



Scanning
and Imaging
Platform

Fast,
Modular
and Versatile

METAFFER

 MetaSystems

METAFER SLIDE SCANNING PLATFORM

Metafer, MetaSystems' slide scanning platform, offers a unique combination of selected scanning hardware and outstanding imaging software, resulting in the most versatile and robust system available for microscope imaging automation.

Versatile

Metafer software is unique in its architecture. Based on a core of highly specialized scanning algorithms, all automated microscopy jobs are defined by sets of parameters bundled up in user-accessible classifiers. Classifiers contain information on hardware and software settings, protocols for intelligent and adaptive autofocus sequences, image processing macros, and also the object features to analyze. Metafer systems can host a virtually unlimited number of classifiers. This concept allows for applying the same Metafer platform to many different assays. Despite this versatility, Metafer software is also very easy to use routinely. Once a workflow has been defined by creating one or more classi-

fiers, the system is operated with just a few mouse clicks. If a higher degree of automation is required, Metafer can even be operated completely unattended with workflow files generated by external databases.

Fast

Metafer's performance is unsurpassed. The slide scanning platform combines state-of-the-art camera technologies with optimized microscope configurations, many different illumination devices, and ultra-precise scanning hardware to achieve unrivaled scanning speed and precision. The renowned MetaSystems CoolCube series is a complete line of high-resolution and ultrahigh-resolution CCD and CMOS cameras. All cameras are available as b/w or color models. For illumination, Metafer users can choose from a variety of devices including white LED lamps and multicolor LED light sources. All pieces of Metafer hardware have been thoroughly tested and were selected based on their outstanding performance.

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Metafer Highlights

■ **Open Platform Architecture**

Flexible scanning configuration, customizable workflow design, and transparent results documentation with many import and export possibilities

■ **High-Speed System**

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 LIMS)

■ **Intelligent Focusing**

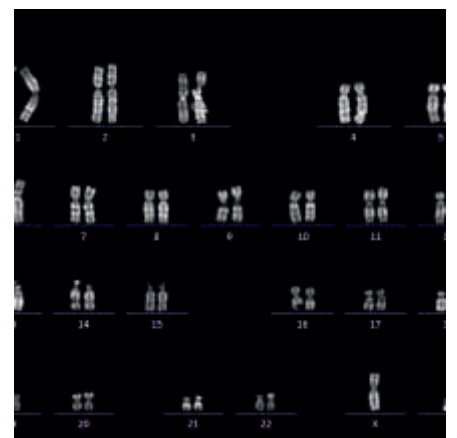
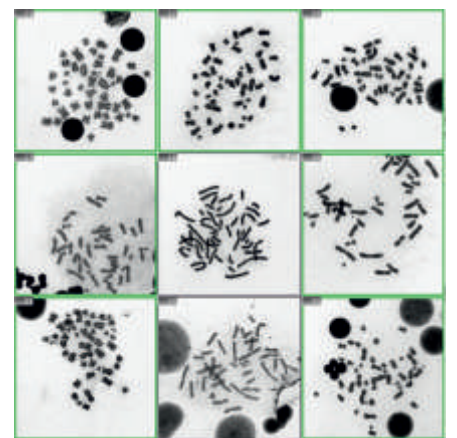
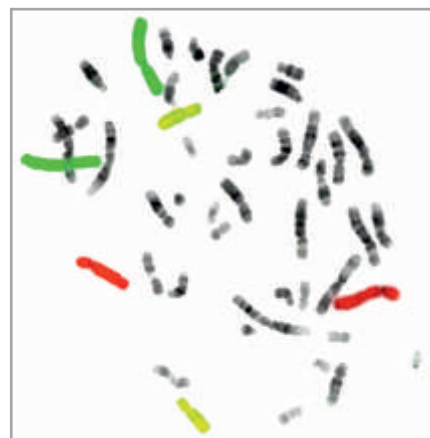
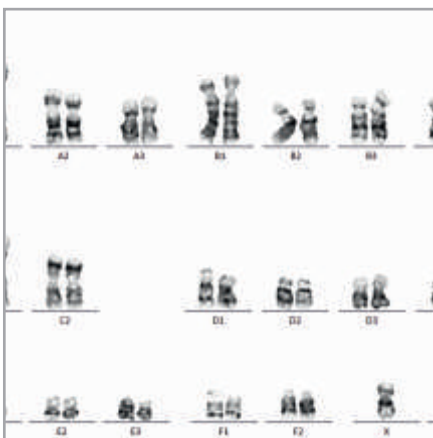
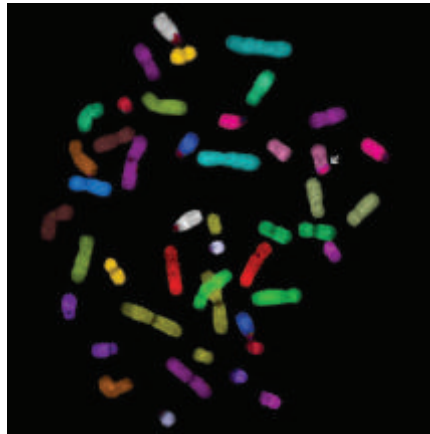
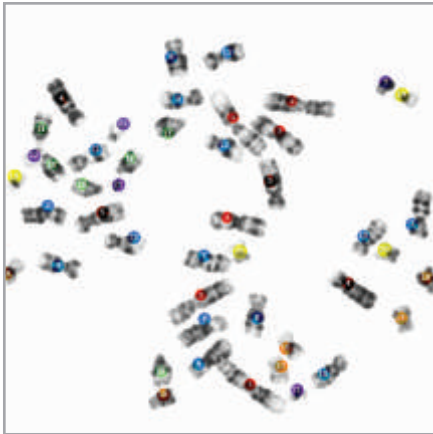
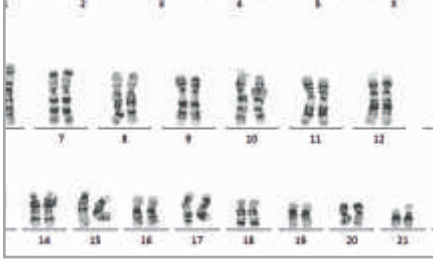
Elaborate autofocus algorithms with automated adaptation to sample thickness and quality, image processing for focusing, and real-time feedback of focusing quality

