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ITALIAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS (AME) POSITION STATEMENT

A STEPWISE APPROACH TO THE DIAGNOSIS OF GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS IN CLINICAL PRACTICE

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DISCLOSURES

Collaboration with

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WHY THIS DOCUMENT

1. Current guidelines are focused on treatment and follow-up of already diagnosed NETs

2. NETs are “rare” but what to do in the many cases of clinical suspicion?

3. The present stepwise work-up is aimed to provide a clinical guide for GEP-NETs diagnosis in everyday practice.

METHODOLOGY

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- The Grading of Recommendations, Assessment, Development, and Evaluation (**GRADE**) system was adopted for the present Position Statement.
- "**Recommendations**" are based on strong evidence "**Suggestions**" on weak evidence
- Levels of evidence (**LoE**) are as follows:
  - very low (⊗○○○)
  - low (⊗⊗○○)
  - moderate (⊗⊗⊗○)
  - and high (⊗⊗⊗⊗)

OUTLINE

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INTRODUCTION

- Why this document
- Methodology
- Definitions and abbreviations
- Classification
  - Grading assessment
  - Pathologic staging

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Outline 2

DIAGNOSTIC TOOLS

- **Histology, cytology, immunohistochemistry, and molecular biology:**
  - Morphologic (cyto-histologic) criteria
  - Immunohistochemistry and molecular biology techniques
  - Working with the pathologist and the pathologic report
  - Genetic assessment
- **Laboratory assessment:**
  - **General markers of NETs**
    - Chromogranin A
    - Other markers
  - **Specific markers**
    - 5-HIAA, Gastrin, Insulin
  - **Other specific markers**

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Outline 3

DIAGNOSTIC TOOLS

Imaging procedures

- **Radiologic procedures**
  - Ultrasonography
  - Multislice CT
  - MRI
- **Nuclear Medicine procedures**
  - SSTR functional imaging
  - PET with other tracers
- **Endoscopic procedures**
  - Upper and lower gastrointestinal NETs
  - Small bowel NETs
  - Pancreatic NETs

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Outline 4

A STEP BY STEP MULTIDISCIPLINARY APPROACH TO CLINICAL DIAGNOSIS

- **Asymptomatic patient: incidental findings**
  - GEP-NET suspected at endoscopy
  - GEP-NET suspected at morphological (US/CT/ MRI) imaging
  - GEP-NET suspected after elevated serum Chromogranin A levels

Outline 5

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- **Symptomatic patient with symptoms due to local effects of GEP-NETs**

  - When to suspect a GEP-NET
  - **Work-up in the patient with local compressive symptoms**
    - Isolated abdominal pain
    - Subocclusive picture
    - Jaundice
    - Gastro-intestinal bleeding

Outline 6

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- **Symptomatic patient with functional syndromes**
  - **Diarrhea and flushing**
    - Clinical approach: when to suspect a GEP-NET
    - Work-up in the patient with suspected carcinoid syndrome
  - **Resistant/relapsing ulcer disease**
    - Clinical approach: when to suspect a GEP-NET
    - Work-up in the patient with suspect gastrinoma
  - **Spontaneous hypoglycemia**
    - Clinical approach: when to suspect a GEP-NET
    - Work-up in the patient with suspect insulinoma

Outline 6

- Work-up in the patient with metastatic disease and unknown primary tumor
- Staging a GEP-NET
- Conclusions

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"More and more patients are going to the Internet for medical advice. To keep my practice going, I changed my name to Dr. Google."

How to manage this long statement?

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- We will review only the Recommandations

- The members of this panel will offer their comments on various flow charts

Back to everyday problems

- What to do when we are faced with an incidentally diagnosed NET?

Asymptomatic patient: incidental finding

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- 3.1.1 GEP-NET suspected at endoscopy
- 3.1.2 GEP-NET suspected at morphological (US/CT/MR) imaging
- 3.1.3 GEP-NET suspected after elevated serum CgA levels

We recommend

- Biopsy as the first diagnostic step in all lesions suspected for GEP-NET;
- Diagnostic work-up to be routinely discussed within a NET multidisciplinary team;
- Against the use of lab test or functional imaging as a first-line diagnostic procedure;
- Careful exclusion of potential interfering physiologic and pharmacological factors in patients with elevated serum CgA levels and no previous NET diagnosis.

