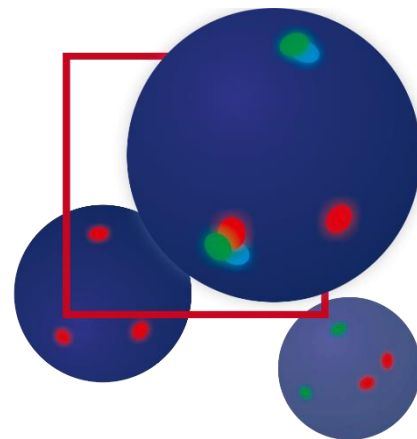


MetaSystems White Paper

META FER CUSTOMIZATION PACKAGE SPOT COUNTING

Optimizing the counting of FISH spots can be a challenging task for laboratories in cytogenetics and hematology. Manual FISH microscopy is often conducted in low-light conditions, leading to fatigue and declining attention. Moreover, there is a lack of comprehensive image documentation and checks according to the four-eyes principle.

By customizing the functionalities of the slide scanning software Metafer, it is possible to replace manual FISH spot counting with a swift workflow involving automated microscopy and interpretation by the expert. The customized workflow includes the use of adapted parameter sets for different probe layouts that enable automated identification and acquisition of nuclei and FISH spots, as well as a high-speed user review step called RapidScore. This allows the expert to swiftly confirm or adjust the suggestions for the spot patterns generated by the software.



Highlights

Stick to Your Procedures!

- Parameter sets for different probe layouts are customized and saved to replace individual settings for samples.
- Various slide layouts including specimens with multiple hybridizations are supported.
- Data is automatically exchanged with a compatible LIMS.

Automate Your Image Acquisition!

- Pre-scan to identify suitable regions on the slide.
- Automated and unattended image acquisition of interphase nuclei and FISH signals.

- Extended focus images show FISH signals in different focus planes.
- External control through scan jobs that map the entire imaging workflow with Search Information Files (SIFs).
- While scanning, an image gallery is created, showcasing nuclei, their FISH signals, and automated FISH count values.
- All outputs are summarized in clearly arranged tables and graphs.
- Optional high-throughput extension is available for automated image acquisition for up to 800 microscope slides.



We appreciate the ability to fine-tune the imaging for the different XCyting Locus-Specific Probes and are pleased with the quality of the XCyting Probes we have validated. We are highly satisfied with the speed of the scans. Our technicians have described using the interactive RapidScore spot counting as fun!

Dr. Cecelia Miller
Assistant Professor



DID YOU KNOW?

Our sister company MetaSystems Probes manufactures the XCyting Locus-Specific Probes that are a great match with the Metafer Customization Package Spot Counting.

www.metasystems-probes.com

Assess Spot Patterns with RapidScore!

- Swift expert review with the programmable RapidScore keyboard that allows instant confirmation or correction of automated outputs with just one keystroke.
- The most frequently used functions and spot patterns are displayed as keys on the RapidScore keyboard.
- Up to five independent analysts are supported in the CellReview blinded reading mode.

Organize Your Digital Workplace!

- Integrated case and image management called Neon with convenient case data displays, reporting, and statistics engine.
- Comprehensive workflow management tools ensure full control over all cases, images, and analyses.
- Configurable dashboard to clearly summarize cases, statuses, case statistics, and much more.
- Multi-user administration with the possibility to define own user roles to manage access.
- Scalable laboratory network of MetaSystems installations to adapt to growing demands and to the respective laboratory environment.

Workflow for FISH Spot Counting

The workflow presented below is intended as an example and can be customized to cover your laboratory needs.

1. Samples from single cell preparations are hybridized, e.g., with the XCyting Locus Specific DNA Probes from MetaSystems Probes.
2. Each slide receives a unique identifier that is linked to the case, either in your LIMS or directly in the case and image management of Metafer.
3. (a) If a LIMS is integrated, a so-called Search Information File (SIF) is written, containing information

on the slide, the hybridization(s), and the probe layout(s).

