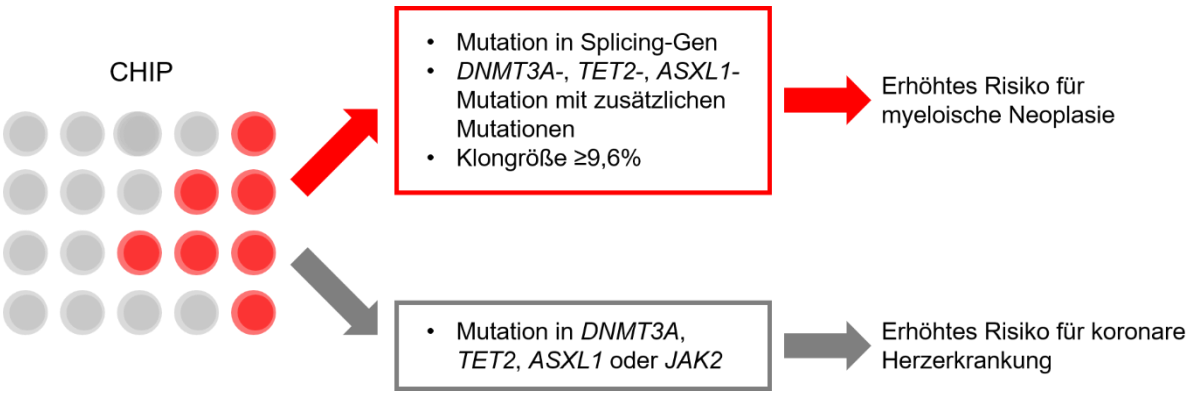
MLL News

February 22, 2022

CHIP highly relevant to individual risk profile for individuals aged ≥80 years

Clonal genetic changes in hematopoietic cells occur with increasing frequency with advancing age, even in individuals without hematological neoplasia. Due to the growing number of individuals aged ≥80 years in our society, the need arises to investigate the clinical relevance of such clonal hematopoiesis of indeterminate potential (CHIP). The focus here is on the relationship between CHIP and the development of myeloid neoplasia or cardiovascular disease for an individual risk assessment and potential early therapeutic intervention.

A recently published study by Rossi and colleagues (Blood 2021;138 (21): 2093–2105) examined blood samples from 1794 individuals aged ≥80 years who have not been diagnosed with hematological neoplasia for mutations in 47 genes implicated in myeloid neoplasia.



Frequency of CHIP and Effect on Survival in Individuals Aged ≥80 Years

- CHIP in approx. 30% of individuals
- The older the individual, the more frequent the occurrence of CHIP
- CHIP more common in individuals with (non-hematological) chronic diseases
- Lower probability of survival for individuals with CHIP, particularly with ≥2 mutations

Approximately 30% of individuals were found to have at least one mutation in one of the genes studied, with the *DNMT3A*, *TET2*, and *ASXL1* genes most frequently affected. The older the individual, the more frequently CHIP mutations were detected. Furthermore, CHIP mutations were approximately three times as common in individuals with non-hematological chronic diseases. In addition, individuals with CHIP had a lower probability of survival, whereby persons with ≥2 mutations exhibited an even less favorable prognosis (observation period of up to 15 years).

Influence of CHIP on Risk of Myeloid Neoplasms

- Absence of CHIP: high negative prediction value
- Number, type, and clone size of mutations as predictive markers for myeloid neoplasms
- Definition of 3 risk groups by mutation status and erythrocyte indices
- High prognostic relevance of mutations for cytopenia of undetermined significance

Rossi and colleagues demonstrated that CHIP mutations influenced the risk of developing a myeloid neoplasm in the cohort studied. The absence of CHIP turned out to be a strong negative predictor. A higher number of mutations as well as mutations in splicing genes (*SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*), *JAK2* mutations, and *DNMT3A*, *TET2*, and *ASXL1* mutations with mutations in additional genes were found to have a strong positive predictive value for the development of myeloid neoplasms. The risk of a myeloid neoplasm also increased when the allele frequency of the mutation was ≥9.6%. Using a risk score based on mutation status, mean red cell volume (MCV >98 fL), and red cell distribution width (RDW >14%), three risk groups for the occurrence of a myeloid neoplasm were defined. The combination of a cytopenia of undetermined significance with specific mutations (clonal cytopenia of unclear significance, CCUS) gave rise to a particularly unfavorable prognosis. Overall survival of individuals with this constellation did not differ from patients with a diagnosed myeloid neoplasm.