■ **Sophisticated Analysis Options**

More than 80 image processing operations, and over 300 algorithms for signal and cell feature analysis

■ **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



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CHROMOSOME IMAGING



Automation of metaphase finding and imaging is one of the most efficient ways for improving throughput and quality in classical cytogenetics. MetaSystems offers a modern and flexible imaging solution for routine applications which is based on automated metaphase finding, intelligent unattended image acquisition, and sophisticated case and image data management tools.

Finding Metaphases

The Metafer-based metaphase finder automatically finds metaphases on any human or non-human metaphase sample. User-trainable classifiers offer an easy method to adapt the search to all kinds of preparations and contrasting methods (Giemsa staining, fluorescence, and even phase contrast). Detected metaphases are displayed in an overview gallery and can be relocated on the microscope stage with just one mouse click.

Acquisition of Images

Once metaphases are detected and their coordinates are stored, Metafer

goes back to those positions and automatically acquires images using high-resolution optics. Up to 12 color channels can be defined for acquisition. Required objectives and/or fluorescence filters are engaged automatically. The immersion oil dispenser prepares slides for the use of high-power lenses. Therefore, the system is perfectly suited for high throughput or even 24/7 operating modes.

Training and Workflow Optimization

Metafer's metaphase finder comes with a number of intelligent training and optimization routines for adapting search algorithms to different scenarios. For instance, search classifiers can be trained to assign quality scores to all metaphases. The automated image acquisition can then be set to automatically select a predefined number of best quality metaphases. This also applies to clonal samples: in this case, Metafer can be set to acquire a number of best metaphases from each single clone.

Data Management

Immediately after acquisition, all metaphases are available on any connected **NEON** case and image management station. Neon records each single image, keeps track of all processing steps, and assigns images to a user. Additionally, metaphases can receive customized labels for further categorization. Images can be directly opened for karyotyping or for FISH analysis. Additionally, lists of metaphase coordinates can be exported to the vernier scales of manual microscopes.



FISH SIGNAL SCORING

MetaSystems, and its sister company MetaSystems Probes (a manufacturer of high-quality DNA probes for routine use and research), work hand in hand to shape integrated analysis solutions for cytogenetics, hematology and oncology. Automated interphase FISH analysis in single cell samples and in tissue sections are integral parts of Metafer's application portfolio. MetaSystems proudly offers RapidScore, the fastest and leanest workflow for precise automated and semi-automated FISH signal analysis. RapidScore dramatically reduces the time to score and evaluate FISH cases.

