



Metafer

Scanning and
Imaging Software

METAFER SLIDE SCANNING SOFTWARE

Metafer, MetaSystems' slide scanning software, is the keystone of a versatile and robust microscopy imaging system. In combination with selected scanning hardware, Metafer enables the automation and standardization of microscopy applications.

Versatile

The Metafer software is unique in its architecture. Based on highly specialized scanning algorithms, all automated microscopy jobs are defined by parameters that are grouped into user-accessible classifiers.

Classifiers contain information about hardware and software settings, protocols for intelligent and adaptive autofocus sequences, image processing macros, and also the object features to be assessed. Thereby, a single Metafer instance can manage an unlimited number of classifiers and thus host

many different applications. Despite its versatility, the Metafer software is very easy to operate in routine. Once a workflow and thus an evaluation standard has been defined, the software is controlled with a few mouse clicks. Installations can then also work completely unattended with workflow files generated by external databases.

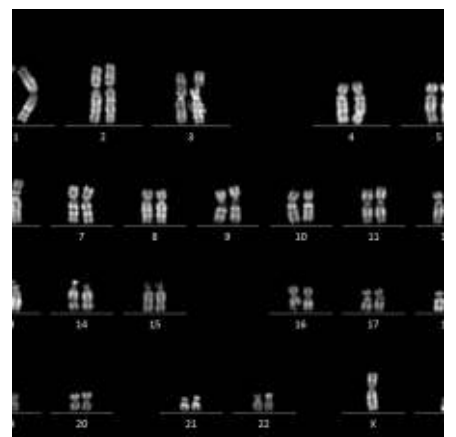
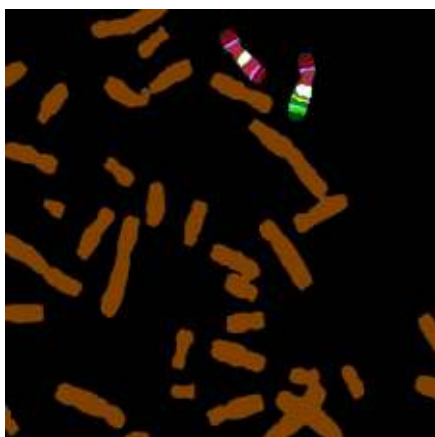
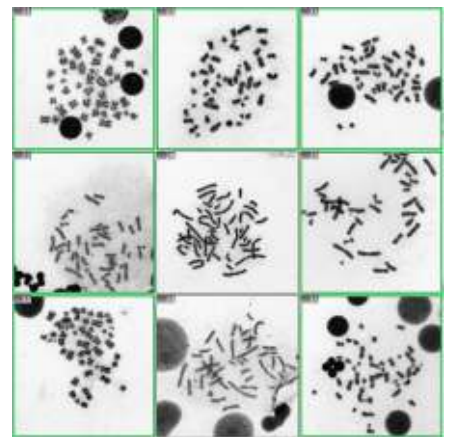
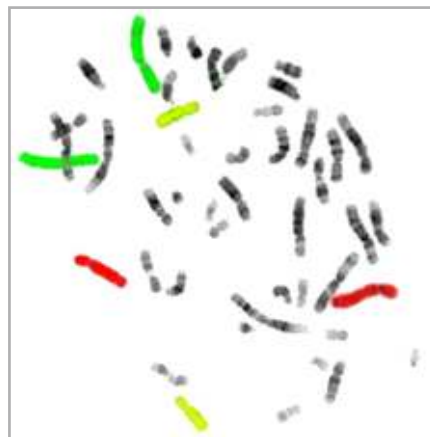
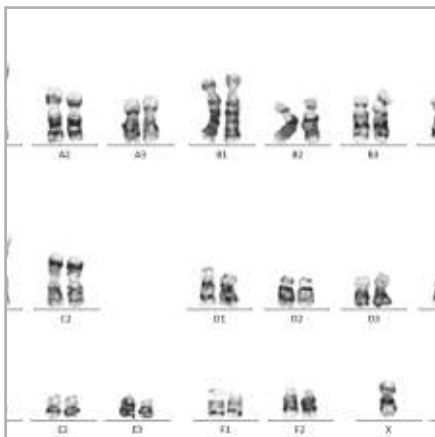
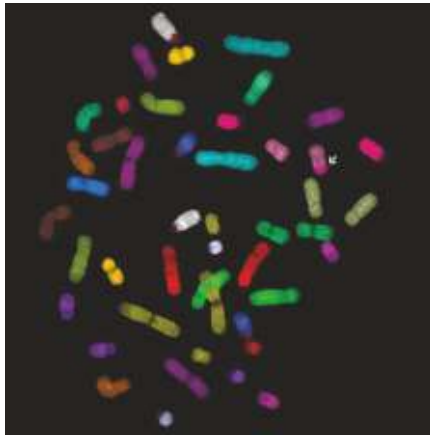
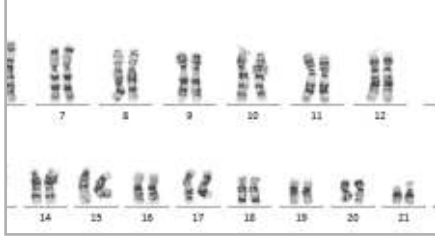
Fast

