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Economic Evaluation

Cost Analysis of Screening for IgA Nephropathy Using Novel Biomarkers

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ABSTRACT

Objectives: IgA nephropathy (IgAN) is the most common primary chronic glomerulonephritis and a major cause of end-stage kidney disease worldwide. Novel biomarkers, including the aberrantly glycosylated IgA1 and glycan-specific antibodies, could be useful in the diagnosis of IgAN. The aim of this study was to assess the cost analysis of IgAN screening using novel biomarkers in addition to the conventional screening compared with conventional screening alone.

Methods: To estimate the medical expense of each strategy related to renal disease for 40 years, we developed an analytical decision model. The decision tree started at "40 years of age with first-time hematuria." It simulated 2 clinical strategies: IgAN screening using the novel biomarkers (group N) and conventional screening (group C). The analysis results were presented as medical expenses from a societal perspective. Discounting was not conducted.

Results: The expected medical expense per person for 40 years was ¥31.2 million (~$291 000) in group N and ¥33.4 million (~$312 000) in group C; hence, expense in group N was lower by ¥2.2 million (~$21 000). In group N, the expected value of IgAN increased by 5.67% points (N 48.44%, C 42.77%) and that of dialysis introduction decreased by 0.85% points (N 19.06%, C 19.91%). In the sensitivity analysis, expenses could be reduced in almost all cases except when renal biopsy using conventional screening was performed at the rate of 73% or higher.

Conclusion: Screening for IgAN using novel biomarkers would reduce renal disease–related expenses.

Keywords: cost analysis, cost-effectiveness, IgA nephropathy, novel biomarkers, screening, chronic kidney disease, end-stage kidney disease.

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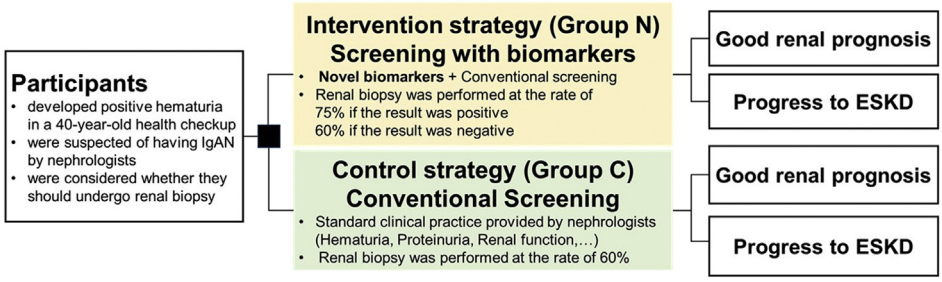
Introduction

The annual number of patients on dialysis has increased worldwide, and it is expected to rise sharply in the next decade.[1] Regarding the incidence rate of treatable end-stage kidney disease (ESKD), many Asian countries including Japan, Taiwan, South Korea, Singapore, and Thailand have the highest grade rate according to the United States Renal Data System.[2] In Japan, the number of patients on dialysis exceeded 330 000 in 2018.[3] Chronic glomerulonephritis is the second most common cause of dialysis introduction after diabetes mellitus,[3] and almost half of its cases are regarded as IgA nephropathy (IgAN). According to an epidemiologic study and genome-wide survey,[4] IgAN is the most common primary chronic glomerulonephritis, and East Asia including Japan has a high prevalence of IgAN. IgAN causes ESKD in 20% to 40% of patients within 10 to 20 years from the onset,[5-7] whereas a previous study showed that 90% cases of IgAN could achieve clinical remission when tonsillectomy and steroid pulse therapy (TSP) was performed within 3 years from the onset in Japan.[8] Therefore, early diagnosis and treatment of IgAN would reduce the number of patients on dialysis with IgAN by preventing progression to ESKD.

Because the annual health checkup is performed mandatorily for almost all Japanese citizens, 70% cases of IgAN are diagnosed as asymptomatic hematuria by screening in Japan. Nonetheless, it is not easy to detect the patients with IgAN in early stages by annual checkup owing to the following 3 reasons: first, detection of presence of hematuria through annual checkups is relatively common, occurring in around 5% and 10% of men and women, respectively[9]; second, hematuria also arises from urological diseases, such as urinary stones and urinary tract infection, many of which are not serious problems, and therefore, detailed examination is not often performed to determine the cause[9]; third, the diagnosis of IgAN requires an invasive renal biopsy. Therefore, presence of hematuria alone at annual checkup often does not lead to a diagnosis of IgAN, and some cases, in which treatment is delayed, lead to ESKD because of missed diagnosis and the subsequent treatment. Thus, an efficient screening for IgAN on diagnosis of hematuria is needed.

Lately, novel biomarkers for IgAN including aberrantly glycosylated IgA1 and glycan-specific antibodies can be measured, and these biomarkers are reportedly associated with disease activity[10] and prognosis.[11-14] Yanagawa et al[15] indicated that biomarkers

Figure 1. Analytical decision tree. The decision tree presents 2 options: the intervention strategy using screening with biomarkers (group N) or the control strategy using conventional screening (group C) for participants with suspected IgAN with first-time hematuria at the age of 40 years. The outcomes (the expected medical expenses, the prevalence of IgAN, and the proportion of dialysis introduction) of each strategy are compared.



