

Annals of Leukemia Research

Review Article

Epigenetic Regulators and Response to Hypomethylating Agents in Higher-Risk Myelodysplastic Syndromes

Kristjan Tamme^{1*}, Franziska Vogel² and Wouter Maes³

¹Department of Medical Oncology, Tallinn University of Technology, Tallinn, Estonia

²Department of Bioinformatics, Charite University Medicine Berlin, Berlin, Germany

³Department of Cytogenetics, KU Leuven, Leuven, Belgium

*Address for Correspondence: Kristjan Tamme, Department of Medical Oncology, Tallinn University of Technology, Tallinn, Estonia

Received: 21 January 2026; Accepted: 12 April 2026; Published: 26 July 2026

Citation of this article: Tamme, K., Vogel, F., Maes, W. (2026) Epigenetic Regulators and Response to Hypomethylating Agents in Higher-Risk Myelodysplastic Syndromes. *Ann Leuk Res*, 7(1): 04-06. doi: 10.5281/zenodo.22247708

Copyright: © 2026 Kristjan Tamme, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Summary

Fewer than half of patients respond to hypomethylating agents, and sequencing has been expected to identify which. It has, but not in the way the field assumed: the mutations that predict response are not the mutations that predict survival, and treating the two questions as one produces a marker that answers neither.

Objectives: To review the published evidence on somatic mutations in epigenetic regulators as predictors of response to hypomethylating agents in higher-risk myelodysplastic syndromes: which mutations predict response, which predict survival, how the two differ, and how the apparent signal depends on how variants are counted.

Material and Methods: Narrative review of sequencing cohorts, randomised trials, meta-analyses and mechanistic work indexed in PubMed and the major haematology journals. Studies were eligible if they reported the association between somatic mutation and response or survival after hypomethylating agent treatment in a defined myelodysplastic syndrome population. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: Sequencing 40 recurrently mutated genes in 213 patients before treatment found that 94 per cent carried at least one driver mutation, most frequently ASXL1 in 46 per cent, TET2 in 27, RUNX1 in 20, TP53 in 18 and DNMT3A in 16 per cent. The overall response rate was 47 per cent and did not differ between azacitidine and decitabine. Clonal TET2 mutation predicted response with an odds ratio of 1.99 ($p = 0.036$) when variants below 10 per cent allele fraction were treated as wild-type, and response was highest in TET2-mutant patients without clonal ASXL1 mutation at an odds ratio of 3.65 ($p = 0.009$). When all variants were counted regardless of allele fraction, TET2 alone ceased to predict response. Mutations of TP53 (HR 2.01, $p = 0.002$) and PTPN11 (HR 3.26, $p = 0.006$) were associated with shorter overall survival but not with drug response.

Conclusion: Response and survival are governed by different mutations, and a patient with TP53 mutation may respond while still dying early. The TET2 signal exists only under a clonality filter, which makes the predictor a variant allele frequency threshold as much as a gene.

Abbreviations: MDS – Myelodysplastic Syndrome, HMA – Hypomethylating Agent, AZA – Azacitidine, DEC – Decitabine, AML – Acute Myeloid Leukaemia, VAF – Variant Allele Frequency, OR – Odds Ratio, HR – Hazard Ratio, WT – Wild-Type, IPSS-R – Revised International Prognostic Scoring System, IPSS-M – Molecular International Prognostic Scoring System, CR – Complete Remission.

Keywords: Myelodysplastic Syndrome; Hypomethylating Agents; TET2; ASXL1; Response Prediction

Introduction

Hypomethylating agents are the standard of care for higher-risk myelodysplastic syndromes and also relieve cytopenia in lower-risk disease [1,2]. Azacitidine prolongs survival against conventional care regimens in higher-risk patients [3], and the two available agents have not been shown to differ from one another in response rate [4].

Only a minority of patients respond, and strong predictors of response have been unknown [4,5]. That gap matters clinically because response takes several cycles to declare itself, during which a non-responding patient is exposed to toxicity and to the opportunity cost of an

alternative approach [1,6].

