

LICENCE CONDITIONS FOR

**ASSISTED REPRODUCTION SERVICE LICENSEES
PROVIDING OR INTENDING TO PROVIDE
PRE-IMPLANTATION GENETIC TESTING
FOR (A) MONOGENIC OR SINGLE GENE DEFECTS
OR (B) CHROMOSOMAL STRUCTURAL
REARRANGEMENTS**

IMPOSED UNDER SECTION 13(1) OF
THE HEALTHCARE SERVICES ACT 2020

1. Application

- 1.1. These licence conditions (“**LCs**”) apply to all persons which have been licensed under the Healthcare Services Act 2020 (the “**HCSA**”) to provide an assisted reproduction service and provide, or intend to provide, as part of that service, the following specified services (such persons referred to as “**Licensees**”):
- a) pre-implantation genetic testing for monogenic or single gene defects (“**PGT-M**”); or
 - b) pre-implantation genetic testing for chromosomal structural rearrangements (“**PGT-SR**”).
- 1.2. For avoidance of doubt:
- a) the defined terms as used in these LCs shall have the meanings ascribed to them in the HCSA and any Regulations made thereunder, unless otherwise stated;
 - b) the requirements in these LCs are without prejudice, and in addition to the requirements imposed under the HCSA as well as any Regulations and other applicable licensing conditions, directions, codes of practice made thereunder; and
 - c) these LCs do not override a healthcare professional's duty to make clinical decisions that are in the best interests of each patient.
- 1.3. Licensees that intend to provide PGT-M or PGT-SR are to (a) make an application to the Director-General of Health (“**DGH**”) for approval to provide PGT-M or PGT-SR pursuant to section 11C of the HCSA, and (b) to obtain the said approval of the DGH pursuant to section 11D of the HCSA, before providing PGT-M and/or PGT-SR services, as the case may be, in compliance with section 9A(2) of the HCSA.

- 1.4 A breach of these LCs may result in regulatory action being taken against Licensees under section 20 of the HCSA, including but not limited to:
- a) suspension or revocation of the Licensee's license to provide an assisted reproduction service;
 - b) shortening the term of the Licensee's licence to provide an assisted reproduction service;
 - c) directing the Licensee to rectify the contravention, or prevent a recurrence of the contravention; and/or
 - d) directing the Licensee to pay a financial penalty.

2. Definition of PGT-M and PGT-SR

- 2.1. For the purpose of these LCs, PGT-M and PGT-SR refer to any clinical treatment and/or laboratory procedure to assess the genetic predisposition of an individual involving:
- a) the biopsy of any cells from a blastocyst which had been created by assisted reproduction ("AR") techniques, to determine the presence or absence of single gene mutations (i.e. monogenic or single gene defects) or chromosomal structural rearrangements that the embryos are at significant risk of inheriting based on family history; and
 - b) the selection of unaffected embryos for transfer into the body of a patient.

3. Acceptable Indications for PGT-M and PGT-SR

- 3.1. The Licensee:
- a) shall only carry out PGT-M and PGT-SR for the specified heritable conditions using the specific genetic tests listed in **Annex A**, or such other conditions as may be approved in writing by the DGH; and
 - b) shall not carry out PGT-M for only a specific sex unless prior approval of the DGH has been sought.
- 3.2. The qualified assisted reproduction practitioner who is the attending physician of the patient receiving an assisted reproduction service from the Licensee may submit an appeal to the DGH to carry out PGT-M or PGT-SR for a condition not listed in **Annex A**. The appeal shall include the following:
- a) details of the patient's condition;
 - b) a report by either a (i) trained genetic counsellor,¹ (ii) a medical practitioner with relevant qualification or training in genetic counselling for that

¹ The genetic counsellor shall have a recognised genetic counselling degree or certification, which is supported or recognised by credible bodies such as the Accreditation Council for Genetic Counselling, Human Genetics Society of Australasia and Genetic Counsellor Registration Board, and has at least 2 years of relevant working experience in clinical genetic counselling.

