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REVIEW

Blood-Based Liquid Biopsy Biomarkers in Pancreatic Neuroendocrine Tumors: A Systematic Review and Narrative Synthesis of Diagnostic, Prognostic, Molecular Profiling, and Monitoring Utility

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Abstract

Introduction: Pancreatic neuroendocrine tumors (PNETs) are biologically heterogeneous neoplasms for which reliable non-invasive biomarkers remain limited. Although tissue-based genomic studies have identified recurrent molecular alterations, the clinical utility of blood-based liquid biopsy in PNETs remains uncertain. **Methods:** A PubMed-based systematic review was conducted following PRISMA 2020 guidelines, with the final search performed on 20 February 2026. Eligible studies investigated blood-based biomarkers in PNETs, including circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), plasma next-generation sequencing (NGS), copy-number alterations (CNAs), and transcript-based multigene assays. Given methodological and clinical heterogeneity, findings were synthesized narratively. One pancreatic neuroendocrine carcinoma case report was included solely as illustrative evidence. **Results:** Six reports were included, comprising five studies providing PNET-specific evidence and one illustrative case report. CNA-based ctDNA analysis demonstrated the strongest prognostic associations, with detectable tumor fraction associated with poorer overall and progression-free survival. Mutation-based plasma NGS identified potentially actionable genomic alterations, although clinical validation remained limited. Total cfDNA showed inconsistent clinical utility. Transcript-based assays, particularly NETest, demonstrated promising diagnostic performance and concordance with imaging-based disease assessment but lacked tumor-specific genomic information for treatment selection. **Conclusions:** Blood-based liquid biopsy biomarkers in *PNET*s demonstrate promising but heterogeneous clinical utility. CNA-Blood-based liquid biopsy approaches show potential for improving PNET management, although their clinical applications differ. CNA-based ctDNA appears promising for prognostication and disease monitoring, while transcript-based assays may support diagnosis and assessment of disease activity. Plasma NGS could provide complementary molecular information in selected patients with advanced disease. However, small study populations, single-database retrieval, assay heterogeneity, and limited prospective validation restrict clinical applicability. Larger multicenter prospective studies with standardized methodologies and clinically relevant endpoints are required before routine implementation.

Keywords: Pancreatic neuroendocrine tumors, Liquid biopsy, Circulating tumor DNA, NETest, Molecular profiling

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Introduction

Pancreatic neuroendocrine tumors (*PNETs*) are heterogeneous neoplasms with clinical behavior ranging from indolent, well-differentiated disease to aggressive metastatic presentations. Modern tissue-based genomic studies have improved understanding of *PNET* biology, including recurrent alterations involving *MEN1, DAXX, ATRX*, and components of the *PI3K/AKT/mTOR* pathway [1, 2]. These biological insights have helped inform targeted therapeutic strategies, including *mTOR* inhibition and tyrosine kinase inhibition in advanced *PNET* [3, 4].

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However, tissue biopsy is invasive, may not be feasible for serial monitoring, and may incompletely capture spatial and temporal tumor heterogeneity.

Liquid biopsy provides a minimally invasive approach for detecting tumor-derived molecular material in the blood. Blood-based approaches include circulating tumor DNA (ctDNA) mutation profiling, total cell-free DNA (cfDNA) quantification, plasma next-generation sequencing (NGS), copy-number alteration (CNA)-based tumor-fraction analysis, circulating tumor cells, and transcript-based multigene expression assays. In *PNETs*, however, the development and clinical application of liquid biopsy face tumor-specific challenges. Well-differentiated *PNETs* may release low quantities of tumor-derived DNA, particularly in localized disease, while their mutational burden may be lower than that observed in many high-grade epithelial malignancies. These characteristics may limit the sensitivity of mutation-based ctDNA assays while increasing the potential value of broader measures of genomic instability or circulating transcriptomic signatures.

