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UNIVERSITÀ DEGLI STUDI DI MILANO

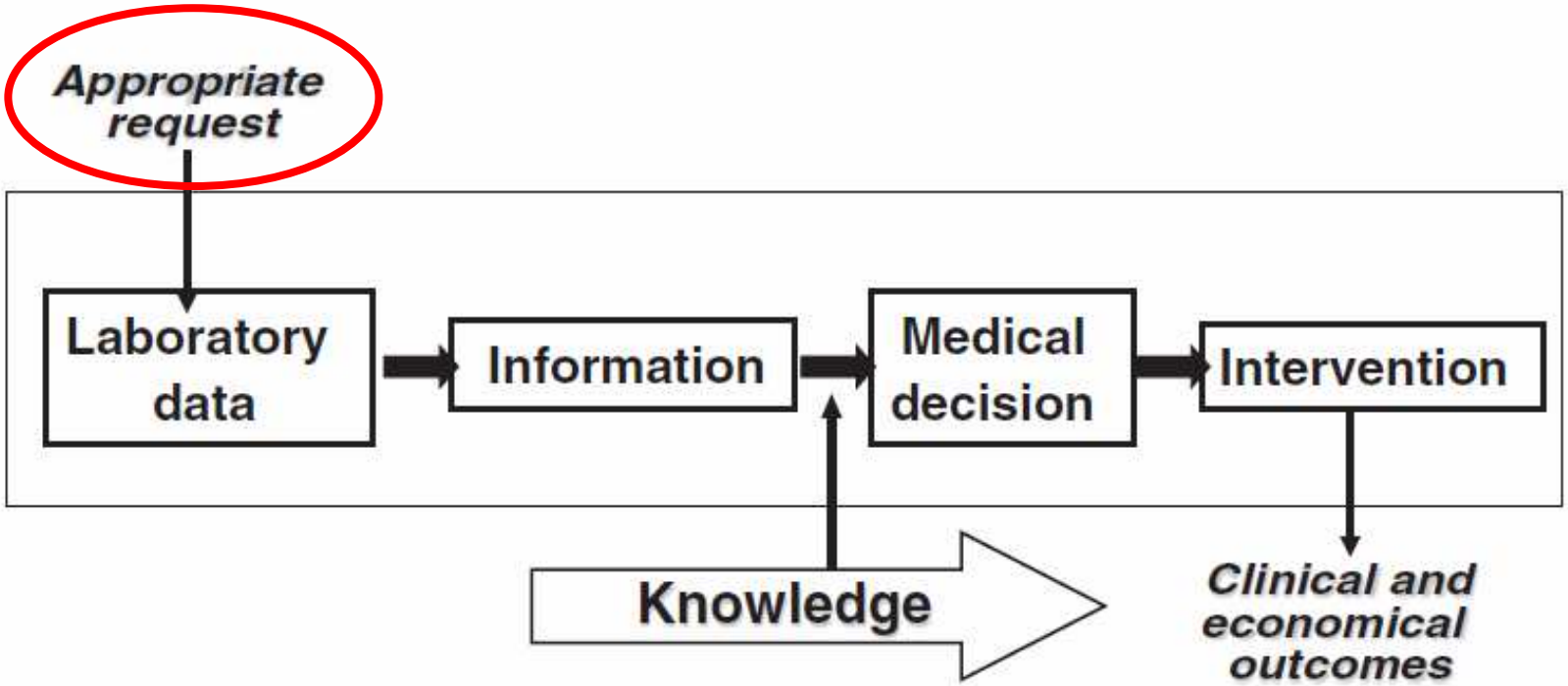
Practical approaches to improve appropriateness of test request

Simona Ferraro

UOC Patologia Clinica,
ASST Fatebenefratelli-Sacco, Milano

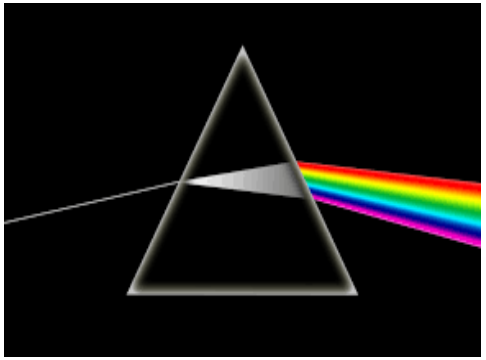
AGENDA

- Definitions
- Reasons for appropriate ordering
- Types of interventions and their application
- Position of guidelines & clinical pathways
- Examples



The appropriate request starts the loop of laboratory testing, in which a laboratory result should enable a decision to be made, which leads to an action being taken, yielding an improved clinical and economic outcome for the patient

Plebani M & Panteghini M, Clinica Chimica Acta 432 (2014) 15.



Appropriateness of test request: The dark side of the moon

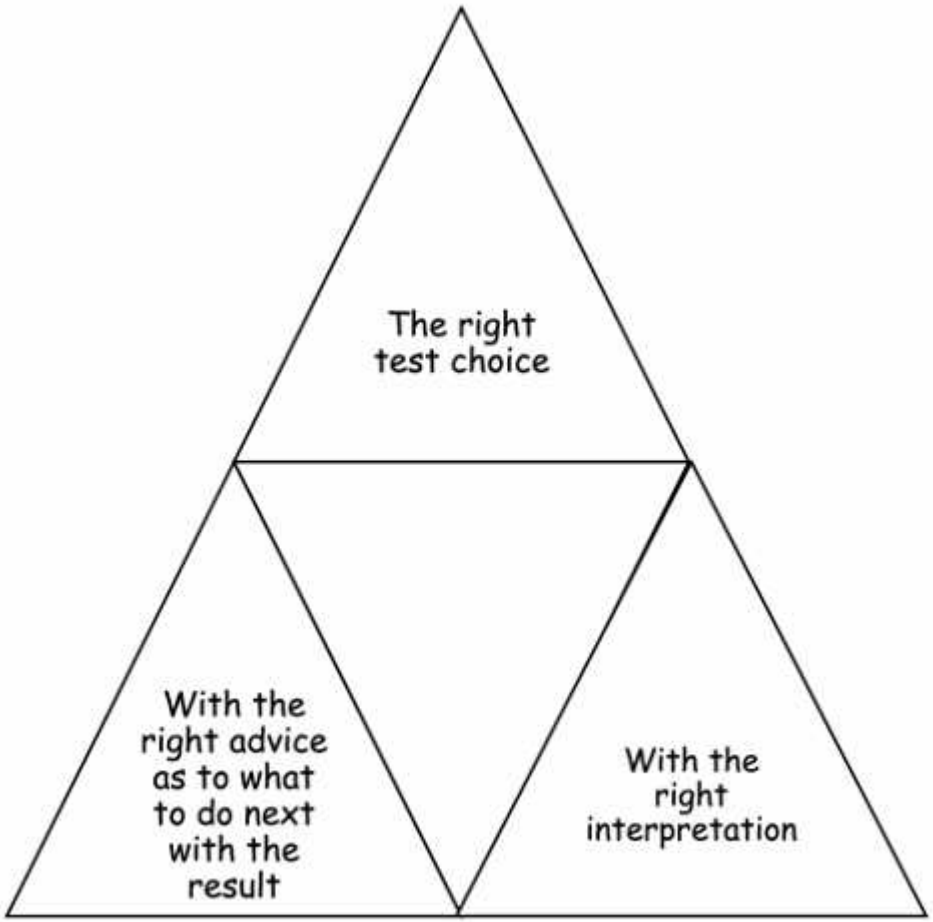


Fig. 1. The triad of elements of value in laboratory information.

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Ferraro S & Panteghini M. Clinical Biochemistry 50 (2017) 555–561

Review

The role of laboratory in ensuring appropriate test requests

Simona Ferraro[a,*], Mauro Panteghini

MAIN QUESTIONS

How can we define inappropriate test?

What is the prevalence of inappropriate testing?

How we can reduce the rate of inappropriate test requests?

