Archival Report

Biological Psychiatry: GOS

Pathway-Specific Polygenic Scores for Predicting Clinical Lithium Treatment Response in Patients With Bipolar Disorder

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ABSTRACT

BACKGROUND: Polygenic scores (PGSs) hold the potential to identify patients who respond favorably to specific psychiatric treatments. However, their biological interpretation remains unclear. In this study, we developed pathway-specific PGSs (PS_{PGSs}) for lithium response and assessed their association with clinical lithium response in patients with bipolar disorder.

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ISSN: 2667-1743

Biological Psychiatry: Global Open Science September 2025; 5:100558 www.sobp.org/GOS

METHODS: Using sets of genes involved in pathways affected by lithium, we developed 9 PS_{PGSs} and evaluated their associations with lithium response in the International Consortium on Lithium Genetics (ConLi^{+}Gen) (N = 2367), with validation in combined PsyCourse (Pathomechanisms and Signatures in the Longitudinal Course of Psychosis) (N = 105) and BipoLife (N = 102) cohorts. The association between each PS_{PGS} and lithium response—defined both as a continuous ALDA score and a categorical outcome (good vs. poor responses)—was evaluated using regression models, with adjustment for confounders. The cutoff for a significant association was $p < .05$ after multiple testing correction.
RESULTS: The PGSs for acetylcholine, GABA (gamma-aminobutyric acid), and mitochondria were associated with response to lithium in both categorical and continuous outcomes. However, the PGSs for calcium channel, circadian rhythm, and GSK (glycogen synthase kinase) were associated only with the continuous outcome. Each score explained 0.29% to 1.91% of the variance in the categorical and 0.30% to 1.54% of the variance in the continuous outcomes. A multivariate model combining PS_{PGSs} that showed significant associations in the univariate analysis (combined PS_{PGS}) increased the percentage of variance explained (R^2) to 3.71% and 3.18% for the categorical and continuous outcomes, respectively. Associations for PGSs for GABA and circadian rhythm were replicated. Patients with the highest genetic loading (10th decile) for acetylcholine variants were 3.03 times more likely (95% CI, 1.95 to 4.69) to show a good lithium response (categorical outcome) than patients with the lowest genetic loading (1st decile).
CONCLUSIONS: PS_{PGSs} achieved predictive performance comparable to the conventional genome-wide PGSs, with the added advantage of biological interpretability using a smaller list of genetic variants.

https://doi.org/10.1016/j.bpsgos.2025.100558

Over the past 15 years, there has been significant progress in the development of polygenic scores (PGSs). Key research areas have been centered around evaluating their potential for disease risk prediction, uncovering the genetic basis of complex diseases, and clinical application for disease screening and drug selection through pharmacogenomics, as well as assessing their cross-population transferability (1–5).

Since the initial implementation of the polygenic theory for assessing the genetic risk of schizophrenia (SCZ) by the International Schizophrenia Consortium in 2009 (1), hundreds of PGSs have been developed and investigated for their association with the risk of common mental health disorders such as SCZ (6), major depressive disorder (MDD) (7), and bipolar disorder (BD) (8). In recent years, PGSs have emerged as a promising tool for understanding the collective influence of common single nucleotide polymorphisms (SNPs) on patients' pharmacological treatment outcomes (9,10). For example, in patients with SCZ, a PGS for SCZ (PGS_{SCZ}) that was significantly associated with antipsychotic treatment outcomes explained 3.2% of the interindividual variability in treatment response (11). Other studies have shown that a PGS_{SCZ} explained 2.0% of the variance in treatment-resistant SCZ (12–15), ∼1% of the variance in antipsychotic-induced weight gain (16,17), nearly 2% of the variance in clozapine-induced myocarditis (18), and 2.7% of the variance in prolonged hospitalization (19). Similarly, in patients with MDD, genetic scores for SCZ, MDD, BD, and neuroticism showed significant associations with antidepressant treatment response (20–23) and resistance (24,25), although each of these scores explained <2% of the variability. Among patients with BD, lithium response was associated with PGSs for SCZ (26), MDD (27), attention-deficit/hyperactivity disorder (28), and lithium responsiveness (29). Combined analysis of SCZ and MDD PGSs with clinical variables resulted in better prediction, with the model accounting for approximately 14% of the variance in lithium treatment response (30), emphasizing the potential clinical relevance of algorithms that combine PGSs with clinical data. This result exceeds the accuracy of any PGSs that have been analyzed individually or in combination using standard measures, which at best have explained up to 5.6% of the variance in psycho-pharmacotherapeutic outcomes, e.g., in resistance to clozapine (31). While PGSs hold significance for research purposes and offer promising clinical implications for the future, their predictive performance remains limited for direct clinical translation (10). Thus, there is a need to utilize novel methods to develop PGSs with better predictive capabilities and to refine existing scores for increased precision.

In this context, newly proposed approaches such as biology-informed polygenic modeling have been evaluated for various traits (32–34). This PGS approach leverages genetic variants based on their relationship to molecular pathways that are linked to the phenotype of interest, thereby enhancing their predictive power and relevance to pharmacogenomics or disease screening (35). For example, an insulin receptor–based PGS targeting the striatum and prefrontal cortex predicted impulsivity and cognitive abilities in children, as well as addiction and dementia risk in adults (32). Similarly, a PGS composed of variants associated with nervous system development and neuron differentiation explained 6.9% of the variance in liability to psychosis in a sample of patients with DSM-IV diagnoses of SCZ or psychosis-related disorders determined by a structured clinical interview. This result surpasses the 3.7% of the variance explained by a conventional PGS_{SCZ} using genome-wide variants (34). Thus, restricting PGSs to genetic variants within biological pathways known to be associated with lithium response may reduce noise from variants with spurious associations and increase the power of polygenic models while explicitly building our mechanistic understanding (36). Furthermore, the biology-informed polygenic approach may facilitate the effort to identify new treatment targets (33,37).

Building on this knowledge, our study adopted the biologically informed strategy and developed pathway-specific PGSs (PS_{PGSs}) for lithium response. We hypothesized that these

scores would improve the prediction of clinical response to lithium and could identify biological targets for future drug development in patients with BD.

METHODS AND MATERIALS

Study Sample Characteristics

The target data for this study were obtained from the International Consortium on Lithium Genetics (ConLi$^+$Gen) cohort (http://www.conligen.org/), a global initiative established to investigate the genetic underpinnings of lithium treatment response in patients with BD. The discovery and target sample included only patients of European ancestry (N = 2367) who received lithium and were followed up for at least 6 months (38). The number of participants in each country is described in our previous study (29).