Existing evidence remains fragmented across small prospective cohorts, pilot studies, retrospective molecular profiling studies, and case-based precision oncology reports. Moreover, liquid biopsy platforms differ substantially in their biological targets and clinical applications. Mutation-based and CNA-based assays primarily aim to detect tumor-derived DNA, whereas transcript-based assays such as NETest assess circulating gene-expression signatures and do not directly provide tumor-specific mutation profiles. A clinically meaningful synthesis therefore requires differentiation of diagnostic performance, molecular profiling capability, prognostic value, and potential utility for longitudinal disease monitoring.

Accordingly, this systematic narrative review evaluates the current evidence on blood-based liquid biopsy biomarkers in *PNETs*, with particular emphasis on their detectability and feasibility, ability to identify molecular alterations and potentially actionable targets, diagnostic performance, association with survival outcomes, and potential role in treatment and disease monitoring.

Materials and Methods

Study Design and Reporting Framework

This review was designed as a systematic narrative review and reported in accordance with the PRISMA 2020 reporting principles [5]. The review protocol was not prospectively registered. Because the eligible studies differed substantially in biomarker platforms, patient populations, disease stages, study designs, and outcome measures, a quantitative meta-analysis was not planned.

Information Source and Search Date

A systematic search of PubMed was conducted for records available up to 20 February 2026. The review was intentionally restricted to PubMed, and this methodological decision is considered a limitation because potentially eligible studies indexed in other databases, including Embase, Scopus, and Web of Science, may not have been identified. Reference lists of eligible articles were also screened manually, when available, to identify potentially relevant additional reports.

Search Strategy

The PubMed search strategy combined terms related to pancreatic neuroendocrine tumors with terms describing blood-based liquid biopsy biomarkers. The search strategy was as follows:

("pancreatic neuroendocrine tumor" OR "*PNET*" OR "pancreatic NET" OR "pancreatic neuroendocrine neoplasm") AND ("liquid biopsy" OR "circulating tumor DNA" OR "ctDNA" OR "cell-free DNA" OR "cfDNA" OR "circulating tumor cells" OR "blood biomarker" OR "NETest")

Filters were applied to restrict the search to human studies published in English. Reference lists of eligible articles were screened manually when appropriate.

Eligibility Criteria

Studies were considered eligible when they included human participants with histologically confirmed *PNET* or an extractable pancreatic neuroendocrine tumor subgroup and evaluated a blood-based liquid biopsy biomarker using plasma or serum. Eligible biomarker approaches included ctDNA, total cfDNA, plasma NGS, CNA-based tumor-fraction analysis, transcript-based multigene assays, or other circulating molecular biomarkers. Studies were required to report at least one clinically relevant outcome, including biomarker detectability, analytical or clinical feasibility, molecular profiling, diagnostic performance, prognostic association, or longitudinal disease monitoring. Original research articles and case reports were eligible when they provided relevant molecular assay data.

Studies were excluded if they were based exclusively on tissue genomic analyses, evaluated non-blood biomarkers, were reviews or editorials without original data, or did not provide extractable *PNET*-specific information. One case report involving pancreatic neuroendocrine carcinoma was retained as illustrative evidence only, because it demonstrated the potential use of plasma-based molecular profiling for treatment selection but did not provide cohort-level evidence of *PNET* biomarker performance. This report was therefore not used to estimate diagnostic, prognostic, or monitoring performance in *PNET*.

Study Selection

Records were screened in two stages, consisting of title and abstract screening followed by full-text assessment for eligibility. The study-selection process is presented in the PRISMA flow diagram (Figure 1). A total of 120 records were identified, of which 14 duplicates were removed. The remaining 106 records were screened by title and abstract, resulting in the exclusion of 95 records. Eleven full-text reports were subsequently assessed for eligibility, of which five were excluded for predefined reasons. Six reports were ultimately retained for qualitative synthesis. No study was eligible for quantitative meta-analysis.

Data Extraction

Data were extracted using a standardized data-extraction form. The extracted variables included first author, publication year, country, study design, total sample size, size of the pancreatic neuroendocrine tumor subgroup, disease stage, biomarker category, assay methodology, availability of serial sampling, clinical endpoints, biomarker detectability, diagnostic performance, prognostic findings, treatment or disease-monitoring findings, and reported actionable molecular alterations, where applicable.

