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Budget impact of incorporating non-invasive prenatal testing in prenatal screening for Down syndrome in Turkey

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ABSTRACT

Objectives: To provide information to the government about the budget impact of implementing non-invasive prenatal testing (NIPT) into prenatal screening strategies to detect Down syndrome (DS) in singleton pregnancies in Turkey; the likely costs or savings associated with NIPT in comparison to the current practice were calculated.

Methods: A decision-analytic model was developed to calculate the cost estimates for 1,309,771 women who gave birth in 2016; 84.8% of whom were <35-years-of-age. The superior combined test (CT) among current strategies is compared with contingent NIPT for women < 35-years-of-age; and usual practice of amniocentesis (AC) for women ≥ 35 years-of-age was replaced with universal NIPT.

Results: When the market price of NIPT (1,077 PPPUS$) is used, contingent NIPT offered to high-risk women < 35-years-of-age adds 34,907,225 PPPUS$; and for women-35 ≥ years-of-age the universal NIPT leads to 142,785,818 PPPUS$ more cost to the government compared to current strategies. The additional costs with NIPT are partially compensated by the cost-savings due to reduction of the number of invasive tests and procedure related losses (17,826,476 PPPUS$ for women < 35-years-of-age and 37,070 PPPUS$ for women ≥ 35-years-of-age). Results are sensitive to the NIPT costs; with a lower cost of NIPT, a total saving would be 33,116,046 PPPUS$ with new strategies.

Conclusions: NIPT might be the choice of prenatal screening strategies if its price is lowered to economically acceptable levels. Until that time, currently accepted protocols seem to be more realistic. On the other hand, decision makers should also consider possible savings and the women's quality of life that can be improved with the new technology.

Introduction

Prenatal screening for common chromosomal abnormalities especially for Down Syndrome (DS) is now a routine part of antenatal care programs in most countries [1]. In Turkey, all pregnant women should be offered one of the antenatal screening tests according to the guideline of the Ministry of Health [2]. Combined test (CT) and triple test (TT) are the most widely used screening approach for women who are under 35 years-of-age [3–5]. Women who are detected for high-risk (≥ 1/250) should undergo invasive tests including amniocentesis (AC), chorionic villus sampling, or cordocentesis for definitive diagnosis. Among all, AC is more commonly performed due to operator's personal preference and technical aspects while CVS has started to replace AC in some centres [6,7]. Since the risk of having a DS child increases with age, AC should be recommended for all women who are above 35 years-of-age, regardless any screening tests [8–10]. There are some maternal and fetal complications of all the techniques, and procedure related loss (PRL) of a healthy fetus is disappointing for parents and physicians [11–13].

Recently, the non-invasive prenatal testing (NIPT) using fetal cell free DNA has become more popular as an alternative screening strategy due to its 99% detection rate, with a false positive rate of 0.09–0.1%. [14–15]. In addition to its higher prediction rates, the NIPT can also reduce the number of invasive procedures and the number of PRLs [16]. Despite its proven advantages, the price of NIPT presents an important barrier for universal adoption. Accordingly, there has been a surge of cost-effectiveness studies conducted in several countries comparing NIPT with other prac-

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tices [17–26]. Most of these studies show that the contingent NIPT as a second-step screening for high-risk patients may result in lower costs via decreasing unnecessary invasive procedures and PRLs [17,19–22,24–28]. In line with these studies, we previously conducted an economic analysis in which we compared the costs and outcomes of current screening strategies and the implementation of NIPT for women under and above the age of 35 in Turkey [27]. The findings were consistent with most of other country studies; as for all age groups NIPT resulted in reducing invasive procedures and PRLs, but was more costly. For women younger than 35 years-of-age, conventional tests followed by the NIPT for high-risk women were more cost-effective. Although these findings are important for decision makers, they also need a detailed analysis for the total cost of implementing new strategies. A Budget Impact Analysis (BIA) addresses this issue by presenting the expected changes in healthcare expenditures after the usage of a new technology. A BIA is also required along with a cost-effectiveness analysis as part of an economic evaluation for reimbursement decisions. A BIA shows the fiscal impact of implementing a new technology and the reimbursement authority will have a clear idea about its affordability [29].

