Precisión de los métodos estadísticos para la detección del síndrome de Down en mujeres panameñas

Accuracy of a Static Screening Method for Down's Syndrome in Panamanian Women

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***Resumen**– Actualmente, el síndrome de Down es la enfermedad genética más común en Panamá, y las estadísticas más recientes indican que en 2010, 474 niños recibieron tratamientos con síndrome de Down en nuestro país. La detección temprana de los pacientes con síndrome de Down es extremadamente importante porque permite aplicar tratamientos clínicos apropiados que reduzcan las complicaciones que tanto la madre como el bebé tienen durante el embarazo[1]. Sin embargo, no hay biomarcadores adaptados a la región, por lo tanto, existen falsos positivos o falsos negativos durante el resultado. Establecer la exactitud de los biomarcadores actuales sería una contribución para determinar que podemos mejorar los métodos de cribado actuales. Este artículo utiliza datos recientes de cien muestras de biomarcadores y la precisión de sus resultados para sacar conclusiones sobre su uso en mujeres panameñas.*

***Palabras claves**– Ingeniería de Software, Salud Electrónica , Síndrome de Down.*

***Abstract**– Currently, the Down syndrome is the most common genetic condition in Panama, and the most recent statistics indicate that in 2010 , 474 children received treatments with Down syndrome in our country. Early detection of Down syndrome patients is extremely important because it allows to apply appropriate clinical treatments that reduce complications which both the mother and the baby occur during pregnancy [1]. Nevertheless, there is no biomarkers adapted to the region, hence exists false positives or false negatives during result. Establish the accuracy of current biomarkers would be a contribution to determine that we can improve on current screening methods. This paper uses recent data from one hundred samples of biomarkers and the accuracy of their results to draw conclusions about its uses in Panamanian women.*

***Keywords**– Software Engineering, eHealth, Down's Syndrome.*

1. Introduction

The Down syndrome [2] was first described in 1866 by John Langdon Down in the United Kingdom and his cause was discovered in 1959 due to chromosomal abnormality known as trisomy 21 however we do not yet know why it happens. Down syndrome is a variable combination of congenital malformations caused by trisomy 21. It is the most commonly recognized genetic cause of mental retardation. Down syndrome occurs at conception, across all ethnic and social groups and to parents of all ages, but the age factor increases the risk more after the mother is 35 years old.

There are three methods currently used to determine the risk of having Downs syndrome being them the demographic, using ultrasound and the biochemical method. In this work, we intent to improve the result obtained in the biochemical methods.

2. Methods for prediction of trisomy 21

There are many factors that increase the risk of having Down's syndrome [3] [4], [5], for example, the age of the mother, if the mother has diabetes or if she smokes, if she has had a previous case of syndrome and her ethnic.

There are a variety of non-invasive and invasive techniques available for prenatal diagnosis of trisomy 21. The methods for estimate of the risk of the existence of trisomy 21 can be divided into invasive and non-invasive test. Invasive diagnosis of trisomy 21 requires sampling of fetal genetic material through amniocentesis or chorionic villus sampling. However, these tests carry a

risk of miscarriage and they are therefore reserved for pregnancies considered to be at high risk of fetal trisomy 21. A Non-invasive prenatal test of trisomy 21 is researched by using ultrasound to measure the amount of fluid at the back of a baby's neck and determines if a baby's nasal bone is present. Babies with chromosomal disorders may accumulate more fluid at the back of their neck during the first trimester.

Another non-invasive prenatal test of trisomy 21 are using fetal specific hormones and proteins biomarkers present in the blood of all pregnant women. This method uses, to calculate the risk, a statistical procedure known as likelihood [6] and it uses a lower and upper limits to determine if the results of the biomarkers are inside or outside of the normal rank. Sometimes the biomarkers results are inside the rank of normal classification but too close to the limits. In these cases, the system shows a negative test but the patients present the illness.

In medical testing, and generally in binary classification, a false positive is an error in data reporting in which a test result improperly indicates presence of a condition, such as a disease (the result is positive), when in reality it is not, while a false negative is an error in which a test result improperly indicates no presence of a condition (the result is negative), when in reality it is present.