Risk-of-Bias and Quality Assessment

Because the included reports addressed different biomarker applications and clinical questions, methodological quality was assessed according to the relevant study domain. Diagnostic accuracy evidence was considered using the principles of the QUADAS-2 framework [6], while prognostic biomarker evidence was considered using the QUIPS domains [7]. The illustrative case report was evaluated according to the principles of the JBI case-report appraisal framework [8]. Quality considerations were used to inform the weighting and interpretation of evidence during the narrative synthesis rather than as automatic exclusion criteria.

Data Synthesis

The included studies were categorized according to their principal biomarker approach: CNA-based ctDNA or tumor-fraction analysis, mutation-based plasma NGS or mutation tracking, total cfDNA quantification, and transcript-based assays. Findings were synthesized narratively across five prespecified clinical domains: biomarker detectability, molecular profiling, diagnostic performance, prognostic value, and potential utility for treatment selection and longitudinal disease monitoring.

Results

Study Selection

The PubMed search identified 120 records. After removal of 14 duplicate records, 106 records underwent title and abstract screening, of which 95 were excluded. Eleven reports were subsequently assessed in full text. Five reports were excluded because they evaluated a tissue-based biomarker (n = 1), were review articles without eligible original data (n = 2), evaluated a non-blood biomarker (cyst fluid; n = 1), or did not provide extractable *PNET*-specific data (n = 1). Six reports were therefore retained for qualitative synthesis. Five of these reports provided direct *PNET*-specific analytic evidence, whereas one pancreatic neuroendocrine carcinoma case report was retained solely as illustrative evidence of plasma-guided treatment selection. No study was included in a quantitative meta-analysis.

Study Characteristics

The six retained reports comprised prospective cohort studies, a prospective pilot study, a retrospective molecular profiling study, a prospective validation study of a transcript-based assay, and one illustrative case report. The characteristics of the included studies are summarized in Table 1. The *PNET*-specific evidence encompassed CNA-based cfDNA/ctDNA analysis, mutation-based ctDNA tracking, targeted plasma NGS, total cfDNA quantification, and transcript-based NETest assessment [9-13].

The report by Szkukalek et al. was retained exclusively as illustrative evidence because it described molecularly

