A Sysmex Group Company

CytoCell

Instructions For Use (IFU)

REF: CE-LPA 003-S / CE-LPA 003

Prenatal 13 and 21 Enumeration Probe Kit

CE IVD
2797

UK CA

PROFESSIONAL USE ONLY

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Intended Purpose

The CytoCell® Prenatal 13 and 21 Enumeration Probe Kit is a qualitative, non-automated, fluorescence *in situ* hybridisation (FISH) test used to detect the chromosome 13q14.2 region and the chromosome 21q22.1 region in Carnoy's solution (3:1 methanol/acetic acid) fixed cells derived from amniotic fluid samples, in enumerating chromosomes 13 and 21 in high-risk pregnancies where Down or Patau syndrome are suspected.

Indications for use

This device is designed as an adjunct to other clinical and laboratory tests in recognised diagnostic and clinical care pathways, such as ultrasound screening and biochemical testing, where knowledge of the copy number status of the chromosome 13q14.2 region and the chromosome 21q22.1 region would be important for patient management.

Limitations

This device is designed to detect chromosomal material which includes the chromosome 13q14.2 and chromosome 21q22.1 regions covered by the green and orange clones in this probe set respectively. Genomic gains or losses outside these regions, or partial losses or gains of these regions may not be detected with this device.
This device is not intended for: use as a stand-alone diagnostic, use as a companion diagnostic, population-based screening, near-patient testing, or self-testing, and has not been validated for sample types, disease types, or purposes outside of those stated in the intended purpose.
This device is intended as an adjunct to other diagnostic laboratory tests and therapeutic action should not be initiated on the basis of the FISH result alone.
Reporting and interpretation of FISH results should be performed by suitably qualified staff, consistent with professional standards of practice, and should take into consideration other relevant test results, clinical and diagnostic information.
This device is intended for laboratory professional use only.
Failure to adhere to the protocol may affect the performance and lead to false positive/negative results.

Principles of the Test

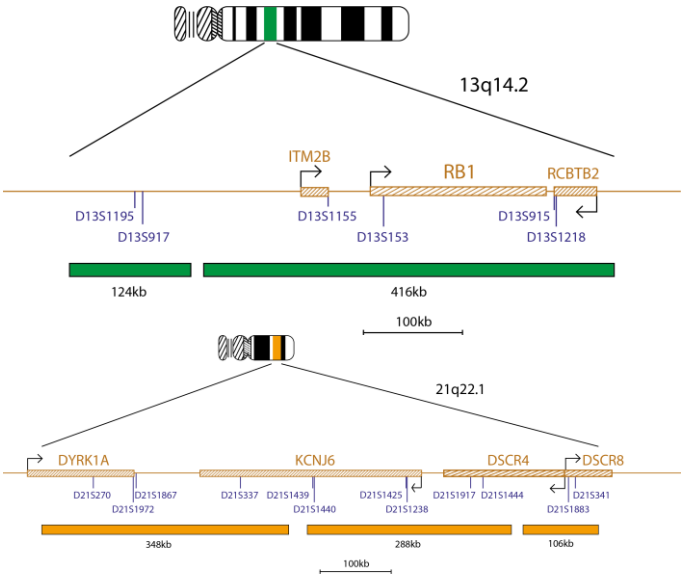
Fluorescence *in situ* hybridisation (FISH) is a technique that allows DNA sequences to be detected on metaphase chromosomes or in interphase nuclei from fixed cytogenetic samples. The technique uses DNA probes that hybridise to entire chromosomes or single unique sequences, and serves as a powerful adjunct to G-banded cytogenetic analysis. This technique can now be applied as an essential investigative tool within prenatal, haematological and solid tumour chromosomal analysis. Target DNA, after fixation and denaturation, is available for annealing to a similarly denatured, fluorescently labelled DNA probe, which has a complementary sequence. Following hybridisation, unbound and non-specifically bound DNA probe is removed and the DNA is counterstained for visualisation. Fluorescence microscopy then allows the visualisation of the hybridised probe on the target material.

