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Tumour Markers in Clinical Oncology: Biochemistry, Classification, Diagnostic Applications, and Emerging Frontiers — A Narrative Review

Ramesh Kumar[1], D. M. Vasudevan[2]

[1]*Department of Clinical Biochemistry, Chief Operating Officer, Metropolis, Kerala, India.* [2]*Research Head, Jubilee Centre for Medical Research, Thrissur.*

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Address for Correspondence
Dr. Ramesh Kumar, Ph.D.,
Department of Clinical Biochemistry,
Chief Operating Officer Metropolis, Kerala, India
drramesh@metropolisindia.com

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ABSTRACT

Background: Cancer exacts a disproportionate burden on global health. Tumour markers — biochemical substances elaborated by malignant cells or induced in the host by tumour — have emerged as indispensable adjuncts in oncological practice. Their detection in blood, urine, or tissue specimens offers a minimally invasive window into tumour biology that complements histopathology and imaging.

Objective: This narrative review synthesises the current evidence on the biochemical basis, clinical classification, diagnostic performance characteristics, and practical clinical applications of established tumour markers, while addressing their documented limitations and the trajectory of next-generation biomarker development.

Methods: A structured narrative review of the English-language literature was conducted using PubMed, Scopus, and MEDLINE databases. Search terms included 'tumour markers', 'cancer biomarkers', 'oncofetal antigens', 'liquid biopsy', 'circulating tumour DNA', and their respective combinations. Guidelines from ASCO, ESMO, and NACB were incorporated to contextualise clinical recommendations.

Results: Among established markers, beta-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP) exhibit the highest sensitivity and specificity for gestational trophoblastic disease and germ-cell tumours, respectively (>95% for both). Prostate-specific antigen (PSA) retains utility for post-treatment surveillance, though its specificity for population screening remains problematic at 25–40%. Emerging liquid-biopsy platforms, including circulating tumour DNA (ctDNA) and cell-free RNA, demonstrate superior lead-time over conventional imaging for recurrence detection in multiple solid tumours.

Conclusion: Tumour markers remain clinically indispensable when interpreted within the framework of histopathological confirmation, cross-sectional imaging, and patient-specific clinical context. The integration of multi-omic liquid biopsy platforms into routine oncological surveillance holds the potential to transform early detection and personalise therapeutic decision-making.

Keywords: tumour markers; cancer biomarkers; oncofetal antigens; circulating tumour DNA; liquid biopsy; clinical oncology; diagnostic accuracy; treatment monitoring

1. INTRODUCTION

Each year, approximately 20 million people receive a new cancer diagnosis worldwide, and nearly 10 million cancer-related deaths are recorded — a toll that underscores the enduring inadequacy of our early-detection infrastructure [1]. Histopathological examination of biopsy material remains the diagnostic gold standard, yet tissue acquisition is invasive, not always feasible, and offers only a static snapshot of a biologically dynamic disease. Herein lies the central appeal of tumour markers: biochemical entities whose concentrations in accessible biological fluids reflect, with varying fidelity, the presence, burden, and trajectory of malignant disease.

The concept of a serum-detectable correlate of tumour activity dates to 1848, when Henry Bence Jones described a distinctive urinary protein subsequently attributed to multiple myeloma — arguably the first tumour marker in clinical history [2]. Over the ensuing century and a half, the repertoire expanded dramatically: from oncofetal antigens resurrected from embryological dormancy, to glycoprotein antigens shed by epithelial mucins, to the molecular era's circulating tumour DNA and liquid biopsy platforms. What unites this diverse class of substances is their biological origin — produced either by malignant cells themselves or by stromal and immune elements reacting to the presence of cancer — and their clinical accessibility, detectable in blood, urine, pleural fluid, cerebrospinal fluid, or tissue.

Yet the clinical enthusiasm surrounding tumour markers has historically outpaced the evidence. Unrealised promises of population-wide screening, driven by markers with suboptimal specificity, generated waves of false-positive results, unnecessary follow-up investigations, and patient anxiety [3]. Professional bodies including the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) have accordingly issued guidelines anchoring tumour marker use within a framework of validated clinical indications — predominantly monitoring of known disease rather than primary screening.

