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Introduction of Products

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Outline and Features of UF-1500, Fully Automated Urine Particle Analyzer

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INTRODUCTION

UF-1500, the fully automated urine particle analyzer (Sysmex Corporation, Kobe, Japan; hereinafter UF-1500) is a down sized model of the UF-5000, UF-4000 and UF-3000 (Sysmex; hereinafter UF-5000). As well as those existing instruments, the UF-1500 can analyze the birefringence of particles [1)] and the nucleic acid content and size information of the cell, coupled with internal structural components, using a blue semiconductor laser (488 nm). Detailed analysis of signal waveforms originating from each particle generates detailed differentiation of casts, epithelial cells, etc. which are equivalent to the results from the UF-5000, UF-4000 and UF-3000 with a smaller footprint. The reagents and differentiation algorithms are consistent with those used with the UF-5000, UF-4000 and UF-3000 analyzers.
Therefore, the UF-1500 is expected to enhance automation of urine sediment analysis in the small sized laboratory, GPs, and urologist offices. The UF-1500 can also serve as a backup instrument for the UF-5000, UF-4000 and UF-3000 analyzers. The UF-1500 is ideal for a small sized laboratory or a site that has limited resources and/or budget since it offers the same quality results and clinical value as the flagship model. Unlike the larger analyzers, body fluid analysis is not available on the UF-1500. Scattergrams and histograms are displayed in the main unit of the UF-1500 without the U-WAM (Urinalysis Work Area Information Management System). A comparison of key specifications between the UF-1500 and UF-5000 is shown in ***Table 1***.

MAIN SPECIFICATIONS

1. External Appearance of the Analyzer

The UF-1500 consists of an analysis section (main unit), a sampler section and a pneumatic unit (***Fig. 1***).

2. Instrument Specifications

The main specifications of the instrument are listed in ***Table 2***.
As with the UF-5000, the UF-1500 utilizes flow cytometry as its measurement principle. The wavelength of the laser light in the UF-1500 is the same as the UF-5000. This enables the UF-1500 to detect smaller particles, equivalent to the UF-5000. The required sample volume for measurement is also the same as the UF-5000.
Numerical results, scattergrams for RBC/X'TAL, WBC/EC1, WBC/EC2, and BACT as well as RBC histograms can be displayed on the UF-1500's main screen without any external device such as the U-WAM. If the U-WAM is connected to the UF-1500, the scattergrams and histograms are the same as those displayed on the UF-5000. (Please refer to ***Table 1***). Additionally, the U-WAM connection provides a cross-check function by generating a REVIEW flag when 2 measured items (any item available in the U-WAM) show a specific feature (a user-defined setting). By connecting the UF-1500 to the U-WAM, linking the U-WAM to a urine test strip analyzer and to the UD-10*, a lab can create a comprehensive urine analysis screening system.

*UD-10 cannot be included in a sample transportation system.

Notes: This article is based on the specifications of the UF-1500 Ver. 00-04 and the UF-5000 Ver. 00-26.
Please note, some specifications, performances and functions described here may vary from region to region due to regulatory affairs, legal matters, or local guidelines. For more details, contact your regional affiliates or distributors.

Table 1 *Comparison of the main specifications between the UF-1500 and UF-5000*

	UF-5000	UF-1500
Parameters**	RBC, WBC, EC, Squa.EC, CAST, BACT, WBC Clumps, Non SEC, Hy.CAST, Path.CAST, X'TAL, YLC, SPERM, MUCUS, RBC-P70Fsc, RBC-Fsc-DW. Large RBC, Small RBC, NL RBC, Lysed RBC, Tran.EC, RTEC, SRC, Atyp.C, SF_TC, CW_TC, CB_TC, SF_OTHERS, CW_OTHERS, DEBRIS, Cond., Osmo	Same as UF-5000
Scattergrams and histograms	Scattergram: RBC/X'TAL*, CAST*, WBC/EC1*, WBC/EC2*, WBC*, YLC/Sperm*, BACT* Histogram: RBC*, WBC*.	Scattergram: RBC/X'TAL, CAST*, WBC/EC1, WBC/EC2, WBC*, YLC/Sperm*, BACT Histogram: RBC, WBC*
Research information	RBC-Info. (RBC morphological information) BACT-Info. (Bacteria Gram dye-affinity information) UTI-Info. (UTI information)	Same as UF-5000
Body fluid analysis	Available	Unavailable
Principle	Flow cytometry using a blue semiconductor laser (488 nm)	Same as UF-5000
Measured signals	Forward scattered light, side scattered light, side fluorescence, depolarized side scattered light	Same as UF-5000
Detection channels	SF ch (for elements without a nucleus) CR ch (for elements with a nucleus)	Same as UF-5000
Throughput	105 samples/hour (max)	60 samples/hour (max)
Aspirated sample volume	0.45 mL (common for all modes)	0.68 mL (sampler mode) 0.52 mL (STAT mode)
Required sample volume	2 mL or 2.5 mL*** (sampler mode) 0.6 mL (STAT mode)	Same as UF-5000

* U-WAM (option in the UF-1500) is required to view those scattergram and histogram.
** Categories of the individual parameters (reportable, non-reportable, quantitative, semi-quantitative, research-use only) may vary depending on the regulatory requirements of each region and/or country.
*** Required sampler volume after auto rinse

Fig. 1 *External appearance of UF-1500*

Table 2 *Specifications of UF-1500*

Name	The fully automated urine particle analyzer, UF-1500
Principle of measurement	Flow cytometry
Analysis targets	Human urine
Throughput	60 samples/hour (max)
Aspirated sample volume	0.68 mL (sampler mode), 0.52 mL (STAT mode)
Required sample volume	2 mL or 2.5 mL* in the sampler mode, 0.6 mL in STAT mode
Data storage capacity**	Analysis results: Maximum 1,000 samples (including scattergrams) Quality control: 2 concentrations × 3 lots (120 plots/lot)
Dimensions (mm)	Analyzer: Approx. 550 (W) × 560 (D) × 630 (H) mm Analyzer (including the sampler (SA-52)***): Approx. 630 (W) × 626 (D) × 630 (H) mm Pneumatic unit: Approx. 280 (W) × 355 (D) × 400 (H) mm
Weight	Analyzer: Approx. 52 kg Analyzer (including the sampler (CV-12)): Approx. 60 kg Pneumatic unit: Approx. 17 kg
Power source	Analyzer : 100 to 240 V AC, 50/60 Hz Pneumatic unit: 100 to 117 V AC, 50/60 Hz
Power consumption	Analyzer : 430 VA or less (including the sampler (SA-52)) Pneumatic unit: 230/280 VA or less (50/60 Hz)

* Required sample volume after auto rinse
** In U-WAM, the data storage capacity is 100,000 samples and 300 plots × 50 files.
*** SA-52 is option.

3. Available Parameters, Measurement Ranges and Units

Depending on the region/country, some of the parameters described here may not be reportable.

Similar to the UF-5000, different analytical methods from conventional ones are available on the UF-1500. This enables labs to benefit from the vast number of detectable signals and advances in optical analysis technologies. Specifically, the system supports improved accuracy of crystal and red blood cell measurements through the detection of depolarized side scattered light [2] and sub-classification of epithelial cells based on particle size, and nucleic acid content. Also, cumulative side scatter signals provide important information specific to cell size coupled with internal structural component information. Analysis of hyaline and non-hyaline casts and mucus elements have been achieved by the use of optical technologies including signal waveform analysis (***Fig. 2***). Furthermore, additional parameters have been added to the menu using these technologies. (***Tables 3***, ***4***). These same features are available on the UF-5000, our flagship model.

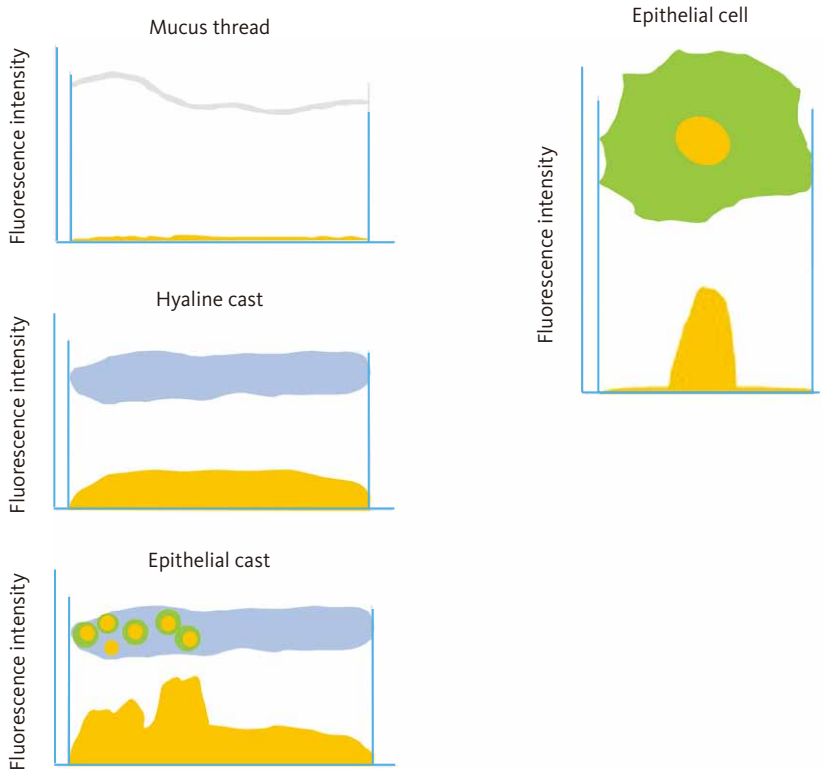


Fig. 2 *Analysis of side fluorescence signal waveforms of various particles*
The shape of the side fluorescence waveform varies depending on the type of urine particles.

