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- ФАРМАКОЭКОНОМИКА ТУБЕРКУЛЕЗА: МЕТОДОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ПРОВЕДЕНИЯ ИССЛЕДОВАНИЙ
- ФИНАНСИРОВАНИЕ СИСТЕМЫ ЗДРАВООХРАНЕНИЯ НА РЕГИОНАЛЬНОМ УРОВНЕ. ВЗАИМОСВЯЗЬ КАЧЕСТВЕННЫХ И КОЛИЧЕСТВЕННЫХ ПОКАЗАТЕЛЕЙ С ВЕЛИЧИНОЙ ФИНАНСИРОВАНИЯ ЗДРАВООХРАНЕНИЯ

Pharmacoeconomics
theory and practice

ECONOMIC EVALUATION OF GENETIC TESTING IN COMBINATION WITH PREVENTIVE DONEPEZIL TREATMENT FOR AMNESTIC MILD COGNITIVE IMPAIRMENT PATIENTS

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Abstract

Objective: To evaluate the cost-effectiveness of genetic screening for Apolipoprotein ε4 (APOE ε4) allele in combination with preventive donepezil treatment in comparison to the standard of care for Amnestic Mild Cognitive Impairment (AMCI) patients in Canada.

Methods: *We performed a cost-effectiveness analysis using a Markov model with a societal perspective and a time horizon of 30 years. For each strategy, we calculated quality-adjusted life years (QALYs) and cost. One-way and probabilistic sensitivity analyses were performed. Expected value of perfect information (EVPI) was conducted to explore the value of future research.*

Results: *The base case results in our exploratory study suggest combined genetic testing and preventive donepezil treatment resulted in a gain of 0.027 QALYs and an incremental cost of CAD $870 compared to standard of care. The incremental cost-effectiveness ratio (ICER) for the base case was $32,585 per QALY. The ICER was sensitive to the and effectiveness of donepezil in slowing rate of progression to AD, Donepezil treatment cost and treatment of AD patients. EVPI analysis showed that additional information on these parameters would be of value.*

Conclusion: *Using presently available clinical evidence, this exploratory study illustrates genetic testing combined with preventive donepezil treatment for AMCI patients may be economically attractive. Since our results were based on a secondary post-hoc analysis, our study alone is insufficient to warrant recommending APOE genotyping in AMCI patients.*

Key words

Pharmacogenetics, Cost-utility analysis, Alzheimer's disease, Donepezil

Introduction

Alzheimer's disease (AD) is a brain degenerative disease, that impairs cognitive function, memory and affecting the daily human activities (1-2). Total expenditure on the treatment of this disease in Canada in 2008 was about $ 15 billion; total time spent by caregivers was approximately 231 million hours (3). Limited success of current health care in the treatment of AD facilitates the search for new ways to slow the progression of the disease at an early stage.

Mild Cognitive Impairment (MCI) is a transitional state between the cognitive abilities of normal aging and the early stages of AD (3). Amnestic variant of mild cognitive impairment (AMCI) is a subtype of the MCI with severe memory impairment, but otherwise intact cognitive function. Patients with these characteristics are at increased risk of AD (4). Progression and development of AD can also accelerate the presence of one or more alleles of apolipoprotein APOE ε4 (5-7). Approximately 24% of the population of patients with MCI in Canada have the genotype ε4/ε4 APOE (8). AMCI patients with two ε4 alleles AROE have 94% chance of developing AD before the age of 80 years (9). Genetic testing for the presence of the APOE ε4 allele and preventive treatment for the group of patients, which has an increased risk of progression of AD, can be an effective way of personal therapy.

One of the ways for slowing cognitive decline in patients with mild to moderate AD is using cholinesterase inhibitors (donepezil, rivastigmine, galantamine, memantine). Although the current standard of MCI patients care not includes these medicine (10), it is assumed that the preventive treatment by using above mentioned drugs at an earlier stage may provide some clinical benefit. A systematic review of the literature in Medline retrieved only two randomized controlled trials (RCTs) that investigated the effect of donepezil in AMCI patients. In the first study, 132 AMCI patients received donepezil treatment for 24 weeks showed no significant improvement in the basic indicators of clinical efficacy, although demonstrated definite improvement in the secondary analysis (11). The second RCT showed that donepezil inhibits onset of AD during the first 12 months of treatment, but after three years of difference between placebo and the effect of donepezil in the rate of progression in AD is not kept (4). Subsequent secondary analysis, noted the obvious benefit of donepezil among carriers of one or more APOE ε4 alleles for the three-year observation period.

