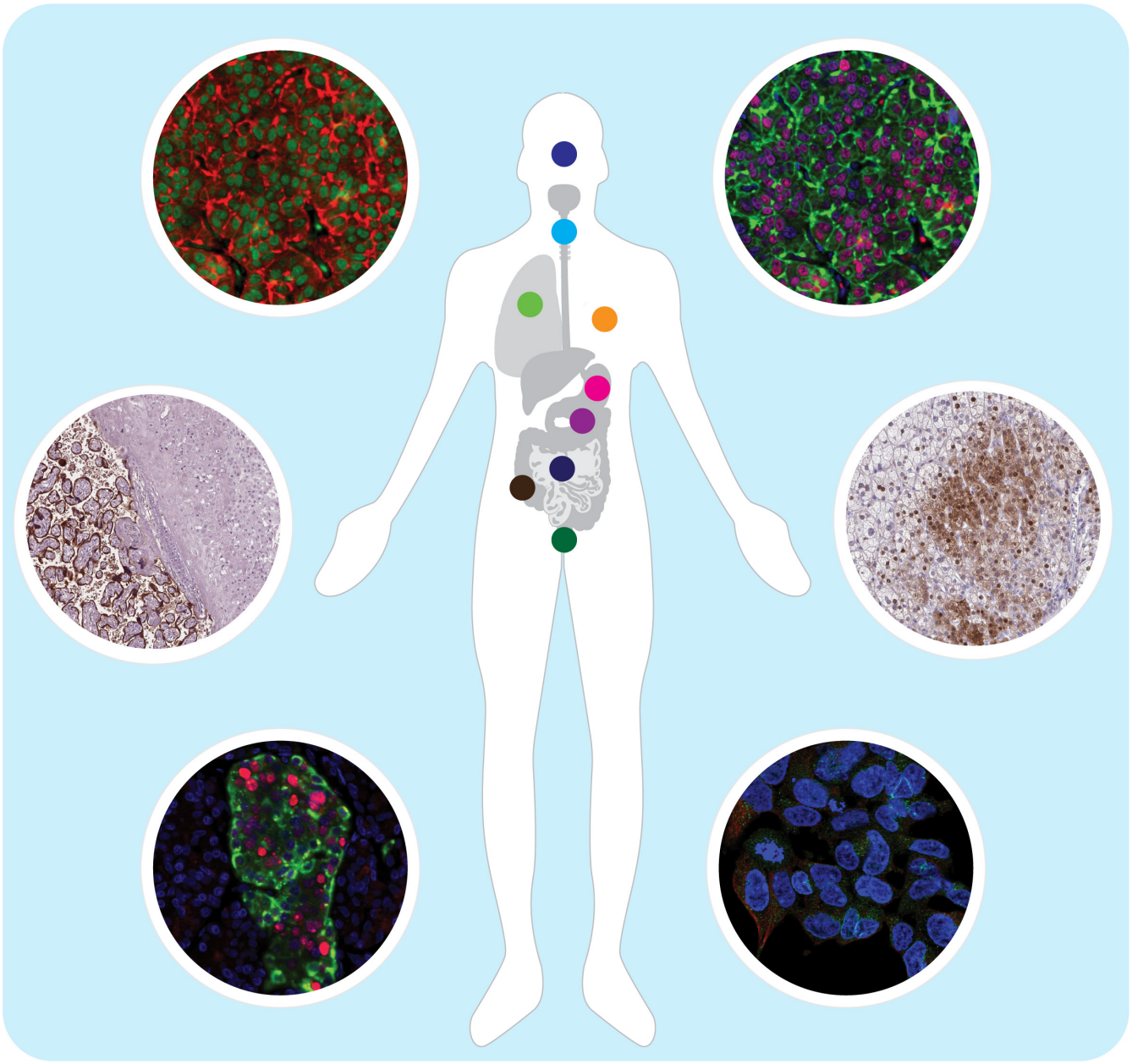
CANCER



NEUROENDOCRINE NEOPLASMS MARKERS

ATLAS ANTIBODIES

Neuroendocrine Neoplasms Markers

Neuroendocrine neoplasms (NENs) constitute a group of tumors that derive from the sensory and secretory neuroendocrine cells of the diffuse endocrine system. There is an unmet need for accurate biomarkers that can be used for NEN diagnosis, prognosis and follow-up, therapy stratification, and evaluation of treatment response. In this white paper, we highlight our newly released PrecisA Monoclonals useful for the immunohistological profiling of NENs.

Classification of NENs is based on tissue of origin, grade of differentiation, malignant potential and TNM staging. NENs are divided into:

- Well-differentiated neuroendocrine tumours (NET) showing either benign or uncertain behavior, e.g. typical and atypical carcinoid.