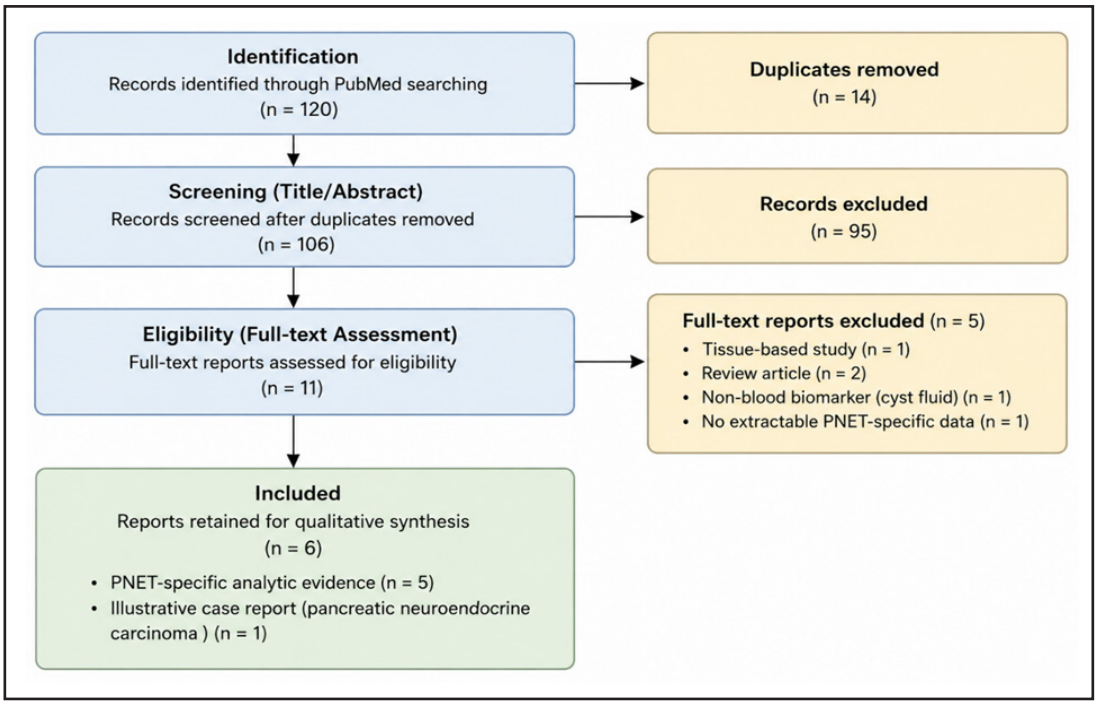


Figure 1. PRISMA Flow Diagram Showing the Identification, Screening, Eligibility Assessment, and Inclusion of Studies Evaluating Blood-based Liquid Biopsy Biomarkers in Pancreatic Neuroendocrine Tumors

guided treatment selection in a patient with metastatic pancreatic neuroendocrine carcinoma [14]. As this report did not provide cohort-level *PNET* biomarker performance data, it was not considered in the assessment of diagnostic, prognostic, or monitoring performance.

Clinical Utility by Biomarker Category

Table 2 summarizes the reported clinical utility of blood-based liquid biopsy biomarkers across the included studies. CNA-based ctDNA and tumor-fraction analysis provided the strongest evidence for prognostic assessment, with detectable tumor-derived signal associated with survival outcomes and disease burden. Mutation-based plasma NGS and ctDNA profiling demonstrated the feasibility of identifying genomic alterations and potentially actionable molecular targets, although their prognostic and predictive utility was not consistently validated. Total cfDNA quantification showed more limited clinical utility when evaluated as a standalone biomarker. In contrast, transcript-based assays, particularly NETest, demonstrated promising diagnostic performance and concordance with imaging and disease status; however, these assays do not provide tumor-specific mutation-level information and therefore have limited utility for direct selection of genotype-matched targeted therapies. Overall, the clinical utility of liquid biopsy in *PNET* appears to vary according to biomarker type, with CNA-based approaches showing the greatest promise for prognostication, transcript-based assays for disease assessment and monitoring, and plasma NGS for molecular profiling.

Risk-of-Bias and Quality Appraisal

Risk-of-bias concerns were primarily related to small sample sizes, heterogeneous study populations, limited reporting of *PNET*-specific data in some cohorts, variability in biomarker platforms and endpoint definitions, and limited use of multivariable analyses for prognostic outcomes. Diagnostic evidence was considered using QUADAS-2 domains, prognostic evidence using QUIPS domains, and the illustrative case report using principles derived from JBI case-report appraisal. Overall, the certainty of evidence was considered limited to moderate, with stronger evidentiary weight assigned to prospective cohort and validation studies reporting survival, diagnostic, or imaging outcomes. Pilot studies were interpreted cautiously because of their small sample sizes and limited statistical power. The Szkukalek et al. case report was considered illustrative only and was not used to infer diagnostic, prognostic, or population-level biomarker performance. The overall quality appraisal and domain-specific concerns are summarized in Table 3.

DNA-based liquid biopsy approaches

Detectability of ctDNA and cfDNA

Tumor-specific ctDNA detectability varied according to the analytical platform and disease context. In the pilot *PNET* study by Boons et al., tumor-specific plasma mutations and copy-number variations (CNVs) were predominantly detectable in patients with metastatic

Table 1. Characteristics of Retained Reports Evaluating Blood-Based Liquid Biopsy Biomarkers Relevant to Pancreatic Neuroendocrine Tumors