The second study showed the possible potential of genetic testing APOE ε4 alleles in patients AMCI having the greatest benefits of targeted therapies. A systematic review of the literature revealed several economic studies (12-15). However, the relationship between gene polymorphism and potential outcomes in these studies has not been reviewed. Therefore, the aim of this study is to assess the potential cost-effectiveness of APOE ε4 testing in combination with donepezil preventive treatment for AMCI patients. The proposed new technique is compared with the existing standard of care for AMCI patients in Canada.

Methods

The model structure

A Markov model was developed to simulate the natural history of the disease in AMCI patients over 30 years time horizon (reflecting the life expectancy of the cohort). Effect of medical intervention on the patient health was expressed in years of quality life (Quality-adjusted Life Years, QALY), which weight length of life with quality of life data – specifically, health state utilities (from 0 to 1). The model simulated a hypothetical cohort of patients AMCI at the age of 70 years who have problems with memory. A hypothetical cohort of patients was divided into two groups: carriers of APOE ε4 gene mutation and patients without such mutations. The model uses a cycle length of 1 year. Each year, patients may progress to either AD or may die of other unrelated causes of disease (Fig. 1). Movement between health (health states) determines the transition probabilities (transition probabilities), obtained by a systematic review of the literature (Table. 1). Costs and effectiveness of medical intervention determined based on the amount of time spent in each patient's health status, with certain costs and utility. Analytical perspective of this study is the perspective of society (societal perspective) of Canada. Discounting rate for costs and effects were 5% per year.

In the targeted therapy strategy, the model begins with the hypothetical cohort receiving an APOE genetic test during a visit to a memory clinic or a neurologist. If the test identifies the patient as a carrier of one or more of the APOE ε4 allele, the patient receives donepezil as a preventive treatment to delay the onset of AD. Non-carriers remain under medical supervision. Since the genetic test works on any good quality DNA, and the procedure and interpretation of the results of the test are quite simple, it is assumed that the specificity and sensitivity of the genetic test for APOE ε4 allele is 100%. In the standard (existing) strategy of patient care, the patients did not receive genetic testing APOE ε4 and preventive treatment, but remain under the supervision of a physician until progression to AD. It is assumed that in both scenarios, patients progressing to AD receive a drug of similar cost and effectiveness to donepezil until they die.

A systematic review to obtain model parameters, including the prevalence of APOE ε4 allele in patients with AMCI, mortality, utility for each health status and costs for patients with AD and MCI was conducted in Medline (16). GRADE method was used to assess the quality of the clinical parameters (17).

