TUMORI NEUROENDOCRINI GASTROINTESTINALI

# COSA CHIEDERE AL LABORATORIO


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**SAN VITO AL TAGLIAMENTO**

**30 GENNAIO 2009**

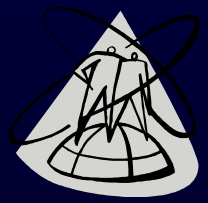
AMBULATORIO
TUMORI NEUROENDOCRINI
GASTROENTEROPANCREATICI

# CORRETTO APPROCCIO DIAGNOSTICO

## ANAMNESI ACCURATA

## MARCATORI TUMORALI

## DIAGNOSTICA CONVENZIONALE



## MEDICINA NUCLEARE

# CARATTERISTICHE DEL MARCATORE TUMORALE PERFETTO

- **Prodotto solamente da un determinato tipo di tumore**
- **Secreto in quantità misurabile in circolo**
- **Rilevabile solo in presenza del tumore**
- **In grado di identificare la proliferazione cellulare maligna prima che questa abbia dato metastasi**

# CARATTERISTICHE DEL MARCATORE TUMORALE PERFETTO

- La quantità di marcatore in circolo dovrebbe essere in rapporto all'entità del tumore
- Le sue variazioni dovrebbero:
  - ✓ riflettere la risposta al trattamento
  - ✓ indicare quando la malattia è in progressione.

# TUMORI NEUROENDOCRINI

**I MARCATORI TUMORALI POSSONO ESSERE**

ASPECIFICI

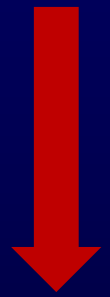
SPECIFICI

# MARCATORI TUMORALI
# SPECIFICI

| | VALORI NORMALI | CUT-OFF |
|---|---|---|
| **Insulina** | **< 15μmol/L** | **> 100** |
| **Gastrina** | **< 40 pmol/L** | **> 200** |
| **Glucagone** | **< 50 pmol/L** | **> 250** |
| VIP | < 30 pmol/L | > 150 |
| **5-HIAA** | **2-8 mg/24h** | **> 20** |

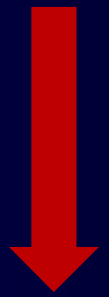
# MARCATORI TUMORALI
## TEST DI STIMOLO

**INSULINOMA**



**TEST AL DIGIUNO**

**GASTRINOMA**



**TEST ALLA SECRETINA**

## Table 2. Protocol for 72-Hour Fast.

1. Date the onset of the fast as of the last ingestion of calories. Discontinue all nonessential medications.
2. Allow the patient to drink calorie-free and caffeine-free beverages.
3. Ensure that the patient is active during waking hours.
4. Measure the levels of plasma glucose, insulin, C peptide, and proinsulin in the same specimen; repeat measurements every six hours until the plasma glucose level is ≤60 mg per deciliter, when the interval should be reduced to every one to two hours.
5. End the fast when the plasma glucose level is ≤45 mg per deciliter (2.5 mmol per liter) and the patient has symptoms or signs of hypoglycemia.
6. At the end of the fast, measure the plasma levels of glucose, insulin, C peptide, proinsulin, β-hydroxybutyrate, and sulfonylurea in the same specimen; then inject 1 mg of glucagon intravenously and measure the plasma glucose level after 10, 20, and 30 minutes. Then feed the patient.
7. When a deficiency is suspected, measure plasma cortisol, growth hormone, or glucagon at the beginning and end of the fast.

