Seminars in Cancer Biology 112 (2025) 112–125

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Pancreatic neuroendocrine neoplasms (pNENs): Genetic and environmental biomarkers for risk of occurrence and prognosis

Matteo Tacelli [a], Manuel Gentiluomo [b], Paolo Biamonte [a,c], Justo P. Castano [d,e,f,g], Maja Cigrovski Berković [h], Mauro Cives [i,j], Sanja Kapitanović [k], Ilaria Marinoni [l], Sonja Marinovic [k], Ilias Nikas [m], Lenka Nosáková [n], Sergio Pedraza-Arevalo [d,e,f,g], Eleonora Pellè [o], Aurel Perren [l], Jonathan Strosberg [o], Daniele Campa [b], Gabriele Capurso [a,c,*]

[a] Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational and Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy
[b] Department of Biology, University of Pisa, Pisa, Italy
[c] Vita-Salute San Raffaele University, IRCCS Ospedale San Raffaele, Milan, Italy
[d] Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Córdoba, Spain
[e] Department of Cell Biology, Physiology, and Immunology, University of Córdoba, Córdoba, Spain
[f] Reina Sofia University Hospital, Córdoba, Spain
[g] CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Córdoba, Spain
[h] Department for Sport and Exercise Medicine, Faculty of Kinesiology University of Zagreb, Zagreb 10000, Croatia
[i] Interdisciplinary Department of Medicine, University of Bari "Aldo Moro", Bari, Italy
[j] Division of Medical Oncology, A.O.U. Consorziale Policlinico di Bari, Bari, Italy
[k] Laboratory for Personalized Medicine, Division of Molecular Medicine, Ruđer Bošković Institute, Zagreb 10000, Croatia
[l] Institute of Tissue Medicine and Pathology, University of Bern, Bern, Switzerland
[m] Medical School, University of Cyprus, Nicosia, Cyprus
[n] Clinic of Internal Medicine - Gastroenterology, JFM CU, Jessenius Faculty of Medicine in Martin (JFM CU), Comenius University in Bratislava, Bratislava, Slovakia
[o] Department of GI Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

ARTICLE INFO

Keywords:
Neuroendocrine neoplasms
Genetic
Risk factors
Radioligand
Somatostatin
NET
NEN
PNET
PanNEN

ABSTRACT

Pancreatic neuroendocrine neoplasms (pNENs) are rare and heterogeneous tumors arising from neuroendocrine cells, representing approximately 10 % of all Gastro-Entero-Pancreatic neuroendocrine neoplasms. While most pNENs are sporadic, a subset is associated with genetic syndromes such as multiple endocrine neoplasia type 1 (MEN1) or von Hippel-Lindau disease (VHL). pNENs are further classified into functioning and non-functioning tumors, with distinct clinical behaviors, prognoses, and treatment approaches. This review explores genetic and environmental biomarkers that influence the risk, prognosis, and therapeutic responses in pNENs. The epidemiology of pNENs reveals an increasing incidence, primarily due to advancements in imaging techniques. Genetic factors play a pivotal role, with germline mutations in MEN1, VHL, and other genes contributing to familial pNENs. Somatic mutations, including alterations in the mTOR pathway and DNA maintenance genes such as DAXX and ATRX, are critical in sporadic pNENs. These mutations, along with epigenetic dysregulation and transcriptomic alterations, underpin the diverse clinical and molecular phenotypes of pNENs. Emerging evidence suggests that epigenetic changes, including DNA methylation profiles, can stratify pNEN subtypes and predict disease progression. Environmental and lifestyle factors, such as diabetes, smoking, and chronic pancreatitis, have been linked to an increased risk of sporadic pNENs. While the association between these factors and tumor progression is still under investigation, their potential role in influencing therapeutic outcomes warrants further study. Advances in systemic therapies, including somatostatin analogs, mTOR inhibitors, and tyrosine kinase inhibitors, have improved disease management. Biomarkers such as Ki-67, somatostatin receptor expression, and O6-methylguanine-DNA methyltransferase (MGMT) status are being evaluated for their predictive value. Novel approaches, including the use of circulating biomarkers (NETest, circulating tumor cells, and ctDNA) and polygenic risk scores, offer promising avenues for non-invasive diagnosis and monitoring. Despite these advancements, challenges remain, including the need for large, well-annotated datasets and validated biomarkers. Future research should integrate multi-omics approaches and leverage liquid biopsy technologies to refine

* Correspondence to: IRCCS San Raffaele Hospital, Vita Salute San Raffaele University, Via Olgettina 60, 20132, Milano, Italy.
E-mail address: capurso.gabriele@hsr.it (G. Capurso).

https://doi.org/10.1016/j.semcancer.2025.03.005
Received 17 January 2025; Received in revised form 7 March 2025; Accepted 19 March 2025
Available online 28 March 2025

diagnostic, prognostic, and therapeutic strategies. Interdisciplinary collaborations and global consortia are crucial for overcoming current limitations and translating research findings into clinical practice. These insights hold promise for improving prevention, early detection, and tailored treatments, ultimately enhancing patient outcomes.

1. Introduction

Neuroendocrine neoplasms (NENs) arise from cells localized in the diffuse neuroendocrine system [1]. Pancreatic neuroendocrine neoplasms (pNENs) are a subgroup of NENs that are believed to originate from the precursors of islet cells and express neuroendocrine markers, such as synaptophysin and chromogranin A [2]. This review aims to provide information about genetic and environmental biomarkers for the risk of occurrence and prognosis of pNENs.

1.1. Epidemiology of pNENs

Pancreatic NENs comprise approximately 10 % of all Gastro-Entero-Pancreatic NENs, with an approximate incidence of 0,5 per 100,000 inhabitants [3]. The incidence of non-functioning pancreatic NENs, which represents approximately 60 %-90 %, has increased over time due to the widespread use of high-quality imaging techniques. However, some functioning pNENs are so rare that only a few cases have been described in literature [4].

1.2. Stratifying pNENs

Most pNENs are sporadic, but some occur as a part of various genetic syndromes, such as multiple endocrine neoplasia type 1 (MEN1) or type 4 (MEN4), or, more rarely, neurofibromatosis type 1 (NF1), von Hippel – Lindau disease (VHL), or tuberous sclerosis complex (TSC) [5]. Pancreatic NENs associated with inherited syndromes are mostly non-functioning [6], except for MEN1 syndrome, in which functional pNENs account for approximately 30 % of the cases.

According to their ability to secrete hormones or peptides that in turn cause a defined clinical syndrome, pNENs are divided into two main groups: non-functioning (70 %) and functioning (30 %) [7]. Some NENs secrete inactive hormonal variants that do not cause symptoms. While these tumors may exhibit positive hormonal expression on immunohistochemical staining, this alone is insufficient for the diagnosis of a functioning NEN, which remains a clinical determination [4]. The most commonly functioning pNENs are insulinomas, which are usually small and rarely malignant (5 % of all cases). Other functioning pNENs include gastrinoma, glucagonoma, VIPoma, GRHoma, ACTHoma, and pNEN-causing carcinoid syndrome [8]. These tumors are rare and usually exhibit malignant behavior.

The two most commonly employed staging systems for PNETs were developed by the European Neuroendocrine Tumors Society (ENETS) and subsequently adopted and refined by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) [9].

Several consensuses exist for the pathological grading system of pNENs (the World Health Organization (WHO) pathological classification, the ENETS guidelines [4], the NANETS consensus [10], the National Comprehensive Cancer Network (NCCN) guidelines [11], and the Chinese Society of Clinical Oncology expert consensus), but the WHO classification is the most used. Based on tumor differentiation and grading, which is defined by the proliferative activity assessed either by mitotic counts or by the rate of cells staining for Ki-67, the 2017 WHO system classified pNENs as well-differentiated NENs (NET G1 if Ki-67 $<$ 3 %, NET G2 if Ki-67 3 %–20 %, and new category NET G3 with Ki-67 $>$ 20 %) and poorly differentiated neuroendocrine carcinomas (NEC G3) [8]. It appears that most of pancreatic NENs G3 develop from low-grade NEN in patients with a history of G1 or G2 pNENs, but the progression from low to high grade is not yet well established and dedicated studies are needed [12]. Pancreatic neuroendocrine carcinomas are rare (10 % of all pNENs), non-functioning, and have not been observed in association with genetic syndromes [12]. There are also special mixed types of pNENs with components of pancreatic ductal or acinar carcinoma, called mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs).

1.3. Prognosis of pNENs

Although the prognosis of patients with pNENs is affected by various factors, they are considered “indolent” tumors, even in metastatic disease, especially when compared with pancreatic adenocarcinoma [13]. In terms of prognosis, it is necessary to distinguish sporadic NENs from NENs associated with genetic syndromes.

The prognosis of sporadic pancreatic NENs is affected by several factors, including tumor size, staging, and grading, as assessed by the proliferative activity expressed by Ki-67 [8]. Numerous studies involving pNENs have reported poorer survival in patients with G3 tumors, regardless of disease stage [14]. Loss of expression of DAXX or ATRX is the best molecular predictor of relapse in R0-resected PanNET [15]. Other specific prognostic factors have also been described, such as the presence of calcifications on imaging, the extent of liver involvement [13,16]. An increasingly reported prognostic marker is anatomical localization of the primary tumor in the pancreas. Tumors located in the pancreatic head/neck have a worse prognosis than tumors located in the body/tail [17,18]. In general, non-functioning pNENs are considered to have a worse prognosis owing to the absence of specific clinical symptoms and delayed diagnosis [18]. However, progress in diagnostic modalities has led to an increased number of asymptomatic small tumors in their early stages [19]. The clinical behavior and outcomes of functioning pNENs differ for each tumor type. Patients with functioning pNENs (except insulinomas) are more frequently metastatic at initial diagnosis than those with non-functioning pNENs [20].

Pancreatic neuroendocrine neoplasms associated with genetic syndromes are generally considered to have a better prognosis and are less aggressive.

2. Risk factors for pNENs development

2.1. Behavioral/exposure factors

The exact mechanisms underlying the development of sporadic pNENs are poorly understood [21]. Over time, lifestyle factors have become increasingly significant in the overall development of cancer. It is estimated that up to 45 % of all cancer cases in the UK are linked to lifestyle choices [22].

Lifestyle factors associated with the development of sporadic pNENs are not well-defined. However, several factors are associated with the risk of developing pNENs. These include diabetes mellitus, family history of cancer, smoking, excessive alcohol consumption, body weight, living in rural areas and chronic pancreatitis [23] (Table 1).

History of diabetes. In a meta-analysis that included 4 cohorts, diabetes emerged as the most significant risk factor for developing pNEN, with an odds ratio (OR) as high as 2.74 [23]. Although all these studies showed a strong link between diabetes and the increased risk of pNENs [24–26], only one of them [24] examined the role of “recent-onset diabetes”, where the association appeared even stronger (OR 45.5; 95 % CI: 5.7–360). It remains uncertain whether diabetes is genuinely a risk

Table 1
Risk Factors for pNENs Development.

Risk Factors	Odds Ratio (OR)	References
Diabetes	General OR: 2.74 (95 % CI: 1.63–4.62) Recent-onset diabetes OR: 45.5 (95 % CI: 5.7–360)	[23,24]
Family history of cancer	OR pancreatic adenocarcinoma: 3.6 (95 % CI: 1.3–10.2) OR hepatobiliary tumors: 2.4 (95 % CI: 1–5.5)	[23–25]
Smoking	OR ever smoking: 1.60 (95 % CI: 1.10–2.33) OR heavy smoking: 2.07 (95 % CI: 1.15–3.73)	[24,25,29, 30]
Alcohol use	OR: 1.39 (95 % CI: 1.07–1.81)	[23–25,27]
Body Mass Index (BMI)	OR: 1.36 (95 % CI: 0.88–2.08)	[24,31]

factor for the development of pNENs or whether this association is a secondary effect related to the presence of pancreatic tumors.

Family history of cancer. A family history of cancer is associated with a two-fold increase in the risk of developing pNENs [23–25]. Regarding specific cancer types, several studies have indicated an elevated risk for individuals with a family history of pancreatic adenocarcinoma (OR, 3.6; 95 % CI: 1.3–10.2) and hepatobiliary tumors (OR 2.4; 95 % CI: 1–5.5) [24], esophageal cancer (OR 5.6; 95 % CI: 1.1–29.6) [25], and sarcoma, ovarian, stomach, and gallbladder cancers [27]. The results regarding family history of pNENs are uncertain. In fact, the two studies that evaluated this positive association included patients with hereditary pNEN, such as those with multiple endocrine neoplasia type 1 (MEN-1) [27,28]. Nonetheless, the increased risk of developing pNENs in individuals with a first-degree family history of cancer could be linked to unidentified genetic factors or shared environmental exposure [23].

Smoking. The relationship between smoking and the development of pNENs is unclear. In the case-control study by Ben et al. [29], both ever smoking (OR 1.60; 95 % CI: 1.10–2.33) and heavy smoking (OR 2.07; 95 % CI: 1.15–3.73) were linked to an increased risk of developing pNENs. In a large case-control study, Capurso et al. [21] showed no significant association between ever smoking and increased pNENs risk, whereas heavy smoking showed a slight increase in risk (OR, 1.5; 95 % CI, 1–2.4). However, in multivariate analysis, neither smoking nor heavy smoking was associated with an increased risk [24]. Hassan et al. [25] also assessed 160 patients with pNEN and found that smoking was not a significant risk factor. Smoking is also related to disease progression. Landry et al. [30] found in their prospective cohort study that tobacco use was linked to poorer survival outcomes in patients with metastatic GI-NENs. Likewise, Ben et al. [29] observed that both ever smoking and heavy smoking were connected to more advanced ENETS stages ($p = 0.035$, $p = 0.002$), indicating that tobacco use is a risk factor for a more aggressive form of pNEN

Alcohol use. In a meta-analysis by Haugvik et al. [23], alcohol use did not appear to be a significant risk factor for pNENs, while heavy alcohol use was identified as a significant risk factor. One study, conducted on 309 cases and 602 controls, suggested that alcohol use might have a protective effect against pNENs development, as it was more common in the control group [27]. However, there were also discrepancies in the odds ratios for smoking and alcohol use between studies conducted in the USA [25] and others included in the meta-analysis [24], likely due to higher proportions of smokers and drinkers in the USA control groups. More extensive and well-designed studies are needed to better understand the relationship between these environmental risk factors and pNENs occurrence.

Body Mass Index. Capurso et al. [24] found no significant difference in the BMI of patients and controls. Valente et al. [31] obtained the same result showing that a higher BMI was not significantly associated with an increased risk of developing pNENs (OR 1.36; 95 % CI: 0.88–2.08).

2.2. Genetic factors

Germline genetic variability plays a role in pNEN development, and common low-penetrance and rare high-penetrance single nucleotide variants (SNVs) have been identified. In the following paragraphs, an updated review of the current knowledge is presented.

2.2.1. Genetic syndromes

The majority of pNENs occur sporadically, with 10 %–22 % of cases being associated with germline mutations. Based on the results of prior studies, it is estimated that more than 10 % of pNEN diagnoses occur in individuals with one of the following four syndromes: MEN1, VHL, NF1, and TSC. Each of these diseases exhibits autosomal dominant inheritance and involves specific causative genes (*MEN1*, *VHL*, *NF1*, *TSC1/2*) [32,33]. Rarely, CDKN1B and MAX germline mutations lead to MEN4 and MEN5 syndromes which include PanNET. 32521546 [34,35]. MAX is involved in tumor suppressor processes within the MYC/MAX/MXD1 pathway

Other germline genetic mutations have been reported in single case reports, which have identified less common mutations in genes known to be causative for different diseases. Aversa et al. reported a case of Li-Fraumeni syndrome caused by germline *TP53* tumor suppressor gene mutations, which also presented with a diagnosis of pNENs [36]. Greidinger and colleagues observed a patient with Cowden syndrome with a deleterious germline mutation in *the PTEN* and *MUTYH* genes. Germline *PTEN* mutations may increase the risk of developing NENs [37]. Neychev et al. also reported a germline *PTEN* mutation in a pNEN case, specifically c.697 C>T (p.R233 *), which caused a premature stop codon in exon 7 [38].