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Figure 1 **Markov process**

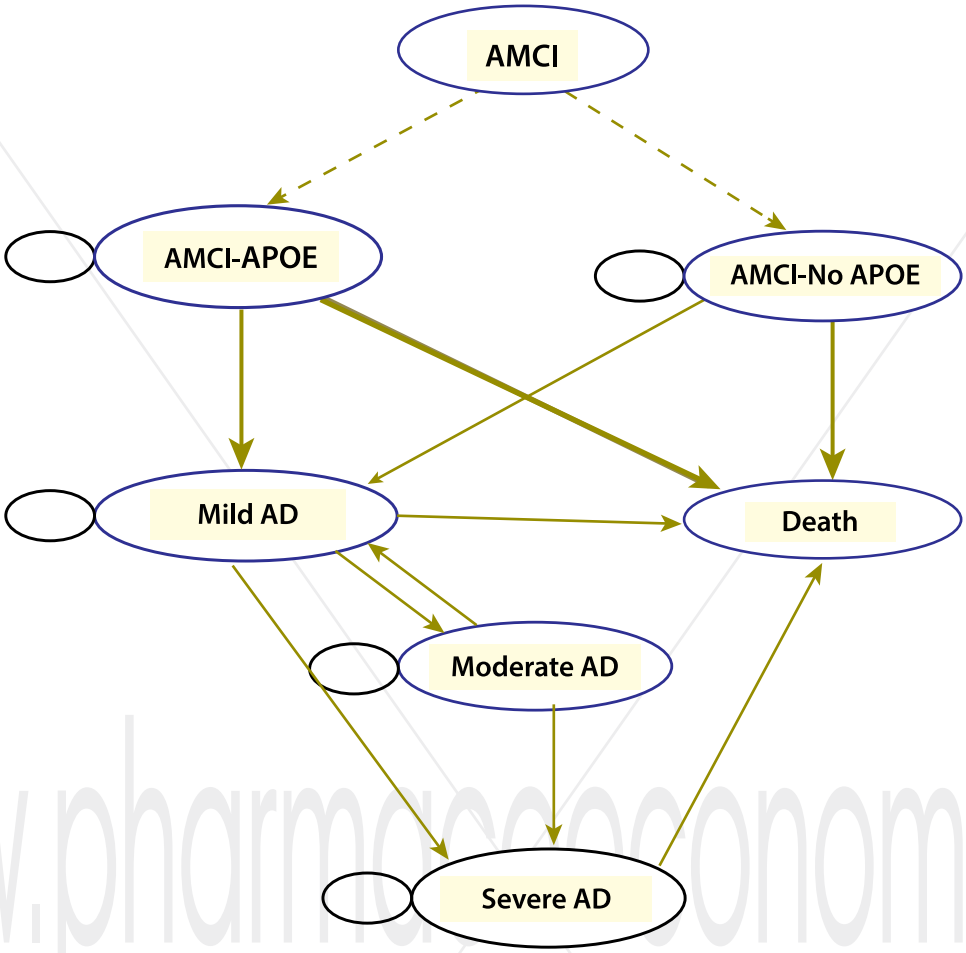


Table 1 Variables used in the model, showing base case values, ranges and data source.

Variable	Base case	Low	High	Distribution	Data source
Probabilities					
Prevalence of APOE ε4 allele	0.24	0.15	0.36	Beta	(8;19)
Adverse events from donepezil	0.17	0.10	0.24	--	(4)
Progression rates to AD					
Targeted Therapy Strategy: **APOE ε4 Carriers + Donepezil**					
1 year	0.080	0.064	0.096	Beta	(4)
2 year	0.185	0.148	0.222	Beta	(4)
3 year	0.320	0.256	0.384	Beta	(4)
4 year	0.189	0.151	0.227	Beta	(4)
5 year and above	0.081	0.065	0.097	Beta	(24)
Standard of Care Strategy: **APOE ε4 Carriers Without Donepezil**					
1 year	0.230	0.184	0.276	Beta	(4)
2 year	0.234	0.187	0.281	Beta	(4)
3 year	0.237	0.190	0.285	Beta	(4)
4 year and above	0.081	0.065	0.097	Beta	(24)
APOE ε4 non-carriers					
1 year	0.130	0.104	0.156	Beta	(4)
2 year	0.057	0.046	0.069	Beta	(4)
3 year	0.061	0.049	0.073	Beta	(4)
4 year and above	0.081	0.065	0.097	Beta	(24)
Progressed to AD					
Mild to Moderate	0.322	0.26	0.39	Beta	(12)
Mild to Severe	0.042	0.03	0.05	Beta	(12)
Moderate to Mild	0.043	0.03	0.05	Beta	(12)
Moderate to Severe	0.339	0.27	0.41	Beta	(12)
Utilities					
AMCI	0.73	0.58	0.88	Beta	(25;26)
Mild AD	0.68	0.54	0.82	Beta	(25-27)
Moderate AD	0.54	0.43	0.65	Beta	(25-27)
Severe AD	0.37	0.30	0.44	Beta	(25-27)
Costs*					
Annual cost of donepezil	$1,916	$1341	$2491	Gamma	(29)
AMCI Surveillance annual cost	$8,391	$5,874	$10,908	Gamma	(30;31;48)
APOE ε4 genetic test cost per sample	$325	$150	$500	Gamma	(32;33)
Annual Mild AD cost	$14,381	$10,067	$18,695	Gamma	(35;36)
Annual Moderate AD cost	$39,142	$27,399	$50,885	Gamma	(35;36)
Annual Severe AD cost	$55,986	$39,190	$72,782	Gamma	(35;36)
Adverse Event cost for Donepezil	$100	$70	$130	Gamma	(34)

*** Costs in Canadian dollars**

APOE ε4 allele prevalence among patients, and MCI

APOE ε4 allele prevalence among MCI patients in Canada (24%) was obtained from the Canadian Study of Health and Aging (CSHA) (8). CSHA study used a definition of «cognitive impairment in the absence of dementia» (Cognitive Impairment, No Dementia), which has similar clinical characteristics with AMCI (18). One of the European research noted APOE ε4 allele prevalence of 15% in the control group and 36% in MCI patients from the specialized clinic (19). Another study noted a higher prevalence of APOE e4 in the south of Europe and reaches from 31.5% to 62.7% in patients with mild cognitive impairment (20). Effect of APOE ε4 alleles increased prevalence was tested with a sensitivity analysis.

The transition probabilities

Data on the mortality rate derived from the Canadian statistical sources (21). It is assumed that the AMCI mortality is the same as the average population. Annual mortality in patients with AD was calculated using the relative risk of mortality in patients of appropriate age from MoVIES trial conducted in the US (23), had a higher risk of mortality in patients with AD than in the AMCI. The scenario where mortality risk of AD was the same as in MCI patients was tested. The model was used by the assumption that the risk of mortality independent of APOE carrier status.