Table 3 *Parameters**

RBC		Red blood cells
	NL RBC	RBC with morphology assumed to be stable
	Lysed RBC	RBC with morphology assumed to be unstable
	RBC-P70Fsc	An indicator of red blood cell size
	RBC-Fsc-DW	An indicator of red blood cell diversity
	Large RBC	Large red blood cell
	Small RBC	Small red blood cell
WBC		White blood cells
	WBC Clumps	White blood cell clumps
EC		Epithelial cells
	Squa.EC	Squamous epithelial cells
	Non SEC	Non-squamous epithelial cells
	Tran.EC	Transitional epithelial cells
	RTEC	Renal tubular epithelial cells
	SRC	Small round cells
Atyp.C		Atypical cells
CAST		Casts
	Hy.CAST	Hyaline casts
	Path.CAST	Non-hyaline casts
BACT		Bacteria
X'TAL		Crystals
YLC		Yeast-like cells
SPERM		Spermatozoa
MUCUS		Mucus
DEBRIS		Debris
Cond.		Conductivity
Osmo.		Osmolality
SF_TC		Total particle count in SF channel
CW_TC		Total particle count in CR channel (WBC)
CB_TC		Total particle count in CR channel (BACT)
SF_OTHERS		Other particle in SF channel
CW_OTHERS		Other particle in CR channel (WBC)

The measured values of semi-quantitatively displayed parameters can be viewed on the research screen. The measured results are displayed in categories, such as "5-9/HPF" in the semi-quantitative display.
Note 1: Certain parameters have the following relationships:
RBC = NL RBC+ Lysed RBC
NL RBC=Large RBC+Small RBC
EC = Squa.EC + Non SEC
Non SEC = Tran.EC + RTEC SRC = RTEC
CAST = Hy.CAST + Path.CAST
Note 2: WBC Clumps is not included in WBC count.
Note 3: Osmolality is calculated from conductivity using a conversion formula.

* Categories of the individual parameters (reportable, non-reportable, quantitative, semi-quantitative, research-use only) vary depending on the regulatory requirements of each region or country.

Table 4 *Research information**

Parameter		Description
RBC-Info.**	Isomorphic?	Undamaged RBC is suspected.
	Dysmorphic?	Damaged RBC or small RBC is suspected.
	Mixed?	RBC suspected that does not meet morphology criteria listed above
UTI-Info.	UTI?	Samples evaluated as having bacterial urinary tract infection (UTI) based on WBC and bacteria counts
BACT-Info.	Gram-positive?	Gram-positive bacteria suspected
	Gram-negative?	Gram-negative bacteria suspected
	Gram-pos/neg?	Gram-positive and Gram-negative bacteria Mix suspected
	Unclassified	Unable to distinctly classify from the distribution

Note 1:
RBC-Info.**: RBC forms Information from the distribution is displayed.
UTI-Info.: Samples suspected of having bacterial urinary tract infection (UTI) from the WBC and bacteria counts.
BACT-Info.: The bacteria Gram dye-affinity suspected based on distribution is displayed.
Note 2:
The algorithm for RBC-Info. [3] and the assessment performance [4] are exactly the same as in UF-5000.

* Categories of the individual parameters (reportable, non-reportable, research-use only) vary depending on the regulatory requirements of each region and/or country.

** Improvements from UF-1000*i* are expected due to enhanced RBC analysis in UF-1500, as well as UF-5000.
Lysed and non-lysed RBCs (total RBCs) are used in UF-5000 and UF-1500 to determine RBC-Info.

4. Linearity, Limit of Blank Value (LoB)[5], Limit of Detection (LoD)[5] and Limit of Quantification (LoQ) [5] (*Tables 5, 6*)

Standardized lab values are based on the assumption that maximum data variation may occur when a sample is prepared and analyzed using recommended specification. Samples may not always meet recommended standards because cellular elements in a native state may react differently from those using prepared particles.

Table 5 *Linearity*
The specifications below are indicated as theoretical values or residual percentages of values measured using a reference analyzer.

Parameters	Linearity
RBC	R^2 = 0.95 or more (2.0 to 20,000.0/μL)
NL RBC	R^2 = 0.95 or more (2.0 to 20,000.0/μL)
WBC	R^2 = 0.95 or more (1.0 to 20,000.0/μL)
WBC Clumps	NA (Semiquantitative)
EC	R^2 = 0.95 or more (1.5 to 250.0/μL)
Squa.EC	R^2 = 0.95 or more (1.0 to 230.0/μL)
Non SEC	R^2 = 0.95 or more (1.5 to 80.0/μL)
Tran.EC	R^2 = 0.95 or more (1.5 to 20.0/μL)
RTEC	R^2 = 0.95 or more (1.5 to 80.0/μL)
CAST	R^2 = 0.95 or more (1.00 to 30.00/μL)
Hy.CAST	R^2 = 0.95 or more (1.00 to 30.00/μL)
Path.CAST	R^2 = 0.95 or more (1.00 to 20.00/μL)
BACT	R^2 = 0.95 or more (5.0 to 10,000.0/μL)
X'TAL	R^2 = 0.95 or more (10.0 to 200.0/μL)
YLC	R^2 = 0.95 or more (35.0 to 2,000.0/μL)
SPERM	R^2 = 0.95 or more (50.0 to 400.0/μL)
MUCUS	NA (Semiquantitative)

Table 6 *Limit of blank value (LoB), limit of detection (LoD) and limit of quantification (LoQ)*

Parameters	Limit of Blank (LoB)	Limit of Detection (LoD)	Limit of Quantitation (LoQ)
RBC	0.5/μL or less	1.0/μL or less	2.0/μL or less
NL RBC	0.5/μL or less	1.0/μL or less	2.0/μL or less
WBC	0.5/μL or less	1.0/μL or less	1.0/μL or less
WBC Clumps	NA (Semiquantitative)	NA (Semiquantitative)	NA (Semiquantitative)
EC	1.0/μL or less	1.5/μL or less	1.5/μL or less
Squa.EC	0.5/μL or less	1.0/μL or less	1.0/μL or less
Non SEC	1.0/μL or less	1.5/μL or less	1.5/μL or less
Tran.EC	1.0/μL or less	1.5/μL or less	1.5/μL or less
RTEC	1.0/μL or less	1.5/μL or less	1.5/μL or less
CAST	0.50/μL or less	1.00/μL or less	1.00/μL or less
Hy.CAST	0.50/μL or less	1.00/μL or less	1.00/μL or less
Path.CAST	0.50/μL or less	1.00/μL or less	1.00/μL or less
BACT	3.0/μL or less	5.0/μL or less	5.0/μL or less
X'TAL	0.5/μL or less	10.0/μL or less	10.0/μL or less
YLC	1.0/μL or less	2.0/μL or less	35.0/μL or less
SPERM	0.5/μL or less	50.0/μL or less	50.0/μL or less
MUCUS	NA (Semiquantitative)	NA (Semiquantitative)	NA (Semiquantitative)

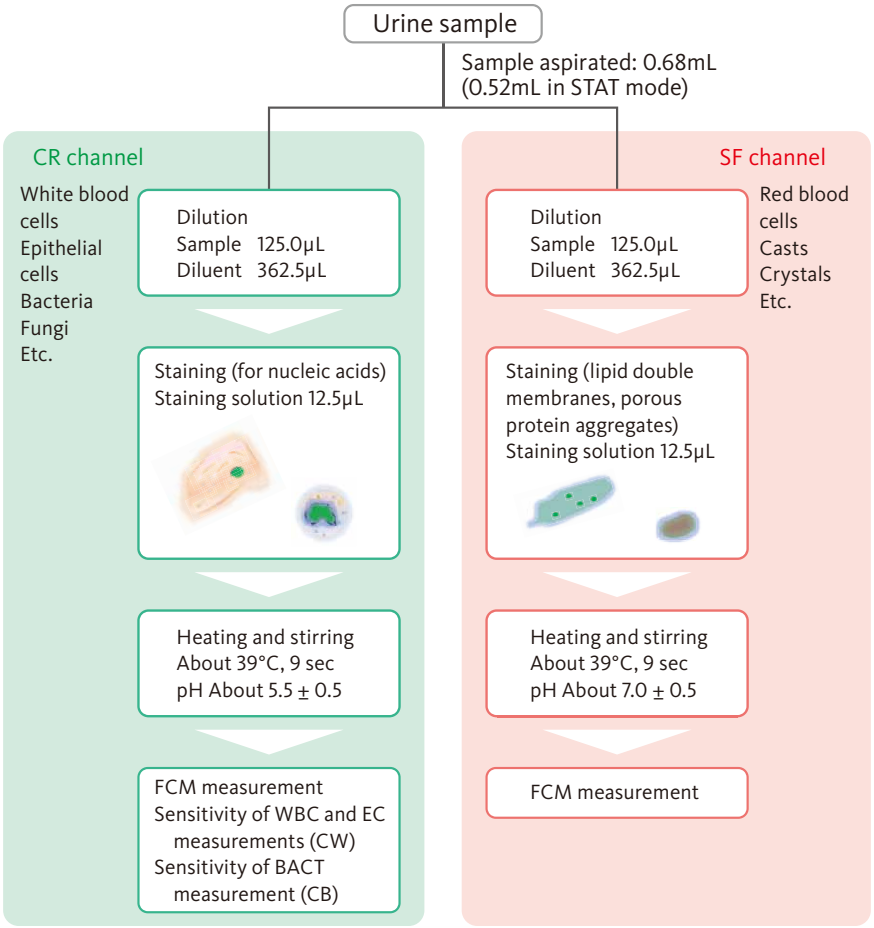
PRINCIPLE OF MEASUREMENT

1. Outline of Measurement Workflow

The analysis workflow of the UF-1500 is shown in ***Fig. 3***. The aspirated sample is mixed with diluent and staining solution, and then analyzed by flow cytometry. The measurements are made in the "SF channel" and "CR channel".
The SF channel measures elements that do not have nucleic acids, such as red blood cells, crystals, and casts. In the CR channel, the red blood cells and crystals are lysed or dissolved, and then all cells with nucleic acids are analyzed including white blood cells, epithelial cells, bacteria, fungi, etc.

2. Functions of the Diluent and Staining Solution in the SF Channel

The sample, along with diluent and staining solution, are mixed in the reaction chamber of the SF channel where they are heated and stirred. In this process, the amorphous salts that affect red blood cell analysis are removed by the chelating function[6] of EDTA-2K present in the diluent. Mucus, mostly attached to bacteria or cells,[7] can cause false positive results for CAST and Path.CAST in UF-1000*i*, which are dispersed by the surfactant. This improvement from UF-1000*i* has reduced the number of false positive results for CASTs. The use of surfactant does not affect red blood cell morphology, epithelial cells, and casts.
In the SF channel, the cellular membranes including internal cellular organisms and porous protein aggregates that constitute the matrix of the cast are stained by a polymethine dye. White blood cells and epithelial cells are extremely fluorescent after staining, which takes them outside the normal measurement range. Casts with inclusions are also significantly stained; however, they can be distinguished from epithelial cells and other elements based on size, internal particle structure, stain intensity of the membrane components and cast matrix, as well as signal waveform analysis results. Given all of these factors, they remain within the expected measurement range of SF channel. Through this mechanism, red blood cells, crystals, hyaline casts and casts with inclusions are measured in the SF channel by flow cytometry.



