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COST-BENEFIT ANALYSIS OF PRENATAL DIAGNOSIS BY MOLECULAR KARYOTYPING VERSUS CONVENTIONAL KARYOTYPING FOR DETECTION OF ANEUPLOIDIES IN RAMATHIBODI HOSPITAL

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ABSTRACT
Objective: To compare the benefit to cost ratio of prenatal diagnosis (PND) for aneuploidy between KaryoLite BACs-on BeadsTM (KL-BoBsTM) and conventional karyotyping techniques in health care purchaser's perspective. Study Design: Health economicevaluation with cost-benefit analysis using decision tree model in prospective study design. **Materials And Methods:** A total of 160 singleton pregnancies with obstetric indications for amniocentesis were enrolled from 11th November 2016 to 11th March 2017 at 16-23 weeks' gestation. Subjects were randomly and equally allocated into 2 groups. All participants were interviewed and completed the questionnaires. Total costs were collected. The benefit in this study was the health state change from relieving of anxiousness described in term of willingness to pay (WTP) for faster turnaround time in each laboratory method. The decision tree model was applied to estimate the ratio of incremental benefit to incremental cost. One way probabilistic sensitivity analyses was applied. **Results:** From the purchaser's perspective view, the incremental benefit to incremental cost ratio when comparing KL-BoBs™ to conventional karyotyping method was 1.48. The incremental benefit was 874 Thai Baht (24.9 US$) more than the incremental cost. The WTP for faster turnaround time which would relieve the participants from anxiousness in conventional karyotyping group was the most powerful parameter using one-way sensitivity analysis. **Conclusion:** KL-BoBs™ technique is valuable in the perspective of pregnant women undergoing amniocentesis for high risk of aneuploidy. The incremental benefit was 1.48-folds higher than incremental cost when comparing KL-BoBs™ to conventional karyotyping method.

KEYWORDS: Prenatal diagnosis, aneuploidies, conventional karyotyping, BACs-on BeadsTM, cost-benefit analysis.

INTRODUCTION
Prenatal diagnosis (PND) for fetal aneuploidy is the most common indication of invasive prenatal tests. Traditionally, the PND of chromosomal abnormality relies on conventional karyotyping method, a cytogenetic analysis procedure which can detect abnormalities on all 23 pairs of chromosomes in term of number, deletions or duplications and structural rearrangement. However, this technique is a labor intensive task and takes around 3-4 weeks to confirm the report.[1] This time consuming process not only raises the anxiety of a couple awaiting for the concluding report, but also could impact some crucial decision and change the course of management. In 2005 Leung WC et al[2] compared the result between rapid aneuploidy testing (RAT) (either QF-PCR or FISH technique) and conventional karyotyping. The results from both methods were concordant 99.1% and suggested that using RAT as a standalone test could be an acceptable alternative method to conventional karyotyping when performed under some indications.

BACs-on Beads™ (BoBs™) is a molecular technique modified from comparative genomic hybridization by using immobilized bacterial artificial chromosome clones attached to dyed fluorescein microspheres beads.[3] KaryoLite BoBs™ (KL-BoBs™) aimed to detect arm-specific aneuploidy of all chromosomes to provide information about the proximal and terminal regions of each chromosome arm.[4] In this study, we decided to use KL-BoB™ because of its ability to detect all aneuploidy. The automaticity of interpretation also significantly decreases the labor of laboratory personnel and can be reported within 72 hours.[5] Previously published literatures[3, 5-6] recommended the use of BoBs™ as the

RAT of choice due to its high sensitivity, specificity, and its ability to detect chromosomal aneuploidy with faster turnaround time. This would aid physicians in making a more rapid medical decision and ease away the couple's anxiety. However, this method lacks the ability to detect balanced rearrangement, low level of mosaicism and triploid.

