Best Practice for Prenatal Genomics

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How will genetic technologies drive the future?
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DISCLOSURE

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BEST PRACTICE FOR PRENATAL GENOMICS

Disclosure information:
Chief Scientific Officer at Institute of Medical Genomics (IMEGEN)
Licensed Laboratory of Panorama Technology (Natera) for NIPD
Reproductive Health and Welfare Societies
Reproductive Health and Welfare Societies

Welfare Societies

- Lack of infectious pandemics
- Antibiotics, vaccines, drugs and treatments evermore effectives
- High impact of birth defects and reproductive problems in the Project of Life
- Maternity delay

30,8 years in 2016
Average Age Of First-Time Moms

Birth defects acquire great importance, becoming the first cause of morbidity and mortality in developed societies
Consequences

- Highly desired babies
- High expectations
- Low tolerance to any deviation that is not expected

The most effective and available tools are…

*Information*

*Prevention*
Preconception Counselling

Objectives

- Risk assessment to minimize or prevent them
  (teratogens, family history, age, ethnic factors, clinical markers or evidences,...)

- Provide information and available options
  (treatments, lifestyle changes, diagnostic or screening tests, alternatives...)

- Facilitate autonomous and informed decision making

- Informed consent

Birth Defects Prevention

- One in every 33 babies (3%) is born with a birth defect
- Are the cause of 20% of all infant deaths
- Not all birth defects can be prevented
- 25% have a genetic cause

Adapted from Stevenson, RE and Hall, J. Human Malformations and Related Anomalies, 2nd ed. 2006
Genetic Birth Defects

- Chromosomal abnormalities: 10-15%
- Single gene disorders: 2-10%

Today, birth defects of genetic cause are only the 25% of the total. New technologies will provide evidences about new genes and genomic causes of birth defects in the next few years.

Nowadays it’s not a technical problem!!!
Genetic Birth Defects

Chromosomal abnormalities

- Aneuploidies (numerical alterations)
- Copy Number Variations (CNVs). Deletions and duplication
- Rearrangements
  - Unbalanced
  - Balanced

All unbalanced chromosome cases in more than 10,000 cases between 2000–2006.

Gene Disorders

- Diseases, syndromes, conditions that could show up during prenatal period or early childhood
- Caused by loss or change of a gene function
- Different type of mutations
  - Point mutations, small insertion or deletions, expansions, etc…
- Genetic heterogeneity:
  - a mutation in different genes can cause the same phenotype
  - Several types of mutations can cause the same phenotype

Molecular Genetics can be considered as a pure handcraft
What’s the goal of our test?

- Research
- Diagnostic
- Screening

This objective can vary depending on the risk assessment:

- Population risk, maternal age,…
- Mother is a carrier, ecographic evidences,…

Our exigence level about technology accuracy will depend on that.
Research

We use the genetic test to corroborate a previous hypothesis, we follow the scientific method

Prenatal Diagnosis doesn’t need surprises nor discoveries!!!
Research

We use the genetic test to corroborate a previous hypothesis, we follow the scientific method.

Diagnostic

We use the genetic test to identify something that previously has been scientifically proven, we use clear evidence-based criteria.

We need to prove or discard evidences.

The highest accuracy is needed.
Research
We use the genetic test to corroborate a previous hypothesis, we follow the scientific method.

Diagnostic
We use the genetic test to identify something that previously has been scientifically proven, we use clear evidence-based criteria.

