Special Article

Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma

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BACKGROUND: Regulatory bodies have approved five biologics for severe asthma. However, regional differences in accessibility may limit the global potential for personalized medicine.

OBJECTIVE: To compare global differences in ease of access to biologics.

METHODS: In April 2021, national prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab were reviewed by severe asthma experts collaborating in the International Severe Asthma Registry. Outcomes (per country, per biologic) were (1) country-specific prescription criteria and (2) development of the Biologic Accessibility Score (BACS). The BACS composite score incorporates 10 prescription criteria, each with a maximum score of 10 points. Referenced to European Medicines Agency marketing authorization specifications, a higher score reflects easier access.

RESULTS: Biologic prescription criteria differed substantially across 28 countries from five continents. Blood eosinophil count thresholds (usually ≥300 cells/μL) and exacerbations were key requirements for anti-IgE/anti−IL-5/5R prescriptions in around 80% of licensed countries. Most countries (40% for dupilumab to 54% for mepolizumab) require two or more moderate or severe exacerbations, whereas numbers ranged from none to four. Moreover, 0% (for reslizumab) to 21% (for omalizumab) of countries required long-term oral corticosteroid use. The BACS highlighted marked between-country differences in ease of access. For omalizumab, mepolizumab, benralizumab, and dupilumab, only two, one, four, and seven countries, respectively, scored equal

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Conflicts of interest: C.M. Porsbjerg has attended advisory boards for AstraZeneca, Novartis, Teva, and Sanofi-Genzyme; has given lectures at meetings supported by AstraZeneca, Novartis, Teva, Sanofi-Genzyme, and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, Novartis, MSD, Sanofi-Genzyme, GlaxoSmithKline, and Novartis; and has received educational and research grants from AstraZeneca, Novartis, Teva, GlaxoSmithKline, ALK, and Sanofi-Genzyme. A.N. Menzies-Gow has attended advisory boards for AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, and Teva, and has received speaker fees from AstraZeneca, Novartis, Roche, Teva, and Sanofi. He has participated in research with AstraZeneca, for which his institution has been remunerated and has attended international conferences with Teva. He has had consultancy agreements with AstraZeneca, Sanofi, and Vectura. M. Al-Ahmad has received advisory board and speaker fees from AstraZeneca, Sanofi, Novartis, and GlaxoSmithKline. R. Al-Lehebi has given lectures at meetings supported by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Sanofi, and participated in advisory board fees from GlaxoSmithKline. A. Altraja has received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Norameda, Novartis, Orion, Sanofi, and Zentiva; and sponsorships from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Norameda, Sanofi, and Novartis; and has been a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi, and Teva. A.S. Belevskiy has received lecture grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Sanofi, and GSK. U.S. Björnsdóttir receives gratuities for lectures/presentations from AstraZeneca, Sanofi, and Novartis. A. Bourdin has received industry-sponsored grants from AstraZeneca/MedImmune, Boehringer-Ingelheim, Cephalon/Teva, GlaxoSmithKline, Novartis, and Sanofi-Regeneron and consultancies with AstraZeneca/MedImmune, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Regeneron-Sanofi, Med-in-Cell, Actelion, Merck, Roche, and Chiesi. G.W. Canonica has received research grants as well as lecture or advisory board fees from A. Menarini, Alk-Albello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas. B.G. Cosio declares grants from Chiesi and GSK; personal fees for advisory board activities from Chiesi, GSK, Novartis, Sanofi, and AstraZeneca; and payment for lectures/speaking engagements from Chiesi, Novartis, GSK, Menarini, and AstraZeneca, outside the submitted work. R.W. Costello has received honoraria for lectures from Aerogen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Teva. He is a member of advisory boards for GlaxoSmithKline and Novartis, has received grant support from GlaxoSmithKline and Aerogen, and has patents in the use of acoustics in the diagnosis of lung disease, assessment of adherence, and prediction of exacerbations. J.M. FitzGerald reports grants from AstraZeneca, GSK, Sanofi Regeneron, and Novartis paid directly to UBC. Personal fees for lectures and attending advisory boards were received from AstraZeneca, GSK, Sanofi Regeneron, Novartis, and Teva. J.A. Fonseca reports grants from or research agreements with AstraZeneca, Mundipharma, Sanofi Regeneron, and Novartis. Personal fees for lectures and attending advisory boards were received from AstraZeneca, GSK, Mundipharma, Novartis, Sanofi Regeneron, and Teva. L.G. Heaney declares he has received grant funding, participated in advisory boards, and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Circassia, Evelo Biosciences, Hoffmann la Roche, GlaxoSmithKline, Novartis, Theravance, and Teva; he has taken part in asthma clinical trials sponsored by Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline, for which his institution received remuneration; and he is the

or higher than the European Medicines Agency reference BACS. For reslizumab, all countries scored lower.
CONCLUSIONS: Although some differences were expected in country-specific biologic prescription criteria and ease of access, the substantial differences found in the current study present a challenge to implementing precision medicine across the world. © 2022 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma &

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Abbreviations used
BACS- Biologic Accessibility Score
BEC- Blood eosinophil count
COFEPRIS- Comisión Federal para la Protección contra Riesgos Sanitarios
EMA- European Medicines Agency
FDA- US Food and Drug Administration
GDP- Gross domestic product
HTA- Health technology assessment
ICS- Inhaled corticosteroids
ISAR- International Severe Asthma Registry
ISC- ISAR Steering Committee
LABA- Long-acting β-agonist
LAMA- Long-acting muscarinic antagonist
LTRA- Leukotriene receptor antagonist
OCS- Oral corticosteroids
SPT- Skin prick test

Key words: *Severe asthma; Biologics access; Biologics eligibility*

INTRODUCTION

Globally, there are currently three major classes of biologics licensed for use for the treatment of patients with severe asthma. These include anti-IgE (omalizumab), anti−IL-5 (mepolizumab and reslizumab)/anti−IL-5 receptor antagonist (benralizumab), and anti−IL-4Rα, which blocks IL-4 and IL-13 (dupilumab).[1] All have been shown to be effective in large randomized controlled trials with carefully selected inclusion and exclusion criteria.[2-5] Some of these criteria differed among biologics, to maximize individual drug response and achieve patient benefits such as reductions in exacerbation rate and oral steroid load.

After successful trials and subsequent regulatory approval, these biologics have become increasingly available to treat severe asthma, facilitating personalized medicine in this subset of patients with asthma. It is important to be able to consider individual patient factors that render patients potentially responsive to biologics.[6] Whereas the principles of personalized or at least stratified medicine are now widely advocated in clinical guidelines, real-world practice and policy may present challenges. Indeed, the European Respiratory Biologics Forum of 2018 noted variation by country in biologic prescriptions owing to differences in national health care systems regarding referral networks, access, and reimbursement policies.[7] All three factors give rise to the hypothesis that despite similar regulatory indications for biologics established by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), there is a high degree of variation in access criteria across these countries. As such, although the efficacy of biologics has been confirmed, whether a patient qualifies for a biologic may depend on the country of residence. To document this variation, a systematic global comparison of access criteria for biologics is required. Importantly, recent evidence suggests that the effect of biologics is poorer with more long-standing asthma, and in patients receiving oral corticosteroids (OCS).[8,9] This suggests that delayed initiation of biologics may have long-term detrimental impacts. This study aimed to analyze national biologic access criteria in countries collaborating with the International Severe Asthma Registry (ISAR)[10] and to compare these with the wider regulatory indications with the newly developed Biologic Accessibility Score (BACS). The ISAR is a multi-country, multicenter, observational initiative that collects data prospectively and retrospectively on patients with severe asthma from tertiary care. It has four governing bodies, of which the ISAR Steering Committee (ISC) is one. The ISC is composed of 46 experts on severe asthma from 28 ISAR collaborating countries, and medical experts from AstraZeneca. Because of the cross-disciplinary global nature of ISAR, its structured and uniform data collection, and its premise of inclusivity and the expertise of the individuals of the ISC, this collaboration provides an appropriate platform to address essential research questions in severe asthma.[11-14]

METHODS

Study design and setting

This study entailed a review of severe asthma biologic prescription criteria and ease of access across 28 countries collaborating with ISAR (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Data sources, survey development, and data collection

We used several data sources to obtain official prescription criteria per biologic and country (Table E1). First, to obtain an initial list of access criteria, publicly available drug regulation authority websites were searched in June 2020. North and Latin American drug regulation authority websites were found through the World Health Organization list of globally identified medicine regulatory authorities. Asian and Oceania drug regulation authorities were compiled from the Regulatory Affairs Professional Society list. If an Asian or Oceanian country was known also to have a separate body that determines reimbursement criteria, this body was used instead (eg, Pharmaceutical Benefits Scheme for Australia, Ministry of Health Drug Advisory Committee for Singapore). For European countries, we used data from health technology assessment (HTA) agencies (eg, National Institute for Health and Care Excellence for the United Kingdom). If a country had specific reimbursement criteria available, those were used. If not, the regulatory criteria (eg, in Europe from the EMA) were used. To determine whether a country had a specific guideline and/or licensing criterion available for the biologics, both the drug name and drug trade name were searched in the search engine of each website (eg, "omalizumab," "Xolair"). All eligibility criteria for biologic initiation were systematically identified from the licensing authorities and aggregated as a table.

Second, to compare these official criteria with the real-life practice of severe asthma specialists, a semistructured survey (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org) was developed and disseminated to severe asthma specialists from the 29 countries collaborating with ISAR. Responses were received from all countries except India, which was eventually removed from the data analysis. This resulted in a response rate of 96.6%. Before dissemination, the survey was reviewed, pilot-tested, and then approved by the project steering committee and the ISC chair. Respondents were given 2 weeks from questionnaire dissemination to complete the survey. In April 2021, tabulated data were resent to the ISC members in ISAR countries to check the criteria for all biologics.

Study outcomes

For each of the 28 countries collaborating with the ISAR, we first assessed the availability of the five biologics (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) and subsequently assessed (1) all individual access criteria per country, per biologic; and (2) the overall ease of access to each biologic, as further specified subsequently. The access or accessibility to severe asthma biologics evaluated in our study refers to the prescription criteria, not to conditions or barriers to access health services in each country.

Biologic Accessibility Score

To summarize and compare overall ease of access for licensed biologics in each country, we created a composite score of biologic access criteria, termed the BACS. To inform the BACS, we first identified all individual access criteria across countries and biologics. This resulted in a list of 18 initial criteria (age, weight, asthma phenotype, blood eosinophil count [BEC], serum IgE, FeNO, allergic asthma diagnostic requirements [eg, skin prick test], background therapy, biologic history, adherence, OCS use, exacerbation history, asthma control, lung function, symptoms, asthma diagnosis, care manager [eg., severe asthma specialist], and correct inhaler technique). Values within the 18 biologic access criteria were simplified according to frequency of use (eg, criteria that were used in only one or two countries, such as weight, were removed) and grouped according to relevancy (eg, symptoms and asthma control) when possible. This resulted in 10 criteria: (1) age, (2) asthma severity and phenotype (eg, eosinophilic), (3) BEC (serum IgE for omalizumab), (4) FeNO, (5) background therapy, (6) adherence (allergic asthma diagnostic requirements for omalizumab), (7) OCS, (8) number of exacerbations, (9) asthma control, and (10) lung function.

Each criterion was then split into clinically relevant categories and scored between 0 and 10, in which 10 represented easiest access and 0 was the most difficult access for each criterion (Table I). The total BACS for each biologic ranged from 0 to 100 and was categorized as 0 for no access; 1 to 20 for very difficult access; 21 to 40 for difficult access; 41 to 60 for moderately difficult access; 61 to 80 for neither difficult nor easy access; and 81 to 100 for easy access. Full details on the categorizations and scoring system for each criterion of the BACS per biologic and per country are provided in Figures E2 to E6 (in this article's Online Repository at www.jaci-inpractice.org).

To put the score into perspective, the percentage of countries with BACS scores lower than the EMA BACS score (based on EMA regulatory criteria) was calculated for each biologic. Of note, we chose EMA over other regulatory bodies (eg, FDA, Therapeutic Goods Administration) because this is the authority that regulates the highest number of countries collaborating with ISAR. Furthermore, for consistency and ease of interpretation, we preferred to use only a single anchor value for comparison.

Descriptive statistics

Final data on prescribing criteria and access were aggregated and summarized through the use of proportions. The denominator used for each prescription criterion was the number of countries licensing that particular drug. An overview of the BACS per biologic in each country showing each biologic prescribing criterion was visualized using spider plots (Figure E7 to E34 in this article's Online Repository at www.jaci-inpractice.org). To provide a global overview per biologic, colored world maps indicating the total BACS category in each ISAR country were created. For each biologic, the relationship between BACS and gross domestic product (GDP) of the ISAR countries for 2019 was assessed using Pearson's correlation testing.

RESULTS

Overview of biologics available

At the time the biologic prescription criteria were reviewed in April 2021, omalizumab, mepolizumab, and benralizumab were each licensed in 28 countries (100%) (Figures E2-E4). All three biologics were fully or partially reimbursed in 96.4% (omalizumab), 92.9% (mepolizumab), and 92.9% (benralizumab) of countries in which they were licensed (Table II). As for reslizumab and dupilumab, they were licensed in 15 (54%) and 20 (71%) of the countries, respectively (Figures E5 and E6), and either fully or partially reimbursed in 73.3% (reslizumab) and 75.0% (dupilumab) of ISAR countries (Table II).

Biologic prescribing criteria

Table III provides an aggregated overview of prescription criteria per biologic across the countries.

Age and phenotype

In most countries, omalizumab and mepolizumab can be prescribed for patients aged 6 years or older, whereas the other three biologics are for ages 12 or 18 years and greater. In 50% (dupilumab) to 73.3% (reslizumab) of countries, there is a requirement for a diagnosis of severe (persistent or eosinophilic) asthma with type 2 inflammation (or allergic sensitization for omalizumab) (Table III).

IgE, allergic diagnostics, BEC, and FeNO

Of the 28 countries, 25 required a serum IgE threshold to start omalizumab (89%); Singapore and Ireland have no criteria in place, and Canada is the only exception because it does not require a threshold. A threshold of 30 or greater or 35 IU/mL was the most common, followed by 70 or greater, 75, or 76 IU/mL. Of the 28 countries, 27 (96%) require a positive serum-specific IgE and/or skin prick test to common aeroallergens to qualify for omalizumab; Ireland has no criteria in place (Table III).

Whereas 64.3% and 42.9% of countries used a BEC threshold of 300 cells/μL or greater in the past 12 months (or ever in the past) for mepolizumab and benralizumab, respectively, for reslizumab the threshold most commonly used to determine eligibility was 400 cells/μL or greater in the past 12 months (66.7%), and for dupilumab it was 150 cells/μL or greater or raised (55.0%). Spain applies a much higher BEC threshold of 500 cells/μL or greater, 400 cells/μL or greater, and 500 cells/μL or greater for mepolizumab, reslizumab, and benralizumab, respectively. Furthermore, three countries (Kuwait, Denmark, and The Netherlands) included sputum eosinophils (>2% or >3%) as an optional alternative to the BEC criterion. Most countries (80.0% to 85.7%) did not use FeNO as a criterion to determine eligibility for omalizumab, mepolizumab, reslizumab, and benralizumab. In contrast, 10 countries (50.0%) required an FeNO threshold to be considered eligible for dupilumab. In addition, five countries (25%) stated that either the elevated BEC or the FeNO value can be used to be eligible for dupilumab. In countries where FeNO was a criterion, thresholds of 20 parts per billion or more, 25 parts per billion or more, or higher were the most common for all countries and biologics.

TABLE I. The BACS scoring system

Criterion	Score
Age, y	
Not required/undecided	10
≥6	8
≥12	4
≥18	0
Severity/phenotype	
Not required/undecided	10
IgE-mediated or type II–driven or eosinophilic	8
Bronchial asthma refractory or uncontrolled allergic	6
Moderate to severe (persistent, eosinophilic, or OCS-dependent)	4
Severe (persistent, eosinophilic, with type II inflammation or allergic)	2
Severe (uncontrolled, uncontrolled plus eosinophilic, uncontrolled allergic, refractory, refractory plus eosinophilic)	0
Serum IgE (IU/mL)	
Not required/undecided	10
≥30, 35, or elevated	8
≥70, 75, or 76	4
≥150	2
≥400	0
BEC (cells/μL)	
Not required/undecided	10
≥150 or raised	8
≥150 in past 12 mo	7
≥150 in past 1 mo	6
≥300 or ≥150 on long-term OCS	5
≥300 in past 12 mo or historical	4
≥300 twice in past 12 mo	3
≥400 or in past 12 mo	2
≥500	0
FeNO (parts per billion)*	
Not required/undecided	10
≥20 or 25 or raised	5
≥50	0
Allergic asthma	
Not required/undecided	10
Skin prick test or radioallergosorbent test	5
Skin prick test and radioallergosorbent test	0
Background therapy	
Not required/undecided	10
ICS	8
High-dose ICS (± LABA or long-term OCS or xanthine or LTRA)	6
Medium-dose ICS/LABA (± LTRA)	5
High-dose ICS/LABA (± LAMA or LTRA)	4
High-dose ICS/LABA (± long-term OCS)	
High-dose ICS/LABA plus one or more other controller (not OCS)	2
High-dose ICS/LABA plus long-term OCS	0
OCS†	
Not required/undecided	10
Long-term OCS use	0
Exacerbations†	
Not required/undecided	10
One or more	8
One or more requiring hospital admission, emergency room visit, or rescue OCS	6
Two or more	4
Two or more requiring hospital admission, emergency room visit, or rescue OCS	3
Three or more	2
Four or more	0
Asthma control	
Not required/undecided	10
Required	0
Lung function	
Not required/undecided	10
FEV_1 ≤80%	8
12% or greater reversibility ± >200 ml FEV_1	6
FEV_1 ≤80% and evidence of reversibility	4
FEV_1 ≤80% and 12% reversibility and airway hyperresponsiveness	2
FEV_1 ≤60%	0
Adherence	
Not required/undecided	10
Required	0

BACS, Biologic Accessibility Score; *BEC*, blood eosinophil count; *ICS*, inhaled corticosteroids; *LABA*, long-acting β-agonist; *LAMA*, long-acting muscarinic antagonist; *LTRA*, leukotriene antagonist; *OCS*, oral corticosteroids.

Rules were formulated to account for blanks and International Severe Asthma Registry Steering Committee (ISC)/guidelines (GL) conflicts during generation of the BACS from the survey. For data pertaining to each criterion per biologic, blanks were assumed not to be required and were given a score of 10 (categorized under Criteria not decided in Table III). If criteria were left blank by ISC members, blanks were supplemented with the GL criteria (when available). If criteria were left blank by European ISC members, blanks were supplemented with the European Medicines Agency criteria, because the European Medicines Agency is the lowest threshold. If both GL and ISC members completed, and there was no overlap in responses, GL criteria were used to fill in gaps or blanks in ISC responses. For overlap and consensus, no further action was required; they were scored as normal. For overlap and disagreement, scoring was done separately to illustrate multiple prescription criteria, and the "best" score was taken, either between the GL and ISC member's responses or between two conflicting ISC members' responses (ie, the highest score) to reflect the true on-the-ground hurdle to biologic prescription and also so as not to inflate the BACS artificially.

*In countries where either the elevated BEC or the FeNO criteria can be used to be eligible for dupilumab, BEC criteria instead of FeNO criteria were used to compute the BACS, and "not required" was stated for FeNO for dupilumab, because there is a more specific gradient in the scoring system for BEC. Otherwise, if BEC criteria were unavailable, the FeNO criteria were used to compute the BACS for dupilumab.

