Cost-Effectiveness of Routine Screening for Autoimmune Encephalitis in Patients With First-Episode Psychosis in the United States

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ABSTRACT

Objective: Autoimmune encephalitis (AE) is a highly treatable neurologic condition that can cause psychosis. Screening for AE is not currently recommended in routine workup for first-episode psychosis (FEP), owing partly to the high cost of testing for AE-associated neuronal autoantibodies.

Methods: This study used a decision-analytic model to estimate the cost-effectiveness of routine serum screening for AE compared with clinically targeted screening in patients with FEP. Model parameters drawn from prior published literature included the prevalence of neuronal autoantibodies in FEP (4.5%), serum autoantibody panel cost (US $291), remission probability with antipsychotics (0.58), and remission probability with immunotherapy for patients diagnosed with AE (0.85). Outcomes included quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratios (ICERs), assessed over a 5-year horizon from the US health care sector and societal perspectives. ICER thresholds of $50,000/QALY to $150,000/QALY were used to define cost-effectiveness. The analysis was conducted between June 2018 and January 2020.

Results: Routine screening led to mean QALY gains of 0.008 among all patients and 0.174 among the subgroup of patients with neuronal autoantibodies. Mean costs increased by $780 from a societal perspective and $1,150 from a health care sector perspective, resulting in ICERs of $99,330/QALY and $147,460/QALY, respectively. Incorporating joint input data uncertainty, the likelihood routine screening has an ICER ≤ $150,000/QALY was 55% from a societal perspective and 37% from a health care sector perspective. The model parameter with the greatest contribution to overall uncertainty was the effectiveness of immunotherapy relative to antipsychotics.

Conclusions: Routine screening for AE in patients with FEP may be cost-effective in the United States. As further immunotherapy effectiveness data become available, a more definitive recommendation to perform routine screening could be warranted.

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Patients presenting with their first episode of psychosis pose a diagnostic challenge: along with clarifying their psychiatric diagnosis, clinicians must assess for treatable medical conditions that could underlie their psychotic symptoms. There are numerous toxicologic, metabolic, infectious, and autoimmune conditions that can manifest with psychosis.[1] Guidelines recommend routine testing for a subset of these conditions,[1,2] though the evidence to support these recommendations is limited.[3]

One cause of psychotic symptoms that has recently sparked great interest is autoimmune encephalitis (AE). AE is a neuroinflammatory condition that is often associated with antibodies directed against neuronal proteins; depending on the specific target, antibodies may be directly pathogenic or an indirect marker of inflammation.[4] Symptoms can include seizures, autonomic dysfunction, cognitive dysfunction, movement disorders, and psychosis.[5] Among patients with anti-NMDA receptor (anti-NMDAR) encephalitis (the best-characterized and most common subtype of AE), psychiatric presentations are common, although most patients go on to develop neurologic symptoms.[6,7] Immunosuppressive treatment is highly effective for such patients, with case series reporting lasting remission in approximately 80% of patients.[7–9]

Given the treatability of AE, accurately diagnosing it could be life-altering for a person with first-episode psychosis (FEP). However, the value of testing for neuronal autoantibodies is limited by the low prevalence of potentially relevant autoantibodies in FEP cohorts (0%–9%)[9–11] and the high cost of testing (approximately $300 for a frequently used autoantibody panel).[12] Unfortunately, several case-control studies evaluating psychiatric patients without focal neurologic findings have failed to find clinical characteristics that can reliably distinguish patients with AE from those without,[11,13] leaving routine testing as the only definitive means of identifying FEP patients with AE. Yet despite its high cost, routine testing for AE could still prove to be a good health-economic value, especially given the potential to avert the long-term costs associated with managing chronic psychosis.[14]

Clinical Points

- Autoimmune encephalitis can cause psychotic symptoms; around 5% of patients with first-episode psychosis have serum autoantibodies associated with autoimmune encephalitis.
- Although testing for serum autoantibodies can be expensive, it may be cost-effective by commonly applied US standards.
- In patients with first-episode psychosis, clinicians should consider performing routine screening for autoimmune encephalitis.

To quantify the costs and clinical benefits of testing for AE, we conducted a decision-analytic modeling study using a newly developed model of FEP evaluation and treatment. Our analysis had two main objectives: (1) to estimate the cost-effectiveness of routine autoantibody testing compared to clinically targeted testing in patients with FEP in the United States and (2) to determine what future research would most effectively reduce uncertainty in the costs and benefits of routine testing and thus better inform clinical decision-making.

METHODS

Overview

We used a decision-analytic model to simulate the clinical and economic consequences of two strategies for detection of AE in a cohort of patients with FEP:

1. *Routine testing*: all patients with FEP are tested for a panel of serum autoantibodies that have been associated with AE.
2. *Clinically targeted testing*: only patients developing neurologic symptoms suggestive of AE are tested.

Under both strategies, patients with positive results for any relevant serum autoantibody undergo further workup to confirm an AE diagnosis[15]; if this diagnosis is confirmed, they are treated with immunotherapy (steroids, intravenous immunoglobulin [IVIG], etc).[4]

We simulated both strategies over a 5-year horizon; this horizon was intended to capture longer-term costs and benefits of AE testing without requiring excessive extrapolation beyond available outcomes data.[7,16] At 5 years, we calculated the mean quality-adjusted life-years (QALYs) and costs accrued by patients under each strategy, using both societal and health care sector perspectives (Supplementary Table 1 in Appendix 1).[17] To reflect their present value, future costs and QALYs were discounted 3% annually.[17]

Using these outcomes, we calculated the incremental cost-effectiveness ratio (ICER) of routine testing, defined as the ratio of its incremental cost to its incremental QALYs (relative to clinically targeted testing). In the United States, previous authors[18,19] have advocated using upper-bound ICER thresholds between $50,000/QALY and $150,000/QALY for defining cost-effective medical interventions. To reflect this, we considered discrete cost-effectiveness thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY in this analysis.

In describing our analysis and results, we adhered to the 2013 Consolidated Health Economic Evaluation Reporting Standards guidelines.[20] As secondary research without identifiable data, this study was exempt from institutional review board regulation. The analysis was conducted between June 2018 and January 2020.

Model Description

We developed a novel state-transition model of FEP diagnosis and treatment for this analysis (Figure 1). The model uses a 3-month cycle length. The model is implemented in Microsoft Excel (Microsoft Corporation); statistical analyses were performed using R and OpenMetaAnalyst.[21]

Patients enter the model at diagnosis of their first psychotic episode. Under the routine screening strategy, all patients are immediately tested for a panel of serum neuronal autoantibodies. Those with negative results are treated with antipsychotic medications and usual psychiatric care. Antipsychotic-treated patients enter health states reflecting either remission or non-remission of psychotic symptoms, with non-remission encompassing both treatment failure and partial symptomatic response.[16] Of note, these health states are intended to accurately capture long-term outcomes of FEP treatment rather than simulate short-term dynamics of remission, non-remission, and relapse.[22]

Patients with positive serum autoantibody screening receive confirmatory workup including neurology consultation, imaging, and further laboratory testing.[15] If this workup fails to confirm the diagnosis of AE, patients receive antipsychotics as described above. If this workup confirms the diagnosis of AE, patients are treated with immunotherapy in addition to psychiatric care, with distinct remission and non-remission rates.[4]