RapidScore

With RapidScore, slides labeled with MetaSystems Probes' signals are fully and automatically scanned by the fluorescence imaging module of Metafer. Dedicated classifiers for each FISH probe identify target nuclei by their morphology and automatically acquire the signals. Metafer's intelligent focusing and image acquisition algorithms analyze the sample quality while the system is scanning, using image pro-

cessing to enhance the results, and acquiring all signal channels as extended focus images. As a result, all signals are well-focused and show the best definition even if the sample quality is poor.

Nuclei picked by Metafer are immediately displayed as a processed gallery image. The original image of the current nucleus and its vicinity is shown, simultaneously. Scores of FISH signals and signal fusions are displayed in the corners of the gallery images. Additionally, Metafer assigns a class number to each nucleus, representing the spot and fusions pattern identified.

One-Click Review

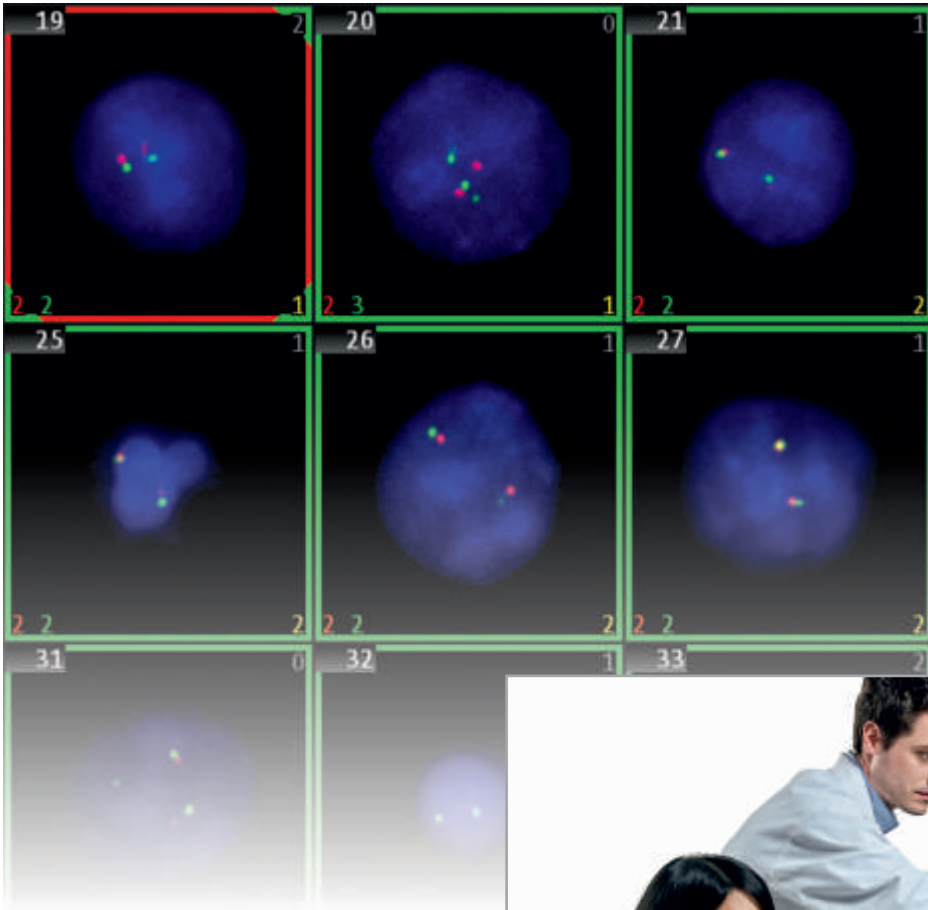
After scanning, results are available on any connected Neon station. With the Metafer review module, the automatically obtained data can be reviewed using the dedicated RapidScore Keyboard. Each key of the keyboard represents one of the signal pattern classes defined in the Metafer classifier. On review, users can change the

pattern of each nucleus simply by pressing the corresponding key. Reviewed nuclei are automatically marked and the new results are displayed in a second diagram.