DEFINITIONS

Appropriate ordering

Doing the right test in the right clinical context

The delivered benefit to the patient exceeds the delivered harm

Inappropriate ordering

Violation of a guideline produced by a government or professional body

Reasons for pursuing the appropriateness of laboratory test requests

Primary endpoint: Improve clinical effectiveness and patient outcome

Primary aim: Reduce the potential for diagnostic errors

Secondary aim: Reduce costs *without* compromising the quality of testing and of related information

Actions:

- ✓Reduce overuse (inappropriate requests)
- ✓Reduce underuse (appropriate request not performed)
- ✓Reduce misuse

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EVERY DAY IS PATIENT SAFETY DAY

Lab-related causes of diagnostic mistakes

- Inappropriate test requested — **Overuse**
- Appropriate test not requested — **Underuse**
- Appropriate test result inaccurate
- Appropriate test result not used properly
  - Knowledge deficit
  - Failure of synthesis (no results integration)
  - Misleading result (unaware of test limitations)

  Misuse
- Appropriate test result delayed/missed

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Adapted from Epner PL et al. BMJ Qual Saf 2013;22:ii6
and Chassin MR & Galvin RW. JAMA 1998;280:1000

Rates of inappropriate testing

Characteristic	Error rate (95% CI)	Difference (95% CI)	n
Subgroup			
Overutilization	20.6 (16.2, 24.9)	(reference)	114
Underutilization	44.8 (33.8, 55.8)	24.2 (12.5, 36.0)	18
Overutilization			
Initial testing	43.9 (35.4, 52.5)	(reference)	18
Repeat testing	7.4 (2.5, 12.3)	−36.5 (−46.4, −26.7)	55
Both	28.0 (22.2, 33.8)	−15.9 (−5.6, −26.3)	41

Zhi M et al. PLoS ONE 2013;8:e78962.

General surgery requesting

38% of all requests from the Dept of Surgery were for panels of ≥4 tumour markers

53% of all requests from the surgical wards were for panels of ≥4 tumour markers

33% of CA125 requests were for male patients

Identified from LIS over 8 months at the University Hospital of Wales – before implementation of local guidance. D Schulenburg-Brand, N Kumar & S Zouwail. Ann Clin Biochem 2013;50:438

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2012 UK National Audit of Tumour Marker Service Provision

What are the most common reasons for rejecting tumour marker requests in your laboratory?

Panel of markers requested	**41%**
CA125 in males	**33%**
Retesting – too soon	**26%**

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Types of interventions to improve appropriateness in test request.

- Developing and disseminating practice care maps (agreed in partnership with clinicians)
- Using the Health Technology Assessment (HTA) approach when guidelines are lacking
- Deleting obsolete tests from laboratory order forms
- Avoiding pathophysiologic duplications and implementing reflex testing
- Applying gating policies and "traffic light" systems (particularly for complex and costly tests)
- Restricting retesting by applying minimum retesting intervals

Ferraro S & Panteghini M. Clinical Biochemistry 50 (2017) 555–561

Pursuing appropriateness of test request in our laboratory

Reflex testing and algorithms (PSA, Bilirubin, ALT, TSH, others)

Periodicity of retesting (e.g. folate/B12 every 6 months, CRP/PCT, D-dimer every 24 h, GGT every 36 h, etc.)

Rules within Computerized Provider Order Entry (CPOE)

Restriction of test request (e.g. procalcitonin)

Implementing local recommendations (e.g. tumor markers, cardiac markers, etc.)

Implementing appropriate assays and differentiating their clinical application (hCG+ hCGβ for oncology/intact hCG for pregnancy)

@ Clinical-Laboratory interface

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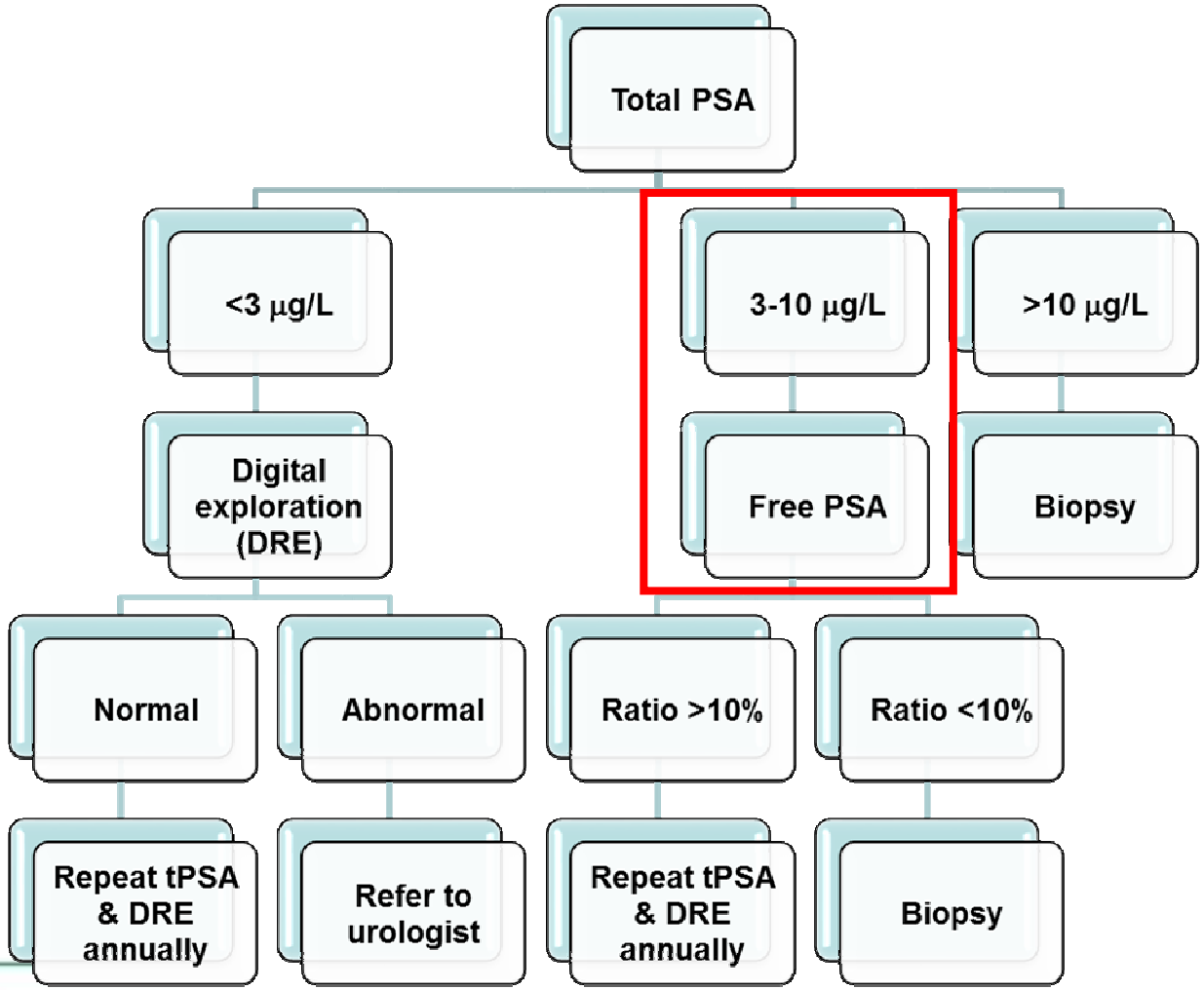
PSA reflex testing

- ✓ **Guidelines recommend the determination of free PSA only when the total PSA concentrations in serum ranges between 3 and 10 μg/L to differentiate benign hyperplasia from prostate cancer.**
- ✓ **By auditing free PSA requests in our institution, in 2006 we reported that only 15% of those complied with this recommendation, with an economic waste for the NHS of ~50,000 € per year.**
- ✓ **This supported the activation of a reflex testing allowing free PSA determination only when total PSA is within the recommended range and labelling as inappropriate the free PSA requests in samples with total PSA exceeding the limits of the recommended interval.**

Investigational algorithm for prostatic cancer



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Ferraro S, Panteghini M. Clin Biochem 2017;50:555

Check for appropriateness of free PSA requests

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Università degli Studi di Milano

DIPARTIMENTO MEDICINA di LABORATORIO
UOC PATOLOGIA CLINICA (LABORATORIO ANALISI CHIMICO-CLINICHE)
Via G.B. Grassi 74 - 20157 MILANO
Telefono (+39) 02.3904.2483 Fax (+39) 02.3904.2896 mail:segreteria.biochimica@hsacco.it
Direttore: Prof. Mauro Panteghini

Determinazione	Risultato	Unità	Limiti di riferimento
INDICATORI BIOCHIMICI DI NEOPLASIA			
S-Antigene prostata specifico (PSA) totale	**0,9**	µg/L	Fino a 3,2 Dopo prostatectomia radicale: <0,01
S-Antigene prostata specifico (PSA) libero	**Richiesta inappropriata**		

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Procalcitonin restricted policy

- PCT can be ordered by ICU as an aid in decision for continuing or stopping of antibiotics
- PCT can be ordered in pediatrics [e.g. neonates with suspected (late-onset) sepsis or children with suspected meningitis]
- For all other clinical wards, PCT requests have to be preventively approved by laboratory specialists, who should be contacted by phone by clinical requestors to discuss about the clinical suspicion supporting the PCT request in addition to other already available tests (e.g., C-reactive protein).