Furthermore, in addition to the germline mutations previously mentioned, other mutations have been identified in studies utilizing multi-gene panels. Scarpa and colleagues conducted whole genome sequencing of 102 pNEN patients and reported germline mutations in 18 patients (17 % of study population) [39]. They reported mutations in the previously mentioned *MEN1*, *VHL*, *MUTYH*, and *CDKN1B* genes and germline mutations in the *BRCA2* and *CHECK2* genes. Another study conducted by Raj et al. on 88 patients identified likely pathogenic germline alterations in 17 patients (19 %) with known cancer susceptibility genes. Eleven mutations in previously reported genes (*MEN1*, *VHL*, *TSC2*, *CHEK2*, and *MUTYH*) and six pathogenic or likely pathogenic germline alterations were identified in novel genes (*APC, RAD50*, *RECQL4*, and *FANCC*) [40]. Finally, the study conducted by Mohindroo et al., which analyzed 106 pNENs, confirmed that approximately 20 % of patients carry pathogenic or likely pathogenic germline alterations, consistent with findings from two previous studies. This percentage increases to 50 % when calculated in a selected population of 132 pNENs with high-risk features, such as young age and family and personal history of cancer [41]. The study by Mohindroo et al. observed germline mutations in previously reported genes (*MEN1, VHL, MUTYH, BRCA2, TP53, RAD50, and RECQL2*) and identified mutations in novel genes (*BRCA1*, *BRIP1, BARD1, MSH2, AXIN2, PALB2, NTHL, BLM, ATM, MSH3, RET, and PR*).

Most reported germline mutations are variants of DNA repair pathways, suggesting that inherited variations in these genes may play a significant role in the development of sporadic pNENs. Current knowledge about rare germline mutations provides some coherent indications regarding which genes might be involved in the predisposition to pNENs. However, these studies highlight different loci within each gene, making it challenging to identify specific mutations that cause pNENs.

2.2.2. Genetic variants and risk of developing pNENs

The impact of common single nucleotide polymorphisms (SNPs) on pNENs susceptibility is largely unexplored because only a small number of studies have been conducted so far. The authors focused on genetic variants of genes involved in cancer-associated processes, such as DNA repair, xenobiotic metabolism, inflammation, and the cell cycle. The

first study was conducted by Berkovic et al., who analyzed the effect of *IL-2* −330 T/G (rs2069762) in 101 gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and 150 controls [42]. The authors observed an association between the rare allele and increased risk (OR 6.32, 95 % CI 1.96–20.31, P = 0.0006). Another study from the same group, in which 60 pNENs and 60 controls were analyzed, reported an association between IL1beta-rs16944 (OR 3.913, 95 % CI 1.24–12.34 P = 0.014) and the risk of developing pNENs [43].

Ter Minassian et al. analyzed 101 pNENs and 432 controls for 1536 SNPs in 355 genes involved in key cellular mechanisms and identified 18 statistically significant associations. Notably 4 were on *CDKN2A* that is located at 9p21.3, which is very close to *CDKN2B*. This region is pleiotropic and its variants, which are associated with PDAC, are thought to regulate the expression of these two genes [44,45]. In an independent study carried out in the context of the Pancreatic Disease Research (PANDoRA) consortium [46,47] Campa and colleagues analyzed 320 pNENs and 4436 controls and identified an association between *CDKN2A*-rs2518719 and risk of developing the disease (OR 2.08, 95 % CI:1.05–4.11, p = 0.035) [48]. This SNP was not in linkage disequilibrium with those found by Ter Minassian, highlighting the importance of this locus in pNENs.

The same group also tested whether polymorphic variants identified through PDAC genome-wide association studies (GWAS) [49–52] were also associated with pNENs susceptibility in a sample of 369 pNENs and 3277 controls. They identified three loci –1q32.1 (NR5A2, rs10919791), 8q24.21 (MIR1208/PVT1, rs1561927) and 13q22.1 (TP63, rs9543325), that showed promising associations, although none were below the threshold considered statistically significant in GWASs ($p < 5 \times 10^{-8}$) [53]. More recently Gentiluomo and colleagues, with samples drawn from PANDoRA (291 pNENs cases and 1686 controls) computed a polygenic risk score (PRS) with 11 SNPs associated with lymphocyte telomere length (LTL) and observed that individuals with longer genetically determined LTL had a higher risk of pNENs when compared with individual with median LTL (OR = 1.99, 95 % CI: 1.33–2.98, p = 0.0008) [54]. LTL has been associated with a plethora of human diseases, and it is interesting to note that for PDAC, the association goes in the opposite direction, that is, shorter LTL is associated with a higher risk [55–59]. The authors also analyzed the individual SNPs that were used to calculate the score and observed an association with TERT-rs2736100 (ORC/A_vs_C/C = 2.03, 95 % CI: 1.42–2.91, $p = 1.06 \times 10^{-4}$), which is a known PDAC susceptibility locus, and with ZNF676-rs409627 (OR C/C_vs_G/G = 2.27, 95 % CI: 1.58–3.27, $p = 8.80 \times 10^{-6}$).

The latest study on pNENs susceptibility was conducted by Marinovic et al. The authors analyzed 68 pNENs and 300 controls for three SNPs of the epidermal growth factor and its receptor (*EGF*-rs4444903, *EGFR*-rs11543848, and *HER2*-rs1136201). The study reports a weak association between EGFR rs11543848 heterozygotes and decreased risk of pNENs (OR 0.118 95 % CI: 0.006–2.036, p = 0.045) [60]. All the associations described in this section are reported in Table 2.

Overall, several polymorphic variants have been proposed to play a role in pNENs genetic susceptibility; however, all have been identified in relatively small cohorts and have not been validated [61]. All these caveats limit the interpretation of these findings. Additionally, no GWAS have been published to date.

3. Molecular changes in pNENs

3.1. Somatic mutations in well differentiated pNENs

Pancreatic NENs are among the tumor entities with the lowest mutational burden [62]. Interestingly, while recurrent mutations were found in 75 % of pNENs > 2 cm, such genomic alterations were found only in 44 % of tumors < 2 cm, suggesting that other unknown mechanisms may be involved in the initial development of these tumors [63]. Nearly 15 % of sporadic pNENs have somatic mutations in genes encoding members of the mTOR pathway, and mutually exclusive mutations have been found in *PTEN* (7.1 %), *TSC1* (2.0 %), *TSC2* (2.0 %), and *DEPDC5* (2.0 %) [39]. *EWSR* translocation rarely results in altered mTOR signalling [39]. *ATM* (ATM serine/threonine kinase) was mutated in 5.5 % of pNENs. ATM is involved in several cellular processes that occur in response to DNA damage, including cell cycle checkpoint control, DNA repair, and apoptosis [64,65]. Almost 40 % of sporadic non-functioning pNENs have mutations in *MEN1*. *MEN1* encodes menin, which recruits the H3K4me3 histone methyltransferase mixed lineage leukemia (MLL1) complex that plays an essential role in chromatin remodelling and gene expression [66]. *MEN1* mutations often occur together with mutations in either *the* death domain-associated protein (DAXX) or *alpha thalassemia/mental retardation syndrome X-linked protein (ATRX)* [67]. DAXX and ATRX form a complex that regulates the deposition of H3K9me3 at heterochromatin regions, such as telomeres and centromeres [68]. While MEN1 mutations occur very early in tumor progression, DAXX/ATRX mutations occur during progression and are usually found in tumors > 2 cm [69,70]. *DAXX/ATRX* mutations correlate with the loss of nuclear expression in tumor tissues [69,71], making immunohistochemistry a cheap tool for indirect mutation detection. pNETs mutated in *DAXX* or *ATRX* are characterized by Alternative Lengthening of Telomeres (ALT) activation, a telomerase-independent mechanism for telomere length maintenance, and genomic instability [69,71], probably due to loss of heterochromatin structure. *DAXX/ATRX-mutant* pNENs have an increased risk of metastasis compared to wild-type pNENs [69]. Additionally, mutations in the histone modifier *SETD2* were found in a further pNENs subset (5 out of 98 mutated) and were found to be mutated in pNETs [39]. Insulinomas show a distinct mutational spectrum compared with non-functioning pNETs. Almost 30 % of insulinomas carry a recurrent somatic T372R gain-of-function mutation in the Ying Yang 1 (*YY1*) transcription factor gene [72]. YY1 regulates the mitochondrial function and insulin/insulin-like growth factor signalling [73,74]. The different mutational spectra between insulinoma and non-functioning pNETs suggest a different susceptibility in the respective cell of origin. Interestingly, malignant insulinomas often harbor *DAXX* and *ATRX* mutations, ALT activation, and high chromosomal instability, indicating transdifferentiation from non-functioning pNET. The expression of the Aristaless-related homeobox (ARX) is also found in both malignant insulinomas and frequently in non-functioning pNET, which supports a common origin of-cells [75]. G3 pNETs have the same drivers, with additional mutations in TP53 in 14 % of cases and loss of RB1 in 7 % of cases [73].

3.2. Somatic mutations in poorly differentiated neuroendocrine carcinomas

Pancreatic neuroendocrine carcinomas (pNECs) are high-grade by definition, poorly differentiated malignancies exhibiting aggressive behavior and poor prognosis [8,77,78]. These rare lesions comprise up to 10 % of pNENs and present most often as sporadic and solitary pancreatic masses [12,79,80]. PNEC tissue sections reveal diffuse sheets or nests of highly atypical small or large cells expressing neuroendocrine markers (e.g., synaptophysin and chromogranin A) in addition to areas of necrosis and abundant mitoses [12,78]. According to the WHO classification, similar to G3 pNETs, they show a Ki-67 proliferative index > 20 % and a mitotic rate > 20/mm2 [77]. However, Ki-67 status is most often higher (>55 %) in pNECs [81,82], which also display a different genomic and transcriptomic profile than G3 pNETs [83]. Interestingly, gastro-entero-pancreatic (GEP) NECs with Ki-67 ≥ 55 % have been associated with shorter survival compared to those with Ki-67 < 55 %, and GEP NECs (regardless of their Ki-67 proliferative index) exhibit a worse prognosis than G3 NETs [83–86].

The two key genetic alterations in pNECs are the inactivation of the TP53 and RB1 tumor suppressor genes [79,87,88]. Consequently, most lesions show an abnormal p53 expression pattern (overexpression or

Table 2
Germline mutations in pNENs.

Category	Gene	Location	Type of mutation	Mutations/Variants	Prevalence in pNENs	Clinical Context	Pathway Involvement	Other Associated Cancers	Mutation Type	Pathogenicity	Reference
Hereditary Syndromes	*MEN1*	11q13	Autosomal dominant	Multiple frameshifts, splice-site mutations, copy number losses	10–22 %	MEN1 Syndrome	DNA repair, cell cycle control	Parathyroid, pituitary tumors	Germline	Pathogenic	[32,33]
	VHL	3p25.3	Autosomal dominant	c.257 C>T (p.P86L) and others	9–17 %	von Hippel-Lindau Syndrome	HIF signaling	Kidney, brain, eye	Germline	Likely pathogenic	[39]
	TSC1/ TSC2	9q34 / 16p13	Autosomal dominant	c.3598 C>T (p.R1200W)	1–9 %	Tuberous Sclerosis	mTOR pathway	Renal angiomyolipomas	Germline	Likely pathogenic	[33]
	NF1	17q11.2	Autosomal dominant	Multiple variants	~10 %	Neurofibromatosis Type 1	RAS signaling	Gliomas, pheochromocytomas	Germline	Pathogenic	[33]
	CDKN1B	12p13.1	Autosomal dominant	Q163X and others	~25 % of gastrinomas and NF-PanNETs	MEN4	Cell cycle regulation	Pituitary adenomas	Germline	Likely pathogenic	[34]
	TP53	17p13.1	Autosomal dominant	c.1009 C>T (p.R337C)	-	Li-Fraumeni Syndrome	Tumor suppressor, DNA repair	Breast, adrenal, brain tumors	Germline	Pathogenic	[36]
	PTEN	10q23.3	Autosomal dominant	c.697 C>T (p.R233 *)	-	Cowden Syndrome	PI3K/AKT/mTOR pathway	Thyroid, breast, endometrial cancer	Germline	Pathogenic	[37,38]
	MAX	14q23.3	Autosomal dominant	Exon 3 deletion	-	Familial	MYC/MAX/MXD1 pathway	Pheochromocytomas	Germline	Likely pathogenic	[35]
	RECQL4	8q24.3	Autosomal recessive	-	-	Rothmund-Thomson Syndrome	DNA helicase	Osteosarcomas	Germline	Likely pathogenic	[40]
	FANCC	9q22.32	Autosomal recessive	-	-	Fanconi Anemia	DNA repair	Leukemia	Germline	Likely pathogenic	[40]
DNA Repair Pathway Genes	*MUTYH*	1p34.1	Autosomal recessive	c.536 A>G (p.Y179C), c.1187 G>A (p.G396D)	5 %	Predisposition to multiple cancer types	Base excision repair	Colorectal cancer	Germline	Pathogenic	[39,40]
	CHEK2	22q12.1	Autosomal dominant	c.1283 C>T (p.S428F), c.1337delA (p.N446Tfs*23), c.470 T > C (p.I157T)	5 %	Moderate penetrance	DNA damage response	Breast, prostate	Germline	Pathogenic	[39,40]
	BRCA2	13q13.1	Autosomal dominant	c.3396_3396del and others	-	Present in high-risk cohort	Homologous recombination repair	Breast, ovarian	Germline	Pathogenic	[39,40]
	ATM	11q22.3	Autosomal dominant	c.3403–1 G>A (splice acceptor)	-	-	DNA damage response	Lymphoid cancers	Germline	Likely pathogenic	[40]
	BRCA1	17q21.31	Autosomal dominant	c.4936del	-	-	DNA repair	Breast, ovarian	Germline	Likely pathogenic	[40]
	BRIP1	17q23.2	Autosomal recessive	c.2392 C>T (p.gln798Ter)	-	DNA repair pathway	DNA repair	Ovarian, breast	Germline	Likely pathogenic	[33]
	BARD1	2q35	Autosomal dominant	c.1921C>T (p.Gln641Ter)	-	DNA repair pathway	DNA repair	Breast, ovarian	Germline	Likely pathogenic	[33]
	MSH2/ MSH3	2p21 / 5q14.1	Autosomal dominant	MSH2: c.1667 T > C (p. Leu556Pro); MSH3: c.2732 T > G (p.Leu911Trp)	-	Lynch syndrome-related	Mismatch repair	Colorectal	Germline	Likely pathogenic	[40]
	PALB2	16p12.2	Autosomal dominant	c.2753 C>A (p.Ser918Ter)	-	DNA repair pathway	Homologous recombination repair	Breast, pancreatic	Germline	Pathogenic	[33]
	RAD50	5q31.1	Autosomal dominant	c.1953delA (p. Lys651AsnfsTer10)	-	DNA repair pathway	DNA repair	Breast	Germline	Likely pathogenic	[33]
Other Relevant Variants	*APC*	5q22.2	Autosomal dominant	I1307K	3 %	Low penetrance	WNT signaling	Colorectal	Germline	Pathogenic	[40]

loss) and RB1 staining loss on immunohistochemistry. In contrast to pNETs, pNEC retain DAXX and ATRX expression [12,79]. KRAS mutations have also been reported as a common molecular event in pNECs [82,89], whereas CDKN2A and SMAD4/DPC4 alterations may also occur, albeit less frequently [79,89]. Notably, KRAS and RB1 mutations have been shown by Hijioka et al. to have a potential predictive value in pNECs regarding their response to platinum-based chemotherapy. The same study also reported that RB1 mutations were significantly associated with a higher therapy response rate in pNECs [82]. Bcl-2 overexpression can also occur in pNECs and has been linked to an elevated Ki-67 index and mitotic count [79].

