GENETICS

First complex decisions

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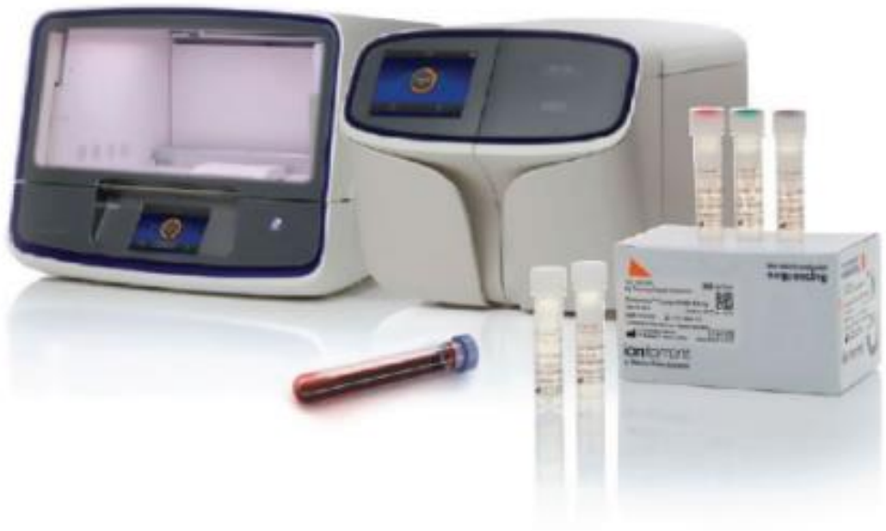
About First Genetics

The only OEM partner of Thermo Fisher Scientific in Russia:

- ❑ Original NGS equipment manufacturer (sequencers and sample preparation stations)
- ❑ Original reagents manufacturer



Main goal? →

Implementation of NGS technology into clinical practice for next directions:

- Preimplantation Genetic Testing for aneuploidy (PGT-A)
- Noninvasive prenatal testing (NIPT)
- Cancer genetic tests

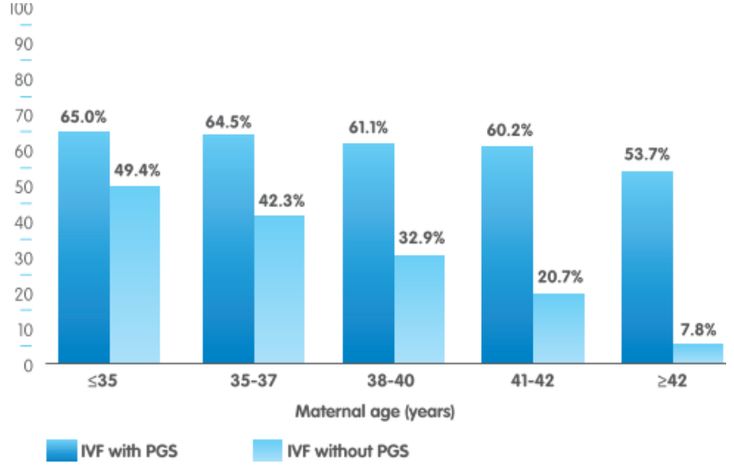
Relevance

Preimplantation Genetic Testing for aneuploidy

24000 tests /year

PGT-A by NGS allows to reduce the number of IVF cycles to achieve the goal:

- ❑ improving the likelihood of implantation and live birth in IVF
- ❑ reducing the risk of miscarriage and multiple pregnancy
- ❑ reducing the risk of having children with certain genetic defects

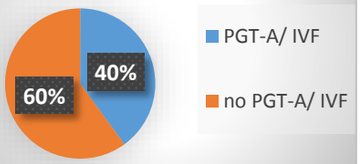


*Internal IGENOMIX data 2016 based on outcomes and 2015 SART data.

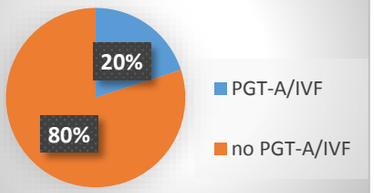
Economic feasibility. Cost reduction for:

- embryo transfer and drug maintenance of pregnancy
- implementing a genetic diagnosis of abortus and potential causes of miscarriage
- keeping a child with chromosomal abnormalities

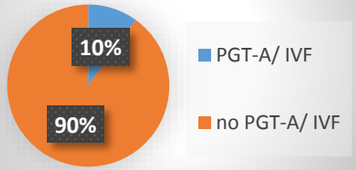
USA



Developed countries



Russian Federation



Questions that are still existing:

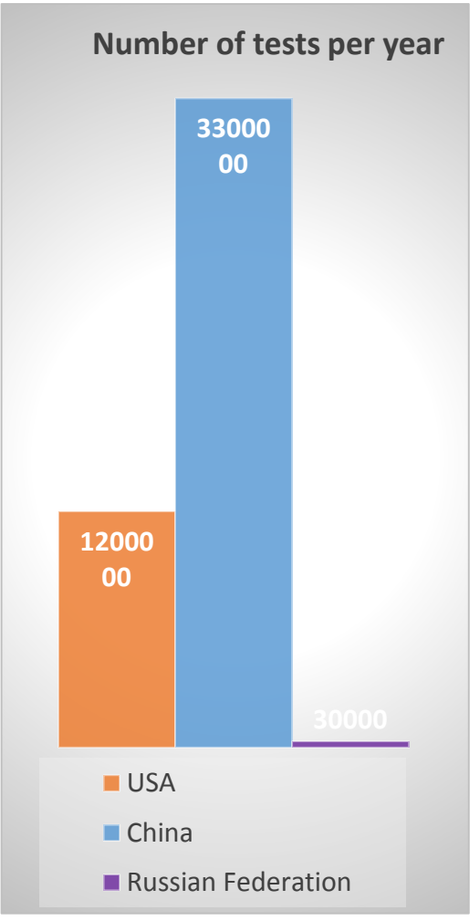
1) improves the efficiency of single embryo transfer/ might discard healthy embryos

2) does embryo testing needed to be registered?

embryo is "not a human“/ embryo is " a human“, in Europe plans to enact a law where the embryo will be recognized by human being

Relevance

Non-invasive prenatal test (NIPT)



- is one of the most promising new areas of screening
- higher Positive Predictive Value
- available through reimbursement in some developed countries (Denmark, Belgium etc.)
- proven effectiveness of test implementation in healthcare abroad
- covered by most health insurance plans for high-risk pregnancies

NIPT by the NGS method has a high sensitivity and specificity in order to be a tool for selecting patients with an increased risk of chromosomal pathology according to the results of combined screening before the appointment of an invasive diagnosis.

Economic feasibility. Cost reduction for:

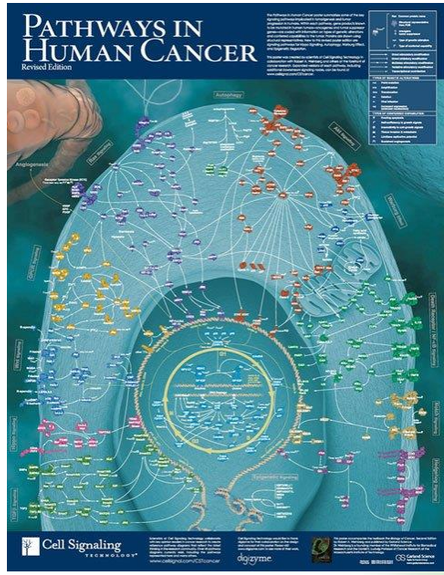
✓ realization of extra invasive genetic diagnosis
✓ drug maintenance of pregnancy and disposal of invasive diagnosis complications
✓ keeping a child with chromosomal abnormalities

Global perspectives on clinical adoption of NIPT, Mollie A. Minear et all., 2015

Relevance

Cancer genetic test

- ❑ the pharmaceutical industry is ahead of the possibilities of diagnostic and screening solutions.
- ❑ relapse and metastasis monitoring tools are not effective enough
- ❑ the cost of treatment is extremely high and the effectiveness of treatment depends largely on the molecular genetic profile of the tumor.



Multigene molecular assay in cancer can help to:

- identify patients who are most likely to benefit from a particular therapeutic product;
- identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product;
- provide relapse and metastasis monitoring (liquid biopsy)
- identify the origin of tumor and differentiate primary focus from metastasis
- predict aggressiveness of (RNA expression)
- genetic susceptibility to cancer

the market is not developed

Companion diagnostics –solution to provide aid in treatment design

Now: time-consuming “step by step” approach with high risk to have no answer

What’s needed: fast validated test gives the most complex information to clinician about patient management with adequate cost

NGS market review

Illumina

MiSeq Dx Instrument

NextSeq 550Dx Sequencing System

NovaSeq 6000 Sequencing System

Life Technologies Corporation

Ion PGM Dx System

Oncomine Dx Target Test

Ion Proton System

OEM Version

Ion GeneStudio S5/S5 Plus

Ion ReproSeq PGS Kit
Oncomine focus kit
Oncomine comprehensive kit
Oncomine mutation load kit

QIAGEN

Gene Reader NGS System

BGI

MGISEQ-2000

MGISEQ-200

Capital Bio

NIPT kit

FDA approved

CE-IVD

CFDA approved

Distribution of NGS technology

- ✓ The number of equipment and reagent kits is limited.
- ✓ Main beneficiary countries are USA, Europe, China
- ✓ Developing countries use the RND result of world leading manufacturers
- ✓ There is no need and economic feasibility to develop own complicated technology NGS solutions
- ✓ Foreign products can only be registered if there are FDA approved or CE-IVD marked, what limits the possibilities of using and distributing RUO (Research use only) NGS technologies.
- ✓ Localization of production may be a solution.

The experience of successful localization of the production of NGS products in the world

Capital Bio
OEM partner of Thermo Fisher in China
NIPT registered in 2013
960 thousand NIPT tests by Capital Bio/ year

Critical points for the localization of foreign production

Device development documentation

Device validation and verification documentation is required for making registration dossier, but manufacturer usually doesn't have it for RUO devices.
As a result full device validation and verification is performed by localizer.