Screening
We use the genetic test to identify a significant health risk, in a large population and for which an effective clinical procedure exists.
Genetic Birth Defects

To summarize…

- Chromosomal abnormalities
  - Aneuploidies (Mainly 21 trisomy)
  - Deletions/duplications
- Gene disorders
  - Gene alterations (monogenic)
  - Gene alterations (multigenic)
## Technologies vs Genetic causes

<table>
<thead>
<tr>
<th>Genetic causes</th>
<th>Karyotyping</th>
<th>Array</th>
<th>NIPT</th>
<th>Specific Molecular tests</th>
<th>Specific Gene panels</th>
<th>Exome /Genome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneuploidies</td>
<td>★★★</td>
<td>★★★</td>
<td>★★★</td>
<td>★★★</td>
<td>★</td>
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<td>Large Structural anomalies</td>
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<td>★</td>
<td>★★★</td>
<td>★</td>
<td>★★★★</td>
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<tr>
<td>Small Structural anomalies</td>
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<td>★★★★</td>
<td>★★★★</td>
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<td>Rearrangements</td>
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<td>★</td>
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<td>★★★</td>
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<tr>
<td>Gene alterations</td>
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<td></td>
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<tr>
<td>Monogenic</td>
<td>★★</td>
<td></td>
<td>★★★</td>
<td>★★★</td>
<td>★★★★</td>
<td>★★★★</td>
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<tr>
<td>Multigenic</td>
<td></td>
<td></td>
<td>★</td>
<td></td>
<td>★★★★</td>
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</tr>
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</table>
New Technologies in Prenatal Genomics

• **Next Generation Sequencing (NGS)**
  Analysis of millions of genomic sequences in only one assay
  Technical Issues to be used in prenatal diagnosis
  - Optimization of technologies and development of precise analysis pipelines
  - Increase of the accuracy (sensibility and specificity)
  - Decrease of prices

• **Non Invasive Prenatal Testing (NIPT)**
  Identification of genetic variations analyzing the cell free fetal DNA in maternal blood
  Technical Issues to be used in prenatal diagnosis
  - Development of deep sequencing technologies and precise quantification algorithms
  - Increase of the accuracy (sensitivity and specificity)
  - Decrease of prices

Nowadays it’s not a technical problem!!!
New Technologies in Prenatal Genomics

Issues to be solved before extensive use of NGS and NIPT

- Technology optimization
- Clinical validation of each technology and new applications
- Adaptation to clinical setting
- To follow Guidelines and Professional Statements
- Prospective and retrospective evaluations
- Data and Knowledge Management
- Ethical Issues. Patient involvement
- Effective Information Delivery
Prenatal Genetics and Genomics

To summarize...

- Chromosomal abnormalities
  - Aneuploidies (Mainly 21 trisomy)
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Prenatal Genetics and Genomics

Genetic Diagnosis

- Accuracy as high as possible
- To follow specific best practice guidelines and procedures
  - Prenatal procedures
    (Valuable samples, prenatal timing, maternal contamination, uncertainty,…)
  - Technology specific
    (Karyotyping, microarray, PCR, sequencing, NGS,…)
  - Disease specific
    (Inherited translocations, inherited diseases, Skeletal Dysplasia, Polycystic Kidney Disease, Noonan,…)

imegen
Prenatal Genetics and Genomics

To summarize…

• Chromosomal abnormalities
  • Aneuploidies (Mainly 21 trisomy)
  • Deletions/duplications

• Gene disorders
  • Gene alterations (monogenic)
  • Gene alterations (multigeneric)
Carrier Screening

Screening

… to identify a **significant health risk**, in a large population and for which an **effective clinical procedure** exists

- We need to identify what and how many diseases should be included in this test. The more number of diseases we include, the more uncertainty we will have
- Sensitivity is not 100%, some mutations could be missed
- Preconception and prenatal Carrier Screening is available
- Genetic counseling is essential (residual risk, uncertainty, …)
ACMG position statement on prenatal/preconception expanded carrier screening

The proper selection of appropriate disease-causing targets for general population-based carrier screening (i.e., absence of a family history of the disorder) should be developed using clear criteria, rather than simply including as many disorders as possible. For a particular disorder to be included in carrier screening, the following criteria should be met:
Carrier Screening