IgAN indicates IgA nephropathy.

might be useful to differentiate IgAN from other glomerular diseases on the basis of the results of 230 cases. Screening for IgAN using these biomarkers in addition to conventional screening may help identify patients with early-stage IgAN and consequently allow us to offer appropriate therapies and prevent ESKD.

Cost-effectiveness analysis (CEA) has gained importance as an approach to evaluating new medical technologies along with highly specialized medical technology and rising medical expenses in Japan and worldwide.[16] The expensive dialysis costs because of the increasing number of patients on dialysis are a big burden in Japan.[17] To prevent introduction of dialysis for patients with IgAN and consequently reduce the high costs, a useful screening method and its CEA are needed. Nonetheless, little is known about the cost-effectiveness of this IgAN screening method using novel biomarkers from a societal perspective. The aim of the study was to evaluate and compare renal disease–related expenses for 40 years when adding novel biomarkers for IgAN screening with that of conventional IgAN screening alone in Japanese clinical settings.

Methods

Model Overview

We developed an analytical decision model to estimate the renal disease–related medical expense of each strategy for 40 years (Fig. 1). The decision tree started at 40 years of age with first-time hematuria and compared 2 kinds of strategies with simulated clinical scenarios: the intervention strategy as screening with novel biomarkers (group N) and the control strategy as conventional screening (group C). Figures 2 and 3 show the clinical flow of diagnosed "IgAN" and "not-IgAN," respectively. The screening strategy with novel biomarkers had 4 components, namely, the result of screening with novel biomarkers (positive or negative), whether renal biopsy was performed or not, the diagnosis by renal biopsy, and the consequent treatment (Figs. 2[A] and 3[A]). The conventional screening strategy had 3 components, namely, whether renal biopsy was performed or not, the diagnosis by renal biopsy, and the consequent treatment (Figs. 2[B] and 3[B]).

Participants

We assumed that it was at the age of 40 years that Japanese people were informed about the first-time hematuria at the annual health checkup along with a diagnosis of suspected IgAN by nephrologists. Then, the nephrologists considered whether the participants should undergo renal biopsy or not, as shown in the details in Figures 2 and 3. The rate of normal renal function (chronic kidney disease [CKD] stage 1 or 2) was assumed to be 80% at baseline and 70% in 5 years, at the point of renal biopsy.

Treatment options depended on the diagnosis "IgAN" or "not IgAN":

1. When the participants received a diagnosis of IgAN, they received tonsillectomy and steroid therapy (TSP) therapy or CKD therapy including renin-angiotensin-system blockade.
2. When the participants received a diagnosis of not-IgAN incorrectly or when they did not receive renal biopsy even though the true diagnosis was IgAN, they received CKD therapy.
3. When the true diagnosis was "not-IgAN," the treatment was not performed.
4. When the renal biopsy was not performed at baseline, it was considered whether the participants should undergo the renal biopsy in 5 years.

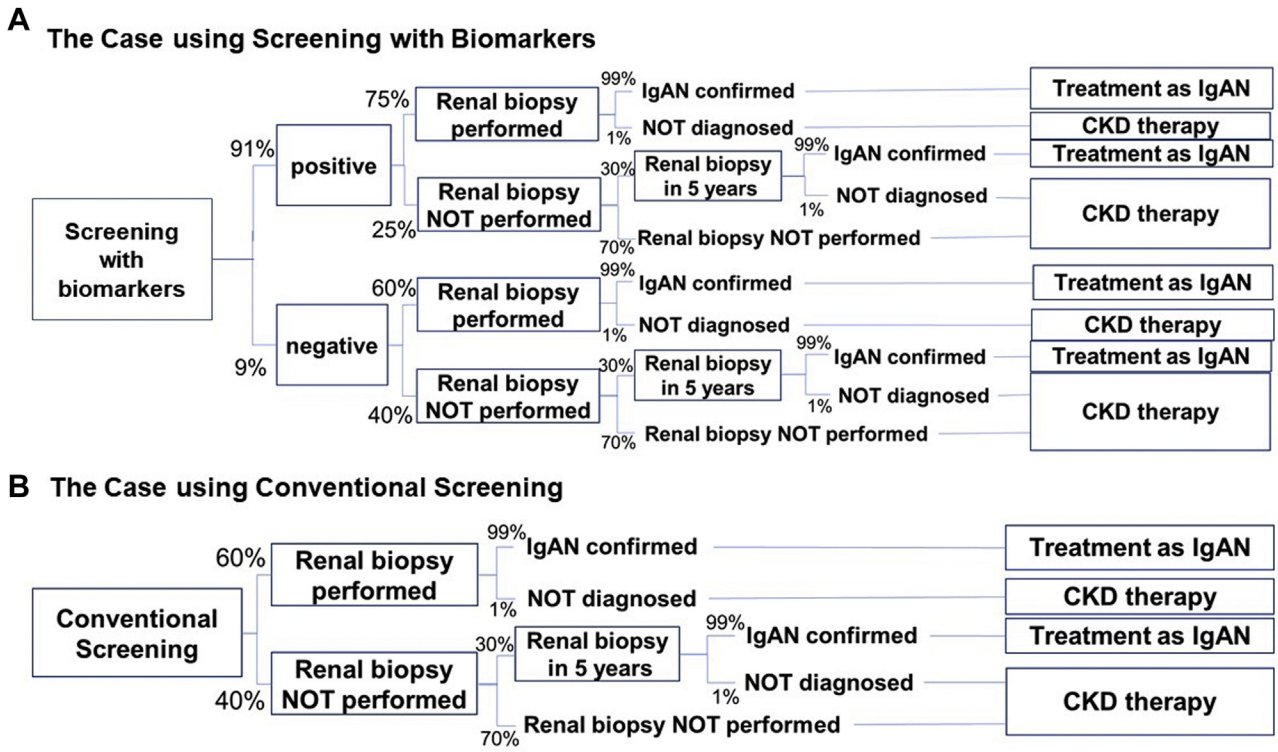
We assumed the clinical flow of each treatment option of IgAN, as shown in Appendix Figures 1 and 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.011. All participants lived until 80 years of age.