The imaging systems managed by Metafer support state-of-the-art camera technologies, many different illumination devices and high-precision scanning hardware. All recommended hardware components have been thoroughly tested by MetaSystems and selected for their excellent performance. The unique combination of selected hardware and state-of-the-art software results in outstanding scanning speed and precision.

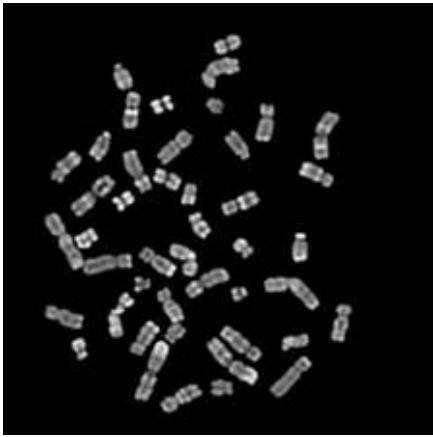


Metafer Highlights

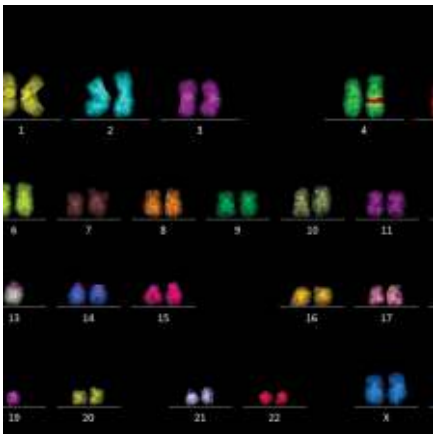
- **Open Architecture**
Flexible scanning configuration, customizable workflow design, and transparent results documentation with many import and export possibilities.
- **High-Speed Scanning**
Optimized algorithms, high-resolution cameras, and modern scanning hardware for highest scanning speed.
- **Optimized for Clinical Routine**
Seamless integration in different working environments, and one-click or remote operation (e.g., by data from laboratory information management systems; LIMS).
- **Intelligent Focusing**
Elaborate autofocus algorithms with automated adaptation to sample thickness and quality, image processing for focusing, and real-time feedback of focusing quality.
- **Sophisticated Investigation Options**
More than 80 image processing operations, and over 300 algorithms for signal and cell feature assessment.
- **Scalability**
Scanning capacities from 8 to 800 slides, optional bar code reader, and immersion oil dispenser to adjust the degree of automation to the requirements.



CHROMOSOME IMAGING



*Automation of microscopy is one of the most efficient ways to increase throughput and improve quality in classical cytogenetics. MetaSystems offers a modern and flexible solution for this purpose. The seamless interaction of **Metafer Metaphase** for exceptionally fast metaphase search, quality-sorted image acquisition, and karyotyping with *Ikaros* software and its patented artificial intelligence-based algorithms is appreciated in many countries as a robust, fast, and reliable aid for everyday laboratory work.*



Finding Metaphases

Metafer Metaphase quickly and reliably finds metaphases on human or non-human metaphase specimens. The unique concept of user-trainable classifiers allows to quickly adapt the search to different specimens and contrasting methods (e.g. Giemsa staining, fluorescence and even phase contrast). Each metaphase found is displayed in an overview gallery and can be relocated on the microscope stage with just one mouse click.

Acquiring images

Found metaphases are stored together with their respective coordinates and can be captured automatically at any time. This is usually done during the search, with the immersion oil dispenser preparing the slides for the use of high-powered objectives. Up to 12 color channels can be defined for imaging. The required objectives and/or fluorescence filters are automatically activated. Therefore, the system operated by Metafer is perfectly suited for high throughput or even 24/7 operation.

Workflow Optimization

Metafer has a number of intelligent training and optimization routines for adapting the search to different scenarios. For instance, search classifiers can be trained to sort metaphases by quality to ensure that only the best ones are selected for acquisition.

