VKGL vereniging klinisch genetische LABORATORIUMDIAGNOSTIEK

VKGL kwaliteitscommissie_Veldnorm

Titel: Richtlijnen verworven cytogenetica	**Doc. code: VKGL_V07**
Subspecialisme: Genoomdiagnostiek - Cytogenetica	**Versie: 03** **Ingangsdatum: 01-12-2021**
Beheerder: Eva van den Berg- de Ruiter **Centrum: UMC Groningen**	

Vakspecifieke toelichting op normelement 5.6 van de ISO15189-2012

Reden voor toelichting:

Als richtlijnen voor de verworven cytogenetica worden gehanteerd: European recommendations and quality assurance for cytogenomic analysis of haematological neoplasms (Rack et al 2019a) and Guidance for reporting the interpretation of cytogenomic test results in haematological neoplasms (Rack et al 2019b).

De WHGD richtlijnen voor verworven cytogenetica zijn een aanvulling op deze recommendations en dienen derhalve in samenhang met deze documenten gelezen te worden, waarbij geldt dat de WHGD richtlijnen en aanvullende afspraken gemaakt tijdens de WHGD vergaderingen leidend zijn voor de Nederlandse praktijk. In overleg met de leden van de WHGD zijn deze richtlijnen opgesteld in het Engels.

Bereik:

Alle Nederlandse en bij de WHGD aangesloten buitenlandse laboratoria die diagnostiek verzorgen
in het kader van cytogenetische analyse t.b.v. verworven chromosoomafwijkingen d.m.v. karyotypering, FISH en andere whole genome mapping technieken.

Definities: n.v.t.

VKGL kwaliteitscommissie_Veldnorm	
Titel: Richtlijnen verworven cytogenetica	**Doc. code: VKGL_V07**
Subspecialisme: Genoomdiagnostiek - Cytogenetica	**Versie: 03** **Ingangsdatum: 01-12-2021**
Beheerder: Eva van den Berg- de Ruiter **Centrum: UMC Groningen**	
Vakspecifieke toelichting op normelement 5.6 van de ISO15189-2012	

Guidelines for Cytogenomic Analysis of Acquired Disorders

Dutch addendum to the European Recommendations by Rack et al 2019a

Authors
Simone Snijder, Berna Beverloo, Anne-Marie van der Kevie-Kersemaekers, Jeroen Knijnenburg, Wilma Kroes, Clemens Mellink, Lucienne Michaux, Daniel Olde Weghuis, Pino Poddighe, Jacqueline Schoumans, Marian Stevens-Kroef, Laura van Zutven, Eva van den Berg

On behalf of the "Landelijk Overleg (former Werkgroep) Hemato-oncologische GenoomDiagnostiek" (WHGD), which is a working party of the Vereniging Klinisch Genetische Laboratoriumdiagnostiek (VKGL).

The guidelines are published at the website of the VKGL (Kwaliteit > Formulieren en documenten > Veldnormen).

Correspondence to: Eva van den Berg, University Medical Center Groningen, e-mail: e.van.den.berg-de.ruiter@umcg.nl

December 2021

VKGL vereniging klinisch genetische LABORATORIUMDIAGNOSTIEK	
VKGL kwaliteitscommissie_Veldnorm	
Titel: Richtlijnen verworven cytogenetica	**Doc. code: VKGL_V07**
Subspecialisme: Genoomdiagnostiek - Cytogenetica	**Versie: 03** **Ingangsdatum: 01-12-2021**
Beheerder: Eva van den Berg- de Ruiter **Centrum: UMC Groningen**	
Vakspecifieke toelichting op normelement 5.6 van de ISO15189-2012	

Index

VKGL kwaliteitscommissie_Veldnorm	
Titel: Richtlijnen verworven cytogenetica	**Doc. code: VKGL_V07**
Subspecialisme: Genoomdiagnostiek - Cytogenetica	**Versie: 03** **Ingangsdatum: 01-12-2021**
Beheerder: Eva van den Berg- de Ruiter **Centrum: UMC Groningen**	
Vakspecifieke toelichting op normelement 5.6 van de ISO15189-2012	

General remarks

These guidelines are a supplement to and should be applied in the context of the "European recommendations and quality assurance for cytogenomic analysis of haematological neoplasms (Rack et al 2019a) and Guidance for reporting the interpretation of cytogenomic test results in haematological neoplasms (Rack et al 2019b).
For issues not covered by the working party WHGD, European Cytogeneticists Association (ECA) guidelines, Rack et al 2019a or 2019b, other VKGL guidelines or local quality systems may apply.

Unless otherwise stated in these guidelines or working party minutes, the ECA and VGKL guidelines should be followed.

Minor changes/additions to these guidelines are documented in the minutes of working party meetings before they are integrated in a new version of the guidelines.

Where reference is made to the International System for human Cytogenomic Nomenclature (ISCN) or World Health Organization (WHO) classification publications, the most recent versions should be used.

General recommendations

- Karyotyping and FISH are increasingly replaced by or supplemented with techniques like array, NGS-based techniques or optical genome mapping. Using these techniques, consideration should be taken about the capacity to detect copy number abnormalities (CNA) and/or balanced structural variants (SV) in the context of the reason for referral and current guidelines.
- To interpret aberrations detected with high resolution techniques in relation to classical karyotyping, in general a threshold of > 5 Mb is applied.
- For the definition of a clone see ISCN 2020 paragraph 11.1.1, page 428 (McGowan-Jordan et al 2020).
- To determine karyotypic complexity, a recommended method of counting chromosome abnormalities is published in ISCN 2020 paragraph 11.4, page 437 (McGowan-Jordan et al 2020). The definition of complexity for prognostic risk assessment is disease-specific. Relevant references are indicated in the disease-specific paragraphs in these guidelines, additional references are mentioned in ISCN 2020 paragraph 11.4.