particular condition and has at least 2 years of relevant working experience in genetic counselling for that particular condition, or (iii) a medical practitioner with relevant qualification or training in clinical genetics and has at least 2 years of relevant working experience in clinical genetics (each, a “**Trained Counsellor**”), detailing:

- i. the counselling provided to the patient and her husband, including other options considered (if there are any), and the likelihood of the patient and her husband having an affected child with the condition if not offered PGT-M or PGT-SR;
 - ii. the reasons for which PGT-M or PGT-SR should be allowed to be carried out for the condition (e.g. the age of onset, severity of condition, penetrance, expressivity and types of treatments available, if any);
 - iii. evidence of the effectiveness of PGT-M or PGT-SR for that particular condition (e.g. scientific publications), where available. To avoid doubt, the Licensee shall take reasonable efforts to ascertain whether such evidence is available and if so, to obtain such evidence; and
- c) the specific CLS Licensee (as defined in paragraph 6.1 below) which the Licensee intends to send the biopsied specimen to for testing, and details of that CLS Licensee’s ability to test for the condition, or alternatively, that CLS Licensee’s ability to acquire the capability to test for the condition.
- 3.3. The Licensee shall ensure that PGT-M and PGT-SR are not carried out in the following circumstances:
- a) for social reasons, e.g. sex selection for non-medical reasons or selection of particular traits due to personal preferences of the prospective parents;
 - b) to alter, or with a view to altering, the genetic constitution of an embryo; or
 - c) when the genetic diagnosis or mode of inheritance is uncertain, e.g. due to genetic or molecular heterogeneity.

4. Requirements Relating to Personnel

As appointed under Regulation 11 of the Healthcare Services (Assisted Reproduction Service) Regulations 2023 (“**AR Regulations**”)

- 4.1. The Licensee shall ensure that the embryo biopsy procedures are carried out by qualified embryologists who are:
- a) familiar with the post-biopsy wash and transfer procedures necessary for successful downstream PGT-M or PGT-SR analysis; and

- b) adequately trained and assessed for competency to perform embryo biopsy for clinical cases, based on the following criteria:²
- i. the completion of pre-clinical training with practice of at least 50 embryo biopsies where all steps of the biopsy procedure are performed under the supervision of an experienced embryologist or the Licensee's chief embryologist (as appointed under Regulation 12 of the AR Regulations);
 - ii. the completion of clinical training with performance of at least 10 embryo biopsies where appropriate evaluation of biopsy outcomes is conducted (e.g. post-biopsy survival of embryo) under the supervision of an experienced embryologist or the Licensee's chief embryologist (as appointed under Regulation 12 of the AR Regulations); and
 - iii. the completion of relevant training on cell washing and certification through single cell pick up validation by the PGT-M/PGT-SR testing laboratory.
- 4.2. The Licensee shall keep proper, complete and accurate records for each personnel's completion of the training and assessment for the criteria set out in paragraph 4.1(b) above.
- 4.3. The Licensee shall ensure that it engages a minimum of two qualified embryologists who meet the criteria as stipulated in paragraph 4.1 above.

5. Facilities and Equipment

- 5.1. The Licensee shall ensure that embryo biopsies are only performed in a dedicated area that complies with all safety and environmental standards, in order to minimise any damaging effects on biological material.
- 5.2. The Licensee shall ensure that all facilities and equipment in the areas referred to in paragraph 5.1 are cleaned with appropriate agents before any biopsy procedure is performed.

6. Laboratories Performing Genetic Testing for PGT-M and/or PGT-SR

- 6.1. The Licensee shall ensure that genetic testing of any biopsied specimen is carried out by a licensee licensed under the HCSA to provide a clinical laboratory service, and approved to perform PGT-M and/or PGT-SR as part of that service (the "**CLS Licensee**").
- 6.2. The Licensee shall:

² For avoidance of doubt, the criteria stipulated in paragraph 4.1(b) do not apply to any existing personnel who, at the time when the conditions titled "Regulatory Terms and Conditions on Assisted Reproduction Centres Providing Pre-Implantation Genetic Testing for Monogenic / Single Gene Defects and Chromosomal Structural Rearrangements Services" took effect on 1 May 2021, were already performing embryo biopsies for clinical cases with an applicable Licensee.