Data on the frequency of progression from MCI to AD in the first 3 years, and the effectiveness of preventive treatment with donepezil for the purpose of delay the onset of AD were obtained from a multicenter, randomized controlled trial (RCT) investigated the effectiveness of preventive treatment with donepezil in AMCI patients from North America (4). The purpose of the clinical study was to compare the frequency of progression in AD patients AMCI who received 10 mg of donepezil daily as preventive treatment (donepezil group) to the placebo group who did not receive preventive treatment. The comparison was performed every 6 months for 3 years, as the primary outcome used onset of AD. Results of RCTs secondary analyzes have shown the advantage of treatment with donepezil in patients with APOE ε4, but had a limited impact on the non-carrier patients. Transition probabilities were derived from the Kaplan-Meier progression curves (4). The primary analysis of clinical studies showed that during the first year, patients receiving donepezil group (APOE ε4 carriers and non carriers) had a lower rate of progression to AD than the placebo group. However, the incidence of progression increased in subsequent years and after three years it become similar to the placebo group.

Due to lack of evidence of donepezil efficacy after 3 years in the model was used conservative scenario - after 3 years donepezil does not slow cognitive decline. Following this scenario the assumption was used that patients receiving donepezil, have a higher rate of progression in the fourth year (18.9% per year) than those who did not receive donepezil (8.1% per year). This is to ensure that by the end of 4 years, all patients had the same cumulative probability of developing AD. In subsequent years, both groups have the same probability of AD (8.1%), which derived from a meta-analysis of the frequency of progression from MCI to AD (24).

Quality of life

Indicators of Quality of life - the utility for health states AMCI and AD were obtained (Table. 1) from the quality of life studies evaluating using Health Utility Index (HUI2) from 679 North American patients at different stages of AD (from AD «questionable» to «terminal») (25-27). For MCI state the average value of utility obtained from 52 patients with a diagnosis of AD «questionable» and evaluated on a scale CDR = 0,5, from the same study were obtained utilities for mild, moderate and severe stages of AD (28).

Resource use and costs

Canadian sources and published literature were used to estimate the resources used and the costs (29-31). Currently, genetic test APOE ε4 is not a standard practice in Canada, therefore, several different sources were used to obtain estimates. In the baseline scenario, a genetic test is $ 325, representing the average value of the service fees of medical laboratories in the United States (32) and the cost of the genetic test indicated in the report of the Ontario Ministry of Health (33). A higher cost of genetic testing was used in the sensitivity analysis. To study the strategy used by the assumption that the APOE ε4 carriers receive daily donepezil 10 mg as a preventive treatment. Gastrointestinal side effects such as diarrhea and nausea are the most common adverse events during treatment with donepezil. It is assumed that 10% patients who receive donepezil have gastrointestinal side effects (4) which requires an average of three visits to the general practitioner. Expenses of doctor visits are calculated based on approved rates of Ontario (34).

A systematic review of the literature on MCI cost identified only one study conducted in Germany (48) converted into Canadian dollars. For the genetic screening strategy, it was assumed that patients identified as APOE ε4 carriers would have several extra physician visits for surveillance compared to non-carriers, because they are at higher risk of developing AD. The annual cost of AD includes hospitalization, medication, outpatient treatment, and productivity losses of caregiver family members. The model uses data on costs for the various stages of AD from the Canadian study (35). All costs are presented in Canadian dollars in 2009, adjusted for inflation and are calculated using the medical component of the Consumer Price Index in Canada (37).

Sensitivity Analysis

Deterministic and probabilistic sensitivity analyzes conducted to assess the uncertainty of the model parameters. One –way sensitivity analysis was performed for all parameters (parameter ranges are shown in Table. 1). In the Probabilistic Sensitivity Analysis «gamma» distribution were used to represent parameters uncertainty for costs because cost data can't be negative. Distribution «beta» was used for the probability and utility, because parameters are located in the range from 0 to 1 (tab. 1). All parameters were carried out random sampling distributions associated with 1000 times the simulation. The analysis was also determined the probability of economic efficiency of each treatment strategy at different thresholds of willingness to pay WTP (Willingness to Pay). To assess the value of additional information, we calculated expected value of perfect information (EVPI) with a 20 year lifespan of the testing technology and partial EVPI (EVPPI) for the input parameters at various WTP thresholds (38). At 24% prevalence of AMCI and the population estimates in Canada, the number of patients and the AMCI age of 70 and older estimated at 275,000 people. Using this population estimate, we estimated the population EVPI at different WTP thresholds.

Results

Base case

In AMCI patients, genetic testing in combination with preventive donepezil treatment for APOE ε4 carriers were more effective (additional increase 0,027 QALY) and more expensive (additional cost $ 870), compared with standard care strategy. Incremental cost-effectiveness ratio (ICER) of genetic testing strategy was $ 32585 for 1 additional QALY (Table. 2). Over the period of time considered in the model, 68% of the patients cohort progressed to the AD.