Data Management

Immediately after acquisition, all metaphases are available on any connected workstation. Metafer records every single image, tracks all processing steps, and assigns images and cases to a user account. At a glance, experts can see in Neon, Metafer's case and image management, which images and cases have been newly created, which ones require attention, and which have already been assessed by a colleague.

RAPID FISH SPOT WORKFLOW

*MetaSystems and its sister company MetaSystems Probes (manufacturer of high-quality DNA and RNA probes for routine and research) work hand in hand to develop integrated analytical solutions for cytogenetics, hematology, and oncology. Automated microscopy of fluorescence in situ hybridizations (FISH) in single cell samples and in tissue sections are integral parts of Metafer's application package portfolio. MetaSystems offers the **RapidScore** technology, a fast and streamlined workflow for swift review of FISH samples. RapidScore dramatically reduces the time required for scoring and evaluating FISH cases.*

Scanning

Slides labeled with FISH probes are automatically scanned by Metafer managed systems. Dedicated classifiers for each FISH probe layout identify target nuclei based on their morphology and automatically acquire the signals. Metafer's intelligent focusing

and image acquisition algorithms analyze sample quality as the system scans and use image processing to improve results. All signal channels are acquired as a focus stack so that signals can be perfectly visualized.

The nuclei selected by Metafer are displayed as processed gallery images. The respective nucleus selected in the gallery is additionally displayed as an unprocessed original image in its vicinity. Each gallery image contains suggestions for a possible signal evaluation, which are also summarized in an interactive histogram. In addition, Metafer assigns a class number to each nuclei, representing the identified spot and fusion pattern.

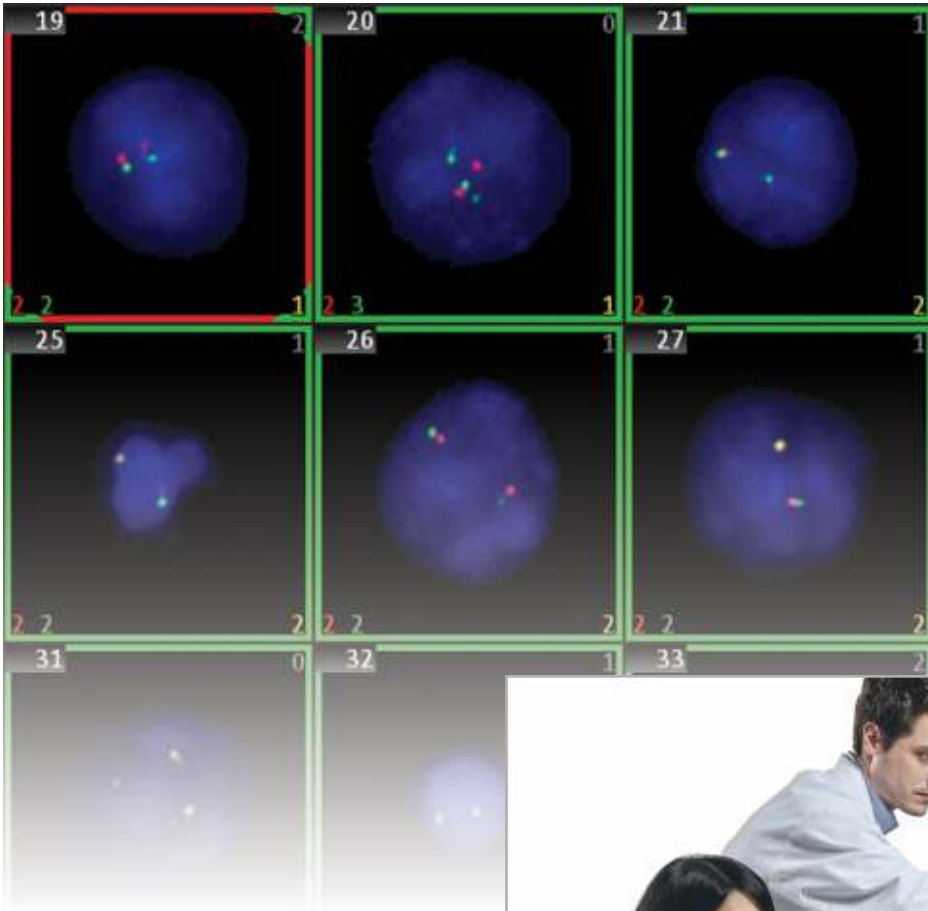
One-Click Review (RapidScore)

Immediately after scanning, the results are available on any connected workstation. The automatically obtained data can now be checked by experts.

