VKGL kwaliteitscommissie_Veldnorm	
Titel: Richtlijnen verworven cytogenetica	**Doc. code: VKGL_V07**
Subspecialisme: Genoomdiagnostiek - Cytogenetica	**Versie: 02** **Ingangsdatum: 18-10-2017**
Beheerder: Simone Snijder **Centrum: UMCU**	
Vakspecifieke toelichting op normelement 5.6 van de ISO15189-2012	

Reden voor toelichting:
Als richtlijnen voor de verworven cytogenetica worden de Europese richtlijnen van de ECA (European Cytogeneticists Association) aangehouden:
☐General Guidelines and Quality Assurance for Cytogenetics (January 2012)
☐Guidelines and Quality Assurance for Acquired Cytogenetics (January 2013).
Beide zijn te vinden op http://e-c-a.eu, onder “guidelines”.
De WHGD richtlijnen voor verworven cytogenetica zijn een aanvulling op de ECA richtlijnen en dienen derhalve in samenhang met de ECA 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 Belgische laboratoria die diagnostiek verzorgen in het kader van cytogenetische analyse t.b.v. verworven chromosoomafwijkingen d.m.v. karyotypering, FISH en array.

Definities: n.v.t.

WHGD Guidelines for (Cyto)genetic Analysis of Acquired Disorders

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

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

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vereniging klinisch genetische LABORATORIUMDIAGNOSTIEK

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Index

GENERAL REMARKS

These WHGD guidelines are a supplement to and should be applied in the context of the "Guidelines and Quality Assurance for Acquired Cytogenetics - Guidelines for cytogenetic analysis of acquired disorders" issued by the European Cytogeneticists Association (ECA Newsletter No. 31 January 2013) and the "General Guidelines and Quality Assurance for Cytogenetics" (ECA Newsletter No. 29 January 2012).
For issues not covered by the WHGD or ECA guidelines, other VKGL guidelines or local quality systems may apply.

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

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

Where reference is made to the International System for Human Cytogenetic nomenclature (ISCN) or World Health Organisation (WHO) classification publications, the most recent versions should be used. The WHO classification by Swerdlow *et al* 2008 should be used in the context of the 2016 revisions (Arber *et al* 2016, Swerlow *et al* 2016, Cazzola 2016).

1. ANALYSIS

1.1. General

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

- WHO classification (Swerdlow *et al* 2008, Arber *et al* 2016, Swerdlow *et al* 2016, Cazzola 2016).
- Heim and Mitelman 2015. Cancer Cytogenetics: Chromosomal and molecular genetic aberrations of tumor cells.
- Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer. Mitelman F, Johansson B and Mertens F. https://cgap.nci.nih.gov/Chromosomes/Mitelman
- Atlas of Genetics and Cytogenetics in Oncology and Haematology. Huret JL *et al*. http://atlasgeneticsoncology.org/

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

1.2. Karyotyping

For these guidelines “karyotyping” is interpreted as whole genome testing and thereby includes array-based techniques. In those cases where the detection of balanced rearrangements is essential, additional FISH tests must be done as mentioned in chapters 2 and 3. See also paragraph 1.4.
For the definition of a clone see ISCN 2016 page 84 (McGowan-Jordan *et al* 2016).

1.3. FISH

Guidelines for FISH analysis are provided in the “General Guidelines and Quality Assurance for Cytogenetics” and “Guidelines and Quality Assurance for Acquired Cytogenetics - Guidelines for cytogenetic analysis of acquired disorders”. In addition local quality systems might apply.

1.4. Microarray

Microarray-based genomic profiling can replace karyotyping for certain leukaemia subgroups. It is for example applied in a diagnostic setting for CLL (Stevens-Kroef *et al* 2014), MM (Stevens-Kroef *et al* 2012), ALL (Simons *et al* 2011) and MDS (Stevens-Kroef *et al* 2017). The currently applied high-resolution microarray platforms exhibit a high sensitivity and allow the detection of copy number abnormalities present in 20% of the cells (Stevens-Kroef *et al* 2014). In addition, microarrays allow the identification of additional abnormalities such as focal copy number aberrations and copy neutral loss of heterozygosity (cnLOH).