- a) submit the following documents to the CLS Licensee performing the genetic testing, prior to the specimen being sent to the CLS Licensee:
 - i. a clinical diagnosis, made by a registered medical practitioner, confirming that either the patient or her husband, or both, carry the gene that causes a heritable condition listed in **Annex A**, or
 - ii. documentation that prior approval of the DGH had been obtained for the patient and her husband to undergo PGT-M or PGT-SR; and
 - iii. a pre-test genetic counselling report, and
- b) ensure that the written informed consents of both the patient and her husband are submitted to the CLS Licensee performing the genetic testing, concurrent with the delivery of the specimens to the CLS Licensee.

7. Patient Information, Counselling and Consent

Requirements relating to Consent (Regulation 25 of the AR Regulations)

- 7.1. The Licensee shall ensure that a patient and her husband seeking PGT-M and/or PGT-SR are provided with adequate information regarding PGT-M and/or PGT-SR, including (but not limited to) the following:
 - a) the procedures and risks associated with the procedures involved, which include in-vitro fertilisation, intracytoplasmic sperm injection and embryo biopsy;
 - b) the findings which patients can expect to receive (e.g. a finding of whether the embryo is normal or abnormal), including incidental findings of any chromosomal abnormality that may be discovered in a PGT-SR test (e.g. abnormality at another chromosome besides the one on which the patient or her husband sought the PGT-SR test for) and the options for follow up (e.g. genetic counselling, discarding of the embryo);
 - c) the reliability of the test to be carried out (in general and for the particular heritable condition being tested), chances of misdiagnosis or false positive/negative results, and possible adverse outcomes that could arise from these issues (e.g. inadvertent transfer of an affected embryo, inadvertent discarding of a healthy embryo);
 - d) any limitations of the test to be carried out (e.g. a PGT-SR test would only detect unbalanced chromosomal rearrangements);
 - e) the Licensee's experience in performing the procedure;
 - f) reproductive options and alternatives for PGT-M and/or PGT-SR (e.g. natural conception with prenatal diagnosis or acceptance of risk without further examination, gamete donation, remaining childless), and the benefits and limitations of PGT-M and/or PGT-SR compared with the alternatives (e.g. additional burden and lowered chances of pregnancy with assisted reproduction treatment compared with natural conception); and

- g) the financial costs involved in PGT-M and/or PGT-SR; and
 - h) the ethical issues involved in PGT-M and/or PGT-SR (e.g. creation and destruction of embryos that test positive for the relevant heritable condition).
- 7.2. Before obtaining the written consents from a patient and her husband for the PGT-M and/or PGT-SR procedure, the Licensee shall ensure that the patient and her husband are provided with the following information on the specific heritable condition and which test it is conducted for:
- a) genetic and clinical information about the specific heritable condition, including the clinical phenotype for each possible genotype where applicable; and
 - b) the likely impact of the heritable condition on those affected and their families.
- 7.3. Before obtaining the written consents from a patient and her husband for the PGT-M and/or PGT-SR procedure, the Licensee shall ensure that the patient and her husband are provided with pre-test genetic counselling by a Trained Counsellor. The Licensee shall ensure that the aforementioned counselling is culturally appropriate and shall include discussion of the following:
- a) genetic risk assessment and recurrence risk;
 - b) the possible outcomes of PGT-M and/or PGT-SR and its implications;
 - c) the likelihood of incidental findings from the PGT-M and/or PGT-SR test, the possible implications of the aforesaid incidental findings, and whether the patient's and her husband's wishes on whether they would want to be informed of any incidental findings from the PGT-M and/or PGT-SR test;
 - d) the likely impact of the genetic condition on the patient's offspring and their family, which includes:
 - i. the rate of degeneration in progressive disorders;
 - ii. the extent of any intellectual impairment;
 - iii. the degree of abnormality associated with the condition;
 - iv. the seriousness of the genetic condition; and
 - v. the availability of effective and affordable therapy, now and in the future;
 - e) the implications of not undergoing PGT-M or PGT-SR; and
 - f) the procedures available as alternatives to PGT-M or PGT-SR.
- 7.4. The Licensee shall ensure that:

- a) the patient and her husband are advised, counselled and informed of all relevant and material information, as specified in paragraphs 7.1 to 7.3 above, not less than 7 days before the patient and her husband give express written consents for the PGT-M or PGT-SR procedure; and
 - b) the aforementioned express written consents be obtained before the PGT-M or PGT-SR is performed.
- 7.5. The Licensee shall ensure that the patient's and her husband's wishes pertaining to incidental findings (as mentioned in paragraph 7.3(c) above) are clearly documented.

