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Research Article

Cost-Benefit Analysis of Screening for Gallstone Disease among Chinese Population in Taiwan

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Abstract. *Purpose:* To explore whether it is worthwhile to launch a routine gallstone disease screening for cholecystectomy prevention among Chinese population from different perspective in Taiwan. *Methods:* The study cohort was conducted with a total of 2,386 healthy adults voluntarily admitted to a teaching hospital for a physical check-up in 2002 in Taiwan. Annual follow-up screenings of gallstone disease then were until 31 December, 2007. The cost-benefit analysis tool of screening for gallstone disease is based on TreeAge software for medical decision analysis. A decision analysis using the Markov Decision Model was constructed to compare different screening regimes for gallstone disease. *Results:* In terms of benefit-cost ratio, the different screening programs for gallstone disease could save New Taiwan Dollars (NTD) from 19.61 to 63.41 in discounted costs for each dollar incurred in different screening years from the societal viewpoint for Taiwan and save NTD from 2.89 to 4.71 in different screening years from health care payer's perspective. The average estimate of willingness-to-pay to translate into benefit yields NTD from 807.8 to 4,039 benefits per case due to gallstone disease screening in different screening years during 10-year follow-up. The net present value of the gallstone disease screening were NTD from −133,736 to −217,689.2 in different screening years. *Conclusion:* It is worthwhile to initial a routine gallstone disease screening of Chinese population for cholecystectomy prevention from the societal perspective but not from consumer decision based on the willingness-to-pay perspective.

Keywords: gallstone disease, cost-benefit analysis, screening

1. Introduction

Gallbladder disease (GSD) has escalated in many countries because of increased dietary consumption of calories and cholesterol [1]. Within the past few years ultrasonographic studies have provided estimates of GSD morbidity and of predisposing factors in various populations [2–4]. Although cholecystectomy still represents the gold standard for symptomatic GSD patients, expectant management may also represent a valid therapeutic approach in GSD patients, depending upon the clinical manifestations of the disease and, in particular, on their changes over time [5]. In Taiwan, the prevalence of open cholecystectomy (OC) and laparoscopic cholecystectomy (LC) were respectively 18.19 and 25.44 per 100,000 in 1996 while OC gradually decreased to 13.21, but LC dramatically increased to 48.35 [6]. In addition, the total treatment cost for OC and LC are U.S. dollars $2,729 and $1,588, respectively [6]. From the viewpoint of preventive medicine, early detection of this disorder by regular screening followed by early treatment could prevent the resulting cholecystectomy.

GSD is matched the Wilson criteria for screening due to it is an important health problem; the disease natural history should be understood; a recognisable latent or early symptomatic stage; a test is easy to perform and interpret, acceptable, accurate, reliable, sensitive and specific; an accepted treatment recognised for the disease; treatment is more effective if started early; a policy on who should be treated; diagnosis and treatment are cost-effective; and case-finding should be a continuous process. Whether screening for GSD is worthwhile is also contingent on whether subjects are willing to pay the ultrasound screening program that would decrease the risk of cholecystectomy. Benefit due to the reduction of disease in cost-benefit analysis is often measured by the human capital approach for which the value of ultrasound screening program is measured by its effect on the patient's disease-free time earning. According to welfare economic theory, the benefit to an individual of a service or an intervention is defined as that individual's maximum willingness to pay (WTP) for the service or intervention [7]. WTP is a contingent valuation and involves using a hypothetical survey to directly ask individuals the maximum amount they are willing to pay for the commodity in question [7, 8]. Because the limitations of medical resources, the government is in a dilemma about whether it is necessary to popularize the ultrasound screening programs into a nationwide program. Our previous study has showed that degree of GSD was the independent factor affecting WTP values in GSD screening [4]. The purpose of this study is to conduct a cost-benefit analysis to determine whether it is worthwhile to launch ultrasound screening program for cholecystectomy prevention among adults in Taiwan.

2. Methods

2.1. Study design and subjects. The data for cost-benefit analysis of GSD screening in this study were derived from a cohort conducted with a total of 2386 healthy adults (1235 males and 1151 females) voluntarily admitted to a northern teaching hospital for a physical check-up between January 2002 and December 2002 in Taiwan. Annual follow-up screenings of GSD then were until 31 December, 2007. Study subjects who participated in at least two GSD screenings were analyzed. All procedures were performed in accordance with the guidelines of our institutional ethics committee and adhered to the tenets of the Declaration of Helsinki. All subjects' information were anonymous. Access to personal records was approved by the hospital human subjects review board at Cheng-Hsin General Hospital, Taipei, Taiwan.

