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Multi-omic profiles of neuroendocrine neoplasms of the pancreas: an integrated landscape

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Abstract

Pancreatic neuroendocrine neoplasms (PanNENs) constitute a heterogeneous group of tumors distinguished by substantial variability in morphology, immunophenotype, molecular characteristics, and clinical behavior. In recent years, the advent of multiple omics-based methodologies has significantly enhanced our understanding of these neoplasms. Integrating histology and genomics with survival analyses has clarified that the fundamental distinction within this disease spectrum lies between well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Furthermore, genomics, transcriptomics, and epigenetic profiling have deepened the granularity of the PanNET landscape, revealing marked differences even within the same diagnostic category, with important clinical implications. For example, *DAXX/ATRX* mutations, activation of the alternative lengthening of telomeres pathway, *BEND2* gene fusions, and an α-cell transcriptional profile are more frequently associated with adverse outcomes. Additional omics approaches, including metabolomics, proteomics, radiomics, and the more recently developed spatially resolved methodologies, are further expanding current knowledge in this challenging field. In this review, we provide an integrated overview of PanNENs, synthesizing insights generated across diverse multi-omics platforms.

Keywords Neuroendocrine, PanNET, PanNEC, Omics, Genomics, Transcriptomics, Metabolomics, Proteomics, Radiomics.

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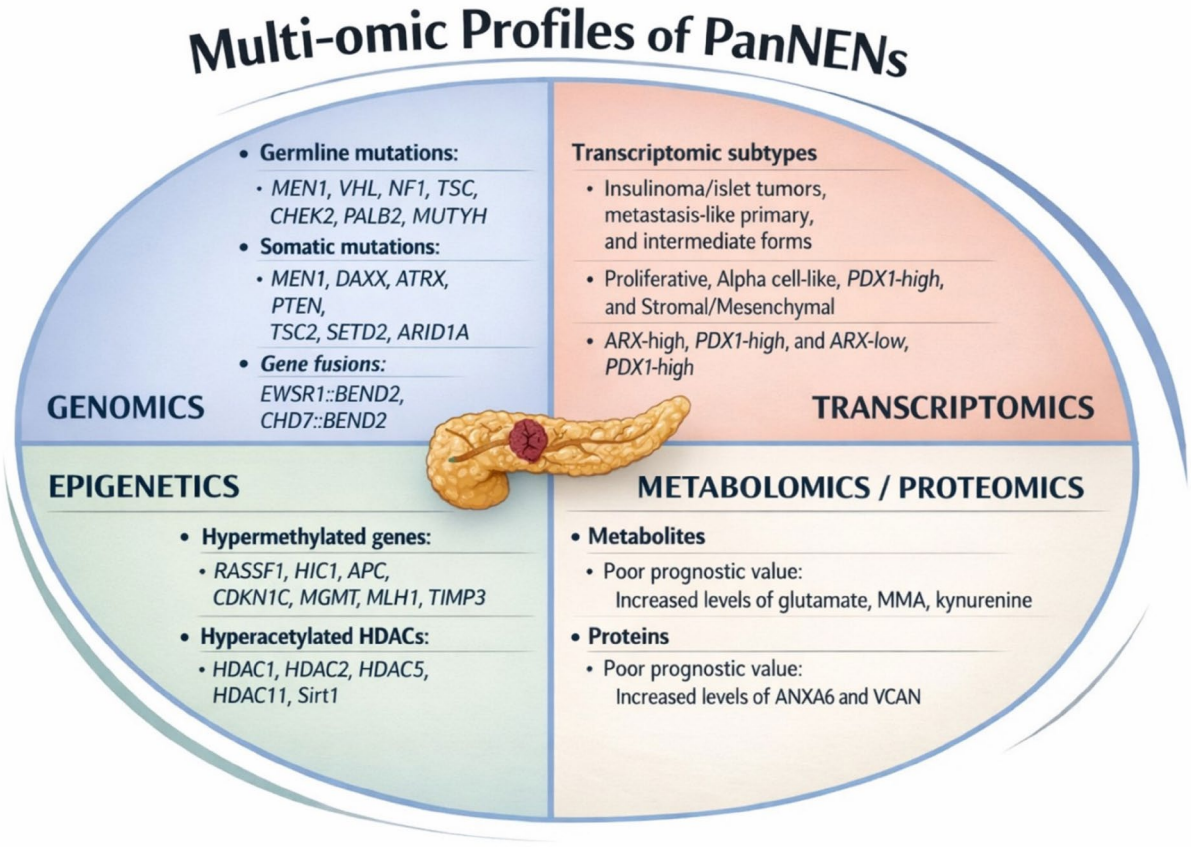
Graphical abstract

This review offers a comprehensive and integrative synthesis of the principal findings across histology, genomics, transcriptomics, epigenetics, metabolomics, proteomics, and radiomics in pancreatic neuroendocrine neoplasms. By integrating multiple omics layers, it advances a more holistic and in-depth characterization of these neoplasms, thereby enhancing the current understanding of their biological complexity.



Background

Neuroendocrine neoplasms (NENs) comprise a heterogeneous group of rare tumors characterized by marked variability in morphology, immunophenotype, molecular landscape, and clinical behavior [1]. Although traditionally associated with specific organs, NENs can arise in virtually any anatomical site, most commonly in the lung, small intestine, and pancreas [1].

Over the past decades, several studies have reported a steadily increasing incidence of NENs, a trend largely attributed to improved diagnostic accuracy and heightened clinical awareness, which has ultimately translated into better patient survival [2–4]. Nonetheless, the diagnosis and clinical management of NENs remain challenging, owing to their biological complexity and the persistent lack of robust, widely validated biomarkers [5].

Gastroenteropancreatic (GEP)-NENs account for approximately 40% of all NENs, with pancreatic NENs (PanNENs) representing 15–20% of this subgroup [6]. Owing to their relative prevalence, the unique biological features of the pancreas —encompassing both exocrine and endocrine functions— and their substantial clinical relevance, PanNENs have historically served as a cornerstone for the development of contemporary NEN taxonomy. Indeed, some of the earliest and most influential insights underpinning current classification systems were derived from studies of PanNENs, providing conceptual frameworks that extend across the broader NEN spectrum [7, 8].

The current World Health Organization (WHO) classification of NENs across all anatomical sites is fundamentally based on the assessment of tumor differentiation and grading, recognizing two major categories: well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). This distinction is pivotal, as it strongly correlates with biological aggressiveness, clinical behavior, and therapeutic response [9]. Notably, the pancreas also represents one

of the most informative models for studying "neuroendocrine differentiation" in non-neuroendocrine malignancies, as entities such as acinar cell carcinoma and pancreatoblastoma frequently exhibit neuroendocrine features at different levels.

In this Review, we provide an integrated overview of the current understanding of PanNENs, with a particular focus on insights derived from recent multi-omics studies. These advances have substantially refined disease stratification and are opening new and compelling avenues not only for basic and translational research but also for clinical decision-making and personalized patient care.

Classification of PanNENs

According to the latest World Health Organization (WHO) classification [9], PanNENs are subdivided into three major categories: well-differentiated PanNETs, further classified into grades 1–3; poorly differentiated PanNECs, which include small-cell and large-cell subtypes; and mixed neuroendocrine/non-neuroendocrine neoplasms (MiNENs). Grading of PanNETs is based on mitotic count and/or the Ki-67 proliferation index (G1: < 2 mitoses/mm² or < 3% Ki-67 index; G2: 2–20 mitoses/mm² or 3–20% Ki-67 index; G3: > 20 mitoses/mm² or > 20% Ki-67 index), whereas PanNECs are, by definition, classified as G3 and are characterized by a mitotic count > 20/mm² or a Ki-67 index > 20% [9].

More recently, sub-grading of G2 PanNETs into G2a (Ki-67 3–< 10%) and G2b (Ki-67 10–20%) has been shown to have striking prognostic significance, with significantly better survival indices for G2a compared to G2b [10]. This finding was confirmed by subsequent analyses [11, 12]. However, such G2a/G2b differences seem to lose relevance once liver metastases develop [12], suggesting the clinical significance in distinguishing G2a vs. G2b only for non-metastatic PanNETs. In contrast to PanNETs, PanNECs are highly aggressive malignancies with a markedly elevated proliferative index, typically exceeding 50–60% [13–16], and consistently exhibit a mitotic count > 20/mm² [9]. In PanNETs, increasing tumor grade correlates with progressively reduced survival [14].

In current clinical practice, more than 90% of PanNETs are classified as non-functioning, as they do not secrete clinically relevant levels of hormones [17]. The remaining subset comprises functioning PanNETs, which release biologically active hormones into the circulation, giving rise to distinct clinical syndromes [18]. Based on the predominant hormone produced, functioning PanNETs are further classified as insulinomas (insulin), gastrinomas (gastrin), glucagonomas (glucagon), somatostatinomas (somatostatin), VIPomas (vasoactive intestinal peptide), as well as serotonin-producing and adrenocorticotropic hormone (ACTH)-producing tumors [18].

Overall, non-functioning PanNETs are associated with a worse prognosis than functioning PanNENs, largely owing to the absence or delayed onset of hormone-related symptoms, which frequently leads to late-stage diagnosis [3, 6].

MiNENs represent a rare tumor category composed of two histologically distinct components: a non-neuroendocrine component (most commonly adenocarcinoma or acinar cell carcinoma) and a neuroendocrine component (typically neuroendocrine carcinoma), each accounting for at least 30% of the total tumor mass. Both components are morphologically identifiable and independently graded [19]. In surgically treated patients, reported 5-year survival rates range from 20% to 60% [19].

Finally, a subset of neoplasms exhibits true dual differentiation within the same tumor cells, detectable at immunohistochemical, molecular, and even ultrastructural levels—for example, with the simultaneous presence of acinar zymogen granules and neuroendocrine granules. These tumors, now designated as "amphicrine" neoplasms by the WHO [9], represent particularly intriguing models for future multi-omics investigations.

Histology of PanNENs

The classical histomorphology of PanNETs is characterized by an organoid growth pattern, most commonly displaying solid, trabecular, nested, or ribbon-like architectural arrangements. PanNETs are typically hypercellular neoplasms composed of monomorphic small- to medium-sized cells with polygonal or cuboidal morphology, eosinophilic cytoplasm, and indistinct cell borders (Fig. 1). Nuclei are usually round to oval, centrally or eccentrically located —occasionally imparting a plasmacytoid appearance— and exhibit the characteristic finely granular "salt-and-pepper" chromatin pattern. Tumoral necrosis is generally absent [20]. In most cases, the stromal component is scant and contains a delicate, richly vascularized network. However, a subset of PanNETs displays prominent stromal sclerosis; notably, serotonin-producing tumors are particularly prone to this feature, underscoring the close interplay between tumor cell phenotype and stromal remodeling [21, 22].