Public health insurance is universal and compulsory in Turkey. Being the sole purchaser of health services for the whole population, the Social Security Institution (SSI) needs information about whether the implementation of NIPT into prenatal screening strategies is affordable or not, and what would be the likely costs or savings that are associated with these strategies. In this study, we calculated the budget impact of the best alternative strategies in prenatal screening including pregnancy follow-up and delivery or termination of pregnancy in Turkey. The main purpose of this study is to provide information to the reimbursement authority (i.e. the SSI) about the budget impact of implementing NIPT into prenatal screening strategies to detect Down syndrome (DS) in singleton pregnancies in Turkey.

Materials and method

A decision-analytic model was developed to calculate the budget impact of implementing NIPT together with the current strategies of prenatal testing to detect DS cases in singleton pregnancies in Turkey. The cost estimates were done for 1309,771 women who gave birth in 2016; 84.8% of whom were under 35 years-of-age. The age-specific risks of DS were obtained from Turkish data [30,31]. The analysis benefited the results of an earlier economic analysis in which the costs and consequences of different screening strategies were compared, and for women under 35 years of age, CT was found to be superior relative to the other strategies [27]. The NIPT was implemented as a second-tier test after the detection of high-risk pregnancies by CT, and we have shown that the NIPT-positive women having AC would result in more cost-effective results. When AC and NIPT for women $\geq$ 35 years-of-age were compared, AC was dominated over NIPT through detecting slightly higher DS cases with a less cost. On the other hand, there was no PRL with NIPT, but AC was calculated to result in more than 200 times PRLs (206 PRL) [27].

In the budget impact analysis, we compared "CT" with "CT+NIPT in high risk cases" for women < 35 years-of-age; and AC with NIPT for women $\geq$ 35 years-of-age. Our model allows all direct costs in relation to the screening of each singleton pregnancy up until the birth, taking into account the risks of PRL and termination of pregnancy (TOP), as well as the costs involved during the course of antenatal care. The estimated costs for each strategy included those directly related to prenatal screening, pregnancy follow-up, and the final outcome (TOP, PRL, vaginal delivery/caesarean section) that are accruing to the government through SSI [30–32]. Hence, the analysis will also provide the information about the cost of antenatal care to the government together with the delivery of singleton pregnant women.

We assumed that all women have full compliance of prenatal screening testing and regular antenatal follow-up. AC was assumed to be the only invasive procedure, and that all women who were detected as high-risk ($\geq$ 1/250) or NIPT-positive would have undergone AC. In the case of DS detection for high-risk women, the patient can decide to terminate or continue the pregnancy. No further tests were assumed, except for the follow-up cost accruing for those who wish to continue their pregnancies. The same procedures in follow-up were assumed to be provided for low-risk or NIPT-negative groups. Fig. 1 shows the decision analytical model for the two age groups.

The model inputs, costs and sources are shown in Table 1. The estimated prevalence of DS according to women's age, termination of pregnancy rate and vaginal / caesarean sections deliveries was obtained from Turkish data [8,30,31]. The characteristics of each screening test, DS-detection and false positive rates were taken from the published literature [1,3–5,10,12]. The regular antenatal care procedures complied with the guideline for prenatal care of the Turkish Ministry of Health [2] were also shown in Table 1 and the costs were assigned accordingly [33]. Since the prices of NIPT are similar due to competition, we take the average prices of NIPT that exist in the market.

The analysis is done from the payer's perspective by taking into account of SSI's reimbursement fee schedule in 2016 [33]. All costs are expressed in purchasing power parity (PPPUS$) terms.