2.2. Screening and diagnosis for gallstone disease. In this study, the sonographic screening results of GSD among participants were diagnosed by a panel of specialists using real-time ultrasound sonography (TOSHIBA nemio SSA-550A, Japan) to examine the abdominal region after fasting for at least 8 hours based on the presence of "movable hyper-echoic material with acoustic shadow. Cases of GSD were classified as follows: single gallbladder stone, multiple gallbladder stones, and cholecystectomy, excluding gallbladder polyps.

In order to set up a consistent diagnosis of GSD between specialists, the Kappa statistic was used to assess the agreement of inter-observer reliability among study specialists. A pilot study was performed using 30 randomly selected healthy subjects other than the study participants. For inter-observer reliability, the Kappa value for diagnosis of GSD between specialists was 0.77 (95%CI: 0.64–0.89).

2.3. Markov decision model and cost-benefit analysis of screening for gallstone disease.

1. The construction of Markov decision model. In this study, the cost-benefit analysis tool of screening for GSD was based on TreeAge software (DATA 3.5, Tree-Age, Inc., Williamstown MA) for medical decision analysis. A decision analysis using the Markov Decision Model was constructed to compare different screening regimes for GSD with no screening group (see Figure 1). TreeAge software is tailored for medical decision analysis using tree structure and influence diagram. Decision tree analysis is a technique for selecting an optimal decision by formulating the problem in tree-structured figure, including decision node, chance node, and value node. An expected value for each node is calculated. The best decision is selected on the basis of expected values. The main reason accounts for why a Markov model, rather than the traditional survival analysis such as accelerated failure time model to estimate parameter is as the traditional survival analysis estimate hazard rate merely based on two state, it is difficult for such a simple model to deal with multi-state disease process. The principle of the Markov chain is applied to the selection of samples from a probability density function to be applied to the disease natural history model. Markov process that assumes that each transition between states follows the "no memory" property of the exponential distribution [9]. In this study, the assumption of no screening group was that except ultrasound screening, subjects still received routine medical care until they become cholecystectomy. According to the theory of stochastic process, the Markov chain model is determined by both the initial state and the transition matrix. The model starts from the decision to screen or not to screen and the overall expected value is based on expected values of end nodes rather than all nodes. For each decision, there are four states of disease natural history of GSD including No GSD, single stone, multiple stones, and cholecytectomy. The initial state distribution is based on the results of the present study. Transition probabilities from one state to another representing the disease natural history of GSD were derived from our empirical estimation, that is, the annual transition probabilities for each stage to the next are as follows: No GSD to single stone 5.05%, single stone to multiple stones 10.00%, and multiple stones to cholecystectomy

13.76% [10]. We assumed the Markov model follows a time-homogeneous distribution, the methods of transition probabilities (the probability of progressing from one state to another state) estimation conducted by Kalbfleisch and Lawless [11], and the algebra for transition probabilities referred to by Chen et al [12]. For each scenario, we calculated the expected probability of subjects aggregate experience that is accumulated in each state during 10-year follow-up.

2. An empirical survey for the estimation of cost and willingness to pay. Costs in this study include direct and indirect cost. Direct costs include cost of GSD screening, cost of regular clinic fee, and treatment cost. Indirect cost includes only productivity loss of the subjects because of time taken off work for treatment. The average time taken off work for treatment was depends on the professions' opinion. In addition, WTP was assessed by the following question: "what is the most price that you would be willing to pay for routine screening for GSD that reduces the risk of cholecytectomy?" The WTP amounts for a routine screening for GSD were elicited by discrete-choice, that is, subjects were presented a single price for a screening program that would yield a specified health change. Subjects either accept or reject the price. By randomly varying the price across a number of different subsamples, the mean WTP could be estimated [4]. To maintain consistency of interview quality, all information on WTP measurements was also collected by one well-trained interviewer. All costs are expressed as New Taiwan Dollars (NTD).

