Journal of the Endocrine Society, 2022, **6**, 1–6
https://doi.org/10.1210/jendso/bvab191
Advance access publication 22 December 2021
Mini-Review

Is There a Role for Biomarkers in Surveillance of Pancreatic Neuroendocrine Neoplasms in Von Hippel-Lindau Disease?

Myrthe R. Naber,[1] Saya Ahmad,[1] Annemarie A. Verrijn Stuart,[2] Rachel H. Giles,[3] Gerlof D. Valk,[1] and Rachel S. van Leeuwaarde[1]

[1]Department of Endocrine Oncology, University Medical Center Utrecht, Utrecht 3584 CX, The Netherlands
[2]Department of Paediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht 3584 EA, The Netherlands; and
[3]Dutch VHL Organization, Utrecht 3503 RD, The Netherlands

Correspondence: Rachel Sara van Leeuwaarde, Department of Endocrine Oncology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht, 3584 CX, The Netherlands. Email: r.vanleeuwaarde@umcutrecht.nl.

Abstract

Von Hippel-Lindau (VHL) disease is an autosomal dominant disorder characterized by the development of multi-organ neoplasms. Among the manifestations of VHL are pancreatic neuroendocrine neoplasms (panNENs). In order to detect these lesions in a timely manner, patients are enrolled in a surveillance program, in accordance with the several existing VHL guidelines. However, these guidelines remain unclear about the role of biomarkers in diagnosing panNENs, despite the benefits a biomarker may offer regarding early detection of new lesions, thereby possibly limiting radiation exposure, and improving quality of life. The aim is to determine which biomarkers might be available in VHL patients and to assess their clinical relevance in diagnosing panNENs in VHL patients.

We searched the databases of PubMed/Medline, Embase, and Web of Science to identify relevant articles. Seven studies assessing the diagnostic or prognostic value of biomarkers were included. The results from these studies were conflicting. Since no evident association between VHL-related panNENs and biomarkers was established in studies with larger study populations, currently biomarkers do not play a significant role in early detection or follow-up for panNENs in VHL patients. The absence of evidence underscores the need for specific research to address this unmet need.

Key Words: Von Hippel-Lindau, pancreatic neuroendocrine tumors, biomarkers, surveillance

Abbreviations: CgA, chromogranin A; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; panNEN, pancreatic neuroendocrine neoplasm; VHL, von Hippel-Lindau.

Von Hippel-Lindau (VHL) disease is a genetic disorder characterized by the growth of cysts and tumors in several organs [1]. Recent data from Denmark showed a birth incidence of 1 in 27 000 [2]. The disease is caused by an autosomal dominant mutation in the VHL tumor suppressor gene located on the short arm of chromosome 3 [1]. This leads to the formation of cysts and hypervascular tumors, as a consequence of VHL's role in regulating angiogenesis [3]. Among the manifestations of VHL are renal cysts, clear cell renal carcinoma, hemangioblastomas of the central nervous system including the retina, pheochromocytomas, endolymphatic sac tumors, mesonephric broad ligament/epididymis cystadenomas, and pancreatic cysts and pancreatic neuroendocrine neoplasms (panNENs) [4]. Abnormalities of the pancreas are common in VHL. A study of 158 VHL patients found that 77% had lesions in the pancreas, of these patients, 70% had cysts and 9% had panNENs [5]. In another study, which included 633 patients, the prevalence of panNENs amounted to 17% [6].

In general, panNENs are divided into functional and nonfunctional tumors. Functional panNENs cause a hormonal hypersecretion syndrome. Nonfunctioning panNENs may present with nonspecific symptoms, such as abdominal pain [7]. In VHL patients, panNENs are generally nonfunctional and may develop into metastatic disease by unnoticed growth [8, 9]. Therefore, it is important to enroll patients in an adequate surveillance program, preferably in a VHL expert center, in order to timely detect these tumors. Several guidelines have been published recommending screening at regular intervals [10-12]. The VHL alliance advises surveillance by means of an abdominal magnetic resonance imaging (MRI) scan every other year starting at age 15 in order to locate developing tumors in the abdomen [12]. However, strong evidence for this frequency of screening is lacking.

