مجلة العلوم الطبية
Journal of Medical Sciences
Published by Sebha University | Journal homepage: www.sebhau.edu.ly/journal/joms

Nuclear Paraspeckle Assembly Transcript 1 and Wnt-Related Transcripts in Breast, Colorectal, Liver and Lung Adenocarcinoma Cohorts: An Exploratory *In Silico* Analysis

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Keywords:
RNA, Long Noncoding
Wnt Signaling Pathway
Gene Expression Profiling
Computational Biology
Neoplasms
Transcriptome

ABSTRACT

Background: Nuclear paraspeckle assembly transcript 1 (*NEAT1*) has been linked experimentally to Wnt/β-catenin signalling, but findings from independent tumour cohorts vary. This study described *NEAT1* tumour–normal expression and its correlations with selected Wnt-related transcripts in public human cancer cohorts.

Methods: Nine Gene Expression Omnibus (GEO) series covering breast, colorectal, liver and lung adenocarcinoma were reanalysed: eight presumed paired series (159 tumour–normal pairs) and one unpaired liver series (five tumour and five normal samples). Gene-level transcripts-per-million (TPM) values were compared with two-sided Wilcoxon signed-rank or Mann–Whitney U tests. Benjamini–Hochberg (BH) adjustment was applied across the nine *NEAT1* p values. Tumour-only Spearman correlations between *NEAT1* and ten Wnt-related transcripts were examined in four cohorts.

Results: Nominal *NEAT1* differences occurred in breast series GSE233242 (41 pairs; $p = 0.0039$; $q = 0.036$) and liver series GSE140845 (5 versus 5; $p = 0.032$; $q = 0.143$); the latter was confounded by hepatitis C background and small group size. Seven of nine group-mean *NEAT1* estimates were positive (exploratory sign test $p = 0.18$). *MMP7* was nominally higher in three colorectal cohorts and one lung adenocarcinoma cohort ($p < 0.05$). Six of ten within-tumour *NEAT1*–Wnt correlations passed within-cohort correction, in one breast cohort only. In GSE103001, the paired-bootstrap 95% confidence interval for the *NEAT1* log2 ratio was −0.204 to +0.635.

Conclusions: These heterogeneous RNA-level findings do not establish Wnt pathway activity or a causal role for *NEAT1*. Count-based sensitivity analyses, robust paired effect estimates and a formal meta-analysis are still needed before broader conclusions are drawn.

نسخة تجميع البقع النووية المجاورة 1 والنسخ المرتبطة بمسار Wnt في مجموعات بيانات سرطان الثدي والقولون والمستقيم والكبد والسرطان الغدي الرئوي: تحليل حاسوبي استكشافي

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الكلمات المفتاحية:
الرنا الطويل غير المشفر
مسار إشارات Wnt
تحليل التعبير الجيني
البيولوجيا الحاسوبية
الأورام
النسخوم

الملخص

الخلفية: رُبط الرنا الطويل غير المشفر NEAT1 تجريبيًا بمسار إشارات Wnt/β-catenin، غير أن نتائج مجموعات الأورام المستقلة متباينة. هدفت الدراسة إلى وصف تعبير NEAT1 في الورم مقارنة بالنسيج الطبيعي، وارتباطه بنسخ مختارة مرتبطة بمسار Wnt في مجموعات سرطانية بشرية عامة.

الطرائق: أُعيد تحليل تسع سلاسل من قاعدة بيانات GEO تشمل سرطان الثدي والقولون والمستقيم والكبد والسرطان الغدي الرئوي: ثماني سلاسل مزدوجة مفترضة (159 زوجًا ورميًا-طبيعيًا) وسلسلة كبدية غير مزدوجة (خمس عينات ورمية وخمس طبيعية). قورنت قيم النسخ لكل مليون (TPM) على مستوى الجين باختبار ويلكوكسون للرتب المؤشرة أو مان–

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Article history: Received 31 October 2026; Revised 03 November 2026; Accepted 18 November 2026; Published online 20 November 2026
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ويتني U ثنائي الاتجاه. وطُبق تصحيح بنجاميني–هوخبيرغ (BH) على قيم p التسع لـ NEAT1، وفُحصت ارتباطات سبيرمان داخل الأورام بين NEAT1 وعشر نسخ مرتبطة بمسار Wnt في أربع مجموعات.

