EMBRYO PROTECTION AUTHORITY

Draft Protocol for Pre-implantation Genetic Testing for Monogenic diseases (PGTM)

1.1 In Malta, PGTM is regulated by the Embryo Protection Authority (EPA). The Authority maintains a list of conditions for which PGTM has been approved, as per table reproduced hereunder:

List of Conditions approved by EPA for PGTM

Finnish Nephrotic Syndrome

Gangliosidosis

Huntington Disease

Joubert Syndrome

Maple Syrup Urine Syndrome

Nemaline Myopathy

Spinal Muscular Atrophy

Tay-Sachs Disease

Walker-Warburg Syndrome

1.2 For conditions not already on the list, the EPA considers a number of factors, including how serious the condition is, the likelihood of it being inherited and the testimony of people affected by the condition before deciding whether to approve it for PGTM testing.

1.3 In order for a new condition to be considered for PGTM testing approval, a couple must have a licensed PGTM clinic apply to the EPA on their behalf.

1.4 When pre-implantation genetic diagnosis (PGTM) is used to combine IVF and genetic testing as a means of avoiding the transmission of a genetic disease, the medical practitioners shall follow the principles of the Ethical Guidelines as per hereunder:

1.4.1 Pre-implantation genetic diagnosis (PGTM) is a technique that may be used to combine IVF and genetic testing as a means of avoiding the transmission of a genetic disease as listed in the protocol. PGTM shall not be allowed for the selection of embryos for eugenic purposes.

1.4.2 PGTM should only be used for the detection of serious genetic conditions as approved by the Authority, and which conditions significantly affect the health of an individual who might be born.

1.5 The use of PGTM should be a matter of discussion between those seeking PGTM (i.e., the prospective parents) and the clinical team on the seriousness of the genetic condition.

1.6 A senior clinical geneticist should be involved in the decision-making process when deciding whether a particular patient should receive treatment involving PGTM.

1.7 The Tissue Establishment offering treatment should ensure that a multidisciplinary team is involved in providing the PGTM service. The team should include reproductive specialists, embryologists, clinical and molecular geneticists, genetic counsellors. It should also maintain close contact with the primary care medical doctor or the referring clinician.

1.8 If the Tissue Establishment offers the PGTM service, the individual responsible for this laboratory should:

(a) hold an appropriate scientific or medical degree

(b) have acquired sufficient experience in an appropriately accredited medical genetics diagnostic laboratory to supervise and be responsible for one, and

(c) be registered with a recognised body by the EPA as a clinical scientist with specific expertise in clinical genetics and is conversant on the nature of tests conducted, the scope and limitations of the tests, accuracy and implications of the tests and the meaning of the test results.

1.9 The Tissue Establishment should ensure that the prospective parents seeking treatment should have access to the clinical geneticists and the genetic counsellors.

1.10 Genetic counselling requires specialist training and knowledge. Tissue Establishments are to ensure, that genetic counselling should only be undertaken by an infertility counsellor if s/he has additional qualification in genetic counselling. In the absence of this, patients should be referred to specialist genetic counselling services. Genetic counselling addresses the risk of patients using their own gametes, but it does not address the emotional issues associated with infertility. Therefore, the Tissue Establishment's counselling service should continue to be available before, throughout and after the investigations, decision-making and treatment.

1.11 The Tissue Establishment should consider the following factors when deciding if PGTM is appropriate in particular cases:

(a) the views of the people seeking treatment in relation to the condition to be avoided, including their previous reproductive experience

(b) the likely degree of suffering associated with the condition

(c) the availability of effective therapy, now and in the future

(d) the speed of degeneration in progressive disorders

(e) the social support available, and

(f) the family circumstances of the people seeking treatment.

1.12 The Tissue Establishment may offer PGTM but withhold the patient's test results (PGTM with non-disclosure). However, this should only be offered under the following conditions:

(a) that patients are given the opportunity to receive genetic counselling on the implications prior to giving consent,

(b) that protocols are established to limit, as far as possible, the risk of unwanted disclosure to the patients. Tissue Establishments should consider using a different embryology laboratory from their own, in order to minimise the number of Tissue Establishment staff who know the patient's genetic status.