Diagnostic flow-chart for NET suspected after high CgA

Discussant: M. Caputo

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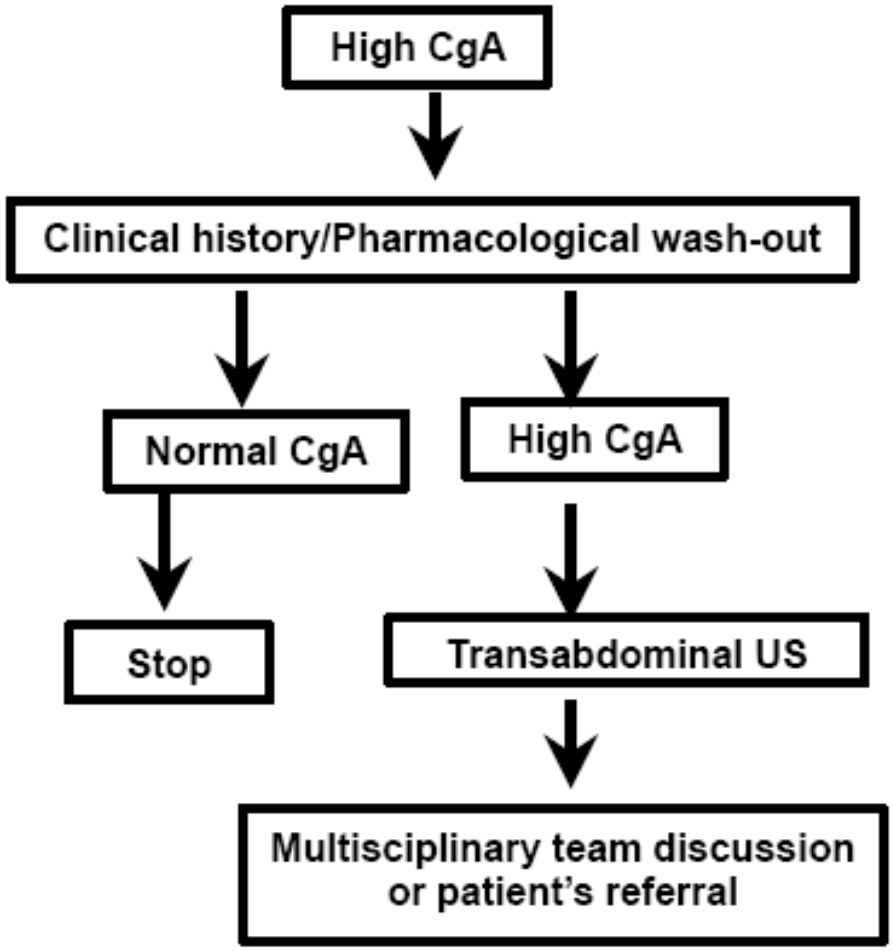

Figure 4
Diagnostic flow-chart for NET suspected after high CgA

Back to everyday problems!

- What should we do when we are faced with a patient that has symptoms compatible with a NET syndrome?

SYMPTOMATIC PATIENT

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- **3.2 Symptomatic patient with symptoms due to local effects of GEP-NETs**
  - Isolated abdominal pain
  - Subocclusive picture
  - Jaundice
  - Gastro-intestinal bleeding

We recommend: an accurate diagnostic work-up should be performed to obtain a histologic or cytologic diagnosis in patients with these symptoms associated with a morphological suspicious imaging

Symptomatic patient with functional syndromes -1

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- **Diarrhea and flushing (Carcinoid Syndrome – CS)**
- Resistant/relapsing ulcer disease (ZES)
- Spontaneous hypoglycemia (Insulinoma)

We recommend for Carcinoid Syndrome

- To rule out other causes of flushing and diarrhea before proceeding with work-up of CS: don't forget a complete history and clinical examination.
- To rely on urinary 5-HIAA for CS diagnosis
- **against** routine use of CgA and NSE assays.

