



Genetics and epigenetics in tumor diagnosis, therapeutics, and prognosis: an editorial

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Cancer is a public health problem globally and is the second-leading cause of death. In the US, it is estimated that there will be ~2,114,850 new cancer patients and 626,140 patient deaths in 2026^[1]. Epigenetics studies the reversible and heritable alterations, including histone modification, DNA methylation, chromatin remodeling, and non-coding RNA, that affect gene function without changing DNA sequence. These alterations could drive cancer development and progression alongside genetic mutations in cancers. Unlike irreversible genetic mutations, these modifications can often be reversed with drugs or are druggable, thus allowing development of novel epigenetic drugs (epidrugs) therapy that reprograms cancer cells back to normal functions. Cancer epigenetics could offer a powerful, non-invasive frontier in oncology for early tumor detection, disease monitoring, risk assessment, precise prognostics, and reversing therapeutic resistance.

TUMOR DETECTION: NON-INVASIVE AND ULTRA-EARLY DIAGNOSIS

Epigenetic alterations, particularly DNA methylation, appear early in carcinogenesis, even earlier than physical lesions detectable by imaging. Because these signatures are stable and detectable in body fluids (blood, urine, stool), they can serve as excellent, non-invasive liquid biopsy markers for early diagnosis, disease monitoring, and screening. Liquid biopsy is a non-invasive and highly sensitive cancer screening approach that detects the methylation patterns of circulating tumor DNA or circulating cell-free DNA (cfDNA) in blood, urine, saliva, or feces. Technologies such as flow cytometry and next-generation sequencing (NGS), mass spectrometry-based approaches, droplet digital PCR (ddPCR), particularly circulating tumor cell analysis (enriched by flow cytometry), cfDNA sequencing, and emerging epigenetic and fragmentomic profiling are in different phases of development that have the potential to revolutionize the approach to detect and treat cancers^[2-4]. Likewise, advances in fragmentomics and histone modification profiling are revealing new



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dimensions of tumor biology that can be captured through liquid biopsy, allowing clinicians to monitor treatment response and measure minimal residual disease (MRD) with unprecedented precision.

Multi-cancer detection (MCD) and Multi-cancer early detection (MCED)

MCD and MCED are new diagnostic tools utilizing epigenomic features to screen for multiple cancers at once, which significantly improve the early detection rate^[5]. Similar to innovative liquid biopsies, MCD/MCED tests can analyze a single blood sample for tumor-derived DNA, RNA, or proteins to detect multiple cancer types simultaneously, often before symptoms appear. These tests aim to improve survival rates by catching cancers earlier, particularly those lacking standard screening methods.

While promising, these tests are not diagnostic and require follow-up confirmation. Currently, there are tests that are still in development or undergoing clinical trials, with some, such as EPISEEK and Galleri® MCED, which is commercially available but has not yet been approved by the U.S. Food and Drug Administration (FDA). EPISEEK is a groundbreaking MCED test that uses a simple blood draw to monitor DNA changes associated with over 60 types of cancer. Galleri® test is used for adults aged 50 and older with an elevated cancer risk^[6].

Examples of tests that are currently in clinical application include the Cologuard and ConfirmMDx. Cologuard is an FDA-approved colorectal cancer screening technology based on fecal DNA methylation. The test can detect aberrantly methylated promoters of genes including Bone Morphogenetic Protein 3 and N-myc Downstream-Regulated Gene 4 (<https://www.cologuard.com/>). Cologuard Plus test was also developed and FDA-approved to reduce false positives. It also scans for mutant KRAS and total human hemoglobin. ConfirmMDx works for prostate cancer at the DNA level to help identify undetected cancers (<https://mdxhealth.com/confirm-mdx-for-patients/>). It uses methylation-specific PCR to detect cancer-associated epigenetic biomarkers, specifically focusing on genes including Adenomatous Polyposis coli, Glutathione S-transferase pi 1, and Ras Association Domain Family Member 1A. ConfirmMDx uses the epigenetic "field effect" or "halo effect" to reduce unnecessary repeat biopsies by up to 30%-40%.

MRD assessment technology

In recent years, the landscape of cancer diagnostics has been fundamentally transformed by the emerging MRD assessment technology. The technology utilizes epigenetic signatures to define tumor subtypes, distinguish benign from malignant tissues, and monitor cancer recurrence.