	CW	CB
	Urine	Urine
Volume measured by FCM (µL)	31.2	4.0
Volume analyzed by FCM (µL)	7.8	1.0

	SF
	Urine
Volume measured by FCM (µL)	31.2
Volume analyzed by FCM (µL)	7.8

Fig. 3 *Outline of analysis work flow*

Table 7 gives an outline of the reagents used in the SF channel.

3. Functions of the Diluent and Staining Solution in the CR Channel

The sample, diluent, and staining solution are mixed, heated, and stirred in the reaction chamber of the CR channel. In this process, crystals are dissolved and removed by mixing EDTA-2K and acetate buffer, both present in the diluent[8]. Additionally, red blood cells are lysed by the surfactant. The use of surfactant here does not significantly affect the morphology of cellular elements such as white blood cells and epithelial cells.

In the CR channel, the surfactant makes small holes on the cell membranes to allow the penetration of the polymethine dye into the cells. The polymethine dye stains the nucleic acids in the cells. White blood cells, epithelial cells, yeast-like cells, spermatozoa, and bacteria are measured by flow cytometry in the CR channel. The nucleic acid content is also determined in this channel. There is a vast difference in the nucleic acid content of human-derived cells compared to non-human-derived cells in urine specimens of humans. This has made it possible to analyze the cells with greater accuracy (***Fig. 4***). A general outline of reagents used in the CR channel is listed in ***Table 8***.

Table 7 *SF channel reagents*

Diluent	Name	UF-CELLPACK™ SF
	Components	HEPES 1.2% 1,2-Benzisothiazolin-3-one, less than 0.01% (preservative) Chelating agent, surfactant
	Functions	Removes amorphous salts which interfere with RBC analysis when mixed with the chelating agent and heated (the chelating action dissociates the divalent cation from the salts and dissolve them). The surfactant disperses the mucus elements.
Stain	Name	UF-Fluorocell™ SF
	Components	Polymethine dye 0.05% Ethylene glycol 99.9%
	Functions	Stains the lipid double membranes of cells, such as red blood cells, and the porous protein aggregate that constitutes the cast matrix

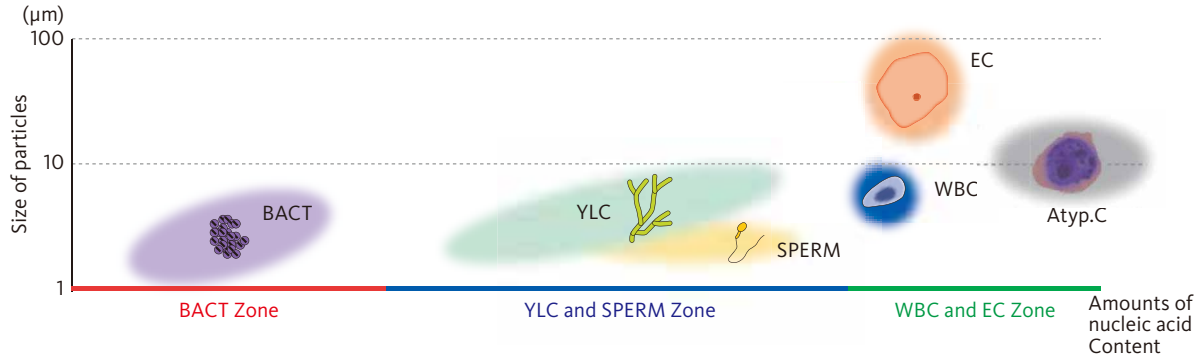


Fig. 4 *Diagrammatic representation of urine particle size and nucleic acid content*

Table 8 *CR channel reagents*

Diluent	Name	UF-CELLPACK™ CR
	Components	Less than 0.1% of acetic acid, surfactant and a chelating agent
	Functions	The surfactant lyses the red blood cells. It makes holes on the cell surface and improves intracellular penetration of the staining solution (cellular elements like white blood cells are not significantly affected). The crystalline elements are mixed with a chelating agent and acetic acid, dissolved and then heated.
Stain	Name	UF-Fluorocell™ CR
	Components	Polymethine dye 0.02% Ethylene glycol 99.9%
	Functions	Staining of nucleic acids

4. Detection and Measurement by Flow Cytometry

Samples mixed with diluent and staining solution are introduced to the flow cell after the process of mixing and heating and then measured by flow cytometry. The sheath flow fluid used in the flow cytometry is described in ***Table 9***. Flow cytometry measurement is performed in both the SF channel and CR channel (CR channel at the sensitivity level for analyzing WBC and EC, and at the sensitivity level for analyzing BACT). Three separate measurements are obtained for each sample. The parameters and analysis methods for each measurement are shown in ***Table 10***, ***Fig. 5***, ***Fig. 6***, and ***Fig. 7***. The forward scattered light (FSC)

Table 9 *Sheath fluid*

Sheath fluid	Name	UF-CELLSHEATH™
	Components	0.14% Tris buffer
	Functions	Creation of sheath flow within the flow cell, washing the hydraulic system of the analyzer

Table 10 *List of optical parameters*

Analysis channel	Optical parameters	Description
SF channel	SF_FSC_P (forward scattered light intensity)	Size / thickness of particles
	SF_FSC_W (forward scattered light signal width)	Length of particles
	SF_FLH_P (side fluorescence intensity (high sensitivity))	Stainability of particles
	SF_FLL_P (side fluorescence intensity (low sensitivity))	
	SF_FLL_W (side fluorescence signal width (low sensitivity))	Length of particles
	SF_FLL_A (side fluorescence signal waveform area (low sensitivity))	Stainability of membrane components and cast matrix
	SF_SSH_P (side scattered light intensity (high sensitivity))	Complexity of internal structure and thickness of particles
	SF_SSL_P (side scattered light intensity (low sensitivity))	
	SF_SSH_A (side scattered light signal waveform area (high sensitivity))	Size information coupled with complexity of internal structure
	SF_DSS_P (depolarized side scattered light intensity)	Intensity of birefringence of particles
CR channel (measured at the sensitivity level for analyzing WBC and EC)	CW_FSC_P (forward scattered light intensity)	Size / thickness of particles
	CW_FSC_W (forward scattered light signal width)	Length of particles
	CW_FLH_P (side fluorescence intensity (high sensitivity))	Stainability of nucleic acids
	CW_FLL_P (side fluorescence intensity (low sensitivity))	
	CW_FLL_A (side fluorescence signal waveform area (low sensitivity))	Amounts of nucleic acid content
	CW_SSH_P (side scattered light intensity (high sensitivity))	Complexity of internal structure and thickness of particles
	CW_SSL_P (side scattered light intensity (low sensitivity))	
	CW_SSH_A (side scattered light signal waveform area (high sensitivity))	Size information coupled with complexity of internal structure
	CW_DSS_P (depolarized side scattered light intensity)	Intensity of birefringence of particles
CR channel (measured at the sensitivity level for analyzing BACT)	CB_FSC_P (forward scattered light intensity)	Size / thickness of particles
	CB_FLH_P (side fluorescence intensity (high sensitivity))	Stainability of nucleic acids
	CB_FLL_P (side fluorescence intensity (low sensitivity))	
	CB_SSH_P (side scattered light intensity (high sensitivity))	Complexity of internal structure and thickness of particles

measurement provides information about the particle size and permeability. The side scattered light (SSC) measurement shows thickness and internal structure of particles. Side fluorescence (FL) measurements provide information about particle stainability while depolarized scattered light (DSS) reflects the intensity of particle birefringence.

As described above, the UF-1500 analysis utilizes a variety of optical parameters. These include signals related to particle birefringence and nucleic acid content which cannot be measured by traditional microscopic analysis. Thus, the analyzer has capabilities that go beyond those of visual observation. In this respect, it is significantly different from the UF-1000*i*.