النتائج: ظهرت فروق اسمية لـ NEAT1 في سلسلة سرطان الثدي GSE233242 (41 زوجًا؛ p = 0.0039؛ q = 0.036) وسلسلة الكبد GSE140845 (5 مقابل 5؛ p = 0.032؛ q = 0.143)، وتأثرت الأخيرة بعدوى التهاب الكبد سي وصغر العينة. وكانت سبعة من تسعة تقديرات لمتوسط NEAT1 موجبة (اختبار الإشارة الاستكشافي p = 0.18). وارتفع MMP7 اسميًا في ثلاث مجموعات قولونية ومجموعة واحدة للسرطان الغدي الرئوي (p < 0.05). واجتاز ستة من عشرة ارتباطات داخل الأورام التصحيحَ في مجموعة ثدي واحدة فقط. وفي GSE103001 امتد فاصل الثقة 95% بإعادة المعاينة المزدوجة لنسبة NEAT1 اللوغاريتمية من −0.204 إلى +0.635.

الاستنتاجات: لا تُثبت هذه النتائج غير المتجانسة على مستوى الرنا نشاط مسار Wnt أو دورًا سببيًا لـ NEAT1. وتلزم تحليلات حساسية قائمة على القراءات الخام، وتقديرات أثر مزدوجة متينة، وتحليل تلوي رسمي قبل استخلاص استنتاجات أوسع.

1. Introduction

Long noncoding RNAs regulate gene expression through several molecular mechanisms. Canonical Wnt/β-catenin signalling contributes to development, homeostasis and cancer phenotypes [1,2]. However, neither a change in pathway-component mRNA nor a correlation with a long noncoding RNA demonstrates pathway activation. Functional readouts require assessment of β-catenin stability, localisation or target-transcription activity.

Nuclear paraspeckle assembly transcript 1 (*NEAT1*) produces distinct isoforms, including non-polyadenylated *NEAT1_2*, which is essential for paraspeckle structure [3]. Earlier colorectal and lung cancer experiments proposed links between *NEAT1* and Wnt regulation [4,5], and similar links have been reported in liver cancer and glioblastoma models [6,7]. Causal effects in selected experimental systems, however, cannot be assumed for bulk human tumour samples. A previous pan-cancer report [8] also supports testing tissue- and cohort-specific expression rather than presuming a universal direction.

This reanalysis adds independent Gene Expression Omnibus (GEO) series, mostly paired comparisons, and separates tumour–normal RNA abundance from within-tumour associations. The Cancer Genome Atlas and Genotype–Tissue Expression resources were not included; consequently, this is neither a comprehensive pan-cancer synthesis nor an external validation study. Differences in library preparation may also alter the relative contribution of *NEAT1_1* and *NEAT1_2* to measured *NEAT1* values.

The objective was to explore whether *NEAT1* is differentially expressed, in either direction, between tumour and comparison tissues in nine selected GEO cohorts, and whether its abundance correlates with a restricted set of Wnt-related transcripts in four within-tumour analyses. The study does not infer functional Wnt activity or clinical prognostic utility.

2. Materials and Methods

2.1. Study design, cohorts and eligibility

This retrospective secondary analysis used GEO series from breast cancer (GSE103001 [9,10], GSE210787 [11,12] and GSE233242 [13,14]), colorectal cancer (GSE104836 [15,16], GSE142279 [17] and GSE50760 [18,19]), hepatocellular carcinoma (HCC; GSE135631 [20] and GSE140845 [21]) and lung adenocarcinoma (GSE87340 [22,23]). Eight comparisons were handled as presumed paired samples (159 pairs in total), and GSE140845 as five tumour versus five independent uninfected normal liver samples. The series were selected from available sample metadata and gene-level expression matrices rather than through a documented systematic search; no reproducible query history or exclusion log is therefore available, and the pairing in GSE210787 could not be independently verified (Supplementary Data S1). Source publications were checked against GEO records where a linked publication existed; series without a published description are cited by accession.