- Thresholds and confidence limits of FISH probes should be established according to (Rack et al 2019a).
- When a whole genome test is performed, negative or positive results for regions specifically relevant for the reason for referral and clinical management should be reported. It is optional to report copy number abnormalities (CNAs) and structural variants (SVs) when >5Mb, irrespective of gene content, or <5 Mb when containing other known or suspected driver cancer genes. Also, CNLOH >10 Mb extending to the telomeres are considered to be acquired abnormalities and may be reported (Schoumans et al 2016, Mikhail et al 2019).
- Amplification is defined as high copy-number gain of sequences, for which standard thresholds typically range from 3–5 fold increases over baseline ploidy (e.g., intrachromosomal amplification of chromosome 21, iAMP21 in B-ALL) to >100 copies per genome and will vary depending on the type of tumor (Mikhail et al 2019).
- Chromothripsis is defined as a copy-number profile that has alternating copy states in a single region - typically a single chromosome or chromosome arm - that contains at least ten distinct alternating copy-number segments (Mikhail et al 2019).
- Intrachromosomal complexity is defined as a summary of chromosomal regions that include more than two copy-number states, are largely confined to a single chromosome or chromosome arm, and contain at least five distinct copy-number segments. If clinically significant abnormalities (tiers 1 or 2) fall within a complex region, they may be reported individually (Mikhail et al 2019).
- Genomic complexity is defined as a pattern of chromosome instability predominantly due to structural alterations resulting in widespread gains and losses of chromosomes or chromosomal regions in the majority of chromosomes (Mikhail et al 2019).
- It should be noted that recent Human Genome Organisation (HUGO) guidelines strongly recommend fusion genes to be written as *BCR::ABL1 (or BCR/ABL1)* and not *BCR-ABL1 (*Bruford et al 2021*)*. This differs from WHO where the fusion genes are written as *BCR-ABL1* (Bruford et al 2020).

Sources

Sources which can be helpful with respect to the visual identification of abnormalities and association with type of haematological malignancies are:

- WHO classification of tumours of haematopoietic and lymphoid tissues (Swerdlow et al 2017).
- Cancer Cytogenetics: Chromosomal and molecular genetic aberrations of tumor cells (Heim and Mitelman 2015).

- Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer (Mitelman F, Johansson B and Mertens F). URL https://mitelmandatabase.isb-cgc.org
- Atlas of Genetics and Cytogenetics in Oncology and Haematology (Huret JL et al). URL http://atlasgeneticsoncology.org
- National protocols are published on the website of HOVON, SKION of Princess Maxima Center (see Appendix B).

Using these sources, one should be aware that there might be more recent publications overruling e.g. prognostic implications.

Reporting

- See publications by Rack et al 2019a and Rack et al 2019b for general guidelines on reporting.
- The interpretation and reporting of loss of the Y chromosome or trisomy 15 can be problematic. Both features are seen in bone marrow cells of elderly patients with no haematological disease but may also occur as markers of neoplastic clones (Hanson et al 2008, Goswami et al 2015).
- In general, it should be stated whether the karyotype is male or female, unless the X and/or Y-chromosome are involved in an aberrant karyotype or no information is available about X and Y.
- In general, limitations of the test should only be mentioned when the test failed to meet the minimal requirements.
- Array based reports should always provide information on the limitations of the test, including resolution, cut off levels for detection of mosaicism and, depending on the platform, a statement that the test will not detect point mutations, balanced rearrangements, polyploidy and copy neutral loss of heterozygosity.
- ISCN: the most recent version of ISCN should be used.
- If a patient is included in an (inter)national trial, use the risk stratification according to the trial protocol (see also minutes of the working party). If these protocols are not applicable, the WHO classification (Swerdlow et al 2017) or GenQA guidelines and recommendations (www.genqa.org) should be applied.
- When relevant the report should refer to previous cytogenetic test results.

Table 5 Reporting times

Rapid test*	95% reported in 3 working days;

	a result should be given in <24h
Urgent referral	95% should be (preliminary) reported within 10 calendar days
Routine referral	95% should be (preliminary) reported within 28 calendar days

* When applicable, usually based on local policy

Myeloproliferative neoplasms
The myeloproliferative neoplasms (MPN) category in the WHO classification (Swerdlow et al 2017 page 10) includes: chronic myeloid leukaemia (CML), chronic neutrophilic leukaemia (CNL), polycythaemia vera (PV), **primary myelofibrosis (PMF), essential thrombocythaemia (ET), chronic eosinophilic leukaemia (CEL), not otherwise specified and mastocytosis.**

Chronic myeloid leukaemia

Diagnosis of CML

- The ELN recommendations for analysis of CML should be followed (Baccarani et al 2013 and 2015). Chromosome analysis is mandatory for CML at diagnosis. Rack et al 2019 strongly recommend that 20 cells are fully analysed to exclude the presence of additional chromosomal abnormalities (ACAs).
- When a translocation t(9;22)(q34;q11) is detected at diagnosis, one can refer in the report to national guidelines (see Appendix B) or Hochhaus et al 2020 for recommendations to the clinician on follow up.
- The prognosis of variant translocations (including those involving other chromosomes in addition to chromosome 9 or 22) is similar to standard t(9;22)(q34;q11) and these patients are considered equally responsive to therapy with tyrosine kinase inhibitors (TKIs).

Follow-up in CML

- **To establish the Cytogenetic Response at least 20 metaphases should be analyzed (Baccarani et al 2013). If the level of Ph-positive cells is close to the boundary of a response category, then it may be necessary to score more than 20 metaphases to establish the level of the positive clone (ACGS guidelines 2011).**
- **It is recommended to describe the Cytogenetic Response in the report according to the criteria as defined by Baccarani et al 2009 (Table 1).**

Table 1 CML Cytogenetic response

Cytogenetic Response	**Ph+ levels**
Complete (CCyR)	No Ph+ metaphases
Partial (PCyR)	1%-35% Ph+ metaphases
Minor (mCyR)	36%-65% Ph+ metaphases
Minimal (minCyR)	66%-95% Ph+ metaphases

None (noCyR)	>95% Ph+ metaphases

- **FISH on blood or bone marrow interphase nuclei could substitute for chromosome banding analysis of marrow cell metaphases only for the assessment of CCyR (complete cytogenetic response), which is then defined by <1% *BCR::ABL1*-positive nuclei of at least 200 nuclei (Baccarani et al 2013).**
- **ACAs may indicate progressive disease. Generally, +8, +Ph, i(17q), +19, +21, +17, 3q26.2, 11q23, -7/del7q, and complex karyotypes are considered High-risk aberrations with a poorer response to TKI's and a negative impact on prognosis (Hochhaus et al 2020, Hehlmann et al 2020). By some groups +8 and +Ph are classified as non-high-risk. In most studies patients with –Y show an outcome not different form patients with no ACA.**
- **Clonal cytogenetic abnormalities in Ph negative (Ph-) cells occurring during treatment are mostly transient and (with the exception of -Y) some studies suggest a negative outcome. Especially monosomy 7 and del(7q) might indicate a risk of developing myelodysplasia or acute leukaemia and justify long-term follow-up bone marrow aspirates (Issa et al 2017).**

Diagnosis of other MPN

- Although diagnosis of MPN is primarily based on somatic mutation analysis and cytogenetic testing is not crucial in this process, the latter may be useful to:
  - exclude (variant) translocation t(9;22)(q34;q11);
  - assess clonality;
  - assess prognosis (especially in primary myelofibrosis);
  - assess disease progression or (risk of) leukaemic transformation.
- Chapter 9 by Vandenberghe and Michaux (Heim et al 2015) gives an overview of cytogenetic aberrations (and mutations) detected in MPN at diagnosis, which may also be indicators of disease progression and leukaemic transformation.
- **See also WHO classification Swerdlow et al 2017, Barbui et al 2018.**

Polycythaemia vera

- The association of specific chromosomal abnormalities with prognosis in PV is summarized by Tang et al 2017.