†In countries where there is specification of the operator "or" between chronic OCS use and exacerbation criteria to be eligible for a particular biologic, exacerbation criteria instead of OCS criteria were used to compute the BACS, and "not required" was stated for OCS for that particular biologic because there is a more specific gradient in the scoring system for exacerbations. When there is chronic OCS use and exacerbation criteria without specification of the operators "or" or "and" to determine eligibility for the biologic, it was assumed to be an "or" operator. Thus, scoring favored the exacerbation criteria and OCS was not indicated as a requirement to be prescribed a particular biologic.

Adherence, asthma control, and lung function

For all biologics except omalizumab, 40.0% to 57.1% of countries had adherence to background therapy as a prescription criterion. Most countries (60.0% to 82.1%) required evidence of poor asthma control. In most countries, a lung function criterion

TABLE II. Biologics license dates and reimbursement status in International Severe Asthma Registry countries with market authorization for their respective biologic (by April 2021)

License date and reimbursement status	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
License dates					
European Medicines Agency license date	October 25, 2005	December 2, 2015	August 16, 2016	January 8, 2018	March 1, 2019*
US Food and Drug Administration license date	June 20, 2003	November 4, 2015	March 23, 2016	November 14, 2017	October 19, 2018†
Reimbursement status, n (%)					
No reimbursement	1 (3.6) SG	2 (7.1) SK, SG	4 (26.7) BR, CN, FR, SK	2 (7.1) SK, SG	5 (25.0) BR, IE, PT, SK, SG
Partial reimbursement	4 (14.3) CN, JP, RU, US	6 (21.4) AR, CN, JP, MX,‡ RU, US	2 (13.3) RU, US	5 (17.9) CN, JP, MX,‡ RU, US	4 (20.0) JP, MX,§ RU, US
Full reimbursement	23 (82.1) AR, AU, BR,‖ BG,¶ CO,# DK, DE, ES, EE, FI,§§ FR, GR, IS, IE,** IT, KW, MX,†† NL, PT, SA, SK, TW, UK	20 (71.4) AU, BR‖, BG,¶ CO,# DK, DE, ES, EE, FI,§§ FR, GR, IS, IE, IT, KW, NL, PT, SA, TW, UK	9 (60.0) DK, DE, ES, EE, FI,§§ IE,** NL, PT, UK	21 (75.0) AR‖‖, AU, BR,‡‡ BG,¶ CO,# DK, DE, ES, EE, FI,§§ FR, GR, IS, IE, IT, KW, NL, PT, SA, TW, UK	11 (55.0) AU, CO,# DK, DE, EE, FI,§§ FR, IT, KW, NL, SA
Total, n	28	28	15	28	20

AR, Argentina; *AU*, Australia; *BG*, Bulgaria; *BR*, Brazil; *CN*, Canada; *CO*, Colombia; *DE*, Germany; *DK*, Denmark; *EE*, Estonia; *ES*, Spain; *FI*, Finland; *FR*, France; *GR*, Greece; *IE*, Ireland; *IN*, India; *IS*, Iceland; *IT*, Italy; *JP*, Japan; *KW*, Kuwait; *MX*, Mexico; *NL*, Netherlands; *PT*, Portugal; *RU*, Russia; *SA*, Saudi Arabia; *SG*, Singapore; *SK*, South Korea; *TW*, Taiwan; *UK*, United Kingdom; *US*, United States.

*Date of extension of indication to severe asthma (first approval, September 26, 2017 for atopic dermatitis).

†Date of extension of indication to severe asthma (first approval, March 28, 2017 for atopic dermatitis).

‡In Mexico, mepolizumab and benralizumab are partially reimbursed only if indication has been approved by the Comisión Federal para la Protección contra Riesgos Sanitarios [COFEPRIS],), as happened recently, by private medical insurance, by the general social security system Instituto Mexicano del Seguro Social at selected tertiary care centers, and by the social security system Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado for those employed by the state, at selected tertiary care centers. For asthma, it is age 12 and 18 years and greater for mepolizumab and benralizumab, respectively.

§In Mexico, dupilumab is partially reimbursed only if the indication has been approved by COFEPRIS (as happened recently), by private medical insurance, and by the IMSS at selected tertiary care centers. For asthma, it is age 12 years and greater.

‖In Brazil, omalizumab and mepolizumab are reimbursed by the public and private health system.

¶In Bulgaria, omalizumab, mepolizumab, and benralizumab are fully reimbursed: 75% by the National Health Insurance Fund and 25% by the Marketing Authorization Holder, according to a patient access scheme, negotiated annually between the National Health Insurance Fund and Marketing Authorization Holder.

#In Colombia, omalizumab, mepolizumab, benralizumab, and dupilumab are fully reimbursed by the National Health System through administrators of the benefit plan (insurers) of the system, and governmental electronic prescription is required.

**In Ireland, omalizumab is reimbursed only in Ireland's publicly funded acute hospitals designated as severe asthma centers.

††In Mexico, omalizumab is partially reimbursed by the public health care system at selected secondary and tertiary care centers. Omalizumab is also partially reimbursed only if the indication has been approved by the COFEPRIS by private medical insurance, by the Instituto Mexicano del Seguro Social at selected tertiary care centers, and by the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado for those employed by the state at selected secondary and tertiary care centers. For asthma, it is age 6 years and greater.

‡‡In Brazil, benralizumab is reimbursed only in the private health system.

§§In Finland, there is no reimbursement system for any drugs administered in the hospital.

‖‖In Argentina, roughly 50% of patients may get full reimbursement or coverage, whereas the other half will get no reimbursement for benralizumab. This is because of the different policies of the health maintenance organization in Argentina. Aside from that, benralizumab is not covered or reimbursed by the public hospitals.

of FEV_1 of 80% predicted or less was most common (46.4%) for omalizumab. For mepolizumab, reslizumab, benralizumab, and dupilumab, only around 13.3% to 32.1% of countries applied a lung function criterion; FEV_1 of 80% or less and documented evidence of reversibility were the most common (Table III).

Background therapy

To qualify for a biologic, most countries required background therapy of at least a high dose of inhaled corticosteroid (ICS) and long-acting β_2-agonist, with or without a long-acting muscarinic antagonist, leukotriene antagonist, or theophylline. Between 0% (reslizumab) and 21% (omalizumab) of countries use long-term OCS as an access criterion (Table III).

Number of exacerbations

In addition to biomarker criteria, approximately half of the countries require two or more exacerbations in the previous year (with hospitalization, an emergency department visit, or treatment with OCS) for a biologic prescription (Table III), with differences among countries and biologics (40% for dupilumab and 54% for mepolizumab). Regarding the number of exacerbations, access to omalizumab in the United Kingdom requires

TABLE III. Percentage of International Severe Asthma Registry countries requiring each biologic criterion (April 2021)

Patient/asthma characteristics	Anti-IgE, n (%)		Anti–IL-5/5R, n (%)						Anti–IL-4R, n (%)	
	Omalizumab (n = 28)		Mepolizumab (n = 28)		Reslizumab (n = 15)		Benralizumab (n = 28)		Dupilumab (n = 20)	
Age, y										
≥6	19.0	(67.9)	12.0	(42.9)	0.0		0.0		0.0	
≥12	5.0	(17.9)	5.0	(17.9)	1.0	(6.7)	2.0	(7.1)	15.0	(75.0)
≥18	0.0		8.0	(28.6)	12.0	(80.0)	23.0	(82.1)	2.0	(10.0)
Not required	1.0	(3.6)	0.0		0.0		0.0		0.0	
Criteria not decided	3.0	(10.7)	3.0	(10.7)	2.0	(13.3)	3.0	(10.7)	3.0	(15.0)
Severity and phenotype										
IgE-mediated or type II –driven or eosinophilic	1.0	(3.6)	1.0	(3.6)	1.0	(6.7)	1.0	(3.6)	2.0	(10.0)
Bronchial asthma refractory or uncontrolled allergic	0.0		0.0		0.0		0.0		0.0	
Moderate to severe (persistent, eosinophilic, or OCS-dependent)	2.0	(7.1)	0.0		0.0		0.0		3.0	(15.0)
Severe (persistent, eosinophilic, with type II inflammation or allergic)	16.0	(57.1)	16.0	(57.1)	11.0	(73.3)	16.0	(57.1)	10.0	(50.0)
Severe (uncontrolled, uncontrolled plus eosinophilic, uncontrolled allergic, refractory, refractory plus eosinophilic)	5.0	(17.9)	8.0	(28.6)	2.0	(13.3)	8.0	(28.6)	3.0	(15.0)
Not required	0.0		0.0		0.0		0.0		0.0	
Criteria not decided	4.0	(14.3)	3.0	(10.7)	1.0	(6.7)	3.0	(10.7)	2.0	(10.0)
Serum IgE (IU/mL)										
≥30, ≥35, or elevated	18.0	(64.3)								
≥70, ≥75, or ≥76	7.0	(25.0)								
≥150	0.0									
≥400	0.0									
Not required	1.0	(3.6)								
Criteria not decided	2.0	(7.1)								
Allergic asthma										
Skin prick test or serum specific IgE	27.0	(96.4)								
Skin prick test and serum specific IgE	0.0									
Not required	0.0									
Criteria not decided	1.0	(3.6)								
Blood eosinophil count (cells/μL)										
≥150 or raised			2.0	(7.1)	0.0		0.0		11.0	(55.0)
≥150 in past 12 mo			0.0		0.0		1.0	(3.6)	1.0	(5.0)
≥150 in past 1 mo			0.0		0.0		0.0		0.0	
≥300 or ≥150 on long-term OCS			4.0	(14.3)	1.0	(6.7)	9.0	(32.1)	3.0	(15.0)
≥300 in past 12 mo or historical			18.0	(64.3)	2.0	(13.3)	12.0	(42.9)	3.0	(15.0)
≥300 twice in past 12 mo			0.0		0.0		0.0		0.0	
≥400 or in past 12 mo			0.0		10.0	(66.7)	1.0	(3.6)	0.0	
≥500			1.0	(3.6)	0.0		1.0	(3.6)	0.0	
Not required			1.0	(3.6)	1.0	(6.7)	1.0	(3.6)	0.0	
Criteria not decided			2.0	(7.1)	1.0	(6.7)	3.0	(10.7)	2.0	(10.0)
FeNO (parts per billion)										

(continued)

TABLE III. *(Continued)*

Patient/asthma characteristics	Anti-IgE, n (%)		Anti–IL-5/5R, n (%)						Anti–IL-4R, n (%)	
	Omalizumab (n = 28)		Mepolizumab (n = 28)		Reslizumab (n = 15)		Benralizumab (n = 28)		Dupilumab (n = 20)	
≥20 or ≥25 or raised	2.0	(7.1)	2.0	(7.1)	1.0	(6.7)	2.0	(7.1)	10.0	(50.0)
≥50	0.0		0.0		0.0		0.0		0.0	
Not required	2.0	(7.1)	2.0	(7.1)	2.0	(13.3)	3.0	(10.7)	7.0	(35.0)
Criteria not decided	24.0	(85.7)	24.0	(85.7)	12.0	(80.0)	23.0	(82.1)	3.0	(15.0)
Adherence										
Required			16.0	(57.1)	7.0	(46.7)	13.0	(46.4)	8.0	(40.0)
Not required			1.0	(3.6)	4.0	(26.7)	2.0	(7.1)	1.0	(5.0)
Criteria not decided			11.0	(39.3)	4.0	(26.7)	13.0	(46.4)	11.0	(55.0)
Asthma control										
Required	23.0	(82.1)	19.0	(67.9)	10.0	(66.7)	18.0	(64.3)	12.0	(60.0)
Not required	1.0	(3.6)	0.0		3.0	(20.0)	1.0	(3.6)	1.0	(5.0)
Criteria not decided	4.0	(14.3)	9.0	(32.1)	2.0	(13.3)	9.0	(32.1)	7.0	(35.0)
Lung function										
FEV_1 ≤80%	13.0	(46.4)	3.0	(10.7)	0.0		2.0	(7.1)	0.0	
≥12% reversibility ± >200 mL FEV_1	1.0	(3.6)	2.0	(7.1)	1.0	(6.7)	1.0	(3.6)	0.0	
FEV_1 ≤80% and evidence of reversibility	6.0	(21.4)	3.0	(10.7)	1.0	(6.7)	3.0	(10.7)	3.0	(15.0)
FEV_1 ≤80% and 12% reversibility and airway hyperresponsiveness	1.0	(3.6)	1.0	(3.6)	0.0		1.0	(3.6)	0.0	
FEV_1 ≤60%	1.0	(3.6)	1.0	(3.6)	0.0		1.0	(3.6)	0.0	
Not required	2.0	(7.1)	1.0	(3.6)	10.0	(66.7)	2.0	(7.1)	1.0	(5.0)
Criteria not decided	4.0	(14.3)	17.0	(60.7)	3.0	(20.0)	18.0	(64.3)	16.0	(80.0)
Background therapy										
ICS	0.0		0.0		0.0		0.0		0.0	
High-dose ICS (± LABA or long-term OCS or xanthine or LTRA)	2.0	(7.1)	1.0	(3.6)	1.0	(6.7)	0.0		2.0	(10.0)
Medium-dose ICS/LABA (± LTRA)	0.0		2.0	(7.1)	3.0	(20.0)	2.0	(7.1)	2.0	(10.0)
High-dose ICS/LABA (± LAMA or LTRA) or high-dose ICS/LABA (± long-term OCS)	21.0	(75.0)	17.0	(60.7)	8.0	(53.3)	20.0	(71.4)	9.0	(45.0)
High-dose ICS/LABA plus one or more other controller (not OCS)	4.0	(14.3)	3.0	(10.7)	2.0	(13.3)	2.0	(7.1)	3.0	(15.0)
High-dose ICS/LABA plus long-term OCS	0.0		2.0	(7.1)	0.0		2.0	(7.1)	1.0	(5.0)
Not required	0.0		0.0		0.0		0.0		0.0	
Criteria not decided	1.0	(3.6)	3.0	(10.7)	1.0	(6.7)	2.0	(7.1)	3.0	(15.0)
Long-term OCS										
Long-term OCS use	6.0	(21.4)	5.0	(17.9)	0.0		3.0	(10.7)	3.0	(15.0)
Not required	4.0	(14.3)	12.0	(42.9)	9.0	(60.0)	14.0	(50.0)	9.0	(45.0)
Criteria not decided	18.0	(64.3)	11.0	(39.3)	6.0	(40.0)	11.0	(39.3)	8.0	(40.0)
Exacerbations										
One or more	0.0		0.0		0.0		0.0		0.0	
One or more requiring hospitalization, emergency room visit, or rescue OCS	5.0	(17.9)	4.0	(14.3)	2.0	(13.3)	3.0	(10.7)	3.0	(15.0)
Two or more	6.0	(21.4)	5.0	(17.9)	4.0	(26.7)	4.0	(14.3)	4.0	(20.0)

(continued)

TABLE III. *(Continued)*

Patient/asthma characteristics	Anti-IgE, n (%)		Anti–IL-5/5R, n (%)						Anti–IL-4R, n (%)	
	Omalizumab (n = 28)		Mepolizumab (n = 28)		Reslizumab (n = 15)		Benralizumab (n = 28)		Dupilumab (n = 20)	
Two or more requiring hospitalization, emergency room visit, or rescue OCS	9.0	(32.1)	10.0	(35.7)	3.0	(20.0)	10.0	(35.7)	4.0	(20.0)
Three or more	0.0		2.0	(7.1)	2.0	(13.3)	3.0	(10.7)	1.0	(5.0)
Four or more	1.0	(3.6)	1.0	(3.6)	1.0	(6.7)	1.0	(3.6)	0.0	
Not required	2.0	(7.1)	1.0	(3.6)	2.0	(13.3)	2.0	(7.1)	2.0	(10.0)
Criteria not decided	5.0	(17.9)	5.0	(17.9)	1.0	(6.7)	5.0	(17.9)	6.0	(30.0)

ICS, inhaled corticosteroids; *LABA*, long-acting β-agonist; *LTRA*, leukotriene receptor antagonist; *OCS*, oral corticosteroids.

four or more exacerbations, whereas in Estonia and The Netherlands, no exacerbations are required. In countries such as Australia and Spain, health care use related to exacerbations is more specified (eg, two or more exacerbations requiring documented use of OCS, or one or more severe exacerbation needing hospitalization).

Biologic Accessibility Score

Figures 1 to 5 present the total BACS for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab for countries that had the specific biologic available as of April 2021. Detailed data per country are provided in Figures E2 to E6.

Omalizumab. Overall, omalizumab is neither easy nor difficult to access in 32% of ISAR countries surveyed (n = 9 of 28), moderately difficult to access in 61% (n = 17 of 28) of ISAR countries, and difficult to access (ie, BACS of 21-40) in Australia (Figure 1). With the exception of Denmark and Finland, all countries surveyed reported a greater hurdle to omalizumab prescription (ie, lower BACS) than the EMA BACS of 69. In absolute terms, the BACS for omalizumab ranged from 39 in Australia to 71 in Denmark (mean, 57).

Mepolizumab. Mepolizumab is difficult to access in Taiwan, Australia, Bulgaria, and The Netherlands (Figure 2). It is neither easy nor difficult to access mepolizumab in 29% of ISAR countries (n = 8 of 28) and moderately difficult to access it in 50% of ISAR countries. Apart from Brazil and Singapore, all countries surveyed reported a greater hurdle to mepolizumab prescription (ie, lower BACS) compared with the EMA BACS of 87. Overall, the BACS for mepolizumab ranged from 26 in Bulgaria to 90 in Brazil (mean, 55).

Reslizumab. Reslizumab is not easily accessible in any ISAR country (Figure 3). It is either difficult or moderately difficult to access in 67% of countries surveyed that had access (n = 10 of 15) and neither easy nor difficult to access in the United States, Germany, South Korea, and Finland. All countries reported stricter prescribing criteria for reslizumab (ie, lower BACS) compared with the EMA derived score (BACS of 76). The BACS for reslizumab ranged from 36 in The Netherlands to 69 in South Korea (mean, 51).

Benralizumab. Benralizumab is not easily accessible in any ISAR country (Figure 4). It is difficult to access in seven of the ISAR countries (25%). Overall, it was either neither easy nor difficult or moderately difficult to access in 75% of ISAR countries (n = 21 of 28). With the exception of Mexico, Brazil, South Korea, and Singapore, all other countries surveyed reported a greater hurdle to benralizumab prescription (ie, lower BACS) compared with the EMA-derived score (BACS of 76). The BACS for benralizumab ranged from 30 in Australia to 80 in Mexico (mean, 54).

Dupilumab. Dupilumab is difficult to access in Colombia and Kuwait (Figure 5). Overall, it is neither easy nor difficult (n = 9) or it is moderately difficult (n = 7) to access in 80% of countries that had access (n = 16 of 20), with a BACS lower than the EMA-derived prescription score (BACS of 65) in 60% of ISAR countries. In absolute values, the BACS for dupilumab ranged from 33 in Colombia to 88 in Mexico (mean, 59).

Correlation of BACS with GDP. For all biologics, no significant correlations were found between BACS and GDP (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

Main findings

This study demonstrated wide variations in severe asthma biologic accessibility across the globe. In addition, it assessed, quantified, and compared ease of access to biologics using the newly developed BACS in 28 countries collaborating with ISAR. Using the BACS, we found that for omalizumab, mepolizumab, benralizumab, and dupilumab, only two, one, four, and seven of the countries, respectively, had access that was equal to or easier than that which be expected from the EMA licensing criteria. Moreover, for reslizumab, we found that all ISAR countries had more stringent access criteria in place than the EMA.

