A Sysmex Group Company

CytoCell

Instructions For Use (IFU)

REF: CE-LPH 026-S / CE-LPH 026

AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion Probe

CE IVD
2797

UK CA

PROFESSIONAL USE ONLY

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Intended Purpose

The CytoCell® AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion Probe is a qualitative, non-automated, fluorescence *in situ* hybridisation (FISH) test used to detect chromosomal rearrangements between the 21q22.1 region on chromosome 21 and the 8q21.3 region on chromosome 8 in Carnoy's solution (3:1 methanol/acetic acid) fixed haematologically-derived cell suspensions from patients with confirmed or suspected acute myeloid leukaemia (AML).

Indications for Use

This device is designed as an adjunct to other clinical and histopathological tests in recognised diagnostic and clinical care pathways, where knowledge of *AML1::ETO (RUNX1::RUNX1T1)* translocation status would be important for clinical management.

Limitations

This device is designed to detect rearrangements with breakpoints in the region covered by the red and green clones in this probe set, which includes the *AML1* and *ETO* (*RUNX1* and *RUNX1T1*) regions. Breakpoints outside this region, or variant rearrangements wholly contained within this region, may not be detected with this device.

This device is not intended for: use as a stand-alone diagnostic, use as a companion diagnostic, prenatal testing, population-based screening, near-patient testing, or self-testing.

This device has not been validated for sample types, disease types, or purposes outside of those stated in the intended purpose.

It 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

The *RUNX1* (*RUNX family transcription factor 1*) gene at 21q22.1 is fused with the *RUNX1T1* (*RUNX1 partner transcriptional co-repressor 1*) gene at Ensembl location 8q21.3, in the t(8;21)(q21.3;q22.1) translocation, found most commonly in patients with acute myeloid leukaemia (AML) FAB (French-American-British classification) type M2.

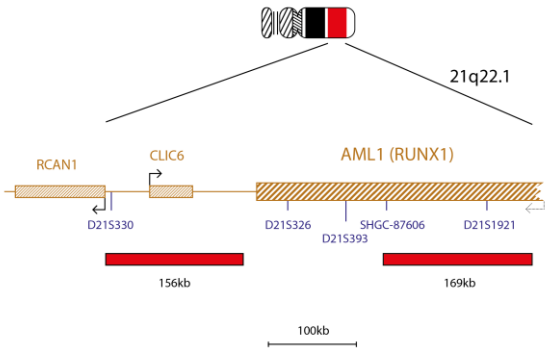
AML with a *RUNX1::RUNX1T1* fusion resulting from a t(8;21)(q21.3;q22.1) translocation is a recognised disease entity according to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia[1]. The translocation is observed in 10%-22% of patients with AML FAB type M2 and 5%-10% of AML cases overall, most commonly in children and young adults[2] and is a good prognostic indicator[3,4,5]. The t(8;21) breakpoint mainly occurs in the intron between exons 5 and 6 just before the transactivation domain and fusion protein created contains the DNA-binding domain of RUNX1 fused to the transcription factor RUNX1T1[2].

In addition to the reciprocal t(8;21) translocation creating the *RUNX1::RUNX1T1* fusion, variant translocations have also been reported. These variant rearrangements may be cryptic and easily overlooked by G-banding; however, FISH can indicate the presence of such rearrangements[2].

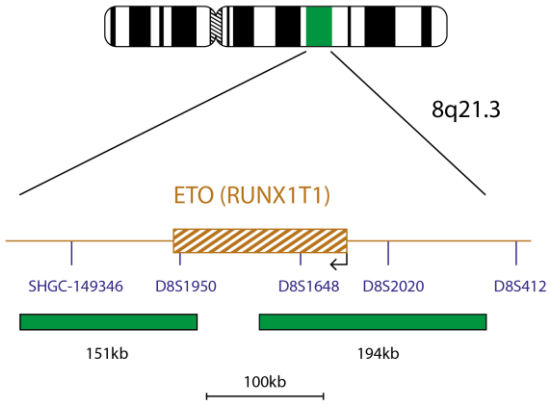
Probe Specification

AML1, 21q22.1, Red
ETO, 8q21.3, Green

CMP-H004 v006.00



CMP-H005 v005.00



The AML1 component consists of a 156kb probe, labelled in red, located centromeric to the *AML1* (*RUNX1*) gene that spans the *CLIC6* gene and a 169kb probe covering part of the *AML1* (*RUNX1*) gene, including markers SHGC-87606 and D21S1921. The ETO (RUNX1T1) component, labelled in green, consists of a 151kb probe covering the centromeric part of the gene and the flanking region and a 194kb probe covering the telomeric part of the gene and the flanking region.

Materials Provided

Probe: 50µl per vial (5 tests) or 100µl per vial (10 tests)
The probes are provided premixed in hybridisation solution (<65% formamide; <20 mg 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

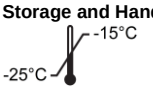
1. For *in vitro* diagnostic use. For laboratory professional use only.
2. Probe mixtures contain formamide, which is a teratogen; do not breathe fumes or allow skin contact. Handle with care; wear gloves and a lab coat.
3. Handle DAPI with care; wear gloves and a lab coat.
4. Do not use if the vial(s) 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
Red	596	615

Ensure appropriate excitation and emission filters that cover the wavelengths listed above are fitted to the microscope. Use a triple bandpass DAPI/green spectrum/red spectrum filter or a dual bandpass green spectrum/red spectrum filter for optimal simultaneous visualisation of the green and red fluorophores.

