LICENCE CONDITIONS FOR

CLINICAL LABORATORY 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 a clinical laboratory service ("**CLS**") and provide, or intend to provide, as part of that service, the following specified services ("**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 These LCs shall supersede and replace the LCs entitled 'Licence Conditions for Clinical Laboratory Service Licensees providing or intending to provide Pre-Implantation Genetic Testing for (A) Monogenic or Single Gene Defects or (B) Chromosomal Structural Rearrangements' issued on 14 March 2025.

1.3 For avoidance of doubt, 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.

1.4 For avoidance of doubt, 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, and codes of practice made thereunder.

1.5 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 CLS licence;

(b) shortening the term of the Licensee's CLS licence;
(c) a direction requiring the Licensee to rectify the contravention, or prevent a recurrence of the contravention; and/or
(d) a direction requiring 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 test and/or laboratory procedure to assess the genetic predisposition of an individual involving:
(a) the evaluation of cells biopsied from early embryos which had been created by assisted reproduction 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 uterus of patients.

3 Acceptable Indications for PGT-M and PGT-SR

3.1 The Licensee shall ensure that PGT-M and PGT-SR are only carried out for the specified inheritable conditions using the specific genetic test listed in **Annex A**, or such other conditions as may be approved in writing by the Director-General of Health ("**DGH**").

3.2 The Licensee shall ensure that PGT-M and PGT-SR are **not** carried out:
(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 alter, the genetic constitution of an embryo; or
(c) when the genetic diagnosis is uncertain, e.g. due to genetic/molecular heterogeneity or uncertain mode of inheritance.

3.3 The Licensee shall ensure that in its provision of PGT-M or PGT-SR:
(a) the Licensee and/or its personnel only accepts specimens that are sent from persons which have been licensed under the HCSA to provide an assisted reproduction service ("**AR Service Licensee**") and provide PGT-M or PGT-SR; and
(b) the Licensee and/or its personnel receives the following documentation:
(i) a clinical diagnosis made by a registered medical practitioner confirming that either the patient or her husband

(or both) carries the gene that causes a condition listed in **Annex A**; or

(ii) where a registered medical practitioner makes a clinical diagnosis confirming that either the patient or her husband (or both) carries the gene that causes a condition not listed in **Annex A**, documentation that prior approval of DGH had been obtained for the patient and her husband to undergo PGT-M or PGT-SR; and

(iii) the pre-test genetic counselling report of both the patient and her husband; and

(iv) the written informed consent of both the patient and her husband accompanying the specimen.

4 Requirements Relating to Personnel

4.1 The Licensee shall ensure that the section leader (as appointed under Regulation 8 of the CLSRS Regulations in respect of its provision of PGT-M or PGT-SR) ("**Section Leader**") has a PhD or equivalent qualifications in the relevant field[1] (e.g. medical genetics, molecular genetics, cytogenetics, genomics) and has at least five years of working experience in molecular genetics or genomics testing or a closely-related field.

4.2 The Licensee shall ensure that genetic testing and associated procedures for the purposes of PGT-M or PGT-SR are carried out by personnel[2] who are:

(a) adequately trained and competent in performing the specific genetic test and associated procedures prior to performing the test (e.g. completion of certified courses in pre-implantation genetic testing analysis); and

(b) assessed for competency to perform each test based on the following criteria:

(i) For each PGT-M test involving target-specific Polymerase Chain Reaction (PCR) with or without whole genome amplification, a minimum of 10 reaction tubes each containing an individually isolated single cell from a defined cell line, together with an equal number of corresponding media blank tubes (where applicable), shall be analysed. There shall be ≥90% amplification success and ≥95%

[1] The candidate should have qualifications and demonstrate training including but not limited to: Mendelian genetics, multifactorial inheritance, DNA structure, chromosome structure, population genetics, mutation rates, ethnicity of disease and genetic mapping in a diagnostic setting.

