# MLL News

08/19/2020

## MLL and Institute of AI for Health of the Helmholtz Center of Munich Announce Research Collaboration

The Munich Leukemia Laboratory and the newly founded Institute of AI for Health (AIH) of the Helmholtz Center of Munich have agreed on comprehensive collaboration for research and development. The primary goal is the implementation of machine learning and artificial intelligence in various areas of leukemia diagnostics.

In the collaborative partnership, the main contribution of Munich Leukemia Laboratory will be its extensive diagnostic and clinical databases and its medical-diagnostic expertise, while the AIH has years of know-how in the field of machine learning applications and data science. Thus, both partners anticipate very high synergistic potential for the joint further development of increasingly data-driven leukemia diagnostics. They are united in the conviction that joint research for the comprehensive implementation of digitalization and artificial intelligence is to be a key element of the collaboration. By pursuing this venture, both parties are expressing their intention to promote scientific progress and the well-being of patients through their work.

For several years now, there have been project-based collaborations between MLL and the Helmholtz Center, such as the AI-based detection of blood cancer cells and the prediction of leukemia subtypes in blood and bone marrow microscopy. Another project is funded by the Federal Ministry of Education and Research and combines the biomedical and AI expertise of both research partners to analyze large amounts of genomic data with the aim of better understanding the molecular basis of leukemia, defining new disease subtypes, and enabling improved personalized treatment of patients.

“Based on the very successful cooperation to date and in view of the great expertise of both partners in their core competencies, the basic arrangement of long-term collaboration in the field of leukemia diagnostics appears to be the fully natural next step,” says Professor Torsten Haferlach of MLL. “We generate gigantic amounts of data every day in routine diagnostics alone. It is only with the help of AI-based methods that systematic analysis and detection of patterns in this data is even conceivable. In this respect, we consider ourselves fortunate to have the AIH of the Helmholtz Center of Munich as an extremely capable partner at our side.”

Carsten Marr, Director of the AIH, feels the same: “With its extensive data and unique expertise, MLL is the perfect partner to advance our AI-based leukemia diagnostics. We are building on cooperation that has already been close in the past and are hoping to put our algorithms to use with MLL. That way, patients can benefit directly from our research.”

The recent founding of the AIH at the Helmholtz Center of Munich is a step that gives further impetus to the previous collaboration between the two partners and is an appropriate step due to the increasing focus on data science and healthcare at the Helmholtz Center of Munich.

Author: Dr. med. Christian Pohlkamp

## Our First Whole Genome Sequencing Report

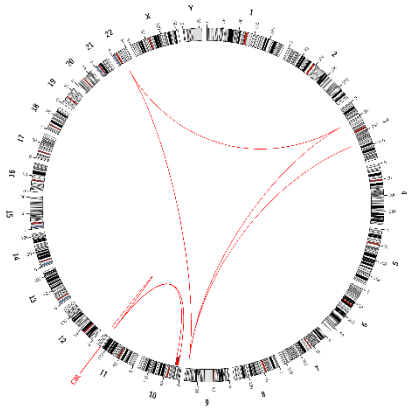
Whole genome sequencing is an established analytical method in research projects and also increasingly in human genetics for the detection of disease-causing genetic alterations. This method is also becoming ever more popular in tumor genetics, as a wide variety of genetic alterations can be investigated with just one analysis. We have transferred all our experience of the last few years to routine diagnostics and have designed a corresponding clinical report of whole genome sequencing, which we were able to send out for the first time in June 2021.

### Whole Genome Sequencing in Routine Diagnostics

Whole genome sequencing (WGS) detects a wide range of genetic alterations in a single analysis: from point mutations to structural alterations to chromosomal copy number alterations. Thanks to our 5,000 genome project, we have been able to acquire a lot of experience in the laboratory in recent years, but primarily in the processing and analysis of the large-scale and extensive data as well. We at MLL have now taken the next step and bundled this experience, transferring it to routine diagnostics and designing a corresponding whole genome sequencing report for it.

### A Report Layout Designed Specifically for Whole Genome Sequencing

The focus of the new layout here is the clear presentation of the results in the report, without diminishing the extent of the data analyzed. In our standard evaluation pipeline, single nucleotide variants (SNVs), structural variants (SVs), copy number variations (CNVs), and copy-neutral loss of heterozygosity (CN-LOH) are investigated and reported. Along with a brief description of the changes found, the findings include a graphi[illegible]Circos plot (see figure).



