MLL News

August 09, 2023

MLL staging diagnostics for unclear cytopenia

One of the most frequent questions in hematological practices and hospitals is the clarification of cytopenias. The causes are manifold, especially in elderly patients, and can be benign or malignant. History and laboratory diagnostics can provide clues to possible causes, but often the picture remains unclear until the indication for bone marrow aspiration is given. After exclusion of reactive conditions, for example, myelodysplastic neoplasia is a common but by no means the only malignant cause of cytopenia. Acute leukemias, lymphomas, plasma cell myelomas and many others can be found in the examination material of corresponding patients.

After bone marrow collection (aspiration and punching recommended), it is often not possible to assess which diagnostic methods are useful for diagnosing and characterizing the potential underlying bone marrow disease at the moment of sending the material to a specialized hematology laboratory. Therefore, MLL offers the option to order a "staged diagnostic workup" (see MLL Request Form). This includes a stepwise examination of the bone marrow aspirate (or blood sample), in the course of which the disease phenotype is first determined using suitable methods (cytomorphology and/or immunophenotyping) or other neoplasms are excluded. Only in the second step a decision is made on suitable methodological additions, especially with regard to the cyto- and molecular genetic characterization of a defined neoplasia or the extended exclusion of a clonal event. The latter is becoming increasingly important in times of newly defined entities such as CHIP and CCUS even in the case of inconspicuous phenotype diagnostics.

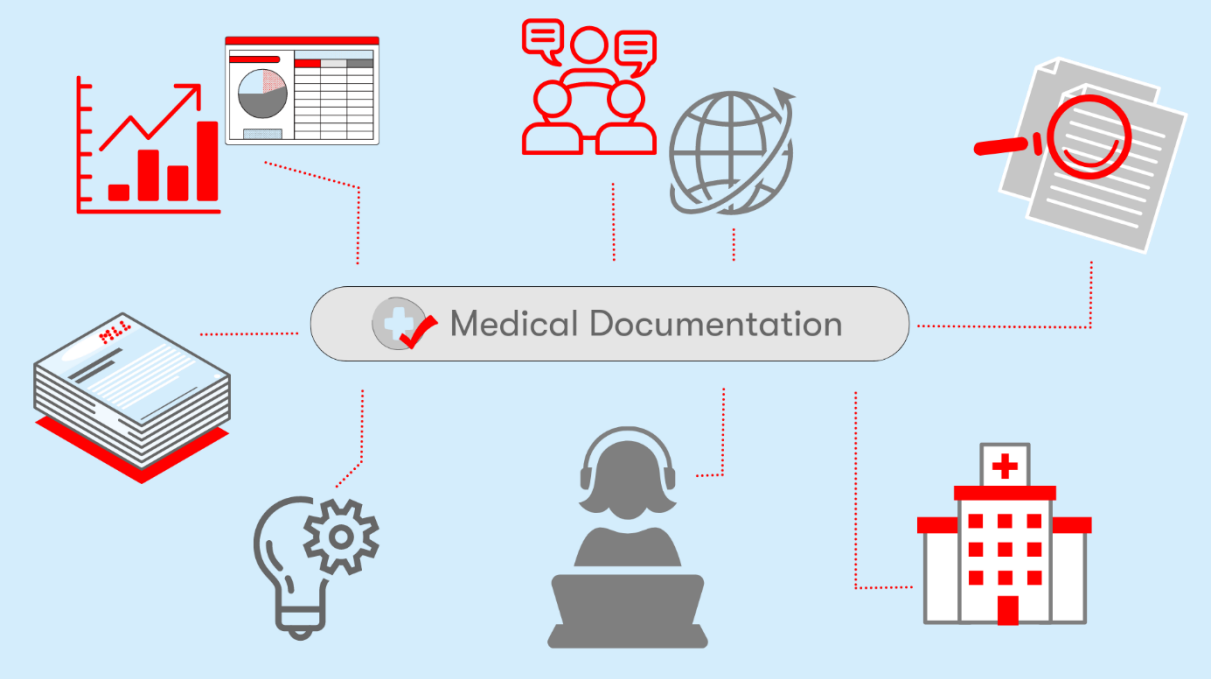
Such a staged approach ensures a more rational and faster use of the highly specific diagnostic armamentarium for patients and avoids additional costs for the healthcare system. A prerequisite for efficient implementation is the immediate processing of the relevant samples upon arrival at the laboratory. Although phenotype diagnosis by cytomorphology and immunophenotyping at MLL has a mean turnaround time of less than

24 hours, additional prioritization is required in view of up to 700 samples/day. Therefore, as part of a plausibility check performed by hematologists and biologists, which is performed for each individual sample immediately upon its arrival at MLL, cases with indications for step diagnostics are immediately assigned to a prioritized workflow. This ensures that the assessment of cytomorphology and immunophenotyping is performed within 2-3 and 4-5 hours, respectively, after sample arrival. If necessary, further diagnostics can then be performed on the fresh sample material within the same day.