With the dedicated RapidScore keyboard, operators can quickly check and correct the proposed results. Each key represents one of the signal pattern classes defined in the Metafer classifier. The reviewed nuclei are automatically marked and the new results are displayed in a second diagram.

Comprehensive Documentation

RapidScore is efficient and flexible. Cases are processed jointly by different scorers, while the software keeps track of all results. If a sample contains signal classes not existing in the classifier's portfolio, it is easy to create and assign a new class. Metafer even suggests the class name based on the automatic evaluation results. Documentation of each cell's analysis history minimizes the need to create multiple slides for the same case. Customizable reports can display a gallery of selected nuclei including their signals, a graph or table of analysis results, and the users.



↑
 RapidScore is a unique technology that combines the reliability of automated signal detection with the flexibility of extremely fast, manual one-click reviewing.

→
 Thanks to Metafer, each single cell is available for review immediately after the scan. Objects can be reviewed as processed gallery images and as unprocessed original images. Users can visualize the single focus levels and the extended focus image of the latter.



MAGAZINES

Slide frame magazines hold 16 frames with 5 slides each, for a total of 80 slides.

A fully equipped SlideFeeder x80* hosts 10 magazines plus one bar code reader.

Each magazine is portable and can easily be taken to the workbench for loading.

SLIDE FEEDER

The rotating module of the SlideFeeder x80* delivers the slide frames to the motorized stage of the microscope.

The device runs unattended and is prepared for 24/7 operation - including intelligent priority sample handling.

AUTOOILER

If the current workflow requires the use of an immersion oil objective, the automated oil dispensing device* is engaged.

Detailed sample dependent macros control optimal oil dispersal for each sample.



* Some hardware components supplied by other manufacturers are not included in MetaSystems IVD products and are therefore not IVD medical devices.



CAMERAS

There are different CoolCube digital camera models* to choose from. All models are available as monochrome or color versions.

The cameras provide seamless automated integration with the Metafer software enabling optimal performance.



MICROSCOPE

Metafer operates a motorized, high-end research microscope* equipped with a stepping-motor stage to enable the finding of objects.

All features of the microscope are directly driven by the Metafer software.



SOFTWARE

The PC based Metafer software controls the scanning hardware and provides a convenient user interface prepared for all-day, routine use. Thanks to the exceptional classifier concept the Metafer software provides the optimal balance between flexibility and standardization.



Study Report

Date of Study: 27.10.2017
 Supervisor: Prof. Hagen, Würzburg

Study Purpose:

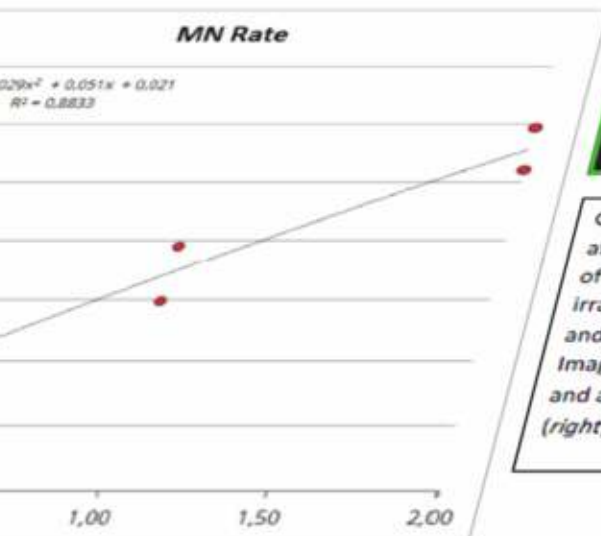
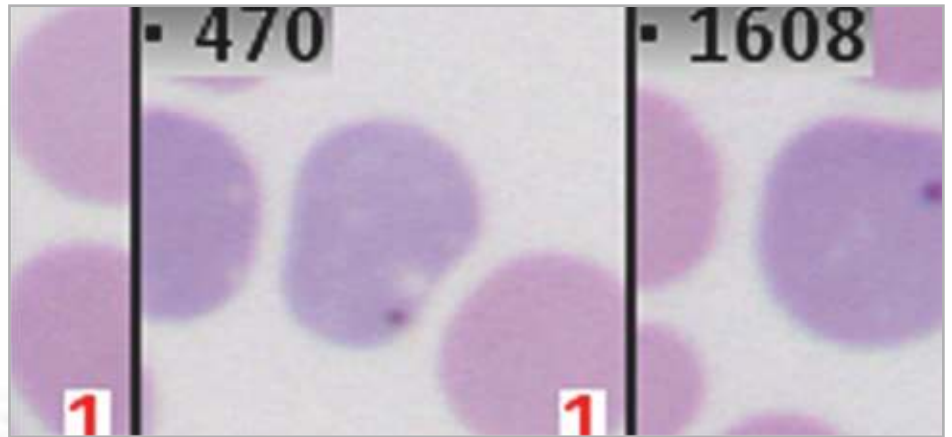
Dose-effect study after direct in-vitro irradiation, with exposure-response relationship, describes the effects of levels of exposure (or doses) to a stressor (here: ionizing dose). The micronucleus test quantifies DNA fragments which are termed micronuclei (MN) in objects during first after-exposure division.