Myelodysplastic syndromes are among the most extensively sequenced haematological malignancies, with recurrent mutations in splicing factors, epigenetic regulators, transcription factors and signalling genes all characterised [7,8,9]. The epigenetic regulators attracted particular attention here because the drugs act on DNA methylation, making a mechanistic link plausible [4,10].

This review sets out which mutations predict response, which predict survival, why those are different questions, and how sensitive the reported associations are to the way variants are counted.

Material and Methods

Search strategy: PubMed and the archives of the major haematology journals were searched for studies of mutation and hypomethylating agent response. Search terms combined myelodysplastic syndrome with hypomethylating agent, azacitidine, decitabine, TET2, ASXL1, DNMT3A, TP53, response prediction and variant allele frequency. Reference lists of retrieved sequencing cohorts and meta-analyses were screened by hand.

Eligibility: Studies were included if they reported the association between somatic mutation and response or survival after hypomethylating agent treatment in a defined myelodysplastic syndrome population, or established the classification and prognostic frameworks against which those associations are read. Studies including acute myeloid leukaemia are cited where identified as such.

Data extraction and handling: Cohort size, sequencing panel, variant allele frequency threshold, response criteria and reported effect estimates were extracted as published. The allele frequency threshold is stated alongside every association, because the principal finding of this review is that several reported associations appear or disappear according to that threshold. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What is mutated: Tumour DNA from 213 patients collected before treatment was sequenced across 40 genes previously shown to be somatically mutated in this disease, covering splicing factors, kinase signalling genes, transcription factors and epigenetic regulators including TET2, DNMT3A, ASXL1 and EZH2 [4]. Mutations were identified in 39 of the 40 genes, and 94 per cent of patients carried at least one [4].

The most frequently mutated genes were ASXL1 in 46 per cent, TET2 in 27, RUNX1 in 20, TP53 in 18 and DNMT3A in 16 per cent, followed by the splicing factor genes (Figure 1) [4]. Overall response was 47 per cent and did not differ between azacitidine and decitabine

[4]. The cohort was representative of trial populations in predicted disease risk and severity of cytopenias [4].

The panel composition matters for interpreting these frequencies. A study covering 40 genes cannot report mutations outside them, and later analyses using broader panels have described a wider landscape of genetic lesions in this disease [9]. Frequencies quoted here therefore describe what that panel could see rather than the full mutational burden.

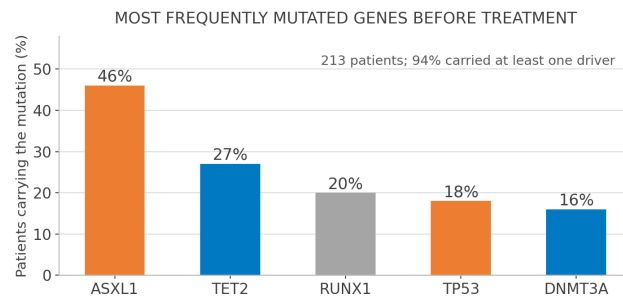


Figure 1: Most frequently mutated genes among 213 patients sequenced before treatment [4]

What predicts response: Clonal TET2 mutation predicted response with an odds ratio of 1.99 ($p = 0.036$), where clonality was defined by treating subclones with allele fraction below 10 per cent as wild-type [4]. Response rates were highest in TET2-mutant patients without clonal ASXL1 mutation, at an odds ratio of 3.65 ($p = 0.009$) (Figure 2) [4].

A systematic review and meta-analysis subsequently confirmed the significant role of TET2 mutation in azacitidine response, and identified the number of driver mutations as an additional determinant, with patients carrying three or more showing significantly lower response rates [11]. Mutations in the DNA methylation pathway and mutation burden therefore both contribute [11].

No mutated gene was significantly associated with decreased response in the primary analysis [4]. Mutations of CBL, often at low allele fraction, were associated with a lower response rate when all variants were counted (HR 0.17, 95% CI 0.04-0.79), but not when low-fraction variants were excluded [4], which is the same threshold sensitivity discussed below.