Since no dividing cells are required, all material types which are expected to contain at least 20% of genetic abnormal cells, can be used.
For the application of genomic array analysis in acquired haematological neoplastic disorders guidelines provided by Schoumans *et al* 2016 are recommended.
In addition, American standards and guidelines can be obtained from Cooley *et al* 2013.

2. MYELOID NEOPLASIA

2.1. CML (chronic myelogenous leukaemia)

Diagnosis
When a translocation t(9;22)(q34;q11) is detected at diagnosis, one can refer in the report to national guidelines (see APPENDIX C or Janssen *et al* 2014) or ELN guidelines (APPENDIX D or Baccarani *et al* 2009) for recommendations to the clinician on follow up.

Follow up studies in CML

- To establish the Cytogenetic Response at least 20 metaphases should be analyzed (Baccarani *et al* 2013). If the level of Ph+ve 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/ACC Guidelines: CML 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

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).

- Wang *et al* 2016 have analysed the prognostic impact of additional chromosomal abnormalities (ACA) in CML:
    - Group 1: trisomy 8, -Y, extra Ph as single abnormalities are associated with a good prognosis;
    - Group 2: i(17q10), -7/del(7q), 3q26.2 as single abnormalities are associated with a poor prognosis;
    - Other single ACA as a group have a survival similar to the good prognostic group;
    - Patients with 2 or more ACA have a survival similar to the poor prognostic group.
- Clonal cytogenetic abnormalities in Ph negative (Ph-) cells, in the absence of dysplasia, do not seem to adversely affect outcome. The exceptions are abnormalities of chromosome 7 (monosomy 7 and del(7q)), where some case reports indicate a risk of myelodysplasia and acute leukaemia and justify long-term follow-up bone marrow biopsies. Other patients with clonal cytogenetic abnormalities in Ph- cells require marrow examination only in case of cytopenias or dysplastic peripheral blood morphology (Baccarani *et al* 2013).

2.2. AML (acute myeloid leukaemia)

Diagnosis

- The 2016 revision of the WHO classification recognizes several entities defined by the presence of recurrent (cyto)genetic abnormalities. See Table 1 in Arber *et al* 2016.
- Table 18 in Arber *et al* 2016 summarizes cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes when ≥20% peripheral blood or bone marrow blasts are present and prior therapy has been excluded.
- SNP array analysis could be considered for detection of acquired CNV analysis or copy neutral loss of heterozygosity (cnLOH).
- FISH analysis to screen for *KMT2A* / 11q23 and *MECOM* / 3q26 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 FISH or array analysis should be performed to screen for monosomy 5/del(5q) and monosomy 7/del(7q).
- In case of a normal karyotype, additional FISH analysis 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, FISH for *NUP98* / 11p15 and *CBFA2T3-GLIS2* could be considered, especially when morphology showed an acute megakaryoblastic leukemia (de Rooij *et al* 2013, Hollink *et al* 2011, Gruber *et al* 2015).

- 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* occur frequently in AML with normal cytogenetics, whereas *TP53* and *KIT* mutations more often are present in AML with abnormal karyotypes.

Interpretation and prognostic implication

- For prognostic implication preferably the ELN recommendations by Döhner *et al* 2017 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, 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/MDS risk classification as a poor risk factor. The definition of a monosomal karyotype 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).

2.3. MDS (myelodysplastic syndrome)

Diagnosis

- When karyotyping is unsuccessful (less than 10 normal metaphases) additional FISH analysis can be considered.
- Microarray based genomic profiling can also be helpful in these cases, and may serve as an alternative for karyotyping and/or FISH (Arenillas *et al* 2013, Stevens-Kroef *et al* 2017).
- MDS can be diagnosed in cases of persistent cytopenia of undetermined origin if a recognized cytogenetic abnormality is present. These abnormalities are specified on page 93 of the WHO classification (Swerdlow *et al* 2008). 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 is recommended.

