PATHOLOGISTS
LANCET LABORATORIES
Key to Diagnostic Excellence
Van Rensburg
Newsletter

Myeloid Next Generation Sequencing (NGS): Uncovering complexity in the genomes of the elderly

Compiled by: Dr Nicole Holland

1st Quarter 2025

Introduction

Myeloid neoplasms have an increased incidence with ageing and include disorders such as myelodysplastic syndromes, acute myeloid leukaemia and chronic myeloproliferative neoplasms (e.g. polycythaemia vera). These are clonal disorders which are characterised by mutations within the stem cells producing blood cells.

Newer technologies have increased our knowledge of the genetic complexity of cancer and our awareness that malignancy is frequently the result of multiple genetic "hits". They have also allowed investigators to detect mutations which are known to be pathogenic, in the absence of overt malignancy. These are found with increasing incidence with ageing and have resulted in the coining of terms such as **A**ging-**R**elated **C**lonal **H**aemopoiesis (**ARCH**) and **C**lonal **H**aemopoiesis of **I**ndeterminate **P**otential (**CHIP**). These changes are of uncertain significance raising the dilemma of what to do with the information.

Myeloid NGS

The diagnosis and classification of myeloid malignancies, together with prognostication and treatment selection, rely heavily on the genetic make-up of the neoplasm. Historically our approach to investigation of mutations has been more directed – the presence of a single DNA mutation or chromosomal translocation will be assessed, e.g. by Fluorescence *In Situ* Hybridization (FISH) or a single PCR test – or less granular, such as the assessment of gross chromosomal aberrations (somatic karyotyping). However, the additional mutations present, which may have prognostic significance, will be missed. In contrast, NGS is massively parallel DNA sequencing – millions of DNA sequences and multiple targets **including RNA rearrangements** will be assessed in a single run. This allows for accurate diagnosis of suspected and unexpected conditions, as well as evaluation of mutations which may be disease modifiers. In the correct setting, the presence of mutations may be the proof of clonality required to confirm the diagnosis of a myelodysplastic syndrome. Important information yielded by Next Generation Sequencing (NGS) includes quantitation of the altered DNA sequence in comparison to the wild-type ("normal") DNA sequence – the **V**ariant **A**llele **F**requency (**VAF**). Once identified, the response of the clone to therapy can be monitored. In addition, malignancies change with the selective pressures of therapy and NGS can be used to monitor for new, previously undocumented mutations indicating clonal evolution.

Use of myeloid NGS in malignancy

- Confirm diagnosis
- Confirm clonality
- Prognostication
- Treatment selection
- Treatment monitoring
- Monitoring for clonal evolution

Clonal haematopoiesis in the absence of haematological malignancy

As people age, acquired mutations can accumulate. Most of these changes are a result of impaired DNA repair or exposure to agents in the environment which induce mutations (e.g. tobacco smoke, radiation, cancer drugs).

Aging-Related Clonal Haemopoiesis (ARCH) refers to the presence of mutations, which are frequently leukaemia-associated, at low percentages (VAFs), usually <2%, without other defined criteria present to make the diagnosis of a haematological malignancy. These clones are referred to as Clonal Haemopoiesis of Indeterminate Potential (CHIP) when the allele frequency is >2%. There is an association of CHIP with a proinflammatory state. Studies have shown an increase in all-cause mortality, increased cardiovascular complications and increased risk of haematological malignancy in older patients with CHIP.

Current recommendations include monitoring of patients with CHIP with 3 - 6 monthly appointments and FBC and differential counts.

References

1. Bacher U, Shumilov E, Flach J, et al. Challenges in the introduction of next-generation sequencing (NGS) for diagnostics of myeloid malignancies into clinical routine use. Blood Cancer J. 2018 Nov 12; 8(11): 113. doi: 10.1038/s41408-018-0148-6.
2. Cho YU. The role of next-generation sequencing in hematologic malignancies. Blood Res. 2024 Mar 6; 59(1): 11. doi: 10.1007/s44313-024-00010-0.
3. Gurbuxani S, Hochman MJ, DeZern AE, Shimamura A. The Times, They Are A-Changing: The Impact of Next-Generation Sequencing on Diagnosis, Classification, and Prognostication of Myeloid Malignancies With Focus on Myelodysplastic Syndrome, AML, and Germline Predisposition. Am Soc Clin Oncol Educ Book. 2023 Jun; 43: e390026. doi: 10.1200/EDBK_390026.
4. Marnell CS, Bick A, Natarajan P. Clonal hematopoiesis of indeterminate potential (CHIP): Linking somatic mutations, hematopoiesis, chronic inflammation and cardiovascular disease. J Mol Cell Cardiol. 2021 Dec; 161: 98 – 105. doi: 10.1016/j.yjmcc.2021.07.004
5. Sekeres MA & Lindsley RC. Clonal hematopoiesis of indeterminate potential (CHIP) and related disorder of clonal haematopoiesis. In: UpToDate, Larson RA (Ed), Wolters Kluwer. (Accessed on February 10, 2025).

design done and printed by: ELECTRONIC LABORATORY SERVICES (PTY) LTD PRINT BUREAU ITEM CODE: N00291
corporate branding/newsletters/sa/2025/N00291 myeloid next generation sequencing (ngs): uncovering complexity in the genomes of the elderly a4 eng simplex 170gsm venus feb2025 | rev000