Diagnostic testing in myeloid malignancies by next-generation sequencing: recommendations from the Commission Personalised Medicine

E. Van Valckenborgh, PhD[1], M. Bakkus, PhD[2], E. Boone, PhD[3], A. Camboni, MD, PhD[4], J-P. Defour, PhD[4], B. Denys, MD[5], H. Devos, MD[6], L. Dewispelaere, MD[7], G. Froyen, PhD[8], A. Hébrant, Ir, PhD[1], P. Heimann, MD, PhD[7], P. Hermans, MD, PhD[9], E. Heylen, PhD[10], K. Jacobs, PhD[11], F. Lambert, MD[12], M. Le Mercier, Apr, PhD[13], E. Lierman, PhD[14], H. Louagie, MD, PhD[11], B. Maes, MD, PhD[8], M-B. Maes, PhD[13], G. Martens, MD, PhD[3], L. Michaux, MD, PhD[14], F. Nollet, PhD[6], H.A. Poirel, MD, PhD[15], G. Raicevic, PhD[1], P. Saussoy, MD, PhD[4], T. Tousseyn, MD, PhD[16], M. Van Den Bulcke, PhD[1], P. Vandenberghe, MD, PhD[17], K. Vandepoele, PhD[5], P. Vannuffel, PhD[18], T. Venken, PhD[10], K. Vermeulen, PhD[13]
On behalf of the ComPerMed haemato working group

SUMMARY

Molecular diagnostics have an increasing impact on diagnosis, risk stratification and targeted treatment in haemato-oncology. In the framework of a pilot study for the implementation of next-generation sequencing in the Belgian healthcare system, the Commission of Personalised Medicine was founded to give professional and evidence-based advice on the molecular analysis in haemato-oncology. This paper describes its recommendations for NGS analysis in myeloid malignancies. In addition, the minimally required set of genes that must be analysed is defined and algorithms for molecular workflow in myeloid malignancies are proposed.

(BELG J HEMATOL 2019;10(6):241-9)

INTRODUCTION

DNA-based next-generation sequencing (NGS), a high-throughput sequencing technology, has recently been implemented by diagnostic laboratories for clinical routine testing in oncology and haemato-oncology.[1] In order to achieve maximal cost-effectiveness, targeted sequencing with limited gene sets is currently the preferred choice. Genes selected in the gene panel are assessed on three criteria: (a) informative for diagnosis according to international guidelines, (b) allowing clinically relevant risk stratification (prognostic) to better assist subsequent counselling, treatment and follow-up and/or (c) identification of suitable markers for

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[1]Belgian Cancer Centre, Sciensano, Brussels, Belgium, [2]Department of Clinical Biology, Haematology Division, Vrije Universiteit Brussel, Universitair Ziekenhuis Brussel, Brussels, Belgium, [3]Laboratory for Molecular Diagnostics, AZ Delta General Hospital, Roeselare, Belgium, [4]Laboratory for Molecular Biology, Cliniques Universitaires Saint-Luc, Brussels, Belgium, [5]Laboratory for Molecular Haematology, Ghent University Hospital, Ghent, Belgium, [6]Laboratoriumgeneeskunde, AZ Sint-Jan Brugge-Oostende AV, Brugge, Belgium, [7]Laboratory for Molecular Haemato-Oncology, LHUB-ULB, Brussels, Belgium, [8]Laboratory for Molecular Diagnostics, Jessa Hospital, Hasselt, Belgium, [9]Clinics of Haematology and Oncology, Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium, [10]Clinical Laboratory, ZNA Middelheim, Antwerp, Belgium, [11]Clinical Laboratory, AZ Sint-Lucas, Ghent, Belgium, [12]Centre for Human Genetics, University Hospitals Liège, Liège, Belgium, [13]Laboratory of Haematology, Antwerp University Hospital, Antwerp, Belgium, [14]Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium, [15]Belgian Cancer Registry, Brussels, Belgium, [16]Department of Pathology, University Hospitals Leuven, Leuven, Belgium, [17]Haematology, University Hospitals Leuven, Leuven, Belgium, [18]Institute of Pathology and Genetics, Gosselies, Belgium.

Please send all correspondence to: E. Van Valckenborgh, PhD, Juliette Wytsmanstraat 14, 1050 Brussels, Belgium, tel: +32 26425496, email: els.vanvalckenborgh@sciensano.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: guidelines, molecular test, myeloid malignancies, next-generation sequencing, recommendations, variant.

Acknowledgement: The authors would like to acknowledge all the ComPerMed experts.

TABLE 1. Definition of levels for diagnostic/prognostic or therapeutic biomarkers and molecular tests, according to the Belgian healthcare system.