Interpretation and prognostic implication

The International Prognostic Scoring System (IPSS, Table 2, derived from Greenberg *et al* 1997) and the revised IPSS (IPSS-R, Table 3, derived from Greenberg *et al* 2012, Schanz *et al* 2012) are important standards for assessing prognosis of primary untreated adult patients with MDS. The cytogenetic contribution to the prognostic score can also be obtained from the >5Mb CNA array result (Stevens-Kroef *et al* 2017). The prognostic score is based on cytogenetics, percentage of bone marrow blasts, cytopenias, hemoglobin, platelets and absolute neutrophil count. It is recommended to describe the cytogenetic contribution to these scoring systems in the laboratory report

Table 2

IPSS	
Prognostic variable	**Cytogenetic abnormality**
0	normal, -Y, del(5q), del(20q)
0.5	all other
1	complex (≥3 abnormalities), or chromosome 7 abnormalities

Table 3

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)

To determine karyotypic complexity, the numbers of karyotype aberrations are counted according to Chun *et al* 2010. The general rule is to count 1 aberration for each item between commas in the nomenclature string. More specifically:

- count 1 aberration for each numerical change (including -Y), balanced translocation and simple structural change;
- count 1 aberration for each complex structural change;
- count 0 for a constitutional aberration, but if in doubt, count 1 aberration;
- when multiple clones are present, add all independent aberrations, but count a single (specific) change only once;
- count 1 aberration for tetraploidy.

2.4. Non neoplastic disorders, MDS related (aplastic anaemia)

This paragraph also includes Fanconi anaemia and childhood MDS.

- Aplastic anaemia (AA) samples should be treated the same as MDS samples.
- In childhood MDS FISH for -7/del(7q) is required.
- In childhood MDS a complex karyotype is associated with a poor prognosis (Goehring *et al* 2010).
- Because MDS/AML is a frequent and severe occurrence in Fanconi anaemia, it is necessary to follow up patients regularly to detect transformation before the onset of an overt MDS/AML. In Fanconi anaemia patients MDS/AML can have an apparently normal karyotype but cryptic chromosomal or genomic abnormalities may be present. Therefore, interphase FISH with probes for 1q, 3q26 and 7q or microarray based genomic profiling for the detection of copy number alterations and interphase FISH with *RUNX1* for the detection of rearrangements is required (Quentin *et al* 2011).

2.5. MPN (myeloproliferative neoplasms excluding CML, but including MDS/MPN) and hypereosinophilic syndrome

Diagnosis

Although diagnosis of myeloproliferative neoplasms (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) leukemic 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 leukemic transformation.

In myeloid (and lymphoid) neoplasms with eosinophilia additional FISH for *PDGFRA* and *PDGFRB*, *FGFR1* and/or *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.

Interpretation and prognostic implication

- Significance of cytogenetic abnormalities in essential thrombocythemia (ET): Gangat *et al* 2009.
- Significance of cytogenetic abnormalities in polycythemia vera (PV): Sever *et al* 2013.
- Significance of cytogenetic abnormalities in primary myelofibrosis (PMF): Tam *et al* 2009, Caramazza *et al* 2011, Wassie *et al* 2014.

3. LYMPHOID NEOPLASIA

In lymphoid (and myeloid) neoplasms with eosinophilia additional FISH for *PDGFRA* and *PDGFRB*, *FGFR1* and/or *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.

3.1. Acute lymphoblastic leukaemia - B or T cell ALL

Diagnosis

- The 2016 revision of the WHO classification recognizes several entities defined by the presence of recurrent (cyto)genetic abnormalities. See Table 1 in Arber *et al* 2016.
- FISH for *BCR-ABL1*, *ETV6-RUNX1* and *KMT2A* rearrangements are required for patients participating in a SKION study, unless molecular techniques for the detection of the fusion transcripts are used.
- 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 (Arber *et al* 2016).
- FISH for *BCR-ABL1* and *KMT2A* rearrangements are required for patients participating in HOVON studies, unless molecular techniques for the detection of the fusion transcripts are used. It is recommended to test for the presence of *ETV6-RUNX1* / t(12;21) in young adults (< 35 year).
- *IKZF1* status will be determined by the SKION laboratory. In case high-density SNP arrays are applied, it is recommended to report the *IKZF1* status in the cytogenetic report (Mullighan *et al* 2009).