[2] This refers to personnel such as medical laboratory technologists or scientists.

overall genotyping accuracy for the relevant genetic loci, and 0% exogenous DNA contamination in the cell-containing tubes, or 0% DNA contamination for all blank tubes (where applicable); and

(ii) For PGT-SR tests involving microarray or low-pass/low-coverage next-generation sequencing analysis, the laboratory personnel shall be assessed for competency prior to performing a clinical case. This shall be accomplished by performing ≥2 trial analysis runs using single cells with known chromosomal aberrations, with successful identification of the specific aberrations.

5 Quality Management System

5.1 The Licensee shall ensure that as part of the quality management system required under Regulation 11 of the CLSRS Regulations, audits on its provision of PGT-M or PGT-SR are carried out, and that corrective and preventive actions for all deficiencies identified are implemented. The following matters shall be documented by the Licensee:

(a) frequency of audits;
(b) the last audit review date; and
(c) the appropriate corrective and preventive measures taken by the Licensee for any deficiencies identified.

5.2 The Licensee shall ensure that supervisory review in relation to its provision of PGT-M or PGT-SR is conducted on records relating to (i) instrument maintenance and functional checks and (ii) quality control. The Licensee shall ensure that corrective actions and troubleshooting actions are performed, where applicable, as part of the supervisory review.

5.3 The Licensee shall ensure that there is a written procedure for escalation of any issues related to its provision of PGT-M or PGT-SR to its Section Leader or its Clinical Governance Officer (as appointed under section 24(2) of the HCSA) ("**CGO**").

Quality Control Measures

5.4 The Licensee shall implement an internal quality control programme, comprising quality control measures, to validate the reliability of its PGT-M or PGT-SR test results. The Licensee shall ensure that the internal quality control programme shall:

(a) include: (i) the analytical test instrument or method, (ii) the selection of appropriate quality control materials, (iii) sample types, (iv)

established acceptance criteria, (v) frequency of quality control and (vi) test volume; and

(b) be performed at least at the frequency stipulated by the manufacturer of the analytical test instrument or method.

5.5 The Licensee shall ensure that as far as reasonably possible, the quality control measures performed by its CLS in relation to a PGT-M or PGT-SR test is conducted in accordance with the procedures used for the testing of that patient specimen ("**test procedures**"), and at the appropriate intervals defined in the test procedures.

5.6 The Licensee shall ensure that for all quality control results in relation to its PGT-M or PGT-SR which are assessed to be unacceptable based on its established acceptance criteria in paragraph 5.4(a):

(a) the results are investigated by the appropriate personnel;

(b) the possible ramifications for patient specimen testing are considered by the Licensee; and

(c) the appropriate corrective and preventive actions are taken to address and rectify the underlying cause for the unacceptable quality control results.

5.7 The Licensee shall ensure that the potency and reliability of reagents used in its provision of PGT-M or PGT-SR shall be tested for acceptable reactivity on each day of use, or as specified by the manufacturer's instruction for use, whichever is applicable, prior to the reporting of any patient results.

5.8 The Licensee shall ensure that all errors or issues detected prior to the conduct of any testing of patient specimens in its provision of PGT-M or PGT-SR are resolved in a timely manner.

External Quality Assessment ("EQA") Programme

5.9 The Licensee shall ensure that samples of a PGT-M or PGT-SR test used for EQA:

(a) are not treated differently from patient samples; and

(b) are processed and tested in accordance with the established standard operating procedures ("**SOPs**") and by the same personnel who performs that test.

5.10 Where commercial EQA programmes for a test method are unavailable, the Licensee shall ensure that its performance of PGT-M or PGT-SR is evaluated by other appropriate and equivalent methods of EQA[3].

5.11 The Licensee shall review all EQA programme results in relation to its provision of PGT-M or PGT-SR, and in the event that unacceptable results are disclosed (including results not graded by an EQA provider), the Licensee shall:

(a) ensure that the unacceptable results are investigated to identify all possible causal factors;

(b) implement the appropriate and effective corrective and preventive actions; and

(c) review the impact of any causal factors identified in paragraph 5.11(a) on the reliability of patients' results reported during the affected period.

5.12 The Licensee shall ensure that all EQA programme reports and, where applicable, investigation reports, in relation to its provision of PGT-M or PGT-SR, shall be reviewed by its CGO or any other suitably qualified personnel designated by the CGO.

