Probabilities in non-invasive prenatal diagnosis (NIPT)

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Program description

This program computes the positive predictive value (PVV, probability of a trisomy given the test results) for use in non-invasive prenatal testing (NIPT). It uses the following inputs:

1. The range of values likely to contain the percentage of fetal DNA (the upper and lower limit may be the same).
2. The *a priori* probability of a trisomy (based on the mother's age, trisomy type (T21, T18, T13) or the combination test).
3. The accuracy of the test measured as a variation coefficient (which is needed because the fraction of fetal DNA in combination with the variation coefficient is used to determine the distance between the null distribution (no trisomy) and the alternative distribution). The variation coefficients for T21, T18 and T13 are generally different.
4. The observed Z-score (computed as a deviation from the average fraction mapped divided by the standard deviation in normal samples).

How to operate the program

This program does not require installation. It can be put on your desktop or in any other directory. You start the program by double clicking the program icon. The current version runs under all versions of Windows. A Linux or Mac version is

available on request from GJ te Meerman. The program is freeware and may be distributed under the GPL V3 license.

The user interface is shown below:

Description of the options

Compute: Compute PVV for an observed Z-score given the *a priori* risk, variation coefficient, fraction of fetal DNA and maternal and gestational age

Exit: Terminate the program

Fields to fill in

A priori risk of a trisomy: The assumed risk for a women to carry a fetus with a trisomy, based on age alone, or on the combination test.

Observed Z-score: The Z-score as computed from the mapping data.

Variation coefficient: Used in combination with the percentage of fetal DNA to compute the distance between the distribution for normal pregnancies and trisomic pregnancies. The variation coefficient for T13 and T18 is typical lower than that for T21 (because the former chromosomes are longer and have more mapped reads, hence an increased accuracy for the fraction mapped to these chromosomes).

Lower and upper limits: These are the lower and upper limits of the fraction of fetal DNA. If you have any results of a test for the percentage of fetal DNA, fill them in here. For example, if the fetal DNA test indicates a percentage between 4% and 8%, and the variation coefficient is 0.5, the lower limit would be 4 and the upper limit 8.

Output to file: If this box is checked, the subsequent results will be stored on a file. The filename needs to be given in a new window that opens after clicking the 'compute' button. After unchecking the box, or if the program is terminated by clicking the 'exit' button, the file will be closed.

Gestational age and maternal age: These values can be filled in to yield an *a priori* probability displayed in the field labeled *a priori* risk. As an alternative for filling in the boxes, the buttons *a priori* risk T21, T18 and T13 use values taken from published tables and interpolate these tables, if necessary, using bivariate linear interpolation. The tables have the form *1:number*, the interpolation is for the 'number' variable.

After filling the boxes, the compute button will perform the risk calculation. The gestational age and maternal age are not given in the output file, only the *a priori* probability result is given. The tables used were taken from Snijders et al. [1, 2].

Underlying mathematics

If no trisomy is present, the Z-score is very closely approximated by a normal N(0,1) distribution. If an expected Z-score is known, derived from a measured fraction of fetal DNA and a variation coefficient of 0.5 for the fraction of reads mapped to a chromosome, this can be filled in directly by setting the lower and upper limits to the same value. Generally, there will be some uncertainty and this can be accounted for by setting the lower and upper limits 1 or 2 percentage points lower viz higher than the expected values. The data given are then used for a Bayesian calculation of the risk of a trisomy, conditional on the observed Z-score ‘Z-observed’ and the *a priori* probability of a trisomy.

The expected Z-score (computed from the percentage of fetal DNA) is assumed to follow a uniform distribution between 1- 30, where the term

Integrate from lower to upper exp(-(Z_expected-Z_observed)^2/2) = Integral*

is integrated to Z_expected from the lower limit to the upper limit. The integration result is computed with a highly accurate procedure for the cumulative distribution of a normal distribution[3, 4]. The integration result is then entered into the formula below for a Bayesian risk calculation:

*PPV= Integral*P_apriori/(Integral*P_apriori+(1-P_apriori*exp(-(Z_observed)^2/2)).*

References:

[1] Snijders RJ, Sundberg K, Holzgreve W, Henry G, Nicolaides KH. Maternal age- and gestation-specific risk for trisomy 21. 1999. Ultrasound Obstet Gynecol.13:167-70.

[2] Snijders RJ, Sebire NJ, Nicolaides KH. Maternal age and gestational age- specific risk for chromosomal defects. 1995 Fetal Diagn Ther. Nov-Dec;10(6):356-67.

[3] Genz A, Numerical computation of rectangular bivariate and trivariate normal and t probabilities, 2004 Statistics and Computing, 14, (3).

[4] Graeme West. Code for accurate computation of the cumulative normal distribution: http://www.codeplanet.eu/files/download/accuratecumnorm.pdf

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