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 haematologically-derived cell suspensions from patients with confirmed or suspected acute myeloid leukaemia (AML), that are prepared according to the laboratory or institution guidelines. 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[6].

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.

FISH Protocol

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

Slide Preparation

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, water baths 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

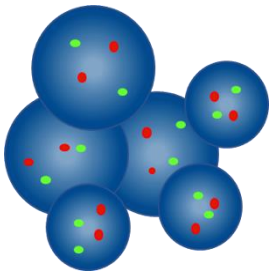
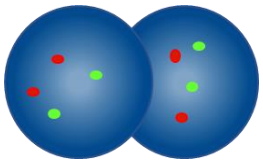
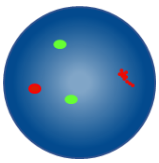
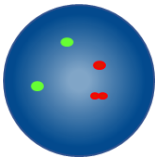
Assessing Slide Quality

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

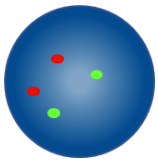
Analysis Guidelines

- 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 score independently 100 nuclei for each sample. The first analyst should start the analysis from the left side of the slide and the second analyst from the right one
- 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
- 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 red signals and two green signals – one of the two red signals is diffuse
	Count as two red signals and two green signals – the gap in one red signal is less than two signal widths

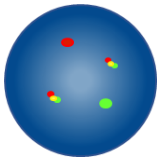
Expected Results

Expected Normal Signal Pattern



In a normal cell, two red and two green signals (2R2G) are expected.

Expected Abnormal Signal Pattern



In a cell with a t(8;21)(q21.3;q22.12) translocation, the expected signal pattern will be one red, one green and two fusions (1R1G2F).

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 the percentage of signals that hybridise to the correct locus and no other location. The analytical specificity was established by analysing a total of 400 target loci. Two chromosomal loci in each of 20 metaphase cells from 5 samples were analysed, giving 400 data points. The analytical specificity was calculated as the number of FISH signals that hybridised to the correct locus divided by the total number of FISH signals hybridised.

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 AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion Probe

Probe	Target	Number of metaphase chromo-somes hybridised	Number of correctly hybridised loci	Analytical Specificity (%)	95% Confidence Interval (%)
AML1, Red	21q22.1	200	200	100	98.12 - 100
ETO, Green	8q21.3	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 200 interphase cells were analysed for each of 25 Carnoy's solution bone marrow fixed cell suspensions that were deemed karyotypically normal, resulting in a minimum of 5000 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 AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion Probe

Number of cells with expected signal patterns	Total number of cells with scoreable signals	Analytical Sensitivity (%)	95% Confidence interval (%)
4965	5000	99.3	99.02, 99.58

Characterisation of Normal Cut-off Values

The normal cut-off value, in association with FISH probes, is the maximum percentage of scoreable interphase cells with a specific abnormal signal pattern at which a sample is considered normal for that signal pattern.

The normal cut-off value was established using samples negative for the rearrangement that the probe is intended to detect and the beta inverse function. For each sample, the signal patterns of 100 interphase nuclei were recorded by two independent analysts, totalling 200 per sample.

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 AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion Probe

Abnormal signal pattern	Number of samples analysed to generate cut-off	Number of nuclei evaluated per sample	Max. no. of false positive signal patterns	Normal cut-off value (%)
1R1G2F	1290	200	1	2.3

Laboratories must verify cut-off values using their own data[7,8].

Reproducibility

Reproducibility studies were performed to establish:

- 3-site Intra-day reproducibility (sample-to-sample)
- 3-site Inter-day reproducibility (day-to-day)
- 3-site Inter-site reproducibility (site-to-site)
- Single site Inter-lot reproducibility (lot-to-lot)

Reproducibility was established by three individual laboratories which tested six blinded samples (two negative for the rearrangement, two low positive samples which were 1 to 3 times the cut-off and two high positive samples which contained more than 45% of cells positive for the rearrangement). The analysis was conducted using two replicates of each sample over the course of five non-consecutive days.

All three sites carried out intra-day, inter-day and inter-site testing using the same lot of probe, whilst one of the sites also carried out inter-lot reproducibility using three different lots of probe.

The reproducibility was calculated using the agreement between the variables examined during each test.

Table 4. Reproducibility for the AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion Probe

Study	Criteria	Result
Intra-/Inter-Day/Inter-Site	90% Agreement Negative Class	100%
	95% Agreement High Positive Class	100%
Inter-Lot	90% Agreement Negative Class	100%
	95% Agreement High Positive Class	100%

Clinical Performance

To ensure that the AML1/ETO (RUNX1/RUNX1T1) Translocation Dual Fusion Probe detects the intended rearrangements, clinical performance was established over five studies on representative samples of the intended population for the product: residual 3:1 methanol/acetic acid-fixed material. The studies had a combined sample size of six hundred and thirty-four (634), with a total of thirty-five (35) positive and five hundred and ninety-nine (599) negative specimens in total across all sites. The concordance/discordance of results was found to meet the acceptance criteria for this study.

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 AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion Probe

Variable	Result
Clinical Sensitivity (true positive rate, TPR)*	99.74%
Clinical Specificity (true negative rate, TNR)*	99.90%
False Positive rate (FPR) = 1 – Specificity*	0.10%

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: 50558449LPH026JH

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