1.13 The Tissue Establishment should document its reasons for offering PGTM with non-disclosure to a patient. This record should include:

(a) written informed consent from the patient to perform PGTM with non-disclosure,

(b) a statement from the people seeking treatment confirming that they have been given the opportunity to receive genetic counselling and that they have, prior to giving consent, received information:

(i) on the risks of inadvertent disclosure,

(ii) that where all embryos are suitable for transfer this is not evidence of the patient's genetic status,

(iii) that where no embryos are suitable for transfer this is not evidence of the patient's genetic status.

1.14 The clinical team of the Tissue Establishment, having discussed with the prospective parents seeking PGTM, and determined the condition to be sufficiently serious to warrant PGTM, need to apply to the Regulatory Authority EPA and provide the EPA with a report prior to starting any PGTM procedure, detailing:

(a) the nature of the genetic condition,

(b) if testing is to be for Polar Body PGTM, Day 3 Blastomere PGTM or on a Day 5 Blastocyst PGTM,

(c) proof that the prospective parents have received genetic counselling and have given a joint informed consent to undergo the procedure,

(d) original or copy of results of genetic testing, karyotypes or other specific testing of the index patient, spouse or partner, children, or other family members (when appropriate),

(e) female reproductive history, gynaecological and fertility status,

(f) male reproductive history, andrological history, fertility status, results of sperm analysis (especially in cases where the genetic disorder(s) for which PGTM is desired has effects on sperm parameters,

(g) reports on health problems of female and male partners that may affect genetic diagnosis, or the outcome of IVF and pregnancy (when appropriate). Health status may need to be re-evaluated over time,

(h) a genetic counselling report

1.15 The Authority, if the condition is listed in the approved conditions, will issue a permission for the prospective parents to undergo PGTM. It is only after an approval is granted that a PGTM procedure can go ahead as per hereunder:

1.15.1 Prospective parents where the woman has not attained thirty-six (36) years of age will be allowed up to a maximum of eight oocytes/embryos to undergo PGTM.

1.15.2 Prospective parents where the woman has attained thirty-six (36) years and have not attained forty-six (46) years of age will be allowed up to a maximum of twelve oocytes/embryos to undergo PGTM.

1.16 The Tissue Establishment should ensure that people seeking PGTM are given the appropriate information about the treatment. This should include:

(a) the process, procedures and possible risks involved in IVF and biopsy procedures when providing a sophisticated genetic test,

(b) the experience of the Tissue Establishment in carrying out the procedure,

(c) that sophisticated genetic tests can reveal additional genetic information about an embryo(s) and that the clinical effect of these findings on a child born may not be known,

(d) All information, oral and written, should be in language that can be understood by a layperson as technical terminology may lead to patient misunderstanding,

(e) Written information about treatment should be available prior to a consultation,

(f) When PGTM involves the treatment of a couple, both partners should, when possible, attend consultations,

(g) An independent interpreter should be present, when necessary, although a family member could act as translator in the absence of an alternative,

(h) Counselling should be offered both before, during and after each IVF/PGTM cycle. The counselling provided should be non-directive and include all reproductive options available to the couple, enabling them to reach their own conclusion about the suitability of treatment,

(i) Costs and timelines should also be discussed to ensure that patients are fully informed of all aspects of IVF and PGTM before treatment starts. The social and psychological impact needs to be considered, especially in couples already responsible for the care of affected children,

(j) Additional counselling may be needed after completion of the laboratory work-up,

(k) Individualised post-consultation letters should contain a summary of the information discussed,

(l)The patients should sign a written informed consent for all procedures they will undergo, and which are PGTM-related.

1.17 The Tissue Establishment should also provide information to those seeking treatment to help them make decisions about their treatment, including:

(a) genetic and clinical information about the condition being tested for,

(b) the likely impact of the condition on those affected and their families,

(c) information about treatment and social support available, and

(d) information from a relevant patient support group or the testimony of people living with the condition, if those seeking treatment have no direct experience of it themselves.