What remains incompletely addressed in the literature, however, is a unified clinical framework that integrates the biochemical classification of tumour markers with their evidence-based diagnostic performance characteristics, practical applications across disease stages, and trajectory toward next-generation molecular platforms. This review aims to address that gap. The primary objective of this narrative review was to synthesise current evidence on the classification, diagnostic performance, clinical applications, and limitations of established tumour markers, and to outline the clinical promise and challenges of emerging biomarker technologies.

2. CLASSIFICATION OF TUMOUR MARKERS

Tumour markers resist a single, universally accepted classification scheme because individual markers may belong to multiple biochemical categories and serve several clinical functions simultaneously. A pragmatic biochemical classification — summarised in Table 1 — provides the most operationally useful framework for clinicians.

Table 1. Biochemical classification of tumour markers with representative examples and primary clinical utility

Category	Representative Markers	Associated Malignancy	Clinical Utility
Oncofetal Antigens	AFP, CEA	HCC, CRC, Germ-cell tumours	Diagnosis, monitoring, recurrence
Hormones & Hormone-related	β-hCG, Calcitonin, PTHrP	Trophoblastic disease, MTC, paraneoplastic syndromes	Diagnosis, staging, monitoring
Glycoproteins / Mucin-associated	CA-125, CA 19-9, CA 15-3, CA 72-4	Ovarian, pancreatic, breast, gastric	Monitoring, recurrence detection
Enzymes & Isoenzymes	PSA, LDH, ALP, NSE	Prostate, lymphoma, bone, SCLC	Diagnosis, prognosis
Molecular / Genomic Markers	BRCA1/2, KRAS, ctDNA, PD-L1	Breast, colorectal, multiple cancers	Targeted therapy, prognosis

2.1 Oncofetal Antigens

Oncofetal antigens are proteins whose expression is normally confined to the developing embryo or fetus and that are re-expressed — through epigenetic derepression — in malignant cells. Alpha-fetoprotein (AFP), synthesised by fetal hepatocytes and yolk-sac cells, is essentially undetectable in healthy adults (reference range <10 ng/mL) [4]. Its elevation above 400 ng/mL carries a specificity exceeding 90% for hepatocellular carcinoma (HCC) in the appropriate clinical setting, and it is incorporated into several staging systems including the Cancer of the Liver Italian Program (CLIP) score [5]. Carcinoembryonic antigen (CEA), first described by Gold and Freedman in 1965, is a glycoprotein expressed during fetal gastrointestinal development and re-expressed by adenocarcinomas of the colon, rectum, stomach, lung, and breast. Its primary clinical role lies not in diagnosis but in post-surgical surveillance of colorectal carcinoma, where a rising CEA level on serial estimation predicts hepatic or pulmonary metastatic recurrence months before cross-sectional imaging becomes positive [6].

2.2 Hormones and Hormone-Related Markers

Certain tumours elaborate hormones either as a physiological extension of their cell of origin or as paraneoplastic phenomena. Beta-human chorionic gonadotropin (β-hCG) is produced physiologically by syncytiotrophoblast cells of the placenta; its production by gestational trophoblastic neoplasms and non-seminomatous germ-cell tumours (NSGCT) makes it one of the most sensitive and specific tumour markers in clinical use [7]. Serial β-hCG quantification guides treatment decisions and defines remission criteria in gestational trophoblastic disease with a precision unmatched elsewhere in oncology. Calcitonin, produced by parafollicular C-cells of the thyroid, is an exquisitely sensitive marker of medullary thyroid carcinoma (MTC) — useful both diagnostically and as a screening tool in families with known RET proto-oncogene mutations [8].

2.3 Glycoproteins and Mucin-Associated Antigens

The cancer antigen (CA) family comprises high-molecular-weight mucin glycoproteins identified

through monoclonal antibody technology. CA-125 (mucin 16, MUC16) is the most extensively studied; elevations above the conventional cutoff of 35 U/mL are observed in approximately 80% of advanced epithelial ovarian cancers, though levels may remain within normal limits in 50% of Stage I disease — a limitation with direct implications for early-detection strategies [9]. CA 19-9, a sialylated Lewis blood group antigen, is most characteristically elevated in pancreatic ductal adenocarcinoma, where it demonstrates sensitivity of 70–80% and specificity of 82–90% for established disease. Critically, patients with the Lewis(a-b-) blood group phenotype — approximately 5–10% of the population — are constitutionally incapable of expressing CA 19-9, rendering the marker uninformative regardless of tumour burden [10]. CA 15-3 and CA 27.29 are mucin-associated antigens used primarily for monitoring metastatic breast carcinoma during systemic therapy, with ASCO guidelines recommending their use in conjunction with symptom assessment and radiological evaluation [11].

