Article:
Newey, P.J. and Newell-Price, J. (2022) MEN1 surveillance guidelines : time to (re)think? Journal of the Endocrine Society, 6 (2). pp. 1-5.

https://doi.org/10.1210/jendso/bvac001

Journal of the Endocrine Society, 2022, **6**, 1–5
https://doi.org/10.1210/jendso/bvac001
Advance access publication 11 January 2022
Perspective

MEN1 Surveillance Guidelines: Time to (Re)Think?

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Abstract

Clinical practice guidelines for patients with multiple endocrine neoplasia type 1 (MEN1) recommend a variety of surveillance options. Given progress over the past decade in this area, it is timely to evaluate their ongoing utility. MEN1 is characterized by the development of synchronous or asynchronous tumors affecting a multitude of endocrine and nonendocrine tissues, resulting in premature morbidity and mortality, such that the rationale for undertaking surveillance screening in at-risk individuals appears robust. Current guidelines recommend an intensive regimen of clinical, biochemical, and radiological surveillance commencing in early childhood for those with a clinical or genetic diagnosis of MEN1, with the aim of early tumor detection and treatment. Although it is tempting to assume that such screening results in patient benefits and improved outcomes, the lack of a strong evidence base for several aspects of MEN1 care, and the potential for iatrogenic harms related to screening tests or interventions of unproven benefit, make such assumptions potentially unsound. Furthermore, the psychological as well as economic burdens of intensive screening remain largely unstudied. Although screening undoubtedly constitutes an important component of MEN1 patient care, this perspective aims to highlight some of the current uncertainties and challenges related to existing MEN1 guidelines with a particular focus on the role of screening for presymptomatic tumors. Looking forward, a screening approach that acknowledges these limitations and uncertainties and places the patient at the heart of the decision-making process is advocated.

Key Words: genetic testing, multiple endocrine neoplasia type 1, MEN1, surveillance, screening, pancreatic neuroendocrine tumor, thymic, bronchial neuroendocrine tumor

Abbreviations: BP, bronchopulmonary; CT, computed tomography; EUS, endoscopic ultrasound; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; NF, nonfunctioning.

Multiple Endocrine Neoplasia Type 1: Definition, Diagnosis and Outcomes

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterized by the occurrence of parathyroid, pituitary, and gastropancreatic neuroendocrine tumors (NETs), although patients may develop other tumor types, most notably thymic and bronchial NETs and adrenocortical tumors. The increased use of genetic testing of potential index cases, as well as the downstream cascade genetic testing of relatives of those harboring pathogenic *MEN1* variants, has resulted in a shift in MEN1 diagnosis to earlier age groups, so affected individuals are frequently asymptomatic and/or disease free at diagnosis. MEN1 is highly penetrant, meaning the vast majority (> 95%) of patients harboring a pathogenic *MEN1* variant will develop clinical manifestations over their lifetime, although there is no clear genotype-phenotype relationship so the particular spectrum of tumors that develops in an individual cannot be predicted. Management of MEN1 is complex, in part related to the synchronous or asynchronous development of tumors affecting multiple tissues. Although some advances in therapy have occurred (eg, proton pump inhibitor therapy for gastrinoma and the Zollinger-Ellison syndrome), MEN1 continues to be associated with significant premature morbidity and mortality, with up to 50% of patients dying prematurely of causes directly related to the disorder, with malignant gastropancreatic and thymic NETs among the leading causes of premature death.

Goals of Management in Multiple Endocrine Neoplasia Type 1 and Rationale for Screening

The overarching goals of management of MEN1 are to minimize the premature morbidity and mortality associated with MEN1-associated tumors by undertaking screening for tumor development, while simultaneously preserving the patients' quality of life. This may be challenging because of the diverse spectrum of tumors that occur, their wide age-related penetrance, and unpredictable disease course. Indeed, clinical practice guidelines published in 2012 recommend an intensive, multifaceted tumor screening program for individuals at high risk of MEN1 (eg, those harboring pathogenic *MEN1* variants), commencing in early childhood and continuing indefinitely [1]. (The 2012 clinical practice guidelines referred to in this article did not constitute an official Endocrine Society guideline document, but rather were synthesized by an international panel of experts in the field of MEN1 based on available evidence at the time of writing.) Intuitively, undertaking frequent screening seems logical, potentially offering regular reassurance to the patient (and clinician) and alleviating the potential fears/anxiety around "missing" early-onset malignant disease. Although such recommendations offer a clear

Received: 9 October 2021. **Editorial Decision:** 30 December 2021. **Corrected and Typeset:** 22 January 2022

structure for care that has been widely adopted, this perspective aims to evaluate their utility and examines whether they achieve their intended goals.