Results

Since NIPT has not been reimbursed currently by the SSI, we use the market price of NIPT (1077 PPPUS$) in the base case analysis. The univariate sensitivity analysis is performed with a parameter that is considered to possibly influence the budget impact analysis. The results would be sensitive to the price of NIPT. In Turkey, the cost of NIPT is more than threefold to that of AC (Table 1). On the other hand, other country studies suggest a reverse relativity; that is the cost of AC is much higher compared to that of NIPT, between 1.3- and 2.5-fold [17,19,21–23]. In the sensitivity analysis, we reduced the price of NIPT to 225 PPP US$ to obtain a similar relativity that was observed in other countries to the cost of AC. With a reduced NIPT price, the cost of AC is 1.5 times higher than the cost of NIPT.

Table 2 illustrates the results of the budget impact analysis of implementing NIPT compared to the current screening practices for both age groups. In the base case scenario when the cost of NIPT is set at 1077 PPPUS$, for women < 35 years-of-age, the contingent NIPT strategy adds 52,705,549 PPPUS$, but saves 17,817,598 PPPUS$ from the costs of invasive tests and 8878 PPPUS$ from the costs of PRL compared to current practice, i.e. CT. Overall, using NIPT after CT increases the total costs of screening and antenatal care for about 5% (CT: 685,967,991 PPPUS$ and CT+NIPT: 720,875,216 PPPUS$). When the cost of NIPT is reduced (225 PPPUS$), the government would make savings by implementing NIPT and the total net savings from new strategy is found to be 6314,063 PPPUS$. For women above the age of 35, when AC is replaced by NIPT, this would lead to 321,165,234 PPPUS$ more cost to the government. However, the results of the sensitivity analyses show that NIPT screening would be cost saving (26,801,984 PPPUS$) when the price of NIPT is lower. The neutrality in cost per woman is achieved for both strategies when the price of NIPT is lower than its market price. For the price of NIPT is 356 PPPUS$ the cost per woman would be 618 PPPUS$ for women < 35 years-of-age and respectively, for the price of NIPT is 360 PPPUS$ 921 PPPUS$ for women $\geq$ 35 years-of-age.