2.4 Enzymes and Isoenzymes

Malignant transformation alters the enzymatic profile of cancer cells in ways that may be reflected in peripheral blood. Prostate-specific antigen (PSA), a serine protease of the kallikrein family, is produced by ductal epithelial cells of the prostate and is the most widely used tumour marker globally. Its sensitivity for prostate cancer detection exceeds 90% at a threshold of 4 ng/mL, though its specificity is markedly limited — benign prostatic hyperplasia, prostatitis, and even vigorous cycling can elevate PSA — generating positive predictive values as low as 25–30% in unselected populations [12]. Lactate dehydrogenase (LDH), a nonspecific marker of cellular injury and turnover, provides prognostic information in diffuse large B-cell lymphoma, testicular germ-cell tumours, and metastatic melanoma. Neuron-specific enolase (NSE) serves as a marker of small-cell lung carcinoma (SCLC) and neuroblastoma, with rising levels correlating with disease progression and falling levels reflecting chemotherapy response [13].

2.5 Molecular and Genomic Markers

The molecular revolution in oncology has yielded a new generation of tissue-based and circulating markers that inform not merely diagnosis but therapeutic targeting. HER2/neu (ERBB2) amplification, detectable by fluorescence in-situ hybridisation (FISH) or immunohistochemistry (IHC) in approximately 15–20% of breast carcinomas, predicts response to trastuzumab-based regimens and identifies a subgroup with intrinsically aggressive behaviour [14]. KRAS and NRAS mutation profiling in metastatic colorectal carcinoma is now a prerequisite for anti-EGFR therapy — patients harbouring RAS mutations derive no benefit from cetuximab or panitumumab and may be harmed by exposure to these agents [15]. The emergence of circulating tumour DNA (ctDNA) — cell-free fragments of tumour-derived DNA detectable in plasma — represents arguably the most significant advance in biomarker science in the past decade, offering dynamic, real-time tumour genomic profiling from a simple blood draw.

3. CLINICAL APPLICATIONS

Tumour markers serve the clinician across five non-mutually exclusive domains: diagnostic supplementation, population screening, treatment response monitoring, recurrence detection, and prognostication. Table 2 summarises the performance characteristics of commonly used markers across these domains.

Table 2. Diagnostic performance characteristics and clinical roles of key tumour markers

Marker	Primary Cancer	Sensitivity (%)	Specificity (%)	Primary Clinical Role
AFP	HCC / Germ-cell	41–65	80–94	Diagnosis, recurrence monitoring
CEA	Colorectal	36–70	87–95	Post-surgical surveillance
CA-125	Ovarian	50–80 (early); >90 (advanced)	75–90	Monitoring treatment response
CA 19-9	Pancreatic	70–80	82–90	Staging, treatment monitoring
PSA	Prostate	90 (>4 ng/mL cutoff)	25–40	Screening (high-risk), recurrence
β-hCG	Trophoblastic / Germ-cell	>95	>95	Diagnosis, therapy response
HER2/neu	Breast	20–30% tumours overexpress	N/A (tissue-based)	Targeted therapy selection

3.1 Role in Diagnosis

No tumour marker currently meets the threshold required for independent diagnostic confirmation of malignancy. Histopathological examination, informed by immunohistochemistry and molecular profiling where indicated, remains the diagnostic standard to which all other investigations are subordinate. That said, tumour markers contribute meaningfully to the pre-biopsy probability assessment and, in certain clinical scenarios, may be near-pathognomonic. An AFP exceeding 1000 ng/mL in a patient with cirrhotic liver and an arterially enhancing hepatic nodule on MRI effectively establishes a diagnosis of HCC according to AASLD criteria, and biopsy is not required before initiating treatment [5]. Similarly, the combination of elevated β-hCG, AFP, and LDH in a young male with a testicular mass is sufficient to begin chemotherapy while awaiting formal pathological classification of germ-cell tumour histology [7].