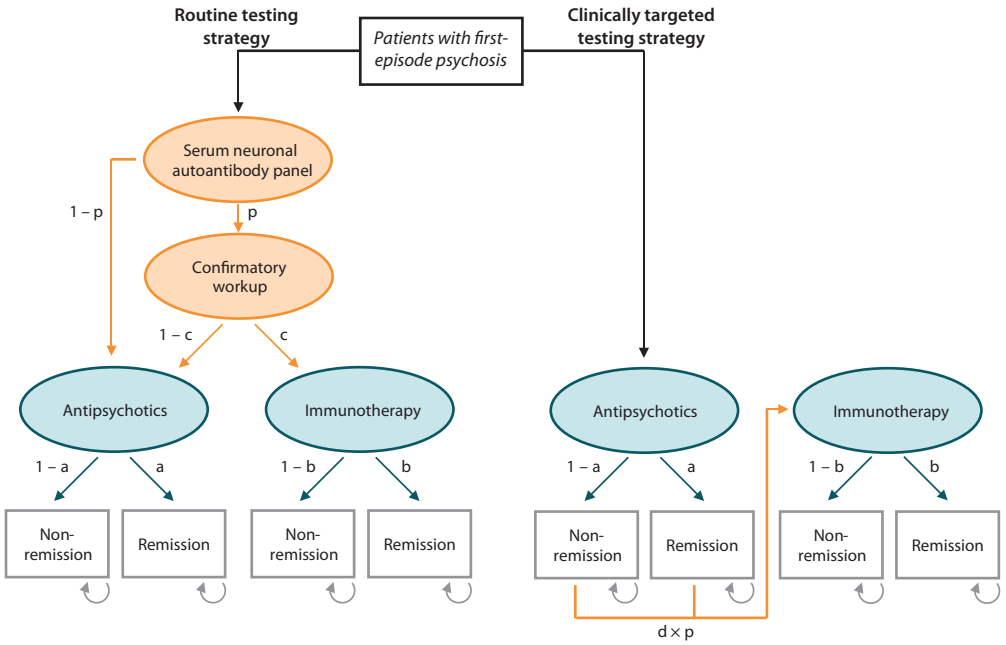
Finally, under the clinically targeted testing strategy, all patients are initially treated with antipsychotic medications. Within the first 3 months, a fraction of patients are diagnosed with AE based on clinical suspicion; these patients incur the costs of screening and confirmatory workup and are then treated with immunotherapy in addition to receiving psychiatric care. On the basis of data suggesting that patients with AE who develop focal neurologic findings do so within several weeks of presentation with psychosis,[9,11] we assumed that clinically targeted diagnosis of AE occurs only within the first 3 months; we varied this assumption in sensitivity analysis.

Model Input Parameters

Base case model input data, sensitivity analysis ranges, and sources are described in the following sections and summarized in Table 1.

Mortality. We did not explicitly simulate patients' demographic characteristics, but instead used mortality and clinical outcomes data that reflect typical FEP patients.[16,23]

Figure 1. Model Structure[a]



[a]The left side of the figure shows the model structure used to simulate the routine screening strategy; the right side shows the structure used to simulate the clinically targeted testing strategy. Rectangles indicate health states; orange ovals and arrows indicate diagnostic testing; blue ovals and arrows indicate treatment. Model parameters are denoted as follows: **p**, serum neuronal autoantibody prevalence in patients with first-episode psychosis; **c**, probability that autoantibody is deemed clinically relevant after further workup; **a**, probability of remission of psychosis with antipsychotic treatment; **b**, probability of remission of psychosis with immunotherapy among patients with clinically relevant neuronal autoantibodies; **d**, probability of clinically targeted diagnosis with autoimmune encephalitis.

Table 1. Model Input Data

Parameter	Base Case Value	Probabilistic Sensitivity Analysis Range	Distribution	References
General				
Annual discount rate, %	3	…	…	17
Time horizon, y	5	…	…	…
Mortality probability, per year				
Year 1 after diagnosis	0.0055	0.0041–0.0068	Normal	23
Year 2 after diagnosis	0.0047	0.0033–0.0061	Normal	23
Year 3+ after diagnosis	0.0035	0.0025–0.0049	Normal	23
Utility by health state				
Remission	0.77	0.75–0.78	Normal	26
Non-remission	0.53	0.52–0.54	Normal	26
Neuronal autoantibody testing				
Serum autoantibody prevalence, percent	4.5	2.0–9.5	Logit-normal	9, 11, 27, 28
Probability autoantibody is clinically relevant	0.76	0.63–0.85	Logit-normal	9, 32, 33
Probability of clinically targeted autoimmune encephalitis diagnosis	0.15	0.01–0.87	Logit-normal	9, 11
Treatment effectiveness, remission probability				
Antipsychotics	0.58	0.53–0.63	Logit-normal	16
Immunotherapy	0.85	0.67–0.94	Logit-normal	7–9, 34, 35
Costs, 2015 US dollars				
Serum autoantibody panel cost	291	…	…	12, 39
Confirmatory workup cost, if serum panel positive	1,084	765–1,402	Normal	32, 39, 41, 42
Immunotherapy cost, per quarter				
Months 1–3	25,217	17,803–32,631	Normal	4, 43, 44
Months 4–6	2,262	1,597–2,927	Normal	4, 43, 44
Months 7–24	1,732	1,223–2,241	Normal	4, 43, 44
Months 25+	123	87–159	Normal	4, 43, 44
Background health care cost, per year				
Remission	17,511	12,363–22,660	Normal	46
Non-remission	24,074	16,997–31,152	Normal	46
Additional societal cost, per year				
Remission	47,319	33,408–61,231	Normal	46–48
Non-remission	58,662	41,416–75,908	Normal	46–48

Mortality data were derived from a 3-year study[23] of 11,713 Kaiser Permanente members aged 16–30 years with a newly diagnosed psychotic disorder. Annual mortality probability was 0.55% in the first year after diagnosis, 0.47% in the second year, and 0.35% in the third year; we assumed the third year value would also apply to years 4 and 5 in our projections. While both FEP and AE are associated with increased mortality, there is limited evidence on the survival benefit of treatment[23,24]; hence, we made the conservative assumption that neither antipsychotic treatment nor immunotherapy would directly impact mortality.[25]

Utility. Utility data were derived from an observational study[26] measuring quality of life (assessed by the EuroQol-5D rating scale) and symptom severity (assessed by the Clinical Global Impressions scale) among 9,340 outpatients with schizophrenia. We grouped Clinical Global Impressions scale scores of 1–3 (normal/minimally/mildly ill, comprising 16% of the cohort at baseline) into our "remission" health state and scores of 4–7 (moderately/markedly/severely/most severely ill, comprising 84% of the cohort at baseline) into our "non-remission" health state. Utility estimates for the two states were 0.77 and 0.53, respectively.

Autoantibody testing. To estimate the prevalence of serum neuronal autoantibodies, we performed a meta-analysis of 4 studies that tested for a panel of neuronal autoantibodies in FEP patients without focal neurologic findings; 2 samples were from the United Kingdom,[11,27] 1 from Australia,[9] and 1 from Finland.[28] In total, 27 of 507 FEP patients were positive for at least 1 disease-relevant neuronal autoantibody, including antibodies against NMDAR, CASPR2, LGI1, AMPAR, and $GABA_AR$.[29] VGKC antibodies in the absence of LGI1 or CASPR2 positivity, and immunoglobulin A (IgA) or IgM without IgG antibodies against NMDAR were not considered clinically relevant.[30,31] A logit-transformed, restricted maximum likelihood meta-analysis of these studies yielded an estimated autoantibody prevalence of 4.5% (95% CI, 2.0%–9.5%) (Supplementary Figure 1 in Appendix 1).

While all aforementioned patients lacked neurologic findings and were diagnosed with AE by routine testing, some of them most likely would have been diagnosed based on clinical suspicion even without routine testing. To estimate the likelihood of this, we performed a meta-analysis of 2 of the aforementioned studies that reported on subsequent development of neurologic findings in patients with positive serum autoantibodies. Lennox et al[11] reported that over 6 months after initial diagnosis, none of 20 patients with disease-relevant serum autoantibodies developed neurologic symptoms, as assessed by their psychiatrists. In contrast, Scott et al[9] reported that 2 of 4 patients with disease-relevant serum autoantibodies developed seizures within 2 weeks of diagnosis. Combining these data yielded an estimated clinically targeted diagnosis probability of 0.152 (95% CI, 0.005–0.871) (Supplementary Figure 2 in Appendix 1).

To estimate the likelihood that a positive serum autoantibody would be deemed clinically relevant after further workup, we performed a meta-analysis of 3 studies[9,32,33] that reported results of further diagnostic workup (including imaging and lumbar puncture) in patients with positive serum autoantibody results. In total, 49 of 64 patients were deemed to have clinically relevant autoantibodies, yielding an estimated probability of 0.756 (95% CI, 0.634–0.847) (Supplementary Figure 3 in Appendix 1).

