ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 November 21; 30(43): 4597-4688

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 30 Number 43 November 21, 2024

EDITORIAL

ORIGINAL ARTICLE

Retrospective Study

META-ANALYSIS

LETTER TO THE EDITOR

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Giovanna Ferraioli, MD, FAIUM, Researcher, Department of Clinical Surgical, Diagnostic and Pediatric Sciences, Medical School University of Pavia, Viale Brambilla 74, Pavia 27100, Italy. giovanna.ferraioli@unipv.it

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJG* as 4.3; Quartile: Q1. The *WJG*'s CiteScore for 2023 is 7.8.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xiao-Mei Zheng*; **Production Department Director:** *Xu Guo*; **Cover Editor:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF
Jian-Gao Fan (Chronic Liver Disease)

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
November 21, 2024

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

POLICY OF CO-AUTHORS
https://www.wjgnet.com/bpg/GerInfo/310

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
https://www.shca.org.cn
https://www.zs-hospital.sh.cn

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2024 November 21; 30(43): 4677-4681

DOI: 10.3748/wjg.v30.i43.4677

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

Improving early diagnosis of multiple endocrine neoplasia type 1 by assessing the gastrointestinal symptoms, hypercalcemia, and elevated serum gastrin

Tsvetelina Velikova, Velik Lazarov

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade C

Novelty: Grade B, Grade B

Creativity or Innovation: Grade C, Grade C

Scientific Significance: Grade B, Grade C

P-Reviewer: Alhamood M; Wei HR

Received: August 17, 2024

Revised: September 29, 2024

Accepted: October 11, 2024

Published online: November 21, 2024

Processing time: 74 Days and 13.4 Hours

Tsvetelina Velikova, Medical Faculty, Sofia University St. Kliment Ohridski, Sofia 1407, Bulgaria

Velik Lazarov, Obstetrics and Gynaecology, Second Specialised Hospital for Obstetrics and Gynaecology "Sheynovo", Sofia 1504, Bulgaria

Corresponding author: Velik Lazarov, MD, Chief Doctor, Obstetrics and Gynaecology, Second Specialised Hospital for Obstetrics and Gynaecology "Sheynovo", 19 ul. Sheinovo, Sofia 1504, Bulgaria. dr.v.lazarov@gmail.com

Abstract

Despite advancements in the field, early diagnosis of multiple endocrine neoplasia type 1 (MEN1) remains unachievable. This letter to the editor highlighted the importance of carefully assessing gastrointestinal symptoms, hypercalcemia, and elevated serum gastrin levels, as suggested by Yuan *et al* in their paper. They focused on a patient with recurrent abdominal pain and diarrhea whose diagnostic path led to establishing a MEN1 diagnosis within a year. This emphasized the need for clinicians to consider MEN1 in patients with similar presentations, particularly when gastrointestinal symptoms persist or recur after discontinuation of proton pump inhibitors, especially knowing that early recognition and intervention are crucial for improving patient outcomes.

Key Words: Multiple endocrine neoplasia type 1; Gastrointestinal symptoms; Hypercalcemia; Early detection; Early diagnosis

Core Tip: Early diagnosis of multiple endocrine neoplasia type 1 (MEN1) is critical for effective management and improved outcomes. This letter underscored the importance of considering MEN1 in patients presenting with recurrent gastrointestinal symptoms, hypercalcemia, and elevated serum gastrin levels. The discussed case demonstrated how a comprehensive diagnostic approach, including imaging studies and blood tests, can lead to timely surgical intervention and accurate diagnosis. Clinicians should remain vigilant for MEN1 in patients with persistent or recurrent symptoms, facilitating early detection and treatment.

Citation: Velikova T, Lazarov V. Improving early diagnosis of multiple endocrine neoplasia type 1 by assessing the gastrointestinal symptoms, hypercalcemia, and elevated serum gastrin. *World J Gastroenterol* 2024; 30(43): 4677-4681
URL: https://www.wjgnet.com/1007-9327/full/v30/i43/4677.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i43.4677