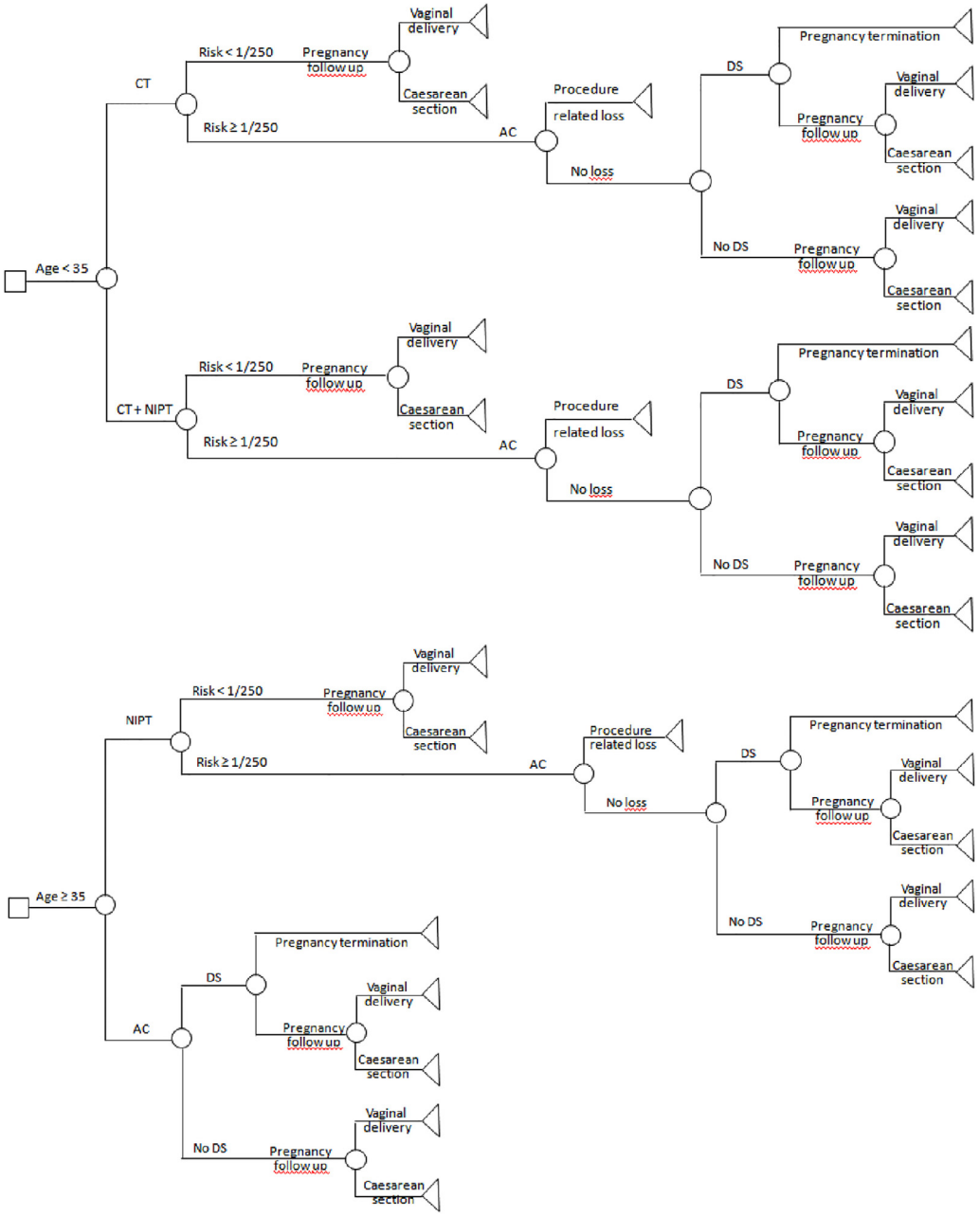

Fig. 1. Decision analytical model of incorporating NIPT in current screening practice for the two age groups.

Discussion

The new technologies can be more effective but they are usually more costly [34]. Budgetary limitations always put pressure on governments for their utilization. The BIA is required by the third party payers, i.e. reimbursement institutions and private health insurance companies in their decisions to include a new technology in their benefit packages. Administrators of national health care budgets, health policy makers and health services planners also benefit from such analysis. Each entity needs clearly presented information on the fiscal impact of the implementation of the new health technology [29].

Most of the prenatal screening tests including “combined test”, “triple test” and NIPT (fetal DNA in maternal blood) targeted not only trisomy-21, but also trisomy-13, trisomy-18 and sex chromosomes. The NIPT test may also cover some hereditary disorders. The spectrum of screening may also be different at different NIPT tests in terms of hereditary disorders. However, trisomy-21 is the main target, as being the most frequent aneuploidy and it is recommended that all women should have screening for trisomy-21 [35,36]. Due to its clinical importance and prevalence NIPT has become such a popular new technology in detecting DS cases in prenatal screening [14–16]. According to the results of cost-effectiveness analyses in many countries including Turkey, NIPT can be implemented at least as a secondary test for women with high-risk in prenatal screening [17,19–22,24–28]. But the government needs to know how much such a strategy costs for a reimbursement decision [29]. Hence, this study takes the initiative to compare NIPT with other screening strategies in Turkey in terms of the costs involved. Nshimyumukiza assessed the budget impact

Table 1
Model inputs, costs and sources.