1	Standard of care biomarker for diagnosis and/or prognosis.* Biomarker predictive of a response or a resistance to a reimbursed drug in Belgium for this indication.
2A	Recommended standard of care biomarker for diagnosis and/or prognosis.** Biomarker predictive of response or resistance to an EMA-approved drug for this indication.
2B	Biomarker predictive of response or resistance to an EMA-approved drug in Belgium for another indication or to a drug for which a clinical trial is available in this indication.
3	Compelling clinical evidence supporting the biomarker for diagnosis and/or prognosis. Biomarker predictive of response or resistance to a drug for which a clinical trial is not available in this indication or to a compassionate use of drug.

* Standard of care: Included in guidelines (for example WHO 2016, ELN, NCCN) AND consensus from ComPerMed experts.
** Recommended standard of care: Clinical evidence based on literature findings AND consensus from ComPerMed experts.

targeted therapy (predictive). Genome profiling studies have significantly increased the knowledge of the genomic landscape of myeloid neoplasms and have led to further integration of genetic information in the updated WHO classification (2016).[2-6] For instance, driver variants in *JAK2, CALR* and *MPL* confirm the presence of a myeloproliferative neoplasm (MPN). *KIT* and *CSF3R* variants are a diagnostic criterion for respectively systemic mastocytosis (SM) and chronic neutrophilic leukaemia (CNL) and *SF3B1* variants for myelodysplastic syndromes (MDS) and MDS/MPN, both with ring sideroblasts. In acute myeloid leukaemia (AML), variants in *CEBPA, NPM1, RUNX1, FLT3* are important for prognostic stratification, and variants in *ASXL1* and *TP53* have an added prognostic value in multiple myeloid malignancies.[7] Recently, *FLT3* and *IDH1/2* variants have demonstrated therapeutic value in AML patients (like FLT3 and IDH1/2 inhibitors) while variants in *TP53* may predict resistance or relapse to lenalidomide in MDS with isolated del(5q).[8-11] Many other variants have been described and reviewed.[12-14]

COMMISSION OF PERSONALISED MEDICINE

For the implementation of NGS and, in a broader context personalised medicine, in the Belgian healthcare system,

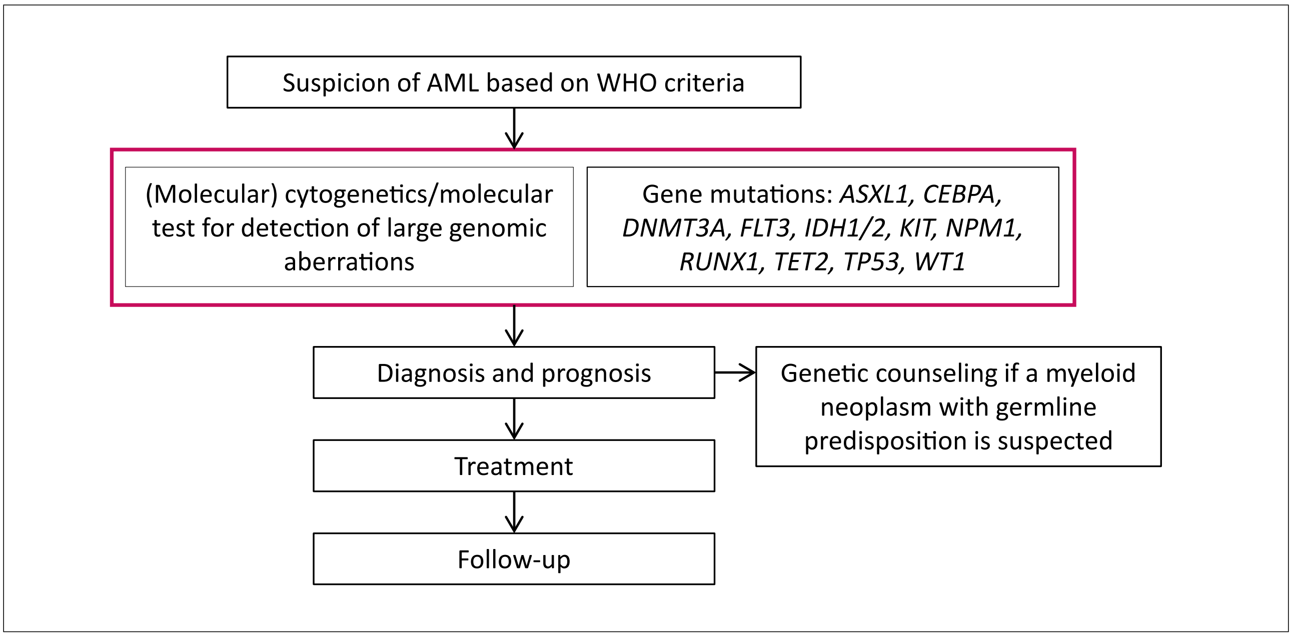

FIGURE 1. Acute myeloid leukemia (AML) algorithm. Molecular tests with level 1 or 2A are represented in a red rectangle.

