

Tumour markers in the laboratory

Closing the Guideline - Practice Gap

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Guidelines...

Encourage

- A collaborative approach
- Dissemination of best practice
- Efficient use of resources

Do not

- Replace clinical experience
- Apply to all patients
- Provide the only solution!

Require

- Proposed recommendations
- Consultation and peer review
- Presentation and publicity
- Dissemination, discussion and implementation → ownership
- Monitoring, evaluation (audit) and review (refinement)

Oosterhuis *et al.* **Evidence-based guidelines in laboratory medicine.**
Clin Chem 2004; 50: 806-818

Closing the Guideline-Practice Gap

- **What guidelines are available?**
- **What recommendations are there and how well have they been implemented?**
 - **Appropriate selection of tumour marker/s**
 - **Pre-analytical requirements**
 - **Analytical issues relevant to clinical practice**
 - **Post-analytical interpretation and reporting**
- **Conclusions**

Some available Guidelines

International

Union Internationale Contre le Cancer (UICC)

International Consensus Conferences (*eg* on Germ cell tumours)

European Group for Tumour Markers (EGTM)

National

American Joint Committee on Cancer (AJCC)

American Society for Clinical Oncology (ASCO)

National Academy of Clinical Biochemistry (NACB)

National Comprehensive Cancer Network (NCCN)

National Council for Clinical Laboratory Standards (NCCLS)

Association of Clinical Biochemists in Ireland (ACBI)

Scottish Intercollegiate Guideline Network (SIGN)

Local

Protocols developed by clinicians and laboratory staff

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NACB recommendations

Cancer	AFP	hCG	CEA	CA125
Germ cell				
• Screening	N	N		
• Diagnosis	Y	Y		
• Prognosis	Y	Y		
• Monitoring	Y	Y		
Colorectal				
• Screening			N	
• Diagnosis			N	
• Prognosis			Y	
• Monitoring			Y	
Ovarian				
• Screening				N
• Diagnosis				N
• Prognosis				Y
• Monitoring				Y

NACB recommendations

Cancer	ER / PR	Her-2 / Neu	CA15.3	CEA	PSA
Breast					
• Selection for therapy	Y	Y			
• Screening			N	N	
• Diagnosis			N	N	
• Prognosis			N	Y	
• Monitoring			Y	Y	
Prostate					
• Screening (with DRE)					Y*
• Diagnosis (with DRE)					Y
• Prognosis					Y
• Monitoring					Y

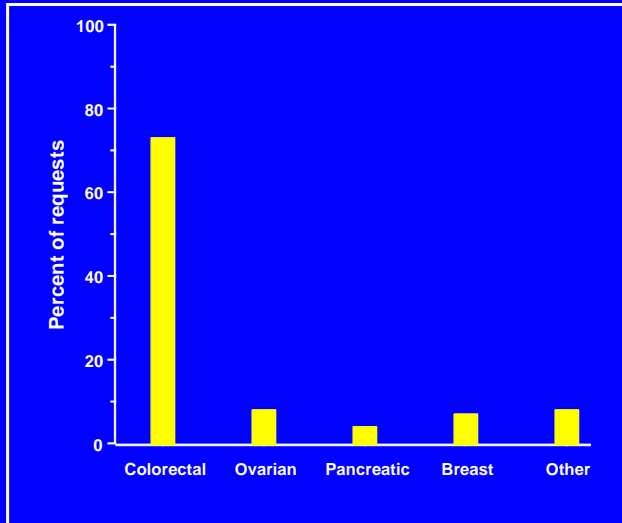
[*On request – not population screening]

Draft NACB recommendations – see www.nacb.org - comments welcome!!!

