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Comprehensive preimplantation genetic detection kit (high-throughput sequencing)

胚胎植入前遗传学一体化检测试剂盒（高通量测序法）

(English Translation)

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Contents

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Foreword

This document is drafted in accordance with the rules set forth in the GB/T 1.1-2020 *Directives for Standardization -- Part 1: Rules for the Structure and Drafting of Standardizing Documents*.

This document was proposed by Shandong University.

This document was prepared by the Guangdong-Hong Kong-Macao Greater Bay Area Standards Innovation Alliance.

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This is the first release.

Introduction

Comprehensive Preimplantation Genetic Testing (PGT) has emerged in recent years and increasingly been implemented in clinical practice. This technology enables the detection of various types of genetic abnormalities for embryos in one test, preventing the implantation of abnormal embryos. Therefore, it can effectively prevent birth defects attributed to chromosomal aneuploidy, monogenic genetic diseases, and chromosomal structural rearrangements, demonstrating significant clinical value and substantial social benefits.

At present, comprehensive PGT technology has advanced considerably, while unified standards of detection kits deriving from this technology remain outstanding. Therefore, to standardize and promote the clinical implementation of comprehensive PGT detection kits, this document is formulated to define the scope, terms, definitions, technical requirements, testing methods, and other particulars. The aim is to facilitate the standardized application of related products, establish well-regulated industrial solutions, and provide clear guidance for clinical users and developers in the field. Ultimately, this initiative seeks to enhance the quality of medical testing.

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Comprehensive preimplantation genetic detection kit (high-throughput sequencing)

1 Scope

This document specifies the terms, definitions, technical requirements, testing methods, labels, instructions, packaging, transportation, and storage requirements for comprehensive preimplantation genetic detection kits (high-throughput sequencing).

This document applies to comprehensive preimplantation genetic detection kits that employ high-throughput sequencing technology to simultaneously detect various genetic abnormalities in preimplantation embryos, including chromosomal aneuploidy, large segmental deletions and duplications, monogenic diseases, and chromosomal structural rearrangements. It includes whole genome amplification, library construction, and may optionally contain high-throughput sequencing reagents. For kits that do not include high-throughput sequencing reagents, manufacturers must specify compatible high-throughput sequencing kits. This document is applicable to comprehensive PGT detection kits that utilize high-throughput sequencing, which is based on single-nucleotide polymorphism (SNP) genotyping, for detecting chromosomal aneuploidy, monogenic diseases, and chromosomal structural rearrangements in preimplantation embryos.

This document is neither applicable to detection kits using microarray technology and single-molecule sequencing-based kits, nor to mitochondrial genetic testing.

2 Normative references

The provisions of the following documents constitute indispensable clauses of this document through normative references in the text. Among them, for referenced documents with dates, only the edition corresponding to the dates is applicable; for referenced documents without dates, the latest edition (including any amendments) is applicable.

GB/T 191 Packaging - Pictorial marking for handling of goods
GB/T 29791.2 In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 2: In vitro diagnostic reagents for professional use
GB/T 30989—2014 Technical regulation of high-throughput gene sequencing
YY/T 1657—2019 Preimplantation chromosomal aneuploidy detection kits (Sequencing).

3 Terms and definitions

The following terms and definitions are applicable to this document.

3.1
preimplantation genetic testing for aneuploidies

Prior to embryo transferred into the uterine cavity, 22 pairs of autosomes and one pair of sex chromosomes are analyzed to determine chromosomal numerical status and copy number variants of biopsied embryonic cells.

3.2
preimplantation genetic testing for monogenic diseases

Prior to embryo transferred into the uterine cavity, specific genetic variants associated with monogenic diseases are analyzed to determine the genetic mutation status of embryonic cells.

3.3
preimplantation genetic testing for structural rearrangements

Prior to embryo transferred into the uterine cavity, chromosomal structure analysis is performed to determine chromosomal structural rearrangements in embryonic cells.