To replicate the findings from ConLi$^+$Gen, we utilized combined data from 2 German cohorts: the PsyCourse (Pathomechanisms and Signatures in the Longitudinal Course of Psychosis) study (N = 105) (39,40) and BipoLife (N = 102) cohorts (41). A detailed sample selection procedure for the replication cohorts is included in Supplemental Methods.

Target Outcome Measure

For both target and replication cohorts, the validated retrospective criteria for long-term treatment response in research subjects, known as the ALDA scale, was used to assess patient's response to lithium treatment (42,43). This score quantifies the degree of improvement during lithium response expressed as a composite measure of change in frequency and severity of mood symptoms (A score). The ALDA scale is adjusted for 5 potential confounding factors that could affect symptom improvement (B scale). These factors include the number (B1) and the frequency (B2) of disease episodes before/off the treatment, the duration of the treatment (B3), and compliance and use of additional medication during the periods of stability. The total ALDA score for each individual was calculated by subtracting the total B score from the total A score. The target outcome, lithium response, was defined as categorical (good response vs. poor response) and continuous outcomes. For the categorical outcome, patients who had a total score $\geq$7 were classified as good responders, and patients with a score $<$7 were classified as poor responders (44). The total ALDA score was used as a continuous lithium response measure after excluding patients with B scores $>$4 or who had missing data. Negative scores were recalibrated as 0. This algorithm has been used in previous studies (26,27,30,45,46) and described in detail elsewhere (44).

Genotyping, Quality Control, and Imputation Procedures for the ConLi$^+$Gen Sample

DNA was extracted from peripheral blood samples collected at 22 participating sites, and samples were genotyped using either Affymetrix or Illumina SNP arrays (44). Prior to imputation, quality control (QC) procedures were implemented on the genotype data using PLINK version 1.9 (47). SNPs with a poor genotyping rate ($<$95%), strand ambiguity (A/T and C/G SNPs), and a minor allele frequency (MAF) $<$10% and SNPs that deviated from Hardy-Weinberg equilibrium ($p < 10^{-6}$) were removed. Individuals with sex inconsistencies between the documented and genotype-derived sex and genetically related individuals were also excluded. The genotypic and QC details of the ConLi$^+$Gen cohort are available elsewhere (44).

The genotype data that passed QC were imputed in the Michigan server separately for each genotyping platform using the Haplotype Reference Consortium reference panel comprising broadly European haplotypes at 39,235,157 SNPs (48). For each cohort, imputation quality procedures were implemented and excluded SNPs of low frequency (MAF $<$ 1%) and low quality (imputation quality score $R^2 < 0.6$). Then, genotype calls for the filtered SNPs were derived and merged using PLINK from the imputed dosage score (47). The genotyping, QC, and imputation procedures for the replication cohorts are provided in Supplemental Methods.

Steps of Developing Pathway-Specific Polygenic Scores

Step 1: Identify Biological Pathways (Targets) of Lithium. To develop a PS_{PGS}, we first conducted a narrative review to identify biological pathways or processes potentially modulated by lithium. In this review, we identified 9 pathways including acetylcholine, GABA (gamma-aminobutyric acid), glutamate, dopamine, calcium channels, mitochondria, circadian rhythm, GSK (glycogen synthase kinase), and NMDA as potential targets for lithium in BD treatment (Supplement).

Step 2: Map Genes and SNPs for Each Biological Pathway. Using the names of pathways relevant to lithium as a search term, we extracted candidate genes in 3 existing databases, specifically Gene Set Enrichment Analysis (https://www.gsea-msigdb.org/gsea/index.jsp), HUGO Gene Nomenclature Committee (https://www.genenames.org/), and Kyoto Encyclopedia of Genes and Genomes (https://www.genome.jp/kegg/). The extracted lists of genes for each pathway are provided in the Supplement. We used MAGMA software (https://ctg.cncr.nl/software/magma) (49), with *–annotate window = 100, 20* (100 kb upstream and 20 kb downstream window), to annotate SNPs to these genes in each pathway. The final list of annotated SNPs that were matched with the target dataset (ConLi$^+$Gen) and included in our analysis were acetylcholine (6247), GABA (2994), glutamate (3840), dopamine (5794), calcium channel (4236), mitochondria (7801), circadian rhythm (6673), GSK (707) and NMDA (641). The lists of genes and SNPs that were included in the final analysis are provided in Supplemental Data. We note that some of the genes/SNPs overlap across pathways.

Step 3: Compute Pathway-Specific Polygenic Scores. To compute PS_{PGSs} for participants in 13 countries involved in the ConLi$^+$Gen, we implemented a widely accepted leave-one-country-out (LOC) procedure (50,51) in which PGSs were calculated for participants of one country at a time (target sample) using genome-wide association study (GWAS) summary statistics from the remaining 12 countries (discovery sample). This iterative procedure was conducted separately for the categorical and continuous measures of lithium response, which resulted in a total of 26 analyses. Each discovery GWAS