Probe Information

Down Syndrome (DS) is an autosomal trisomy that is caused by the presence of a third (partial or total) copy of chromosome 21 and is characterised by variable intellectual disability, muscular hypotonia, and joint laxity, often associated with a characteristic facial dysmorphism and various anomalies such as cardiac, gastrointestinal, neurosensorial or endocrine defects[1,2]. DS is one of the leading causes of intellectual disability worldwide and these patients also face various health issues including learning and memory, congenital heart diseases (CHD), Alzheimer's diseases (AD), leukaemia, cancers and Hirschsprung disease (HD)[1]. DS has high genetic complexity and phenotype variability[1]. At 16 weeks gestation of pregnancy, the incidences of DS pregnancies are 1 in 1050 for mothers aged 20 years, 1 in 620 for mothers aged 30 years and 1 in 70 for mothers aged 40 years[3]. Patau Syndrome (PS) is a chromosomal anomaly caused by the presence of an extra chromosome 13 and is characterised by brain malformations (holoprosencephaly), facial dysmorphism, ocular anomalies, postaxial polydactyly, visceral malformations (cardiopathy) and severe psychomotor retardation[2]. PS is associated with phenotypic holoprosencephaly and midline fusion abnormalities due to defective fusion of the prechordal mesoderm in the embryonic stage[4]. At 16 weeks gestation of pregnancy, the incidence of PS pregnancies are 1 in 11 000 for mothers aged 20 years, 1 in 6500 for mothers aged 30 years and 1 in 700 for mothers aged 40 years[3].

Probe Specification

13 unique sequence, 13q14.2 Green
21 unique sequence, 21q22.1 Orange



The green probe mix contains a 124kb probe and a 416kb probe that spans the *ITM2B*, *RB1* and *RCBTB2* genes. The orange probe mix covers a region on 21q22.1 from the *DYRK1A* gene to the *DSCR8* gene.

Materials Provided

Probe: 50µl per vial (5 tests) or 100µl per vial (10 tests).
The probes are provided premixed in hybridisation solution (<65% formamide; <20mg dextran sulfate; <10% of 20x saline-sodium citrate (SSC)) and are ready to use.

Counterstain: 150µl per vial (15 tests)
The counterstain is DAPI Antifade ES (0.125µg/ml DAPI (4,6-diamidino-2-phenylindole) in glycerol-based mounting medium).

Warnings and Precautions

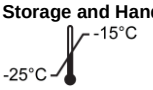
1. For *in vitro* diagnostic use. For laboratory professional use only.
2. Probe mixtures contain formamide, which is a teratogen; do not breathe fumes or allow skin contact. Handle with care; wear gloves and a lab coat.
3. Handle DAPI with care; wear gloves and a lab coat.
4. Do not use if the vial(s) are damaged, or the vial contents are compromised in any way.
5. Follow local disposal regulations for your location along with recommendations in the Safety Data Sheet to determine the safe disposal of this product. This also applies to damaged test kit contents.
6. Dispose of all used reagents and any other contaminated disposable materials following procedures for infectious or potentially infectious waste. It is the responsibility of each laboratory to handle solid and liquid waste according to their nature and degree of hazardousness and to treat and dispose of them (or have them treated and disposed of) in accordance with any applicable regulations.
7. Operators must be capable of distinguishing the colours red, blue, and green.
8. Failure to adhere to the outlined protocol and reagents may affect the performance and lead to false positive/negative results.
9. The probe should not be diluted or mixed with other probes.
10. Failure to use 10µl of probe during the pre-denaturation stage of the protocol may affect the performance and lead to false positive/negative results.

11. All products should be validated before use.
12. Internal controls should be carried out by using unaffected cell populations in testing samples.

Temperature Definitions

- -20°C / Frozen / In the Freezer: -25°C to -15°C
- 37°C: +37°C ± 1°C
- 72°C: +72°C ± 1°C
- 75°C: +75°C ± 1°C
- Room Temperature (RT): +15°C to +25°C

Storage and Handling



The kit should be stored between -25ºC to -15ºC in a freezer until the expiry date indicated on the kit label. The probe and counterstain vials must be stored in the dark.