TO THE EDITOR

We were delighted to read the high-quality case-based article by Yuan *et al*[1] published in the *World Journal of Gastroenterology*. The main focus of this article was the early detection of multiple endocrine neoplasia (MEN) type 1. The authors presented a case report of a patient in whom MEN1 was detected early. At the same time, the presenting symptoms were recurrent abdominal pain and diarrhea. After performing computed tomography of the parathyroid glands (demonstrating hyperfunctioning parathyroid lesion), a gastroscopy (suggesting a duodenal bulge and ulceration), ultrasound endoscopy (revealing a hypoechoic lesion in the duodenal bulb), and further blood tests (hypercalcemia and hypophosphatemia and elevated levels of serum gastrin), the surgery was performed. Pathological analysis of the surgical specimens demonstrated a parathyroid adenoma after parathyroidectomy and a neuroendocrine tumor (NET) after duodenal bulbectomy, establishing the definitive diagnosis in approximately a year. The authors discussed the case through literature research, providing a scientific basis for early detection of MEN1 by suggesting the possibility of the condition in patients with gastrointestinal symptoms accompanied by hypercalcemia and hypophosphatemia.

CURRENT SITUATION AND CHALLENGES OF MEN1 DIAGNOSTICS

The latest research by Yuan *et al*[1] raised important questions regarding the challenges in MEN1 diagnostics and why it usually takes several years. MEN1 is a rare genetic disorder that affects approximately 1 in 30000 individuals. This condition is inherited in an autosomal dominant manner, meaning that a single copy of the altered gene in each cell is sufficient to cause the disorder. MEN1 affects males and females equally and shows no significant geographical, racial, or ethnic preferences[2].

MEN1 is characterized by the development of tumors in multiple endocrine glands. The most common types of tumors associated with MEN1 include: Parathyroid tumors, which lead to primary hyperparathyroidism and elevated calcium levels in the blood; pituitary tumors, which can produce excess hormones resulting in conditions such as prolactinoma, acromegaly, or Cushing's disease; and pancreatic NETs, which can produce hormones like insulin, gastrin, and glucagon, leading to clinical syndromes such as Zollinger-Ellison syndrome or insulinoma. Additionally, MEN1 can also involve less common tumors in the adrenal glands, thymus, and bronchial tubes[3]. Diagnosing MEN1 involves a combination of clinical evaluation, biochemical tests, imaging studies, and genetic testing[4]. Since MEN1 is an autosomal dominant inherited syndrome caused by germline mutations in the *MEN1* gene that predisposes carriers to variable risk of development of tumors in diverse non-endocrine and endocrine organs, most MEN1 carriers develop main tumors between 5 years and 80 years with at least one initiating around 20-30 years (50%-60%), and invariably 94% of *MEN1* carriers have developed one or more disease manifestations at the age of 50 years[5].

The process typically begins with a thorough clinical evaluation where a healthcare provider assesses symptoms and conducts physical examinations to identify signs of endocrine tumors. Biochemical tests are then performed to measure hormone levels in the blood, such as calcium, prolactin, and gastrin, which can indicate the presence of endocrine tumors. Imaging studies, including magnetic resonance imaging, computed tomography scans, and ultrasound, visualize tumors in the endocrine glands. Finally, genetic testing is conducted to identify mutations in the *MEN1* gene, which can confirm the diagnosis, especially in individuals with a family history of the disorder. This comprehensive approach ensures accurate diagnosis and helps plan appropriate management and treatment strategies for patients with MEN1[6].

Clinical practice guidelines for MEN1 diagnosis from 2021 by Thakker *et al*[7] on behalf of the Endocrine Society was further discussed for updates by Newey and Newell-Price in 2022[2]. Current recommendations advise a rigorous clinical, biochemical, and radiological monitoring program starting in early childhood for individuals with a clinical or genetic diagnosis of MEN1, aiming for early detection and treatment of tumors. While it may be assumed that such screening improves patient outcomes, there is limited strong evidence supporting several aspects of MEN1 management. Additionally, there are potential risks from unnecessary interventions or tests that lack proven benefits. The psychological and financial impacts of intensive screening remain largely unexplored. Although screening is crucial in MEN1 care, this perspective emphasizes the uncertainties and challenges surrounding current guidelines, particularly regarding the detection of presymptomatic tumors. A future approach that considers these limitations and actively involves patients in

decision-making is recommended. In line with this, differential diagnoses of MEN1 include Von Hippel-Lindau syndrome, neurofibromatosis type 1, tuberous sclerosis complex, and multiple endocrine neoplasia type 4[8].

Therapy for MEN1 focuses on managing the symptoms and complications caused by the various tumors associated with the disorder. This often requires a multidisciplinary approach involving different medical specialties to address the diverse manifestations of MEN1[6].