Accumulated prevalence vs No diseases

Number of diseases
Carrier Screening

Disorder selection

- Carrier frequency 1 in 100 or greater
- Well-defined phenotype
- Suppose detrimental effect on quality of life
- Cause cognitive impairment
- Require surgical or medical intervention
- Early onset
- Should be able to be diagnosed prenatally and ‘actionable’
  - Antenatal intervention to improve perinatal outcomes
  - Changes to delivery management
  - Patents education about special care needs after birth

- Should not be included adult onset conditions

Carrier Screening

Guidelines

- Test should be available after counseling on its limitation (residual risk), benefits and alternatives, ideally before pregnancy
- Appropriate disorder selection
- Consanguinity
- More prevalent diseases (Cystic Fibrosis, SMA, thalassemias and globinopathies) should be offered independently ethnicity or screening strategy

To summarize…

- Chromosomal abnormalities
  - Aneuploidies (Mainly 21 trisomy)
  - Deletions/duplications ★

- Gene disorders
  - Gene alterations (monogenic)
  - Gene alterations (multigenic)
Microarray (CNVs Screening)

Guidelines

- **Genetic Counseling and specific Informed consent** are required, including discussion about VOUS, non paternity, consanguinity, adult onset, technical limitations, etc
- A focused design of regions associated to known syndromes is useful to reduce VOUS
- Algorithm for variant reporting and interpretation should be established before test
- Parental samples are recommended wherever possible

Prenatal Genetics and Genomics

To summarize…

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Non Invasive Prenatal Diagnosis

Relative amount of DNA mapping to chromosome of interest

Amt. of DNA detected as % of expected

Maternal DNA

Fetal DNA

Maternal Copy (x2)
Maternal Copy (x1)
Fetal Copy (x2)
Fetal Copy (x1)
Fetal Copy (x2)
Fetal Copy (x1)
disomy
trisomy
## Non Invasive Prenatal Diagnosis

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Screening Procedure</th>
<th>Detection Rate (%)</th>
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<tr>
<td>1st Trimester</td>
<td>NT Ultrasound</td>
<td>64-70</td>
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<tr>
<td>1st Trimester</td>
<td>1st Trimester Blood Screen → NT Ultrasound</td>
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</tr>
<tr>
<td>2nd Trimester</td>
<td>Triple Screen</td>
<td>69</td>
</tr>
<tr>
<td>2nd Trimester</td>
<td>Quadruple Screen</td>
<td>81</td>
</tr>
<tr>
<td>Integrated Screen</td>
<td>1st Trimester Blood Screen → NT Ultrasound →  2nd Trimester Blood Screen</td>
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<tr>
<td>Serum Integrated Screen</td>
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**False Positive Rate:** 5%
## Non Invasive Prenatal Diagnosis

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<th>Process 2</th>
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### False Positive Rate:
- **5%**

**ACOG Practice Bulletin No. 77, January 2007**

1st Trimester (<10 weeks)  
**Cell freeDNA**  
**99**

**ACOG Practice Bulletin No. 163, May 2016**

**False Positive Rate:**  
0.5%
Non Invasive Prenatal Test Recommendations:

- **Genetic Counseling** to optimize patient decision making,
- **NIPS is the most sensitive screening option for** traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes)
- Laboratories should provide readily visible and clearly stated **DR, SPEC, PPV, and NPV** for conditions being screened
- Laboratories should Include a clearly visible **fetal fraction** on NIPS report
- Laboratories should specify the **reason for a no-call** when reporting NIPS result
- **NIPS to screen for autosomal aneuploidies other than those** involving chromosomes 13, 18, and 21 is **not recommended**
- To deter patients from selecting sex chromosome aneuploidy in the absence of a clinical indication
- **NIPS to screen for genome-wide CNVs** is not recommended
- **Offering diagnostic testing when a positive screening test result is reported after NIPS**
CONCLUSIONS

• Genetic Counseling (Pre and post test)
  o Updated information, knowledge management
  o Delivery information to patient

• Objective of the test (Diagnosis vs Screening)

• To follow specific guidelines and professional position statements

• New technologies and applications should be validated and evaluated potential harms before use
Thank you very much