Material:

Human lymphocytes (healthy donors).

Total No. of Scans: 8

Case	Scan	Consent	Date	Total	Bi-Nucl.	Micronucl.	Cells w/ MN	MN/Cell
2017-10-01		0.0 Gy	27.10.2017 13:38:46	638	21	617	0	0.0000
2017-10-01	G	0.0 Gy	27.10.2017 11:22:42	6591	1273	5318	44	0.0416
2017-10-01	B	0.5 Gy	27.10.2017 13:36:54	436	305	131	15	0.0492
2017-10-01	H	0.5 Gy	27.10.2017 13:10:57	4001	695	4006	28	0.0432
2017-10-01	I	1.0 Gy	27.10.2017 13:14:32	6540	1164	5416	61	0.0593
2017-10-01	J	1.0 Gy	27.10.2017 13:13:38	5890	756	5134	50	0.0760
2017-10-01	A	2.0 Gy	27.10.2017 13:37:54	770	77	693	8	0.1039
2017-10-01	D	2.0 Gy	27.10.2017 13:41:30	1061	557	504	64	0.1185



Gallery images of bi-nucleated cells after exposure to X-rays. Addition of Cytochalasin B directly after irradiation suppresses cytokinesis and results in cells with two nuclei. Images show undamaged cell (left) and a cell with one micronucleus (right).

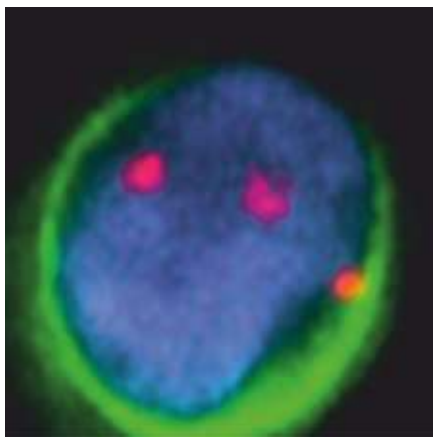
Since the installation of the first Metafer version over thirty-five years ago, Metafer has been continuously optimized and now also detects objects other than metaphases and FISH signals. Today, every system managed by Metafer is capable of detecting cells, nuclei, subcellular structures, or other items in an unattended manner. Metafer users can choose from more than 300 parameters to specify their target objects. As with metaphase finding, each detected object is displayed in the gallery for immediate review. Metafer is therefore utilized worldwide for fast, reproducible, and reliable object detection.

0DlsXMDSUAAABAA7FaBhW8DSUACCAgAJwDYnAHPRYRl



Based on more than 300 feature detection algorithms, Metafer offers robust tools to quantify markers like micronuclei in rodent erythrocytes for the in vivo micronucleus assay.

The ability to combine different markers in a single assay allows for an increased detection precision. For example, to detect circulating tumor cells, immune-based markers and FISH signals can be analyzed in the same multichannel scan.



Application Package

Finding Rare Events

Finding extremely rare cells on slides requires assessing multiple cell features simultaneously. Metafer's flexibility allows for combining multiple criteria together accurately defining the target cells. Thanks to the unique Metafer classifier concept, it is possible to set up a detection workflow that combines morphology criteria with specific markers, such as for the cell membrane, as well as with FISH signals.



OBJECT RECOGNITION, QUANTIFICATION & CHARACTERIZATION

Application Packages

Quantifying DNA Damage

DNA damage quantification represents a routine tool in genetic toxicology and radiation biology. However, observed effects can be very subtle. Automation of microscopy in analysis has proven helpful in standardizing tests and facilitating international collaboration. Metafer's flexibility and precise evaluation standards make it one of the most important automation solutions for toxicology and biological dosimetry.