Treatment effectiveness. On the basis of a meta-analysis of long-term outcomes of FEP (mean follow-up = 5.5 years),[16] we used a probability of remission with antipsychotic treatment of 0.579. To estimate the effectiveness of immunotherapy, we performed a meta-analysis of 5 studies[7–9,34,35] that reported treatment outcomes for FEP patients with no neurologic findings and positive neuronal autoantibodies who received immunotherapy plus antipsychotics. All studies were case series or small prospective cohorts (Supplementary Table 2 in Appendix 1). In total, 27 of 30 patients achieved symptomatic remission, yielding an estimated probability of 0.846 (95% CI, 0.665–0.938) (Supplementary Figure 4 in Appendix 1). For comparison, in a cohort of 501 patients with anti-NMDAR encephalitis (not restricted to FEP patients),[7,24] approximately 80% achieved good functional outcomes with immunotherapy.

Costs. We used Medical Care Expenditure indices from the Bureau of Economic Analysis to inflate costs from prior years to 2015 US dollars (USD), the most recent year available for these indices.[36,37] To deflate costs from later years, we used Personal Consumption Expenditure indices compiled by the Federal Reserve.[38]

The cost of a serum neuronal autoantibody panel was calculated by applying unit costs from the Centers for Medicare and Medicaid Services (CMS) Clinical Diagnostic Laboratory Fee Schedule[39] to the individual components of Mayo Clinic Laboratories' serum AE panel (test ID: ENS2).[12] This yielded a total cost of $291 per panel; we varied this cost in sensitivity analysis.

For patients with a positive serum autoantibody panel, further workup included a neurology consultation (averaging 1 initial evaluation and 1.8 follow-up evaluations)[40]; brain magnetic resonance imaging with and without contrast; a 1-hour electroencephalogram (EEG); serum albumin and IgG quantitation; and a lumbar puncture, with cerebrospinal fluid studies including cell count and differential, glucose, protein, albumin, culture, gram stain, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) polymerase chain reaction (PCR), IgG quantitation, and a spinal fluid AE panel (Mayo Clinic Laboratories test ID: ENC2).[15,32,41] Laboratory test costs in this confirmatory workup were derived from the CMS Clinical Diagnostic Laboratory Fee Schedule[39]; costs of physician evaluations, procedures, and imaging were derived from the CMS Physician Fee Schedule.[42] Summing these components yielded a total cost of $1,084 per confirmatory workup; in sensitivity analysis, we assumed a standard error equal to 15% of this mean estimate.

Estimating the aggregate cost of immunotherapy used to treat AE is challenging, as patients receive multiple

successive and/or concurrent medications,[24] treatment choices differ greatly by institution and individual provider,[35] and the costs of specific treatments vary widely (eg, $75 for a methylprednisolone infusion vs $2,293 for an IVIG infusion).[4,43,44] To address this heterogeneity, we based our costing analysis around treatment frequency from an observational study[24] of 501 patients with anti-NMDAR encephalitis; 91% received steroids, 75% IVIG, 35% plasma exchange, 22% rituximab, 18% cyclophosphamide, and 7% other medications including azathioprine and mycophenolate. For each treatment, we used doses and dosing intervals suggested in the literature[4] and derived unit costs from online databases[43,45] and prior costing analyses[44]; full details are provided in Supplementary Table 3 in Appendix 1. In total, we estimated mean quarterly costs of $25,217 for months 1–3, $2,262 for months 4–6, $1,732 for months 7–24, and $123 thereafter.

We derived background health care costs (including antipsychotic medications, other medications, and outpatient, inpatient, and emergency department services) for FEP patients from an observational cohort study of 389 people with schizophrenia.[46] Over 12 months, patients with remission had a mean quarterly health care cost of $4,378, as compared with $6,019 among patients without remission.

When performing analyses from a societal perspective, we also incorporated criminal justice, lost productivity, and caregiver burden costs.[45] To estimate criminal justice and lost productivity costs, we used data from the same observational study that provided health care cost estimates.[46] Twelve months after enrollment, the fraction of patients reporting being arrested in the previous 6 months was 0.05 for those with remission versus 0.04 for those without; the fractions reporting being the victim of a crime in the preceding 4 weeks were 0.05 and 0.11, respectively, and the fractions with paid employment were 0.29 and 0.21, respectively. We applied costs of $22,385 per arrest, $5,430 per victimization, and $47,255 per year of unemployment, drawn from a study evaluating the total economic burden of schizophrenia in the United States.[47] Finally, to estimate the societal cost of unpaid caregiving, we used data from a 2015 survey conducted by the National Alliance for Caregiving.[48] Caregivers of individuals with "mild" or "moderate" psychotic disorders (N = 106) spent a mean of 10.5 hr/wk of caregiving (95% CI, 8.5–12.4 hr/wk) as compared with 16.0 hr/wk (95% CI, 14.7–17.3 hr/wk) among those whose illness was categorized as "severe." In our model, we applied these values to patients in the remission and non-remission states using an hourly cost of $23 (mean hourly wage in the United States) for the 65% of patients in contact with family caregivers.[47]

Sensitivity Analyses

To quantify the uncertainty in our results and assess their robustness to alternative modeling assumptions, we performed several types of sensitivity analysis. In probabilistic sensitivity analysis, the model was run using input parameter values drawn at random from each parameter's uncertainty distribution (Table 1); we compiled model results across 10,000 iterations of this process to estimate aggregate uncertainty in our results.

In scenario sensitivity analysis, we assessed the effects of several alternative modeling and input parameter assumptions on our results. Scenarios included the following:

- Serum autoantibody panel cost varied between $100 and $500
- Clinically targeted diagnosis probability of 0.02 per cycle after the first cycle
- Only patients with anti-NMDAR IgG on serum autoantibody panel receive further workup or immunotherapy; using the 4 studies included in our overall meta-analysis,[9,11,27,28] we estimated a prevalence of anti-NMDAR IgG in FEP patients of 2.8% (95% CI, 1.6–4.8) (Supplementary Figure 5 in Appendix 1)
- Likelihood serum autoantibody is deemed clinically relevant varied between 0.5 and 1.0
- Time horizon of 10 years

Finally, we used value-of-information analysis to assess each model parameter's contribution to overall uncertainty in our results. We used the generalized additive regression method developed by Strong et al[49] to calculate expected value of partial perfect information (EVPPI) for groups of parameters. For a given set of parameters, EVPPI estimates the upper limit of the economic value of better informing a medical decision by eliminating uncertainty in those parameters; hence, parameters with higher EVPPI contribute more to decision uncertainty and may represent a more valuable topic of future research.[50]

RESULTS

Model Validation

To assess the external validity of our model, we compared model projections to independent estimates from the literature. Estimates of mean per-person annual health care costs over 24 months after FEP diagnosis include $20,066, $21,828, and $22,338, from 3 independent claims-based studies of commercially-insured patients with newly diagnosed schizophrenia[51–53] and $13,498 from the usual-care arm of an FEP early intervention trial.[54] Of note, the latter study measured resource utilization via patient interview, and hence may have underestimated total costs. For comparison, our model projected a mean per-person annual health care cost of $20,278.

Because our model uses an aggregate, long-term estimate of treatment effectiveness as input data,[16] there were no adequate validation targets available for clinical outcomes.

Base Case

Base case results are shown in Table 2. Among all patients, routine autoantibody screening increased the fraction of life-years spent in remission from 58.1% to 58.8%; among the subgroup of patients with neuronal autoantibodies, remission

Table 2. Base Case Results

Variable	Clinically Targeted Testing	Routine Testing	Difference[a]
Fraction of time spent in remission, %			
All patients	58.1	58.8	0.7
Autoantibody-positive patients	61.9	78.1	16.1
Autoantibody-negative patients	57.9	57.9	0
Mean QALYs			
All patients	3.053	3.061	0.008
Autoantibody-positive patients	3.095	3.269	0.174
Autoantibody-negative patients	3.051	3.051	0
Mean costs, 2015 USD			
Total cost, societal perspective	331,410	332,190	780
Total cost, health care sector perspective	93,030	94,190	1,150
Cost components			
Autoimmune encephalitis testing cost	10	340	330
Immunotherapy cost	260	1,310	1,040
Background health care cost	92,760	92,540	−220
Additional societal cost	238,380	238,010	−380
Incremental cost-effectiveness ratios, USD/QALY			
Societal perspective	…	…	99,330
Health care sector perspective	…	…	147,460

[a]Due to rounding, some values in this column do not appear equal to the difference between values in the other two columns.
Abbreviations: QALY = quality-adjusted life-year, USD = US dollars.

increased more markedly, from 61.9% to 78.1% of life-years. These increases in remission translated into quality-adjusted survival gains of 0.008 QALYs for the entire cohort and 0.174 QALYs for patients with neuronal autoantibodies.