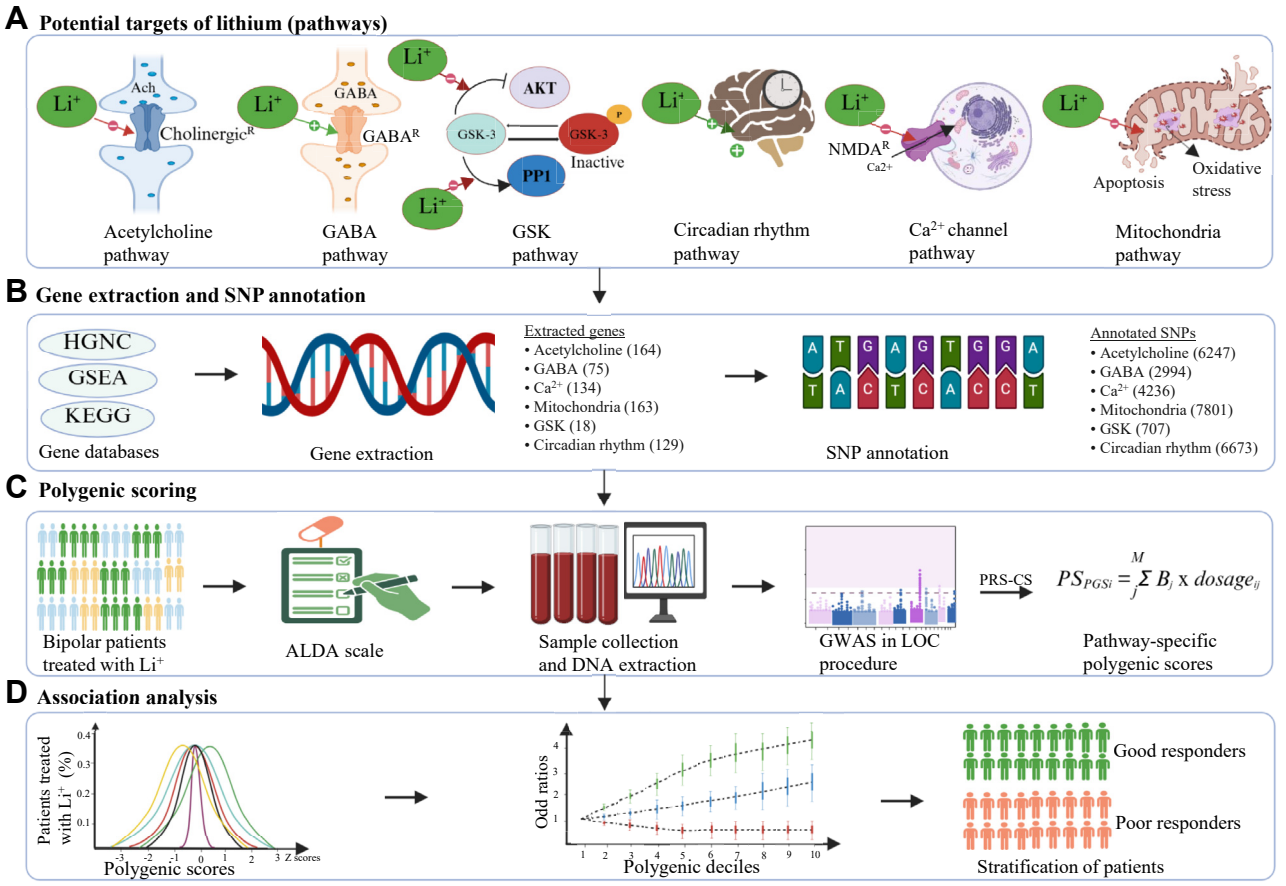

Figure 1. Examples of potential targets of lithium (pathways) and detailed steps of the data analysis process. Ach, acetylcholine; Ca^{2+}, calcium ion; GABA, gamma-aminobutyric acid; GSEA, Gene Set Enrichment Analysis; GSK, glycogen synthase kinase; GWAS, genome-wide association study; HGNC, HUGO Gene Nomenclature Committee; KEGG, Kyoto Encyclopedia of Genes and Genomes; Li^+, lithium; LOC, leave-one-country-out; PRS-CS, polygenic risk score with continuous shrinkage; PS_{PGS}, pathway-specific polygenic score; SNP, single nucleotide polymorphism.

was performed using PLINK, with regression models adjusted for age, sex, chip type, and the first 4 principal components (PCs). Each of the PS_{PGSs} was computed using the polygenic risk score with continuous shrinkage (PRS-CS) method, which incorporates continuous shrinkage priors on effect sizes and accounts for linkage disequilibrium among SNPs (52). In the replication analysis, a summary GWAS data from the full ConLi$^+$Gen was used as the discovery sample (29) to compute PS_{PGSs} in the combined PsyCourse (39,40) and BipoLife (41) samples. Additional details on the development of PS_{PGSs} are provided in Supplemental Methods.

Table 1. Characteristics of the Study Cohorts and Participants

Cohort	*N*	Sex, Female	Age (SD)	ALDA Score, Mean (SD)	Good Response to Lithium, *N* (%)
ConLi$^+$Gen	2367	1369	47.53 (13.73)	4.12 (3.15)	660 (27.88%)
BipoLife	102	49	49.87 (13.62)	4.52 (2.93)	29 (28.43%)
PsyCourse	105	42	46.91 (12.64)	3.80 (2.87)	24 (22.86%)

ConLi$^+$Gen, International Consortium on Lithium Genetics; PsyCourse, Pathomechanisms and Signatures in the Longitudinal Course of Psychosis.

Step 4: Association Analysis. Finally, the associations between each of the PS_{PGSs} and lithium response were evaluated using linear regression analysis for the continuous outcome and binary logistic regression analysis for the categorical outcome. Each association analysis was adjusted for age, sex, chip type, and the first 4 PCs. The cutoff for a statistically significant association was $p < .05$ after correction for multiple testing using the Benjamini-Hochberg procedure (53). To evaluate the combined effect of multiple PS_{PGSs} on lithium response, we utilized a multivariate regression model considering only PS_{PGSs} that showed a significant association with lithium response in the univariate model. The performance of this combined PS_{PGS} model was compared with the conventional genome-wide PGS model that uses genome-wide variants of lithium responsiveness. This analysis was conducted using *r2redux* R package (54). We also performed elastic-net regularization with 5-fold nested cross-validation in the

Table 2. The Association of Pathway-Specific Polygenic Scores With Clinical Lithium Treatment Response in Patients With Bipolar Disorder (*N* = 2367)