Building local recommendations and taking actions: examples

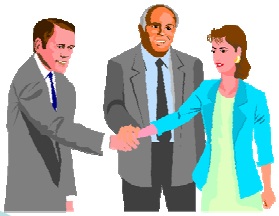
Control tumor marker requests by local consensus pathways (based on internatl/natl guidelines)
→ phone call for abnormal request discussion

Control folate/B12 requests and retesting by local guidelines & documents (based on HTA approach)
→ CPOE

HCG for cancer diagnosis/monitoring vs. pregnancy → Implementation of appropriate assays and differentiation of their application
→ phone call for request management

SYSTEMATIC SEARCH OF SCIENTIFIC EVIDENCE

GUIDELINES
(recommendation for care)



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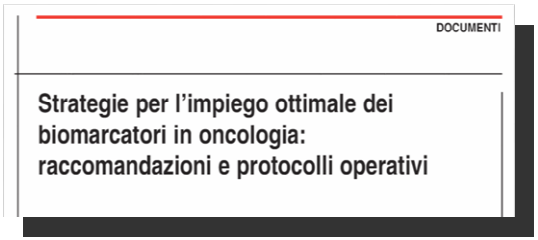
CARE MAPS/CLINICAL PATHWAYS
(efficiency of care)



OUTCOMES
(efficacy of care)

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Panteghini M et al, Biochim Clin 2005;29:419-28

General concepts and main outcomes supporting local recommendations for the correct use of tumor markers

Basic concepts

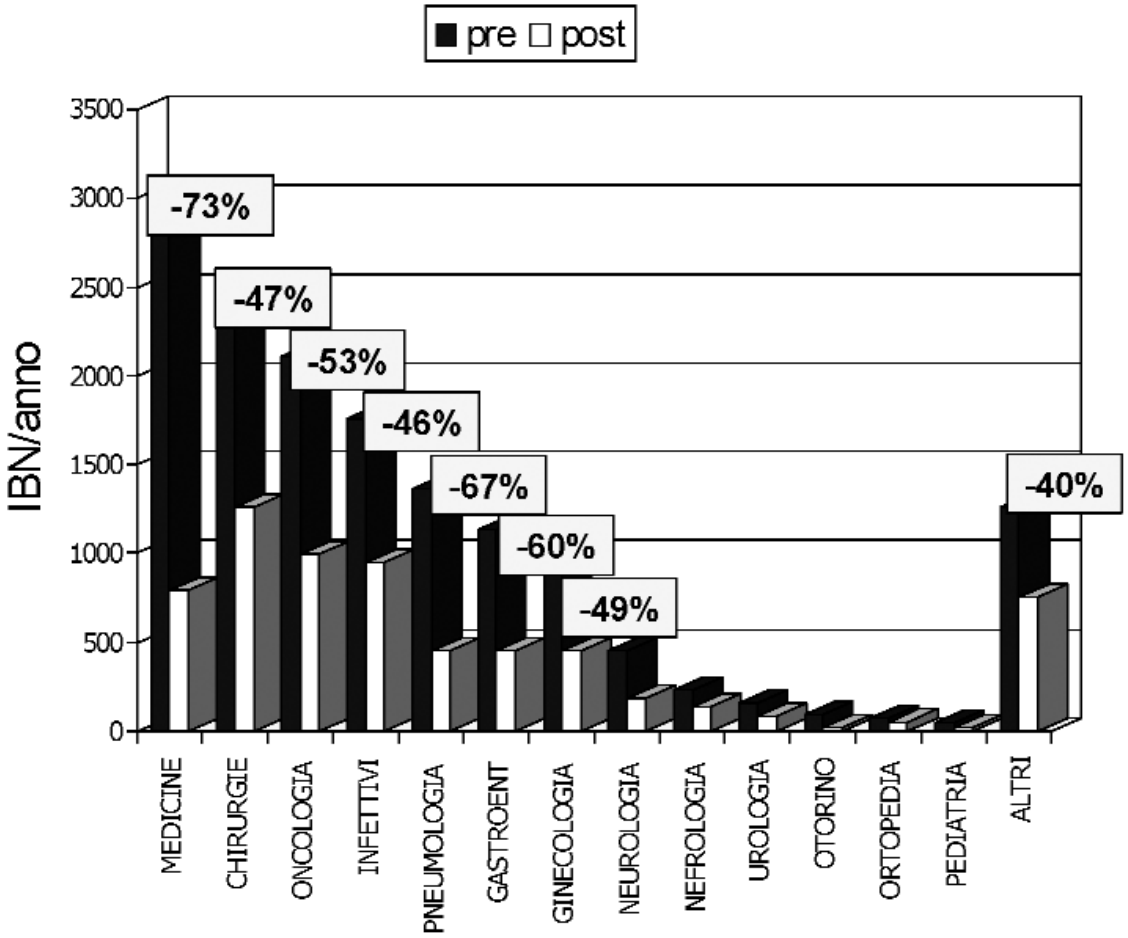
- With few exceptions, TMs should not be requested and used for diagnostic purposes
- When appropriately used, TMs may provide relevant information on treatment efficacy and on residual disease after treatment
- In general, organ-appropriate TMs exist and one TM is enough for disease evaluation and monitoring

Main outcomes

- To homogenise the possible clinical benefits associated to the TMs request
- To decrease the rate of inappropriateness of TMs request (e.g., requests performed for tumour diagnosis or use of TMs not recommended for specific tumours)
- To decrease costs both direct and indirect, i.e., economic and social, associated with the TMs inappropriate use, with consequent better rationalization of resources.

Ferraro S, Panteghini M. Clin Biochem 2017;50:555

Implementing recommendations on correct use of tumor markers largely decrease the number of ordered tests, without any impact on clinical outcome



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Dolci A et al. biochimica clinica, 2008, vol. 32, n. 3 181.

Tumor Marker Ordering: Do Not Lose Control

A Prospective Clinical Trial

Simona Ferraro, BSc, Roberta Mozzi, MD, and Mauro Panteghini, MD

From the Clinical Pathology Unit, 'Luigi Sacco' University Hospital, and Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy.

Key Words: Tumor markers; Test request; Appropriateness; Diagnosis; Efficacy

Am J Clin Pathol October 2015;144:649-658

Objectives: *In this study, we evaluated the extent of inappropriate tumor marker (TM) ordering in a secondary care setting, approximately 6 years after the introduction of local guidelines, and we identified the main factors potentially influencing clinicians when performing an inappropriate TM request.*

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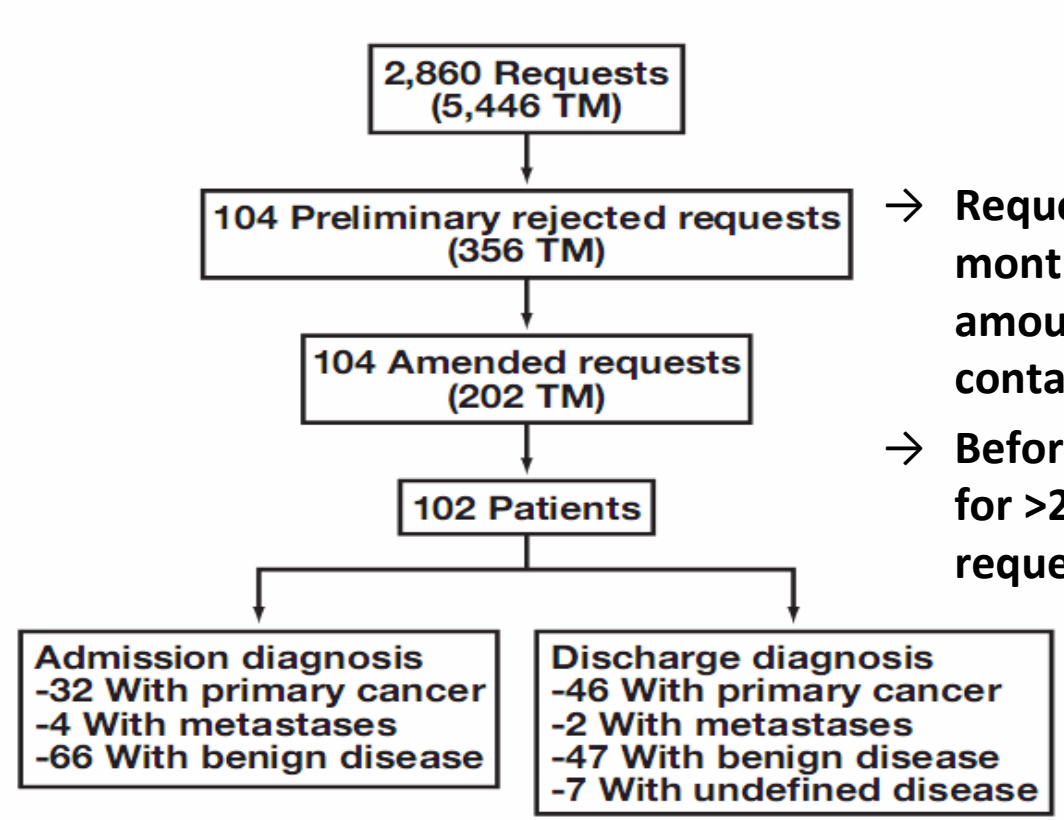
In general, we recommend that one TM is usually enough for disease management, and thus we established that no more than two different TMs should be requested in the same transaction.