RapidScore is extremely efficient and flexible. Cases can be shared between different scorers, and Neon will automatically keep track of all results. If a sample has signal classes which are not part of the classifier's portfolio, it is very easy to create and assign a new one. Metafer even proposes the class name based on the automated scoring results. The documentation of each cell's analysis history in Neon minimizes the requirement of making multiple slides for the same case. Comprehensive customizable reports can show a gallery of selected nuclei including their signals, a diagram or a table of the analysis results, and, of course, the users who have scored the case.

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↑
 RapidScore is a unique technology to combine 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

Metafer's slide frame magazines hold 16 frames with 5 slides each (80 slides in total). 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.

FEEDER MODULE

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

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.



CAMERAS

Metafer users can choose between four different CoolCube digital camera models. All models are available as monochrome or color versions.

The outstanding performance of MetaSystems' CoolCube cameras is optimally exploited by Metafer.

MICROSCOPE

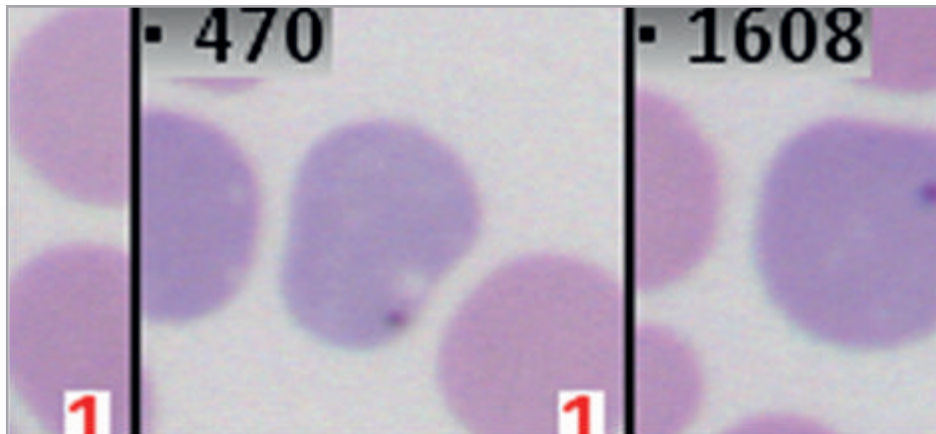
Metafer integrates a motorized, high-end research microscope equipped with a stepping-motor stage of the highest precision.

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 each Metafer provides the optimal balance between flexibility and standardization.





Study Report: MN2017-10-01

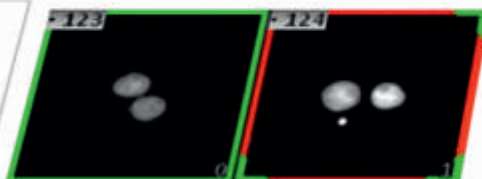
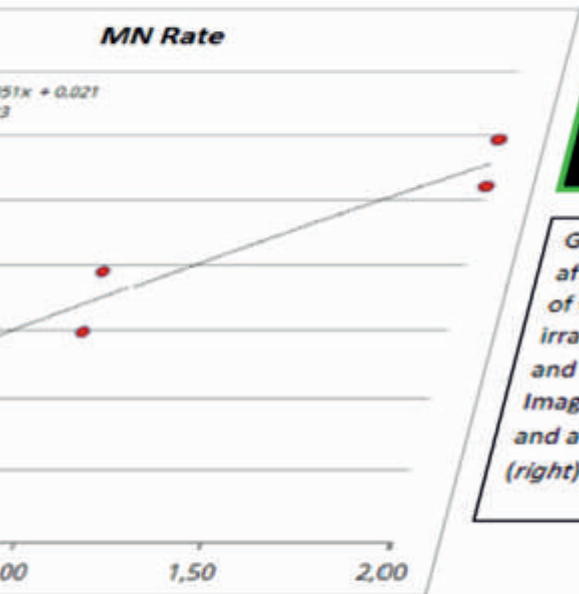
Date of Study: 27.10.2017
 Supervisor: Prof. Hagen, Walter

Study Purpose:
 Dose-effect study after direct in-vitro irradiation with X-rays. The dose-response relationship, or exposure-response relationship, describes the change in effect on an organism caused by differing levels of exposure (or doses) to a stressor (here: ionizing irradiation) after a certain exposure time, or dose. The micronucleus test quantifies DNA fragments which are turned in small nucleus shaped micronuclei during first after-exposure division.

