

Abuse of Tumor Marker in Taiwan

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Definition of Tumor Marker

- *A substance that is*
 1. *Present or produced by the tumor itself*
 2. *Or produced by the host in response to a tumor*

that can be used to determine the presence of a tumor based on measurement in the blood or secretion
- *Chromosome abnormality that can lead to identify the type of a tumor, or the risk of developing that tumor..*

Tsung SH: Alpha-fetoprotein in patients with lung cancer metastasized to liver. Arch. of Pathol. 99:267-269, 1975

Classification of Tumor Markers

- 1.Enzymes.
- 2.Ectopic hormones.
- 3.Oncofetal antigens.
- 4.Proteins.
- 5.Mucin tumor markers.
- 6.Blood group antigen related markers.
- 7.Oncogene and suppresser gene markers.
- 8.Others



Several Characteristics define an Ideal Tumor Marker

- 1. Should not be present in health or in benign diseases.*
- 2. Should be present frequently enough and early enough in the development of a malignancy to be useful in screening for that cancer.*
- 3. Should be produced by the tumor cells and be readily detectable in body fluid.*
- 4. Should directly reflect the bulk of malignancy and be detectable even when there is no clinical evidence of tumor.*
- 5. Should correlate with the results of anticancer therapy*

The Value of Tumor Markers

- *In monitoring cancer therapy.*
- *In detecting recurrence.*
- *Not in screening for cancer.*

市面上常見健檢套餐

- A. 陽春麵: 身高、體重、視力、血壓血球、肝腎功能、血糖、膽固醇、尿酸。(NT700)
- B. 榨菜肉絲麵: A+(心電圖、胸部X光、膽道功能、高低密度脂蛋白、甲狀腺功能、尿液、糞便、肝炎指標)。
(NT1000~3000)
- C. 大滷麵: B+(上下消化道內視鏡，癌症指標、胸腹X光、腹部超音波、各科會診、醫師解說)。
(NT20,000~50,000)
- D. 什錦海鮮麵: C+(核磁共振、正子造影、功能醫學、基因檢查、各科名醫會診、養生套餐、SPA, 美女白衣天使親切服務...)。
(NT100,000~~~)

健檢市場大力推銷

- 很大商機。
- 堵人財路。

名詞解釋

D+: 有病 D-: 沒病 T+: 檢查陽性 T-: 檢查陰性

| | D+(100) | D-(100) |
|----|---------|---------|
| T+ | a(90) | b(5) |
| T- | c(10) | d(95) |

- Sensitivity: 敏感度 $a / (a+c)$
→ 有病的人檢查後結果顯示有病的百分比
- Specificity: 特異性 $d / (b+d)$
→ 沒病的人檢查後結果顯示沒病的百分比
- False positive : 偽陽性 $b / (b+d)$
→ 沒病的人檢查後結果顯示有病的百分比
- False negative : 偽陰性 $c / (a+c)$
→ 有病的人檢查後結果顯示沒病的百分比

敏感度及特異性低

- 胎兒蛋白為例(AFP)