→ **Requests containing >2 TMs. During the 21-month audit, the rate of rejected requests amounted to 3.6%. Each blocked request contained a median of 3 TMs (up to 7).**

→ **Before making any decision, orders asking for >2 TMs were always discussed with the requesting clinicians.**

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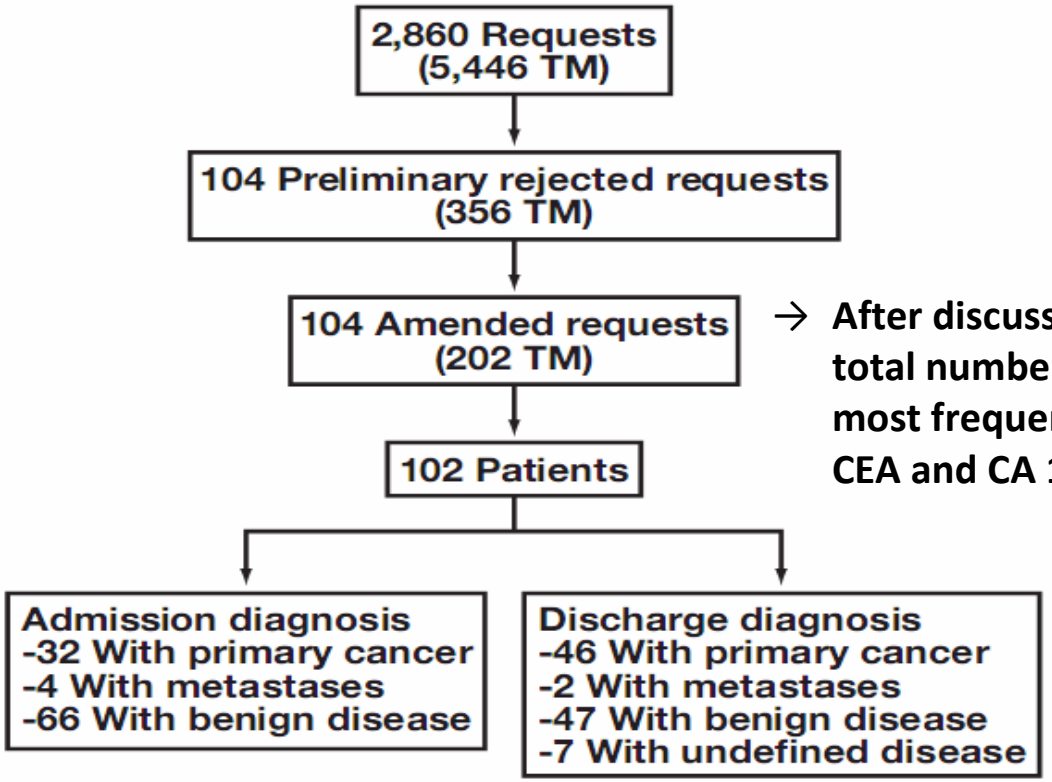

→ **After discussion with requesting clinicians, the agreed total number of TM requests decreased of –43.3%. The most frequent and inappropriate requested TMs were CEA and CA 19.9.**

Numbers and Results of Tumor Markers (TMs) Present in the Automatically Blocked Requests Before and After the Discussion With Clinicians[a]

Characteristic	CEA	CA 19.9	AFP	CA 125	CA 15.3	PSA	NSE	CYFRA 21.1	SCCA	CgA	β-hCG
No. of TMs as recorded in the rejected requests	95	66	57	36	29	29	22	8	7	5	3
No. of TMs in the reviewed requests	71	43	20	17	15	16	12	6	0	1	1
Achieved reduction, %	–25.3	–34.8	–64.9	–52.8	–48.3	–44.8	–42.9	–25.0	–100	–80.0	–66.7
Median (25th-75th percentiles) results of measured TMs after the request revision	1.3 (2.6-4.2) µg/L	18 (5-102.5) kU/L	3 (2-4.5) µg/L	16 (11-25) kU/L	24 (17-34.5) kU/L	1.6 (0.5-2.8) µg/L	14.5 (11-22) µg/L	2.1 (1.4-8.8) µg/L		120 µg/L	<0.1 U/L
No. (%) of positive results	17 (23.9)	16 (37.2)	3 (15)	4 (23.5)	5 (33.3)	4 (25)	4 (33.3)	2 (33.3)		1 (100)	0 (0)

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Tumor Marker Ordering: Do Not Lose Control

A Prospective Clinical Trial

Simona Ferraro, BSc, Roberta Mozzi, MD, and Mauro Panteghini, MD

From the Clinical Pathology Unit, 'Luigi Sacco' University Hospital, and Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy.

Key Words: Tumor markers; Test request; Appropriateness; Diagnosis; Efficacy

Am J Clin Pathol October 2015;144:649-658

Results: *The inappropriateness of requests appeared to be linked to the need for more education and knowledge on their clinical applicability and limitations. The clinical motivation was generally associated with patients displaying nonspecific signs/symptoms (ie, weight loss with worsening general conditions), having an incidentally positive result to some recently performed TM tests, or being tested by a TM to avoid more expensive diagnostic imaging procedures.*

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Impact and dimension of TM inappropriateness

- The new cases of tumors per year in Milan are 7,846.
- The total number of tumors amounts to 62,832.
- If we subtract the number of incident from prevalent cases, we obtain the number of patients (~55,000) who could potentially be tested twice per year for monitoring by using preferentially a single TM, as reported in current guidelines.

- Accordingly, the total number of expected TM tests per year in Milan should be around 110,000 plus approximately 16,000 (7,846 × 2) needed to accurately establish the baseline TM values in newly diagnosed subjects for following up the disease.
- By comparing the expected total number of TM determinations per year (~126,000) with the number of TMs actually performed in clinical laboratories of Milan (~350,000), we can roughly estimate that performed TM tests currently exceed the justified ones by approximately 3-fold.

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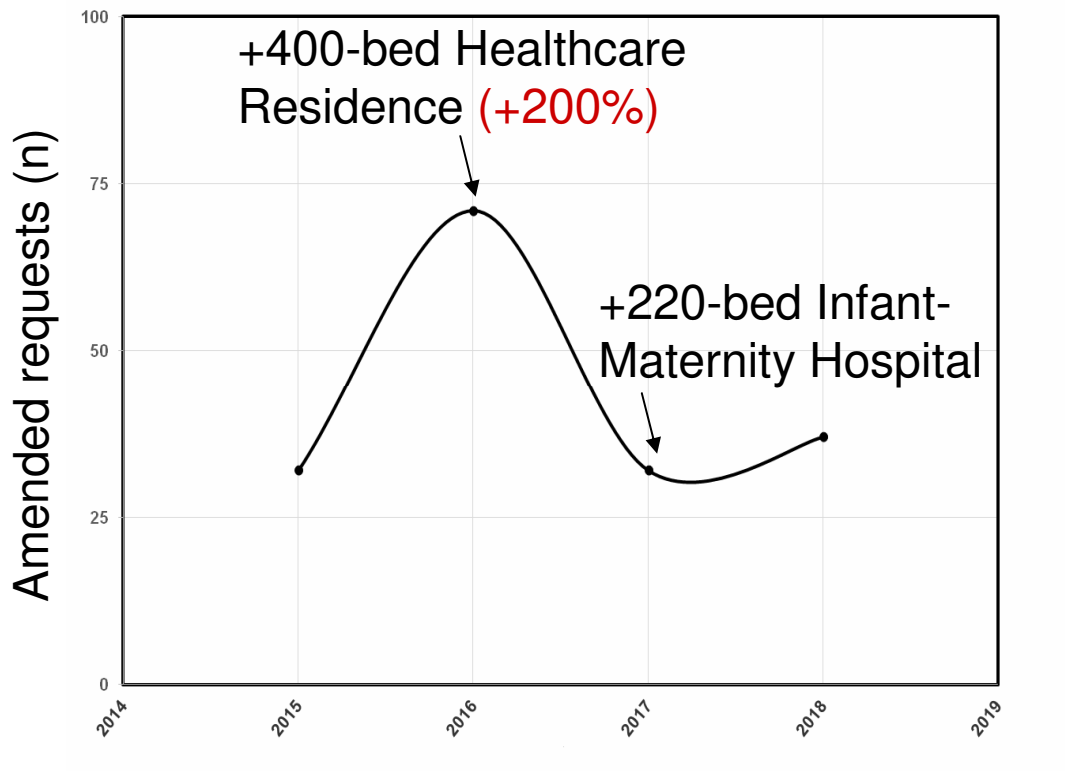
Ferraro S et al. Am J Clin Pathol 2015;144:649