Interpretation

Although all ISAR countries assessed in this study had access to the same trial data and follow similar licensing pathways, we observed significant differences in clinical prescription criteria. These differences subsequently resulted in biologic accessibility variation across countries. Some variation can be attributed to country-specific circumstances, but it might also reflect a lack of consensus regarding which patients benefit most from which biologic. To our knowledge, no previous studies systematically compared biologic access across so many countries. Earlier studies mostly assessed the proportions of patients who were eligible for one or more severe asthma biologics in single countries such as Canada and Brazil.[15,16] Others looked only at reimbursement and costs of severe asthma biologics over time in Bulgaria.[17] All of these single country studies are relevant to

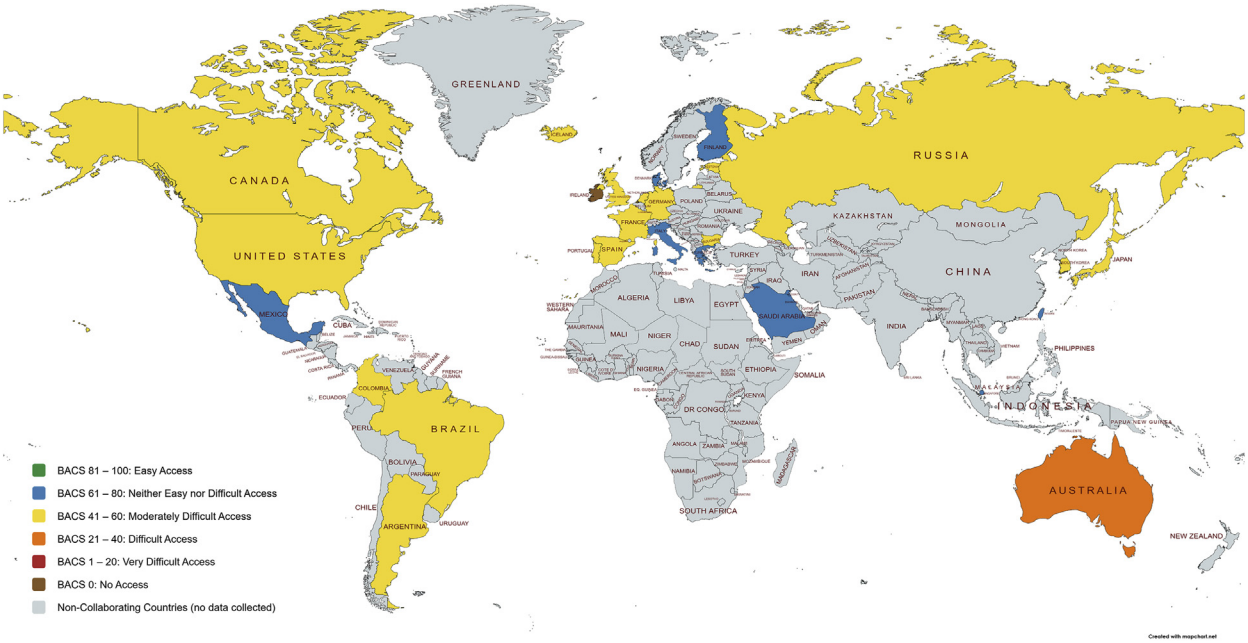

FIGURE 1. Omalizumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.

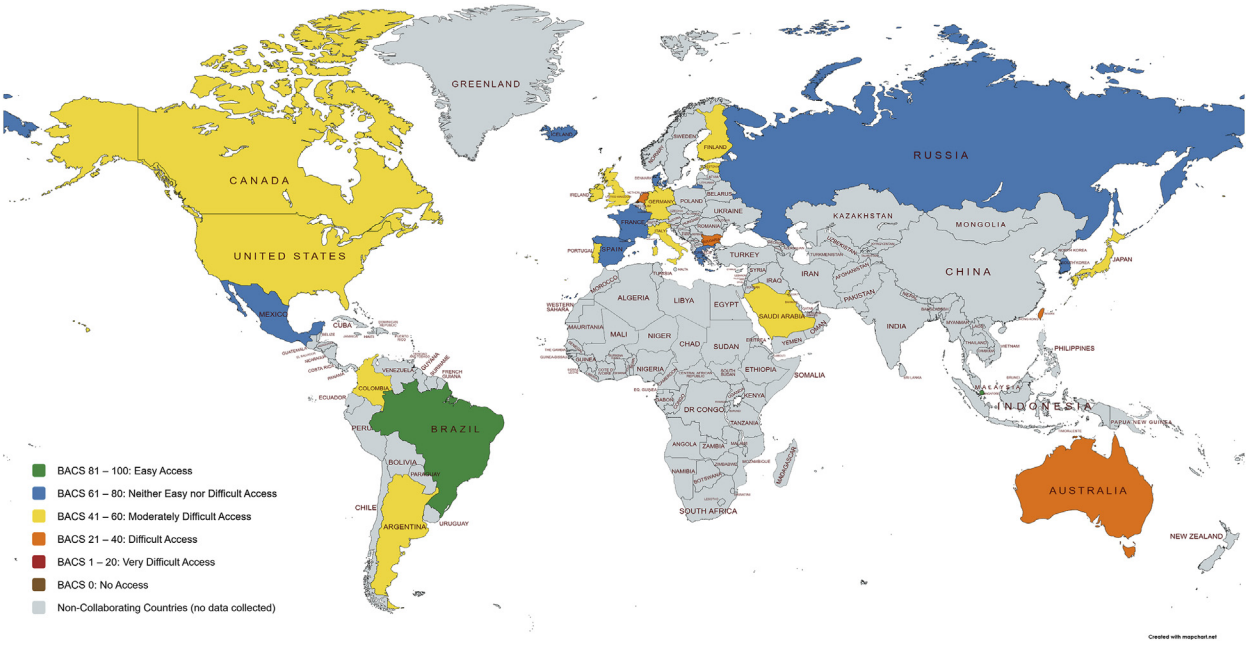

FIGURE 2. Mepolizumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.

inform within-country policy, but they limit direct cross-country comparisons regarding access or comparisons with our study. The Identification and Description of sEvere Asthma patients in a cross-sectionaL study assessed eligibility for three biologics (omalizumab, reslizumab, and mepolizumab) across six countries (Australia, Canada, France, Germany, the United Kingdom, and the United States).[18] That study demonstrated that the percentage of patients eligible for omalizumab depended on the country access criteria (eg, European criteria of 30% and US, Canadian, or Australian criteria of 40% for patients in the cohort to be eligible). A similar variation was found for reslizumab and mepolizumab, but no in-depth comparison of prescription criteria and their relationship to access was provided.

Regarding ease of access in our study, there were variations among biologics (the mean BACS ranged from 57 for omalizumab to 55 for mepolizumab, 51 for reslizumab, 54 for benralizumab, and 59 for dupilumab) and among countries (the BACS ranged from 26 in Bulgaria to 90 in Brazil for mepolizumab). Numerous countries had no access (corresponding to a BACS of 0 [Figures 1-5]). Multiple factors may have a role in the eligibility

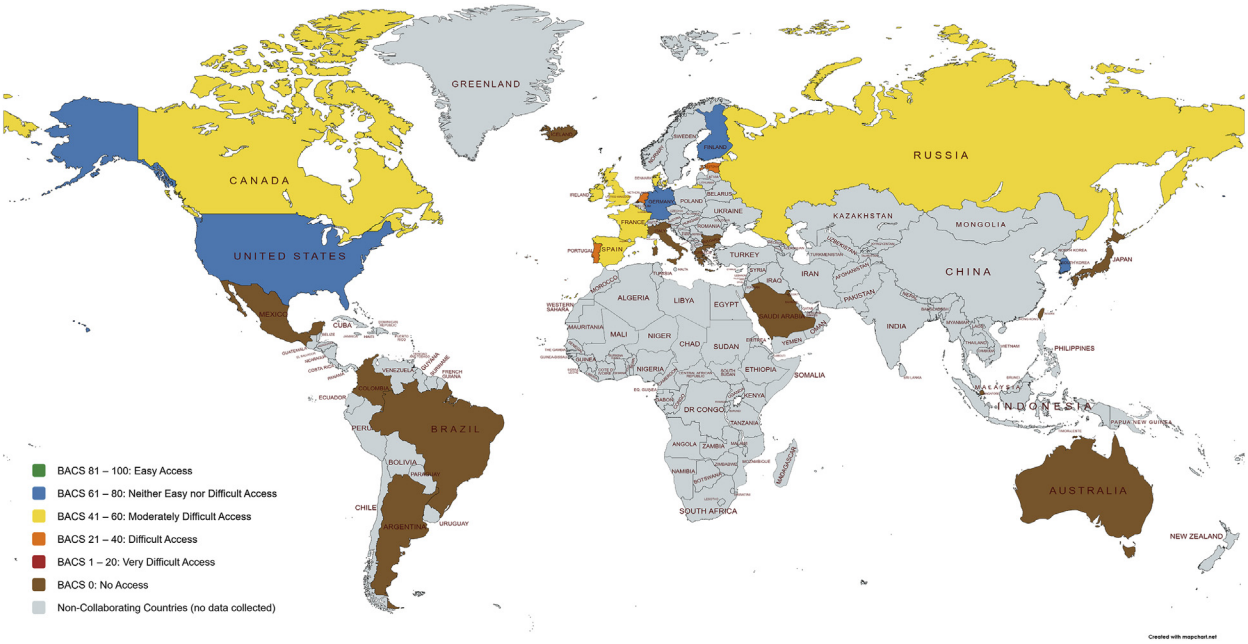

FIGURE 3. Reslizumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.

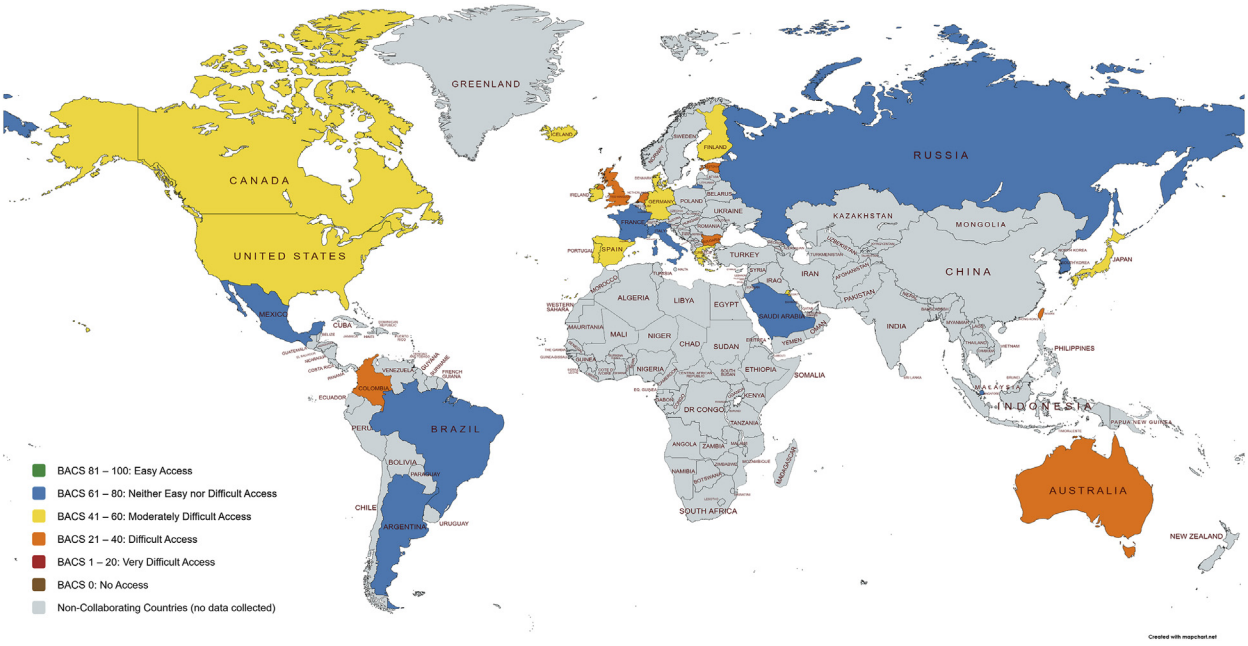

FIGURE 4. Benralizumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.

for reimbursement, including (1) clinical drug characteristics (eg, efficacy, safety), (2) clinical guideline recommendations, (3) economic implications of the drugs (eg, cost, cost-effectiveness, budget impact), and (4) regulatory systems (eg, financing of health systems and HTA guidelines, and time between regulatory approval and reimbursement). Regulatory procedures usually are not aligned with reimbursement procedures. Licensing is often a central procedure (eg, by EMA or the FDA), but reimbursement is a national, state, or even insurer or health plan–specific procedure. This means that patients with similar clinical criteria may have different accessibility to biologics (ie, in which prescription criteria are based on provincial or state reimbursement policies, such as in Canada, the United States, or France) owing to different reimbursement criteria.

Looking more closely at the criteria underlying the BACS, we observed a large variation in clinical criteria applied. The main drivers of differences were biomarkers (BEC, FeNO, and IgE thresholds), exacerbation requirements (ranging from zero

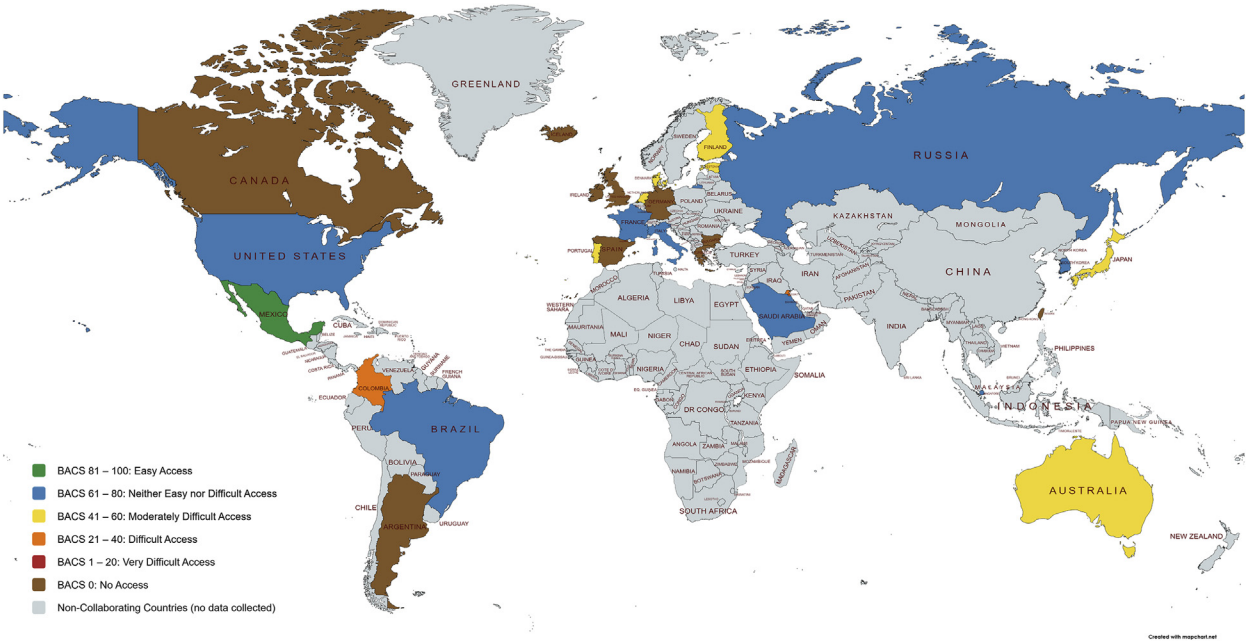

FIGURE 5. Dupilumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.

to four), the need for long-term OCS, severity, asthma control, and adherence to background therapy. Interestingly, some prescription criteria included OCS use, although registration trials did not show a steroid-sparing effect.[19] These different clinical factors may be partly driven by differences in clinical trial inclusion and exclusion criteria as well as national severe asthma guidelines and restrictive criteria initiated at a local level. Notably, the process for evidence ranking in these guidelines can be different, but the frequency of updates may also differ so that some guidelines may consider some more recent randomized controlled trials and real-world evidence when making their recommendations compared with others. Finally, creating guidelines is often a matter of consensus in which experience, expertise, and opinions of individual committee members may be different across countries, especially in the absence of head-to-head comparisons among these biologics. Regarding the overall wealth of a country as an explanation for BACS variation, we first assessed whether GDP per capita might be a factor; however, both a visual inspection and formal correlation testing of the data showed no significant trend (Table E2). In fact, some countries with a higher GDP, such as the United Kingdom, have stricter HTA guidelines in place, making biologics more difficult to access than in countries with a lower GDP, such as Colombia. Therefore, we hypothesize that for payer system factors such as HTA criteria, whether the state (eg, in the United Kingdom) or private insurance of a regional system (eg, in the United States or Canada) pays for the biologic has a role. Another observation supporting the importance of wider system factors is that the oldest biologic (ie, omalizumab) (Table II) is also the easiest to access. Because this is also the biologic available in the highest number of countries, the relatively long time that reimbursement has been available may partly explain this higher BACS.

Generally, we hypothesize that many of the additional access criteria are employed to enhance cost-effectiveness and lower the budget impact of biologics. Indeed, most of the biologics have not been shown to be cost-effective in the full trial population but are cost-effective only when carefully targeted.[20] However, we acknowledge that many of the cost-effectiveness analyses may be unable to capture the full benefit of biologics, including avoidance of the long-term complications of OCS and work productivity-related outcomes.[21] Also, most long-term cost-effectiveness analyses may not consider the lowering of biologics prices in the future (eg, driven by the development of biosimilars). Still, these additional criteria may significantly restrict the real-world use of biologics within some countries, with health disparities partially depending on income and access to specialists.[22]

Another comment should be made regarding the incorporation of adherence to background therapies as a prescription criterion. In several severe asthma national guidelines, nonadherence to ICS should be ruled out before a severe asthma diagnosis is made. Recent studies showed that low adherence rates to ICS/long-acting β-agonists were observed before the start of additional severe asthma treatments.[23,24] In addition, the loss of adherence to ICS during the use of mepolizumab is associated with a suboptimal response to treatment.[25] As such, to ensure biologics are used in the most appropriate patients and in the most cost-effective manner, objective and effective methods (eg, the use of smart inhalers or FeNO suppression) to identify and manage poor adherence to inhaled therapies as well as ensure good inhaler technique and the appropriate treatment of comorbidities should be required before considering a biologic.[26-29]

Strengths and limitations

A major strength of this study is that we included 28 countries spread over five continents, thus providing the world's largest systematic overview of biologic prescription criteria. Structured reviews of health authority databases and guidelines, combined with the use of a survey with local prescribers of biologics to verify real-world practice, ensured data quality and

representativeness. This included the use of a quantitative consensus-based BACS based on a transparent set of clinical access criteria that can be used for future benchmarking of ISAR countries and may also be expanded to other countries.

Some limitations should be noted. First, this survey provides a snapshot of the current status of reimbursement and access criteria for the biologics because they may vary over time. The BACS was calculated only for a country with the specific biologic available by April 2021 using criteria reported by severe asthma specialists (ie, not reimbursement agencies). To overcome this potential limitation, the BACS will be periodically updated and will be available at the ISAR website[10] to ensure access to up-to-date information and future benchmarking. Second, although we aimed for clinically relevant categories within the scoring of each access criterion, some level of arbitrariness is involved that may require further validation, wider consensus in scoring of the BACS, and associations of the BACS with better asthma care outcomes to be established. Third, regarding generalizability, although in most countries access criteria are uniformly applied (eg, the United Kingdom), some countries had variability within the country, depending on (local) health plans (eg, the United States, Canada), which warrants caution in interpretation. Although detailed payer plans which focused on general prescription criteria, they may be addressed in BACS updates. Besides prescription criteria, one method used to enhance cost-effectiveness and affordability is the use of stopping criteria for biologics. This means that after a certain number of weeks, effectiveness should be established by a specialist physician before the biologic should be continued. We acknowledge the existence of differences in biologic stopping criteria, but this was beyond the focus of the current study.