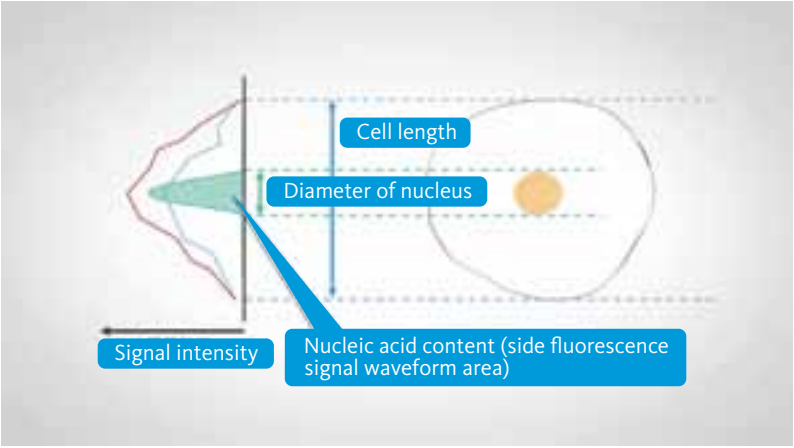


Fig. 5 *Signal waveforms obtained by UF-1500*

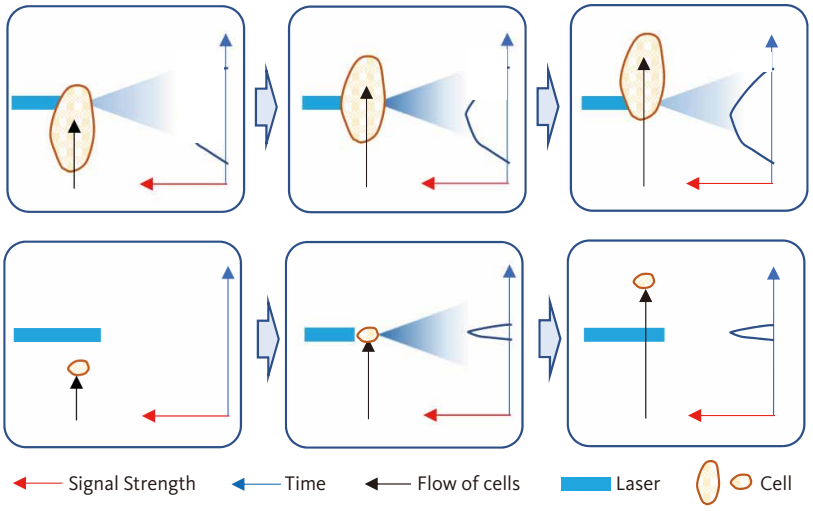


Fig. 6 *How signal waveform generation works in the UF-1500*

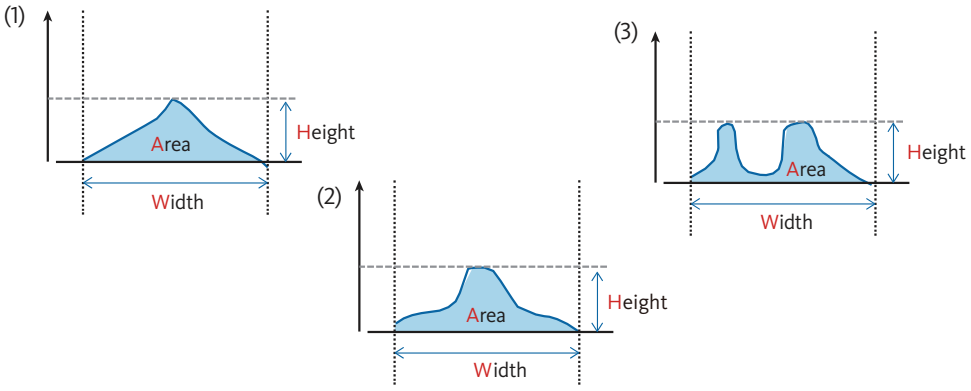


Fig. 7 *Signal waveform analysis by the UF-1500*

As seen in the example shown in ***Fig. 5***, the x-axis represents side fluorescence in the CR channel with an area under the curve (presented as green area) reflecting the nucleic acid content. When the x-axis shows side scattered light, the area (surrounded by green line) reflects particle size along with internal structure content. When the x-axis shows side fluorescence in SF channel, the width (along with vertical axis) of the curve (indicated by a purple line) reflects the "length*" of the particle. (*The maximum width of the individual particle) ***Fig. 6*** demonstrates how the signal waveform is obtained for both large and small particles.
Even when the height, width and the area of the curve are the same (***Fig. 7 (1)***, ***(2)*** and ***(3)***), if the signal waveform shape differs, then the particle classifications are different. This analytical capability contributes to improved differentiation of a CAST from a MUCUS classification.
Information on particle birefringence is obtained by analyzing depolarized side scatter light. Polarized light is light in which the plane of oscillation, i.e., plane of polarization of all light waves, is the same. Laser light is basically polarized light[9]. Many solid substances, including crystals, exhibit the birefringent property. As shown in ***Fig. 8***, inside the birefringent substance, the light speed of the polarization light, with its polarization plane indicated as a blue arrow, is different from that with its polarization plane indicated as a green arrow. Due to the property of the material, when a substance is irradiated by the Laser light, the plane of polarization changes (***Fig. 9***). Therefore, if we place a polarized filter upstream from the photo-multiplier to

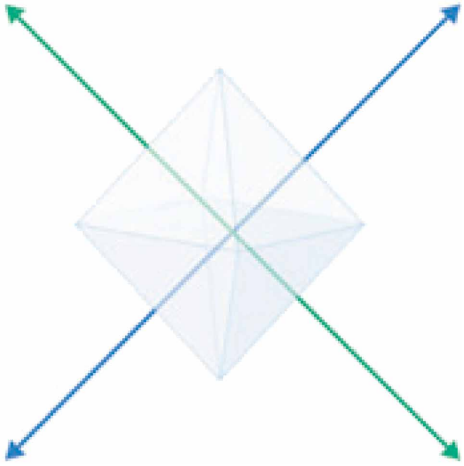


Fig. 8 *A substance having birefringence property*

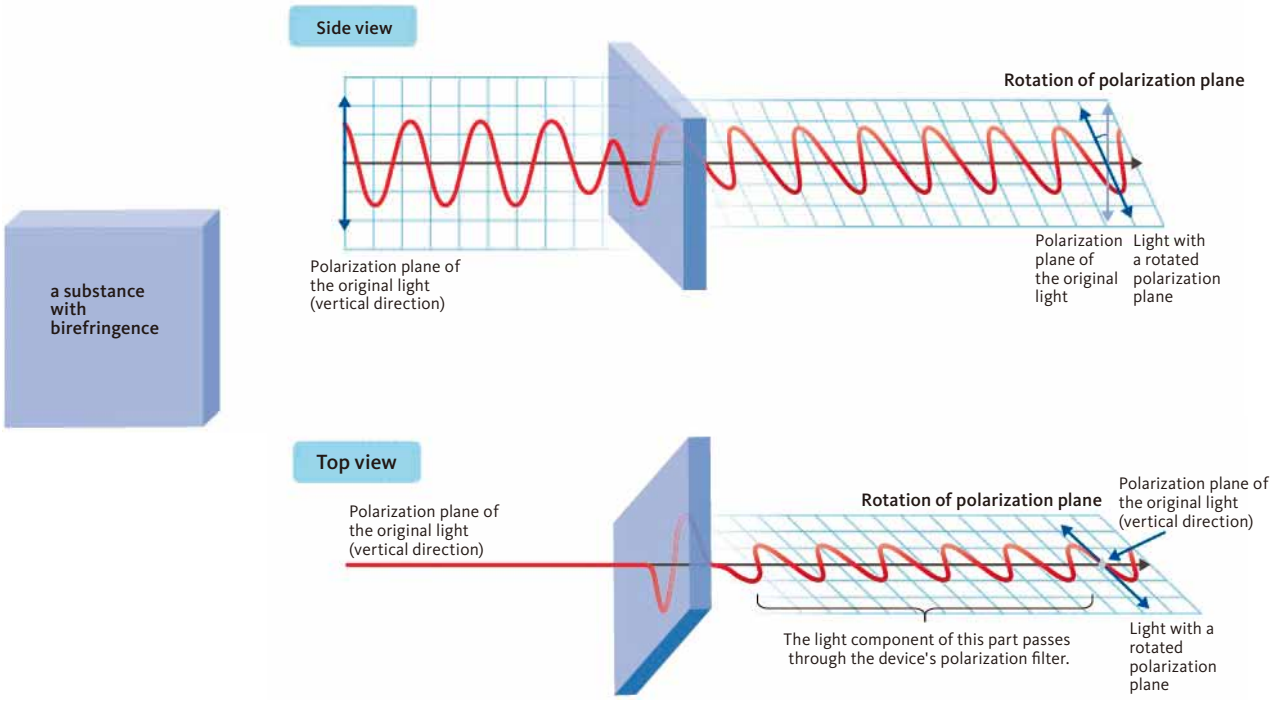


Fig. 9 *3-dimensional figure of "depolarization"*

block light, since the polarization planes are equal, the analyzer only detects the one that changed. (***Fig. 10***). In other words, the UF-1500 captures the equivalent signal obtained by the polarized light microscope. Subsequently, it can obtain essential information from particles such as crystals that can be observed under polarized light microscopes.

5. Scattergram Analysis

The intensity, width, waveform area, waveform forward scattered light, side fluorescence, side scattered light and depolarized side scattered light are obtained by flow cytometry for each particle. The measurements are analyzed and the particles are differentiated using algorithms that take into account all of these components. The results of this analysis (differential classification) are displayed as scattergrams.

1) RBC/X'TAL Scattergram [SF Channel SF_SFC_P/SF_FLH_P (Not displayed by UF-1500 or UF-5000)]

This scattergram is not shown in the UF-1500 or the UF-5000; however, the channel measurements are used in the UF-1000*i* (***Fig. 11***). Crystals typically show a lower staining intensity compared to red blood cells. White blood cells and epithelial cells, which have a nucleus and a higher staining intensity, appear on the right side of the scattergram, and thus can be separated from particles without nuclei. CASTs (including Path.CAST) are distributed at a relatively low intensity of forward scattered light. Although the actual forward scattered light intensity, which reflects particle size corresponding to particle type, may change depending on the particle permeability and the amount of scattered light. Therefore, the forward scattered light intensity for dehemoglobinized red blood cells is thought to be weaker even if the size is

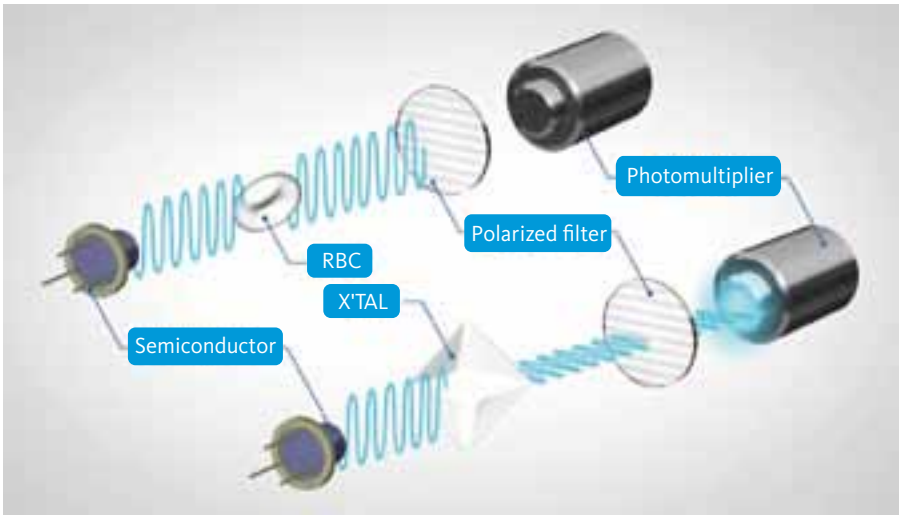


Fig. 10 *Diagram showing detection of depolarized side scattered light*

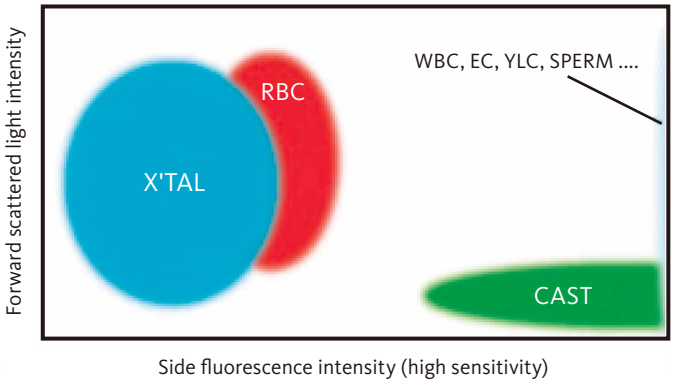


Fig. 11 *The RBC/X'TAL Scattergram (not displayed in the UF-1500 or the UF-5000)*

the same. If the particle size is larger than the width of the laser beam, only the irradiated portion (cross-section) of the particle will be reflected as forward scattered light intensity. This is because the central part of the flow cell has the highest flow rate, and the particles move along the long axes in the flow direction. The likely reasons that CASTs display a relatively low forward scattered light intensity are (1) permeability and (2) light intensity reflects the cross-sectional area of large particles.