Thailand is a developing country with high variation of household income. The expanding population results in higher demand for the public health care system. Data from Rajanukul institute of Thailand[7] showed that the number of patients to receive conventional karyotyping should not exceed 20,000 cases per year due to limitation of resource and lab personnel. Pattanaphesaj J, et al[7] stated that in the simulation model, the genetic technicians may have to analyze conventional karyotyping around 87,000 cases per year. It appears that the demand for PND is far exceeded the limited resource of work force and the alternative genetic testing that required less manpower might be essential. While BoBs™ is relatively new in Thailand and usage is still limited in clinical practice, Ramathibodi hospital is the first hospital in Thailand to adopt this new technique and it has been on the PND service since 2013 but still in a limited number of cases requesting this technique. Data from previous studies[3, 4-6] had compared the abilities of both techniques but the studies in health economic perspective have never been conducted before. This study aimed to evaluate cost-benefit analyses of PND between KL-BoBs™ and conventional karyotyping technique in health care purchaser perspective in term of the willingness to pay (WTP) to relieve anxiousness due to faster turnaround time from alternative diagnosis procedure.

MATERIALS AND METHODS

Study population

This study was conducted from 11th November 2016 to 11th March 2017 at Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand. The study was reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects, based on the Declaration of Helsinki, Mahidol University (EC_600108). Singleton pregnant women attending the antenatal care clinic with obstetric indication for amniocentesis were counseled and invited to join the study with written informed consents.

Inclusion criteria included all of the followings: 1) maternal age of 18 years or greater, 2) gestational age between 16 and 23 weeks based on well-defined last menstrual period or fetal biometry from ultrasound scanning in the first half of pregnancy, 3) having obstetric indication for amniocentesis, and 4) proficiency in the Thai language. Exclusion criteria was self resignation from the study.

Study design

In this study, the cost-benefit analysis (CBA) method was chosen. The way to express the outcome or benefit was health stage change which was usually described in term of willingness to pay (WTP). We decided to use WTP to represent the benefit because there was no difference in clinical outcome between these 2 methods such as the aneuploidy detection rate, adverse effect to their fetuses or mothers. Donaldson C [8] aforementioned that the WTP technique could be used to derive values from patients receiving various ways of treatment and to aid in priority setting across patient groups.

Sample size

The sample size was calculated from pilot study implementing 10 subjects in each group to receive the interview. WTP was calculated in term of mean and standard deviation and represented in Thai Baht. Mean and standard deviation of conventional karyotype group and KL-BoB™ group are 522, 630 and 239, 247 Thai Baht (14.9, 18.0 and 6.8, 7.0 US$), respectively. The calculated sample size was 80 subjects in each group with 0.05 of alpha error and 0.8 of power (calculated by n4Studies program version 1.4.0).

Method

The questionnaire was created, reviewed and validated by 5 experts in maternal fetal medicine division, human genetic and health economic divisions. It was tried-out by 30 pregnant women and tested for reliability using Cronbach's alpha formula. The calculated alpha coefficient is 0.75. The questionnaire contained 2 sections including demographic data and health stage change by interviewing. The health stage change consisted of WTP for each day of faster result from both methods (conventional karyotyping or KL-BoBs™) and their faster turnaround time in days of result expectation.

Subjects were randomized by block of four techniques and equally allocated into 2 groups. The participants in group 1 answered the questionnaires as if they were to receive conventional karyotyping, whereas those in the group 2 completed the questionnaires as if they were to receive KL-BoBs™. All participants received pre-test counselling from the same researcher and completed the answers in demographic data. The health stage change was obtained from researcher interviewing under the assumed circumstances: singleton, maternal aged 35 years or greater, turnaround time more than 24 hours. The questionnaires were collected for analysis. Then, all participants underwent amniocentesis and were provided antenatal care according to Ramathibodi hospital standard protocol. If the gestational age was beyond 21 weeks, they were counselled to perform fetal cord blood sampling for conventional karyotyping or perform amniocentesis for molecular karyotyping technique (KL-BoBs™ or QF-PCR). The advantage, disadvantage and risk of complications were counseled.

Statistical analysis
Demographic data was reported as mean and percentage. We used decision tree model which was an economic evaluation model suitable for short term diagnosis or screening decision**.** The decision tree model was developed to analyze the cost-benefit between conventional karyotype or KL-BoBs™ technique (Figure 1). The cost parameters in this model included 1) direct medical cost which consisted of the cost of conventional karyotyping or KL-BoBs™ technique from the year 2016 to 2017 and the medical service with ultrasonography which were 4,000, 6,000 and 1,050 Thai Baht (114.2, 171.4 and 30.0 US$), respectively, 2) direct non-medical cost including participants' expense for food and transportation during the visit to antenatal clinic and 3) indirect cost referring to amount of total income loss during the visit to antenatal clinic. All costs have been converted to 2016 American $ with the rate of 35.00 Thai Baht per US$.[9]