Application Package

Forensic Sperm Scanning

Examination of sperm in forensic samples is a helpful but time-consuming method to convict perpetrators of sexual crimes. With the help of artificial intelligence, Metafer supports forensic laboratories in clearing their often large backlog of unprocessed cases. In addition to the actual search for sperm cells, the software also provides comprehensive documentation of all results.

SAMPLE IMAGING & VIRTUAL SLIDES

Metafer combines the advantages of a flexible software architecture with a fully equipped, motorized microscope and modern, high-quality imaging automation. When digitizing tissue samples, a system managed by Metafer is therefore not restricted to just some magnifications or contrasting modes.

Sample Digitization

Metafer automatically generates high quality images of samples under transmitted light conditions, fluorescence, phase contrast, polarized light or dark field imaging. Images can be composed of an unlimited number of focal planes. In addition, there is basically no restriction on the choice of magnifications, and even oil objectives are supported.

Comprehensive Viewer

Images and metadata can be visualized and annotated off-site with the Metafer **VViewer**. The viewer allows easy navigation over the image and even virtual focusing on the screen. If an

image contains different color channels (e.g., a transmitted light image and one or more fluorescence channels), they can be visualized separately. Color separations can even be shown side by side and synchronized in position and magnification. Information about cells and signals, individual subregions of the tissue, user annotations, alignment marks and much more are stored together with the virtual slide.