**Service F.J., N Engl J Med. 1995**

# CRITERI DIAGNOSTICI

## GASTRINOMA

**pH gastrico < 2**

**Gastrina > 1000 pg/ml**

**GASTRINOMA**

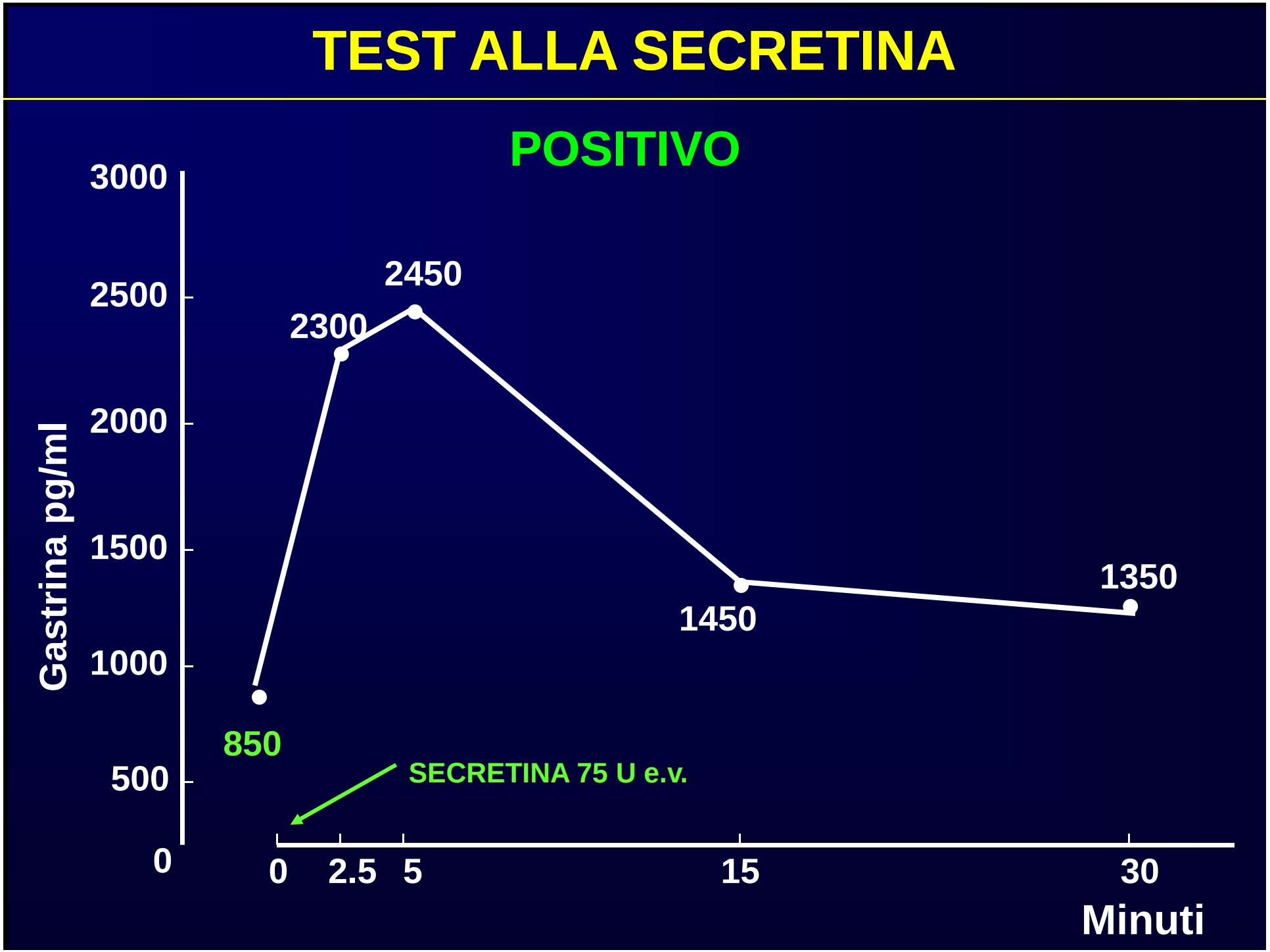
**pH gastrico < 2**

**Gastrina = 100-1000 pg/ml**

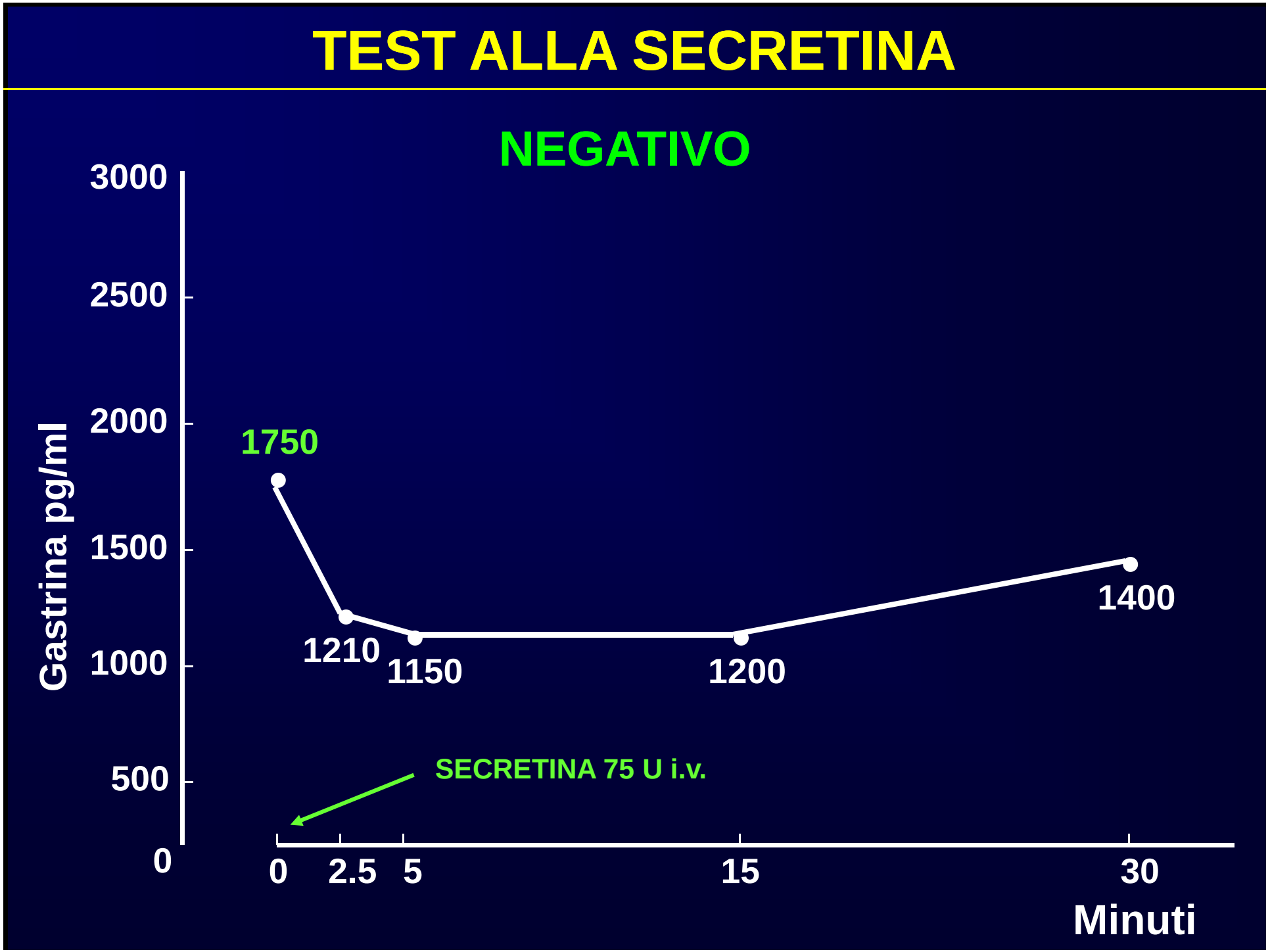
**GASTRINOMA ?**

**TEST ALLA SECRETINA**

# TEST ALLA SECRETINA



# TEST ALLA SECRETINA



# CAUSES OF HYPERGASTRINEMIA

## HYPERGASTRINEMIA WITH HYPERCHLORHYDRIA

- Zollinger-Ellison syndrome → sporadic
  → associated with
  MEN 1

- Antral G-cell hyperplasia
- Excluded gastric antrum syndrome
- Gastric outlet obstruction
- Small intestinal resection

# CAUSES OF HYPERGASTRINEMIA

## HYPERGASTRINEMIA WITH HYPOCHLORHYDRIA

- Chronic Atrophyc Gastritis type A
  1. Idiopathic
  2. Autoimmune → pernicious anemia
     → other autoimmune disorders