敏感度 68%

特異性 60%

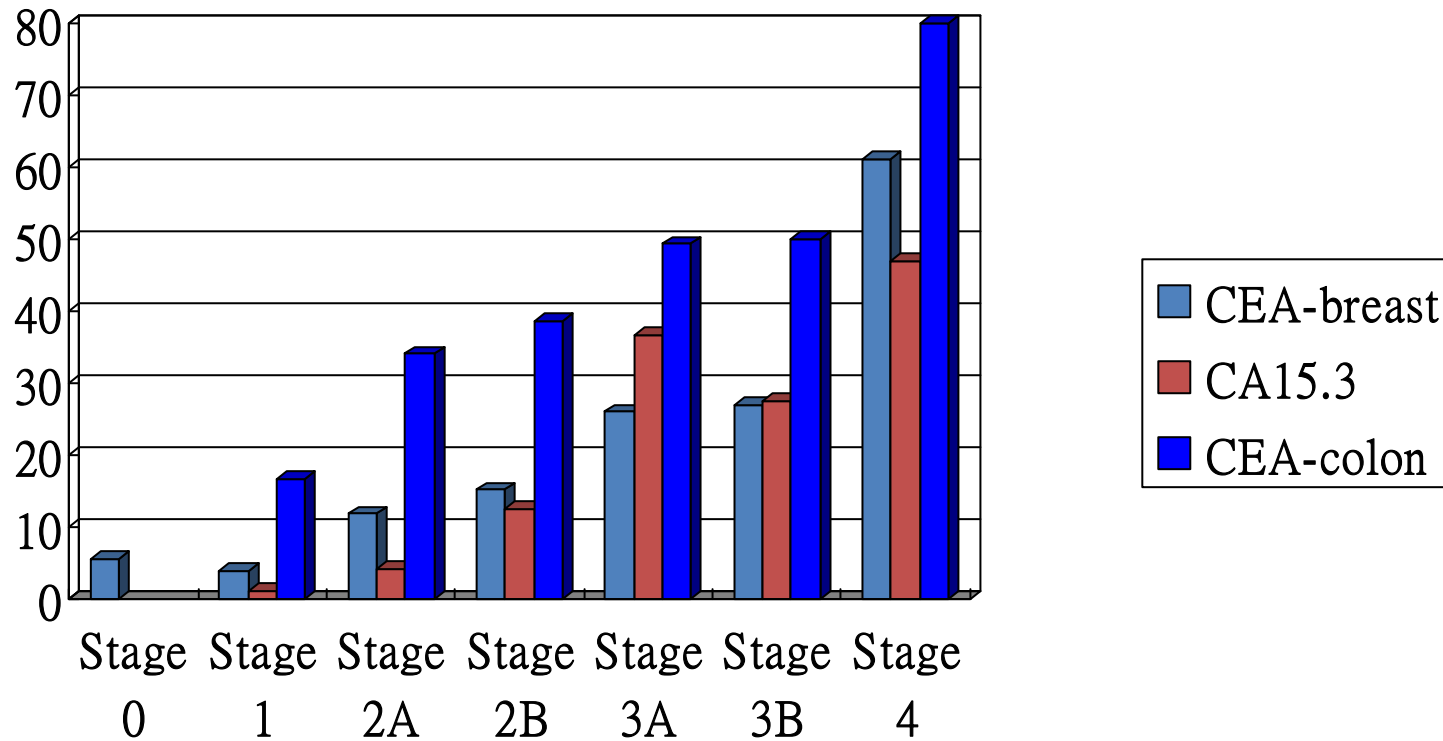
- 前列特異抗原(PSA)

敏感度 34.9%

特異性 63.1%

Incidence of Elevation

CEA-breast=76/660=11.5% CEA-colon=130/285=45% CA15.3=130/661=6.8%
SYSCC 1990=1998



腫瘤標誌不能當健檢用

- 是作為治療反應與復發的指標。

例外

- 特定的族群有些價值；例如**B**肝帶原者，**C**肝的病人。

To screen for diseases

- Indicate whether or not a disease is present in its early or subclinical stages in an otherwise healthy person.

1. General screen :Cervical Pap smears

2. Targeted screen :AFP, SGPT for HCC

- *The characteristics of the tests used for screen*

1.High sensitivity, high specificity.

2.Cheap

3.Easy to perform.

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(NT100,000~~~)

Hereditary Breast Cancer

- Approximately 5~10% of breast cancer results from inherited mutation of the tumor suppressor gene (BRCA)
- Early age onset (<40 years of age)

Breast Cancer Gene (BRCA)

- **BRCA-1**
- BRCA-2

The consequence of Abuse of Tumor Markers

Screening for cancer in healthy person

- 在臨床工作中，相信有不少同仁也注意到，偶而會遇到一些所謂的“病人”，抱著一個較高於參考值的血清CA19-9濃度(eg. >37U/mL)，或CEA >4 ng/ml，來個“全省走透透”以及“全身找透透”，就是找不到一個癌症。

Table 1. Non-malignant cause of CA 19-9 elevation

- Obstructive jaundice
- Acute liver failure
- and acute hepatitis
- Chronic liver disease
- Alcoholic liver disease
- Non-alcoholic liver disease
- Cirrhosis
- Gallstones
- Acute cholangitis
- Pancreatitis
- Diabetes mellitus
- Interstitial pulmonary disease
- Rheumatoid arthritis
- Endometriosis
- -----

