impact the outcome of AML patients other than those with t(15;17), t(8;21), or inv(16) or t(16;16). The monosomal karyotype subgroup is defined by the presence of at least two autosomal monosomies (loss of chromosomes other than Y or X) or a single autosomal monosomy with additional structural abnormalities.

For patients lacking prognostic cytogenetic abnormalities, such as those with CN-AML, outcome prediction uses mutated or aberrantly expressed genes. *NPM1* mutations without concurrent presence of *FLT3*-ITD, and *CEBPA* mutations, especially if concurrently present in two different alleles, have been shown to predict favorable outcome, whereas *FLT3*-ITD predicts poor outcome. Given the proven prognostic importance of *NPM1* and *CEBPA* mutations and *FLT3*-ITD, molecular assessment of these genes at diagnosis has been incorporated in AML management guidelines by the National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN). The same markers have also been incorporated in the definitions of the genetic groups of the ELN standardized reporting system, which are based on both cytogenetic and molecular abnormalities and used for comparing clinical features and treatment response among subsets of patients reported in different studies (Table 132-2). More recently, the prognostic impact of the genetic groups recognized by the ELN reporting system has been demonstrated. Thus, these genetic groups may also be used for risk stratification and treatment guidance.

In addition to *NPM1* and *CEBPA* mutations and *FLT3*-ITD, other molecular aberrations (Table 132-3) may in the future be routinely used for prognostication in AML and incorporated in the WHO classification and the ELN reporting system. Among these prognostic mutated genes are those encoding receptor tyrosine kinases (e.g., v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog [*KIT*]), transcription factors (i.e., *RUNX1* and Wilms tumor 1 [*WT1*]), and epigenetic modifiers (i.e., additional sex combs like transcriptional regulator 1 [*ASXL1*], DNA (cytosine-5-)-methyltransferase 3 alpha [*DNMT3A*], isocitrate dehydrogenase 1 (NADP+), soluble [*IDH1*] and isocitrate dehydrogenase 2 (NADP+), mitochondrial [*IDH2*], lysine (K)-specific methyltransferase 2A [*KMT2A*, also known as *MLL*], and tet methylcytosine dioxygenase 2 [*TET2*]). Although *KIT* mutations are almost exclusively present in CBF AML and impact adversely the outcome, the remaining markers have been reported primarily in CN-AML. These gene mutations have been shown to be associated with outcome in multivariable analyses independently from other prognostic factors. However, for some of them, the prognostic impact (e.g., *TET2* mutations) or the type (adverse vs favorable) of prognostic impact (e.g., *IDH1*, *IDH2*) has been found in the majority, but not in all, of the reported studies.

An independent prognostic impact remains to be determined for mutated genes that are either associated primarily with unfavorable cytogenetic aberrations (e.g., *TP53*) or are found with a relatively lower frequency in AML patients like those encoding epigenetic modifiers (e.g., enhancer of zeste 2 polycomb repressive complex 2 subunit [*EZH2*]), phosphatases (e.g., protein tyrosine phosphatase, non-receptor type 11 (*PTPN11*]), putative transcription factors (e.g., PHD finger protein 6 [*PHF6*]), splicing factors (e.g., U2 small nuclear RNA auxiliary factor 1 [*U2AF1*]), and proteins involved in chromosome segregation and genome stability (e.g., structural maintenance of chromosomes 1A [*SMC1A*] or structural maintenance of chromosomes 3 [*SMC3*]). Finally, other mutated genes are recognized as predictors of treatment response to distinct therapies rather than prognosticators; for example, neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*) and Kirsten rat sarcoma viral oncogene homolog (*KRAS*) predict a better response to high-dose cytarabine in CBF AML.

In addition to gene mutations, deregulation of the expression levels of coding genes and of short noncoding RNAs (microRNAs) have been reported to provide prognostic information (Table 132-3). Overexpression of genes such as brain and acute leukemia, cytoplasmic (*BAALC*), v-ets avian erythroblastosis virus E26 oncogene homologue (avian) (*ERG*), meningioma (disrupted in balanced translocation) 1 (*MN1*), and MDS1 and EVI1 complex locus (*MECOM*, also known as *EVI1*) have been found to be predictive for poor outcome, especially in CN-AML. Similarly, deregulated expression levels of microRNAs, naturally occurring noncoding RNAs that have been shown to regulate the expression of proteins involved in hematopoietic differentiation and survival pathways by degradation or translation inhibition of target coding RNAs, have been associated with prognosis in AML. Overexpression of *miR-155* and *miR-3151* has been found to affect outcome adversely in CN-AML, whereas overexpression of *miR-181a* predicts a favorable outcome both in CN-AML and cytogenetically abnormal AML.

Because prognostic molecular markers in AML are not mutually exclusive and often occur concurrently (>80% patients have at least

TABLE 132-2 EUROPEAN LEUKEMIANET RECOMMENDED STANDARDIZED REPORTING FOR CORRELATION OF CYTOGENETIC AND MOLECULAR GENETIC DATA IN AML WITH CLINICAL DATA[a]

Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	–5 or del(5q); –7; abn(17p); complex karyotype (≥3 abnormalities)

[a]H Döhner et al: Blood 115:453, 2010.

Abbreviation: ITD, internal tandem duplication.

TABLE 132-3 MOLECULAR PROGNOSTIC MARKERS IN AML

Gene Symbol	Gene Location	Prognostic Impact
Genes Included in the WHO Classification and ELN Reporting System		
NPM1 mutations	5q35.1	Favorable
CEBPA mutations	19q13.1	Favorable
FLT3-ITD	13q12	Adverse
Genes Encoding Receptor Tyrosine Kinases		
KIT mutation	4q12	Adverse
FLT3-TKD	13q12	Adverse
Genes Encoding Transcription Factors		
RUNX1 mutations	21q22.12	Adverse
WT1 mutations	11p13	Adverse
Genes Encoding Epigenetic Modifiers		
ASXL1 mutations	20q11.21	Adverse
DNMT3A mutations	2p23.3	Adverse
IDH mutations (*IDH1* and *IDH2*)	2q34 & 15q26.1	Adverse
MLL-PTD	11q23	Adverse
TET2 mutations	4q24	Adverse
Deregulated Genes		
BAALC overexpression	8q22.3	Adverse
ERG overexpression	21q22.3	Adverse
MN1 overexpression	22q12.1	Adverse
EVI1 overexpression	3q26.2	Adverse
Deregulated MicroRNAs		
miR-155 overexpression	21q21.3	Adverse
miR-3151 overexpression	8q22.3	Adverse
miR-181a overexpression	1q32.1 and 9q33.3	Favorable

Abbreviations: AML, acute myeloid leukemia; ELN, European LeukemiaNet; ITD, internal tandem duplication; PTD, partial tandem duplication; TKD, tyrosine kinase domain; WHO, World Health Organization.