Biomarkers have not yet been validated to identify VHL-related panNENs. The USA-based VHL Alliance and the Dutch VHL guideline do not mention the use of biomarkers for panNENs in the screening program developed for *VHL* gene mutation carriers, yet the Danish National VHL guidelines advise annual testing of chromogranin A (CgA) [10-12]. Biochemical testing is a routine procedure in the diagnostic approach to sporadic panNENs. Even in nonfunctional panNENs, hormone levels may be elevated, such as CgA, pancreatic polypeptide (PP), neuron-specific enolase (NSE), vasoactive intestinal peptide (VIP), gastrin, insulin, and glucagon, whereby these may be markers of subclinical disease [7, 13]. The diagnostic objectives of these biomarkers are presented in Table 1. CgA is a biomarker commonly used for gastroenteropancreatic

Received: 29 August 2021. 17November2021**Editorial Decision:** 16 December 2021. **Corrected and Typeset:** 17 January 2022

neuroendocrine tumors, although it can be falsely elevated by several factors, which are explained in Table 2. The most common causes of falsely elevated CgA are use of proton pump inhibitors (PPIs), atrophic gastritis, and impaired kidney function [14]. The European Neuroendocrine Tumor Society (ENETS) consensus guideline recommends measuring CgA in nonfunctional panNENs. If elevated, it is useful for evaluating treatment response and detecting progression and recurrence at an early stage [15]. Assuming that the etiology of VHL-related and sporadic panNENs overlap, this approach might be valuable in the VHL population.

Recently, a systematic review on the diagnostic and management strategies for panNENs in VHL was published by our research group [20]. However, this article did not include an overview of the potential utility of biomarkers. Because the role of biomarkers in diagnosing panNENs in *VHL* gene mutation carriers is unclear and as current guidelines propose conflicting recommendations, this article aims to further investigate the additional value of biomarkers in diagnosing panNENs in VHL.

Methods

For this review the electronic databases of PubMed/Medline, Embase, and Web of Science were searched in February 2021. Keywords used for the search can be found in Table 3, and the full search string is made available by the authors upon request. The literature search was reviewed by an experienced librarian. Case reports and reviews were excluded and only articles written in English, Dutch, French, and German were included. There was no restriction in year of publication.

Only original articles reporting on the diagnostic or prognostic value of biomarkers were included. Studies had to include a minimum of 5 VHL patients with (suspected) panNEN, who were either clinically or genetically diagnosed with VHL. Articles including both sporadic and VHL-associated pancreatic lesions were deemed eligible if it was possible to extract data of VHL patients separately. In addition, eligible articles found by snowball method, in which references of key articles are examined, were also included.

All identified articles were entered into Rayyan QCRI and duplicates were removed. Title/abstract of all studies were

Table 1. Biochemical biomarkers used for panNEN diagnosis [16-18]

Biomarker	Source	Sensitivity (%)	Specificity (%)	Diagnostic objective
Chromogranin A	Serum	60-87	72-85	GEP-NET
Pancreatic polypeptide	Plasma	31-63	67-81	PanNEN
Neuron-specific enolase	Plasma	33	73	GEP-NET
5-hydroxyindole acetic acid	Urine	70	90	Carcinoid syndrome
		52-68	89-98	SI NET
Gastrin	Serum	94[a]	100[a]	Gastrinomas, Zollinger-Ellison syndrome
Insulin	Serum/plasma	52-94	92-100	Insulinomas
Glucagon	Plasma	na	na	Glucagonomas
Vasoactive intestinal peptide	Serum	na	na	VIPomas

Abbreviations: GEP-NET, gastroenteropancreatic neuroendocrine tumor; na, not available; PanNEN, pancreatic neuroendocrine neoplasm; SI NET, small intestinal neuroendocrine tumor.
[a]When measured during a provocative test using > 120 pg/mL as cutoff.

Table 2. Factors known to increase CgA levels [14, 19]

Factor	Explanation
Gastric disorders	PPI treatment, atrophic gastritis. Lack of gastric acid leads to hypersecretion of CgA.
Impaired kidney function	Reduced renal clearance of CgA.
Cardiovascular	Chronic heart failure, acute coronary syndromes, hypertension. CgA is increased by inflammation and cardiac overload.
Rheumatoid diseases	Rheumatoid arthritis, systemic lupus erythematosus. CgA correlates with TNF-alfa receptors and generalized inflammation.
Gastrointestinal disease	Inflammatory bowel disease, irritable bowel syndrome.
Other	CgA is known to increase after food intake and exercise in healthy individuals.
Hepatic failure	Nonalcoholic fatty liver disease. CgA correlates with serum inflammatory markers.

