Critical Laboratory information and Disclaimer:

Considerations and challenges of preimplantation genetic diagnosis .

- Patients should be counselled on IVF procedures, possible prenatal diagnosis (a chorionic villus sampling/CVS or amniocentesis) even if PGD/PGS is performed.
- Even with a successful IVF and PGD procedure, pregnancy is not guaranteed after transfer, and a term or near-term delivery is also not guaranteed.
- Removal of a single cell without breaking it or causing serious damage is technically difficult. Damage to the embryo (projected to be 0.1%) may accidentally occur during removal of the cell.
- Analysis of a single cell has limitations, and misdiagnosis resulting from mosaicism (when the embryo has cells with different compositions) may occur. For this reason, prenatal diagnosis with either a CVS or amniocentesis should be considered to confirm the condition of the fetus.
- A relatively large number of eggs or embryos may be found to be abnormal, thus leaving only a few or no healthy embryos for transfer.
- For aneuploidy (numeric) screening, not all chromosomal or genetic abnormalities can be diagnosed with PGD because only a restricted number of chromosomes can be examined at one time during the course of a single procedure.
- Currently, only a specific examination of a single biopsied cell is available. A single cell cannot be screened for multiple genetic conditions.
- Some chromosome disorders may not be amenable to PGD due to an unavailability of suitable FISH locus specific or area specific probes for a specific chromosome disorder (i.e. chromosome deletions, or translocations). In the case of deletions and / or balanced chromosome translocations couples must have a chromosome analysis specifically to confirm detailed chromosome breakpoints. The process of validating and confirming the correct choice of FISH probes for such a procedure can take several weeks.

Considerations and challenges of preimplantation genetic screening

Although initially heralded as a method to identify and avoid aneuploidy in embryos of women at increased risk asa result of advanced maternal age, recent studies suggest that success might be limited. Most considerations and challenges listed in the PGD section also apply to PGS.

- **Technical limitations**: Currently, FISH offers evaluation of less than half of the 23 chromosomes; usually only 5 are analyzed for the most commonly occurring numeric chromosome abnormalities. It must be noted that studies demonstrate that up to 25% of aneuploid embryos are characterized as normal because the abnormal chromosomes were not analyzed.
- **No or inconclusive results:** Approximately 30% of cells removed for screening may yield no or inconclusive results as a result of difficult technical protocols.
- **Limitation of single cell analysis:** If nondisjunction occurs during meiosis, then all the cells in an embryo are aneuploidic. However, if disjunction occurs at mitosis, then two or more cell lines may be present in the embryo. Thus, a mosaic embryo with normal and abnormal cells may be misdiagnosed with the present single cell biopsy technique.
- **"Self-correction":** Self-correction refers to evidence that mosaic embryos are able to halt the proliferation of abnormal cells and that many embryos identified as aneuploid will survive and be re-identified as normal.

- **Benefits:** Results for PGS for advanced maternal age are mixed. Couples with recurrent pregnancy loss and established balanced translocation may benefit from PGS.

- **Current recommendations:** Current recommendations state that available evidence does not support the use of PGS to improve live-birth rates for advanced maternal age, recurrent pregnancy loss, or implantation failure.
- **Fetal malformation rates:** To date there are no reports of increased fetal malformation rates or other identifiable problems in babies born from IVF with PGD/PGS. However, the presentation of other abnormalities later in life as a consequence of the PGD/PGS procedure (biopsy) is possible.
- **Pregnancy rate:** Due to a reduction in the number of embryos available for embryo transfer, patients should be counselled that IVF with PGD/PGS may result in a lower pregnancy rate than if IVF is performed without PGD/PGS.

Disclaimer:

1. No tests will be performed without the patients reading and signing the "Critical Laboratory information and Disclaimer" form.

2. Where the FISH procedure is performed, the embryo every endeavour will be made to exclude numeric chromosome abnormalities of tested chromosomes.

3. For specific requests, e.g. translocations and deletions, every reasonable effort will be made to ensure exclusion of unbalanced chromosome abnormalities. For this, selected locus and area specific DNA FISH probes will be used.

6. It MUST be noted that in spite of spending a considerable amount of money in performing a PGD cycle, there is **no certainty** that a pregnancy will result.

7. While every effort is made to exclude human and / or technical errors, Unistel Medical Laboratories (Pty) Ltd. do not accept any responsibility for human or technical error. Should gross negligence be proven the claim shall not exceed the value of the contract.

8. Unistel Medical Laboratories (Pty) Ltd. and all its employees shall in no event be liable for loss of income, profits or for incidental, special or consequential damages, whether direct or indirect, arising from the acceptance and action taken on the grounds of the Analysis Report.

9. Unistel Medical Laboratories (Pty) Ltd. do not warrant or make any representations regarding the success of the full procedure in producing a successful conception after transfer of selected embryo's that have been biopsied and the sectioned blastomeres tested.

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PATIENT SIGNATURE SPOUSE / PARTNER SIGNATURE

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DATE WITNESS