			Categorical Outcome			Continuous ALDA Score		
Pathways	No. of Genes	No. of SNPs	aOR (95% CI)	*p*	Pseudo R^2, %	β (95% CI)	*p*	R^2, %
Acetylcholine	164	6247	1.34 (1.22 to 1.49)	3.54×10^{-8}[a]	1.91%	0.38 (0.26 to 0.51)	3.24×10^{-9}[a]	1.54%
GABA Receptor	76	2994	1.15 (1.05 to 1.27)	9.14×10^{-3}[a]	0.34%[a]	0.15 (0.03 to 0.28)	.03[a]	0.30%
Calcium Channel	134	4236	1.10 (0.99 to 1.21)	.11	0.29%	0.18 (0.06 to 0.31)	.01[a]	0.30%
Mitochondria	163	7801	0.82 (0.74 to 0.91)	7.42×10^{-4}[a]	1.05%	−0.19 (−0.30 to −0.09)	1.02×10^{-4}[a]	1.16%
Glutamate	92	3840	0.98 (0.89 to 1.08)	.77	0.25%	0.09 (−0.03 to 0.22)	.21	0.20%
Circadian Rhythm	129	6673	1.09 (0.99 to 1.21)	.10	0.62%	0.16 (0.04 to 0.29)	.01	0.20%
Dopamine	155	5794	1.03 (0.94 to 1.14)	.59	0.01%	0.12 (−0.01 to 0.23)	.11	0.01%
GSK	18	707	1.09 (0.99 to 1.21)	.15	0.15%	0.24 (0.13 to 0.37)	1.85×10^{-4}[a]	0.60%
NMDA	11	641	0.93 (0.84 to 1.02)	.14	0.01%	0.04 (−0.09 to 0.17)	.67	0.01%
Combined PS_{PGS}	942	38,933	NA	<.01[a]	3.71%	NA	<.01[a]	3.18%
Genome-Wide PGS			1.14 (1.03 to 1.27)	4.13×10^{-9}[a]	2.87%	0.45 (0.31 to 0.57)	2.41×10^{-7}[a]	2.69%

A statistically significant association was determined at $p < .05$ after correction for Benjamini-Hochberg multiple testing. The observed R^2 in the categorical outcome is transformed to a liability scale. The analysis models were adjusted for age, sex, chip type, and the first 4 principal components. R^2 represents the variance explained by polygenic scores. The combined PS_{PGS} represents a multivariate analysis of PS_{PGSs} with p values < .05 in the univariate analysis at least either of lithium response, i.e., acetylcholine, GABA, calcium signaling, mitochondria, circadian rhythm, and GSK potential pathways. The genome-wide PGS represents a PGS for genome-wide variants of lithium responsiveness for lithium treatment response in a leave-one-country-out procedure.

aOR, adjusted odds ratio; GABA, gamma-aminobutyric acid; GSK, glycogen synthase kinase; NA, not applicable; PS_{PGS}, pathway-specific polygenic score; SNP, single nucleotide polymorphism.

[a]Denotes significant association after correction for multiple tests.

continuous outcome model to mitigate potential overestimation of the performance of combined PS_{PGSs} in the multivariate analysis using ordinary least squares regression. Furthermore, we implemented a stratified analysis by dividing the ConLi$^+$Gen sample into deciles, ranging from the lowest to the highest polygenic loading for each PS_{PGS}. The proportion of phenotypic variance explained (R^2) by each PS_{PGS} was calculated as the difference in R^2 between the model fit with specific PGSs and covariates and the model with only covariates. For the categorical outcome, McFadden's pseudo R^2 was calculated as a measure of model performance (55). The observed R^2 values were subsequently transformed to the liability (56), assuming a lithium responsiveness prevalence of 30% (44,57) and responders to nonresponders ratio within both the target and replication cohorts.

Figure 1 shows examples of potential targets of lithium (pathways) and detailed steps of the data analysis process.

RESULTS

Description of Study Participants

Our discovery analysis included data from 2367 patients with BD treated with lithium for at least 6 months. Nearly 60% of the participants were female; the mean age (SD) was 47.53 (13.73) years. Six hundred sixty (27.9%) patients had a good response to lithium treatment (defined as an ALDA score ≥7), and the

Table 3. The Association of Pathway-Specific Polygenic Scores With Clinical Lithium Treatment Response Among Patients With Bipolar Disorder in Replication Cohorts (Combined PsyCourse and BipoLife Cohorts) (*N* = 207)

			Categorical Outcome			Continuous Outcome		
Pathways	No. of Genes	No. of SNPs	aOR (95% CI)	*p*	Pseudo R^2, %	β (95% CI)	*p*	R^2, %
Acetylcholine	164	6247	1.21 (0.88 to 1.67)	.09	0.95%	0.24 (−0.15 to 0.64)	.22	0.22%
GABA	76	2994	1.53 (1.09 to 2.14)	.01[a]	2.74%	0.57 (0.18 to 0.96)	.01[a]	3.31%
Calcium Channel	134	4236	0.96 (0.69 to 1.33)	.79	0.05%	0.25 (−0.14 to 0.65)	.21	0.30%
Mitochondria	163	7801	0.96 (0.70 to 1.33)	.83	0.03%	−0.13 (−0.52 to 0.27)	.51	0.01%
Circadian Rhythm	92	3840	0.99 (0.72 to 1.37)	.94	0.02%	0.40 (0.01 to 0.79)	.04[a]	1.38%
Glutamate	129	6673	0.98 (0.71 to 1.35)	.88	0.02%	0.29 (−0.10 to 0.68)	.15	0.54%
Dopamine	155	5794	1.07 (0.78 to 1.47)	.67	0.13%	−0.20 (−0.60 to 0.19)	.31	0.01%
GSK	18	707	1.13 (0.82 to 1.58)	.44	0.33%	0.01 (−0.39 to −0.40)	.96	0.01%
NMDA	11	641	1.13 (0.77 to 1.69)	.81	0.03%	0.13 (−0.26 to 0.52)	.52	0.01%

The cutoff for statistical significance was $p < .05$ after Benjamini-Hochberg procedure correction for multiple testing. The analysis models were adjusted for age, sex, chip type, and the first 4 principal components. The observed R^2 in the categorical outcome is transformed to a liability scale. aOR is from the total sample (before decile stratification). R^2 indicates variance explained by polygenic scores.

aOR, adjusted odds ratio; GABA, gamma-aminobutyric acid; GSK, glycogen synthase kinase; PsyCourse, Pathomechanisms and Signatures in the Longitudinal Course of Psychosis; SNP, single nucleotide polymorphism.

[a]Denotes significant association after correction for multiple tests.