A bar code label is generated with information on the case, the slide designation, the probe(s), and the slide layout used.

Metafer reads the bar code of the slide, connects to the corresponding SIF, and starts scanning.

(b) Without LIMS connection, the user loads the respective SIF manually, and starts the Metafer scanning procedure.

4. FISH spots are captured in focus stacks, and the software generates an extended focus image and a proposed spot pattern for each captured nucleus.

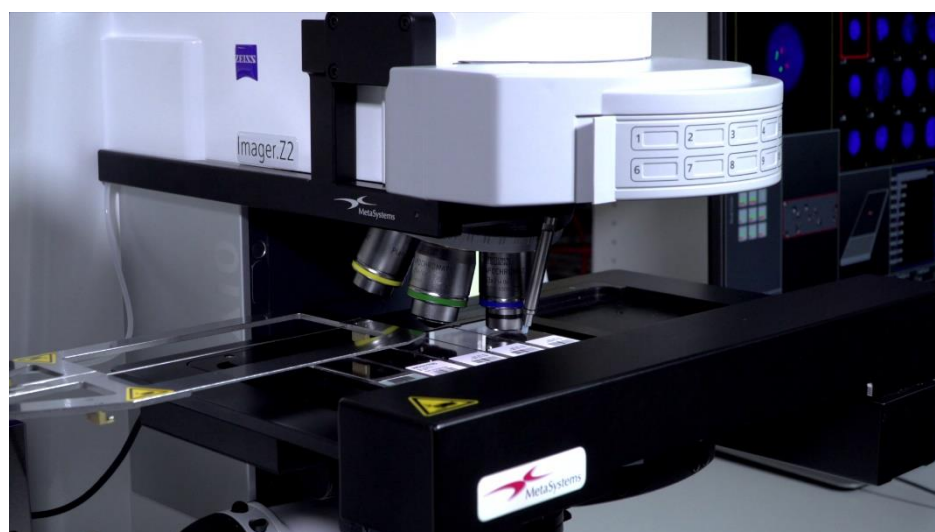


Figure 1: With the optional extension for high-throughput scanning, continuous 24/7 operation is possible. Up to 800 slides can be automatically scanned in one run with the SlideFeeder x80 as optional add-on. The SlideFeeder x80 is a robotic system for exchanging slides and can hold up to 10 magazines, each with 16 frames for 5 slides, plus a bar code reader. The capacity of the SlideFeeder x80 is thus scalable. The bar code reader interprets frame and slide bar codes to start scanning processes adapted to user needs. In combination with the automated immersion oil dispenser called AutoOiler, a high degree of automation can be achieved.

5. Once the scan is finished, the workflow status of the respective case is changed automatically, indicating that the images are ready for expert review.
6. The cytogenetic expert opens the scan file on Metafer or on one of the connected workstations, and gets access to the gallery of detected nuclei with the proposed spot counts.
7. Using the information stored in the parameter sets, the RapidScore keyboard displays the spot patterns matching the probe layout on its programmable LCD keys.
8. The expert either confirms or corrects the automated findings with a single keystroke for each nucleus on the RapidScore keyboard.
9. On reviewing, Metafer generates a summary of the confirmed results and marks each checked cell.
10. If the expert identifies additional spot patterns, they can be interactively added at any time.
11. If more than one scorer is involved, the CellReview functionality offers the possibility of a blinded assessment with up to five independent evaluations.
12. Once finished reviewing, a supervisor can confirm the results and close the case. The workflow stage will be adapted automatically.

13. Results are either printed in a report or sent back to a connected LIMS.

The RapidScore Keyboard- Swift Review by the Expert

One highlight of RapidScore is the programmable RapidScore keyboard with 32 LCD keys. The most common commands and spot patterns are automatically displayed depending on the selected parameter set used for imaging the respective slide.

The expert performs an interpretation of the spot patterns from nucleus to nucleus by swiftly confirming or correcting the automated output with a single keystroke.