In clinical practice, it is important to distinguish G3 NETs from NECs, which differ in their molecular biology, prognosis, and response to platinum-based chemotherapy [8,77,82]. In addition to histomorphology, an immunohistochemical panel comprising p53, RB1, DAXX, and ATRX is useful [12,85]. Interestingly, a recent study reported that pNEC tissues often exhibit p16 overexpression (diffuse strong immunopositivity with the E6H4 clone) in contrast to G3 pNENs [89] linked to RB1 inactivation.

PD-L1 levels and tumor mutational burden (TMB) are predictive biomarkers of response to immunotherapy [90–92]. Cavalcanti et al. reported that G3 GEP NENs exhibited higher PD-L1 levels with immunohistochemistry in both tumor and immune cells, at significant levels [93]. Furthermore, Busico et al. showed that PD-L1 expression in tumor-infiltrating lymphocytes was significantly higher in GEP NECs with Ki-67 $\geq$ 55 % [86]. Notably, NECs have been significantly associated with a higher TMB than NETs in general [94], and G3 NETs in particular [83].

3.3. Epigenetics and cell of origin of pNENs

In addition to the mutations described above, epigenetic dysregulation is emerging as an important feature of pNENs that contributes to their progression. Epigenetic changes are an emerging hallmark of cancer, enabling tumor cells to acquire a malignant phenotype through plasticity [95] (Table 3). Epigenetic changes include DNA methylation and histone modifications. DNA methylation can be assessed easily in paraffin-embedded clinical specimens, making this analysis a powerful tool for diagnostic applications. Epigenetic profiles, including DNA methylation, are shaped during cell differentiation and highly conserved in specific non-neoplastic tissues. Indeed, DNA methylation profiles can be used to identify the organ of origin in cases of metastasis from unknown primary adenocarcinomas as well as in patients with neuroendocrine tumors [96].

Specifically, the promoters of tumor-suppressor genes were found to be hypermethylated and silenced in pNET [62]. In addition, global methylation changes are a feature of pNETs with loss of DAXX/ATRX expression [97].

Recently, analysis of super-enhancer profiles associated with H3K27ac has defined three pNET subtypes [98]. One group expressed the ARX transcription factor (alpha-like), another group expressed the PDX1 transcription factor (beta-like), and a small group was positive for both transcription factors. ARX and PDX1 regulate the differentiation of normal α- and β-cells, respectively.

In addition, DNA methylation profiles can stratify these three subtypes of pNETs with different genetic backgrounds, cells of origin, and clinical outcomes, termed alpha-like, beta-like, and intermediate tumors. β-like tumors were epigenetically very similar to α-cells, enriched for *MEN1* mutations, and smaller than 2 cm. β-like tumors are epigenetically very similar to α-cells and mainly insulinomas. Intermediate tumors were large tumors, enriched for *MEN1* and *DAXX/ATRX* (ADM) mutations, and progressively lost cell differentiation, yet maintained some cell features, suggesting progression from alpha-like to intermediate ADM tumors [99]. Accordingly, the β-like and intermediate tumors were positive for ARX, whereas the β-like tumors were positive for PDX1. These data suggest that β- like tumor originates from α-cells and that they may progress into intermediate acquisition of DAXX/*ATRX* mutations. Intermediate tumors have an increased risk of relapse compared with both α- and β-like tumors.

Additionally, DNA methylation can distinguish pNET G3 from pNEC [100]. While non-functional pNETs G3 epigenetically resemble α- cells, pNECs are closer to acinar cells, suggesting two distinct cells of origin.

Beyond, general DNA methylation dysregulation also specific histone markers have been found to be dysregulated in pNETs. Loss of H3K36me3 and ARID1A has been observed in metastatic pNETs [101]. EZH2 expression is highly upregulated in high-grade pNECs [102].

Epigenetic changes are reversible, and hence represent a potential opportunity for therapy. Indeed, promising results have been obtained in *MEN1* mouse models using BET inhibitors or knockdown of KDM5 (histone demethylase) [103,104]. Further studies are needed to address the potential of epigenetic therapy for pNENs. Additionally, DNA methylation can be assessed using liquid biopsies, thereby opening new frontiers for diagnostic applications.

3.4. Transcriptomics of pNENs

Historically, transcriptomic approaches have been employed to understand the molecular cues underlying tumoral pathologies, as well as to better classify them and identify biomarkers and therapeutic targets, with the ultimate goal of improving their clinical management. In pNENs, while transcriptomics has not been as thoroughly developed and applied as in other tumoral pathologies with a higher incidence, several studies have contributed significantly to this regard.

In a recent study, Ramos-Rodríguez et al. combined RNA sequencing with ChIP-seq and whole genome sequencing (WGS) data to analyze insulinomas and discovered a uniform tumoral phenotype around non-coding regulation of gene expression affecting the insulin secretion pathway and tumor-related genes [105]. Some of the included samples were previously published by Wang et al., who sequenced insulinomas to obtain insights to improve diabetes treatment and showed alterations in gene expression regulators [106]. In a different study, Wong and collaborators analyzing 5 metastatic pNETs presented a diversity of signalling pathways activation, highlighting their characteristic heterogeneity [107]. Along these lines, Greenberg et al. found that

Table 3
Epigenetics of Pancreatic Neuroendocrine Neoplasms.

Gene	Tumor	Percentage	Function	Molecular features	Epigenetic profiles	References
MEN1	NF/Glucagon producing	37 %	Epigenetic regulation	Low CNV, Loss of chromosome 11 only	alpha-like	[39,99]
DAXX	NF	22 %	Epigenetic regulation	High CNV, ALT	Intermediate-ADM	[39,99]
ATRX	NF	10 %	Epigenetic regulation	High CNV, ALT	Intermediate-ADM	[39,62]
PTEN		7 %	mTOR pathway	Variable CNV	undefined	[39]
SETD2		6 %	Epigenetic regulation	Variable CNV	undefined	[39]
DEPCDC5		2 %	mTOR pathway	Variable CNV	undefined	[39]
TSC1		2 %	mTOR pathway	Variable CNV	undefined	[39]
TSC2		2 %	mTOR pathway	Variable CNV	undefined	[39]
ATM		5,50 %	DNA repair	Variable CNV	undefined	[32]
YY1	Insulinoma	30 %	Transcription factor	Low CNV	beta-like	[72,116]

metastatic tumors exhibited activated immune cell signalling pathways compared to localized disease [108]. With a mutational view, Chan et al. found differential transcriptomic profiles between ATRX-DAXX-MEN1 mutated and non-mutated pNETs with marked alterations in endocrine-related pathways, concluding that these mutant tumors may originate from transdifferentiation [109]. Similarly, Quevedo et al. found that ATRX-DAXX-MEN1 mutant pNETs exhibit defects in centromere cohesion and chromosome missegregation [110]. However, most transcriptomic studies of pNETs have focused on clustering and biomarker searching. A large study on GEP-NECs by Yachida et al. showed that pNECs are not a single entity, but several subgroups can be distinguished based on transcriptomics among other omics [88]. They also showed a 3-group clustering of pNETs based on ARX, MEN1, and PDX1 expression, exhibiting differential clinical and cellular features. In line with this, ARX and PDX1 were found by Cejas et al. to characterize subtypes of non-functioning pNETs, partially resembling different islet cell types associated with specific clinical outcomes [98]. Using different experimental approaches, Chun and Hanahan used RIP1-TAG2 mice to find pro- and anti-invasive molecules in pNENs [111]; later, Sadanandam et al. used a similar approach to classify murine pNENs into well-differentiated islet/insulinoma tumors (IT) and metastasis-like primary (MLP) and then applied this classification to human tumors, finding distinctive phenotypic, clinical, and pathologic properties [112]. A more recent study used these molecular subtypes to study immune-related genes and their associations with clinical outcomes [113]. Similarly, transcriptomics, together with other omics, were used by Yang et al. to cluster pNETs into four different groups associated with phenotypes and clinical parameters [114]. Moreover, gene expression and the presence of mutations served to probe into the differences between G3 NETs and NECs [83], between serotonin-secreting pNETs and other pan-ileal NETs [115], and between insulinomas and non-functioning pNETs [116].

In a search for biomarkers and therapeutic targets, glycosylation status was transcriptionally studied by Xiao et al., who found several related molecules associated with prognostic features (survival, differentiation, and metastasis), highlighting EGFR as a biomarker for lower overall survival [117]. In an independent study, Miki et al. found that extracellular matrix (ECM)-related genes may be used as predictive markers for postoperative recurrence in G1 and G2 pNETs [118]. Different and independent studies based on other gene expression techniques showed the potential of PAX6 as a predictive biomarker for liver metastasis after surgery [119] and the SWI/SNF component ARID1A as a biomarker for unfavorable prognosis [120]. On the other hand, Alvarez et al. used transcriptomics to create clusters of pancreatic and other NETs to find tumoral master regulators that could be pharmacologically targeted [121], leading to incorporate entinostat as a new treatment for GEP-NETs. Similarly, Scott et al. sequenced metastases and primary tumors and identified a number of altered factors involved in cell proliferation and survival that could be targeted by specific drugs [122], while Xiao et al. showed several dysregulated genes in pNETs that could be used as targets of 12 different drugs, with special relevance to EGFR inhibitors [123]. Notably, coding gene expression has also been investigated in pNENs. Several studies have used miRNAs and lncRNAs to classify tumors [124–126] as blood biomarkers [127] or to better understand their molecular biology [128–130]. In addition, recent studies have uncovered the relevant role of RNA processing, particularly alternative splicing, as a novel regulatory layer in pNETs pathobiology (NOVA1, CELF4, reviewed by Blázquez-Encinas et al. [131]). Finally, single-cell transcriptomics is gaining importance in most fields, including pNETs. A few studies have shown vast heterogeneity in cellular compartments and activated signalling pathways among pNETs with different malignancy features [132,133].

4. Biomarkers for pNENS prognosis

4.1. Role of circulating biomarkers

Circulating biomarkers have been intensively investigated as possible prognostic predictors in patients with pNENs (Table 4). Secretory peptides including insulin, glucagon, gastrin etc. are effective serum indicators of tumor activity, but their utility is limited to functioning tumors [134]. Patients with suspected hormonal syndromes should be tested for hormone levels. If elevated, the hormone concentration may be monitored over time and used as a tumor marker, with rising hormone levels being associated with suboptimal disease control and worse prognosis [135]. Among markers common to well-differentiated pNENs there is Chromogranin A (CgA), a glycoprotein stored within secretory vesicles and released with peptides and amines from neuroendocrine cells [136]. The clinical utility of CgA determination for prognostication in patients still remains debatable [137]. Studies that investigated the effects of CgA levels on survival were mainly retrospective and focused on patients with advanced disease. Overall, high levels of CgA appear to correlate with poor survival outcomes in patients with GEP-NENs [138–140]. False-positive elevations of CgA can occur in several conditions, including chronic corpus atrophic gastritis, renal insufficiency, inflammatory bowel disease, and chronic treatment with proton pump inhibitors (PPIs) [141]. Moreover, the use of multiple CgA assays (different antibodies, CgA epitopes, detection techniques, etc.) limits the reproducibility and comparability of CgA measurements across different laboratories [142]. Other secretory proteins can function as tumor markers in patients with pNENs. These include pancreastatin and neuron-specific enolase (NSE) in well-differentiated and poorly differentiated pNENs, respectively. Pancreastatin is a breakdown fragment of CgA that is not falsely elevated by chronic PPI use [143]. Several studies have reported a significant correlation between abnormal levels of pancreastatin and poor survival outcomes [144,145]. NSE is a glycolytic enzyme that is present in the cytoplasm of highly proliferating neuroendocrine cells [146]. Elevated NSE levels have a negative prognostic value, although it should be noted that most studies evaluating biomarkers are related to small cell lung cancer rather than high-grade extrapulmonary NENs [147].

New blood biomarkers for pNEN patients include NETest, circulating tumor cells (CTCs), and circulating tumor DNA (ctDNA). The NETest, a blood multi-gene RNA transcript assay, utilizes a 2-step protocol of RNA isolation and cDNA production to integrate the expression of 51 separate genes defining NEN biology through a PCR-based test [148]. The NETest has been shown to outperform CgA measurement in terms of diagnostic accuracy and can predict disease progression as well as disease relapse after curative surgery. Numerous studies have demonstrated the prognostic ability of baseline NETest scores in patients with NENs [149]. However, different test cut-offs have been applied over time, ultimately limiting the possibility of interpreting the study findings in terms of

Table 4
Incomplete list of circulating Pancreatic Neuroendocrine Neoplasms biomarkers.

Biomarker	Sensitivity	Specificity	References
Chromogranin A	43–100 %	10–96 %	[216–218]
Chromogranin B	57–99 %	Up to 100 %	[217,219,220]
Pancreastatin	64 %	58–100 %	[217,221]
Pancreatic polypeptide	31–63 %	Up to 67 %	[222,223]
NSE	33 %	Up to 100 %	[224]
Insulin*	Up to 100 %	< 20 %	[225]
Gastrin#	Up to 100 %	< 20 %	[225]
CTCs	21 %	95 %	[150,226]
ctDNA	62 %	100 %	[152]
NETest	90–98 %	90–98 %	[148,227,228]

*In insulinomas
#In gastrinomas

prognostication. The presence of CTCs has been shown to have prognostic relevance in patients with pNENs [150]. A significant association was also observed between early post-treatment changes in CTC counts and overall survival [151]. ctDNA is the fraction of cell-free DNA that is released into circulation by tumor cells via apoptosis, necrosis, and active secretion. The presence of ctDNA in the plasma of NEN patients has been reported to be associated with worse overall survival, whereas increased fractions of ctDNA have been associated with poorer progression-free survival [152]. While the NETest has been independently validated by numerous groups internationally, CTCs and ctDNA still require extensive validation before routine clinical implementation.

4.2. Cytokines and growth factors in pNENs

In addition to oncogenes and tumor suppressors related directly to tumor growth [67,153], cytokines, chemokines, and growth factors (GFs) play pivotal roles in the regulation of signalling pathways that are crucial for tumor formation and progression [154]. They are involved in the regulation of both pro- and anti-tumor activities, such as inflammation, cell growth, differentiation, survival, angiogenesis, and invasion, and therefore represent an important research area [155,156].

A number of pro-inflammatory cytokines and chemokines were found to be increased in either tumor or plasma samples of pNEN patients such as interleukin (IL)-6 [157,158], IL-8 [159] and its receptors C-X-C motif chemokine receptor 1 and 2 (CXCR1, CXCR2) [160,161], CXCR4 [162], C-X-C motif chemokine ligand 12 (CXCL12) [161,163], CXCL10 and monocyte chemoattractant protein-1 (MCP-1) [164] when compared to healthy controls. Nevertheless, information about their pro- or anti-tumorigenic role or a correlation between tumor grade, size, stage, and cytokine levels is lacking. Takahashi et al. showed that higher serum CXCL12 chemokine levels correlated with worse progression-free survival in patients with pNENs [165], Zurita et al. [163], and Jiménez-Fonseca et al. [166] reported that both CXCL12 and IL-8 levels could be useful non-invasive markers of sunitinib treatment response. In the case of metastatic pNENs, RNASeq data showed enriched scores for IFN-γ, IFN-α, TNF-α, and IL-6, suggesting an important role for these cytokines in tumor progression; however, this should be further studied [108].