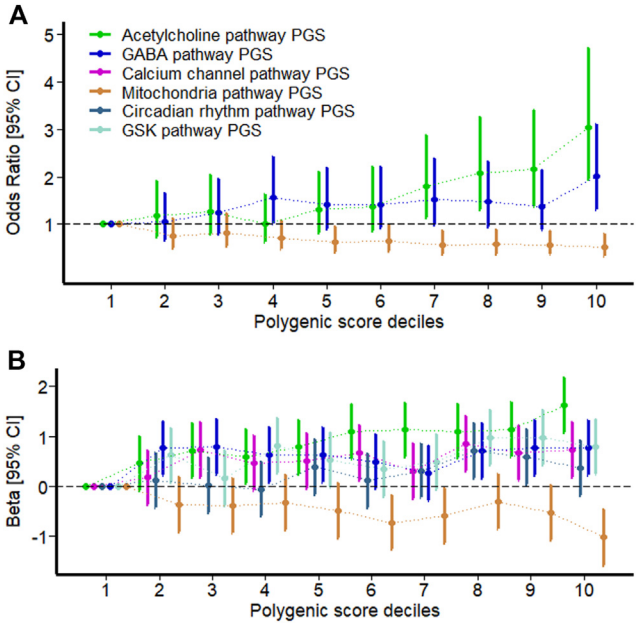

Figure 2. Trends in the odds ratios for favorable lithium treatment response [with the categorical **(A)** and beta coefficeints in the continuous **(B)** outcomes in patients with bipolar disorder, comparing patients with a high pathway-specific PGS, deciles (2nd–10th) with patients with the lowest genetic scores (1st decile; $n = 2367$)] for the pathways that had a significant association after multiple testing. The dot points and error bars represent the odds ratios and 95% CIs for the respective polygenic deciles. The PGS deciles that crossed an odds ratio of 1 on the y-axis in the categorical outcome **(A)** and a beta coefficient of 0 in the continuous outcome **(B)** are not statistically significant. GABA, gamma-aminobutyric acid; GSK, glycogen synthase kinase; PGS, polygenic score.

mean (SD) ALDA total score was 4.12 (3.15). Among the replication cohort participants, 48.0% of the BipoLife participants and 40% of the PsyCourse participants were female. About 28% of patients in the BipoLife cohort and 23% of patients in the PsyCourse cohort had a good response to lithium treatment (Table 1).

Associations of Pathway-Specific Polygenic Scores With Clinical Lithium Treatment Response

BD patients with higher PGSs for acetylcholine genetic variants (ACh_{PGS}) were more likely to have a good lithium treatment response than BD patients with lower PGSs; adjusted odds ratio (aOR) = 1.34 (95% CI, 1.22 to 1.49; $p = 3.54 \times 10^{-8}$; pseudo $R^2 = 1.91\%$) for the categorical outcome and $\beta = 0.38$ (95% CI, 0.26 to 0.51; $p = 3.24 \times 10^{-9}$; $R^2 = 1.56\%$) for the continuous outcome (Table 2). In the stratified analysis, patients with the highest genetic loading for ACh variants (10th decile) were 3.03 times more likely (95% CI, 1.95 to 4.69) to have a good lithium response than patients with the lowest genetic loading (1st decile) (Figure 2). Similarly, BD patients with higher PGSs for GABA genetic variants ($GABA_{PGS}$) were more likely to have a good lithium treatment response than BD patients with lower $GABA_{PGS}$; aOR = 1.15 (95% CI, 1.05 to 1.27; $p = 9.14 \times 10^{-3}$; pseudo $R^2 = 0.34\%$) for the categorical outcome and $\beta = 0.15$ (95% CI, 0.03 to 0.28; $p = .03$; $R^2 = 0.30\%$) for the continuous outcome (Table 2). In the stratified analysis, patients with the highest genetic loading for GABA variants (10th decile) were 2.01 times more likely (95% CI, 1.30 to 3.09) to have a good lithium treatment response than patients with the lowest genetic loading (1st decile) (Figure 2). Higher PGSs for calcium channel variants ($Ca^{2+}{}_{PGS}$) in BD patients were significantly associated with the continuous lithium response ($p = .01$, $R^2 = 0.3\%$) but not with the categorical measure ($p = .11$) (Table 2). The PGS for GSK genetic variants (GSK_{PGS}) and the PGS for circadian rhythm genetic variants (CIR_{PGS}) were positively associated with better lithium response—with continuous outcome ($p = 1.84 \times 10^{-4}$; $R^2 = 0.6\%$) and ($p = .01$, $R^2 = 0.2\%$), respectively, but not with the categorical outcome. In contrast, the increased genetic variance within mitochondria genes was associated with poorer lithium response—categorical ($p = 7.42 \times 10^{-4}$; pseudo $R^2 = 1.05\%$) and the continuous outcomes ($p = 1.02 \times 10^{-4}$; $R^2 = 1.16\%$) in the PGS for mitochondria genetic variants ($MITO_{PGS}$). With a decreasing trend across deciles, BD patients with the highest genetic loadings for mitochondria variants (10th decile) had 52% lower odds of responding to lithium than patients with the lowest genetic loadings (1st decile); aOR = 0.52 (95% CI, 0.33 to 0.80) (Figure 2). The remaining PS_{PGSs} were not significant. The full stratified analysis is presented in the Supplement.

Combined Modeling of Pathway-Specific Polygenic Scores

The multivariate modeling combining PS_{PGSs} that showed a significant association in univariate analysis (combined PS_{PGS}) explained 3.71% of the variance in the categorical and 3.18% in the continuous lithium responses. These results were higher than the variance explained by each of the PS_{PGSs}. To compare the predictive performance of PGSs developed from the pathway-specific approach with the conventional genome-wide method, we developed a PGS for lithium responsiveness ($Li^{+}{}_{PGS}$) using a similar LOC procedure. The $Li^{+}{}_{PGS}$ explained significant variance in the categorical (pseudo $R^2 = 2.87\%$) and continuous (pseudo $R^2 = 2.69\%$) outcomes (Table 2). When comparing these $Li^{+}{}_{PGS}$ R^2 values with the combined PS_{PGS}, no statistically significant difference was found for either the categorical (R^2 difference = 84%; $p = .58$, non-nested model) or the continuous (R^2 difference = 0.49%; $p = .88$, non-nested model) lithium treatment outcomes. These findings indicate that the combined PS_{PGS} resulted in model performance that was comparable to that of the conventional genome-wide PGS (see Supplement). Furthermore, the elastic-net regularization regression model resulted in 2.98% of the variability in the continuous outcome being explained, which is very similar to the results in the multivariate analysis using ordinary least squares regression ($R^2 = 3.18\%$) (Supplement).