1.18 If the person seeking treatment has already been given information about the particular genetic disorder, for example from another genetics Tissue Establishment, the Tissue Establishment need not provide this information again. However, the Tissue Establishment should ensure that the information has been provided to a satisfactory standard of breadth and clarity.

1.19 Before providing PGTM, the Tissue Establishment should ensure that those seeking treatment have had sufficient opportunity to fully consider the possible outcomes of genetic testing and their implications.

1.20 Embryos from which biopsies have been taken or resulting from gametes from which biopsies have been taken, should not be transferred with any other (non-biopsied) embryos in the same treatment cycle.

1.21 Embryos that after biopsies have been carried out result that they have a gene that will develop a serious disease, cannot be discarded as per the Embryo Protection Act, thus, such embryos are to be cryopreserved in a dedicated storage facility, separate from embryos not diagnosed with the disease.

1.22 Any embryos, that after undergoing PGTM biopsies have inconclusive diagnosis, are to be clearly labelled and cryopreserved in the same dedicated storage facility as the embryos diagnosed with the disease.

1.23 Any embryos that after undergoing PGTM result that they are not diagnosed with the disease being tested for but might be carriers of that disease can be transferred into the prospective parents requiring treatment and are to be cryopreserved with the embryos not diagnosed with the disease

1.24 The use of an embryo known to have a gene of a serious disease as described above, should be subject to consideration of the welfare of any resulting child and should have approval from the Authority. Prior to use, the prospective parents must give their consent, after receiving adequate information for same use.

1.25 Embryos known to have a gene of serious disease as described above, will only be placed for adoption once an effective treatment for same disease has been found.

1.26 If a Tissue Establishment decides that it is appropriate to provide treatment services to a woman using an embryo known to have a gene of a serious disease as described above, it should document the reason for the use of that embryo and inform the Authority without due delay.

1.27 The Tissue Establishment should have an adequate labelling system, written or barcoded (electronic), with two unique patient identifiers plus the embryo/cell(s) number is used to match the sample's diagnostic result with the embryo from which that sample was taken. This should ensure traceability throughout the IVF and PGTM process until reporting of the final results.

1.28 The labelling system should be comprehensible and practical for both the IVF and PGTM centres. Printed sticker labelling may be superior to pens, as labelling should be legible and uneditable.

1.29 Labelling and sample identification should be confirmed for critical and high-risk steps by an independent observer and signed

1.30 After biopsy, the sample may be analysed in house or sent for genetic testing in another centre

1.31 The PGTM work-up report should contain at least the following information:

(a) administrative information including

(i) title or name of the report;

(ii) number of the report (as used for document control, when available);

(iii) pagination including the actual and total number of pages (the patient identifier and report name/number must be present on each additional page);

(iv) full date of the report;

(v) name and address of the physician referring the patient;

(vi) identification of the person(s) performing the diagnosis/authorising the release of the report and their signature;

(vii) identity of the IVF/PGTM centre with full contact details;

(b) patient (male and female)/sample identification:

(i) full given name(s) and surname, or unique patient identification code;

(ii) unequivocal date of birth;

(iii) gender;

(c) specific for the preclinical work-up report:

(i) date of DNA sample collection;

(ii) date of DNA sample arrival in the laboratory;

(iii) samples and genetic status of relevant family members can be mentioned only with their informed consent and should be in accordance with general data protection regulations (GDPR) and/or local privacy regulations;

(d) restatement of the clinical question, i.e., the indication(s) being requested for analysis, the type of required testing, the referral reason, parental karyotypes/genomes;

(e) specification of genetic tests used:

(i) brief information on the methods used in the analysis;

(ii) full details of the extent of the tests, including software, where appropriate;

(iii) where a commercially available kit is used, this should be clearly identified in the report, including the reference and version of the kit.

(f) a clear description and interpretation of results;

(g) a clear summary of the results;

(h) error rates/limitations of the test/misdiagnosis (a general figure should be stated for the overall cycle/treatment).

1.32 Before starting a clinical PGTM cycle, relevant documents should be available, labelling of samples should be checked, and genetic counselling provided to the prospective parent/s.

1.33 The PGTM laboratory should ensure that it has clearly documented procedures for all steps of the examination process (explicit instructions and a summary of validation results) and release of results (diagnosis, reporting, embryo transfer policy). These procedures should be covered in a service-level agreement between the PGTM and IVF centres.