3.4
effective reads

The data obtained from high-throughput sequencing undergo quality control and unique alignment to the reference genome sequence. After this processing, the number of analyzable sequences (reads) constitutes the effective reads.

The number of high-throughput sequencing reads can be used to align to the reference genome sequence uniquely after data quality control.
Note: In this document, the unit for effective reads is denoted as 'M', where 1M represents 1,000,000.
[Source: YY/T 1657-2019, Preimplantation chromosomal aneuploidy detection kits (Sequencing), Section 3.2]

3.5
genome coverage

The proportion of the reference genome's physical length covered by effective reads obtained through high-throughput sequencing relative to the total length of the reference genome.

Genome coverage is termed as the proportion of physical length of effective reads to the total length of the reference genome by high-throughput sequencing.
[Source: YY/T 1657-2019, Preimplantation chromosomal aneuploidy detection kits (Sequencing), Section 3.3)

3.6
copy number variation

Copy number variation is the fragment of deletions or duplications occurring in the genome.
Note: In this document, the size of abnormal fragments is denoted as ‘Mb’, where 1 Mb represents a fragment length of 1,000,000 bases.

[Source: YY/T 1657-2019, Preimplantation chromosomal aneuploidy detection kits (Sequencing), Section 3.4]

3.7
mosaicism

An individual is composed of two or more genetically distinct cell lines derived from a single fertilized oocyte.

3.8
allelic dropout rate

For non-identical homozygous loci across the whole genome sequence of both parents, the proportion of loci where one allele was expected but undetected in genotyping analysis of the embryos.

3.9
informative haplotyping loci

Informative haplotyping loci is termed as single-nucleotide polymorphism (SNP) loci that can effectively be distinguished between the two haplotypes during haplotyping analysis.

3.10
informative haplotyping window

A sequencing window contains two or more informative haplotyping loci within a 1Mb region during haplotyping analysis.

4 Abbreviations

The following abbreviations are applicable to this document:
PGT-A: preimplantation genetic testing for aneuploidies
PGT-M: preimplantation genetic testing for monogenic diseases
PGT-SR: preimplantation genetic testing for structural rearrangements

5 Technical requirements

5.1 Appearance

The product documentation shall be legible and complete, with unambiguous labels of product name, batch/lot number, and expiry date. All tubes of reagent must have intact packaging, clear labels, and no leaks or breakage.

5.2 Quality of library construction

When tested with national reference materials or company reference materials, the failure rate of the library construction kit shall not exceed 3.0%.

Note 1: The requirements of company reference materials for comprehensive preimplantation genetic detection kits are specified in Appendix A. National reference materials shall comply with officially released standards.

Note 2: For currently available national or company reference materials, the failure rate of the library construction kit shall not exceed 3.0%.

5.3 Quality control of effective reads amount and genome coverage

For PGT-A analysis, uniquely aligned effective reads shall be no less than 1M, and genome coverage shall be no less than 4%.

5.4 Quality control of informative haplotyping loci and informative haplotyping window

For PGT-M linkage analysis, a minimum of two informative haplotype loci are required within 1Mb upstream and downstream of the target gene.

For PGT-SR linkage analysis, 98% of the genome shall be covered by informative haplotype windows.

Note: Flanking regions within 1Mb of telomeres, centromeres, highly repetitive sequences, and pseudogenes are exempt. All other genomic regions should satisfy the requirements above.

5.5 Allelic dropout (ADO) rate

For PGT-M or PGT-SR linkage analysis, the ADO rate shall not exceed 10%.

5.6 Concordance rate of reference materials tested for PGT-A, PGT-M, and PGT-SR

When tested using national or manufacturer’s reference materials, the kit must meet the following:

PGT-A: detect chromosomal aneuploidy or CNVs ≥4Mb;

PGT-M: detect haplotypes carrying pathogenic variants;

PGT-SR: detect haplotypes carrying structural rearrangements;

Negative controls: yield negative results.

The concordance rate shall be 100% for all types of reference materials described above.