Abbreviations: CgA, chromogranin A; PPI, proton pump inhibitors; TNF-alfa, tumor necrosis factor alfa.

Table 3. Keywords of the search

Biomarker OR *CgA* OR *PP* OR *somatostatin* OR *glucagon* OR *insulin*	*NET* OR *endocrine tumor* OR *carcinoid* OR *nonfunctioning tumor* OR *neuroendocrine neoplasm*	*Pancreas* OR *duodenopancreatic* OR *pNET* OR *gastroenteropancreatic*

independently screened by 2 reviewers (S.A. and M.R.N.), after which potentially relevant articles were independently examined in full text for inclusion based on the aforementioned eligibility criteria. Reasons for exclusion were noted for articles examined in full text. Disagreement between the 2 authors was resolved by consensus. If consensus could not be achieved, a third reviewer was consulted (R.S.v.L.).

Included articles examining biomarkers as primary research question were assessed for risk of bias and applicability adhering to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. The QUADAS-2 tool addresses risk of bias in 4 domains: patient selection, index test, reference test, and flow and timing. For the first 3 domains, concerns regarding applicability are also assessed.

Results

After screening a total of 6 004 records, 6 studies were eligible for inclusion (Fig. 1).The study by Tirosh et al was the only study to primarily investigate the association between biomarkers and extent of disease. Therefore, this was the only study assessed for risk of bias and applicability. Risk of bias and concerns regarding applicability were considered low. However, concerns regarding flow and timing were regarded as unclear, because only 23 out of 28 VHL patients were analyzed for the biomarkers VIP and PP. Characteristics of all included studies can be found in Table 4.

The study by Tirosh et al, a multicenter, prospective cohort study, was most applicable for this review. The following biomarkers were assessed in 24 evaluable VHL patients with panNENs: CgA, PP, neuron-specific enolase, VIP, gastrin, glucagon, and 24-hour 5-hydroxyindoleacetic acid (5-HIAA) urine levels. A positive correlation was reported between tumor volume and plasma VIP ($r = 0.5$, $P = 0.02$) and PP levels ($r = 0.7$, $P < 0.001$) [21]. The study by Weisbrod et al was also applicable for this review and represented a larger VHL cohort. Of note, the population studied by Weisbrod et al partially overlapped with the cohort examined by Tirosh et al. The biomarkers CgA and PP were related to greatest tumor diameter. In contrast with the study by Tirosh et al, no association was found between PP levels and tumor size [22].

Furthermore, Weisbrod et al found a trend indicating an inverse relationship between serum CgA and tumor size. In contrast to the negative trend, Prasad et al observed a trend toward higher mean CgA concentrations in patients with panNENs than in those without, although only 2 out of the 11 patients showed a CgA concentration above the upper limit of normal, 1 of whom used proton pump inhibitors and had renal insufficiency [23]. The remaining studies that reported on CgA levels did not find an association between CgA and panNENs in the VHL population [24-26]. Sadowski et al found no association between uptake on fluorodeoxyglucose–positron emission tomography (FDG-PET) and CgA levels [25]. The other 2 studies mainly described whether CgA levels