2) RBC/X'TAL Scattergram
[SF channel SF_FSC_P/SF_DSS_P]

This scattergram shows the intensity of the depolarized side scattered light, a signal detected by the UF-1500 as well as the UF-5000. It is mainly used to differentiate RBCs from X'TALs (***Fig. 12***). The lateral placement of crystals and red blood cells is reversed compared to the SF_FSC_P/SF_FLH_P scattergram (***Fig. 11***). RBCs appear as red dots at a low-intensity zone of depolarized side scattered light on the RBC/X'TAL scattergram. As red blood cells do not have birefringence, the depolarized side scattered light intensity is very low. Crystals appear as aqua blue dots on the same scattergram. The depolarized side scattered light intensity reflects the birefringence of the crystals. Therefore, the higher the crystal intensity, the more the dots will shift right on the scattergram. Red blood cells, which have very low, depolarized side scattered light intensity, appear on the left side. On the UF-1000*i*, red blood cells and crystals are differentiated using side scattered light intensity, which has limitations because some red blood cells and crystals exhibit similar light intensity. Therefore, the depolarized side scattered light measurement was introduced on both the UF-1500 and the UF-5000, as an effective means of resolving this problem. As described above, depolarized side scattered light reflects particle birefringence so a more precise differentiation of red blood cells from crystals was possible with the UF-1500 and UF-5000. The proven fluorescent signal used for differential classification on the UF-1000*i* is now a feature on the UF-1500 and UF-5000 analyzers. Similar to the UF-1000*i*, both the UF-1500 and the UF-5000, generate red blood cell histograms based on forward scattered light intensity and RBC morphological information (RBC-Info.). ***Fig. 13*** demonstrates an example of RBC-Info. analysis using a red blood cell histogram. Here, RBC-Fsc-DW and RBC-P70Fsc obtained from the red blood cell histogram, are plotted on the Judging figure in the top right on ***Fig. 13***, and then RBC-Info. is differentiated. The result of RBC- Info. (in ***Fig. 13***) is "Isomorphic?" because the width of the red blood cell histogram is narrow and plotted in the high Fsc area. In this case, RBC morphology is identical to the RBC in the blood vessel. If the horizontal location of the red blood cell histogram is in the lower Fsc area or the width is wider, the result of the RBC-Info. becomes "Mixed?" or "Isomorphic?"

3) CAST Scattergram
(Only available when U-WAM is connected.)
[SF channel SF_FLL_A/SF_FLL_W]

This scattergram displays the differentiation results of Path.CAST, Hy.CAST and MUCUS (***Fig. 14***). Hy.CAST particles appear as dark green dots on the CAST scattergram. As the total dye uptake is lower in Hy.CAST compared to Path.CAST, the side fluorescence waveform area of the former falls between those of MUCUS and Path.CAST. Path.CAST particles appear as yellowish-green dots on the scattergram. The more inclusions in casts, the stronger the stainability. Therefore, the side fluorescence waveform area of a Path.CAST is larger than that of a Hy.CAST. MUCUS appears as brown dots on the scattergram. Mucus threads are dispersed by the surfactant in UF-CELLPACK™-SF. Therefore, the side fluorescence signal waveform area, which reflects the total dye uptake in the SF channel, is smaller than that of Hy.CAST.

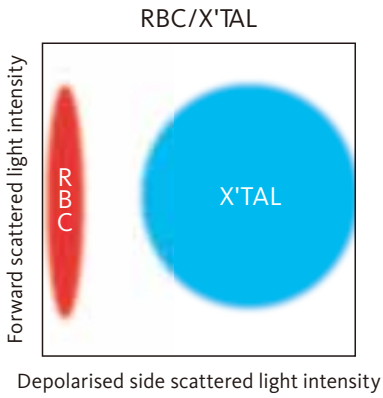
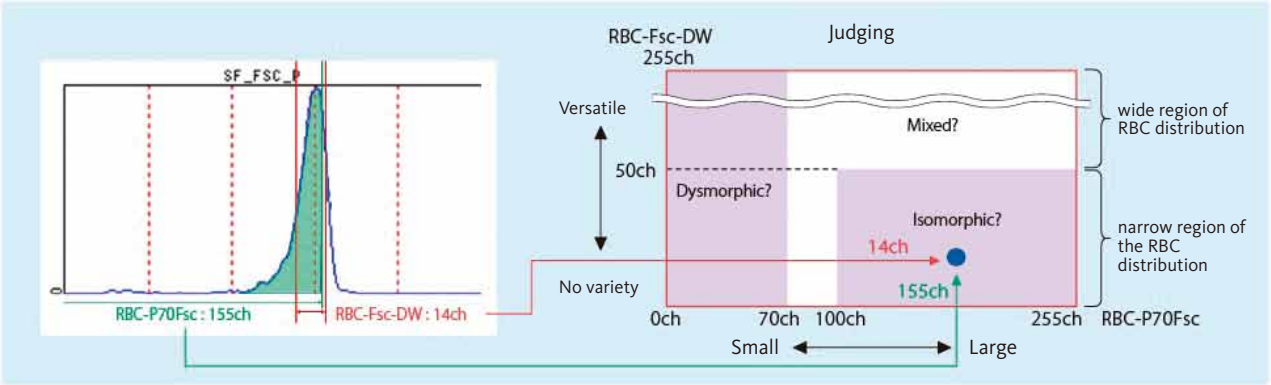


Fig. 12 *The RBC/X'TAL Scattergram*

Isomorphic?

Applying the values of RBC-P 70 Fsc and RBC-Fsc-DW to the figure of the judging method, Isomorphic? will be.



Item name	Value (/μc, h)
RBC	442.6
RBC-P70Fsc	155
RBC-Fsc-DW	14
Large RBC	428.5
Small RBC	11.1
NL RBC	439.6
Lysed RBC	3.0

The distribution of Large RBC and Small RBC on histograms and scattergrams are shown in the figure below.

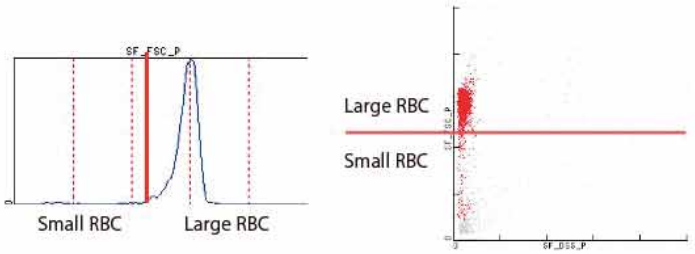


Fig. 13 *Example of RBC-Info. analysis using red blood cell histogram*

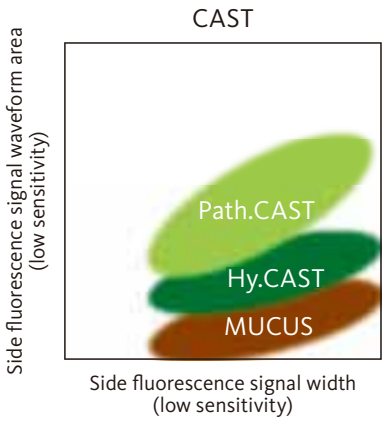


Fig. 14 *The CAST Scattergram*

Here, the side fluorescence signal waveform area represents the sum total of fluorescent intensity. The greater the inclusion of cast particles, the higher the total fluorescent intensity. As the mucus threads are dispersed by the diluent, which remains unraveled, the total fluorescence intensity is also low (***Fig. 15***).
The side fluorescence signal width can represent the length of the particles. Due to the high fluorescence intensity in the SF channel, the entire cast is stained even if it is a hyaline cast. The method of displaying the side fluorescence signal width as the particle length is the same on the UF-1000*i* (as well as the UF-5000). Path.CAST, Hy.CAST and MUCUS are distributed diagonally towards the upper right area on the scattergram because the accumulated particle fluorescence intensity becomes larger as the length increases.

Signal waveform analysis and side scattered light information are also used for the actual differentiation of Path.CAST, Hy.CAST and MUCUS. However, to simplify interpretation of the plots, the same type of scattergram used in the UF-1000*i* has been used in the UF-1500 (and UF-5000).