The FISH probe, DAPI Antifade ES counterstain, and Hybridisation Solution remain stable throughout the freeze-thaw cycles experienced during normal use (where one cycle constitutes the vial's removal from and replacement into the freezer) - 5 cycles for the 50µl (5 tests) vial of FISH probe, 10 cycles for the 100µl (10 tests) vial of FISH probe, and 15 cycles for the 150µl (15 tests) vial of counterstain. Exposure to light should be minimised and avoided wherever possible. Store components in the light proof container provided. Components used and stored under conditions other than those stated on the labelling may not perform as expected and may adversely affect the assay results. All efforts must be made to limit exposure to light and temperature changes.

Equipment and Materials Necessary but not Supplied

Calibrated equipment must be used:

1. Hotplate (with a solid plate and accurate temperature control up to 80ºC)
2. Calibrated variable volume micropipettes and tips range 1µl - 200µl
3. Water bath with accurate temperature control at 37ºC and 72ºC
4. Microcentrifuge tubes (0.5ml)
5. Fluorescence microscope (Please see Fluorescence Microscope Recommendation section)
6. Phase contrast microscope
7. Clean plastic, ceramic or heat-resistant glass Coplin jars
8. Forceps
9. Calibrated pH meter (or pH indicator strips capable of measuring pH 6.5 – 8.0)
10. Humidified container
11. Fluorescence grade microscope lens immersion oil
12. Bench top centrifuge
13. Microscope slides
14. 24x24mm coverslips
15. Timer
16. 37ºC incubator
17. Rubber solution glue
18. Vortex mixer
19. Graduated cylinders
20. Magnetic stirrer
21. Calibrated thermometer

Optional Equipment not Supplied

1. Cytogenetic drying chamber

Reagents Needed but not Supplied

1. 20x saline-sodium citrate (SSC) Solution
2. 100% Ethanol
3. Tween-20
4. 1M Sodium hydroxide (NaOH)
5. 1M Hydrochloric acid (HCl)
6. Purified water

Fluorescence Microscope Recommendation

Use a 100-watt mercury lamp or equivalent and oil immersion plan apochromat objectives 60/63x or 100x for optimal visualisation. The fluorophores used in this probe set will excite and emit at the following wavelengths:

Fluorophore	$Excitation_{max}$ [nm]	$Emission_{max}$ [nm]
Green	495	521
Orange	551	572

Ensure appropriate excitation and emission filters that cover the wavelengths listed above are fitted to the microscope. The triple bandpass filter DAPI/FITC/TRITC is optimal for viewing the green and orange fluorophores as well as counterstain simultaneously. The triple bandpass filter DAPI/FITC/Texas Red can also be used to view both fluorophores and DAPI simultaneously.

Check the fluorescence microscope before use to ensure it is operating correctly. Use immersion oil that is suitable for fluorescence microscopy and formulated for low auto fluorescence. Avoid mixing DAPI antifade with microscope immersion oil as this will obscure signals. Follow manufacturers' recommendations in regards to the life of the lamp and the age of the filters.

Sample Preparation

The kit is designed for use on Carnoy's solution (3:1 methanol/acetic acid) fixed cells derived from amniotic fluid samples, in enumerating chromosomes 13 and 21 in high-risk pregnancies where Down or Patau syndrome are suspected, that are prepared according to the laboratory or institution guidelines. Amniotic fluid sample collection should be performed according to the laboratory or institution guidelines. Samples that appear bloody or brown should not be used, since they may contain maternal blood and may lead to false results. Prepare air dried samples on microscope slides according to standard cytogenetic procedures. The AGT *Cytogenetics Laboratory Manual* contains recommendations for specimen collection, culturing, harvesting and for slide making[5].

Solution Preparation

Ethanol Solutions

Dilute 100% ethanol with purified water using the following ratios and mix thoroughly:

- 70% Ethanol - 7 parts 100% ethanol to 3 parts purified water
- 85% Ethanol - 8.5 parts 100% ethanol to 1.5 parts purified water

Store the solutions for up to 6 months at room temperature in an airtight container.

2xSSC Solution

Dilute 1 part 20xSSC Solution with 9 parts purified water and mix thoroughly. Check pH and adjust to pH 7.0 using NaOH or HCl as required. Store the solution for up to 4 weeks at room temperature in an airtight container.