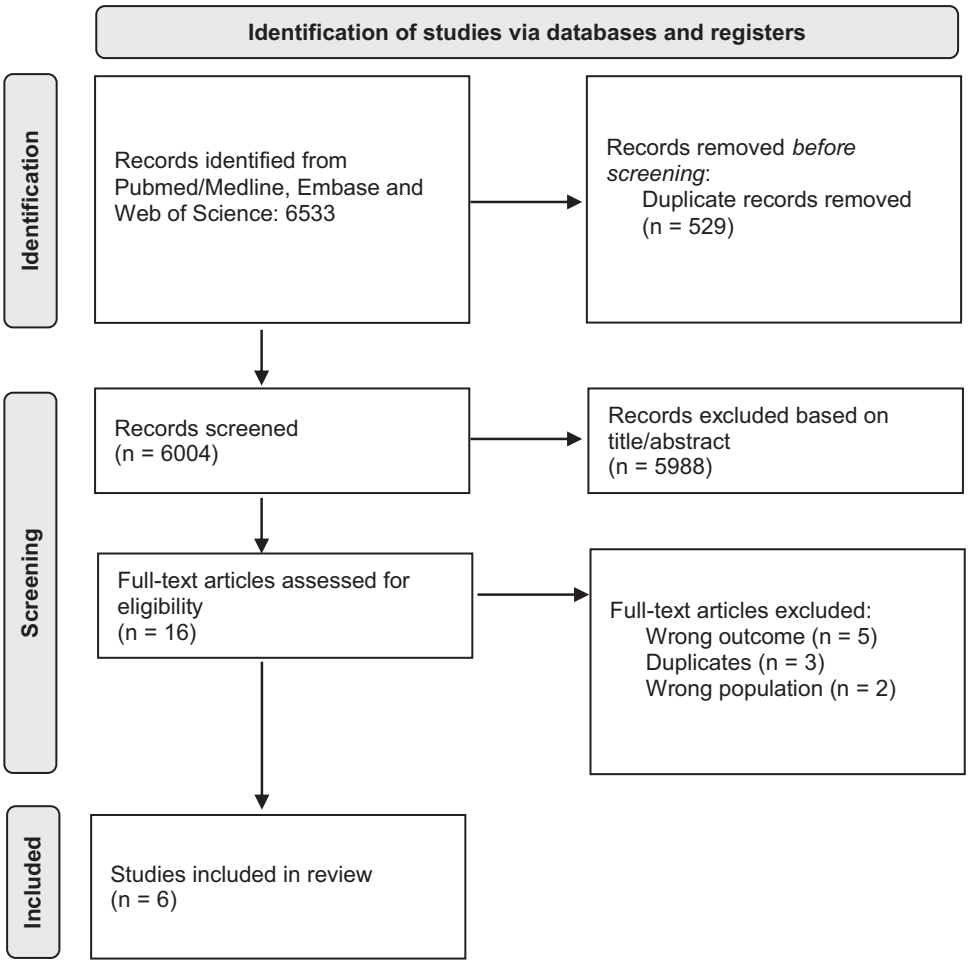

Figure 1. PRISMA flow diagram of identified studies.

Table 4. Characteristics of all studies assessing diagnostic or prognostic value of biomarkers for pNETs in VHL patients

Authors, year	Country	Multicenter/single center	Institute	Number of VHL patients with pNETs	Biomarkers	Method of establishing diagnosis
Weisbrod et al., 2014	USA	Multicenter	NIH Clinical Center	87	CgA, PP	CT
Tirosh et al., 2017	USA	Multicenter	NIH Clinical Center	24	CgA, PP, NSE, VIP, gastrin, glucagon, 5-HIAA	PET/CT
van Asselt et al., 2016	The Netherlands	Multicenter	University Medical Centers	22	EUS, PET	CT or MRI
Sadowski et al., 2014	USA	Multicenter	NIH Clinical Center	109	FDG-PET	CT
Prasad et al., 2016	Germany	Single center	Interdisciplinary Centre of Metabolism, Charité-Universitätsmedizin Berlin	17	PET/CT	CT or MRI
Kitano et al., 2011	USA	Multicenter	NIH Clinical Center	69	18F-FDG, 18F-DOPA PET	CT and MRI
Blansfield et al., 2007	USA	Single center	NIH Clinical Center	108	Insulin, glucagon, PP, and VIP	Pathology or CT and MRI

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; CgA, chromogranin A; CT, computed tomography; EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; F-DOPA, fluorodopa; MRI, magnetic resonance imaging; NIH, National Institutes of Health; NSE, neuron-specific enolase; PET, positron emission tomography; PP, pancreatic polypeptide; VIP, vasoactive intestinal peptide.

were elevated [24, 26]. Overall, these results do not suggest that CgA values are substantially altered in VHL-associated panNENs.

Van Asselt et al referred to a study on biomarkers in 108 VHL patients with panNENs, conducted by Blansfield et al. They studied the natural history of panNENs in VHL patients, including biochemical investigation. However, since the investigation of biomarkers was not reported in the abstract or keywords, this study was not identified by our search. Biochemical investigations included serum levels of insulin, glucagon, PP, and VIP, none of which were indicative for presence of a panNEN in any of the subjects. Furthermore, it was noted that none of the patients had functioning tumors and therefore proposed to test serum hormone levels only when patients exhibit symptoms suggestive of a functioning panNEN [6].

