

11.3% with an ICS/LABA combination. Current therapy at 6 months was not notably different between prevalent and incident patients, with the only exception of the ICS/LABA combination was being used more frequently in prevalent patients than in incident patients (16.2% vs 7.7%) (Table S3).

## Secondary Endpoint results

Overall, lung function improved over the 6-month observational period, as evidenced by the increase in pre-bronchodilator FEV<sub>1</sub> (Table 3). When the pre-bronchodilator FEV<sub>1</sub> at 6 months was compared with that at enrollment in 206 patients, a mean increase of 140 mL was observed (Table 3), and one-quarter of the patients exhibited an increase of at least 300 mL.

At enrollment, 45.9% of patients with COPD reported a significant level of dyspnea, with an mMRC score  $\geq 2$ . At the 6-month follow-up, this value was reduced to 23.5% (Table 3). The mMRC scores at enrollment and at the 6-month follow-up are summarized in Table S4. Overall, the mMRC score decreased by at least one point in 40% of the patients and remained unchanged in 53.9%.

**Table 3** Summary of Secondary Endpoint Results for Eligible Patients at Enrollment and at the 6-month Follow-up

Variable	N	Value
<b>FEV<sub>1</sub> pre-bronchodilator (L)</b>		<b>Mean (SD)</b>
At enrollment	341	1.88 (0.58)
At the 6-month follow-up	208	2.00 (0.60)
Change	206	0.14 (0.39)
<b>FEV<sub>1</sub> (%), pre-bronchodilator</b>		<b>Mean (SD)</b>
At enrollment	341	71.3 (16.3)
At the 6-month follow-up	208	75.3 (15.7)
Change	206	3.9 (13.6)

(Continued)

**Table 3** (Continued).

Variable	N	Value
<b>FVC (L), pre-bronchodilator</b>		<b>Mean (SD)</b>
At enrollment	341	3.02 (0.87)
At the 6-month follow-up	208	3.06 (0.92)
Change	206	0.06 (0.48)
<b>FEV<sub>1</sub>/FVC (%), pre-bronchodilator</b>		<b>Mean (SD)</b>
At enrollment	341	62.5 (6.2)
At the 6-month follow-up	208	65.4 (8.3)
Change	206	3.0 (7.5)
<b>mMRC dyspnea of score of <math>\geq 2</math></b>		<b>n (%)</b>
At enrollment	344	158 (45.9%)
At the 6-month follow-up	332	78 (23.5%)
<b>CAT score</b>		<b>Mean (SD)</b>
At enrollment	344	16.4 (5.0)
At the 6-month follow-up	331	12.9 (5.3)
Change	331	-3.6 (4.8)
<b>Exacerbations frequency</b>		<b>% of patients</b>
At enrollment	344	23.2%
Annualized 6-month	332	7.8%
Change <sup>†</sup>	332	15.4%

**Notes:** <sup>†</sup>Absolute reduction, with a relative reduction of 34%. CAT score ranges between 0 and 40. Higher CAT scores represent worse health.

**Abbreviations:** CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub> (L), forced expiratory volume in 1 second (in Liters); FEV<sub>1</sub> (%), forced expiratory volume in 1 second (as a percentage of the predicted value); FEV<sub>1</sub>/FVC (%), ratio of forced expiratory volume in 1 second to forced vital capacity (as a percentage); FVC (L), forced vital capacity (in Liters); mMRC, modified Medical Research Council; N, total number of patients; n, number of patients in each category; SD, standard deviation.

In terms of the impact of COPD on patients' lives, the patients' health status and quality of life improved noticeably over the 6-month study period, as evidenced by a mean decrease of 3.6 points in the CAT score (Table 3). Notably, the CAT score decreased by at least 6 points in one-quarter of the patients.

During the observation period, 3.9% (n = 13/332) of the patients experienced 14 exacerbations (10 mild and 4 moderate), resulting in an approximate annualized exacerbation rate of 7.8%. This represents a meaningful drop from the 23.2% incidence rate in the year before recruitment, indicating an absolute reduction of 15.4% and a 34% reduction in the annualized relative risk over the 6-month period (Table 3). Notably, none of these reported exacerbations required admission to the ER or hospitalization.

## Discussion

To the best of our knowledge, the ASTER study was the first COPD study conducted in a GP setting in Italy, providing real-world evidence of clinical practice for patients with COPD managed according to Nota 99, which confers GP with

a critical responsibility in the COPD management. The study findings highlight the importance of treatment pathways, and the public health implications of appropriate COPD management.

The findings of the ASTER study provide a detailed overview of the evolving treatment patterns for patients with COPD. Over the course of the study, there was a noticeable shift towards combination therapy, with a substantial number of patients switching from monotherapy with LABA or LAMA to LABA/LAMA combination therapy. Similarly, the majority of patients who were initially treated with ICS/LABA combination therapy, switched to LABA/LAMA therapy. This shift towards LABA/LAMA therapy as well as the observed improvements in the CAT and mMRC scores suggests the effectiveness of these treatments in managing symptoms and improving the quality of life of patients with COPD. These real-world results are consistent with prior randomized controlled studies that demonstrated the effectiveness of LAMA/LABA therapy for patients with COPD.<sup>24,25</sup> Overall, the results of the ASTER study suggest that the implementation of Nota 99 may positively influence clinical practices on COPD treatment. The absence of severe exacerbations requiring hospitalization suggests that enhanced patient management and treatment regimens are effective in preventing severe episodes. This is also consistent with previous research indicating that treatment with LABA/LAMA therapy is more effective than monotherapy in preventing all COPD exacerbations.<sup>26</sup> Although no formal hypothesis was established, our findings indicate that intervention according to Nota 99, as implemented in the ASTER study, has the potential to avoid an exacerbation episode for every six patients correctly diagnosed and treated over a year.