In addition to the usual clinical information, we particularly require a sufficient amount of sample material (10-15 ml of heparin and EDTA each) from the colleagues sending in the samples. In addition, the scope of the methods used within the scope of a step-by-step diagnosis can be specified on our examination order, e.g. in order to limit the costs for inpatients.

If you have any questions regarding the request for step-by-step diagnostics in MLL, we will be happy to assist you in the usual manner by telephone (+49 89 99017-0) or via email info@mll.com .

Author: Christian Pohlkamp, M.D.



The MLL introduces itself - our medical documentation

"Medical documentation - what exactly do you do?" is a question we get from time to time from MLL colleagues and external partners. We are a small and central department that is networked with all areas of MLL and has a wide range of tasks.

Tasks of the department

MLL is the central laboratory for more than 20 international studies. A major core topic of our work is the coordination of these clinical studies. Our department is involved in the entire multi-year process of a study: In the preparatory phase, coordination takes place with the diagnostic areas so that it is clear which analyses and findings are to be performed and generated for the various study samples. Often, new IT processes also have to be established

for this purpose. In the further course, we are in close contact with the study sponsors: We transmit data on samples received, initial results and clarify questions about individual submissions. After completion of a study, we organize the shipment of patient material if necessary or initiate subsequently requested analyses.

Another important task of our department is the management of clinical patient data, i.e. therapy and survival data, which we receive from our referring colleagues.

In addition, we have access to the extensive database of the MLL, in which all analyses and results of the last 18 years are stored. We query the appropriate data sets from the database for specific questions. Thus, we are also regularly involved in current research projects. In addition, we undertake statistical evaluations and graphical representations of the data.

We maintain our internal publications database, assist colleagues in submitting publications, and provide training on statistical and database programs.

In addition, we take care of the documentation for the clinical studies at the MLL MVZ, our hematology care center affiliated with the MLL. Here, we work closely with the colleagues at the MLL MVZ.

We do not have a "typical" working day. Of course, there are regularly recurring tasks; however, new requests and medium-term projects provide variety every day. Due to our diverse line-up and the many different areas of responsibility, it is possible to get involved in projects that suit one's personal and professional interests.

The team and outlook

Currently, our team consists of five colleagues: Jeannette Beyer, Irene Fuhrmann (technical director), Sarah Koch, Dr. rer. nat. Miriam Lenk and Wenke Shearer. The department is headed by Dr. rer. nat. Sabit Delic. All employees have different professional backgrounds: from documentalist to study nurse to biologist.

We want to further advance automation in our department - making small daily work steps easier, but also rethinking large processes and defining long-term strategies. For this further development, an expansion of our team is currently being planned.

Author: Irene Fuhrmann

Clonal hematopoiesis risk score

The molecular genetic detection of clonal hematopoiesis by sequencing allows us to better understand the early phase of the development of myeloid neoplasms. The prevalence of clonal hematopoiesis is strongly age-dependent, ranging from 10-20% of the population over 60 years of age, so we are increasingly confronted with this question in the workup of blood count abnormalities. The WHO classification 2022 distinguishes clonal hematopoiesis of indeterminate potential (CHIP) and clonal cytopenia of indeterminate significance (CCUS) as myeloid precursor lesions. The risk of progression from clonal hematopoiesis to full-blown myeloid neoplasia depends on the number and type of underlying mutations and clone size. In addition, the presence of unexplained hematopoietic changes, especially unexplained cytopenia (i.e., diagnosis of CCUS rather than CHIP), is the major risk factor for hematologic progression. However, no generally accepted prognostic models have been available to accurately predict individual risk.

In a recently published study (Weeks LD et al, NEJM Evid 2023;2(5)), the risk of progression of clonal hematopoiesis was investigated in a large cohort of 438,890 subjects from the U.K. Biobank and a Clonal Hematopoiesis Risk Score (CHRS) was established. Prognostically unfavorable variables included defined high-risk mutations (*SRSF2*, *SF3B1*, *ZRSR2*, *IDH1*, *IDH2*, *FLT3*, *RUNX1*, *JAK2*, and *TP53*), detection of multiple mutations, a clone size of at least 20% variant allele frequency (VAF), a red cell distribution width (RDW) of ≥15%, macrocytosis defined as mean red cell volume (MCV) of ≥100 fl, the presence of cytopenia (CCUS vs. CHIP) and an age ≥65 years. In contrast, the presence of a *DNMT3A* mutation alone is a prognostically favorable factor in CHRS. The weighted sum of these factors results in a CHRS score, on the basis of which individuals with clonal hematopoiesis are classified into the risk categories of low (score ≤9.5), intermediate (score 10-12), and high (score ≥12.5). For individuals in the lowest risk category (approximately 90% of all individuals with clonal hematopoiesis), the 10-year risk of developing a hematologic neoplasm was <1% and thus only marginally increased compared with individuals without clonal hematopoiesis. In contrast, the 10-year progression rates in the intermediate (approximately 10% of all individuals with clonal hematopoiesis) and high risk categories (approximately 1% of all individuals with clonal hematopoiesis) were 8% and 52%, respectively, in a clinically relevant range, which was also reflected accordingly in overall survival.