Total societal costs increased by $780 per patient with routine testing, and total health care sector costs increased by $1,150 per patient. These increases were driven largely by the cost of immunotherapy for patients with AE (cost increase $1,040), with a smaller contribution from AE testing (cost increase $330). Background health care costs (–$220) and additional societal costs (–$380) both declined with routine testing.

From a societal perspective, routine testing had an ICER of $99,330/QALY versus clinically targeted testing; from a health care sector perspective, routine testing had an ICER of $147,460/QALY.

Sensitivity and Uncertainty Analyses

In probabilistic sensitivity analysis (Figure 2), the likelihood that routine testing is cost-effective at a cost-effectiveness threshold of $150,000/QALY was 55.3% from a societal perspective and 37.4% from a health care sector perspective. With lower thresholds, the likelihood of cost-effectiveness declined, reaching 14.9% and 0.5%, respectively, at a threshold of $50,000/QALY.

In scenario sensitivity analyses, routine testing maintained a moderate probability of being cost-effective under a range of alternative modeling assumptions. At a cost-effectiveness threshold of $150,000/QALY, routine testing had >35% likelihood of being cost-effective from a societal perspective under all scenarios examined (Figure 3A); from a health care sector perspective, this value was >20% under all scenarios examined (Figure 3B). Notably, extending the time horizon to 10 years substantially increased the likelihood of cost-effectiveness to 82.0% (societal) and 78.1% (health care sector).

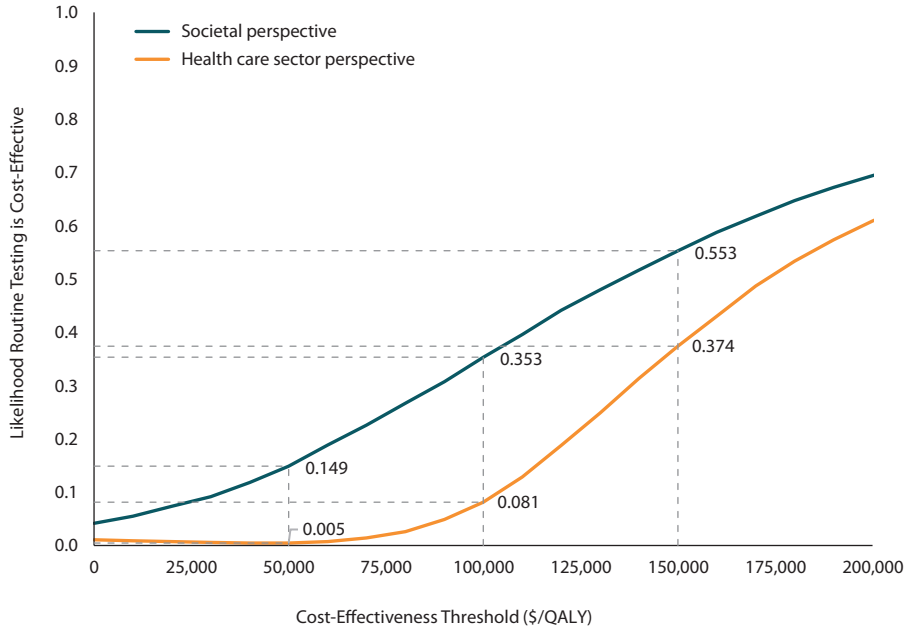
In value-of-information analysis (Supplementary Figure 6 in Appendix 1), we found that the effectiveness of immunotherapy versus antipsychotics had the greatest contribution to overall uncertainty, under both societal and health care sector perspectives (mean per-person EVPPIs $87 and $101, respectively, at a cost-effectiveness threshold of $150,000/QALY). Other model parameters with mean per-person EVPPI >$10 included the cost of immunotherapy, background health care costs, additional societal costs, the prevalence of serum autoantibodies, and the probability of clinically targeted AE diagnosis.

DISCUSSION

We performed a decision-analytic modeling analysis to evaluate the cost-effectiveness of routine screening for AE in patients with FEP. We found that routine screening could markedly improve clinical outcomes (increasing remission from 62% to 78% among patients with neuronal autoantibodies) at an acceptable cost-effectiveness ratio (societal ICER $99,330/QALY, health care sector ICER $147,460/QALY). For comparison, similar ICER estimates have been reported for a comprehensive FEP early-intervention program ($84,570/QALY).[54]

Applying recommendations from the American College of Cardiology[19] and expert opinion in the health care cost-effectiveness field,[18] these ICER estimates suggest that routine testing for AE should be designated "intermediate value" or simply "cost-effective." However, our findings come with substantial uncertainty: incorporating joint input parameter uncertainty, we estimate an approximately 40%–60% likelihood (depending on perspective) that this ICER falls below the "intermediate value" threshold of $150,000/QALY.[19] Overall, our results suggest that screening for AE in patients with FEP could provide an acceptable health-economic value, but given the uncertainty in our findings,

Figure 2. Probabilistic Sensitivity Analysis[a]



[a]The x-axis shows a range of possible cost-effectiveness thresholds, expressed in dollars per quality-adjusted life-year (QALY). The y-axis indicates the likelihood that routine autoantibody screening would be deemed cost-effective at a given cost-effectiveness threshold, based on probabilistic sensitivity analysis consisting of 10,000 model runs. The blue and orange curves show the likelihood of cost-effectiveness under societal and health care perspectives. Dotted lines and numbers on the plot indicate the likelihood of cost-effectiveness at specific cost-effectiveness thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY.

a definitive recommendation to routinely screen for AE in FEP is not warranted.

The model parameter with the single greatest contribution to overall uncertainty in our analysis was the relative effectiveness of immunotherapy versus antipsychotics in FEP patients with AE. This finding reflects the current paucity of data on immunotherapy efficacy in FEP patients, and it suggests that rectifying this evidence gap will be critical to better informing clinical decision-making. Notably, a trial in the United Kingdom, the Study of Immunotherapy in Antibody Positive Psychosis (SINAPPS2),[35,55] is currently enrolling patients with FEP and positive serum autoantibody screens, who will be randomized to immunotherapy versus placebo (in addition to antipsychotics). Our analysis suggests that this trial's findings (expected in 2022) could significantly refine AE diagnosis and treatment recommendations in FEP.