Study	Year	Country	Study design	Population	Disease stage	Biomarker type	Assay method	Serial sampling	Main clinical endpoints
Boons et al. [9]	2018	Belgium	Prospective pilot study	10 PNET patients	Localized and metastatic	ctDNA mutation tracking and CNV assessment	Tumor/germline whole-exome sequencing; plasma ddPCR; shallow whole-genome sequencing	Limited	ctDNA detectability and association with tumor burden
Zakka et al. [10]	2020	United States	Retrospective molecular profiling study	165 pancreatic NET patients within a 320-patient neuroendocrine neoplasm cohort	Advanced/ metastatic	ctDNA mutation profiling	Guardant360 targeted NGS panel	Limited	Genomic landscape and potentially actionable alterations
Malczewska et al. [11]	2019	Poland	Prospective validation study	67 PNET patients within a 111-patient NET cohort	Mixed	Transcript-based multigene assay (NETest)	Multigene mRNA PCR assay	Yes	Diagnostic accuracy, imaging concordance, and discrimination of progressive versus stable disease
Boons et al. [12]	2022	Belgium	Prospective cohort study	21 pancreatic neuroendocrine neoplasm patients within a 43-patient plasma cohort	Metastatic	cfDNA/ctDNA and CNA-based tumor fraction	Shallow whole-genome sequencing with ichorCNA	Yes, longitudinal	Overall survival, progression-free survival, tumor fraction, and diagnostic classification
Oversoe et al. [13]	2022	Denmark	Prospective cohort study	20 pancreatic NET patients within a 70-patient small-intestinal or pancreatic NET cohort	Mixed, predominantly low-grade	Total cfDNA	ddPCR quantification	Yes, approximately every 6 months	Overall survival, progression-free survival, and PRRT monitoring
Szkukalek et al. [14]	2021	Hungary	Case report; illustrative evidence	One patient with metastatic pancreatic neuroendocrine carcinoma	Metastatic	cfDNA-based molecular profiling	591-gene NGS panel with computational decision support	No	Treatment selection and radiologic response; not used to estimate PNET biomarker performance

Table 2. Clinical Utility of Blood-Based Liquid Biopsy Biomarkers in PNET-Related Evidence

Study	Biomarker category	Detectability	Molecular profiling	Diagnostic performance	Prognostic value	Treatment / monitoring	Actionable targets
Boons et al. [12] (2022)	ctDNA/CNA-based tumor fraction	CNA-based tumor fraction was detectable in 62% of pancreatic neuroendocrine neoplasm samples in the extracted data	CNA landscape and tumor-fraction estimation	AUC = 0.79 for distinguishing pancreatic neuroendocrine neoplasms from pancreatic adenocarcinoma in the extracted data	Higher tumor fraction was associated with poorer outcomes; OS HR = 5.6 in univariate analysis and HR = 4.5 in multivariate analysis; lower PFS probability was also reported (p = 0.035 in the extracted data)	Serial assessment demonstrated increasing tumor fraction with disease burden	No direct drug-matching claim
Boons et al. [9] (2018)	ctDNA mutation tracking and CNV assessment	ctDNA was predominantly detectable in patients with metastatic PNET	Tumor-specific mutations and CNVs were identified	Not reported	Findings were suggestive but limited by the small sample size	Variant allele fraction increased with tumor burden in the extracted data	Not evaluated
Zakka et al. [10] (2020)	Targeted plasma NGS	Alterations were detected in 87.5% of cases in the extracted data	Broad genomic profiling, including selected genomic gains and losses	Not reported	Not reported	Serial mutation assessment was feasible in a subset of patients	Potentially actionable alterations were identified
Oversoe et al. [13] (2022)	Total cfDNA quantification	cfDNA levels were elevated compared with controls in the extracted data	No tumor-specific molecular profiling	Not reported	Weak or inconsistent prognostic signal; no clear OS association was identified in the extracted data	No significant PRRT-monitoring signal was demonstrated in the extracted data	No
Malczewska et al. [11] (2019)	Transcript-based multigene assay (NETest)	High assay positivity; sensitivity reported as 99%	Gene-expression signature; does not provide mutation-level profiling	Sensitivity = 99%; specificity = 95%; AUC = 0.89–0.96 in the extracted data	Differentiated progressive disease from stable disease	Strong concordance with imaging and disease status was reported	Not mutation-based
Szkukalek et al. [14] (2021) †	Large-panel cfDNA NGS; illustrative case	High tumor fraction was reported in a single metastatic pancreatic neuroendocrine carcinoma case	591-gene NGS panel; 38 variants were detected	Not applicable	Not applicable	Radiologic stabilization followed molecularly informed treatment selection	Everolimus was selected based on PI3K/mTOR-pathway alterations in the reported case