The utility of tumour markers in diagnosing carcinoma of unknown primary (CUP) deserves specific mention. A panel including AFP, β-hCG, PSA, CA-125, CA 19-9, CEA, and NSE, interpreted alongside immunohistochemistry of the biopsy specimen, can direct site-of-origin workup and occasionally identify treatable primary tumours — particularly germ-cell tumours — that would otherwise be managed empirically and less effectively [16].

3.2 Screening and Early Detection

The theoretical appeal of tumour marker-based population screening — identifying cancer before symptoms arise, when curative intervention is most feasible — has proven difficult to realise in practice. The fundamental statistical challenge is that even a highly specific marker (specificity 99%) applied to a low-prevalence population (cancer prevalence 0.1%) generates nine false-positive results for every true positive, exposing the majority of screen-positive individuals to unnecessary investigation and attendant anxiety [3].

PSA screening for prostate cancer remains the most debated example. The European Randomized Study of Screening for Prostate Cancer (ERSPC) demonstrated a 21% reduction in prostate cancer-specific mortality with PSA-based screening, but at the cost of substantial overdiagnosis and overtreatment of indolent, clinically insignificant cancers [12]. Current USPSTF and EAU guidelines therefore recommend shared decision-making rather than universal screening, reserving PSA testing for informed men aged 50–69 years at average risk and earlier in those with a family history of prostate cancer or African ancestry. CA-125 for ovarian cancer screening in the general population has similarly failed to demonstrate mortality benefit in large randomised trials, including the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), and is not recommended for population-based screening [9].

Exceptions apply in genetically defined high-risk populations. Annual AFP measurement and hepatic ultrasound in patients with liver cirrhosis — regardless of aetiology — reduces HCC mortality and is endorsed by multiple hepatology societies [5]. Serial calcitonin measurement and RET mutation screening constitute the standard of care in families with Multiple Endocrine Neoplasia type 2 (MEN2) [8].

3.3 Monitoring Treatment Response

Serial quantitative measurement of tumour markers during systemic therapy or radiotherapy constitutes their most evidence-supported clinical application. The principle is straightforward: a declining marker level reflects effective tumour cytoreduction, while a stable or rising level signals treatment failure or emerging resistance. The kinetics of decline may carry independent prognostic significance. In testicular NSGCT, a half-life of AFP exceeding 7 days during induction chemotherapy — when the expected half-life is 5–7 days — predicts poor response and may warrant early regimen intensification [7]. In epithelial ovarian cancer, CA-125 nadir levels after platinum-based chemotherapy correlate with progression-free survival; the GCIG CA-125 criteria define a 50% reduction from baseline as the biochemical equivalent of a partial response [17].

CEA monitoring during treatment of metastatic colorectal carcinoma is endorsed by ASCO, with measurements recommended every 3 months during active systemic therapy. A CEA surge — a transient early rise followed by subsequent decline — is recognised as a potential marker of tumour lysis rather than progression in the first 4–8 weeks of biological therapy, and clinicians are advised against premature treatment cessation based solely on this phenomenon [6].

3.4 Detection of Recurrence

Among all clinical applications, surveillance for post-treatment recurrence may represent the setting where tumour markers provide the greatest net benefit. The lead time conferred — the interval between biochemical recurrence and clinical or radiological recurrence — allows earlier therapeutic intervention at a point when disease burden remains lower and treatment options broader.

In colorectal carcinoma, serial post-operative CEA measurement identifies hepatic metachronous metastases with a lead time of 4–6 months over CT surveillance in approximately 30% of cases, enabling curative-intent resection in a proportion of patients who would otherwise present with unresectable disease [6]. In prostate carcinoma, PSA recurrence after radical prostatectomy is defined as a value exceeding 0.2 ng/mL confirmed on two separate occasions; this PSA relapse definition triggers evaluation for salvage radiotherapy or androgen deprivation, and its prognostic subclassification (PSA doubling time, time to recurrence from surgery) guides therapeutic urgency [12]. Importantly, the biochemical recurrence of AFP or β-hCG in a germ-cell tumour survivor mandates urgent imaging and reinduction chemotherapy, as these tumours retain high chemosensitivity even at relapse [7].