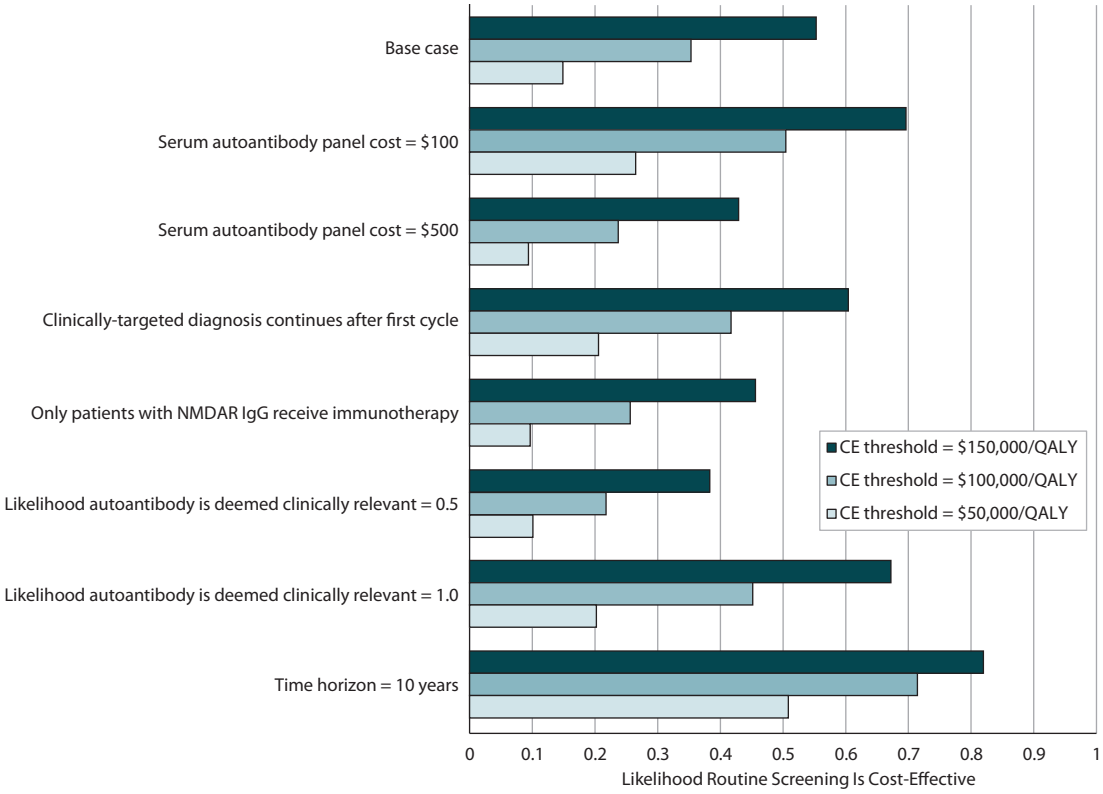
Limitations

Our results should be interpreted in the context of several limitations. There is controversy in the literature surrounding whether neuronal autoantibodies are truly disease-causing in FEP[29]: while some authors have reported high rates of autoantibodies in FEP patients[11] and excellent immunotherapy outcomes,[8,9,35] others have failed to find autoantibodies in FEP samples[28] or reported similar prevalence in FEP and control samples.[27] By providing the first placebo-controlled outcomes data on AE treatment in FEP, the aforementioned SINAPPS2 trial[35,55] should be instrumental in addressing these discrepancies; in the meantime, we have incorporated all available data (positive and negative) into our modeling analysis.

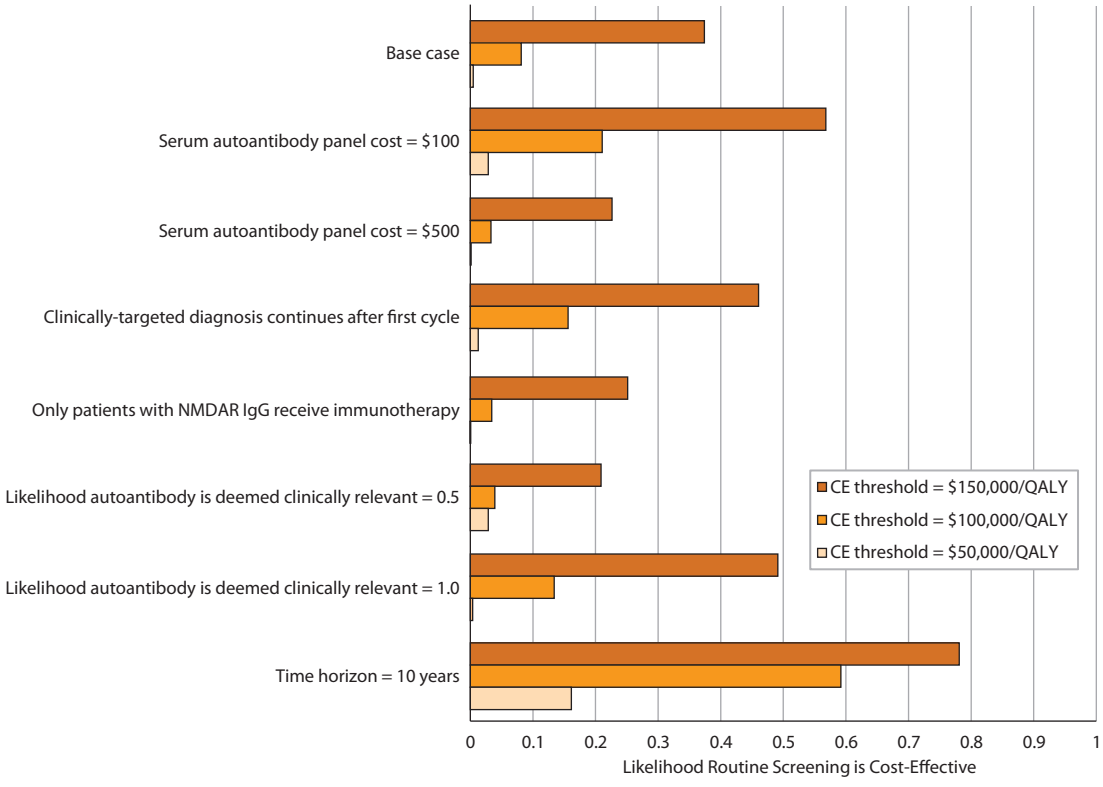
There are multiple limitations to our model's input data. First, data on AE treatment outcomes extending beyond 3 years in patients with FEP are lacking.[7,9] To avoid excess extrapolation, we thus used a relatively short 5-year time horizon, which may fail to capture relevant longer-term outcomes and changes in treatment effectiveness; indeed, sensitivity analysis using a 10-year horizon improved the cost-effectiveness of routine AE screening. Our estimates of immunotherapy efficacy,[7–9,34,35] the likelihood autoantibodies are deemed clinically relevant,[32] and the likelihood of clinically-targeted AE diagnosis[9,11] are based on sample sizes below 100; in the absence of alternative data sources, we address this issue by incorporating appropriately broad confidence intervals into our uncertainty analyses. Alternative approaches to AE screening, such as routine cerebrospinal fluid or EEG testing or systematic use of clinical "red flags" to guide testing, might prove to be superior to routine serum testing[56]; however, there were insufficient data available to assess the cost-effectiveness of these approaches. In addition, there were no data to inform the efficacy of antipsychotics in patients with AE versus the broader FEP population, or the efficacy of immunotherapy in patients diagnosed with AE via routine testing versus clinically targeted testing; again, we expect the SINAPPS2 trial[55] will provide critical insight into these issues. Finally, our model is inherently simplified and does not capture the

Figure 3. Scenario Sensitivity Analysis From (A) a Societal Perspective and (B) a Health Care Sector Perspective[a]

A. Scenario sensitivity analysis, societal perspective



B. Scenario sensitivity analysis, healthcare sector perspective



[a]The y-axis in each figure shows several scenarios consisting of specific alternative modeling assumptions simulated in sensitivity analysis. The x-axis in each figure indicates the likelihood that routine autoantibody screening would be deemed cost-effective under each scenario according to the cost-effectiveness thresholds indicated in the legend.

Abbreviations: CE = cost-effectiveness, IgG = immunoglobulin G, NMDAR = *N*-methyl-D-aspartate receptor, QALY = quality-adjusted life-year.

full complexity of clinical factors such as family caregivers' quality of life or long-term cognitive impairment associated with delayed treatment of autoimmune encephalitis.[48,57]

CONCLUSIONS

In this decision-analytic modeling analysis, we found that routine screening for AE in patients with FEP may be cost-effective in the United States, though there is substantial uncertainty around this finding. To reduce uncertainty, further research into the efficacy of immunotherapy in this population is needed. Until such data are available, our results suggest that routine screening could provide an acceptable clinical and health-economic value, but a definitive recommendation to perform routine AE screening in FEP patients is not currently warranted.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Psychosis section. Please contact Ann K. Shinn, MD, MPH, at ashinn@psychiatrist.com.