- 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 (Stergianou *et al* 2005, Hagemeijer *et al* 2010).
- High-density SNP arrays may be used instead of karyotyping or FISH for the detection of unbalanced abnormalities. However, when applying arrays, the recommended FISH for the translocations must be performed (Simons *et al* 2011).

Follow up studies
When a genetic abnormality is identified on a diagnostic sample by interphase FISH, interphase FISH is the recommended technique for follow up.

National protocols are published on the SKION and HOVON websites (see APPENDIX C).

Interpretation and prognostic implication
- 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 (Holmfeldt *et al* 2013).
- For prognostic implication different risk classification can be used (e.g. Harrison *et al* 2011, Moorman *et al* 2014, Gazahvi *et al* 2015, comprising both cytogenetic and genetic abnormalities), 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, MRD). This should specifically mentioned in the report.

3.2. Mature B-cell Neoplasms

3.2.1. CLL (chronic lymphocytic leukaemia)

To assign CLL patients into clinically relevant prognostic subgroups one of the following techniques is recommended:
- FISH with probes for *TP53* / 17p13 preferably in combination with *ATM* / 11q22.
- Array with focus on prognostic significant abnormalities that may affect clinical management (*TP53* / del(17p13)).

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Notes

- According to (inter)national guidelines additional *TP53* mutation analysis is required (see appendix C and D). This analysis can be done in any lab (hematology, pathology or genetics); it is recommended that the results are combined or refer to each other.
- Clinical trials may still demand FISH for the detection of 13q14-deletions and trisomy 12.
- Optional: FISH for t(11;14)(q13;q32) on request or based on clinical trials.
- Follow up: array or FISH, depending on the results of preceding analysis.

Risk stratification

For prognostication and therapy consequences respectively see Table 4 (Schoumans *et al* 2016) and "Richtlijn CLL" (http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html).

Table 4

Risk factors	Genes	Prognosis*	Consequences for therapy (HOVON)	Reference
deletion 17p or TP53 mutation**	*TP53*	very poor	yes	Döhner *et al* 1997 Zenz *et al* 2012
deletion 11q	*ATM, BIRC3*	adverse	no	Dohner *et al* 1997 Zenz *et al* 2012 Rose-Zerilli *et al* 2014
deletion 13q14 type I	*MIR, DLEU*	favorable	no	Ouillette *et al* 2011a Parker *et al* 2011
deletion 13q14 type II	*RB1, MIR, DLEU*	favorable (shorter survival)	no	Ouillette *et al* 2011a Parker *et al* 2011
trisomy 12		intermediate/ favorable	no	Hurley *et al* 1980
complex genome (CNA***>3)		adverse	no	Ouillette *et al* 2011b Edelmann *et al* 2012 Schweighofer *et al* 2013
no aberrations		intermediate	no	

* based on Schoumans *et al* 2016. ** cut-off level 10% (Pospisilova *et al* 2012).
*** All CNA>5 Mb and CNA<5 Mb when recurrent and/or clinical relevant for referral reason.

Interpretation and prognostic implication

- Malek *et al* 2013.

- Rodriguez-Vicente *et al* 2013.
- Puiggros *et al* 2014. (NB: by personal communication with one of the authors from Puiggros *et al* 2014: the definition of type I/II deletions should be:
  Type I = small deletion (*RB1* present);
  Type II = large deletion (*RB1* deleted).

3.2.2. B- and T-cell lymphomas

To diagnose NHL cases into clinically relevant prognostic subgroups the following techniques are recommended:

- Karyotyping and/or FISH on fresh biopsy material or smears.
- FISH on FFPE material only (5µm sections).

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.

Notes

- Table 5 shows suggested loci for FISH detection in specific 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 (karyotyping or FISH) depends on the results of the preceding analysis.