Beyond conventional morphology, several histological variants of PanNETs have been increasingly recognized. These include oncocytic, plasmacytoid, lipid-rich, and hepatoid variants, which are often associated with a more aggressive biological behavior, as well as paraganglioma-like and ductulo-insular variants, which tend to follow a more indolent clinical course. Other patterns, such as pseudoglandular, peliotic, and sclerotic variants, have been described, although their clinical significance remains incompletely defined [20]. The growing

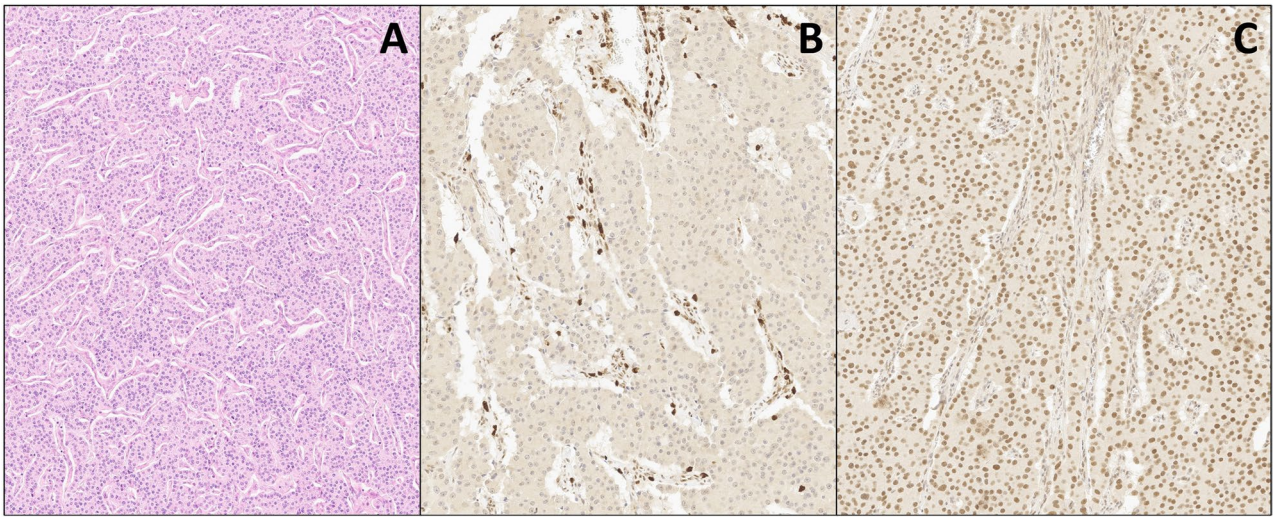


Fig. 1 Histology. Representative histological images of a G1 pancreatic neuroendocrine tumor (**A**, hematoxylin-eosin, original magnification 4x) along with loss of expression of DAXX at immunohistochemistry (**B**, original magnification 20x) and retained ATRX expression (**C**, original magnification 20x)

recognition of these morphological variants further emphasizes the central role of histology in the diagnostic and prognostic stratification of NENs. In this context, the growth pattern at the tumor–host interface may also carry prognostic implications, as PanNETs with pushing borders are generally associated with more favorable outcomes, whereas infiltrative growth patterns correlate with increased aggressiveness [23, 24].

Immunohistochemistry (IHC) provides essential support for the diagnosis of PanNETs. As epithelial neoplasms, PanNETs typically express cytokeratins, most commonly cytokeratins 7, 8, and 18. They also show diffuse positivity for canonical neuroendocrine markers, including synaptophysin and chromogranin A (CgA). Additional markers useful for confirming neuroendocrine differentiation include insulinoma-associated protein 1 (INSM1), CD56, CD200, neuron-specific enolase (NSE), and protein gene product 9.5 (PGP9.5) [25–27]. Importantly, the IHC panel must always include Ki-67 (clone: MIB-1), which is indispensable for tumor grading. In PanNETs, Ki-67 labeling is often heterogeneous, frequently with areas displaying values below 20%.

In contrast, the histomorphology of PanNECs differs markedly from that of PanNETs. PanNECs typically exhibit a solid growth pattern composed of large, irregular sheets or nests of tumor cells, associated with infiltrative margins, a desmoplastic stromal response, and extensive tumoral necrosis, often with geographic or comedo-like features. Cytologically, PanNECs are composed of highly atypical cells with a high nucleus-to-cytoplasm ratio. Two major subtypes are recognized based on cell size: small-cell PanNECs, composed of small cells with hyperchromatic nuclei and finely granular chromatin, and large-cell PanNECs, characterized by markedly atypical cells with abundant cytoplasm and pleomorphic nuclei with prominent nucleoli [28–32].

From an immunohistochemical perspective, PanNECs typically retain cytokeratin expression, similar to their well-differentiated counterparts; however, neuroendocrine markers such as synaptophysin and, in particular, CgA may show only focal or weak staining. Ki-67 remains a critical diagnostic parameter and usually demonstrates uniformly high proliferative indices [9]. Additional immunohistochemical patterns that are diagnostically informative include aberrant p53 expression, most commonly manifesting as diffuse nuclear accumulation, and loss of retinoblastoma protein (Rb) expression. Moreover, PanNECs may exhibit loss of SMAD4, a feature commonly observed in pancreatic ductal adenocarcinoma, supporting their phylogenetic proximity to adenocarcinomas and reinforcing the concept that PanNECs represent the neuroendocrine counterpart of conventional pancreatic carcinomas [33].

The histological diagnosis of mixed neuroendocrine/non-neuroendocrine neoplasms (MiNENs) relies on the identification of at least two morphologically distinct components, one neuroendocrine and one non-neuroendocrine, most commonly showing ductal or acinar differentiation. While IHC is indispensable for confirming lineage differentiation, careful morphological assessment remains the cornerstone of diagnosis. Notably, the Ki-67 index of the NEC component has emerged as a relevant prognostic modifier [34]. Intriguingly, acinar cell carcinomas frequently display substantial neuroendocrine differentiation, either as a discrete neuroendocrine component or, more commonly, as an intermediate histomorphological phenotype with overlapping acinar and neuroendocrine features, often accompanied by expression of neuroendocrine markers. These tumors exemplify the

concept of "amphicrine" neoplasms, in which the same tumor cells exhibit both acinar and neuroendocrine differentiation [35, 36].

Finally, emerging digital pathology approaches and artificial intelligence–based algorithms are increasingly contributing to the histopathological evaluation of PanNENs. These technologies have shown excellent performance in the assessment of tumor margins, including the distinction between pushing and infiltrative growth patterns, as well as in the quantification of the Ki-67 index, providing more standardized measurements and significantly reducing interobserver variability [24, 37, 38].

Genomics of PanNENs

Germline mutations

PanNETs reflect the contribution of both rare, high-penetrance germline alterations and more common, low-penetrance variants. Below, we summarize the most clinically and biologically informative findings.

Rare high-penetrance germline mutations

Inherited cancer predisposition syndromes driven by germline alterations represent a key framework for understanding PanNET oncogenesis. Approximately 15–20% of PanNETs develop in the context of pathogenic germline variants affecting tumor suppressor genes, corresponding to established hereditary syndromes, including multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC) [39–45].

Beyond these canonical conditions, additional germline variants have been described in patients developing PanNETs, including *RET* [41], *PTEN* [46, 47], *PALB2* [48], and *CHEK2* [49]. PanNETs can also rarely arise as part of Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*) [50, 51], familial atypical multiple mole melanoma syndrome (*CDKN2A*) [52, 53], Li–Fraumeni syndrome (*TP53*) [54], and succinate dehydrogenase–associated disease (*SDHx*) [55]. Among functioning PanNETs, germline *MAFA* variants have been reported in insulinomas [56], whereas germline *GCGR* variants underlie glucagon cell hyperplasia and neoplasia [57]. Of note, PanNETs arising in these hereditary settings often develop on a background of dysplastic-like islet cell proliferations and frequently present as multifocal lesions, providing an invaluable model for multi-omics dissection of early tumorigenesis [58].

Large-scale sequencing studies have further consolidated —and expanded— this germline landscape. In a cohort of familial PanNETs, pathogenic germline variants were identified in 17% of patients across multiple genes, including *MEN1*, *MUTYH*, *CDKN1B*, *PTEN*, *CHEK2*, *VHL*, and *BRCA2* [59]. Another study, analyzing patients with metastatic PanNETs but not in a familial setting, detected pathogenic or likely pathogenic germline variants in 16% of cases, involving *MEN1*, *TSC2*, *VHL*, *CHEK2*, *MUTYH*, and *APC* [60]. Two additional studies published in 2023 provided further granularity. The first, focusing on young patients with PanNETs (G1–G2; age 14–50 years at diagnosis), identified germline variants in *MUTYH*, *MEN1*, *RECQL4*, *ERCC3*, *XPC*, and *SLX4* [61]. The second examined high-grade PanNENs (22 G3 PanNETs and 18 PanNECs), reporting germline variants in *FANCA* (one G3 PanNET), *MYOC* (two PanNECs and one G3 PanNET), and *MUTYH* (one PanNEC and one G3 PanNET) [62].

A more recent study stratified patients into a high-risk cohort (early onset, personal or family history of cancer, or syndromic features) and an unselected cohort. In the high-risk cohort (n = 132), 33% of patients (n = 44) harbored germline variants, most frequently involving *MEN1* (n = 25; 56%), followed by DNA repair genes (n = 8; 18%), and *MSH2* (n = 3; 7%). In the unselected cohort (n = 106), germline variants were identified in 21% (n = 22) of patients, enriched for DNA repair genes (n = 9; 40%) and *MEN1* (n = 8; 36%) [63]. Collectively, these data support the implementation of germline testing in routine clinical practice for patients with PanNENs, particularly in those with early-onset disease and/or multiple PanNETs, in whom the probability of detecting a pathogenic germline alteration is highest [44, 64–66].

Importantly, integrating morphology with genomics suggests that specific histological features can serve as clues to underlying germline alterations. The clear cell variant of PanNET is classically associated with VHL syndrome, cystic changes are more frequently encountered in MEN1-associated tumors, and psammomatous bodies are characteristic of pancreatoduodenal somatostatinomas associated with NF1. Serotonin-producing tumors appear to preferentially involve the large duct system, often causing duct obstruction and showing a propensity for prominent stromal sclerosis. These genotype–phenotype correlations underscore the value of integrative frameworks to refine risk assessment and optimize clinical management [67, 68].

Along these lines and with regard to the clinical criteria guiding the implementation of germline testing, current European guidelines indicate that although most NENs across different anatomical sites are sporadic, a hereditary background should be particularly considered in the case of PanNETs [69]. These guidelines recommend germline genetic testing in patients with multiple NENs, in those with a family history of NENs or related syndromic conditions, and in young patients (< 40 years of age). Notably, the National Comprehensive Cancer Network guidelines further suggest that germline testing should at least be considered in all patients diagnosed with PanNETs [70]. Taken together, current guidelines and the most relevant evidence from the literature support the

consideration of germline testing in all patients with PanNETs. This recommendation becomes particularly compelling when one or more of the following conditions are present: (i) age < 40 years at diagnosis; (ii) the occurrence of a NEN in another anatomical site or of another tumor within the spectrum of hereditary syndromes associated with PanNETs (e.g., clear cell renal cell carcinoma for VHL syndrome); (iii) the presence of multiple PanNETs; (iv) a family history of NENs or of tumors associated with hereditary syndromes involving PanNETs; and (v) histopathological features suggestive of syndromic PanNETs, including cystic changes, clear cell morphology, or the presence of psammomatous bodies.

Common germline variants

Evidence supporting a role for common single-nucleotide variants (SNVs) in PanNEN susceptibility remains limited and derives largely from candidate-gene association studies rather than genome-wide association studies (GWAS) [71], reflecting the rarity of PanNENs and the challenge of assembling adequately powered cohorts to detect low-penetrance effects.

In the largest case–control analysis to date (320 PanNET cases and 4,436 controls), a variant (rs2518719) in the *CDKN2A/2B* locus was associated with increased PanNET risk [72]. Homozygosity for the minor allele was associated with more than twofold increased risk relative to other genotypes, and functional studies suggested that this SNV may alter binding of neuron-restrictive silencer factor, providing a mechanistic link between neuroendocrine differentiation programs and tumorigenesis [72]. Another study investigated telomere-length genetics through a polygenic "teloscore" based on 11 telomere-length–associated SNVs, showing an almost twofold increased risk in individuals within the highest teloscore quintile, with ZNF676-rs409627 and *TERT*-rs2736100 emerging as major contributors [73]. These findings implicate telomere maintenance and genome stability as plausible modulators of PanNET development.

The same research group also explored whether PDAC GWAS loci associate with PanNEN susceptibility [73–77]. In a cohort including 369 cases and 3,277 controls, variants at 1q32.1 (*NR5A2*, rs10919791), 8q24.21 (MIR1208/PVT1, rs1561927), and 13q22.1 (*TP63*, rs9543325) showed suggestive associations with PanNET risk, although none met the conventional threshold for genome-wide significance. The possibility of shared germline susceptibility between PDAC and PanNEN is intriguing but requires substantially larger studies to be established.

Several additional association studies performed over the past 15 years remain underpowered and largely unvalidated in independent cohorts [71]. Moreover, limited pharmacogenomic data suggest that germline variation in angiogenesis-related pathways may modulate outcomes: two SNVs in VEGFR3 (rs307826 and rs307821) were associated with poorer overall survival in patients with metastatic well-differentiated PanNETs treated with sunitinib [63, 78].

Overall, although comprehensive GWAS are still lacking, targeted studies have highlighted biologically plausible pathways —including cell-cycle regulation, telomere maintenance, and angiogenesis— that may influence susceptibility and clinical behavior. The field has shifted from viewing PanNENs as predominantly sporadic tumors to recognizing a substantial contribution of germline genetics to disease pathogenesis, presentation, and potentially therapeutic response. The observation that 21–33% of apparently "sporadic" PanNET patients harbor pathogenic germline variants may reshape genetic testing and counselling strategies [63]. However, key challenges remain, including replication across diverse populations, functional validation of candidate variants, and development of clinically deployable decision-support tools. Ultimately, the goal is to translate germline discoveries into improved risk stratification, earlier detection, and more personalized management.