Several studies have highlighted the role of vascular endothelial growth factors (VEGFs), major regulators of angiogenesis, and ANG-2, a facilitator of VEGF-dependent angiogenesis, as it has been shown that they are highly expressed in pNENs, and their high levels correlate with disease progression [160,167–169]. A similar role was also suggested for fibroblast growth factors (FGFs) and their receptors [170,171], while elevated placental growth factor (PlGF) was associated with better survival [172]. Even though it was only shown in a mouse model that deficiency in macrophage growth factor (CSF-1) disrupts pancreatic neuroendocrine tumor development [173], the importance of this growth factor and the above-mentioned factors is strengthened by the fact that surufatinib, a potent tyrosine kinase inhibitor targeting VEGFRs, FGFR1, and CSF-1R, showed clinically meaningful antitumor activity, including tumor shrinkage, in advanced pNENs, at least in the Chinese population [174].

In addition, serum concentrations of some other cytokines and GF, such as IL-2, IL-10, IL-1β, IL-18, TNF, epidermal growth factor (EGF) family, and transforming growth factor-beta (TGF-β), differed between neuroendocrine neoplasms (NENs) and controls; however, it should be taken into account that the included patients were a combination of pNENs and other neuroendocrine tumors [42,175–178].

Little is known about the cellular production and alteration of cytokines and GFs in pNEN, and further research is required to clarify the mechanisms through which these molecules contribute to pNEN tumorigenesis, since they have already been shown to be promising biomarkers of tumor progression and therapeutic response.

4.3. Do exposure factors or commonly prescribed drugs influence progression?

There are multiple therapeutic options for the treatment of pNENs with different mechanisms of action that often overlap. Patients with similar general characteristics and pNENs of the same stage and grade can be treated using different therapies. Conversely, it is also known that, even with the same disease and treatment, therapeutic responses can vary significantly.

In recent years, preclinical oncology research has focused on investigating possible explanations for the lack of response to available therapies. It has been demonstrated that neoplastic cells can develop resistance to systemic therapies, a resistance that may be present either at diagnosis (primary) or developed over time through the selection of genetically predisposed clones (secondary). This phenomenon has been observed in various cancers, including lung cancer, melanoma, and prostate cancer, although most available studies have focused on breast cancer, likely due in part to the prevalence of the disease, which allows for large-scale studies [179–184].

This has led researchers to question the main factors explaining these variations. It has been suggested that both "tumor-related" factors, such as the degree of differentiation of the neoplasm or the stage of the disease, and "patient-related" factors, such as smoking, obesity, or the use of medications (typically statins or metformin, which are the most studied), could play a role. Moreover, the therapies used to treat the tumors themselves may be risk factors for the development of chemoresistance, as neoplastic cells can develop defense systems through complex mechanisms of gene and protein expression, ensuring their survival.

With regard to GEP-NENs, it is well established that factors intrinsic to the neoplasm (such as grade, stage, and disease burden) can influence treatment responses. However, little research has been conducted to investigate whether "patient-related" factors can affect therapeutic outcomes. The most significant evidence to date on this topic comes from a retrospective study, which showed that patients treated with everolimus or somatostatin analogs, who were also on metformin for pre-existing type 2 diabetes, had a significant two-fold increase in progression-free survival (PFS) compared to non-diabetic patients, suggesting a protective role of metformin [185].

Regarding other possible chronic therapies commonly used by patients for comorbid conditions, such as statins, COX-2 inhibitors, insulin, or beta-blockers, the available data are very limited and mostly anecdotal. For example, in pancreatic adenocarcinoma, the role of these drugs is supported by studies with a moderate level of evidence, including meta-analyses based on large cohort studies [186], and such evidence is largely derived from preclinical studies [18,187].

5. Prognostic response factors to pNENs systemic therapies

Systemic therapies for pancreatic neuroendocrine neoplasms (pNENs) encompass a heterogeneous group of compounds [188]. Although numerous prognostic factors have been shown to correlate with outcomes, such as disease stability, PFS, and overall survival (OS), high-quality data are largely lacking to determine which factors are predictive (specifically correlating with outcomes from a particular therapy).

Somatostatin analogs (SSAs) have been approved for the treatment of well-differentiated, low- to intermediate-grade NETs [189,190]. A plurality of patients enrolled in the CLARINET phase III registration trial (45 %) had a pancreatic primary tumor [200]. Currently, there are no proven predictive factors of response to SSAs in patients with pNETs, although it is likely that somatostatin receptor expression (SSTR) correlates with the antiproliferative effect of SSAs. The CLARINET study was limited to tumors with a ki-67 < 10 %. These data indicate substantially lower durations of disease stability in tumors with higher proliferative activity. However, information from single-arm studies is insufficient to indicate whether ki-67 is prognostic, predictive, or purely

prognostic [191,192].

Peptide receptor radionuclide therapy (PRRT) delivers radioactive particles to somatostatin receptor-expressing tumors [193,194]. The Phase III NETTER-1 trial is the largest published study utilizing PRRT in patients with NETs, confirming the role of PRRT in prolonging PFS in patients with midgut NETs [195]. Several studies have confirmed the efficacy of PRRT in patients with pNENs [196], including a large retrospective analysis, which showed a median OS of 63 months (95 % CI, 55–72 months) and a median PFS of 29 months (95 % CI, 26–33 months) in 443 GEP-NEN patients [197]. The NETTER-2 trial highlighting that first-line 177Lu-Dotatate plus octreotide LAR significantly extended median progression-free survival (by 14 months) in patients with grade 2 or 3 advanced gastroenteropancreatic neuroendocrine tumors, supporting its role as a new standard of care in this population [198].

SSTR expression on 68Ga-DOTA-PET correlates with the response to PRRT [199] and is therefore a key predictive factor [200]. 18F-FDG PET is a known prognostic factor for NENs [201,202]. Many studies indicate that a high 18F-FDG SUVmax is associated with poor outcomes and high rates of disease progression; however, the extent to which this test is predictive versus merely prognostic remains unclear [210,211].

A retrospective multicenter study showed that treatment with upfront PRRT in patients with enteropancreatic neuroendocrine tumors who had experienced disease progression with SSA treatment was associated with significantly improved survival outcomes compared with upfront chemotherapy or targeted therapy [203].

A circulating biomarker aimed at predicting the response to PRRT has recently been developed. This test, called the PRRT predictive quotient (PPQ), integrates the circulating expression of genes involved in growth factor expression and metabolism in peripheral blood with tumor grade to generate a prediction classifier. The test identifies individuals likely to respond to PRRT (defined as objective response or disease stabilization) and has shown 95 % accuracy in predicting PRRT efficacy. The fact that this test was non-prognostic in small cohorts of patients treated with SSA or on observation suggests that it might be specifically predictive of PRRT efficacy rather than prognostic [204]. However, further validation studies are ongoing.

The other treatments included everolimus and sunitinib. The effectiveness of the mTOR inhibitor everolimus in patients with advanced low- to intermediate-grade pNETs was demonstrated in the Phase III RADIANT-3 trial [205]. Currently, there are no well-defined predictive factors for everolimus use.

Sunitinib is a tyrosine kinase inhibitor approved for the treatment of pNETs [206]. An analysis of the association between pre-treatment plasma levels of angiogenic biomarkers and clinical outcomes showed that high baseline SDF-1α was associated with worse PFS, OS, and lower rates of disease stabilization or response, and high sVEGFR-2 was associated with longer OS ($P > 0.05$). It is unclear whether these factors are predictive or merely prognostic [163].

Chemotherapy is associated with a high objective response rate in pNETs. The ECOG2211 trial was a prospective, randomized phase II study investigating temozolomide (TEM) versus capecitabine and temozolomide (CAPTEM) in advanced well-differentiated grade 1 and 2 pNETs. Treatment with CAPTEM resulted in improved PFS compared to temozolomide monotherapy [207]. The O6-methylguanine-DNA methyltransferase (MGMT) enzyme is a factor that predicts the methylation. The correlation between MGMT expression and the response to temozolomide has been well established in brain tumors, but findings in neuroendocrine tumors (NETs) have been inconsistent [208]. Analysis of MGMT status in the ECOG-ACRIN E2211 trial revealed that MGMT deficiency, determined by either low IHC expression or promoter methylation, was predictive of an objective radiographic tumor response. However, the lack of a non-temozolomide control arm prevented a definitive conclusion on whether MGMT deficiency is predictive of more clinically relevant endpoints, such as PFS or OS.

Another single-center prospective observational study demonstrated an association between MGMT promoter methylation status and PFS [209]. Moreover, low MGMT expression was associated with a radiological objective response ($P = 0.04$) and improved PFS (HR=0.35, $P = 0.01$) in 43 patients with progressive well-differentiated pNET [210]. In contrast, a retrospective analysis of 143 patients with advanced pNET treated with CAPTEM showed that objective treatment response was not influenced by MGMT expression; however, the number of patients with available tissue for analysis may have been insufficient to reach statistical significance [211].

Mutations in VHL lead to the accumulation of HIF-α, and consequently, the development of tumors in multiple organs, including pNENs [212]. Belzutifan is a small molecule that inhibits the hypoxia-inducible factor (HIF) pathway. A study on belzutifan in patients with RCC incidentally noted a high rate of shrinkage of localized pNETs [213,214]. A case report of a patient with VHL and metastatic pancreatic NET showed a near-complete response to Belzutifan therapy [222]. Prospective trials of belzutifan in advanced NETs (including pNETs) are ongoing, and it is currently unclear whether somatic VHL mutations predict the response to this drug [215].

6. Conclusion

The identification and characterization of genetic and environmental biomarkers have significantly improved our understanding of pNENs, offering valuable tools for diagnosis, prognosis, and personalized treatment strategies.

Genetic biomarkers play a crucial role in differentiating pNEN subtypes, assessing prognosis, and guiding therapeutic decisions. Mutations in p53, RB1, DAXX, and ATRX help distinguish G3 neuroendocrine tumors (NETs) from neuroendocrine carcinomas (NECs), aiding in appropriate classification and treatment selection. p16 overexpression is a characteristic feature of pNECs, while DAXX/ATRX loss is associated with global DNA methylation changes, which can influence tumor progression and epigenetic-based treatment strategies.

In the context of immunotherapy, PD-L1 levels and tumor mutational burden (TMB) serve as predictive biomarkers, with higher levels observed in NECs, suggesting a greater likelihood of response to immune checkpoint inhibitors. Epigenetic dysregulation, particularly tumor-suppressor gene hypermethylation, contributes to pNEN progression, providing potential targets for epigenetic therapies.

Transcriptomic studies have further refined pNEN classification and risk assessment. ARX and PDX1 define distinct pNET subtypes, while PAX6 has been identified as a predictor of liver metastasis. The SWI/SNF complex component ARID1A is associated with poor prognosis, and extracellular matrix (ECM)-related genes can help predict postoperative recurrence. Additionally, glycosylation-related molecules, including EGFR, correlate with lower overall survival, making them potential therapeutic targets. Other molecular factors, such as alternative splicing regulators (NOVA1, CELF4) and non-coding RNAs (miRNAs, lncRNAs), further define pNEN biology and may offer novel prognostic indicators.

Predictive biomarkers are essential for tailoring treatment strategies and maximizing therapeutic efficacy. Somatostatin receptor expression (SSTR) is a key factor in determining the efficacy of somatostatin analogs (SSAs), although no definitive predictive biomarker has been established. The PRRT predictive quotient (PPQ), a circulating biomarker integrating gene expression and tumor grade, has demonstrated 95 % accuracy in predicting response to peptide receptor radionuclide therapy (PRRT), facilitating treatment selection.

In chemotherapy, O6-methylguanine-DNA methyltransferase (MGMT) deficiency, identified through low IHC expression or promoter methylation, has been associated with a better response to temozolomide, although its prognostic significance remains under investigation.

Non-invasive biomarkers are gaining relevance in clinical practice for diagnosis, prognosis, and treatment monitoring. The NETest, a multigene blood-based assay, has shown superior diagnostic accuracy compared to Chromogranin A (CgA) and can predict disease progression

and relapse. While circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) hold promise as prognostic markers, they require further validation before routine implementation.

Additionally, single-cell transcriptomics and liquid biopsy technologies, including the analysis of circulating tumor DNA and exosomes, represent promising frontiers for real-time disease monitoring and personalized treatment adjustments.

Despite significant progress, challenges remain in translating genetic and environmental biomarkers into routine clinical practice. The limited availability of large, well-annotated datasets hampers biomarker validation, necessitating multi-institutional collaborations and global consortia. Future research should focus on integrating multi-omics approaches to refine biomarker-based classification and treatment selection.

In conclusion, the application of genetic and predictive biomarkers is transforming the clinical management of pNENs. These biomarkers not only improve diagnostic accuracy and risk stratification but also enable personalized treatment approaches. Moving forward, a holistic strategy combining genetic, environmental, and clinical data will be crucial to optimizing patient outcomes and advancing precision medicine in pNENs.

Funding

GC received fundings from AIRC: 2015 IG 17177, 2021 IG 26201.

Declaration of Competing Interest

No conflict of interest.

Data availability

No data was used for the research described in the article.