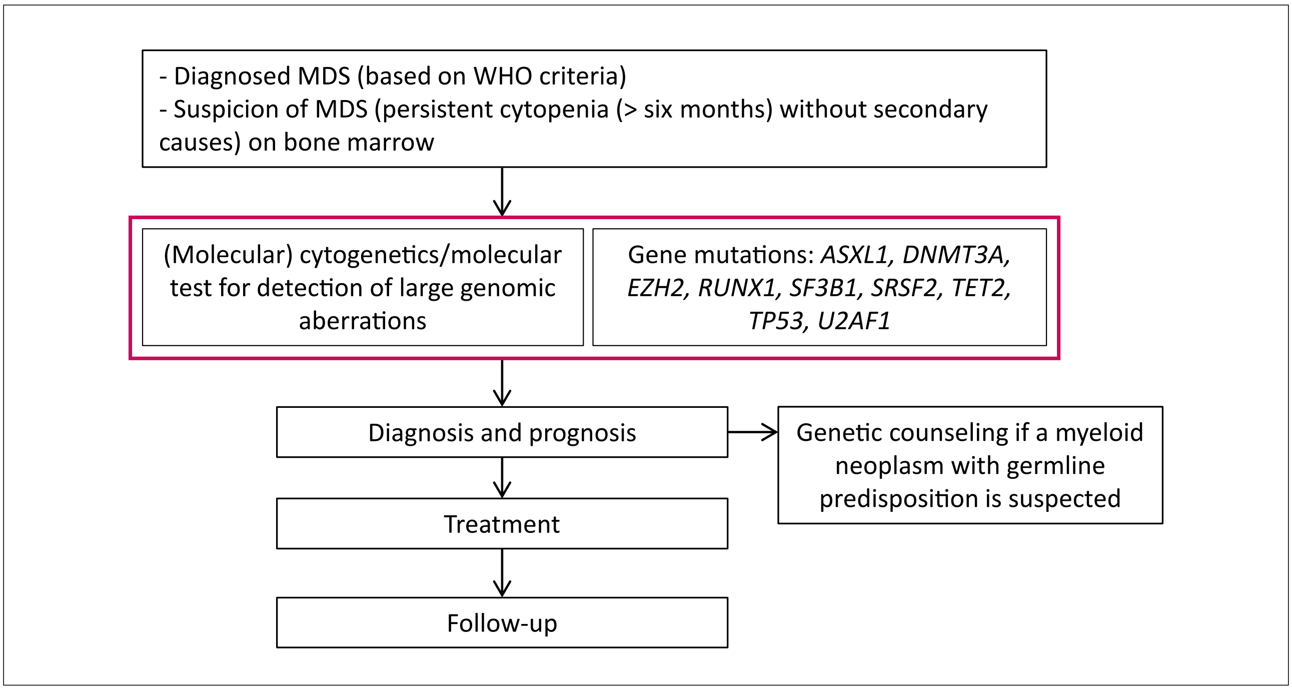

FIGURE 2. Myelodysplastic syndrome (MDS) algorithm. Molecular tests with level 1 or 2A are represented in a red rectangle.

a multidisciplinary committee of experts was created by Sciensano and designated as the 'Commission of Personalised Medicine' or 'ComPerMed'.[15] The commission is composed of experts with different backgrounds (molecular biologists, clinical biologists, pathologists, geneticists and oncologists) who are active in Belgian university and non-university hospitals. The mission of the ComPerMed is to provide evidence-based advice to policy makers on the relevance and reimbursement of innovative solutions in personalised medicine. In this framework, a first version of generic recommendations for the 'wet bench' part and 'dry' or 'bio-informatics' part of targeted NGS was published.[16] In addition, the commission establishes guidelines for molecular testing that have an added value in the diagnosis and treatment of patients, to facilitate reimbursement decisions.[17] Information on the ComPerMed and its projects is available on the website *www.compermed.be*.