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Supplementary Material

Article Title: Cost-Effectiveness of Routine Screening for Autoimmune Encephalitis in Patients With First-Episode Psychosis in the United States

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Appendix 1

Supplementary Table 1: Impact inventory

Sector	Type of impact	Included in this analysis from given perspective?	
		Healthcare sector	**Societal**
Formal healthcare sector			
Health	Health outcomes		
	Longevity effects	No	No
	Health-related quality of life effects	**Yes**	**Yes**
	Other health effects (e.g. adverse effects)	No	No
	Medical costs		
	Third-party payers	**Yes**	**Yes**
	Out-of-pocket	**Yes**	**Yes**
	Future related medical costs	**Yes**	**Yes**
	Future unrelated medical costs	**Yes**	**Yes**
Informal healthcare sector			
Health	Patient-time costs	No	No
	Unpaid caregiver-time costs	No	**Yes**
	Transportation costs	No	No
Non-healthcare sector			
Productivity	Unemployment due to illness	No	**Yes**
Criminal justice	Victimization of patients	No	**Yes**
	Arrests of patients	No	**Yes**

Supplementary Table 2: Studies of immunotherapy for autoimmune encephalitis in first-episode psychosis

Author and year	N before/after exclusion	Reasons for exclusion	Treatments received	Remission definition	N with remission (non-excluded patients)	Follow-up duration
Kayser 2013[1]	5/4	*1 patient*: "unknown" treatment	Steroids, IVIG, rituximab, azathioprine, mycophenolate	"Full recovery"	4	24-37 months
Zandi 2014[2]	9/9	None	Steroids, plasma exchange, IVIG, rituximab, mycophenolate	Modified Rankin Scale 0-1	7	Not specified
Yoshimura 2017[3]	22/9	*10 patients*: neurologic findings (e.g. dysphasia, gait instability) *1 patient*: prior HSV encephalitis *2 patients:* previously described in Kayser 2013[1]	Steroids, plasma exchange, IVIG, rituximab, azathioprine, mycophenolate	"Much improved" or "very much improved"	9	Not specified
Scott 2018[4]	6/2	*2 patients*: seizures *1 patient*: positive VGKC antibody, negative LGI1 and CASPR2 *1 patient*: no treatment received	Steroids, IVIG, azathioprine	"No psychosis"	2	18-30 months
Lennox 2019[5]	10/6	*4 patients*: positive VGKC antibody, negative LGI1 and CASPR2	Steroids, plasma exchange, IVIG	"Dramatic improvement"	5	Mean 46 days (SD 26)

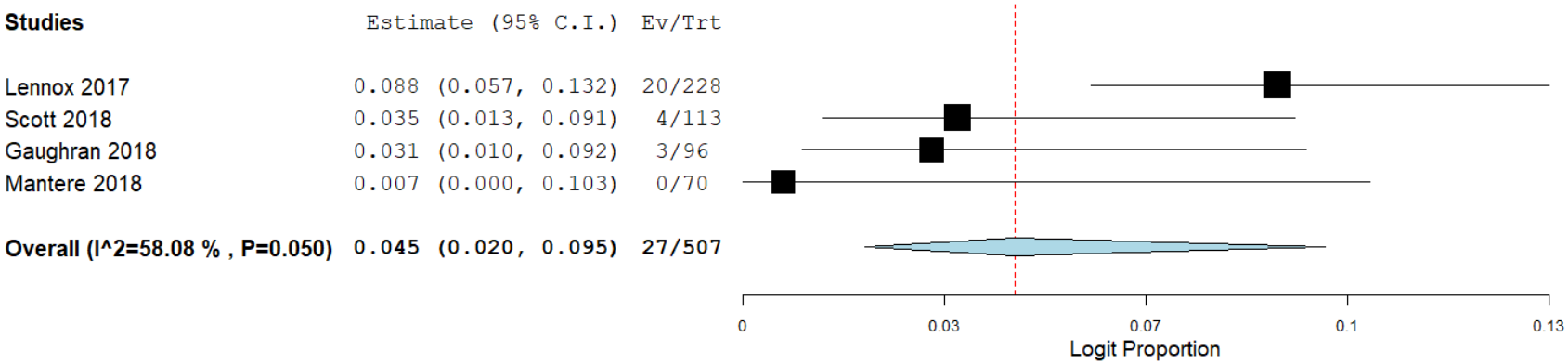
IVIG, intravenous immune globulin; HSV, herpes simplex virus; VGKC, voltage-gated potassium channel; LGI1, leucine-rich glioma inactivated 1; CASPR2, contactin-associated protein-like 2

Supplementary Table 3: Immunotherapy costs and use frequency

Treatment	Proportion receiving[6]	Dosing[7]	Cost per dose, 2015 USD	Quarterly cost, 2015 USD			
				Months 1-3	Months 4-6	Months 7-24	Months 25+
Steroids	0.91	*Methylprednisolone* 1,000 mg/day IV for 3 days, then 1,000 mg/week IV for 7 weeks Followed by *prednisone* 60 mg/day for 3 months, then 20 mg/day thereafter	Methylprednisolone: 75 per infusion[8,9] Prednisone: 0.08 per 10 mg[9]	747	45	15	15
IVIG	0.75	0.4 g/kg/day for 5 days, then 0.4 g/kg/week for 7 weeks	2,293[8]	27,518	–	–	–
Plasma exchange	0.35	Every other day for 5 total treatments	1,030[8]	5,148	–	–	–
Cyclophosphamide	0.18	1,300 mg/month IV for 6 months	955[8,9]	2,865	2,865	–	–
Rituximab	0.22	1,000 mg/week IV for 2 doses, repeated every 6 months for 24 months	7,358[8,10]	7,358	7,358	7,358	–
Azathioprine *Mycophenolate*	0.07	150 mg/day (maintenance treatment) 2,000 mg/day (maintenance treatment)	6[9] 30[9]	–	1,631	1,631	1,631
			Weighted average:	25,217	2,262	1,732	123

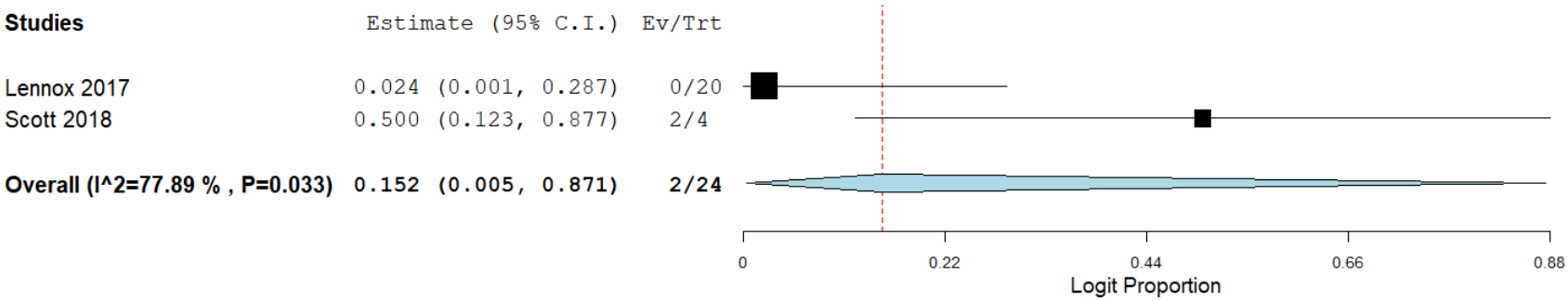
USD, United States dollars; IV, intravenous; IVIG, intravenous immune globulin

Supplementary Figure 1: Serum neuronal autoantibody prevalence in first-episode psychosis



