MLL News

02/18/2020

New MLL Findings Portal Allows Findings to be Viewed Online

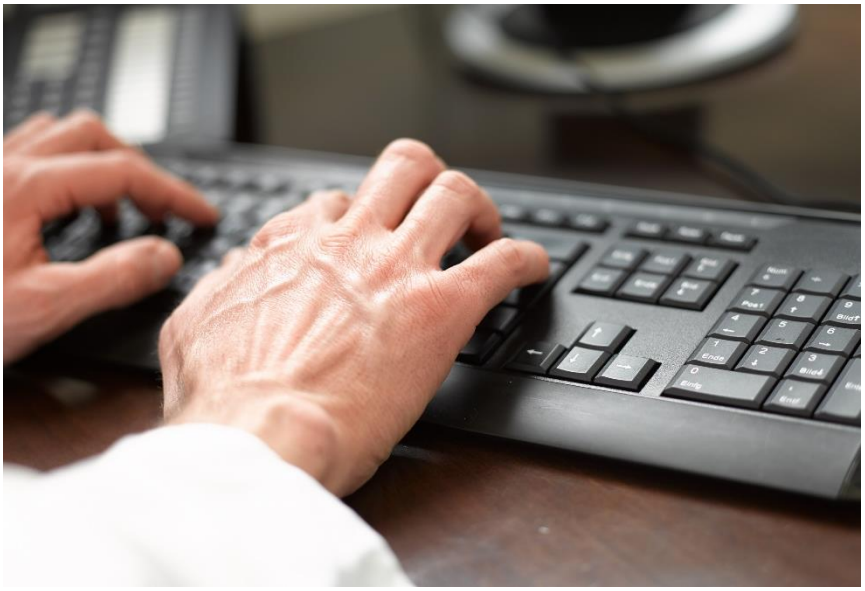
In the age of digital transformation, it appears increasingly anachronistic to communicate findings by fax. In addition, frequent technical problems make them difficult to receive. That is why MLL is now offering a web-based findings portal in which all findings are available for download as a PDF document.

Specific data security standards, including the new GDPR, need to be taken into account for this. You can register either on the MLL website (www.mll.com) or directly with us over the phone. We will first provide you with a user name and the data protection terms / general terms and conditions via email. After you send us your written consent by email, fax, or letter, a password will then be mailed to you separately, which you will need to change once you log in for the first time. There is also a procedure for the loss or misuse of a password.

We hope that this new procedure will avoid technical bottlenecks with the communication of findings and will make it much easier to obtain older findings as well. The goal is to provide you with complete digital findings and documentation management. As an option, you can also set up an email alert to inform you whenever new findings have been finalized.

Feel free to contact us if you have any questions or further suggestions. It is also possible to **order sample shipment material** online now.

In addition, we want to remind you again of our digital portal for entering orders. You can find this at **"MLL Portals" on our website.**



Assessing Sequence Variants

Sequencing technologies have developed rapidly in the last few years. It is possible to sequence an entire genome or a larger panel within just a few days. At the MLL, data from the sequencing machine is loaded to our private cloud in real time and automatically preprocessed using the very latest algorithms. These algorithms compare the sequence of four bases (the nucleotides A, C, G, and T) obtained for individual patients to a reference sequence. It quickly becomes apparent that no one patient is identical to any other. An individualized sequence assessment is a prerequisite for personalized diagnostics and therapy.

In the past, sequence alterations were typically assigned to two categories: *"Mutations"* and *"Polymorphisms"*. Most of the sequence differences – the ones we see on a daily basis – are polymorphisms. These occur in the population with varying frequencies, are transmitted, and, according to what we know today, usually have nothing to do with any subsequent diseases. They explain blood type features or hair and eye color, for example. Acquired mutations are different. These are caused by errors introduced whilst copying the double stranded DNA during cell division. Targeted therapies as well as cell-based and/or animal models that extensively characterize the function of the more frequently occurring acquired mutations such as *JAK2* V617F or *BRAF* V600E already exist.

However, the rapid increase in sequencing data from healthy and a wide variety of diseased tissues has made it clear that there is a broad spectrum between mutations that are clearly associated with diseases and non-pathogenic polymorphisms. Just because a change has occurred during the course of disease does not automatically make it the cause (or the "driver") of the disease. Some changes are merely byproducts of rapid cell division or of a defective DNA repair mechanism and are referred to as "passenger" alterations. In addition, a patient may have been born with a change that favors the development of the disease or influences the response to medications. Making it even more difficult is the fact that individual genes (e.g. *TET2*) exhibit such a diverse mutational landscape that functional characterization of each individual mutation is often not feasible.

For this reason, scientists prefer to use the term "*variant*" instead of *mutation or polymorphism*. Every day we face the challenge of interpreting each patient's variants in the overall clinical context. To do this, we employ the most advanced technical resources. Thanks to artificial intelligence, we are better able to predict the function of a variant (see Hutter *et al.* ASH 2019). Moreover, the GnomAD database project enables us to compare each change with data from more than 100,000 individuals with just one click of the mouse.

Even so, it still happens that we are the first in the world to detect a variant or that the data is contradictory. A comparison with germ line material can be helpful in these cases. To do this we collect a buccal swab and a sample of fingernail. If no evidence of the variant can be found in these samples, we then assume that the variant has been acquired and is therefore only present in the leukemic cell and its precursors. This type of variant serves as a marker of outcome, as it should no longer be present following successful therapy.

Once such a variant becomes better described, we can use this information to help subsequent patients. That is the reason why we have been collecting all mutations, variants, and polymorphisms for more than 14 years. We have access to this expanding wealth of information for each new case and this contributes to improve the diagnostics for each individual patient every day.