Recommendations for future research, policy, and research

In its current form, the BACS allows clinicians and regulators to assess ease of access to biologics in their own country, and by its provision of insights into intercountry variation, it may serve to push harmonization of access criteria and help support international biologic access equality. Importantly, to validate the BACS and expand its future use, the association of the BACS with national asthma outcomes (eg, OCS use, hospital admissions) should be addressed in future studies. Ultimately, the BACS may then become useful as an educational tool to encourage timely and appropriate biologic prescription to improve outcomes and reduce costs. Structured and comparable real-world data as collected in ISAR could contribute to these outcome studies. Countries not covered in the ISAR survey are also encouraged to further external validation of the BACS.

Conclusions

This study showed a high degree of variability in the criteria used to prescribe severe asthma biologics globally. These differences resulted in profound differences in ease of access to biologics across countries. To ensure the availability of personalized treatment options for patients with severe asthma independently of the country of residence, standardization of prescribing and access criteria is recommended.

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ONLINE REPOSITORY

TABLE E1. International Severe Asthma Registry countries and data sources used to obtain official prescription criteria per biologic and country

International Severe Asthma Registry country	Country-specific guideline/licensing body	Guidance available from country-specific body?	Licensing body (only if guideline unavailable)
Argentina	National Administration of Drugs, Food, and Medical Devices	No	—
Australia	Pharmaceutical Benefits Scheme	Yes[E1]	
Brazil	Brazilian Health Regulatory Agency	Yes[E2]	
Canada	Canadian Agency for Drugs and Technology in Health	Yes[E3]	
Japan	Pharmaceuticals and Medical Devices Agency	Yes[E4]	
Mexico	Mexican Secretariat of Health	Yes[E5]	
Singapore	MOH Drug Advisory Committee	No	
United Kingdom	NICE	Yes[E6]	
Colombia	Colombia National Food and Drug Surveillance Institute	No	Manufacturer
Korea	Ministry of Food and Drug Safety	No	
Kuwait	Kuwait Drug and Food Control Administration	No	US Food and Drug Administration[E9]
Saudi Arabia	Saudi Food and Drug Authority	No	
Taiwan	Food and Drug Administration (Taiwan)	No	
United States	Insurer-dependent	No	
Bulgaria	Bulgarian Drug Agency	No	European Medicines Agency[E10]
Denmark	Danish Medicines Agency	No	
Estonia	State Agency of Medicines	No	
Finland	Finnish Medicines Agency Fimea	No	
France	National Agency for the Safety of Medicines and Health Products	No	
Germany	Germany's Federal Institute for Drugs and Medical Devices	No	
Greece	National Organisation for Medicines	No	
Iceland	Lyfjastofnun	No	
Ireland	Monthly Index of Medical Specialities Ireland	No	
Italy	Italian Medicines Agency	No	
Portugal	National Authority of Medicines and Health Products	Yes[E7]	
Russia	Russian Federal Services for Surveillance in Health Care	No	
Spain	Spanish Agency of Medicines and Medical Products	No	
The Netherlands	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose	Yes[E8]	

Criteria	Anti-IgE	Anti-IL5		Anti-IL5R	Anti-IL4Rα
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Availability of biologic	☐ Licenced ☐ Reimbursed full ☐ Reimbursed partial ☐ Compassionate programme ☐ Not yet available (no need to complete rest of column)	☐ Licenced ☐ Reimbursed full ☐ Reimbursed partial ☐ Compassionate programme ☐ Not yet available (no need to complete rest of column)	☐ Licenced ☐ Reimbursed full ☐ Reimbursed partial ☐ Compassionate programme ☐ Not yet available (no need to complete rest of column)	☐ Licenced ☐ Reimbursed full ☐ Reimbursed partial ☐ Compassionate programme ☐ Not yet available (no need to complete rest of column)	☐ Licenced ☐ Reimbursed full ☐ Reimbursed partial ☐ Compassionate programme ☐ Not yet available (no need to complete rest of column)
	other, specify ____	other, specify ____	other, specify ____	other, specify ____	other, specify ____
Total number of asthma exacerbations in the last 12 months	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A
	other, specify ____				
Number of asthma exacerbations *requiring oral corticosteroids* in the last 12 months	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A
	other, specify ____	other, specify ____	other, specify ____	other, specify ____	other, specify ____
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Number of asthma exacerbations *requiring A&E attendance or hospital admission* in the last 12 months	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A	☐ ≥1, OR ☐ ≥2 ☐ ≥3 ☐ ≥4 ☐ N/A
	other, specify ____	other, specify ____	other, specify ____	other, specify ____	other, specify ____
Background therapy	☐ Medium dose ICS + LABA ☐ High dose ICS + LABA ☐ Add-on LAMA ☐ Add-on LTRA ☐ Add-on maintenance OCS ☐ Continuous OCS ☐ Other biologic therapy ☐ N/A	☐ Medium dose ICS + LABA ☐ High dose ICS + LABA ☐ Add-on LAMA ☐ Add-on LTRA ☐ Add-on maintenance OCS ☐ Continuous OCS ☐ Other biologic therapy ☐ N/A	☐ Medium dose ICS + LABA ☐ High dose ICS + LABA ☐ Add-on LAMA ☐ Add-on LTRA ☐ Add-on maintenance OCS ☐ Continuous OCS ☐ Other biologic therapy ☐ N/A	☐ Medium dose ICS + LABA ☐ High dose ICS + LABA ☐ Add-on LAMA ☐ Add-on LTRA ☐ Add-on maintenance OCS ☐ Continuous OCS ☐ Other biologic therapy ☐ N/A	☐ Medium dose ICS + LABA ☐ High dose ICS + LABA ☐ Add-on LAMA ☐ Add-on LTRA ☐ Add-on maintenance OCS ☐ Continuous OCS ☐ Other biologic therapy ☐ N/A
	other, specify ____	other, specify ____	other, specify ____	other, specify ____	other, specify ____
Adherence to previous therapy	☐ Poor; on the basis of medication records ☐ Poor; clinical impression ☐ N/A	☐ Poor; on the basis of medication records ☑ Poor; clinical impression ☐ N/A	☐ Poor; on the basis of medication records ☐ Poor; clinical impression ☐ N/A	☐ Poor; on the basis of medication records ☐ Poor; clinical impression ☐ N/A	☐ Poor; on the basis of medication records ☐ Poor; clinical impression ☐ N/A
	other, specify ____	other, specify ____	other, specify ____	other, specify ____	other, specify ____
Biomarker profile in the last 12 months					
Eosinophil count	N/A	☐ ≥150 cells/μL, OR ☐ ≥300 cells/μL, OR ☐ ≥400 cells/μL ☐ N/A	☐ ≥150 cells/μL, OR ☐ ≥300 cells/μL, OR ☐ ≥400 cells/μL ☐ N/A	☐ ≥150 cells/μL, OR ☐ ≥300 cells/μL, OR ☐ ≥400 cells/μL ☐ N/A	☐ ≥150 cells/μL, OR ☐ ≥300 cells/μL, OR ☐ ≥400 cells/μL ☐ N/A
	other, specify ____	other, specify ____	other, specify ____	other, specify ____	other, specify ____
Serum IgE	☐ ≥150 IU/mL, OR ☐ ≥400 IU/mL, OR ☐ N/A	N/A	N/A	☐ ≥150 IU/mL, OR ☐ ≥400 IU/mL, OR ☐ N/A	☐ ≥150 IU/mL, OR ☐ ≥400 IU/mL, OR ☐ N/A
	other, specify ____>/=30 IU/ml	other, specify ____	other, specify ____	other, specify ____	other, specify ____
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
FeNO	☐ ≥25 ppb, OR ☐ ≥50 ppb, OR ☐ N/A	☐ ≥25 ppb, OR ☐ ≥50 ppb, OR ☐ N/A	☐ ≥25 ppb, OR ☐ ≥50 ppb, OR ☐ N/A	☐ ≥25 ppb, OR ☐ ≥50 ppb, OR ☐ N/A	☐ ≥25 ppb, OR ☐ ≥50 ppb, OR ☐ N/A
	other, specify ____	other, specify ____	other, specify ____	other, specify ____	other, specify ____
Allergic asthma (RAST/SPT)	☐ RAST Positive ☐ SPT Positive ☐ N/A	☐ RAST Positive ☐ SPT Positive ☐ N/A	☐ RAST Positive ☐ SPT Positive ☐ N/A	☐ RAST Positive ☐ SPT Positive ☐ N/A	☐ RAST Positive ☐ SPT Positive ☐ N/A
Asthma control (ACQ/ACT/GINA asthma control score)	☐ Partially uncontrolled ☐ N/A	☐ Partially uncontrolled ☐ N/A	☐ Partially uncontrolled ☐ N/A	☐ Partially uncontrolled ☐ N/A	☐ Partially uncontrolled ☐ N/A
Lung function	☐ ≥12% airway reversibility to SABA ☐ ≤80% FEV1 ☐ N/A	☐ ≥12% airway reversibility to SABA ☐ ≤80% FEV1 ☐ N/A	☐ ≥12% airway reversibility to SABA ☐ ≤80% FEV1 ☐ N/A	☐ ≥12% airway reversibility to SABA ☐ ≤80% FEV1 ☐ N/A	☐ ≥12% airway reversibility to SABA ☐ ≤80% FEV1 ☐ N/A
	other, specify __airway hyperresponsiveness > 20% decline in FEV1 during a direct bronchial provocation test or > 15% decline during an indirect bronchial provocation test, or, peak expiratory flow (PEF) variability > 15% between the 2 highest and 2 lowest peak expiratory flow rates during 14 days	other, specify ____airway hyperresponsiveness > 20% decline in FEV1 during a direct bronchial provocation test or > 15% decline during an indirect bronchial provocation test, or, peak expiratory flow (PEF) variability > 15% between the 2 highest and 2 lowest peak expiratory flow rates during 14 days	other, specify ____	other, specify ____airway hyperresponsiveness > 20% decline in FEV1 during a direct bronchial provocation test or > 15% decline during an indirect bronchial provocation test, or, peak expiratory flow (PEF) variability > 15% between the 2 highest and 2 lowest peak expiratory flow rates during 14 days	other, specify ____
Any other criteria, please specify	Total dose OCS in 12 months >	Total dose OCS in 12 months >/= 500 mg		Total dose OCS in 12 months >/= 500 mg	
	☐ N/A	☐ N/A	☐ N/A	☐ N/A	☐ N/A

FIGURE E1. Survey disseminated to International Severe Asthma Registry Steering Committee members. *A&E*, accident and emergency; *ACQ*, Asthma Control Questionnaire; *ACT*, Asthma Control Test; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroids; *LABA*, long-acting β-agonist; *LAMA*, long-acting muscarinic antagonist; *LTRA*, leukotriene receptor antagonist; *N/A*, not available; *OCS*, oral corticosteroids; *ppb*, parts per billion; *RAST*, radioallergosorbent test; *SABA*, short-acting β_2-agonist; SPT, skin prick test.

Country*	Data Source	Age	Severity/ Phenotype	Serum IgE	FeNO	Allergic Asthma	Background Therapy	OCS	Exacerbations	Asthma Control	Lung Function	BACS
Denmark	ISC only	8	2	8	10†	5	4	10	4	10	10	71
Finland	ISC only	8	2	8	10†	5	4	10†	4	10†	8	69
EMA	**GL**	**8**	**2**	**8**	**10†**	**5**	**4**	**10†**	**4**	**10†**	**8**	**69**
Mexico	GL & ISC	8	0	8	10†	5	6	10†	10†	0	10†	67
Singapore	ISC only	4	2	10†	10†	5	4	10†	4	10†	8	67
Kuwait	ISC only	10†	10†	8	10†	5	4	10†	3	0	4	64
Saudi Arabia	ISC only	10†	10†	8	10†	5	4	10†	3	0	4	64
Greece	ISC only	8	2	4	10†	5	4	10†	3	10†	8	64
Italy	ISC only	8	2	4	10†	5	4	10†	10†	0	8	61
Taiwan	ISC only	4	2	8	10†	5	6	10†	10†	0	6	61
Brazil	GL & ISC	10	2	8	10†	5	4	10	3	0	8	60
Canada	CADTH	4	4	10	10†	5	2	10†	10†	0	4	59
France	ISC only	8	2	8	10†	5	4	10†	4	0	8	59
Japan	ISC only	8	0	8	10†	5	2	10†	6	0	10	59
Spain	ISC only	8	2	8	10†	5	4	10†	3	0	8	58
Russia	ISC only	8	2	8	10	5	4	10†	6	0	4	57
Portugal	GL & ISC	8	0	8	10†	5	4	10†	4	0	8	57
Colombia	ISC only	8	0	8	10†	5	4	10	6	0	4	55
Estonia	ISC only	8	8	4	10†	5	2	0	10	0	8	55
Germany	ISC only	8	2	4	10†	5	4	10†	4	0	8	55
UK	GL & ISC	8	2	8	10†	5	4	10	0	0	8	55
South Korea	ISC only	8	2	4	10†	5	2	10†	3	0	8	52
USA	ISC & FDA	8	4	8	10†	5	4	0	3	0	10†	52
Iceland	ISC only	8	2	4	5	5	4	10†	3	0	8	49
Argentina	ISC only	4	10†	8	10†	5	4	0	3	0	4	48
Netherlands	NVALT	8	2	4	5	5	4	0	10	0	10†	48
Bulgaria	ISC only	8	2	8	10†	5	4	0	6	0	0	43
Australia	GL & ISC	4	0	8	10	5	4	0	6	0	2	39

*Ireland: Not defined in national criteria; †Criteria undecided

FIGURE E2. Biologic Accessibility Score (BACS) specification for omalizumab by country. *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

Country	Data Source	Age	Severity/ Phenotype	BEC	FeNO	Adherence	Background Therapy	OCS	Exacerbations	Asthma Control	Lung Function	BACS
Brazil	ISC only	8	2	10†	10†	10†	10†	10†	10†	10†	10†	90
EMA	**GL**	**8**	**2**	**7**	**10†**	**10†**	**10†**	**10†**	**10†**	**10†**	**10†**	**87**
Singapore	ISC only	4	2	10†	10†	10†	10†	10†	10†	10†	10†	86
Russia	ISC only	8	2	8	10	0	5	10†	10†	10†	10†	73
France	ISC only	8	2	4	10†	10†	4	10	4	10†	10†	72
South Korea	ISC only	10†	2	4	10†	10†	5	10†	10†	0	10†	71
Mexico	GL & ISC	4	0	4	10†	10†	10†	10†	10†	0	10†	68
Iceland	ISC only	8	2	4	5	10†	4	10†	3	10†	10†	66
Spain	ISC	8	8	0	10†	10	6	10†	3	0	8	63
Denmark	ISC only	8	2	4	10†	0	4	10	4	10†	10†	62
Greece	ISC only	8	2	4	10†	0	4	10†	3	10†	10†	61
Italy	ISC only	8	2	4	10†	10†	4	10	4	0	8	60
Japan	ISC only	8	0	4	10†	10†	2	10†	6	0	10†	60
Germany	ISC only	8	2	4	10†	0	4	10†	10	0	10†	58
Kuwait	ISC only	10†	10†	5	10†	0	4	10	3	0	4	56
USA	ISC & FDA	8	2	5	10†	0	4	10	3	0	10†	52
Ireland	ISC only	0	0	4	10†	0	4	10	3	10†	10	51
Finland	ISC only	4	2	10	10†	10†	0	0	4	0	10†	50
Argentina	ISC only	0	10†	4	10†	10†	4	0	3	0	8	49
Estonia	ISC only	8	2	5	10†	0	2	10	2	0	10†	49
UK	GL & ISC	0	0	4	10†	0	4	10	0	10†	10†	48
Canada	CADTH	0	2	4	10†	10†	2	10	3	0	6	47
Portugal	GL & ISC	4	0	4	10†	0	4	10†	4	0	10†	46
Saudi Arabia	ISC only	10†	10†	4	10†	0	4	0	3	0	4	45
Colombia	ISC only	0	0	8	10†	0	4	10	6	0	4	42
Netherlands	NVALT	0	2	5	5	0	4	10	3	0	10†	39
Taiwan	ISC only	0	0	4	10†	0	0	10	2	0	6	32
Australia	GL & ISC	4	0	4	10	0	4	0	6	0	2	30
Bulgaria	ISC only	0	2	4	10†	0	4	0	6	0	0	26

†Criteria undecided

FIGURE E3. Biologic Accessibility Score (BACS) specification for mepolizumab by country. *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

Country	Data Source	Age	Phenotype	BEC	FeNO	Adherence	Background Therapy	OCS	Exacerbations	Asthma Control	Lung Function	BACS
Mexico	GL	0	0	10†	10†	10†	10†	10†	10†	10†	10†	80
Brazil	GL & ISC	0	2	5	10†	10†	10†	10†	10†	10†	10†	77
South Korea	ISC only	10†	2	10	10†	10†	5	10†	10	0	10†	77
Singapore	ISC only	0	2	10†	10†	10†	4	10†	10†	10†	10†	76
EMA	**GL**	**0**	**2**	**10†**	**10†**	**10†**	**4**	**10†**	**10†**	**10†**	**10†**	**76**
Argentina	ISC only	0	10†	5	10†	10†	4	10	3	10†	10†	72
Saudi Arabia	ISC only	10†	10†	5	10†	10†	4	10	3	0	4	66
Italy	ISC only	0	2	5	10†	10†	4	10	4	10†	10†	65
France	ISC only	0	2	4	10†	10†	4	10	3	10†	10†	63
Russia	ISC only	0	2	5	10	0	5	10†	10†	10†	10†	62
Germany	ISC only	0	2	4	10†	10	4	10†	10	0	10†	60
USA	ISC & FDA	4	2	5	10†	10†	4	10	3	0	10†	58
Kuwait	ISC only	10†	10†	5	10†	0	4	10	3	0	4	56
Denmark	ISC only	0	2	4	10†	0	4	10	4	10	10	54
Canada	CADTH	0	2	7	10†	10†	4	0	10†	0	10†	53
Spain	ISC only	0	8	0	10†	10	4	10†	3	0	8	53
Japan	ISC only	0	0	4	10†	10†	2	10†	6	0	10†	52
Greece	ISC only	0	0	4	10†	0	4	10†	3	10†	10†	51
Ireland	ISC only	0	0	4	10†	0	4	10	3	10†	10	51
Finland	ISC only	0	2	10†	10†	10†	0	0	4	0	10†	46
Iceland	ISC only	0	2	4	5	10†	4	10†	3	0	8	46
Portugal	GL & ISC	0	0	5	10†	0	4	10†	4	0	10†	43
UK	GL	0	2	4	10†	0	4	10	0	0	10†	40
Netherlands	NVALT	0	2	5	5	0	4	10	3	0	10†	39
Colombia	ISC only	0	0	4	10	0	4	10	6	0	4	38
Estonia	ISC only	0	2	2	10†	0	2	10	2	0	10†	38
Bulgaria	ISC only	0	2	4	10†	0	4	10	2	0	0	32
Taiwan	ISC only	0	0	4	10†	0	0	10	2	0	6	32
Australia	GL & ISC	4	0	4	10	0	4	0	6	0	2	30

†Criteria undecided

FIGURE E4. Biologic Accessibility Score (BACS) specification for benralizumab by country. *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