What Makes a Good Tumor Screening/ Surveillance Program?

Although the terms *screening* and *surveillance* are frequently used interchangeably in the context of MEN1, it is important to consider the different aspects of clinical monitoring. Management of patients with MEN1 includes detection of presymptomatic tumors, diagnosis of manifestations presenting with signs and symptoms, and monitoring of tumors once diagnosed. Here, the focus is primarily on the role of screening for presymptomatic disease, although possible changes to the screening approach are considered once tumors are identified.

Successful cancer screening programs typically involve the detection of tumors at a presymptomatic stage to facilitate evidence-based interventions that improve patient outcomes (eg, reduced mortality). This requires many elements, including an understanding of the natural disease course; precise, validated tests that facilitate early tumor detection; and the availability of evidence-based interventions known to improve patient outcomes (ie, following positive test results). Furthermore, the screening methods need be cost-effective and acceptable to patients, with the benefits outweighing any associated harms (https://www.cancer.gov/about-cancer/screening/hp-screeningoverview-pdq; https://www.gov.uk/government/publications/evidencereview-criteria-national-screening-programmes/criteria-forappraising-the-viability-effectiveness-and-appropriateness-of-ascreening-programme).

So how does the MEN1 screening program perform? At the outset, it should be stated that there is no strong-evidence base supporting the screening components of MEN1 guidelines, although an absence of such evidence per se should not detract from their use. It is, however, important to examine each element required for a successful screening program in the context of MEN1.

Over the last decade, several high-quality descriptive studies based on national MEN1 patient registries (eg, DutchMEN, French-GTE registries) have provided important information regarding the natural history of the disorder [2-4]. Despite this progress, fundamental gaps in knowledge are a potential barrier to successful screening. Most strikingly, for several tumor types (eg, gastrinoma, nonfunctioning [NF] pancreatic NETS, bronchopulmonary [BP] NETs) it is not possible to differentiate the subset of tumors destined to run an aggressive disease course from those with more indolent behavior.

Screening is also reliant on accurate diagnostic tests. While the diagnosis of symptomatic functioning tumors (eg, prolactinoma, insulinoma) is based on a combination of standardized biochemical and radiological tests, screening for several of the MEN1-associated tumors in the presymptomatic phase (eg, NF pancreatic NETs, thymic/BP-NETs) is more challenging. For example, although recommended in MEN1 guidelines, fasting gut hormones and chromogranin A have a low sensitivity and specificity for diagnosis of NF pancreatic NETs such that they have little utility in this setting, while for thymic and BP NETs there are no reliable biomarkers of early disease, so diagnosis is reliant on interval imaging (discussed later).

Once diagnosed, there is a lack of high-quality evidence guiding the treatment of several MEN1-associated tumors, such that their optimal treatment remains controversial (eg, the timing and extent of parathyroid surgery for primary hyperparathyroidism, medical vs surgical management for gastrinoma, the size criteria employed for surgical intervention for NF pancreatic NETS, surveillance vs intervention for small BP NETs). In addition, some treatment recommendations are extrapolated from their sporadic counterpart tumors, which may be unreliable. For example, recent studies indicate that MEN1-associated BP NETs have a better prognosis than the equivalent sporadic tumors, unexplained by differences in baseline characteristics [4]. Thus, the lack of high-quality evidence guiding treatment decisions for several MEN1-associated tumors calls into question the value of intensive screening, limitations that were acknowledged in the 2012 guidelines. Indeed, these guideline recommendations were never intended to be applied as a "gold-standard" template for care, but rather a suggested framework from which it may be reasonable to deviate. As such, it is important that clinicians (as well as insurance providers and medical litigators) recognize that the guidelines do not represent a rigid protocol, but rather constitute a starting point from which physicians can and should exercise their clinical judgment, while taking into account the patient perspective and resource setting.