0.4xSSC Solution

Dilute 1 part 20xSSC Solution with 49 parts purified water and mix thoroughly. Check pH and adjust to pH 7.0 using NaOH or HCl as required. Store the solution for up to 4 weeks at room temperature in an airtight container.

2xSSC, 0.05% Tween-20 Solution

Dilute 1 part 20xSSC Solution with 9 parts purified water. Add 5µl of Tween-20 per 10ml and mix thoroughly. Check pH and adjust to pH 7.0 using NaOH or HCl as required. Store the solution for up to 4 weeks at room temperature in an airtight container.

Recommended Slide Pretreatment [5].

1. Immerse the slide prepared from 3:1 methanol/acetic acid-fixed cells derived from amniotic fluid samples in 2xSSC for 1 hour at 37ºC.
2. Place the slide in freshly made pepsin working solution (5mg of pepsin added to 100ml of 0.01M HCl) for 13 minutes at 37ºC.
3. Immerse the slide in phosphate buffered saline (PBS) at RT for 5 minutes.
4. Immerse the slide in post fixation solution (0.95% formaldehyde: 1.0ml of 37% formaldehyde, 0.18g of $MgCl_2$ and 39.0ml of PBS) for 5 minutes at RT.
5. Immerse the slide in PBS at RT for 5 minutes.
6. Immerse the slide in 70% ethanol at RT. Allow the slide to stand in the ethanol wash for 2 minutes.
7. Remove the slide from 70% ethanol. Repeat step 6 with 80% ethanol, followed by 100% ethanol.
8. Allow to air dry.

FISH Protocol

(Note: Ensure that exposure of the probe and counterstain to laboratory lights is limited at all times).

Slide Preparation (skip this step if the slide was pretreated according to the protocol above)

1. Spot the cell sample onto a glass microscope slide. Allow to dry. (**Optional, if using a cytogenetic drying chamber**: The chamber should be operated at approximately 25°C and 50% humidity for optimal cell sample spotting. If a cytogenetic drying chamber is not available, use a fume hood as an alternative).
2. Immerse the slide in 2xSSC for 2 minutes at room temperature (RT) without agitation.
3. Dehydrate in an ethanol series (70%, 85% and 100%), each for 2 minutes at RT.
4. Allow to dry.

Pre-Denaturation

5. Remove the probe from the freezer and allow it to warm to RT. Briefly centrifuge tubes before use.
6. Ensure that the probe solution is uniformly mixed with a pipette.
7. Remove 10µl of probe per test, and transfer it to a microcentrifuge tube. Quickly return the remaining probe to the freezer.
8. Place the probe and the sample slide to prewarm on a 37ºC (+/- 1ºC) hotplate for 5 minutes.
9. Spot 10µl of probe mixture onto the cell sample and carefully apply a coverslip. Seal with rubber solution glue and allow the glue to dry completely.

Denaturation

10. Denature the sample and probe simultaneously by heating the slide on a hotplate at 75ºC (+/- 1ºC) for 2 minutes.

Hybridisation

11. Place the slide in a humid, lightproof container at 37ºC (+/- 1ºC) overnight.

Post-Hybridisation Washes

12. Remove the DAPI from the freezer and allow it to warm to RT.
13. Remove the coverslip and all traces of glue carefully.
14. Immerse the slide in 0.4xSSC (pH 7.0) at 72ºC (+/- 1ºC) for 2 minutes without agitation.
15. Drain the slide and immerse it in 2xSSC, 0.05% Tween-20 at RT (pH 7.0) for 30 seconds without agitation.
16. Drain the slide and apply 10µl of DAPI antifade onto each sample.
17. Cover with a coverslip, remove any bubbles and allow the colour to develop in the dark for 10 minutes.