2.1 Biochemical Method

Prenatal screening for trisomy21 based on the analysis of biochemical markers in maternal serum has become an established part of obstetric practice in many countries. The screening or screening is a probabilistic technique is applied to a specific population to determine the risk or probability that the object under study suffer from a particular disease. The same is done by setting specific markers and benchmarks to compare the results against the average of the values of the population. When the values of the MOM for its acronym in English Multiple of Median varies relative to the standard, the result is considered positive as presented in figure 1.

2.2 Demographic Method

The calculation of risk is based on the method of calculating risk Likelihood [7] published by Palomaki and Haddow combining the a priori risk for maternal age obtained from the meta-analysis of Cuckle HS, Wald NJ and Thompson, with the likelihood ratio.
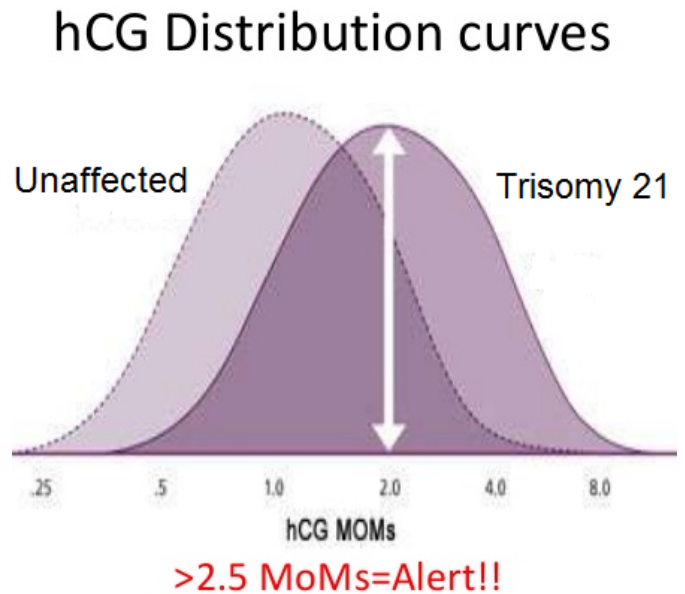

Figure 1. Model.

2.3 Ultrasound Method

By this method , as presented in the presence or absence of the nasal bone is determined and the measurements obtained in the ultrasound vs standard measures pertaining to the week of gestation compared established [8], [9]. If the measurements are outside the average range, it stipulates that there is a risk of trisomy 21. The increased thickness of the nuchal translucency, when the measurement exceeds the thickness of 3mm, is associated with an increased risk of abnormalities chromosomal which in our case is associated with trisomy 21.

3. Accuracy and precision of bio-markers

Biological markers "*biomarkers*" have been defined by Hulka and colleagues [10] as *"cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids"*. However, it is known that no measure is perfect and all measurements have some error associated with them.

It should verify the validity and determine "the sensitivity of that marker" and "predictive power" to check what number of false positives or false negatives can result in a clinical diagnosis.

Accuracy is how close a measurement comes to the truth, represented as a bullseye above. Accuracy is determined by how close a measurement comes to an existing value that has been measured by many, many scientists.

Precision is how close a measurement comes to another measurement. Precision is determined by a statistical method called a standard deviation.

	Accurate	Inaccurate (Systematic Error)
Precise		
Imprecise (Reproductible Error)		

Figure 2. Explanation of Accuracy and Precision.

This classic diagram in figure 2 illustrates the possible combinations of accuracy and precision. The precision measurements both exhibit tight grouping near some portion of the dartboard. The accurate measurements are near the center. To determine if a value is accurate compare it to the accepted value. As these values can be anything a concept called percent error has been developed.

Find the difference (subtract) between the accepted value and the experimental value, then divide by the accepted value as show equation 1.

$$error = (accepted - \exp erimental) / accepted * 100 \quad (1)$$

To determine if a value is precise find the average of your data, then subtract each measurement from it as show equation 2. This provides a table of deviations.

$$deviation = (average - actual) \quad (2)$$

Standard deviation is how much, on average, each measurement differs from each other, formalized as standard deviation = (deviations for all measurements added together) / number of measurements. A high standard deviation indicates low precision and a low standard deviation indicates high precision. Then average the deviations will give you a value called uncertainty, a

positive or negative value that says how precise the measurement is.

Uncertainty analysis aims to make a technical contribution to decision-making through the quantification of uncertainties in the relevant variables, alike sensitivity analysis. Throughout the following sections deviation values and uncertainty of the data used is calculated.