Our first clinical report of whole genome sequencing involved CML in blast crisis, which, besides a complex 3-way translocation between chromosomes 3, 9, and 22 leading to the *BCR-ABL1* fusion transcript, revealed a second additional *KMT2A-MLLT10* translocation between chromosomes 10 and 11. In addition, a mutation (SNV) in *CBL* and the loss of chromosomal material from chromosome 10 was able to be identified.

In our Circos plot, the chromosomes are listed in circular form, translocations are represented by red connecting lines, gains (blue) and losses (red) are marked inside the chromosome circle, and the gene with a mutation is labeled at its position in the genome. This graphical representation of the results is intended to give the treating physician a quick overview of the genome-wide alterations. Naturally – as usual – this report also contains the relevant alterations in text form, tables with detailed information, and the resulting interpretation with regard to diagnosis and prognosis.

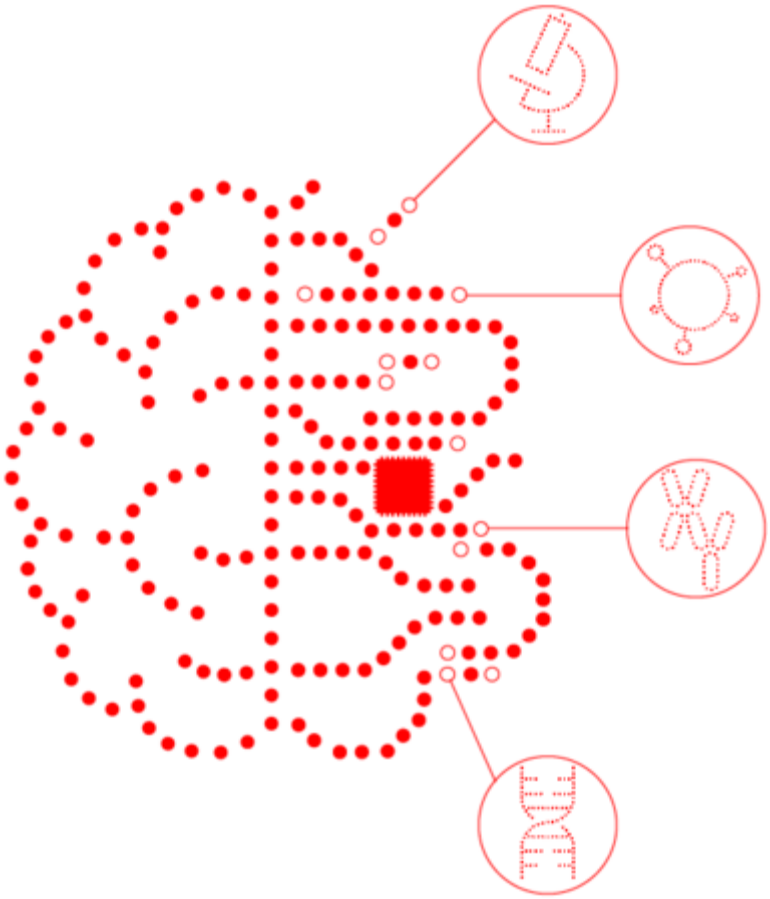
### The First Clinical Report Has Been Sent Out

We are pleased to announce that, in mid-June, we were able to send out the first clinical report on whole genome sequencing in the new layout with the added graphic. The additional information that whole genome sequencing can bring will become clear in the future. It is therefore all the more gratifying that for complex cases and diseases such as multiple myeloma and acute lymphatic leukemia (ALL), we are already able to contribute to the further development of diagnostic methods, collect therapy-controlling findings, and clearly present the results in a disease-relevant way through whole genome sequencing and transcriptome analyses.

Author: Dr. Manja Meggendorfer

## MTLAs, doctors and artificial intelligence at MLL – a good team!

We take artificial intelligence (AI) for granted these days and often use it in our everyday lives without noticing. But what does this mean for diagnostics – today and in the future? At MLL, artificial intelligence is used in various areas of diagnostics and is constantly being further developed. This not only saves time but will also facilitate the training of new staff in the future and expand opportunities for global collaboration. The aim is to provide patients with easier access to precise and rapid diagnoses and thus access to the best possible therapy.



