Redefining Cut-Points for High Symptom Burden of the Global Initiative for Chronic Obstructive Lung Disease Classification in 18,577 Patients With Chronic Obstructive Pulmonary Dis...

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Redefining Cut-Points for High Symptom Burden of the Global Initiative for Chronic Obstructive Lung Disease Classification in 18,577 Patients With Chronic Obstructive Pulmonary Disease

Dionne E. Smid MSc1,6, Frits M.E. Franssen MD, PhD1,2, Maria Gonik PhD3, Marc Miravitlles MD, PhD4, Ciro Casanova MD5, Borja G. Cosio MD6, Pilar de Lucas-Ramos MD, PhD7, Jose M. Marin MD8, Cristina Martinez MD9, Isabel Mir MD10, Joan B. Sordinio MD, PhD11, Juan P. de Torres MD12, Alvar Agusti MD13, Nart B. Atalay PhD14, Julia Billington MSc15, Afroditi K. Boutou MD, PhD16,17, Stefanie Brighenti-Zogg PhD18, Emma Chaplin BSc19, Samantha Coster PhD20, James W. Dodd PhD21, Selina Dürr MSc18, Alberto Fernandez-Villar PhD22, Miriam T.J. Groenen MSc1, Miguel Guimarães PhD23, Karel Hejduk PhD24, Victoria Higgins MSc25, Nicholas S. Hopkinson PhD26, Nobuyuki Horita MD, PhD27, Sarah Houben-Wilke PhD1, Daisy J.A. Janssen MD, PhD1, Melissa Jhein PhD28, Rudolf Joerres PhD29, Annika Karch MSc30, Julia L. Kelly PhD31,32, Yu-Il Kim MD, PhD33, Hiroshi Kimura PhD34, Vladimir Koblizeck MD, PhD35, Janwillem H. Kocks MD36, Samantha S.C. Kon PhD37,38, Namhee Kwon PhD39, Inês Ladeira PhD23, Sang-Do Lee PhD40, Joerg D. Leuppi PhD18, Nicholas Locantore PhD41, José L. Lopez-Campos MD, PhD32,43, William D-C Man MD, PhD38, Lana Maricic MD, PhD44, Laura Mendoza MSc45, David Miedinger MD, PhD18, Florin Mihaltan MD, PhD46, Seigo Minami MD, PhD47, Thys van der Molen MD, PhD36, Trevor J. Murrells MSc20, Nienke Nakken MSc1, Yu Nishijima PhD47,48, Ian J. Norman PhD20, Barbora Novotna MD, PhD45, Denis E. O'Donnell MD, FRCP49, Yoshitaka Ogata PhD47, Eanes D. Pereira MD, PhD50, James Piercy MSc25, David Price PhD, FRCPG51,52, Chaicharn Pothirat MD53, Natya Raghavan MD54, Thomas Ringbaek PhD55, Dimitar Sajkov PhD56, Naseh Sigari PhD27, Sally Singh PhD19, Mark Small BSc25, Guilherme F. da Silva PT58, Rebecca J. Tanner MSc29, Joanna G. Tisliyannni MD, PhD59,60, Baykal Tulek MD, PhD61, Nikolaos Tzanakis MD, PhD62, Lowie E.G.W. Vanleferen MD, PhD1,2, Henrik Watz MD, PhD63, Katherine A. Webb MSc49, Emiel F.M. Wouters MD, PhD1,2, Guogang G. Xie MD, PhD54, Masanori Yoshikawa MD, PhD34, Martijn A. Spruit PhD, PT, FERS1,65,66

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Background: Patients with chronic obstructive pulmonary disease (COPD) can be classified into groups A/C or B/D based on symptom intensity. Different threshold values for symptom questionnaires can result in misclassification and, in turn, different treatment recommendations. The primary aim was to find the best fitting cut-points for Global initiative for chronic Obstructive Lung Disease (GOLD) symptom measures, with an modified Medical Research Council dyspnea grade of 2 or higher as point of reference.
Methods: After a computerized search, data from 41 cohorts and whose authors agreed to provide data were pooled. COPD studies were eligible for analyses if they included, at least age, sex, post-bronchodilator spirometry, modified Medical Research Council, and COPD Assessment Test (CAT) total scores.