Country**	Data Source	Age	Phenotype	BEC	FeNO	Adherence	Background Therapy	OCS	Exacerbations	Asthma Control	Lung Function	BACS
EMA	**GL**	**0**	**2**	**10**	**10†**	**10**	**4**	**10**	**10**	**10**	**10**	**76**
South Korea	ISC only	10†	2	2	10†	10†	5	10†	10	0	10†	69
Finland	ISC only	0	2	10	10†	10	5	10	0	10	10	67
Germany	ISC only	0	2	5	10†	10	4	10†	10	0	10	61
USA	ISC & FDA	0	2	2	10†	10†	4	10	3	10†	10†	61
Spain	ISC only	0	8	2	10†	10	4	10†	4	0	10	58
Denmark	ISC only	0	2	4	10†	0	2	10	4	10	10	52
France	ISC only	0	2	2	10†	10	4	10	4	0	10	52
Ireland	ISC only	0	0	2	10	0	4	10	6	10	10	52
Canada	CADTH	0	2	2	10†	10†	4	10†	3	0	6	47
Russia	ISC only	4	2	4	10	0	5	10†	6	0	4	45
UK	GL	0	2	2	10†	0	6	10	2	0	10	42
Portugal	GL & ISC	0	0	2	10†	0	4	10	4	0	10	40
Estonia	ISC only	0	2	2	10†	0	2	10	2	0	10	38
Netherlands	NVALT	0	2	2	5	0	4	10	3	0	10	36

**Brazil: Approved, but not commercialized; †Criteria undecided

FIGURE E5. Biologic Accessibility Score (BACS) specification for reslizumab by country. *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

Country***	Data Source	Age	Phenotype	BEC	FeNO	Adherence	Background Therapy	OCS	Exacerbations	Asthma Control	Lung Function	BACS
Mexico	GL & ISC	4	4	10†	10†	10†	10†	10†	10†	10†	10†	88
Italy	ISC only	4	2	8	10	10†	6	10	4	10†	10†	74
Brazil	GL & ISC	4	2	8	5	10†	4	10†	10†	10†	10†	73
Russia	ISC only	4	4	8	10	0	5	10†	10†	10†	10†	71
Singapore	ISC only	4	2	8	5	10†	10†	0	10†	10†	10†	69
USA	ISC & FDA	4	4	8	5	10†	4	10	3	10†	10†	68
France	ISC only	4	2	8	5	10†	6	10†	10†	0	10†	65
EMA	**GL**	**4**	**2**	**8**	**5**	**10†**	**6**	**10†**	**10†**	**0**	**10†**	**65**
Saudi Arabia	ISC only	10†	10†	8	5	10†	4	10	3	0	4	64
South Korea	ISC only	4	2	8	5	10†	5	10	10	0	10†	64
Germany	ISC only	0	2	5	10	10	4	10†	10	0	10†	61
Japan	ISC only	4	0	8	5	10†	2	10†	6	0	10†	55
Finland	ISC only	4	8	8	10	10†	0	0	4	0	10†	54
Estonia	ISC only	4	8	7	10	0	2	10	2	0	10†	53
Denmark	ISC only	4	2	4	5	0	2	10	4	10	10	51
Portugal	GL & ISC	4	2	5	10	0	4	10†	4	0	10†	49
Australia	GL & ISC	4	0	4	10	0	4	10	6	0	10†	48
Netherlands	NVALT	4	2	8	5	0	4	10	3	0	10†	46
Kuwait	ISC only	10†	2	5	10†	0	4	0	3	0	4	38
Colombia	ISC only	0	0	4	5	0	4	10	6	0	4	33

***Ireland: Not defined in national criteria; †Criteria undecided

FIGURE E6. Biologic Accessibility Score (BACS) specification for dupilumab by country. *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

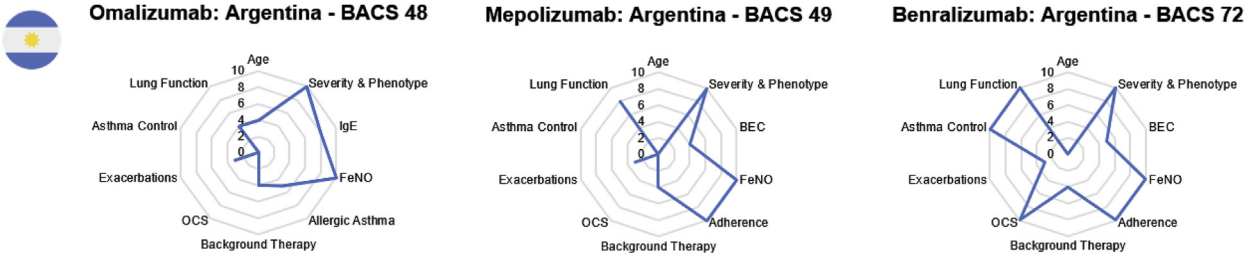

FIGURE E7. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, and benralizumab in Argentina. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

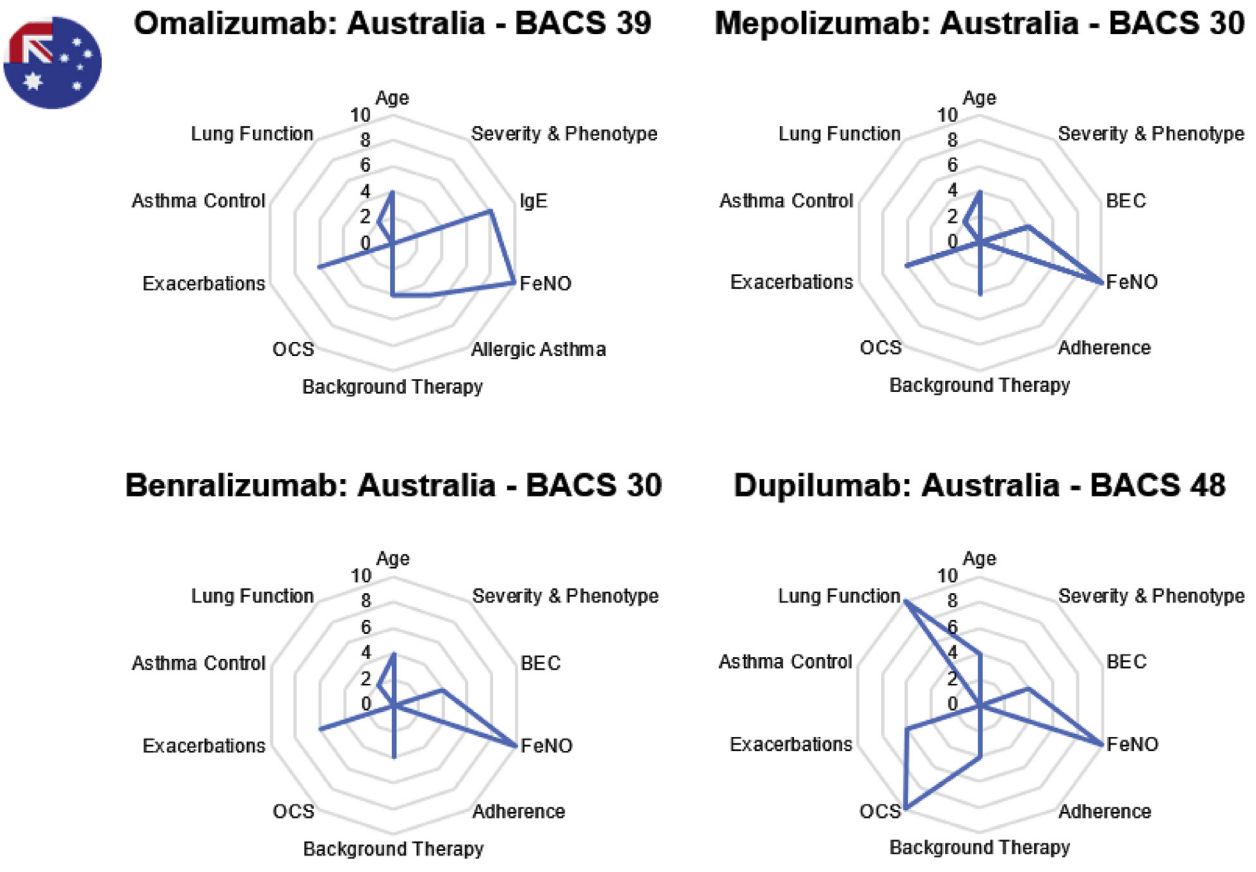

FIGURE E8. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, and benralizumab in Australia. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

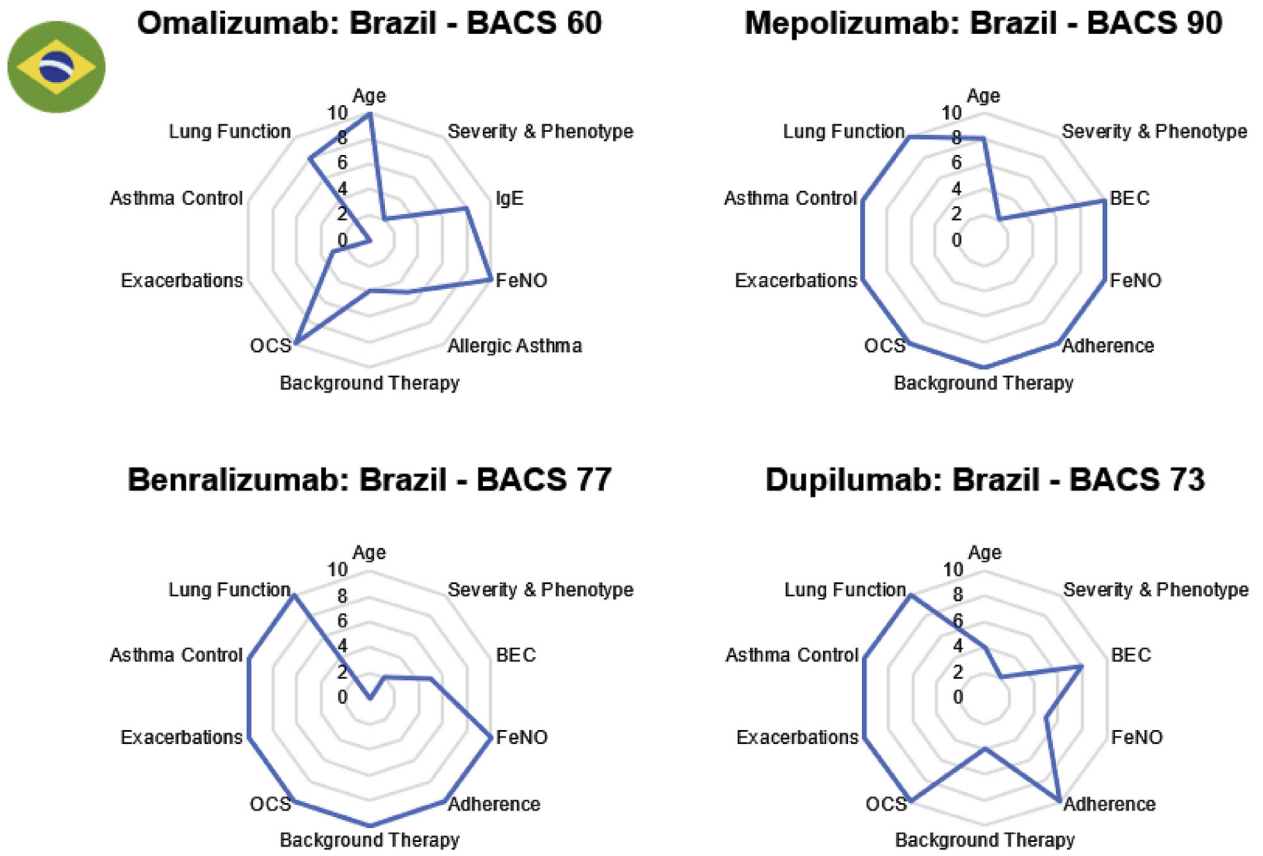

FIGURE E9. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, benralizumab, and dupilumab in Brazil. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

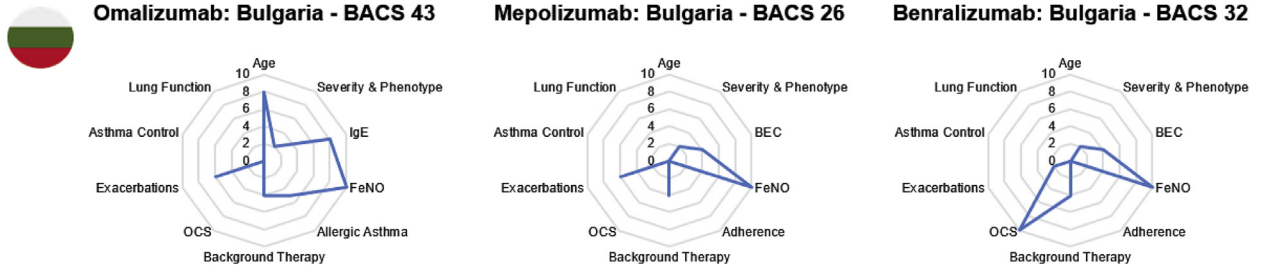

FIGURE E10. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, and benralizumab in Bulgaria. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

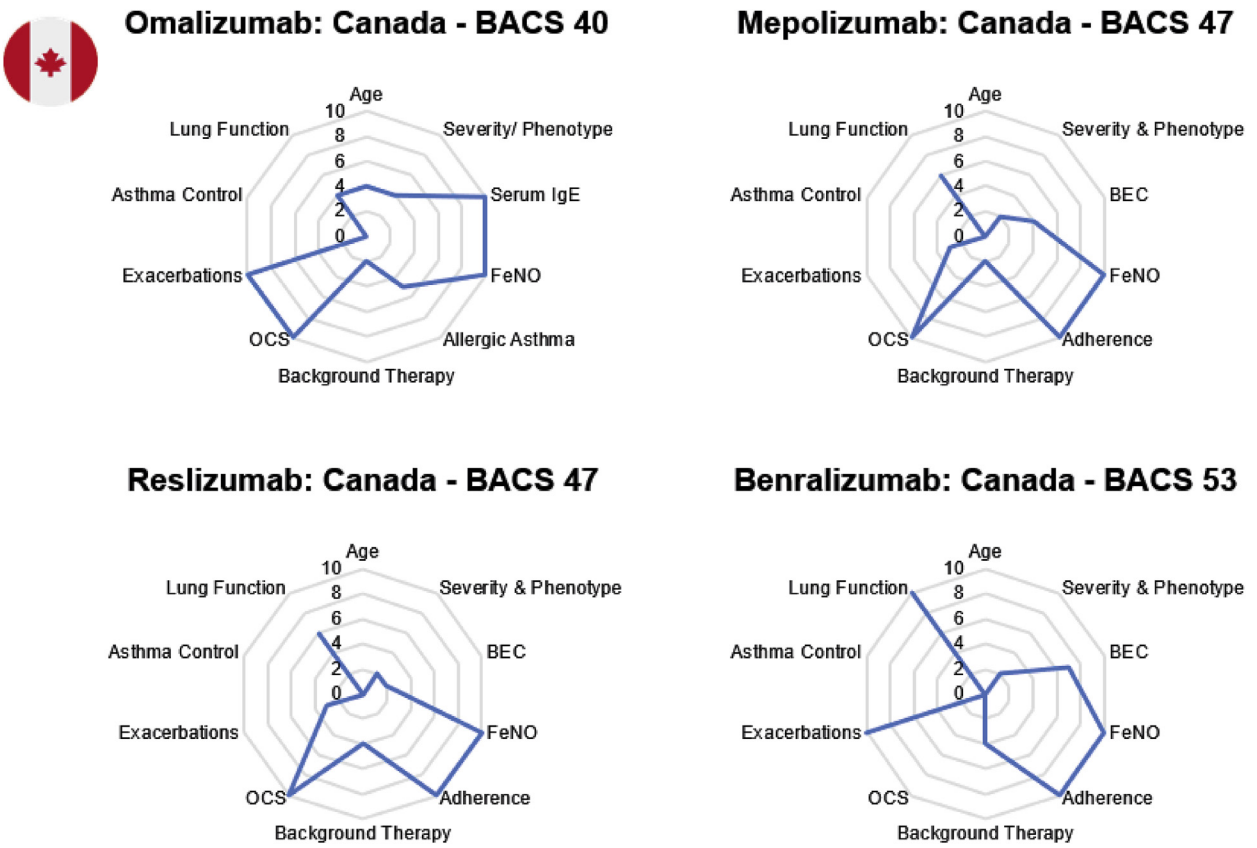

FIGURE E11. Spider plots depicting the variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, and benralizumab in Canada.

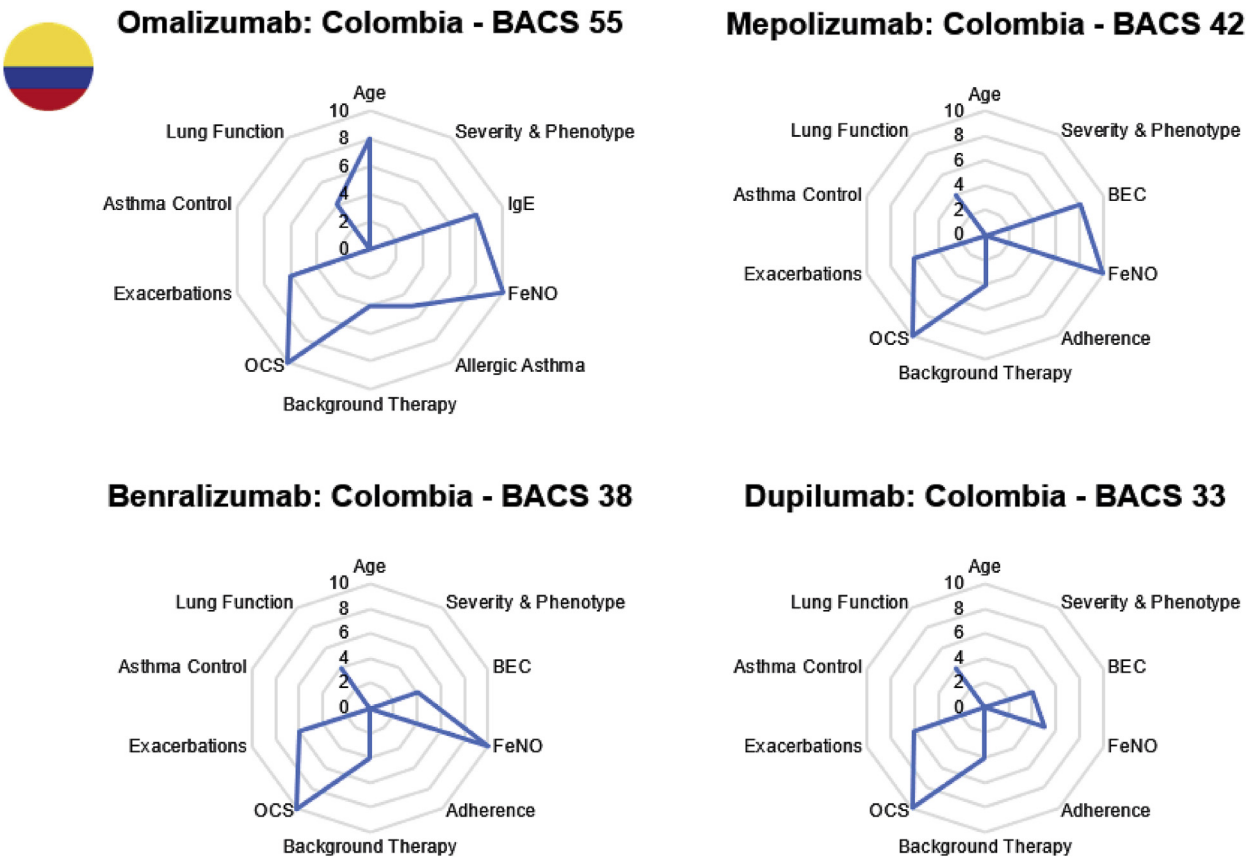

FIGURE E12. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, benralizumab, and dupilumab in Colombia. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