Somatic mutations

Next-generation sequencing has profoundly accelerated the characterization of somatic alterations in PanNENs. Over the past decade, a subset of recurrent mutations has emerged as molecular hallmarks of PanNETs and PanNECs, informing taxonomy within the neuroendocrine spectrum and beyond.

The first large-scale whole-exome sequencing study of sporadic PanNETs (predominantly G1/G2) identified recurrent somatic mutations in *MEN1*, *DAXX* or *ATRX*, *PTEN*, and *TSC2* across 68 surgically resected tumors [79], and provided an early, clear distinction between PanNET and PDAC mutational landscapes [79]. A subsequent whole-genome and RNA-sequencing study confirmed these findings and further delineated at least four recurrently perturbed pathways: DNA damage repair (including *MUTYH*, *CHEK2*, *BRCA2*), chromatin remodeling (including *MEN1*, *SETD2*, *ARID1A*, *MLL3*, *SMARCA4*), telomere maintenance (including *TERT* and *DAXX/ATRX*), and PI3K–mTOR signaling (including *PTEN*, *TSC2*, *TSC1*, *DEPDC5*, and *EWSR* fusions) [59]. Structural rearrangements inactivating tumor suppressors (including *ARID2*, *CDKN2A*, and *SETD2*) and gene fusions (including *EWSR1*:*BEND2/FLI*, *TSC1*:*TMEM71*, and *CHD7*:*BEND2*) further underscored the genomic complexity of PanNETs [59].

ATRX and *DAXX* alterations are mutually exclusive in PanNETs. Although initially linked to favorable outcomes [79], subsequent large series demonstrated that biallelic inactivation is associated with genomic instability,

increased metastatic risk, early postoperative recurrence, and worse prognosis [80–82]. In the evolutionary trajectory of PanNET, these alterations typically arise later [83] and are strongly associated with alternative lengthening of telomeres (ALT) (Fig. 2) [84]. ALT is a telomerase-independent mechanism used by several malignancies, including PanNETs, to overcome telomere shortening and sustain proliferation [84–86]. In PanNETs, ALT is a robust adverse prognostic marker and supports clinical risk stratification, including in small (< 2.0 cm) G1 tumors [81, 82, 85, 87–89]. ALT status can also support assignment of pancreatic origin in neuroendocrine metastases of unknown primary [85] and can be assessed using fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH). The adverse prognostic impact of *DAXX/ATRX* alterations and ALT has also been confirmed in functioning PanNETs, including insulinomas and glucagonomas [90–93].

Compared with G1–G2 PanNETs, the genomic landscape of G3 PanNETs has been less extensively characterized. Available studies report alterations involving *MEN1*, *DAXX/ATRX*, *PTEN*, *TSC2*, *SETD2*, *TP53*, *RNF213*, *APC*, *PRKAR1A*, *ARID1A*, and *LRP1B* [94–97]. Typically, G3 PanNETs do not harbor *RB1* alterations, whereas *TP53* mutations may be present in a subset. Rarely, the acquisition of co-alterations in *TP53* and/or *RB1* can represent a late event in the evolutionary trajectory of PanNETs and appears to enable progression toward PanNEC-like neoplasms (Fig. 2) [98]. Emerging evidence suggests that p53-altered PanNETs may be more prone to aggressive evolution, including transformation into overt PanNECs [16, 99]. NEC-like transformation has also been reported after neoadjuvant therapy in association with newly acquired *TP53* mutations [99]. These observations suggest that PanNET, specifically those in advanced stages of progression, and PanNEC may represent biological compartment that only rarely overlap or communicate. In the vast majority of cases, however, PanNETs and PanNECs remain distinct entities with characteristic histologic, genomic, and clinical features.

Consistent with this distinction, PanNECs typically harbor alterations in *TP53* and *RB1*, together with changes frequently encountered in PDAC, including *CDKN2A*, *SMAD4*, and *KRAS* [32, 94–97, 100]. Only limited differences have been observed between small-cell and large-cell PanNECs; variants in *BRAF*, *MYC*, and *ARID1A* appear to be more frequent in large-cell tumors [97]. Overall, genomic studies indicate that PanNECs are genetically and phenotypically closer to PDAC than to PanNETs [96], supporting their classification as a distinct

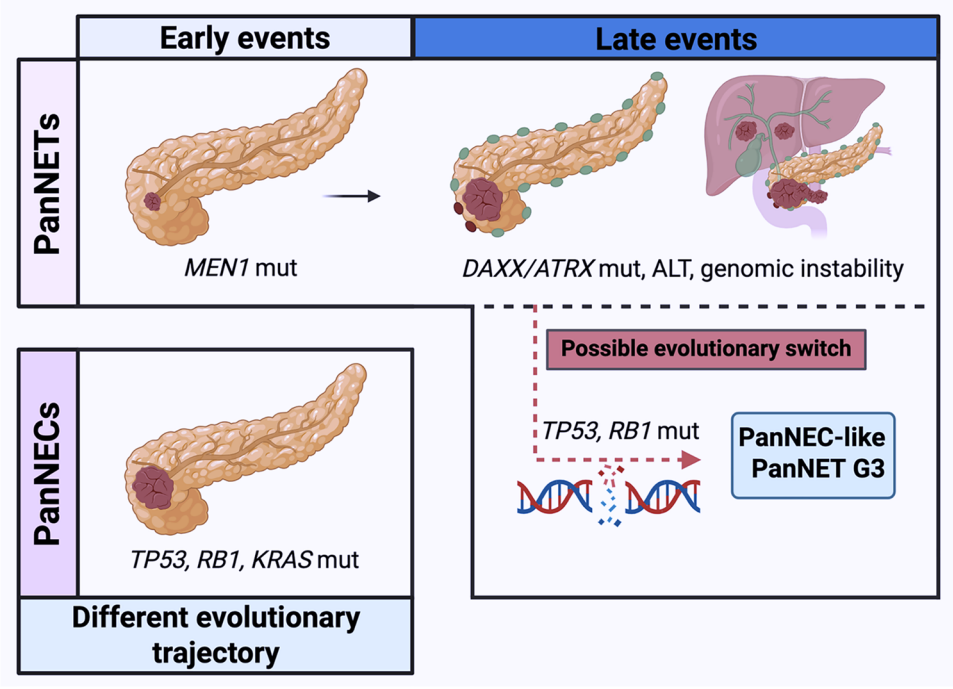


Fig. 2 Evolutionary trajectories of PanNETs and PanNECs. As shown, in well-differentiated PanNETs (top panel), early tumorigenesis is commonly driven by *MEN1* mutations, followed by additional alterations involving *DAXX/ATRX* mutations and activation of ALT. These events contribute to chromosomal/genomic instability and tumor progression. Within this framework, an alternative evolutionary trajectory may occur in cases harboring *TP53/RB1* alterations, potentially leading to PanNEC-like PanNET G3. In contrast, poorly differentiated PanNECs (bottom panel) are typically characterized by alterations in *TP53*, *RB1*, and a limited number of additional genes (including *KRAS*), thus showing a molecular profile closer to PDAC. The existence of a clear stepwise molecular progression for PanNECs remains uncertain. Abbreviations: PanNETs; pancreatic neuroendocrine tumors; PanNECs: pancreatic neuroendocrine carcinomas; ALT: alternative lengthening of telomeres; PDAC: pancreatic ductal adenocarcinoma

entity and suggesting different cells of origin for PanNETs and PanNECs [58, 101].

From a diagnostic standpoint, these genomic distinctions have been translated into practical immunohistochemical panels to complement morphology in differentiating G3 PanNET from PanNEC. Alongside Ki-67, these panels typically include p53 and Rb as PanNEC-associated markers, with p16 and SMAD4 as potentially informative adjuncts, and MEN1 and DAXX/ATRX as supportive markers of PanNET lineage (Fig. 1) [69, 94, 102, 103]. Particularly, in PanNECs, the typical findings at the immunohistochemical level include a homogeneously high Ki-67 (usually > 55%) and the aberrant expression of p53 (usually overexpressed in cancer cells) and Rb (typically lost) [32, 33, 37, 69, 94, 102]. Additional immunohistochemical features that further support a diagnosis of PanNEC include strong and diffuse p16 expression, reported in approximately 60–70% of cases, and loss of SMAD4 expression, observed in up to 30–40% of cases [32, 33, 94]. In contrast, PanNETs display distinct immunohistochemical alterations that parallel their underlying genomic landscape and are not encountered in PanNECs. These include loss of MEN1 expression and mutually exclusive loss of DAXX or ATRX expression [59, 69, 80, 81, 102].

Finally, recurrent copy-number variations (CNVs) have been described, including losses on chromosomes 1, 3, 6 (harboring *DAXX*), 10q, 11 (harboring *MEN1*), and 22q, and gains on chromosomes 4, 5, 7, 12q, 14, 17, 19, and 20 [6, 104–106]. These CNVs have also demonstrated significant prognostic relevance. Indeed, two independent studies reported highly concordant findings, identifying three groups of PanNETs defined by specific CNV patterns, and above all loss of heterozygosity (LOH), with prognostic implications [107, 108]. The first group is characterized by an isolated LOH of chromosome 11 and is associated with a more favorable clinical outcome. Tumors within this category typically harbor biallelic inactivation of *MEN1*. A second group is defined by a pattern of widespread aneuploidy, characterized by recurrent LOH affecting the same (at least) eight chromosomes (1, 2, 3, 6, 10, 11, 16, and 22). This genomic profile is associated with poorer prognosis and is enriched for mutations in *MEN1* and, particularly, in *DAXX* or *ATRX*. Finally, a third group has been described as a heterogeneous "basket" category. Although it shares some similarities with the aneuploid group, it encompasses tumors with highly variable CNV profiles, ranging from relatively flat patterns to markedly fragmented genomes. Consistent with this genomic heterogeneity, the clinical behavior of this group is variable but tends to be more aggressive in most cases.

Somatic alterations in MiNENs largely recapitulate the molecular features of their constituent components [109]. The non-neuroendocrine component typically harbors hallmark alterations of the corresponding carcinoma subtype, including *KRAS*, *TP53*, *SMAD4*, and *CDKN2A* in PDAC [110], and alterations involving *APC*, *BRCA* genes, and mismatch repair (MMR) genes in acinar cell carcinomas [111–114]. The neuroendocrine component, most often a neuroendocrine carcinoma, has been reported to harbor mutations in *KRAS*, *PCK1*, *MLL3*, *GNAS*, *TP53*, *KDR*, *JAK3*, *BRAF*, and *CCND1* [35, 115–118]. Shared driver events across both components provide strong support for a common cell of origin, and further highlight the conceptual and biological distance between PanNECs and PanNETs. The key genomic features of PanNENs are summarized in Fig. 3.

Transcriptomics of PanNENs

Transcriptomic analyses have markedly advanced the understanding of PanNENs, enabling the identification of biologically meaningful molecular subtypes and revealing candidate biomarkers and potential therapeutic vulnerabilities. One of the earliest insights derived from transcriptome profiling of PanNETs was the recognition of α-cell versus β-cell lineage programs. In 2018, Chan and colleagues analyzed RNA expression profiles from 33 PanNETs and demonstrated transcriptional similarities to either α or β cells of normal pancreatic islets, suggesting that PanNETs may originate from distinct endocrine lineages [119]. Consistent with this observation, expression of the transcription factors *ARX* and *PDX1* was strongly associated with α-cell and β-cell identity, respectively [120, 121].