3. Cost-benefit analysis and discount rate. Using the human-capital approach, net cost (saving) for different screening programs of GSD, taking direct cost and indirect cost into account, was calculated. Benefit-cost ratios were calculated as the reduction cholecytectomy costs divided by the cost of the screening programs. Using WTP approach, net present value (NPV) was also calculated on the basis of the total benefit (calculated by the WTP method) minus screening cost of GSD. To take time preference into account, that is, receiving benefit earlier and incurring cost later, we discounted all costs and benefits to the present value at 5% annually.

3. Results

Of the 2386 study cohort, 1379 subjects attended at least two sonographic check-ups: 719 (52.1%) subjects had two consultations+, 416 (30.2%) subjects had three, and 244 (17.7%) subjects underwent four or more check-ups during the five year period. The overall response rate was about 57.8, and the mean follow-up time was 3.66±0.78 years. The baseline information of study subjects with GSD at initial screening shows in Table 1.

The annual direct cost, annual indirect cost, WTP value, and annual transition probability in decision analysis of GSD screening are shown in Table 2. Direct costs include screening cost, regular clinics' fees, laparoscopic cholecystectomy, and hospitalizations and others. Indirect cost represents lost productivity according to patient's disease state, estimated using the Gross Domestic Product (GDP) value in 2011.

Table 1: The baseline characteristics of gallstone disease at first screening among study subjects between 2002 and 2007 ($n = 1379$).

Variables	Number (%) or mean±SD
Categorical variables	
Sex	
Male	701 (50.8)
Female	678 (49.2)
Age (yrs)	
<40	421 (30.5)
40–49	386 (28.1)
50–59	293 (21.2)
60–69	152 (11.0)
≥70	127 (9.2)
Each state of gallstone disease	
No gallstone	1296 (94.0)
Single stone	26 (1.9)
Multiple stones	36 (2.8)
Cholecystectomy	21 (1.5)
Continuous variables	
Fasting plasma glucose (mg/dl)	95.2 ± 24.0
Body mass index (Kg/m^2)	23.6 ± 3.6
Systolic blood pressure(mmHg)	121.3 ± 17.2
Diastolic blood pressure(mmHg)	78.4 ± 12.8
Total cholesterol(mg/dl)	212.4 ± 35.5
Triglyceride (mg/dl)	133.0 ± 111.4
Uric acid (mg/dl)	6.4 ± 3.0
AST (U/L)	29.2 ± 17.9
ALT (U/L)	31.5 ± 30.6
Creatinine (mg/dl)	1.01 ± 0.33
BUN (mg/dl)	14.2 ± 5.8

Table 3 shows total discounted direct costs and indirect costs using the human capital approach. Annual screening, biennial screening, 3-yearly screening, 4-yearly screening, and 5-yearly screening regimens could save NTD38,073, NTD24,356, NTD17,693, NTD16,114, and NTD12,407 per case in discounted direct costs (except screening cost), respectively. From payer's perspective, the discounted net total direct costs for GSD screening program were NTD-24,893, NTD-17,766, NTD-13,300, NTD-12,819, and NTD-9,771 for annual screening, biennial screening, 3-yearly screening, 4-yearly screening, and 5-yearly screening, respectively. The discounted indirect costs saved per case by GSD screening program were NTD220,345, NTD185,222, NTD179,125, NTD163,143, and NTD154,745 for annual screening, biennial screening, 3-yearly screening, 4-yearly screening, and 5-yearly screening, respectively. This yield NTD245,238 (annual screening), NTD202,988 (biennial

