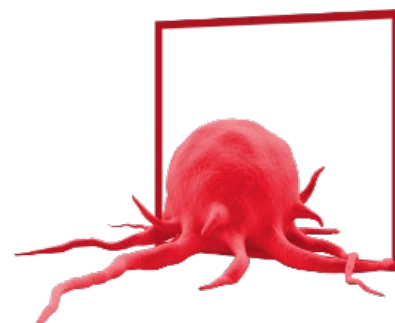


## MetaSystems White Paper

# AUTOMATED SOLUTIONS FOR CANCER GENETICS

*MetaSystems – Innovative Solutions for Automated Microscope-based Imaging*

As diverse as the manifestations of cancer are the research approaches used by laboratory experts in cancer genetics worldwide to prevent, identify, and tackle the disease. MetaSystems has more than 35 years of experience in automated slide scanning for medicine and life sciences. Automated workflows can be customized for occupational cancer studies and genetic toxicology (in vitro micronucleus assay and the Comet assay), for cancer genetics (karyotyping and fluorescence in situ hybridization), and for therapy monitoring (detection of rare tumor cells). Time-consuming and tedious manual steps can be accelerated or even completely avoided with automated microscopy. Turnaround times can be reduced, and experts have more time to focus on complex tasks.



## Highlights

*Automation is key to standardization and reduction of processing times.*

- Brightfield and fluorescence illumination for different techniques on the same imaging system.
- Unattended slide scanning of up to 800 slides possible.
- Standardized templates for reporting.
- Sophisticated case and image management.
- Integration to a Laboratory Information Management System (LIMS) possible.
- Software add-on available for GLP compliance.
- Network of installations scalable to growing demands.

## Introduction

Cancer is still the second leading cause of death worldwide. The disease kills nearly 10 million people each year, with over 3.7 million lives that could be saved with appropriate strategies for

prevention, early detection, and timely and high-quality treatment. World Cancer Day is an international day celebrated on February 4 to raise awareness and fight against the unequal distribution of detection and treatment options, any form of misinformation, and stigmatization.



*Figure 1: Fully automated scanning system run by the Metafer software. The installation shows an application-specific adaptation to the in vitro micronucleus assay. Hardware add-ons for high-volume scanning allow unattended scanning of up to 800 slides.*

Microscopy is a key technology in numerous areas of cancer diagnostics and is considered by many to be a gold standard. Unfortunately, many microscope-based evaluation techniques are time-consuming and complex if they must be performed manually. This ties up trained experts, who are thus prevented from carrying out more advanced work. With automatable microscopy aids, professional digital imaging, and artificial intelligence substantial parts of the manual work steps can nowadays be completely or partially automated. Doctors, biologists, and other healthcare providers thus get more time to spend on the actual result analysis.

For more than 35 years, MetaSystems has helped cancer diagnostic experts improve and simplify their microscope-based workflows. MetaSystems installations have since evolved into laboratory-wide solutions in many areas of cancer diagnostics. The network of installations is scalable to grow with future demands. By linking to an existing LIMS (Laboratory Information Management System), the microscopy solution seamlessly integrates into the laboratory environment.

## Prevention

### *Occupational Toxicology*

In many occupations, workers are at risk of exposure to potentially carcinogenic substances. Preventing cancer therefore involves identifying these sources of danger and quantifying their effects on the body to take

appropriate protective measures. The so-called micronucleus test makes it possible to detect the effects that potentially carcinogenic substances have on human DNA [1]. For this purpose, for example, nasal mucosa or buccal cells of persons who are occupationally exposed to potentially harmful substances can be examined.

This relatively simple microscope-based screening method allows for detecting DNA-damaging effects in large populations. This is even more true if evaluation of the tests is expedited and standardized by means of automation. MetaSystems' Metafer software offers a range of application packages for the automation of toxicological tests. In addition to the micronucleus test, the Comet assay should be mentioned here, which makes the effect of substances on DNA directly detectable on a single cell basis.

## Diagnostics

If cancer is suspected, early and accurate diagnosis is essential. Just as there are many different types of cancer, there are also many ways to identify them. Among all the methods, cytogenetics in particular enables direct detection and localization of changes in the genome [3].

### *Intelligent Karyotyping*

Karyotyping provides a very detailed and complex insight into the state of chromosomes. Unfortunately, evaluation and assessment are equally complex and require elaborate

procedures, perfect organization of workflows, and expert knowledge for evaluation.



*Figure 2: The screen shows the Ikaros software, which uses artificial intelligence to provide karyogram suggestions rapidly and reliably for the expert's review.*

Innovations in Deep Learning have launched the next generation of digital karyotyping. The advanced algorithms in the karyotyping software Ikaros simplify the entire preparation process for karyotype analysis, from chromosome separation to classification. This method replaces tedious manual processing steps and helps the experts focus on the actual analysis and drastically shortens turnaround times.

### *Rapid FISH Spot Workflow*

Fluorescence in situ Hybridization (FISH) can be used to specifically mark regions in the genome known to be affected by rearrangements in certain cancers (for example, leukemias). The evidence is provided microscopically by detecting and quantifying specific signal patterns. Routine evaluation of such spot patterns takes time, but fortunately can be easily automated [4].