A pivotal transcriptomic study subsequently identified three major PanNEN subtypes: insulinoma/islet tumors, metastasis-like primary (MLP) tumors, and intermediate tumors [122]. Insulinoma/islet tumors, largely composed of insulinomas, represented the least aggressive subgroup and were characterized by transcriptional programs linked to hormone production. In contrast, MLP tumors were enriched among aggressive and metastatic cases, frequently associated with liver or lymph node dissemination, and exhibited upregulation of *ENPP2* and of genes involved in stromal remodeling, hypoxia, and pancreatic progenitor programs, while lacking functional hormone secretion. In a subsequent analysis, the MLP subtype was further shown to be enriched for an immune-high phenotype, characterized by broad activation of immune-related genes and increased expression of immune checkpoint molecules, including *PD-L1* and *PD-L2*, highlighting potential responsiveness to immunotherapeutic strategies in this specific subgroup [123]. Intermediate tumors comprised mainly non-functioning, well-differentiated PanNETs and displayed a distinct transcriptomic profile enriched for *MEN1* and *DAXX/ATRX* alterations, with upregulation of *ENPP2* gene

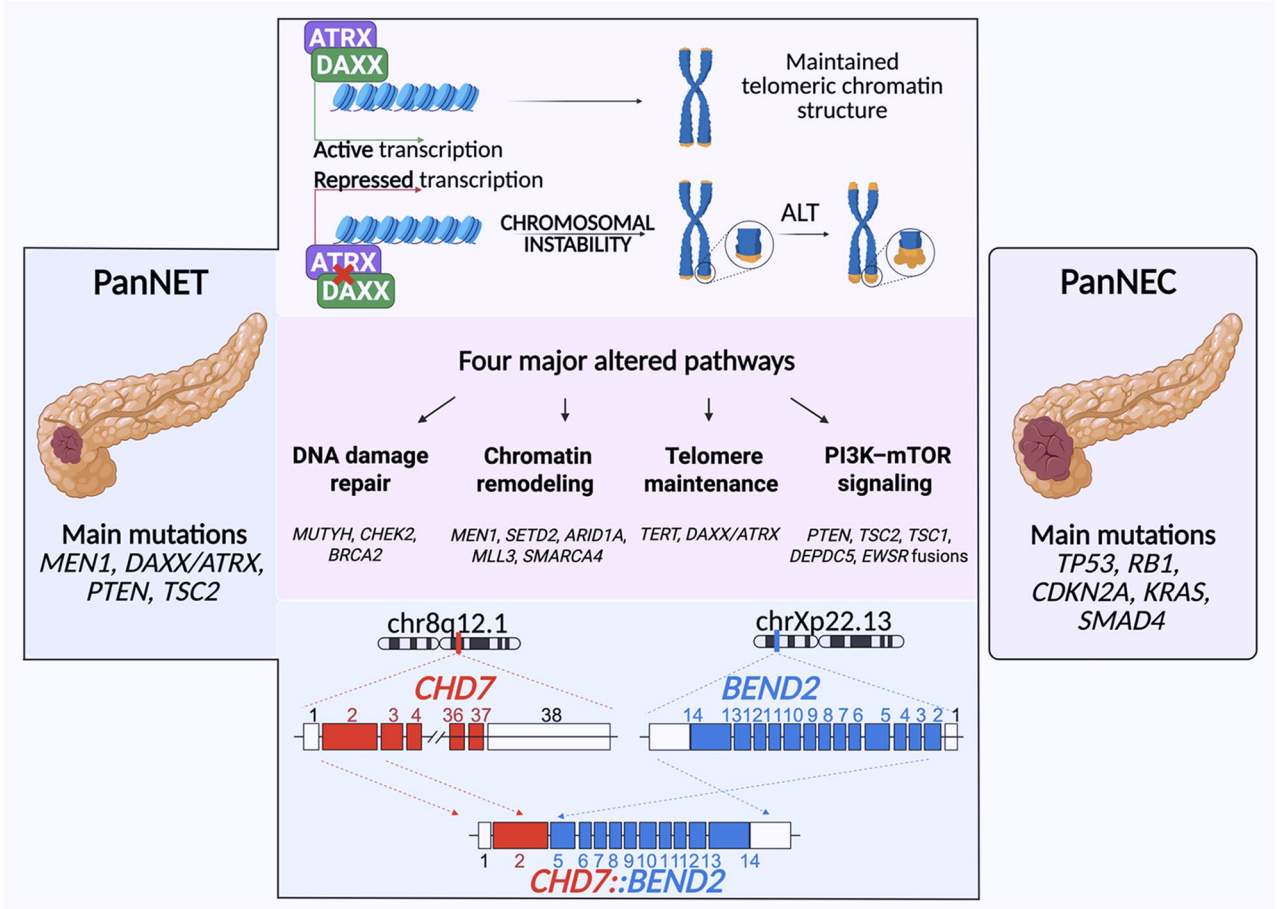


Fig. 3 Genomics of PanNENs. The key somatic mutations identified in PanNENs are reported. Key mutations in PanNETs include *MEN1* and *DAXX/ATRX*, as well as *PTEN* and *TSC2*, although the latter are less frequently altered (left panel). Activation of ALT in PanNETs is strictly associated with *DAXX/ATRX* mutational status (upper middle panel). The four major pathways altered in PanNETs are also depicted, together with a schematic representation of a specific fusion gene identified in a subset of cases (*CDH7*::*BEND2*). The right panel shows the key mutations characterizing PanNECs, with *TP53* and *RB1* the most prominent. Abbreviations: PanNENs: pancreatic neuroendocrine neoplasms; PanNETs: pancreatic neuroendocrine tumors; PanNECs: pancreatic neuroendocrine carcinomas; ALT: alternative lengthening of telomeres

(usually at higher levels than those observed in MLP tumors) [122].

An additional integrative transcriptomic–proteomic analysis delineated four PanNEN subtypes: proliferative, α-cell-like, *PDX1*-high, and stromal/mesenchymal [123]. The proliferative subtype showed high expression of cell cycle–related genes at both the mRNA and protein levels, including enrichment of *MYC* targets, G2/M checkpoint genes, and *E2F* targets, and was predominantly composed of G3 PanNETs and PanNECs, correlating with poor overall survival. The α-cell-like subtype exhibited high *ARX* expression, enrichment of oxidative phosphorylation pathways, and increased abundance of mitochondrial proteins, and was frequently associated with *MEN1* and *DAXX/ATRX* mutations. The *PDX1*-high subtype was characterized by enrichment of pancreatic progenitor markers, including *PDX1* and *NEUROG3*. Finally, the stromal/mesenchymal subtype showed activation of epithelial-to-mesenchymal transition (EMT) and immune-related pathways, with prominent involvement of Hippo signaling [124]. Independent studies subsequently confirmed the existence of α-cell-like and *PDX1*-high PanNET subtypes [119, 120].

Importantly, transcriptomic profiles differ substantially between PanNETs with and without *MEN1–ATRX–DAXX* alterations [119]. Tumors harboring these mutations exhibited increased expression of liver-associated genes (including *APOH*, *ALDH1A1*, *FGB*, *APOC3*) and components of complement and coagulation cascades (including *SERPINA1*, *FGA*, *F10*, *CP*, *MT3*), compared with wild-type tumors. A hepatic transcriptional signature was subsequently shown to correlate with α-cell programming and poorer clinical outcomes [125]. In this context, hepatoid PanNETs —known to express hepatocellular markers such as Hep Par-1 and arginase by immunohistochemistry—represent a particularly intriguing model for further investigation.

A landmark transcriptomic study specifically addressed the distinction between G3 PanNETs and PanNECs using RNA sequencing [33]. Analysis of 30 non-functioning PanNETs and 14 PanNECs revealed clearly separable molecular subtypes. PanNETs clustered into three groups: one characterized by high *ARX* expression and frequent *MEN1* inactivation, a second enriched for *PDX1* expression, and a third showing co-expression of *ARX* and *PDX1*, which was notably associated with immune checkpoint activation [33]. In parallel, PanNECs segregated into two molecular subtypes. The first, termed "ductal-type," displayed high expression of pancreatic ductal lineage markers such as *SPP1* and *CFTR*, frequent *KRAS* mutations, and overexpression of transcription factors including *SOX2*, *ASCL1*, *NKX2-1*, *EZH2*, and *E2F1*. The second, designated "acinar-type," was defined by predominant expression of *PTF1A*, recurrent alterations in WNT signaling, frequent *CDKN2A* loss, and upregulation of acinar-related transcription factors such as *PTF1A*, *GATA4*, *NR5A2*, and *RBPJL* [33].

It is important to emphasize that acinar cell carcinomas frequently display neuroendocrine morphology and immunoreactivity, leading to potential misclassification as PanNECs and vice versa. Indeed, in the largest expert-based reassessment of PanNECs, only 44 of 120 initially classified cases were ultimately confirmed as true PanNECs, with the remainder reclassified predominantly as acinar cell carcinomas or other malignancies [126]. Accordingly, some tumors categorized as "acinar-type" PanNECs in transcriptomic studies may in fact represent acinar carcinomas with neuroendocrine differentiation.

The most recent whole-transcriptome sequencing study of 73 non-functioning PanNETs identified six distinct molecular clusters, with cluster 6 emerging as particularly noteworthy [127]. Tumors within this cluster exhibited aggressive clinicopathological features, including high grade, lymphovascular invasion, and distant metastases. Notably, five tumors in this cluster harbored recurrent *BEND2* fusion genes (*CHD7::BEND2* and *EWSR1::BEND2*; Fig. 3), which were mutually exclusive with *ATRX/DAXX* alterations and strongly associated with poor prognosis. *BEND2*, a chromatin remodeling gene, can be detected by immunohistochemistry, and tumors harboring these fusions frequently showed gastrin immunoreactivity without clinically relevant hormone secretion [127].

Single-cell RNA sequencing (scRNA-seq) approaches have only recently been applied to PanNENs but have already provided important insights. A longitudinal scRNA-seq analysis of over 24,000 cells from primary and metastatic lesions in a patient with G2 PanNET revealed progressive transitions from a neuroendocrine-like state to more proliferative and drug-resistant phenotypes. This evolution was accompanied by a gradual increase in expression of *IGFBP3*, *PCSK1*, *CXCL16*, *SMOC1*, and *FGF14*. In an independent cohort of 46 surgically resected G1/G2 PanNETs, combined immunohistochemical expression of *PCSK1* and *SMOC1* was associated with particularly poor prognosis, suggesting that dual positivity may identify patients at high risk of postoperative recurrence [128].

Another scRNA-seq study interrogated the cellular heterogeneity of non-functioning PanNETs by profiling more than 123,000 cells from primary tumors, adjacent normal tissue, and liver metastases. This analysis identified 12 major cell populations within the tumor microenvironment and revealed marked heterogeneity among endocrine tumor cells, particularly with respect to copy-number variations (CNVs). Cells with high CNV burden activated oncogenic pathways such as mTOR signaling, whereas CNV-neutral cells more closely resembled normal endocrine cells. The study also identified microenvironmental populations associated with metastasis, including regulatory T cells and IL-32–expressing fibroblasts [129].

Transcriptomic data on functioning PanNENs remain limited. A dedicated study of serotonin-producing PanNETs demonstrated a *PDX1*-high/*ARX*-low transcriptional profile resembling β cells, together with upregulation of serotonin biosynthesis and fibrosis-related pathways, including TGF-β signaling and collagen deposition. These tumors occupied an intermediate position between non-functioning PanNETs and ileal neuroendocrine tumors within transcriptomic taxonomies [22].

Finally, transcriptomic analyses of ACTH-producing PanNETs identified recurrent gene fusions in a subset of cases. RNA-targeted sequencing detected *EWSR1::BEND2* fusions in two tumors (one G1 and one G3 PanNET), a *TFG::ADGRG7* fusion in one G3 PanNET, and a *KMT2A::BCOR* fusion in another G3 PanNET. Notably, all fusion-positive cases were wild type for *MEN1* and *ATRX/DAXX* [130]. The principal transcriptomic features of PanNETs are summarized in Fig. 4.

Epigenetics of PanNENs

Epigenetic dysregulation has emerged as a major contributor to the pathogenesis of PanNENs [131]. Unlike genetic alterations, epigenetic mechanisms regulate gene expression without changing the underlying DNA sequence, primarily through DNA methylation, chromatin remodeling, and histone modifications [132–135]. In PanNENs, these processes are tightly interconnected and have been consistently linked to tumor progression, prognosis, and therapeutic response [132].