Parameter	Number of live births in 2016	Prevalence of DS cases (per 10,000)	Source
Women < 35	1110,638	6.78	[30,31]
Women ≥ 35	199,133	28.41	[30,31]

Screening tests	DS-detection rate (%)	False-positive rate (%)	Source
CT	90.00	4.30	[5]
NIPT	99.20	0.09	[15]
AC	100.00	0.00	[6]
Probability of procedural related loss due to AC	0.11		[6]
Termination of pregnancy, DS confirmed	86		[8,31]
Rate of cesarean	53.1		[32]

Costs (PPP US$)[a]	Baseline		Source
CT	30		[33]
Ultrasound	12		[33]
NIPT	1077	225	[NIPT suppliers]
AC	338		[33]
Polyclinic visit	12		[2,33]
Vaginal delivery–no complications[b]	338		[33]
Cesarean delivery–no complications[b]	381		[33]
Pregnancy loss[b]	169		[33]
Termination of pregnancy[b]	258		[33]
Antenatal Follow-up (before prenatal tests)[c]	33		[2,33]
Antenatal Follow-up (after prenatal tests)[c]	154		[2,33]

DS: Down Syndrome; CT: First trimester combined test; NIPT: Noninvasive prenatal testing; AC: Amniocentesis.
[a] Costs are expressed in PPP US$ using National Currency (TRY) per USD: 1,2,999,412 (https://stats.oecd.org/Index.aspx?DataSetCode=SNA_TABLE4.PPPs are the currency conversion rates that are used to eliminate the price levels and cost of living variations between countries so that the purchasing power of different currencies are equalized (http://www.oecd.org/std/prices-ppp/purchasingpowerparities-frequentlyaskedquestionsfaqs.htm#FAQ1).
[b] Costs of hospital stay are included.
[c] The procedures during follow-up before prenatal screening are based on the Ministry of Health Antenatal Care Guideline and involve the following: one doctor visit, complete blood count, urinalysis, thyroid stimulating hormone, ABO and Rh test, ferritin level; after screening 7 doctor visits with 3 ultrasonography, 2 urinalysis, 2 complete blood count, glucose challenge test, nonstress test and tetanus vaccine (assumed to be done for all women).

Table 2
Budget impact analysis of implementing NIPT compared to current screening practice (PPPUS$).

	Current practice: CT	Contingent NIPT: CT+NIPT	Cost difference: Contingent NIPT – Current practice	Current practice: CT	Contingent NIPT: CT+NIPT	Cost difference: Contingent NIPT – Current practice
Baseline results				Lower NIPT price		
Women < 35 years-of-age				Women < 35 years-of-age		
Screening tests	59,310,752	112,016,301	52,705,549	59,310,752	70,795,014	11,484,262
Invasive tests	18,084,836	267,238	−17,817,598	18,084,836	267,238	−17,817,598
Pregnancy Loss (PRL)	9011	133	−8,878	9,011	133	−8,878
Other[a]	608,563,393	608,591,678	28,285	608,563,393	608,591,678	28,285
Total	685,967,991	720,875,216	34,907,225	685,967,991	679,653,929	−6,314,063
Women ≥ 35-years-of-age				Women ≥ 35-years-of-age		
	Current practice: AC	Universal NIPT	Cost difference: NIPT – Current practice	Current practice: AC	Universal NIPT	Cost difference: Universal NIPT – Current practice
Screening tests	74,402,518	216,835,009	142,432,491	74,402,518	47,247,207	−27,155,310
Invasive tests	0	276,459	276,459	0	276,459	276,459
Pregnancy Loss (PRL)	37,071	1	−37,070	37,071	1	−37,070
Other[a]	108,902,757	109,016,695	113,938	108,902,757	109,016,695	113,938
Total	183,305,275	326,165,234	142,859,958	183,342,345	156,540,362	−26,801,984

[a] Other includes costs of elective termination, vaginal and cesarean delivery, antenatal follow-up.

of implementing NIPT in DS screening Programme in Quebec using the similar approach; decision analytical model[37]. In our model, we also included costs directly related to antenatal follow-up and the final outcome; pregnancy termination, PRL and delivery. Hence, our analysis also provides the total cost estimates of prenatal care with delivery in addition to the total cost of prenatal screening strategies of singleton pregnancies. The recent analysis assessing the financial impact of introducing NIPT as a contingent test done according to the Italian National Health Service perspective also calculated the total direct costs associated with the diagnosis and management of pregnant women, but NIPT was detecting trisomies 21, 13 and 18 [38].