CHIP and Chronic Inflammatory Disease or Coronary Heart Disease in Individuals Aged ≥80 Years

The risk of coronary heart disease was also higher in individuals with CHIP mutations. *DNMT3A*, *TET2*, *ASXL1*, or *JAK2* mutations turned out to be high-risk mutations which, in addition, also indicated an increased risk of rheumatoid arthritis.

The study by Rossi and colleagues demonstrates the significance of CHIP for individual risk assessment and prognosis, particularly in older individuals. A mutation analysis may be particularly useful for further classification of an unexplained cytopenia. Based on research findings such as these, we are constantly considering adjustments and additions to our diagnostic services in order to identify potential risk factors at an early stage.

Author: Dr. Isolde Summerer

CLL: The more complex the karyotype, the less favorable the prognosis

Chronic lymphocytic leukemia (CLL) is the most common leukemic disease in Central Europe. In addition to clinical prognostic factors, a number of genetic risk factors have a negative impact on response rate and overall survival.

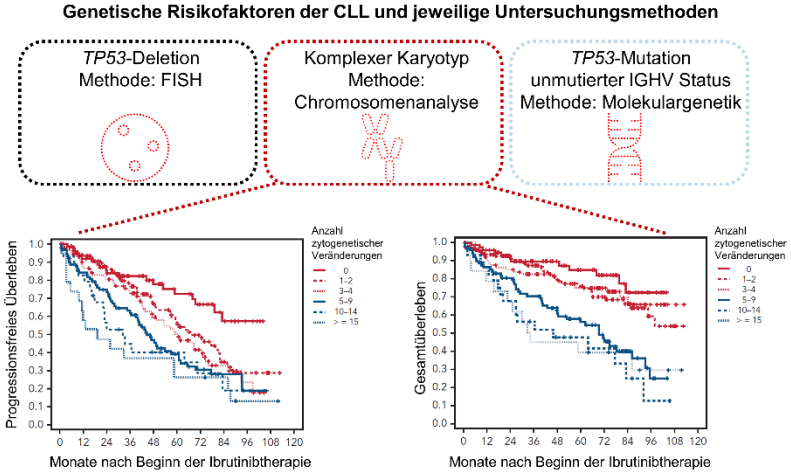


Abbildung (nach Kittai et al, Blood. 2021;138(23):2372-2382): Gezeigt sind die nach Onkopedia Leitlinien beschriebenen genetischen Risikofaktoren der CLL sowie die für die jeweilige Detektion verwendete Untersuchungsmethode. Der Einfluss des komplexen Karyotyps auf sowohl das progressionsfreie Überleben (links) als auch auf das Gesamtüberleben (rechts) wurde von Kittai et al. detailliert aufgeschlüsselt, indem das Überleben von mit Ibrutinib behandelten CLL Patienten abhängig von der Anzahl an chromosomalen Veränderungen untersucht wurde.

Genetic Risk Factors of CLL

The Onkopedia guidelines[1] recommend testing for the following genetic risk factors before initiating therapy:

1. *TP53* deletion (del(17p13))
2. *TP53* mutation
3. Complex karyotype
4. Unmutated IGHV status

The presence of at least one of these risk factors influences the therapy of patients, because in these cases the use of BTK inhibitors (e.g. ibrutinib) or the combination of venetoclax/obinutuzumab is recommended in first-line therapy[1].

Complex Karyotype as a Prognostic Factor

Approximately 20% of all CLL patients exhibit a complex karyotype, but the number of aberrations starting from which the strongest prognostic effect is observed has long been debated[2,3]. New data now further breaks down this relationship by examining the survival of 456 CLL patients treated with ibrutinib based on the number of chromosomal alterations[4]. The patients were divided into subgroups based on the number of aberrations at initial diagnosis (0, 1-2, 3-4, 5-9, 10-14, ≥15). The authors were then able to show that karyotype complexity is a continuous variable for survival: Patients with 1-2 aberrations showed a progression-free survival of 67 months, the presence of 5-9 aberrations reduced this to 45 months, and with ≥15 alterations it further decreased to 19 months. Thus, it is clear that it is not only the presence of a complex karyotype *per se*, but also the number of alterations which has an influence on the prognosis. For some patients, samples were also analyzed during the course of the disease. Here it also became clear that an increase in chromosomal alterations was associated with a poorer prognosis.