References

[1] Z.Y. Ma, Y.F. Gong, H.K. Zhuang, Z.X. Zhou, S.Z. Huang, Y.P. Zou, et al., Pancreatic neuroendocrine tumors: a review of serum biomarkers, staging, and management, World J. Gastroenterol. 26 (19) (2020 May 21) 2305–2322.
[2] A.T. Scott, J.R. Howe, Evaluation and management of neuroendocrine tumors of the pancreas, Surg. Clin. North Am. 99 (4) (2019 Aug) 793–814.
[3] B. Lawrence, B.I. Gustafsson, A. Chan, B. Svejda, M. Kidd, I.M. Modlin, The epidemiology of gastroenteropancreatic neuroendocrine tumors, Endocrinol. Metab. Clin. North Am. 40 (1) (2011 Mar) 1–18 (vii).
[4] J. Hofland, M. Falconi, E. Christ, J.P. Castaño, A. Faggiano, A. Lamarca, et al., European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes, J. Neuroendocr. 35 (8) (2023 Aug) e13318.
[5] L. Magi, M. Marasco, M. Rinzivillo, A. Faggiano, F. Panzuto, Management of functional pancreatic neuroendocrine neoplasms, Curr. Treat. Options Oncol. 24 (7) (2023 Jul) 725–741.
[6] R.T. Jensen, M.J. Berna, D.B. Bingham, J.A. Norton, Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies, Cancer 113 (7) (2008) 1807–1843.
[7] R.T. Jensen, G. Cadiot, M.L. Brandi, W.W. de Herder, G. Kaltsas, P. Komminoth, et al., ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes, Neuroendocrinology 95 (2) (2012) 98–119.
[8] I.D. Nagtegaal, R.D. Odze, D. Klimstra, V. Paradis, M. Rugge, P. Schirmacher, et al., The 2019 WHO classification of tumours of the digestive system, Histopathology 76 (2) (2020 Jan) 182–188.
[9] Y. You, J.Y. Jang, S.C. Kim, Y.S. Yoon, J.S. Park, C.K. Cho, et al., Validation of the 8th AJCC cancer staging system for pancreas neuroendocrine tumors using Korean Nationwide Surgery Database, Cancer Res Treat. 51 (4) (2019 Oct) 1639–1652.
[10] A.I. Vinik, E.A. Woltering, R.R.P. Warner, M. Caplin, T.M. O'Dorisio, G. A. Wiseman, et al., NANETS consensus guidelines for the diagnosis of neuroendocrine tumor, Pancreas 39 (6) (2010 Aug) 713–734.
[11] M.H. Shah, W.S. Goldner, A.B. Benson, E. Bergsland, L.S. Blaszkowsky, P. Brock, et al., Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology, J. Natl. Compr. Cancer Netw. JNCCN 19 (7) (2021 Jul 28) 839–868.
[12] B. Konukiewitz, M. Jesinghaus, A. Kasajima, G. Klöppel, Neuroendocrine neoplasms of the pancreas: diagnosis and pitfalls, Virchows Arch. 480 (2) (2022 Feb) 247–257.
[13] F. Panzuto, E. Merola, M.E. Pavel, A. Rinke, P. Kump, S. Partelli, et al., Stage IV Gastro-entero-pancreatic neuroendocrine neoplasms: a risk score to predict clinical outcome, Oncologist 22 (4) (2017) 409–415.
[14] D.L. Miao, W. Song, J. Qian, Z.G. Zhu, Q. Wu, C.G. Lv, et al., Development and validation of a nomogram for predicting overall survival in pancreatic neuroendocrinetumors, Transl. Oncol. 11 (5) (2018) 1097–1103.
[15] W.M. Hackeng, L.A.A. Brosens, J.Y. Kim, R. O'Sullivan, Y.N. Sung, T.C. Liu, et al., Non-functional pancreatic neuroendocrine tumours: ATRX/DAXX and alternative lengthening of telomeres (ALT) are prognostically independent from ARX/PDX1 expression and tumour size, Gut 71 (5) (2022) 961–973.
[16] M. Falconi, B. Eriksson, G. Kaltsas, D.K. Bartsch, J. Capdevila, M. Caplin, et al., ENETS Consensus Guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors, Neuroendocrinology 103 (2) (2016) 153–171.
[17] T. Feng, W. Lv, M. Yuan, Z. Shi, H. Zhong, S. Ling, Surgical resection of the primary tumor leads to prolonged survival in metastatic pancreatic neuroendocrine carcinoma, World J. Surg. Oncol. 17 (1) (2019) 54.
[18] L. Lee, T. Ito, R.T. Jensen, Prognostic and predictive factors on overall survival and surgical outcomes in pancreatic neuroendocrine tumors: recent advances and controversies, Expert Rev. Anticancer Ther. 19 (12) (2019) 1029–1050.
[19] S. Crippa, S. Partelli, G. Zamboni, A. Scarpa, D. Tamburrino, C. Bassi, et al., Incidental diagnosis as prognostic factor in different tumor stages of nonfunctioning pancreatic endocrine tumors, Surgery 155 (1) (2014) 145–153.
[20] R.T. Jensen, L. Bodei, J. Capdevila, A. Couvelard, M. Falconi, S. Glasberg, et al., Unmet needs in functional and nonfunctional pancreatic neuroendocrine neoplasms, Neuroendocrinology 108 (1) (2019) 26–36.
[21] M. Bogaards, A.M. May, F.A. Hassan, G.D. Valk, R.S. van Leeuwaarde, Lifestyle factors and development and natural course of gastroenteropancreatic neuroendocrine tumors: a review of the literature, Neuroendocrinology 113 (4) (2023) 381–394.
[22] D.M. Parkin, L. Boyd, L.C. Walker, 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010, Br. J. Cancer 105 (2(2) (2011) S77–S81.
[23] S.P. Haugvik, P. Hedenström, E. Korsæth, R. Valente, A. Hayes, D. Siuka, et al., Diabetes, smoking, alcohol use, and family history of cancer as risk factors for pancreatic neuroendocrine tumors: a systematic review and meta-analysis, Neuroendocrinology 101 (2) (2015) 133–142.
[24] G. Capurso, M. Falconi, F. Panzuto, M. Rinzivillo, L. Boninsegna, R. Bettini, et al., Risk factors for sporadic pancreatic endocrine tumors: a case-control study of prospectively evaluated patients, Am. J. Gastroenterol. 104 (12) (2009) 3034–3041.
[25] M.M. Hassan, A. Phan, D. Li, C.G. Dagohoy, C. Leary, J.C. Yao, Risk factors associated with neuroendocrine tumors: A U.S.-based case-control study, Int J. Cancer 123 (4) (2008) 867–873.
[26] I. Onwere, T. O'Dorisio, S.M. O'Dorisio, B. DeYoung, M. Yusuf, Risk factors for sporadic pancreatic neuroendocrine tumors (PNETs): a single-center case control study, Pancreas 39 (2) (2010) 279.
[27] T.R. Halfdanarson, W.R. Bamlet, R.R. McWilliams, T.J. Hobday, P.A. Burch, K. G. Rabe, et al., Risk factors for pancreatic neuroendocrine tumors: a clinic-based case-control study, Pancreas 43 (8) (2014) 1219–1222.
[28] H.X. Zhan, L. Cong, Y.P. Zhao, T.P. Zhang, G. Chen, Risk factors for the occurrence of insulinoma: a case-control study, Hepatobiliary Pancreat. Dis. INT HBPD INT 12 (3) (2013) 324–328.
[29] Q. Ben, J. Zhong, J. Fei, H. Chen, L. Yv, J. Tan, et al., Risk factors for sporadic pancreatic neuroendocrine tumors: a case-control study, Sci. Rep. 6 (2016) 36073.
[30] C.S. Landry, C.R. Scoggins, K.M. McMasters, R.C.G. Martin, Management of hepatic metastasis of gastrointestinal carcinoid tumors, J. Surg. Oncol. 97 (3) (2008) 253–258.
[31] R. Valente, A.J. Hayes, S.P. Haugvik, P. Hedenström, D. Siuka, E. Korsæth, et al., Risk and protective factors for the occurrence of sporadic pancreatic endocrine neoplasms, Endocr. Relat. Cancer 24 (8) (2017) 405–414.
[32] V. Corbo, I. Dalai, M. Scardoni, S. Barbi, S. Beghelli, S. Bersani, et al., MEN1 in pancreatic endocrine tumors: analysis of gene and protein status in 169 sporadic neoplasms reveals alterations in the vast majority of cases, Endocr. Relat. Cancer 17 (3) (2010) 771–783.
[33] C. Mohindroo, F. McAllister, A. De Jesus-Acosta, Genetics of pancreatic neuroendocrine tumors, Hematol. Oncol. Clin. North Am. 36 (5) (2022) 1033–1051.
[34] A. Frederiksen, M. Rossing, P. Hermann, C. Ejersted, R.V. Thakker, M. Frost, Clinical Features of Multiple Endocrine Neoplasia Type 4: Novel Pathogenic Variant and Review of Published Cases, J. Clin. Endocrinol. Metab. 104 (9) (2019) 3637–3646.
[35] S. Petignot, A.F. Daly, E. Castermans, E. Korpershoek, I. Scagnol, P. Beckers, et al., Pancreatic neuroendocrine neoplasm associated with a familial MAX deletion, Horm. Metab. Res Horm. Stoffwechs. Horm. Metab. 52 (11) (2020) 784–787.
[36] J.G. Aversa, F.B. De Abreu, S. Yano, L. Xi, D.W. Hadley, I. Manoli, et al., The first pancreatic neuroendocrine tumor in Li-Fraumeni syndrome: a case report, BMC Cancer 20 (1) (2020) 256.
[37] A. Greidinger, S. Miller-Samuel, V.N. Giri, M.S.A. Woo, S. Akumalla, C. Zeigler-Johnson, et al., Neuroendocrine tumors are enriched in cowden syndrome, JCO Precis Oncol. (4) (2020). PO.19.00241.
[38] V. Neychev, S.M. Sadowski, J. Zhu, M. Allgaeuer, K. Kilian, P. Meltzer, et al., Neuroendocrine tumor of the pancreas as a manifestation of cowden syndrome: a case report, J. Clin. Endocrinol. Metab. 101 (2) (2016) 353–358.

[39] A. Scarpa, D.K. Chang, K. Nones, V. Corbo, A.M. Patch, P. Bailey, et al., Whole-genome landscape of pancreatic neuroendocrine tumours, Nature 543 (7643) (2017) 65–71.
[40] N. Raj, R. Shah, Z. Stadler, S. Mukherjee, J. Chou, B. Untch, et al., Real-time genomic characterization of metastatic pancreatic neuroendocrine tumors has prognostic implications and identifies potential germline actionability, JCO Precis Oncol. 2018 (2018). PO.17.00267.
[41] C. Mohindroo, S. Baydogan, P. Agarwal, R.D. Wright, L.R. Prakash, M.E. Mork, et al., Germline testing identifies pathogenic/likely pathogenic variants in patients with pancreatic neuroendocrine tumors, Cancer Prev. Res Philos. Pa 17 (7) (2024) 335–342.
[42] M.C. Berković, M. Jokić, J. Marout, S. Radosević, V. Zjacić-Rotkvić, S. Kapitanović, IL-2–330 T/G SNP and serum values-potential new tumor markers in neuroendocrine tumors of the gastrointestinal tract and pancreas (GEP-NETs), J. Mol. Med Berl. Ger. 88 (4) (2010) 423–429.
[43] M. Cigrovski Berković, T. Catela Ivković, J. Marout, V. Zjačić-Rotkvić, S. Kapitanović, Interleukin 1β gene single-nucleotide polymorphisms and susceptibility to pancreatic neuroendocrine tumors, DNA Cell Biol. 31 (4) (2012) 531–536.
[44] M. Giaccherini, R. Farinella, M. Gentiluomo, B. Mohelnikova-Duchonova, E. F. Kauffmann, M. Palmeri, et al., Association between a polymorphic variant in the CDKN2B-AS1/ANRIL gene and pancreatic cancer risk, Int J. Cancer 153 (2) (2023) 373–379.
[45] D. Campa, M. Pastore, M. Gentiluomo, R. Talar-Wojnarowska, J. Kupcinskas, E. Malecka-Panas, et al., Functional single nucleotide polymorphisms within the cyclin-dependent kinase inhibitor 2A/2B region affect pancreatic cancer risk, Oncotarget 7 (35) (2016) 57011–57020.
[46] D. Campa, M. Gentiluomo, A. Stein, M.N. Aoki, M. Oliverius, L. Vodičková, et al., The PANcreatic Disease ReseArch (PANDoRA) consortium: Ten years' experience of association studies to understand the genetic architecture of pancreatic cancer, Crit. Rev. Oncol. Hematol. 186 (2023) 104020.
[47] D. Campa, C. Rizzato, G. Capurso, N. Giese, N. Funel, W. Greenhalf, et al., Genetic susceptibility to pancreatic cancer and its functional characterisation: the PANcreatic Disease ReseArch (PANDoRA) consortium, Dig. Liver Dis. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liver 45 (2) (2013) 95–99.
[48] D. Campa, G. Capurso, M. Pastore, R. Talar-Wojnarowska, A.C. Milanetto, L. Landoni, et al., Common germline variants within the CDKN2A/2B region affect risk of pancreatic neuroendocrine tumors, Sci. Rep. 6 (2016) 39565.
[49] E.J. Childs, E. Mocci, D. Campa, P.M. Bracci, S. Gallinger, M. Goggins, et al., Common variation at 2p13.3, 3q29, 7p13 and 17q25.1 associated with susceptibility to pancreatic cancer, Nat. Genet 47 (8) (2015) 911–916.
[50] L. Amundadottir, P. Kraft, R.Z. Stolzenberg-Solomon, C.S. Fuchs, G.M. Petersen, A.A. Arslan, et al., Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer, Nat. Genet 41 (9) (2009) 986–990.
[51] G.M. Petersen, L. Amundadottir, C.S. Fuchs, P. Kraft, R.Z. Stolzenberg-Solomon, K.B. Jacobs, et al., A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22, 1, 1q32. 1 5p15. 33. Nat. Genet 42 (3) (2010) 224–228.
[52] B.M. Wolpin, C. Rizzato, P. Kraft, C. Kooperberg, G.M. Petersen, Z. Wang, et al., Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer, Nat. Genet 46 (9) (2014) 994–1000.
[53] O. Obazee, G. Capurso, F. Tavano, L. Archibugi, A. De Bonis, W. Greenhalf, et al., Common genetic variants associated with pancreatic adenocarcinoma may also modify risk of pancreatic neuroendocrine neoplasms, Carcinogenesis 39 (7) (2018) 969.
[54] M. Gentiluomo, G. Capurso, L. Morelli, S. Ermini, C. Pasquali, A. Latiano, et al., Genetically determined telomere length is associated with pancreatic neuroendocrine neoplasms onset, Neuroendocrinology 112 (12) (2022) 1168–1176.
[55] D. Campa, A. Felici, C. Corradi, G. Peduzzi, M. Gentiluomo, R. Farinella, et al., Long or short? Telomere length and pancreatic cancer and its precursor lesions, a narrative review, Mutagenesis (2023) gead034.
[56] M. Giaccherini, M. Gentiluomo, M. Fornili, E. Lucenteforte, L. Baglietto, D. Campa, Association between telomere length and mitochondrial copy number and cancer risk in humans: A meta-analysis on more than 300,000 individuals, Crit. Rev. Oncol. Hematol. 167 (2021) 103510.
[57] D. Campa, C. Rizzato, R. Stolzenberg-Solomon, P. Pacetti, P. Vodicka, S.P. Cleary, et al., TERT gene harbors multiple variants associated with pancreatic cancer susceptibility, Int J. Cancer 137 (9) (2015) 2175–2183.
[58] D. Campa, B. Mergarten, I. De Vivo, M.C. Boutron-Ruault, A. Racine, G. Severi, et al., Leukocyte telomere length in relation to pancreatic cancer risk: a prospective study, Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res Cosponsored Am. Soc. Prev. Oncol. 23 (11) (2014) 2447–2454.
[59] D. Campa, M. Matarazzi, W. Greenhalf, M. Bijlsma, K.U. Saum, C. Pasquali, et al., Genetic determinants of telomere length and risk of pancreatic cancer: a PANDoRA study, Int J. Cancer 144 (6) (2019) 1275–1283.
[60] S. Marinović, M. Cigrovski Berković, V. Zjačić-Rotkvić, S. Kapitanović, Analysis of polymorphisms in EGF, EGFR and HER2 genes in pancreatic neuroendocrine tumors (PNETs), Cancer Genet 266–267 (2022) 44–50.
[61] D. Campa, O. Obazee, M. Pastore, F. Panzuto, V. Liço, W. Greenhalf, et al., Lack of Association for Reported Endocrine Pancreatic Cancer Risk Loci in the PANDoRA Consortium, Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res Cosponsored Am. Soc. Prev. Oncol. 26 (8) (2017) 1349–1351.
[62] A. Di Domenico, T. Wiedmer, I. Marinoni, A. Perren, Genetic and epigenetic drivers of neuroendocrine tumours (NET), Endocr. Relat. Cancer 24 (9) (2017) R315–R334.
[63] M. Cives, S. Partelli, R. Palmirotta, D. Lovero, B. Mandriani, D. Quaresmini, et al., DAXX mutations as potential genomic markers of malignant evolution in small nonfunctioning pancreatic neuroendocrine tumors, Sci. Rep. 9 (1) (2019) 18614.
[64] F.A. Derheimer, M.B. Kastan, Multiple roles of ATM in monitoring and maintaining DNA integrity, FEBS Lett. 584 (17) (2010) 3675–3681.
[65] Y. Shiloh, Y. Ziv, The ATM protein kinase: regulating the cellular response to genotoxic stress, and more, Nat. Rev. Mol. Cell Biol. 14 (4) (2013) 197–210.
[66] S.K. Agarwal, S.C. Guru, C. Heppner, M.R. Erdos, R.M. Collins, S.Y. Park, et al., Menin interacts with the AP1 transcription factor JunD and represses JunD-activated transcription, Cell 96 (1) (1999) 143–152.
[67] Y. Jiao, C. Shi, B.H. Edil, R.F. de Wilde, D.S. Klimstra, A. Maitra, et al., DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors, Science 331 (6021) (2011) 1199–1203.
[68] P.W. Lewis, S.J. Elsaesser, K.M. Noh, S.C. Stadler, C.D. Allis, Daxx is an H3.3-specific histone chaperone and cooperates with ATRX in replication-independent chromatin assembly at telomeres, Proc. Natl. Acad. Sci. USA 107 (32) (2010) 14075–14080.
[69] I. Marinoni, A.S. Kurrer, E. Vassella, M. Dettmer, T. Rudolph, V. Banz, et al., Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors, Gastroenterology 146 (2) (2014) 453–460.e5.
[70] R.F. De Wilde, C.M. Heaphy, A. Maitra, A.K. Meeker, B.H. Edil, C.L. Wolfgang, et al., Loss of ATRX or DAXX expression and concomitant acquisition of the alternative lengthening of telomeres phenotype are late events in a small subset of MEN-1 syndrome pancreatic neuroendocrine tumors, Mod. Pathol. 25 (7) (2012) 1033–1039.
[71] Y. Jiao, C. Shi, B.H. Edil, R.F. De Wilde, D.S. Klimstra, A. Maitra, et al., *DAXX / ATRX*, *MEN1*, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors, Science 331 (6021) (2011) 1199–1203.
[72] Y. Cao, Z. Gao, L. Li, X. Jiang, A. Shan, J. Cai, et al., Whole exome sequencing of insulinoma reveals recurrent T372R mutations in YY1, Nat. Commun. 4 (2013) 2810.
[73] J.T. Cunningham, J.T. Rodgers, D.H. Arlow, F. Vazquez, V.K. Mootha, P. Puigserver, mTOR controls mitochondrial oxidative function through a YY1-PGC-1alpha transcriptional complex, Nature 450 (7170) (2007) 736–740.
[74] S.M. Blättler, J.T. Cunningham, F. Verdeguer, H. Chim, W. Haas, H. Liu, et al., Yin Yang 1 deficiency in skeletal muscle protects against rapamycin-induced diabetic-like symptoms through activation of insulin/IGF signaling, Cell Metab. 15 (4) (2012) 505–517.
[75] W.M. Hackeng, L.A.A. Brosens, K.M.A. Dreijerink, Aggressive versus indolent insulinomas: new clinicopathological insights, Endocr. Relat. Cancer 30 (5) (2023) e220321.
[77] N. Assarzadegan, E. Montgomery, What is New in the 2019 World Health Organization (WHO) Classification of Tumors of the Digestive System: Review of Selected Updates on Neuroendocrine Neoplasms, Appendiceal Tumors, and Molecular Testing, Arch. Pathol. Lab Med 145 (6) (2021) 664–677.
[78] O. Basturk, L. Tang, R.H. Hruban, V. Adsay, Z. Yang, A.M. Krasinskas, et al., Poorly differentiated neuroendocrine carcinomas of the pancreas: a clinicopathologic analysis of 44 cases, Am. J. Surg. Pathol. 38 (4) (2014) 437–447.
[79] S. Yachida, E. Vakiani, C.M. White, Y. Zhong, T. Saunders, R. Morgan, et al., Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors, Am. J. Surg. Pathol. 36 (2) (2012) 173–184.
[80] L.H. Tang, O. Basturk, J.J. Sue, D.S. Klimstra, A Practical Approach to the Classification of WHO Grade 3 (G3) Well-differentiated Neuroendocrine Tumor (WD-NET) and Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) of the Pancreas, Am. J. Surg. Pathol. 40 (9) (2016) 1192–1202.
[81] H. Kim, S. An, K. Lee, S. Ahn, D.Y. Park, J.H. Kim, et al., Pancreatic high-grade neuroendocrine neoplasms in the Korean population: a multicenter study, Cancer Res Treat. 52 (1) (2020) 263–276.
[82] S. Hijioka, W. Hosoda, K. Matsuo, M. Ueno, M. Furukawa, H. Yoshitomi, et al., Rb Loss and KRAS mutation are predictors of the response to platinum-based chemotherapy in pancreatic neuroendocrine neoplasm with Grade 3: a Japanese Multicenter Pancreatic NEN-G3 study, Clin. Cancer Res J. Am. Assoc. Cancer Res 23 (16) (2017) 4625–4632.
[83] V. Angerilli, G. Sabella, M. Simbolo, V. Lagano, G. Centonze, M. Gentili, et al., Comprehensive genomic and transcriptomic characterization of high-grade gastro-entero-pancreatic neoplasms, Br. J. Cancer 131 (1) (2024) 159–170.
[84] M. Milione, P. Maisonneuve, F. Spada, A. Pellegrinelli, P. Spaggiari, L. Albarello, et al., The clinicopathologic heterogeneity of grade 3 gastroenteropancreatic neuroendocrine neoplasms: morphological differentiation and proliferation identify different prognostic categories, Neuroendocrinology 104 (1) (2017) 85–93.
[85] H. Elvebakken, A. Perren, J.Y. Scoazec, L.H. Tang, B. Federspiel, D.S. Klimstra, et al., A Consensus-Developed Morphological Re-Evaluation of 196 High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms and Its Clinical Correlations, Neuroendocrinology 111 (9) (2021) 883–894.
[86] A. Busico, P. Maisonneuve, N. Prinzi, S. Pusceddu, G. Centonze, G. Garzone, et al., Gastroenteropancreatic high-grade neuroendocrine neoplasms: histology and molecular analysis, two sides of the same coin, Neuroendocrinology 110 (7–8) (2020) 616–629.