- Poorly differentiated neuroendocrine carcinoma (NEC), displaying high-grade malignancy, e.g. large cell neuroendocrine carcinoma and small cell carcinoma.

NETs are further graded according to proliferation score (G1-G3), while NECs are all G3 and are further subdivided into large and small cell carcinoma based on the histology.

In this white paper, we use “NEN” to include all tumor types.

NENs consist of a spectrum of heterogeneous tumors affecting neuroendocrine cells (the cells that release hormones into the bloodstream and act as an interface between the endocrine system and the nervous system). Thereby, NENs are either epithelial or neural in origin.

Although NENs may arise almost in every organ, they are predominately found in the gastrointestinal (48%) and bronchopulmonary (25%) systems, followed by pancreas (9%) reflecting the high density of neuroendocrine cells in these organs.

Some specific types of NETs include:

- Neuroendocrine tumor of the gut
- Neuroendocrine tumor of the lung (typical and atypical carcinoid)
- Neuroendocrine carcinoma of the lung (large or small cell type)
- Pituitary neuroendocrine tumors (PitNET)
- Merkel cell carcinoma (neuroendocrine carcinoma of the skin)
- Pancreatic neuroendocrine tumors (islet cell cancer)
- Pheochromocytoma of the adrenal gland

The survival is determined by several parameters, including the localization of the primary tumor, tumor size, presence of vascular invasion, necrosis, metastasis, and grade.

In addition, metastases are found in 20.8% of NENs at presentation and in another 38% after the initial diagnosis [(1)].

Morphological differentiation characteristics (well- or poorly-differentiated) is at the moment the most important prognostic factor for NENs, along with grade (proliferation degree, G1-G3) and stage (early or advanced).

However, there is a need for sensitive and specific tumor biomarkers, and the interest in molecular and immunohistochemical profiling of NENs is increasing since morphology alone is not sufficient [(2)].

Most NENs produce and secrete a multitude of proteins (including hormones and amines) that can be detected by immunohistochemistry (IHC).

In case of silent (non-hormone producing) tumors, assessment of transcription factors can be of help for correct diagnosis and classification [(3)].

Thus, along with the rapid development of next-generation sequencing and imaging techniques, IHC holds the top position as the most routinely used histopathological method in clinical settings to diagnose NENs.

The crucial need of new biomarkers in the management of NENs

NENs management remains a challenge due to a number of aspects such as lack of profound knowledge of the biology of the disease, late clinical presentation, and the scarcity of effective treatment options.

A correct diagnosis is imperative for the patient to obtain the most efficient treatment. The immunohistochemical assessment of the complex biomarkers expression patterns in targeted biopsies is instrumental in all phases of the diagnostic process, such as differentiation (neuroendocrine or epithelial origin) and proliferation (grading and staging) (Table 1).

In fact, the ultimate NEN diagnosis can only be established with tissue biopsy and further tumor grading based on the combination of Ki-67 proliferative index with cell mitotic rate.

Ki67 index and mitotic rate (Fig 1) is the standard routine for measuring NEN proliferation to define the tumor grade [4]. In addition, Ki67 has both prognostic and predictive value in NENs. Thus, Ki67 proliferation index >2% is a significant predictor of progression-free survival [5].

Also, selection of systemic therapies is partly based on the Ki67 rate [6,7].

A critical limitation in the management of NENs is posed by the lack of accurate immunohistochemical markers for classification, monitoring of therapy's efficacy, and providing a prognostic assessment of disease progression.

Most NENs produce and secrete a multitude of proteins that can be detected by IHC [8,9]. These include, most importantly, chromogranin A (CgA or CHGA) and synaptophysin (SYP), which are considered the most specific markers of NENs differentiation, SYN being more sensitive and CHGA more specific [10].

In addition, expression of CD56 (cluster of differentiation 56, also known as NCAM1) and neuron-specific enolase (NSE) are adequate evidence of neuroendocrine differentiation [11,12].

Also, CD57 is commonly used as marker for some NENs, namely pheochromocytoma and extra-adrenal paraganglioma and a useful marker for diagnosing Merkel cell carcinoma [13].

These markers, however, offer little help in the determination of NEN's primary location when this is unknown.

Moreover, highly proliferative NENs recurrently lose the ability to express CHGA and SYP making the diagnosis particularly challenging on small biopsies of metastatic lesions.

In case of metastasis, employment of IHC stains for transcription factors and hormonal products may be effective in identifying the primary site of tumor origin [14].