Primary myelofibrosis

- **Cytogenetic findings are incorporated in several prognostic models for PMF (see PMF guideline** www.hematologienederland.nl **for the most recent recommendations on using these models. See also Tefferi et al 2021).**
- **The DIPSS Plus score (based on Gangat et al 2011) can be applied to all PMF patients and defines an unfavorable karyotype as: a complex karyotype or sole or two abnormalities that include +8, -7/del(7q), i(17q), -5/del(5q), del(12p), inv(3) or 11q23 rearrangements.**
- **The MIPSS70+ version 2.0 score (Tefferi et al 2018, Guglielmelli et al 2018) can be applied to all patients aged 70 years or younger, who are candidate for allo-stemcell transplantation (SCT). Cytogenetic abnormalities are classified according to Table 3 in Tefferi et al 2018:**
  - Favorable risk : normal karyotype or sole abnormalities 20q-, 13q-, +9, chromosome 1 translocation/duplication or sex chromosome abnormality (incl. –Y).
  - Unfavorable risk : all other abnormalities (including sole abnormalities +8, 7q-, translocations not involving chromosome 1, two abnormalities not including a VHR abnormality, single or multiple 5q-, complex karyotype without a VHR abnormality, monosomal karyotype without a VHR abnormality or sole abnormalities not otherwise specified).
  - Very high risk (VHR) : single or multiple abnormalities with -7, inv(3)/3q21, i(17q), 12p-/12p11.2, 11q-/11q23, autosomal trisomies other than +8 or +9.

Essential thrombocythaemia

- **Chromosome aberrations in ET have been found to be non-specific with limited clinical and prognostic significance (Gangat et al 2009).**

Mastocytosis

- In case of a suspected mastocytosis additional FISH for *PDGFRA* rearrangements might be considered.

Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement

- **In myeloid and lymphoid neoplasms with eosinophilia additional FISH for *PDGFRA*, *PDGFRB*, *FGFR1* and/or *JAK2 (PCM1::JAK2),* may be useful to detect cryptic aberrations or to confirm the involvement of these loci because these gene rearrangements may have implications for therapy choices (Swerdlow et al 2017 page 72).**

Myelodysplastic/myeloproliferative neoplasms

- **This category in the WHO classification (Swerdlow et al 2017 page 81) includes:** chronic myelomonocytic leukaemia (CMML), atypical CML (aCML), juvenile myelomonocytic leukaemia (JMML), **myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis, and myelodysplastic/myeloproliferative unclassifiable.**

Chronic myelomonocytic leukaemia

- In case of a suspected CMML with eosinophilia rearrangements of *PDGFRA*, *PDGFRB*, *FGFR1* or *PMC1::JAK2* translocation should be excluded.
- The association of specific chromosomal abnormalities with overall survival and risk of evolution to acute myeloid leukaemia (AML) is summarized by Itzykson et al 2018.

Myelodysplastic syndrome

Diagnosis

- When karyotyping is unsuccessful (less than 10 normal metaphases) additional FISH analysis can be considered.
- Array-based, whole genome sequencing (WGS) based tests and optical genome mapping are good alternatives for karyotyping and/or FISH (Schoumans et al 2016, Mikhail et al 2019; Neveling et al 2021).
- MDS can be diagnosed in cases of persistent cytopenia of undetermined origin if a recognized cytogenetic abnormality is present. These abnormalities are specified in the WHO classification Tables 6.01, 6.03 and 6.05 (Swerdlow et al 2017 pages 101-105). Note that a +8, del(20q) and -Y are not considered definitive evidence for MDS in the absence of morphological features.
- Single or two cell loss of chromosomes 5 and/or 7 poses a particular problem in karyotyping of MDS samples. To discriminate between 'random loss' and clonal abnormality, FISH or another appropriate additional test is recommended.
- This paragraph also includes samples for MDS screening in patients with bone marrow failure syndromes (e.g. aplastic anaemia, Fanconi anaemia) and should be treated the same as MDS samples.

Interpretation, prognosis and/or risk stratification

- The Revised International Prognostic Scoring System IPSS-R (Table 2), derived from Greenberg et al 2012, Schanz et al 2012 are important standards for assessing prognosis of primary untreated adult patients with MDS.

- In case array, optical genome mapping, or WGS data are available, CNA <5Mb, SV <5Mb, and copy-neutral loss of heterozygosity (CN-LOH) should not be included in the prognostic score.
- If only array or other copy number-based data are available, a note should be added that a test for inv(3)/t(3q26) is required for a full cytogenetic contribution to the IPSS-R.
- The prognostic score is based on cytogenetics, percentage of bone marrow blasts, cytopenias, haemoglobin, platelets and absolute neutrophil count. It is recommended to describe the cytogenetic contribution to these scoring systems in the laboratory report.

Table 2 MDS IPSS-R classification

IPSS-R	
Prognostic variable	**Cytogenetic abnormality**
0	-Y, del(11q)
1	normal, del(5q), del(12p), del(20q), double including del(5q)
2	del(7q), +8, +19, i(17q), any other single or double independent clones
3	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities
4	Complex: >3 abnormalities

Some cases of myeloid neoplasm occur in association with inherited or *de novo* germline mutations characterized by specific and genetic and clinical findings, such as bone marrow failure syndromes and the telomere biology disorders. In addition, there are disorders with predisposition to MDS or AML. For a list of these disorders see Swerdlow et al 2017 Table 7.01 and 7.03 pages 123 and 127. For recommendations for diagnosis and treatment see Raaijmakers et al 2018.

Acute myeloid leukaemia

Diagnosis

- The 2017 revision of the WHO classification recognizes several entities defined by the presence of recurrent (cyto)genetic abnormalities in acute myeloid leukaemia (AML) (Swerdlow et al 2017 page 10).
- SNP array analysis could be considered for detection of acquired CNA analysis or CN-LOH.
- Screening for 11q23 *KMT2A* and 3q26 *MECOM* rearrangements is highly recommended (*MECOM* rearrangements are very rare in childhood AML) as these abnormalities have a prognostic impact, and may be cryptic by banding analysis.
- If karyotyping has failed, additional screening with other techniques should be performed for monosomy 5/del(5q) and monosomy 7/del(7q).
- In case of a normal karyotype, additional screening could be performed to exclude cryptic *PML::RARA*, *CBFB::MYH11* or *RUNX1::RUNX1T1* rearrangements, depending on the morphological subtype.