- Antisecretory agents
  $H_2$-antagonists
  $H^+ K^-$ ATPase inhibitors

# ACIDO 5-IDROSSI-INDOLACETICO

## 5-HIAA URINARIO

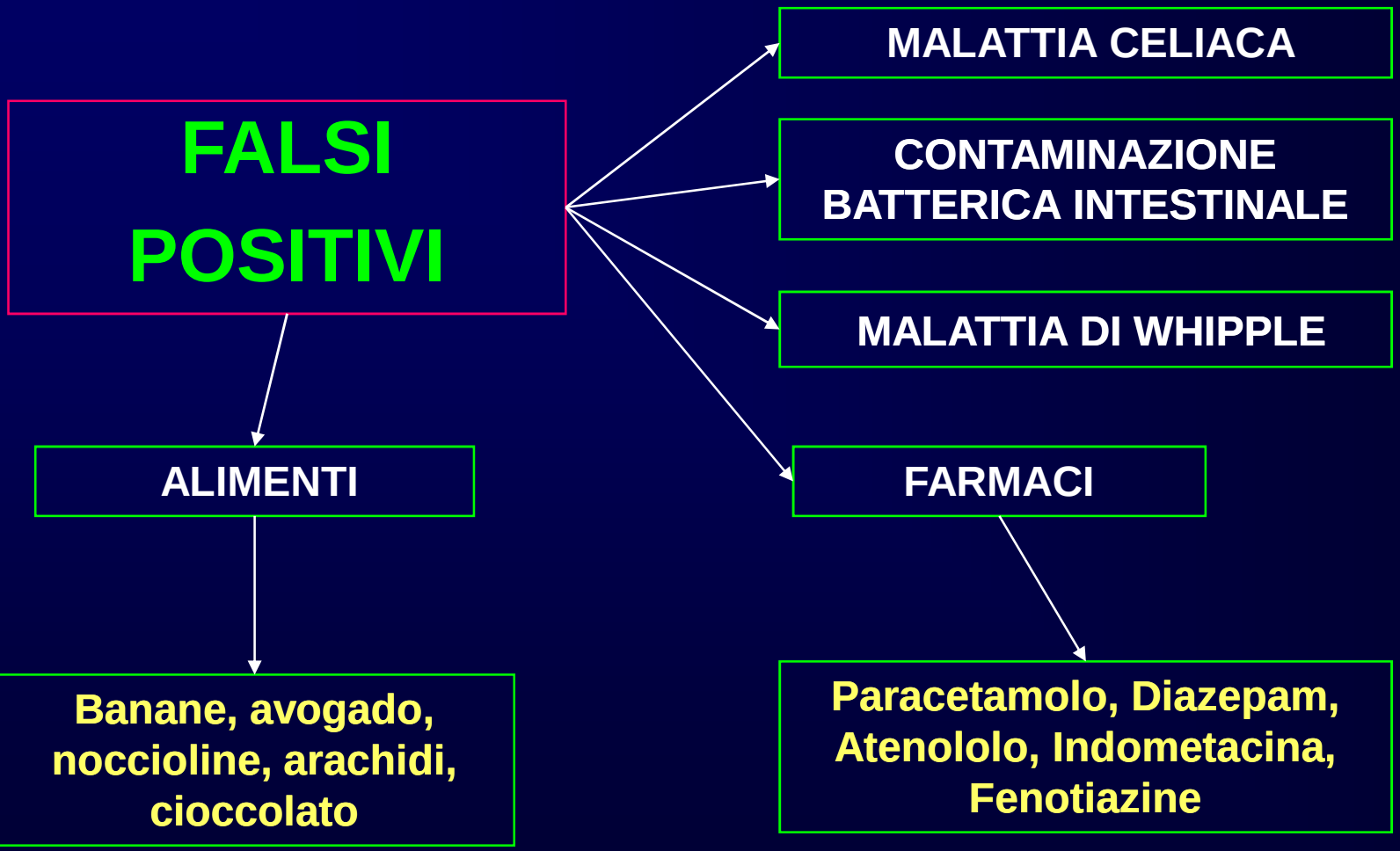
n. v. = 2- 8 mg / 24 hrs

cut-off > 20 mg / 24 hrs

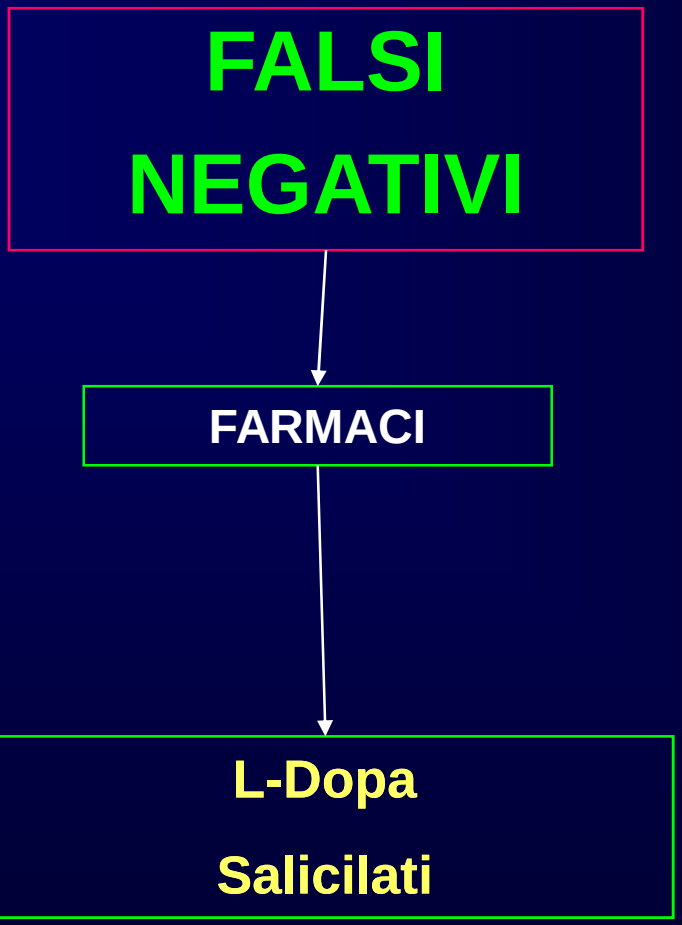
| | |
|---|---|
| SENSIBILITA’ | 65 - 75% |
| SPECIFICITA’ | 90 - 100% |