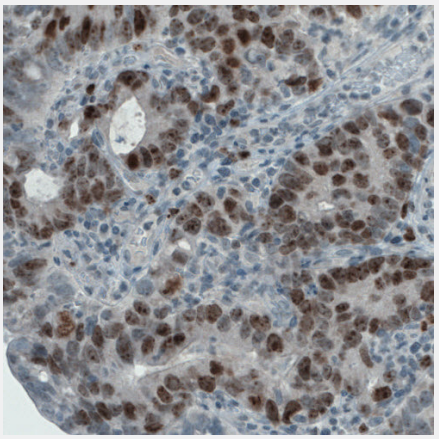


Figure 1. Immunohistochemical staining of human stomach cancer using the monoclonal antibody **Anti-MKi67 (AMAb90870)** shows strong immunoreactivity in tumor cells, in brown.

Table 1. Overview of NENs diagnose in targeted biopsies (first generation markers)

Scope	IHC markers
Confirmation of neuroendocrine nature	***Markers for neuroendocrine differentiation:*** Chromogranin A, Synaptophysin, CD56, CD57, UCHL1, NSE
Confirmation of epithelial origin	***Markers for epithelial differentiation:*** Cytokeratins AE1/AE3, CAM5.2, CK18, CK8
Grading and staging	***Marker for tumor proliferation:*** Ki-67

Examples of second-generation IHC markers for NENs differentiation

Standard laboratory assessment, when diagnosing a NET, relies mostly on CHGA, NSE, SYP, and CD56. However, while virtually all carcinoids are positive for SYP and CHGA, their expression is highly variable in NENs.

The advent of second-generation NEN markers for use in IHC has considerably expanded the pathology toolbox, constituting markers that often retain expression even in poorly differentiated NECs.

From a biological context, the second generation IHC NEN markers (functionally distinct from CHGA and SYP) are more consistent in terms of expression even if the NEN downregulates its secretory machinery as part of the dedifferentiation process.

Second-generation IHC markers for NEN include i.a. ISL1, INSM, SECG, and OTP (figs 2-7). As non-NENs rarely express these antigens, their specificity makes them welcome additions to the clinical practice [15].

ISL1

ISL1 (or ISLET1) is a transcription factor involved in the differentiation of the neuroendocrine pancreatic cells. It binds the insulin gene promoter and regulates insulin gene expression.

Hence, ISL1 is a reliable standard marker of pancreatic well-differentiated NENs [16] but is also commonly found in well and poorly differentiated NENs of extra-pancreatic origin [17]. Thus, recently, a combination of SATB2, ISL1 and TTF1 has been proposed to differentiate rectal from other gastrointestinal and lung well-differentiated NETs [18].

INSM1

The nuclear transcription factor INSM1 (insulinoma-associated protein 1) is a novel sensitive and specific marker that has recently demonstrated excellent sensitivity and specificity for NETs differentiation in various anatomic sites.

INSM1 is more sensitive than SYP/CHGA in NECs. Thus, 91-95% of small and large cell NECs express INSM1 [19]. In addition, nuclear expression pattern of INSM1 offers an advantage in interpretation over first generation markers, which are all cytoplasmic.

INSM1 may be used as a standalone, first-line marker for tumors of the head and neck [20], as well as in primary NENs of the gastrointestinal tract, appendix, and pancreas [21]. Thus, it is positive in pancreatic NET, and negative in pancreatic ductal adenocarcinoma [22] and in gynecologic high-grade neuroendocrine carcinomas [23, 24].

INSM1 is also expressed in lung carcinoids (small cell neuroendocrine carcinoma) [25, 26].

Notably, for pulmonary NENs, INSM1 has been proposed as a more sensitive marker than conventional neuroendocrine markers of the first generation [27].

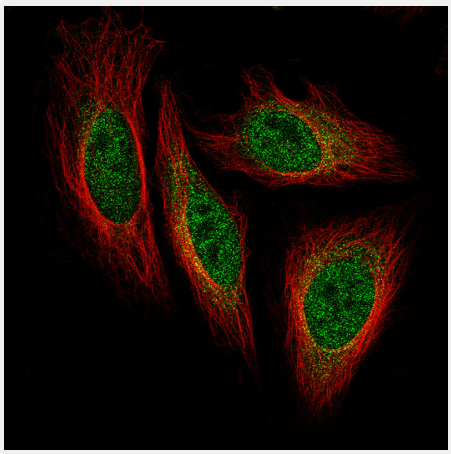


Figure 2. Immunofluorescence staining of HeLa cells using the monoclonal antibody **Anti-ISL1 (AMAb91729)**, showing localization to nucleoplasm and cytosol in green. Microtubules are visualized in red.