Requirements relating to post-test counselling

- 7.6. The Licensee shall ensure that all the Licensee's patients and their husbands who have undergone PGT-SR are offered the option of post-test genetic counselling, particularly in the event of any incidental findings. If desired by the patient or her husband, post-test genetic counselling shall be provided by a Trained Counsellor, and shall include discussion of the following:
- a) the results of the genetic test and the interpretation of these results;
 - b) the implications of the test results on the patient or her husband as the case may be; and
 - c) any psychological, social and ethical issues or concerns that the patient or her husband may have as the case may be.

8. Prohibition of disclosure of information

- 8.1. The Licensee shall ensure that the following information is **not disclosed** to any of the Licensee's patients and/or their husbands:
- a) the sex of the tested embryo, unless the Licensee has obtained the DGH's prior written approval in accordance with paragraph 3.1(b) above; and
 - b) other genetic traits which are not related to the heritable condition at paragraph 3.1 above, except for incidental findings of any chromosomal abnormality detected from a PGT-SR test where the patient and her husband have indicated a wish to be informed of any incidental findings.

9. Quality Control and Management

Quality Management System (Regulation 10 of the AR Regulations)

- 9.1. The Licensee shall ensure, as part of its quality management system established in relation to its provision of PGT-M and/or PGT-SR services, that the following are monitored on a regular and systematic basis:
- a) the proportion of cells damaged during embryo biopsy;
 - b) the proportion of embryos for which a diagnosis was not obtained;

- c) the misdiagnosis rate;
- d) the implantation rate;
- e) the spontaneous abortion rate;
- f) the clinical pregnancy rate;
- g) the take-home baby rate; and
- h) the multiple pregnancy rate.

9.2. The Licensee shall ensure that it conducts regular evaluations of the competency of all personnel involved in performing the different steps of PGT-M and/or PGT-SR against clinical outcomes of the embryos which were tested, as part of its quality management system.

10. Other Requirements

10.1. The Licensee shall comply with all relevant requirements, including for record retention, under the HCSA and any applicable Regulations and Guidelines issued thereunder.

11. Reporting to the DGH

11.1. The Licensee shall furnish to the DGH such information as the DGH may from time to time require regarding the processes and procedures carried out for PGT-M and/or PGT-SR for regulatory compliance and inspection purposes.

**LIST OF ALLOWABLE CONDITIONS FOR WHICH PGT-M AND PGT-SR
CAN BE CARRIED OUT**

**A. PGT-M using Polymerase Chain Reaction (PCR)-based single cell
tests for the following genetic diseases:**

I. Autosomal Dominant Conditions

1. Autosomal Dominant Dilated Cardiomyopathy (*TTN*)
2. Autosomal Dominant Retinitis Pigmentosa (*PRPF3*)
3. Breast-ovarian cancer, familial, susceptibility to, 1 (*BRCA1*)
4. Breast-ovarian cancer, familial, susceptibility to, 2 (*BRCA2*)
5. Facioscapulohumeral muscular dystrophy 1 (*FSHD1*)
6. Familial adenomatous polyposis 1 (*APC*)
7. Hereditary Pancreatitis (*PRSS1*-related highly penetrant pathogenic variants only i.e. p.Asn29Ile and p.Arg122His)
8. Huntington disease (*HTT*)
9. Li-Fraumeni syndrome (*TP53*)
10. Marfan syndrome (*FBN1*)
11. Multiple endocrine neoplasia, type 1 (*MEN1*)
12. Multiple endocrine neoplasia, type 2A (*RET*)
13. Myotonic dystrophy, type 1 (*DMPK*)
14. Osteogenesis imperfecta, type V (*IFITM5*)
15. Polycystic kidney disease 1 (*PKD1*)
16. Polycystic kidney disease 2 (*PKD2*)
17. Rhabdoid tumor predisposition syndrome 1 (*SMARCB1*)
18. Spinocerebellar ataxia, type 2 (*ATXN2*)
19. Spinocerebellar ataxia, type 3 (*ATXN3*)
20. Tuberous sclerosis 2 (*TSC2*)
21. Von Hippel-Lindau Syndrome (*VHL*)