Continuing to pursue appropriateness of tumor marker requests after the acquisition of other hospitals



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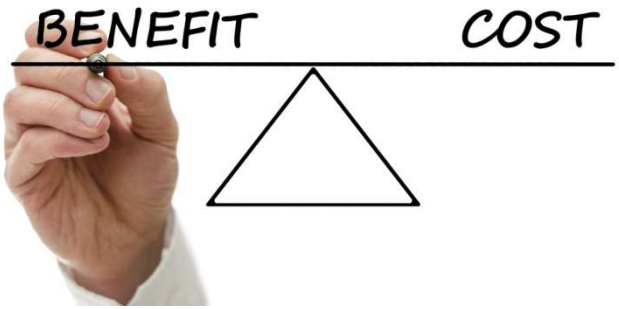
When using HTA approach?



No Guidelines
No EBM indications

High rate of test requests
Budget restriction

Action: curbing test request

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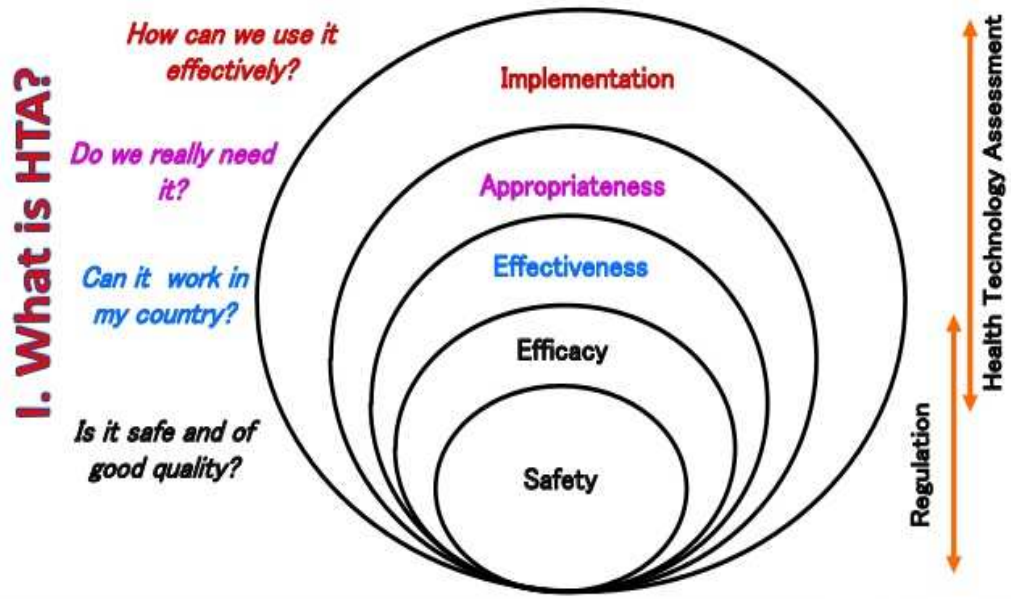
HTA Reasoning

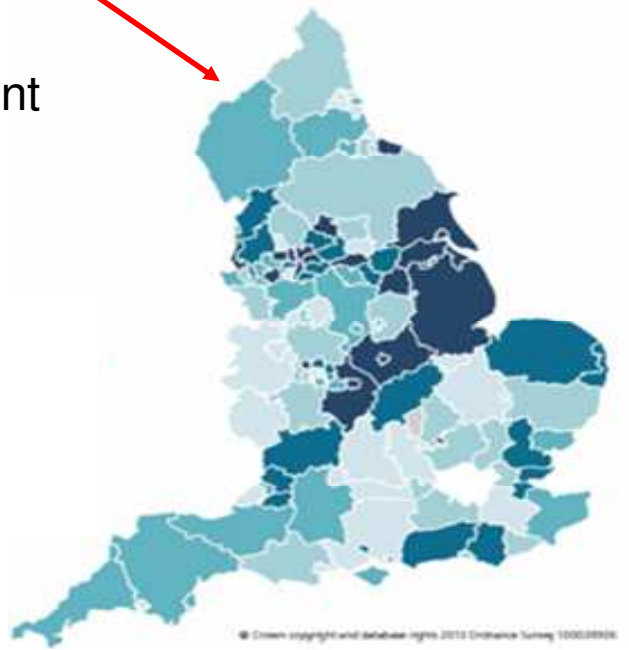


HTA Core Model DOMAINS
1. Health problem and current use of technology
2. Description and technical characteristics
3. Safety
4. Clinical effectiveness
5. Costs and economic evaluation
6. Ethical analysis
7. Organisational aspects
8. Patient and social aspects
9. Legal aspects

B12: an (unexpected) diagnostic challenge

- Laboratories have determined B_{12} status using serum B_{12} test for 50 years, yet:
  - large variation in annual rate of use of test: from 1.8 to 131.3 by GPs per 1000 practice population in UK (2012)
  - delayed diagnosis for a proportion of B_{12} deficient patients
  - burden on healthcare system includes time, multiple consultations, repeat laboratory tests

NHS Atlas of Variation in Diagnostic Services



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Our laboratory B12 workload

Audit

The current workload in our laboratory is ~5,000 B12 tests per year.

Marker distribution

By considering the reference interval of B12 assay in use by our laboratory (Roche Modular EVO system: 190–665 ng/L), we may report the percentage of test results for marker concentrations as follows: <190 ng/L (6.8%), 190–665 ng/L (74.7%), 666–2000 ng/L (17.4%) and >2000 ng/L (0.1%).

Reasons for request

As 92.2% of tested subjects exhibited physiologic or elevated B12 concentrations, it can be assumed that the test is mostly used to screen for vitamin deficiency or in subjects undergoing cobalamin supplementation.

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Ferraro S et al. Clin Chem Lab Med 2014;52:767

Searching for recommendations

No guidelines have been released by the Hematology Societies.

- **The *American Academy of Neurology* recommends the evaluation of serum B12, with MMA, and with or without Hcy, for all patients suspected for polyneuropathy.**

- **The *American Dietetic Association and Dietitians of Canada* and the *Society of Obstetricians and Gynaecologists of Canada* did not report any suggestion about diagnosis of cobalamin deficiency, but only recommendations for B12 intake in categories at risk (e.g. vegetarians and pregnant women, respectively).**

DE GRUYTER DOI 10.1515/cclm-2013-0738 — Clin Chem Lab Med 2014; 52(6): 767–777

Review

Simona Ferraro*, Roberta Mozzi and Mauro Panteghini

Tracing a roadmap for vitamin B_{12} testing using the health technology assessment approach

Table 2 Synopsis of main items to be considered for improving the appropriateness of vitamin B_{12} (B12) testing demand.

- Serum B12 testing has a relatively low capability to exclude vitamin deficiency
- Distinguishing subjects with normal and cobalamin-deficient conditions by a single threshold level of serum B12 concentrations (e.g., the lower reference limit) can be clinically misleading
- The knowledge of analytical issues as well as the introduction on the market of harmonized immunoassays are mandatory to reliably improve the identification of cobalamin deficiency
- According to ethical concerns and association with adverse outcome occurrences, hemodialysis patients and pregnant women have emerged as those groups preferentially requiring B12 testing

Interpret B12 test results in terms of 'risk for deficiency':

<100 ng/L, probable B12 deficiency, needing immediate supplementation;

<300 ng/L, possible B12 deficiency;

300-400 ng/L, unlikely B12 deficiency;

>400 ng/L, B12 deficiency excluded.

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Clin Chem Lab Med 2017; 55(9): 1262–1275 DE GRUYTER

Review

Simona Ferraro*, Andrea Panzeri and Mauro Panteghini

Tackling serum folate test in European countries within the health technology assessment paradigm: request appropriateness, assays and health outcomes

The cost-effectiveness of the test is maximized when the request is oriented to subjects suggestive/at risk for deficiency, becoming low if the test is used as a screening tool or for monitoring of vitamin intake/supplementation. Because the individual folate status has a key role in ensuring normal development, physiologic growth and maintenance of optimal health, the evaluation of its serum levels has to be retained in the clinical use in non-fortified countries, boosting for more appropriate request, and evidence from countries following fortification policies should be cautionary interpreted.