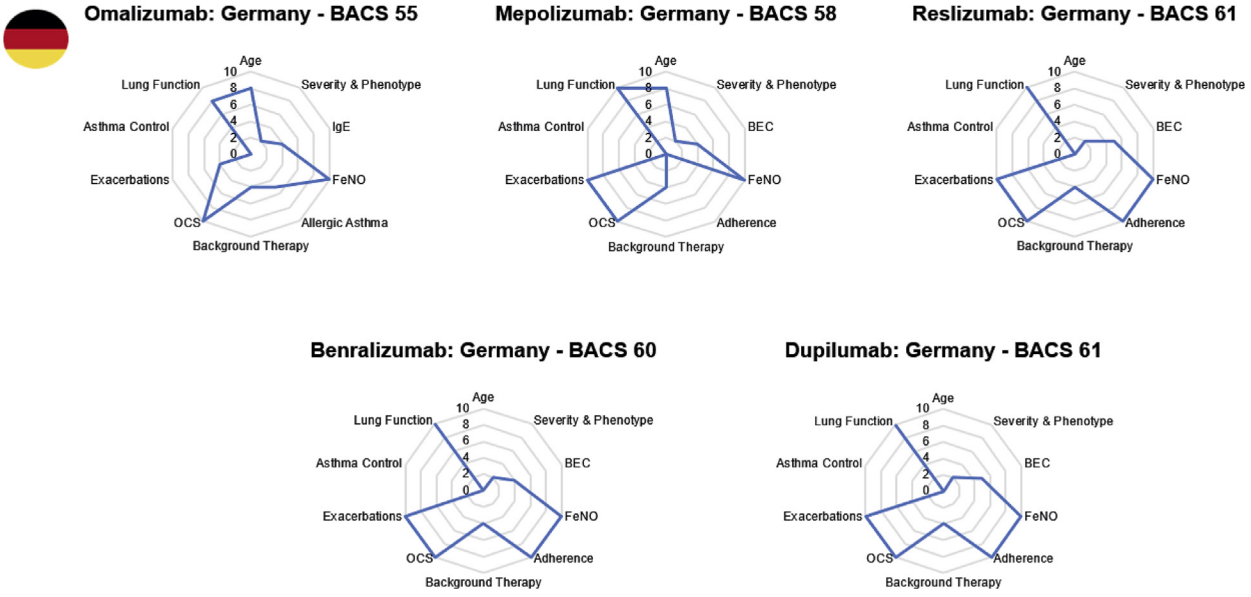

FIGURE E13. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab in Germany. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

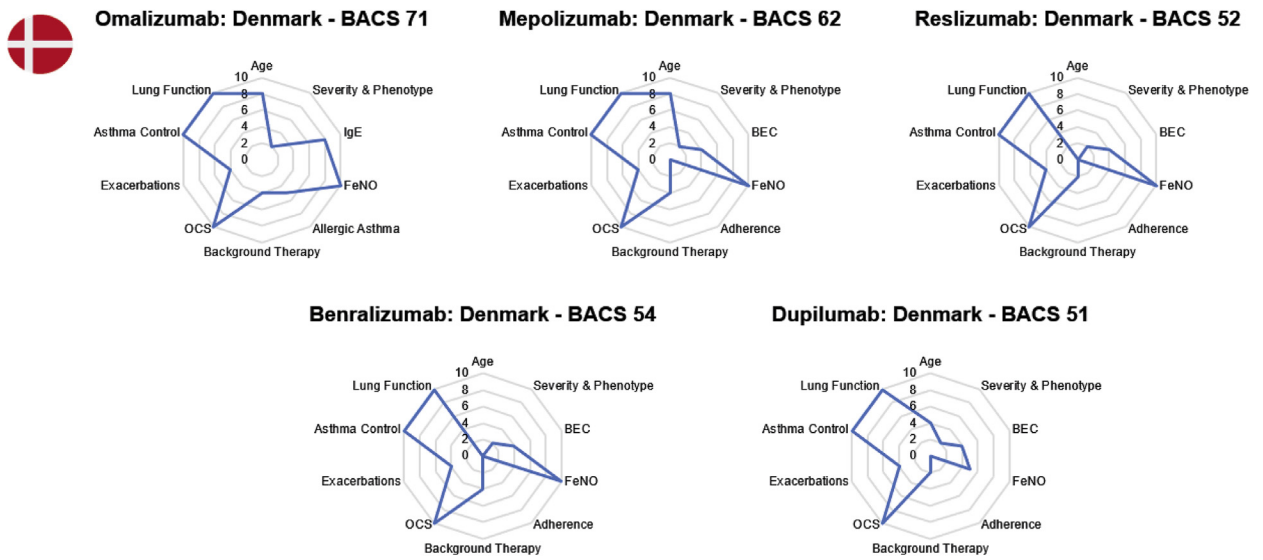

FIGURE E14. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab in Denmark. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

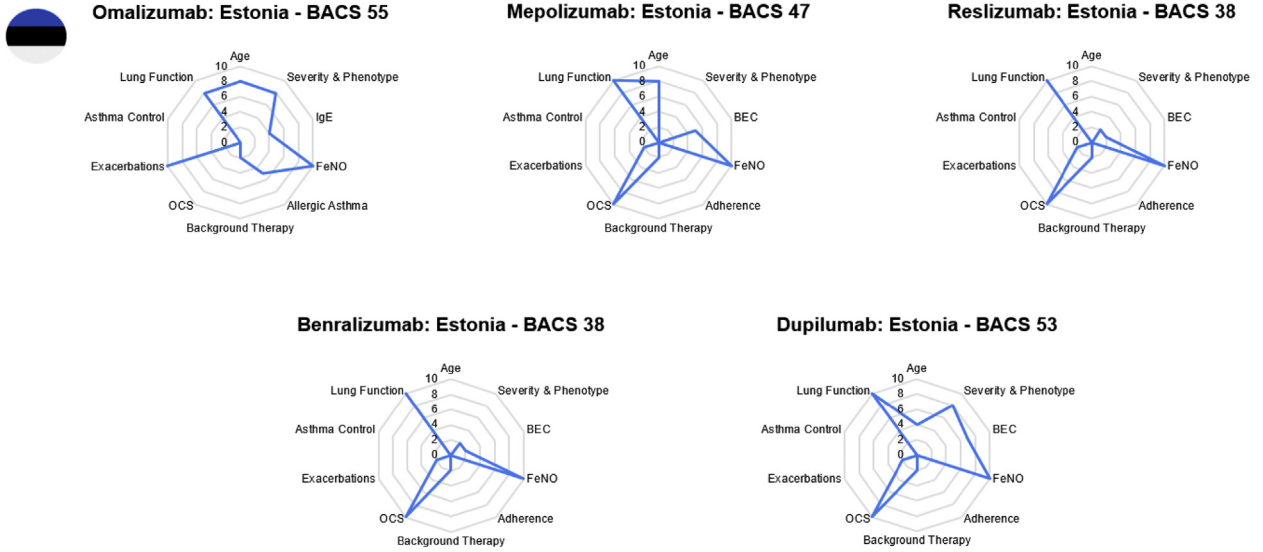

FIGURE E15. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab in Estonia. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

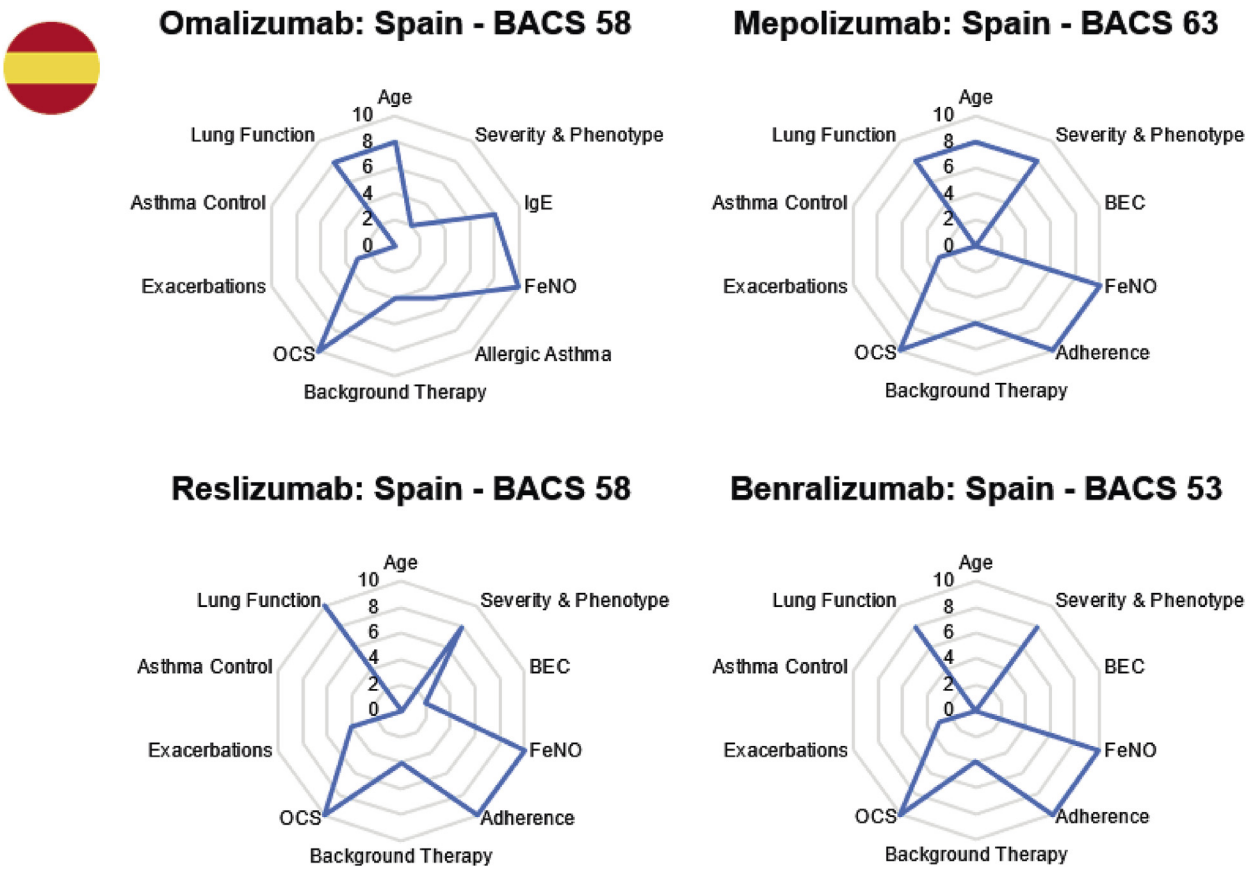

FIGURE E16. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, and benralizumab in Spain. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

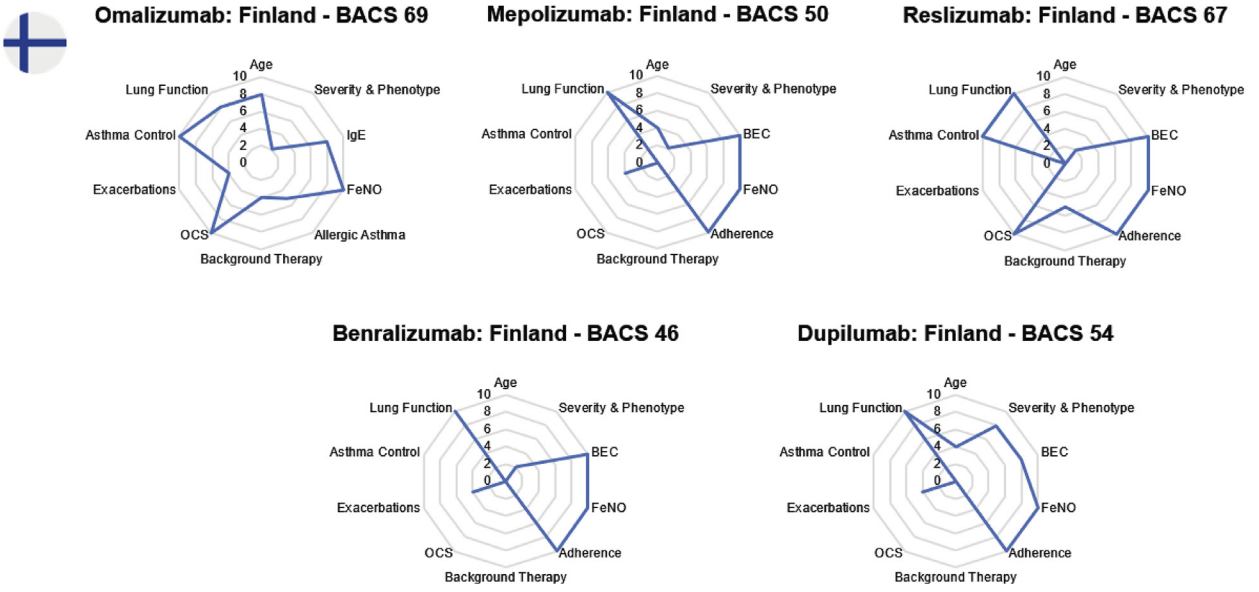

FIGURE E17. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab in Finland. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

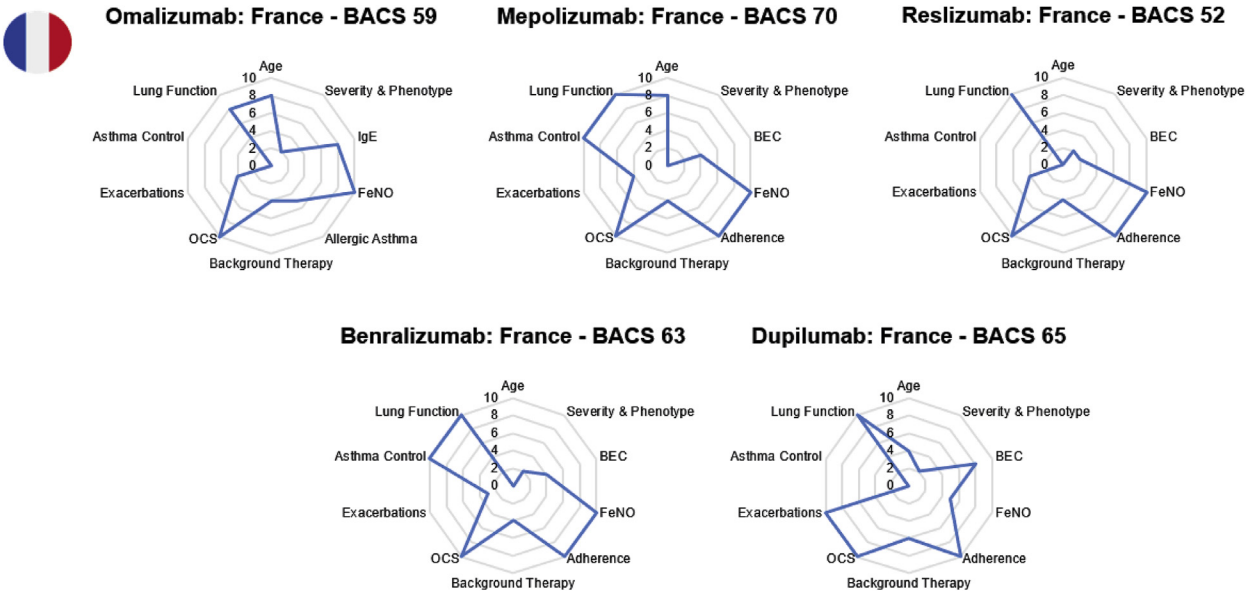

FIGURE E18. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab in France. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

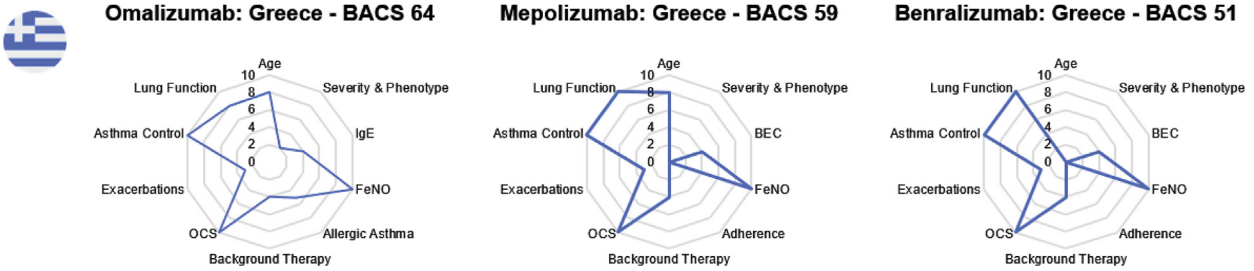

FIGURE E19. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab and mepolizumab in Greece. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

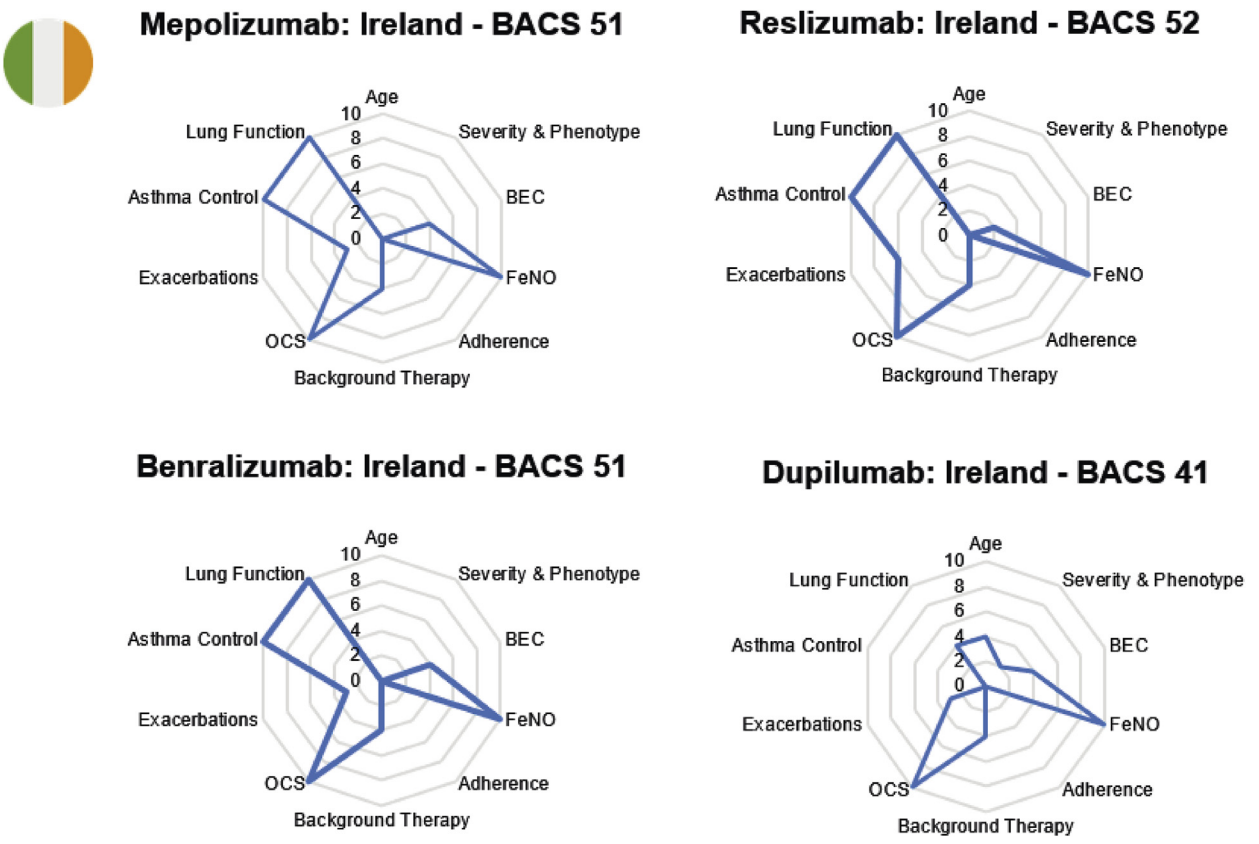

FIGURE E20. Spider plots depicting variability in biomarkers and prescription criteria for mepolizumab, reslizumab, benralizumab, and dupilumab in Ireland. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