The direction of the ASXL1 effect deserves precision. ASXL1 mutation was not itself associated with reduced response in the primary analysis; rather, its presence removed the benefit conferred by clonal TET2 mutation [4]. The interaction is between the two genes rather than an independent adverse effect of one, which is why the combined category outperforms either considered alone.

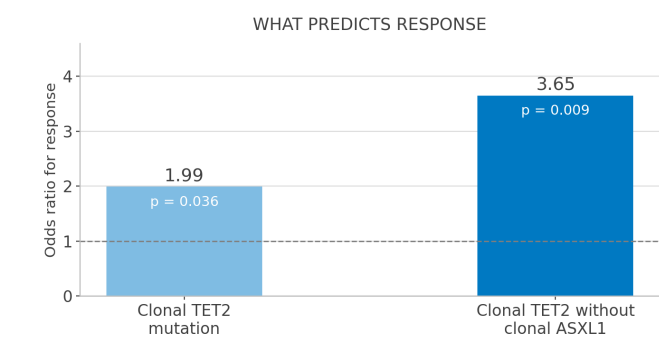


Figure 2: Odds ratios for response by TET2 and ASXL1 status [4]

Study	n	Question	Principal reported finding
Fenaux et al. 2009 [3]	Randomised	Efficacy	Azacitidine prolongs survival in higher-risk disease
Bejar et al. 2011 [7]	Cohort	Prognosis	Point mutations carry independent prognostic effect
Bejar et al. 2014 [4]	213	Response	Clonal TET2 predicts response; TP53 predicts survival
Welch et al. 2016 [12]	Cohort	Decitabine	Higher response with TP53 mutation on 10-day schedule
Meta-analysis 2017 [11]	Pooled	Response	TET2 role confirmed; driver number matters
Bernard et al. 2022 [13]	Cohort	Prognosis	Molecular prognostic scoring system derived

Table 1: Principal studies reviewed, with the question addressed and the finding as reported by the original investigators

What predicts survival, and does not predict response: Mutations of TP53 were associated with shorter overall survival (HR 2.01, p = 0.002), as were the rarer mutations of PTPN11 (HR 3.26, p = 0.006), and neither predicted drug response (Figure 3) [4]. Survival among patients with complex karyotype was strongly associated with TP53 mutation status specifically [4].

This is the dissociation at the centre of the field's difficulty. A patient carrying a TP53 mutation is no less likely to respond to a hypomethylating agent than one without, and is nonetheless substantially more likely to die [4,14]. Response and survival are answering different questions, and a single molecular marker that conflates them will mislead in one direction or the other.

TP53-mutated disease has since been recognised as a distinct entity in current classifications rather than a risk modifier [15,16], with median survival of five to ten months and reduced response to induction chemotherapy, hypomethylating agents and

venetoclax-based regimens alike [14,17]. The molecular prognostic scoring system incorporates mutation status into survival prediction directly [13].

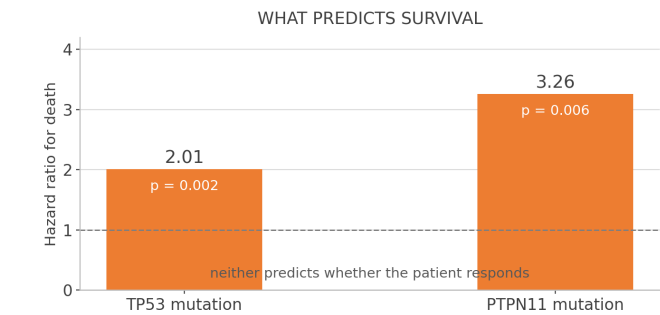


Figure 3: Hazard ratios for death by TP53 and PTPN11 status, neither predicting response [4]

The signal depends on how variants are counted: The TET2 finding was obtained by treating variants below 10 per cent allele fraction as wild-type, on the reasoning that subclones at that level would not have been detected by earlier sequencing methods [4]. When all mutations were considered regardless of allele fraction, TET2 mutation alone was no longer predictive of response (HR 1.58, 95% CI 0.86-2.89) (Figure 4) [4].