Symptomatic patient with functional syndromes - 2

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- **Diarrhea and flushing (CS)**
- Resistant/relapsing ulcer disease (ZES)
- Spontaneous hypoglycemia (Insulinoma)

We recommend for CS

- Contrast-enhanced abdominal CT or MRI as initial imaging according to local availability and expertise. If negative, use thoracic CT.
- Functional imaging by SRS or PET, according to local availability, for localization of tumor and metastasis and characterization of SSTR status.
- Echocardiography at diagnosis and at yearly interval.

Diagnostic flow-chart for suspected carcinoid syndrome

Discussant: F. Angelini

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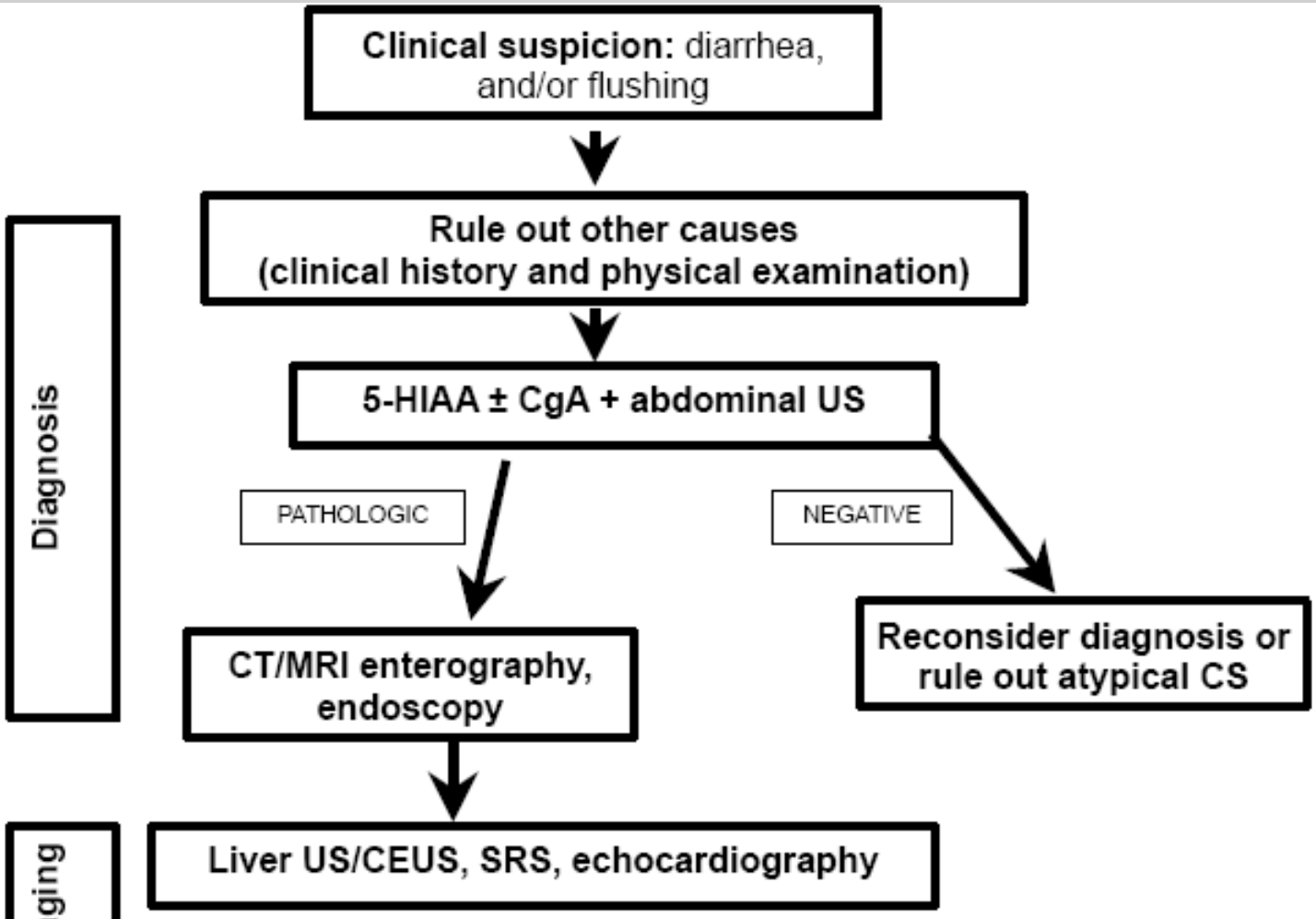