Potential Harms of Screening

Screening recommendations for MEN1 encompass the simultaneous evaluation for different tumor types over the majority of the patient's lifetime, resulting in a considerable burden of investigation (Fig. 1). These investigations are not without potential harms, either direct or indirect. For example, direct iatrogenic harms may result from a high cumulative burden of ionizing radiation from imaging modalities used for screening or downstream investigation of abnormal findings, which may paradoxically contribute to an increased cancer risk. Indeed, patients with MEN1 may "accumulate" radiation doses in excess of those associated with increased cancer risk (ie, > 50-100 mSv) [5]. Similarly, there are concerns over repeated exposure to gadolinium-based contrast agents, which may be deposited in the central nervous system with uncertain long-term effects. Direct harms may also arise from invasive procedures such as endoscopic ultrasound (EUS; eg, hemorrhage, perforation, pancreatitis), which need to be considered if widely deployed for screening. Other harms are harder to quantify; for example, screening tests associated with false-positive results (eg, imaging tests identifying incidental/nonspecific abnormalities) may result in substantial downstream investigation, and unwarranted intervention. In contrast, false-negative tests may provide unfounded reassurance. Even when screening tests are accurate, there is a danger of overdiagnosis and overtreatment, with interventions of unproven benefit performed for tumors unlikely to cause morbidity; endocrine surgery (eg, pancreatic, thoracic, pituitary resections) is associated with high rates of early and late complications.

The clinical decision processes in MEN1 are likely influenced by multiple psychological factors. For example, following the identification of a tumor, patient anxiety may result in a preference for intervention over surveillance.