## Cytomorphology

In the area of blood smear analysis, AI was developed in cooperation with AWS on the basis of a self-created training database that can generate differential blood counts within a few seconds. To this end, 300–500 cells per smear are photographed at high resolution and fully automatically with a MetaSystems scanner, stored as individual images, and classified by an algorithm. The median accuracy of this process is already 94% (Fig. 1). Lower values mainly occur with cell types that are difficult to differentiate even for experienced physicians and MTAs because they are in transitional stages of maturation. Critical-pathological cell types and those that cannot be determined with certainty can be marked by the AI and checked by doctors and MTAs. Since January 2021, blood smears of each case are scanned by AI and evaluated by humans and AI together. The comparison makes it possible for the clinical benefit to be assessed in a prospective study and enables AI to be included in routine practice (BELUGA study, NCT04466059). AI-based analysis of bone marrow cells is already part of current research and development as well.

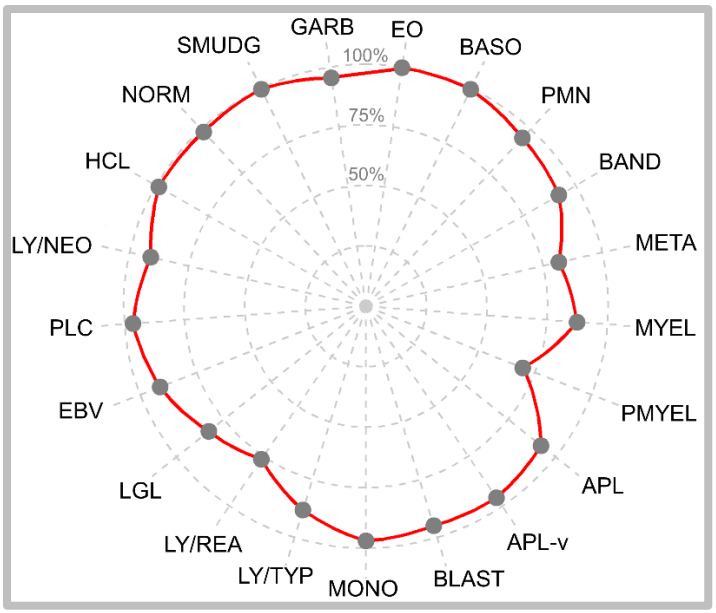



Figure 1 from: Pohlkamp et al. Machine Learning (ML) Can Successfully Support Microscopic Differential Counts of Peripheral Blood Smears in a High Throughput Hematology Laboratory. Blood 2020; 136 (Supplement 1): 45–46.

## Immunophenotyping

In the BELUGA study, both immunophenotyping data and cytomorphology data are collected. The AI for classifying lymphomas that has been developed by MLL in collaboration with AWS uses raw flow cytometric matrix data and allows for the prediction of diagnoses without prior manual visualization. Its use was able to be extended from mature B-cell neoplasms to other entities – the results are promising and of high precision, especially for multiple myeloma. One current challenge is the analysis of subpopulations within the sample, as is needed in myelodysplastic syndrome, for example. This could be remedied by an analysis where the existence of an entity is determined in a first step and subclassifications are studied by means of defined features in a second step.

## Chromosome Analysis

The automatic generation of karyograms was already introduced into the routine at MLL in 2019. The AI for this has been steadily further developed, which has so far allowed the processing time of 1–3 minutes per karyogram (by very experienced staff) to be reduced to 31 seconds and a single mouse click. Copy number aberrations (CNAs) are automatically detected by the AI, and derivative chromosomes are prepared for manual assignment by a staff member. The precision for chromosome detection is 98.6%, and the majority of findings are made within 5 days (Fig. 2).