We assumed renal prognosis of participants as follows:

1. When the disease activity of IgAN was sustained continuous remission, participants had a good renal prognosis throughout their lives, and no recurrence happened.
2. When the participants did not obtain the remission of IgAN, the renal prognosis was the following depending on their renal function at the time of renal biopsy:
    1. When the renal function at the biopsy was in CKD stage 1 or 2, participants developed ESKD 20 years later and received dialysis for 20 years.
    2. When the renal function at the biopsy was in CKD stage 3 or below, participants developed ESKD 10 years later and received dialysis for 30 years.
3. When the true diagnosis was "not-IgAN," their renal prognosis was good throughout their lives despite no treatment.

Figure 4 shows the assumption of the IgAN prognosis of each treatment option depending on the renal function at the biopsy. The rate of TSP therapy was 55% when the participants were in CKD stage 1 or 2 and 45% when they were in CKD stage 3 or below. A good prognosis of TSP therapy was obtained at the rate of 80% when the participants were in CKD stage 1 or 2 and 75% when they were in CKD stage 3 or below, whereas a good prognosis of

Figure 2. Clinical flow when true diagnosis is IgAN. The proportion of patients with "true IgAN" was 60%. (A) The case using screening with biomarkers. The proportion of positive results with "true IgAN" of screening with biomarkers was 91%, which was defined as the value of sensitivity of screening with novel biomarkers. Renal biopsy was performed in 75% of patients with positive results and 60% of those with negative results, and 30% of patients who did not undergo renal biopsy at baseline received the procedure in 5 years. Definitive IgAN diagnosis was obtained in 99% of renal biopsies, which was defined as the value of sensitivity of renal biopsy. When the diagnosis was IgAN, TSP therapy or CKD therapy was performed. When the diagnosis of IgAN was not obtained by renal biopsy or when renal biopsy was not performed, CKD therapy was performed. (B) The case using conventional screening. Renal biopsy was performed at the rate of 60%, and 30% of those who did not undergo renal biopsy at baseline received the procedure in 5 years. Definitive IgAN diagnosis was obtained in 99% of renal biopsies, which was defined as the value of sensitivity of renal biopsy. When the diagnosis was IgAN, TSP therapy or CKD therapy was performed. When the diagnosis of IgAN was not obtained by renal biopsy or when renal biopsy was not performed, CKD therapy was performed.



CKD indicates chronic kidney disease; IgAN, IgA nephropathy; TSP, tonsillectomy and steroid pulse.

CKD therapy was obtained at the rate of 65% when the participants were in CKD stage 1 or 2 and 55% when they were in CKD stage 3 or below. When the diagnosis of IgAN was not obtained incorrectly or renal biopsy was not performed, the good prognosis was obtained at the rate of 55%, and the remaining 45% developed ESKD 10 years later and underwent dialysis for 30 years.

Intervention Strategy

A screening for IgAN using novel IgAN-specific biomarkers (galactose-deficient IgA1, galactose-deficient IgA1 antibodies, and galactose-deficient IgA1 immune complexes) was performed in addition to the conventional strategy. This new screening strategy consisted of the level of each biomarker in addition to clinical findings including the degree of hematuria, proteinuria, and renal function. According to the research report, the sensitivity and specificity of this screening method were 91% and 81%, respectively.[15,18] The nephrologists used the method before renal biopsy only to determine the indications for renal biopsy. The renal biopsy was assumed to be performed in 75% or 60% of patients with positive or negative results, respectively. The clinical flow after renal biopsy using screening with novel biomarkers was the same as the clinical flow using the conventional screening.

Control Strategy

The standard clinical practice provided by nephrologists (including the degrees of hematuria, proteinuria, and renal function) was performed as the conventional screening. The renal biopsy was assumed to be performed in 60% of patients.