18. View with a fluorescence microscope (see **Fluorescence Microscope Recommendation**).

Procedural Recommendations

1. Baking or ageing of slides may reduce signal fluorescence.
2. Hybridisation conditions may be adversely affected by the use of reagents other than those provided or recommended by Cytocell Ltd.
3. Use a calibrated thermometer for measuring temperatures of solutions, waterbaths and incubators as these temperatures are critical for optimum product performance.
4. The wash concentrations, pH and temperatures are important as low stringency can result in non-specific binding of the probe and too high stringency can result in a lack of signal.
5. Incomplete denaturation can result in lack of signal and over denaturation can also result in non-specific binding.
6. Over hybridisation can result in additional or unexpected signals.
7. Users should optimise the protocol for their own samples prior to using the test for diagnostic purposes.
8. Suboptimal conditions may result in non-specific binding that may be misinterpreted as a probe signal.

Interpretation of Results

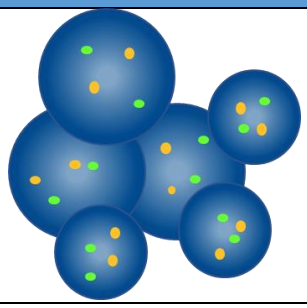
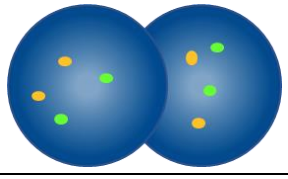
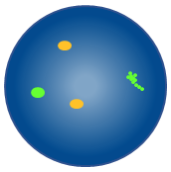
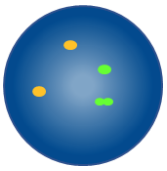
Assessing Slide Quality

The slide should not be analysed if:

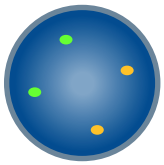
- Signals are too weak to analyse in single filters - in order to proceed with analysis, signals should appear bright, distinct and easily evaluable
- There are high numbers of clumped/overlapping cells obstructing the analysis
- >50% of the cells are not hybridised
- There is excess of fluorescent particles between cells and/or a fluorescent haze that interferes with the signals - in optimal slides the background should appear dark or black and clean
- Cell nucleus borders cannot be distinguished and are not intact

Analysis Guidelines

- Two analysts should analyse and interpret each sample. Any discrepancies should be resolved by assessment by a third analyst
- Each analyst should be suitably qualified according to recognised national standards
- Each analyst should independently score sufficient nuclei from each sample so that combined analysts' scores meet minimal criteria as specified by institutional, regional or national guidelines. The first analyst should start the analysis from the left side of the slide and the second analyst from the right.
- Each analyst should document their results in separate sheets
- Analyse only intact nuclei, not overlapped or crowded nuclei or nuclei covered by cytoplasmic debris or high degree of autofluorescence
- Avoid areas where there is excess of cytoplasmic debris or non-specific hybridisation
- Signal intensity may vary, even with a single nucleus. In such cases, use single filters and/or adjust the focal plane
- In suboptimal conditions signals may appear diffuse. If two signals of the same colour touch each other, or the distance between them is no greater than two signal widths, or when there is a faint strand connecting the two signals, count as one signal
- When analysing dual-colour breakapart probes, if there is a gap between the red and green signal no greater than 2 signals width apart, count as not rearranged/fused signal
- When analysing three-colour breakapart probes, if there is a gap between any of the 3 signals (red, green, blue) no greater than 2 signals width apart, count as not rearranged/fused signal
- If in doubt about whether a cell is analysable or not, then do not analyse it

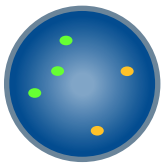
Analysis Guidelines	
	Do not count – nuclei are too close together to determine boundaries
	Do not count overlapping nuclei – all areas of both nuclei are not visible
	Count as two orange and two green signals – one of the two green signals is diffuse
	Count as two orange and two green signals – the gap in one green signal is less than two signal widths

Expected Normal Signal Pattern

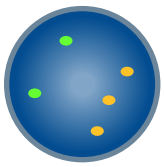


In a normal cell, two green and two orange (2G2O) are expected.

Expected Abnormal Signal Pattern(s)



In a cell with trisomy 13, three green and two orange signals (3G2O) will be expected.



In a cell with trisomy 21, two green and three orange signals (2G3O) will be expected.

Other signal patterns are possible in aneuploid/unbalanced specimens.