3.1. Biochemical markers

A Biochemical marker is any measurable biological chemical parameter, which allows to know, for example, the state of a disease or drug response.

Many proteins in the maternal circulation have been found during the time of pregnancy [11]. Many of these are made or modified by the placenta. Differences in levels of some of the proteins have been observed in patients carrying a fetus with Down syndrome and certain other chromosome abnormalities.

The discovery of these slight differences in protein levels has been largely based on observation- we really don't know why they work in most cases. Nevertheless, we can take advantage of these differences in screening protocols. These are referred to as biochemical markers. Certain patterns of biochemical markers have been associated with fetal Down syndrome as well as other conditions.

It is important to know that these proteins change during pregnancy, so interpretation requires a knowledge of the gestational age. Also, the effectiveness of these proteins varies with gestational ages. For example, differences in protein levels may be observed during the second trimester but not the first, while other proteins show differences during the first trimester but not the second.

3.2. Range of the biochemical markers

As mentioned in [12] the current screening methods utilize an upper and lower limit to group a healthy population. The chemical markers results are compared with these limits. Based on this comparison, if two of this group of conditions is presented, the algorithm will throw a positive case. Let say in the test, the AFP has a MoM of 0.48 (Lower than 0.5) and the HCG has a MoM is 2.62 (Greater than 2.5) the algorithm will mark the test as positive with Down's syndrome [13]. If the values of the MoMs are inside the range, the test diagnostic will be negative. The condition's value for each marker are presented in the table 1.

Table 1. Ranges and Meanings of Biomarkers.

Marker	Conditions Value
AFP MoM	Bad if less than 0.5 to 2.5
UE3 MoM	Bad if less than 0.5 to 2.5
HCG-T	Bad if greater than 2.5
INH-A	Bad if greater than 2.5

3.3. Link accuracy probability

The proposed method is based in the study of the bad ranges in the chemical markers with the aim to use the obtained values of the three markers which gives us more reliability in the decision toked.

As mentioned above the algorithm makes a comparison of the markers, if two markers of the three give us acceptable values, then the result will be negative. Also, if two markers give us abnormal values, then the test is marked as positive with high risk. The omission of one marker could lead us to those states which have values with false positives or false negatives so we need at least three of them.

The difference in the number of markers used influences the result obtained in the calculation of the standard deviation and therefore in the precision due to the error contained. For example, with the values Unconjugates Estriol UE3 = 0.49, Alpha Fetoprotein AFP = 0.52, and Human Chorionic Gonadotropin HCG = 2.50, we can obtain different results depending of the markers used. Table 2 contains the results in the standard deviation and the error when using two or three markers.

**Table 2.** Markers, Standard Deviation and Errors.

Markers	Standard Deviation	Error
UE3, AFP	0.505	56.8376068
UE3, HCG	1.495	-27.7777778
AFP, HCG	1.51	-29.0598291
UE3, AFP, HCG	1.17	0

Figure 3 and 4 shows the corresponding graphs to the values obtained in the table 2.

These values were calculated using a sample of the chemical markers of one hundred patients with difference age and ethnic.
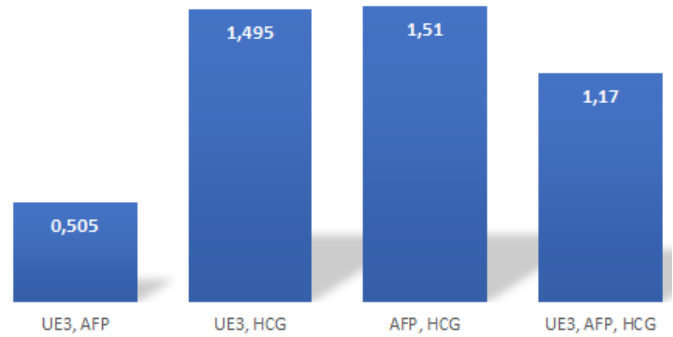
Figure 3. Standard Deviation Calculation Graph when using two or three markers.
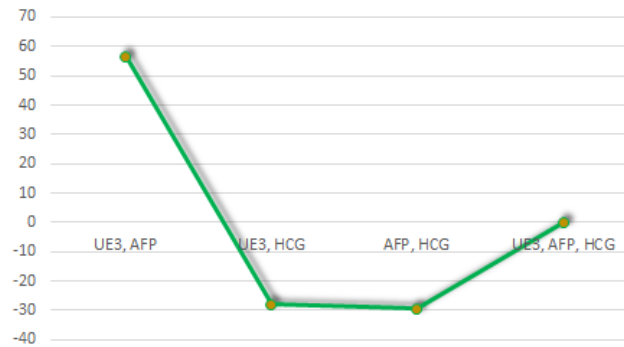
Figure 4. Error calculation when using two or three markers.