Main outcomes: Receiver operating characteristic curves and the Youden index were used to determine the best calibration threshold for CAT, COPD Clinical Questionnaire, and St. Geoges Respiratory Questionnaire total scores. Following, GOLD A/B/C/D frequencies were calculated based on current cut-points and the newly derived cut-points.

Findings: A total of 18,577 patients with COPD [72.0% male; mean age: 66.3 years [standard deviation 9.6]] were analyzed. Most patients had a moderate or severe degree of airflow limitation (GOLD spirometric grade 1, 10.9%; grade 2, 46.6%; grade 3, 32.4%; and grade 4, 10.3%). The best calibration threshold for CAT total score was 18 points, for COPD Clinical Questionnaire total score 1.9 points, and for St. Georges Respiratory Questionnaire total score 46.0 points.

Conclusions: The application of these new cut-points would reclassify about one-third of the patients with COPD and, thus, would impact on individual disease management. Further validation in prospective studies of these new values are needed.

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specifity of the binary classification for different cut-points of the GOLD symptom measures. The cut-point, which satisfied the optimal criterion of the Youden index, was referred as the best calibration threshold. The optimal cut-points were calculated for CAT total score, CCQ total score, and SGRQ total score. A software environment R v 3.1.0 was used. The ROC function from the pROC package was used to visualize the ROC curves and calculate the best thresholds.

Graphs were created using GraphPad Prism v 6 (GraphPad Software Inc. San Diego, CA). Statistics were performed using SPSS for Windows, v 20.0 (IBM Corp, Armonk, NY). A P value of ≤ 0.01 was interpreted as statistically significant, to obtain a greater statistical power than the usual P value of < 0.05.

Results

Overall, 337 reports were identified, of which 63 were eligible (Figure 1). Forty-five author groups were able and willing to participate. Finally, 41 datasets were included in the patient level pooled analysis. At the time of inclusion, 3 articles were published with the dataset of the COPD History Assessment In Spain (CHAIN) cohort; 3 articles used the Adelphi Respiratory Disease Specific Program dataset (one of which is from another subcohort than the other 2 articles), 1 author group published 2 articles with the same dataset, and 1 dataset did not have recently measured FEV1 (% predicted). In addition, the COPD and SYstemic consequences-COmorbidities NETwork (COSYCONET) steering committee approved to share their cohort baseline data. Table 1 provides all details per study.

Demographic and clinical characteristics of 18,577 patients with COPD are presented in Table 2. Most patients had a moderate or severe degree of airflow limitation. Spirometric grade 2 was the most prevalent (46%). Using the GOLD 2017 cut-points, the majority of patients were classified in the high-symptom B/D groups: mMRC, 55.3%; CAT, 83.6%; CCQ, 78.8%; and SGRQ 83.0%.

The degree of airflow limitation correlated weakly-to-moderately with the mMRC dyspnea grade (r = − 0.40, P < 0.001), CAT total score (r = − 0.26, P < 0.001), CCQ total score (r = − 0.37, P < 0.001), and SGRQ total score (r = − 0.36, P < 0.001; Figure 2). Moreover, the symptom measures interrelated strongly, with the Pearson product-moment correlation coefficients ranging from 0.540 to 0.799 (all P < 0.001; Figure 3).

New Cut-Points

Figure 4 shows the newly proposed cut-points. A CAT cut-point of 18 points, a CCQ cut-point of 1.9 points, and a SGRQ cut-point of 46.0 points reached the highest sensitivity and specificity vs the mMRC dyspnea grade of 2 or higher as point of reference.