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The serum folate test is inappropriately ordered when:

a) there is no specific risk condition/suspicion for folate deficiency/inadequate status;

b) the subject is undergoing or has recently undergone folic acid supplementation;

c) retesting at 3–6 months to evaluate the actual correction of the deficit after intake discontinuation.

By applying these recommendations on the current folate testing strategy applied in our institution, we can estimate a ~50% saving in laboratory costs.

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Ferraro S et al. Clin Chem Lab Med 2017;55:1262

The problem of the heterogeneity of guideline recommendations

Tumor Marker	Tumor Origin	Clinical Scenario					
		Screening	Differential Diagnosis	Initial Workup	Response to Treatment	Disease Progression	Disease Monitoring
CA 19.9	Gastric	NA	NA	NA	NA	NA	NA
	Colorectal	No	No	No	NA	No	No
	Ovarian (mucinous)	NA	NA	NA	NA	NA	NA
	Pancreatic	No	Yes/no[c]	Yes/no[d]	Yes	Yes	Yes
	Biliary tract	No	No	Yes	NA	NA	NA
	Bladder	NA	NA	NA	NA	NA	NA
CA 15.3	Breast	No	No	Yes/no[e]	No	No	Yes/no[f]
CA 125	Ovarian (serous)	Yes/no[g]	Yes	Yes	Yes	Yes	Yes
PSA	Prostatic	No	Yes	Yes	Yes	Yes	Yes
CEA	Gastric	NA	NA	NA	NA	NA	NA
	Colorectal	No	No	Yes/no[h]	NA	Yes	Yes
	Breast	No	No	Yes/no[e]	No	No	Yes/no[i]
	Pancreatic	No	No	No	No	Yes/no[j]	Yes/no[j]
	Lung	No	No	No	No	No	No
	Biliary tract	No	No	Yes	No	No	No
AFP	Ovarian (nonepithelial)	No	Yes (<40 y)	Yes	Yes	Yes	Yes
	Liver	Yes	Yes	Yes	NA	Yes	NA
	Testicular	NA	Yes	Yes	Yes	Yes	Yes
SCCA	Cervical	No	No	Yes	NA	Yes/no[k]	NA
	Pharynx (squamous)	No	No	No	No	No	No
NSE	Lung (small cell)	No	No	No	No	No	No
CYFRA 21.1	Lung (squamous)	No	No	No	No	No	No
CgA	Gastrointestinal (neuroen	No	Yes	Yes	NA	Yes	Yes
β-hCG	Ovarian (choriocarcinoma	No	Yes	Yes	Yes	Yes	Yes
	Testicular	NA	Yes	Yes	Yes	Yes	Yes

[g] Yes—for high-risk patients and together with transvaginal echography (NACB)/no (ECOG, AIOM, NCCN, SIGN, NACB, ACOG).

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Guidelines aim to achieve the “right balance”

Hazards of under-testing

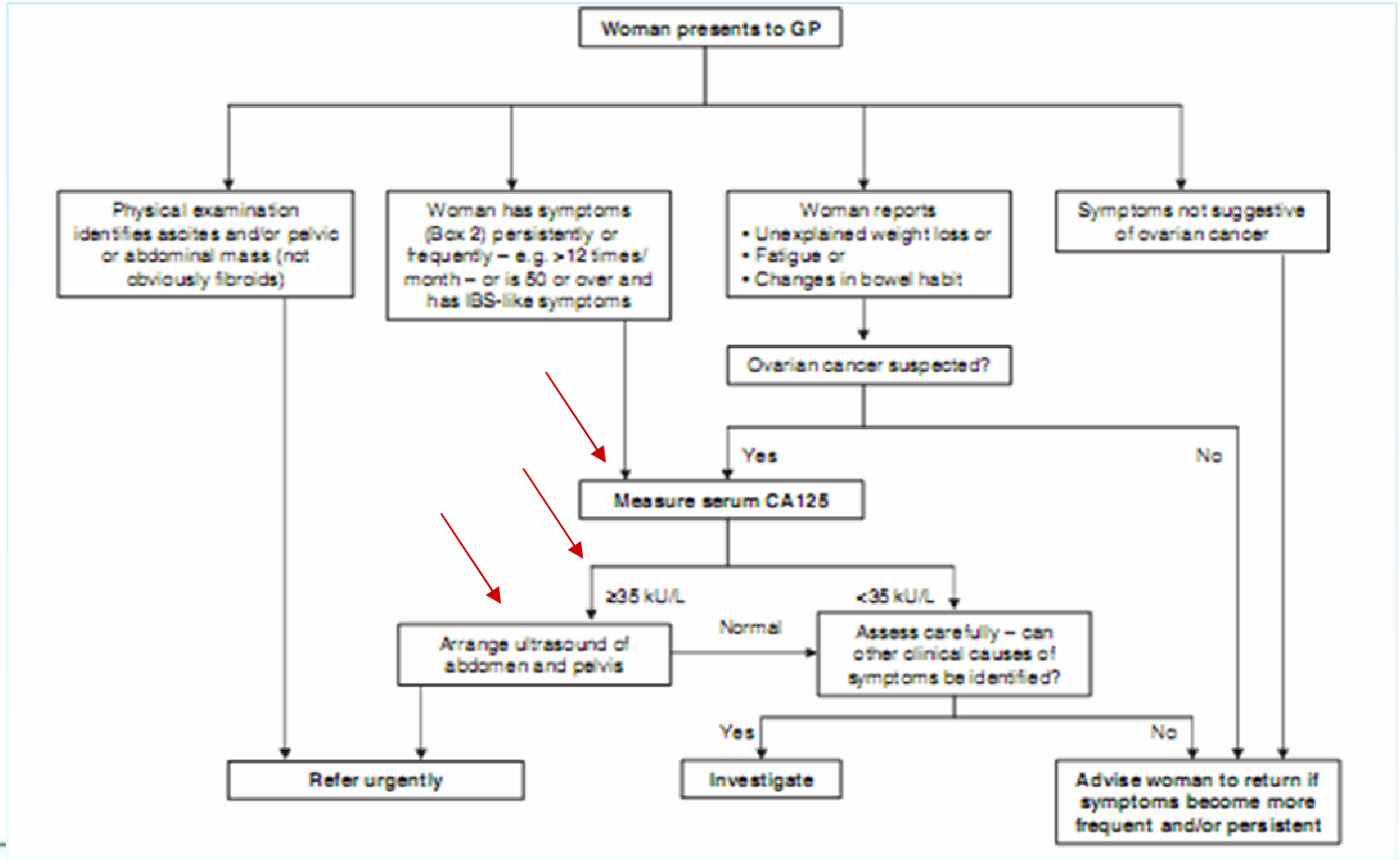
- Failure to identify disease (or recurrence) early enough to enable effective treatment
- Lack of consistency in health care provision

Hazards of over-testing

- Additional investigations due to false-positive results
- Complications of diagnosis and/or treatment
- Psychosocial effects of the test itself

Strategy for ovarian cancer detection 2011

National Institute for Health and Clinical Excellence



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Requirement of an OvCa screening strategy

- According to gynaecological oncologist expectations, the test must have a minimum PPV of 10% (i.e., no more than 9 false positives for each true positive).
- To achieve this in post-menopausal women, the screening test must have a sensitivity of >75% and specificity of >99.6%.

CA125

Ferraro S et al. J Clin Pathol 2013;66:273.

Predictive values of CA125 for the diagnosis of OvCa in women presenting with symptoms to primary care

[estimated disease prevalence in primary care, 0.23%]

Cutoff value	NPV	PPV
35 kU/L	99.9%	<1%

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UK audit of effectiveness of NICE guidelines

Frimley Park & St George's
- CA125 requests increased by 34% post-NICE guidelines
- e-records suggest that 16 patients with CA125 >35 kU/L were not investigated further

University Hospital Coventry
- CA125 requests increased by 130% post-NICE guidelines
- 10% of primary care requests inappropriate – asymptomatic women

Whiston Hospital
- CA125 requests increased by 80% post-NICE guidelines
- 24% of primary care requests inappropriate and 13% had no clinical details

Leeds Teaching Hospitals
- Majority of GP patients with CA125 >35 kU/L are being managed appropriately
- Positive predictive value 20x higher than expected

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Still unanswered questions

- How well are the NICE guidelines being followed in routine practice?
- Are women with OvCa seen by gynae-oncologists more quickly?
- Has the proportion of women with curable Stage I cancers increased?