Faster turnaround time was the most obvious difference between these 2 methods. In Ramathibodi hospital, the final result report from conventional karyotyping method and BoBs™ method took 21 and 7 days, respectively. The definition of benefit in this study is health stage change from relieving of anxiousness described in term of WTP for their faster-turnaround-day result multiplied by faster-turnaround-day result expectation. Cost-benefit between 2 methods was calculated by using the following equations:

1) Ratio of incremental benefit to incremental cost = (Δ Benefit /Δ Cost) and

2) Difference of incremental benefit to incremental cost = (Δ Benefit – Δ Cost).

Δ Benefit = the difference of mean faster-turnaround-day results multiplied by mean WTP of each group. = **-** (B2-B1)

Δ Cost = the difference of total costs calculated from summation of direct medical, direct non-medical and indirect cost of each intervention. = (C2-C1)

Data was analysed by Microsoft Excel (TreePlan Student). The benefit to cost ratio when comparing KL-BoBs™ to conventional karyotyping technique was calculated. If the ratio is greater or equal to 1 and benefit was more than calculated cost, the alternative technique would be considered as valuable in participants' perspective. One-way sensitivity analysis was also conducted to determine the individual impact of each input parameter value on cost-benefit ratios.

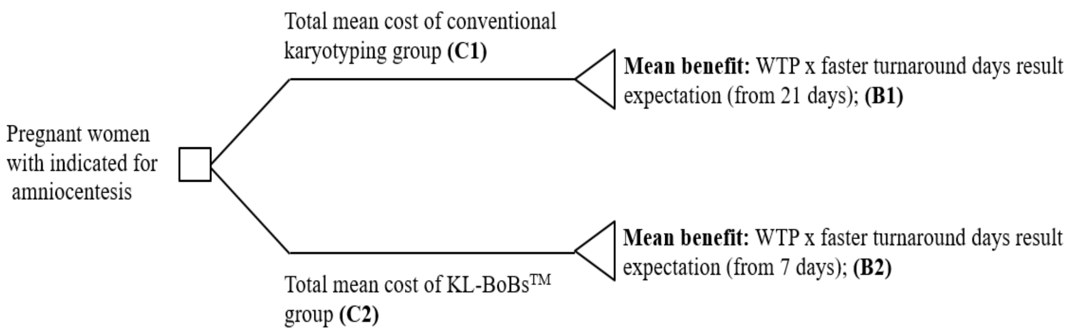

Figure 1: The decision tree model.
The first arm represented cases with reference method (conventional karyotyping) while the second arm revealed cases with alternative method (KL-BoBs™).

RESULT
During the study period, 160 pregnancies were enrolled as shown in Figure 2. The distribution of real obstetric indication for amniocentesis was shown in Table 1**.** No participant resignation from the study. After allocation by block of 4 technique, they were categorized into group 1 or 2 as shown in Table 1. There was no statistically significant difference in maternal demographic data or their socioeconomic status. The mean maternal age was 36.8 +/- 3 years. Most of them graduated with bachelor's degree and were under universal coverage health payment program. Fifty four percent received antenatal care at Ramathibodi hospital while the remaining was referred from private hospitals or other government hospitals. Advanced maternal age was the most common obstetric indication performing amniocentesis resulting in 86.3 percent. Mean gestational age for amniocentesis was 18^{+6} weeks. The participants' and their families' income, cost of traveling, food cost and total loss of participants' income were not statistically significant.

Table 2 demonstrates total cost parameters including 1) direct medical cost 2) direct non-medical cost and 3) indirect cost. All cost values were summed in total. The benefit in term of participants' anxiousness relieved in monetary value was also reported. The participant's faster turnaround time (days) of conventional karyotyping and KL-BoBs™ were 9.8 and 4.1 days, respectively. All results were represented in Thai Baht and US$. The difference of total costs between methods was 1,803.5 Thai Baht (51.5 US$). The difference of benefit between methods was 2,677.5 Thai Baht (76.5 US$).

The data in Figure 3 showed the benefit to cost ratio (∆ Benefit / ∆ Cost) comparing KL-BoBs™ to conventional karyotyping method**.** The benefit to cost ratio comparing KL-BoBs™ to conventional karyotyping method were above 1 yielding the ratio of 1.48, with WTP 874 Thai Baht (24.9 US$) more than the calculated cost respectively.