Material:
 Human lymphocytes (healthy donors).

Number of Scans: 8

Scan	Comment	Date	Total	Bi-Nucl.	Mono-Nucl.	Cells w/ MN	MN Rate
1	0.0 Gy	27.10.2017 13:38:46	638	21	617	0	0.0000
2	0.0 Gy	27.10.2017 11:22:42	6591	1273	5318	44	0.0416
3	0.5 Gy	27.10.2017 13:36:54	436	305	131	15	0.0492
4	0.5 Gy	27.10.2017 13:10:57	4901	695	4206	28	0.0432
5	1.0 Gy	27.10.2017 13:14:32	6580	1164	5416	61	0.0593
6	1.0 Gy	27.10.2017 13:13:38	5890	756	5134	50	0.0780
7	2.0 Gy	27.10.2017 13:37:54	770	77	693	8	0.1039
8	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 first Metafer model was installed over thirty years ago, the system has been continuously optimized and now also detects objects other than metaphases and FISH signals. Today, every Metafer system is capable of detecting cells, nuclei, subcellular structures, or other items while unattended. Metafer users can choose from more than 300 parameters to specify their target objects. Like in the metaphase finder mode, each detected object is displayed in the gallery allowing for immediate review. Therefore, Metafer is utilized worldwide wherever swift, reproducible and reliable object recognition is required.

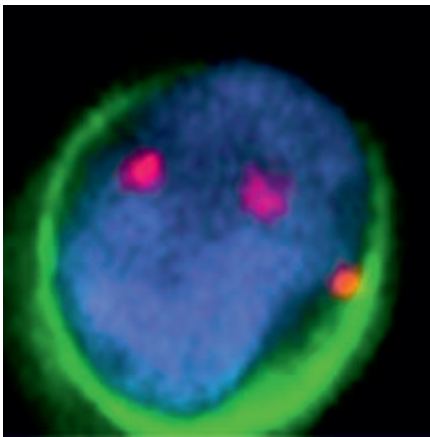
METAFER





Based on more than 300 feature detection algorithms, Metafer reliably quantifies markers like micronuclei in rodent erythrocytes for the *in-vivo* micronucleus assay.

The possibility to combine different markers in a single assay allows for increasing the precision of detection. To detect circulating tumor cells, for example, immune-based markers and FISH signals are analyzed in the same multi-channel scan.



OBJECT RECOGNITION, QUANTIFICATION & CHARACTERIZATION

Finding Rare Events

To find extremely rare cells on microscope slides, such as residual tumor cells in blood, this often requires the correlation of different markers and features. The flexibility of Metafer allows for combining multiple criteria which together precisely define the target cells.

Based on the unique strengths of the Metafer classifier concept, it is possible

to set up a detection workflow which combines morphology criteria with membrane markers and FISH signals.

Quantifying Objects

There are various assays available for the quantification of residual DNA damage in cells which were exposed either to chemical substances or to ionizing radiation. Though the design of these assays was done based on manual scoring methods, it has been

easily possible to design protocols which replace the manual observation with an automated analysis by Metafer. Consequently, Metafer became the most versatile tool for the analysis of microscope-based genetic toxicology assays and for retrospective biological dosimetry. The outstanding speed of the system, in combination with the unrivaled reproducibility, made Metafer a standard for these fields of work in many countries.

SAMPLE IMAGING & VIRTUAL SLIDES

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

Sample Digitization

Metafer generates outstanding high-quality images from all samples under transmitted light conditions, fluorescence, and even from samples contrasted with phase contrast, polarized light, or dark field. Images can be composed of an unlimited number of focus planes and can hold information about cells and signals, single subsections of the tissue, user annotations, alignment marks, and much more. Images and metadata can be visualized and annotated off-site with the dedicated viewer software, or with an internet browser. Since focus planes are stored separately, it is possible to virtually move through the sample along the Z axis. If an image contains different color channels (for example a transmit-

ted light image and also a number of fluorescence channels) they can be visualized separately. Of course, the viewer also offers various tools to enhance and optimize the images.