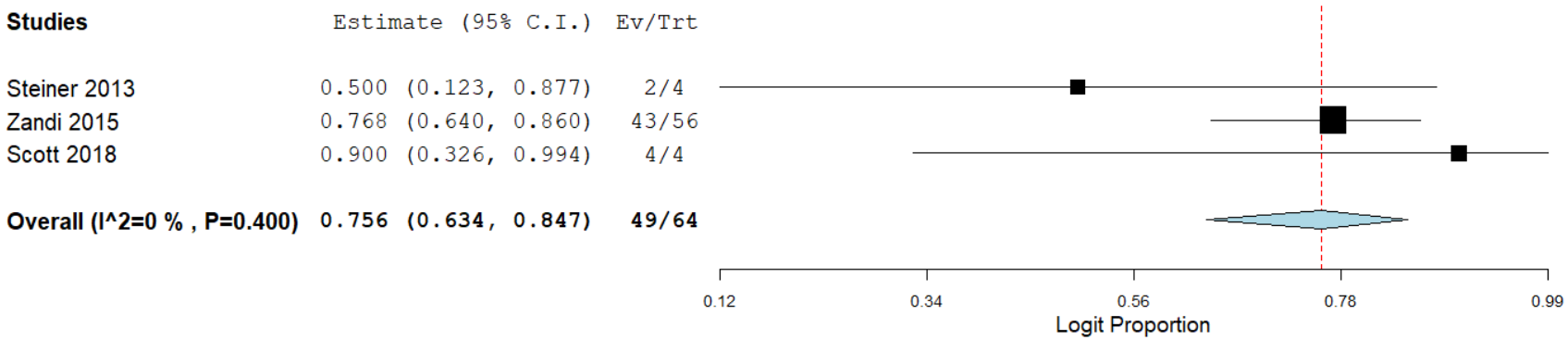
Forest plot showing the estimated prevalence of disease-relevant serum neuronal autoantibodies in patients with first-episode psychosis and no focal neurologic findings from 4 prospective cohorts. The red dashed line denotes the mean estimate; the blue diamond denotes the 95% confidence interval. VGKC antibodies in the absence of LGI1 or CASPR2 positivity were not considered disease-relevant (6 patients from Lennox 2017, 1 patient from Scott 2018).

Supplementary Figure 2: Probability of clinically-targeted diagnosis of autoimmune encephalitis in first-episode psychosis



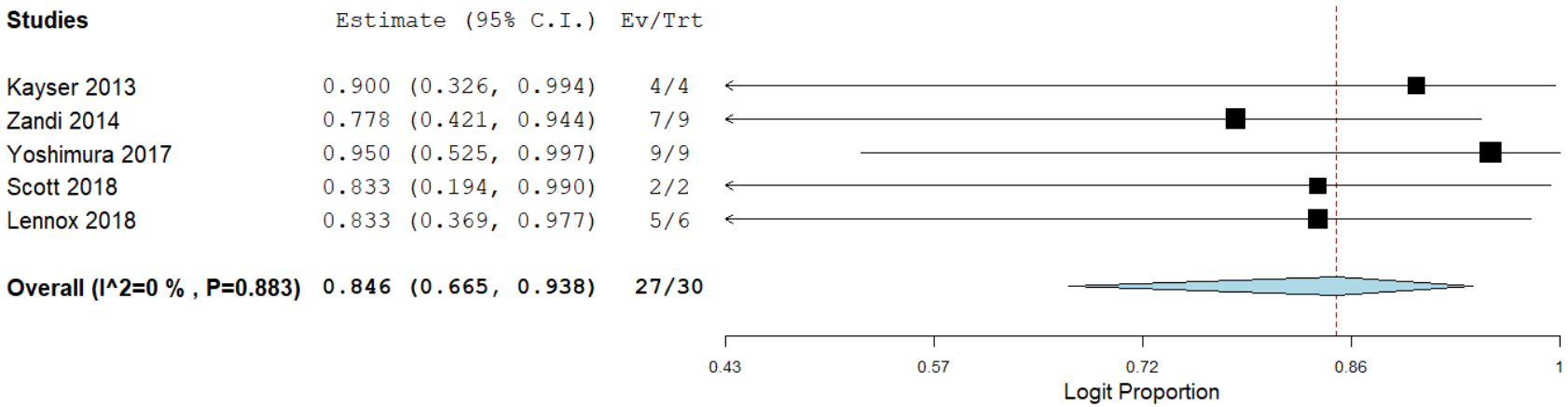
Forest plot showing the estimated probability that patients with first-episode psychosis and serum neuronal autoantibodies would be diagnosed with autoimmune encephalitis in the absence of a routine screening policy. The red dashed line denotes the mean estimate; the blue diamond denotes the 95% confidence interval. Data are drawn from 2 prospective studies which reported the number of first-episode psychosis with serum autoantibodies (based on routine screening) who subsequently developed focal neurologic findings.

Supplementary Figure 3: Likelihood serum neuronal autoantibody is deemed clinically relevant



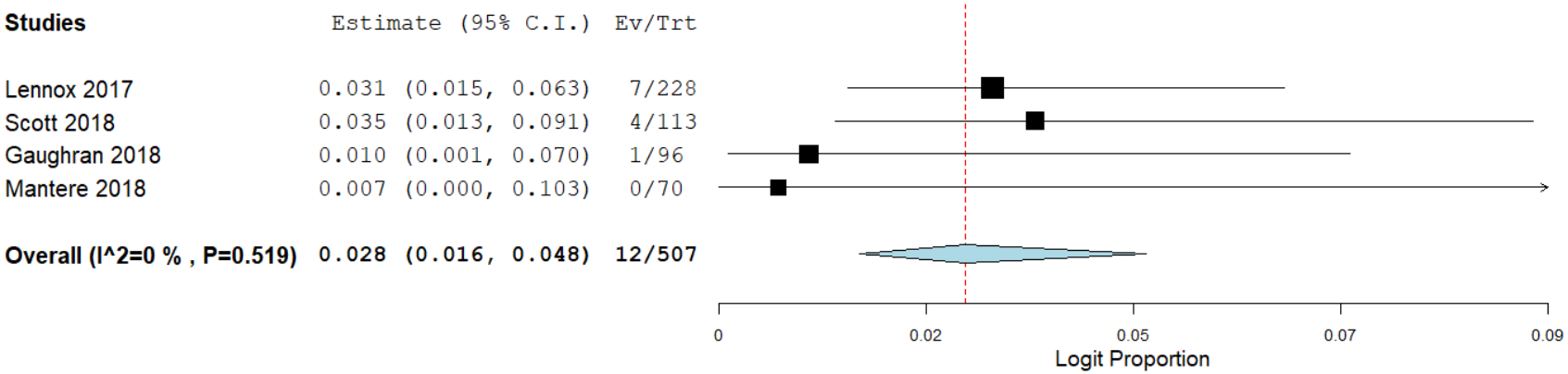
Forest plot showing the estimated likelihood that serum neuronal autoantibodies are deemed clinically relevant after further diagnostic workup. The red dashed line denotes the mean estimate; the blue diamond denotes the 95% confidence interval. Data are drawn from 3 studies reporting the results of further diagnostic workup including MRI, EEG, and lumbar puncture among individuals with neuronal autoantibodies on serum testing.

Supplementary Figure 4: Effectiveness of immunotherapy for autoimmune encephalitis in first-episode psychosis