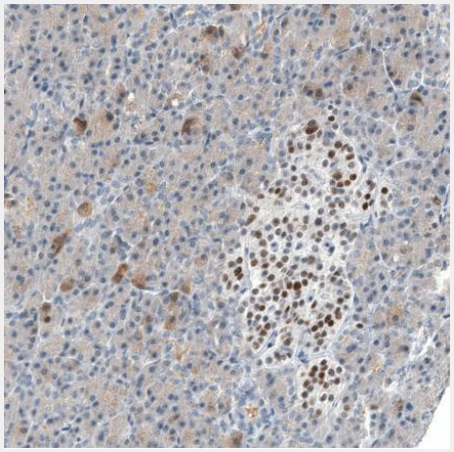


Figure 3. Immunohistochemical staining of human pancreas sing the monoclonal antibody **Anti-INSM1 (AMAb91727)** shows strong nuclear positivity in islets of Langerhans, in brown.

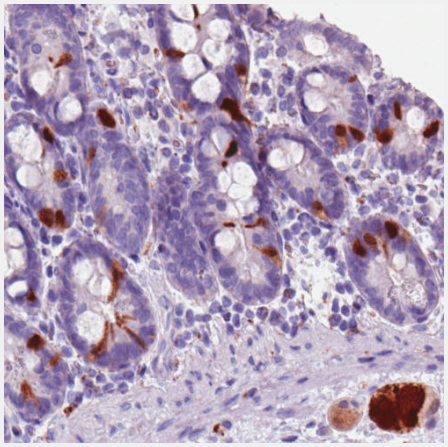


Figure 4. Immunohistochemical staining of human duodenumu sing the monoclonal antibody **Anti-SCGN (AMAb90630)** shows strong immunoreactivity in the neuroendocrine cells as well as in the local ganglionic cells, in brown.

SCGN

Secretagogin (SCGN or SECG) is a calcium-binding protein highly expressed in neuroendocrine cells, postulated to control cell proliferation via calcium signals.

High SCGN expression is found in the cytosol and nuclei of well-differentiated NENs and carcinoid metastases originating from different organs, as well as in NENs from the lung, pancreas, and adrenal glands promoting SCGN as a novel marker of NETs differentiation [28]. Moreover, pancreatic endocrine tumors, including gastrinomas, vipomas, carcinoids, and insulinomas, also highly express SCGN [29].

SCGN is more sensitive and specific in large cell neuroendocrine carcinoma than first-generation markers such as CD56, CHGA, and SYN [30].

OTP

Orthopedia homeobox protein (OTP) is a nuclear transcription factor with a well-defined role in embryonic neurodevelopment. OTP was suggested as diagnostic and prognostic marker for pulmonary NENs, being strongly expressed in NET cells (typical and atypical carcinoid) but not in NECs (LCNEC and SCLC) of the normal bronchus/bronchiole or any other normal tissues, except for hypothalamus [31-33].

OTP was shown to be twice as sensitive as TTF-1 in detecting pulmonary carcinoid tumors [34]. High OTP expression is a highly sensitive and specific marker for favourable prognosis of pulmonary carcinoid tumors [31].

In summary, first-generation markers such as CHGA and SYP are still considered the gold standard in endocrine pathology. However, the combined IHC analysis utilising second-generation markers may constitute additional sensitive and specific clinical use panels. This appears to be a promising approach for identifying tumors with NEN differentiation and a potential tool for NEN diagnosis (Table 2 and Fig.7).

The combination of classical and new IHC markers should thus be part of the clinical routine arsenal to improve the diagnostic capability, as well as aid in therapy stratification and clinical follow-up.

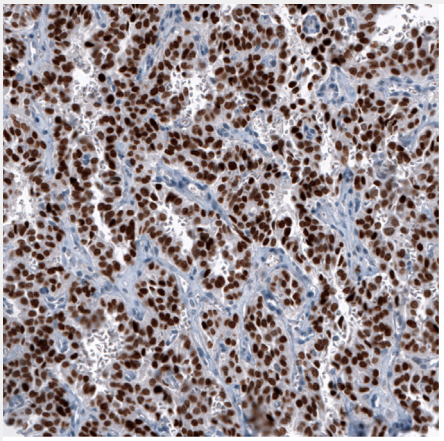


Figure 5. Immunohistochemical staining of human lung tumor (typical carcinoid) using the **Anti-OTP** monoclonal antibody (AMAb91696) shows strong nuclear positivity in tumor cells, in brown.