Figure 9
Diagnostic flow-chart for suspected carcinoid syndrome

Symptomatic patient with functional syndromes -1

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- Diarrhea and flushing (CS)
- **Resistant/relapsing ulcer disease (Zollinger Ellison Syndrome - ZES)**
- Spontaneous hypoglycemia (Insulinoma)

Consider ZES in case of:

- Recurrent, severe or familial peptic ulcer disease;
- Or peptic ulcer disease:
  - without *HP*
  - associated severe GERD
  - resistant to treatment
  - associated with complications, with endocrinopathies or diarrhea
  - with prominent gastric folds at endoscopy

Symptomatic patient with functional syndromes -2

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- Diarrhea and flushing (CS)
- **Resistant/relapsing ulcer disease (ZES)**
- Spontaneous hypoglycemia (Insulinoma)

We recommend

- Exclusion of all other causes of hypergastrinemia before proceeding with the diagnostic work-up.
- Fasting serum gastrin as the initial test to support the clinical suspicion of ZES
- Secretin test when the diagnosis of ZES is unclear/ controversial
- Tumor localization procedures with biochemically established ZES.
- MEN-1 Syndrome be suspected in patients with refractory peptic ulcer disease or a confirmed ZES.

Diagnostic flow-chart for suspected gastrinoma

Discussant: A. Faggiano - D. Berretti

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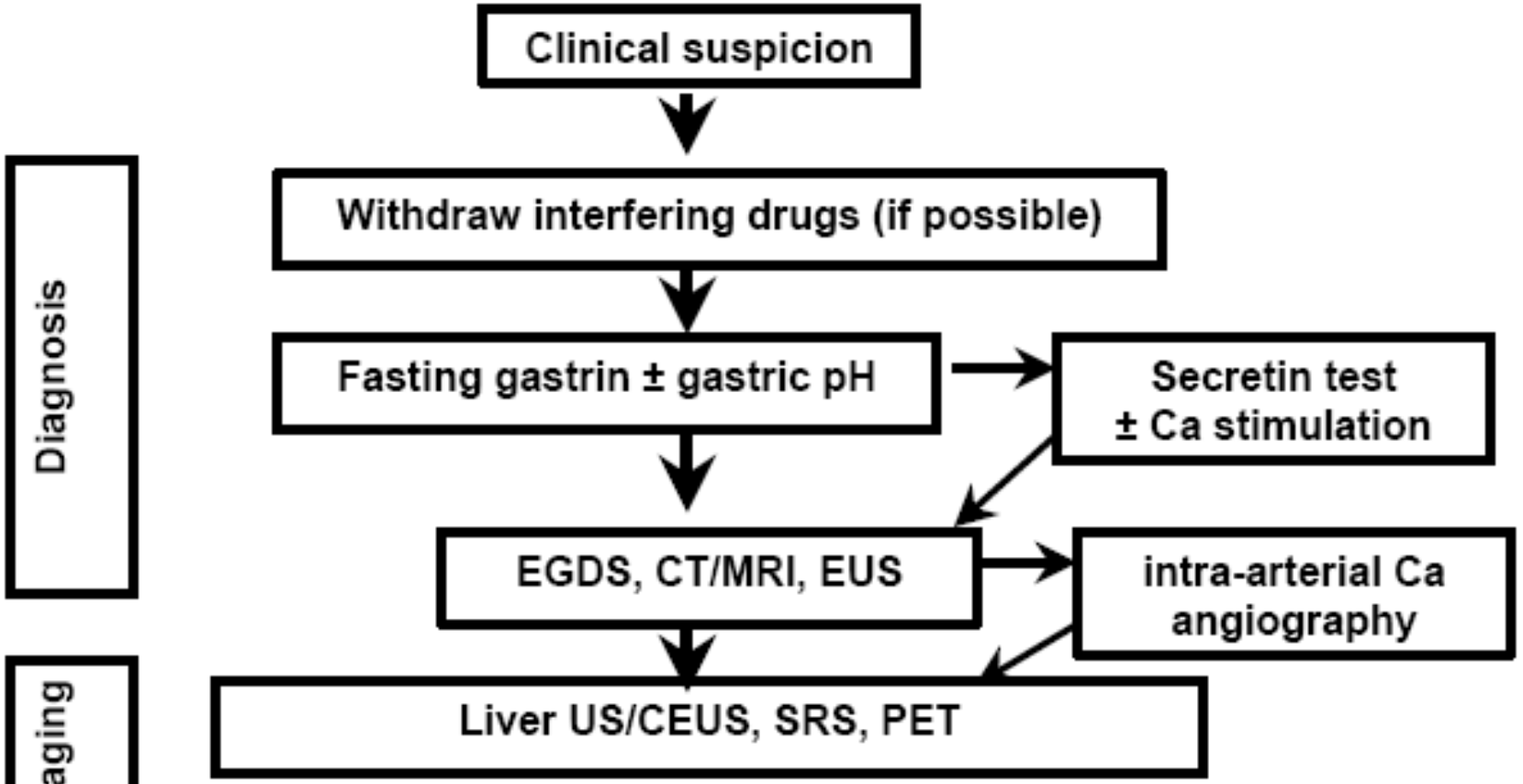