Discussion

This article is the first to present an overview of previous research in VHL patients reporting on biomarkers in relation to panNENs. At this time the role of biomarkers seems limited, with no evident association between VHL-related panNENs and biomarkers in larger study populations [6, 22]. However, the number of studies is few and therefore conclusions must be drawn with care. Current evidence shows a limited role for biomarkers to diagnose panNENs in VHL. Therefore, assessment of hormone levels should be restricted to patients who have symptoms suggestive of a functioning panNEN.

Weisbrod et al found an inverse relationship between CgA and tumor size. It is hypothesized that this could be the result of an increasing percentage of tumor volume not synthesizing and secreting CgA. However, as can be seen in Table 2, several factors are known to influence CgA, and patients with these disorders should be excluded from studies regarding CgA. The authors did not specify whether this population was excluded. Moreover, VHL patients have an increased risk of developing clear cell renal carcinoma, which is managed with surgery. Thus, this population is at risk for developing an impaired kidney function after treatment of clear cell renal carcinoma.

For comparison, studies on the accuracy of biomarkers have been performed in patients with multiple endocrine neoplasia type 1 (MEN1), where a substantial part of the population have a nonfunctioning panNEN. Van Treijen et al conducted a systematic review on this topic and found that the diagnostic value of biomarkers to detect panNENs was low [27]. Studies by de Laat et al and Qui et al found AUCs of 0.48-0.66 for CgA, 0.64 for PP, and 0.58-0.77 for glucagon [28, 29]. It was therefore concluded that these biomarkers are of inadequate diagnostic value and should not be used in the screening programs for nonfunctioning panNENs in the MEN1 population. In addition, the diagnostic value of these biomarkers in MEN1 patients is low even when combined or adjusted for age, tumor size, or tumor number [27]. Although panNENs have a higher prevalence in MEN1 as well as another genetic driver, results from the MEN1 population may be extrapolated to VHL patients.

Recently, an extensive review was published regarding biomarkers for panNENs management [17]. In line with the present study, this review concluded that monoanalytes, the biomarkers researched in our review, were of poor sensitivity

and specificity. However, this review directs the attention to circulating RNA. Compared with cell-free DNA and circulating tumor cells, circulating microRNA seems less expensive and more accessible [17]. Therefore, this method could be of future interest to the VHL community.

Strengths

This article is the first comprehensive review on biomarkers for panNENs in VHL. In order to achieve an overview of the literature on biomarkers in VHL patients, an extensive search string was composed, which intentionally did not include VHL as search term, in order to discover studies on sporadic panNENs that also included VHL patients. VHL is a rare disease and to identify all possibly relevant articles, prognostic as well as diagnostic studies were included. This search strategy has resulted in detection of additional studies which did not primarily investigate biomarkers, but nonetheless reported on them.

Limitations

A few studies, although they did fit our inclusion criteria, were missed by our search, because their index terms did not include biomarker, CgA, PP, somatostatin, glucagon, or insulin [5, 30, 31]. However, these studies did report on elevated levels of several biomarkers in their VHL populations. Hammel et al describes increased serum levels of somatostatin, 8 and 20 times the upper limit of normal, in 2 of the 5 VHL patients with panNENs who underwent complete biochemical investigations [5]. In the study by Yamasaki et al, 3 out of 10 cases showed increased levels of several neuroendocrine hormones: these were, respectively, PP; somatostatin and serotonin; and gastrin, serotonin, and adrenocorticotropic hormone [30]. On the contrary, Erlic et al did not find elevated levels of gastrin, C peptide, and insulin in 16 VHL patients [31]. These 3 studies reported on a small number of patients, which limits their value in comparison with studies investigating the correlation between biomarkers and panNENs in larger populations, which did not report conclusive evidence [6, 22].

Future Directions

Surveillance for panNENs and other manifestations in VHL patients is an intensive and lifelong necessity. Fundamental to the screening programs in the current era are the imaging modalities such as MRI and computed tomography (CT). Availability of biomarkers would be ideal to reduce the burden of imaging and to help monitor disease progression; however, the biomarkers reported in this review seem to lack diagnostic or prognostic value. Nonetheless, other biomarkers may well aid future VHL surveillance; candidates for this purpose might be identified by new technologies, such as RNA sequencing or serum proteomics.