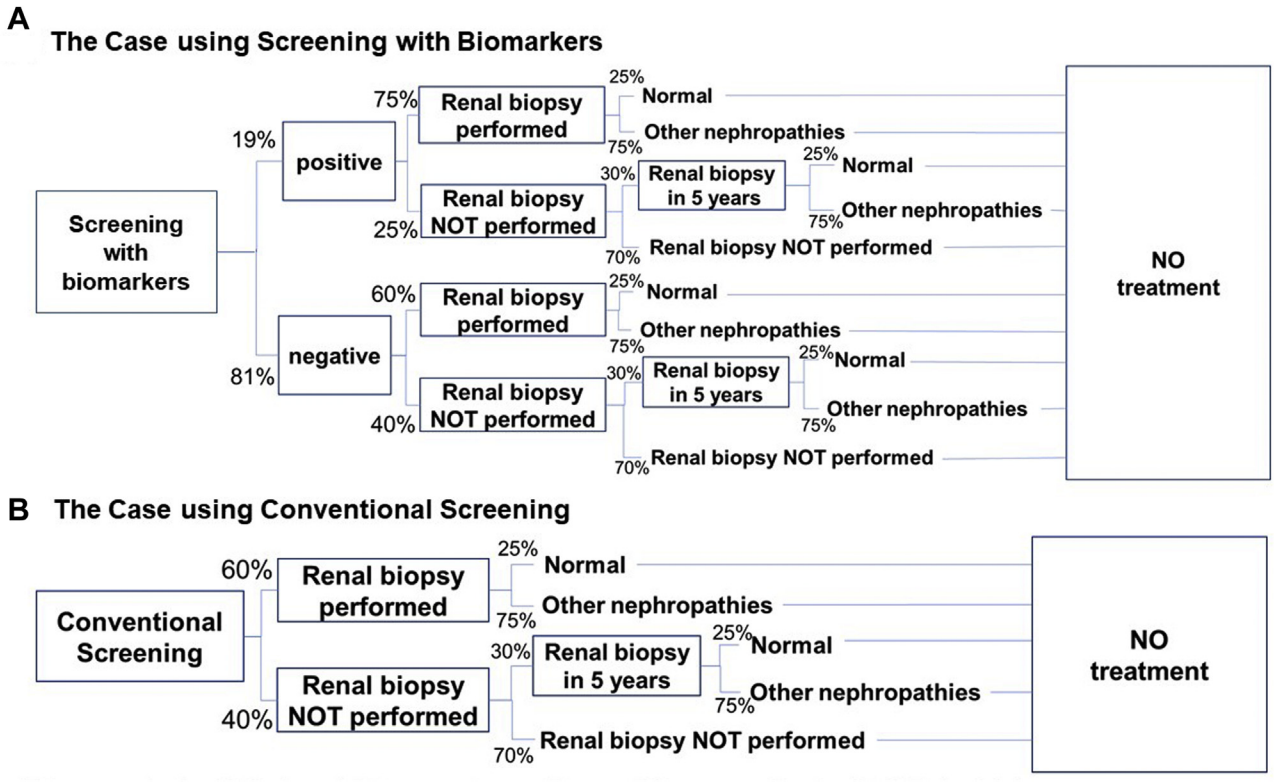
Outcome

The primary outcome was the renal disease–related medical expense of each strategy for 40 years. For the clinical effectiveness, the incremental prevalence of IgAN diagnosis and the incremental proportion of dialysis introduction thereafter were obtained.

Model Inputs

The clinical scenarios and variables were created by specialists in the Japanese Society of Nephrology. The inputs of the clinical variables in the analysis are presented in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.011 and those of the cost variables are presented in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.011. We searched the literature by a systematic review, extracted the relevant documents, and applied

Figure 3. Clinical flow when true diagnosis is "not-IgAN." The proportion of patients with true "not IgAN" was 40%. (A) The case using screening with biomarkers. The proportion of negative results of screening with biomarkers in true "not IgAN" was 81%, which was defined as the value of specificity of screening with novel biomarkers. Renal biopsy was performed in 75% of patients with positive results and 60% of those with negative results, and 30% of those who did not undergo renal biopsy at baseline received this procedure in 5 years. Renal biopsy diagnosed that 25% had normal tissue and 75% had glomerular disease other than IgAN. The treatment was not performed because the renal prognosis was good in either case. (B) The case using conventional screening. Renal biopsy was performed at the rate of 60%, and 30% of patients who did not undergo renal biopsy at baseline received the procedure in 5 years. Renal biopsy diagnosed that 25% had a normal tissue, and 75% had glomerular disease other than IgAN. The treatment was not performed because the renal prognosis was good in either case.



IgAN indicates IgA nephropathy.

the representative figures.[15,18–24] Interstudy variability reflected the maximum and minimum values in the deterministic sensitivity analysis. We used figures by referring to unpublished research reports and conference reports when the corresponding previous documents were missing. The cost variables were defined by Japanese medical expenses, which were based on discussion in the Central Social Insurance Medical Council. Each cost variable was calculated according to the clinical scenarios. Hospitalization costs were defined by referring to the Diagnosis Procedure Combination data at Juntendo University Hospital. Dialysis costs were cited from previous literature.[23] The variables were reviewed and corrected by 4 specialists (expert panel) and then consensus was obtained from the whole research meeting (March, September, and December, 2019).