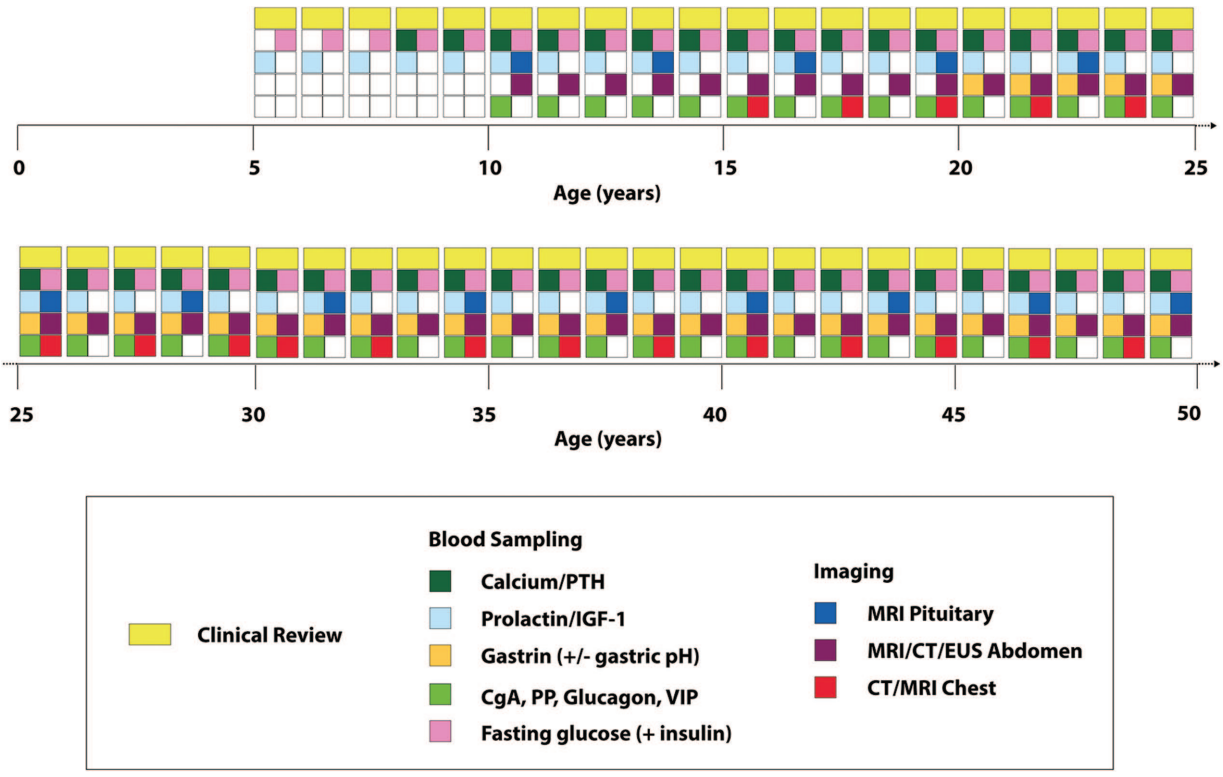

Figure 1. Cumulative burden of MEN1 screening over the patient life course. Current MEN1 screening guidelines recommend regular clinical, biochemical and radiological surveillance commencing in childhood (ie, from age 5 y) and continuing indefinitely through adult life (until age 50 y shown) [1]. Applying such a screening schedule would result in a patient undergoing approximately 200 blood tests and approximately 70 surveillance scans by age 50 years. Notably, this schedule of recommended screening does not include any additional downstream investigation required as a consequence of positive findings (ie, additional tumor localization/monitoring studies). CgA, chromogranin A; CT, computer tomography; EUS, endoscopic ultrasound; IGF-1, insulin-like growth factor 1; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; PP, pancreatic polypeptide; PTH, parathyroid hormone; VIP, vasoactive intestinal peptide.

Likewise, a decision to intervene with surgery or to undertake additional investigations may assuage the anxieties of the clinician, whose fears frequently mirror those of their patients [6]. Likewise, fear that deviating from a recommended guideline increases exposure to litigation may override clinical judgment. Screening for cancer may raise additional psychological issues. For several sporadic cancers, fear of cancer itself is reported to deter a proportion of individuals from participation in screening. Although there is little available evidence on the extent of this phenomenon in MEN1, anecdotally many patients report anxiety around test attendance and receiving investigation results. Further study is also required to better understand the consequences of frequent surveillance on quality of life. In this regard, it may be important to consider the legacy of personal family history; the patients' perspective may be influenced by the disease course in affected family members, which in turn may shape their views on screening. Indeed, many MEN1 patients display a high fear of disease occurrence, which may be alleviated or exacerbated by frequent screening.

Multiple Endocrine Neoplasia Type 1 Screening: Areas of Controversy

When to Start Screening?

Current recommendations for screening are based on the youngest reported ages of the respective manifestations and account for rare adverse outcomes in the pediatric age group. Thus, clinical and biochemical screening is recommended annually in children at risk of MEN1 from approximately age 5 years, with regular radiological imaging of the pancreas and pituitary from approximately age 10 years (see Fig. 1) [1]. Although a series of recent studies has reported a higher than previously recognized penetrance of tumors in children and young people with MEN1, the value of screening to detect presymptomatic disease remains uncertain. The majority of clinically important early-onset tumors present symptomatically (eg, prolactinoma, insulinoma, Cushing disease), and in this setting investigation should not be delayed. However, the role for detecting asymptomatic tumors is less clear. For example, although biochemical primary hyperparathyroidism has a penetrance of approximately 50% to 75% by age 21 years, the evidence base supporting early intervention is weak. The age to commence pancreatic imaging for NF pancreatic NETs is also controversial. A recent study estimated an approximately 2.5% and approximately 5% risk of a clinically relevant tumor at ages 13.5 and 17.8 years, respectively [7]. Thus, determining the age at which to start screening should represent a balance between the potential burdens/risks of screening with the small chance of "missing" a clinically relevant tumor. For young children who are well (eg, absence of symptoms, normal growth), it may be reasonable to avoid all investigation (even including genetic testing) until the midteenage years and even then, following baseline investigation, a less frequent screening regimen is likely to be suitable for many patients.