Table 3. Domain-Specific Quality Appraisal and Influence on Synthesis

Study	Appraisal frame	Main considerations for this review question	Overall concern	Influence on synthesis
Boons 2022 [12]	QUIPS- oriented prognostic	Prospective design and longitudinal sampling support prognostic inference; however, cohort size and metastaticenriched population limit generalizability to localized PNET.	Moderate High for out-	Weighted as strongest prognostic and monitoring evidence.
Boons 2018 [9]	appraisal QUIPS/ adapted feasibility appraisal feasibility	Pilot design and 10-patient PNET sample limit precision; useful for biological feasibility and stage- dependent detectability.	come inference; moderate for	Used mainly for detectability and proof-of-concept mutation/CNV tracking.
Zakka 2020 [10]	Adapted observational molecular- profiling appraisal	Large pancreatic NET subgroup supports profiling feasibility; retrospective design and limited survival- response linkage restrict prognostic or predictive conclusions.	Moderate for profiling; high for outcome inference	Used for genomic land- scape/ actionability, not for survival conclusions.
Oversoe 2022 [13]	QUIPS- oriented prognostic appraisal	Prospective sampling supports evaluation of cfDNA; total cfDNA lacks tumor specificity and the pancreatic subgroup is modest.	Moderate to high	Used to support limited standalone value of total cfDNA.
Malczewska 2019 [11]	QUADAS-2-oriented diagnostic	Prospective validation and imaging concordance support diagnostic/monitoring interpretation; assay is transcript-based and biologically distinct from	Moderate High	Weighted as strongest diagnostic/ disease-activity evidence, not as genomic profiling
Szkukalek 2021 [14]	appraisal JBI case- report appraisal	ctDNA. Single case; cannot estimate diagnostic, prognostic, or monitoring accuracy. It demonstrates plausibility of plasma-guided treatment selection only.		evidence. Illustrative only; excluded from PNET performance conclusions.

disease, supporting the concept that ctDNA shedding in *PNET* is influenced by tumor burden and disease stage [9]. In a subsequent longitudinal CNA-based study, genome-wide cfDNA profiling and tumor-fraction estimation demonstrated a stronger clinical signal in metastatic neuroendocrine neoplasms, including a pancreatic subgroup [12]. By contrast, total cfDNA concentration measured without tumor-specific attribution appeared less clinically informative, as circulating DNA may originate from both tumor and non-tumor biological processes [13].

Molecular profiling and actionable alterations

Mutation-based plasma next-generation sequencing (NGS) enabled broad genomic characterization in neuroendocrine neoplasms, including a substantial pancreatic NET subgroup [10]. This approach is clinically attractive because it can identify potentially actionable genomic alterations and can be repeated longitudinally to monitor molecular evolution. However, the available evidence has not yet established its ability to predict survival or treatment response specifically in *PNET*. The case report by Szkukalek et al. demonstrated that large-panel plasma sequencing may facilitate molecularly informed treatment selection in an individual patient with advanced pancreatic neuroendocrine carcinoma; however, such evidence should not be generalized to *PNET* populations [14].

Prognostic value

The strongest prognostic evidence among DNA-based approaches came from CNA-based ctDNA and tumor-fraction analysis. Detectable tumor fraction was associated with shorter overall survival and progression-free survival in the longitudinal study by Boons et al. [12]. This finding is biologically plausible because CNA-based approaches capture broader genomic instability signals rather than depending on the presence of individual point mutations. Nevertheless, these findings require validation in larger, prospectively followed, *PNET*-specific cohorts, particularly in patients with localized disease and those undergoing post-resection surveillance.