Among epigenetic mechanisms, DNA methylation represents the most extensively investigated in PanNENs. This process involves the covalent addition of a methyl

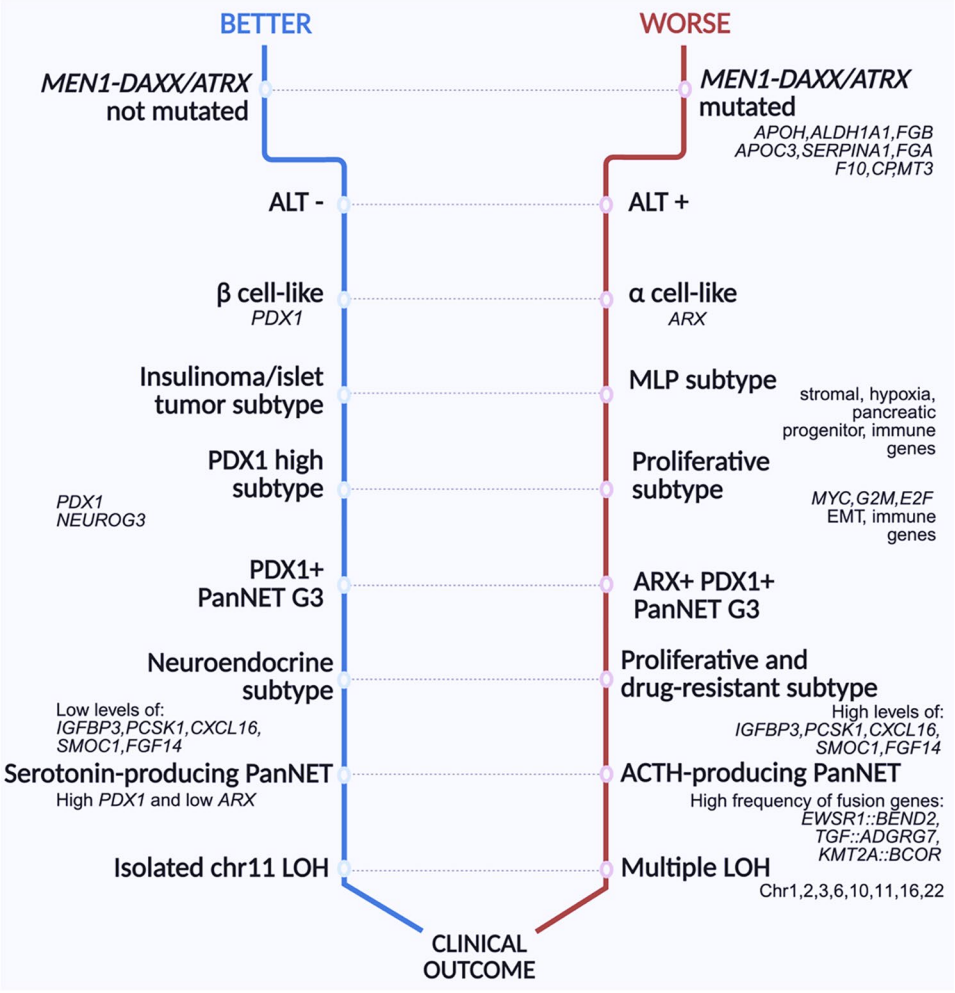


Fig. 4 Transcriptomics of PanNETs. This figure highlights the main subtypes of PanNETs, also based on the analysis of their transcriptome, and their association with clinical outcomes. In the final section, copy number variation data were incorporated as an initial step toward multi-omics integration. Abbreviations: PanNETs: pancreatic neuroendocrine tumors; ALT: alternative lengthening of telomeres; MLP: metastasis-like primary; EMT: epithelial-to-mesenchymal transition; ACTH: adrenocorticotropic hormone, chr: chromosome; LOH: loss of heterozygosity

group to the 5-carbon position of cytosine residues, predominantly within CpG dinucleotides, catalyzed by DNA methyltransferases (DNMTs) [136, 137]. DNA methylation represses transcription by inhibiting transcription factor binding and recruiting methyl-CpG–binding proteins, which promote chromatin condensation and the establishment of transcriptionally inactive heterochromatin [138]. In pancreatic neuroendocrine tumors (PanNETs), global DNA methylation levels are inversely correlated with tumor grade [139]. Multiple studies have demonstrated hypermethylation of tumor suppressor and regulatory genes —including *RASSF1*, *HIC1*, *APC*, *CDKN1C*, *CDKN2A*, *MGMT*, *MLH1*, *TIMP3*, *BRCA1*, *SSTR5-AS1*, and *VHL*— in association with aggressive behavior and metastatic potential [140–152].

Along these lines, the analysis of methylation profiles may also have a significant diagnostic impact. Indeed, a recent investigation showed a very accurate diagnostic prediction of methylation profiling among non-ductal histologies in pancreatic tumors [153]. This analysis may be a significant tool, particularly in cases of challenging differential diagnoses and/or in the preoperative setting. The study of methylation profiles in PanNETs has also brought some novelties regarding the field of cell-of-origin and is intimately connected with the activation of specific transcription factors. Moreover, assessment of *MGMT* promoter methylation status may have a predictive role in identifying patients more likely to benefit from temozolomide-based therapies. However, further evidence and more refined validation are still required to establish this role conclusively [69].

PanNETs harboring *MEN1–ATRX/DAXX* alterations exhibit DNA methylation and gene expression signatures resembling α cells, with high ARX protein expression, whereas PDX1 —a key β-cell transcription factor— is suppressed through promoter methylation [119].

Consistently, chromatin immunoprecipitation sequencing (ChIP-seq) analyses of H3K27ac-marked enhancers in primary non-functioning PanNETs identified two major epigenomic subtypes resembling α and β pancreatic islet cells [120]. Distant relapses occurred almost exclusively in *ARX*$^{+}$/*PDX1*$^{-}$ tumors and, within this subgroup, predominantly in cases exhibiting alternative lengthening of telomeres (ALT). In contrast, β-cell–like PanNETs were associated with more favorable clinical outcomes [121]. Based on *PDX1* promoter methylation status, two epigenetic subtypes —A and B— were identified, corresponding to α-like and β-like tumors, respectively, and displaying distinct clinicopathological features, chromosomal alteration patterns, and prognoses, with subtype A showing significantly worse outcomes [154]. Regarding CNVs, both subtypes A and B frequently displayed chromosomal gains involving chromosomes 5, 7, 9, and 13. However, subtype A was characterized by multiple LOH of chromosomes 1, 2, 6, 10, 11, 16, and 22, whereas subtype B primarily clustered cases with isolated LOH of chromosome 11 [154]. Overall, CNV profiles inferred from methylation array data were largely consistent with those derived from SNP array analyses and previously described in the genomic section.

Genome-wide DNA methylation profiling of 125 primary G1–G2 PanNETs further refined this classification, identifying three major groups reflecting α-like, β-like, and intermediate phenotypes [155]. As expected, α-like tumors expressed *ARX* and were enriched for *DAXX/ATRX* loss, whereas β-like tumors expressed *PDX1*, were enriched of isolated LOH of chromosomal 11 and were generally indolent. Intermediate tumors, either negative for both transcription factors or expressing *ARX* alone, exhibited the highest risk of recurrence. Interestingly, compared to the other two subgroups, intermediate tumors were enriched of copy number events and recurrent whole chromosomal loss [155].

An array-based methylation study of CpG sites within promoter regions of sporadic PanNETs identified three additional epigenetic subgroups (T1–T3) [156]. The T1 subgroup included functioning PanNETs with wild-type *ATRX*, *DAXX*, and *MEN1*. The T2 subgroup comprised tumors harboring *ATRX*, *DAXX*, and *MEN1* mutations, recurrent chromosomal losses, larger tumor size, and poorer prognosis; notably, this group showed hypomethylation of the *MGMT* gene body, associated with increased *MGMT* expression [156]. The T3 subgroup included G1 PanNETs with *MEN1* mutations and isolated chromosome 11 loss and was associated with favorable histopathological features [156].

DNA methylation profiling has also proven useful in distinguishing G3 PanNETs from PanNECs. A recent study identified three methylation-based groups, with well-differentiated PanNETs clustering predominantly in groups A and C, and PanNECs in group B, which was associated, as expected, with the poorest survival outcomes [157]. Mutations typically associated with PanNETs (*MEN1*, *DAXX*, *ATRX*, *TSC2*) were enriched in group A and absent in group B, whereas group B exclusively harbored *KRAS* and *SMAD4* alterations [157].

Collectively, epigenetic studies delineate at least two major PanNET subtypes: (i) a β-cell–like subtype characterized by *PDX1* hypomethylation, absence of ALT, isolated LOH of chromosome 11, and favorable prognosis, and (ii) an α-cell–like subtype defined by ARX expression, frequent *MEN1* mutations, multiple LOH of chromosomes 1, 2, 6, 10, 11, 16, and 22, and more aggressive behavior. Several studies also support the existence of an intermediate group, marked by *DAXX/ATRX* alterations, ALT positivity, increased genomic instability with a higher number of copy number events, reduced *MGMT* expression, and a hybrid methylation profile, suggesting potential sensitivity to alkylating agents such as temozolomide [119, 120, 122, 124, 158]. Notably, when integrating histology with genomic and epigenetic data, *DAXX/ATRX* status and ALT remain the most powerful prognostic modifiers in PanNETs [80].

Epigenetic regulation in PanNENs extends beyond DNA methylation. Mutations in chromatin modifiers such as *SETD2*, *MEN1*, and *DAXX/ATRX* influence not only methylation patterns but also histone modification and genomic stability [159–164]. DNA methylation occurs within a complex chromatin landscape that is tightly regulated by histone modifications [165]. Histone acetylation reduces DNA–histone interactions and promotes transcription, whereas histone deacetylation mediated by histone deacetylases (HDACs) leads to chromatin compaction and gene silencing [165]. Overexpression of several HDACs, including HDAC1, HDAC2, HDAC5, HDAC11, and Sirt1, correlates with higher tumor grade, increased proliferation (Ki-67 index), and poorer survival in PanNETs [104, 166].

Epigenetic data on functioning PanNENs are more limited and largely focused on insulinomas. Targeted methylome sequencing of approximately 30,000 CpG sites within the 11p15.5–p15.4 region containing the *INS* gene revealed that insulinomas largely retain a β-cell–like methylation profile, consistent with their cellular origin, but also display 2,545 differentially methylated CpG sites [167]. The most pronounced changes clustered within four regions of chromosome 11p15, indicating epigenetic reprogramming diverging from canonical β-cell regulation. These findings suggest that *INS* promoter methylation may drive insulin expression independently of classical PDX1-driven β-cell specification [167]. Interestingly, in insulinomas, the *SYT8*/*TNNI2* locus, which is likely involved in the activation of the insulin gene promoter, was found to be hypomethylated. At the same

time, the *INS*/Insulin-like growth factor 2 (*IGF2)* locus was found to be hypermethylated [167].

Clinically, most insulinomas exhibit indolent behavior, small size, and *PDX1* expression, a phenotype consistently supported by epigenetic analyses. However, a subset of insulinomas shows aggressive behavior, larger size, and expression of ARX —a transcription factor absent in normal β cells but present in α and γ cells [90, 91]. These tumors often present with delayed symptomatology, suggesting reduced or late-acquired insulin secretion, and share epigenetic and transcriptional features with non-functioning PanNETs that co-express ARX and PDX1 [90, 91]. Although methylation data on glucagonomas are still lacking, their large size, aggressive behavior, and frequent co-expression of ARX and PDX1 suggest epigenetic similarities with non-functioning PanNETs and aggressive insulinomas [92].

Finally, epigenetic alterations have also been described in other functioning PanNETs. In a cohort of 44 gastrinomas of various origins, including pancreatic tumors, 52% exhibited hypermethylation of a 5′ CpG island within the *CDKN2A* promoter, in the absence of gene mutation or deletion; however, this alteration did not correlate with clinicopathological parameters [168].

Overall, epigenetic profiling holds substantial potential for clinical translation in PanNENs. Integration of DNA methylation and histone modification data may improve prognostic stratification, refine α- versus β-cell–like classification, support challenging diagnostic distinctions —including between G3 PanNETs and PanNECs and among non-ductal neoplasms— and identify tumors with aggressive behavior and increased metastatic risk. The principal epigenetic features of PanNETs are summarized in Fig. 5.