Figure 10
Diagnostic flow-chart for suspected gastrinoma

Symptomatic patient with functional syndromes

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- Diarrhea and flushing (CS)
- Resistant/relapsing ulcer disease (ZES)
- **Spontaneous hypoglycemia (Insulinoma)**

Consider insulinoma

- After exclusion of all alternative causes of hypoglycemia.
- As a probable cause in patients with predominant chronic neuroglycopenic symptoms, recurrent fasting hypoglycemia, and weight gain
- In patients with acute, especially if recurrent, change in mental status

Symptomatic patient with functional syndromes

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- Diarrhea and flushing (CS)
- Resistant/relapsing ulcer disease (ZES)
- **Spontaneous hypoglycemia (Insulinoma)**

We recommend

- using the simultaneous evaluation of blood glucose, insulin and C-peptide to detect endogenous hyperinsulinemic hypoglycemia.
- prolonged fasting (up to 72 h) for a more accurate testing
- using imaging and localization tests only after the biochemical diagnosis of insulinoma
- **against the** use of stimulation tests for insulin.

WORK-UP IN THE PATIENT WITH METASTATIC DISEASE AND UNKNOWN PRIMARY TUMOR

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- The presence of liver metastases dramatically worsens the prognosis
- Survival rate at 5 years ranges from 13 to 54% with untreated metastatic liver disease
- The major prognostic factors shared by the different types of GEP-NETs are Ki-67 or mitotic index, size and/or distant metastases and histologic findings

We recommend

- A detailed clinical and family history to elicit signs or symptoms that could point to the primary site.
- Biopsy at the metastatic site with histologic and IHC examination as a first step.
- Selecting specific morphologic and functional examinations for the work-up based on signs and symptoms.

Diagnostic flow-chart in the patient with metastatic disease and unknown primary tumor