MRD assessments can be peripheral blood-based, bone marrow-based, and imaging-based techniques. Bone marrow-based next-generation flow cytometry and NGS with a minimum sensitivity of 10^{-5} (1 aberrant cell per 100,000 total cells analyzed) remain the current standard for MRD assessment in cancers, particularly in multiple myeloma (MM)^[2]. Mass spectrometry-based methods, such as intact protein mass spectrometry (MALDI-TOF assays like MASS-FIX and EXENT) and clonotypic peptide mass spectrometry (EasyM and M-Insight), have emerged as highly sensitive peripheral blood-based MRD assessment tools for relatively non-invasive dynamic MRD detection. Newer technologies such as circulating tumor cell analysis using enriched flow cytometry, cfDNA sequencing, ddPCR, and emerging epigenetic and fragmentomic profiling are also under extensive study and have the potential to revolutionize detection and treatment of cancers. Clinical trials exploring the role of MRD in guiding cancer therapy are ongoing and are expected to identify the optimal technique for MRD monitoring in clinical practice.

CANCER TREATMENT: RESTARTING THE CANCER SUPPRESSION SWITCH

Since epigenetic alterations are not permanent modifications to the DNA sequences, they can be druggable, making them a key focus for cancer therapy. The so-called epidrugs aim to reset the gene expression program of tumor cells and restore the activity of tumor suppressor genes or inhibit oncogenes by targeting

Table 1. Epidrugs that are FDA-approved for cancer therapeutics

Drug name	Target	Approved	Year	Approved cancer indication	Reference
Azacitidine (Onureg, Vidaza)	DNA methyltransferase (DNMT)	Yes	2004	Acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), and juvenile myelomonocytic leukemia	[8,9]
Decitabine (Dacogen)	DNMT	Yes	2006	AML, MDS and CMML	[8,9]
Vorinostat (SAHA)	Histone deacetylase (HDAC)	Yes	2006	Cutaneous T-cell lymphoma (CTCL)	[8,9]
Romidepsin (FK288)	HDAC	Yes	2009	CTCL	[8,9]
Belinostat (PXD101)	HDAC	Yes	2014	Peripheral T-cell lymphoma (PTCL)	[8,9]
Panobinostat (LBH589)	HDAC	Yes	2015	Multiple myeloma and CTCL	[8,9]
Tazemetostat (Tazverik)	Histone methyl transferase EZH2	Yes	2020	Epithelioid sarcoma and follicular lymphoma	[8,9]
Enasidenib (IDHIFA)	Metabolic epigenetic regulator (IDH2)	Yes	2017	IDH2-mutant AML	[9]
Ivosidenib (Tibsovo)	Metabolic epigenetic regulator (IDH1)	Yes	2018	IDH1-mutant AML	[9]
Olutasidenib (Rezlidhia)	IDH1	Yes	2022	IDH1-mutant AML	[9]
Ivosidenib/Azacitidine	IDH1/DNMT1	Yes	2022	IDH1-mutated AML	[9]
Voranigo (Vorasidenib)	IDH1/IDH2	Yes	2024	Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation	[10]
Revumenib (Revuforj)	Menin-KMT2A interaction/NPM1 mutation	Yes	2024/2025	Refractory acute leukemia with KMT2A translocations (KMT2Ar) and NPM1 mutation	[11,12]
Ziftomenib (Komzifti)	Menin-NPM1 mutation	Yes	2025	Relapsed or refractory AML with NPM1 mutation	[13]
Dordaviprone (Modeyso)	H3K27M mutation	Yes	2025	A protease activator harboring an H3K27M mutation for various cancers	[14]
Treosulfan (Grafapex)	DNA cross-linking in cancer cells	Yes	2025	In combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation for AML and MDS	[15]

epigenetic marks. Epidrugs include histone deacetylase inhibitors (HDACi), DNA methyltransferase inhibitors (DNMTi), histone methyltransferase inhibitors (HMTi), and bromodomain and extra-terminal motif protein inhibitors (BETi)^[7]. By inhibiting "writers" (such as DNMTs), "erasers" (such as HDACs), or "readers" (such as BET proteins), abnormally silenced tumor suppressor genes can be reactivated, or oncogenes can be inactivated.

Epidrugs

Epidrugs are a class of therapeutic agents that modify the structure of DNA and chromatin to reverse abnormal gene expression without altering the underlying DNA sequences. Primarily used in cancer treatment to reactivate silenced tumor suppressor genes, these compounds target enzymes like histone deacetylases (HDACs) and DNA methyltransferases (DNMTs). Table 1 shows epigenetic-based drugs that are approved by the FDA. These drugs in the treatment of cancer were also recently summarized by Suraweera *et al.*^[8] and Scandolaro *et al.*^[9], and we also updated the newest information.

