Newborn Screening: Results of a 17-year NBS Program in Mexico

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Background

The inborn errors of metabolism (IEM) are a group of more than 1,000 rare inherited disorders resulting from a defect in the functioning of intermediate metabolic pathways.\textsuperscript{1} Although, these are known as rare diseases, as a group they become a relevant cause of morbidity and mortality; with an accumulated prevalence of 1:800 newborns.\textsuperscript{2,3} Newborn screening (NBS) is fundamental for the early diagnosis of IEM and other disorders; however, only a few can be early diagnosed. \textsuperscript{4,5}

Individually rare, their cumulative prevalence is thought to be high. Global reports present a lack of standardization, leading to disparities when comparing different programs. Those differences involve coverage (both panel and geographically), laboratory methodologies, among others.\textsuperscript{3,4}

Latin America has been improving its NBS programs.\textsuperscript{5} Particularly, the NBS covers 80\% of newborns in Mexico and it mainly targets congenital hypothyroidism (CH). One of the obstacles our country faces is its health system segmentation, in which private NBS programs with a broader disease panel comprises a small percentage of the population and cannot be comparable to each other.\textsuperscript{6}

Currently, there is still a challenge upon coverage, implementation uniformity and evaluation, causing an uncertain panorama of IEM prevalence. Therefore, we present the results of a private NBS program recorded to date with the broadest panel available in Mexico (50+ IEM and other disorders), on account of the use of a specialized software developed in-house.

Objective

To report the results of Genomi-k’s NBS program in Mexico providing a surrogate prevalence of screened disorders.
Materials and Methods

We retrospectively analyzed Genomi-k’s ~300,000 newborns reports performed from October 2004 to June 2021. All newborns were evaluated for ~50 disorders. Furthermore, after 2012, almost 30% were also assessed for SCID and for six lysosomal storage diseases (i.e., Pompe, Fabry, Hurler, Niemann Pick A/B, Krabbe, and Gaucher diseases).

For these tests, dried blood spots (DBS) were taken by venipuncture between the neonates’ first 24 to 72 hours of life, and the samples were then placed on filter paper. The DBS were processed by PerkinElmer Genomics Laboratories in the USA. The technologies performed were MS/MS for fatty acid β-oxidation defects (FAOD), amino acid metabolism disorders (AA), organic acidemias (OA), and lysosomal storage diseases (LSD).

Additionally, other biochemical techniques - i.e. fluoroimmunoassay, fluorometry, and isoelectric focusing- for endocrine disorders, hemoglobinopathies, galactose disorders, and cystic fibrosis (CF), Polymerase chain reaction (PCR) was used for severe combined immunodeficiency (SCID) through TREC’s quantification, as well as for the detection of 5 variants related to glucose-6-phosphate dehydrogenase deficiency (G6PD). PCR extended to the confirmation of genetic variants for various conditions, including hemoglobinopathies.

The results analyses consisted of the estimation of an overall and individual prevalence of IEM and other disorders in Genomi-k’s NBS program.

Results

The results of this program encompass the following:

- In 17 years, our program presented an overall prevalence of 4.5 : 1,000 newborns for the screened disorders (Figure 1).
- On the basis of the ~300,000 newborns who were tested for more than 50 conditions, the most frequent diagnoses were: G6PD, CH, and CAH (Figure 2).
- On the other hand, the LSD group showed the highest prevalence in comparison to other groups (i.e., AA, FAOD, OA, and Hb) (Figure 1-2)
- More than 50% of abnormal results in the initial screening comprehend only aminoacid and acylcarnitine profiles, G6PD, as well as Hemoglobinopathies (Figure 1). The large sum of abnormal profiles might be attributed to the physiological changes the newborn is experiencing, while the hemoglobin conditions may be explained by the molecular techniques applied.
- Naturally, the previous considerations led to a significant reduction of abnormal results in the NBS repetition. In other words, more NBS results within the normal limits were obtained (Figure 1).
- In general, a 17% of patients were lost to follow-up due to difficulties in establishing communication with the parents or other (Figure 1).
- Overall, the NBS resulted in a ~50% PPV, varying among screened conditions (Figure 1).