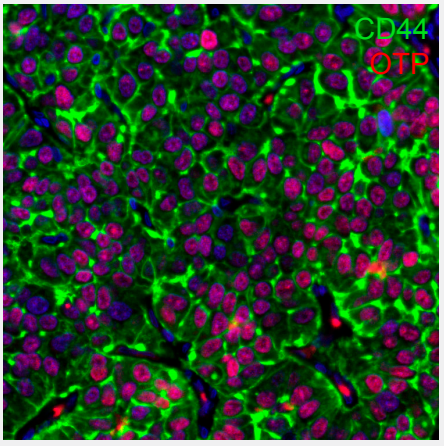


Figure 6. Multiplexed IHC-IF staining of human lung tumor (atypical carcinoid) using **Anti-OTP** monoclonal antibody AMAb91695 (nuclear, in red) and Anti-CD44 polyclonal antibody HPA005785 (in green). Nuclei are counterstained by DAPI (in blue).

Table 2. Schematic overview of tissue-specific expression patterns in some NETs for first- and second-generation markers

Human Tissue	CHGA 1st Gen.	SYP 1st Gen.	ISL1 2nd Gen.	INSM1 2nd Gen.	SECG 2nd Gen.	OTP 2nd Gen.
Lung	+	+	+	+	+	+
Pancreas	+	+	+	+	+	n.d.
Small Intestine	+	+	n.d.	+	+	n.d.
Pheochromocytoma/paraganglioma	+	+	+	+	n.d.	n.d.
Colorectum	n.d.	+	+	+	+	n.d.

CHGA (Chromogranin A); SYP (Synaptophysin); ISL1(ISL LIM Homeobox 1); INSM1(INSM Transcriptional Repressor 1); SECG (Secretagogin). n.d.= not detected