The Role of Chromosomal Analysis in Risk Stratification for CLL

Although several guidelines (e.g., Onkopedia) recommend analysis of the complex karyotype before initiating therapy, chromosomal analysis has not yet been established as an integral part of CLL diagnostics. FISH (fluorescence in situ hybridization) analyses to detect frequent or prognostically relevant alterations are routinely performed, but cannot determine the total number of aberrations because a genome-wide analysis is not possible with FISH. The new data not only demonstrates the importance of the complex karyotype as a continuous prognostic marker, but also underscores the role of chromosomal analysis in CLL diagnostics, both for the initial diagnosis and over the course of the disease. In principle, whole-genome sequencing (WGS) analyses can be considered as an alternative method. However, this is currently not yet a standard option in CLL diagnostics for cost reasons.

References

[1]https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/chronic-lymphocytic-leukemia-cll/@@guideline/html/index.html

[2]Haferlach C, Dicker F, Schnittger S, Kern W, Haferlach T. Comprehensive genetic characterization of CLL: a study on 506 cases analysed with chromosome banding analysis, interphase FISH, IgV(H) status and immunophenotyping. Leukemia. 2007; 21(12):2442-2451.

[3]Baliakas P, Jeromin S, Iskas M, et al; ERIC, the European Research Initiative on CLL. Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. Blood. 2019;133(11):1205-1216.

[4]Kittai AS, Miller C, Goldstein D, et al. The impact of increasing karyotypic complexity and evolution on survival in patients with CLL treated with ibrutinib. Blood. 2021;138(23):2372-2382.

Author: Dr. Anna Stengel

Client communication and digital portals – Introducing our customer support

Each day, hundreds of blood and bone marrow samples from different doctor's offices, medical care centers, and clinics arrive at MLL. In addition to a consistently high testing quality, working closely together with our clients is very important for us as a diagnostic laboratory. Fast and reliable communication, both internally and externally, plays a fundamental role here, which we are constantly trying to optimize along with the necessary digital processes.

The first point of contact for this is our "Customer Support" department (Julia Hennig, julia.hennig@mll.com). By networking with other departments as well as regular and intensive discussions with our physicians, biologists, IT specialists, and data protection officers, our Customer Support department is always up to date across all disciplines and is able to quickly resolve questions or forward them to the right contact person.

Day-to-Day Tasks of the Customer Support Department

A core daily task of the Customer Support department is the maintenance of client data and the documentation of supplementary information. This includes the best contact options (phone numbers, email addresses, etc.) to ensure reliable communication. Furthermore, where desired, individual preferences for the testing methods are stored for each client. Armed with this information, the responsible employees are able to carry out and allocate the orders from our clients as specified and in a medically appropriate manner. This data is also required and taken into account in the plausibility check performed by medical staff for each incoming test request.

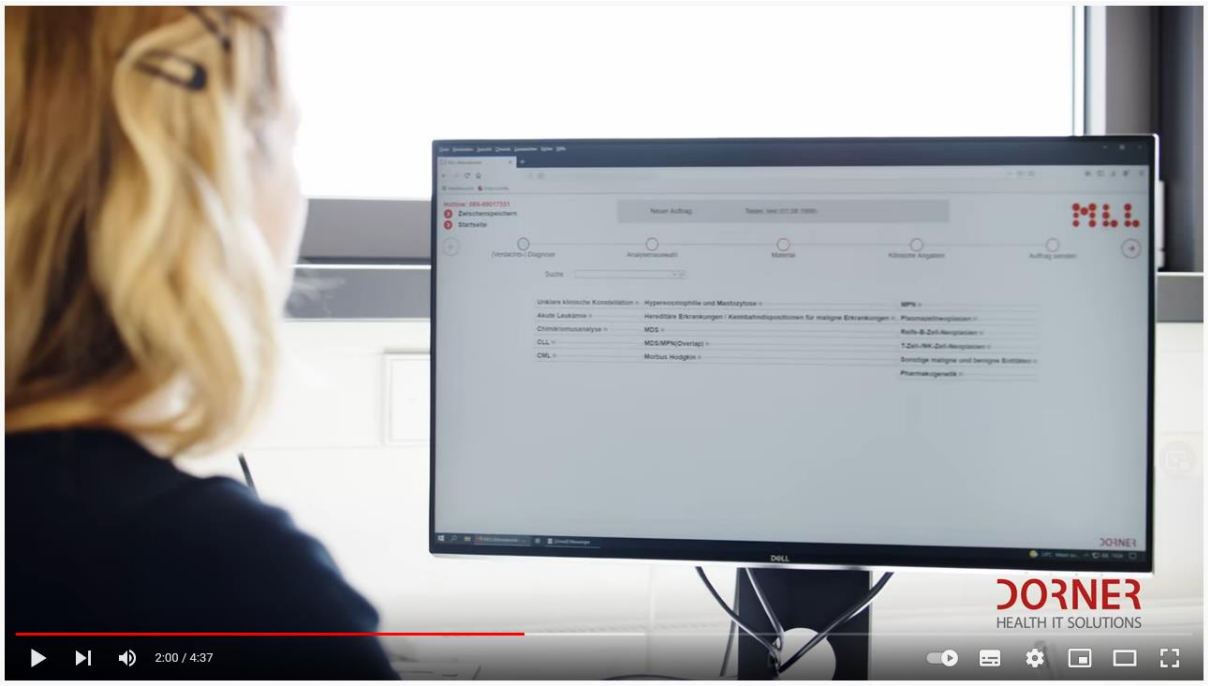
Such information helps us to reach you promptly if necessary, but also helps to avoid any unnecessary further questions. We would therefore be very grateful if you would support us in this respect, and also proactively provide us with this information. In addition, regular communication with our Sample Receipt and administration office is important for our Customer Support department in order to identify potential problems and challenges regarding the transmission of findings and sample material at an early stage.