4) *WBC/EC1 Scattergram*
[CR channel CW_FSC_W/CW_SSH_A]
WBC/EC2 Scattergram
[CR channel CW_FSC_W/CW_FLL_A]

ECs and WBCs are displayed in these scattergrams (***Fig. 16***, ***17***).
The forward scattered light signal width reflects particle

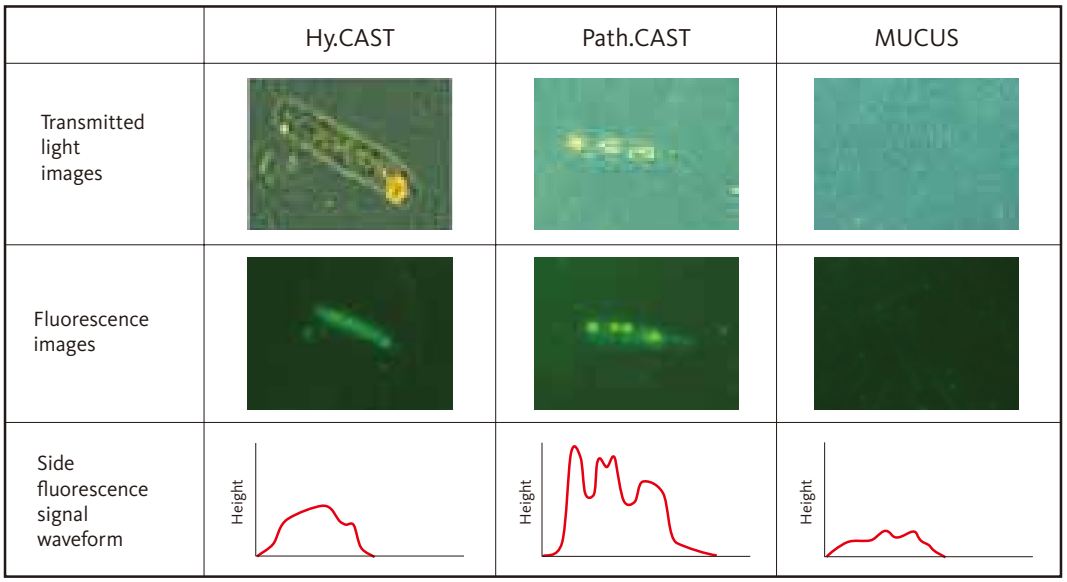


Fig. 15 *Stained images and side fluorescence signal waveforms of casts and mucus*

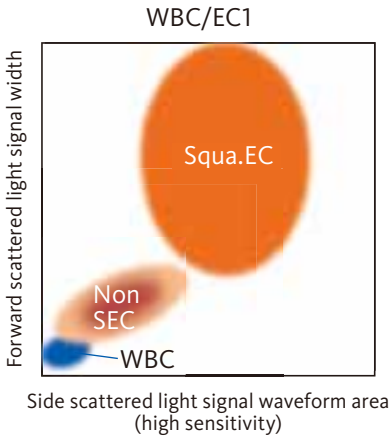


Fig. 16 *The WBC/EC1 Scattergram*

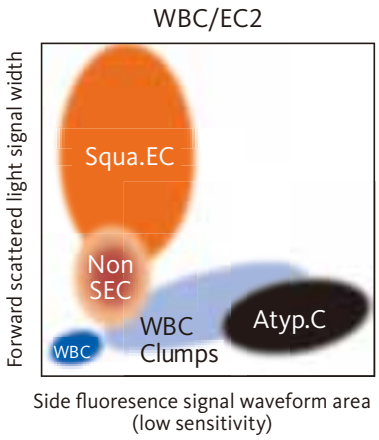


Fig. 17 *The WBC/EC2 Scattergram*

length and the side scattered light signal waveform area reflects size coupled with internal structural component information. The side fluorescence signal waveform area reflects the nucleic acid content. (As nucleic acid is present not only in the nucleus but also in the mitochondria, in cells with an abundance of intracellular organelles the value of the side fluorescence signal waveform area becomes slightly larger.)

The WBC/EC1 scattergram (***Fig. 16***) reflects cell morphology. It gives size information that is coupled with internal structural components of the cell, in relation to the particle length (long axis dimension).

The WBC/EC2 scattergram (***Fig. 17***) reflects the particle length and the nucleic acid content. WBCs appear as blue dots which converge in the bottom left area on the WBC/EC1 and WBC/EC2 scattergrams. WBC Clumps appear as pale blue dots on the WBC/EC1 and WBC/EC2 scattergrams. WBC clumps have a larger side fluorescence signal waveform area compared to WBCs because clumps have more nucleic acid content. The larger the clumps, the greater the nucleic acid content and size. Therefore, the dot distribution spreads up and to the right on the scattergram.

On the WBC/EC1 scattergrams, ECs appear as orange (Squa.EC), pale orange (Squa.EC) or reddish brown (RTEC) dots, representing the total epithelial cell count measured by the analyzer. Squa.ECs appear as orange-colored dots on the WBC/EC1 and WBC/EC2 scattergrams. The Squa.EC analyzer count mainly consists of superficial layer squamous epithelial cells in the range of about 60 - 100 μm. The nucleic acid content is low and the size information is small relative to the particle length (dimension along the long axis of the cell). Therefore, compared to other kinds of epithelial cells, the side fluorescence signal waveform and side scattered light signal waveform areas are relatively smaller with respect to the forward scattered light signal width which reflects the particle length. Typically, Squa.ECs have low nucleic acid content relative to particle length. Non SECs, on the other hand, appear as reddish brown or pale orange dots on the WBC/EC1 scattergram. Their size data is large relative to the particle length. Non SECs have high nucleic acid content relative to their length and appear as light orange dots on the WBC/EC2 scattergram.

Non SECs are further classified into Tran.ECs and RTECs. Tran.ECs appear as pale orange dots and RTECs appear as reddish-brown dots on the WBC/EC1 scattergrams. Tran.ECs and RTECs appear in the same area of the scattergram using the particle length (forward scattered light signal width) and nucleic acid content (side fluorescence signal waveform area) or the particle length (forward scattered light signal width) and the size coupled with internal structural content information. (side scattered light signal waveform area). However, both Tran.ECs and RTECs can be differentiated based on nucleic acid content (side fluorescence signal waveform area) and the size coupled with internal structural content information (side scattered light signal waveform area). This principle is based on the fact that for a given cell size, Tran.ECs tend to have more nucleic acid content than RTECs. (***Fig. 18***)

Apart from above-mentioned ECs (Squa.EC and Non SEC), Atyp.C (atypical cells) also appears as black dots on the right side of the WBC/EC2 scattergram. Atyp.C includes cells with abnormally high nucleic acids and larger fluorescence signal waveform areas such as atypical cells, intraplasmic inclusion-bearing cells, and virus infected cells. Compared to Tran.ECs and RTECs as previously described, the Atyp.C particle length (forward scattered light signal width) and the size coupled with internal structural component information (side scattered light signal waveform area) are nearly equivalent.

5) WBC Scattergram [CR channel CW_FLL_P/CW_SSH_P]

(Only available when U-WAM is connected.)

In the WBC scattergram, the vertical axis is the side fluorescence intensity (low sensitivity), which reflects the nucleic acid stainability. The horizontal axis is the side scattered light intensity (high sensitivity), which reflects internal structure complexity and particle thickness (***Fig. 19***).

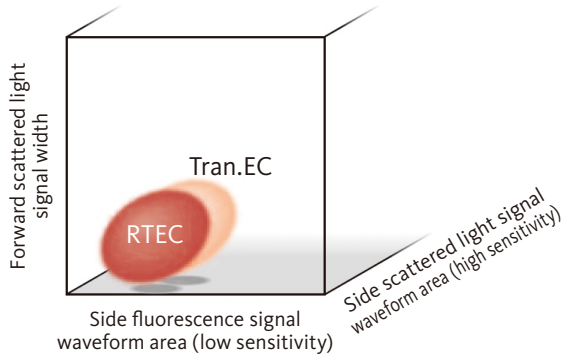


Fig. 18 *3-dimensional figure to show the discrimination between Tran. EC and RTEC (not available in the UF-1500)*

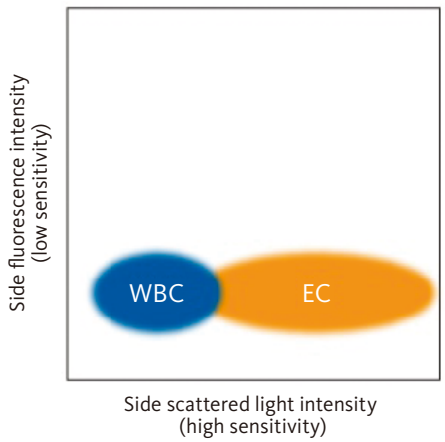


Fig. 19 *The WBC Scattergram*

In this scattergram, WBCs and ECs are displayed. Here, the smaller the nucleic acid content, the lower the location of the dots on the scattergram. The thicker the size or more complex the internal cell structure of the cells, the dots will be located more to the right on the scattergram. This scattergram is also expected to be used for research use only results, i.e., the study of the location of WBC dots, comparing with the nature of the WBC, examined by microscopy etc.

6) WBC Histogram
(Only available when U-WAM is connected.)

The WBC histogram shows the distribution of white blood cells based on side scattered light intensity which reflects particle complexity and thickness of the internal structures (***Fig. 20***). This histogram is also expected to be used only for research, i.e., the study of the distribution of WBC histogram, comparing with the nature of the WBC, examined by microscopy etc. Through our internal study, it was suggested that the side scattered light histogram shows more variation depending on the patient, than the one using the forward scattered light.

7) YLC/SPERM Scattergram
(Only available when U- WAM is connected.)
[CR channel CW_FSC_P/CW_FLH_P]

This scattergram displays YLC and SPERM (***Fig. 21***). YLC appears as pale green dots on the YLC/SPERM scattergram. Several nuclei are included by a chain of YLC and the amount of nucleic material is dependent on the state of budding. The cell size and nucleic acid content increase as the budding process advances. Both forward scattered light intensity and side fluorescence intensity increase as the budding progresses. When this occurs, the dot distribution spreads diagonally upward and to the right on the scattergram.
SPERM, on the other hand, appears as pale-yellow dots on the YLC/SPERM scattergram. The heads of spermatozoa are normally uniform in size. Therefore, the forward scattered light intensity and staining intensity are constant. The horizontal distribution spread of spermatozoa on the scattergram is due to the characteristic features of the YLC/SPERM scattergram. Waveform analysis is also used for differentiating SPERM.