Possible solution:

- ✓ to develop special criteria for localized production
- ✓ to perform only technical and clinical trials for localized devices which are widely used all over the world

Critical points for NGS validation

Unique features of NGS

- ❑ Specific purpose - an indication of the analyte, each of which must be validated
- ❑ The NGS method allows to determine a huge number of analytes (mutations, aneuploidy, etc.) and it is not possible to confirm all of them.
- ❑ The advantage of the NGS method is the ability to determine an unspecified parameter for analysis and the ability to determine a variety of parameters. The formulation of a specific purpose narrows down the potentialities of the method.
- ❑ Lack of the reference method. Comparison between possible methods are available for one parameter.
- ❑ NGS allows to identify not only the most common, but also rare analytes, it may be impossible to collect a sample group.

Solution:

- ✓ **to form a more general purpose of medical device with the designation of primary and end points.**
- ✓ **to prepare a document that will indicate the minimum number of samples are needed to test.**
- ✓ **to develop special requirements for the registration of NGS products.**

Critical points for NGS validation

Clinical trials

1. Preimplantation Genetic Testing for aneuploidy

- ✓ limited amount of biomaterial - each embryo can be divided into a limited number of parts.
- ✓ euploid embryos are almost unavailable for testing.
- ✓ the clinical trials providers have to get reversion of rights on the embryo from the parents.
- ✓ the selected method of comparison (FISH) is applicable for only 5 chromosomes at the maximum at the same time
- ✓ the selected method of comparison (FISH) is very expensive

2. Non-invasive prenatal test (NIPT)

- ✓ NGS method allows to identify microdeletions and microduplications but it is not possible to announce to be afraid of FPR
- ✓ the conformation of positive result should be performed by invasive method (amniocentesis), that pregnancy woman can sign away

3. Cancer genetic tests

- ✓ low quality FFPE samples make RNA extraction process quite difficult
- ✓ the lack of the reference standards for NGS with confirmed frequent and rare mutations
- ✓ the lack of referent method for non-common mutations

Summary

- ✓ From our point of view localization of foreign production is only possible solution to solve a wide range of clinical applications NGS technology

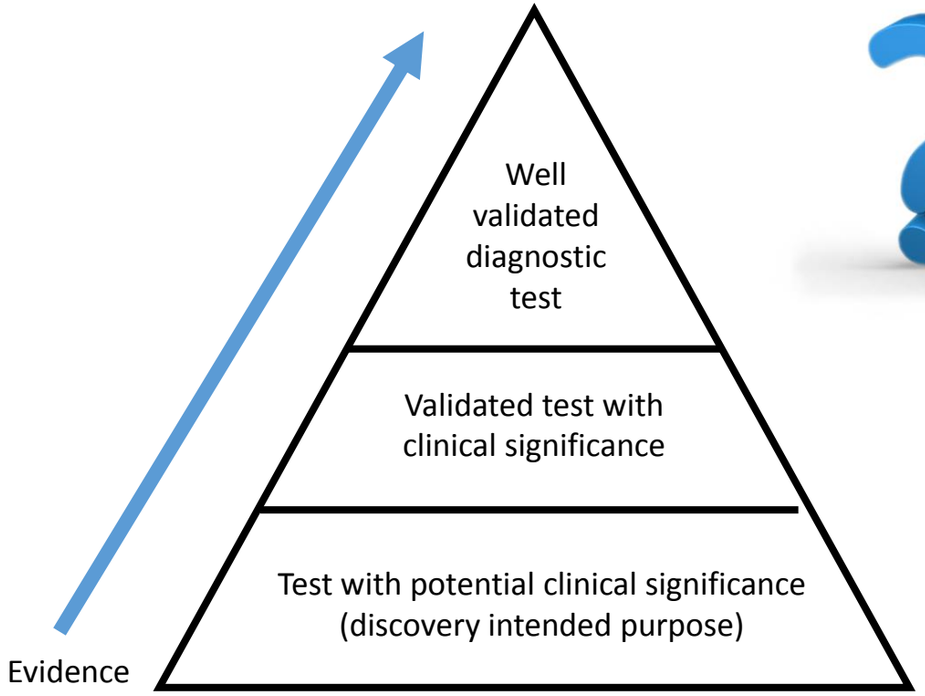
- ✓ NGS technology is completely different because it gives huge amount of data. It makes necessary the development of special requirements for the registration of NGS products.

- ✓ We focused on NGS technology implementation in clinical performance where we have limitative criteria:

  PGT – presence/absence of chromosomal abnormality in all 24 chromosome;
  NIPT – presence/absence of chromosomal abnormality in 5 chromosome;
  Cancer genetic test – identification of mutations in certain genes associated with oncogenesis.

One step forward

NGS technology is extensively used for whole genome and whole exome sequencing the result of which are random findings. There are no limitative criteria in this case.



Probably one more approach to registration requirements development is needed

Спасибо за внимание

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