Replication Analysis

Using the combined datasets from PsyCourse and BipoLife, we found a statistically significant association between the $GABA_{PGS}$ and lithium treatment response, both for the categorical ($p < .01$, pseudo $R^2 = 2.74\%$) and the continuous ($p = .01$, $R^2 = 3.30\%$) outcomes, replicating the findings from the above analysis. The results showed that patients with BD who

had higher $GABA_{PGSs}$ were 1.53 times more likely (95% CI, 1.09 to 2.14) to have a good lithium treatment response than patients with lower $GABA_{PGSs}$ (for the categorical outcome). For the continuous outcome, each 1-unit increase in the $GABA_{PGS}$ was associated with a 0.57-point increase in the ALDA score (95% CI, 0.18 to 0.96). The CIR_{PGS} was also significantly associated with the continuous lithium response ($p = .01$, $R^2 = 1.38$). Each 1-unit increase in the CIR_{PGS} was associated with a 0.40-point increase in the ALDA score (95% CI, 0.01 to 0.79). The association results of the PGSs for other potential biological pathways were not replicated. The full replication analysis results are available in Table 3.

DISCUSSION

For the first time, we developed biologically informative PS_{PGSs} in well-characterized datasets and evaluated their association with lithium treatment response in patients with BD. Building on a previous study (29) that utilized the conventional genome-wide PGS approach, the current analysis targeted genetic variants mapped within acetylcholine, GABA, calcium channel, mitochondria, glutamate, circadian rhythm, dopamine, NMDA, and GSK pathways that are characterized as potential pharmacological targets in the treatment of BD (58,59). We found that BD patients with higher genetic loading of variants within the acetylcholine, GABA, calcium channel, GSK, and circadian rhythm pathways were more likely to respond to lithium treatment. In contrast, individuals with higher loading for genetic variants in the mitochondria pathway were less likely to respond to lithium. Our stratified analysis showed that patients with the highest genetic loading for acetylcholine, GABA, and calcium channel pathway variants (in the 10th decile) had a good lithium treatment response compared with patients with the lowest genetic loading (in the 1st decile), with an increasing trend of lithium treatment responsiveness across the 1st decile to the 10th decile. The trend was reversed in the mitochondria pathway.

Combined modeling of PS_{PGS} explained 3.71% of the phenotypic variance in categorical and 3.18% in the continuous lithium response, comparable to the predictive power of the conventional polygenic model developed using genome-wide variants (29). While these approaches appear comparable in predictive performance, the PS_{PGS} has advantages over the traditional whole genome polygenic approach in that it uses biological information to optimize the number of SNPs in each pathway or biological phenotype of interest (e.g., circadian rhythm, mitochondrial function) (60). The process of modeling individual genetic variation in lithium-related pathways attempts to enrich the selection of biologically significant variants at the pathway level, making PS_{PGS} more biologically interpretable in comparison to conventional genome-wide PGS (60). Moreover, PS_{PGS} could make the process of drug repurposing more efficient through its focus on specific genes in each pathway that are associated with pharmacogenomic outcomes of interest (61). The pathway-specific polygenic approach also prioritizes variants that may contribute to higher heritability estimates and the detection of enriched and functionally relevant GWAS signals by minimizing noise variants and leveraging the genetic variation across multiple potential biological pathways, thereby achieving better clinical utility (62–65). Combining these scores with clinical data may further increase the variance explained, thereby improving their clinical utility (30).

In terms of the direction of associations with lithium treatment response, ACh_{PGS}, $GABA_{PGS}$, $Ca^{2+}{}_{PGS}$, CIR_{PGS}, and GSK_{PGS} were positively associated. The positive associations between ACh_{PGS}, $GABA_{PGS}$, and lithium response are consistent with evidence suggesting that lithium acts to correct deficits in acetylcholine and GABA neurotransmission (58,59,66,67). A similar association between lithium treatment response and $Ca^{2+}{}_{PGS}$ is consistent with evidence of disruption of cellular calcium concentrations in patients with BD (68). Lithium is known to attenuate calcium release and regulate intracellular calcium levels in hippocampal neurons, thereby reducing excitotoxicity (69). Regarding the circadian rhythm pathway, lithium is widely recognized for its efficacy in improving sleep rhythm by increasing amplitude and slowing rhythm cycles (70,71). Good lithium responders show higher amplitude sleep cycle (72) and lithium has been found to correct rhythm abnormalities in patients with BD (73,74). The positive association between GSK_{PGS} and lithium treatment response aligns with previously reported functional enrichment of the PI3K-Akt signaling pathway, which involves GSK-3β and is associated with response to lithium (75). From the above evidence, a higher genetic loading for lithium response appears to be related to better treatability.

On the other hand, the increased genetic variance within mitochondrial genes was associated with poorer lithium treatment response. Evidence suggests that patients with BD may experience reductions in mitochondrial enzyme levels and overall mitochondrial health, resulting in reduced bioenergetic capacity (76). Mitochondrial gene expression tends to be lower in the postmortem brains of patients with BD and is rescued specifically in lithium responders via a number of potential mechanisms including expression of electron transport chain proteins, second messenger systems such as protein kinase A, protein kinase C and in intracellular potassium and calcium regulation (76–78). Studies in induced pluripotent stem cell–derived neuron culture suggest that lithium may act to correct hyperexcitability via these mechanisms (76). The significant association between $MITO_{PGS}$ and lithium treatment response underscores the centrality of mitochondrial health in lithium's mechanism of action. The relationship between our negative association of these genes with lithium response and protein expression networks needs further exploration.

Pathway-specific PGSs have been employed in several studies to enhance risk stratification in psychiatry (79–82). For example, Grama *et al.* (79) investigated whether behavior- and neuronal-related gene sets, previously implicated in SCZ, were associated with subcortical volumes. They found that PGS derived from an abnormal behavior gene set was associated with right thalamic volume, and this association was robust across *p*-value thresholds, unlike the finding from a genome-wide approach (79). Warren *et al.* (80) also studied the relationship between the genome-wide PGS_{SCZ} and the neurotransmitter PGSs (glutamate, GABA, dopamine, and serotonin) with psychotic disorder presentation. In this study, there was no significant association between individual symptom measures and the PGS_{SCZ}, while glutamate and GABA pathway PGSs were associated with psychosis case

status, and a dopamine pathway PGS was significantly associated with poorer global functioning in participants with psychosis (80). Other studies have shown that a PGS for oxidative stress pathway significantly differentiated individuals with early psychosis status from control individuals (82), and a dopamine pathway PGS has been implicated in the pathophysiology of SCZ (81).