Feldman 1986

# ACIDO 5-IDROSSI-INDOLACETICO



# ACIDO 5-IDROSSI-INDOLACETICO



# TUMORI NEUROENDOCRINI

## MARCATORI TUMORALI ASPECIFICI

# MARCATORI TUMORALI
# ASPECIFICI

ENOLASI NEURONO-SPECIFICA (NSE)

GONADOTROPINA CORIONICA UMANA (HCG) $\alpha$, $\beta$

POLIPEPTIDE PANCREATICO (PP)

TUMOR M2-PIRUVATO KINASI (TM2-PK)

CROMOGRANINA A (CgA)

# NSE SENSITIVITY AS CIRCULATION MARKERS FOR NET

| NET | NSE SENSITIVITY % |
|---|---|
| CARCINOID | 47, 38 |
| PANCREAS ISLET CELL TUMOURS | 43, 31 |
| GASTRINOMA | 44, 33 |
| CARCINOID MIDGUT | 50 |
| SMALL CELL LUNG CARCINOMA | 74, 61, 85, 62 |
| LIMITED DISEASE | 45, 77 |
| EXTENSIVE DISEASE | 68, 85 |

Seregni E, Q J Nucl Med 2000

# CROMOGRANINA A

VOLUME 25 · NUMBER 15 · MAY 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Chromogranin A: Is It a Useful Marker of Neuroendocrine Tumors?

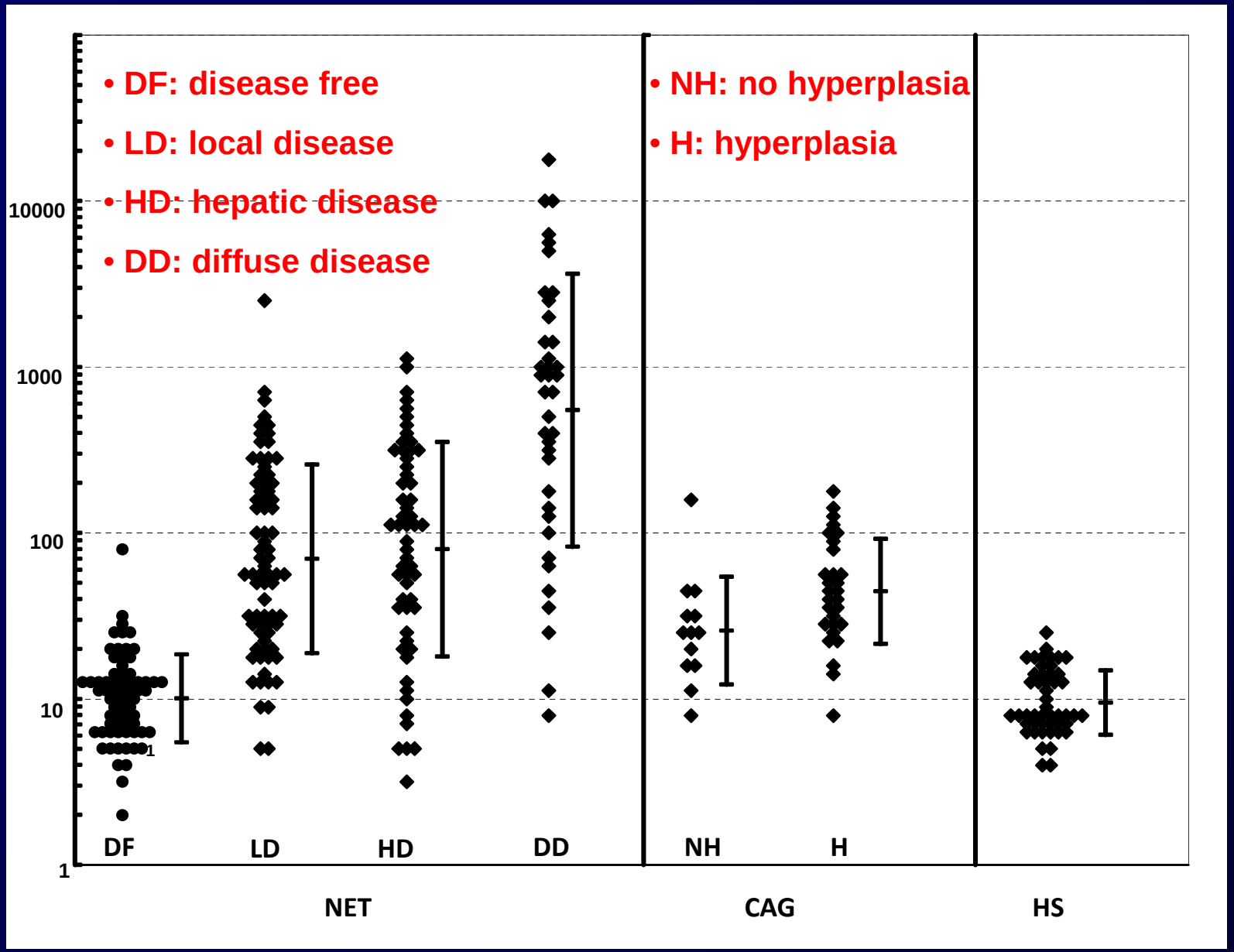
*Davide Campana, Francesca Nori, Lidya Piscitelli, Antonio Maria Morselli-Labate, Raffaele Pezzilli, Roberto Corinaldesi, and Paola Tomassetti*

