

# CLEFT RR- New App to Calculate Recurrence Risk in Cleft Lip and Palate

**Rosa Helena Wanderley Lacerda**

Universidade Federal da Paraíba: Universidade Federal da Paraíba

**Alice Castro Guedes Mendonça**

Universidade Federal da Paraíba: Universidade Federal da Paraíba

**Rebeca Andrade Laurentina**

Universidade Federal da Paraíba

**Paulo Germano Cavalcanti Furtado**

Universidade Federal da Paraíba

**Vitor Marques Figueiras**

Universidade Federal da Paraíba: Universidade Federal da Paraíba

**Alexandre Rezende Vieira** (✉ [alexandre\\_vieira@pitt.edu](mailto:alexandre_vieira@pitt.edu))

University of Pittsburgh School of Dental Medicine <https://orcid.org/0000-0003-3392-6881>

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## Research Article

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# Abstract

**Background:** The impact of the birth of a child with cleft lip and palate generates a concern in the family related to care and the child's future. The opportunity to clarify the recurrence risk arouses high interest in families and adult individuals born with orofacial clefts and it contributes to decisions regarding family planning.

**Results:** The purpose is to present the **Cleft Recurrence Risk (Cleft RR)**, which aims to facilitate health professionals to quickly calculate the recurrence risk considering the ancestry, cleft type, sex, and family history. After defining parameters the application development follows the steps: development, prototyping, and documentation. The validation of the calculated data was performed by comparing the results of 100 cases undergoing genetic counseling at the cleft lip and palate treatment center obtained by the manual method. The results were obtained by the mobile app method; the data were submitted to the Bland-Altman statistics and a high concordance was found.

**Conclusions:** The mobile app for use by healthcare professionals proved to be simple to use, easy to apply, and provided accurate results. Cleft RR is an App for smartphones developed for genetic counseling in cleft lip and palate, supplementary use by health professionals, and should not replace professional performance.

## Background

Cleft lip and palate are the most common congenital anomalies in the human face and the incidence varies among races<sup>1,2</sup> and cleft type. The greatest incidence takes place in Asia (China, Japan) 2.1:1000, an average of 1:650 for Brazil.<sup>3,4,5</sup>, followed by Europe 1:1000, America 1:1000, South Africa 1:2500. The etiology of non-syndromic orofacial clefts is multifactorial and complex with a polygenic model that involves many genes with small effects and environmental interference<sup>6,7,8</sup>.

Individuals born with cleft lip and palate may face difficulties in speech function, nutrition, facial aesthetics, facial growth, psychological function, and long-term and interdisciplinary care<sup>9,10</sup>. The impact of the birth of a child with cleft lip and palate generates a concern in the family related to care, the child's future and risk of recurrence<sup>11-15</sup>, and a high degree of stress during treatment<sup>10</sup>. The opportunity to clarify the recurrence risk arouses high interest in families and adult individuals born with orofacial clefts and it contributes to decisions regard to family planning<sup>13,14</sup>.

For decades, studies have sought to define the risks of recurrence with more precision and specificity. Difficulties regarding sample size, genotyping and patient follow-up limit many of the studies that sometimes analyze the risk of recurrence considering only sex, type of cleft and degree of relatives or only type of cleft and degree of kinship<sup>15-26</sup>. Tolarová et al. carried out several studies analyzing the empirical risk of cleft recurrence in a North American population considering the sex of the affected

person, degree of kinship, type of cleft and the child's sex, contributing significantly to the progress of genetic counseling<sup>27-29</sup>.

The idea of developing a resource to make it easier to calculate the recurrence risk considering the family history and ancestry emerged with the observation of a genetic counseling service in a cleft lip and palate center notice that more than 90% of the patients or their parents have a high interest to know about the recurrence risk of cleft lip and palate in their families.

The technology in genetics has been increasingly used, and resources have been developed to allow and simplify and interpreting data<sup>30</sup>. Mobile applications (Apps) to access health and health care are utilized<sup>31</sup> and more than eighty Apps were developed to access information related to genetics/genomics for resources, risk assessments, references/ resources, clinical tools, lifestyle recommendations, provision of genetic tests<sup>33</sup>. Some Apps were developed related to cleft lip and/or palate, about lifestyle, cleft care, education and treatment.