1.34 The IVF Centre should ensure that the method used for PGTM should have been previously implemented, tested, and validated in the PGTM centre.

1.35 Clinical results are to be reviewed and signed or electronically validated by a suitably qualified person (name, qualification, date).

1.36 The PGTM clinical cycle report contains an interpretation of the clinical results and guidance on which embryos are genetically transferable. The same recommendations apply as specified for the preclinical work-up report, together with the following items:

(a) unique cycle/treatment code;

(b) date of oocyte retrieval;

(c) date of biopsy;

(d) date of biopsy sample arrival in the laboratory;

(e) information on the sample type (including number of samples and controls);

(f) unique ID number for each cycle and/or biopsy sample tested;

(g) indication for PGTM.

1.37 When scoring results from polar body (PB) testing, it is recommended to report what was detected in each PB and then infer the oocyte diagnosis. It is recommended to test both PBs.

1.38 When scoring results from blastomere/trophectoderm (TE) testing, it is recommended to report what was detected in the sample and then infer the embryo diagnosis.

1.39 A written or electronic report should be securely transmitted to the IVF centre to ensure transfer and/or cryopreservation of the correct embryos. Results should not be communicated orally.

1.40 Reporting time should be kept as short as possible and when fresh transfer is intended, reporting time should be adapted to allow the IVF centre to organise the embryo transfer.

1.41 The report should be clear, concise, accurate and easily understandable by non-geneticists and that the overall result and interpretation (including transfer recommendation) are presented per embryo.

1.42 In case of no diagnosis and re-biopsy to try and obtain a result, this should be included in the report.

1.43 The final clinical cycle report must be signed by appropriately qualified (authorised) personnel (name, qualification, date), and the clinical cycle results are discussed with the couple before embryo transfer.

1.44 The report is stored in the patient file in the both the PGTM and the IVF centre, according to local regulations and a copy of which is sent to the Regulatory Authority EPA together with cryopreservation details of the embryos that can be transferred as well as the cryopreservation details of the embryos diagnosed with the disease.

1.45 Tissue establishments should compare PGTM live birth rates and matched non-PGTM [routine IVF or intracytoplasmic sperm injection (ICSI)] live birth rates within that IVF centre.

1.46 When in-house genetic analysis is not feasible, transport PGTM is an option. In transport PGTM, patients have the IVF treatment (oocyte retrieval, embryo culture, biopsy and transfer, pregnancy follow-up) at their local IVF centre, but genetic testing is performed at a collaborating PGTM centre with significant experience in PGTM.

1.47 The IVF centre and PGTM centre should have in place an official agreement (Service-Level Agreement) dealing with legal, insurance and accountability issues about the transport PGTM procedures.

1.48 Transportation companies entitled to transport biopsied material should certify their suitability to transport the biopsied material, provide the likelihood of a sample loss or sample delivery delay and provide actions taken against these risks.

1.49 The IVF centre and outsourced PGTM centre should make arrangements to ensure that patients have had adequate PGTM counselling.

1.50 The IVF centre and PGTM centre should have in place a set of clinical/laboratory validated protocols, including tubing/spreading protocols, and shipment protocols specifying approximate transportation time and ensuring cell and/or DNA integrity.

1.51 In addition, practical and logistic arrangements on who will be responsible for the various stages of the PGTM treatment should be clearly established.

1.52 The IVF centre and PGTM centre should delineate clear and sufficient lines of communication as documented in written procedures and compliant with the GDPR during all stages of a transport PGTM treatment.

1.53 The IVF/PGTM centres should agree on the feasibility, the number, and the timing of transport PGTM cycles and define a schedule.

1.54 All diagnostic results and reports are sent in written form (complying with the GDPR).

1.55 PGTM centres should be accredited and certified, as PGTM is of a multidisciplinary nature, the various units involved should each be accredited/certified for their defined tasks and according to the most appropriate quality standards. For each unit, responsibilities should be clearly outlined/described and transition of responsibility from one unit to the other during the PGTM process should be well defined and guaranteed.