In this experience, our NBS had a high specificity (99.97%) and sensitivity (near 100%).
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**Births**
- Newborn Screening
- NBS Result
- NBS Repetition
- Follow-up
- Diagnostic Testing

**Biochemical and/or Molecular Tests**
1. +95% Screened Newborns 24-72h of age (<28 days since birth)
2. +93% NBS results <7 days since DBS sampling

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### Table: Newborn Screening Results

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Screened Newborns</th>
<th>(Abnormal Results) Screening per 10,000 newborns</th>
<th>Screening Repetition WNL (%)</th>
<th>Lost to follow-up vs. 1st Abnormal Screening (%)</th>
<th>Confirmed Newborns (per 10,000)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>+310</td>
<td>42.89</td>
<td>↓↓↓ 96.3%</td>
<td>8.3%</td>
<td>0.8</td>
<td>50%</td>
</tr>
<tr>
<td>FAOD</td>
<td>+308</td>
<td>31.39</td>
<td>↓↓↓ 91.5%</td>
<td>13.1%</td>
<td>0.3</td>
<td>13%</td>
</tr>
<tr>
<td>GAL</td>
<td>+299</td>
<td>2.01</td>
<td>↓ 70.5%</td>
<td>17.8%</td>
<td>0.3</td>
<td>56%</td>
</tr>
<tr>
<td>BIOT</td>
<td>-961</td>
<td>16.95</td>
<td>↓↓↓ 91.4%</td>
<td>17.8%</td>
<td>0.3</td>
<td>23%</td>
</tr>
<tr>
<td>CH</td>
<td>+115</td>
<td>15.74</td>
<td>↓ 61.6%</td>
<td>22.6%</td>
<td>5.1</td>
<td>85%</td>
</tr>
<tr>
<td>CAH</td>
<td>+355</td>
<td>3.4</td>
<td>↓ 63.1%</td>
<td>16.5%</td>
<td>0.8</td>
<td>66%</td>
</tr>
<tr>
<td>CF</td>
<td>-4,701</td>
<td>12.14</td>
<td>↓↓↓ 74.6%</td>
<td>22.9%</td>
<td>1.1</td>
<td>35%</td>
</tr>
<tr>
<td>G6PD*</td>
<td>-4,446</td>
<td>35.77</td>
<td>-</td>
<td>0.3%</td>
<td>32.4</td>
<td>91%</td>
</tr>
<tr>
<td>Hb*</td>
<td>-4,446</td>
<td>94.46</td>
<td>↓ 89.7% **</td>
<td>0.4%</td>
<td>0.2</td>
<td>86%</td>
</tr>
<tr>
<td>SCID</td>
<td>+9,486</td>
<td>3.47</td>
<td>↓↓↓ 89.5%</td>
<td>57.9%</td>
<td>0.1</td>
<td>25%</td>
</tr>
<tr>
<td>LSD</td>
<td>+2,867</td>
<td>28.68</td>
<td>↓ 63.2%</td>
<td>9.8%</td>
<td>2.8</td>
<td>26%</td>
</tr>
</tbody>
</table>

**Figure 1.** Results of the 17 years of the NBS program in Mexico, including total number of screened patients per condition and relevant results regarding those requiring follow-up.

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* Analysis for G6PD consisted of an allele-specific PCR for 5 genetic variants; while the Hemoglobinopathies (Hb) were confirmed with an allele-specific PCR after abnormal isoelectrofocusing results (S, C, D, E variants only).

** This percentage only represents those NBS results that required a repetition.

**Discussion**

Overall, the estimated prevalence in this study requires segmentation for a more accurate comparison to the literature; nevertheless, it may seem higher when compared to reported prevalences (e.g., 1:800 newborns as an international reference \(^2\,^3\)). In Mexico, there is insufficient epidemiological information to contrast the data we are presenting herein.

Individually, in this study G6PD was present in 32.4:10,000 newborns, positioning this disorder as the most prevalent among this population. Even though there are differences among reported prevalences, G6PD may seem as the most common condition in Mexico.\(^8\)

Congenital hypothyroidism, situated as the second most common disorder in our study, presented a similar prevalence as the one published by Redón et al. for a Mexican population (4.3:10,000 newborns)\(^9\) and is consistent with the prevalence presented worldwide\(^12\).

Additionally, our estimated CAH prevalence is similar to the prevalence described by Hinojosa-Treco et al. (1.2 : 10,000 newborns)\(^11\).

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*Figure 2. Representative distribution of confirmed patients with a metabolic disorder or other condition in this NBS program.*

Conclusion

The well-defined and standardized process implemented from the collection of samples to delivering a result, was essential for the compilation of data used in this analysis. Additionally, the high-quality standards incorporated in our specialized software enhanced the reliability of the program, and in consequence the results.

As the patient’s prognosis is proportional to early diagnosis and treatment, we recommend the inclusion of these biomarkers within any NBS program in Mexico. It is necessary to have more extensive epidemiological studies to show a clearer picture regarding the prevalence and distribution of the IEM and other conditions detected by the NBS.

References


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