Analysis Method

The model assumes a societal perspective. We considered only direct medical expenses related to renal disease. The expenses were calculated for 40 years in each strategy. Discounting was not conducted. Deterministic one-way sensitivity analysis was performed and expressed as a tornado diagram.

We conducted sensitivity analysis on the basis of each of the following case scenarios: (1) the rate of the TSP therapy was 80% when the participants were in CKD stage 1 or 2, (2) the proportion of the good prognoses was 99% when the participants with CKD stage 1 or 2 received TSP therapy, and (3) both scenario 1 and 2. The analysis was performed by the software TreeAge Pro 2019, R1 (Tree Age Software Inc., Williamstown, MA).

Ethical Consideration

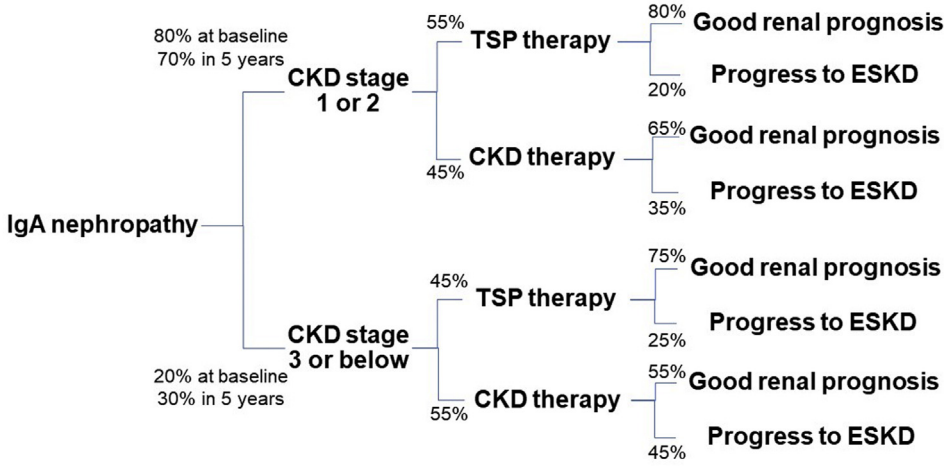
This study did not need the approval of the Ethics Committee because all data used in the analysis were based on existing materials, including published articles and research reports. The authors have no conflict of interest to declare. This evaluation followed all criteria of the Consolidated Health Economic Evaluation Reporting Standards reporting guidelines.

Results

Main Results

The total expected medical expense per person for 40 years was ¥31.2 million (~$291 000) in group N and ¥33.4 million (~$312 000) in group C. The expense in group N was lower by ¥2.2 million (~$21 000, equivalent to 6.65% of that in group C) than that in group C. Moreover, through screening with novel biomarkers, the

Figure 4. Treatment and prognosis in IgAN. The proportion of patients with CKD stage 1 or 2 at diagnosis was 80% at baseline and 70% in 5 years. The rate of TSP therapy was 55% in CKD stage 1 or 2 and 45% in CKD stage 3 or below, that is, CKD therapy was performed at the rate of 45% in CKD stage 1 or 2 and 55% in CKD stage 3 or below. A good prognosis of TSP therapy was obtained at the rate of 80% in CKD stage 1 or 2 and 75% in CKD stage 3 or below, whereas a good prognosis of CKD therapy was obtained at the rate of 65% in CKD stage 1 or 2 and 55% in CKD stage 3 or below.



CKD indicates chronic kidney disease; IgAN, IgA nephropathy; TSP, tonsillectomy and steroid pulse.

expected value of diagnosed IgAN increased by 5.67% points (group N 48.44%, group C 42.77%), and thereafter, that of dialysis introduction decreased by 0.85% points (group N 19.06%, group C 19.91%). Furthermore, the expected dialysis period in group N was 0.21 years shorter than that in group C (group N 4.86 years, group C 5.07 years), as shown in Table 1.

Sensitivity Analysis

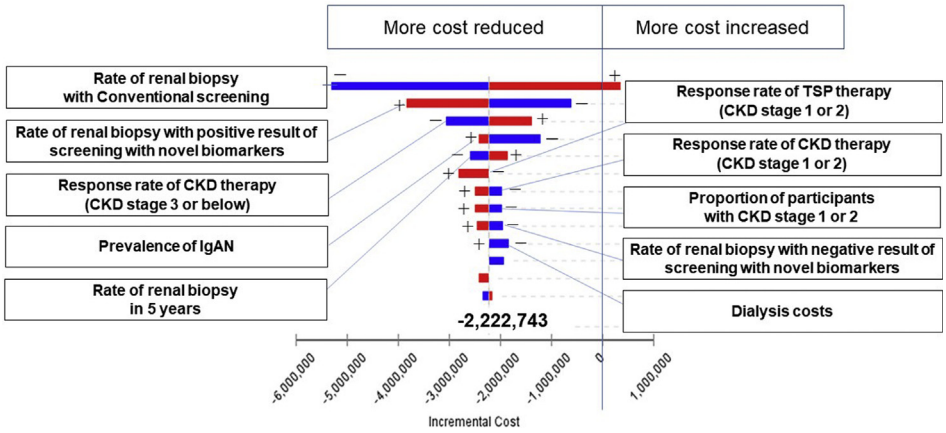
In the tornado diagram (Fig. 5), which illustrates the results of deterministic one-way sensitivity analysis about how degree of the expenses could be reduced by screening with novel biomarkers, the expenses could be reduced in almost all cases except

Table 1. Results of base-case and sensitivity analysis.