**Table 1.** CgA Plasma Levels in the Three Groups of Participants

| Group | No. of Participants | CgA Level (U/L) | | *P* | Effect (%) | |
|---|---|---|---|---|---|---|
| | | Mean | SD | | Estimate | 95% CI |
| NETs | 238 | 428.1 | 1,584.3 | | | |
| Compared with CAG patients | | | | .114 | 153.5 | 90.1 to 261.6 |
| Compared with healthy participants | | | | < .001 | 606.7 | 367.3 to 1,000.0 |
| CAG* | 42 | 50.1 | 41.2 | < .001 | 395.3 | 201.8 to 774.5 |
| Healthy participants | 48 | 10.5 | 4.7 | — | — | — |

NOTE. Comparisons among the groups were made using one-way analysis of variance. $P < .001$ among the three groups.
Abbreviations: CgA, chromogranin A; SD, standard deviation; NET, neuroendocrine tumor; CAG, chronic atrophic gastritis.
*$P$ values and effect estimates compared with healthy participants.

**Distribution of Chromogranin A in 238 endocrine tumor (NET) patients, in 42 chronic atrophic gastritis subjects (CAG) and in 48 healthy subjects (HS).**




Campana D., JCO; 25(15) May 2007

**Table 2.** CgA Plasma Levels in the Subgroups of NET and CAG Patients

| Group | No. of Patients | CgA Level (U/L) | | *P* | Effect (%) | |
|---|---|---|---|---|---|---|
| | | Mean | SD | | Estimate | 95% CI |
| NET | | | | | | |
| Diffuse disease | 38 | 2,055.5 | 3,539.4 | | | |
| Compared with hepatic disease | | | | < .001 | 687.3 | 398.5 to 1,185.4 |
| Compared with local disease | | | | < .001 | 786.2 | 468.2 to 1,320.2 |
| Compared with disease free | | | | < .001 | 5,452.6 | 3,218.5 to 9,237.4 |
| Hepatic disease | 57 | 187.2 | 237.4 | | | |
| Compared with local disease | | | | .563 | 114.4 | 72.4 to 180.7 |
| Compared with disease free | | | | < .001 | 793.3 | 497.1 to 1,266.1 |
| Local disease* | 75 | 163.5 | 312.5 | < .001 | 693.5 | 448.5 to 1,072.4 |
| Disease free | 68 | 12.3 | 10.7 | — | — | — |
| CAG | | | | | | |
| Hyperplasia† | 29 | 56.7 | 41.0 | .032 | 172.7 | 105.2 to 283.6 |
| No hyperplasia | 13 | 35.3 | 39.2 | — | — | — |