Due to the high complexity to understand the recurrence risk in non-syndromic cleft lip and palate, we developed the **Cleft Recurrence Risk (Cleft RR)**, the first App in genetic counseling for cleft lip and/or palate which aims to facilitate health professionals to quickly calculate the recurrence risk considering the ancestry, cleft type, sex and family history and thus encourage to the implementations of genetic counseling in cleft lip and palate centers around the world.

## **Implementation**

This study follows the CONSORT-EHEALTH check-list<sup>34</sup>.

The application development followed steps to build consistent numbers taking into account the differences in frequency of clefts around the world, cleft type, cleft, gender and family history The steps are described in Figure 1.

## **Methods**

### **● Bibliographic Search And Reference Numbers Definition**

The definition of reference numbers for calculating the risk of recurrence was carried out with a literature search in the PubMed, Web of Science, Scopus and SciELO databases: (((cleft lip and palate) OR (cleft lip)) OR (cleft palate)) AND (recurrence risk)) AND (risk). We found several studies that analyzed the incidence and recurrence of clefts, mainly in American and European populations<sup>1,2,18-24,29</sup>.

### **● Defining Parameters To Calculate The Recurrence Risk:**

Cleft lip and palate incidence for each ancestry were considered as the reference value (Table 1). Thus, 1:2500 was used as a reference in isolated cleft palate for all ancestries.

Table 1  
Reference value pattern in cleft lip with or without palate according to ancestry.

	%	Absolute values	
		1/ number of births	
Asian	0.2	1/	500
Brazil	0.15	1/	650
American	0.1	1/	1000
European	0.1	1/	1000
African	0.04	1/	2500

The variables' incidence, family history, ancestry<sup>1,24</sup>, gender, and cleft type were considered to determine the risk calculation using the numbers from Tolarová et al.<sup>29</sup> and the increased risk, according to Tables 2 and 3.

In cases with 2 or more individuals with non-syndromic oral clefts with first degree kinship were considered as autosomal recessive or dominant.

Table 2  
Proportional increases in the values in Table 1 in relation to the reference value of the population studied (1:1000).

Cleft type and gender	Risk to have a sibling			Risk to have a child		
	Brother	Sister	Sibling total	Son	Daughter	Child total
Male unilateral	22.5	13.5	18.4	49.1	22.7	36
Male bilateral	41.7	44.1	42.9	115.4	48.8	86
Female unilateral	52.6	31.3	42.9	45.5	30.5	38
Female bilateral	157.8	71.4	121.2	172.4	76.9	127.3
Total	39.1	26.7	33.4	64.1	31.1	48.2

Table 3

Extra configuration based on Table 2. If there is more than one affected individual in the household, the risk of recurrence changes according to this table. P=parents; S=number of unaffected children R=number of affected children.

Extra configuration / Cleft lip with or without palate			
If there is history	Multiply by		
	M	F	T
P0 S1 R1	0.9	0.8	0.93
P0 S0 R2	It implies autosomal recessive inheritance		25%
P1 S0 R1	It implies autosomal dominant inheritance		50%
P1 S1 R1	It implies autosomal dominant inheritance		50%
P1 S0 R2	It implies autosomal dominant inheritance		50%
P2 S0 R0	7.8	9.5	8.96
P2 S0 R1	It implies autosomal dominant inheritance		50%
P2 S1 R1	It implies autosomal dominant inheritance		50%
P2 S0 R2	It implies autosomal dominant inheritance		50%

## 1- APP development

### 1.1 - Backend development of the application

After collecting the data by the user requesting the application - explained in point “1.3 - User data collection” - we automated the calculations, aiming to optimize the query result, as well as improve its visualization. Then we used the Node JS environment to implement the API (Application Programming Interface), containing the application logic. By not saving any user data, it is worth noting that we do not work with any database of any kind.

### 1.2 - Frontend development of the application

In order to build an accessible and inclusive application, we sought to build an environment with colors and designs that work with the application's theme, but we also sought to build a smooth journey for the user. To do so, we used images that work with the lip clefts, and seeking inclusion using (for example) the representation of different ethnic groups. In order to make the application more accessible, we have sought to be as pragmatic as possible with regard to the questions, mostly multiple choice, transforming the user's journey into a short journey, but which includes all the necessary points for the calculation.

### 1.3 – User data collection

As shown above, we need some information in order to generate a result. Among them are information on the child's biological parents, their ethnicity, as well as collecting data relating to the family (to look for a hereditary factor). There is also the collection of the disease history to check if there is any other problem that makes the calculation impossible, as it is a case outside the work curve of the application.