Variables	Base case	Case scenario 1	Case scenario 2	Case scenario 3
Expected renal disease–related medical expense, ¥				
Screening with biomarkers	31 177 576	29 544 370	26 383 791	22 571 591
Conventional screening	33 400 319	31 971 183	29 205 520	25 869 657
Incremental expected renal disease–related medical expense, ¥	−2 222 743	−2 426 813	−2 821 729	−3 298 066
%	−6.65	−7.59	−9.66	−12.75
Dialysis introduction, %				
Screening with biomarkers	19.06	17.62	15.06	11.80
Conventional screening	19.91	18.65	16.41	13.56
Incremental expected number of dialysis participants				
People per 100 000 people	−850	−1030	−1350	−1760
Expected dialysis period, y				
Screening with biomarkers	4.860	4.393	3.880	3.229
Conventional screening	5.065	4.814	4.365	3.796
Incremental expected dialysis period, y	−0.205	−0.421	−0.485	−0.567
Expected diagnosed IgAN				
Screening with biomarkers	48.44	48.44	48.44	48.44
Conventional screening	42.77	42.77	42.77	42.77
Incremental expected diagnosed IgAN				
people per 100 000 people	5670	5670	5670	5670

IgAN indicates IgA nephropathy.

Figure 5. Tornado diagram. The tornado diagram illustrates deterministic one-way sensitivity analysis, showing which uncertain valuables are influential to medical expenses that could be reduced by screening with novel biomarkers. Ten major influential variables were presented and are ordered, as shown, according to the magnitude of the medical expenses that could be reduced: the rate of renal biopsy with conventional strategy, the rate of renal biopsy with screening with novel biomarkers, the response rate of CKD therapy in CKD stage 3 or below, the prevalence of IgAN, the rate of renal biopsy in 5 years, the response rate of TSP therapy in CKD stage 1 or 2, the response rate of CKD therapy in CKD 1 or 2, the proportion of participants with CKD stage 1 or 2, and the dialysis costs. The incremental costs are presented by red bars when increasing the variables or by blue bars when decreasing the variables.



CKD indicates chronic kidney disease; IgAN, IgA nephropathy; TSP, tonsillectomy and steroid pulse.

when renal biopsy using the conventional screening was performed at a rate of 73% or higher. The tornado diagram also indicates that the rate of renal biopsy for both screening strategies, the response rate for both TSP and CKD therapies, the prevalence of IgAN, the proportion of participants with CKD stage 1 or 2, and the dialysis costs were major influential variables.

In particular, the higher rate of renal biopsy using novel biomarkers and lower rate of renal biopsy using the conventional strategy were provided, which in turn could lead to a greater reduction in expenses. Moreover, the higher the success rate of both therapies in CKD stage 1 or 2 and the lower the success rate of both therapies in CKD stage 3 or below, the more prevalence of diagnosis with IgAN, the more the proportion of CKD stage 1 or 2 and the higher the dialysis costs were provided, the more expenses could be reduced.

In the assumed case scenario analysis, when the rate of TSP therapy in CKD stage 1 or 2 increased to 80% and the achieved clinical remission rate increased to 99%, the expected expense in group N was lower by ¥3.3 million (~$30 000, equivalent to 12.75% of that in group C) than that in group C, the expected value of the dialysis decreased by 1.76% points (group N 11.80%, group C 13.56%), and the expected dialysis period was 0.57 years shorter (group N 3.23 years, group C 3.80 years), as shown in Table 1.

Discussion

In this study, we demonstrated that screening for IgAN with novel biomarkers reduced the expected medical expense per person for 40 years by ¥2.2 million (~$21 000, equivalent to 6.65% of that of the conventional screening) among participants with first hematuria with suspected IgAN at 40 years old. Our results suggested that screening for IgAN with novel biomarkers can help diagnose IgAN in the early stages and thus provide timely and appropriate therapy to participants and help prevent induction of dialysis because of IgAN. To our knowledge, this is the first study to conduct a cost analysis on the IgAN screening method.

To assess a long diverse clinical history of chronic diseases or a future medical technology, expert opinion as well as randomized controlled study could be useful to make an analytic model with higher reliability and validity. We developed an analytic decision model on the basis of the 40-year clinical course of IgAN, referenced by an expert panel's opinions. The formal method to solve these situations is termed "structured expert disciplines."[25] Unfortunately, we could not use the structured consensus method when making the analytical decision model, nevertheless, we tried to increase the validity of this model by the expert panel's consideration and consensus of the research group.