5.13 The Licensee shall ensure that maintains an audit trail at each critical step of analysis in its provision of PGT-M or PGT-SR. These critical steps include but are not limited to:

(a) specimen verification;

(b) determination of specimen quality (e.g. extracted DNA, embryonic tissue);

(c) quality control for mutation detection;

(d) quality checks for biparental inheritance, exogenous contamination and allele dropout;

(e) checks on the run parameters of the tests where applicable;

(f) verification at all sample transfer steps; and

(g) delivery of test report, which entails verification and interpretation of test results, results transfer, and the preparation, review and approval of the report in accordance with paragraphs 8.1 and 8.2 below.

5.14 The Licensee shall establish a process for reviewing and informing the Ministry of Health of any possible errors in its processes relating to its provision of PGT-M or PGT-SR, including but not limited to any incidental

[3] Examples of other appropriate and equivalent methods of EQA include but are not limited to inter-laboratory comparison, method comparison or split sample testing.

findings of non-maternity, non-paternity or non-familial in biopsied embryos.

6 Facilities and Equipment

6.1 The Licensee shall ensure that it takes adequate measures to eliminate or minimise the risk of contamination of its PGT-M or PGT-SR, including but not limited to the following:

(a) physical segregation within its approved permanent premises where PGT-M or PGT-SR is provided in, from other parts of the premises (e.g. DNA or molecular laboratory) that handles other biological samples or genomic DNA; and

(b) performing PGT-M or PGT-SR in an area within its approved permanent premises which is dedicated solely for single cell analysis.

6.2 The Licensee shall ensure that there is a contingency plan to carry out the PGT-M or PGT-SR tests in the event of any equipment failure immediately before or during the performance of the PGT-M or PGT-SR test.

7 Testing

7.1 The Licensee shall ensure that it has procedures in place to minimise the occurrence of DNA contamination from external sources in Polymerase Chain Reaction (PCR)-based PGT-M tests.

8 Test Reports

8.1 The Licensee shall ensure that each of its final PGT-M or PGT-SR test reports includes:

(a) results interpretation, including incidental findings of any chromosomal abnormality discovered from a PGT-SR test (including the chromosome number and type of chromosomal abnormality, which should be stated in the report only where both the patient and her husband had expressly indicated a wish for incidental findings to be reported);

(b) test limitations; and

(c) recommendation for genetic counselling by qualified personnel and further tests, where appropriate.

8.2 The Licensee shall ensure that the following information is **excluded** from any of its PGT-M or PGT-SR final reports, and is not disclosed (whether verbally or in writing) to any of the personnel of the AR Service Licensee

described in paragraph 3.3(a) above, the patient, her husband or any other unauthorised parties:

(a) sex of the tested embryo, unless the AR Service Licensee has obtained DGH's prior written approval; and

(b) other genetic traits which are not related to the inheritable condition at paragraph 3.1 above, except for incidental findings of any chromosomal abnormality detected from a PGT-SR test.

9 Reporting to DGH

9.1 The Licensee shall furnish to DGH such information as DGH may from time to time require regarding its provision of PGT-M or PGT-SR.

ANNEX A

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. Breast-ovarian cancer, familial, susceptibility to, 4 (*RAD51D*)
6. Facioscapulohumeral muscular dystrophy 1 (FSHD1)
7. Familial adenomatous polyposis 1 (*APC*)
8. Hereditary Pancreatitis (*PRSS1*-related highly penetrant pathogenic variants only i.e. p.Asn29Ile and p.Arg122His)
9. Huntington disease (HTT)
10. *INS*-related permanent neonatal diabetes
11. Li-Fraumeni syndrome (TP53)
12. Lynch syndrome 2 (MLH1)
13. Maple Syrup Urine Disease (MSUD)
14. Marfan syndrome (FBN1)
15. Multiple endocrine neoplasia, type 1 (MEN1)
16. Multiple endocrine neoplasia, type 2A (*RET*)
17. Myotonic dystrophy, type 1 (*DMPK*)
18. Osteogenesis Imperfecta, type I (*COL1A1*)
19. Osteogenesis imperfecta, type V (*IFITM5*)
20. *PALB2*-cancer predisposition syndrome (*PALB2*)
21. *Plakophilin-2* (*PKP2*) (to exclude embryos affected with 2 pathogenic *PKP2* gene variants)
22. Polycystic kidney disease 1 (*PKD1*)
23. Polycystic kidney disease 2 (*PKD2*)
24. Rhabdoid tumor predisposition syndrome 1 (*SMARCB1*)
25. Spinocerebellar ataxia, type 2 (*ATXN2*)
26. Spinocerebellar ataxia, type 3 (*ATXN3*)
27. *STAT3* Hyper IgE Syndrome (*STAT3*-HIES)
28. Tuberous sclerosis 2 (*TSC2*)
29. Von Hippel-Lindau Syndrome *(VHL)*