Sensitivity analysis

Because of the uncertainty of the parameters, one-way sensitivity analysis was applied to manage and adjust the benefit to cost ratio when each parameter was changed. This statistical analysis was conducted to determine the impact of each parameter value. The result was shown in Figure 4. The WTP for faster turnaround time which would relieve the participants from anxiousness in conventional karyotyping group is the most significant effect factor on our benefit to cost ratio. Other influential factors included faster turnaround time in days of result expectation, total losing income, laboratory cost, additional cost for traveling and food while visiting antenatal clinic, cost of medical service and ultrasonography.

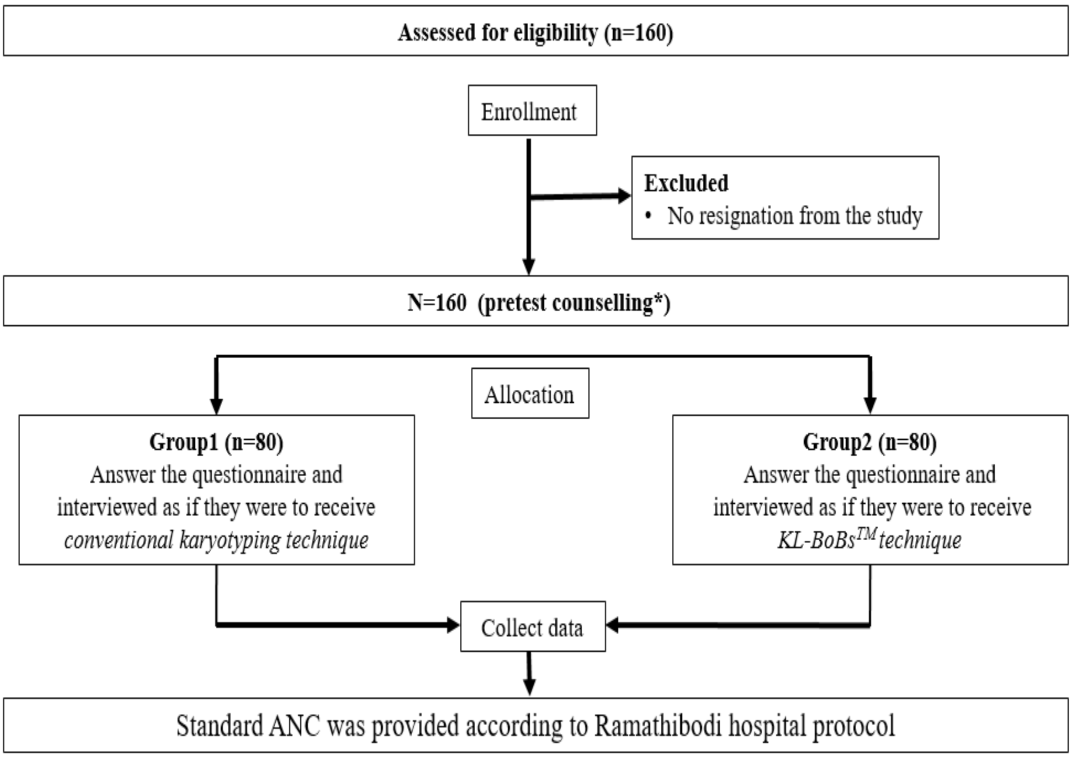

Figure 2: Flow chart of the population of the study.

* Under the assumed circumstances: singleton, maternal aged 35 years or greater, turnaround time more than 24 hours.

Abbreviation; ANC = antenatal care

Table 1: Maternal demographic data, obstetric data and socioeconomic status (Total N = 160).