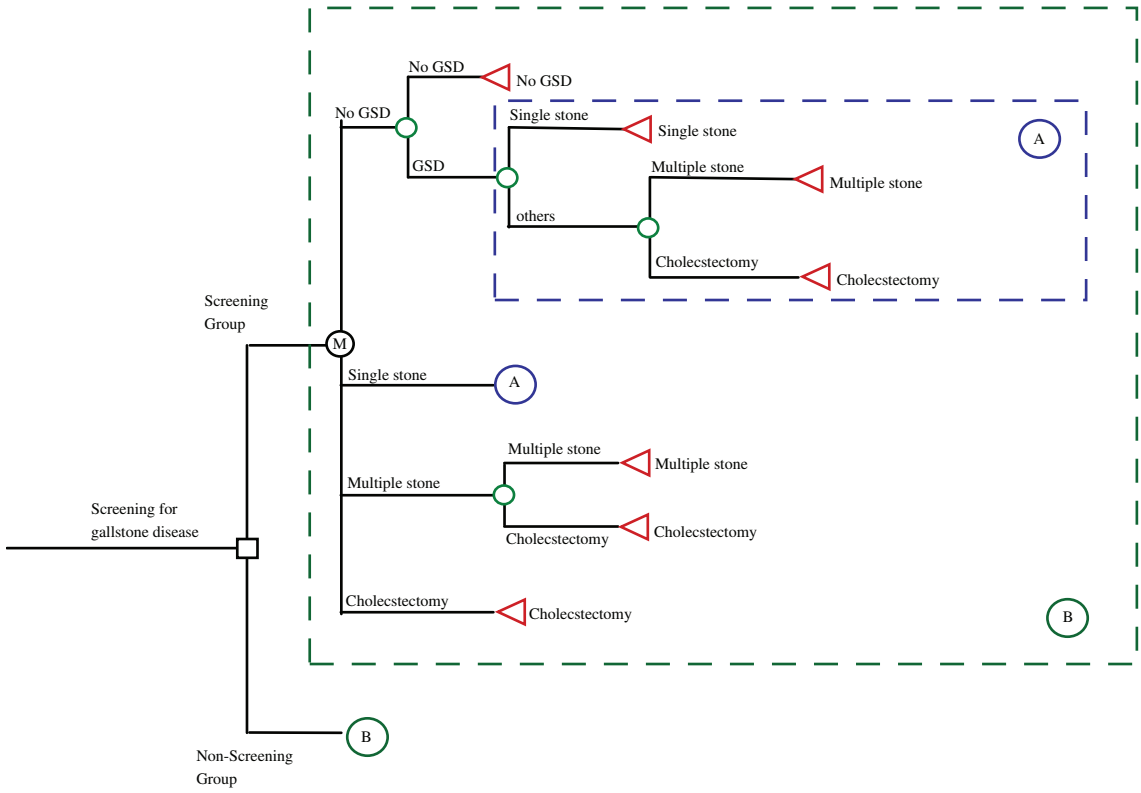

Figure 1: Markov decision model for cost-benefit analysis of gallstone disease screening.

screening), NTD192,425 (3-yearly screening), NTD175,962 (4-yearly screening), and NTD154,745 (5-yearly screening) net saving per case due to GSD screening program from the societal perspective (P-value < 0.0001).

As Table 4 shows, GSD screening programs could save NTD19.61 (annual screening), NTD31.80 (biennial screening), NTD44.80 (3-yearly screening), NTD53.21 (4-yearly screening), and NTD63.41 (5-yearly screening) from the societal viewpoint and save NTD2.89 (annual screening), NTD3.70 (biennial screening), NTD4.03 (3-yearly screening), NTD3.89 (4-yearly screening), and NTD4.71 (5-yearly screening) in discounted costs for each NTD dollar incurred in GSD screening programs from health care payer's perspective.

The average estimate of WTP in order to reduce blindness as shown in Table 2 is NTD403.9. Translating this figure into benefit yields NTD4,039 (annual screening), NTD2,019.5 (biennial screening), NTD1,346.3 (3-yearly screening), NTD1,009.8(4-yearly screening), and NTD807.8 (5-yearly screening) benefit per case due to GSD screening during 10-year follow-up. The NPV of the screening programs, taking indirect cost into account, were NTD-133,736, NTD-178,005.5, NTD-189,241.7, NTD-206,041.2, and NTD-217,689.2 of annual screening, biennial screening, 3-yearly screening, 4-yearly screening, and 5-yearly screening, respectively.

4. Discussion

4.1. Implications of cost-benefit analysis for gallstone disease screening. Few population-based studies have attempted to quantify the cost and benefit of GSD screening programs in Taiwan. This study used cost-benefit analysis to assess whether a GSD screening program against non-screening group is worthwhile in Taiwan from different perspectives. The results indicate that indirect costs play an important role in the evaluation of the GSD screening program. Annual screening program could save the most (NTD220,345) per case in discounted indirect costs compared with non-screening group. From health care payer's perspective, the discounted net cost for annual screening was NTD24,893 per case. This indicate that the benefit from the annual screening program of GSD could not outweigh the cost incurred in the GSD screening program from health care payer's perspective. Taking indirect cost into account, the NTD245,238 net saving per case suggest the annual screening program is rather worthwhile from the societal perspective (P-value <0.0001).