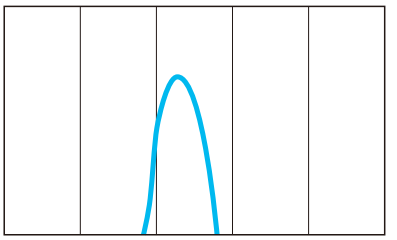


Fig. 20 *The WBC Histogram*

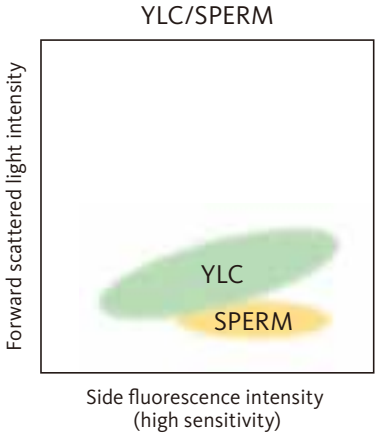


Fig. 21 *The YLC/SPERM Scattergram*

8) BACT Scattergram

[CR channel CB_FSC_P/CB_FLH_P]

This scattergram displays BACT and DEBRIS (***Fig. 22***). The forward scattered light sensitivity of detection has been enhanced using the blue semiconductor laser. Also, the use of stain has increased the stainability difference between BACT and DEBRIS (side fluorescence intensity). As a result, the UF-1500, as well as UF-5000 has an improved ability to detect small bacteria such as Pseudomonas aeruginosa compared to the UF-1000*i*. Studies confirmed that the shape (angle of distribution of the dots) of clusters in the BACT scattergram may vary depending on the type of bacteria present. BACT appears as purple-colored dots on the BACT scattergram. Sensitivity level measurements are used for detection of bacteria in the CR channel.

DEBRIS are fine components such as cell fragments. They are counted as DEBRIS to separate them from the BACT count which strengthens the analytical accuracy of the BACT parameter. DEBRIS appears as gray dots on the BACT scattergram.

The UF-1500 displays Bacteria Gram dye-affinity information (BACT-Info.) estimated from the scattergram. The side fluorescence intensity reflects the differences in the cell wall constituents, such as the peptidoglycan layer of the bacteria cells (***Fig. 23***). Gram-positive bacteria, which have a thick peptidoglycan layer, generally show higher forward scattered light intensity than Gram-negative

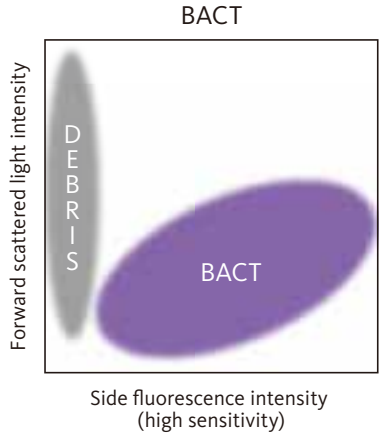
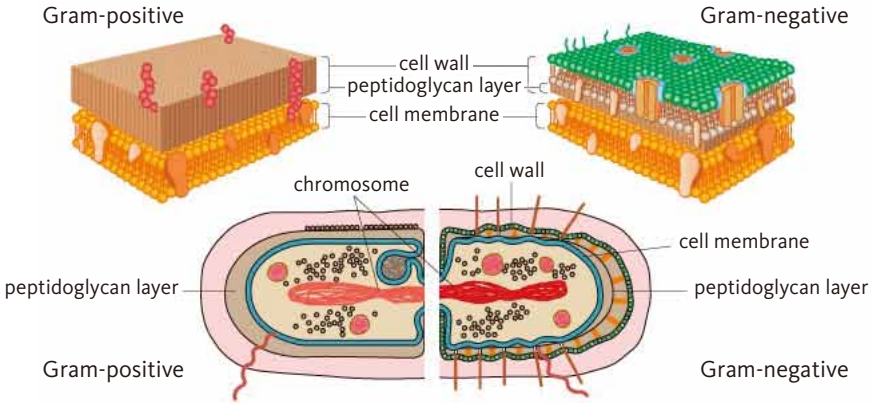


Fig. 22 *The BACT Scattergram*



	Gram-positive bacteria	Gram-negative bacteria
peptidoglycan layer	thick	thin

Fig. 23 *Structure of cell wall in Gram-positive and Gram-negative bacteria*

bacteria. The side fluorescence intensity reflects the amount of dye that has penetrated into the bacterial cell, which is affected by differences in the cell wall structure. For Gram-positive bacteria, side fluorescence intensity is lower due to the smaller amount of dye that penetrates the bacterial cell. On the other hand, side fluorescence intensity for Gram-negative bacteria is higher due to a larger amount of dye penetration. BACT-Info. is displayed as one of four potential messages: "Gram-positive?", "Gram-negative?", "Gram-pos/neg?" and "Unclassified" (***Table 11***, ***Fig. 24***).

To provide additional research information, UTI-Info. is also available with the UF-1500 as well as the UF-5000. Based on the combination of white blood cell and bacterial counts, either UTI-Info. (UTI Information) or "UTI?" is displayed. "UTI?" is displayed for samples that exceed the default setting threshold for WBC (10/mL) and BACT (10/mL). The threshold setting is programmable and can be changed.

Table 11 *Interpretation of BACT-Info.*

Information	Meaning of Message
Gram-positive?	Bacteria with low Side fluorescence signal intensity and high forward scattered light signal intensity are present.
Gram-negative?	Bacteria with high Side fluorescence signal intensity and low forward scattered light signal intensity are present.
Gram-pos/neg?	Mixed bacteria are present.
Unclassified	Signal information alone is not enough to make an accurate decision.

If the number of BACT or WBC is below the set value, no judgment is made.
BACT- Info. Initial setting for output is WBC 10/μL or more and BACT 100/μL or more.

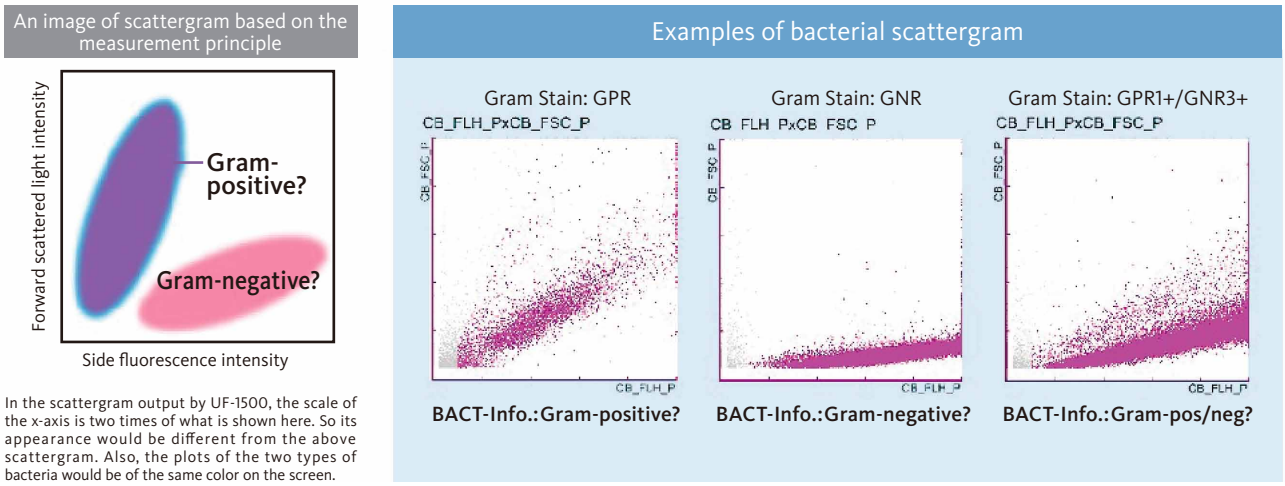


Fig. 24 *Detection of BACT-Info.*

DISPLAY AND OUTPUT OF ANALYSIS RESULTS

As described above, the intensity, width, waveform area, waveform forward scattered light, side fluorescence, side scattered light and depolarized side scattered light are obtained by flow cytometry for each particle. The measurements are analyzed and the particles are differentiated using algorithms that take into account all these results.

The results screen on the analyzer's main unit displays the analysis findings (quantitative and semiquantitative), comments, scattergrams, and the research parameters. (***Fig. 25***). When the analyzer is connected to the U-WAM, all scattergrams are available (***Fig. 26***). The main unit can also be connected to a printer to show results (results of both reportable and research parameters can be obtained, but printing research parameters is restricted by an access authorization feature).

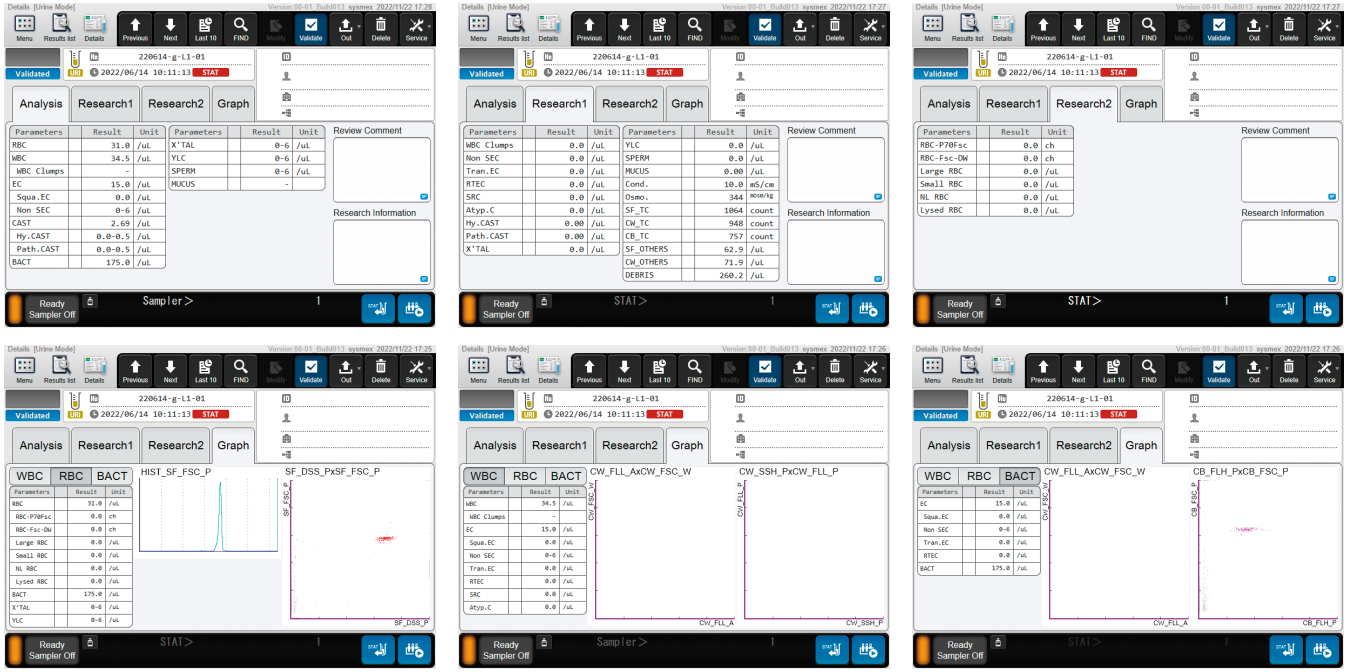


Fig. 25 *Analysis results screen (UF-1500)*
The display screen may differ based on local regulations.