Frequency Distribution

GOLD A/B/C/D frequencies based on current cut-points and the newly derived cut points are shown in Figure 5. Compared with the existing CAT cut-point (≥ 10 points), the new cut-point (≥ 18 points) re-classified 30.2% of the GOLD B/D patients into GOLD A/C. Compared

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**Table 1**

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<th>Total number of articles: n= 337</th>
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<td>Articles with required data: n= 63</td>
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<tr>
<td>Accessible data: n= 45</td>
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<tr>
<td>Suitable articles: n= 40</td>
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<tr>
<td>Total number of datasets: n= 41</td>
</tr>
<tr>
<td>Total number patients: 23,927</td>
</tr>
<tr>
<td>Total number patients with minimal required data: 18,577</td>
</tr>
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n= 1,569 FEV1/FVC (%) ≥ 70
n= 2,053 FEV1 % predicted < 10 or ≥ 120 or missing
n= 145 no mMRC dyspnea score
n= 1,300 no CAT total score
n= 229 age (years) < 40 or year missing
n= 54 gender missing

**Figure 1.** Flow diagram of subject inclusion.
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<tr>
<th>Dataset Resource</th>
<th>Lead author</th>
<th>Journal/year</th>
<th>Country</th>
<th>Cohort</th>
<th>GOLD stage, n (%)</th>
<th>Sex (male), n (%)</th>
<th>Age, y</th>
<th>Current smoker, n (%)</th>
<th>Pack-y</th>
<th>FEV1 (% pred.)</th>
<th>FEV1/FVC (%)</th>
<th>LTOT, n (%)</th>
<th>Exacerbations previous 12 mo &gt;2, n (%)</th>
<th>Hospitalizations previous 12 mo &gt;1, n (%)</th>
<th>mMRC dyspnea grade &gt;2, n (%)</th>
<th>CAT total score, points</th>
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<td>Qual Life Res, 2015</td>
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<td>-</td>
<td>-</td>
<td>104 (94.5)</td>
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<td>54.0 (11.2)$^{b}$</td>
<td>-</td>
<td>24 (12.1)</td>
<td>9 (8.2)</td>
<td>44 (44.5)</td>
<td>163.8 (8.2)</td>
<td>134 (2.1)</td>
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<td>41 (67.2)</td>
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<td>38.4 (19.2)$^{p}$</td>
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<td>41.2 (22.0-63.0)$^{p}$</td>
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BMI, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; CHAIN, COPD History Assessment In SpaiN; COPD, chronic obstructive pulmonary disease; COSYCONET, COPD and SYstemic consequences-COmorbidities NETwork; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HEED, Health-Related Quality of Life in COPD in Europe Study; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GSK, GlaxoSmithKline; IQR, interquartile range; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council dyspnea scale; SD, standard deviation; SGRQ, St. George’s Respiratory Questionnaire; UK, United Kingdom.

Values expressed as mean (SD), median (IQR) or number of patients (%).

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Country

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<th>Hospitalizations previous, 12 mo ≥ 2, n (%)</th>
<th>mMRC dyspnea grade, ≥ 2, n (%)</th>
<th>CAT total score, points</th>
<th>CCQ total score, points</th>
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Values expressed as mean (SD), median (IQR) or number of patients (%).

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Country

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<th>Pack-y</th>
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<th>FEV₁ (% pred.)</th>
<th>FEV₁/FVC (%)</th>
<th>LTOT, n (%)</th>
<th>GOLD stage, n (%)</th>
<th>Exacerbations previous, 12 mo ≥ 2, n (%)</th>
<th>Hospitalizations previous, 12 mo ≥ 2, n (%)</th>
<th>mMRC dyspnea grade, ≥ 2, n (%)</th>
<th>CAT total score, points</th>
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<th>II</th>
<th>III</th>
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<th>Exacerbations previous, 12 mo ≥, n (%)</th>
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**Values expressed as mean (SD), median (IQR) or number of patients (%).**