In addition, using the WTP approach, the present study shows it is not worthwhile to have screening for GSD from the perspective of WTP due to the negative result of NPV value. It should be noted that the WTP approach is a contingent-valuation method that reflects consume surplus

Table 2: Cost assumptions, willingness-to-pay value, transition probabilities in decision analysis of screening for gallstone disease.

Parameter	Value
Annual direct cost (NT dollars)	
Screening cost[1]	1,382
Regular clinics fee[2]	509
Laparoscopic cholecystectomy	11,710
Hospitalizations and others	26,825
Total	40,426
Annual indirect cost (NT dollars)	
Gross Domestic Product, GDP	635,670
Willingness-to-pay value(NT dollars) [4]	
No gallstone disease	248.4 ± 178.9 (95%CI: 216.4-280.4)
Single stone	335.3 ± 208.19 (95%CI: 298.1-372.5)
Multiple stones	382.2 ± 221.89 (95%CI: 342.5-421.9)
Cholecystectomy	470.5 ± 192.89 (95%CI: 436.0-505.0)
Total	403.9 ± 238.09 (95%CI: 361.3-446.5)
Annual transition probability (%) [10]	
No gallstone diseaseSingle stone	5.05
Single stoneMultiple stones	10.00
Multiple stonesCholecystectomy	13.76

[1]Screening cost includes clinician's fee, ultrasound examination, SMA-12 test, and manpower cost.
[2]Regular clinics fee includes clinician's fee and pharmacist's fee.

of getting GSD screening. Since the mean estimate of WTP (NTD403.9) for the GSD screening program was far below the current expense for direct costs of GSD screening (NTD1,318) per case. This suggests that they could not get any surplus from the purchase of screening program. This accounts for why the results of NPV is negative. If the estimate of WTP is raised to NTD1,500, this means that if people have to pay only NTD1,318 for benefits they value at NTD1,500 then they get a surplus of NTD192 from the purchase of screening for GSD. Results from the WTP suggest that the study population are willing to pay for the screening program is lower than the benefit they value. In terms of consumer decision based on the perspective of WTP, it may not be worthwhile to launch a GSD screening program.

4.2. The efficiency and advantage for routine gallstone disease screening. Economic evaluations were criticized commonly by decision makers for ignoring budget impacts, about which decision makers desperately concerned. Payers could get into financial difficulty if they adopt too many cost-effectiveness interventions and affordability, which depended on the overall volume of patients, is therefore a prime concern [5, 13]. In addition, evidence-based studies also suggested that screening for and treating GSD is extremely cost-effective. A screening program in Chile for gallbladder disease in a high risk population achieves significant benefits at a low incremental cost and acceptable cost-effectiveness. The incremental cost-effectiveness ratio of universal screening/elective intervention, high risk intervention, and selective screening strategy were US$ 180, US$147, and US$481, respectively [14]. To take both cost and efficacy into consideration, prevention programs aimed at GSD screening result in both substantial federal budgetary savings and highly cost-effective health care.

4.3. Methodological considerations. Although using a follow-up study design could reduce selection bias and increase statistical power, using primary information and calculating both direct and indirect costs help us estimate the true benefit of GSD screening more closely than has been possible before. There are still some critiques raised form this study. First, there were 1007 (42.2%) failed to complete the series of assessment. People who lost to follow-up during the five year period were older (50.2 ± 10.8 years vs. 45. ± 9.9 years, $P< 0.0001$), higher SBP (127.9 ± 21.0 mmHg vs. 120.7 ± 19.1 mmHg, $P < 0.0001$), and higher fasting plasma glucose (102.6 ± 25.1 mg/dl vs. 95.2 ± 24.0 mg/dl, $P < 0.0001$) than did the participants. Second, only five-year follow-up period, we could not have enough sample size to predict all of the effects of GSD screening on disease variations and we did not explicitly consider the sensitivity and specificity of the GSD screening tests. Third, the sonographic examination is technique dependent to the examiner. Although the Kappa value for the agreement of interobserver reliability seemed acceptable [14], non-differential misclassification-bias identification still could have occurred. We did not estimate the variational sonographic examination cost and cholecystectomy fee in different year and decreasing as the technologic development in this study. Forth, the screening cost and regular clinics fee are referenced by the National Health Insurance System in Taiwan, however, the potential information bias of the manpower cost due to the hospital-based study design, that is, of it not being exactly representative of the whole general practice. Further, it should be noted that the estimates used in this analysis were based on relatively small samples, that is, the aggregate estimates may reflect a reasonable population, but not all Chinese populations. Finally, we did not estimate the how the covariates such as number of co-morbidities influence the each stage on the screening efficacy of different intervals for GSD and

Table 3: Cost-benefit analysis using the human-capital approach of different screening programs for gallstone disease.