Total cfDNA demonstrated weaker and less consistent prognostic utility. Oversoe et al. reported elevated cfDNA levels in patients with NETs but did not demonstrate a strong standalone association with treatment monitoring or survival among low-grade pancreatic or small-intestinal NET subgroups [13]. This distinction suggests that tumor-specific measurements or tumor-fraction estimates may provide greater clinical information than total circulating DNA concentration alone.

Treatment monitoring

Longitudinal evidence was most supportive of CNA-based monitoring of tumor-fraction dynamics. Increasing tumor fraction was associated with a lower probability of progression-free survival in the available longitudinal data [12]. Serial mutation-based plasma NGS also demonstrated dynamic acquisition and loss of genomic alterations in selected patients, although formal validation against radiographic treatment response remained limited [10]. Similarly, total cfDNA did not demonstrate a reliable signal for monitoring response to peptide receptor radionuclide therapy (PRRT) in the available data [13].

Transcript-based liquid biopsy

The NETest transcript-based assay demonstrated the strongest diagnostic and disease-activity signal among the retained studies. In the prospective validation study by Malczewska et al., NETest showed high sensitivity and specificity, strong concordance with imaging findings, and the ability to distinguish progressive from stable disease [11]. Importantly, NETest is biologically distinct from ctDNA-based assays because it measures circulating gene-expression signatures rather than tumor-specific

DNA alterations. Accordingly, its potential clinical role is better framed in terms of diagnosis and disease-activity assessment rather than mutation-directed treatment selection.

Comparative clinical interpretation

Taken together, the available evidence suggests that different liquid-biopsy modalities may serve complementary clinical roles. CNA-based ctDNA and tumor-fraction analysis currently provide the most consistent prognostic and treatment-monitoring signals. Mutation-based plasma NGS offers broad molecular profiling and may identify potentially actionable alterations, but robust *PNET*-specific evidence linking these findings to survival or treatment response remains limited. Total cfDNA concentration alone appears insufficient as a standalone biomarker. Transcript-based assays, particularly NETest, demonstrate promising diagnostic and disease-activity assessment performance but represent a biologically distinct approach from DNA-based tumor profiling. Therefore, these modalities should be considered complementary rather than interchangeable, with their clinical utility interpreted according to the specific question being addressed.

Discussion

This review indicates that blood-based liquid biopsy in pancreatic neuroendocrine tumors (*PNETs*) is promising but remains at an early stage of clinical development. The available evidence is limited, methodologically heterogeneous, and largely derived from patients with advanced or metastatic disease. Among the reviewed approaches, CNA-based ctDNA and tumor-fraction analysis showed the most consistent prognostic and treatment-monitoring signals, whereas total cfDNA concentration alone appeared less informative. Mutation-based plasma NGS demonstrated potential for genomic profiling and identification of actionable alterations, but robust *PNET*-specific prognostic or predictive validation remains lacking. Transcript-based NETest showed strong diagnostic and disease-activity signals and good concordance with imaging; however, it represents a biologically distinct approach from ctDNA-based genotyping and should therefore not be interpreted as equivalent to DNA-based tumor profiling.

Biological and clinical interpretation

The variable performance of ctDNA assays in *PNETs* is likely influenced by tumor biology. Compared with highly proliferative carcinomas, many well-differentiated *PNETs* may release relatively small amounts of tumor-derived DNA into the circulation. This limitation may be particularly relevant in localized or low-volume disease and may explain why mutation-based ctDNA detection appears more feasible in patients with metastatic or high-burden disease. CNA-based approaches may partially address this limitation by capturing broader patterns of genomic instability and estimating tumor fraction. Nevertheless, whether these approaches provide superior sensitivity across the full spectrum of *PNET* disease remains to be established in larger, *PNET*-specific cohorts.

Clinical implications

The current evidence supports a potential tiered model of clinical utility. For diagnosis and assessment of disease activity, transcript-based assays such as NETest currently demonstrate the strongest evidence. For prognostic assessment and longitudinal monitoring, CNA-based ctDNA and tumor-fraction analysis appear particularly promising. Mutation-based plasma NGS may be useful for molecular profiling in selected patients with advanced disease, particularly when tissue is unavailable, insufficient, or no longer representative of the current disease state. In contrast, total cfDNA concentration alone should not currently be considered a robust standalone biomarker for *PNET* management.