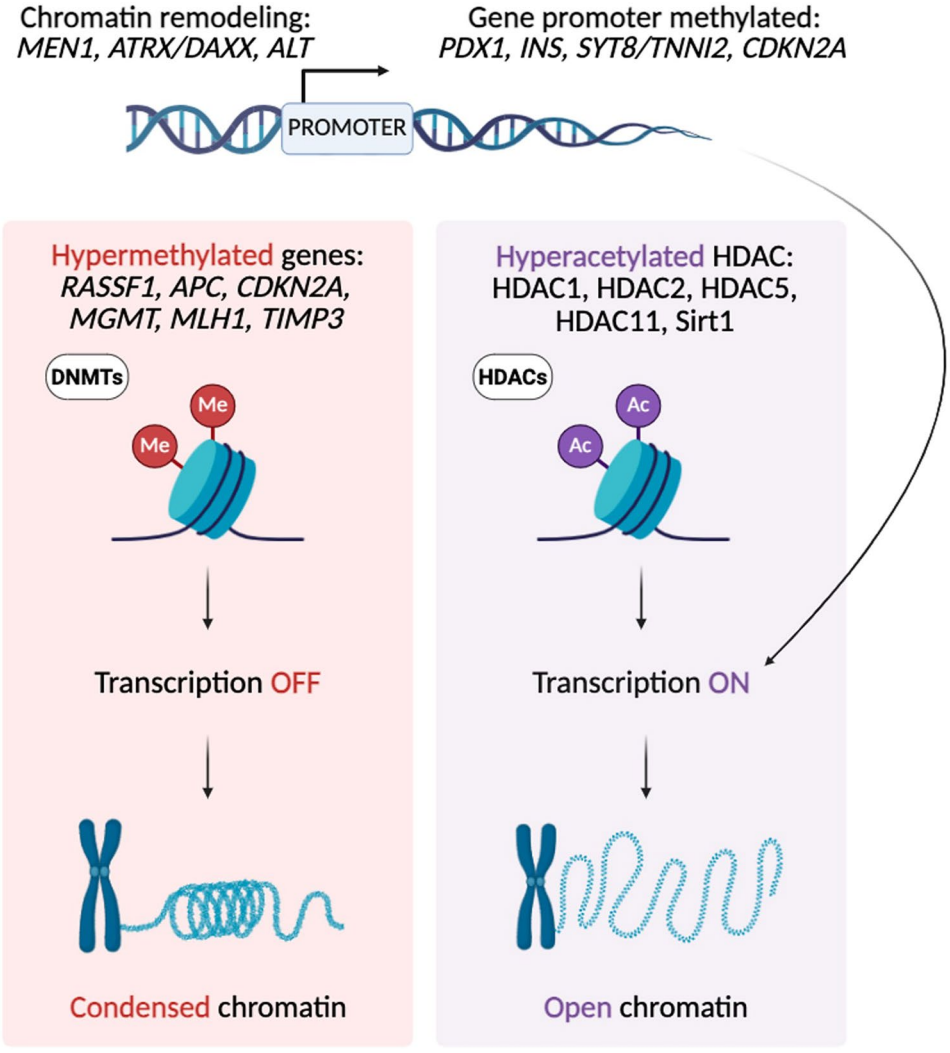


Fig. 5 Epigenetics of PanNETs. The main epigenetics modifications in PanNETs are shown, highlighting crucial contributions of chromatin remodeling, methylation, and acetylation. Abbreviations: PanNETs: pancreatic neuroendocrine tumors; ALT: alternative lengthening of telomeres; DNMTs: DNA methyltransferases. HDACs: histone deacetylases

Metabolomics and proteomics of PanNENs

Metabolomics

Metabolomics offers a unique advantage over genomic approaches by capturing the integrated output of gene–environment interactions and enabling the comprehensive identification of metabolites in biological fluids and tissues, including blood, urine, and tumor samples (Fig. 6). As such, metabolomic profiling provides a functional readout of tumor biology that is closely linked to phenotype and disease behavior.

The first metabolomic study in PanNETs analyzed urine samples from a small cohort of patients (seven G1 and three G2 PanNETs) using mass spectrometry. Compared with healthy controls, patients with PanNETs exhibited reduced urinary levels of creatine, citrate, and hippuric acid, suggesting alterations in energy metabolism and gut microbiota–related pathways [169].

Subsequent studies expanded these observations. In a targeted metabolomic analysis of 99 metabolites in patients with localized and metastatic PanNETs, 38 metabolites were found to be significantly upregulated, including methylmalonic acid, uracil, and 2-hydroxyhexanoic acid [170]. Among these, methylmalonic acid (MMA) emerged as a potential marker of disease progression, with significantly higher serum levels observed in metastatic patients. Functional experiments further demonstrated that MMA promotes tumor cell migration and invasiveness by inducing EMT through activation of inhibin βA, which was also associated with shorter overall survival [170].

More recently, plasma metabolomic profiling of 76 patients with PanNETs, compared with 38 healthy controls, revealed increased levels of phosphoglyceride metabolites and decreased levels of acylcarnitines, consistent with enhanced fatty acid oxidation in PanNETs [171]. Patients with metastatic disease showed additional metabolic shifts, including elevated glutamate levels and reduced lipid metabolites [171]. Notably, syndromic MEN1 patients with PanNETs displayed a distinct metabolic signature characterized by reduced amino acid and fatty acid oxidation metabolites and increased levels of metabolites associated with leucine catabolism, suggesting genotype-specific metabolic reprogramming [171].

Metabolomic data are also available for functioning PanNETs. In a study analyzing urine samples from 18 patients with G1–G2 PanNETs—including seven functioning tumors (four insulinomas, two gastrinomas, and one glucagonoma)—proton nuclear magnetic resonance spectroscopy revealed significant alterations in tryptophan metabolism [172]. Levels of downstream tryptophan metabolites, such as astrigonelline, nicotinic acid, and hippuric acid, were reduced in PanNETs compared with controls, whereas upstream metabolites, including tryptophan itself and kynurenine, were increased [172, 173]. These findings point to dysregulation of tryptophan catabolism as a recurring metabolic feature of PanNETs.

Proteomics

Proteomics —the large-scale study of protein expression, structure, function, post-translational modification, and interaction networks— provides a critical complement to genomic and transcriptomic analyses by directly interrogating the functional effectors of tumor biology (Fig. 6) [174–178].

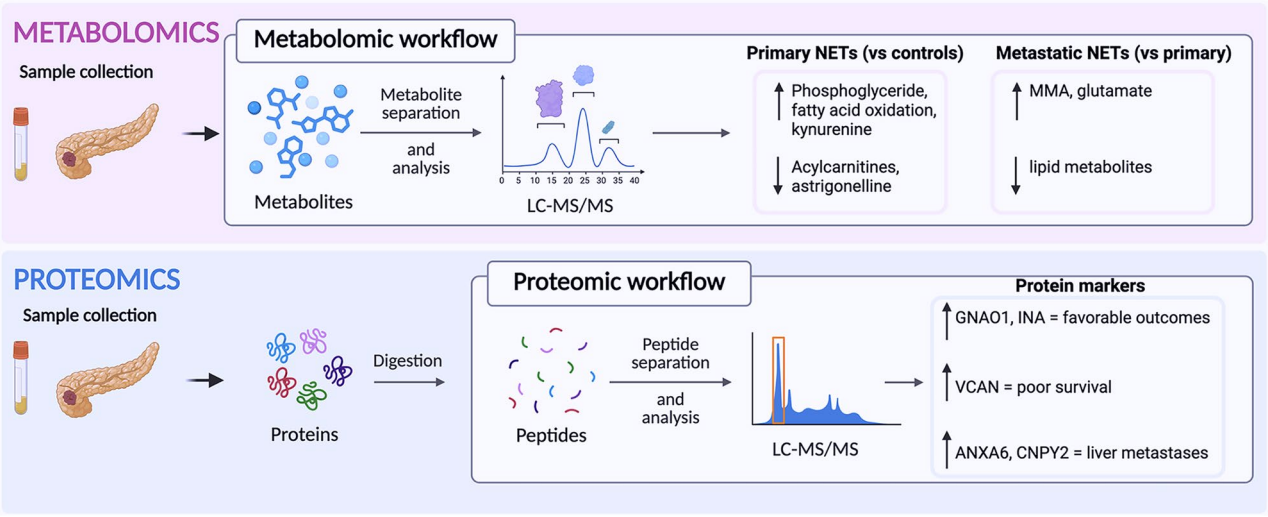


Fig. 6 Metabolomics and Proteomics of PanNETs. The metabolomic and proteomic workflows applied to PanNETs are summarized, together with their major findings. Metabolomic analyses enable discrimination between primary and metastatic PanNETs, whereas proteomic profiling can be used for prognostic stratification. Abbreviations: PanNETs: pancreatic neuroendocrine tumors; LC-MS: liquid chromatography–mass spectrometry; MMA: methylmalonic acid; GNAO1: guanine nucleotide-binding protein subunit α; INA: α-internexin; VCAN: versican core protein; ANXA6: annexin A6; CNPY2: canopy FGF signaling regulator 2

The first proteomic investigation in PanNETs analyzed paired primary tumors and matched liver metastases from seven patients (four G2 and three G3 PanNETs), quantifying more than 2,000 proteins [179]. This study identified 33 proteins selectively upregulated in primary PanNETs and 76 proteins enriched in liver metastases. Among the latter, annexin A6 (ANXA6) and canopy FGF signaling regulator 2 (CNPY2) were validated as potential biomarkers of metastatic progression, showing an inverse correlation with liver recurrence-free survival [179].

Integration of proteomics with transcriptomics has further refined PanNEN classification. As discussed above, a combined transcriptomic–proteomic study identified four major PanNEN subtypes: proliferative, α-cell-like, PDX1-high, and stromal/mesenchymal [124]. Building on this integrative framework, a proteogenomic analysis compared the proteomes of 37 genomically characterized primary PanNETs with nine normal pancreatic samples, quantifying over 7,000 proteins [108]. In this study, G3 PanNETs formed a distinct proteomic cluster, whereas G1–G2 tumors showed greater heterogeneity. Unsupervised clustering identified four proteomic subtypes (P1–P4), with G3 PanNETs confined to the P2 subtype. Notably, the P2 and P3 subtypes were enriched for hypoxia, EMT, inflammatory signaling, and metabolic reprogramming pathways, as well as for genomic alterations involving DNA damage repair genes, chromatin remodelers (including *DAXX/ATRX*), ALT activation, and mTOR signaling, and were associated with poorer survival outcomes [108].

A more comprehensive proteogenomic study recently characterized 108 treatment-naïve non-functioning PanNETs (G1 = 30, G2 = 74, G3 = 4) through integrated genomic, transcriptomic, proteomic, and phosphoproteomic profiling [180]. This analysis provided functional insights into key driver alterations, identifying centromere protein V (CENPV) as a mediator of *MEN1* alterations, a finding validated in conditional *Men1* knockout mouse models. Machine learning–based analyses identified a three-protein prognostic signature, in which high expression of GNAO1 and INA correlated with favorable outcomes, whereas elevated VCAN expression was associated with poorer survival [180].

Proteomic and phosphoproteomic stratification further delineated four molecular subtypes (C1–C4) with distinct biological and clinical features. C1 tumors showed strong activation of SNAI2-mediated EMT and inflammatory pathways and were associated with the poorest prognosis. C2 tumors were enriched for metabolic pathways, including oxidative phosphorylation, and were predominantly α-cell-like PanNETs harboring *DAXX/ATRX* alterations. C3 tumors exhibited upregulation of proliferative programs, including *MYC* and *E2F* targets, G2/M checkpoint, and DNA repair pathways, with *SMARCC1* identified as a key transcriptional regulator; this subgroup was more frequently β-cell-like and expressed higher levels of PDX1. C4 tumors were characterized by activation of VHL-mediated hypoxia, glycolysis, and myogenesis pathways, along with suppression of oxidative phosphorylation, and were associated with the most favorable outcomes. Importantly, drug screening in patient-derived organoids identified cyclin-dependent kinase 5 (CDK5) as a broadly actionable target and CACNA1D as a subtype-specific vulnerability in C2 tumors [180].

Proteomic studies have also provided insights into functioning PanNETs. A comparative analysis of six indolent and six metastatic insulinomas, validated by immunohistochemistry in an independent cohort of 62 insulinomas, identified higher expression of ALDH1A1 and VDAC1 and reduced expression of tumor protein D52 (TPD52) in metastatic lesions [181]. Low TPD52 expression emerged as a strong, independent predictor of poor overall survival [181].

In another study, the proteome of plasma samples from three patients with functioning PanNETs (two patients with metastatic glucagonomas and another one with non-metastatic insulinoma) was analyzed, along with 62 control samples [182]. Peptides related to glucagon and its secretory machine distinguished the two glucagonomas from the insulinoma and the controls, suggesting a potential role as an additional tool for the differential diagnosis of functioning PanNETs [182].