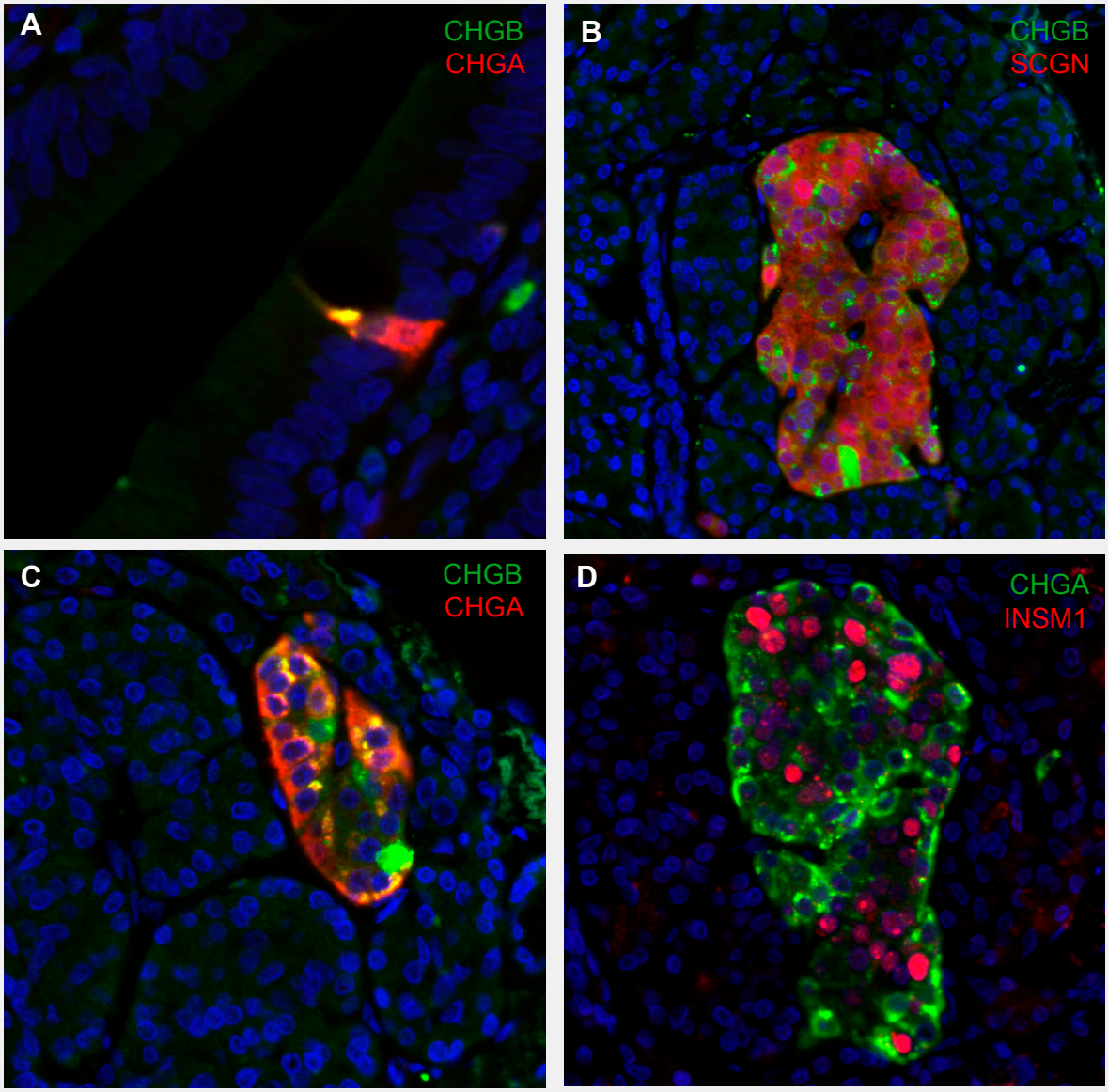


Figure 7.

A. Multiplexed IHC-IF staining of human duodenum showing CHGB and CHGA expression in enteroendocrine cell, using the **Anti-CHGB** monoclonal antibody AMAb91709 (cytoplasmic, in green) and the **Anti-CHGA** polyclonal antibody HPA017369 (cytoplasmic, in red). Note colocalisation of markers in the enteroendocrine cell. Nuclei are counterstained by DAPI (in blue).

B. Multiplexed IHC-IF staining of human pancreas showing CHGB and SCGN expression in pancreatic islet, using the **Anti-CHGB** monoclonal antibody AMAb91709 (cytoplasmic, in green) and the **Anti-SCGN** monoclonal antibody AMAb90632 (cytoplasmic and nuclear, in red). Nuclei are counterstained by DAPI (in blue).

C. Multiplexed IHC-IF staining of human pancreas showing CHGB and CHGA expression in pancreatic islet, using the **Anti-CHGB** monoclonal antibody AMAb91709 (cytoplasmic, in green) and the **Anti-CHGA** polyclonal antibody HPA017369 (cytoplasmic, in red). Nuclei are counterstained by DAPI (in blue).

D. Multiplexed IHC-IF staining of **human pancreas** showing INSM1 and CHGA expression in pancreatic islet, using the **Anti-INSM1** monoclonal antibody AMAb91727 (nuclear, red) and the **Anti-CHGA** polyclonal antibody HPA017369 (cytoplasmic, green). Nuclei are counterstained by DAPI (blue).