Screening for Nonfunctioning Pancreatic Neuroendocrine Tumors

The 2012 guidelines recommend that surgery be considered for tumors larger than 1 cm (or rapidly growing tumors) although the evidence base for the recommendation is weak. The majority of retrospective cohort studies indicate that the risk of metastatic disease increases substantially for tumors greater than 2 cm, with the majority of smaller tumors running an indolent course. Thus, in the absence of validated predictive biomarkers of tumor behavior, decisions regarding the management of NF pancreatic NETS are predominantly size based, with 2 cm advocated by most as a suitable threshold for surgery [8]. Thus, the primary goal of screening should be the detection of clinically significant tumors, with the value of detecting small NF tumors (eg, < 1 cm) uncertain given that intervention is unlikely to be recommended for most patients in this setting. Current guidelines recommend annual imaging with computed tomography (CT), magnetic resonance imaging (MRI), or EUS, with each modality reported to have good sensitivity for detection of tumors >1cm, such that the safety and acceptability of the test should be the primary concern, with periodic MRI appearing to have the least potential for harm, especially if noncontrast diffusion-weighted imaging sequences are used. Furthermore, given that the majority of NF tumors evolve slowly with low growth rates, a less frequent interval of surveillance (eg, every 2-3 y) is likely to be acceptable for most patients in whom imaging remains negative. However, it is important to highlight that a low percentage of MEN1 patients with small NF tumors may still develop metastatic disease. Thus, following the identification of small NF tumors, it may be reasonable to adapt the surveillance regimen for risk stratification, initially repeating imaging at an earlier time point (eg, 6-12 mo) to assess for a "rapid" growth, or employing other modalities such as 18f-fluorodeoxyglucose–positron emission tomography (^{18}F-FDG-PET/CT) or EUS (ie, with fine-needle aspirate) to identify higher-grade tumors, although these latter approaches require further validation in MEN1 cohorts. Furthermore, some clinicians may suggest somatostatin analogue therapy to reduce the chances of tumor growth, and with joint decision-making, intervention may be justifiable even if the tumors are below a given size "threshold." Judicious use of ^{68}Galllium DOTATATE PET/CT may be of value in detecting occult metastatic disease in those in whom intervention is being considered, but has limited utility as a serial surveillance tool because of a high ionizing radiation burden.

Screening for Bronchopulmonary and Thymic Neuroendocrine Tumors

Current MEN1 guidelines suggest imaging for BP and thymic NETs every 1 to 2 years with CT or MRI but acknowledges the uncertainty of this approach (ie, weak recommendation, very low-quality evidence) [1]. Recent studies report radiologic evidence of BP NETs in approximately 25% of MEN1 patients, but that such tumors are typically associated with low growth rates and an excellent overall survival with little excess mortality [3, 4, 9]. Although occasional tumors display a more aggressive disease course, the current evidence calls into question the value of frequent screening in asymptomatic patients, particularly because there is little evidence to support intervention for small, stable lesions. At most, periodic evaluation (eg, with MRI) to detect larger lesions may be appropriate, although the relative merits and limitations of screening should be discussed with the patient. If small BP NETs are detected, there is a lack of evidence to guide further surveillance, although initial interval assessment for rapid growth and/or FDG avidity may help identify tumors on an aggressive disease course.

Current estimates suggest that thymic NETS affect only 3% to 5% of patients with MEN1, with the prevalence and sex distribution dependent on the population under study [10]. For example, thymic NETS occur predominantly in male MEN1 patients in Europe and North America (male-to-female ratio = ~ 10:1), although a more even sex distribution is reported in Asian populations. Thymic NETs may also cluster in MEN1 families, although this cannot be relied on for screening purposes. Although infrequent tumors, thymic NETs are typically associated with an aggressive disease course and high mortality (~ 30% 10-y survival), and may evolve quickly, so current guidelines suggest frequent CT or MRI (eg, every 1-2 y). Thus, the number of scans needed to identify cases in asymptomatic patients is high, and therefore decisions regarding screening should be individualized to the patient. Where screening is deemed appropriate, MRI at least avoids the potential high cumulative radiation doses associated with CT.