Radiomics of PanNENs

Radiomics is an emerging research field that focuses on the extraction of quantitative features from biomedical images through advanced computational analysis. These radiomic features capture tissue characteristics that are not appreciable by visual inspection and can be integrated with clinical, histological, genomic, or proteomic data to construct predictive and decision-support models. Radiomic features are commonly categorized into first-, second-, and higher-order features. First-order features describe the distribution of voxel intensities within a region of interest using basic statistical measures, such as mean, median, and percentiles. Second-order features characterize spatial relationships between neighboring voxels through texture matrices, including grey-level co-occurrence and grey-level run-length matrices; finally, higher-order features are derived from the application of filters or mathematical transformations to the image [183, 184].

The potential clinical utility of radiomics in PanNETs has been explored across several domains, including lesion characterization and differential diagnosis, prediction of tumor grade, and estimation of treatment response and clinical outcomes. Although the number

of radiomics studies in PanNETs has increased substantially over the past decade, results have often been inconsistent. A meta-analysis by Staal et al. demonstrated that most radiomics studies in PanNETs were of low methodological quality, with a median radiomics quality score of 2 (corresponding to 5.6%), largely due to the lack of prospective design, external validation, and data sharing [185]. These findings underscore the need for more rigorously designed studies. Nonetheless, several promising radiomics models have emerged.

Imaging characterization of PanNETs is generally straightforward, owing to their typical hyperenhancing appearance during the arterial phase across imaging modalities. Diagnostic challenges arise in hypovascular PanNETs, a feature influenced by tumor size, grade, and functionality [186–188]. In such cases, differentiation from pancreatic ductal adenocarcinoma (PDAC) is critical, given the markedly different therapeutic strategies and prognoses. Radiomics has shown potential in this setting. Most studies, primarily based on computed tomography (CT), reported higher minimum, mean, median, percentile, and entropy values and lower skewness in PanNETs compared with PDACs [189–192]. Combined models integrating radiomic and clinical features outperformed radiomics-only approaches, achieving areas under the curve (AUCs) of 0.83–0.88 compared with 0.79–0.87 [192].

Radiomic analyses of apparent diffusion coefficient (ADC) maps derived from magnetic resonance imaging (MRI) have also been investigated. Lower ADC entropy, skewness, and kurtosis were reported in PanNETs compared with PDACs [193], findings that were confirmed using intravoxel incoherent motion MRI, achieving an AUC of 0.93 for differential diagnosis [194]. Radiomics has additionally shown value in distinguishing PanNETs from solid pseudopapillary neoplasms, particularly in lesions ≤ 30 mm with overlapping imaging features. In this context, radiomics-based models significantly outperformed expert radiologists, with accuracies of 86–92% versus 65–78%, respectively [195–197].

Prediction of PanNET grade has been one of the most extensively explored applications of radiomics. CT-based models demonstrated good diagnostic performance, with reported AUCs ranging from 0.74 to 0.96, depending on the grading thresholds applied [198–204]. Models combining radiomics with clinical variables consistently outperformed radiomics-only approaches [205–207]. Although first-order features were frequently selected, results were conflicting, with some studies reporting lower entropy in high-grade tumors [199, 208] and others reporting higher entropy in G2/G3 tumors [209]. MRI-based studies mainly focused on identifying G2/G3 tumors and achieved similarly robust performance [207, 210]. Kurtosis emerged as a recurrent predictor of tumor grade across multiple modalities [210–213].

Positron emission tomography (PET)/CT-based radiomics has also yielded encouraging results. High diagnostic accuracy was reported for differentiation between G1 and G2 PanNETs (AUC 0.90–0.92) [214]. On ^{68}Ga-labeled somatostatin analog PET/CT, higher skewness and kurtosis were associated with non-response to peptide receptor radionuclide therapy (PRRT) [215], whereas higher entropy correlated with improved progression-free and overall survival after PRRT [216]. Additional CT-based studies identified lower entropy and higher skewness as predictors of favorable outcomes [209, 217, 218]. A deep-learning model applied to CT-derived radiomics features achieved superior performance in predicting recurrence (AUC 0.77) compared with conventional machine-learning and combined clinical–radiomic models [219]. The principal radiomic findings in PanNETs are summarized in Fig. 7.

A particularly promising application of radiomics is the assessment of the recently described infiltration grade

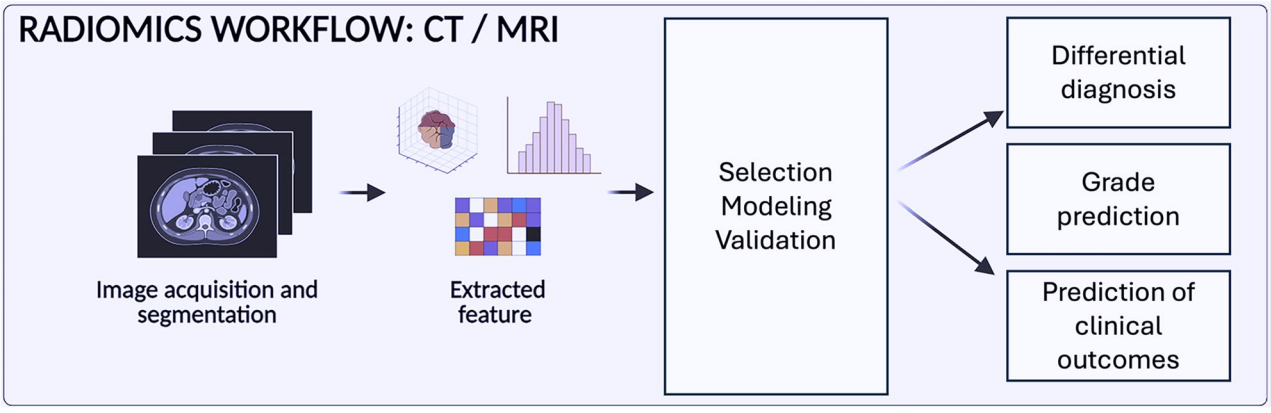


Fig. 7 Radiomics of PanNENs. Overview of radiomics workflow in PanNENs, starting with imaging acquisition and segmentation, followed by radiomic features extraction (e.g., entropy, skewness, and kurtosis). The potential fields of radiomics-based analysis include differential diagnosis, tumor grading prediction, and prognostic stratification. Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging

of PanNETs, which reflects the degree of invasiveness at the tumor–host interface [23, 24, 220]. This parameter has emerged as a stronger prognostic factor than traditional markers such as Ki-67. Radiomic quantification of infiltrative growth patterns represents a low-hanging yet potentially impactful opportunity for refining risk stratification and guiding personalized management strategies.

Other omics on the launch pad

The recent advent of spatially resolved omics technologies is opening new frontiers in cancer research and reshaping the understanding of tumor biology. Among these, spatial transcriptomics (ST) enables the mapping of gene expression within its native tissue architecture, allowing interrogation of the spatial relationships between tumor cells and components of the tumor microenvironment, including stromal and immune populations. These approaches are particularly relevant for addressing critical challenges in oncology, such as therapy resistance, tumor dormancy, and disease relapse [221, 222]. A first exploratory application of ST to PanNETs has recently been reported, revealing spatially distinct gene expression patterns of tumor and stromal cells associated with tumor grade, including differential expression of metalloproteinases [223]. In particular, the authors characterized and compared gene expression profiles of both the neoplastic epithelial compartment and the α-smooth muscle actin (α-SMA)–expressing stromal compartment in three G1, four G2, and one G3 PanNETs [223]. ST-based analysis of the α-SMA–positive stromal cells revealed enrichment of pathways related to extracellular matrix (ECM) remodeling and structural organization, whereas tumor cell–specific gene expression signatures were predominantly associated with proliferative and cell cycle–related programs. Comparative analyses across the three histological grades further demonstrated grade-dependent transcriptional heterogeneity in both tumor and stromal compartments, underscoring dynamic bidirectional interactions during disease progression. Notably, tumor cells located in regions characterized by abundant adjacent α-SMA–expressing stromal cells—potentially corresponding to the infiltrative tumor front or tumor capsule—exhibited marked upregulation of matrix metalloproteinase-9 expression in the G3 PanNET. Collectively, these findings substantiate the concept that both neoplastic and stromal compartments act as active and cooperative drivers of PanNET biology. In particular, the enhanced invasive capacity usually observed in G3 PanNETs may, at least in part, reflect increased expression of ECM-degrading enzymes, including metalloproteinases, within spatially defined tumor–stroma interfaces. To advance our understanding of PanNENs, further investigations leveraging ST are warranted. Such studies should aim to comprehensively characterize the immune microenvironment and to delineate the spatially resolved intra-tumoral heterogeneity, lineage identity, and functional states of neoplastic cells, while systematically elucidating the complex cellular and molecular interactions across these distinct yet interdependent compartments. The integration of these multidimensional datasets will provide a critical framework for the development of future mechanistic studies and for the implementation of innovative translational and therapeutic strategies.

Spatial proteomics represents another rapidly evolving modality, offering advantages over ST such as a robust single-cell resolution with maintained tissue morphology and direct use of canonical protein markers for accurate cell and structure typing [224]. Thus, when applied to the study of PanNENs, this methodology has the potential to further expand and refine the conceptual and technological framework provided by ST, opening new avenues for the spatially resolved dissection of tumor architecture and microenvironmental interactions. In parallel, spatial metabolomics allows the direct localization of small molecules —including metabolites, lipids, glycans, and peptides— within tissue sections, adding an additional functional layer of information [224]. However, the complexity and scale of data generated by spatial omics pose substantial analytical and interpretative challenges, particularly with regard to clinical translation [221]. Consequently, artificial intelligence–based approaches are increasingly recognized as essential companions to spatial technologies, enabling efficient management of high-dimensional datasets, extraction of meaningful patterns, and development of predictive models [221].

Within the broader landscape of artificial intelligence–driven methodologies, pathomics has recently emerged as a novel omics discipline. By applying computational and machine-learning approaches to digitized histopathological slides, pathomics enables large-scale quantitative extraction of morphological features, effectively transforming routine pathology images into high-dimensional omics data. This approach holds particular promise for standardizing assessment of parameters such as Ki-67 index, mitotic count, and tumor infiltration margins [24, 37, 225, 226]. Collectively, these emerging omics platforms are poised to substantially expand the investigative toolkit available for PanNEN research and hold great promise for advancing understanding of this complex disease spectrum.

Towards integration

The integration of multiple omics layers is poised to profoundly reshape our understanding of PanNENs, enabling a shift beyond traditional classifications based solely on histopathological and clinical features. This integrative approach finds its most comprehensive application

in PanNETs (Fig. 8; Table 1). The combined analysis of genomic, transcriptomic, epigenetic, metabolomic, and proteomic data now allows the reconstruction of the biological architecture of these tumors as a complex and dynamic system, in which distinct molecular alterations drive specific phenotypes and cellular lineages. Accordingly, PanNETs should no longer be regarded as a single disease entity with variable degrees of aggressiveness, but rather as a heterogeneous group of biologically distinct tumors characterized by defined cellular programs and evolutionary trajectories.

At the genomic level, PanNETs exhibit a relatively limited mutational burden compared with other solid tumors, with recurrent alterations predominantly affecting *MEN1*, *DAXX*, and *ATRX*. However, the biological relevance of these mutations becomes fully apparent only when integrated with transcriptomic and epigenetic data. Transcriptomic profiling has uncovered distinct molecular signatures reflecting divergent endocrine differentiation programs, with tumors polarized toward α-cell, β-cell, or intermediate (hybrid) identities. These transcriptional programs are supported by specific epigenetic landscapes, including ARX activation and PDX1 promoter methylation in the α-cell group, which appear to function as molecular switches governing cell identity. Of note, CNVs also appear to play a central role in delineating distinct PanNET subtypes. In particular, β-cell–like tumors are characterized by enrichment of isolated LOH of chromosome 11, whereas α-cell–like tumors exhibit recurrent, multiple LOH affecting chromosomes 1, 2, 3, 6, 10, 11, 16, and 22. In contrast, intermediate tumors display a markedly more heterogeneous CNV landscape.