II. Autosomal Recessive Conditions

22. Adrenal hyperplasia, congenital, 1 (*CYP21A2*)
23. Alkuraya-Kucinkas syndrome (*KIAA1109*)
24. Alpha-thalassemia (*HBA2* and *HBA1*, but excluding deletional HbH disease and all other milder forms, such as alpha-thalassemia silent carrier or alpha-thalassemia carrier)
25. Autosomal Recessive Alport Syndrome (ARAS) (*COL4A4*)
26. Autosomal Recessive Congenital Titinopathy (*TTN*)
27. Autosomal Recessive Polymicrogyria (*ADGRG1*)
28. Beta-thalassemia (*HBB*)

**LIST OF ALLOWABLE CONDITIONS FOR WHICH PGT-M AND PGT-SR
CAN BE CARRIED OUT**

29. Bile acid synthesis defect, congenital, type 2 / delta(4),3-oxosteroid 5-beta-reductase deficiency (*AKR1D1*) – only for couples with gene mutation leading to null enzyme activity
30. Ceroid lipofuscinosis, neuronal, 1 (*PPT1*)
31. Ehlers-Danlos syndrome, kyphoscoliotic type, 1 (*PLOD1*)
32. Galactosemia 1 / classical galactosemia (*GALT*)
33. Gaucher disease, type 1 (*GBA*)
34. Glycogen storage disease II, classical infantile form / Pompe disease (*GAA*)
35. Harlequin ichthyosis (*ABCA12*)
36. Herlitz junctional epidermolysis bullosa (*LAMB3*)
37. Infantile osteopetrosis, autosomal recessive 1 (*TCIRG1*)
38. Leigh Syndrome (Infantile Subacute Necrotising Encephalopathy) due to mitochondrial complex IV deficiency (*SURF1*)
39. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (*HADHA*)
40. Matthew Wood syndrome / Microphthalmia, syndromic 9 (*STRA6*)
41. Meckel Syndrome, Type 6 / Joubert syndrome 9 (*CC2D2A*)
42. Netherton syndrome (*SPINK5*)
43. Pierson syndrome (*LAMB2*)
44. Pseudo-TORCH syndrome 1 (*OCLN*)
45. Renal Tubular Dysgenesis (*REN*)
46. Sensenbrenner syndrome / Cranioectodermal dysplasia 1 (*IFT122*)
47. Short-rib thoracic dysplasia 3 with or without polydactyly (*DYNC2H1*)
48. Sickle Cell Anaemia (*HBB*)
49. Spinal muscular atrophy, Type 1 and Type 2 (*SMN1*)
50. Sulfite oxidase deficiency, isolated (*SUOX*)
51. Wolcott-Rallison syndrome (*EIF2AK3*)

III. X-linked Conditions

52. Agammaglobulinemia, X-linked 1 (*BTK*)
53. Coffin-Lowry syndrome (*RPS6KA3*)
54. Duchenne/Becker muscular dystrophy (*DMD*)
55. Fabry disease, classic form (*GLA*)
56. Fragile X syndrome (*FMR1*)
57. Hemophilia A (*F8*)
58. Hemophilia B (*F9*)
59. Hydrocephalus, X-linked / MASA syndrome (*L1CAM*)
60. Incontinentia pigmenti / Bloch-Sulzberger syndrome (*IKBK*)