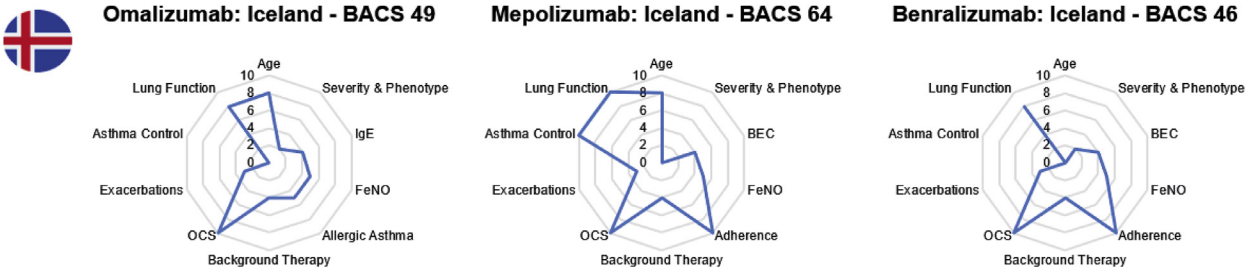

FIGURE E21. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, and benralizumab in Iceland. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

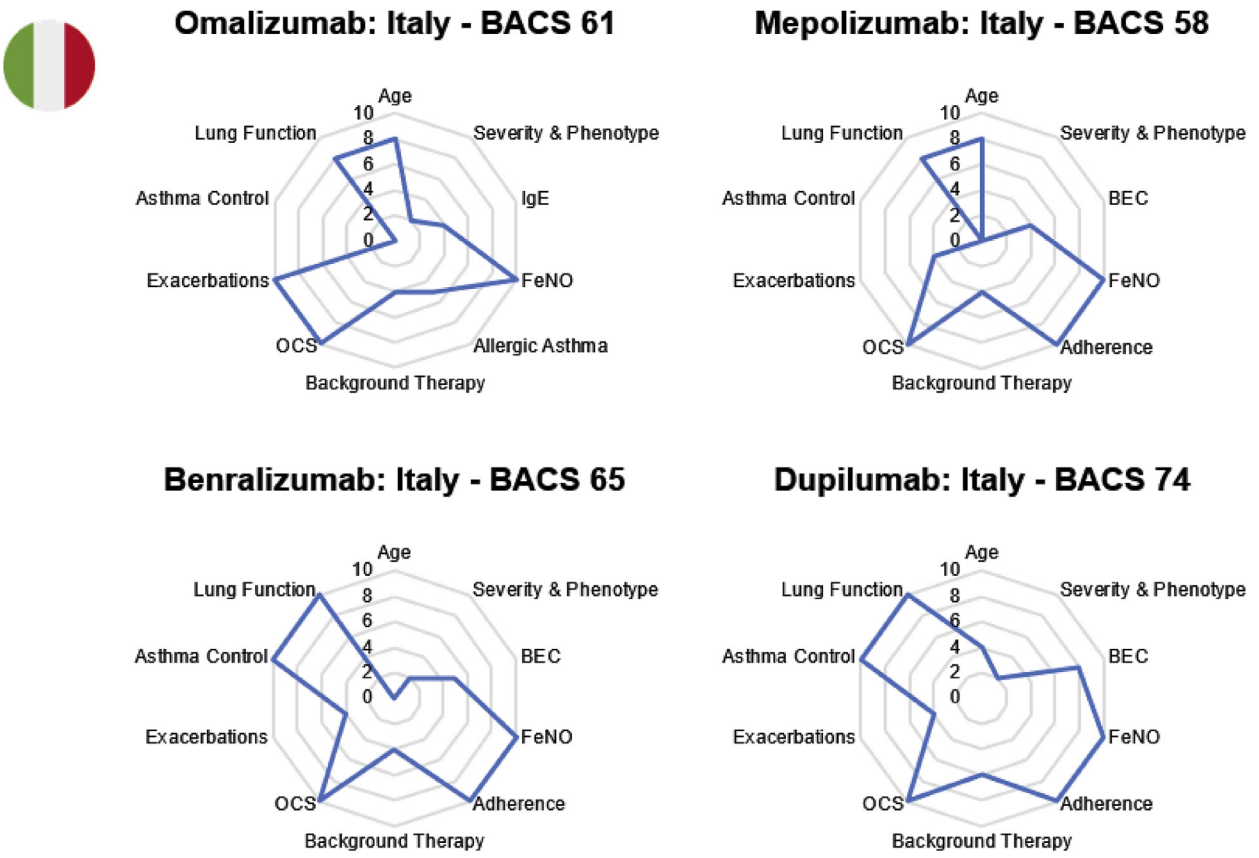

FIGURE E22. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, benralizumab, and dupilumab in Italy. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

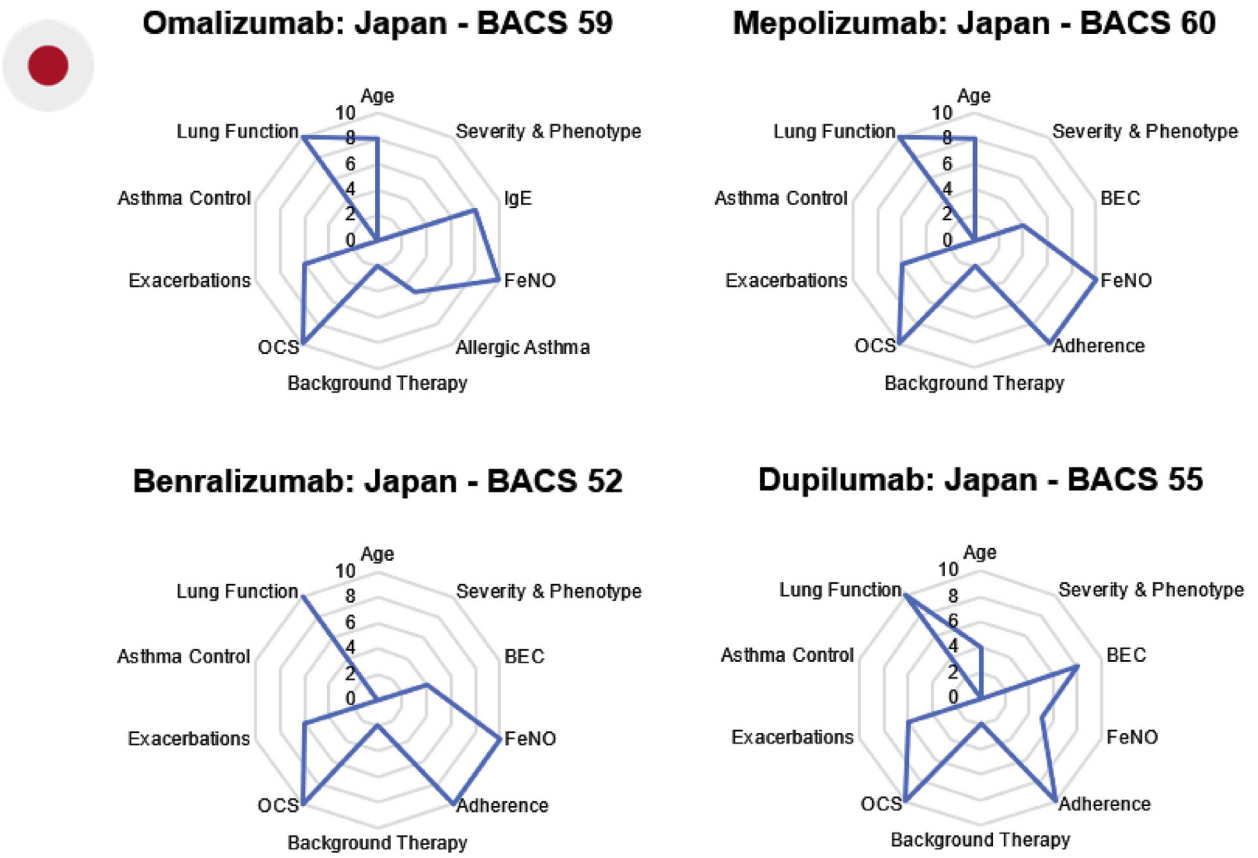

FIGURE E23. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, benralizumab, and dupilumab in Japan. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

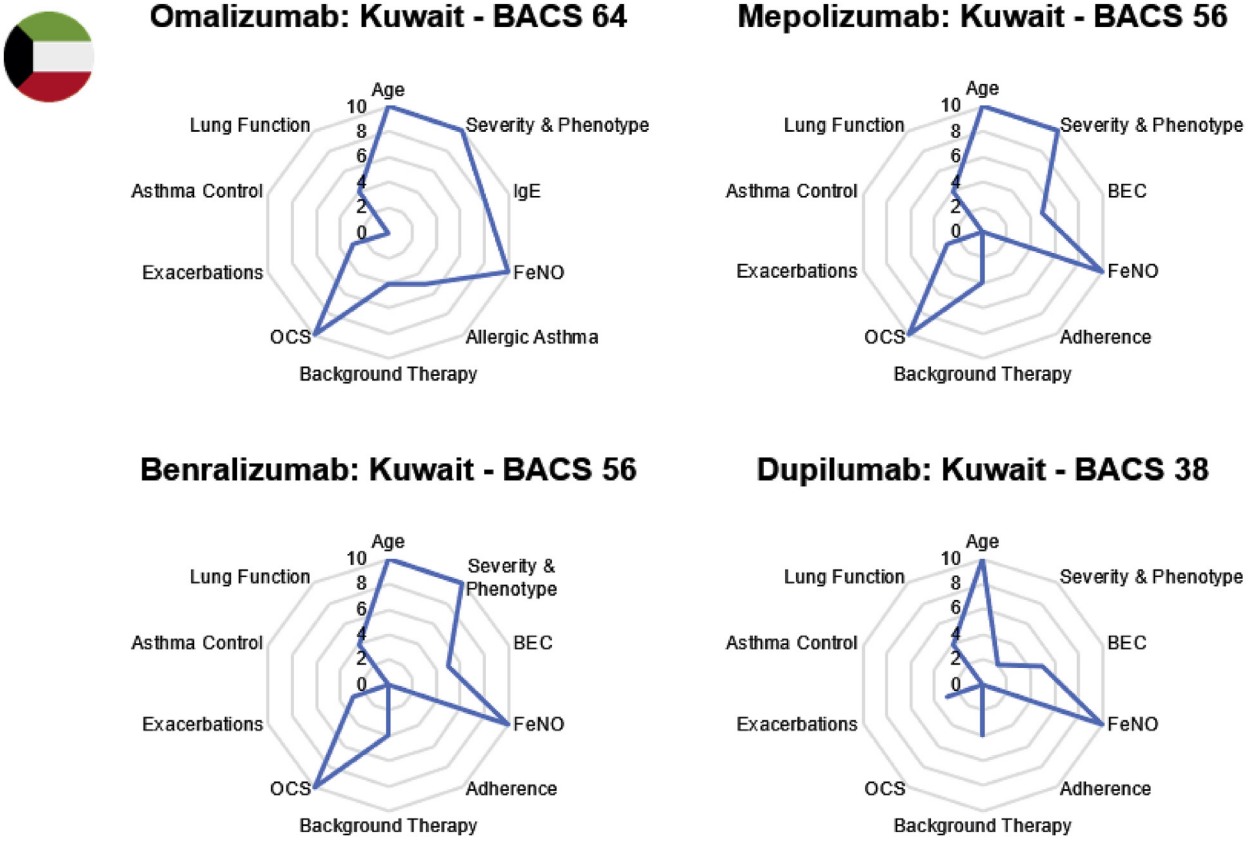

FIGURE E24. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, benralizumab, and dupilumab in Kuwait. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

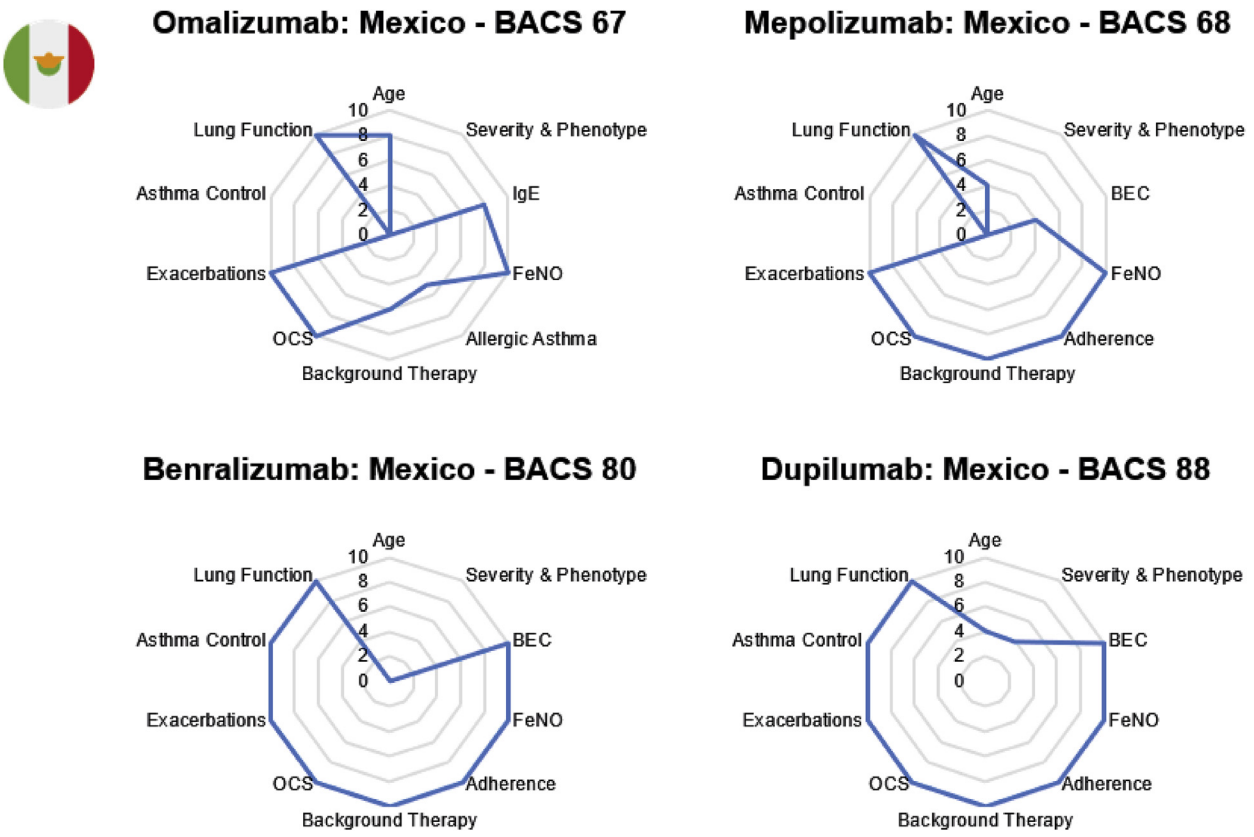

FIGURE E25. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, benralizumab, and dupilumab in Mexico. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

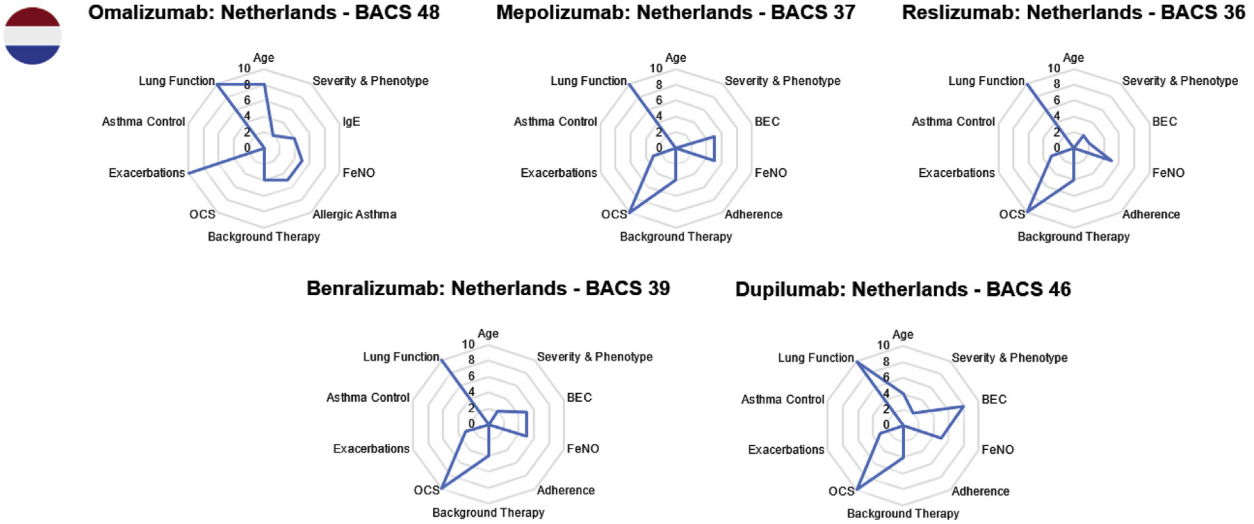

FIGURE E26. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab in The Netherlands. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

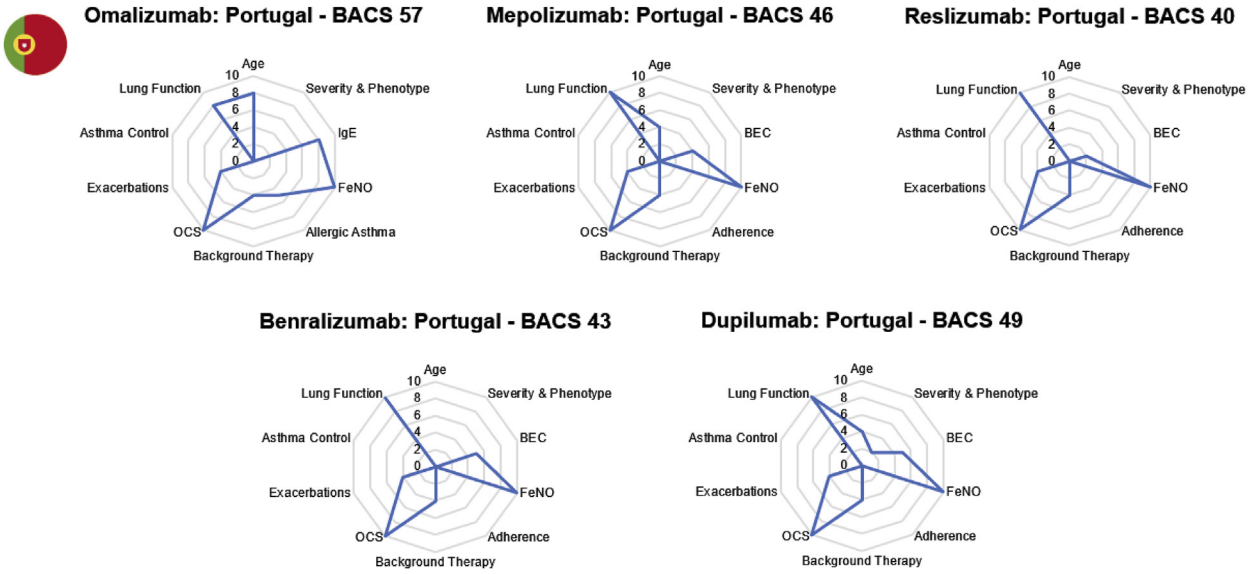

FIGURE E27. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab in Portugal. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