Other examples of the development of PS_{PGSs} in cardiovascular medicine have showcased their potential in personalizing treatment approaches. For example, a PGS for calcium signaling pathways together with phosphatidylinositol/inositol phosphate pathways was associated with hypertensive status, suggesting that their regulation could be a target for prevention and treatment of hypertension (83). PGSs tailored to pharmacodynamic pathways of angiotensin-converting enzyme (ACE) inhibitors (84) and β blockers, respectively, have enhanced patient selection for ACE inhibitors and predicted mortality in patients with heart failure (85). Similarly, a pharmacogenomic polygenic response score developed with 31 genes associated with adenosine diphosphate–based platelet reactivity during clopidogrel treatment has been applied to predict major adverse cardiovascular events and cardiovascular death in patients with coronary artery disease treated with clopidogrel (86).

Based on the evidence presented in our study and the literature summarized above, PS_{PGSs} hold promise for the future of precision psychiatry by refining patient treatment stratification and improving treatment efficacy through leveraging genetic information across specific pharmacological pathways. PS_{PGS}-based stratification of patients as likely good and poor responders could reduce delays in delivering effective treatment and associated burden. Serious side effects of long-term lithium therapy, including chronic renal failure, hypothyroidism, and mortality due to toxicity (87), could also be minimized.

Limitations

While our study provides novel and robust support for the use of PS_{PGS} methods, the results should be interpreted in conjunction with some limitations. First, the $ConLi^{+}Gen$ cohort's retrospective study design introduces challenges in determining associations between a PS_{PGS} and lithium response without a placebo arm. However, the B scale in the ALDA score measures and weights the effect of confounding factors such as treatment duration, number and frequency of mood episodes off treatment, compliance, and use of concomitant psychotropics while on lithium. Second, only participants of European ancestry were included, and these results may not be generalized to other ancestrally diverse populations. Third, while our general strategy for pathway selection was based on the narrative review, we included cholinergic and glutamatergic pathways identified in our previous work with the same sample, highlighting the need for external replication of these pathways (29). The PsyCourse and BipoLife cohorts are genuine replications not used in the previous analysis and therefore mitigate this issue somewhat. Fourth, we used relatively small cohorts for the replication analysis, suggesting that the failure to replicate results for acetylcholine, calcium signaling, and mitochondrial pathways may be subject to type II error. Large and diverse cohorts are needed to further explore and replicate our findings. Fifth, our search was not exhaustive, and we may have excluded important biological pathways implicated in lithium pharmacology.

Conclusions

By focusing on biologically relevant genetic variants, PS_{PGS} for lithium response has shown predictive capabilities comparable to those of the conventional genome-wide PGS, but with the advantage of using fewer SNPs and providing biological interpretability. While the variance in lithium treatment response explained by these models is still small, at best 3.71%, future models may include an expanded range of lithium-specific pathways to improve accuracy, reaching an effect size relevant to stratifying individuals by genetic risk for personalization of lithium treatment. Our study invites further investigation of how proteins including acetylcholine, GABA, calcium signaling, mitochondria, GSK, glutamate, and circadian rhythm pathways interact at the molecular level to define lithium treatment response. Replication in larger cohorts, including cohorts of participants of non-European ancestry, is required to establish the clinical utility of PS_{PGSs}.

ACKNOWLEDGMENTS AND DISCLOSURES

ATA is supported by the National Health and Medical Research Council (NHMRC) Emerging Leadership Investigator (Grant No. 2021–2008 000). NTS is a recipient of the University of Adelaide Research Scholarship. The primary sources of support were the Deutsche Forschungsgemeinschaft (DFG) (Grant Nos. RI 908/7-1, FOR2107, and RI 908/11-1 [to MR] and 246/10-1 [to MMN]) and Intramural Research Program of the National Institute of Mental Health (Grant No. ZIA-MH00284311). The genotyping was funded in part by the German Federal Ministry of Education and Research (BMBF) through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders) under the auspices of the e:Med Programme (grants awarded to TGS, MR, and MMN). The BipoLife (Improving Recognition and Care in Critical Areas of Bipolar Disorders) study was funded by BMBF (to principal investigators [PIs]: FBer, PR, MBa, AR, SK-S, TGS, JW, GJ, AJF, and MLam). UH was supported by the European Union's Horizon 2020 Research and Innovation Programme (PSY-PGx; Grant Agreement No. 945151). Some data and biomaterials were collected as part of 11 projects (Study 40) that participated in the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative. From 2003 to 2007, the PIs and co-investigators were Indiana University, Indianapolis, Indiana, Grant No. R01 MH59545, John Nurnberger, M.D., Ph.D., Marvin J. Miller, M.D., Elizabeth S. Bowman, M.D., N. Leela Rau, M.D., P. Ryan Moe, M.D., Nalini Samavedy, M.D., Rif El-Mallakh, M.D. (at University of Louisville), Husseini Manji, M.D. (at Johnson & Johnson), Debra A. Glitz, M.D. (at Wayne State University), Eric T. Meyer, Ph.D., M.S. (at Oxford University, United Kingdom), Carrie Smiley, R.N., Tatiana Foroud, Ph.D., Leah Flury, M.S., Danielle M. Dick, Ph.D (at Virginia Commonwealth University), Howard Edenberg, Ph.D.; Washington University, St. Louis, Missouri, Grant No. R01 MH059534, John Rice, Ph.D, Theodore Reich, M.D., Allison Goate, Ph.D., Laura Bierut, M.D. Grant No. K02 DA21237; Johns Hopkins University, Baltimore, M.D., Grant No. R01 MH59533, Melvin McInnis, M.D., JRD, Jr., M.D., Dean F. MacKinnon, M.D., FMM, M.D., JBP, M.D., PPZ, Ph.D., Dimitrios Avramopoulos, and Jennifer Payne; University of Pennsylvania, Pennsylvania, Grant No. R01 MH59553, Wade Berrettini, M.D., Ph.D.; University of California at San Francisco, California, Grant No. R01 MH60068, William Byerley, M.D., and Sophia Vinogradov, M.D.; University of Iowa, Iowa, Grant No. R01 MH059548, William Coryell, M.D., and Raymond Crowe, M.D.; University of Chicago, Illinois, Grant No. R01 MH59535, Elliot Gershon, M.D., Judith Badner, Ph.D., FJM, M.D., Chunyu Liu, Ph.D., Alan Sanders, M.D., Maria Caserta, Steven Dinwiddie, M.D., Tu Nguyen, Donna Harakal; University of California at San Diego, California, Grant No. R01 MH59567, JK, M.D., Rebecca McKinney, B.A.; Rush University, Illinois, Grant No. R01 MH059556, William Scheftner, M.D., Howard M. Kravitz,