One of the projects of the ComPerMed was to advice on the NGS use in myeloid malignancies. The aim was to define the myeloid malignancies that benefit from NGS testing, the required genes to be analysed, and the workflows of molecular tests to be followed during the work-up of these malignancies. A similar methodology was used as described for solid tumours.[18] Different levels were defined to categorize the molecular tests and genes according to standard (levels 1 and 2A) versus investigational clinical implication (levels 2B and 3)(*Table 1*). For each neoplasm, the experts of the ComPerMed defined algorithms outlining stepwise approaches of level 1 and 2A molecular tests. In case of NGS analysis, the minimally required genes, categorised as level 1 and 2A, were determined. Algorithms are given in *Figures 1-5* and are also available on the website *www.compermed.be* together with a description of the molecular tests as well as the cancer incidence (provided by the Belgian Cancer Registry). As this is an evolving field, it is required to keep the guidelines up-to-date. Once a year, they will be revised and updated if necessary. Additional updates are possible when requested by experts. Based on this exercise for myeloid malignancies, ComPerMed recommendations were formulated in the section below.

RECOMMENDATIONS

- For patients older than 70 years, a consensus on the added value of a NGS analysis for the patients' management should be reached at a multidisciplinary oncology consult (MOC).
- The minimally required genes (level 1 and 2A) to be investigated with NGS per disease are given in *Table 2*. Details on the regions/exons to be analysed can be found in the test descriptions on the website *www.compermed.be*.
- *Table 3* gives an overview of all genes listed in *Table 2* together with their most important clinical impact. Some of the genes in this list are known to be involved in inherited predisposition (marked with an asterisk in *Table 3*). However, not all the genes currently associated with 'Myeloid neoplasms with germline predisposition' are included in the ComPerMed panels described in this paper. For