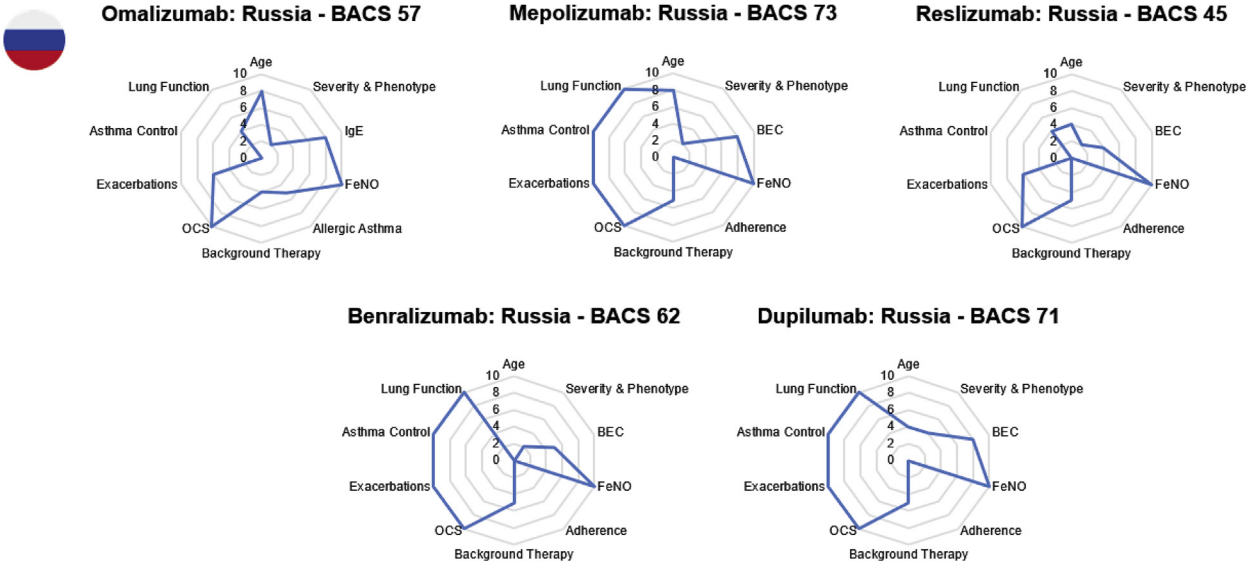

FIGURE E28. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab in Russia. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

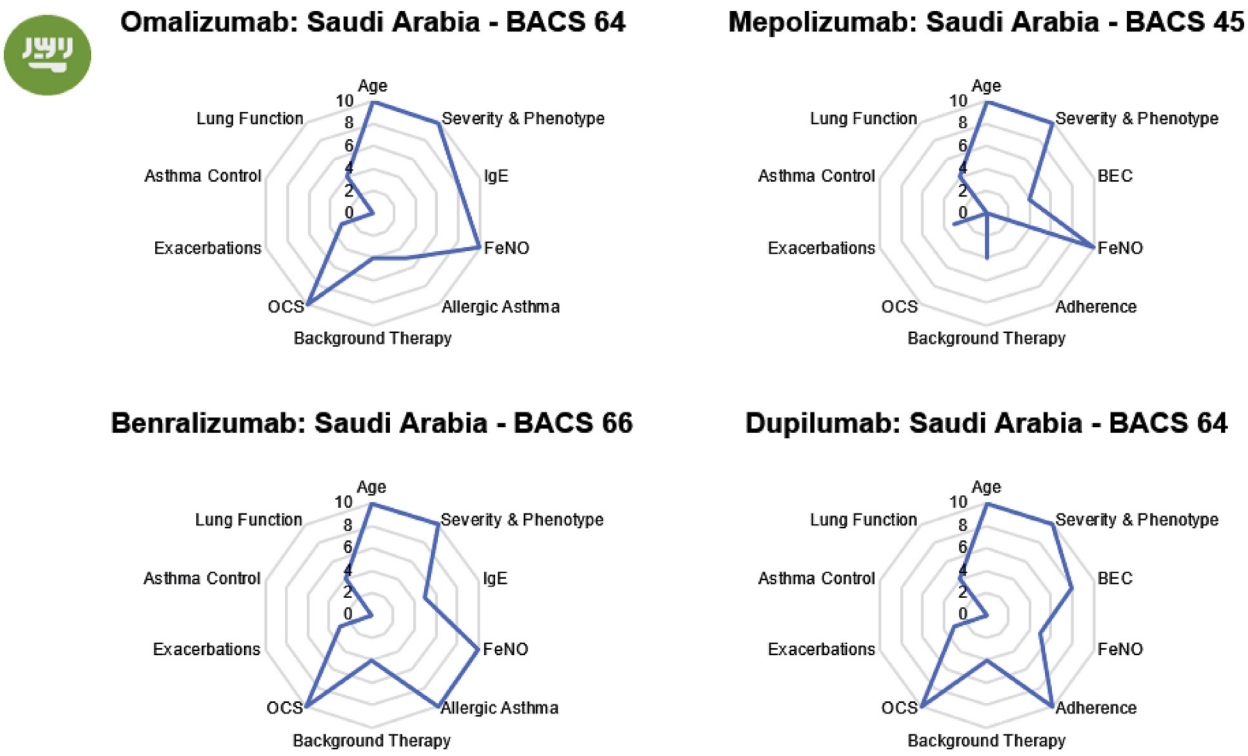

FIGURE E29. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, benralizumab, and dupilumab in Saudi Arabia. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

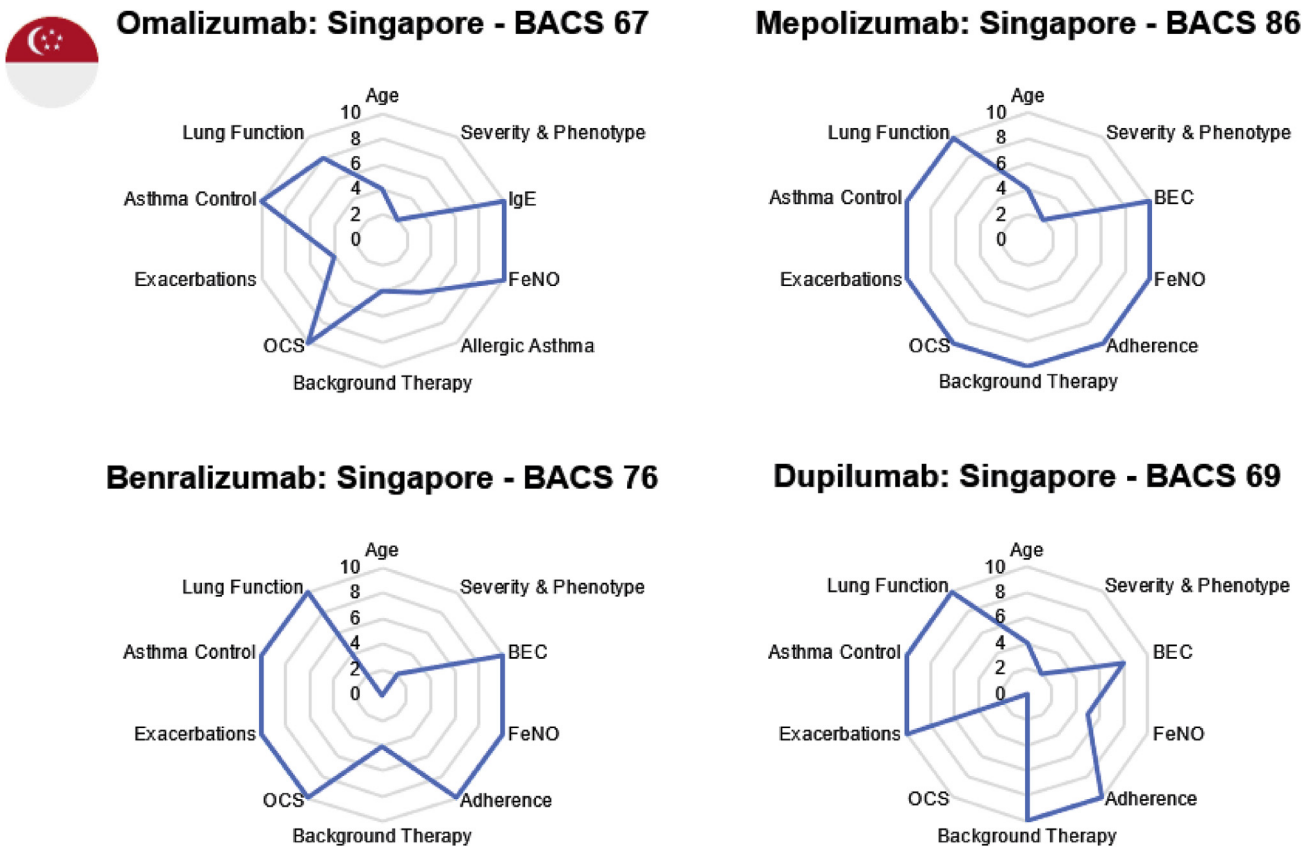

FIGURE E30. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, benralizumab, and dupilumab in Singapore. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

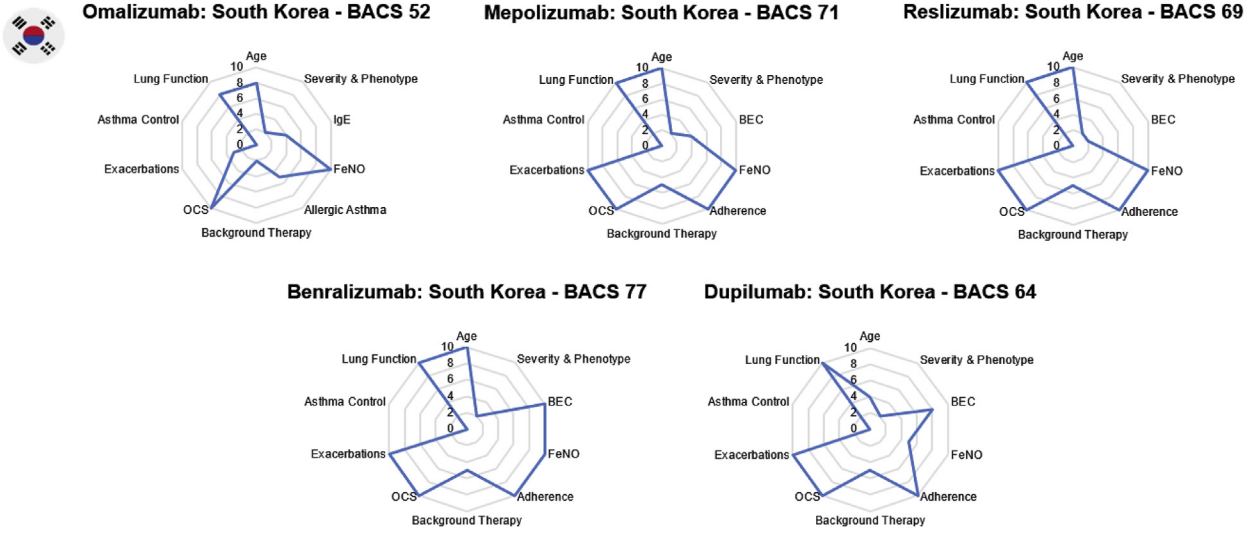

FIGURE E31. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab in South Korea. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

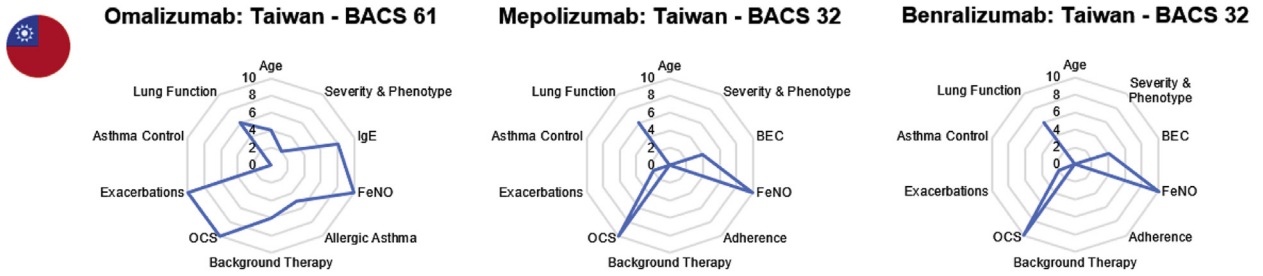

FIGURE E32. Spider plots depicting Biologic Accessibility Score (BACS) for omalizumab, mepolizumab, and benralizumab in Taiwan. *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

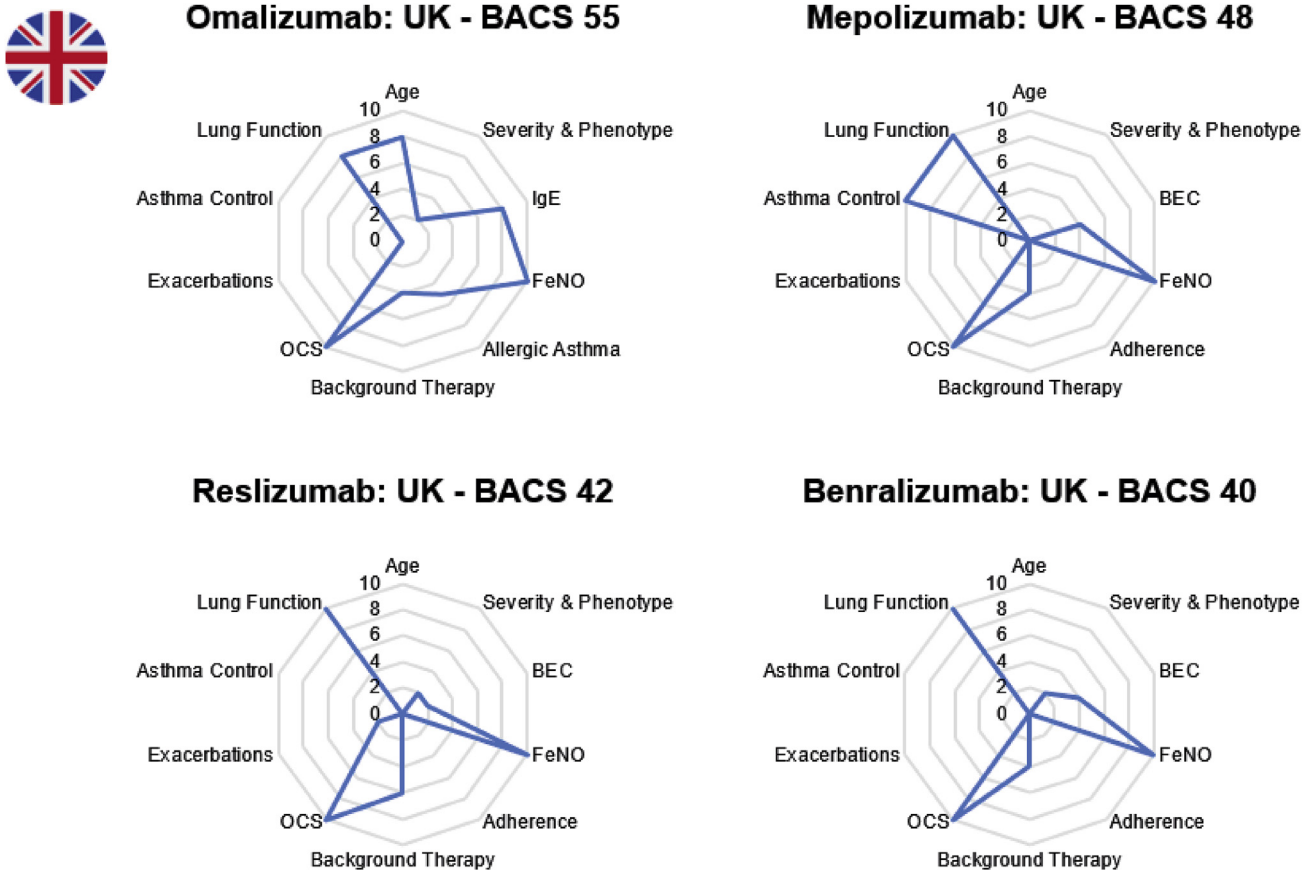

FIGURE E33. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, and benralizumab in the United Kingdom. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

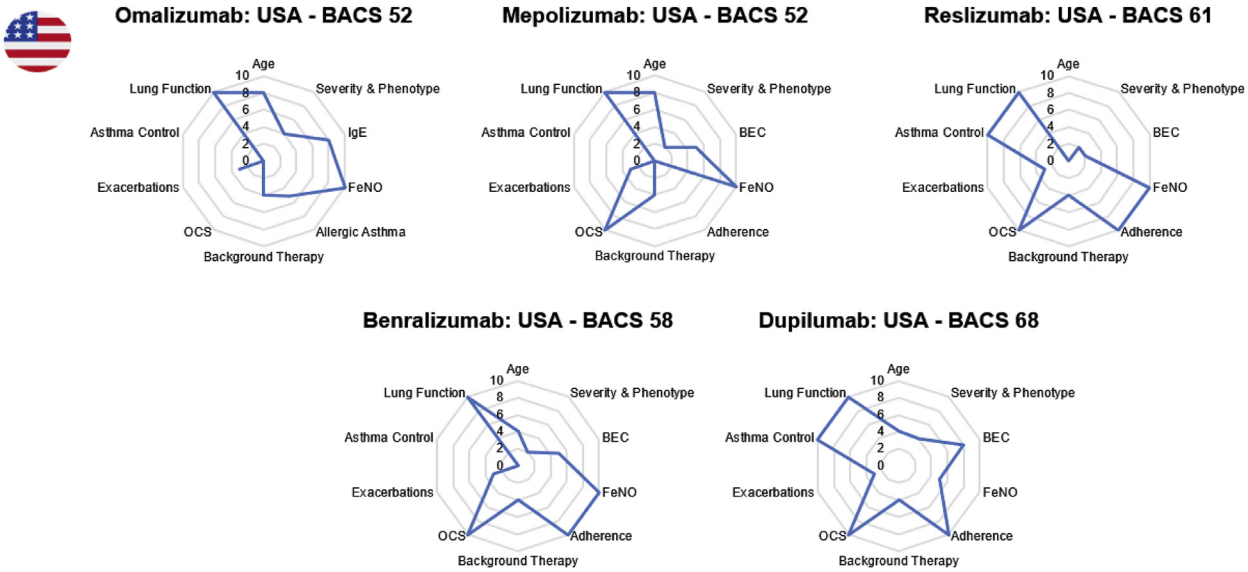

FIGURE E34. Spider plots depicting variability in biomarkers and prescription criteria for omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab in the United States. *BACS*, Biologic Accessibility Score; *BEC*, blood eosinophil count; *OCS*, oral corticosteroids.

TABLE E2. Correlations between gross domestic product* and Biologic Accessibility Score

Statistical variable	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Pearson's *r*	0.006	0.000	0.243	−0.162	−0.127
P (two-tailed)	.978	1.000	.402	.420	.605

*Most recent gross domestic product per capita data per country was extracted from the World Bank website.[E11]

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