Discussant: G. Bizzarri, A Crescenzi

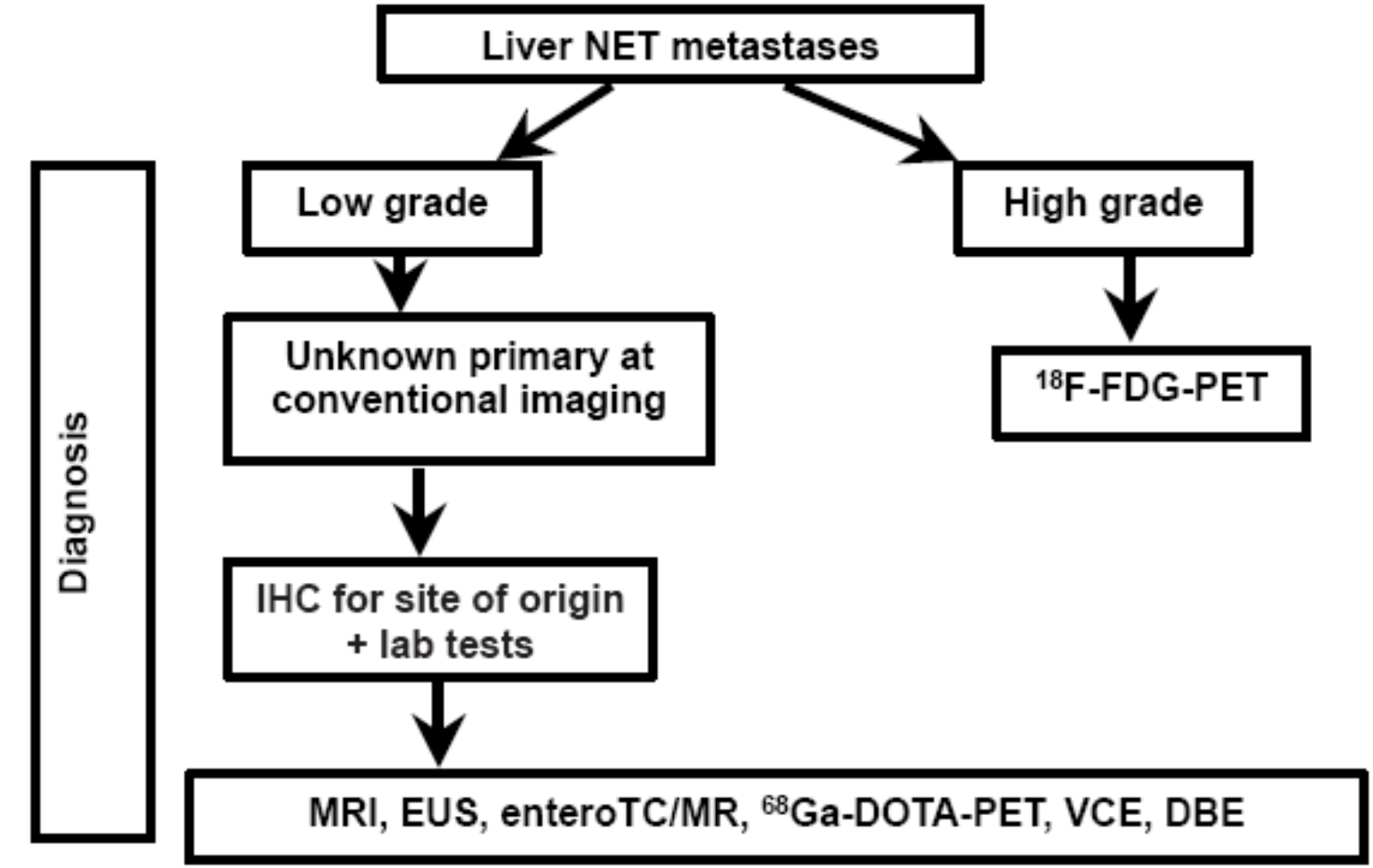

Figure 12

Diagnostic flow-chart in the patient with metastatic disease and unknown primary tumor

STAGING A GEP-NET

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- Evaluation of disease extension has a pivotal role in treatment planning.
- Pre-treatment staging should include morphologic and functional imaging.

We recommend

- Chest-abdomen CT or abdomen MRI in pre-treatment staging of GEP-NETs. Perform Entero TC and colonoscopy in patients with jejuno-ileum
- ^{68}Ga-DOTA-peptides-PET-CT for functional staging of differentiated GEP-NETs, or, if not available, ^{111}I-pentetreotide (Octreoscan®) scintigraphy.
- EUS study before resection of gastric polyps >1 cm and duodenal polypoid lesions.
- We **suggest** ^{18}F-FDG-PET-CT for staging of G3 and selected G2 GEP-NETs.

CONCLUSIONS

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- Up to 60% of GEP-NETs are initially asymptomatic and can develop insidiously.
- a wide variation in disease outcome and extremely variable natural history contributes to the difficulty in diagnosing and managing GEP-NETs.

We recommend

a multidisciplinary team model to improve the diagnostic and staging process and to offer the best opportunity to improve outcome for the patients

CONCLUSIONS

- Implementations and updates of this document will hopefully cover the many still grey areas in the field.

- AME hopes that this Position Statement will be useful for all the clinicians that face the problem of NET diagnosis.

Thanks