Iowa well-differentiated NET Site of Origin Classifier

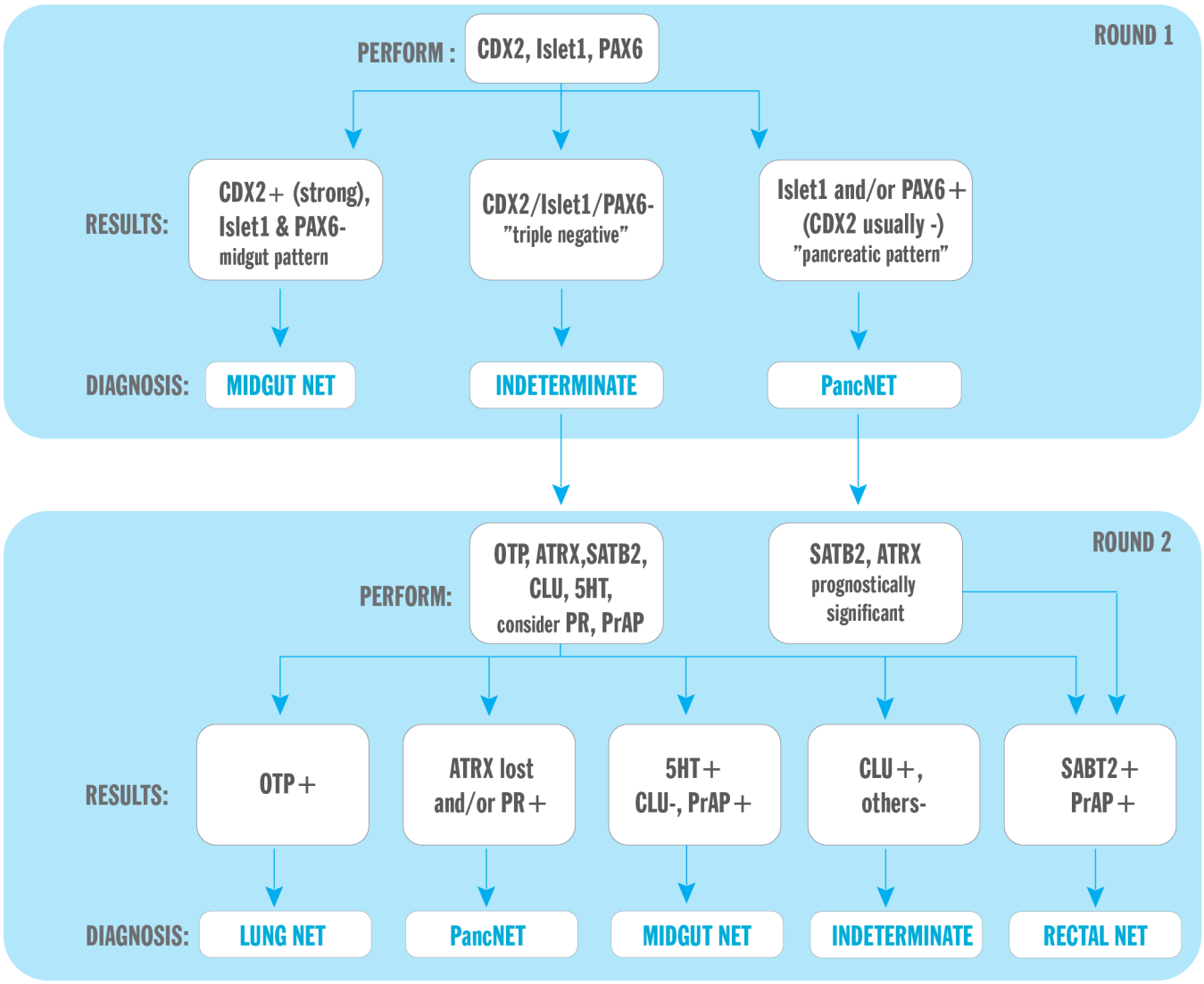


Figure 8. University of Iowa Immunohistochemical Algorithm for Well-Differentiated Neuroendocrine Tumor Site of Origin. This algorithm assumes positivity for one or more general neuroendocrine marker and for a broad-spectrum epithelial marker. "Round 1" IHC staining is geared toward detecting CDX2, Islet 1, PAX6, PAX8, while "Round 2" IHC staining is geared toward detecting OTP, ATRX,SABT2, PrAp and others specific markers.

Reference:

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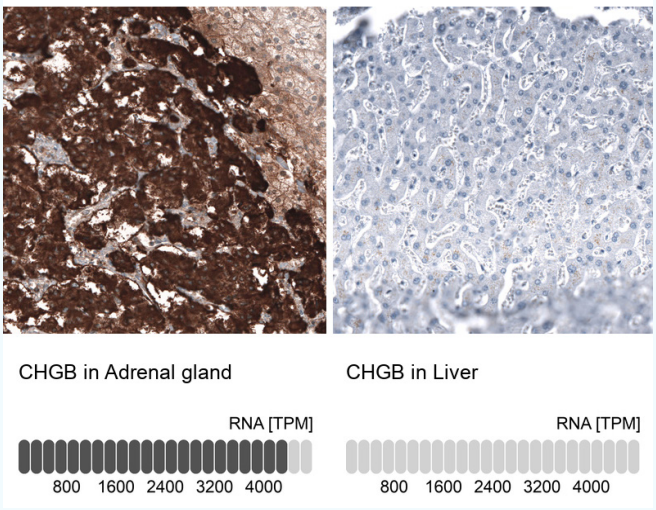
Table 3. PrecisA Monoclonal NEN markers.

Product Name	Protein Name	Product Number	Isotype	Validated Applications
Anti-ATRX	alpha thalassemia/mental retardation syndrome X-linked	AMAb90784	IgG1	IHC, WB*, ICC-IF
Anti-CHGB	Chromogranin B	AMAb91709	IgG1	IHC*
		AMAb91710	IgG1	IHC*, ICC-IF
Anti-EGRF	Epidermal growth factor receptor	AMAb90816	IgG1	IHC, WB
		AMAb90819	IgG1	WB
Anti-GATA3	Gata binding protein 3	AMAb91525	IgG2a	IHC*, WB, ICC-IF
Anti-INSM1	INSM Transcriptional Repressor 1	AMAb91727	IgG1	IHC
Anti-ISL1	ISL LIM homeobox 1	AMAb91729	IgG2a	ICC-IF
Anti-OTP	Homeobox protein orthopedia	AMAb91695	IgG1	IHC
		AMAb91696	IgG1	IHC, ICC-IF
Anti-PAX6	Paired box 6	AMAb91372	IgG1	IHC, ICC-IF
Anti-PAX8	Paired box 8	AMAb91488	IgG1	IHC, WB, ICC-IF
Anti-PNMT	Phenylethanolamine n-methyltransferase	AMAb91711	IgG1	IHC*
Anti-SATB2	SATB homeobox 2	AMAb90635	IgG1	IHC*, WB
		AMAb90678	IgG2a	IHC*, WB
		AMAb90679	IgG1	IHC, WB, ICC-IF
Anti-SCGN	Secretagogin, EF-hand calcium binding protein	AMAb90632	IgG2a	IHC
		AMAb90630	IgG1	IHC, WB

* Products with enhanced validation for indicated application

ENHANCED VALIDATION: AN ADDITIONAL LAYER OF SECURITY IN ANTIBODY VALIDATION

Enhanced Validation



Enhanced validation offers increased security of antibody specificity in a defined context. By using 5 different enhanced validation methods we validate our antibodies for each combination of protein, sample, and application.