- In case of a normal karyotype in childhood AML additional screening for 11p15 *NUP98* and *CBFA2T3::GLIS2* could be considered, especially when morphology showed an acute megakaryoblastic leukaemia (Swerdlow et al 2017 Table 8.01 page 131).
- Mutations are increasingly important in AML with impact on the risk classification for the patient (Grimwade et al 2016). *NPM1*, *FLT3*, *CEBPA*, *RUNX1* and *ASXL1* mutations occur frequently in AML with normal cytogenetics, whereas *TP53* and *KIT* mutations more often are present in AML with abnormal karyotypes (Swerdlow et al 2017 Table 8.02 pages 146-149).

Some cases of myeloid neoplasm occur in association with inherited or *de novo* germline mutations characterized by specific and genetic and clinical findings, such as bone marrow failure syndromes and the telomere biology disorders. In addition, there are disorders with predisposition to MDS or AML. For a list of these disorders see Swerdlow et al 2017 Table 7.01 and 7.03 pages 123 and 127. For recommendations for diagnosis and treatment see Raaijmakers et al 2018.

Interpretation, prognosis and/or risk stratification

- For prognostic implication preferably the European Leukemia Network (ELN) recommendations by Döhner et al 2017 (see Table 3) for the impact on risk classification for AML (comprising both cytogenetic and genetic abnormalities) should be used as a guideline when reporting risk associated with a certain abnormality, unless the patient was included in a trial for which a risk classification scheme is provided. The risk classification provided by a laboratory specialist clinical genetics is a provisional one as other factors influence the final risk (e.g. molecular data, minimal residual disease (MRD)). This should specifically be mentioned in the report, especially in the case of normal karyotypic results.
- Several trials include the presence of a monosomal karyotype (MK) in their AML or MDS risk classification as a poor risk factor. The definition of a MK is the presence of two or more distinct autosomal monosomies or one single autosomal monosomy in the presence of structural abnormalities, excluding marker and ring chromosomes (Breems et al 2008).
- Complex karyotype in AML is defined as three or more unrelated chromosome abnormalities in the absence of one of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR::ABL1* (Döhner et al 2017).

Table 3 ELN risk stratification by genetics

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*,*MECOM*(*EVI1*) -5 or del(5q); -7; -17/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type *NPM1* and *FLT3*-ITD^{high}† Mutated *RUNX1*¶ Mutated ASXL1¶ Mutated *TP53*#

‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.
‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).
¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
#TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Acute lymphoblastic leukaemia/lymphoma

Diagnosis

- The 2017 revision of the WHO classification recognizes several entities defined by the presence of recurrent (cyto)genetic abnormalities in acute lymphoblastic leukaemia/lymphoma (ALL/LBL) (Swerdlow et al 2017 page 10).
- FISH for t(12;21) can also be used to detect hyperdiploidy (>50 chromosomes), or intrachromosomal amplification of chromosome 21 (iAMP21), characterized by amplification of a portion of chromosome 21. iAMP21 is defined as interphase FISH with a probe for the *RUNX1* gene showing 5 or more copies of the gene or 3 or more extra copies on a single abnormal chromosome 21 in metaphase FISH analysis (Swerdlow et al 2017 pages 208-209).
- Additional screening for *BCR::ABL1* and *KMT2A* rearrangements is required for adult patients participating in HOVON studies. It is recommended to test for the presence of *ETV6::RUNX1* / t(12;21) in young adults (< 25 year), see Rack et al 2019 Table 3.
- In T-ALL cases, *BCR::ABL1* FISH can be used to determine the presence of the *BCR::ABL1* fusion, but also for the detection of *ABL1* amplification. Amplification of *ABL1* is indicative for the presence of *NUP214::ABL1* episomes. The presence or absence of *ABL1* amplification should be stated in the report, as this might influence treatment decisions in T-ALL (Rack et al 2019).
- High-density SNP arrays may be used instead of karyotyping or FISH for the detection of unbalanced abnormalities. However, when applying arrays, the relevant translocations must be investigated by FISH or alternative techniques (Rack et al 2019, Mikhail et al 2019).
- Children aged 1-18 years should be diagnosed and classified according to the ALL Together1 protocol (in the Netherlands started in July 2020).
  It is expected that this protocol will also be applied to (young) adults in the near future.
- The ALL Together1 protocol includes screening for t(9;22) *BCR::ABL1*, t(12;21) *ETV6::RUNX1*, 11q23.3 *KMT2A*, 9q34.1 *ABL1*, 1q25.2 *ABL2*, 5q32 *PDGFRB/CSF1R*, t(17;19) *TCF3::HLF*, hypodiploidy, hyperdiploidy and iAMP21.
  A CNA profile should be determined based on copy number aberrations of *BTG1*, *CDKN2A*, *CDKN2B*, *EBF1*, *ETV6*, *IKZF1*, *PAX5*, *RB1* and the PAR1-region (*P2RY8::CRLF2*).

Interpretation, prognosis and/or risk stratification

- For patients treated according to the ALL Together1 protocol the relevant genetic markers should be reported before day 15 after start treatment as they might have

consequences for risk stratification. Results should be classified as High Risk genetics or no High Risk genetics, and the CNA profile as good risk (GR) or poor risk (PR). Details are provided in the ALL Together1 protocol.

- Risk categories in adult ALL are defined in treatment guideline ALL (HOVON website, version 16JUN2020, paragraph 3 Table 4). High Risk applies when:
  - t(9;22) *BCR::ABL1*;
  - 11q23.3 *KMT2A* rearrangements;
  - Low hypodiploidy/near-triploidy
  - Complex structural and numerical chromosomal aberrations (≥ 5), NO hyperdiploidy.
- Alternatively, for prognostic implication the publication of Moorman et al 2014 can be used.
- Hyperdiploid karyotypes mostly come from gain of chromosomes in a diploid cell line, but near-haploid or low hypodiploid clones can double and appear as hyperdiploid/near-triploid. The prognosis for these two entities is different (Rack et al 2019).

Chronic lymphocytic leukaemia/small lymphocytic lymphoma

Diagnosis

To assign chronic lymphocytic leukaemia (CLL) patients into clinically relevant prognostic subgroups one of the following techniques is recommended on peripheral blood lymphocytes (Rack et al 2019):

- FISH with probes for 17p13.1 *TP53* preferably in combination with 11q22.3 *ATM*.
- SNP-array or other genome wide tests with focus on prognostic significant abnormalities that may affect clinical management (*TP53*: del(17p13.1) and/or CN-LOH for 17p) (Schoumans et al 2016; Chun et al 2018).
- Additional analysis (e.g. karyotyping, FISH for t(11;14)(q13;q32)) can be done on request or based on clinical trials.
- According to (inter)national guidelines additional *TP53* mutation analysis and *IGHV* mutation status is required (IW-CLL guidelines Hallek et al 2018). This analysis can be done in any accredited laboratory (hematology, pathology or genetics).