Our results showed that the screening for IgAN with novel biomarkers reduced ¥2.2 million (~$21 000). This reduction was equivalent to 8% of the expected lifelong medical expenses among Japanese people.[26] Because annual increase of the national medical expenses is an urgent financial problem, an 8% reduction for the medical expenses only by using a new screening method for a single disease would have a considerable beneficial social impact in Japan. The increase of population and medical expenses with CKD because of IgAN are also a global issue; therefore, this screening with novel biomarkers would offer a similar benefit worldwide as in Japan.

Recently, trends in treatment for IgAN have been changed. The results of a national questionnaire survey in 2008 suggested that TSP therapy was performed in more cases of IgAN.[27] In this study, the variables for treatment selection and the prognosis for IgAN were based on the results of a multicentered large study conducted from 2002 to 2004.[24] We conducted the sensitivity analysis similar to the current clinical situation, in which TSP therapy was performed more highly with a better response rate. According to this analysis, the expected medical expense was reduced by ¥3.3 million ($30 000), equivalent to 12% of the expected lifelong medical expenses among Japanese people. This result suggested that screening for IgAN with novel biomarkers would be more useful in the current clinical situation.

One-way sensitivity analysis using a tornado diagram showed that the rate of renal biopsy was the most influential variable. This is partially because the indications for renal biopsy in cases

"with hematuria, without proteinuria" is controversial. A bigger difference emerged in the rates of renal biopsy between previous reports, and uncertainty caused by this difference could make the rate of renal biopsy the most influential variable. Interestingly, as shown in the tornado diagram (Fig. 5), the direction of the amount of incremental medical expenses was opposite between the rate of the renal biopsy using the screening for IgAN with novel biomarkers and that of the conventional screening. The biomarkers could help to determine the indication for renal biopsy more correctly for participants with suspected IgAN and help in efficient diagnosis of IgAN. The prevalence of IgAN was another influential variable. The expected value of diagnosed IgAN increased as the prevalence of IgAN increased, and thus, the more the patients with IgAN, the more the expenses could be reduced. This finding indicated that screening with novel biomarkers is more useful in areas with a higher prevalence of IgAN, including Japan and East Asia.

This study has several limitations. First, the sensitivity and specificity of the novel biomarkers, which calculated diagnostic accuracy, might be overestimated because participants of the study were included from patients with IgAN and healthy subjects (2-gate type study). Nonetheless, both sensitivity and specificity of screening with novel biomarkers were less influential variables in the tornado diagram (Fig. 5), and therefore, the final result would not change markedly. Moreover, we investigated it in the case of broader range of sensitivity and specificity of the screening with novel biomarkers from –20% and confirmed that there was not a significant impact on the final result, even if the impact size of the sensitivity became bigger as shown by the seventh grade in the other tornado diagram (see Appendix Figure 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.011). The reliability of biomarkers for screening IgAN was rarely reported because of the lack of consistency. Because IgAN has marked disease heterogeneity in its clinical and pathological features, there is a variety of epidemiology, clinical presentation, disease progression, and long-term outcome across ethnic populations around the world,[28] and therefore, it could be difficult to find patients with IgAN effectively by simple and common biomarkers worldwide. It might be necessary to combine various biomarkers differently depending on the target population to increase sensitivity. Second, the analytical model did not consider the several medical expenses of surgical complications of tonsillectomy or CKD-induced cardiovascular diseases. Nonetheless, the expenses due to these complications would be less influential because an absolute reduction of expenses is obtained by possible reduction of permanent expensive dialysis costs due to prevention of ESKD. Future studies on a detailed CEA using the Markov model are needed to investigate a long and diverse clinical course of IgAN. Third, tonsillectomy is routinely performed only in Japan and is not usually performed in Western countries, and almost all articles about the effects of tonsillectomy were reports from Japan. Nevertheless, recent reviews describe that immunological evidence supporting the usefulness of tonsillectomy as a treatment for IgAN is gradually accumulating.[29,30] Moreover, there is a report about the randomized controlled trial of tonsillectomy in patients with IgAN other than Japanese.[31] Thus, we considered that our result could be increasingly applied to patients with IgAN in future.

Conclusion

A screening method with the novel IgAN-specific biomarkers would reduce the expected renal disease–related medical expense among individuals with suspected IgAN.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2021.07.011.

Article and Author Information

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REFERENCES

1. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet*. 2015;385(9981):1975–1982.
2. USRDS Reference Tables. The United States Renal Data System. https://adr.usrds.org/2020/reference-tables. Accessed March 5, 2021.
3. Therapy-current status of chronic dialysis therapy in Japan in 2018. The Japanese Society for Dialysis Therapy. https://docs.jsdt.or.jp/overview/Published2020. Accessed March 5, 2021.
4. Magistroni R, D'Agati VD, Appel GB, Kiryluk K. New developments in the genetics, pathogenesis, and therapy of IgA nephropathy. *Kidney Int*. 2015;88(5):974–989.
5. Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research Group on Progressive Renal Diseases. *Am J Kidney Dis*. 1997;29(4):526–532.
6. Manno C, Strippoli GF, D'Altri C, Torres D, Rossini M, Schena FP. A novel simpler histological classification for renal survival in IgA nephropathy: a retrospective study. *Am J Kidney Dis*. 2007;49(6):763–775.
7. Schena FP. Immunoglobulin A nephropathy with mild renal lesions: a call in the forest for physicians and nephrologists. *Am J Med*. 2001;110(6):499–500.
8. Ieiri N, Hotta O, Sato T, Taguma Y. Significance of the duration of nephropathy for achieving clinical remission in patients with IgA nephropathy treated by tonsillectomy and steroid pulse therapy. *Clin Exp Nephrol*. 2012;16(1):122–129.