The 5 methods are: genetic validation, orthogonal validation, validation by independent antibodies, recombinant expression validation, and migration capture MS validation.

Left: Example of orthogonal validation of protein expression using IHC by comparison of the staining signal to the RNA-seq data (TPM) of corresponding target in high and low expression tissues. The image shows the immunohistochemistry analysis in human adrenal gland and liver tissues using the Anti-CHGB (AMAb91709) antibody. Corresponding CHGB RNA-seq data (TPM) are presented for the same tissues.

Table 4. NEN markers for site of origin

Site of origin	Marker	Product Name	Product Number	Clonality	Validated Applications
Duodenal	ISL-1	Anti-ISL1	AMAb91729	Monoclonal	ICC-IF
	PDX-1	Anti-PDX1	HPA059146	Polyclonal	IHC*, ICC-IF
	CDX-2	Anti-CDX2	HPA045669	Polyclonal	ICC-IF
Hindgut Rectal	SATB2	Anti-SATB2	AMAb90679	Monoclonal	IHC*, WB, ICC-IF
	Peptide YY	Anti-PYY	HPA010973	Polyclonal	IHC*
	CDX-2	Anti-CDX2	HPA045669	Polyclonal	ICC-IF
	ISL-1	Anti-ISL1	AMAb91729	Monoclonal	ICC-IF
Midgut	CDX-2	Anti-CDX2	HPA045669	Polyclonal	ICC-IF
	INA	Anti-INA	HPA008057	Polyclonal	IHC*, WB, ICC-IF
	Ki67	Anti-MKI67	AMAb90870	Monoclonal	IHC, ICC-IF
Pancreatic, Small intestine	ISL-1	Anti-ISL1	AMAb91729	Monoclonal	ICC-IF
	PDX-1	Anti-PDX1	HPA059146	Polyclonal	IHC*, ICC-IF
	CDX-2	Anti-CDX2	HPA045669	Polyclonal	ICC-IF
Paraganglioma	Tyrosine Hydroxylase	Anti-TH	AMAb91112	Monoclonal	IHC
	GATA-3	Anti-GATA3	AMAb91525	Monoclonal	IHC*, WB, ICC-IF
Parathyroid	PTH	Anti-PTH	HPA048540	Polyclonal	IHC*
	GATA-3	Anti-GATA3	AMAb91525	Monoclonal	IHC*, WB, ICC-IF
Pituitary	Pit-1	Anti-SLC20A1	HPA035834	Polyclonal	IHC
	T-pit	Anti-TBX19	AMAb91409	Monoclonal	IHC
	SF-1	Anti-NR5A1	AMAb91540	Monoclonal	IHC, WB, ICC-IF
Pulmonary	TTF-1	Anti-TTF-1	HPA054837	Polyclonal	IHC, WB, ICC-IF
	POU2F3	Anti-POU2F3	HPA019652	Polyclonal	IHC*, WB*
	SYP	Anti-SYP	HPA002858	Polyclonal	IHC*, WB
	INSM1	Anti-INSM1	AMAb91727	Monoclonal	IHC
	OTP	Anti-OTP	AMAb91696	Monoclonal	IHC, ICC-IF
		Anti-OTP	AMAb91695	Monoclonal	IHC
Rectal	PAX6	Anti-PAX6	AMAb91372	Monoclonal	IHC, ICC-IF
	PAX8	Anti-PAX8	AMAb91488	Monoclonal	IHC, WB, ICC-IF
	SECG	Anti-SCGN	AMAb90630	Monoclonal	IHC, WB
	INSM1	Anti-INSM1	AMAb91727	Monoclonal	IHC
Thyroid	TTF-1	Anti-TTF-1	HPA054837	Polyclonal	IHC, WB, ICC-IF
	CALCA	Anti-CALCA	HPA064453	Polyclonal	IHC*, WB
Thoracic	INSM1	Anti-INSM1	AMAb91727	Monoclonal	IHC
	CD56	Anti-NCAM1	HPA039835	Polyclonal	IHC*, WB, ICC-IF

* Products with enhanced validation for indicated application

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