Surgery is a primary treatment option for many MEN1-related tumors. For instance, parathyroidectomy is commonly performed to treat hyperparathyroidism caused by parathyroid tumors. Similarly, surgical removal of pancreatic NETs and pituitary tumors may be necessary to control hormone overproduction and alleviate symptoms[9].

Medications play a crucial role in managing hormone levels and symptoms. For example, proton pump inhibitors can reduce stomach acid production in gastrinoma patients, while medications like dopamine agonists can help control prolactin levels in patients with prolactinomas. Hormone replacement therapy may also be required if endocrine glands are removed or damaged during surgery[10].

Radiation therapy may be employed for certain types of tumors, such as pituitary adenomas, particularly when surgery is not feasible or if the tumor recurs after surgery. This approach helps to shrink the tumors and control hormone production[11].

Regular monitoring is essential for patients with MEN1 due to the risk of developing new tumors over time. Lifelong surveillance, including periodic biochemical tests and imaging studies, is necessary to detect any new or recurrent tumors early and effectively manage existing ones. Managing MEN1 presents several difficulties and challenges (Figure 1). One of the primary challenges is early detection. Since MEN1 can cause a variety of tumors in different endocrine glands, regular and comprehensive screening is essential but can be burdensome for patients. Early detection is critical to prevent complications, but the need for frequent monitoring can be stressful and time-consuming[12].

Genetic counseling is another significant challenge. Given the hereditary nature of MEN1, genetic counseling is essential for affected families to understand the risks and implications of the disorder. However, the psychological impact of genetic testing and the potential for discovering that other family members are at risk can be profound and complex to manage[13].

Treatment complications also pose a challenge. Surgical and medical treatments for MEN1-related tumors can have significant side effects and complications. For example, parathyroid surgery can lead to hypocalcemia (low calcium levels), and managing hormone levels with medications can be complex and require careful monitoring to avoid adverse effects[8].

Quality of life is a significant concern for patients with MEN1. The chronic nature of the disorder, the need for ongoing treatment, and the constant monitoring can significantly impact the quality of life for patients and their families. The psychological burden of living with a genetic disorder that predisposes individuals to multiple tumors can be substantial [14].

In summary, while advances in genetic testing and treatment options have improved outcomes for patients with MEN1, the disorder still presents significant challenges (Table 1) in terms of early detection, genetic counseling, treatment complications, and maintaining quality of life.

In line with this, Yuan *et al*[1], by providing a case report of a patient exhibiting nonspecific gastrointestinal symptoms, hypercalcemia, and elevated serum gastrin levels, raised awareness for diagnosing MEN1 within just 1 year from the onset of such symptoms. Given that MEN1 can present with a variety of clinical symptoms and is often misdiagnosed, it is crucial to consider MEN1 as a possibility in patients with gastrointestinal symptoms, particularly if symptoms reoccur after discontinuing proton pump inhibitors. Early suspicion, diagnosis, and treatment are essential in improving patient outcomes.

This case underscored the importance of considering MEN1 in patients presenting with recurrent gastrointestinal symptoms, hypercalcemia, and elevated serum gastrin levels, even when these symptoms overlap with more common conditions. By raising clinical suspicion for MEN1 in such cases, earlier diagnosis and intervention can be achieved, potentially preventing disease progression. Incorporating this diagnostic approach into routine clinical practice may lead to earlier detection of MEN1-associated tumors, altering the current reliance on later-stage diagnosis and improving long-term outcomes through timely treatment.

CONCLUSION

Early diagnosis of MEN1 remains a significant challenge due to its diverse and often nonspecific clinical presentation. The discussed case highlighted how gastrointestinal symptoms, when combined with hypercalcemia and elevated serum gastrin levels, should prompt consideration of MEN1. However, the overlap of these symptoms with more common conditions often leads to delays in diagnosis. This underscores the need for heightened clinical awareness and a thorough, multidisciplinary approach to evaluation. By recognizing the potential for MEN1 early in the diagnostic process, clinicians can improve outcomes through timely intervention. Yet, the rarity and variability of the condition demand ongoing vigilance and education in the medical community.