5.7 Concordance rate of reference materials with mosaicism

When tested using national or manufacturer’s reference materials with mosaicism, the detection rate shall meet the following:

Reference materials with a mosaic level of 30%, the detection rate shall be more than 30%;

Reference materials with a mosaic level of 70%, the detection rate shall be more than 60%.

5.8 Concordance rate of reference materials with triploidy

When tested using national or manufacturer’s reference materials with triploidy, the detection rate shall be 100%.

5.9 Reproducibility of reference materials

Solution 1: Perform three replicated tests using the same batch of kits on national or manufacturer’s reference materials, yielded results shall meet all criteria specified in Sections 5.2~5.8.

Solution 2: Perform tests on replicated national or manufacturer’s reference materials, yielded results shall reach a 100% concordance rate.

6 Testing method

6.1 Appearance

Under natural light, the appearance of kit components shall meet the requirements given in

6.2 Quality of library construction

Quality of library construction is decided by testing the national or company reference materials and shall meet the requirements given in 5.2.

6.3 Quality control of effective reads amount and genome coverage

According to instructions of the kit, quality control of effective reads amount and genome coverage is decided by testing the national or company reference materials and shall meet the requirements given in 5.3.

6.4 Quality control of informative haplotyping loci and informative haplotyping window

According to instructions of the kit, quality control of informative haplotyping loci and informative haplotyping window is decided by testing the national or company reference materials and shall meet the requirements given in 5.4.

6.5 Allelic dropout (ADO) rate

According to instructions of the kit, allelic dropout (ADO) rate is decided by testing the national or company reference materials and shall meet the requirements given in 5.5.

6.6 Concordance rate of reference materials tested for PGT-A, PGT-M, and PGT-SR

According to instructions of the kit, concordance rate of reference materials tested for PGT-A, PGT-M, and PGT-SR is decided by testing the national or company reference materials and shall meet the requirements given in 5.6.

6.7 Concordance rate of reference materials with mosaicism

According to instructions of the kit, concordance rate of reference materials with mosaicism is decided by testing the national or company reference materials and shall meet the requirements given in 5.7.

6.8 Concordance rate of reference materials with triploidy

According to instructions of the kit, concordance rate of reference materials with triploidy is decided by testing the national or company reference materials and shall meet the requirements given in 5.8.

6.9 eproducibility of reference materials

According to instructions of the kit, reproducibility of reference materials is decided by conducting three replicated tests using the same batch of kits on national or company reference materials, or conducting tests on replicated national or manufacturer’s reference materials, and shall meet the requirements given in 5.9.

7 Labels and Instructions for Use

Compliance with the regulation of GB/T 29791.2.

8 Packaging, Transportation, and Storage

8.1 Packaging

Symbols for packaging, transportation, and storage must conform to regulations of GB/T 191. Packaging containers shall maintain well sealed, complete, no leaks, and no breakage.

8.2 Transportation

Reagent kits shall be transported in strict compliance with the manufacturer's specifications. The following protective measures should be adopted: moisture-resistant containment, prohibition of compressive loading, protection against UV radiation and precipitation, isolation from corrosive agents such as acidic/alkaline, and integrity maintenance of both inner and outer packaging.

8.3 Storage

Maintain storage conditions as specified in the manufacturer's recommendations.

Appendix A
(Informative)
Manufacturer’s reference materials documentation for comprehensive preimplantation genetic testing

【Development Institution】Shandong University
【Batch No.】SDU-YTH-202410
【Appearance】Colorless liquid (gDNA sample)
【Intended Use】These reference materials represent the first batch developed, which are derived from gDNA extracted from human whole blood and products of conception. Its intended applications include performance evaluation of comprehensive preimplantation genetic testing (PGT) technologies. In addition, it is also applicable for individual evaluation of chromosomal aneuploidy detection (PGT-A), monogenic diseases detection (PGT-M), and structural rearrangements detection (PGT-SR). It is certified for whole genome amplification (WGA) followed by next-generation sequencing (NGS). (Note: Users employing alternative methodologies must independently validate their suitability.)
【Composition & Specifications】Aliquoted in 2.5 μL/tube, 30 tubes/set, including: seven tubes of mimic whole-genome DNA samples (250 pg/μL), twenty-one tubes of mimic embryonic cell DNA (20 pg/μL), and two tubes of blank controls (PBS). Detailed specifications are provided in Table A.1.