Where Do We Go From Here? A Patient-Centered, Evidence-Based Approach

Although this perspective has focused on some of the challenges and potential detrimental aspects of screening, it does not intend to portray a nihilistic view with regard to its value. Rather, it aims to highlight the limited evidence base surrounding several aspects of MEN1 care, while emphasizing some of the harms that might arise directly or indirectly from well-intentioned investigation. These uncertainties related to screening are unlikely to be resolved until the evidence base is strengthened. This requires large, multicenter, international longitudinal studies reporting standardized phenotype and outcome data, as well as the development of improved biomarkers predicting tumor behavior and disease course. In the meantime, a screening approach that employs joint decision-making with the patient and promotes the use of carefully considered investigation is encouraged. This is not in fact a significant departure from existing guidelines [1], which state: "The nature and timing of screening will depend on local resources, clinical judgement and patient preference," although this message may have become somewhat obscured by the intensive schedule of screening suggested.

So, how should MEN1 screening be performed? Although there are no clear answers to some of the dilemmas raised, we suggest the application of several guiding principles to individualize the approach to the patient.

1. Undertake regular clinical assessment and investigate relevant symptoms: Although many of the manifestations of MEN1 present with symptomatic features, these are easily overlooked (eg, indigestion as a symptom of gastrinoma, "funny-turns" resulting from hypoglycemia and insulinoma). At clinical review, sufficient time should be allowed to explore all symptoms of MEN1-related tumors, and when identified these should be investigated promptly.

2. Screening in asymptomatic MEN1 patients should focus on the detection of clinically important tumors for which there is the strongest case for intervention. It is important to remain focused on the detection of clinically important disease (eg, NF pancreatic NETs > 2 cm). Based on current available evidence, a reduced frequency of radiological screening is likely to be appropriate for several tumor types, and in some instances the value of undertaking any screening remains uncertain (eg, for BP NETs).
3. Where screening identifies small tumors not requiring immediate treatment (eg, small NF pancreatic NETs), initial follow-up should aim to risk stratify such lesions. Initially, more intensive screening may be appropriate to identify fast-growing/higher-grade tumors requiring intervention. In contrast, tumors demonstrating indolent behavior on serial imaging are likely suitable for less frequent surveillance.
4. Decisions regarding screening frequency and modality should account for the patient's views. To achieve this, the clinician requires sufficient knowledge of the disorder to counsel the patient appropriately so that genuinely informed choices can be made. Thus, it remains important that clinicians caring for patients with MEN1 see many affected patients to have sufficient expertise in the disorder, and where this is not possible (eg, in remote/rural settings), the responsible clinician have access to such expertise (eg, ability to refer to an experienced regional/national multidisciplinary team).
5. Minimize the exposure to investigations/intervention associated with direct harms. The substantial burden of investigation over the patient's lifetime should ensure that investigations with the lowest possible harms are employed. An awareness of the cumulative burden of ionizing radiation received by the patient is important. There should be an avoidance of "knee-jerk" investigations and the clinician's instinct to do more rather than less may need to be resisted.
6. Consider patient-specific factors. The clustering of specific manifestations in MEN1 kindreds, differences in sex distribution of manifestations (eg, thymic NETs), and possible genetic anticipation in MEN1 kindreds [11] strengthens the argument for tailoring screening schedule to the individual.
7. Acknowledge and accept a degree of uncertainty: MEN1 is a complex disorder and clinical judgment remains an essential component of management. Intensive screening/surveillance does not necessarily resolve uncertainty and in some instances may fuel it. Open and honest discussion with the patient regarding all aspects of care, including areas of uncertainty, is required. Furthermore, it is important to recognize that current screening methods will not avoid all adverse outcomes, as the inability to differentiate indolent from aggressive trajectories for some tumor types means there will be patients who develop advanced disease despite apparent optimal care
8. Consider the psychological effects of screening. An awareness of psychological factors may help joint decision-making. Recognition that patient and clinician anxiety may drive investigation and intervention may help avoid overtreatment. In contrast, identifying patients disengaged from follow-up and exploring the reasons for nonattendance may facilitate reengagement.

Acknowledgments

P.J.N. was a contributing author to clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1) published in 2012. P.J.N. and J.N.P. would like to thank Ms. Jo Grey, CEO of AMEND, for her review of the manuscript. P.J.N. would like to thank Ms. Hannah Vennard, who helped conceive the idea for Fig. 1.

Disclosures

At the time of writing P.J.N. held a Scottish Senior Clinical Fellowship (SCAF/15/01) funded by the Chief Scientist Office (UK), NRS Scotland, and University of Dundee.

Data Availability

Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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