Smart Workflow

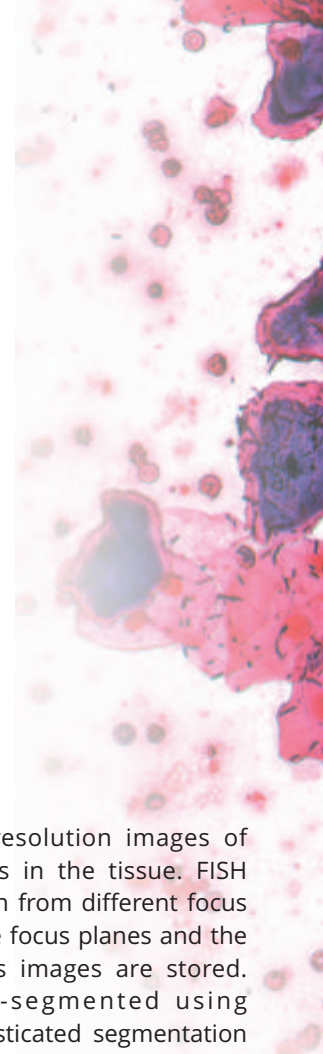
Metafer offers a number of smart scanning and analysis workflows for the pathologist. Due to the flexibility of the system, it is easy to digitize and match two consecutive tissue sections. Regions marked on a digital image taken from an IHC / H&E sample are automatically transferred to the image of a neighboring section. Metafer's algorithms match the regions even if images are rotated, mirrored or distorted. Once determined, the region can be acquired and analyzed by Metafer, for example, with the TissueFISH tool.

TissueFISH

The Metafer TissueFISH tool applies the advantages of RapidScore to the analysis of FISH signals in tissue sections. For TissueFISH, Metafer

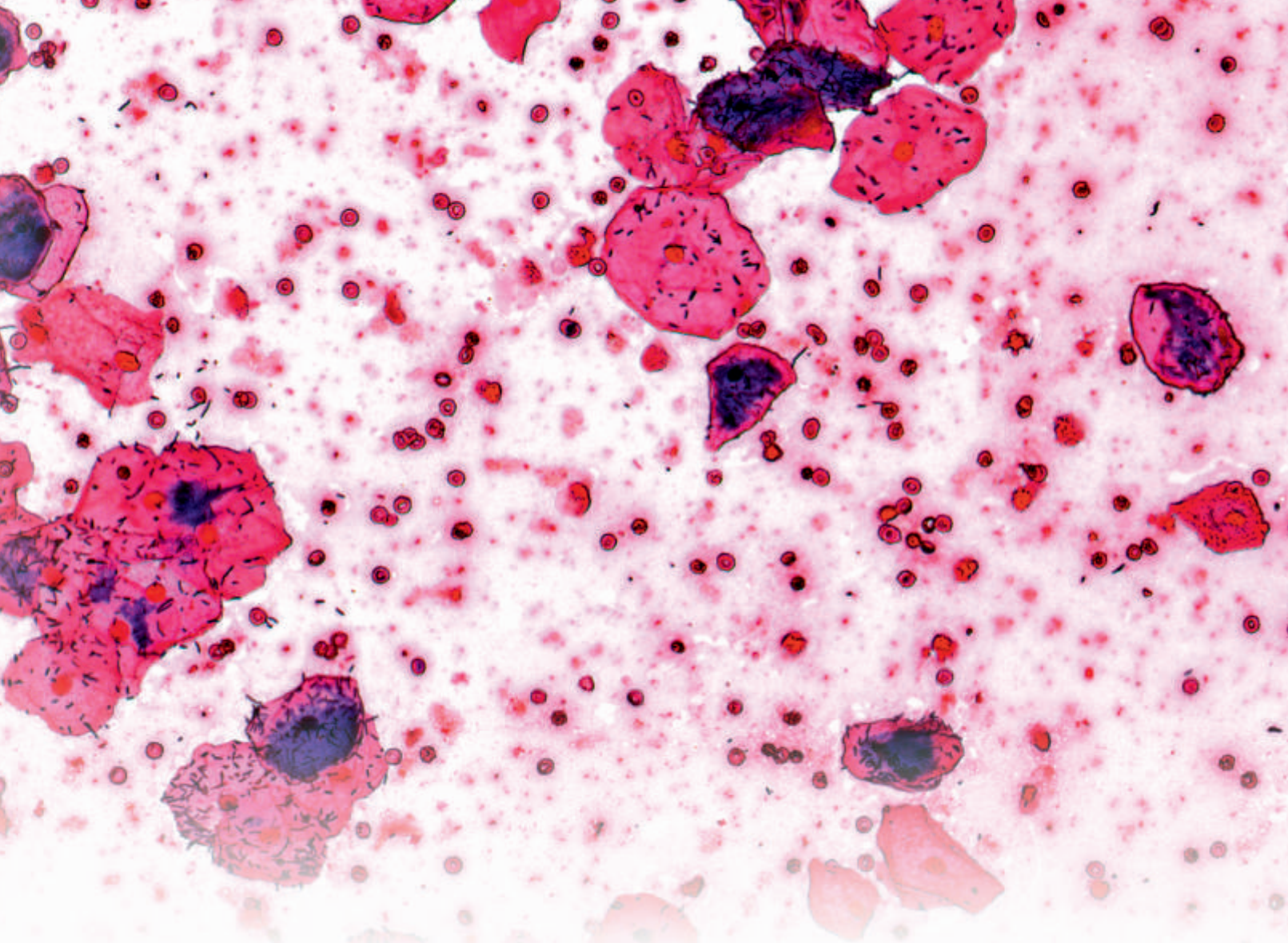
acquires high-resolution images of selected regions in the tissue. FISH signals are taken from different focus levels and single focus planes and the combined focus images are stored. Cells are pre-segmented using Metafer's sophisticated segmentation algorithms. After the acquisition, the user can open each image in the dedicated TissueFISH software. With the mouse, or with an interactive pen, single cells can be encircled and marked for analysis. If the intelligent cell segmentation tool is chosen, the software automatically detects the contour of the nuclei within the user-selected circle. Nuclei pre-segmented by the software can easily be marked with just a mouse click.