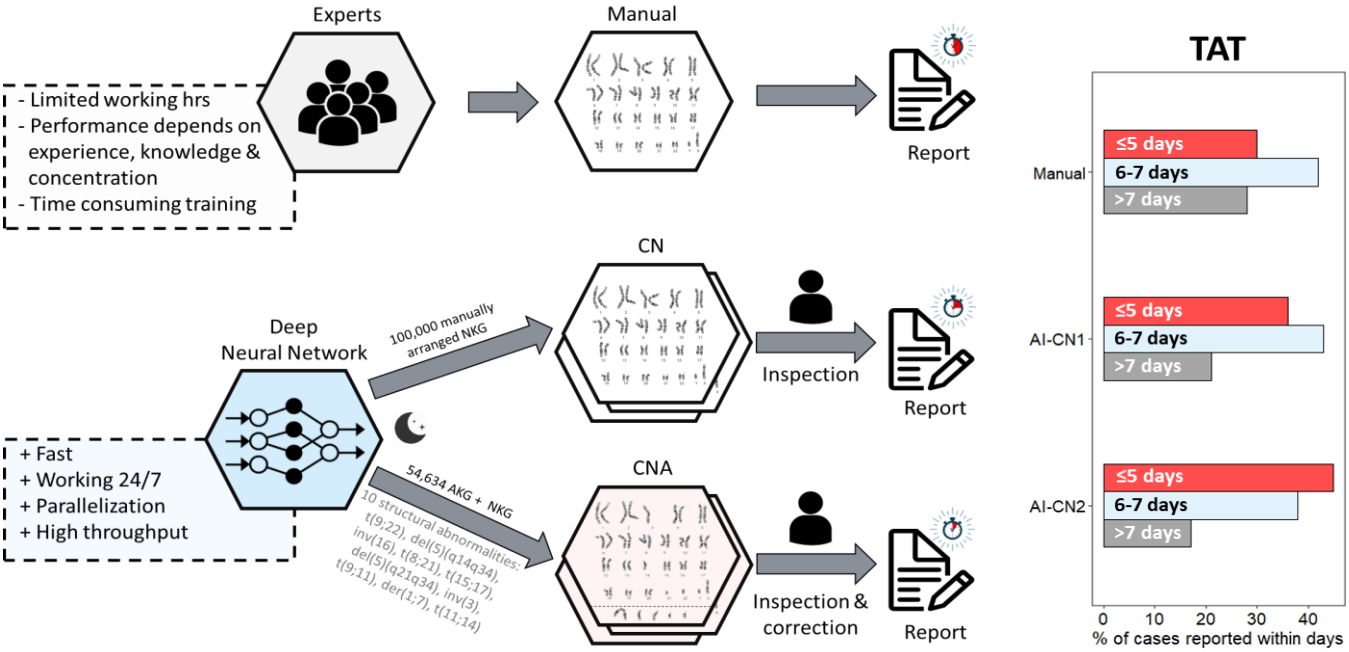



Figure 2 from: Haferlach et al. Artificial Intelligence Substantially Supports Chromosome Banding Analysis Maintaining Its Strengths in Hematologic Diagnostics Even in the Era of Newer Technologies. Blood 2020; 136 (Supplement 1): 47–48.

## Molecular Genetics

Molecular genetics is playing an increasingly important role in diagnostics. Sequencing in particular gives deep insight into the biology of disease patterns. However, there are also new challenges. Not every mutation identified is relevant for the disease pattern. When assessing the pathogenicity, the MLL Predictor a specially developed AI, can assist the diagnostician significantly.
The next step in molecular genetic diagnostics is genome-wide approaches. However, the data generated by sequencing the complete genome and transcriptome exceeds the possibilities of manual analyses. This is where AI can help and increase the output of this data considerably. In collaboration with AWS MLL is developing an algorithm that uses 5 aberration types to make a diagnostic prediction. To this end, genetic structural variants, single nucleotide variants (SNVs), copy number variants (CNVs), gene fusions, and gene expression data are read into the tool and evaluated by the AI. The algorithm has high precision already, especially for genetically unique entities. Current training is increasingly focused on genetically less well-defined entities that pose a major challenge to the algorithm.

Author: Dr. Constanze Kühn

## Medical Work at the Munich Leukemia Laboratory

What does it mean to be a doctor at the Munich Leukemia Laboratory? We are repeatedly confronted with the most diverse ideas that mainly have one thing in common: They do not correspond with reality. For example, pipetting samples has never been part of a doctor's work, let alone in times of full automation. Nor is a PhD or other academic awards a prerequisite for working at MLL in any way. The following article intends to paint a realistic picture of medical work at MLL.

We have already reported on the role of doctors at MLL in the past. However, just like our diagnostic methods, medical work here is also subject to the changes of time and progress.

### Interfaces between Diagnostics and Clinical Routine

Currently, 12 doctors – most of them hematologists – are working at MLL. They bring many years of clinical experience and contribute to the management of routine and to further development and innovation. Their traditional fields of application range from practical activities in our MLL MVZ GmbH medical care center (formerly MHP Munich Hematology Practice) to cytomorphological and flow cytometric diagnostics to the integrative reporting of all analyses carried out here. An important part of the job involves case discussions with our senders from clinics and practices.

Thus, a doctor at MLL functions as a highly interesting interface between hematological laboratory diagnostics and clinical application as targeted patient care.

### A Special Workplace

It is often necessary to assess complex constellations of findings. This is made possible by a specially adapted laboratory information system that ensures rapid viewing and interpretation of even extensive panel findings. A doctor at MLL is largely relieved of bureaucratic tasks as well; the focus is on the specialized hematological work. This makes the work rich in content and widely varied every single day.