Our analysis differs from these studies by taking into consideration two age groups; women under 35 years and women 35

years or older as the risk of having a child with DS increases with women's age and screening strategies and costs associated with different subgroups may affect the new intervention's budget impact. The current study attempted to find the cost difference between introducing NIPT into prenatal screening for trisomy 21 and current screening strategies for these two age groups. As a result, the budget impact analysis shows that with its current market price, NIPT strategies have higher costs compared to the current practice. However, some savings can be achieved owing to a lower number of women undergoing invasive diagnostic procedures. Under the condition of proposed low price of NIPT, NIPT option comes out as the best cost-saving strategy compared to the current screening approach. Similar findings were obtained in Quebec study; contingent NIPT was cost saving compared to the current screening approach and cost-savings were reinforced if the cost of NIPT was reduced [37]. The results are thus sensitive to the price of NIPT, the fees paid by the SSI for AC, and the various assumptions made with respect to the costs included and the preferences in relation to prenatal tests. The analysis done in Italian setting calculated increase in detection of trisomies by 3% through implementing contingent NIPT which would result in cost reductions in pregnancy management arising mainly from due to lower number of invasive tests performed and decreased complications accordingly at the current NIPT price in the market [38].

Our study has some limitations. First we assumed that all women complied to undergo prenatal tests and had similar preferences. There is no published study in relation to women's preferences to prenatal screenings, especially women's attitude after a definitive DS diagnosis. Such studies are difficult to perform due to social values and religious reasons as well as ethical concerns in Turkey. Since we do not have this information, we had to assume that all pregnant women would undergo prenatal screening. In our decision-analytical model, we only take the PRL due to AC into account and assumed no other complications such as chorioamnionitis, leakage of amniotic fluid, fetal needle injury and cell culture failure. In addition, we also assumed the same follow-up procedures for low and high-risk pregnancies.

Since we aimed to calculate costs to the government, we included only direct costs of screening tests, costs related to PRL, elective termination of pregnancies, delivery, and antenatal care, although there are other costs involved. For example, the lifetime costs of DS live-births are also important from an individual and a societal point of view, and in a longer time period, some of them would accrue to the government [39]. The quality of life of women and families should also be considered in providing better healthcare within budgetary limitations [34]. Future research should address the valuation of quality of life as well as other ethical and legal issues in prenatal screening and women's preferences, attitudes and perceptions to prenatal screening. In addition, the costs and clinical outcomes for inclusion of detecting other chromosomal abnormalities should also be considered in economic evaluations.

In Turkey, obstetricians tend to offer AC for all pregnant women older than 35 years old to avoid legal consequences in case of adverse outcomes. Having highly accurate non-invasive prenatal screening test such as NIPT with a lower cost is therefore should be of interest for the government in Turkey. Despite its limitations we aimed to present the short-term outcomes of prenatal screening strategies so that the policy makers are informed in a transparent way about the possible consequences of introducing NIPT. The findings will enable the Social Security Institution to assess the financial impact of introducing NIPT into prenatal screening strategies to the government budget. Our analysis can also be used for budgetary allocations, and also provides input for better management of antenatal care programmes for the Ministry of Health.

CRediT authorship contribution statement

Zeynep Guldem Okem: Writing - original draft. **Gokcen Orgul:** Formal analysis, Data curation, Writing - review & editing. **Berna Tari Kasnakoglu:** Writing - review & editing. **Mehmet Cakar:** Formal analysis. **Mehmet Sinan Beksac:** Writing - review & editing.

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