Gene-level transcripts-per-million (TPM) matrices generated by the National Center for Biotechnology Information (NCBI) pipeline against human genome build GRCh38.p13, with Entrez GeneID mapping [24], were analysed in Google Colaboratory (Google LLC, Mountain View, CA, USA). Unnormalised count matrices and FASTQ reads were not analysed, so count-based sensitivity analyses with DESeq2 or edgeR were not performed [25]. Supplementary Data S1 lists all 328 included GSM sample identifiers (159 putative or established tumour–normal pairs, plus 10 independent samples of hepatitis C virus (HCV)-associated HCC and normal liver). Public GEO descriptions document total RNA/rRNA depletion for GSE103001 and GSE135631 and poly(A) enrichment for GSE50760; sequencing protocols are incompletely recorded for the remaining series. These preparations may differ in their sensitivity to *NEAT1* isoforms.

Of the 43 GSE233242 specimen pairs described at accession level, 41 complete pairs were analysed: pair 19 lacks tumour GSM7416151 and pair 22 lacks normal GSM7416157 in the NCBI TPM matrix, and the two remaining unpaired samples were excluded from paired tests. GSE50760 contains 18 primary tumour–normal pairs and 18 metastatic samples, which were excluded from this contrast. GSE87340 represents 27 matched lung adenocarcinoma/normal pairs (54 samples), consistent with GEO metadata. GSE210787 was handled as six putative pairs based on column order, and this pairing

requires external confirmation.

No prospective sample-size calculation was conducted because group sizes were fixed by data availability. Small datasets are underpowered for moderate effects; therefore, a nonsignificant test cannot be taken as evidence that a *NEAT1* difference is absent. Adjacent non-tumour tissues may carry field effects and are not equivalent to healthy donor tissues, especially in hepatitis-associated liver disease. GSE233242 includes 29 luminal A, 3 luminal B, 2 human epidermal growth factor receptor 2 (HER2)-enriched and 9 triple-negative pairs at accession level; subgroup comparisons were not attempted within the 41 complete pairs.

2.2. Transcript targets and correlation analysis

The predefined exploratory RNA panel consisted of *NEAT1* and ten Wnt-related genes (*MMP7*, *CTNNB1*, *GSK3B*, *APC*, *AXIN1*, *LRP6*, *FZD7*, *DVL2*, *MYC* and *CCND1*). Most panel members are pathway components rather than canonical response genes, and *MMP7*, *MYC* and *CCND1* can also be regulated independently of Wnt. This panel is therefore not a validated Wnt pathway-activity score. No *AXIN2*-based signature, gene set variation analysis (GSVA), single-sample gene set enrichment analysis (ssGSEA), tumour purity adjustment or isoform-specific quantification was performed.

Tumour-only Spearman correlations were computed for four cohorts: GSE103001 breast (n = 22 tumours), GSE87340 lung adenocarcinoma (n = 27), GSE135631 liver (n = 15) and GSE142279 colorectal (n = 20). For each cohort, ten *NEAT1*–target rho coefficients, nominal p values and within-cohort Benjamini–Hochberg (BH)-adjusted q values were obtained (40 tests in total; Supplementary Data S2). Approximate 95% confidence intervals (CIs) for rho were derived descriptively by Fisher z-transformation of the rounded coefficients.

2.3. Statistical analysis

Two-sided Wilcoxon signed-rank tests were used for paired GEO comparisons and a two-sided Mann–Whitney U test for the independent GSE140845 groups. Log2 fold-change (log2FC) values were computed as log2[(mean tumour TPM + 10^{-9})/(mean normal TPM + 10^{-9})]. This mean-ratio statistic is sensitive to outliers and to values near zero and is not a paired effect estimate. Exact test settings (handling of ties and zero differences, approximation method), individual medians and interquartile ranges, CIs and software package versions were not recorded in the original outputs. The BH method [26] was applied to the nine *NEAT1* p values, treated as a prespecified single-gene family across cohorts; q denotes the BH-adjusted p value. This is neither a correction across all 99 gene-by-cohort tests nor a count-based differential-expression analysis, and the within-cohort Spearman q values represent separate testing families. In addition, all 99 printed gene-by-cohort p values were adjusted by BH within each gene across the nine cohorts and across the full 99-test family (Supplementary Data S4). Because some p values were printed as 0.000000, 5×10^{-7} was used as a conservative upper bound, and the resulting q values are approximate screening values rather than model-based tests. All human expression findings are exploratory.