3.5 Prognostic Significance

Baseline tumour marker levels at the time of diagnosis correlate with disease stage, tumour burden, and — in several cancer types — overall survival. International Germ Cell Cancer Collaborative Group (IGCCCG) classification stratifies germ-cell tumour patients into good-, intermediate-, and poor-prognosis categories based on histology, site of primary tumour, and serum levels of AFP, β-hCG, and LDH — a prognostic schema that directly informs chemotherapy regimen selection and intensity [7]. In SCLC, baseline NSE levels above 25 ng/mL predict inferior response rates and shorter overall survival. In hepatocellular carcinoma, AFP levels at diagnosis are incorporated into the CLIP score, GALAD score, and Milan criteria for transplant eligibility determination [5].

4. LIMITATIONS

4.1 Analytical Limitations

Tumour marker assays are subject to a range of analytical interferences that may produce erroneous results. Heterophilic antibodies — human anti-mouse antibodies (HAMA) present in patients previously exposed to murine monoclonal antibodies used in diagnostic imaging or therapy — can cross-react with the immunoglobulin components of immunometric assays, producing spuriously elevated results, particularly for CA-125 and CEA [18]. The hook effect — paradoxical assay underestimation when very high analyte concentrations saturate both capture and detection antibodies simultaneously — may cause dangerously low readings in patients with markedly elevated β-hCG, with implications for trophoblastic disease management. Assay standardisation remains imperfect across manufacturer platforms; a patient's CA 19-9 result from one laboratory may not be directly comparable with a value obtained elsewhere, complicating longitudinal monitoring [10].

4.2 Clinical Limitations — Specificity

Elevation of tumour markers in benign, non-malignant conditions constitutes the most clinically consequential limitation. CA-125 may be elevated in endometriosis, pelvic inflammatory disease, hepatic cirrhosis, and in the first trimester of pregnancy — conditions that share target demographics with ovarian cancer and that generate

precisely the population most likely to be referred for elevated CA-125 values [9]. CEA rises in active inflammatory bowel disease, hepatic steatosis, and in cigarette smokers. AFP is physiologically elevated throughout pregnancy and in hepatitis and cirrhosis. PSA elevations in prostatitis and BPH are sufficiently common as to have prompted the development of derivative indices — PSA density, PSA velocity, free-to-total PSA ratio, and prostate health index — designed to improve specificity without sacrificing sensitivity [12].

4.3 Clinical Limitations — Sensitivity

Not all histological subtypes of a given cancer produce their expected marker. Mucinous ovarian carcinomas may produce minimal CA-125, and endometrioid histology is associated with lower CA-125 elevations than serous subtypes [9]. AFP elevation occurs in only 41–65% of HCC cases and may be absent in fibrolamellar carcinoma entirely. Approximately 30% of colorectal carcinomas produce insufficient CEA to exceed the normal reference range at diagnosis, and this proportion is higher in right-sided tumours and in poorly differentiated histology [6]. The biological heterogeneity of malignant clonal populations — with marker-positive and marker-negative subclones coexisting within a single tumour — ensures that no single circulating analyte can capture the full phenotypic complexity of the disease.

5. EMERGING FRONTIERS AND FUTURE PERSPECTIVES

5.1 Liquid Biopsy and Circulating Tumour DNA

Circulating tumour DNA (ctDNA) — fragmented tumour-derived DNA released into the bloodstream through apoptosis, necrosis, and active secretion — has emerged as one of the most transformative biomarker platforms in contemporary oncology. Unlike conventional protein markers, ctDNA carries the specific somatic mutational signature of the tumour from which it derives, enabling dynamic, non-invasive profiling of tumour genomics across the natural history of disease. Ultra-sensitive detection platforms — including digital droplet PCR (ddPCR) and next-generation sequencing (NGS)-based approaches — can detect ctDNA at fractional allele frequencies below 0.01%, capturing minimal residual disease (MRD) states that are entirely invisible to conventional imaging [19].

In colorectal carcinoma, ctDNA detection in plasma at 4 weeks post-resection identifies patients at high risk of recurrence with a hazard ratio exceeding 10 compared with ctDNA-negative patients, outperforming post-operative CEA in both sensitivity and prognostic precision [20]. In early-stage breast carcinoma, ctDNA detection during or after adjuvant chemotherapy provides a molecular bellwether of metastatic relapse months to years before clinical presentation. Clinical trials are now investigating ctDNA-directed treatment intensification or de-escalation — an approach that may deliver personalised therapy at the individual patient level rather than the population cohort level [19].