Further careful audit is required

Further issue: How to manage TM requests for mixed OvCa?

Ovarian cancer: recognition and initial management

Clinical guideline
Published: 27 April 2011
nice.org.uk/guidance/cg122

NICE guideline

1.2 *Establishing the diagnosis in secondary care*

1.2.1 Tumour markers: which to use?

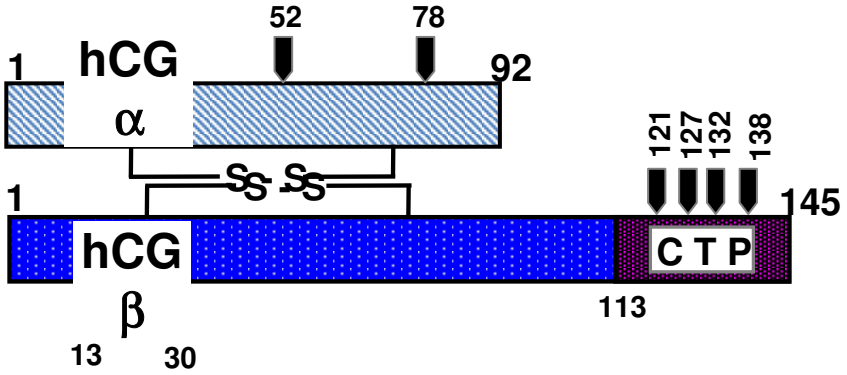
1.2.1.1 Measure serum CA125 in secondary care in all women with suspected ovarian cancer, if this has not already been done in primary care.

1.2.1.2 In women under 40 with suspected ovarian cancer, measure levels of alpha fetoprotein (AFP) and beta human chorionic gonadotrophin (beta-hCG) as well as serum CA125, to identify women who may not have epithelial ovarian cancer.

3/4 MARKERS for rule-in non-epithelial OvCa (prevalence, 10% of all OvCa cancers)!

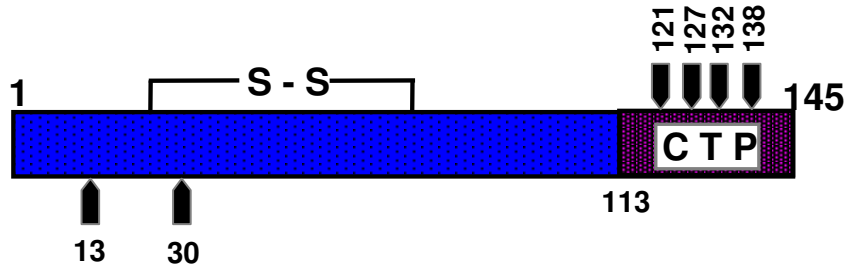
hCG assay methods measure different molecular forms: primarily three types of assays

1



Intact hCG assay

2



Free β-subunit assay

3

'Total' hCG assay – measures intact hCG + free β-subunit

hCG results are often misinterpreted

Clinical Chemistry 54:4
761–764 (2008)

Are Laboratories Reporting Serum Quantitative hCG Results Correctly?

Zhimin (Tim) Cao,[1*] Robert Rej[1,2]

Intact hCG results reported by 22/235 labs (9.3%) registered as using a "total" method

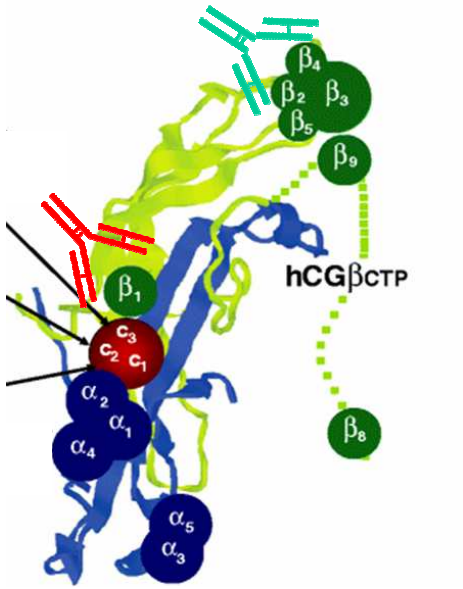
Total hCG results reported by 8/61 labs (13.1%) registered as using an "intact" method

Recommended MAb combinations for immunoassay construction for oncology purposes

Assay specifically recognizing: hCG + hCG β

β_1 capture MAb with β_2 or β_4 detection MAbs

Such assays can be constructed using pairs of MAbs directed against the cystine knot-associated epitope β_1 (Asp10, Asp60, and Gln89) in combination with epitopes β_2 or β_4 located at the top of β loops 1+3 of hCG β



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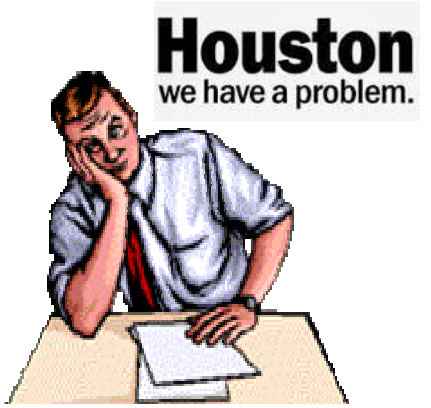
Berger P et al. Tumor Biol 2013;34:4033

hCG assays built on this design are not yet commercially available.



By applying a pragmatic approach, one can recommend *as a minimum requirement for oncology* application the use of an assay characterized by an equal detection of hCG and hCGβ, considering that trophoblastic tumors produce intact hCG and that hCGβ may predominate as well, frequently being the only form in the serum of patients with germ cell tumors, banning in oncology the use of assays not detecting hCGβ.

Ferraro S et al. Clin Chem 2018;64:270

APPLIED STEPS:

1) Identification of suspected inappropriate requests (e.g., intact HCG in post-menopausal age, in males, etc.)

2) Retrieving clinical motivations: call clinician, gynecologist oncologist, oncologist

3) Replacing intact HCG with HCG+β if oncological motivation

→ In two years, 25% of requests have been corrected

The step forward:

Improving appropriateness of TM requests in pediatric oncology

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Rought indications

Table 1. Clinical applications and available pediatric reference intervals for 11 key circulating tumor biomarkers.

Marker	Clinical relevance: Pediatric cancer	Clinical relevance: Adult cancer[a]	Available pediatric reference intervals
AFP	Monitoring of sacroccygeal teratomas [Pauniaho et al. *(3)*]; prognosis of germ cell tumors [Baranzelli et al. *(2)*]	Diagnosis and prognosis of hepatocellular carcinoma patients [Duffy *(30)*]	Reference intervals established by CALIPER using previous generation Abbott Diagnostics AFP assay [Bailey et al. *(9)*]
Anti-Tg	Currently unknown	Monitoring of thyroid disease, including thyroid cancer [Ringel and Nabhan *(36)*]	95th percentile for individuals from birth to 20 years reported [Taubner et al. *(24)*]
CA15-3	Currently unknown	Surveillance of breast cancer patients after diagnosis [Duffy *(30)*]	None reported
CA19-9	Increased in some malignant germ cell tumors and immature teratomas [Lahdenne et al. *(7)*]	Monitoring of pancreatic cancer [Duffy *(30)*]; used, in combination with CEA, in diagnosis and follow-up of colorectal and gastrointestinal cancer patients [Lahdenne and Heikinheimo *(37)*]	Reference intervals available for children birth to 1.5 years [Lahdenne et al. *(7)*]
CA125	Potential to aid in monitoring of patients with sacroccygeal teratomas [Pauniaho et al. *(3)*]; increased concentrations observed in children with non-Hodgkin lymphoma [Kutluk et al. *(38)*]	Used, in combination with HE4, to aid in diagnosis and monitoring of ovarian cancer patients [Li et al. *(4)*]	Reference intervals available for children birth to 1.5 years [Lahdenne et al. *(7)*]
CEA	Currently unknown	Monitoring of colon cancer patients posttreatment [Duffy *(30)*]	None reported
HE4	Currently unknown	Used, in combination with CA125, to aid in diagnosis and monitoring of ovarian cancer patients [Li et al. *(4)*]; potential prognostic factor in lung cancer [Yamashita et al. *(39)*]	None reported
ProGRP	Currently unknown	Monitoring tool for lung cancer patients undergoing treatment and in remission [Yamashita et al. *(39)*]	None reported
SCC	Increased in various skin, esophageal, lung, head, and neck cancers [Torre *(40)*]	Can help determine prognosis for cervical cancer patients [Torre *(40)*]	None reported
Free and total PSA	Currently unknown	Used in prostate cancer screening efforts, prognosis, and monitoring [Duffy *(30)*]	95th percentile of total PSA for individuals aged birth to 18 years reported [Randell et al. *(22)*]

[a] Relates to cancers that typically occur in the adult population, although they may still occur in pediatric patient.