*a*145 missing; *b*717 missing; *c*28 missing; *d*2 missing; *e*153 missing; *f*10 missing; *g*35 missing; *h*2 missing; *i*1 missing; *j*29 missing; *k* 98 missing; *l*98 missing; *m*1 missing; *n*57 missing; *o*319 missing; *p*3 missing; *q*62 missing; *r*37 missing; *s*4 missing; *t*1 missing; *u*2 missing.
with the existing CCQ cut-point (≥1 point), the new cut-point (≥1.9 points) re-classified 23.9% of the GOLD B/D patients into GOLD A/C. Compared to the existing SGRQ cut-point (≥25 points), the new cut-point (≥46 points) re-classified 34.3% of the GOLD B/D patients into GOLD A/C.

Discussion

Healthcare professionals should be aware of the fact that the choice of symptom measure influences classification, and, in turn, also specific treatment recommendation in patients with COPD. Using mMRC ≥2 points as a reference, a CAT cut-point of 18 points, CCQ cut-point of 1.9 points, and SGRQ cut-point of 46.0 points reached the highest agreement. Implementation of these newly derived cut-points will influence the management of individual patients and the design and interpretation of clinical studies.

Recommendations

As the newly derived cut-points reached the highest sensitivity and specificity with the mMRC dyspnea grade of 2 or higher, guidelines committees may need to consider the use of a mMRC dyspnea grade 2 or higher, a CAT total score of 18 points or higher, a CCQ total score of 1.9 points or higher, or a total SGRQ score of 46.0 points or higher to classify patients with COPD as symptomatic (ie, GOLD B or D; Figure 6). This recommendation is supported by the fact that a CAT total score ≥10 points already occurs in 50% of current or former smokers without having any airway obstruction.76 The newly derived cut-points enable healthcare professionals to classify the largest proportion of patients into the same GOLD quadrant regardless of their choice of symptom measure.
Fig. 3. Correlation between symptom measures

Fig. 4. ROC curves showing best pairwise classification thresholds. A) Best pairwise classification threshold between mMRC ≥2 points and the CAT; B) best pairwise classification threshold between mMRC ≥2 points and the CCQ; best pairwise classification threshold between mMRC ≥2 points and the SGRQ.
Clinical Consequences

Future studies are needed to assess the effectiveness of bronchodilators in COPD patients with and without symptoms, using the newly derived cut-points. For example, GOLD A patients are advised to use short-acting bronchodilators, whereas GOLD B patients are advised to use long-acting bronchodilators. Therefore, the new cut-points may reduce the prescription of long-acting bronchodilators in patients who are currently GOLD B, and will become GOLD A by applying the new cut-points. Obviously, the question arises what to do with COPD patients with a mMRC grade below 2 and a CAT score between 10 (current cut-point) and 18 points (newly derived cut point)? This combination of scores suggests that these patients suffer from other symptoms than dyspnea, which can most probably not be treated satisfactorily with the current pulmonary drug therapy.

The newly proposed cut-points may also affect recruitment criteria for upcoming trial designs. Indeed, studies that previously applied the current cut-points, will have an overrepresentation of GOLD B or D patients. Sillen et al showed that there is a lot of heterogeneity in GOLD group D, when applying the existing cut-points. In turn, adjusting cut-points of the symptom measures to the newly derived cut-points will increase baseline homogeneity of patient populations within observational COPD studies and intervention trials.

The current analysis confirms that the degree of airflow limitation only moderately correlates with the symptom measures. So, the degree of symptom burden cannot accurately be derived from spirometry. Therefore, healthcare professionals need to regularly assess symptoms in patients with COPD. Indeed, a change in symptom scores may even have a prognostic value in patients with COPD.