Total N = 160	**Group 1*, N = 80**	**Group 2**, N = 80**	**p-value**
Maternal age (years), (mean, SD)	37.1 +/- 4.5	36.4 +/- 3.2	
Education (degree), (n, %)			0.35
Lower than bachelor	28 (35.0)	25 (31.2)	0.37
Bachelor	42 (52.5)	44 (55.0)	
Higher than bachelor	10 (12.5)	11 (13.8)	
Health insurance (n, %)			
UC	30 (37.5)	32 (40.0)	0.89
CSMBS	24 (30.0)	21 (26.3)	
Private	26 (32.5)	27 (33.7)	
ANC (n, %)			
Ramathibodi hospital	45 (56.2)	42 (52.5)	0.11
Government hospital	4 (5.0)	4 (5.0)	0.86
Private hospital	31 (38.8)	34 (42.5)	

GA (weeks and days), (mean, SD)	18^{+5} +/- 1^{+3}	18^{+3} +/- 1^{+4}	
OB indication for amniocentesis (n, %) Positive DS screening Structural anomaly by USG Advanced maternal age Positive DS screening+structural anomaly by USG Positive DS screening+advanced maternal age Structural anomaly by USG+advanced maternal age Positive DS screening+structural anomaly by USG++ advanced maternal age	 2 (2.5) 3 (3.7) 69 (86.3) 1 (1.3) 2 (2.5) 3 (3.7) 0 (0)	 3 (3.7) 3 (3.7) 69 (86.3) 1 (1.3) 1 (1.3) 3 (3.7) 0 (0)	0.88
Participant's income (THB/ US$)***, (mean, SD)	21,951.0, 7,868.7/ 627.1, 224.8	23,428.1, 10,820.7/ 669.3, 309.1	0.10
Family's income (THB/ US$)***, (mean, SD)	22,965.0, 10,327.1/ 656.1, 295.0	22,088.7, 13,697.5/ 631.1, 391.3	0.64
Traveling and food cost (THB/ US$)***, (mean, SD)	355.1, 130.7/ 10.1, 3.7	267.5, 123.9/ 7.6, 3.5	0.08
Total losing income (THB/ US$)***, (mean, SD)	953.6, 245.6/ 27.2, 7.0	844.7, 218.4/ 24.1, 6.2	0.58

* **Group 1:** Pregnant women who answered the questionnaire and were interviewed as if they were to receive conventional karyotyping technique.
** **Group 2:** Pregnant women who answered the questionnaire and were interviewed as if they were to receive KL-BoBs™ technique.
***All costs have been converted to 2016 American $ with the rate of 35.00 Thai Baht per US$ [9].
Abbreviation; GA = gestational age, UC = universal coverage, CSMBS = civil servant medical benefit scheme, OB = obstetric, DS = Down's syndrome, USG = ultrasonography

Table 2: Total cost and benefit components.

Cost components and benefit	**Costs (THB/ US$)***		
	Mean	**SD**	**lower-upper**
Group 1* (n=80)			
Direct medical cost Laboratory costs Medical supply, USG cost	 4,000/ 114.2 1,050/ 30.0	 0 0	 3,600-4,400/ 102.8- 125.7 945-1,155/ 27.0-33.0
Direct non-medical cost			
Traveling and food cost	355.1/ 10.1	130.7/ 3.7	68-549/ 1.9- 15.6
Indirect cost			
Total losing income	953.6/ 27.2	245.6/ 7.0	450.0-1,695.9/ 12.8- 48.4
WTP Faster turnaround time result (days)	488.3/ 13.9 9.8	235.7/ 6.7 3.7	210.8-1,050.0/ 6.0- 30.0 6.1-13.5
Group 2** (n=80)			
Direct medical cost Laboratory costs Medical supply, USG cost	 6,000/ 171.4 1,050/ 30.0	 0 0	 5,400-6,600/ 154.2- 188.5 945-1,155/ 27.0- 33.0
Direct non-medical cost			
Traveling and food cost	267.5/ 7.6	123.9/ 3.5	90.0-472.7/ 2.5- 13.5
Indirect cost			
Total losing income	844.7/ 24.1	218.4/ 6.2	387.7-1,628.0/ 11.0- 46.5
WTP Faster turnaround time result (days)	514.1/ 14.6 4.1	220.4/ 6.3 1.3	155.0-1,000/ 4.4- 28.5 2.8-5.4

* **Group 1:** Pregnant women who answered the questionnaire and were interviewed as if they were to receive conventional karyotyping technique.
** **Group 2:** Pregnant women who answered the questionnaire and were interviewed as if they were to receive KL-BoBs™ technique.
***All costs have been converted to 2016 American $ with the rate of 35.00 Thai Baht per US$ [9].
Abbreviation; USG = ultrasonography, WTP=willingness to pay