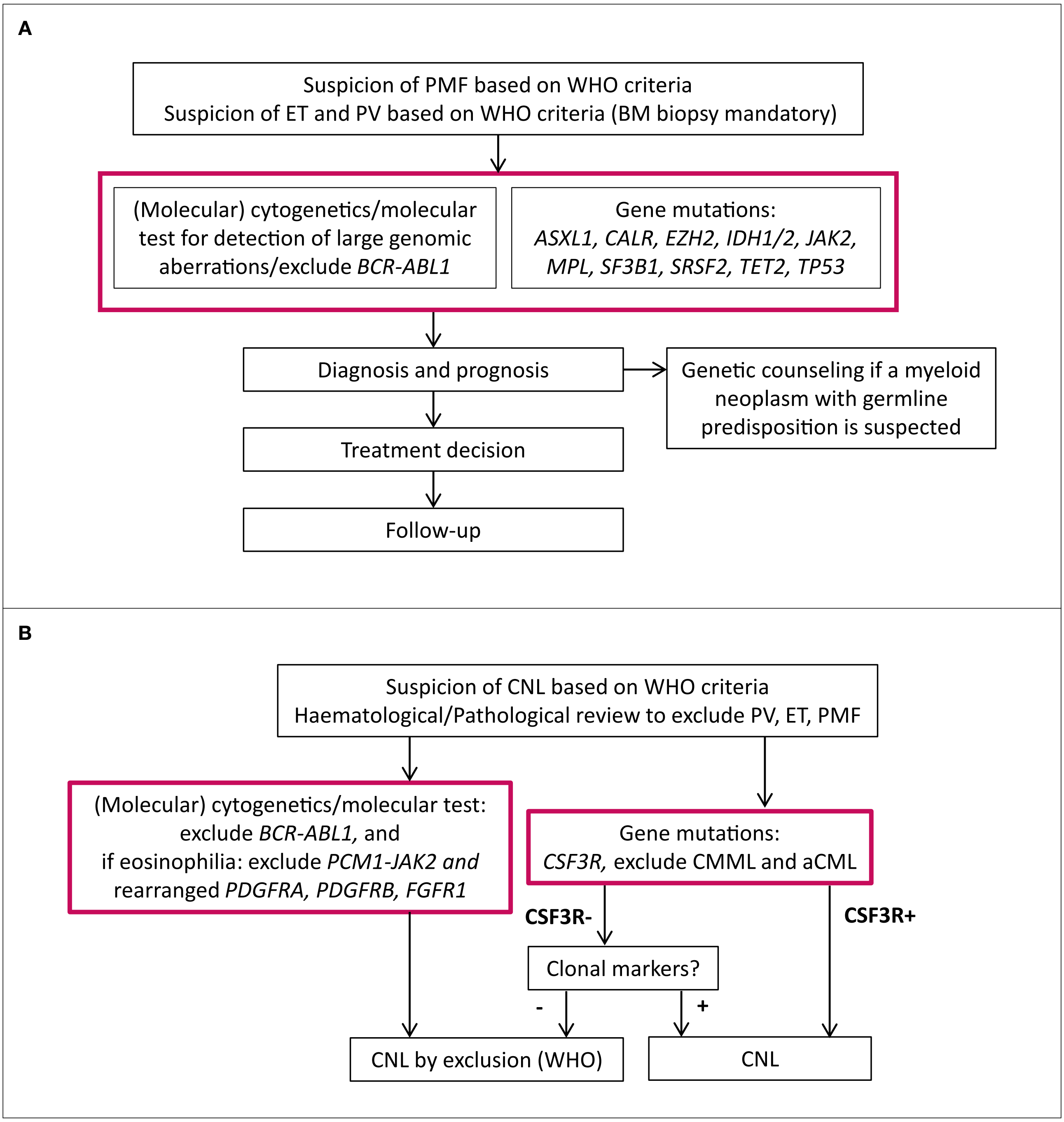

FIGURE 3. Myeloproliferative neoplasms (MPN) algorithms. **A:** Prefibrotic and overt fibrotic primary myelofibrosis (PMF), essential thrombocythemia (ET), polycythemia vera (PV); **B:** Chronic neutrophilic leukaemia (CNL). Molecular tests with level 1 or 2A are represented in a red rectangle.

patients with potential inherited conditions, dedicated guidelines have been described extensively elsewhere.[19,20] In these suspected cases, a more comprehensive NGS analysis for germline variants is mandatory (see below).

- For differential diagnosis purposes, it is useful to analyse a combination of genes from several myeloid neoplasms. Moreover, as several myeloid neoplasms show significant overlap in their gene aberrations, the standard use of a single 'pan-myeloid' NGS panel for all myeloid neoplasms may account for a valuable and cost-effective strategy in the diagnostic work-up of any myeloid neoplastic subentity. This approach has already been implemented by several laboratories.[1]
- The inclusion of level 2B and 3 genes in the NGS analysis is optional.
- NGS analysis must be performed on DNA extracted from

bone marrow. However, in PMF, NGS analysis on blood is a good alternative in case of a dry tap bone marrow aspirate. For AML work-up, the analysis can also be performed on peripheral blood if ≥20% leukemic blasts are found in peripheral blood.

- To support diagnosis of MDS, NGS analysis on bone marrow with suspicious morphology is recommended if there is a persistent cytopaenia (>6 months) and if secondary causes are excluded. In cases with a conclusive MDS diagnosis, NGS has an added prognostic value. In case of PV and ET, NGS analysis is recommended if the BM morphology is suspicious. Many labs use NGS to efficiently analyse for the diagnostically important *JAK2* V617F, *JAK2* exon 12, *CALR* and *MPL* mutations and to search for other gene mutations in triple-negative cases (*JAK2*-, *CALR*-, *MPL*-) that would definitely prove the neoplastic nature of the condition. In addition, mutation-enhanced international prognostic systems are recently proposed and will also require NGS for its application.[21] Currently, NGS analysis for PV and ET is not reimbursed by the INAMI/RIZIV but in view of the increasing clinical validity this will be reconsidered after yearly review by the ComPerMed.
- In SM, the bone marrow is almost always involved, so morphological and molecular analysis on a bone marrow biopsy is essential. *KIT* D816V analysis should be performed with a highly sensitive test (limit of detection (LOD) <0.01%) prior to NGS analysis.[22] Sequencing the whole *KIT* coding sequence using NGS might be considered for diagnostic purposes in patients with a high suspicion of SM if no mutation is detected at codon 816. The high LOD of NGS (typically 1 to 5 %) should be taken into account as a limitation of this approach, especially in cases with low-level bone marrow involvement (for example <10% mast cells). NGS analysis for other myeloid neoplasm associated mutations should be performed for prognostic purposes in *KIT* D816V-positive patients presenting with advanced disease, more specifically for SM with an associated haematological neoplasm (SM-AHN) requiring therapy, aggressive SM (ASM) and mast cell leukaemia (MCL). Currently, NGS analysis for SM is not reimbursed by the INAMI/RIZIV.
- The GC-rich *CEBPA* TAD domain is a well-known difficult locus to analyse with NGS and might require another technique to achieve complete coverage and high accuracy.