Although not a typical biomarker, telomere length was encountered during the search as a possible valuable tool. Telomere length has been examined to investigate the age-related tumor risks in VHL patients. VHL patients showed significantly shorter telomere length than their healthy family controls. Moreover, patients with shorter telomeres had significantly increased age-related risks of developing panNENs. These results highlight a possible role for telomere length as a risk factor for panNENs [32]. However, methods for diagnosing panNENs were not specified in this study and therefore results should be interpreted with caution. Nonetheless, telomere length may well be an interesting topic for future research, as it might help to identify patients with an increased risk of developing panNENs and who therefore may need earlier and more frequent surveillance programs.

Currently, surveillance in VHL patients relies heavily on imaging modalities and patients are exposed to excessive cumulative radiation over the course of their lives [33]. Identification of biomarkers will facilitate more dynamic testing to support pancreas-sparing interventions, which would not only greatly improve the quality of life of these patients but also would facilitate earlier detection of new lesions.

The evolution from static imaging opportunities at predesignated time points not based on evidence or natural history of the individual tumor to biomarkers would fundamentally change surveillance practice, with considerably less impact on patients' quality of life.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Disclosures

The authors have nothing to disclose. The authors declare that there is no conflict of interest.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Feletti A, Anglani M, Scarpa B, *et al*. Von Hippel-Lindau disease: an evaluation of natural history and functional disability. *Neuro Oncol*. 2016;18(7):1011-1020.
2. Binderup ML, Galanakis M, Budtz-Jørgensen E, *et al*. Prevalence, birth incidence, and penetrance of von Hippel-Lindau disease (vHL) in Denmark. *Eur J Hum Genet*. 2017;25(3):301-307.
3. Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. *J Clin Oncol*. 2004;22(24):4991-5004.
4. Maher ER, Neumann HP, Richard S. Von Hippel–Lindau disease: a clinical and scientific review. *Eur J Hum Genet*. 2011;19(6):617-623.
5. Hammel PR, Vilgrain V, Terris B, *et al*. Pancreatic involvement in von Hippel-Lindau disease. The Groupe Francophone d'Etude de la Maladie de von Hippel-Lindau. *Gastroenterology*. 2000;119(4):1087-1095.
6. Blansfield JA, Choyke L, Morita SY, *et al*. Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (pNETS). *Surgery*. 2007;142(6):814-818.e2.
7. Massironi S, Sciola V, Peracchi M, *et al*. Neuroendocrine tumors of the gastro-entero-pancreatic system. *World J Gastroenterol*. 2008;14(35):5377-5844.
8. De Mestier F, Gaujoux S, Cros J, *et al*. Long-term prognosis of resected pancreatic neuroendocrine tumors in von Hippel-Lindau disease is favorable and not influenced by small tumors left in place. *Ann Surg*. 2015;262(2):384-388.
9. Krauss T, Ferrara AM, Links TP, *et al*. Preventive medicine of von Hippel–Lindau disease-associated pancreatic neuroendocrine tumors. *Endocr Relat Cancer*. 2019;25(9):783-793.
10. Binderup ML, Bisgaard ML, Harbud V, *et al*. von Hippel-Lindau disease (vHL) — National clinical guideline for diagnosis and surveillance in Denmark. *Dan Med J*. 2013;60(12):B4763.