Table 5

Lymphoma	Gene(s) / rearrangement	Chromosome loci
Mantle cell lymphoma (MCL)	*CCND1-IGH*	t(11;14)(q13;q32)
MCL negative for t(11;14)	*CCND2* *CCND3*	12p13 6p21
Follicular lymphoma (FL)	*BCL2-IGH*	t(14;18)(q32;q21)
Burkitt lymphoma (BL)	*MYC-IGH* *IGK* *IGL*	t(8;14)(q24;q32) 2p11 22q11
Diffuse large B-cell lymphoma (DLBCL)	*BCL2-IGH* *BCL6* *MYC*	t(14;18)(q32;q21) 3q27 8q24
High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* translocations (formerly Double hit /Triple hit lymphoma in WHO 2008)	*BCL2-IGH* *BCL6* *MYC*	t(14;18)(q32;q21) 3q27 8q24
Primary mediastinal B-cell lymphoma (PMBL)	*REL* *JAK2*	2p13-p12 9p24
Mucosa-associated lymphoid tissue lymphoma (MALT) / Marginal zone lymphoma (MZL)	*MALT1-IGH* *BIRC3-MALT1* *BCL10* *FOXP1*	t(14;18)(q32;q21) t(11;18)(q21;q21) 1p22 3p14 +8, +13
Splenic MZL (SMZL)		del(7q)
ALK-positive large B-cell lymphoma	*ALK*	2p23
Anaplastic large cell lymphoma (ALCL)	*ALK*	2p23
Hepatosplenic T-cell lymphoma		del(7q)
Classic Hodgkin lymphoma (CHL)	*JAK2*	9p24 triploidy detection
Lymphocyte-predominant Hodgkin lymphoma (LPHL)	*BCL6*	3q27

For Hodgkin lymphoma (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 and SKION websites (see APPENDIX C). For a British guideline in lymphoma diagnostics see APPENDIX D.

Relevant publications on diagnostics and classification of NHL and HL are Vos *et al* 2012, Kluin *et al* 2009, Hebeda *et al* 2010, Lam 2008, Kerst *et al* 2007, Aukema *et al* 2014, Aukema *et al* 2011, Pasqualucci *et al* 2014, Swerdlow *et al* 2016.

3.2.3. Plasma cell myeloma

- The WHGD has decided to perform array and/or interphase FISH on enriched plasma cells from whole bone marrow aspirates. Plasma cells have to be collected using magnetic beads: the CD138-positive fraction has to be isolated.
- In 2016 the International Myeloma Working Group (IMWG) 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).
- The WHGD and Dutch Myeloma Working Group (Zweegman *et al* 2011) have decided to perform an extended panel of targets: del(1p32) / *CDKN2C*, gain(1q) / *CKS1B*, t(4;14) / *IGH-FGFR3* fusion, del(13q), t(14;16) / *IGH-MAF* fusion, del(17p) / *TP53*, and ploidy status. Testing for 1p21-p22 (*MTF2,TMED5*), 1p12 (*FAM46C*), t(11;14) / *IGH-CCND1* fusion and t(14;20) / *IGH-MAFB* fusion are optional.
- When array is performed, copy number abnormalities (CNA) mentioned above should be reported. It is optional to report other CNA when >5Mb, irrespective of gene content, or <5Mb when recurrent and/or containing genes clinical relevant for referral reason. Also cnLOH >10Mb extending to the telomeres are considered to be acquired abnormalities and may be reported (Schoumans *et al* 2016).
- When establishing the ploidy status by FISH, FISH has to be performed for any 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.
- Number of cells to be counted with FISH: n=200 for numerical abnormalities and n=100 for structural abnormalities. If a FISH result is abnormal then respectively n=100 and n=50 is sufficient.
- For FISH positive cut-off levels are relatively conservative: 10% for fusion or break-apart probes, 20% for numerical abnormalities (Ross *et al* 2012).

4. BONE MARROW FROM SOLID TUMOUR CASES

Guidelines for cytogenetic investigations in solid tumour cases are described in Hastings *et al* 2016.

5. 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 WHGD working party). If these protocols are not applicable, the WHO classification (Swerdlow *et al* 2008, Swerdlow *et al* 2016, Arber *et al* 2016) or CEQAS guidelines (www.ceqas.org) should be applied. For several disease groups additional references are given in paragraphs 2 and 3.
- When relevant the report should refer to previous cytogenetic test results.