Table A.1 Composition of the reference materials for comprehensive preimplantation genetic testing

No.	Type of specimen	Type of reference materials	Genetic constitutions	Remark
1	Mimic embryonic DNA	Negative reference materials	46,XX	-
2	Mimic embryonic DNA	Replicated reference materials	46,XX	Replicate of sample No.1
3	Mimic embryonic DNA	Replicated reference materials	46,XX	Replicate of sample No.1
4	Mimic embryonic DNA	Negative reference materials	46,XX	-
5	Mimic embryonic DNA	Negative reference materials	46,XX	-
6	Mimic embryonic DNA	Reference materials for PGT-A	47,XY,+15	-
7	Mimic embryonic DNA	Replicated reference materials	47,XY,+15	Replicate of sample No.6
8	Mimic embryonic DNA	Replicated reference materials	47,XY,+15	Replicate of sample No.6
9	Mimic embryonic DNA	Reference materials	47,XX,+21	-

		for PGT-A		
10	Mimic embryonic DNA	Reference materials for PGT-A	47,XX,+11	-
11	Mimic embryonic DNA	Reference materials for PGT-A	seq[GRCh37]del(13)(q33.3q34) chr13:g.109370001_115070000del	5.7 Mb
12	Mimic embryonic DNA	Reference materials for PGT-A	seq[GRCh37]del(X)(p21.1p11.4) chrX:g.35760001_41460000del	5.7 Mb
13	Mimic embryonic DNA	Reference materials for PGT-A	seq[GRCh37]del(X)(p11.4p11.3) chrX:g.39960001_44010000del	4.05 Mb
14	Mimic gDNA from peripheral blood	Reference materials for PGT-SR	46,XY	Paternal father
15	Mimic gDNA from peripheral blood	Reference materials for PGT-SR	46,XX,t(4;12)(p12;q23)	Paternal mother
16	Mimic gDNA from peripheral blood	Reference materials for PGT-SR	46,XY,t(4;12)(p12;q23)	Paternal
17	Mimic gDNA from peripheral blood	Reference materials for PGT-SR	46,XX	Maternal
18	Mimic embryonic DNA	Reference materials for PGT-SR	46,XX, non-carrier	Sample pending testing
19	Mimic gDNA from peripheral blood	Reference materials for PGT-M	*GJB2*(NM_004004.6) c.299_300del, heterozygous	Mother of the proband
20	Mimic gDNA from peripheral blood	Reference materials for PGT-M	*GJB2*(NM_004004.6) c.94C>T, heterozygous	Father of the proband
21	Mimic gDNA from peripheral blood	Reference materials for PGT-M	*GJB2*(NM_004004.6) c.299_300del and c.94C>T, compound heterozygous	Proband
22	Mimic embryonic DNA	Reference materials for PGT-M	*GJB2*(NM_004004.6) c.299_300del, heterozygous	Sample for measurement
23	Mimic embryonic DNA	Reference materials with mosaicism	seq(X)×1[0.7],(15)×3[0.3]	Sample with mosaicism
24	Mimic embryonic DNA	Reference materials with mosaicism	seq(X)×1[0.7],(14)×3[0.3]	Sample with mosaicism
25	Mimic embryonic DNA	Reference materials with mosaicism	seq(15)×3[0.3],(21)×3[0.7]	Sample with mosaicism
26	Mimic embryonic DNA	Reference materials with triploidy	69,XXY	Triploidy
27	Mimic embryonic DNA	Reference materials for PGT-A	47,XX,+22	-
28	Mimic embryonic DNA	Reference materials for PGT-A	47,XX,+18	-
29	Blank control		Blank control	-
30	Blank control		Blank control	-

Note: The manual of reference materials is revised per batch/lot when necessary.

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