D.O., M.P.H., Diana Marta, B.S., Annette Vaughn-Brown, M.S.N., R.N., and Laurie Bederow, M.A.; NIMH Intramural Research Program, Bethesda, Maryland, Grant No. 1Z01MH002810-01, FJM, M.D., LK, Psy.D., Sevilla Detera-Wadleigh, Ph.D., Lisa Austin, Ph.D., Dennis L. Murphy, M.D.; Howard University, William B. Lawson, M.D., Ph.D., Evarista Nwulia, M.D., and Maria Hipolito, M.D. This work was supported by the National Cancer Institute (Grant No. P50CA89392) and the National Institute on Drug Abuse (Grant No. 5K02DA021237). The Canadian part of the study was supported by the Canadian Institutes of Health Research (Grant No. 166098), as well as grants from Genome Canada and Research Nova Scotia (to MAl). Collection and phenotyping of the Australian UNSW sample by PBM, PRS, JMF, and AW was funded by Australian NHMRC Program (Grant No. 1037196). The collection of the Barcelona sample was supported by the Centro de Investigación en Red de Salud Mental (CIBERSAM), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), and the Centres de Recerca de Catalunya Programme/Generalitat de Catalunya (Grant Nos. PI080247, PI1200906, PI12/00018, 2014SGR1636, and 2014SGR398). The Swedish Research Council, Stockholm County Council, Karolinska Institutet, and the Söderström-Königska Foundation supported this research through grants awarded to LB, LF, CL, and MScha. The collection of the Geneva sample was supported by the Swiss National Foundation (Grant Nos. Synapsy 51NF40-158776 and 32003B-125469). The collection of the Romanian sample was supported by an Executive Agency for Higher Education, Research, Development and Innovation Funding (U.E.F.I.S.C.D.I.), Romania grant (to MG-S).

We thank all patients who participated in the study, and we appreciate the contributions of the clinicians, scientists, research assistants, and study staff who helped in the patient recruitment, data collection, and biological sample preparation of the studies. We are also indebted to the members of the ConLi$^+$Gen Scientific Advisory Board (http://www.ConLi+Gen.org/) for critical input over the course of the project. Angel's pilot work, as part of her honors thesis, provided the foundation for designing this project, and we gratefully acknowledge her contribution. The analysis of this study was carried out using the high-performance computational capabilities of the University of Adelaide's Phoenix Supercomputer https://www.adelaide.edu.au/phoenix/.

ATA conceived and designed the project and secured a fellowship to lead the study. NTS developed the research proposal, conducted the statistical analysis, interpreted the findings, and drafted the manuscript. ATA, SRC, and KOS provided supervision and critically reviewed the data analysis steps and article draft. All authors contributed genetic and clinical data, provided feedback, and made significant intellectual contributions to the article.

All data used in this analysis are available to ConLi$^+$Gen members. See http://www.conligen.org/ for more information. The following software were used: PRS-CS (see https://github.com/getian107/PRScs), MAGMA (https://ctg.cncr.nl/software/magma), PLINK 2 (https://zzz.bwh.harvard.edu/plink/tutorial.shtml). The custom codes used in this study will be made available upon reasonable request to the corresponding author.

EV has received grants and served as consultant, adviser, or continuing medical education (CME) speaker for the following entities: AB-Biotics, Allergan, Angelini, Astra Zeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), and the Stanley Medical Research Institute. MBa has received grants from the DFG and BMBF and served as consultant, adviser, or CME speaker for the following entities: Allergan, Aristo, Janssen, Lilly, Lundbeck, neuraxpharm, Otsuka, Sandoz, Servier, and Sunovion outside the submitted work. SK-S has received grants and served as consultant, adviser, or speaker for the following entities: Medice Arzneimittel Pütter GmbH and Shire/Takeda. BTB has received grants and served as consultant, adviser, or CME speaker for the following entities: Astra Zeneca, Bristol-Myers Squibb, Janssen, Lundbeck, Otsuka, Servier, the National Health and Medical Research Council, the Fay Fuller Foundation, and the James and Diana Ramsay Foundation. SRC has received grants and served as consultant, adviser, or CME speaker for the following entities: Otsuka Australia, Lundbeck Australia, Janssen-Cilag Australia, and Servier Australia. TKa received honoraria for lectures, manuscripts, and/or consultancy from Kyowa Hakko Kirin Co., Ltd.; Eli Lilly Japan K.K.; Otsuka Pharmaceutical Co., Ltd.; GlaxoSmithKline K.K.; Taisho Toyama Pharmaceutical Co., Ltd.; Dainippon Sumitomo Pharma Co., Ltd.; Meiji Seika Pharma Co., Ltd.; Pfizer Japan Inc.; Mochida Pharmaceutical Co., Ltd.; Shionogi & Co., Ltd.; Janssen Pharmaceutical K.K.; Janssen Asia Pacific; Yoshitomiyakuhin; Astellas Pharma Inc.; Wako Pure Chemical Industries, Ltd.; Wiley Publishing Japan; Nippon Boehringer Ingelheim Co., Ltd.; Kanae Foundation for the Promotion of Medical Science; MSD K.K.; Kyowa Pharmaceutical Industry Co., Ltd.; and Takeda Pharmaceutical Co., Ltd. TKa also received a research grant from Takeda Pharmaceutical Co., Ltd. PF has received grants and served as consultant, adviser, or CME speaker for the following entities Abbott, GlaxoSmithKline, Janssen, Essex, Lundbeck, Otsuka, Gedeon Richter, Servier, and Takeda as well as the German Ministry of Science and the German Ministry of Health. ER has received grants and served as consultant, adviser, or CME speaker for the following entities: Janssen and Institut Allergosan. MLan declares that, over the past 36 months, he has received lecture honoraria from Lundbeck and served as a scientific consultant for EPID Research Oy; he declares no other equity ownership, profit-sharing agreements, royalties, or patents. KAk has received consulting honoraria from Taisho Toyama Pharmaceutical Co., Ltd. In 2021, JZ served as an adviser for Biogen concerning Aducanumab (Alzheimer's disease). All other authors report no biomedical financial interests or potential conflicts of interest.

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Received Mar 18, 2025; revised May 28, 2025; accepted Jun 3, 2025.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsgos.2025.100558.

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