Table 2 **Incremental cost-effectiveness of a genetic test for the APOE ε4 allele in combination with preventive donepezil treatment in Amnestic Mild Cognitive Impairment (AMCI) patients (Costs in Canadian dollars)**

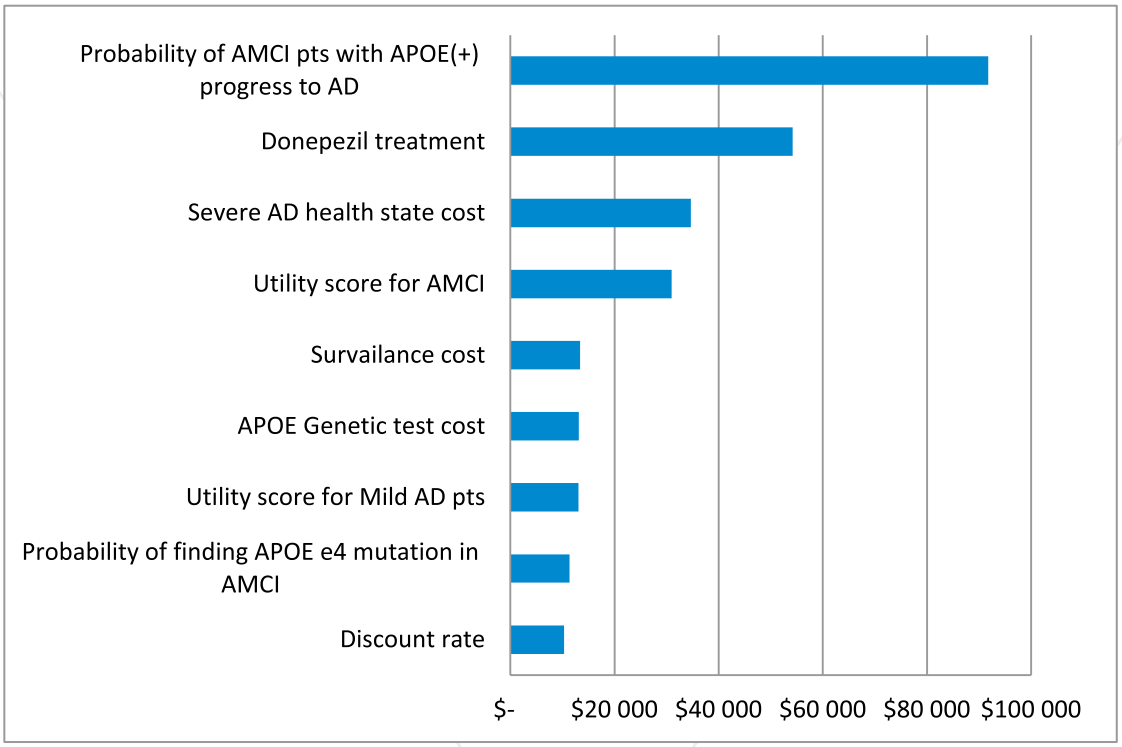
Strategy	Cost	Quality-adjusted life years (QALYs)	Δ $ / ΔQALY
Screening + preventive drug treatment	145,569	4.980	--
No screening	144,699	4.953	--
Difference	870	0.027	32,585

Sensitivity Analysis

One –way sensitivity analysis showed that the model results are most sensitive to the probability of patients with AMCI mutation and APOE ε4 progression to AD (the effectiveness of treatment with donepezil), donepezil treatment costs and costs of AD treatment (Fig. 2). The model results are less sensitive to the utility, the discount rate and the cost of the genetic test.

The study analyzed different scenarios. In the scenario where the frequency of progression does not depend on the status of APOE ε4 and depends only on the methods of treatment, ICER increased to $ 109,005 per additional QALY. In another scenario, when the time horizon of the analysis was limited to three years, ICER decreased slightly (to $ 26,587) per additional QALY. One study found that individuals with MCI are 1.74 times more likely to die than those without cognitive impairment (22). If the annual risk of mortality in patients with MCI was 1.74 times higher than in the general population, the ICER would drop to $ 18,582 for an additional QALY. In the scenario with the same level of mortality in the AMCI and AD patients, ICER is $ 30,659 per additional QALY. If you increase the value of the genetic test 3 times, taking into account the fact that in the future can new risk factors of AD caused by genetic mutations will be discovered, ICER increases to $ 56,935 for an additional QALY. When using the Weibull and exponential distributions for the parameter probability of progression of AMCI patients to AD, ICER becomes negative. Probabilistic sensitivity analysis showed that the majority of the 1,000 simulations ICER, were located mainly in the east and only a few in the western quadrants with the center near the origin of the cost-effectiveness plane (Fig. 3). At the threshold of the effectiveness of $ 50,000 per additional QALY, 62% of the simulations (ICER) were cost-effective (Figure 3 and 4).