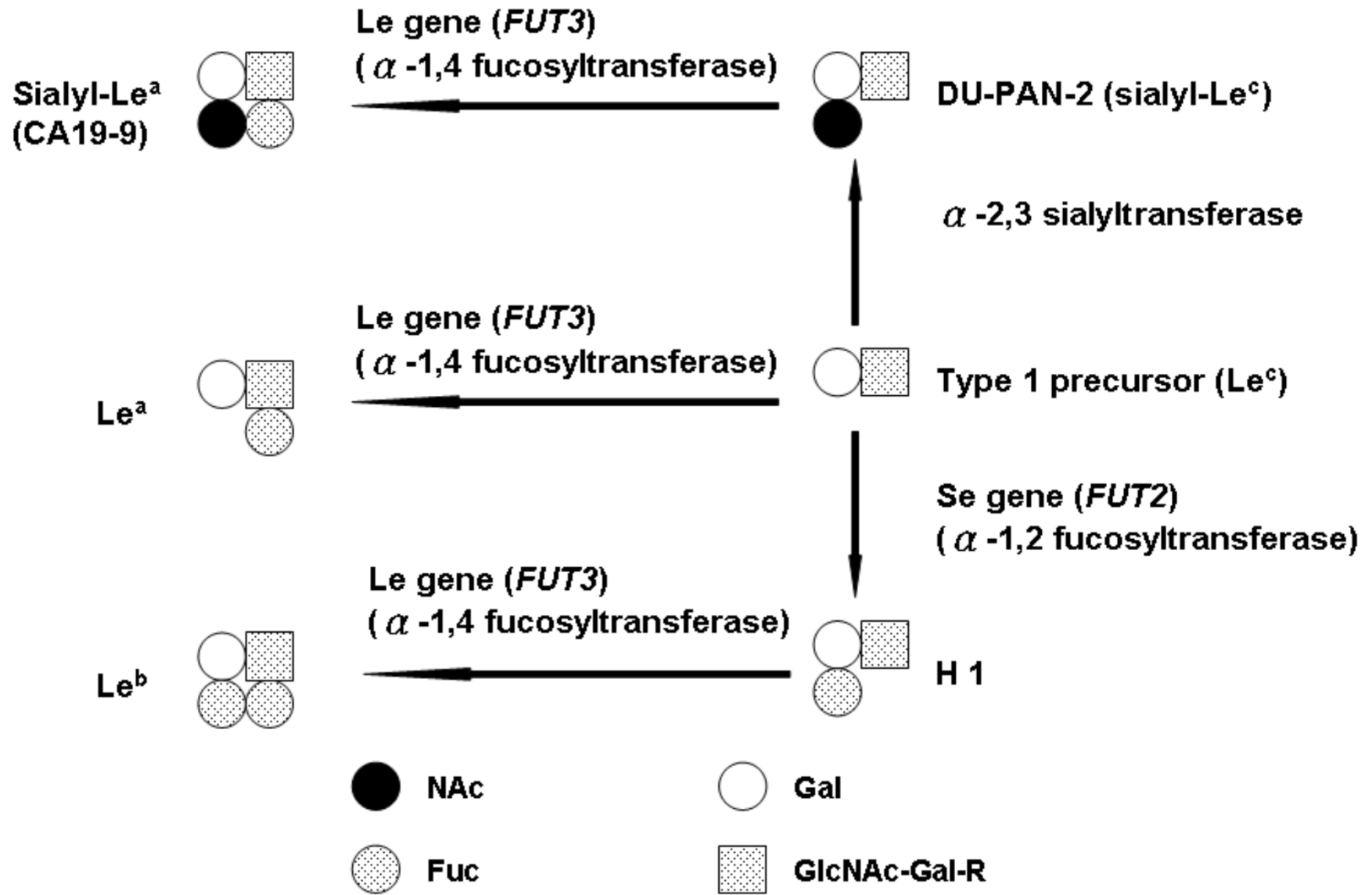


Figure 1. Biosynthetic pathways of type 1 blood group antigens.