The combined category survived the change: TET2-mutant, ASXL1-wild-type patients retained a significant association with increased response even when all variants were counted (HR 2.37, 95% CI 1.00-5.58), though with a lower bound touching unity [4]. The predictor is therefore not simply TET2 mutation but clonal TET2 mutation in the absence of clonal ASXL1 mutation.

Because the association appears and disappears with the threshold, the clonality filter is part of the biomarker rather than a preprocessing step. Any laboratory applying a different sensitivity or a different cutoff is testing a different marker, and recommendations for sequencing studies in this disease address exactly this kind of methodological variation [18].

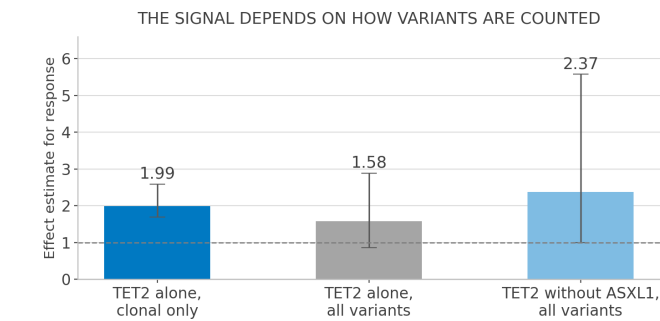


Figure 4: How the TET2 association changes with the variant counting rule [4]

Mutation	Predicts response?	Predicts survival?
Clonal TET2	Yes, OR 1.99	Not reported as independent [4]
Clonal TET2 without clonal ASXL1	Yes, OR 3.65	Not reported [4]
TET2 counting all variants	No	Not reported [4]
TP53	No	Yes, HR 2.01 [4,14]
PTPN11	No	Yes, HR 3.26 [4]
Three or more drivers	Lower response	Not separately reported [11]

Table 2: Which mutations answer which question

Corroboration and contradiction across cohorts: The TET2 finding did not arise in isolation. An earlier French analysis reported that TET2 mutation affected response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukaemia [21], and a separate study examined the impact of molecular mutations on response to methyltransferase inhibitors across myelodysplasia and related neoplasms [22]. Later work found somatic mutations predictive of outcome after hypomethylating therapy in an independent cohort [24].

Attempts to build predictive models from these signals have followed. Genomic biomarkers of resistance have been derived using machine learning approaches [25], and integrative genomics has been applied to identify the molecular basis of resistance rather than only its correlates [26]. Neither has produced a marker in routine use.

TP53 mutation in this disease correlates strongly with chromosome 5 abnormalities and with adverse prognosis [23], which is consistent with the finding that survival among complex karyotype patients tracked TP53 status specifically [4]. Prognostic scoring systems have accordingly moved from morphology and cytogenetics [20] toward molecular variables [13].

Why TET2 loss might sensitise: The association has a mechanistic candidate. TET2 encodes an enzyme that hydroxylates 5-methylcytosine, and its impairment in myeloid cancers alters the methylation landscape directly [28]. Loss increases haematopoietic stem cell self-renewal and drives myeloid transformation in murine models [29], so a TET2-mutant clone is plausibly more dependent on aberrant methylation than a wild-type one and correspondingly more sensitive to its reversal.

ASXL1 acts through a different route, promoting transformation by loss of polycomb-mediated gene repression [30], which offers a reason why the combination behaves differently from either alone. Myelodysplastic syndrome and secondary acute myeloid leukaemia display distinctive patterns and abundance of aberrant methylation [27], which is the substrate these agents act on.

Agent and schedule	Population	Established by
Azacitidine, 7 days	Higher-risk disease	Randomised survival benefit [3,31]
Decitabine, 3 days	Advanced disease	Randomised outcome improvement [32]
Decitabine, 5 days	Advanced disease	Multicentre evaluation [33]
Oral azacitidine	Lower-risk, transfusion dependent	Randomised placebo-controlled trial [34]

Table 3: Hypomethylating agent schedules and the evidence establishing each

What follows treatment failure: The clinical urgency of prediction comes from what happens when these agents stop working. Outcome after azacitidine failure in higher-risk disease is poor [6], and management at that point has been addressed as a distinct problem [2,35]. A marker identifying non-responders before several cycles have elapsed would change the sequence in which options are offered rather than merely the prognosis given [5,25].