The proposed method integrates the three markers with the aim to obtain more precision in the result due that sometimes the used method presents a gap when the values are too close to the limits. For example, if we take the same patient having a MoM of AFP of 0.51 and HCG 2.49, values that are inside the healthy range, the algorithm will throw a negative Downs syndrome test. However, both markers are very close of the limits so in these cases, it is most likely that the patient present a Down's syndrome condition.To work with these three markers is necessary to focus in the proximity of the value that each marker presents to the limits for to compute the result. That is important because when more near is the value of the marker to its limits increase the probability that the patient has Down Syndrome. An example of this case is shown in figure 5:
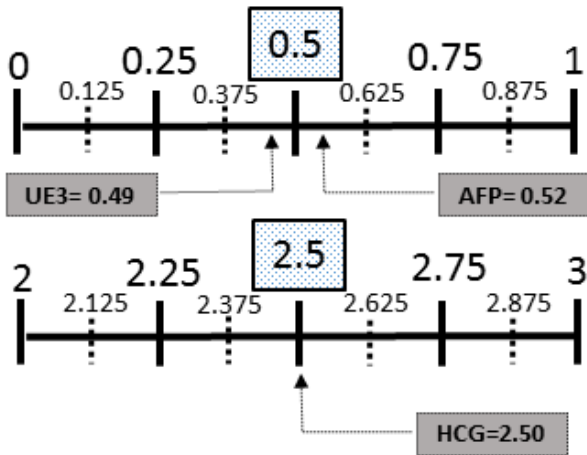
Figure 5. Example of a positive false.

With this value, the test indicates that the patient does not has Down Syndrome but its markers are too close to the limits which state that the possibility to suffer it is high. The decision is taken based on the result of the MoM's value of the three markers. That's means that each one has influence on a third part of the global result. This condition leads us to assign equal percent to each one of the markers. The percent is calculated for both, the Lower Limit and Upper Limit markers, taking in consideration the way in which the percent increase for each type of chemical marker, until achieving the 100 percent as shown in the figure 7. We could not apply the same calculation condition for the lower and upper limit because the actual rank is not from 0 to 2.5. The current rank starts from 0.5 to 2.5 so the formula changes.
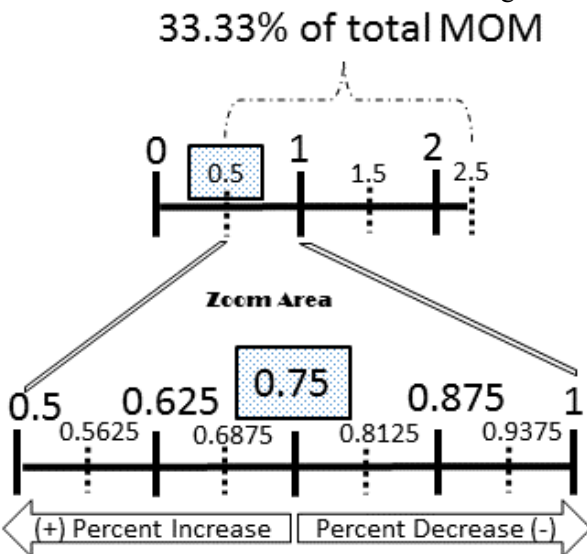