Figure 2: The programmable RapidScore keyboard allows instant confirmation or correction of automated outputs with just one keystroke.

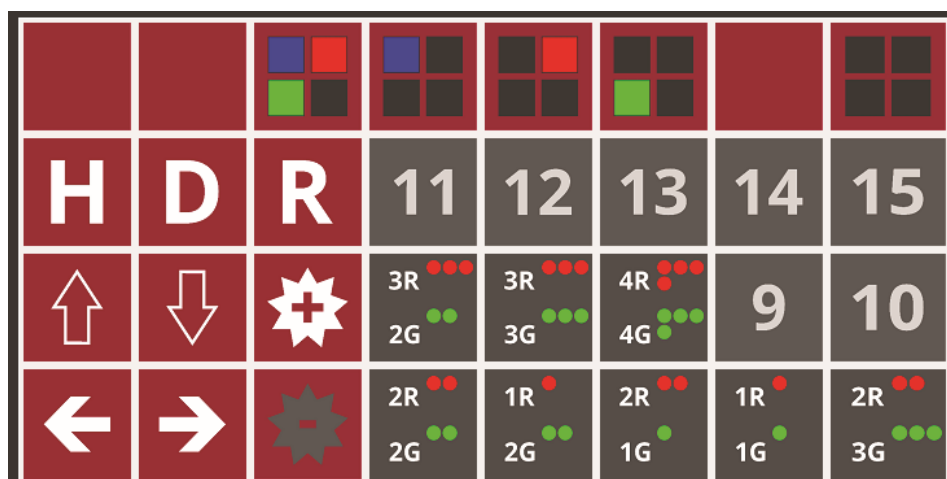


Figure 3: Example layout for the RapidScore keyboard.

The top row contains buttons for adjusting the color channels displayed. The left section features controls for navigating through the gallery of nuclei (left/right arrows) and for moving through the focus planes (up/down arrows). Above these controls, there are options for highlighting, deleting, and rejecting nuclei. The +/- keys are used to adjust the brightness of the RapidScore keyboard.

The gray section on the right provides a set of keys corresponding to the respective probe layout (in this case: dual color amplification/deletion). Each key is designated for a specific spot pattern class, allowing users to confirm or correct automated suggestions. The numbered keys serve as placeholders, ready to accommodate any new spot pattern classes that may be introduced by the user.

The keyboard also provides other useful keys. For example, the reviewer can use the keyboard to move through the individual focus planes of a captured nucleus and to display the individual color channels. In this way, the most frequently required functions are combined in a compact keyboard to enable ergonomic working.

Case Study: Time Saving in Hands-on Operations

Summary

Customized functionalities of the Metafer software enabled users in a U.S. laboratory to perform the analysis of the investigated probe panels faster

than with a purely manual, paper-based workflow.

Materials and Methods

A commercial customer specialized in cancer treatment based in the United States of America conducted a case study involving three XL Probe panels manufactured by MetaSystems Probes:

- **Chronic lymphocytic leukemia (CLL):** ATM/P53, CEN12 and 13q/q(3 colors), CCND1/IGH(DFDC),
- **Myelodysplastic syndrome (MDS):** 5p/q/q(3colors), CEN7/7q, CEN8 and 20q/q(3 colors), MLL+(BA), and

- **Non-Hodgkin lymphoma (NHL):** BCL6+(BA), MYC+(BA), CCND1/IGH(DCDF), IGH+(BA), IGH/BCL2(DCDF), MALT1+(BA).

In total, 12 cases with multiple probe panels per case were investigated. Samples were hybridized following the recommended standard protocol for XL Probes. 200 nuclei per sample have been scored manually or using the Metafer software.

As the slide scanning and image acquisition was done fully automated with the Metafer-operated scanning system without user interaction, the laboratory compared the pure hands-on time for spot counting with or without the Metafer software. Please note that the scan time is not shown in the results as it is not a manual step. In this case study, the average scan time with Metafer was approximately three minutes per slide.