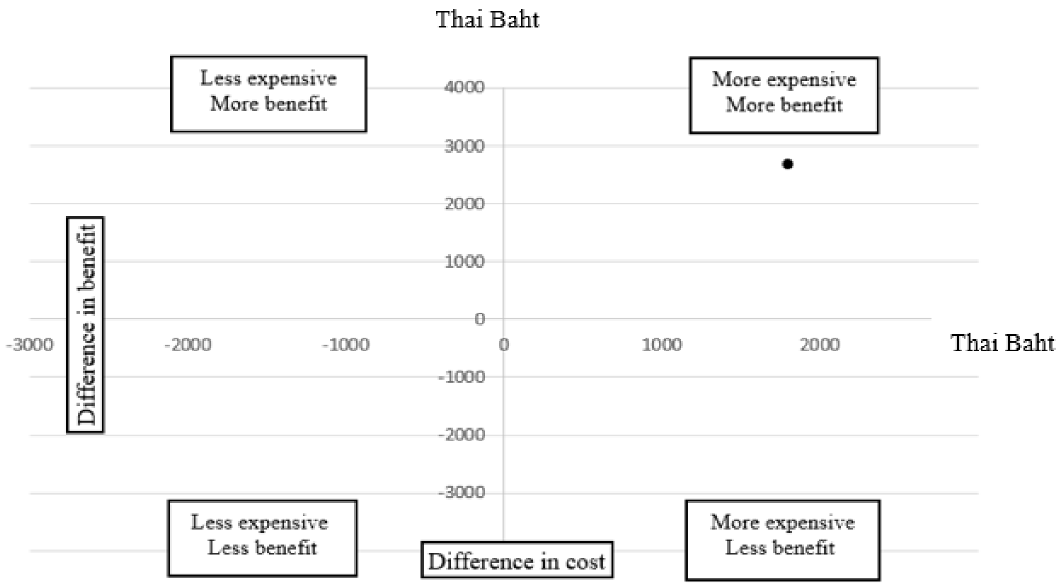

Figure 3: Incremental benefit to incremental cost ratio of the participants (ΔB/ΔC=1.48). Abbreviation; B=benefit, C=cost

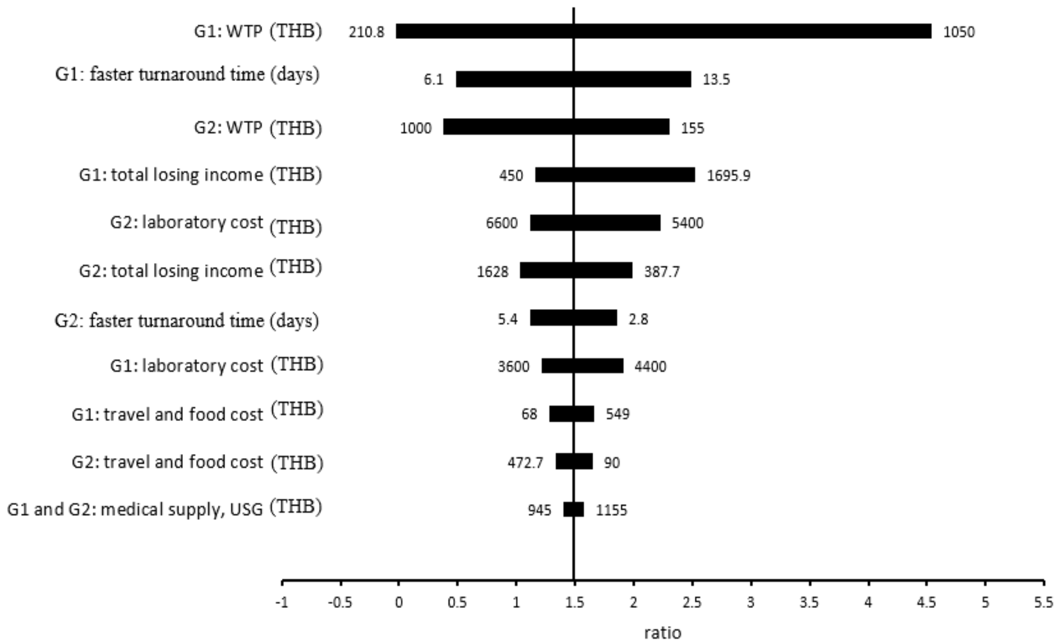

Figure 4: One-way sensitivity analysis.