Interpretation, prognosis and/or risk stratification

- Results for 17p13.1 *TP53* must be reported (for therapy consequences) and results for 13q14 *RB1/MIRs/DLEU*, 11q22.3 *ATM/BIRC3*, trisomy 12 and highly complex genome (5 or more abnormalities) are recommended to report (IW-CLL guidelines Table 1 in Hallek et al 2018, Baliakas et al 2019, Leeksma et al 2021).

- For prognostication and therapy consequences see Schoumans et al 2016, Chun et al 2018, Mikhail et al 2019, Baliakas et al 2019, Leeksma et al 2021 and “Richtlijn chronisch lymfatische leukemie”.
- Highly complex karyotype/array profile with 5 or more abnormalities is an independent adverse prognosticator and related to dismal clinical outcomes, independent of clinical stage, *TP53* aberrations or *IGHV* mutation status (Baliakas et al 2019, Leeksma et al 2021).
- Patients with complex karyotype including +12, (+18),+19 displayed an exceptionally indolent profile and should not be marked as complex (Baliakas et al 2019).
- Counting complexity (following Schoumans et al 2016, Leeksma et al 2021): only copy number aberrations (CNAs) ≥5Mb should be included in the determination of complexity of the array profile; the established CLL CNAs being 11q22.3 *ATM* and 17p13.1 *TP53* and 13q14 *RB1/DLEU* will be called even when <5 Mb.
- Putative chromothripsis (and intrachromosomal complexity) events (where no size limit of > 5Mb is used) were counted as one event (Leeksma et al 2021, Mikhail et al 2019).

Lymphomas

Diagnosis

- To detect clinically relevant prognostic subgroups in non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL) karyotyping and/or FISH on fresh biopsy material or smears is recommended.
- To detect infiltration in bone marrow:
  - Karyotype 50 metaphases or,
  - Karyotype 20 metaphases and perform additional FISH if applicable.
    When FISH is performed, bone marrow smears are preferred to bone marrow cultures.
- Table 4 shows suggested loci for specific detection in lymphoma subtypes.
- It is highly recommended to perform FISH for translocation detection of high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* translocations (formerly double/triple hit).
- The preferred method for follow-up depends on the results of the preceding analysis.
- For HL it is recommended to perform FISH on rare giant cells, e.g. centromere 8 for detection of (near-)triploidy.

National protocols are published on the HOVON websites and for a British guideline in lymphoma diagnostics see Appendix B.

For relevant publications on diagnostics and classification of NHL and HL see Swerdlow et al 2017.

Table 4 Gene rearrangements in lymphomas

Lymphoma	**Gene(s) / rearrangement**	**Chromosome loci**
Mantle cell lymphoma (MCL)	*IGH::CCND1*	t(11;14)(q13;q32)
MCL negative for t(11;14)	*CCND2* *CCND3*	12p13 6p21
Follicular lymphoma (FL)	*(IGH::)BCL2*	t(14;18)(q32;q21)
Burkitt lymphoma (BL)	*IGH::MYC* *IGK* *IGL*	t(8;14)(q24;q32) 2p11 22q11
Burkitt-like lymphoma with 11q aberration		11q23.2-23.3 11q24.1-qter
Diffuse large B-cell lymphoma (DLBCL)	*(IGH::)BCL2* *BCL6* *MYC*	t(14;18)(q32;q21) 3q27 8q24 See also Swerdlow et al 2017 Table 13.23 page 295
High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* translocations (formerly Double hit /Triple hit lymphoma)	*(IGH::)BCL2* *BCL6* *MYC*	t(14;18)(q32;q21) 3q27 8q24
Primary mediastinal B-cell lymphoma (PMBL)	*REL* *JAK2* *CIITA*	2p13-p12 9p24 16p13.13
Mucosa-associated lymphoid tissue lymphoma (MALT) / Marginal zone lymphoma (MZL)	*IGH::MALT1* *BIRC3::MALT1* *BCL10* *FOXP1*	t(14;18)(q32;q21) t(11;18)(q21;q21) 1p22 3p14 +3, +18
Splenic MZL (SMZL)		del(7q) i(7)(q10)
Anaplastic large cell lymphoma (ALCL), *ALK* positive	*ALK*	2p23 See also Swerdlow et al 2017 Table 14.10 page 417
Hepatosplenic T-cell lymphoma		del(7q)

Classic Hodgkin lymphoma (CHL)	*JAK2*	9p24 triploidy detection
Lymphocyte-predominant Hodgkin lymphoma (LPHL)	*BCL6*	3q27

Multiple myeloma

Diagnosis

- The WHGD has decided to perform array, interphase FISH, optical genome mapping and/or whole genome sequencing on enriched plasma cells from whole bone marrow aspirates in multiple myeloma (MM).
- The International Myeloma Working Group (IMWG) and the European Myeloma Network (EMN) recommends testing for prognostic relevant abnormalities: del(17p) / *TP53*, t(4;14) *IGH*::*FGFR3* fusion and t(14;16) *IGH*::*MAF* fusion (Sonneveld et al 2016, Caers et al 2018).
- The WHGD and Dutch Myeloma Working Group (Minnema et al 2021, in preparation) have decided to perform an extended panel of targets: del(1p32) *CDKN2C*, gain(1q) *CKS1B*, t(4;14) *IGH::FGFR3*, del(13q), t(14;16) *IGH*::*MAF*, del(17p) *TP53*, and ploidy status.
- On request of the physician testing for t(11;14) *IGH::CCND1* will be performed.
- Testing for 1p21-p22 (*MTF2,TMED5*), 1p12 (*FAM46C)* deletion and t(14;20) *IGH::MAFB* is optional.
- When establishing the ploidy status by FISH, FISH must be performed for at least two chromosomes out of 3, 5, 9, 11 and 15.
- If a normal FISH result is observed for an IGH break-apart probe, no additional FISH testing is required. In the report it must be stated that the t(4;14) and t(14;16) are not observed. In case the IGH break-apart probe shows an abnormal result, additional FISH for t(4;14) and t(14;16) is required.
- The clone-size of the del(17p) must be mentioned in the report.

Appendix A References

Baccarani M, Cortes J, Pane F, Niederweiser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silvert RT, Goldman J, Hehlmann R; European LeukemiaNet. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 2009;27(35):6041–51, PMID 19884523.

Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperly JF, Cervantes F, Clark RE, Cortes JE, Guilhot F, Hjorth-Hansen H, Hughes TP, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Martinelli G, Mayer J, Muller MC, Niederwieser D, Pane F, Radich JP, Rousselot P, Saglio G, Saussele S, Schiffer C, Silver R, Simonsson B, Steegmann JL, Goldman JM, Hehlmann R. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 2013;122(6):872-84, PMID 23803709.

Baccarani M, Castagnetti F, Gugliotta G, Rosti G. A review of the European LeukemiaNet recommendations for the management of CML. Ann Hematol 2015;94:141-7, PMID 25814080.

Baliakas P, Jeromin S, Iskas M, Puiggros A, Plevova K, Nguyen-Khac F, Davis Z, Rigolin GM, Visentin A, Xochelli A, Delgado J, Baran-Marszak F, Stalika E, Abrisqueta P, Durechova K, Papaioannou G, Eclache V, Dimou M, Iliakis T, Collado R, Doubek M, Calasanz MJ, Ruiz-Xiville N, Moreno C, Jarosova M, Leeksma AC, Panayiotidis P, Podgornik H, Cymbalista F, Anagnostopoulos A, Trentin L, Stavroyianni N, Davi F, Ghia P, Kater AP, Cuneo A, Pospisilova S, Espinet B, Athanasiadou A, Oscier D, Haferlach C, Stamatopoulos K; ERIC, the European Research Initiative on CLL. Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. Blood 2019;133(11):1205-16, PMID 30602617.

Barbui T, Tefferi A, Vannucchi AM, Passamonti F, Silver RT, Hoffman R, Verstovsek S, Mesa R, Kiladjian JJ, Hehlmann R, Reiter A, Cervantes F, Harrison C, Mc Mullin MF, Hasselbalch HC, Koschmieder S, Marchetti M, Bacigalupo A, Finazzi G, Kroeger N, Griesshammer M, Birgegard G, Barosi G. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. Leukemia 2018;32(5):1057-69, PMID 29515238.

Breems DA, Van Putten WL, De Greef GE, Van Zelderen-Bhola SL, Gerssen-Schoorl KB, Mellink CH, Nieuwint A, Jotterand M, Hagemeijer A, Beverloo HB, Löwenberg B. Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. J Clin Oncol. 2008;26(29):4791-7, PMID 18695255.

Bruford EA, Braschi B, Denny P, Jones TEM, Seal RL, Tweedie S. Guidelines for human gene nomenclature. Nat Genet 2020;52(8):754-8, PMID 32747822.

Bruford EA, Antonescu CR, Carroll AJ, Chinnaiyan A, Cree IA, Cross NCP, Dalgleish R, Gale RP, Harrison CJ, Hastings RJ, Huret JL, Johansson B, Le Beau M, Mecucci C, Mertens F, Verhaak R, Mitelman F. HUGO Gene Nomenclature Committee (HGNC) recommendations for the designation of gene fusions. Leukemia 2021; Epub ahead of print, PMID 34615987.

Caers J, Gardenet L, Kortüm M, et al. European Myeloma Network recommendations on tools for the diagnosis and monitoring of multiple myeloma: what to use and when. Haematologica 2018;103(11):1772-1784, PMID 30171031.

Chun K, Wenger GD, Chaubey A, Dash DP, Kanagal-Shamanna R, Kantarci S, Kohle R, Van Dyke DL, Wang L, Wolff DJ, Miron PM. Assessing copy number aberrations and copy-neutral loss-of-heterozygosity across the genome as best practice: An evidence-based review from the Cancer Genomics Consortium (CGC) working group for chronic lymphocytic leukemia. Cancer Genet 2018;228-229:236-50, PMID 30554732.

Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, Dombret H, Ebert BL, Fenaux P, Larson RA, Levine RL, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz M, Sierra J, Tallman MS, Tien HF, Wei AH, Löwenberg B, Bloomfield CD. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424-447, PMID 27895058.

Gangat N, Tefferi A, Thanarajasingam G, Patnaik M, Schwager S, Ketterling R, Wolanskyj AP. Cytogenetic abnormalities in essential thrombocythemia: prevalence and prognostic significance. Eur J Haematol. 2009;83(1):17-21, PMID 19236446.

Gangat N, Caramazza D, Vaidya R, George G, Begna K, Schwager S, Van Dyke D, Hanson C, Wu W, Pardanani A, Cervantes F, Passamonti F, Tefferi A. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol 2011;29(4):392-7, PMID 21149668.

Goswami RS, Liang CS, Bueso-Ramos CE, Hu S, Goswami M, Yin CC, Lu G, Medeiros J, Tang G. Isolated +15 in bone marrow: Disease-associated or a benign finding? Leuk Res 2015;39:72-6, PMID 25435027.

Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, Bennett JM, Bowen D, Fenaux P, Dreyfus F, Kantarjian H, Kuendgen A, Levis A, Malcovati L, Cazzola M, Cermak J, Fonatsch C, Le Beau MM, Slovak ML, Krieger O, Luebbert M, Maciejewski J, Magalhaes SM, Miyazaki Y, Pfeilstöcker M, Sekeres M, Sperr WR, Stauder R, Tauro S, Valent P, Vallespi T, van de Loosdrecht AA, Germing U, Haase D. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454-65, PMID 22740453.

Grimwade D, Ivey A, Huntley BJP. Molecular landscape of acute myeloid leukemia in younger adults and its clinical relevance. Blood 2016;127(1):29-41, PMID 26660431.

Guglielmelli P, Lasho TL, Rotunno G, Mudireddy M, Mannarelli C, Nicolosi M, Pacilli A, Pardanani A, Rumi E, Rosti V, Hanson CA, Mannelli F, Ketterling RP, Gangat N, Rambaldi A, Passamonti F, Barosi G, Barbui T, Cazzola M, Vannucchi AM, Tefferi A. MIPSS70: Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis. J Clin Oncol 2018;36(4):310-8, PMID 29226763.

Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, Hillmen P, Keating M, Montserrat E, Chiorazzi N, Stilgenbauer S, Rai KR, Byrd JC, Eichhorst B, O'Brien S, Robak T, Seymour JF, Kipps TJ. iwCLL Guidelines for diagnosis, indications for treatment, response assessment and supportive management of CLL. Blood 2018;131(25):2745-60, PMID 29540348.

Hanson CA, Steensma DP, Hodnefield JM, Nguyen PL, Hoyer JD, Viswanatha DS, Zou Y, Knudson RA, Van Dyke DL, Ketterling RP. Isolated trisomy 15: a clonal chromosome abnormality in bone marrow with doubtful hematologic significance. Am J Clin Pathol 2008;129(3):478-85, PMID 18285273.