3. Results

3.1. *NEAT1* expression in human tumour cohorts

Across the nine human comparisons, two nominal *NEAT1* p values were < 0.05 (Table 1; Fig. 1): GSE233242 (41 complete pairs; group-mean log2FC +0.624; p = 0.003948) and GSE140845 (5 tumours versus 5 independent normal samples; +2.135; p = 0.031746). The corresponding BH-adjusted q values across the nine *NEAT1* p values were approximately 0.0355 and 0.1429, so one of the nine comparisons passed this limited correction. Model-based estimates with 95% CIs were not available for the nine cohorts, and this summary is not a meta-analysis.

Table 1. Human GEO cohorts, group-mean *NEAT1* estimates and BH correction across the nine *NEAT1* p values

GEO series	Cancer	Samples	log2FC	Nominal p	q
GSE103001	Breast, ER+	22 pairs	+0.196	0.702	0.766
GSE210787	Breast	6 putative pairs*	−0.360	0.312	0.539
GSE233242	Breast, mixed	41 pairs	+0.624	0.00395	0.0355
GSE104836	Colorectal	10 pairs	+0.396	0.105	0.317
GSE142279	Colorectal	20 pairs	+0.311	0.33	0.539
GSE50760	Colorectal	18 pairs	−0.027	0.766	0.766
GSE135631	Liver, HBV-related	15 pairs	+0.464	0.359	0.539
GSE140845	Liver, HCV-related	5 T, 5 N (unpaired)	+2.135	0.0318	0.143
GSE87340	Lung adenocarcinoma	27 pairs	+0.098	0.47	0.604

ER+, oestrogen receptor-positive; HBV, hepatitis B virus; HCV, hepatitis C virus; T, tumour; N, normal; log2FC, log2 ratio of group-mean TPM values; p, unadjusted two-sided rank-test p value; q, BH-adjusted p value across the nine *NEAT1* comparisons only. Values are exploratory and are not count-based paired fold-change estimates. *Patient matching between normal and tumour samples in GSE210787 requires confirmation.

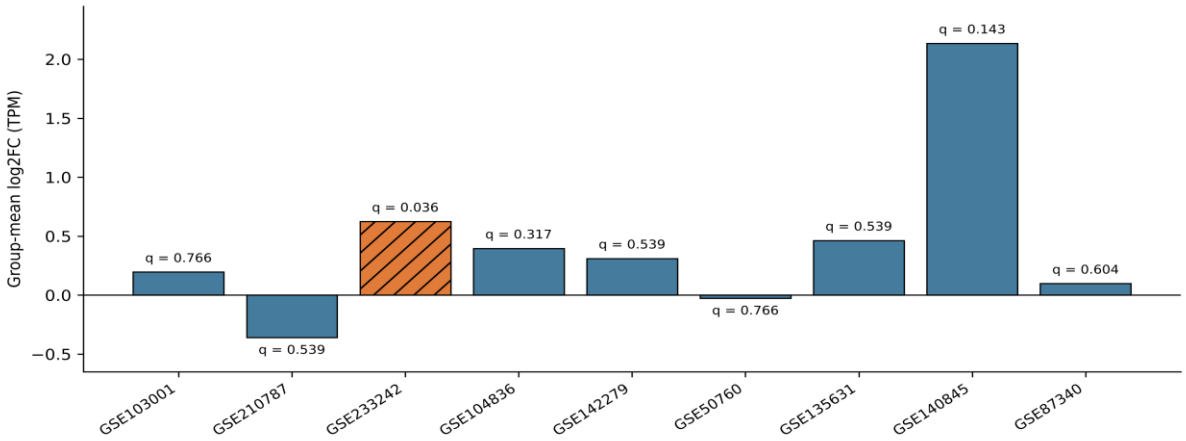

Fig. 1. Group-mean *NEAT1* log2FC across nine human cohorts, with *q* values from BH correction across the nine *NEAT1 p* values. The hatched orange bar indicates $q < 0.05$. Estimates carry no CIs and should not be interpreted as meta-analytic effects.

As a transcript-level positive control, *MMP7* showed nominal tumour-associated elevation in three colorectal comparisons (GSE104836, $p = 0.0020$; GSE142279, $p = 1.9 \times 10^{-6}$; GSE50760, $p = 7.6 \times 10^{-6}$) and in the lung adenocarcinoma cohort (GSE87340, $p = 2.0 \times 10^{-6}$) (Fig. 2). These Wilcoxon-test results are not formal measures of Wnt pathway activation, and the large group-mean fold changes require recomputation with a robust pseudocount and paired effect estimator before they are treated as effect sizes. *NEAT1* was not nominally different in these four cohorts, and the tumour–normal contrasts established no direct association between *NEAT1* and *MMP7*. A W statistic of 0 at the exact-test floor in the 10-, 20- and 18-pair colorectal cohorts is consistent with positive paired *MMP7* differences in every pair, although this was not verified against sample-level data.