Table 2 .Combinations of secretor and Lewis genotypes
and resulting erythrocyte phenotypes.

| Secretor genotype | Lewis genotype | Erythrocyte Phenotype | ABH in saliva | Frequency (%) (15, 20) | | |
|--|----------------|-----------------------|---------------|------------------------|-------|--------|
| | | | | Whites | Black | Taiwan |
| Se/Se or Se/se | Le/Le or Le/le | Le (a-b+) | + | 72 | 55 | 67 |
| se/se | Le/Le or Le/le | Le (a+b-) | - | 22 | 23 | 0 |
| Se/Se or Se/se or se/se | le/le | Le (a-b-) | + | 6 | 22 | 8 |
| Se ^w /Se ^w or Se/Se ^w | Le/Le or Le/le | Le (a+b+) | - | rare | rare | 25 |

Tumor Markers的另一個問題

- *Interference in immunoassay
could be a threat !*

In modern clinical chemistry laboratory, immunoassay plays a very important role

◆ Tumor markers

AFP CEA CA 19.9 CA 125 hCG PSA

◆ Hormones:

TSH T4 T3 FSH LH Prolactin Estradiol

◆ Drugs:

Gentamycin Amikacin Digoxin Theophyllin Methotrexate

◆ Others:

Hepatitis profile , viral antigens, cytokin

No diagnostic test is flawless, and unfortunately this also applies to immunoassay

◆ *Recent literature has documented false-positive or false-negative results in immunoassay due to interference by endogenous substances, such as*

- *Heterophil antibodies*
- *Autoantibodies against thyroid hormones*
- *Antinuclear antibodies*
- *Rheumatoid factor*

An example of falsely elevated serum level of hCG

Rotmensch S, Cole LA: Lancet 2000;355:712

Report of 12 patients

School of Medicine, Yale University

Patient: A woman, aged 23 years, was seen by her family physician because of irregular menses.

Past history: one unsuccessful pregnancy.

Initial serum hCG 251 IU/ml

repeated hCG fluctuated between 215-218 in 6 months time span

Gynecology oncologist was consulted

She underwent systemic investigation for metastasis----- negative

She received 2 courses of methotrexate hCG level unaltered

She then received combination chemotherapy with

etoposide methotrexate actinomycin D cyclophosphamide

hCG persistently elevated

She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy—negative results, hCG remained unchanged

PET scan: suggested a metastatic lesion in the lung with an enlarged left lymph node

Thoracotomy and lymph node excision---negative

Similar cases have been reported

- **Olsen TG,et al: Falsely elevated human hCG leading to unnecessary therapy.**

Obst Gynecol 2001;98:843

- **A similar case at University of Washington resulting in a 16 million dollars law suit**

Braunstein GD: False-positive serum hCG results

causes, characteristics, & recognition

Am J Obstet Gynecol 2002;187:217

U of California, Cedars-Sinai Medical Center

An IgM lambda antibody to E. Coli produces false-positive results in multiple immunometric assays