[87] J. Arakelyan, D. Zohrabyan, P.A. Philip, Molecular profile of pancreatic neuroendocrine neoplasms (PanNENs): opportunities for personalized therapies, Cancer 127 (3) (2021) 345–353.
[88] S. Yachida, Y. Totoki, M. Noë, Y. Nakatani, M. Horie, K. Kawasaki, et al., Comprehensive genomic profiling of neuroendocrine carcinomas of the gastrointestinal system, Cancer Discov. 12 (3) (2022) 692–711.
[89] S.E. Umetsu, S. Kakar, O. Basturk, G.E. Kim, D. Chatterjee, K.W. Wen, et al., Integrated genomic and clinicopathologic approach distinguishes pancreatic grade 3 neuroendocrine tumor from neuroendocrine carcinoma and identifies a subset with molecular overlap, Mod. Pathol. J. U S Can. Acad. Pathol. Inc. 36 (3) (2023) 100065.
[90] A. Marabelle, M. Fakih, J. Lopez, M. Shah, R. Shapira-Frommer, K. Nakagawa, et al., Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study, Lancet Oncol. 21 (10) (2020) 1353–1365.
[91] J.H. Strickler, B.A. Hanks, M. Khasraw, Tumor mutational burden as a predictor of immunotherapy response: is more always better? Clin. Cancer Res J. Am. Assoc. Cancer Res 27 (5) (2021) 1236–1241.
[92] J.C.F. Quintanilha, M.H. Storandt, R.P. Graf, G. Li, R. Keller, D.I. Lin, et al., Tumor mutational burden in real-world patients with pancreatic cancer: genomic alterations and predictive value for immune checkpoint inhibitor effectiveness, JCO Precis Oncol. (7) (2023) e2300092.
[93] E. Cavalcanti, R. Armentano, A.M. Valentini, M. Chieppa, M.L. Caruso, Role of PD-L1 expression as a biomarker for GEP neuroendocrine neoplasm grading, Cell Death Dis. 8 (8) (2017) e3004.
[94] M. Liu, N. Li, H. Tang, L. Chen, X. Liu, Y. Wang, et al., The mutational, prognostic, and therapeutic landscape of neuroendocrine neoplasms, Oncologist 28 (9) (2023) e723–e736.
[95] D. Hanahan, Hallmarks of cancer: new dimensions, Cancer Discov. 12 (1) (2022) 31–46.
[96] W.M. Hackeng, K.M.A. Dreijerink, W.W.J. De Leng, F.H.M. Morsink, G.D. Valk, M.R. Vriens, et al., Genome methylation accurately predicts neuroendocrine tumor origin: an online tool, Clin. Cancer Res 27 (5) (2021) 1341–1350.
[97] I. Marinoni, A. Wiederkeher, T. Wiedmer, S. Pantasis, A. Di Domenico, R. Frank, et al., Hypo-methylation mediates chromosomal instability in pancreatic NET, Endocr. Relat. Cancer 24 (3) (2017) 137–146.
[98] P. Cejas, Y. Drier, K.M.A. Dreijerink, L.A.A. Brosens, V. Deshpande, C.B. Epstein, et al., Enhancer signatures stratify and predict outcomes of non-functional pancreatic neuroendocrine tumors, Nat. Med 25 (8) (2019) 1260–1265.
[99] A. Di Domenico, C.P. Pipinikas, R.S. Maire, K. Bräutigam, C. Simillion, M. S. Dettmer, et al., Epigenetic landscape of pancreatic neuroendocrine tumours reveals distinct cells of origin and means of tumour progression, Commun. Biol. 3 (1) (2020) 740.
[100] T. Simon, P. Riemer, A. Jarosch, K. Detjen, A. Di Domenico, F. Bormann, et al., DNA methylation reveals distinct cells of origin for pancreatic neuroendocrine carcinomas and pancreatic neuroendocrine tumors, Genome Med 14 (1) (2022) 24.
[101] S. Roy, W.A. LaFramboise, T.C. Liu, D. Cao, A. Luvison, C. Miller, et al., Loss of chromatin-remodeling proteins and/or CDKN2A associates with metastasis of pancreatic neuroendocrine tumors and reduced patient survival times, Gastroenterology 154 (8) (2018) 2060–2063.e8.
[102] S.L. April-Monn, V. Andreasi, M. Schiavo Lena, M.C. Sadowski, C. Kim-Fuchs, M. C. Buri, et al., EZH2 inhibition as new epigenetic treatment option for pancreatic neuroendocrine neoplasms (PanNENs), Cancers 13 (19) (2021) 5014.
[103] W. Lin, J. Cao, J. Liu, M.L. Beshiri, Y. Fujiwara, J. Francis, et al., Loss of the retinoblastoma binding protein 2 (RBP2) histone demethylase suppresses tumorigenesis in mice lacking Rb1 or Men1, Proc. Natl. Acad. Sci. USA 108 (33) (2011) 13379–13386.
[104] K.E. Lines, M. Stevenson, P. Filippakopoulos, S. Müller, H.E. Lockstone, B. Wright, et al., Epigenetic pathway inhibitors represent potential drugs for treating pancreatic and bronchial neuroendocrine tumors, Oncogenesis 6 (5) (2017) e332.
[105] M. Ramos-Rodríguez, M. Subirana-Granés, R. Norris, V. Sordi, Á. Fernández, G. Fuentes-Páez, et al., Implications of noncoding regulatory functions in the development of insulinomas, Cell Genom. 4 (8) (2024) 100604.
[106] H. Wang, A. Bender, P. Wang, E. Karakose, W.B. Inabnet, S.K. Libutti, et al., Insights into beta cell regeneration for diabetes via integration of molecular landscapes in human insulinomas, Nat. Commun. 8 (1) (2017) 767.
[107] H.L. Wong, K.C. Yang, Y. Shen, E.Y. Zhao, J.M. Loree, H.F. Kennecke, et al., Molecular characterization of metastatic pancreatic neuroendocrine tumors (PNETs) using whole-genome and transcriptome sequencing, Cold Spring Harb. Mol. Case Stud. 4 (1) (2018) a002329.
[108] J. Greenberg, J. Limberg, A. Verma, D. Kim, X. Chen, Y.J. Lee, et al., Metastatic pancreatic neuroendocrine tumors feature elevated T cell infiltration, JCI Insight 7 (23) (2022) e160130.
[109] C.S. Chan, S.V. Laddha, P.W. Lewis, M.S. Koletsky, K. Robzyk, E. Da Silva, et al., ATRX, DAXX or MEN1 mutant pancreatic neuroendocrine tumors are a distinct alpha-cell signature subgroup, Nat. Commun. 9 (1) (2018) 4158.
[110] R. Quevedo, A. Spreafico, J. Bruce, A. Danesh, S. El Ghamrasni, A. Giesler, et al., Centromeric cohesion failure invokes a conserved choreography of chromosomal mis-segregations in pancreatic neuroendocrine tumor, Genome Med 12 (1) (2020) 38.
[111] M.G.H. Chun, D. Hanahan, Genetic deletion of the desmosomal component desmoplakin promotes tumor microinvasion in a mouse model of pancreatic neuroendocrine carcinogenesis, PLoS Genet 6 (9) (2010) e1001120.
[112] A. Sadanandam, S. Wullschleger, C.A. Lyssiotis, C. Grötzinger, S. Barbi, S. Bersani, et al., A cross-species analysis in pancreatic neuroendocrine tumors reveals molecular subtypes with distinctive clinical, metastatic, developmental, and metabolic characteristics, Cancer Discov. 5 (12) (2015) 1296–1313.
[113] K. Young, R.T. Lawlor, C. Ragulan, Y. Patil, A. Mafficini, S. Bersani, et al., Immune landscape, evolution, hypoxia-mediated viral mimicry pathways and therapeutic potential in molecular subtypes of pancreatic neuroendocrine tumours, Gut 70 (10) (2021) 1904–1913.
[114] K.C. Yang, S.E. Kalloger, J.J. Aird, M.K.C. Lee, C. Rushton, K.L. Mungall, et al., Proteotranscriptomic classification and characterization of pancreatic neuroendocrine neoplasms, Cell Rep. 37 (2) (2021) 109817.
[115] T. Depoilly, R. Leroux, D. Andrade, R. Nicolle, M. Dioguardi Burgio, I. Marinoni, et al., Immunophenotypic and molecular characterization of pancreatic neuroendocrine tumors producing serotonin, Mod. Pathol. J. U S Can. Acad. Pathol. Inc. 35 (11) (2022) 1713–1722.
[116] X. Hong, S. Qiao, F. Li, W. Wang, R. Jiang, H. Wu, et al., Whole-genome sequencing reveals distinct genetic bases for insulinomas and non-functional pancreatic neuroendocrine tumours: leading to a new classification system, Gut 69 (5) (2020) 877–887.
[117] Z. Xiao, H. Xu, J.R. Strosberg, R. Lu, X. Zhu, S. Deng, et al., EGFR is a potential therapeutic target for highly glycosylated and aggressive pancreatic neuroendocrine neoplasms, Int J. Cancer 153 (1) (2023) 164–172.
[118] M. Miki, T. Oono, N. Fujimori, T. Takaoka, K. Kawabe, Y. Miyasaka, et al., CLEC3A, MMP7, and LCN2 as novel markers for predicting recurrence in resected G1 and G2 pancreatic neuroendocrine tumors, Cancer Med 8 (8) (2019) 3748–3760.
[119] A. Kudo, K. Akahoshi, S. Ito, T. Akashi, S. Shimada, T. Ogura, et al., Downregulated pancreatic beta cell genes indicate poor prognosis in patients with pancreatic neuroendocrine neoplasms, Ann. Surg. 271 (4) (2020) 732–739.
[120] X. Han, W. Chen, P. Chen, W. Zhou, Y. Rong, Y. Lv, et al., Aberration of ARID1A is associated with the tumorigenesis and prognosis of sporadic nonfunctional pancreatic neuroendocrine tumors, Pancreas 49 (4) (2020) 514–523.
[121] M.J. Alvarez, P.S. Subramaniam, L.H. Tang, A. Grunn, M. Aburi, G. Rieckhof, et al., A precision oncology approach to the pharmacological targeting of mechanistic dependencies in neuroendocrine tumors, Nat. Genet 50 (7) (2018) 979–989.
[122] A.T. Scott, M. Weitz, P.J. Breheny, P.H. Ear, B. Darbro, B.J. Brown, et al., Gene expression signatures identify novel therapeutics for metastatic pancreatic neuroendocrine tumors, Clin. Cancer Res J. Am. Assoc. Cancer Res 26 (8) (2020) 2011–2021.
[123] Y. Xiao, G. Xu, J.M. Cloyd, S. Du, Y. Mao, T.M. Pawlik, Predicting novel drug candidates for pancreatic neuroendocrine tumors via gene signature comparison and connectivity mapping, J. Gastrointest. Surg. J. Soc. Surg. Aliment Trac. 26 (8) (2022) 1670–1678.
[124] V.K. Grolmusz, A. Kövesdi, K. Borks, P. Igaz, A. Patócs, Prognostic relevance of proliferation-related miRNAs in pancreatic neuroendocrine neoplasms, Eur. J. Endocrinol. 179 (4) (2018) 219–228.
[125] N. Panarelli, K. Tyryshkin, J.J.M. Wong, A. Majewski, X. Yang, T. Scognamiglio, et al., Evaluating gastroenteropancreatic neuroendocrine tumors through microRNA sequencing, Endocr. Relat. Cancer 26 (1) (2019) 47–57.
[126] C. Thorns, C. Schurmann, N. Gebauer, H. Wallaschofski, C. Kümpers, V. Bernard, et al., Global microRNA profiling of pancreatic neuroendocrine neoplasias, Anticancer Res 34 (5) (2014) 2249–2254.
[127] C. Vicentini, F. Calore, G. Nigita, P. Fadda, M. Simbolo, N. Sperandio, et al., Exosomal miRNA signatures of pancreatic lesions, BMC Gastroenterol. 20 (1) (2020) 137.
[128] M. Ji, L. Tang, R. Ding, L. Shi, A. Liu, D. Chen, et al., Long noncoding RNA-mRNA expression profiles and validation in pancreatic neuroendocrine neoplasms, Clin. Endocrinol. (Oxf.) 92 (4) (2020) 312–322.
[129] H.Q. Zhou, Q.C. Chen, Z.T. Qiu, W.L. Tan, C.Q. Mo, S.W. Gao, Integrative microRNA-mRNA and protein-protein interaction analysis in pancreatic neuroendocrine tumors, Eur. Rev. Med Pharm. Sci. 20 (13) (2016) 2842–2852.
[130] M. Ji, Y. Yao, A. Liu, L. Shi, D. Chen, L. Tang, et al., lncRNA H19 binds VGF and promotes pNEN progression via PI3K/AKT/CREB signaling, Endocr. Relat. Cancer 26 (7) (2019) 643–658.
[131] R. Blázquez-Encinas, M.T. Moreno-Montilla, V. García-Vioque, F. Gracia-Navarro, E. Alors-Pérez, S. Pedraza-Arevalo, et al., The uprise of RNA biology in neuroendocrine neoplasms: altered splicing and RNA species unveil translational opportunities, Rev. Endocr. Metab. Disord. 24 (2) (2023) 267–282.
[132] Y. Zhou, S. Liu, C. Liu, J. Yang, Q. Lin, S. Zheng, et al., Single-cell RNA sequencing reveals spatiotemporal heterogeneity and malignant progression in pancreatic neuroendocrine tumor, Int J. Biol. Sci. 17 (14) (2021) 3760–3775.
[133] S.E. Hoffman, T.W. Dowrey, C. Villacorta Martin, K. Bi, B. Titchen, S. Johri, et al., Intertumoral lineage diversity and immunosuppressive transcriptional programs in well-differentiated gastroenteropancreatic neuroendocrine tumors, Sci. Adv. 9 (39) (2023) eadd9668.
[134] T.R. Halfdanarson, J. Rubin, M.B. Farnell, C.S. Grant, G.M. Petersen, Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors, Endocr. Relat. Cancer 15 (2) (2008) 409–427.
[135] M. Cives, J.R. Strosberg, Gastroenteropancreatic neuroendocrine tumors, CA Cancer J. Clin. 68 (6) (2018) 471–487.
[136] D.T. O'Connor, L.J. Deftos, Secretion of chromogranin A by peptide-producing endocrine neoplasms, N. Engl. J. Med 314 (18) (1986) 1145–1151.
[137] V. Marotta, M.C. Zatelli, C. Sciammarella, M.R. Ambrosio, M. Bondanelli, A. Colao, et al., Chromogranin A as circulating marker for diagnosis and