The manual, paper-based procedure of the laboratory consisted of the following steps:

1. Loading slides on the manual microscope.
2. Preparing the microscope, e.g.: set filters, apply immersion oil, and adjust the light source.
3. Manual spot counting of 200 nuclei.
4. Completing the paper-based worksheet with the results.
5. Manual image capture and processing of two to three images.
6. Export and print the images for documentation.

The Metafer-based workflow with RapidScore included the following hands-on steps:

1. Loading slides on Metafer-operated microscope.
2. Selecting the appropriate parameter sets for imaging with Metafer.
3. Using RapidScore to analyze 200 nuclei.
4. Exporting 200 images and result data to XML files for documentation.

Results and Conclusion

Figure 4 shows the direct comparison of hands-on time for manual, paper-based scoring (gray columns) and the Metafer-based workflow with RapidScore (red columns). Each pair of columns represents a different probe or probe panel. Table 1 summarizes the relative time savings for the analyzing 200 nuclei.

The laboratory's study results show that the Metafer-based workflow with RapidScore took significantly less time than manual, paper-based analysis in all experiments. On average, the use of RapidScore saved more than 40% of time in hands-on work.

The results of this study indicate that Metafer with RapidScore is a fast and convenient method to combine automatic software-generated suggestions for spot patterns and the interactive user review using the RapidScore keyboard.

Sources

The laboratory that performed the case study presented in this publication would like to remain anonymous. However, if there is a need, we are more than willing to put you in contact with customers who use our products in routine. Do not hesitate to [contact us or our sales partners through our website](#) for more information.

About MetaSystems

For more than 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?

If you would like to continue reading about the Metafer Customization Package Spot Counting, we invite you to visit the [download section on our website](#).

Would you like to know more? Do not hesitate to [contact us or our sales partners through our website](#) for more information.