Discussion

Two findings sit at the centre of this literature and they are frequently conflated. Clonal TET2 mutation, particularly without clonal ASXL1, predicts whether a patient responds [4,11]. TP53 and PTPN11 mutations predict how long a patient survives and say nothing about whether they respond [4]. These are different clinical questions and they have different molecular answers.

The practical consequence is specific. A TP53-mutated patient should not be denied a hypomethylating agent on the grounds that they will not respond, because the data do not support that inference [4]. They should be counselled that response, if achieved, is unlikely to translate into prolonged survival, and alternative strategies should be explored in parallel rather than sequentially [14,17].

Why the counting rule is part of the biomarker

A biomarker that is significant under one variant allele frequency threshold and not under another is not fully specified by naming the gene [4]. TET2 mutation predicted response at a 10 per cent cutoff and did not predict it when all variants were counted, and the CBL association ran in the opposite direction under the same two rules [4].

This is the same difficulty that has affected other quantitative molecular markers, where a measurement with a sound biological basis proves unusable because laboratories applying different assays produce different values [18,19]. Reporting the sequencing depth, the panel and the allele frequency cutoff alongside the result is what would make these findings transferable.

The contradictory TP53 signal

One analysis found higher response rates among patients with TP53 mutation than without, which appears to contradict the finding that TP53 does not predict response [12]. Two features of that study explain the difference: 77 per cent of the patients were diagnosed with acute myeloid leukaemia rather than myelodysplastic syndrome, and the regimen was a ten-day course of decitabine, which is unusual in this disease [11,12].

The reconciliation offered in the literature is that available data support treating patients with TP53 or EZH2 mutation with hypomethylating agents, while their expected low survival argues for exploring other strategies in this group [11]. Response and survival again pull in different directions, and both are worth stating to a patient.

Study limitations

The limitations belong to the underlying literature. The principal cohort comprises 213 patients across two treatment sites, and several reported associations rest on small mutated subgroups such as PTPN11 at 4 per cent and CBL at low allele fraction [4]. Response criteria differ between studies and between the two agents' registration trials [1,3]. The sequencing panel covered 40 genes, so mutations outside it could not contribute and later studies using broader panels are not directly comparable [4,7,13]. Analyses combining myelodysplastic syndrome with acute myeloid leukaemia populations report findings that may not transfer [11,12]. And classification criteria for the disease and for TP53-mutated entities changed across the period covered, so the populations differ between studies [15,16].

Two gaps deserve naming. No trial has randomised treatment selection by TET2 and ASXL1 status, so the predictive value remains observational [4,11]. And no study reviewed here establishes whether an alternative strategy improves survival in TP53-mutated patients who do respond, which is the group the response and survival dissociation identifies most sharply [4,14].

Conclusion

Fewer than half of patients with myelodysplastic syndrome respond to hypomethylating agents, at 47 per cent with no difference between azacitidine and decitabine. Clonal TET2 mutation predicts response with an odds ratio of 1.99, rising to 3.65 in the absence of clonal ASXL1 mutation, and three or more driver mutations predicts lower response. Mutations of TP53 and PTPN11 predict shorter survival, at hazard ratios of 2.01 and 3.26, and predict nothing about response. Response and survival are separate questions with separate molecular answers, and a TP53-mutated patient may respond and still die early. The TET2 association exists only when variants below 10 per cent allele fraction are excluded, which makes the counting

rule part of the biomarker rather than a technicality, and means the result does not transfer between laboratories applying different thresholds.

Acknowledgements

The authors thank the sequencing cohorts and trial groups whose published analyses form the substance of this article.

Funding

No dedicated funding from public, commercial or charitable sources supported this review.

Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

References

1. Fenaux, P., Haase, D., Santini, V., Sanz, GF., Platzbecker, U., Mey, U. (2021) Myelodysplastic syndromes: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 32(2): 142-156.
2. Santini, V. (2019) How I treat MDS after hypomethylating agent failure. *Blood*, 133(6): 521-529.
3. Fenaux, P., Mufti, GJ., Hellstrom-Lindberg, E., Santini, V., Finelli, C., Giagounidis, A., et al. (2009) Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol*, 10(3): 223-232.
4. Bejar, R., Lord, A., Stevenson, K., Bar-Natan, M., Pérez-Ladaga, A., Zaneveld, J., et al. (2014) TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. *Blood*, 124(17): 2705-2712.
5. Lee, EJ., Zeidan, AM. (2015) Genome sequencing in myelodysplastic syndromes: can molecular mutations predict benefit from hypomethylating agent therapy? *Expert Rev Hematol*, 8(2): 155-158.
6. Prebet, T., Gore, SD., Esterni, B., Gardin, C., Itzykson, R., Thepot, S., et al. (2011) Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. *J Clin Oncol*, 29(24): 3322-3327.
7. Bejar, R., Stevenson, K., Abdel-Wahab, O., Galili, N., Nilsson, B., Garcia-Manero, G., et al. (2011) Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med*, 364(26): 2496-2506.
8. Papaemmanuil, E., Gerstung, M., Malcovati, L., Tauro, S., Gundem, G., Van Loo, P., et al. (2013) Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood*, 122(22): 3616-3627.
9. Haferlach, T., Nagata, Y., Grossmann, V., Okuno, Y., Bacher, U., Nagae, G., et al. (2014) Landscape of genetic lesions in 944 patients with