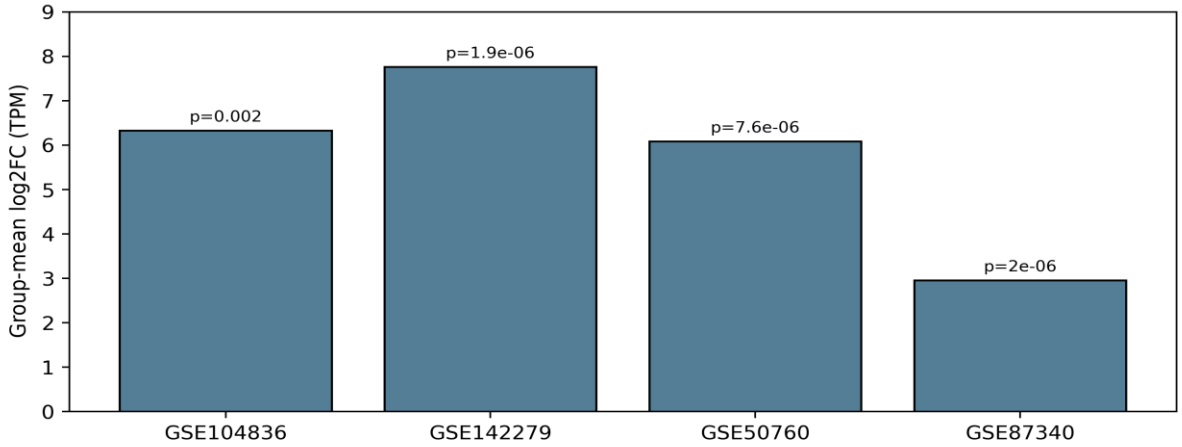

Fig. 2. Group-mean *MMP7* log2FC in three colorectal cohorts and one lung adenocarcinoma cohort, with nominal *p* values. Group-mean ratios are sensitive to low TPM values, and the figure is not a measure of Wnt activity.

3.2. Tumour-only correlations

All 40 tumour-only *NEAT1*–Wnt-panel Spearman coefficients, with nominal *p* and within-cohort BH-adjusted *q* values, are given in Supplementary Data S2 and summarised in Table 2. Six of ten associations in GSE103001 passed $q < 0.05$: *GSK3B* (rho = +0.569), *APC* (+0.599), *AXIN1* (+0.485), *LRP6* (+0.597), *DVL2* (+0.569) and *CCND1* (+0.477). No association survived correction in GSE87340, GSE135631 or GSE142279. The accompanying Fisher-transform CIs are approximate. These correlations do not establish canonical Wnt activation or *NEAT1* causality, and the positive correlations with the destruction-complex transcripts *APC* and *AXIN1* caution against equating coexpression with pathway activation.

Table 2. Within-tumour Spearman tests between *NEAT1* and ten Wnt-related transcripts

GEO series	Cancer	Tumour n	$q < 0.05$ (of 10)	Genes with $q < 0.05$
GSE103001	Breast	22	6	*GSK3B*, *APC*, *AXIN1*, *LRP6*, *DVL2*, *CCND1*
GSE87340	Lung	27	0	None
GSE135631	Liver	15	0	None
GSE142279	Colorectal	20	0	None

Ten genes per cohort were tested with within-cohort BH adjustment. All 40 rho, nominal *p* and *q* values, with approximate Fisher-z 95% CIs, are given in Supplementary Data S2. This tumour-only panel is not a Wnt-activity assay.

3.3. Paired-bootstrap sensitivity analysis in GSE103001

In GSE103001, the 22 paired *NEAT1* TPM observations reproduced the original group means (normal 66.845 TPM; tumour 76.555 TPM), with Wilcoxon signed-rank W = 114 and $p = 0.702385$. The log2 ratio of group means was +0.196. Paired bootstrap resampling of the 22 patient indices with replacement (40,000 replicates; fixed seed 20261119) gave a percentile 95% CI of −0.204 to +0.635 for this ratio, which crosses zero. This is a descriptive, nonparametric sensitivity interval for a single cohort, not a DESeq2/edgeR estimate or a pooled cross-cancer CI (Supplementary Data S3).