covinsky M,etal:Clin Chem46:2000

Washington University

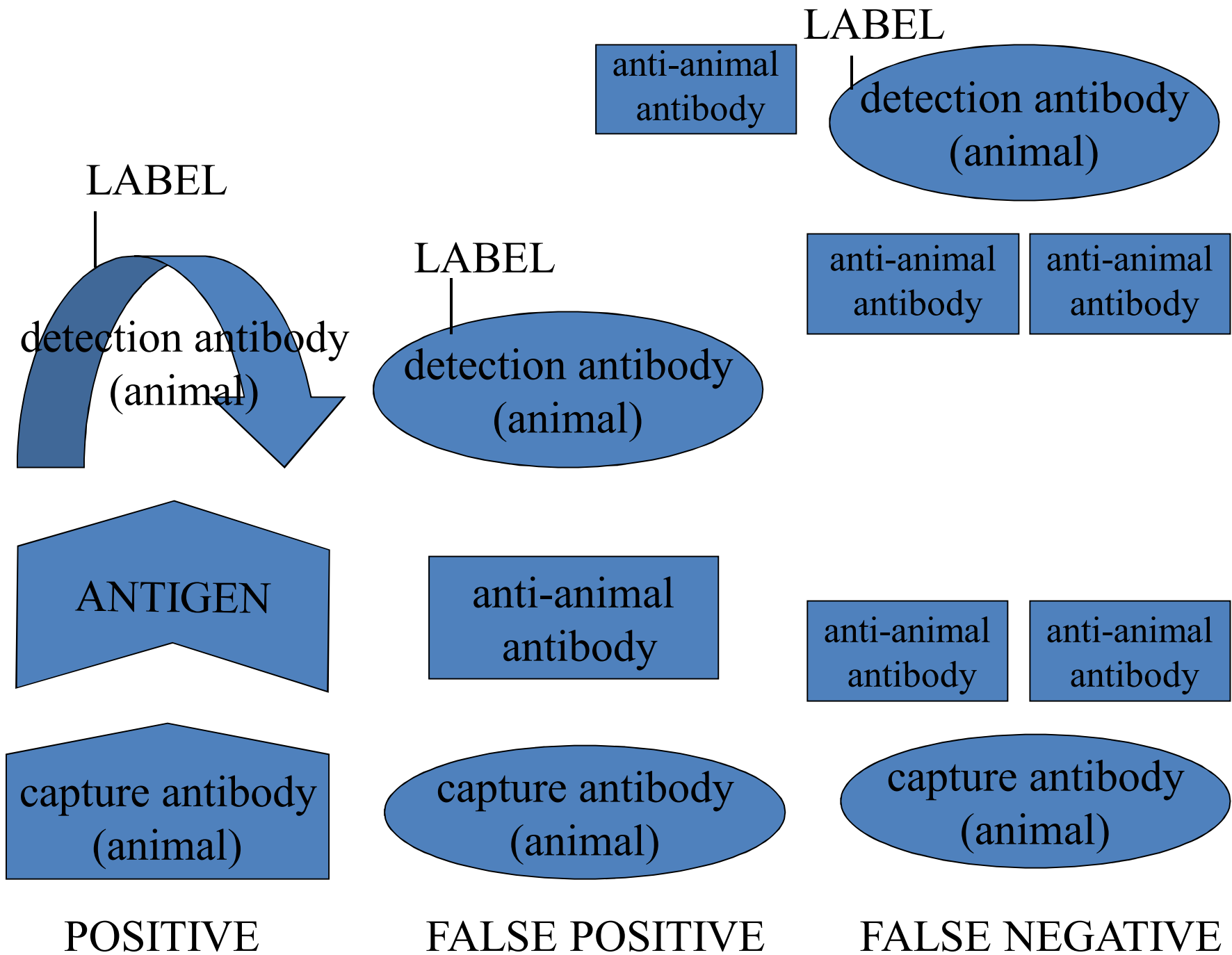
- ***A 56 year-old white male was admitted to the hospital because of urethral obstruction due to BPH. His hospital course was complicated with E.coli septicemia. On the 3rd day of hospitalization, a cardiac Troponin I was ordered because the pt complained of jaw pain. The result was 235 ug/L***

Effect on other immunometric assays

| <i>assay</i> | <i>untreated</i> | <i>Incubated with killed E.coli</i> |
|-------------------|------------------|-------------------------------------|
| <i>Troponin I</i> | <i>235ug/L</i> | <i>6 ug/L</i> |
| <i>TSH</i> | <i>14 IU/L</i> | <i>1.8IU/L</i> |
| <i>AFP</i> | <i>41</i> | <i>6 ug/L</i> |
| <i>CA-125</i> | <i>225 ug/L</i> | <i>17 ug?l</i> |
| <i>hCG</i> | <i>17 IU/L</i> | <i>< 5 IU/L</i> |

Heterophil Antibodies

- 1. *Definition:*
- 2. *May arise as a consequence of intimal contact, either intentional or unintentional, with animals*
Antigenic reactions are triggered by close proximity to the animal species concerned, either by handling, inhalation of fur or other cutaneous products.
- 3. *May arise by the injection of monoclonal antibody that are used as vehicle to target tumors, either for visualization or chemotherapy.*