Fig.2 **One -way sensitivity analysis**



The expected value of the complete information

The total Expected Value of Perfect Information (EVPI) was $ 909 and $ 976 per patient at WTP thresholds of $ 50,000 and $ 100,000 for an additional QALY, respectively (Fig. 5). EVPI for the target population of 275 000 people in Canada, reaches a maximum value of about $ 250 million at the threshold of WTP $ 50,000, then after a slight downturn begins to steadily increase after $ 60,000 (Fig. 6). Partial EVPI parameters varies depending on various thresholds WTP (Fig. 5). At the WTP threshold of $ 50,000 per QALY, additional information on AMCI progression rate , cost of donepezil treatment and monitoring of AMCI patients will be useful for further research. With corresponding partial EVPIs being quite low, conducting additional research on quality of life estimates, the cost of genetic testing and side effects would be of little value.

Fig.3 **Results of Monte Carlo simulation on Cost-effectiveness plane**

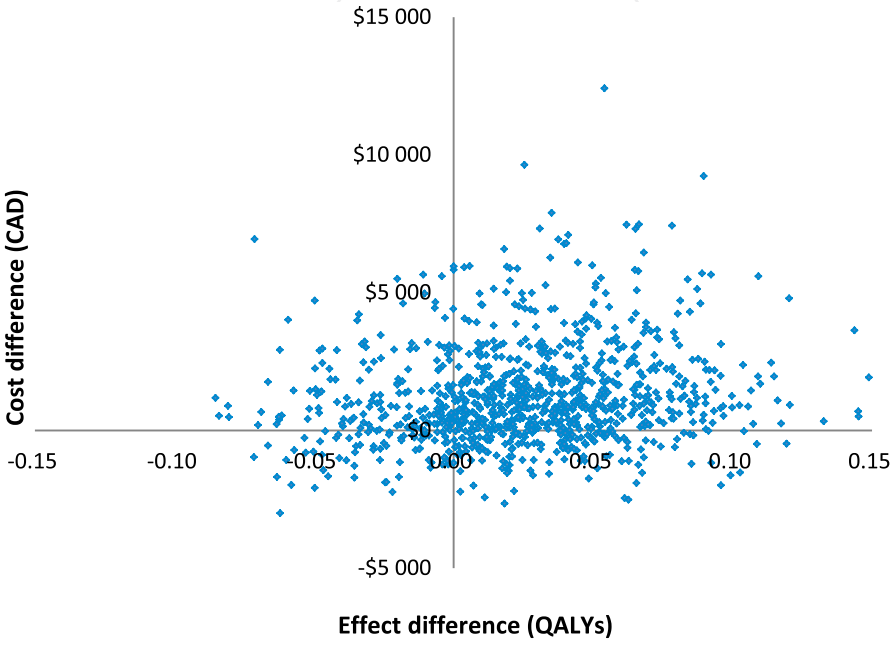


Fig.4 **Cost - effectiveness Acceptability Curve**

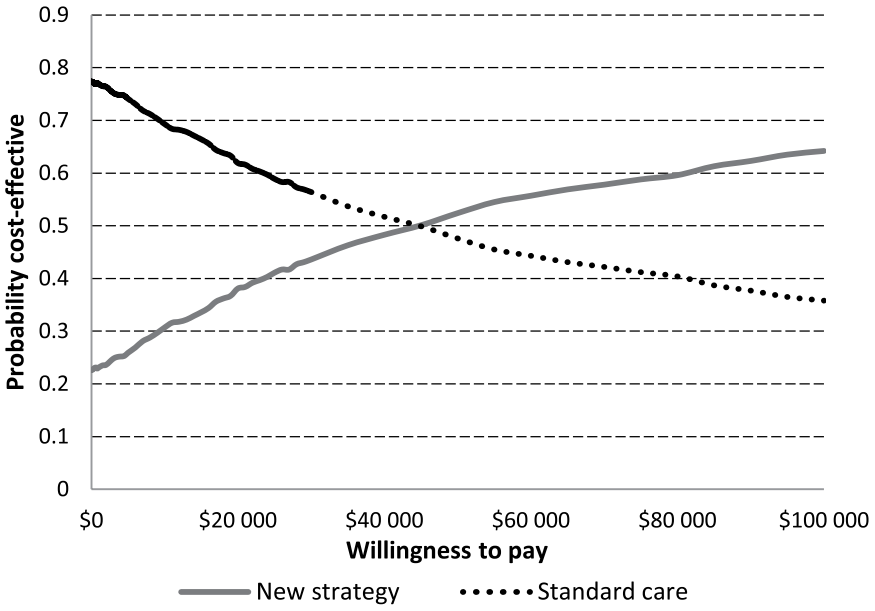


Fig.5 **Population EVPI**

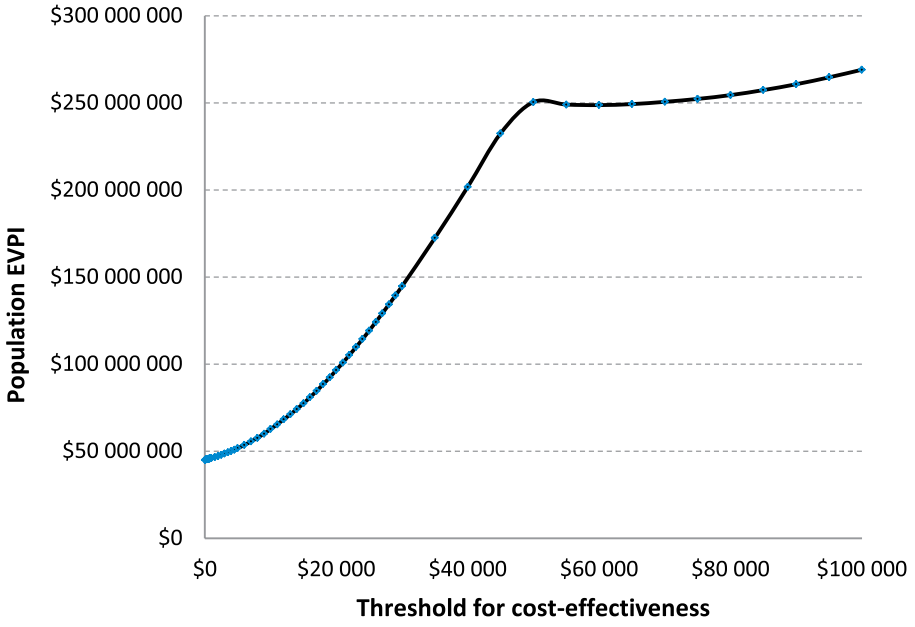
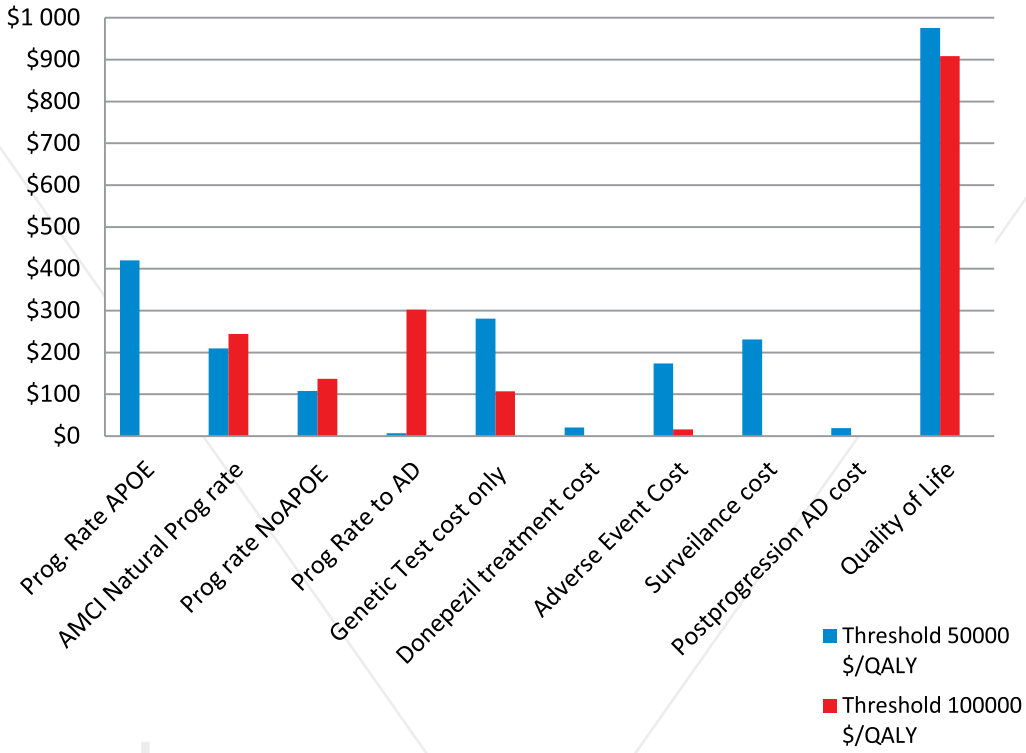