"In my first few weeks here, I was able to examine a range of hematological neoplasms that would not have come up at a clinic even over a period of years," explains Prof. Dr. Rainer Ordemann, who moved to MLL from UK Dresden in 2020. "The combination of clinical activity with state-of-the-art diagnostic and IT-based methods gives a vivid impression of the medicine of tomorrow."

## Insights into the Future of Medicine

MLL has always paid a great deal of attention to the close interlinking of routine and research. This ensures that new scientific findings are promptly incorporated into the diagnostics offered. One increasingly significant aspect is the implementation of artificial intelligence in all areas of the laboratory. The vast amounts of diagnostic data that is generated each day at MLL provides a valuable basis for the use of AI tools. Here as well, hematologists are heavily involved in many projects.

Nevertheless, the following applies with regard to research activities: Everything is possible, but nothing has to be. Those who feel at home in patient care and diagnostics are just as welcome as ambitious scientists.

Anyone who changes over to MLL from a clinic or practice today will certainly find a significantly different environment than what was true three, four, or five years ago. The constant development and innovation are continually changing the face of MLL, making it a more exciting place to work for hematologists than ever before. And, by the way, we offer an excellent work-life balance – in one of the most beautiful cities in Germany...

Author: Dr. Christian Pohlkamp

## MHP Becomes MLL MVZ GmbH

We have changed the legal form of our MHP Munich Hematology Practice to “MLL MVZ GmbH.” All general terms and conditions and our address will remain the same, and the contact persons at our company with whom you are familiar will continue to be responsible for and available to you as before. We are looking forward to continued good and close collaboration!

## Important dates

### Oncological Symposium 2021

Save the date: The successful symposium series "Oncological Symposium 2021— From Biomarkers to Therapy" will enter its third round on November 5, 2021. The event offers insights into modern oncological precision medicine, which combines innovative diagnostic methods and therapeutic strategies into a greater whole. The symposium will take place virtually and, if circumstances allow, also as a face-to-face event at the MLL Münchner Leukämielabor. You can now reserve your seat.

More information and a link for registration can be found here.

## Shaping the Medicine of Tomorrow Together

In order to expand our dedicated team, we are looking for medical specialists (m/f/d) with a focus on hematology/oncology, laboratory medicine, or pathology for the area of cytomorphology or immunophenotyping and for biologists (m/f/d) with a focus on cytomorphology – to start immediately or at any time.

You can find all information about the job posting, the application, and other job offers here.

## Most Recent Publications with MLL Involvement

- Bendig S et al. *Whole genome sequencing demonstrates substantial pathophysiological differences of MYC rearrangements in patients with plasma cell myeloma and B-cell lymphoma*. Leuk Lymphoma. 2021. Open publication
- Cappelli et al. *Indeterminate and oncogenic potential: CHIP vs CHOP mutations in AML with NPM1 alteration*. Leukemia. 2021. Open publication
- Genescà E et al. *Adverse prognostic impact of complex karyotype (≥3 cytogenetic alterations) in adult T-cell acute lymphoblastic leukemia (T-ALL)*. Leuk Res. 2021. Open publication
- Haferlach C et al. *The diverse landscape of fusion transcripts in 25 different hematological entities*. Leuk Lymphoma. 2021. Open publication
- Haferlach T et al. *Genome Sequencing in Myeloid Cancers*. N Engl J Med. 2021;384(25):e106. Open publication
- Jobanputra V et al. *Clinical interpretation of whole-genome and whole-transcriptome sequencing for precision oncology*. Semin Cancer Biol. 2021. Open publication
- Martelli MP et al. *NOVEL NPM1 EXON 5 MUTATIONS AND GENE FUSIONS LEADING TO ABERRANT CYTOPLASMIC NUCLEOPHOSMIN IN AML*. Blood. 2021. Open publication

- Meggendorfer M et al. *Analytical Demands to Use Whole-Genome Sequencing in Precision Oncology*. Semin Cancer Biol. 2021. Open publication
- Rosenquist R et al. *Clinical utility of whole-genome sequencing in precision oncology*. Semin Cancer Biol. 2021. Open publication
- Rossi M et al. *Clinical relevance of clonal hematopoiesis in the oldest-old population*. Blood. 2021. Open publication
- Simonetti G et al. *Integrated genomic-metabolic classification of acute myeloid leukemia defines a subgroup with NPM1 and cohesin/DNA damage mutations*. Leukemia. 2021. Open publication
- Walter W et al. *Clinical application of whole transcriptome sequencing for the classification of patients with acute lymphoblastic leukemia*. BMC Cancer. 2021; 21(1):866. Open publication

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