11. Hes FJ, van der Luijt RB. Von Hippel-Lindau disease: protocols for diagnosis and periodical clinical monitoring. National Von Hippel-Lindau Disease Working Group. *Ned Tijdschr Geneeskd*. 2000;144(11):505-509.
12. *VHL Alliance*. *The VHL Handbook*. 5th ed. Scotts Valley, California, USA: CreateSpace Independent Publishing Platform; 2015.
13. Ehehalt F, Saeger HD, Schmidt CM, *et al*. Neuroendocrine tumors of the pancreas. *Oncologist*. 2009;14(5):456-467.
14. Gut P, Czarnywojtek A, Fischbach J, *et al*. Chromogranin A – unspecific neuroendocrine marker. Clinical utility and potential diagnostic pitfalls. *Arch Med Sci*. 2016;12(1):1-9.
15. Falconi M, Eriksson B, Kaltsas G, *et al*. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology*. 2016;103(2):153-171.
16. Sansone A, Lauretta R, Vottari S, *et al*. Specific and non-specific biomarkers in neuroendocrine gastroenteropancreatic tumors. *Cancers*. 2019;11(8):1113.
17. Bocchini M, Nicolini F, Severi S, *et al*. Biomarkers for pancreatic neuroendocrine neoplasms (PanNENs) management – an updated review. *Front Oncol*. 2020;10:831.
18. Oberg K, Couvelard A, Delle Fave G, *et al*. ENETs consensus guidelines for the standards of care in neuroendocrine tumors: biochemical markers. *Neuroendocrinology*. 2017;105(3):201-211.
19. Bo Wu, P, Zhi Deng, *et al*. Increased plasma CgA levels associated with non alcoholic fatty liver disease. *Turk J Gastroenterol*. 2015;26(5):404-407.
20. Ahmad S, Naber M, Giles R, *et al*. Diagnostic and management strategies for pNETs in Von Hippel-Lindau: a systematic review. *Endocr Relat Canc*. 2021;28(3):151-160.
21. Tirosh A, Papadakis G, Millo C, *et al*. Association between neuroendocrine tumors, biomarkers and primary tumor site and disease type based on total 68Ga-DOTATATE-avid tumor volume measurements. *Eur J Endocrinol*. 2017;176(5):575-582.
22. Weisbrod A, Kitano M, Thomas F, *et al*. Assessment of tumor growth in pancreatic neuroendocrine tumors in von Hippel Lindau syndrome. *J Am Coll Surg*. 2014;218(2):163-169.
23. Prasad V, Tiling N, Denecke T, *et al*. Potential role of (68) Ga-DOTATOC PET/CT in screening for pancreatic neuroendocrine tumour in patients with von Hippel-Lindau disease. *Eur J Nucl Med Mol Imaging*. 2016;43(11):2014-2020.
24. Asselt S van, Brouwers AH, Dullemen HM van, *et al*. Potential value of EUS in pancreatic surveillance of VHL patients. *Eur J Endocrinol*. 2016;174(5):611-620.
25. Sadowski SM, Weisbrod AB, Ellis R, *et al*. Prospective evaluation of the clinical utility of 18-Fluorodeoxyglucose PET CT scanning in patients with Von Hippel-Lindau-associated pancreatic lesions. *J Am Coll Surg*. 2014;218(5):997-1003.
26. Kitano M, Millo C, Rahbari R, *et al*. Comparison of 6-18F-fluoro-L-DOPA, 18F-2-deoxy-D-glucose, CT, and MRI in patients with pancreatic neuroendocrine neoplasms with von Hippel-Lindau disease. *Surgery*. 2011;105(6):1122-1128.
27. van Treijen MJC, van Beek DJ, van Leeuwaarde RS, *et al*. Diagnosing nonfunctional pancreatic NETs in MEN1: the evidence base. *J Endocr Soc*. 2018;2(9):1067-1088.
28. de Laat J, Pieterman C, Weijmans M, *et al*. Low accuracy of tumor markers for diagnosing pancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1 patients. *J Clin Endocrinol Metab*. 2013;98(10):4143-4145.
29. Qui W, Christakis I, Silva A, *et al*. Utility of chromogranin A, pancreatic polypeptide, glucagon and gastrin in the diagnosis and follow-up of pancreatic neuroendocrine tumours in multiple endocrine neoplasia type 1 patients. *Clin Endocrinol (Oxf)*. 2016;85(3):400-407.
30. Yamasaki I, Nishimori I, Ashida S, *et al*. Clinical characteristics of pancreatic neuroendocrine tumors in Japanese patients with von Hippel-Lindau disease. *Pancreas*. 2006;33(4):382-385.
31. Erlic Z, Ploeckinger U, Cascon A, *et al*. Systematic comparison of sporadic and syndromic pancreatic islet cell tumors. *Endocr Relat Cancer*. 2010;17(4):875-883.
32. Wang J, Peng S, Ning X, *et al*. Shorter telomere length increases age-related tumor risks in von Hippel-Lindau disease patients. *Cancer Med*. 2017;6(9):2131-2141.
33. Graff J. Patient perspectives on radiation dose. *J Am Coll Radiol*. 2014;11(3):243-245.