The Rapid FISH Spot Workflow developed by MetaSystems enables the combination of optimized FISH probes, rapid automated acquisition of cells and their signal patterns, and a unique review step that allows the automated acquisition suggestions to be confirmed or corrected in the least amount of time. The workflow consists of three essential parts. First, the samples, whether from single cell preparations or tissue sections, are hybridized with DNA-FISH probes (XL probes) from our sister company MetaSystems Probes. These probe kits allow for shortest hybridization times (RapidHyb) and show signals that are optimized for automated imaging. RapidScan, scanning of slides and detection of nuclei, can be done fully automated using the Metafer software. FISH spots are captured in focus stacks, and the software generates a proposed spot pattern for each captured nucleus. With the third step, RapidScore, the expert interactively reviews the spot patterns with the help of the innovative RapidScore keyboard. The keys on this instrument

automatically adjust to the FISH probe arrangement, allowing the user to confirm or correct the automatic results with just one keystroke.

The Rapid FISH Spot Workflow, an application package for the Metafer scanning software, is thus a routine workflow designed to support swift and professional cancer diagnostics. The method impresses with its ability to combine fast yet high-quality hybridization with automated imaging and a review step by experts in such a way that the final evaluation can be performed in just a few minutes.

## Therapy Monitoring

### *Rare Cell Detection*

If a patient is diagnosed with cancer and therapy is started, it is essential for the success of treatment to regularly check the effectiveness of the measures taken. In addition to reapplying the methods already used for diagnosis (for instance, the examination of FISH signals), there are also

methods designed to find the rare tumor cells present in the patient's peripheral blood. The problem here is that these cells are extremely rare, making them virtually undetectable by manual methods.

A combination of enrichment of the tumor cells in culture, use of specific markers, and automatic detection of the cells using Metafer software has proven to be a possible way out of this dilemma. This so-called Rare Cell Detection procedure helps the experts to continuously monitor the success of their therapy measures [5].

## Conclusion

The automation of microscopy as an aid in cancer diagnostics not only speeds up many procedures, but also contributes to the standardization of processes. Not to be forgotten is the fact that when Metafer scanning software is used, each work step and each examined cell is stored in the form of images and records of analysis. This automatically creates an archive with all data, which can be used as a basis for the final diagnosis by the physicians.

## Sources

[1] Maxim Asanov, Stefano Bonassi, Stefania Proietti, Varvara I. Minina, Carlo Tomino, Randa El-Zein (2021) Genomic instability in chronic obstructive pulmonary disease and lung cancer: A systematic review and meta-analysis of studies using the micronucleus assay, Mutation Research/Reviews in



Figure 3: With the Rapid FISH Spot Workflow, the expert interactively checks the spot patterns using the RapidScore keyboard (shown in the center of the image). The keys of this device automatically adapt to the arrangement of the FISH probes, allowing the user to confirm or correct the automatic proposals with just one keystroke.

Mutation Research, 787, DOI: 10.1016/j.mrrev.2020.108344.

[2] Kirsty Meldrum, Stephen J. Evans, Ulla Vogel, Lang Tran, Shareen H. Doak & Martin J. D. Clift (2022) The influence of exposure approaches to in vitro lung epithelial barrier models to assess engineered nanomaterial hazard, *Nanotoxicology*, 16:1, 114-134, DOI: 10.1080/17435390.2022.2051627.

[3] Eigil Kjeldsen (2022) Congenital Aneuploidy in Klinefelter Syndrome with B-Cell Acute Lymphoblastic Leukemia Might Be Associated with Chromosomal Instability and Reduced Telomere Length, *Cancers* 2022, 14(9), 2316; DOI:10.3390/cancers14092316.

[4] Semjon Sidorov, Lara Fux, Katja Steiner, Samyo Bounlom, Sabrina Traxel, Tarik Azzi, Arbeneshe Berisha, Christoph Berger, Michele Bernasconi, Felix K. Niggli, Yvonne Perner, Sugeshnee Pather, Werner Kempf, David Nadal, Simone Bürgler (2022) CD4 + T cells are found within endemic Burkitt lymphoma and modulate Burkitt lymphoma precursor cell viability and expression of pathogenically relevant Epstein-Barr virus genes, *Cancer Immunology, Immunotherapy* volume 71, pages1371–1392; DOI: 10.1007/s00262-021-03057-5.

[5] Peter Ping Lin (2018) Aneuploid CTC and CEC, *Diagnostics* 2018, 8(2), 26; DOI: 10.3390/diagnostics8020026.

## About MetaSystems

For 35 years, MetaSystems has been developing and producing innovative solutions for automated microscopy-based imaging for the healthcare and biotechnology sectors. Our headquarters are located in the southwest of Germany in the Rhine-Neckar metropolitan region near Heidelberg.

We are a global company with an international team working in Germany and in our subsidiaries in North and South America, Europe, India, and China. Our customers can be found in institutes, hospitals, and universities in over 100 countries around the world.

We continuously develop our products in close connection with our users, thus combining innovation with tradition. Our modern approaches include an advanced workflow management that grows with your requirements and the use of artificial intelligence. In many segments, this has enabled us to achieve an international top position on the market.

## Want to Know More?

MetaSystems offers innovative solutions for automated microscopy imaging for numerous applications with brightfield and fluorescence illumination.

Would you like to know more about how MetaSystems uses artificial intelligence? Please contact us at [info@metasystems-international.com](mailto:info@metasystems-international.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 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.

The presented solutions are application-specific adaptations of the Metafer software. It is possible that further adaptations to specific specimen conditions are necessary.

Please contact us for further information.

## CONTACT US

OR YOUR LOCAL  
**MetaSystems**  
REPRESENTATIVE



[metasystems-international.com](https://metasystems-international.com)