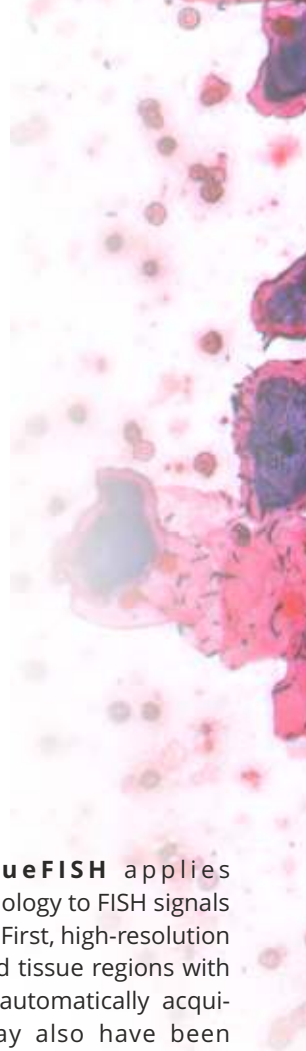
Smart Workflow

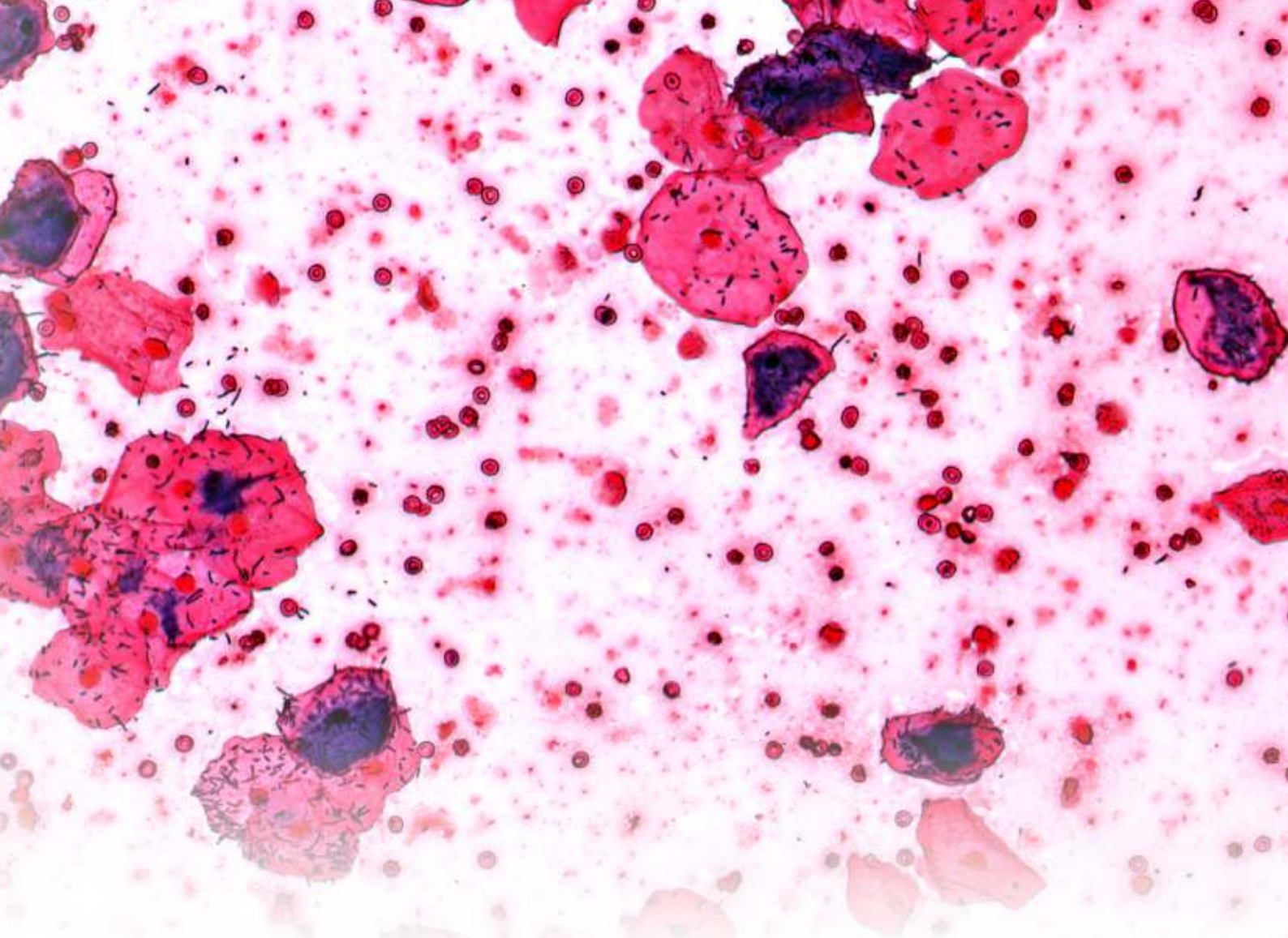
Metafer offers pathologists and other specialists a range of intelligent scanning and analysis options. The flexibility of the software makes it easy to digitize and match two consecutive tissue sections. Areas marked on a digital image of an IHC/H&E specimen are automatically transferred to the image of an adjacent section. Metafer's algorithms match regions even when images are rotated, flipped or distorted. Once the region is determined, it can be captured and evaluated with the TissueFISH package, for example.

FISH in Tissues

Metafer TissueFISH applies **RapidScore** technology to FISH signals in tissue sections. First, high-resolution images of selected tissue regions with FISH signals are automatically acquired. Regions may also have been selected on adjacent, differently stained sections; in this case, Metafer handles the transfer to the current section. Cells are pre-segmented using Metafer's advanced segmentation algorithms. After acquisition, the user can open each image in the dedicated Metafer TissueFISH application package and mark individual cells for analysis using the mouse or an interactive pen.

Immediately upon selecting a nucleus, the software's algorithms generate a suggested score. In the course of this process, a gallery image is created and the evaluation suggestions are added to the data histogram. Once all suitable nuclei are obtained from the current image, the user is prompted to proceed to the next camera image.





After finishing all fields, or after collecting enough cells for the assay, the gallery can be reviewed using the innovative and swift **RapidScore** technology.

TMA

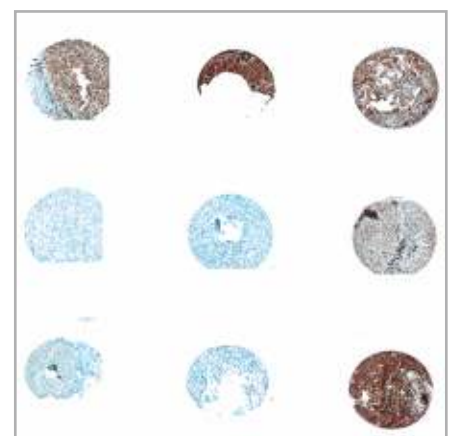
All tissue imaging features of Metafer can also be applied to tissue microarrays (TMAs). The intelligent TMA tool of Metafer uses special algorithms to match the structural layout of any TMA with the actual image. Metafer then offers several tools to assign the core designations to each single nucleus analyzed and to prepare the resulting data for single core reporting.



Metafer automates the acquisition of high-quality images from microscope samples, for example from Gram slides.



The Metafer software provides several tools to help match neighboring tissues and assign images and results to tissue microarray (TMA) cores.