**LIST OF ALLOWABLE CONDITIONS FOR WHICH PGT-M AND PGT-SR
CAN BE CARRIED OUT**

61. Kennedy's disease (*AR*) (alleles with more than or equal to 38 CAG repeats only)
62. Lowe oculocerebrorenal syndrome (*OCRL*)
63. Ocular albinism (*GPR143*)
64. Severe combined immunodeficiency (*IL2RG*)
65. WAS-related disorder

B. PGT-SR using PCR-based single cell tests or comprehensive 24-chromosome analysis test kits that perform only low-pass/low-coverage sequencing for the following structural rearrangements:

I. Robertsonian Translocations

1. rob(13;14)(q10;q10)
2. rob(13;15)(q10;q10)
3. rob(13;21)(q10;q10)
4. rob(15;21)(q10;q10)
5. rob(14;21)(q10;q10)

II. Reciprocal Translocations

6. t(1;4)(p31;q33)
7. t(1;4)(q43;q23)
8. t(1;6)(q25;p22.1)
9. t(1;7)(p36.1;p15.1)
10. t(1;9)(p10;p10)
11. t(1;9)(p10;q10)
12. t(1;10)(p32;q11.2)
13. t(1;11)(p13.3;q21)
14. t(1;13)(p12;q14.1)
15. t(1;15)(p.34.1-34.2;q24)
16. t(1;16)(q12;q24)
17. t(1;16)(q23~24;p12)
18. t(1;19)(p36.2;p13.2)
19. t(2;3)(q37.1;p21.3)
20. t(2;5;14)(p23;q31.1;q32.2)
21. t(2;7)(q33;p13)
22. t(2;8)(q35;q22.3)
23. t(2;10)(q12;q24.3)

**LIST OF ALLOWABLE CONDITIONS FOR WHICH PGT-M AND PGT-SR
CAN BE CARRIED OUT**

24. t(2;11)(q35;q21)
25. t(2;11)(q37.1;q23.1)
26. t(2;15)(p13;q22-24)
27. t(2;19)(q14.1;p13.3)
28. t(2;19)(q32.1;q13.4)
29. t(3;4)(q25.3;q21.2)
30. t(3;9)(q21;q22.3)
31. t(4;7)(p14;p11.2)
32. t(4;7)(p16.3;p22.1)
33. t(4;15)(q12;q13)
34. t(4;15)(q12;q15)
35. t(5;9)(p13;p22)
36. t(5;11)(q31.1;q21)
37. t(5;20)(p15.2;q13.3)
38. t(6;7)(q25.3;q32)
39. t(6;13)(q14;q32)
40. t(6;17)(q22.3;q24)
41. t(6;22)(p21.3;q13.1)
42. t(7;11)(p21;q23.3)
43. t(7;15)(q21.2;q26.1)
44. t(8;9)(q24.1~24.22;p22)
45. t(8;11)(p11.2;q13.3)
46. t(8;17)(q24.21;q21.3)
47. t(8;22)(p11.2;q13.3)
48. t(10;11)(p15;p13)
49. t(11;14)(q23.1;q32.3)
50. t(11;21)(q24.2;q22.2)
51. t(11;22)(q23;q11.2)
52. t(12;15)(q15;q11.2)
53. t(12;15)(q24.1;q26.1)
54. t(12;22)(p11.2;q11.2)
55. t(16;17)(q23;q12)

III. Inversions

56. inv(1)(p36.1q42.3)
57. inv(2)(p11q13)
58. inv(9)(p12;q13)
59. inv(10)(p15q11.2)

ANNEX A

LIST OF ALLOWABLE CONDITIONS FOR WHICH PGT-M AND PGT-SR CAN BE CARRIED OUT

- 60. inv(11)(p15.4;q24)
- 61. inv(13)(p11.2q14.1)

IV. Miscellaneous

- 62. mos del(11)(q14.2q23.2)
- 63. del(22)(q11.2q11.2)
- 64. del(X)(q25q28)
- 65. der(15)t(Y;15)(q12;p11.2)
- 66. dic(12;22)(p11;p13), der(21)t(12;21)(p11;q10)
- 67. mos dup(8)(q24.13q24.3)
- 68. mos X/XY
- 69. mos X/XX
- 70. mos X/XXX/XX
- 71. mos XXXXX/XX