#### 1.4- Documentation stage

Consisted of preparing a term of use for the application and a privacy policy.

After all of these steps, the risk of recurrence is calculated and expressed as a percentage and proportion considering the risk of recurrence in females, males and regardless of gender (total risk).

## 2- Testing APP

- Automation and Validation

The numbers and the calculation were included in an excel doc and a first automation was tested to validate the numbers using 100 cleft cases that had received genetic counseling with a manual calculation. The app development began after validating the numbers.

The calculation is based on the proportional increase in the risk of recurrence in relation to the risk of the general population, and the proportion of the increase is maintained in changing the population risk (reference value). Thus, the calculations can be performed with the standard reference values (Table 1) or with reference values suggested by the author that best suits the analyzed population.

## Results

The validation of the calculated data was performed by comparing the results of 100 cases undergoing genetic counseling at the cleft lip and palate treatment center obtained by the manual method with the results obtained by the mobile app method; the data were submitted to the Bland-Altman statistics (Figure 1) and we found a high level of agreement between methods, the difference mean was in the 0 (confidence interval -0.006 to 0.04). The mobile app for use by healthcare professionals proved to be simple to use, easy to apply and provided accurate results.

## Conclusion

Cleft RR is an App for smartphones developed for genetic counseling in cleft lip and palate with free access and supplementary use by health professionals and should not replace professional performance.

## Abbreviations

**Cleft RR:** Cleft Recurrence Risk

**App:** Mobile applications

## Declarations

**Ethics approval and consent to participate:** This study was approved by a Lauro Wanderley University Hospital- Universidade Federal da Paraíba ethics committee (CAAE12853919.0.0000.5188/P 3.470.922). Consent was obtained from a parent or guardian for participants under 16 years old.

**Consent for publication:** parents and guardians signed the informed consent to use the genetic counseling data

**Availability of data and materials:** Not applicable.

**Competing interests:** The authors declare that they have no competing interests.

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**Author Contribution:** AV Conceptualization, study design wrote the first draft of the manuscript, RHWL ACGM, RAL app design, data collection. RHWL, VMF and PGF interpreted and analyzed data. All authors contributed to the article and approved the submitted version.

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## Clinical significance

The possibility of enabling elements through creating digital resources which facilitate treatment center teams to be able to carry out genetic counseling in a simple and effective way provides advances in assistance to families affected with cleft lip and palate.

## Availability and Requirements

Project name: Cleft Recurrence Risk ( Cleft RR)

Project home page: <https://drive.google.com/file/d/11dBo9wLf2ndUGeVy0HTxLJTVQfv9zc4c/view?usp=sharing>

Operating system(s): Android e iOS;

Programming language: JavaScript with frameworks NodeJs and React Native

Other requirements: Not applicable.

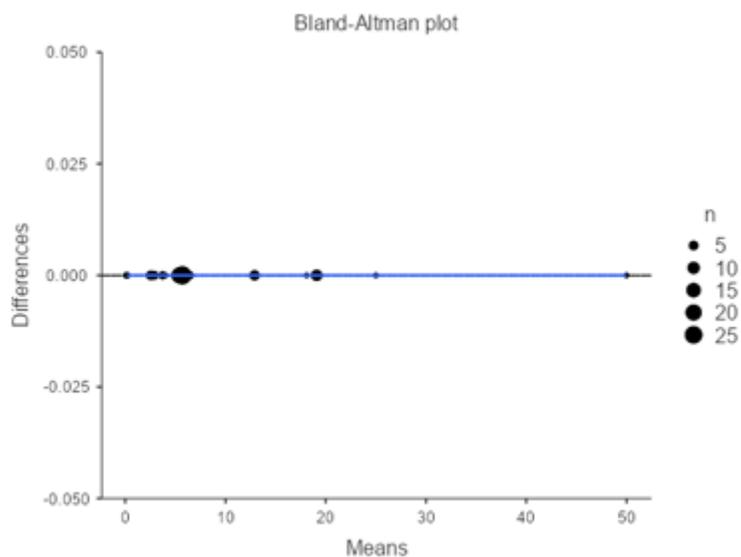
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## Figures



**Figure 1**

Bland-Altman plot to compare the manual method to calculate de recurrence risk and the calculate by the mobile app Cleft RR. In "Y" axis, diferences and in "X" axis the means. Diference Against the mean ( tick solid middle line) of manual and app method (confidence interval = -0.006 a 0.04).