VERSATILITY & MODULARITY

Versatility

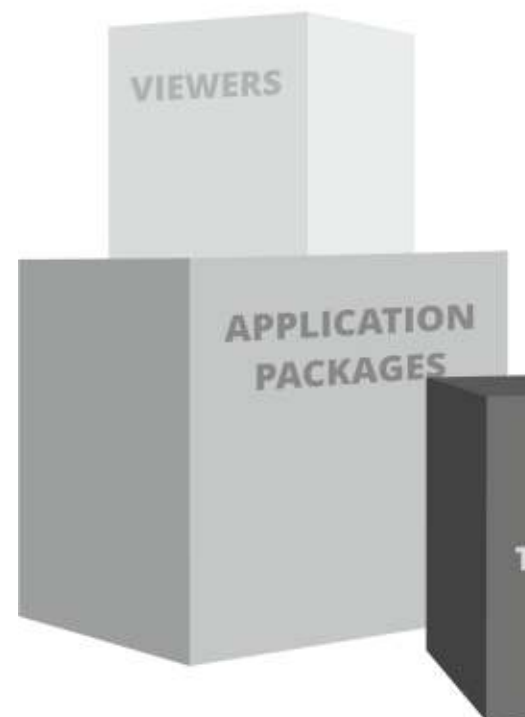
Metafer's various modules and application packages support the easy configuration of multi-user environments with separate imaging, analysis, and review stations for decentralized work. This modularity facilitates easy adaptation to specific needs. Moreover, different applications can be performed on the same installation.

With solutions by MetaSystems, it is possible to expand the scalable multi-user network at any time and adapt it to future needs. This is supported by the fact that each Metafer module is equipped with the sophisticated case and workflow management technology Neon. The Neon case and data management engine ensures maximum data security, easy and safe access to all content, and customizable workflow and user management.

Modularity

Building customized Metafer installations is very easy, as a wide range of basic modules, analysis modules, application packages, and technologies are available.

Each Metafer installation is designed around one of the base modules. Depending on the application, these can then be supplemented by various additional application packages that give the installation its special capabilities.



METAFER PACKAGES

Base Modules

Solid Groundwork

Base Modules all come with Neon, the integrated case and image management technology, and many imaging and display functions. The choice of base module determines whether the installation is a scanning application, an image acquisition solution, a relocation or a review station.

Analysis Modules

Toolshed

Analysis Modules extend any Metafer installation by supporting the user in searching for metaphases (**Metafer Metaphase**), in evaluating cells and other objects (**Metafer MetaCyte**) or in finding rare cells at highest speed (**Metafer RCDetect**).

Viewers

Images On Stage

Metafer VSViewer displays composite images (virtual slides), provides many tools for easy image navigation, supports focus stacking, manages annotations and scan regions, displays color separations and modified colors, and provides easy functions for tissue matching.

Application Packages

Specialist Imaging

Our **Application Packages** offer tailored settings and functions to support experts in the fields of cytogenetics, hematology, toxicology, radiation biology, forensics, and more. They represent application-specific adaptations of the software.

Technologies

Smart Helpers

Functions to support artificial intelligence (Deep Neural Networks; DNNs), case and data management, image stitching, bar code reading, integration of HL7 or DICOM, and GLP are called **Technologies**. Moreover, the support of high-resolution cameras and remote analysis in networks is available.



ANALYSIS
MODULES

BASE
MODULES

TECHNOLOGIES



WORLDWIDE

AMERICAS

USA, Medford

info@metasystems.org

Argentina, Buenos Aires

info@metasystems-latam.com

OFFICES

EUROPE

Germany, Altlusheim

info@metasystems-international.com

Italy, Milan

info@metasystems-italy.com

ASIA

China, Hong Kong

info@metasystems-asia.com


China, Taizhou

info@metasystems-china.com

India, Bangalore

info@metasystems-india.com

The described functions refer to the following software versions: **Ikaros 6.3** | **Metafer 4.3**

☹️  MetaSystems software and system products are classified as in vitro diagnostic medical devices (IVD) in the European Union in accordance with the Regulation (EU) 2017/746 or Directive 98/79/EC, respectively, and carry the CE label unless otherwise indicated. Use all MetaSystems IVD products only within the scope of their intended purpose.

MetaSystems products are used in many countries worldwide. Depending on the regulations of the respective country or region, some products may not be used for clinical diagnostics.

Some hardware components supplied by other manufacturers are not included in MetaSystems IVD products and are therefore not IVD medical devices.

Application packages are application-specific adaptations of the Metafer software. It is possible that further adaptations to specific specimen conditions are necessary.

CONTACT US

OR YOUR LOCAL
MetaSystems
REPRESENTATIVE



metasystems-international.com

MetaSystems Hard & Software GmbH

Robert-Bosch-Str. 6
68804 Altlusheim | Germany

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