Currently, there are not many FDA-approved epidrugs. Although Treosulfan belongs to the DNA alkylating agents and inhibits tumor cells by directly modifying the DNA structure, this kind of drug could be classified as genetic/epigenetic modification therapy.

Additionally, since chemotherapy faces drug resistance, natural small molecules or compounds such as Isoflavonoids can be an interesting alternative in cancer therapeutics^[16,17]. Studies should investigate the potential of natural and synthetic compounds as anti-cancer agents including epidrugs^[18-20].

Combinational therapy and reversal of drug resistance

Furthermore, synergistic effects are provided for therapy and reversal of drug resistance. Epidrugs are often used in combination with chemotherapy or immunotherapy to activate the antitumor immune response by inducing a "viral mimicry" response or to make drug-resistant cells sensitive to traditional therapies again. For example, DNMTi can enhance tumor immunogenicity by inducing a "viral mimicry" effect (activating endogenous retroviruses), thereby improving the efficacy of PD-1/PD-L1 inhibitors.

Epigenetic interventions can also reverse cancer drug resistance by altering the epigenetic landscape (episensitization), and thus restoring sensitivity to conventional chemo- or endocrine therapies. In breast cancer, epigenetic interventions can resensitize tumor cells that have developed resistance to conventional chemotherapy or endocrine therapy. For example, HDACi combined with tamoxifen can induce apoptosis in drug-resistant cells in breast cancer^[21].

Challenges in solid tumors

While effective in hematological malignancies, targeting epigenetics in solid tumors faces challenges such as poor drug delivery, resistance/off-target effects, high cellular heterogeneity, and the need for more specific predictive biomarkers.

PROGNOSTIC ASSESSMENT: ACCURATE PREDICTION OF RISK AND EFFICACY

Prognostics is the clinical assessment of a patient's treatment outcomes, including the probability of cancer progression, recurrence, or survival. Epigenetic markers can more accurately predict a patient's cancer progression, therapy response, survival and relapse risk than traditional staging^[7].

For example, O⁶-methylguanine-DNA methyltransferase (MGMT) promoter methylation acts as a critical biomarker in GBM. Specifically, silencing MGMT gene due to promoter methylation leads to decreased DNA repair capacity, enhanced sensitivity to temozolomide (TMZ) chemotherapy, and results in improved overall survival^[22]. Thus, MGMT promoter methylation serves as a key predictor of response to TMZ chemotherapy in GBM.

Clinically, Graded Prognostic Assessment (GPA) for brain metastases^[23] or Palliative Prognostic Score (PaP)^[24] are validated tools which assign numerical risk scores based on factors such as functional status (Karnofsky Performance score) and disease extent. The GPA is used to estimate survival and guide treatment for patients with brain metastases, while the PaP is used to predict 30-day survival in advanced cancer patients.

CONCLUSION AND PERSPECTIVES

Multi-omics integration, computational models, and artificial intelligence (AI) contribute to the development of novel strategies for early cancer detection, risk stratification, MRD monitoring, and precise prognostics. Computational approaches are revolutionizing the field, with deep learning frameworks now capable of predicting metastatic potential from primary tumor methylation data, while AI-driven deconvolution techniques enable the dissection of tumor methylation profiles to uncover the immune and stromal components of the tumor microenvironment, which is key to predicting treatment response. cfDNA methylation signatures have emerged as highly sensitive biomarkers for MCED offering a promising route

for non-invasive screening across multiple tumor types. Similarly, advances in fragmentomics and histone modification profiling are revealing new dimensions of tumor biology that can be performed through liquid biopsy, allowing clinicians to monitor treatment response and detect MRD with unprecedented precision. Cell-free chromatin state tracing (cf-EpiTracing) may provide early diagnosis, molecular subtyping and prognostic prediction by revealing disease origin and therapy responses^[25].

CRISPR-based epigenome editing will provide a powerful experimental toolkit to validate candidate regulatory regions and epigenetic drivers identified in large-scale datasets. Tang *et al.*^[26] systematically reviewed the advances using CRISPR-based molecular biosensing for pathogen detection and early tumor screening. They summarized the technological evolution of device integration, including automated and closed microfluidics to portable systems to achieve point-of-care testing.