management of neuroendocrine neoplasms: more flaws than fame, Endocr. Relat. Cancer 25 (1) (2018) R11–R29.
[138] S. Krogh, H. Grønbæk, A.R. Knudsen, P. Kissmeyer-Nielsen, N.E. Hummelshøj, G. Dam, Predicting progression, recurrence, and survival in pancreatic neuroendocrine tumors: a single center analysis of 174 patients, Front Endocrinol. 13 (2022) 925632.
[139] H.J. Tsai, C.F. Hsiao, J.S. Chang, L.T. Chen, Y.J. Chao, C.J. Yen, et al., The prognostic and predictive role of chromogranin a in gastroenteropancreatic neuroendocrine tumors - a single-center experience, Front Oncol. 11 (2021) 741096.
[140] W.C. Chou, J.S. Chen, Y.S. Hung, J.T. Hsu, T.C. Chen, C.F. Sun, et al., Plasma chromogranin A levels predict survival and tumor response in patients with advanced gastroenteropancreatic neuroendocrine tumors, Anticancer Res 34 (10) (2014) 5661–5669.
[141] J.M. Conlon, Granin-derived peptides as diagnostic and prognostic markers for endocrine tumors, Regul. Pept. 165 (1) (2010) 5–11.
[142] L. Pedersen, M. Nybo, Preanalytical factors of importance for measurement of Chromogranin A, Clin. Chim. Acta Int J. Clin. Chem. 436 (2014) 41–44.
[143] D. Raines, M. Chester, A.E. Diebold, P. Mamikunian, C.T. Anthony, G. Mamikunian, et al., A prospective evaluation of the effect of chronic proton pump inhibitor use on plasma biomarker levels in humans, Pancreas 41 (4) (2012) 508–511.
[144] S.K. Sherman, J.E. Maxwell, M.S. O'Dorisio, T.M. O'Dorisio, J.R. Howe, Pancreastatin predicts survival in neuroendocrine tumors, Ann. Surg. Oncol. 21 (9) (2014) 2971–2980.
[145] D. Strosberg, E.B. Schneider, J. Onesti, N. Saunders, B. Konda, M. Shah, et al., Prognostic impact of serum pancreastatin following chemoembolization for neuroendocrine tumors, Ann. Surg. Oncol. 25 (12) (2018) 3613–3620.
[146] L. Mariën, O. Islam, S. Chhajlani, W. Lybaert, M. Peeters, G. Van Camp, et al., The quest for circulating biomarkers in neuroendocrine neoplasms: a clinical perspective, Curr. Treat. Options Oncol. 24 (12) (2023) 1833–1851.
[147] C.M. Korse, B.G. Taal, A. Vincent, M.L.F. van Velthuysen, P. Baas, J.C.G. M. Buning-Kager, et al., Choice of tumour markers in patients with neuroendocrine tumours is dependent on the histological grade. A marker study of Chromogranin A, Neuron specific enolase, Progastrin-releasing peptide and cytokeratin fragments, Eur. J. Cancer Oxf. Engl. 1990 48 (5) (2012) 662–671.
[148] I.M. Modlin, M. Kidd, M. Falconi, P.L. Filosso, A. Frilling, A. Malczewska, et al., A multigenomic liquid biopsy biomarker for neuroendocrine tumor disease outperforms CgA and has surgical and clinical utility, Ann. Oncol. J. Eur. Soc. Med Oncol. 32 (11) (2021) 1425–1433.
[149] G. Puliani, V. Di Vito, T. Feola, F. Sesti, R. Centello, C. Pandozzi, et al., NETest: a systematic review focusing on the prognostic and predictive role, Neuroendocrinology 112 (6) (2022) 523–536.
[150] M.S. Khan, A. Kirkwood, T. Tsigani, J. Garcia-Hernandez, J.A. Hartley, M. E. Caplin, et al., Circulating tumor cells as prognostic markers in neuroendocrine tumors, J. Clin. Oncol. J. Am. Soc. Clin. Oncol. 31 (3) (2013) 365–372.
[151] M.S. Khan, A.A. Kirkwood, T. Tsigani, H. Lowe, R. Goldstein, J.A. Hartley, et al., Early changes in circulating tumor cells are associated with response and survival following treatment of metastatic neuroendocrine neoplasms, Clin. Cancer Res J. Am. Assoc. Cancer Res 22 (1) (2016) 79–85.
[152] G. Boons, T. Vandamme, L. Mariën, W. Lybaert, G. Roeyen, T. Rondou, et al., Longitudinal Copy-Number Alteration Analysis in Plasma Cell-Free DNA of Neuroendocrine Neoplasms is a Novel Specific Biomarker for Diagnosis, Prognosis, and Follow-up, Clin. Cancer Res J. Am. Assoc. Cancer Res 28 (2) (2022) 338–349.
[153] D.C. Chung, S.B. Brown, F. Graeme-Cook, M. Seto, A.L. Warshaw, R.T. Jensen, et al., Overexpression of cyclin D1 occurs frequently in human pancreatic endocrine tumors, J. Clin. Endocrinol. Metab. 85 (11) (2000) 4373–4378.
[154] H. Zhao, L. Wu, G. Yan, Y. Chen, M. Zhou, Y. Wu, et al., Inflammation and tumor progression: signaling pathways and targeted intervention, Signal Transduct. Target Ther. 6 (1) (2021) 263.
[155] M. Yi, T. Li, M. Niu, H. Zhang, Y. Wu, K. Wu, et al., Targeting cytokine and chemokine signaling pathways for cancer therapy, Signal Transduct. Target Ther. 9 (1) (2024) 176.
[156] N. Zhang, Y. Li, Receptor tyrosine kinases: biological functions and anticancer targeted therapy, MedComm 4 (6) (2023) e446.
[157] M.C. Berković, M. Jokić, J. Marout, S. Radosević, V. Zjacić-Rotkvić, S. Kapitanović, IL-6–174 C/G polymorphism in the gastroenteropancreatic neuroendocrine tumors (GEP-NETs), Exp. Mol. Pathol. 83 (3) (2007) 474–479.
[158] Y. Yang, L. Yang, Y. Li, Neuropilin-1 (NRP-1) upregulated by IL-6/STAT3 signaling contributes to invasion in pancreatic neuroendocrine neoplasms, Hum. Pathol. 81 (2018) 192–200.
[159] M.E. Pavel, G. Hassler, U. Baum, E.G. Hahn, T. Lohmann, D. Schuppan, Circulating levels of angiogenic cytokines can predict tumour progression and prognosis in neuroendocrine carcinomas, Clin. Endocrinol. (Oxf.) 62 (4) (2005) 434–443.
[160] F. Hussain, J. Wang, R. Ahmed, S.K. Guest, E.W.F. Lam, G. Stamp, et al., The expression of IL-8 and IL-8 receptors in pancreatic adenocarcinomas and pancreatic neuroendocrine tumours, Cytokine 49 (2) (2010) 134–140.
[161] T. Tecimer, J. Dlott, A. Chuntharapai, A.W. Martin, S.C. Peiper, Expression of the chemokine receptor CXCR2 in normal and neoplastic neuroendocrine cells, Arch. Pathol. Lab Med 124 (4) (2000) 520–525.
[162] R.A. Werner, A. Weich, T. Higuchi, J.S. Schmid, A. Schirbel, M. Lassmann, et al., Imaging of chemokine receptor 4 expression in neuroendocrine tumors - a triple tracer comparative approach, Theranostics 7 (6) (2017) 1489–1498.
[163] A.J. Zurita, M. Khajavi, H.K. Wu, L. Tye, X. Huang, M.H. Kulke, et al., Circulating cytokines and monocyte subpopulations as biomarkers of outcome and biological activity in sunitinib-treated patients with advanced neuroendocrine tumours, Br. J. Cancer 112 (7) (2015) 1199–1205.
[164] I. Boemi, S. Piccini, F.S. Colombo, V. Smiroldo, A. Zerbi, G. Capretti, et al., Alteration of the immunophenotype and cytokine profiles in patients affected by neuroendocrine neoplasms, Endocrine 83 (3) (2024) 810–823.
[165] Y. Takahashi, Y. Akishima-Fukasawa, N. Kobayashi, T. Sano, T. Kosuge, Y. Nimura, et al., Prognostic value of tumor architecture, tumor-associated vascular characteristics, and expression of angiogenic molecules in pancreatic endocrine tumors, Clin. Cancer Res J. Am. Assoc. Cancer Res 13 (1) (2007) 187–196.
[166] P. Jiménez-Fonseca, M.N. Martín, A. Carmona-Bayonas, A. Calvo, J. Fernández-Mateos, M. Redrado, et al., Biomarkers and polymorphisms in pancreatic neuroendocrine tumors treated with sunitinib, Oncotarget 9 (97) (2018) 36894–36905.
[167] K.M. Detjen, S. Rieke, A. Deters, P. Schulz, A. Rexin, S. Vollmer, et al., Angiopoietin-2 promotes disease progression of neuroendocrine tumors, Clin. Cancer Res J. Am. Assoc. Cancer Res 16 (2) (2010) 420–429.
[168] Hansel DE, A. Rahman, J. Hermans, R.R. de Krijger, R. Ashfaq, C.J. Yeo, et al., Liver metastases arising from well-differentiated pancreatic endocrine neoplasms demonstrate increased VEGF-C expression, Mod. Pathol. J. U S Can. Acad. Pathol. Inc. 16 (7) (2003) 652–659.
[169] J. Zhang, Z. Jia, Q. Li, L. Wang, A. Rashid, Z. Zhu, et al., Elevated expression of vascular endothelial growth factor correlates with increased angiogenesis and decreased progression-free survival among patients with low-grade neuroendocrine tumors, Cancer 109 (8) (2007) 1478–1486.
[170] A. Chaudhry, K. Funa, K. Oberg, Expression of growth factor peptides and their receptors in neuroendocrine tumors of the digestive system, Acta Oncol. Stock. Swed. 32 (2) (1993) 107–114.
[171] S. La Rosa, S. Uccella, S. Erba, C. Capella, F. Sessa, Immunohistochemical detection of fibroblast growth factor receptors in normal endocrine cells and related tumors of the digestive system, Appl. Immunohistochem. Mol. Morphol. AIMM 9 (4) (2001) 319–328.
[172] G. Hilfenhaus, A. Göhrig, U.F. Pape, T. Neumann, H. Jann, D. Zdunek, et al., Placental growth factor supports neuroendocrine tumor growth and predicts disease prognosis in patients, Endocr. Relat. Cancer 20 (3) (2013) 305–319.
[173] S.M. Pyonteck, B.B. Gadea, H.W. Wang, V. Gocheva, K.E. Hunter, L.H. Tang, et al., Deficiency of the macrophage growth factor CSF-1 disrupts pancreatic neuroendocrine tumor development, Oncogene 31 (11) (2012) 1459–1467.
[174] J. Xu, L. Shen, C. Bai, W. Wang, J. Li, X. Yu, et al., Surufatinib in advanced pancreatic neuroendocrine tumours (SANET-p): a randomised, double-blind, placebo-controlled, phase 3 study, Lancet Oncol. 21 (11) (2020) 1489–1499.
[175] M. Cigrovski Berković, T. Čačev, T. Catela Ivković, J. Marout, M. Ulamec, V. Zjačić-Rotkvić, et al., High VEGF serum values are associated with locoregional spread of gastroenteropancreatic neuroendocrine tumors (GEP-NETs), Mol. Cell Endocrinol. 425 (2016) 61–68.
[176] L. Geisler, T. Hellberg, J. Lambrecht, H. Jann, J. Knorr, J. Eschrich, et al., Inflammatory cytokines associated with diagnosis, tumor grade and prognosis in patients with neuroendocrine tumors, J. Clin. Med 11 (20) (2022) 6191.
[177] D. Herman Mahečić, M. Cigrovski Berković, V. Zjačić-Rotkvić, T. Čačev, S. Kapitanović, M. Ulamec, Inflammation-related cytokines and their roles in gastroenteropancreatic neuroendocrine neoplasms, Bosn. J. Basic Med Sci. 20 (4) (2020) 445–450.
[178] S. Krishnamurthy, Y. Dayal, Immunohistochemical expression of transforming growth factor alpha and epidermal growth factor receptor in gastrointestinal carcinoids, Am. J. Surg. Pathol. 21 (3) (1997) 327–333.
[179] M. Persson, M. Simonsson, A. Markkula, C. Rose, C. Ingvar, H. Jernström, Impacts of smoking on endocrine treatment response in a prospective breast cancer cohort, Br. J. Cancer 115 (3) (2016) 382–390.
[180] S. Chellappan, Smoking cessation after cancer diagnosis and enhanced therapy response: mechanisms and significance, Curr. Oncol. 29 (12) (2022) 9956–9969.
[181] S. Riondino, V. Formica, E. Valenzi, C. Morelli, V. Flaminio, I. Portarena, et al., Obesity and breast cancer: interaction or interference with the response to therapy? Curr. Oncol. 30 (1) (2023) 1220–1231.
[182] C. Chayangsu, J. Khorana, C. Charoentum, V. Sriuranpong, J. Patumanond, A. Tantraworasin, Development of clinical prediction score for chemotherapy response in advanced non-small cell lung cancer patients, Healthcare 11 (3) (2023) 293.
[183] S. O'Grady, J. Crown, M.J. Duffy, Statins inhibit proliferation and induce apoptosis in triple-negative breast cancer cells, Med Oncol. 39 (10) (2022) 142.
[184] Ú.C. Mc Menamin, L.J. Murray, C.M. Hughes, C.R. Cardwell, Statin use and breast cancer survival: a nationwide cohort study in Scotland, BMC Cancer 16 (1) (2016) 600.
[185] S. Pusceddu, C. Vernieri, M. Di Maio, R. Marconcini, F. Spada, S. Massironi, et al., Metformin use is associated with longer progression-free survival of patients with diabetes and pancreatic neuroendocrine tumors receiving everolimus and/or somatostatin analogues, Gastroenterology 155 (2) (2018) 479–489.e7.
[186] Miyaki C., Lynch L.M. An Update on Common Pharmaceuticals in the Prevention of Pancreatic Cancer. Cureus [Internet]. 2022 May 30 [cited 2024 Nov 26]; Available from: ⟨https://www.cureus.com/articles/96124-an-update-on-common-pharmaceuticals-in-the-prevention-of-pancreatic-cancer⟩.
[187] A.J. León-González, J.M. Jiménez-Vacas, A.C. Fuentes-Fayos, A. Sarmento-Cabral, A.D. Herrera-Martínez, M.D. Gahete, et al., Role of metformin and other metabolic drugs in the prevention and therapy of endocrine-related cancers, Curr. Opin. Pharm. 60 (2021) 17–26.