3.4. Exploratory 99-test panel and library preparation

The nine-cohort × eleven-gene matrix of *p* values and group-mean ratios (99 tests), with BH screening *q* values within each gene and across the full 99-test family, is provided in Supplementary Data S4. Differences in library preparation between cohorts (Supplementary Data S5) preclude attributing cross-cohort differences to cancer biology alone.

4. Discussion

The principal limitation is inferential: most results derive from rank tests on TPM values and group-mean abundance ratios rather than count-based paired modelling, so genome-wide inference and model-based CIs for all nine cohorts are unavailable. The limited BH adjustment across nine preselected *NEAT1* tests does not replace false discovery rate (FDR) control in a differential-expression analysis. A paired-bootstrap interval could be computed only for GSE103001, the single cohort with available sample-level *NEAT1* values, and it is not a substitute for count-based analysis or a nine-cohort meta-analysis.

The recurrent *MMP7* signal is consistent with existing knowledge of colorectal oncogenic signalling and is useful mainly as a positive-control observation; it does not imply *NEAT1* regulation. The targeted panel is not a validated readout of canonical Wnt activity, and transcript abundance cannot resolve β-catenin localisation or the distinct functions of *NEAT1_1* and non-polyadenylated *NEAT1_2* [27,28]. The documented use of total-RNA/rRNA-depleted and poly(A)-selected protocols across cohorts may strongly bias comparisons.

Within-tumour correlations were not adjusted for tumour purity or immune and stromal proportions, and equivalent normal-tissue correlations were not available for all nine cohorts. Because *NEAT1* also participates in inflammatory and anti-tumour immune programmes [29–33], differences in immune infiltration could contribute to these associations. The six FDR-significant associations are limited to one breast cohort and are insufficient to claim a conserved *NEAT1*–Wnt association.

Further limitations include an incomplete record of the original search and data-acquisition dates, uncertain same-patient pairing in GSE210787, unavailability of the original count matrices, and the absence of per-cohort model-based uncertainty estimates needed for a random-effects meta-analysis. Sequencing library preparation, cancer subtype, hepatitis status and transcript isoform coverage are potential effect modifiers.

5. Conclusions

In selected public human cancer GEO series, *NEAT1* RNA-level contrasts and limited Wnt-related transcript comparisons were inconsistent across study settings, and only one of nine *NEAT1* comparisons passed BH adjustment across the nine *NEAT1 p* values. The analysis is observational, lacks a formal pooled effect estimate and does not measure canonical Wnt pathway activity. A reproducible count-based paired sensitivity analysis, complete association statistics, robust CIs and external validation are required before judging whether *NEAT1* is a reliable cross-cohort signal.

Acknowledgements

The authors thank the researchers who deposited their data in GEO. This work is derived from the first author's MSc thesis, Libyan Academy for Postgraduate Studies, Tripoli, Libya.

Declarations

Author contributions: N.K.A.A.: Investigation, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. A.F.A.: Supervision, Conceptualization, Writing – review & editing. All authors read and approved the final manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest: The authors declare that they have no conflicts of interest.

Ethics approval and consent to participate: Not applicable. This study was a secondary analysis of publicly available, de-identified GEO datasets; no participants were recruited, no new human or animal specimens were obtained and no interventions were undertaken. Ethics approval and consent for the source studies were the responsibility of the original investigators.

Data availability: The datasets analysed are publicly available in GEO under accessions GSE103001, GSE210787, GSE233242, GSE104836, GSE142279, GSE50760, GSE135631, GSE140845 and GSE87340 [9,11,13,15,17,18,20–22]. Sample identifiers, correlation statistics, bootstrap inputs and the 99-test matrix are provided as supplementary material. Further data are available from the corresponding author upon reasonable request.

Use of generative AI: During the preparation of this work the authors used OpenAI ChatGPT (GPT-6) to assist with restructuring and language editing of the thesis-derived manuscript, translation of

the Arabic abstract and preparation of publication-format files. All research findings originated from the first author's thesis. The authors reviewed and edited the output and take full responsibility for the content of the publication.

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