Strengths and Limitations

The pooled, multicenter, multinational, patient level dataset with a large number of patients and global coverage is a major strength. Indeed, this resulted in a heterogeneous sample of patients with COPD, also including a high number of patients with a low mMRC dyspnea grade (grade 0: 2183 patients; grade 1: 6122 patients), patients with a mild degree of airflow limitation (spirometric grade 1: 2029 patients), and 1,122 patients younger than 50 years of age. Moreover, patients were recruited from various care settings (ie, primary care, general population, hospital outpatients). This makes the results more generalizable.

A limitation of the current study is that the largest proportion of patients was male (72.0%). Although this seems to over-represent the male sex, it is probably a reliable representation of the current COPD population in the participating cohorts. Less data were available for the CCQ total score (2047 patients) and SGRQ total score (6159 patients). Furthermore, the definition of COPD, current, former or never smoker and the definition of exacerbations and hospitalizations could differ between studies. Finally, the mMRC dyspnea grade solely captures symptoms of dyspnea, which may, together with spirometry and history of exacerbations/hospitalizations, be a suitable guidance for treatment recommendations. Nevertheless, mMRC dyspnea scale may
be too limited to truly understand the impact of COPD. Indeed, symptoms like fatigue, pain and insomnia, may also occur in patients with COPD. Therefore, CAT, CCQ, or SGRQ may be preferred to more broadly characterize the daily symptoms of patients with COPD. Obviously, when CAT, CCQ, and SGRQ are applied for the binary classification of high vs low symptoms, there will be discrepancy between these symptom measures. So, the GOLD Scientific Committee may want to consider the choice of 1 symptom measure or applying the worst scoring questionnaire to classify patients into groups A/C or B/D.

Conclusions

To objectively define a symptom burden score equivalent to a mMRC dyspnea grade of 2 or higher, a CAT total score of ≥18 points, a CCQ total score of ≥19 points, or a SGRQ total score of ≥46 points should be used. Following this grading, about one-third of the patients in GOLD groups B/D are re-classified to GOLD groups A/C. This implies that guidelines committees may consider adapting our evidence-based cut-points of symptom measures.

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55. Mihaltan F.


58. Mihaltan F.


Appendix A

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Appendix B

All authors completed the ICMJE uniform disclosure form and declare:


Dr Agusti reports grants and personal fees from Astra-Zeneca, and personal fees from GlaxoSmithKline (GSK), grants from MSD, grants and personal fees from Menarini, personal fees from Novartis, personal fees from TEVA, personal fees from Chiesi (outside the submitted work).

Dr Casanova has participated in speaking activities, industry advisory committees, and other activities related to industry sources by AstraZeneca, Esteve, Rovi, Gebro-Pharma, GlaxoSmithKline plc, and Novartis AG during the period 2014–2016.

Dr Franssen reports grants from GlaxoSmithKline, grants from Lung Foundation Netherlands during the conduct of the study.

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Dr Kimura reports personal fees from Nippon Boehringer Ingelheim Co (outside the submitted work).

Dr Koblizek reports grants from Czech Ministry of Health no. 15/14/NAP, grants from Czech Ministry of Health no. 5/15/NAP, grants from Angelini, CZ, grants from GlaxoSmithKline, CZ, non-financial support from Pfizer, CZ, grants from Takeda, CZ,
grants from Novartis, CZ, grants from AstraZeneca, CZ, grants from Boehringer Ingelheim, CZ, during the conduct of the study; grants and personal fees from AstraZeneca, CZ, personal fees from Berlin-Chemie, CZ, grants and personal fees from Boehringer Ingelheim, CZ, and RCV, personal fees from GlaxoSmithKline, CZ, personal fees from Angelini, CZ, personal fees from Mundipharma, UK, grants and personal fees from Novartis, CZ, grants and personal fees from Takeda, CZ (outside the submitted work).