9. Japanese Clinical Practice Guidelines for hematuria diagnosis 2013. Japanese Society of Nephrology. www.jsn.or.jp/guideline/pdf/hugl2013.pdf. Accessed March 5, 2021.
10. Suzuki Y, Matsuzaki K, Suzuki H, et al. Serum levels of galactose-deficient immunoglobulin (Ig) A1 and related immune complex are associated with disease activity of IgA nephropathy. *Clin Exp Nephrol*. 2014;18(5):770–777.
11. Camilla R, Suzuki H, Dapra V, et al. Oxidative stress and galactose-deficient IgA1 as markers of progression in IgA nephropathy. *Clin J Am Soc Nephrol*. 2011;6(8):1903–1911.
12. Zhao N, Hou P, Lv J, et al. The level of galactose-deficient IgA1 in the sera of patients with IgA nephropathy is associated with disease progression. *Kidney Int*. 2012;82(7):790–796.
13. Berthoux F, Suzuki H, Thibaudin L, et al. Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. *J Am Soc Nephrol*. 2012;23(9):1579–1587.
14. Chen P, Yu G, Zhang X, et al. Plasma galactose-deficient IgA1 and C3 and CKD progression in IgA nephropathy. *Clin J Am Soc Nephrol*. 2019;14(10):1458–1465.
15. Yanagawa H, Suzuki H, Suzuki Y, et al. A panel of serum biomarkers differentiates IgA nephropathy from other renal diseases. *PLoS One*. 2014;9(5), e98081.
16. Fukuda T. A pilot program of implementing health technology assessment to decision making in Japan. *Jpn J Pharmacoepidemiol*. 2018;23(1):3–10.
17. Wang J, Zhang L, Tang SC, et al. Disease burden and challenges of chronic kidney disease in North and East Asia. *Kidney Int*. 2018;94(1):22–25.
18. Suzuki H. [Aberrantly glycosylated IgA1 as a useful biomarker in IgA nephropathy]. *J Clin Exp Med (Japanese)*. 2015;255:1095–1100.
19. Hoshino Y, Kaga T, Abe Y, et al. Renal biopsy findings and clinical indicators of patients with hematuria without overt proteinuria. *Clin Exp Nephrol*. 2015;19(5):918–924.
20. Lee HM, Hyun JI, Min JW, et al. The natural course of biopsy-proven isolated microscopic hematuria: a single center experience of 350 patients. *J Korean Med Sci*. 2016;31(6):909–914.
21. Kim BS, Kim YK, Shin YS, et al. Natural history and renal pathology in patients with isolated microscopic hematuria. *Korean J Intern Med*. 2009;24(4):356–361.
22. Ubara Y, Kawaguchi T, Nagasawa T, et al. Kidney biopsy guidebook 2020 in Japan. *Clin Exp Nephrol*. 2021;25(4):325–364.
23. Fukuhara S, Yamazaki C, Hayashino Y, et al. The organization and financing of end-stage renal disease treatment in Japan. *Int J Health Care Finance Econ*. 2007;7(2-3):217–231.
24. Hirano K, Matsuzaki K, Yasuda T, et al. Association between tonsillectomy and outcomes in patients with immunoglobulin A nephropathy. *JAMA Netw Open*. 2019;2(5):e194772.
25. Soares MO, Sharples L, Morton A, Claxton K, Bojke L. Experiences of structured elicitation for model-based cost-effectiveness analyses. *Value Health*. 2018;21(6):715–723.
26. Lifelong medical expenses. https://www.mhlw.go.jp/content/shougai_h28.pdf. Ministry of Health, Labor and Welfare. Accessed March 5, 2021.
27. Matsuzaki K, Suzuki Y, Nakata J, et al. Nationwide survey on current treatments for IgA nephropathy in Japan. *Clin Exp Nephrol*. 2013;17(6):827–833.
28. Rodrigues JC, Haas M, Reich HN. IgA nephropathy. *Clin J Am Soc Nephrol*. 2017;12(4):677–686.
29. Harabuchi Y, Takahara M. Recent advances in the immunological understanding of association between tonsil and immunoglobulin A nephropathy as a tonsil-induced autoimmune/inflammatory syndrome. *Immun Inflamm Dis*. 2019;7(2):86–93.
30. Yang X, Zhu A, Meng H. Tonsillar immunology in IgA nephropathy. *Pathol Res Pract*. 2020;216(7):153007.
31. Yang D, He L, Peng X, et al. The efficacy of tonsillectomy on clinical remission and relapse in patients with IgA nephropathy: a randomized controlled trial. *Ren Fail*. 2016;38(2):242–248.