Informed Consent to Carry out Preimplantation Genetic Testing (PGT)

1) Reasons and purpose of using preimplantation genetic testing (PGT)

Preimplantation genetic testing – PGT („Preimplantation Genetic Testing“) represent testing for genetic diseases of IVF embryos before transferring the embryos into the patient‘s uterus, i.e. prior to the implantation. These testing are recommended based on genetic counseling where an increased risk of genetic abnormalities exists. When these technologies are used, not fresh embryos, but frozen ones are transferred, after test results are known.

PGT-M („PGT for monogenic/single gene defects“)
PGT-M is technology being used in the case of already detected hereditary disease in the family of the infertile couple. It allows pre-implantation detection of gene mutations (changes) associated with specific hereditary disease of which one or both partners are carriers, and which could occur in the family (e.g. cystic fibrosis).

PGT-SR („PGT for chromosomal structural rearrangements”)
In the case of carriers of chromosomal rearrangements, PGT-SR serves to detect embryos with abnormality in an unbalanced form where parts of chromosomes are redundant or missing.

PGT-A („PGT for aneuploidies“)
PGT-A is technology which allows to detect acquired deviations in chromosome number or size (these are blocks of about hundreds of genes) that prevent the proper development of the embryo organs and are often associated with spontaneous abortion (such as Down syndrome). Without PGT-A, we would not get this information and this could result in transfer of such embryos that cannot give rise to a normal course of pregnancy. This way we can exclude the most frequent variations in chromosome number and reduce the risk of miscarriage or birth of a child with a severe chromosomal defect. At the same time the success rate of in vitro fertilization is increased, because only embryos with a negative test result are being transferred into the uterus.

PGT cannot be used for gender selection, except for by geneticist indicated cases in serious gender-related genetic diseases. If such a disease is not present in the family, the information about gender tests is not stated in the report for the patients.

2) Description of proposed methods and procedures

i. Chromosomal PGT (PGT-A and PGT-SR)

Humans usually have in each cell nucleus 46 chromosomes (bodies, visible under a microscope) of typical shapes on which genes are located. Variations in the number or structure of chromosomes usually affect more genes and may be associated with recurrent miscarriages, birth defects or mental and physical development disorders. Chromosomal defects can be present in any of the partners, or they can occur newly and randomly. The risk of these new defects increases significantly with the age of parents. For proving chromosomal defects there are mostly used methods enabling to examine in detail all the chromosomes with the use of a microchip (array), or by determining the sequence of the genetic alphabet letters (sequencing). In some cases, microscopic FISH technology is used. Its principle is to assess the binding (hybridization) of color-coded probes to corresponding sections of chromosomes.

In what cases it is advisable to perform chromosomal testing:

- One of the parents carries a balanced chromosomal rearrangements. This means that he is healthy and has a complete set of genes, but certain blocks of genes are located in the wrong place on the chromosome. Embryos with an unbalanced chromosomal defect with the above mentioned consequences develop from the part of germ cells (oocytes or sperm).
- Selection of gender which is determined by the presence of gender chromosomes labeled Xand Y. It is carried out only in cases when it is possible to prevent serious genetic gender-related diseases.
- Vyšetření náhodně vzniklých změn počtu chromozomů embrya (PGT-A - screening aneuploidií).
- Testing of randomly generated changes in the embryo chromosomes number (PGT-A).
  PGT-A may be considered e.g. in the case of repeated failures of assisted reproduction, in couples with recurrent miscarriages, in elderly couples or in substantial reduction in fertility of the partner.

ii. PGT-M

The cause of many serious hereditary diseases is a disorder of a particular gene, a change (mutation) in the sequece of letters in the genetic alphabet (DA sequences). If such mutation is detected in a family with a hereditary disease, PGT-M may be carried out. In order to increase PGT reliability, also hereditary changes in DA (markers) in the vicinity of the mutations that are not directly related to the disease and are found in all persons. y testing of other family members, group of DA markers that are inherited together with the mutation (so called Risk haplotype) may be determined, and this can be used in making diagnosis more accurate.

In what cases it is advisable to perform gene PGT-M:

- In addition to diseases manifesting themselves by multiple defects prenatally or after birth, gene PGT-M may be considered in couples with a significant risk of the disease which manifests itself fully until later in life, such as proven hereditary susceptibility to cancer.
- In the occurrence of a disease that is treatable by stem cell transplantation it is possible, through gene PGT-M, to select an embryo, from which a sibling (savior) may grow with stem cells suitable for transplantation (i.e. genetically healthy and having the same combination of HLA alleles).

Indications (reasons) for testing and chosen testing method chosen in the case of the embryo / embryos of the pair are as follows: (to be ticked by physician)

[_] Finding of genetically balanced embryos in parents with chromosomal rearrangement (PGT-SR)

[_] Testing for monogenic disease (PGT-M):

[_] Gender selection un gender-related diseases: Transfer of embryos female [_] male [_]

[_] Detection of aneuploidy of all chromosomes (PGT-A)

[_] Other

The above-mentioned tests will be followed by genetic counseling, during which the couple will be provided proper interpretation of the test results.

Unused diagnostic material (DNA) obtained from the embryos retrieval will be preserved for additional tests.

3) Potential complications and risks, risks of unexpected findings for the couple and genetically related persons

Like all laboratory methods, also PGT has its limitations:

- in the early stage of embryo development, the number and structure of chromosomes as well as of individual genes, must be in all cells identical (mosaicism)
- Testing fails in 2–5% of the embryos.
- Laboratory error and false-negative or false-positive result of PGT is even not ruled out.
- Although retrieval of a few cells usually does not cause harm to the embryo, it cannot be excluded that it may rarely happen.