Evidence gaps

Several important evidence gaps remain. First, most available studies have focused on advanced or metastatic disease, whereas evidence in localized *PNET* and in the post-resection minimal residual disease setting remains limited. Second, substantial methodological heterogeneity exists across studies, including the use of digital droplet PCR, targeted NGS, shallow whole-genome sequencing, and multigene transcript-based assays. Third, relatively few studies have systematically integrated liquid-biopsy findings with radiographic response, functional imaging, tumor grade, tumor burden, and treatment line. Finally, longitudinal sampling intervals and thresholds defining clinically meaningful changes in circulating biomarkers have not been standardized.

Strengths and limitations of this review

A major strength of this review is its *PNET*-focused synthesis across several liquid-biopsy modalities, with separate consideration of diagnostic, prognostic, molecular-profiling, and treatment-monitoring applications. The review also distinguishes DNA-based tumor profiling from transcript-based assays and gives greater interpretive weight to cohort-level evidence than to illustrative case reports.

Several limitations should be acknowledged. The literature search was restricted to PubMed; therefore, relevant studies indexed exclusively in Embase, Scopus, Web of Science, conference proceedings, or other databases may have been missed. The number of eligible studies was also relatively small. Furthermore, several included studies enrolled broader neuroendocrine neoplasm populations with pancreatic subgroups, meaning that some findings cannot be considered exclusively *PNET*-specific. Considerable heterogeneity in assay platforms, study populations, and clinical endpoints precluded quantitative meta-analysis. Finally, risk-of-bias assessments were used primarily to inform narrative interpretation and weighting of the available evidence; these assessments may require updating if additional studies or full-text information become available.

Future directions

Future research should prioritize multicenter, prospective validation of CNA-based ctDNA and tumor-fraction monitoring in well-characterized *PNET* cohorts. Plasma NGS panels should be optimized for genomic alterations and pathways relevant to *PNET* biology and evaluated systematically against tissue genotyping, radiological and functional imaging, treatment response, and survival outcomes. Transcript-based assays should be investigated alongside DNA-based approaches to determine whether they provide complementary rather than interchangeable information.

Minimal residual disease detection after curative-intent surgery represents a particularly important unmet clinical need. Future studies should also adopt standardized blood-sampling schedules, prespecified thresholds for clinically meaningful biomarker changes, and clearly defined clinical endpoints. Such standardization would facilitate comparison across studies and help determine whether liquid biopsy can ultimately be incorporated into routine *PNET* surveillance and treatment decision-making.

In conclusion, blood-based liquid biopsy biomarkers in *PNETs* demonstrate emerging but heterogeneous clinical utility. CNA-based ctDNA and tumor-fraction analysis currently provide the strongest evidence for prognostic assessment and longitudinal monitoring. Mutation-based plasma NGS offers valuable molecular-profiling capabilities and may identify potentially actionable alterations, whereas total cfDNA concentration alone appears to have limited standalone clinical value. Transcript-based assays such as NETest show promising diagnostic and disease-activity performance but represent a biologically distinct biomarker strategy.

Despite these encouraging findings, the current evidence remains insufficient to support broad routine implementation of liquid biopsy in *PNET* management. Larger, prospective, multicenter studies involving well-defined *PNET* populations are required to validate clinical utility, establish standardized thresholds and sampling strategies, and determine whether these biomarkers can improve individualized surveillance and treatment decisions.

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None.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

AUC: area under the curve; cfDNA: cell-free DNA; CNA: copy-number alteration; ctDNA: circulating tumor DNA; ddPCR: droplet digital polymerase chain reaction; NGS: next-generation sequencing; NET: neuroendocrine tumor; pNEC: pancreatic neuroendocrine carcinoma; *PNET*: pancreatic neuroendocrine tumor; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRRT: peptide receptor radionuclide therapy; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2; QUIPS: Quality in Prognosis Studies

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