Moreover, this case emphasized the importance of integrating MEN1 into the differential diagnosis of gastrointestinal symptoms, especially in the presence of biochemical abnormalities like hypercalcemia and elevated gastrin. This approach may refine clinical guidelines by encouraging earlier genetic screening and imaging in patients with similar symptom clusters. Additionally, by adopting a proactive stance in identifying MEN1, this case supported the call for further research on cost-effective diagnostic strategies that can mitigate the economic burden of intensive surveillance without compromising early detection. Ongoing education and updated clinical guidelines that stress the importance of

Table 1 Challenges in multiple endocrine neoplasia type 1 diagnosis and suggestions for improvement

Challenge	Description	Suggestions for improvement
Nonspecific symptoms	MEN1 often presents with vague symptoms like abdominal pain, diarrhea, and fatigue	Increase clinical awareness and consider MEN1 in differential diagnosis for patients with these symptoms
Overlap with common conditions	Symptoms such as hypercalcemia and gastrointestinal issues can be mistaken for more common diseases	Encourage routine screening for MEN1 markers in patients with persistent symptoms
Genetic testing accessibility	Limited access to genetic testing in some regions hinders early diagnosis	Expand genetic testing programs and offer counseling to at-risk individuals and their families
Delayed diagnosis	MEN1 diagnosis is often delayed due to its rarity and complex presentation	Implement standardized protocols for early screening and referral to specialized centers
Multisystem involvement	MEN1 affects multiple endocrine glands, complicating diagnosis, and management	Foster a multidisciplinary approach to care, involving endocrinologists, surgeons, and geneticists
Inconsistent surveillance practices	Variation in follow-up and surveillance across institutions	Establish uniform guidelines for ongoing monitoring and management of patients with MEN1
Psychosocial impact	The diagnosis of MEN1 can lead to significant psychological stress for patients	Provide mental health support and counseling services as part of comprehensive care

MEN1: Multiple endocrine neoplasia type 1.

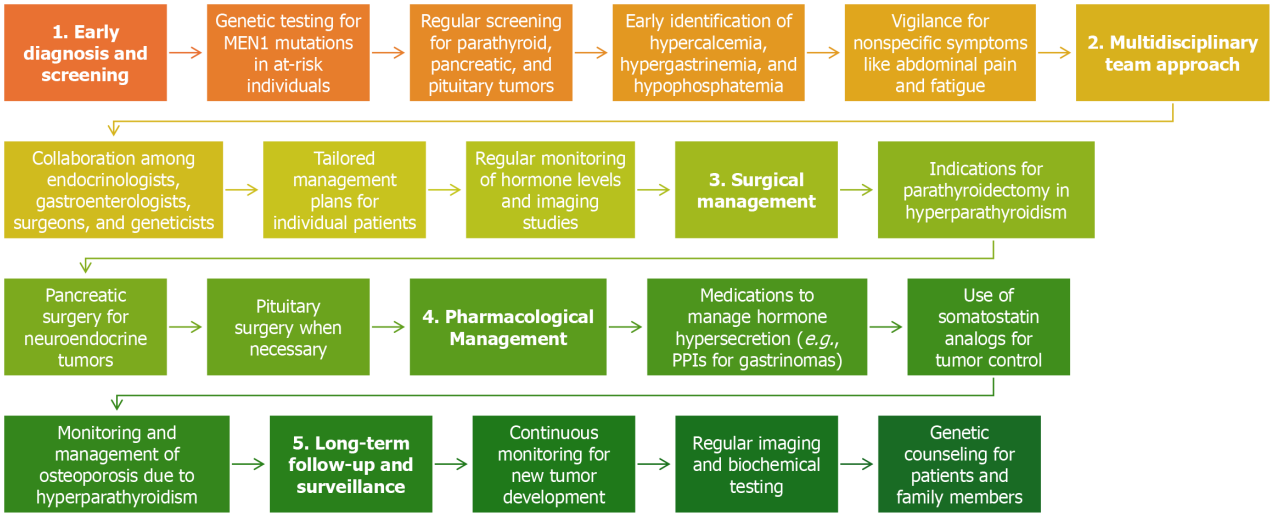

Figure 1 Comprehensive management of multiple endocrine neoplasia type 1. MEN1: Multiple endocrine neoplasia type 1; PPIs: Proton pump inhibitors.

early recognition may lead to improved management and patient outcomes.

FOOTNOTES

Author contributions: Velikova T wrote the original draft; Lazarov V contributed to conceptualization, writing, reviewing, and editing; All authors read and approved the final version of the manuscript.

Supported by the European Union-Next Generation EU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, No. BG-RRP-2.004-0008.

Conflict-of-interest statement: The authors declare having no conflicts of interest.

Country of origin: Bulgaria

ORCID number: Velik Lazarov 0009-0006-0976-5132.