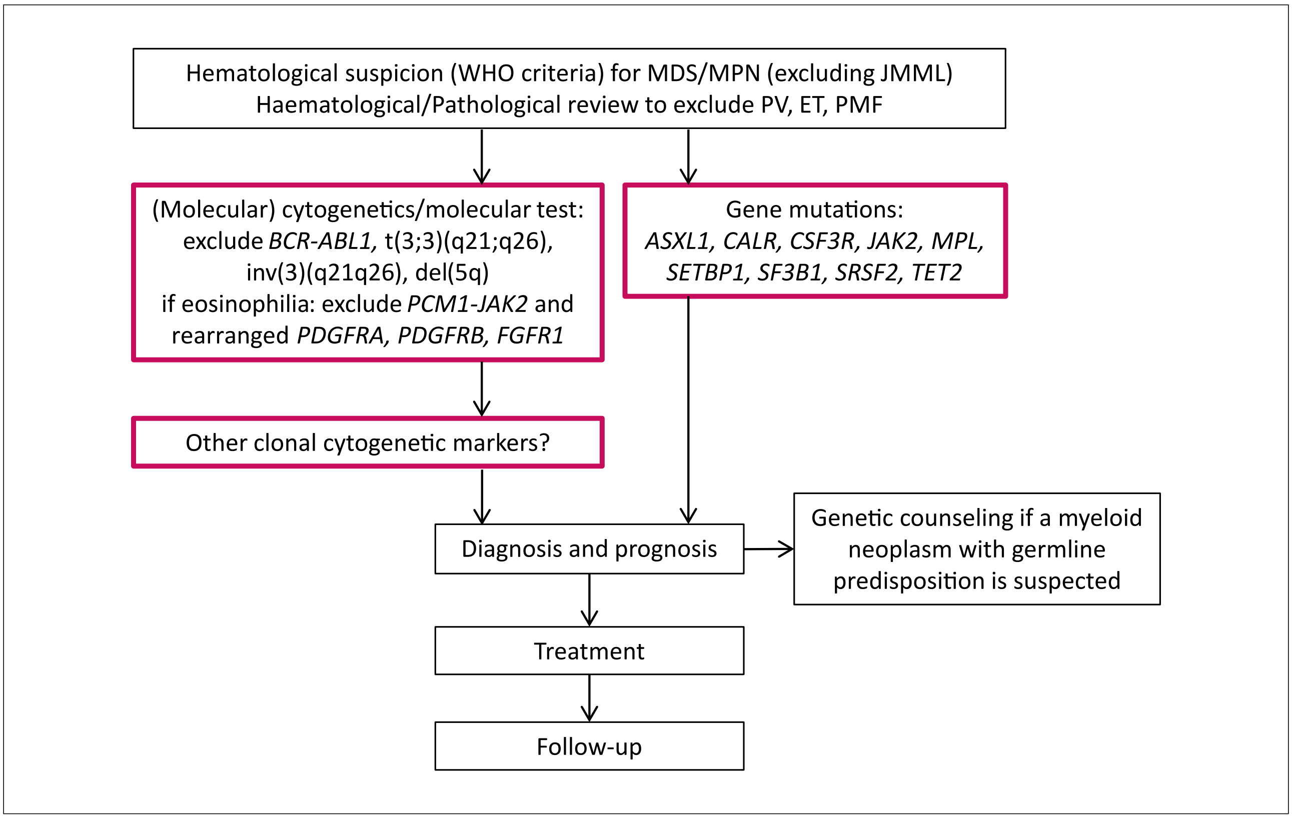

FIGURE 4. Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN) algorithm (not for juvenile myelomonocytic leukaemia). MDS/MPN includes chronic myelomonocytic leukaemia (CMML), atypical chronic myeloid leukaemia (aCML), MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) and MDS/MPN, unclassifiable (MDS/MPN-U). Molecular tests with level 1 or 2A are represented in a red rectangle.

TABLE 2. The minimal genes (level 1 and 2A) to be investigated with NGS per disease.

Disease type	Minimal genes (level 1 and 2A)
AML	*ASXL1, CEBPA, DNMT3A, FLT3, IDH1, IDH2, KIT, NPM1, RUNX1, TET2, TP53, WT1*
MDS	*ASXL1, DNMT3A, EZH2, RUNX1, SF3B1, SRSF2, TET2, TP53, U2AF1*
PMF, ET, PV	*ASXL1, CALR, EZH2, IDH1, IDH2, JAK2, MPL, SF3B1, SRSF2, TET2, TP53*
CNL	*ASXL1, CALR, CSF3R, JAK2, MPL, SETBP1, SF3B1, SRSF2, TET2*
MDS/MPN (excluding JMML)	*ASXL1, CALR, CSF3R, JAK2, MPL, SETBP1, SF3B1, SRSF2, TET2*
SM: advanced cases and KIT D816V negative suspicious SM cases	*ASXL1, CBL, KIT, KRAS, NRAS, RUNX1, SRSF2, TET2*

AML: acute myeloid leukaemia, MDS: myelodysplastic syndrome, PMF: primary myelofibrosis, ET: essential thrombocythemia, PV: polycythaemia vera, CNL: chronic neutrophilic leukaemia, MDS/MPN: myelodysplastic/myeloproliferative syndromes, JMML: juvenile myelomonocytic leukaemia, SM: systemic mastocytosis.