- Dr Kwon reports to be a full time employee from GlaxoSmithKline (outside the submitted work).
- Dr Lee reports personal fees from Astra, personal fees from Pfizer, personal fees from GlaxoSmithKline (GSK), personal fees from Bayer (outside the submitted work).
- N. Locantore is an employee and shareholder of GlaxoSmithKline (GSK).
- Dr Man reports grants from Pfizer Ltd (outside the submitted work).
- Dr Miravitlles has received speaker fees from Almirall, Boehringer Ingelheim, AstraZeneca, Chiesi, GlaxoSmithKline, Menarini, Teva, Grifols, and Novartis, and consulting fees from Almirall, Bayer Schering, Boehringer Ingelheim, GlaxoSmithKline, Gedeo Pharma, CSL Behring, Cipla, Medimmune, Teva, Takeda, Novartis, and Grifols.
- Dr van der Molen owns the copyright of the CCQ and was involved in the development of the CAT.
- Dr Novotna reports grants from Czech Ministry of Health no. 15/14/NAP, grants from Czech Ministry of Health no. 5/15/NAP, grants from Angelini, CZ, grants from GlaxoSmithKline, CZ, non-financial support from Pfizer, CZ, grants from Takeda, CZ, grants from Novartis, CZ, grants from Astra Zeneca, CZ, grants from Boehringer Ingelheim, CZ, during the conduct of the study.
- Dr O'Donnell reports grants from Queen's University, grants from Ontario Thoracic Society, grants from Canadian Respiratory Research Network (supported by grants from the Canadian Institutes of Health Research (CIHR) - Institute of Circulatory and Respiratory Health; Canadian Lung Association (CLA)/Canadian Thoracic Society (CTS); British Columbia Lung Association; and Industry Partners Boehringer Ingelheim Canada Ltd, AstraZeneca Canada Inc., and Novartis Canada Ltd.), grants from CIHR (subsire), grants and personal fees from GlaxoSmithKline (GSK), grants and personal fees from Boehringer Ingelheim, grants and personal fees from AstraZeneca (outside the submitted work).
- Dr Price reports board membership with Aerocrine, Almirall, Amgen Inc., AstraZeneca plc, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis International AG and Teva, consultancy with Almirall, Amgen Inc., AstraZeneca plc, Boehringer Ingelheim, Chiesi, GlaxoSmithKline plc, Meda, Mundipharma, Napp, Novartis International AG, Pfizer, Inc., and Teva, grants and unrestricted funding for investigator-initiated studies (conducted through Research in Real-Life Ltd and Observational and Pragmatic Research Institute Pte Ltd) from UK National Health Service, British Lung Foundation, Aerocrine, AKL Ltd, Almirall, AstraZeneca plc, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline plc, Meda, Merck & Co., Inc., Mundipharma, Napp, Novartis International AG, Orion, Pfizer, Inc., Respiratory Effectiveness Group, Takeda, Teva, and Zentiva, payments for lectures/speaking from Almirall, AstraZeneca plc, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline plc, Kyorin, Meda, Merck & Co., Inc., Mundipharma, Novartis International AG, Pfizer, Inc., Skyepharma, Takeda, and Teva, payment for manuscript preparation from Mundipharma and Teva, payment for travel/accommodations/meeting expenses from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis International AG, and Teva, funding for patient enrolment or completion of research from Almirall, Chiesi, Teva, and Zentiva, payment for the development of educational materials from GlaxoSmithKline plc, Novartis International AG, outside the submitted work; In addition, Dr Price has a patent AKL Ltd. pending and has shares in AKL Ltd which produces phytopharmaceuticals. He owns 80% of Research in Real Life Ltd (which is subcontracted by Observational and Pragmatic Research Institute Pte Ltd), 75% of the social enterprise Optimum Patient Care Ltd and 75% of Observational and Pragmatic Research Institute Pte Ltd.
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- Prof Spruit discloses receiving personal remuneration for consultancy and/or lectures from Boehringer Ingelheim, GSK, and AstraZeneca outside the scope of this work.