S-Editor: Chen YL
L-Editor: Filipodia
P-Editor: Zheng XM

REFERENCES

1 **Yuan JH**, Luo S, Zhang DG, Wang LS. Early detection of multiple endocrine neoplasia type 1: A case report. *World J Gastroenterol* 2024; **30**: 3247-3252 [PMID: 39086634 DOI: 10.3748/wjg.v30.i26.3247]
2 **Newey PJ**, Newell-Price J. MEN1 Surveillance Guidelines: Time to (Re)Think? *J Endocr Soc* 2022; **6**: bvac001 [PMID: 35079671 DOI: 10.1210/jendso/bvac001]
3 **de Laat JM**, van Leeuwaarde RS, Valk GD. The Importance of an Early and Accurate MEN1 Diagnosis. *Front Endocrinol (Lausanne)* 2018; **9**: 533 [PMID: 30254610 DOI: 10.3389/fendo.2018.00533]
4 **Kamilaris CDC**, Stratakis CA. Multiple Endocrine Neoplasia Type 1 (MEN1): An Update and the Significance of Early Genetic and Clinical Diagnosis. *Front Endocrinol (Lausanne)* 2019; **10**: 339 [PMID: 31263451 DOI: 10.3389/fendo.2019.00339]
5 **Lourenço DM Jr**, de Herder WW. Editorial: Early Genetic and Clinical Diagnosis in MEN1. *Front Endocrinol (Lausanne)* 2020; **11**: 218 [PMID: 32351454 DOI: 10.3389/fendo.2020.00218]
6 **Pieterman CRC**, Valk GD. Update on the clinical management of multiple endocrine neoplasia type 1. *Clin Endocrinol (Oxf)* 2022; **97**: 409-423 [PMID: 35319130 DOI: 10.1111/cen.14727]
7 **Thakker RV**, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML; Endocrine Society. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab* 2012; **97**: 2990-3011 [PMID: 22723327 DOI: 10.1210/jc.2012-1230]
8 **Singh G**, Mulji NJ, Jialal I. Multiple Endocrine Neoplasia Type 1. 2023 Jul 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan- [PMID: 30725665]
9 **van Beek DJ**, Nell S, Verkooijen HM, Borel Rinkes IHM, Valk GD; (on behalf of the DutchMEN study group), Vriens MR; International MEN1 Insulinoma Study Group. Surgery for multiple endocrine neoplasia type 1-related insulinoma: long-term outcomes in a large international cohort. *Br J Surg* 2020; **107**: 1489-1499 [PMID: 32352164 DOI: 10.1002/bjs.11632]
10 **Hu X**, Guan J, Wang Y, Shi S, Song C, Li ZP, Feng ST, Chen J, Luo Y. A narrative review of multiple endocrine neoplasia syndromes: genetics, clinical features, imaging findings, and diagnosis. *Ann Transl Med* 2021; **9**: 944 [PMID: 34350259 DOI: 10.21037/atm-21-1165]
11 **van Vliembergen ENM**, Eijkelenkamp H, Valk GD, Vriens MR, Meijer GJ, Intven MPW, de Laat JM. Precision radiotherapy using MR-linac for pancreatic neuroendocrine tumors in MEN1 patients (PRIME): a protocol for a phase I-II trial, and systematic review on available evidence for radiotherapy of pNETs. *Front Endocrinol (Lausanne)* 2023; **14**: 994370 [PMID: 37305036 DOI: 10.3389/fendo.2023.994370]
12 **Marini F**, Giusti F, Tonelli F, Brandi ML. Management impact: effects on quality of life and prognosis in MEN1. *Endocr Relat Cancer* 2017; **24**: T227-T242 [PMID: 28733468 DOI: 10.1530/ERC-17-0203]
13 **Giusti F**, Marini F, Brandi ML. Multiple Endocrine Neoplasia Type 1. 2005 Aug 31. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993– [PMID: 20301710]
14 **van Leeuwaarde RS**, Pieterman CRC, May AM, Dekkers OM, van der Horst-Schrivers AN, Hermus AR, de Herder WW, Drent ML, Bisschop PH, Havekes B, Vriens MR, Valk GD. Health-Related Quality of Life in Patients with Multiple Endocrine Neoplasia Type 1. *Neuroendocrinology* 2021; **111**: 288-296 [PMID: 32365349 DOI: 10.1159/000508374]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com