[188] M. Cives, E. Pelle', J. Strosberg, Emerging treatment options for gastroenteropancreatic neuroendocrine tumors, J. Clin. Med 9 (11) (2020) 3655.
[189] M.E. Caplin, M. Pavel, J.B. Ćwikła, A.T. Phan, M. Raderer, E. Sedláčková, et al., Lanreotide in metastatic enteropancreatic neuroendocrine tumors, N. Engl. J. Med 371 (3) (2014) 224–233.
[190] A. Rinke, H.H. Müller, C. Schade-Brittinger, K.J. Klose, P. Barth, M. Wied, et al., Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group, J. Clin. Oncol. J. Am. Soc. Clin. Oncol. 27 (28) (2009) 4656–4663.
[191] A. Faggiano, A.C. Carratù, E. Guadagno, S. Tafuto, F. Tatangelo, F. Riccardi, et al., Somatostatin Analogues according to Ki67 index in neuroendocrine tumours: an observational retrospective-prospective analysis from real life, Oncotarget 7 (5) (2016) 5538–5547.
[192] E. Merola, T. Alonso Gordoa, P. Zhang, T. Al-Toubah, E. Pellè, A. Kolasińska-Ćwikła, et al., Somatostatin analogs for pancreatic neuroendocrine tumors: any benefit when Ki-67 Is $\geq$ 10%? Oncologist 26 (4) (2021) 294–301.
[193] M. Cives, J. Strosberg, Radionuclide therapy for neuroendocrine tumors, Curr. Oncol. Rep. 19 (2) (2017) 9.
[194] F. Panzuto, M. Albertelli, M.L. De Rimini, F.M. Rizzo, C.M. Grana, M. Cives, et al., Radioligand therapy in the therapeutic strategy for patients with gastro-entero-pancreatic neuroendocrine tumors: a consensus statement from the Italian Association for Neuroendocrine Tumors (Itanet), Italian Association of Nuclear Medicine (AIMN), Italian Society of Endocrinology (SIE), Italian Association of Medical Oncology (AIOM), J. Endocrinol. Invest 48 (1) (2025) 23–36.
[195] J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, et al., Phase 3 Trial of ^{177} Lu-dotatate for midgut neuroendocrine tumors, N. Engl. J. Med 376 (2) (2017) 125–135.
[196] J. Ramage, B.G. Naraev, T.R. Halfdanarson, Peptide receptor radionuclide therapy for patients with advanced pancreatic neuroendocrine tumors, Semin Oncol. 45 (4) (2018) 236–248.
[197] T. Brabander, W.A. Van Der Zwan, J.J.M. Teunissen, B.L.R. Kam, R.A. Feelders, W.W. De Herder, et al., Long-Term Efficacy, Survival, and Safety of [177Lu-DOTA0,Tyr3]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors, Clin. Cancer Res 23 (16) (2017) 4617–4624.
[198] S. Singh, D. Halperin, S. Myrehaug, K. Herrmann, M. Pavel, P.L. Kunz, et al., 177Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study, Lancet Lond. Engl. 403 (10446) (2024) 2807–2817.
[199] M. Miederer, S. Seidl, A. Buck, K. Scheidhauer, H.J. Wester, M. Schwaiger, et al., Correlation of immunohistopathological expression of somatostatin receptor 2 with standardised uptake values in 68Ga-DOTATOC PET/CT, Eur. J. Nucl. Med Mol. Imaging 36 (1) (2009) 48–52.
[200] C. Kratochwil, M. Stefanova, E. Mavriopoulou, T. Holland-Letz, A. Dimitrakopoulou-Strauss, A. Afshar-Oromieh, et al., SUV of [68Ga]DOTATOC-PET/CT predicts response probability of PRRT in neuroendocrine tumors, Mol. Imaging Biol. 17 (3) (2015) 313–318.
[201] B. Nilica, D. Waitz, V. Stevanovic, C. Uprimny, D. Kendler, S. Buxbaum, et al., Direct comparison of 68Ga-DOTA-TOC and 18F-FDG PET/CT in the follow-up of patients with neuroendocrine tumour treated with the first full peptide receptor radionuclide therapy cycle, Eur. J. Nucl. Med Mol. Imaging 43 (9) (2016) 1585–1592.
[202] S. Oh, V. Prasad, D.S. Lee, R.P. Baum, Effect of Peptide Receptor Radionuclide Therapy on Somatostatin Receptor Status and Glucose Metabolism in Neuroendocrine Tumors: Intraindividual Comparison of Ga-68 DOTANOC PET/CT and F-18 FDG PET/CT, Int J. Mol. Imaging 2011 (2011) 1–7.
[203] S. Pusceddu, N. Prinzi, S. Tafuto, T. Ibrahim, A. Filice, M.P. Brizzi, et al., Association of upfront peptide receptor radionuclide therapy with progression-free survival among patients with enteropancreatic neuroendocrine tumors, JAMA Netw. Open 5 (2) (2022) e220290.
[204] L. Bodei, M.S. Kidd, A. Singh, W.A. Van Der Zwan, S. Severi, I.A. Drozdov, et al., PRRT genomic signature in blood for prediction of 177Lu-octreotate efficacy, Eur. J. Nucl. Med Mol. Imaging 45 (7) (2018) 1155–1169.
[205] J.C. Yao, M.H. Shah, T. Ito, C.L. Bohas, E.M. Wolin, E. Van Cutsem, et al., Everolimus for advanced pancreatic neuroendocrine tumors, N. Engl. J. Med 364 (6) (2011) 514–523.
[206] E. Raymond, L. Dahan, J.L. Raoul, Y.J. Bang, I. Borbath, C. Lombard-Bohas, et al., Sunitinib malate for the treatment of pancreatic neuroendocrine tumors, N. Engl. J. Med 364 (6) (2011) 501–513.
[207] P.L. Kunz, N.T. Graham, P.J. Catalano, H.S. Nimeiri, G.A. Fisher, T.A. Longacre, et al., Randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors (ECOG-ACRIN E2211), J. Clin. Oncol. 41 (7) (2023) 1359–1369.
[208] M.E. Hegi, A.C. Diserens, T. Gorlia, M.F. Hamou, N. De Tribolet, M. Weller, et al., *MGMT* gene silencing and benefit from temozolomide in glioblastoma, N. Engl. J. Med 352 (10) (2005) 997–1003.
[209] N. Brighi, G. Lamberti, E. Andrini, C. Mosconi, L. Manuzzi, G. Donati, et al., Prospective evaluation of MGMT-promoter methylation status and correlations with outcomes to temozolomide-based chemotherapy in well-differentiated neuroendocrine tumors, Curr. Oncol. 30 (2) (2023) 1381–1394.
[210] J. Cros, O. Hentic, V. Rebours, M. Zappa, N. Gille, N. Theou-Anton, et al., MGMT expression predicts response to temozolomide in pancreatic neuroendocrine tumors, Endocr. Relat. Cancer 23 (8) (2016) 625–633.
[211] M. Cives, M. Ghayouri, B. Morse, M. Brelsford, M. Black, A. Rizzo, et al., Analysis of potential response predictors to capecitabine/temozolomide in metastatic pancreatic neuroendocrine tumors, Endocr. Relat. Cancer 23 (9) (2016) 759–767.
[212] V. Haase, The VHL tumor suppressor: master regulator of HIF, Curr. Pharm. Des. 15 (33) (2009) 3895–3903.
[213] E. Jonasch, F. Donskov, O. Iliopoulos, W.K. Rathmell, V.K. Narayan, B. L. Maughan, et al., Belzutifan for renal cell carcinoma in von Hippel–Lindau disease, N. Engl. J. Med 385 (22) (2021) 2036–2046.
[214] E. Pelle, T. Al-Toubah, B. Morse, J. Strosberg, Belzutifan in a patient With VHL-associated metastatic pancreatic neuroendocrine tumor, J. Natl. Compr. Cancer Netw. JNCCN 20 (12) (2022) 1285–1287.
[215] T. Else, E. Jonasch, O. Iliopoulos, K.E. Beckermann, V. Narayan, B.L. Maughan, et al., Belzutifan for von Hippel–Lindau Disease: Pancreatic Lesion Population of the Phase 2 LITESPARK-004 Study, Clin. Cancer Res 30 (9) (2024) 1750–1757.
[216] M. Stridsberg, K. Oberg, Q. Li, U. Engström, G. Lundqvist, Measurements of chromogranin A, chromogranin B (secretogranin I), chromogranin C (secretogranin II) and pancreastatin in plasma and urine from patients with carcinoid tumours and endocrine pancreatic tumours, J. Endocrinol. 144 (1) (1995) 49–59.
[217] M. Stridsberg, K. Oberg, Q. Li, U. Engström, G. Lundqvist, Measurements of chromogranin A, chromogranin B (secretogranin I), chromogranin C (secretogranin II) and pancreastatin in plasma and urine from patients with carcinoid tumours and endocrine pancreatic tumours, J. Endocrinol. 144 (1) (1995) 49–59.
[218] V. Marotta, V. Nuzzo, T. Ferrara, A. Zuccoli, M. Masone, L. Nocerino, et al., Limitations of Chromogranin A in clinical practice, Biomark. Biochem Indic. Expo. Response Susceptibility Chem. 17 (2) (2012) 186–191.
[219] M. Stridsberg, B. Eriksson, B. Fellström, G. Kristiansson, E. Tiensuu Janson, Measurements of chromogranin B can serve as a complement to chromogranin A, Regul. Pept. 139 (1–3) (2007) 80–83.
[220] M. Miki, T. Ito, M. Hijioka, L. Lee, K. Yasunaga, K. Ueda, et al., Utility of chromogranin B compared with chromogranin A as a biomarker in Japanese patients with pancreatic neuroendocrine tumors, Jpn J. Clin. Oncol. 47 (6) (2017) 520–528.
[221] S. Rustagi, R.R.P. Warner, C.M. Divino, Serum pancreastatin: the next predictive neuroendocrine tumor marker, J. Surg. Oncol. 108 (2) (2013) 126–128.
[222] F. Panzuto, C. Severi, R. Cannizzaro, M. Falconi, S. Angeletti, A. Pasquali, et al., Utility of combined use of plasma levels of chromogranin A and pancreatic polypeptide in the diagnosis of gastrointestinal and pancreatic endocrine tumors, J. Endocrinol. Invest 27 (1) (2004) 6–11.
[223] T. Walter, L. Chardon, X. Chopin-laly, V. Raverot, A.G. Caffin, J.A. Chayvialle, et al., Is the combination of chromogranin A and pancreatic polypeptide serum determinations of interest in the diagnosis and follow-up of gastro-entero-pancreatic neuroendocrine tumours? Eur. J. Cancer Oxf. Engl. 1990 48 (12) (2012) 1766–1773.
[224] E. Bajetta, L. Ferrari, A. Martinetti, L. Celio, G. Procopio, S. Artale, et al., Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors, Cancer 86 (5) (1999) 858–865.
[225] B. Eriksson, K. Oberg, M. Stridsberg, Tumor markers in neuroendocrine tumors, Digestion 62 (1) (2000) 33–38.
[226] M.S. Khan, T. Tsigani, M. Rashid, J.S. Rabouhans, D. Yu, T.V. Luong, et al., Circulating tumor cells and EpCAM expression in neuroendocrine tumors, Clin. Cancer Res J. Am. Assoc. Cancer Res 17 (2) (2011) 337–345.
[227] T. Al-Toubah, M. Cives, T. Valone, K. Blue, J. Strosberg, Sensitivity and specificity of the NETest: a validation study, Neuroendocrinology 111 (6) (2021) 580–585.
[228] I.M. Modlin, M. Kidd, L. Bodei, I. Drozdov, H. Aslanian, The clinical utility of a novel blood-based multi-transcriptome assay for the diagnosis of neuroendocrine tumors of the gastrointestinal tract, Am. J. Gastroenterol. 110 (8) (2015) 1223–1232.