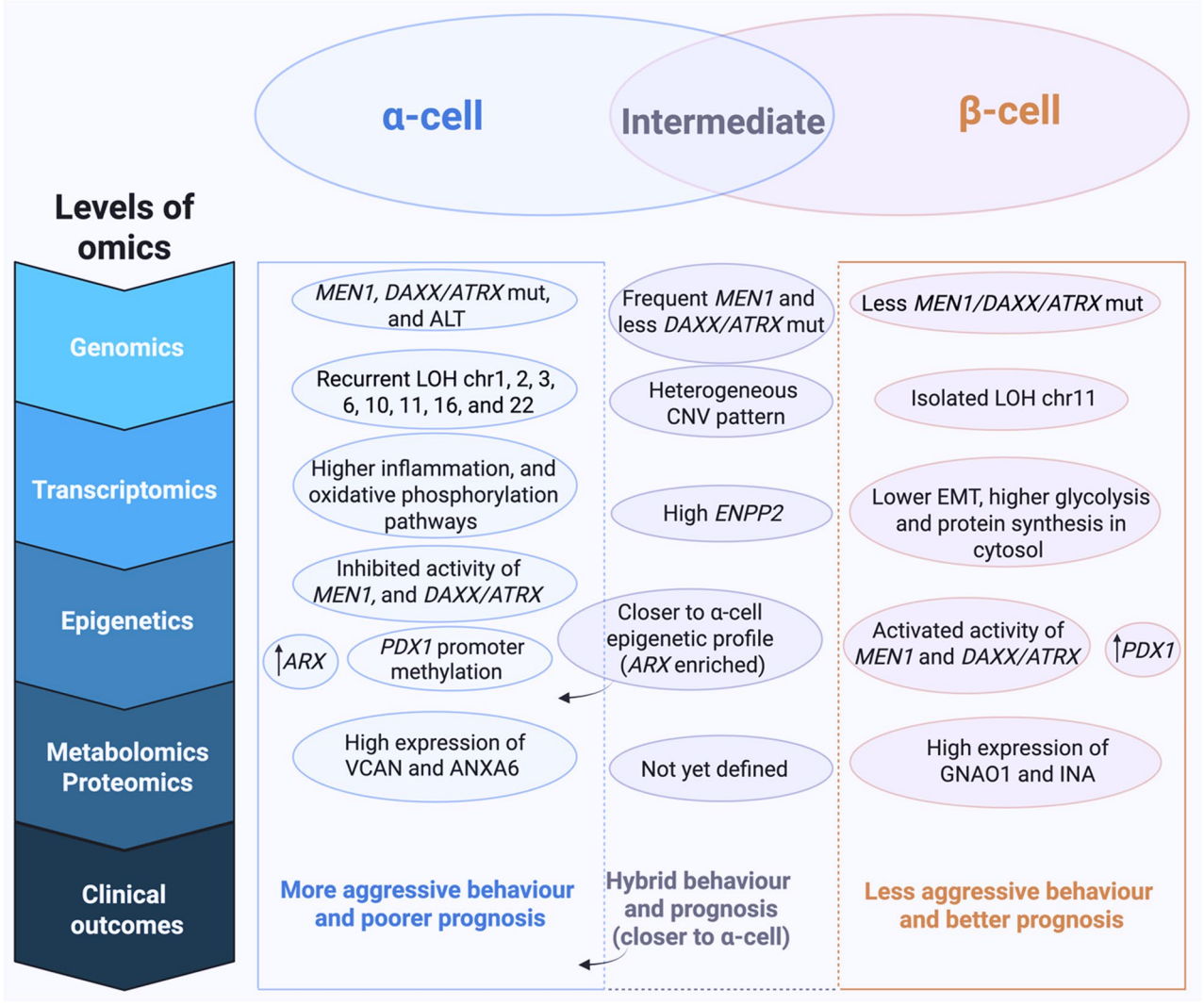


Fig. 8 Multi-omic integration panel for PanNETs. This figure offers an integrated overview of the composite multi-omics levels of PanNETs, highlighting the most distinctive profiles that are oriented based on α-cell, β-cell, and intermediate nature. Abbreviations: ALT: alternative lengthening of telomeres; *ENPP2*: Ectonucleotide Pyrophosphatase/Phosphodiesterase 2; EMT: epithelial-to-mesenchymal transition; VCAN: versican core protein; ANXA6: annexin A6; GNAO1: guanine nucleotide-binding protein subunit α; INA: α-internexin

Table 1 Integrative overview of multi-omics layers in PanNETs, presented in relation to their prognostic relevance

	Features associated with poorer survival	Features associated with better survival
Lineage cell identity	α-cell lineage and intermediate tumors	β-cell lineage
Genomics	*MEN1*, *DAXX/ATRX* mut and ALT; recurrent LOH of chr1,2,3,6,10,11,16, and 22; higher number of CNV events and/or heterogeneous CNV pattern	Less *MEN1/DAXX/ATRX* mut; isolated LOH chr11
Transcriptomics	Higher inflammation and oxidative phosphorylation pathways	Lower EMT, higher glycolysis and protein synthesis in cytosol
Epigenetics	Inhibited activity of *MEN1/DAXX/ATRX; PDX1* promoter hypermethylation; α-like methylation/enhancer state	Activated activity of *MEN1/DAXX/ATRX; PDX1* epigenetic activation state
Metabolomics / Proteomics	High blood levels of VCAN and ANXA6	High blood levels of GNAO1 and INA
Lineage protein markers	Positive for ARX, IRX2, and TM4SF4	Positive for PDX1, NEUROG3, and INS

Abbreviations. *PanNETs* pancreatic neuroendocrine tumors, *ALT* alternative lengthening of telomeres, *LOH* loss of heterozygosity, *chr* chromosome, *CNV* copy-number variation, *EMT* epithelial-to-mesenchymal transition, *VCAN* Versican core protein, *ANXA6* Annexin A6, *GNAO1* Guanine nucleotide-binding protein subunit α, *INA* α-internexin, *INS* insulin

Proteomic analyses add a further layer of functional resolution. Tumors with an α-cell signature display enhanced activation of inflammatory pathways and oxidative phosphorylation, accompanied by high expression of proteins such as VCAN and ANXA6, which are associated with a more invasive phenotype. In contrast, β-cell–like tumors display a metabolic profile biased toward glycolysis and protein synthesis, with increased expression of GNAO1 and INA, and are associated with a clinically less aggressive behavior. These lineage-specific functional differences would remain largely unrecognized without a cross-layer, multi-omics approach capable of linking initiating genetic events to downstream cellular programs. Collectively, this integrated framework supports the existence of three distinct lineage entities within PanNETs: α-cell, β-cell, and intermediate tumors.

Overall, the α-cell group is characterized by functional inactivation of *MEN1*, *DAXX*, and *ATRX*, presence of ALT phenotype, multiple LOH affecting chromosomes 1, 2, 3, 6, 10, 11, 16, and 22, ARX protein expression, *PDX1* promoter methylation, and a transcriptomic profile enriched in oxidative stress and inflammatory pathways, features that correlate with poor prognosis. Conversely, the β-cell lineage retains tumor suppressor gene activity, expresses PDX1 protein, harbors isolated LOH of chromosome 11, and displays a more differentiated metabolic program centered on glycolysis, consistent with a more indolent clinical course. Between these two extremes, an "intermediate" population emerges, exhibiting hybrid and plastic features that may represent either a transitional state or an independent lineage. From a clinical perspective, the major implication of this framework lies in the potential for more refined prognostic stratification, a critical need in PanNETs given their marked biological heterogeneity and wide variability in survival outcomes. In surgically resectable disease, multi-omics profiling may aid in identifying high-risk tumors that could benefit from more aggressive surgical strategies rather than active surveillance. In metastatic settings, integrative omics analyses may inform therapeutic decision-making, including the identification of surgical opportunities in oligometastatic patients with more biologically indolent tumors.

Indeed, while the clinical implementation of the multi-omics revolution is still awaited, some immediate clinical applications can already be envisaged: (i) implementation of germline testing in patients with PanNETs, at least in cases with a well-founded clinical suspicion, as discussed in the relevant section of this manuscript; (ii) assessment of *DAXX*/*ATRX* mutational status, or at minimum the corresponding immunohistochemical evaluation, and/or detection of ALT by FISH in small PanNETs (< 2 cm), to help guide clinical decision-making (i.e., surgical resection versus active surveillance), as well as in resected tumors for prognostic stratification and refinement of follow-up strategies, including shorter surveillance intervals for biologically more aggressive tumors; and (iii) evaluation of *MGMT* promoter methylation in the metastatic setting as a potential predictive biomarker for temozolomide-based therapies, while acknowledging that further studies are required to fully elucidate its clinical utility.

Finally, it is essential to highlight that this integrative multi-omics knowledge provides a valuable foundation for basic and translational research aimed at uncovering novel actionable alterations beyond those currently addressed by precision oncology approaches.

Conclusions

PanNENs constitute a highly heterogeneous group of neoplasms, with persistent grey areas across diagnostic, biological, and clinical domains. The application of multi-omics technologies has nonetheless led to substantial progress in dissecting the complex molecular, cellular, and microenvironmental landscape of these tumors. Moving forward, a key priority will be the effective integration of multi-omics data into unified analytical frameworks, enabling a more holistic and patient-centered approach. Such integration is essential to accelerate

the translation of research advances into routine clinical practice, ultimately improving prognostication, risk stratification, therapeutic decision-making, and patient outcomes.

Abbreviations

PanNENs	Pancreatic neuroendocrine neoplasms
PanNETs	Pancreatic neuroendocrine tumors
PanNECs	Pancreatic neuroendocrine carcinomas
MiNENs	Mixed neuroendocrine/non-neuroendocrine neoplasms
NENs	Neuroendocrine neoplasms
GEP	Gastroenteropancreatic
NETs	Neuroendocrine tumors
NECs	Neuroendocrine carcinoma
VIP	Vasoactive intestinal peptide
ACTH	Adrenocorticotropic hormone
IHC	Immunohistochemistry
INSM1	Insulinoma-associated protein 1
NSE	Neuron-specific enolase
PGP9.5	Protein gene product 9.5
SDHx	Succinate dehydrogenase
SNVs	Single-nucleotide variants
GWAS	Genome-wide association studies
PDAC	Pancreatic ductal adenocarcinoma
ALT	Alternative lengthening of telomeres
FISH	Fluorescent in situ hybridization
CISH	Chromogenic in situ hybridization
CNVs	Copy-number variations
LOH	Loss of heterozygosity
MLP	Metastasis-like primary
ENPP2	Ectonucleotide pyrophosphatase/phosphodiesterase 2
EMT	Epithelial-to-mesenchymal transition
scRNA-seq	Single-cell RNA sequencing
DNMTs	DNA methyltransferases
HDACs	Histone deacetylases
INS	Insulin
IGF2	Insulin-like growth factor 2
MS	Mass spectrometry
MMA	Methylmalonic acid
ANXA6	Annexin A6
CNPY2	Canopy FGF signaling regulator 2
CENPV	Centromere protein V
GNAO1	Guanine nucleotide-binding protein subunitα
INA	α-internexin
VCAN	Versican core protein
CDK5	Cyclin-dependent kinase 5
CACNA1D	Calcium voltage-gated channel subunit α1D
VDAC1	Voltage-dependent anion-selective channel 1
CT	Computed tomography
AUC	Areas under the curve
ADC	Apparent diffusion coefficient
MRI	Magnetic resonance imaging
PET	Positron emission tomography
68Ga-SSA	Gallium-68 labeled somatostatin analog tracer
SP	Spatial transcriptomics
α-SMA	α-smooth muscle actin
ECM	Extracellular matrix

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MB, AS, CL: study conception; MB, AG, SV, SDF, AS, CL: study design; all authors: review of the literature; all authors: interpretation and discussion of findings; MB, AG, SV, SDF, AS, CL: writing (original draft); all authors: writing (review, editing) and final approval of the submission in this current version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable (review of the literature).

Consent for publication
Not applicable (review of the literature).

Competing interests
All the authors have no competing interest that can influence the results and/or discussion reported in this paper. Regarding competing interest outside this study, the full disclosure is as follows: Aldo Scarpa reports honoraria from Incyte, MSD, and Medica (consulting and speaker bureau) and Claudio Luchini reports honoraria from Astellas (consulting and advisory board), and from Bayer, MSD, Gilead sciences, and Medica s.r.l. (consulting and speaker bureau). The other authors have no competing interest to declare.

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