Hehlmann R, Voskanyan A, Lauseker M, Pfirrmann M, Kalmanti L, Rinaldetti S, Kohlbrenner K, Haferlach C, Schlegelberger B, Fabarius A, Seifarth W, Spieß B, Wuchter P, Krause S, Kolb HJ, Neubauer A, Hossfeld DK, Nerl C, Gratwohl A, Baerlocher GM, Burchert A, Brümmendorf TH, Hasford J, Hochhaus A, Saußele S, Baccarani M; SAKK and the German

CML Study Group. High-risk additional chromosomal abnormalities at low blast counts herald death by CML. Leukemia 2020;34(8):2074-86, PMID 32382082.

Heim S and Mitelman F (Eds): Cancer cytogenetics: Chromosomal and molecular genetic aberrations of tumor cells. Fourth edition, 2015.

Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, Clark RE, Cortes JE, Deininger MW, Guilhot F, Hjorth-Hansen H, Hughes TP, Janssen JJWM, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Mayer J, Nicolini F, Niederwieser D, Pane F, Radich JP, Rea D, Richter J, Rosti G, Rousselot P, Saglio G, Saußele S, Soverini S, Steegmann JL, Turkina A, Zaritskey A, Hehlmann R. European LeukemiaNet2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020;34(4):966-84, PMID 32127639.

Huret J. Atlas of Genetics and Cytogenetics in Oncology and Haematology. URL http://atlasgeneticsoncology.org

Issa GC, Kantarjian HM, Gonzalez GN, Borthakur G, Tang G, Wierda W, Sasaki K, Short NJ, Ravandi F, Kadia T, Patel K, Luthra R, Ferrajoli A, Garcia-Manero G, Rios MB, Dellasala S, Jabbour E, Cortes JE. Clonal chromosomal abnormalities appearing in Philadelphia chromosome-negative metaphases during CML treatment. Blood 2017;130(19):2084-91, PMID 28835440.

Itzykson R, Fenaux P, Bowen D, Cross NCP, Cortes J, De Witte T, Germing U, Onida F, Padron E, Platzbecker U, Santini V, Sanz GF, Solary E, Van de Loosdrecht A, Malcovati L. Diagnosis and Treatment of Chronic Myelomonocytic Leukemias in Adults : Recommendations From the European Hematology Association and the European LeukemiaNet. HemaSphere 2018;2 (6):e150, PMID 31723789.

Leeksma AC, Baliakas P, Moysiadis T, Puiggros A, Plevova K, Van der Kevie-Kersemaekers AM, Posthuma H, Rodriguez-Vicente AE, Tran AN, Barbany G, Mansouri L, Gunnarsson R, Parker H, Van den Berg E, Bellido M, Davis Z, Wall M, Scarpelli I, Österborg A, Hansson L, Jarosova M, Ghia P, Poddighe P, Espinet B, Pospisilova S, Tam C, Ysebaert L, Nguyen-Khac F, Oscier D, Haferlach C, Schoumans J, Stevens-Kroef M, Eldering E, Stamatopoulos K, Rosenquist R, Strefford JC, Mellink C, Kater AP. Genomic arrays identify high-risk chronic lymphocytic leukemia with genomic complexity: a multi-center study. Haematologica 2021;106(1):87-97, PMID 31974198.

McGowan-Jordan J, Hastings RJ, Moore S (Eds): ISCN 2020: an international system for human cytogenomic nomenclature (2020). Karger, Basel.
Minnema MC, Ruinemans-Koerts J, Jacobs JFM, Broijl A, Stevens-Kroef M, Poddighe PJ, Nijhof IS, van der Velden VHJ, Bloem AC, Lam K, Zijlstra-Baalbergen JM, Zwezerijnen B. Diagnostiek richtlijn Multipel Myeloom, 2021, in preparation.

Mikhail FM, Biegel JA, Cooley LD, Dubuc AM, Hirsch B, Horner VL, Newman S, Shao L, Wolff D, Raca G. Technical laboratory standards for interpretation and reporting of acquired copy-number abnormalities and copy-neutral loss of heterozygosity in neoplastic disorders: a joint consensus recommendation from the American College of Medical Genetics and Genomics (ACMG) and the Cancer Genomics Consortium (CGC). Genet Med 2019;21(9):1903-16, PMID 31138931.
Mitelman F, Johansson B and Mertens F (Eds.). Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer. https://mitelmandatabase.isb-cgc.org

Moorman AV, Enshaei A, Schwab C, Wade R, Chilton L, Elliott A, Richardson S, Hancock J, Kinsey SE, Mitchell CD, Goulden N, Vora A, Harrison CJ. A novel integrated cytogenetic and genomic classification refines risk stratification in pediatric acute lymphoblastic leukemia. Blood 2014;124(9):1434-44, PMID 24957142.

Neveling K, Mantere T, Vermeulen S, Oorsprong M, van Beek R, Kater-Baats E, Pauper M, van der Zande G, Smeets D, Olde Weghuis D, Stevens-Kroef MJPL, Hoischen A. Next-generation cytogenetics: Comprehensive assessment of 52 hematological malignancy genomes by optical genome mapping. Am J Hum Genet. 2021;108(8):1423-35, PMID 34237281.

Raaijmakers MHGP, Joosten M, Wouters BJ, Beverloo BH, Valk PJM. Genetische predispositie voor myeloïde maligniteiten: diagnostiek en beleid. Ned Tijdschr Hematol 2018;15:208-17, URL https://www.ariez.nl/wp-content/uploads/2018/08/208-17.pdf

Rack KA, van den Berg E, Haferlach C, Beverloo HB, Costa D, Espinet B, Foot N, Jeffries S, Martin K, O'Connor S, Schoumans J, Talley P, Telford N, Stioui S, Zemanova Z, Hastings RJ. European recommendations and quality assurance for cytogenomic analysis of haematological neoplasms. Leukemia 2019a;33(8):1851-1867, PMID 30696948.

Rack K, van den Berg E, Haferlach C, Beverloo B, Espinet B, Foot N, Martin K, O'Connor S, Schoumans J, Talley P, Stioui S, Zemanova Z, Luquet I, Hastings R.Guidance for reporting the interpretation of cytogenomic test results in haematological neoplasms. Atlas Genet

Cytogenet Oncol Haematol 2019b;23(12):353-55, URL http://atlasgeneticsoncology.org/Deep/GuidanceReportInterpretationCytogenomicID20150.html.

