Proceedings of the 2014 Winter Simulation Conference
A. Tolk, S. Y. Diallo, I. O. Ryzhov, L. Yilmaz, S. Buckley, and J. A. Miller, eds.

THE OPTIMAL RISK CUTOFF VALUES FOR DOWN SYNDROME SCREENING CONSIDERING WOMEN'S PREFERENCES

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ABSTRACT

Prenatal screening for Down syndrome (DS) based on biomarker levels provides expectant parents with an estimated risk of a DS baby. The risk cutoff value of a prenatal screening test determines the detection and false positive rates and the selection of follow-up procedures, such as an invasive diagnostic test. Women who consider prenatal screening might face two undesirable outcomes: undetected DS live births (DSL) and procedure-related fetal losses (EFL). One-size-fits-all risk cutoff values, such as 1/270, are commonly used in DS screening to recommend diagnostic tests. However, evidence suggests that different women have different preferences about the pregnancy outcomes. The objective of this study is to find the optimal risk cutoff values for DS screening. As no closed-form solutions exist, we use Monte Carlo simulation to solve the proposed model. We find that age-specific risk cutoff values outperform one-size-fits-all risk cutoff values.

1 INTRODUCTION

Down syndrome (DS) is a common type of chromosomal abnormality. Integrated screening strategy for pregnant women is non-invasive and assesses the risk of having a DS baby. A woman with a risk higher than the risk cutoff value typically undergoes an invasive diagnostic test, such as amniocentesis with a fetal loss rate of 0.1-0.5% (Odibo et al. 2008, Caughey et al. 2006), as a follow-up procedure to confirm that her fetus is affected. A low risk cutoff value reduces false negative rate but increases false positive rate, and a high risk cutoff value acts in the opposite direction. One-size-fits-all risk cutoff values are commonly used in DS screening. However, Mulvey et al. (2003) report that older and younger women present opposite preferences to the two undesirable outcomes from screening, i.e. undetected DS live births (DSL) due to false negatives, and euploid procedure-related fetal losses (EFL) due to false positives. The risk cutoff values should balance the two adverse outcomes. To the best of our knowledge, the question of how risk cutoff values should be set to capture women's various preferences remains unanswered. In this study, we propose a generic model that addresses optimizing the risk cutoff values in DS screening considering women's preferences and perform a case study to numerically demonstrate that age-specific risk cutoff values outperform one-size-fits-all risk cutoff values.

2 MATHEMATICAL MODEL

We divide pregnant women into three age groups, indexed by k, namely below 25 years ($k = 1$), between 25 and 34 years ($k = 2$) and above 34 years ($k = 3$). The optimization model seeks to find a vector of risk cutoff

values $X = (x_1, x_2, x_3)$ to minimize a preference-weighted sum of DSL and EFL, where a higher weight corresponds to a more undesirable outcome. We formulate a discrete optimization problem in (1)-(2).

$$\min \quad \sum_{k=1}^{3} w_{k1} DSL_k(X) + \sum_{k=1}^{3} w_{k2} EFL_k(X) \tag{1}$$

$$\text{s.t.} \quad x_k \in \left\{ \frac{1}{2000}, \frac{1}{1999}, \frac{1}{1998} \ldots, \frac{1}{2} \right\} \ \forall k \in \{1,2,3\}, \tag{2}$$

where $DSL_k(X)$ and $EFL_k(X)$ denote the expected number of DSL and EFL respectively, and w_{k1} and w_{k2} denote the weights assigned to DSL and EFL respectively, for age group k. The problem doesn't have any closed-form solutions, so we utilize Monte Carlo simulation to evaluate the objective value. Note that randomness exists when we use simulation. We can achieve a satisfactory precision as we gradually increase the number of evaluations. At the same time, we want to eliminate inferior solutions as early as possible to save computational efforts. In particular, when the entire 95% CI of a solution is higher than the upper bound of 95% CI of another solution, we eliminate the former solution from consideration. As a result, a two-stage heuristic algorithm of sequential eliminations is developed to eliminate inferior solutions and looks for near optimal solutions.

3 NUMERICAL RESULTS

The number of live births in the U.S. is approximately four million per year (Centers for Disease Control and Prevention 2010). As a case study, we set $w_{11} = 0.5, w_{12} = 1.5, w_{21} = 1.0, w_{22} = 1.0, w_{31} = 1.5, w_{32} = 0.5$, which are in line with the trend of age-specific preferences reported in Mulvey et al. (2003). The estimated optimal age-specific risk cutoff values are $X^* = (\frac{1}{166}, \frac{1}{482}, \frac{1}{1368})$ and the estimated optimal one-size-fits-all risk cutoff value is $x^* = \frac{1}{536}$. By using age-specific risk cutoff values rather than the one-size-fits-all risk cutoff value, we can decrease EFL by 44.7 on average for women below 25 years and decrease DSL by 60.2 on average for women above 34 years, out of four million pregnant women. The numerical study suggests that the optimal solutions converge as iterations increase.

4 CONCLUSION

In this study, we formulate a discrete optimization problem to select the optimal risk cutoff value of integrated screening for Down syndrome with respect to women's preferences. We provide a heuristic approach to achieve near optimal solutions and reduce unnecessary objective function evaluations for inferior solutions. We find that age-specific risk cutoff values for DS screening have a great potential to improve the pregnancy outcomes and patient satisfaction.

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