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II. Autosomal Recessive Conditions

30. Adrenal hyperplasia, congenital, 1 (*CYP21A2*)
31. Alkuraya-Kucinskas syndrome (*KIAA1109*)
32. 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**)
33. Autosomal Recessive Alport Syndrome (ARAS) (*COL4A4*)
34. Autosomal Recessive Congenital Titinopathy (*TTN*)
35. Autosomal Recessive Polymicrogyria (*ADGRG1*)
36. Bardet Biedl syndrome, *BBS2*-related
37. Beta-thalassemia (*HBB*)
38. 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
39. Ceroid lipofuscinosis, neuronal, 1 (*PPT1*)
40. Developmental and Epileptic Encephalopathy 44 (DEE 44), UBA5 gene
41. Ehlers-Danlos syndrome, kyphoscoliotic type, 1 (*PLOD1*)
42. Galactosemia 1 / classical galactosemia (*GALT*)
43. Gaucher disease, type 1 (*GBA*)
44. Glycogen storage disease II, classical infantile form / Pompe disease (*GAA*)
45. Harlequin ichthyosis (*ABCA12*)
46. Herlitz junctional epidermolysis bullosa (*LAMB3*)
47. Infantile osteopetrosis, autosomal recessive 1 (*TCIRG1*)
48. Leber Congenital Amaurosis 9 (LCA9)
49. Leigh Syndrome (Infantile Subacute Necrotising Encephalopathy) due to mitochondrial complex IV deficiency *(SURF1)*
50. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (*HADHA*)
51. *MANBA*-related Mannosidosis beta
52. Matthew Wood syndrome / Microphthalmia, syndromic 9 (*STRA6*)
53. Meckel Syndrome, Type 6 / Joubert syndrome 9 *(CC2D2A)*
54. Netherton syndrome (*SPINK5*)
55. Pierson syndrome (*LAMB2*)
56. Pontocerebellar hypoplasia type 7 (PCH7)
57. Pseudo-TORCH syndrome 1 (*OCLN*)
58. Renal Tubular Dysgenesis *(REN)*
59. Renal tubular dysgenesis (*AGT*-related)
60. Sensenbrenner syndrome / Cranioectodermal dysplasia 1 (*IFT122*)

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61. Short-rib thoracic dysplasia 3 with or without polydactyly (*DYNC2H1*)
62. Sickle Cell Anaemia (*HBB)*
63. Spinal muscular atrophy, Type 1 and Type 2 (*SMN1*)
64. Sulfite oxidase deficiency, isolated (*SUOX*)
65. Wolcott-Rallison syndrome (*EIF2AK3*)

III. X-linked Conditions

66. Agammaglobulinemia, X-linked 1 (*BTK*)
67. Coffin-Lowry syndrome (*RPS6KA3*)
68. Duchenne/Becker muscular dystrophy (*DMD*)
69. Fabry disease, classic form (*GLA*)
70. Fragile X syndrome (*FMR1*)
71. Hemophilia A (*F8*)
72. Hemophilia B (*F9*)
73. Hydrocephalus, X-linked / MASA syndrome (*L1CAM*)
74. Incontinentia pigmenti / Bloch-Sulzberger syndrome (*IKBKG*)
75. Kennedy's disease (*AR*) (alleles with more than or equal to 38 CAG repeats only)
76. Lowe oculocerebrorenal syndrome (*OCRL*)
77. Ocular albinism (*GPR143*)
78. Severe combined immunodeficiency (*IL2RG*)
79. *WAS*-related disorder
80. X-linked hypophosphatemia (XLH)