Known Relevant Interferences / Interfering Substances

No known relevant interferences / interfering substances.

Known Cross-Reactivity

No known cross-reactivity.

Serious Incident Reporting

For a patient/user/third party in the European Union and in countries with identical regulatory regime (Regulation (EU) 2017/746 on *In vitro* Diagnostic Medical Devices); if, during the use of this device or as a result of its use, a serious incident has occurred, please report it to the Manufacturer and to your National Competent Authority.

For serious incidents in other countries, please report it to the Manufacturer and, if applicable, to your National Competent Authority.

Manufacturer vigilance contact: vigilance@ogt.com

For EU National Competent Authorities, a list of vigilance contact points can be found at:

https://health.ec.europa.eu/medical-devices-sector/new-regulations/contacts_en

Specific Performance Characteristics

Analytical Specificity

Analytical specificity is defined as the percentage of signals that hybridise to the correct locus and no other location. Four chromosomal loci in each of 20 metaphase cells from five samples were analysed, giving 400 data points. The location of each hybridised probe was mapped and the number of metaphase chromosome FISH signals that hybridised to the correct locus was recorded.

The analytical specificity of each probe in the kit was calculated as the number of metaphase chromosome FISH signals hybridised to the correct locus divided by the total number of metaphase chromosome FISH signals hybridised, this result was multiplied by 100, expressed as a percentage and given with a 95% confidence interval.

Table 1. Analytical Specificity for the Prenatal 13 and 21 Enumeration Probe Kit

Target	Number of metaphase chromosomes hybridised	Number of correctly hybridised loci	Analytical Specificity	95% Confidence Interval
21q22.1	200	200	100%	98.12% - 100%
13q14.2	200	200	100%	98.12% - 100%

Analytical Sensitivity

Analytical sensitivity is the percentage of scoreable interphase cells with the expected normal signal pattern. A minimum of 50 interphase cells were analysed for each of 25 fixed cell suspensions from amniotic fluid samples from karyotypically normal males or females that were confirmed as having a normal complement of chromosomes 13 and 21 by FISH or karyotype, resulting in a minimum of 1250 nuclei scored for each sample type. The sensitivity data was analysed based on the percentage of cells showing a normal expected signal pattern and expressed as a percentage with a 95% confidence interval.

Table 2. Analytical Sensitivity for the Prenatal 13 and 21 Enumeration Probe Kit

Sample Type	Sensitivity Criteria	Sensitivity Result
Amniotic fluid	>95%	96.24% (94.84-97.64%)

Characterisation of Normal Cut-off Values

The normal cut-off is defined as the percentage of cells exhibiting a false positive signal pattern at which an individual would be considered normal and not consistent with a clinical diagnosis. A minimum of 50 interphase cells were analysed for each of 25 fixed cell suspensions from amniotic fluid samples from karyotypically normal males or females that were confirmed as having a normal complement of chromosomes 13 and 21 by FISH or karyotype, resulting in a minimum of 1250 nuclei scored for each sample type.

The cut-off value was determined using the β-inverse (BETAINV) function in MS Excel. It was calculated as the percentage of interphase cells showing a false positive signal pattern using the upper bound of a one-sided 95% confidence interval of the binomial distribution in a normal patient sample.

Table 3. Characterisation of Normal Cut-off Values for the Prenatal 13 and 21 Enumeration Probe Kit

Sample Type	Cut-off Result
Amniotic Fluid	8.97%

Laboratories *must* verify cut-off values using their own data, and in accordance with any institutional, regional or professional best practice guidelines which might apply within their diagnostic setting [6,7].

Precision

The precision of this product has been measured in terms of intra-day precision (sample-to-sample), inter-day precision (day-to-day) and single-site inter-lot precision (lot-to-lot).

Three (3) samples were used to assess the precision of this product: one normal amniotic fluid, one Low Positive trisomy 13 amniotic fluid (3G2O) and one Low Positive trisomy 21 amniotic fluid (2G3O). The Low Positive amino fluid samples were contrived by using a proportion of the normal amniotic fluid sample and spiking this with a known positive amniotic fluid sample, with the aim of creating a low positive sample in the range of 2-4x cut-off.