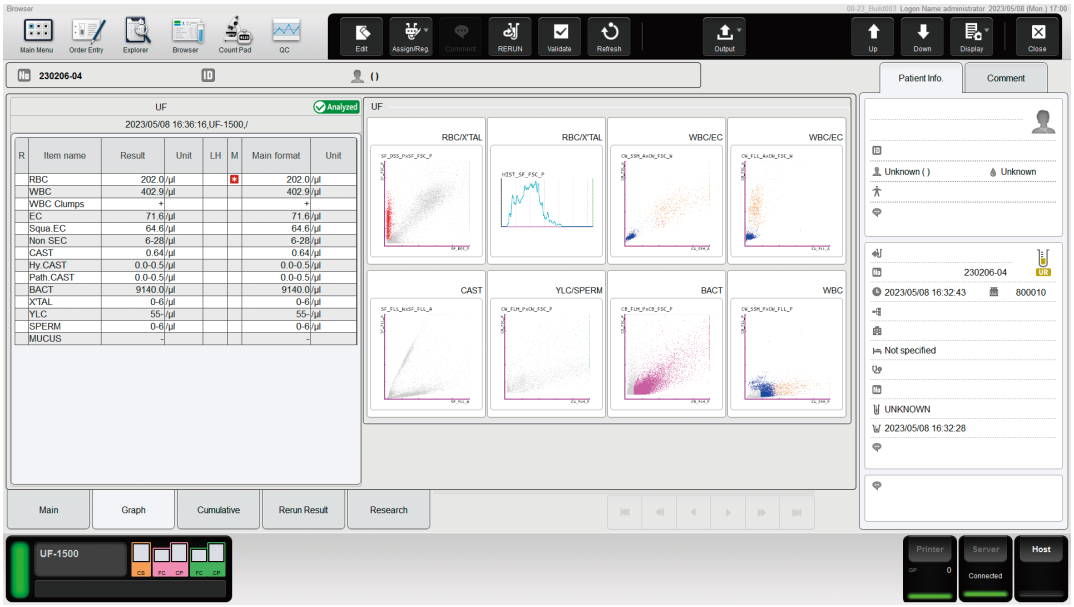


Fig. 26 *Analysis results (scattergram) screen (UF-1500)*
The display screen may differ based on local regulations.

FUNCTIONS OF ANALYZER

The functions of the analyzer main unit are as follows.

- Sampler measurement and stat measurement
- Data storage capacity for analysis results
- Quality control
- Anti-carryover

In cases where RBC or WBC is ≥ 10,000/μL or BACT is ≥ 1,000/μL, the anti-carryover function is activated to perform auto rinses (these thresholds can be adjusted in the analyzer setting screen).

- Flagging of low-reliability data (abnormal classification, abnormal conductivity, etc.)
- Threshold setting and flagging functions for abnormal (positive) samples and REVIEW samples
- Automatic recognition of the lot number and validity from the IC tag of the reagents (staining solutions)
- Barcode recognition for reagents and controls (reading of lot number and reference values)
- Automatic monitoring of remaining reagent volumes
- Automatic start-up function (optional)

QUALITY CONTROL AND CONTROL MATERIALS

Consistent with the UF-1000*i* and UF-5000, the UF-1500 has quality control functions. The X-bar and/or the L-J control functions can be implemented. UF-CONTROL™ (***Table 12***) is a quality control material for the analyzer. It is available in two levels, UF-CONTROL™-H and UF-CONTROL™-L. The lot information for the control material can be obtained by scanning the barcode on the assay sheet that comes with the UF-CONTROL™ using the hand-held reader.

For implementing quality control, first, select the control material and the specified lot number on the analyzer screen. The control material is then placed in the sample cup and set in the STAT sample holder, where the measurement is made.

The analysis results can be viewed on both the QC chart screen and the radar chart screen. (***Fig. 27***). The analyzer main unit keeps a record of results from 2 concentrations × 3 lots (120 plots/lot), and when the U- WAM is connected, 300 plots × 50 files can be stored in WAM.

The purpose of internal quality control testing, using the quality control function, is to verify analyzer repeatability. The analyzer is calibrated during production and periodically during scheduled maintenance checks. The internal quality control is used to verify whether the analyzer performed according to specifications at the indicated performance level. Target values and upper and lower limits provided on control material assay sheets are used as indices of accuracy while conducting routine quality control. However, these should not be used as indices for evaluating routine quality control results. The internationally recognized CLSI C24-A3 [10] guidelines from the Clinical and Laboratory Standards Institute (CLSI), state "the assay values provided by the manufacturers should be used only at the start of internal quality control, and ideally, the target values and limits may be determined using 20 measurements made on different days". Therefore, for internal quality control of the UF-1500, the assay sheet ranges may be taken as an approximate guideline and the target values and limits should preferably be set based on actual measured values. Given the principle of measurement used by this analyzer, the results obtained from sensitivity parameters, such as SF_FSC_P, have greater importance than the results of particle count analysis from control materials. The analyzer results are more accurate because if the sensitivity parameter shows a large change, the scattergram distribution is altered, making it difficult to achieve the designed differential classification performance. All particle counts measured by the analyzer are believed to be accurate based on the RBC and WBC control counts.

Table 12 *UF-CONTROL™*

Name	UF-CONTROL™
Components	UF-CONTROL™-H: Particulate component 0.4% (W/W)
	UF-CONTROL™-L: Particulate component 0.1% (W/W)
Functions	Controls materials for quality control of Sysmex fully automated urine particle analyzer and fully automated urine particle digital imaging device
Remarks	Contains latex particles

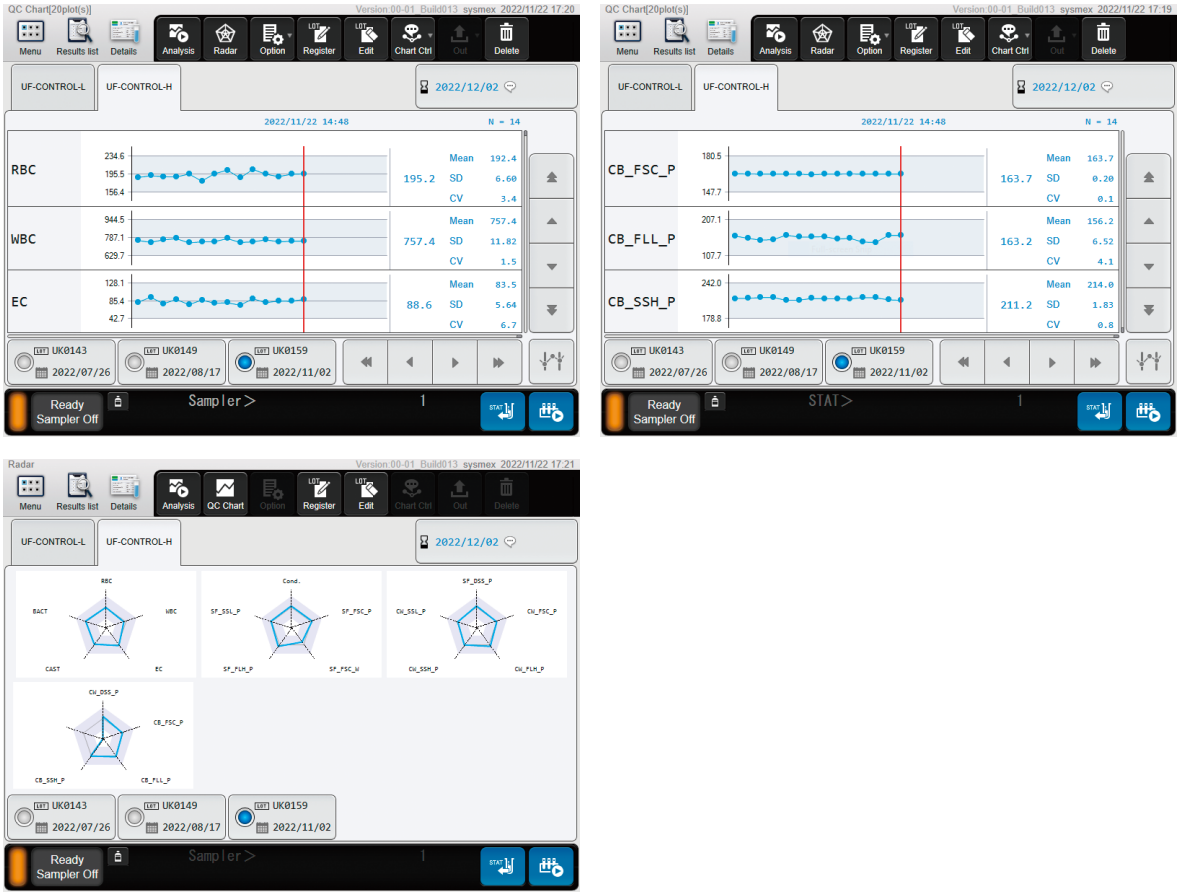


Fig. 27 *QC screen*

CONCLUSION

In summary, the UF-1500 has a smaller footprint and a lower cost point but utilizes the same advanced technology as the UF-5000, our flagship model. Since the UF-5000 was launched, there have been many publications showing the clinical value of the automated analyzer for kidney disease, UTIs, bladder cancer and other conditions [11-44]. These findings and benefits are also applicable to UF-1500. Even though the UF-1500 is new to the market, the clinical evidence that has been shared globally also applys to the UF-1500. Therefore, the UF-1500 is expected to contribute to automation of urine sediment analysis in small-sized laboratories as well as general practitioner (GPs) and urology offices. Additional features such as the automated start-up function are available that can further enhance lab efficiency. We believe the UF-1500's advanced analysis capabilities will improve laboratory productivity and promote clinical value. It remains possible with future clinical research, such as comparison of analyzer findings with guideline-based criteria, that automated analyzers may provide new evidence-based test information. Automated laboratory technology may play a pivotal role in point-of-care testing and not be positioned merely as screening devices before proceeding with further microscopic urine sediment analysis.

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