5.1. Reporting times

Table 6

Urgent referrals	95% should be (preliminary) reported within 10 calendar days
Routine referrals	95% should be (preliminary) reported within 28 calendar days

ACKNOWLEDGEMENTS

No WHGD supplement

APPENDICES

A. INDICATIONS FOR CYTOGENETIC ANALYSIS

No WHGD supplement

B. REFERENCES

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C. NATIONAL GUIDELINES

CML (chronic myelogenous leukaemia)

http://www.hovon.nl/upload/CML-richtlijnen%20versie%20HOVON%20website%20juli%202014.pdf

Acute lymphoblastic leukaemia - B or T cell ALL

https://www.skion.nl/voor-professionals/behandelrichtlijnen/protocollen/100/all-11/?pid=ac-p

CLL (chronic lymphocytic leukaemia)

http://www.hovon.nl/behandeladvies/behandeladvies-leukemie/cll.html

http://www.hovon.nl/studies/studies-per-ziektebeeld/cll.html

B- and T-cell lymphomas

http://www.hovon.nl/behandeladvies/behandeladvies-lymfomen/nhl/richtlijnen-lymfomen/pathologie.html

http://www.hovon.nl/behandeladvies/behandeladvies-lymfomen/

https://www.skion.nl/voor-professionals/behandelrichtlijnen/protocollen/per-ziektebeeld/246/maligne-lymfomen/

Plasma cell myeloma

http://www.hovon.nl/studies/studies-per-ziektebeeld/mm.html

D. INTERNATIONAL/EUROPEAN STANDARDS

General

http://www.acgs.uk.com/committees/quality-committee/best-practice-guidelines/

CML (chronic myelogenous leukaemia)

http://www.acgs.uk.com/media/765597/acc_cmlmpn_bp_jul2011_v1.00.pdf

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

AML (acute myeloid leukaemia)

http://www.acgs.uk.com/media/765567/acc_aml_mds_bp_mar2012_1.00.pdf

MDS (myelodysplastic syndrome)

http://www.acgs.uk.com/media/765567/acc_aml_mds_bp_mar2012_1.00.pdf

CLL (chronic lymphocytic leukaemia)

http://www.ericll.org/pages/ericguidelines

B- and T-cell lymphomas

http://www.bcshguidelines.com/documents/Lymphoma_disease_app_bcsh_042010.pdf

E: ABBREVIATIONS

AA	Aplastic anaemia
ACA	A**dditional chromosomal abnormalities**
ACC	Association for Clinical Cytogenetics, see also ACGS
ALL	Acute lymphoblastic leukaemia
ACGS	Association for Clinical Genomic Science, see also ACC
AML	Acute myeloid leukaemia
CEQAS	Cytogenetic External Quality Assessment Service
CLL	Chronic lymphocytic leukaemia
CML	Chronic myelogenous leukaemia
cnLOH	Copy neutral loss of heterozygosity
CNA	Copy number aberration
CNV	Copy number variation
ECA	European Cytogeneticists Association
ELN	European Leukemia Network
ET	Essential thrombocythemia
FFPE	Formalin-fixed, paraffin-embedded
FISH	Fluorescence in situ hybridisation
HL	Hodgkin lymphoma
HOVON	Stichting Hemato-Oncologie voor Volwassenen Nederland
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
ISCN	International System for human Cytogenetic Nomenclature
MDS	Myelodysplastic syndrome
MK	Monosomal karyotype
MM	Multiple myeloma
MPN	Myeloproliferative neoplasm
MRD	Minimal residual disease
NHL	Non-Hodgkin lymphoma
PMF	Primary myelofibrosis
PV	Polycythemia vera
SKION	Stichting Kinderoncologie Nederland
SNP	Single nucleotide polymorphism
VKGL	Vereniging Klinisch Genetische Laboratoriumdiagnostiek
WHGD	Werkgroep Hemato-oncologische GenoomDiagnostiek
WHO	World Health Organisation

F: REQUIRED TESTS FOR CLINICAL TRIALS

Requirements for specific tests for regular diagnostics and/or for (inter)national clinical trials are documented in the minutes of WHGD meetings (document “Lijst met trials).