Confirmation of interference

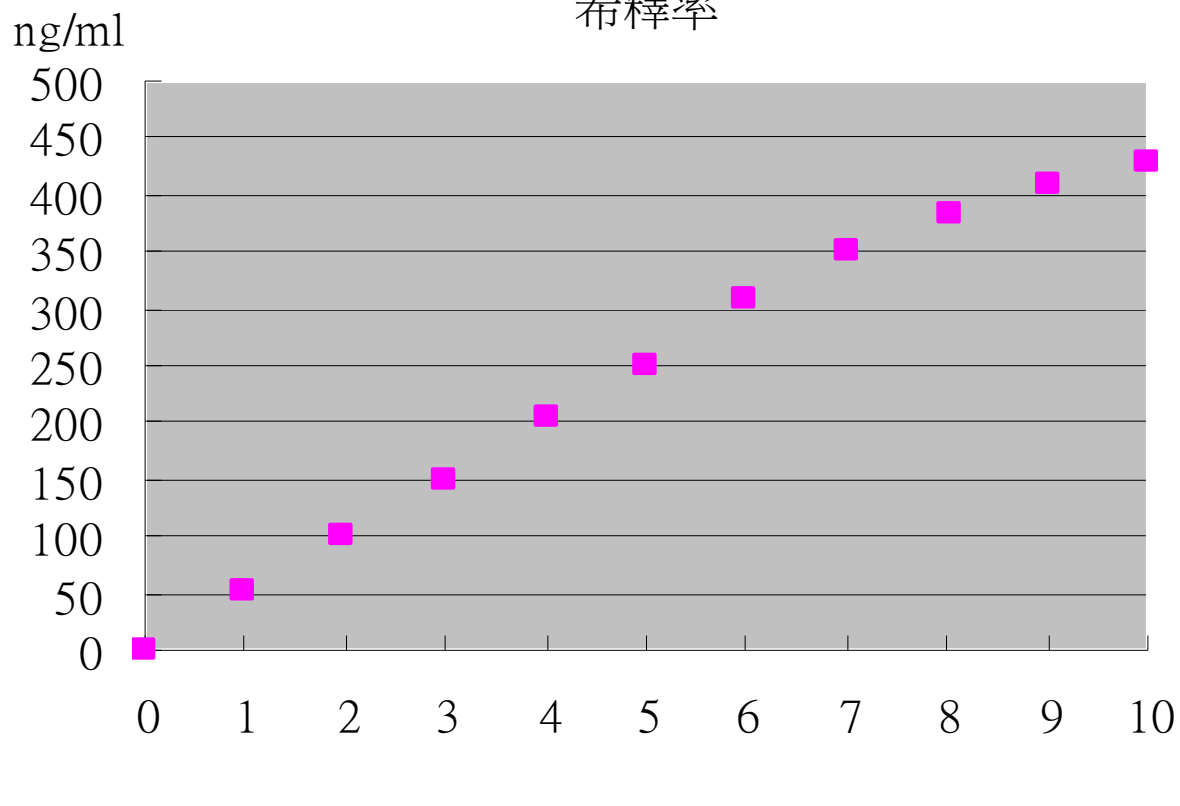
suspicion of interference should be raised when the test results disagree with the clinical presentation

- **1. Test the same sample with a different method.**
- **2. Dilution tests.**
- **3. Attempt to identify the antibody, and remove it, if present.
then, repeat the test.**
- **4. In case of hCG, analyze the serum and urine sample simultaneously.**

項目:AFP
 機種:Axsym
 檢體1:High unit serum
 試藥:Abbott Reagent
 備考:MEIA Method

解決辦法

希釋率



檢體:

| | 0/10 | 1/10 | 2/10 | 3/10 | 4/10 | 5/10 | 6/10 | 7/10 | 8/10 | 9/10 | 10/10 |
|-----------|------|-------|-------|------|------|-------|-------|------|-------|-------|-------|
| 0 | 0 | 49.5 | 98 | 146 | 205 | 255 | 312 | 348 | 389 | 415 | 432 |
| 0 | 0 | 51.6 | 103 | 152 | 201 | 248 | 305 | 352 | 378 | 400 | 427 |
| 0 average | 0 | 50.55 | 100.5 | 149 | 203 | 251.5 | 308.5 | 350 | 383.5 | 407.5 | 429.5 |

The Clinical Impacts

- ✓ **1. Misdiagnosis leading to unnecessary therapy.**
- ✓ **2. Inappropriate diagnostic intervention, wasting enormous amount of medical resources.**
- ✓ **3. Inappropriate treatment.**
- ✓ **4. Malpractice law suit.**

累了一小時了休息吧！



謝謝！