To establish the inter-day and intra-day precision, the samples were evaluated over 10 non-consecutive dates and to establish the lot-to-lot precision, Three (3) lots of the product were evaluated on three(3) replicates of the same samples. The results were presented as the overall agreement with the predicted negative class (for the negative samples).

Table 4. Reproducibility and Precision for the Prenatal 13 and 21 Enumeration Probe Kit

Variable	Sample type	Agreement
Intra-day and inter-day precision	Amniotic fluid Negative	100%
	Amniotic fluid Low Positive Trisomy 13 (3G2O)	100%
	Amniotic fluid low Positive Trisomy 21 (2G3O)	96.7%
Lot-to-lot precision	Amniotic fluid Negative	88.9%
	Amniotic fluid Low Positive Trisomy 13 (3G2O)	100%
	Amniotic fluid low Positive Trisomy 21 (2G3O)	100%

Clinical Performance

To ensure that the product detects intended rearrangements, clinical performance was established over three studies on representative samples of the intended population for the product: Residual 3:1 methanol/acetic acid-fixed material from prenatal amniotic fluid samples. The sample size for the study was 172 specimens, with a population of 15 trisomy 13 positive and 157 trisomy 13 negative specimens, and a total of 109 trisomy 21 positive and 63 trisomy 21 negative specimens. The results were compared to the known status of the sample. The probe correctly identified the status of the samples in all instances.

The results of these tests were analysed in order to provide clinical sensitivity, clinical specificity and false positive rate (FPR) values for positive signals, using a one-dimensional approach.

Table 5. Clinical Performance for the Prenatal 13 and 21 Enumeration Probe Kit

Variable	Result
Clinical Sensitivity (true positive rate, TPR)	100.0%
Clinical Specificity (true negative rate, TNR)	100.0%
False Positive rate (FPR) = 1 – Specificity	0.00%

Summary of Safety and Performance (SSP)

The SSP shall be made available to the public via the European database on medical devices (Eudamed), where it is linked to the Basic UDI-DI.
Eudamed URL: https://ec.europa.eu/tools/eudamed
Basic UDI-DI: 50558449LPA003GL

If Eudamed is not fully functional, the SSP shall be made available to the public upon request by emailing SSP@ogt.com.

Additional Information

For additional product information, please contact the CytoCell Technical Support Department.
T: +44 (0)1223 294048
E: techsupport@cytocell.com
W: www.ogt.com

References

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3. Gardner, R. and Amor, D. Gardner and Sutherland's Chromosome Abnormalities and Genetic Counseling. 5th ed: OUP USA, 2018
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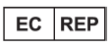
7. Wiktor AE, Dyke DLV, Stupca PJ, Ketterling RP, Thorland EC, Shearer BM, Fink SR, Stockero KJ, Majorowicz JR, Dewald GW. *Preclinical validation of fluorescence in situ hybridization assays for clinical practice*. Genetics in Medicine. 2006;8(1):16–23.

Symbols Glossary

EN ISO 15223-1:2021 - "Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements" (© International Organization for Standardization)		
Symbol	**Title**	**Reference Number(s)**
	**en:** Manufacturer	5.1.1
	**en:** Authorized representative in the European Community/European Union	5.1.2
	**en:** Use-by date	5.1.4
	**en**: Batch code	5.1.5
	**en:** Catalogue number	5.1.6
	**en:** Keep away from sunlight	5.3.2
	**en:** Temperature limit	5.3.7
	**en:** Consult instructions for use	5.4.3
 ogt.com/IFU	**en:** Consult electronic instructions for use	5.4.3
	**en:** Caution	5.4.4
	**en:** *In vitro* diagnostic medical device	5.5.1
	**en:** Contains sufficient for <n> tests	5.5.5
	**en:** Unique Device Identifier	5.7.10
EDMA symbols for IVD reagents and components, October 2009 revision		
Symbol	**Title**	**Reference Number(s)**
	**en:** Contents (or contains)	N/A

Patents and Trademarks
CytoCell is a registered trademark of Cytocell Limited.

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IFU Version History
V001.00 2023-01-11: New IFU for Regulation (EU) 2017/746.