- myelodysplastic syndromes. *Leukemia*, 28(2): 241-247.
10. Sperling, AS., Gibson, CJ., Ebert, BL. (2017) The genetics of myelodysplastic syndrome: from clonal haematopoiesis to secondary leukaemia. *Nat Rev Cancer*, 17(1): 5-19.
 11. Tobiasson, M., McLornan, DP., Karimi, M., Dimitriou, M., Jansson, M., Ben Azenkoud, A., et al. (2016) Mutations in the DNA methylation pathway and number of driver mutations predict response to azacitidine in myelodysplastic syndromes. *Oncotarget*, 7(16): 22103-22115.
 12. Welch, JS., Petti, AA., Miller, CA., Fronick, CC., O'Laughlin, M., Fulton, RS., et al. (2016) TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med*, 375(21): 2023-2036.
 13. Bernard, E., Tuechler, H., Greenberg, PL., Hasserjian, RP., Arango Ossa, JE., Nannya, Y., et al. (2022) Molecular international prognostic scoring system for myelodysplastic syndromes. *NEJM Evid*, 1(7): EVIDoa2200008.
 14. Daver, NG., Maiti, A., Kadia, TM., Vyas, P., Majeti, R., Wei, AH., et al. (2022) TP53-mutated myelodysplastic syndrome and acute myeloid leukemia: biology, current therapy, and future directions. *Cancer Discov*, 12(11): 2516-2529.
 15. Khoury, JD., Solary, E., Ablu, O., Akkari, Y., Alaggio, R., Apperley, JF., et al. (2022) The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*, 36(7): 1703-1719.
 16. Arber, DA., Orazi, A., Hasserjian, RP., Borowitz, MJ., Calvo, KR., Kvasnicka, HM., et al. (2022) International consensus classification of myeloid neoplasms and acute leukemias. *Blood*, 140(11): 1200-1228.
 17. Kantarjian, H., Kadia, T., DiNardo, C., Daver, N., Borthakur, G., Jabbour, E., et al. (2021) Acute myeloid leukemia: current progress and future directions. *Blood Cancer J*, 11: 41.
 18. Cazzola, M., Della Porta, MG., Malcovati, L. (2013) The genetic basis of myelodysplasia and its clinical relevance. *Blood*, 122(25): 4021-4034.
 19. Malcikova, J., Tausch, E., Rossi, D., Sutton, LA., Soussi, T., Zenz, T., et al. (2018) ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia: update on methodological approaches and results interpretation. *Leukemia*, 32(5): 1070-1080.
 20. Greenberg, PL., Tuechler, H., Schanz, J., Sanz, G., Garcia-Manero, G., Solé, F., et al. (2012) Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*, 120(12): 2454-2465.
 21. Itzykson, R., Kosmider, O., Cluzeau, T., Mansat-De Mas, V., Dreyfus, F., Beyne-Rauzy, O., et al. (2011) Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. *Leukemia*, 25(7): 1147-1152.
 22. Traina, F., Visconte, V., Elson, P., Tabarroki, A., Jankowska, AM., Hasrouni, E., et al. (2014) Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms. *Leukemia*, 28(1): 78-87.
 23. Kulasekararaj, AG., Smith, AE., Mian, SA., Mohamedali, AM., Krishnamurthy, P., Lea, NC., et al. (2013) TP53 mutations in myelodysplastic syndrome are strongly correlated with aberrations of chromosome 5, and correlate with adverse prognosis. *Br J Haematol*, 160(5): 660-672.
 24. Jung, SH., Kim, YJ., Yim, SH., Kim, HJ., Kwon, YR., Hur, EH., et al. (2016) Somatic mutations predict outcomes of hypomethylating therapy in patients with myelodysplastic syndrome. *Oncotarget*, 7(35): 55264-55275.
 25. Nazha, A., Sekeres, MA., Bejar, R., Rauh, MJ., Othus, M., Komrokji, RS., et al. (2019) Genomic biomarkers to predict resistance to hypomethylating agents in patients with myelodysplastic syndromes using artificial intelligence. *JCO Precis Oncol*, 3: PO.19.00119.
 26. Unnikrishnan, A., Papaemmanuil, E., Beck, D., Deshpande, NP., Verma, A., Kumari, A., et al. (2017) Integrative genomics identifies the molecular basis of resistance to azacitidine therapy in myelodysplastic syndromes. *Cell Rep*, 20(3): 572-585.
 27. Figueroa, ME., Skrabanek, L., Li, Y., Jiemjit, A., Fandy, TE., Paietta, E., et al. (2009) MDS and secondary AML display unique patterns and abundance of aberrant DNA methylation. *Blood*, 114(16): 3448-3458.
 28. Ko, M., Huang, Y., Jankowska, AM., Pape, UJ., Tahilian, M., Bandukwala, HS., et al. (2010) Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. *Nature*, 468(7325): 839-843.
 29. Moran-Crusio, K., Reavie, L., Shih, A., Abdel-Wahab, O., Ndiaye-Lobry, D., Lobry, C., et al. (2011) Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. *Cancer Cell*, 20(1): 11-24.
 30. Abdel-Wahab, O., Adli, M., LaFave, LM., Gao, J., Hricik, T., Shih, AH., et al. (2012) ASXL1 mutations promote myeloid transformation through loss of PRC2-mediated gene repression. *Cancer Cell*, 22(2): 180-193.
 31. Silverman, LR., Demakos, EP., Peterson, BL., Kornblith, AB., Holland, JC., Odchimar-Reissig, R., et al. (2002) Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the Cancer and Leukemia Group B. *J Clin Oncol*, 20(10): 2429-2440.
 32. Kantarjian, H., Issa, JP., Rosenfeld, CS., Bennett, JM., Albitar, M., DiPersio, J., et al. (2006) Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer*, 106(8): 1794-1803.
 33. Steensma, DP., Baer, MR., Slack, JL., Buckstein, R., Godley, LA., Garcia-Manero, G., et al. (2009) Multicenter study of decitabine administered daily for 5 days for advanced myelodysplastic syndrome. *J Clin Oncol*, 27(23): 3842-3848.
 34. Garcia-Manero, G., Santini, V., Almeida, A., Platzbecker, U., Jonasova, A., Silverman, LR., et al. (2021) Phase III, randomized, placebo-controlled trial of CC-486 with best supportive care in patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk myelodysplastic syndromes. *J Clin Oncol*, 39(13): 1426-1436.
 35. Sekeres, MA., Taylor, J. (2022) Diagnosis and treatment of myelodysplastic syndromes: a review. *JAMA*, 328(9): 872-880.