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;3)(p34;p21)

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7. t(1;4)(p31;q33)
8. t(1;4)(q43;q23)
9. t(1;6)(q25;p22.1)
10. t(1;7)(p36.1;p15.1)
11. t(1;8)(q43;q22.3)
12. t(1;9)(p10;p10)
13. t(1;9)(p10;q10)
14. t(1;10)(p32;q11.2)
15. t(1;11)(p13.3;q21)
16. t(1;13)(p12;q14.1)
17. t(1;15)(p.34.1-34.2;q24)
18. t(1;16)(q12;q24)
19. t(1;16)(q23~24;p12)
20. t(1;19)(p36.2;p13.2)
21. t(2;3)(q37.1;p21.3)
22. t(2;5;14)(p23;q31.1;q32.2)
23. t(2;7)(q33;p13)
24. t(2;8)(q35;q22.3)
25. t(2;10)(q12;q24.3)
26. t(2;11)(q35;q21)
27. t(2;11)(q37.1;q23.1)
28. t(2;12)(q13;q15)
29. t(2;15)(p13;q22-24)
30. t(2;19)(q14.1;p13.3)
31. t(2;19)(q32.1;q13.4)
32. t(3;4)(q25.3;q21.2)
33. t(3;9)(q21;q22.3)
34. t(3;15)(p10;p10)
35. t(3;17)(q21;p13)
36. t(4;7)(p14;p11.2)
37. t(4;7)(p16.3;p22.1)
38. t(4;8)(q22;p23.2)
39. t(4;9)(p16.3;p13)
40. t(4;15)(q12;q13)
41. t(4;15)(q12;q15)
42. t(4;16)(p15.3;p13.3)
43. t(5;7)(p12;q31.3)

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44. t(5;8)(q23.3;q23)
45. t(5;9)(p13;p22)
46. t(5;11)(q31.1,q21)
47. t(5;20)(p15.2;q13.3)
48. t(6;7)(q25.3;q32)
49. t(6;13)(q14;q32)
50. t(6;17)(q22.3;q24)
51. t(6;22)(p21.3;q13.1)
52. t(7;11)(p21;q23.3)
53. t(7;15)(q21.2;q25)
54. t(7;15)(q21.2;q26.1)
55. t(7;19)(p22;p13.1)
56. t(8;9)(q24.1~24.22;p22)
57. t(8;11)(p11.2;q13.3)
58. t(8;12)(q23;q13.2)
59. t(8;17)(q24.21;q21.3)
60. t(8;22)(p11.2;q13.3)
61. t(10;11)(p15;p13)
62. t(11;14)(q23.1;q32.3)
63. t(11;21)(q24.2;q22.2)
64. t(11;22)(q23;q11.2)
65. t(12;15)(q15;q11.2)
66. t(12;15)(q24.1;q26.1)
67. t(12;22)(p11.2;q11.2)
68. t(16;17)(q23;q12)
69. t(Y;9)(q12;q21.12)

III. Inversions

70. inv(1)(p36.1q42.3)
71. inv(2)(p11q13)
72. inv(8)(p11.2q22.1)
73. inv(9)(p12;q13)
74. inv(10)(p15q11.2)
75. inv(11)(p15.4;q24)
76. inv(13)(p11.2q14.1)

IV. Miscellaneous

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

77. mos del(11)(q14.2q23.2)
78. del(22)(q11.2q11.2)
79. del(X)(q21.2q26)
80. del(X)(q25q28)
81. der(14;15)(q10;q10)
82. der(15)t(Y;15)(q12;p11.2)
83. dic(12;22)(p11;p13), der(21)t(12;21)(p11;q10)
84. dup(X)(q13.1q21.1)
85. mos dup(8)(q24.13q24.3)
86. mos X/XY
87. mos X/XX
88. mos X/XXX/XX
89. mos XXXXX/XX