NOTE. Comparisons among the subgroups were made using one-way analysis of variance.
Abbreviations: CgA, chromogranin A; NET, neuroendocrine tumor; CAG, chronic atrophic gastritis; SD, standard deviation.
**P* values and effect estimates compared with disease free.
†*P* values and effect estimates compared with no hyperplasia

**Table 3.** CgA Plasma Levels in NET Patients According to the Site of Tumor

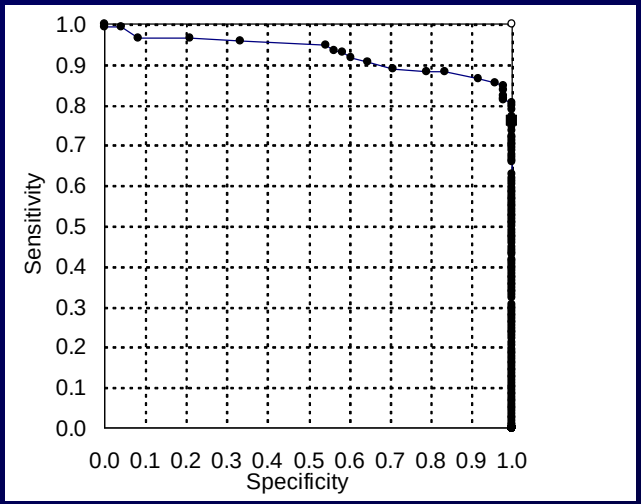
| Tumor Site | No. of Patients | CgA Level (U/L) | |
|---|---|---|---|
| | | Mean | SD |
| Lung | 20 | 46.3 | 94.6 |
| Stomach | 14 | 78.0 | 69.2* |
| Pancreas | 94 | 322.2 | 952.7* |
| Intestine | 85 | 380.1 | 1,224.9* |
| ZES | 25 | 1,490.5 | 3,819.3 |

NOTE. Comparisons among the subgroups were made using one-way analysis of variance. Overall $P < .001$ among the five localizations.
Abbreviations: CgA, chromogranin A; NET, neuroendocrine tumor; SD, standard deviation; ZES, Zollinger-Ellison syndrome.
*No significant differences ($P = .780$) were detected at the post hoc analysis among patients with stomach, pancreas, and intestinal tract neoplasia.

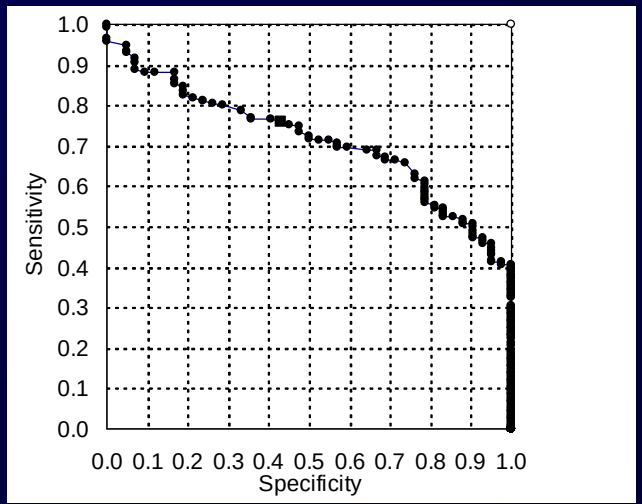
Campana D., JCO; 25(15) May 2007

## Results of the ROC curve analysis comparing different groups of patients

| | AUC±SE | Best cut-off range (U/L) | Sensitivity | Specificity |
|---|---|---|---|---|
| NETs vs. HS | 0.928±0.017 | 18-19 | 85.3% | 95.8% |
| Neoplasia vs. no neoplasia | 0.865±0.020 | 31-32<br>84-87 | 75.3%<br>55% | 84.2%<br>95% |
| NETs: diffuse vs. limited disease | 0.805±0.047 | 281-282<br>564-603 | 71.1%<br>55% | 78.8%<br>95% |




NETs vs HS




NETs vs CAG

Campana D., JCO; 25(15) May 2007

# CHROMOGRANIN A

## FALSE POSITIVE

RENAL FAILURE

LIVER FAILURE

ATROPHIC GASTRITIS

INFLAMMATORY BOWEL DISEASE

NEOPLASMS

DRUGS (PPI)