In addition, one of the most important tasks is supporting and maintaining our digital portals. We currently offer two digital portals for our clients:

The findings portal and the digital order entry, our order entry system.

While the findings portal uses a web-based solution, the order entry requires the additional setup and implementation of the necessary connection to the AIS/KIS(physician/hospital information system) and – where desired – subsequent expansion to additional computers or locations. After establishing the connection, a convenient and entirely digital test request can then be submitted by the physician.

This video provides information on the most important aspects of our order entry system.



All the details concerning registration, a test account for trying out the system, and a tutorial video are available at www.mll.com/orderentry.

Of course, we very much hope that you are satisfied with our diagnostic service and our digital portals at all times. However, should you have any criticism, feel free to contact our customer support (befundportal@mll.com or orderentry@mll.com) with your feedback.

Future & Perspectives

We have developed our digital portals for various reasons. On the one hand, it is essential for us to make order submission and communicating findings as straightforward, user-friendly, and environmentally friendly as possible. With our portals, we also offer a service that solves the most frequently asked questions from clients: Have my samples arrived? What is the status of my analyses and when can I expect the initial results? Can you re-send me older findings?

The COVID-19 pandemic and the 2021 flood disaster have shown us how important it is to be able to view findings digitally at any time and from any location.

In addition, digitalization and automation are also playing an increasingly important role in healthcare. A few years ago, for example, sending a fax was still the most common means of communication, but digital formats are increasingly taking over. This is why it will continue to be our goal in the future to constantly develop the portals with all their possibilities and to consistently expand and improve the way we communicate with clients.

Should you have any questions about the portals or any other concerns, please do not hesitate to contact us. Feel free to contact us via email or phone at:

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Research Report 2021

Even though the last two years have been dominated by the pandemic, we never lost sight of our scientific goals. We therefore took the opportunity to summarize our 2021 research findings for you. To make it easier to read and to better communicate our data, we've included various graphical representations and summaries.

> Click here for the Research Report 2021

Most Recent Publications with MLL Involvement

- Berger D et al. Secondary basophilic leukemia in Ph-negative myeloid neoplasms: A distinct subset with poor prognosis. Neoplasia. View publication
- Gurnari C et al. A study of TERT rare variants in myeloid neoplasia. Hematol Oncol. 2022. View publication
- Müller H et al. Aberrant somatic hypermutation of CCND1 generates non-coding drivers of mantle cell lymphomagenesis. Cancer Gene Ther. 2022. View publication
- Simonsen AT et al. Acute myeloid leukemia displaying clonal instability during treatment: implications for measurable residual disease assessments. Exp Hematol. 2022. View publication
- Tettero JM et al. Technical Aspects of Flow Cytometry-based Measurable Residual Disease Quantification in Acute Myeloid Leukemia: Experience of the European LeukemiaNet MRD Working Party. Hemasphere. 2021;6(1):e676. View publication
- Wagner-Ballon O et al. ELN iMDS flow working group validation of the monocyte assay for chronic myelomonocytic leukemia diagnosis by flow cytometry. Cytometry B Clin Cytom. 2021. View publication
- Weiß E et al. Identification of a specific immunophenotype associated with a consistent pattern of genetic mutations including SRFS2 and gene expression profile in MDS. Cytometry B Clin Cytom. 2022. View publication

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