Before the decision to undergo PGT, it is necessary to realize also further facts:

- For PGT it is necessary in vitro fertilization with hormonal treatment of women, oocytes retrieval carried out by transvaginal puncture (through the vaginal wall) under ultrasound control and laboratory manipulation with embryos.
- PGT cannot guarantee successful IVF, i.e. embryo attachment to the uterus and emergence of pregnancy. Embryo attachment to the uterus is not guaranteed even after the transfer of embryo of excellent quality. If pregnancy occurs, it may result, as after natural fertilization, in miscarriage, ectopic pregnancy, fetal death or birth of fetus with a congenital defect. After PGT, it must be expected that the number of embryos suitable for transmission will be after discarding of genetically unsuitable embryos even lower than normal (the number of embryos suitable for the transfer into the uterus on the fifth day after the standard IVF without PGT is usually lower than five), and therefore also chance of getting pregnant. After the performance of PGT, the laboratory may even discard all embryos as genetically unsuitable, and another cycle of IVF must be undergone.
- When searching a suitable sibling – savior in PGT, the probability of the suitable embryo is lower than 20% (1/5).
- When pregnancy is proved, its successful completion is not guaranteed. PGT is focused on a particular disease, it is not therefore excluded that suspicion of another genetic defect during pregnancy or in the newborn will be expressed.
- In connection with the performance of PGT and within the family history there is a risk of unexpected findings for the couple and their genetically related persons with medically significant genetic risk (relatives in direct line who are grandparents, parents and their children, and indirect one, when the level of risk is determined according to the degree of relatedness and type of genetic disease).

Performing preimplantation genetic diagnosis does not replace the standard prenatal testing performed in all pregnant women to detect developmental defects and genetic diseases of the fetus (ultrasound and biochemical screening). We recommend to confirm additionally each PGT-M and PGT-SR by chorionic villus sampling during the first trimester of pregnancy (chorial biopsy) or testing of amniotic fluid (amniocentesis) during the second trimester of pregnancy.

4) Alternatives to the method

The above described prenatal diagnosis of amniotic fluid or placenta in the first trimester (chorionic villus sampling) or second trimester (amniocentesis) of pregnancy. Some genetic defects in the fetus during pregnancy can be detected even by non-invasive testing, using imaging techniques (ultrasound, magnetic resonance imaging) or by analysis of free DNA in maternal blood.

5) Data on the impact on health, including the health of future generations, limitations in the usual way of life and ability to work, treatment regimen

In these methods the couple must undergo the assisted reproduction treatment regimen (in vitro fertilization - IVF) although their fertility is normal. The patient‘s organism may respond inappropriately to hormonal treatment necessary to obtain a larger number of oocytes, so called „Hyperstimulation Syndrome.“ During the oocytes retrieval complications may occur, and the introduction of suitable embryo may result in ectopic pregnancy. In PGT all embryos may be found to be unfit for transfer. **In order not to influence the result of PGT, it is necessary for couples who can conceive also naturally, to practice safe sex.**

6) Declaration of the couple – consent to the examination

We declare that we were informed by our treating physician fully and in good time on our state of health, on reasons for planned examination. We were acquainted by physician in detail and in comprehensible form with the course and nature of proposed examination, its advantages and success rate. We also declare that we were comprehensibly informed by physician about consequences and possible risks of this technology, its alternatives including the risks and consequences thereof, as well as other important examination-related circumstances. Physician also informed us about possible limitations in the way of life and ability to work after performance of this method and about our right to freely decide on provision of this examination.

We agree that abnormal embryos, i.e. embryos diagnosed as unfit for transfer will be excluded from storage and will not be transferred.

We could ask the physician about everything what we did not understand. Physician answered all our additional question clearly and comprehensibly. We have understood all items of the mentioned advice as well as the answers to the additional questions, and have no additional queries.

We declare that we have been informed that in accordance with Section 28 (1) of Act No. 372/2011 Coll., on health services, we have the right to freely decide on the procedure in providing health services, unless other legislation excludes this right. We agree to carrying out the above examination.

We further declare that we have informed the physician about all facts important for the assessment of our state of health and for the choice of the optimal treatment regimen (especially health data). We accept warning that in case of falsehood of this statement, both provider of the health services and treating physician will not be liable for the consequences caused thereby. We undertake that if any substantial change occurs, we will inform the Health Services Provider immediately in writing.

We declare that we have been acquainted with the price of the examination, and should it not be covered by public health insurance, we undertake to pay it to the Health Services Provider based on the tax document in due time and manner.

Patient‘s name:

Personal ID number:

ID:

Address:

Email:

Tel:

Date:

Signature:.....

Patient‘s name:

Personal ID number:

ID:

Address:

Email:

Tel:

Date:

Signature:.....

7) Physician‘s statement:

I declare that I have explained the patient and her partner the content of this instruction in a clear and comprehensible manner, especially I have acquainted them with their state of health, scheduled examination, the course of the treatment, subsequent limits and intervention-related risks.

The patient and her partner were also informed, beyond the above mentioned, about risks and potential complications of PGT and with in vitro fertilization with respect to their state of health. They understood this instruction, and had opportunity to put questions to physician providing instructions, and these questions were comprehensibly answered.

In ..... on .....

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Physician‘s name and signature