Attached Figures and Tables

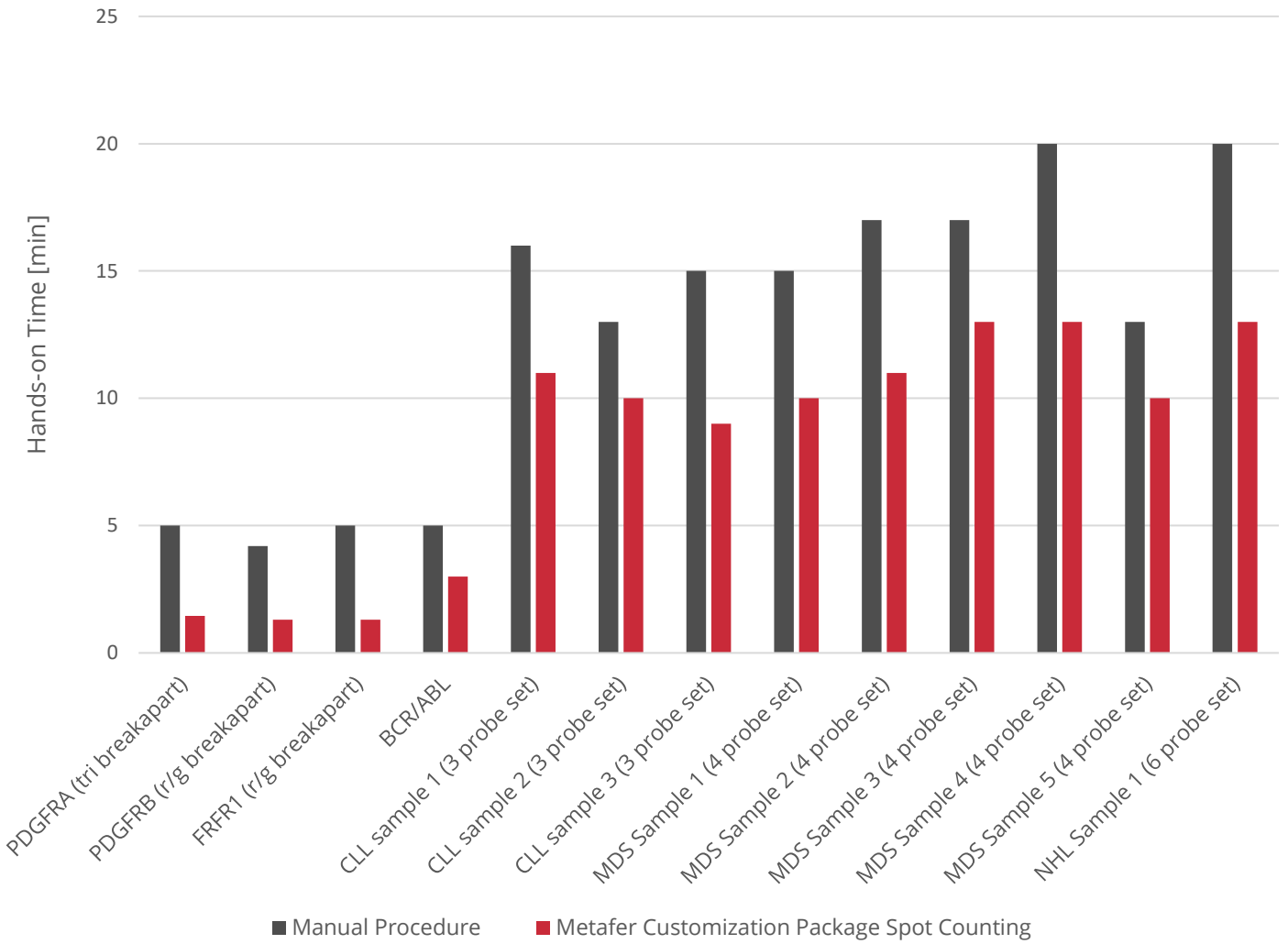


Figure 4: Comparison of hands-on times using manual, paper-based counting (gray columns) and the Metafer software (red columns) for the tested probes or probes panels.

Table 1: Relative time saving of hands-on work using the Metafer software compared to manual, paper-based analysis.



Sample	Time Saved (min.)	Time Saved [%]
PDGFRA	3.55	71.00
PDGFRB	2.9	69.05
FRFR1	3.7	74.00
BCR/ABL	2	40.00
CLL sample 1	5	31.25
CLL sample 2	3	23.08
CLL sample 3	6	40.00
MDS Sample 1	5	33.33
MDS Sample 2	6	35.29
MDS Sample 3	4	23.53
MDS Sample 4	7	35.00
MDS Sample 5	3	23.08
NHL Sample 1	7	35.00
Average time saving over all samples		41.05



Figure 5: Metafer-driven slide scanning installation for interphase FISH spot imaging. This includes a motorized microscope fitted with one or two cameras, along with a stepping motor stage. To enhance scanning capabilities, an automated slide-feeding robotic device (SlideFeeder x80; positioned on the left) can supply up to 800 slides per run to the microscope stage. Additionally, a barcode reader is integrated to automate slide identification and allocate samples to respective cases and Search Information Files (SIFs).

MetaSystems software provides, among other functions, features to assist users with image processing. These include, but are not limited to, the use of machine and deep learning algorithms for pattern recognition. The output generated in this process should be regarded as preliminary suggestions and, in any case, mandatorily requires review and assessment by trained experts.

MetaSystems offers **Customization Packages** for application workflows that have been successfully implemented for customer labs using standard Metafer platform functionality. It is expected that they can be implemented for other customer labs using similar workflows and slide preparation procedures. If a Customization Package is purchased, MetaSystems product specialists will – based on their experience from other similar application cases - support the customer lab in adapting the Metafer software configuration to their needs. The performance of the solution will depend on the quality of the customer slides and the expertise of the users, MetaSystems cannot specify or guarantee any performance parameters. The validation of the solution for clinical use is the sole responsibility of the customer lab.

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