In the absence of guidelines, consensus documents contain indications about the use of tumor markers in pediatrics

Management of Pediatric Malignant Germ Cell Tumors: ICMR Consensus Document

Sandeep Agarwala[1] · Aparajita Mitra[1] · Deepak Bansal[2] · Gauri Kapoor[3] · Tushar Vora[4] · Maya Prasad[4] · Girish Chinnaswamy[4] · Brijesh Arora[4] · Venkatraman Radhakrishnan[5] · Siddharth Laskar[6] · Tanvir Kaur[7] · Rupinder Singh Dhaliwal[7] · G. K. Rath[8] · Sameer Bakhshi[9]

J Clin Oncol 22:3663-3668

Treatment of Children and Adolescents With Stage II Testicular and Stages I and II Ovarian Malignant Germ Cell Tumors: A Pediatric Intergroup Study—Pediatric Oncology Group 9048 and Children's Cancer Group 8891

Paul C. Rogers, Thomas A. Olson, John W. Cullen, Deborah F. Billmire, Nayas Marina, Frederick Rescorla, Mary M. Davis, Wendy B. London, Stephen J. Lauer, Roger H. Giller, and Barbara Cushing

Pediatr Blood Cancer 2010;54:532–537

Teratoma With a Malignant Somatic Component in Pediatric Patients: The Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) Experience

Pediatr Blood Cancer 2014;62:1202–1208

Mature and Immature Teratoma: A Report From the Second Italian Pediatric Study

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SOCIETE INTERNATIONALE D'ONCOLOGIE PEDIATRIQUE

SIOP

INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

SIOPEL 6

A multi-centre open label randomised phase III trial of the efficacy of Sodium Thiosulphate in reducing ototoxicity in patients receiving Cisplatin chemotherapy for

STANDARD RISK HEPATOBLASTOMA

International Childhood Liver Tumour Strategy Group – SIOPEL

Version 2- April 2008

Start Date: 15/12/2007	**Final MREC approval date: 15/06/2007**
EUDRACT Number: 2007-002402-21	**MREC Amendment approval date: 07/07/2008**
CTA Number: 21275/0235/001-0001	

SIOPEL
Childhood Liver Tumours Strategy Group - SIOPEL

Children's Cancer and Leukaemia Group Data Centre
University of Leicester
3rd Floor, Hearts of Oak House
9 Princess Road West, Leicester, LE1 6TH, United Kingdom
(Tel: +44 116 249 4460 - Answering machine)
(Fax: + 44 116 254 9504)

In cooperation with Swiss Institute for Applied Cancer Research Coordination Centre and in collaboration with Adherex

DE GRUYTER Clin Chem Lab Med 2018; aop

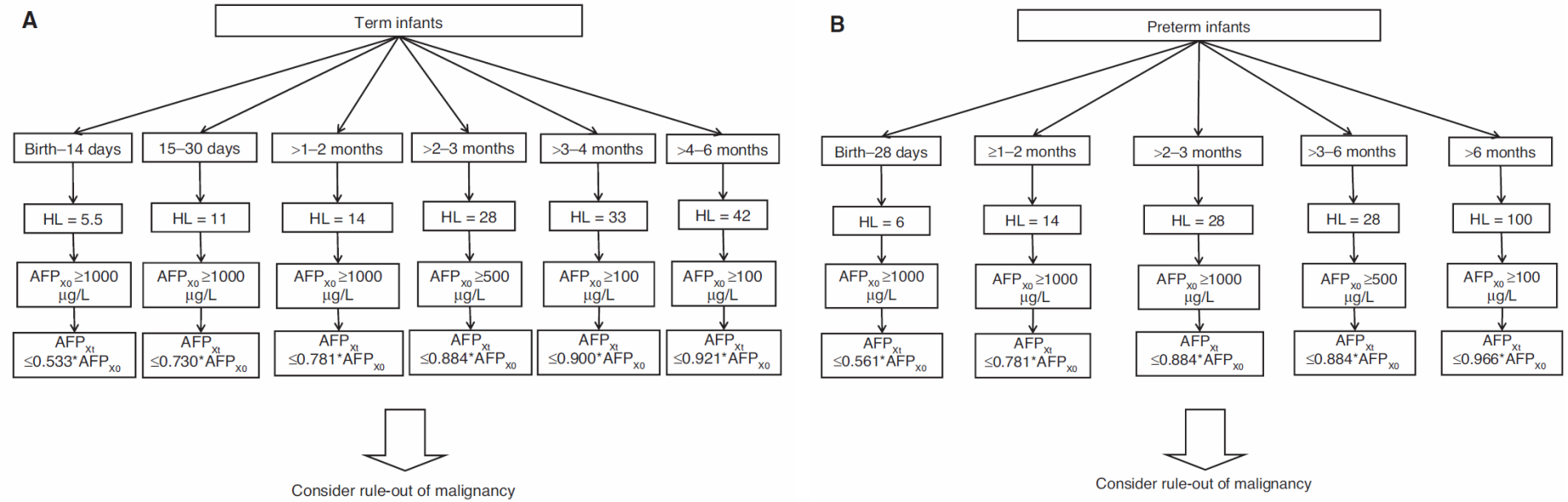
Review

Simona Ferraro*, Andrea Panzeri, Federica Braga and Mauro Panteghini

Serum α-fetoprotein in pediatric oncology: not a children's tale

The inability of defining robust RI in the first months of life made difficult, if not impossible, using upper reference limits for ruling out malignancies with a single AFP result.

Revising interpretation criteria *using algorithms for ruling out malignancy according to serum AFP concentrations measured baseline and 5 days later in term (A) and preterm (B) infants of different ages using appropriate marker half-life (HL).*



Effectiveness of Practices to Support Appropriate Laboratory Test Utilization

A Laboratory Medicine Best Practices Systematic Review and Meta-Analysis

Am J Clin Pathol 2018;149:197-221

Matthew Rubinstein, MS,[1] Robert Hirsch, PhD,[2] Kakali Bandyopadhyay, PhD,[3] Bereneice Madison, PhD,[1] Thomas Taylor, MS,[1] Anne Ranne, PhD,[1] Millie Linville, MS,[3] Keri Donaldson, MD, MSCE,[4] Felicitas Lacbawan, MD, FCAP, FACM,[5] and Nancy Cornish, MD[1]

- Outcomes:
  - Number of tests (eg, number of test orders, number of tests performed)
  - Costs/charges (eg, cost of test orders, cost of tests performed, cost per diagnosis, overall health care costs)
  - Turnaround time (eg, where reduction in the number of inappropriate tests may not be relevant)
  - Diagnostic yield and diagnostic detection rate
  - Length of hospital stay
  - Other patient-related outcomes (eg, patient satisfaction, patient safety events related to delayed or incorrect diagnosis, adverse drug reactions, readmission rates, morbidity, and mortality)

It is difficult to actually measure the impact of practices supporting appropriate ordering

Summary of Practice Recommendations

Practice Category	Practice Recommendation
CPOE	Use of CPOE is recommended as a best practice to support appropriate clinical LTU
CDSS/CDST	No recommendation for or against due to insufficient evidence is made for CDSS/CDST as a best practice to support appropriate clinical LTU
Education	No recommendation for or against due to insufficient evidence is made for education as a best practice to support appropriate clinical LTU
Feedback	No recommendation for or against due to insufficient evidence is made for feedback as a best practice to support appropriate clinical LTU
Reflex testing	Use of reflex testing practices is recommended as a best practice to support appropriate clinical LTU
Test review	No recommendation for or against due to insufficient evidence is made for test review as a best practice to support appropriate clinical LTU
LTU team	No recommendation for or against due to insufficient evidence is made for LTU team as a best practice to support appropriate clinical LTU
Combined practices	Use of combined practices is a recommended as a best practice to support appropriate clinical LTU

CDSS/CDST, clinical decision support systems/tools; CPOE, computerized provider order entry; LTU, laboratory test utilization.

Relevance of appropriateness in modern laboratory medicine to:

- ✓ Focus on efficacy and effectiveness in addition to efficiency
- ✓ Link laboratory testing to clinical and economic outcomes
- ✓ Underline the role of laboratory specialists in improving the quality of test request and interpretation of results

Pursuing and maintaining appropriate test requests is a daily achievement.

Laboratory specialists should continuously operate in:

–building recommendations to close the gaps between guidelines and clinical practice;

–retrospective auditing of data.

THANK YOU

FOR YOUR ATTENTION!

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