5.2 Proteomics and Multi-Analyte Panels

Single-marker platforms are inherently limited by the biological heterogeneity of malignant disease. Multi-analyte protein panels that combine several individually suboptimal markers through algorithmic scoring have demonstrated superior diagnostic performance in early detection studies. The OVA1 panel (combining CA-125 with transthyretin, apolipoprotein A1, beta-2 microglobulin, and transferrin) achieves sensitivity exceeding 92% for malignant ovarian masses when used to triage adnexal masses pre-operatively, significantly outperforming CA-125 alone [21]. The ROMA (Risk of Ovarian Malignancy Algorithm) integrates CA-125 and human epididymis protein 4 (HE4) with menopausal status to risk-stratify women with pelvic masses more effectively than either marker in isolation [17].

5.3 Methylomics and Epigenetic Biomarkers

Tumour-specific aberrant DNA methylation patterns are detectable in cell-free DNA long before a tumour reaches a clinically detectable size. Multi-cancer early detection (MCED) tests — epitomised by the Galleri assay (GRAIL), which analyses methylation signatures of over 1 million CpG sites across the genome — have demonstrated the capacity to detect over 50 cancer types from a single blood draw, with specificity exceeding 99% and a tissue-of-origin classifier accuracy of approximately 89% [22]. Large-scale implementation trials, including the NHS-GRAIL study in the United Kingdom, are currently evaluating the real-world performance of MCED testing, with results anticipated to reshape the early-detection paradigm within the next decade.

5.4 Artificial Intelligence and Biomarker Integration

The clinical interpretation of multi-analyte biomarker panels, genomic signatures, and longitudinal monitoring data exceeds the analytical capacity of unaided human cognition. Machine learning algorithms — particularly those trained on large, prospectively collected biomarker datasets with linked clinical outcomes — offer the prospect of integrating hundreds of analyte values with imaging features, clinical metadata, and genomic data to generate calibrated risk predictions at the individual patient level. AI-driven interpretation of PSA kinetics combined with MRI-based prostate imaging reports (PI-RADS scores) has demonstrated improved specificity for clinically significant prostate cancer in retrospective validation cohorts [12]. Prospective validation in ethnically diverse, real-world populations remains essential before such tools can be responsibly deployed at scale.

6. CONCLUSION

Tumour markers occupy a well-established and irreplaceable position in the modern oncological armamentarium — not as standalone diagnostic instruments, but as contextually powerful adjuncts that inform clinical decision-making when interpreted alongside pathological, radiological, and clinical data. Their greatest validated utility lies in treatment response monitoring and post-treatment surveillance for recurrence, where serial quantitative estimation provides dynamic, accessible, and cost-effective information about disease trajectory. Prognostic stratification — particularly in germ-cell tumours, HCC, and prostate carcinoma — represents a second domain where established markers have

demonstrably influenced treatment algorithms and patient outcomes.

The limitations of conventional protein-based markers — low specificity in benign conditions, incomplete sensitivity across histological subtypes, and assay variability — are real and must temper clinical enthusiasm for their uncritical deployment. The emerging liquid biopsy technologies, multi-cancer early detection platforms, and AI-integrated diagnostic systems address many of these limitations in principle, though prospective validation in diverse populations and rigorous health-economic analysis are prerequisites for responsible clinical implementation.

The clinician who understands the biochemical basis, performance characteristics, appropriate indications, and interpretive caveats of tumour markers will deploy them judiciously — avoiding both the diagnostic nihilism of dismissing them as unreliable and the diagnostic overreach of treating them as infallible oracles. In this measured deployment lies their greatest contribution to patient care.

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AUTHOR CONTRIBUTIONS

Conceptualisation: R.K. Literature search and synthesis: R.K. Writing – original draft: D.M.V. Writing – review and editing: R.K. Final approval of manuscript: R.K.

CONFLICT OF INTEREST

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DATA AVAILABILITY

No primary data were generated or analysed in the preparation of this review. All evidence cited is available in the published literature referenced herein.

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