	Screening group	Non-screening group	Net cost	*P*-value for t-test
Annual screening				
Direct cost				
Screening cost	13,180	0	13,180	
Other cost	74,792	112,865	–38,073	
Total	87,972	112,865	–24,893	
Indirect cost	49,803	270,148	–220,345	
Total (Direct + Indirect cost)	137,775	383,013	–245,238	<0.0001
Biennial screening				
Direct cost				
Screening cost	6,590	0	6,590	
Other cost	88,509	112,865	–24,356	
Total	95,099	112,865	–17,766	
Indirect cost	84,926	270,148	–185,222	
Total (Direct + Indirect cost)	180,025	383,013	–202,988	<0.0001
3-yearly screening				
Direct cost				
Screening cost	4,393	0	4,393	
Other cost	95,172	112,865	–17,693	
Total	99,565	112,865	–13,300	
Indirect cost	91,023	270,148	–179,125	
Total (Direct + Indirect cost)	190,588	383,013	–192,425	<0.0001
4-yearly screening				
Direct cost				
Screening cost	3,295	0	3,295	
Other cost	96,751	112,865	–16,114	
Total	100,046	112,865	–12,819	
Indirect cost	107,005	270,148	–163,143	
Total (Direct + Indirect cost)	207,051	383,013	–175,962	<0.0001
5-yearly screening				
Direct cost				
Screening cost	2,636	0	2,636	
Other cost	100,458	112,865	–12,407	
Total	103,094	112,865	–9,771	
Indirect cost	115,403	270,148	–154,745	
Total (Direct + Indirect cost)	218,497	383,013	–164,516	<0.0001

Table 4: The benefit-cost ratio estimates of different screening programs for gallstone disease.

	Benefit-cost ratio			
	Payer's perspective		Society perspective	
Annual screening	2.89	(38,073/13,180)	19.61	((38,073 + 220,345)/13,180)
Biennial screening	3.70	(24,356/6,590)	31.80	((24,356 + 185,222)/6,590)
3-yearly screening	4.03	(17,693/4,393)	44.80	((17,693 + 179,125)/4,393)
4-yearly screening	3.89	(12,819/3,295)	53.21	((12,819 + 163,143)/3,295)
5-yearly screening	4.71	(12,407/2,636)	63.41	((12,407 + 154,745)/2,636)

investigate possible associations between benefit-cost ratio and whether the person belongs in screening group or not, what is his/her age, how many times was the person screened. Further study of those inadequately represented is needed.

5. Conclusion

In conclusion, this study revealed that it is worthwhile to launch a routine GSD screening program of Chinese population for cholecystectomy prevention from the societal

perspective but not from consumer decision based on the perspective of WTP.

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I am pleased to share with you that **Nuclear Receptor Research** is now a reality as an open access peer-reviewed journal devoted to publishing high-quality, original research and review articles covering all aspects of basic and clinical investigations involving members of the nuclear receptor superfamily. **Nuclear Receptor Research** has an editorial board comprised of a group of renowned scientists from around the world. Board members are committed to make **Nuclear Receptor Research** a vibrant forum showcasing global efforts in this ever-expanding area of research.

We believe that the impact and visibility of papers related to nuclear receptors will be significantly enhanced by appearing in a journal devoted exclusively to nuclear receptors. In addition, it is hoped that **Nuclear Receptor Research** will serve as a catalyst to encourage collaborative studies as well as to foster interdisciplinary initiatives within this expansive and dynamic field. For these reasons, I invite you to consider **Nuclear Receptor Research** (**http://www.agialpress.com/journals/nrr/**) as a vehicle to share your novel research findings as well as your vision for the future of nuclear receptor research with your colleagues around the world.

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