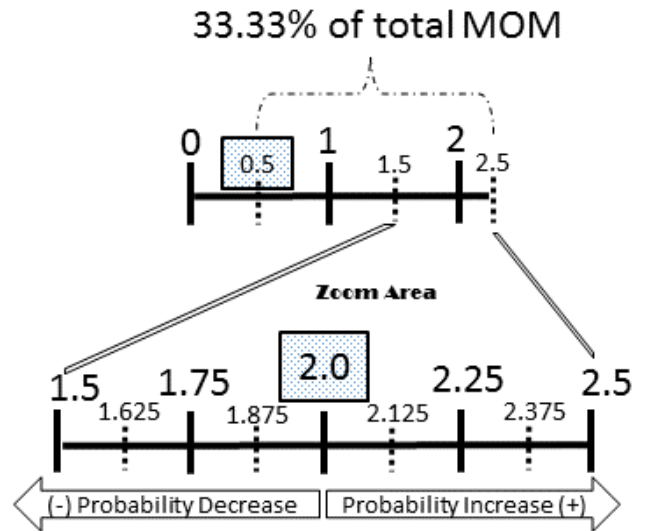**Figure 6.** Risk increment direction for LL biomarkers.

Figure 7. Risk increment direction for UL biomarkers.

Each marker has a limit value given for the range of a healthy population we use this range for to compute the new values for each marker. The next equations compute the rate of confidence for each marker according to the limit value. That is, markers whose limits value are below 0.5 denominate as Lower Limits Rate of Confidence (LL) are compute by equation 3 and the marker whose MoMs limits is upper than 2.5 denominate as Upper Limits Rate of Confidence (UL) is compute by equation 4.

$$LL = \left(\frac{1\text{-Marker MoM's Value}*0.3333}{\text{Lower limit value}} \right) \quad (3)$$

$$UL = \left(\frac{(\text{Marker MoM's Value -1})*0.3333}{\text{Upper limit value -1}} \right) \quad (4)$$

Applying the result obtained of the previous equations we can compute one result of the three markers denominate Test Rate of Confidence (TRC). Equation 5 compute this final result.

$$TCR = \sum UL + LL \quad (5)$$

To compute the Test Rate of Confidence (TRC) with the above equations the following test shown in table 3 was selected from our sample data.

Table 3. Sample data to compute the test rate of confidence TCR.

AFP	UE3	HCG
0.57438	0.66835	2.39302

Applying the equation 3 and 4 for the results of the patient presented in the table 3, the percentage of confidence for each marker is calculated in the equation 6, 7 and 8.

$$AFP = \left(\frac{(1\text{-}0.57438)*0.3333}{0.5\text{-}1} \right) = 28.37\% \quad (6)$$

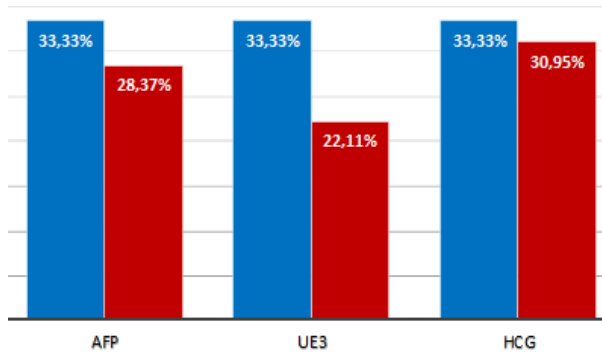$$UE3 = \left(\frac{(1\text{-}0.66835)*0.3333}{0.5} \right) = 22.11\% \quad (7)$$

$$HCG = \left(\frac{(2.39302\text{-}1)*0.3333}{2.5\text{-}1} \right) = 30.95\% \quad (8)$$

After, the confidence rate of the equation 5 is calculated as shown in equation 9:

$$TCR = \sum UL + LL$$
$$TCR = 28.37\% + 22.11\% + 30.95\% \quad (9)$$
$$TCR = 81.49\%$$

Figure 8. Acceptance rate obtained for each marker.

4. Results

The sum of the value of the confidence rate for all the markers is 81.43%. Even though the normal test will throw a negative Downs syndrome result because the MoMs are inside the healthy range, based on this method, we could argue that the mother present a high risk of having a baby with this aneuploidy. Figure 8 shown graphically the high risk of this values.

5. Conclusion

This work presents a mathematical model to calculate a percentage rate of confidence of the current static method applied to calculate the risk of having Down's syndrome or not. This percentage rate of confidence will provide to the specialist a clue of how accurate the test is, even though it throws a correct output or a false positive or false negative case.

The intention of this work is to provide a second layer of estimation to improve the risk estimation and facilitate the work of the gynecologist and fetal screening health specialist.

6. Acknowledgment

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