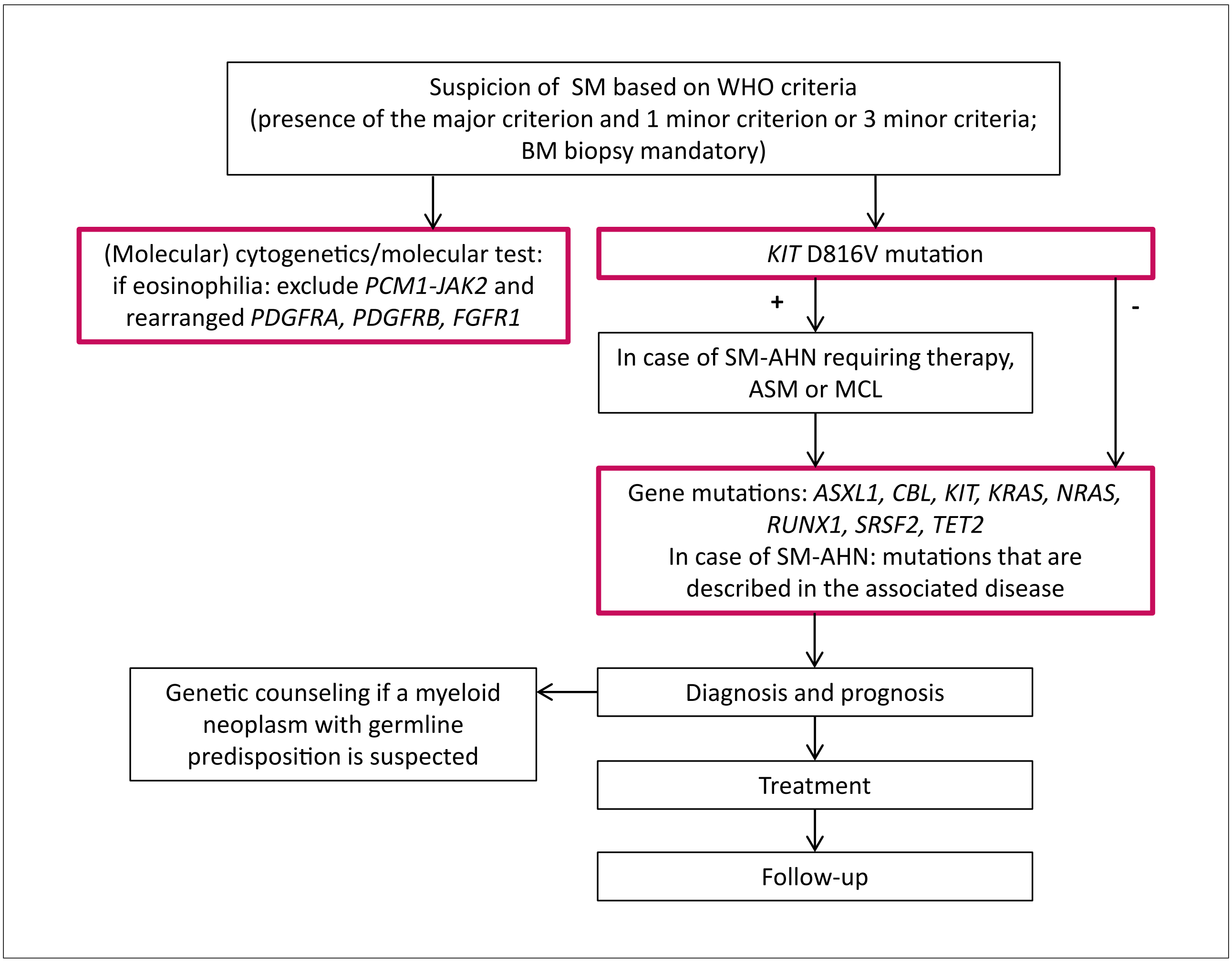

FIGURE 5. Systemic mastocytosis (SM) algorithm. Molecular tests with level 1 or 2A are represented in a red rectangle. *SM-AHN: SM with associated haematological neoplasm; ASM: aggressive SM; MCL: mast cell leukaemia.*

TABLE 3. An overview of current level 1 and 2A genes with their most important clinical impact in myeloid cancers.[7,9,10,12,13,22-25-27]