Mapping the epigenetic regulatory networks that drive cancer initiation, progression, and therapy resistance remains a critical challenge. In gastrointestinal cancer, Huang *et al.*^[27] systematically illustrated the epigenetic dysregulation for providing hints in clinical translation. G-quadruplexes (G4s) are non-canonical secondary structures formed by guanine-rich DNA or RNA strands by Hoogsteen hydrogen bonds that help control gene replication, transcription, and RNA translation. DHX36, a member of the DEAD/H box superfamily, is a main helicase that unwinds G4s of target genes^[28,29]. Abnormal G4 regulation by helicases should be linked to cancer pathways and progression epigenetically, making them targets for new diagnostics, prognostics, and treatments^[30,31]. The DHX36-m6A-G4 axis might play roles in health and disease in an epigenetic way^[31,32].

Single-cell multi-omics (such as scRNA-seq + scATAC-seq) combined with bulk data will dissect the intratumoral heterogeneity and identify epigenetically distinct cell states. Li *et al.*^[33] reviewed precision management in chronic myeloid leukemia by single-cell sequencing. Furthermore, advanced techniques like ATAC-seq and ChIPmentation allow for rapid assessment of chromatin accessibility, providing high-precision, personalized diagnostics. Emerging technologies such as third-generation sequencing and spatial epigenomics now enable direct and spatial measurements of DNA methylation and chromatin accessibility, opening new possibilities for correlating epigenetic signatures with tissue architecture.

The field of pharmacoepigenomics is rapidly advancing, leveraging epigenetic markers to predict response to targeted epigenetic therapies and guide combination treatment strategies. Computational epigenetics can accelerate the identification of new therapeutic candidates by exploiting known epigenetic signatures and drug-epigenome interactions.

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Fu J is a Section Editor of the *Journal of Translational Genetics and Genomics* and also serves as a Guest Editor for the Special Issue "Power of Epigenetics in Tumor Detection, Treatment, and Prognosis", Fu J was not involved in any steps of editorial processing, notably including reviewers' selection, manuscript handling and decision making. Wu RC declares that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

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Not applicable.

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REFERENCES

1. Siegel RL, Kratzer TB, Wagle NS, Sung H, Jemal A. Cancer statistics, 2026. *CA Cancer J Clin.* 2026;76:e70043. DOI PubMed PMC
2. Mohan Lal B, Kumar SK. New approaches for measurable residual disease assessment in multiple myeloma: integrating NGS, mass spectrometry, and next-generation flow cytometry to monitor treatment response. *Curr Hematol Malig Rep.* 2026;21:4. DOI PubMed
3. Park M, Lim DJ, Kim H, et al. Complementary roles of next-generation flow and next-generation sequencing for measurable residual disease assessment in multiple myeloma. *J Korean Med Sci.* 2026;41:e5. DOI PubMed PMC
4. Lin X, Liu B, Wu J, et al. Circulating tumor DNA in breast cancer: from technological foundation to clinical implementation. *Cancer Treat Rev.* 2026;144:103108. DOI
5. Kahwati LC, Avenarius M, Brouwer L, et al. Multicancer detection tests for screening: a systematic review. *Ann Intern Med.* 2025;178:1591-604. DOI
6. Schrag D, Beer TM, McDonnell CH, et al. Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study. *Lancet.* 2023;402:1251-60. DOI PubMed PMC
7. Oliver J, Garcia-Aranda M, Chaves P, et al. Emerging noninvasive methylation biomarkers of cancer prognosis and drug response prediction. *Semin Cancer Biol.* 2022;83:584-95. DOI
8. Suraweera A, O'byrne KJ, Richard DJ. Epigenetic drugs in cancer therapy. *Cancer Metastasis Rev.* 2025;44:37. DOI PubMed PMC
9. Scandolaria TB, Siqueira IVM, Ribeiro Pinto LF, Soares-Lima SC. The power and the promise of epigenetic drugs in oncology. *Front Genet.* 2026;16:1622115. DOI PubMed PMC
10. Barbato MI, Barone AK, Aungst SL, et al. FDA approval summary: vorasidenib for IDH-mutant grade 2 astrocytoma or oligodendroglioma following surgery. *Clin Cancer Res.* 2025;31:4412-8. DOI PubMed PMC
11. Issa GC, Aldoss I, Dipsio J, et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. *Nature.* 2023;615:920-4. DOI
12. Syed YY. Revumenib: first approval. *Drugs.* 2025;85:577-83. DOI PubMed
13. Chang L, Wang M, Zhang H, et al. Synthesis and clinical application of small-molecule drugs approved by FDA in 2025. *Med Res Rev.* 2026;46:1543-73. DOI
14. Blair HA. Dordaviprone: first approval. *Drugs.* 2025;86:101-9. DOI PubMed
15. Peña M, Lazzari L, Martínez DF, et al. Treosulfan/fludarabine versus thiotepa/busulfan/fludarabine for allogeneic haematopoietic cell transplantation in lymphoma in the post-transplant cyclophosphamide era: AGETH-TC study. *Br J Haematol.* 2026;208:1017-26. DOI
16. De Moraes E Sousa E, Luciano MCDS, De Souza GC, et al. Isoflavonoids and epigenetic modulation: therapeutic insights for cancer treatment. *Chem Biodiversity.* 2026;23:e03446. DOI PubMed PMC
17. Wang Y, Xie Q, Tan H, et al. Targeting cancer epigenetic pathways with small-molecule compounds: Therapeutic efficacy and combination therapies. *Pharmacol Res.* 2021;173:105702. DOI
18. Ashraf W, Ahmad T, Reynold N, et al. Natural and synthetic anticancer epidrugs targeting the epigenetic integrator UHRF1. *Molecules.* 2023;28:5997. DOI PubMed PMC
19. Khan MA, Tania M, Fu J. Epigenetic role of thymoquinone: impact on cellular mechanism and cancer therapeutics. *Drug Discov Today.* 2019;24:2315-22. DOI PubMed
20. Zhang F, Zhang L, Dong Y, et al. ADAM9 in cancer: a comprehensive analysis of mutation, prognostic value, expression and TQFL12-induced inhibition. *J Transl Genet Genom.* 2026;10:140-55. DOI