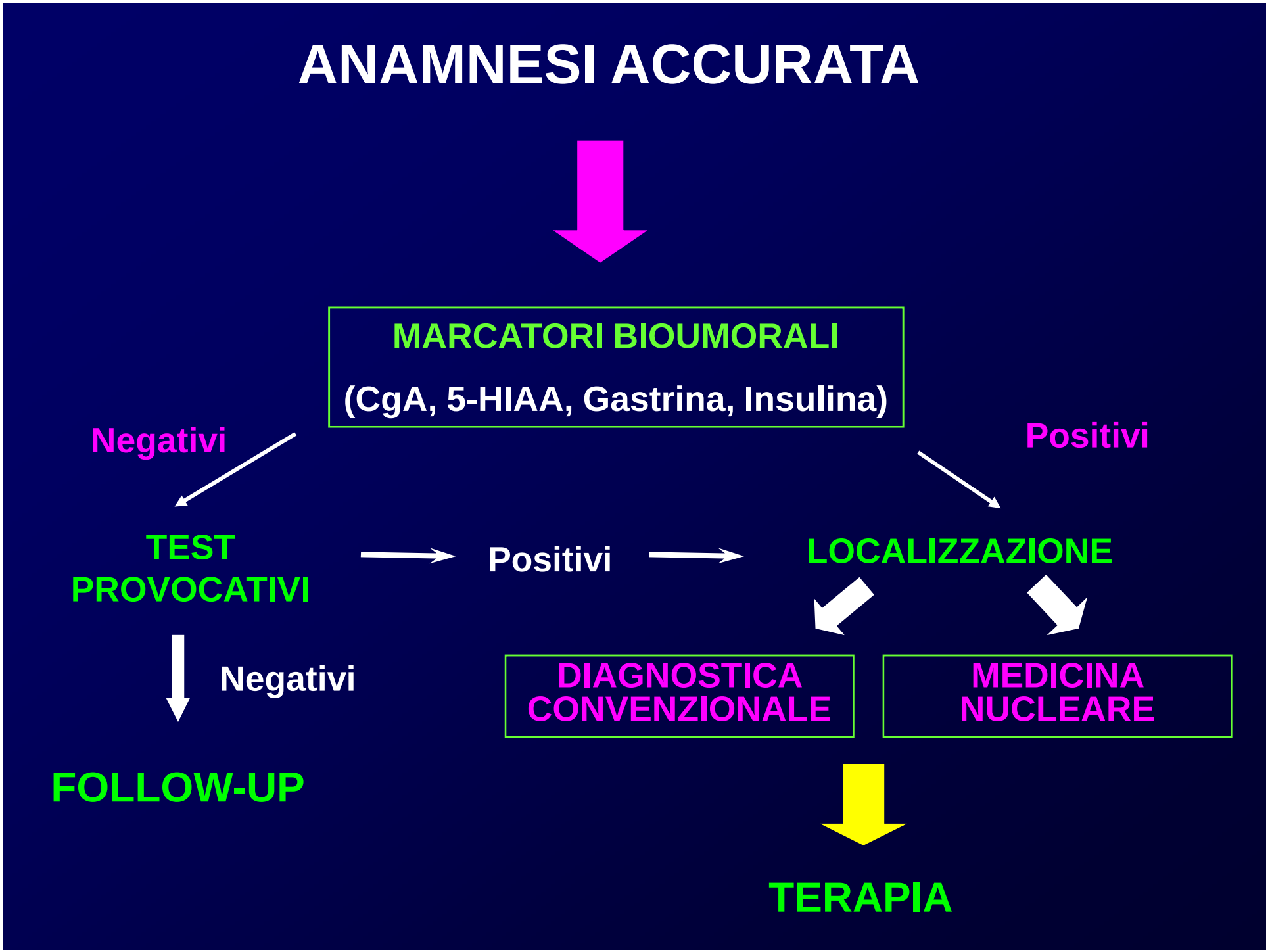
STRESS

INTENSE PHYSICAL ACTIVITY

PREGNANCY

HYPERTENSION

PARKINSON SYNDROME


ANAMNESI ACCURATA
MARCATORI BIOUMORALI
(CgA, 5-HIAA, Gastrina, Insulina)
Negativi
Positivi
TEST PROVOCATIVI
Positivi
LOCALIZZAZIONE
Negativi
DIAGNOSTICA CONVENZIONALE
MEDICINA NUCLEARE
FOLLOW-UP
TERAPIA