Abbreviation; G1= group 1 (answer the questionnaire and interviewed as if they were to receive conventional karyotyping technique), G2= group 2 (answer the questionnaire and interviewed as if they were to receive KL-BoBs^{TM} technique), WTP = willingness to pay, USG = ultrasonography

DISCUSSION

This economic evaluation study showed that *under assumed circumstances*, the KL-BoBs^{TM} technique was beneficial in term of relieving their anxiousness by faster turnaround time result regarding the perspective of pregnant women undergoing amniocentesis for high risk of aneuploidy. The incremental benefit was higher than incremental cost when comparing KL-BoBs^{TM} to conventional karyotyping method by1.48-folds. In the sensitivity analysis for each parameter, the most significant factor affecting on benefit to cost ratio was WTP for faster turnaround time in conventional karyotyping group, meaning their anxiousness was the most potential influence on this result.

There were two published literatures about economic evaluation in PND. The first study[10] was performed by using computer simulation in Canadian women with positive prenatal screening test. It compared cost effectiveness of RAT (either QF-PCR or FISH technique) to conventional karyotyping technique. This study focused on evaluating the clinically significant missed chromosome abnormalities and the impact of detecting missed chromosome abnormalities. This study concluded that RAT was the most effective strategy in government perspective. The second study[7] was conducted in Thai pregnant women using computer simulation. This study focused on finding the best way in societal and government perspectives to diagnose Down syndrome. The study compared in 4 scenarios of prenatal Down syndrome screening and diagnosis. Any positive prenatal screening tests following by amniocentesis was the most appropriate financial and practical option. Both studies were conducted under computer simulation but the prospective study design for evaluation of cost benefit analysis in PND testing had never been conducted in Thailand.

Ramathibodi hospital is the first hospital in Thailand to adopt BoBs™ technique. This technique gives information in total number of chromosomes and can potentially change the decision from cordocentesis to amniocentesis in pregnant women with gestational age which is approaching to viability. The cordocentesis has higher risk of procedure related fetal abortion. It appears that this reliable molecular method is faster and provides more benefit in healthcare purchaser perspective even though it costs more than conventional karyotyping technique.

Since 2004, Thailand Ministry of Public Health has declared that advanced maternal age was considered to be the indication for invasive PND. This announcement is still valid at the present day and some parts of Thailand. However, the American collage of obstetrician and gynecologists (ACOG)[11] encouraged all pregnant women should be offered prenatal assessment for aneuploidy by screening or diagnostic testing regardless of maternal age or other risk factors. Furthermore, the Society for Maternal-Fetal Medicine (SMFM)[12] recommends that chromosomal microarray analysis (CMA) be offered when genetic analysis is performed in cases with fetal structural anomalies with discuss the benefits and limitations of CMA and conventional karyotype. The pre- and posttest counseling should be performed by trained genetic counselors, geneticists, or other expert providers. In addition, the CMA may include probes that cover the whole genome, or may be targeted with concentrated coverage in known disease-causing region of the genome and more limited coverage of the rest of the genome. In parts of structurally normal fetuses with indication for invasive prenatal testing, both SMFM[12] and ACOG[13] recommend that either fetal karyotype or chromosomal microarray analysis (CMA) can be performed regardless of maternal age. In the near future, with well co-operation between medical providers and the government support. The need for invasive PND may be reduce. The resource and lab personnels may be sufficient for increasing demands.

The strength of this study was the first economic evaluation of cost benefit analysis in PND testing with prospective study design in Thailand. There were study limitations since only questionnaires were used as a study tool and the results of benefit in term of WTP was calculated altogether without categorization by obstetric indications. However, it explored the trend of need and value of procedures in the health care purchaser perspective and may have a potential to be a model for future studies. Further larger scale multicenter study with actual use of these methods and categorization of participants according to obstetric indication might be required. Additional survey from provider's, social and government perspective might also be valuable.

CONCLUSION
KL-BoBs™ technique is valuable in the perspective of pregnant women undergoing amniocentesis for high risk of aneuploidy. The incremental benefit was 1.48-folds higher than incremental cost when comparing KL-BoBs™ to conventional karyotyping method.

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Conflict of interest
No conflict of interest related to this article

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