Fig.6 **Partial EVPI**



Discussion

In the presented model, genetic testing APOE ε4 in combination with donepezil preventive treatment is more expensive and more effective than the AMCI standard care strategy. The benefit of the targeted therapy strategy, conferred through a reduction in progression to AD among APOE ε4 allele carriers during the first three years, is translated into an average gain equivalent to 10 days of quality adjusted life per patient. Although the effect size may appear small, it is comparable to QALYs gained in studies for other recognized health interventions, such as pharmacogenetic testing in the clinical management of schizophrenia (4 days) (39) or adjuvant treatment in postmenopausal women with breast cancer (25 days) (40). The additional costs of $ 870 per patient in combination with efficiency in 0,027 QALY resulted in a net ICER $ 32,585 per additional QALY. This means that a targeted therapy can be a cost-effective intervention, if the willingness to pay more than $ 33,000 for an additional QALY.

The comparative benefit of the targeted therapy strategy versus the standard of care in AMCI patients is based on two important clinical parameters: (i) an elevated risk of developing AD among carriers of APOE ε4 alleles compared to non-carriers; and (ii) delayed progression to AD with donepezil preventive treatment specifically among APOE ε4 allele carriers. Several studies have found an association between APOE ε4 carriers and the development of AD (6, 41-43). However, the APOE ε4 genetic test can't guarantee a sufficiently high accuracy of forecasting the development of AD in patients with MCI, and that reduces its use in practice. Despite the fact that the indicators of clinical effectiveness were obtained from a large RCT (4), they are based on the results of the secondary analysis, and the authors do not believe that the results have a statistical power to recommend targeted therapy for implementation. In addition, the effectiveness of treatment with donepezil APOE ε4 carriers among yet is quite controversial (44). EVPI analysis results indicate the need for additional research on the evaluation of efficiency in order to reduce the uncertainty of parameters.

The annual rate of progression (12%) in APOE ε4 carriers and non- carriers, calculated on the basis of the RCT (4). This rate is similar to the rate of progression (13%) reported among the observed patients in the clinic specializing in the treatment of memory disorders (45). The same study noted a 3% incidence of progression to AD in the population. Baseline progression in AD, used in the model is higher than the rate of progression of the population, the appropriateness of modeling high rates based on the fact that genetic testing of patients expected to spend in the hospital among patients with memory disorders, where traditionally the higher rate.

To date, this is the first economic evaluation of genetic testing in combination with donepezil preventive treatment in AMCI patients. The results of this study can't be compared with the results of other economic evaluations of donepezil treatment of patients with AD because in our study, the additional benefits of a new intervention for APOE ε4 carriers achieved for the state of MCI progression to AD. The only economic valuation of donepezil treatment for patients MCI not stratify patients APOE ε4 status and use only hypothetical performance indicators and the utility value of the published literature (15). The results of this study confirmed the hypothesis of the effectiveness of preventive treatment with donepezil for high-risk individuals.

This study has several limitations. Firstly, there is limited evidence of reducing the progression of AD treatment with donepezil APOE ε4 carriers. Therefore, the value of this study is to develop an algorithm of economic evaluation of targeted therapy in preventing the onset of AD in the MCI population, which can be used when there will be more evidence. Secondly, surveillance cost is used for AMCI patients from a German study of costs associated with MCI in primary care (46) and a population of elderly patients (mean 81 y.) than patients in the model cohort therefore defined cost components might be differ. Third, in order to avoid selection bias, the model does not use a higher mortality rate among patients with AD who have ε4 allele AROE (47). In the case of high mortality in patients with AD presence of APOE ε4, economic evaluation will be even more favorable. Finally, in clinical practice, there are no universally accepted criteria for the diagnosis of mild cognitive impairment (MCI). Not quite clear distinction between this term and other clinical definitions of cognitive dysfunctions such as «cognitive impairment without dementia,» «mild cognitive decline» and «age-related decline in cognitive function» associated with aging (48).

In the future, genetic testing APOE ε4 allele in combination with other clinical measures may be useful for identifying potential risk groups AD. Such information will help predict who may develop AD, which will be important when preventive measures become available.

Conclusions

Our study is based on the hypothesis that among APOE ε4 carriers, preventive donepezil treatment could potentially delay progression from AMCI to AD. Given this possibility, the model was created for the study of genetic testing for APOE ε4 in combination with donepezil preventive treatment in Canada. Cost-effectiveness of a new medical intervention depends on the effectiveness of preventive treatment with donepezil in slowing the progression of MCI, and in AD among

carriers of APOE ε4. The results are of a preliminary nature, as more evidence of effective targeted therapy in delaying progression to AD becomes available, the economic evaluation estimates can be updated with new data.

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