21. Raha P, Thomas S, Thurn KT, Park J, Munster PN. Combined histone deacetylase inhibition and tamoxifen induces apoptosis in tamoxifen-resistant breast cancer models, by reversing Bcl-2 overexpression. *Breast Cancer Res.* 2015;17:26. DOI PubMed PMC
22. Szyllberg M, Sokal P, Śledzińska P, et al. MGMT promoter methylation as a prognostic factor in primary glioblastoma: a single-institution observational study. *Biomedicines.* 2022;10:2030. DOI PubMed PMC
23. Sperduto PW, De B, Li J, et al. Graded prognostic assessment (GPA) for patients with lung cancer and brain metastases: initial report of the small cell lung cancer GPA and update of the non-small cell lung cancer GPA including the effect of programmed death ligand 1 and other prognostic factors. *Int J Radiat Oncol Biol Phys.* 2022;114:60-74. DOI PubMed PMC
24. Scarpi E, Nanni O, Maltoni M. Development and validation of the PaP score nomogram for terminally ill cancer patients. *Cancers.* 2022;14:2510. DOI PubMed PMC
25. Chen X, Meng X, Zhang W, et al. Cell-free chromatin state tracing reveals disease origin and therapy responses. *Nature.* 2026;653:599-610. DOI PubMed PMC
26. Tang Z, Yan S, Xu S, et al. Advances in CRISPR-based molecular biosensing: from pathogen detection to early tumor screening. *J Transl Genet Genom.* 2026;10:343-68. DOI
27. Huang Z, Ma R, Xiao Z, Zhou X. Epigenetic dysregulation of gastrointestinal tumors. *J Transl Genet Genom.* 2026;10:442-61. DOI
28. Fu JJ, Li LY, Lu GX. Molecular cloning and characterization of human DDX36 and mouse Ddx36 genes, new members of the DEAD/H box superfamily. *Sheng Wu Hua Xue Yu Sheng Wu Wu Li Xue Bao.* 2002;34:655-61. Available from: <https://pubmed.ncbi.nlm.nih.gov/12198572/> [Last accessed on 13 Oct 2026].
29. Chen MC, Tippana R, Demeshkina NA, et al. Structural basis of G-quadruplex unfolding by the DEAH/RHA helicase DHX36. *Nature.* 2018;558:465-9. DOI PubMed PMC
30. Wei C, Xu D, Cheng J, et al. DHX36 plays an oncogenic role in breast cancer progression and invasiveness. *Sci Rep.* 2025;16:1156. DOI PubMed PMC
31. El-Far A, Cheng J, Fu L, et al. Decoding the DHX36-m6A-G4 axis: exploring its role in health and disease through epigenetic and molecular insights. *J Transl Genet Genom.* 2026;10:89-118. DOI
32. Zhang Y, Zhao J, Chen X, et al. DHX36 binding induces RNA structurome remodeling and regulates RNA abundance via m6A reader YTHDF1. *Nat Commun.* 2024;15:9890. DOI PubMed PMC
33. Li X, Chen R, Huang Y, et al. Single-cell sequencing in precision management of chronic myeloid leukemia. *J Transl Genet Genom.* 2026;10:386-400. DOI

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