More information can be found here.

The Use of Artificial Intelligence at MLL Munich Leukemia Laboratory

Whether a search engine or digital assistant is involved, artificial intelligence (AI) has long been a part of our day-to-day work. There are success stories in imaging-based diagnostics thanks to AI as well. Preliminary studies, for example, indicate that the classification of medical findings using AI is equivalent to traditional methods*. While AI will never replace medical work, it will support it in significant ways. What this can look like in specific cases and how MLL utilizes the potential of AI to advance hematological diagnostics can be seen from application examples from the MLL departments.

To begin with, AI must learn to identify characteristic features in a dataset. In a training phase, the AI runs through iterative cycles of training and validation until it is finally able to recognize the relevant characteristics autonomously and precisely and to produce a classification. It is also true of AI that practice makes perfect – the training dataset just needs to be big enough.

Cytomorphology

In the area of cytomorphology, MLL is working to prepare a database that will initially include around half a million annotated single-cell images of peripheral blood cells. Using this, AI will learn to prepare a differential blood count based on blood smears in preparation for the MTA. Planned as the next step is the automated analysis of bone marrow.

Chromosomal Analysis

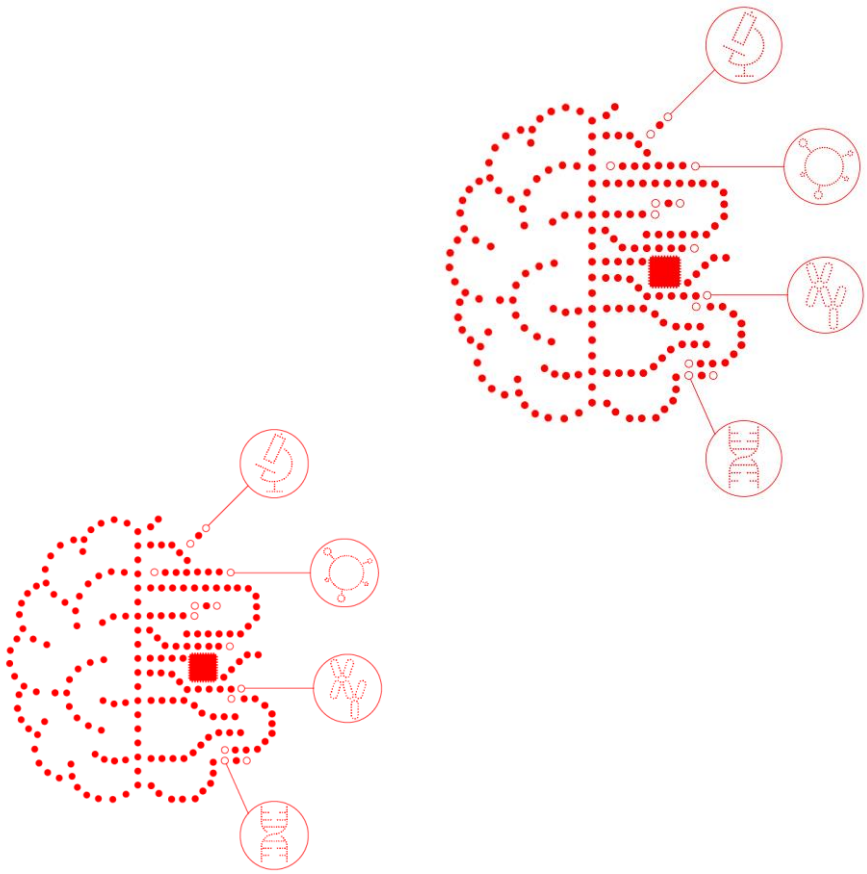
AI has already been supporting MLL in this since the summer of 2019. Based on metaphase images, AI identifies chromosomes, isolates them, and places them in the correct order and orientation in the karyogram. Each karyogram prepared in this way is carefully checked, and any errors are rectified manually. AI support saves a lot of time, which the employees can use for interpreting the data and characterizing complex aberrations. Together with its cooperation partner MetaSystems, MLL is working on continuously improving AI for conventional chromosome analysis.

Immunophenotyping

AI used for this application, was developed jointly with the working group of Professor Krawitz (University of Bonn) and is already proving to be a specialist in classifying mature B-cell neoplasias. In a feasibility study conducted over several months, the analysis of raw data from routine flow cytometry assays was compared in parallel and independently by the MTA, physicians/biologists as well as by AI. So far, AI only makes predictions concerning the diagnosis instead of producing findings, but it also indicates how probable the specific diagnosis is and which one would be the second most probable. At a predictive confidence of >95%, AI correctly detected the presence of mature B-cell neoplasia in 99.7% of cases and also provided a correct class allocation 99.3% of the time (Kern et al. 2019 ASH Abstract 886). At present, the goal is to expand the diagnostic spectrum to all other areas of immunophenotyping, including marrow/cortex differentiation using AI.

Molecular Genetics

Evidence of mutations in a gene panel of interest can be of great importance for diagnosis, risk assessment and even for the selection of therapies for hematological neoplasias. However, the interpretation of detected gene variants poses a considerable challenge in many cases – because not every gene variant is relevant to disease. The AI tool developed at



Important Dates

Save the date: Oncology Symposium 2020

In the wake of the resounding success of the 2019 Oncology Symposium “From Biomarker to Therapy Recommendation”, plans are currently being drawn up for the 2020 Oncology Symposium. Experts from the field of diagnostics met in 2019 to report on the important role of biomarkers as a guide for personalized medical approaches and to give insights into their experience in oncological diagnostics.

The successful format will be continued on **11/13/2020**. **Simply register now free of any obligations.**

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