Schanz J, Tüchler H, Solé F, Mallo M, Luno E, Cervera J, Granada I, Hildebrandt B, Slovak ML, Ohyashiki K, Steidl C, Fonatsch C, Pfeilstöcker M, Nösslinger T, Valent P, Giagounidis A, Aul C, Lübbert M, Stauder R, Krieger O, Garcia-Manero G, Faderl S, Pierce S, Le Beau MM, Bennett JM, Greenberg P, Germing U, Haase D. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol 2012;30(8):820-9, PMID 22331955.

Schoumans J, Suela J, Hastings R, Muehlematter D, Rack K, van den Berg, Beverloo H, Stevens-Kroef M. Guidelines for genomic array analysis in acquired haematological neoplastic disorders. Genes Chrom Cancer 2016;55(5):480-91, PMID 26774012.

Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, Chng WJ, Moreau P, Attal M, Kyle RA, Caers J, Hillengas J, San Miguel J, van de Donk NW, Einsele H, Bladé J, Durie BG, Goldschmidt H, Mateos MV, Palumbo A, Orlowski R. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood 2016;127(24):2955-62, PMID 27002115.

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J (Eds). WHO classification of tumours of haematopoietic and lymphoid tissues (revised 4th edition). IARC: Lyon 2017.

Tang G, Hidalgo Lopez JE, Wang SA, Hu S, Ma J, Pierce S, Zuo W, Carballo-Zarate AA, Yin CC, Tang Z, Li S, Medeiros LJ, Verstovsek S, Bueso-Ramos CE. Characteristics and clinical significance of cytogenetic abnormalities in polycythemia vera. Haematologica 2017;102(9):1511-8, PMID 28473622.

Tefferi A, Nicolosi M, Mudireddy M, Lasho TL, Gangat N, Begna KH, Hanson CA, Ketterling RP, Pardanani A. Revised cytogenetic risk stratification in primary myelofibrosis: analysis based on 1002 informative patients. Leukemia 2018;32(5):1189-99, PMID 29472717.

Tefferi A. Primary myelofibrosis: 2021 update on diagnosis, risk-stratification and management. Am J Hematol 2021;96(1):145-62, PMID 33197049.

VKGL vereniging klinisch genetische LABORATORIUMDIAGNOSTIEK	
VKGL kwaliteitscommissie_Veldnorm	
Titel: Richtlijnen verworven cytogenetica	**Doc. code: VKGL_V07**
Subspecialisme: Genoomdiagnostiek - Cytogenetica	**Versie: 03** **Ingangsdatum: 01-12-2021**
Beheerder: Eva van den Berg- de Ruiter **Centrum: UMC Groningen**	
Vakspecifieke toelichting op normelement 5.6 van de ISO15189-2012	

Appendix B National and international guidelines and organisations

General

https://hematologienederland.nl/kwaliteit/richtlijnen/

https://hovon.nl/en

https://www.e-c-a.eu/en/GUIDELINES.html

https://www.leukemia-net.org/home/

https://www.acgs.uk.com/quality/best-practice-guidelines/

Myeloproliferative neoplasms

https://hovon.nl/_asset/_public/TreatmentGuidelines/TreatmentGuidelines_Leukemia/hovon-cml-richtlijn-14-04-2018_geautoriseerd.pdf

http://www.leukemia-net.org/content/leukemias/cml/recommendations/index_eng.html

http://www.mipss70score.it/

Myelodysplastic syndrome

https://hovon.nl/_asset/_public/TreatmentGuidelines/TreatmentGuidelines_Leukemia/Richtlijnen-MDS.pdf

Acute myeloid leukaemia

https://hovon.nl/_asset/_public/TreatmentGuidelines/TreatmentGuidelines_Leukemia/AML-richtlijn-versie-2021-06-29-definitief.pdf

Acute lymphoblastic leukaemia/lymphoma

https://hovon.nl/_asset/_public/TreatmentGuidelines/TreatmentGuidelines_Leukemia/Richtlijn-ALL-volwassenen2020.pdf

ALL Together1 – A treatment study protocol of the ALLTogether Consortium for children and young adults (1-45 years of age) with newly diagnosed acute lymphoblastic leukaemia (ALL). Heyman et al. Most recent version available through the Princess Maxima Center, Bilthoven, the Netherlands.

Chronic lymphocytic leukaemia/ small lymphocytic lymphoma

https://hematologienederland.nl/wp-content/uploads/2020/05/2020_02_10_CLL-richtlijn-geautoriseerd-2020_05_26.pdf

https://hovon.nl/_asset/_public/TreatmentGuidelines/TreatmentGuidelines_Leukemia/CLL-richtlijn-final-09-06-2021.pdf

http://www.ericll.org/tp53_aberrations/#

Lymphomas

https://hovon.nl/en/treatment-guidelines/lymphoma

Multiple myeloma

https://hovon.nl/en/treatment-guidelines/myeloma

Appendix C Abbreviations

AA	Aplastic anaemia
ACA	A**dditional chromosomal abnormalities**
ACC	Association for Clinical Cytogenetics, see also ACGS
ACGS	Association for Clinical Genomic Science, see also ACC
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
CEL	**Chronic eosinophilic leukaemia**
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CNA	Copy number abnormality
CNL	**chronic neutrophilic leukaemia**
CN-LOH	Copy-neutral loss of heterozygosity
DIPPS	Dynamic International Prognostic System
ECA	European Cytogeneticists Association
ELN	European Leukemia Network
ET	Essential thrombocythaemia
FFPE	Formalin-fixed, paraffin-embedded
FISH	Fluorescence in situ hybridisation
GenQA	Genomic Quality Assessment
HL	Hodgkin lymphoma
HOVON	Stichting Hemato-Oncologie voor Volwassenen Nederland
HUGO	Human Genome Organisation
IMWG	International Myeloma Working Group
IPSS-R	Revised International Prognostic Scoring System
ISCN	International System for human Cytogenomic Nomenclature
JMML	Juvenile myelomonocytic leukaemia
MDS	Myelodysplastic syndrome
MIPPS	Mutation enhanced International Prognostic System
MK	Monosomal karyotype
MLPA	Multiplex ligation-dependent probe amplification
MM	Multiple myeloma
MPN	Myeloproliferative neoplasm
MRD	Minimal residual disease
NGS	Next-Generation Sequencing
NHL	Non-Hodgkin lymphoma
PMF	Primary myelofibrosis

PV	Polycythaemia vera
SCT	Stem cell transplantation
SKION	Stichting Kinderoncologie Nederland
SNP	Single nucleotide polymorphism
SV	Structural variant
TKI	Tyrosine Kinase Inhibitors
VKGL	Vereniging Klinisch Genetische Laboratoriumdiagnostiek
WGS	Whole Genome Sequencing
WHGD	Werkgroep Hemato-oncologische Genoomdiagnostiek
WHO	World Health Organization