The ASTER study emphasizes the pivotal role played by Italian GPs in COPD management. With resources and clear guidelines, GPs can effectively diagnose, treat, and monitor patients with COPD, reducing the disease's impact and improving long-term outcomes. Continuous training and resources are essential for GPs to provide optimal care. Comparative analyses with practices in other countries<sup>27–29</sup> reveal that Nota 99 promotes structured COPD management, allowing for a proactive rather than reactive strategy by providing clear guidance on the correct diagnostic process, prevention, and management of COPD. According to the ASTER study, 94.4% of newly diagnosed patients with COPD were untreated at the time of enrollment, highlighting that COPD is often overlooked. Improved diagnostic procedures in primary care are essential. Active research and surveillance by GPs can help develop precise diagnostic tools and protocols, ensuring accurate and prompt treatment. Routine case findings and early detection strategies are critical to improve COPD management outcomes.

Although the ASTER study provides valuable insights, it has the following limitations. As a real-life, non-interventional study with prospective data collection, there are inherent biases to consider. Information and selection biases may have influenced the outcome as respondents may have been influenced by GPs or their own beliefs about meeting GP expectations. Additionally, the inclusion criteria required patients to be able to read and write in Italian and fill out questionnaires on their own, which may have disqualified some patients and reduced the generalizability of the findings. Furthermore, GPs' participation in the trial may have encouraged them to adhere more rigorously to treatment recommendations, potentially diverging from "real-world" treatment practices (known as the Hawthorne effect). However, efforts were made to mitigate these biases, including consecutive patient enrollment and regional diversity in site selection.

The study's findings may have limited applicability to the broader Italian patient population with COPD because of the study's recruitment strategies and specific eligibility criteria. Despite the efforts taken to choose locations from various geographic regions and ensure representative sampling, the enrolled patients may not fully represent Italy's COPD patient community. As a result, the findings should be interpreted with caution, taking into account potential selection bias.

## Conclusion

The proactive identification of patients with COPD in a general practice setting may allow for early detection, effective treatment, and better clinical outcomes. In ASTER study, the application of AIFA's Nota 99, which empowers GPs to initiate the most effective therapy when needed, was associated with meaningful improvements in patient outcomes in this study. This suggests that GPs in Italy should actively identify patients with COPD, especially those who may not pay attention to their symptoms because of lack of awareness. Such a proactive approach could result in earlier interventions,

more effective disease management, and, eventually, improved patient outcomes. However, future studies using public health system administrative registries or large clinical databases could confirm the ASTER results, accurately define their dimensions, and reduce potential biases, verifying if the promising outcomes are consistent in general medical practice in Italy.

## Abbreviations

AIFA, Italian Medicines Agency; ASTER, Italian observational prospective multicenter study; CAT, COPD Assessment Test; CI, Confidence Interval; COPD, Chronic obstructive pulmonary disease; GPP, Good Pharmacoepidemiology Practice; ER, Emergency room; FEV<sub>1</sub>, Forced expiratory volume in 1 second; FVC, Forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GP, General practitioner; ICS, Inhaled corticosteroids; ISTAT, Italian Institute of Statistics; LABA, Long-acting beta-agonists; LAMA, Long-acting muscarinic antagonists; mMRC, modified Medical Research Council; SABA, Short-acting beta-agonists; SAMA, Short-acting muscarinic antagonists; Nota 99, Italian Medicine Agency's guideline for managing mild-to-moderate COPD by GPs.

## Data Sharing Statement

Anonymized individual participant data and study documents can be requested for further research from <https://www.gsk-studyregister.com/en/>.

## Ethics Approval and Informed Consent

This study complies with the Declaration of Helsinki. Informed consent was obtained before initiating this study. The ethics committee of each participating study center has received approval through the Coordinator Research Ethics Committee (Comitato Etico Lazio 1, Rome, Italy), and the individual study centers have received approval from the following ethical committees: Comitato Etico Interaziendale - ASL Alessandria; Comitato Etico Area Vasta Centro - USL Toscana Centro; Comitato Etico Area Vasta Sud Est - USL Toscana Sud Est; Comitato Etico Interprovinciale Area 1 ASL BT; CESC delle Province di Verona e Rovigo; Comitato Etico di Brescia; CET Regione Abruzzo; Comitato Etico - ARES Sardegna; CET Regionale dell'Umbria; Comitato Etico Regione Marche; Comitato Etico Lazio 1; Comitato Indipendente di Etica Medica - ASL Brindisi; Comitato Etico Regione Calabria Area Centro; Comitato Etico Campania Centro; Comitato Etico di Messina; Comitato Etico Indipendente - ASL Bari; CET Marche - AOU delle Marche.

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## Author Contributions

All authors contributed to the study conception or design and/or data analysis and interpretation. All authors were involved in the writing, reviewing, and final approval of the manuscript and agreed to be accountable for all aspects of the work.

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## Disclosure

M.V., C.S., D.C., and B.G. are employees of GSK and hold stock options. G.G. and U.A. have no conflicts of interest to declare. R.P. has received consulting fees from GSK Italy and holds stock options from GSK SpA. The authors report no other conflicts of interest in this work.

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