Immediately with the selection or marking of a nucleus, Metafer applies automated analysis settings to it; a gallery image is generated, and the analysis results are added to the data histogram. If all suitable nuclei from the current image are obtained, the user is asked to proceed with the next camera



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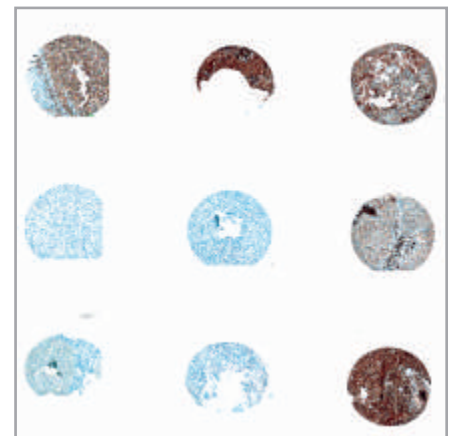
field. After finishing all fields, or after collecting enough cells for the assay, the gallery can be reviewed using the innovative and swift RapidScore procedure.

TMA

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

↑
Metafer generates high-quality images from microscope samples, for example from Gram slides.

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



METAFER APPLICATIONS*

Clinical Cytogenetics, Hematology, Oncology

Metafer and the Neon case and image data management tool were created to optimize routine work in small, medium sized and large laboratories. Decentralized data and workflow management, high-throughput slide scanning for metaphases and interphases, karyotyping, FISH and multicolor FISH analysis stations, and a growing portfolio of FISH probes from MetaSystems Probes take the tedious parts of routine image analysis away, thus providing the staff more time to complete the more discerning tasks.



Toxicology and Radiation Protection

Standardization of analysis is the core benefit of Metafer for DNA damage quantification. Metafer, having removed scoring bias from toxicology tests and biological dosimetry, opens the path to inter-laboratory comparisons of quantitative biological data. As a result, the system is part of the methodology of many international radiation protection networks and pre-clinical tests for chemical toxicology are often based on Metafer analyses.



Microbiology

Rapid identification of pathogens is crucial for successful treatment of infectious diseases. MetaSystems Indigo, the microbiology brand of MetaSystems, offers several imaging tools to support infectious disease management and, in consequence, to help reduce hospitalization costs.

Direct Multiplex Imaging (DMI) is a novel molecular platform technology that precisely and reproducibly identifies and differentiates pathogens. The assay is performed on microscope slides and is evaluated on the Metafer system. Used together with automated digitization of Gram stained samples, DMI results provide valuable information to facilitate a fast decision-making process for the selection of appropriate antibiotics. Additionally, Metafer detects and counts mycobacteria in standard blood smear preparations.