The CHRS risk score for clonal hematopoiesis allows improved prediction of progression risk in individuals with CHIP and CCUS based on simple blood count variables and molecular genetic NGS examination of a myeloid gene panel. While the corresponding analyses can in principle be performed in peripheral blood, the combination of an unclear cytopenia and the detection of a somatic mutation still indicates a bone marrow biopsy to clarify the presence of an already manifest myelodysplastic neoplasia (MDS) or other hematologic neoplasia.

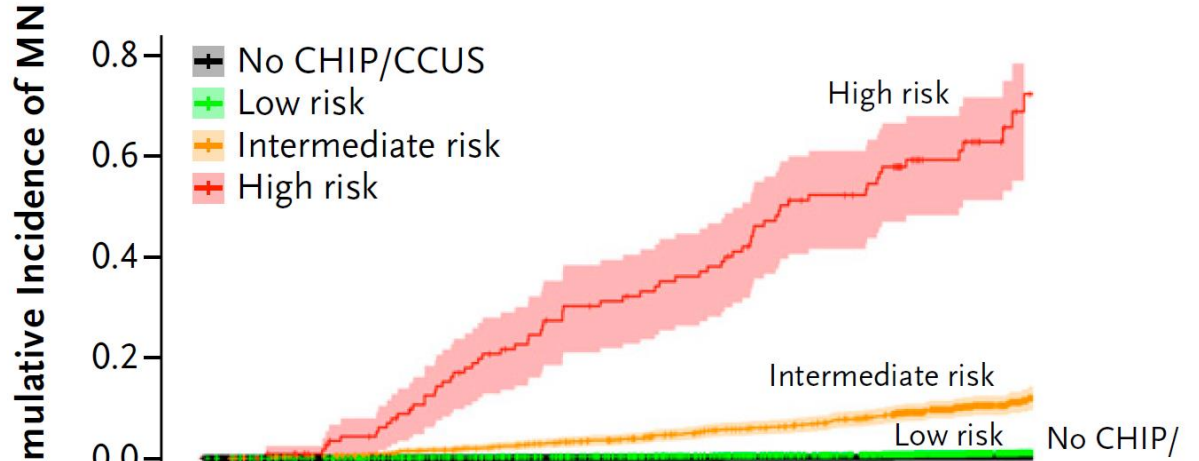
Table: CHRS values (Weeks et al. 2023).

Table 2. CHRS Values.*

Prognostic Variable	0.5	1	1.5	2	2.5
Single *DNMT3A*	Present	Absent			
High-risk mutation		Absent			Present
Mutation number		1		≥2	
Variant allele fraction		<0.2		≥0.2	
Red cell distribution width		<15			≥15
Mean corpuscular volume		<100			≥100
Cytopenia		CHIP	CCUS		
Age (yr)		<65	≥65		

* CCUS denotes clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential; and CHRS, clonal hematopoiesis risk score.

Figure: Cumulative curves for incidence of MN according to CHRS risk category (Weeks et al. 2023).



References

- Weeks LD et al. Prediction of risk for myeloid malignancy in clonal hematopoiesis. NEJM Evid 2023;2(5).

Author: PD Gregor Hörmann, MD, PhD

Invitation to the Oncology Symposium 2023

The Trillium Academy cordially invites you to the fifth Oncology Symposium. Themed "From Biomarker to Therapy", the event will take place on Friday, October 6, 2023, at our premises at the MLL Munich Leukemia Laboratory. The symposium will be offered in a hybrid format (on-site and livestream). Our newsletter subscribers will benefit from a discount code on the event price.

Click here for registration and program

Microscopy courses MADE

The Würmtal Laboratory and the MLL Munich Leukemia Laboratory are jointly organizing - and for the first time in cooperation - the microscopy course series MADE (Microscopy, Analysis, Discussion, Wrapping). The course "MADE for the future" will take place from 21.10. to 23.10.2023 and from 10.11. to 12.11.2023.

Click here for registration and program

Recent publications with MLL participation

- de Almeida JG et al. Computational analysis of peripheral blood smears detects disease-associated cytomorphologies. Nat Commun. 2023. Open publication
- D'Amico S et al. Synthetic Data Generation by Artificial Intelligence to Accelerate Research and Precision Medicine in Hematology. JCO Clin Cancer Inform. 2023. Open publication
- Metzgeroth G et al. Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions: reevaluation of the defining characteristics in a registry-based cohort. Leukemia. 2023. Open publication

- Sakuma M et al. UBA1 Non-M41 Variants Are More Aggressive than UBA1 M41 Variants in Their Haematological Manifestations. EMJ Hematology. 2023.
  Open publication
- Stengel A et al. Interplay of TP53 allelic state, blast count and complex karyotype on survival of patients with AML and MDS. Blood Adv. 2023. Open publication.

➢ Click here for all publications

MLL Münchner Leukämielabor GmbH Max-Lebsche-Platz 31
81377 München, Germany
Phone: +49 89 990 17 0
Fax: +49 89 990 17 111 E-Mail: info@mll.com
Internet: www.mll.com