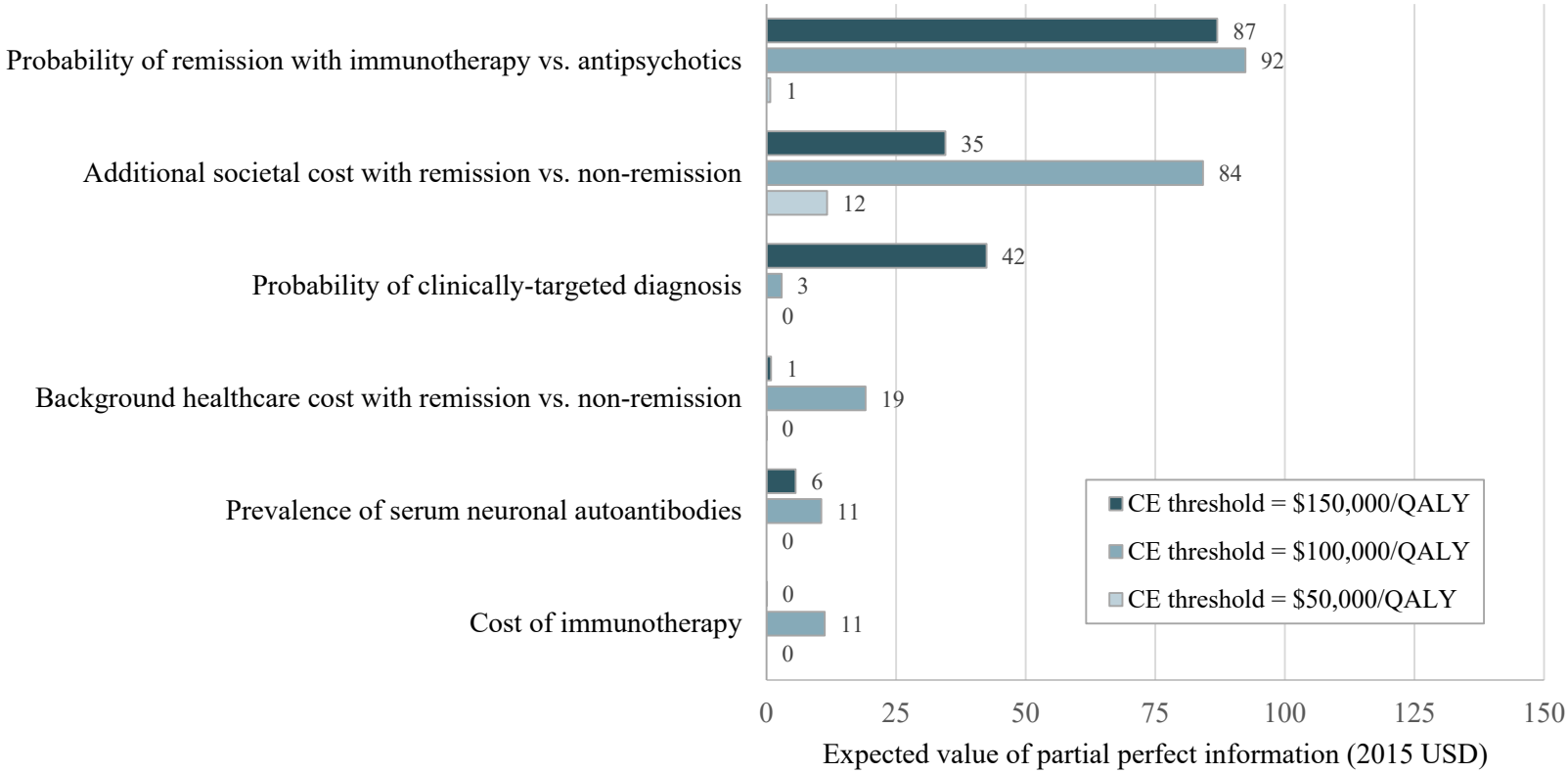
Forest plot showing the estimated probability of remission of psychotic symptoms among first-episode psychosis patients with autoimmune encephalitis treated with immunotherapy. The red dashed line denotes the mean estimate; the blue diamond denotes the 95% confidence interval. Data are drawn from 5 studies reporting treatment outcomes among first-episode psychosis patients without focal neurologic findings who were diagnosed with autoimmune encephalitis and treated with immunotherapy.

Supplementary Figure 5: Serum anti-NMDAR IgG prevalence in first-episode psychosis



Forest plot showing the estimated prevalence of IgG antibodies against the NMDA receptor in patients with first-episode psychosis and no focal neurologic findings from 4 prospective cohorts. The red dashed line denotes the mean estimate; the blue diamond denotes the 95% confidence interval.

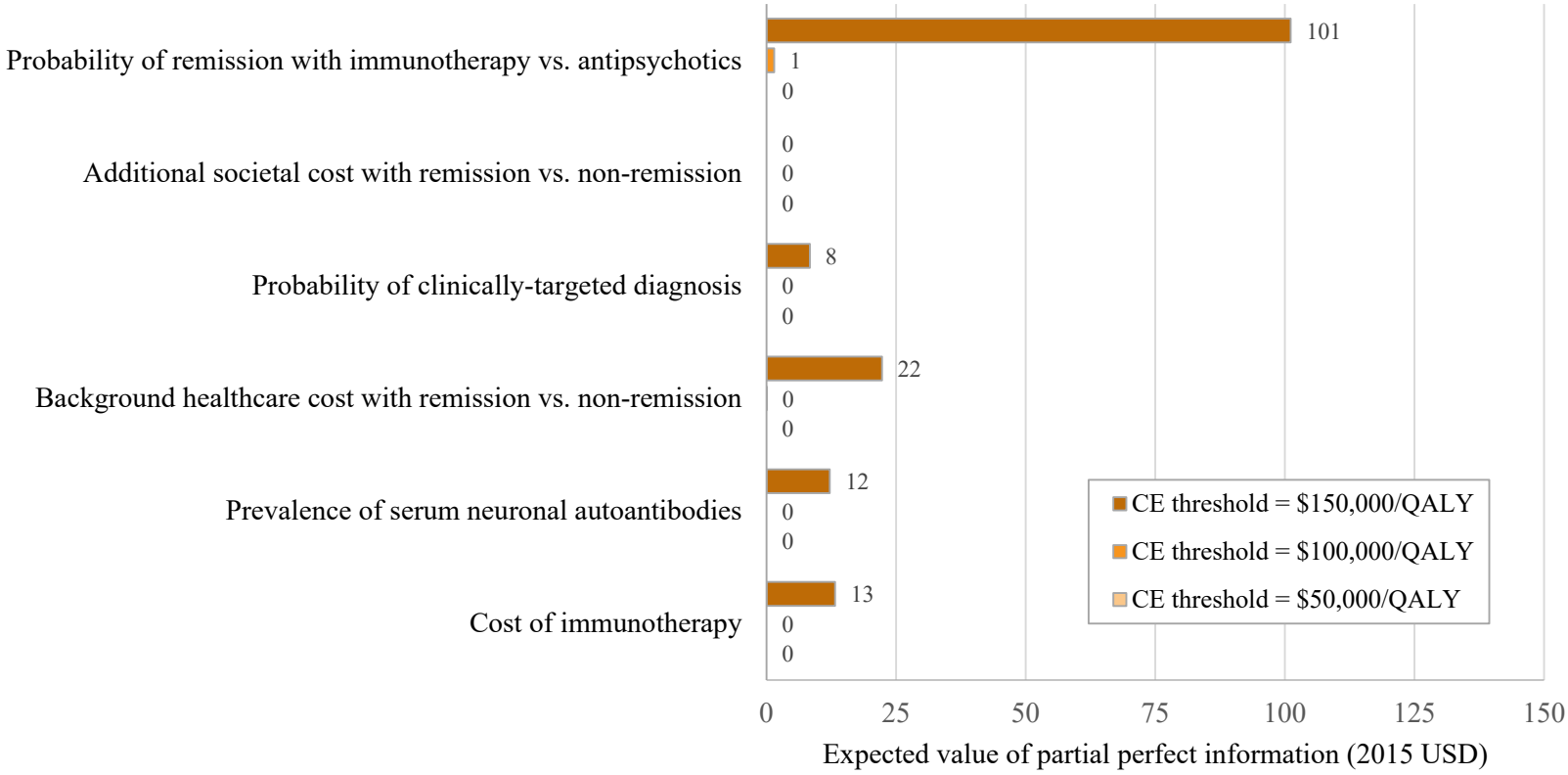
Supplementary Figure 6a: Value-of-information analysis, societal perspective



Horizontal bars show the societal expected value of partial perfect information (EVPPI) for parameter groups displayed on the vertical axis; cost-effectiveness thresholds used for EVPPI calculations are indicated in the legend. All parameter groups with EVPPI ≥$10 for at least one perspective/threshold are shown. Additional parameter groups which did not produce an EVPPI ≥$10 include: annual mortality probability; utility with remission vs. non-remission; likelihood serum autoantibody is deemed clinically relevant after confirmatory workup; cost of confirmatory workup.

CE threshold, cost-effectiveness threshold; QALY, quality-adjusted life-year

Supplementary Figure 6b: Value-of-information analysis, healthcare sector perspective



Horizontal bars show the healthcare sector expected value of partial perfect information (EVPPI) for parameter groups displayed on the vertical axis; cost-effectiveness thresholds used for EVPPI calculations are indicated in the legend. All parameter groups with EVPPI ≥$10 for at least one perspective/threshold are shown. Additional parameter groups which did not produce an EVPPI ≥$10 include: annual mortality probability; utility with remission vs. non-remission; likelihood serum autoantibody is deemed clinically relevant after confirmatory workup; cost of confirmatory workup.

CE threshold, cost-effectiveness threshold; QALY, quality-adjusted life-year

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