Pathology

With the slide scanning platform Metafer, MetaSystems offers an extensive toolbox to digitize, analyze, and share larger microscopic samples such as tissue sections. Using sophisticated algorithms, Metafer generates high-quality digital copies of a slide. Images provide focus stacks and all relevant meta data (such as information on the location of cells). Users can create their own annotations, generate snapshots from the main image, and display different color channels separately on the same screen. Dedicated software tools allow users to interpret tissue micro-array cores, or to match consecutive tissue sections. Neon integrates all workflow components and keeps track of the process.

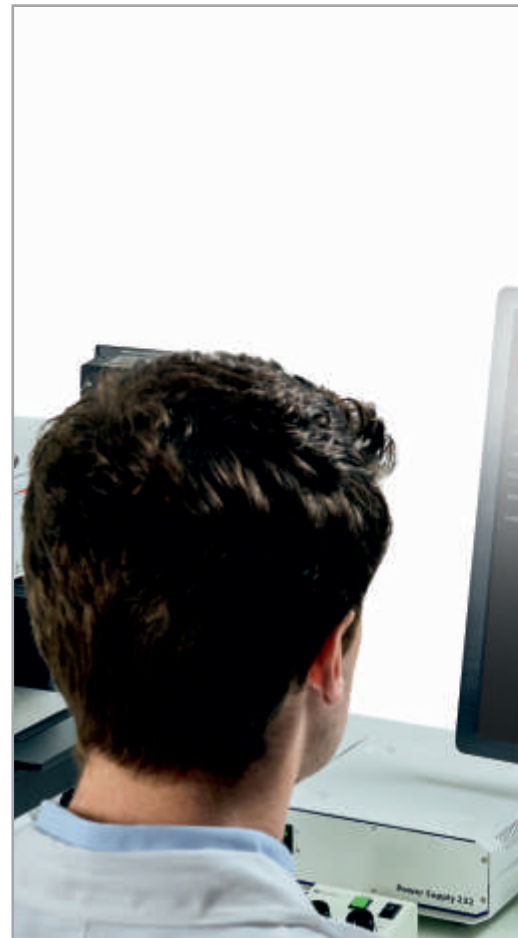


* MetaSystems products are used in many countries worldwide. Depending on the regulations of the respective country or region, some products may not be used for clinical diagnostics. In Europe, MetaSystems devices are CE certified in-vitro diagnostics (IVD) devices. In the United States of America (USA), MetaSystems has received a 510(k) clearance for the Ikaros karyotyping system. All other MetaSystems instruments are intended to be used for research only.

MORE ...

Are you facing an imaging automation task which was not mentioned here? It is likely that Metafer can help. Contact MetaSystems today to learn more about the specific solution for your imaging problem.

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METAFER



NEON



Neon, a tool for flexible and consistent image and case data management, is the backbone of MetaSystems workstations. It was designed to collect data from different sources, and to unite them to form an efficient and well structured workflow. Neon reliably manages cases, images, and results of Metafer systems, single workstations, and of large multi-user installations. It guarantees that all relevant information is visible whenever and wherever it is needed. Neon's powerful and flexible workflow settings facilitate seamless integration with existing routines and allow for the use of a variety of different imaging applications.

Data and Workflow Management

Neon organizes and displays information in an extremely efficient and customizable way. Neon users always have access to exact information on case status, history of images, analysis results, and much more. Data import and export, even with customized data fields and global, cross-application reports, facilitate daily work.

Neon helps to achieve maximum control over all imaging and data handling procedures. Patients, physicians, and technicians benefit from consistent documentation, secure handling of sensitive data, and user-friendliness in all procedures. Neon's flexibility assures seamless integration of the system with existing procedures. Analysis steps, for example, can be individually defined, and then composed to represent the complete workflow. In analysis, each stage of the workflow can either be assigned to a case manually (by authorized users), or automatically based on predefined conditions.

Image Management

Images acquired by Metafer can be identified based on the information on their bar code labels: Neon ensures that the sample information is automatically merged with the respective case.

Results Documentation

Neon also offers two strong tools to summarize and report all data: the powerful case statistics package and the reporting engine with graphic template editor. The statistics package can be used to query all data and to summarize the results graphically and as tables. Results of queries can also be implemented in report templates. Reports can be printed, saved as a PDF files, or exported to external software; this allows for the results of the analyses to be provided to clients, or shared with colleagues around the world.



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