Genes	DIAGNOSTIC		PROGNOSTIC		THERANOSTIC		
	WHO criterion	Supportive	Poor	Favourable	Higher drug sensitivity	Lower drug sensitivity	Clinical responses with targeted treatment
ASXL1 #	PMF	CMML	AML, MDS, PMF, CMML, Advanced SM				
CALR	ET, PMF	MDS/MPN-RS-T					
*CBL**			Advanced SM				
*CEBPA**				AML with biallelic mutations of *CEBPA*			
CSF3R	CNL						
*DNMT3A** #			certain subgroups of AML and MDS				
EZH2	PMF		MDS, PMF				
FLT3			AML with high *FLT3*-ITD allelic ratio		FLT3 inhibitors with standard chemotherapy in *FLT3* mutated AML		
IDH1/IDH2	PMF		PMF				relapsed or refractory AML
JAK2	ET, PV, PMF	MDS/MPN-RS-T					
*KIT**	SM		AML with t(8;21), and maybe in inv(16)				
KRAS/NRAS			Advanced SM				
*MPL**	ET, PMF	MDS/MPN-RS-T					
NPM1				AML without *FLT3*-ITD			
*RUNX1**			AML, MDS, Advanced SM				
SETBP1		CMML, aCML	CMML				
SF3B1	PMF, MDS-RS, MDS/MPN-RS-T			MDS-RS			
SRSF2	PMF	CMML	MDS, Advanced SM				
*TET2** #	PMF	CMML	some subtypes of AML				
*TP53**			AML, MDS, PMF, ET, PV			lenalidomide in del(5q) MDS	
U2AF1			MDS				
WT1			AML				

* Genes involved in inherited predisposition to myeloid malignancies. Not all genes associated with ‘Myeloid neoplasms with germline predisposition’ are included in the table.

[#] Low frequency variants might be detected in older patients due to clonal haematopoiesis of indeterminate potential (CHIP) or age-related clonal haematopoiesis (ARCH).[28]

KEY MESSAGES FOR CLINICAL PRACTICE

1. **The Commission of Personalised Medicine defined a minimal list of genes to be analysed for each indication.**
2. **NGS analysis is useful for the diagnosis, prognosis and/or treatment of myeloid malignancies.**
3. **For patients older than 70, a multidisciplinary oncology consult is required to discuss and reach a consensus on the clinical relevance and added value of a NGS analysis.**
4. **Bone marrow is the recommended sample for performing NGS.**
5. **A combination of NGS analysis with cytogenetics and/or other molecular tests is required in several myeloid neoplasms and integration with the clinical history. Other pertinent laboratory data is mandatory for a correct clinical interpretation.**
6. **For now, NGS is only reimbursed in the indication of AML, PMF, CNL and MDS/MPN.**

- The analysis of long insertions/deletions has proven difficult by NGS. Therefore, an additional molecular method might be required to cover all possible internal tandem duplications in *FLT3*, as these are regularly over 100 bp.[23]
- Targeted DNA-based NGS analysis alone is not sufficient as the sole tool for genomic characterization. Indeed, a combination of (molecular) cytogenetics and/or molecular testing for the detection of large genomic aberrations (genomic imbalances, translocations, inversions) is required for proper diagnosis, prognosis, treatment and/or decision-making. For the diagnosis of CNL, PMF, ET, PV and MDS/MPN neoplasms, the presence of the *BCR-ABL1*-fusion gene (Philadelphia chromosome) should be excluded. In the diagnostic work-up of CNL, MDS/MPN and SM with coinciding eosinophilia, a negative status should be demonstrated for PCM1-JAK2, PDGFRA-, PDGFRB- and FGFR1-fusion genes. For accurate AML sub classification and prognostication, the detection of several translocations/inversions (for example t(15;17)(q22;q11-12)/PML-RARA, t(8;21)(q22;q22.1)/RUNX1-RUNX1T1, inv(16)(p13.1q22)/CBFB-MYH11, etc.) is mandatory. NGS performed on RNA is expected to become a valuable alternative method for the detection of these fusion genes.
- Genetic counselling should be considered if a myeloid neoplasm with germline predisposition is suspected. In those cases a more comprehensive NGS analysis is mandatory with a panel including genes such as *GATA2, ANKRD26, DDX41, ETV6, TERT, TERC,* etc. (for the complete list see WHO).[2] Potential germline variants should be confirmed using a non-haematopoietic source of DNA.
- Any genetic information, either obtained by NGS or by any other molecular or cytogenetic technique should always be interpreted in the context of the clinical, haematological, morphological and immunophenotypic findings that are available for the patient. Integration of all these different types of information by haematology experts warrants accurate diagnosis and WHO sub classification, prognostication and therapeutic management.

CONCLUSION

Similar to the recommendations for solid tumours, the ComPerMed formulated in this paper recommendations for NGS analysis in haematological myeloid malignancies in the framework of a pilot study for the reimbursement of NGS analyses.[18,24] The purpose of the study is to facilitate high-quality NGS in the Belgian healthcare system for (haemato-) oncology that allows a precise and harmonised decision-making by providing detailed information for diagnosis, prognosis and treatment. Further initiatives of the ComPerMed aim at the harmonisation of the biological classification, clinical interpretation and reporting of the NGS results.

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