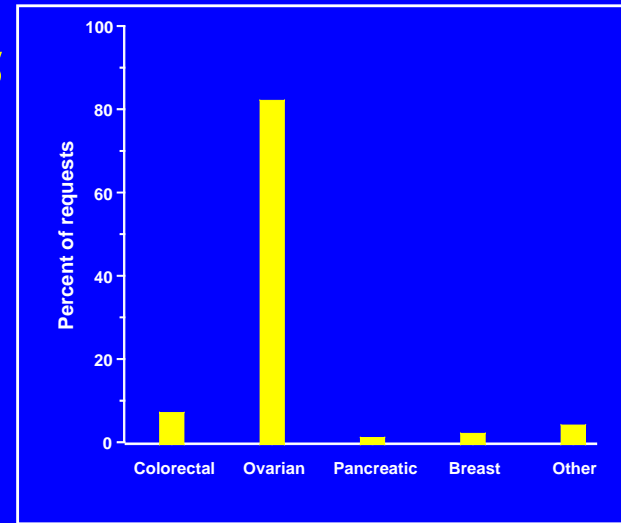
Practice Guidelines for Tumor Marker Use in the Clinic. Clin Chem 2002; 48: 1151-1159

Audit of choice of test

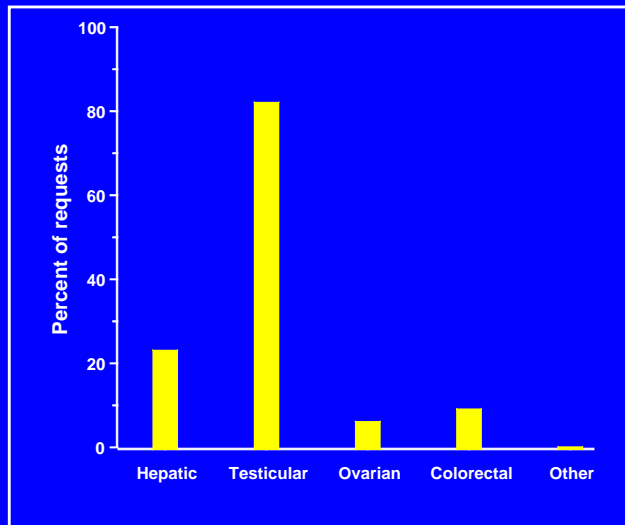
CEA



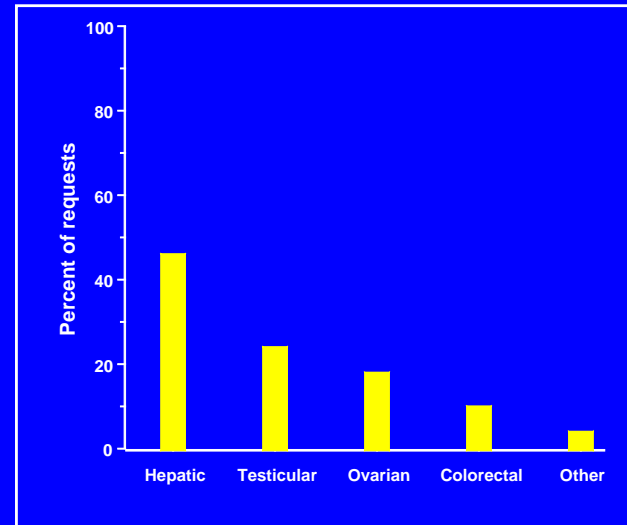
CA125



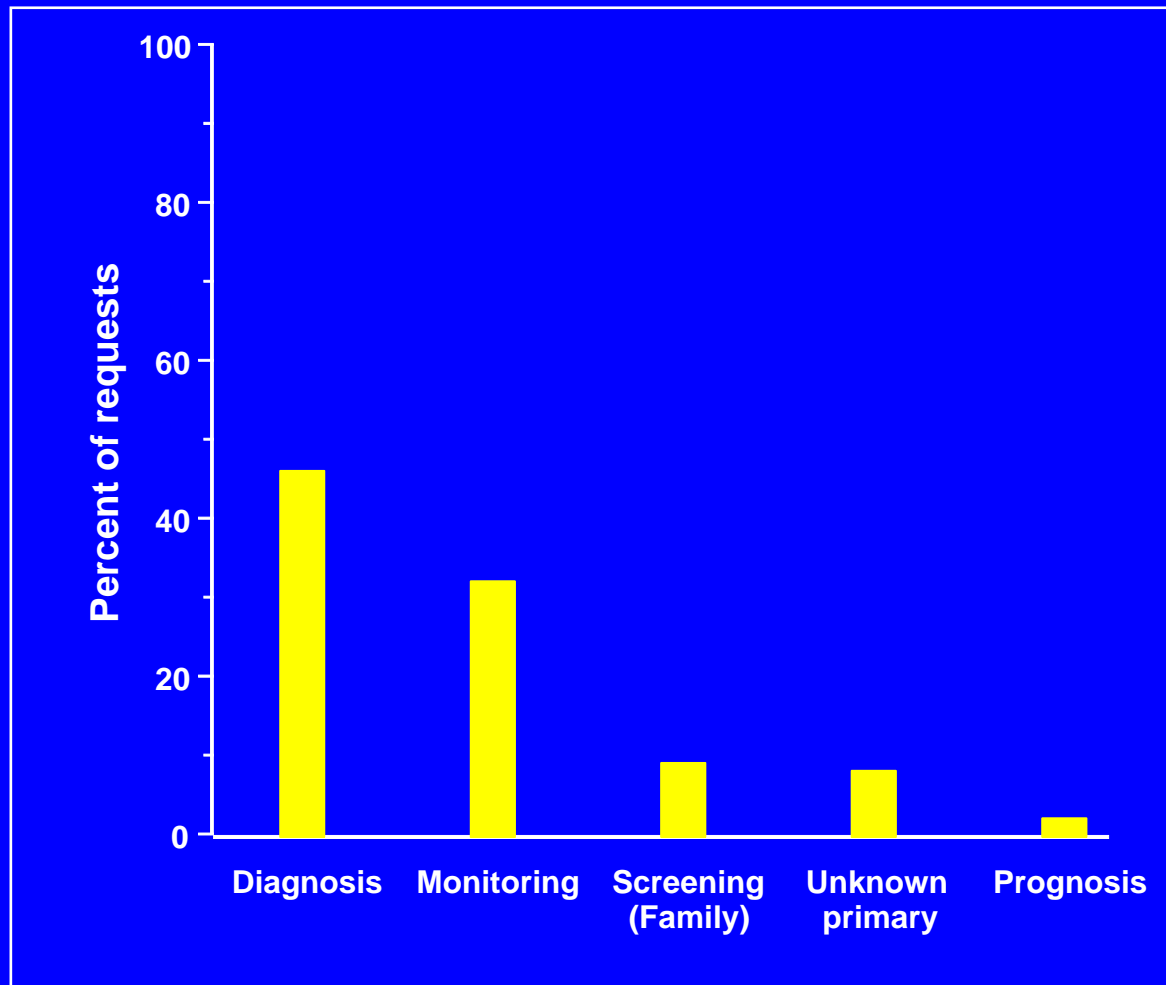
hCG



AFP



Reasons for requests



Summary: Choice of marker

- **Considerable guidance is available regarding appropriate choice of marker.**
- **Available audit data suggest request patterns are generally sensible.**
- **However there is little information about how tumour markers are being used for staging or monitoring in routine practice (outside clinical trials).**

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Pre-analytical quality

- **Correct specimen / i.d. / etc.**
- **Type and stability of specimen**
 - Suitable blood collection tubes
 - Appropriate storage conditions
- **Timing of specimen collection**
 - ↑ PSA in urinary tract infection
 - ↑ CA125 during menses
 - ↑ CA125 post-peritoneal trauma
 - ↑ AFP / hCG post chemotherapy
- **Effect of other treatment**
 - MAbs → HAMA → false results
- **Effect of medical conditions**
 - ↑ CA19.9 in cholestasis
 - ↑ (?) CEA, TPS in renal failure

CAP / CDC study (1995)

- ~41% errors in pre-analytical
cf ~4% in analytical phase

Minimizing pre-analytical errors requires

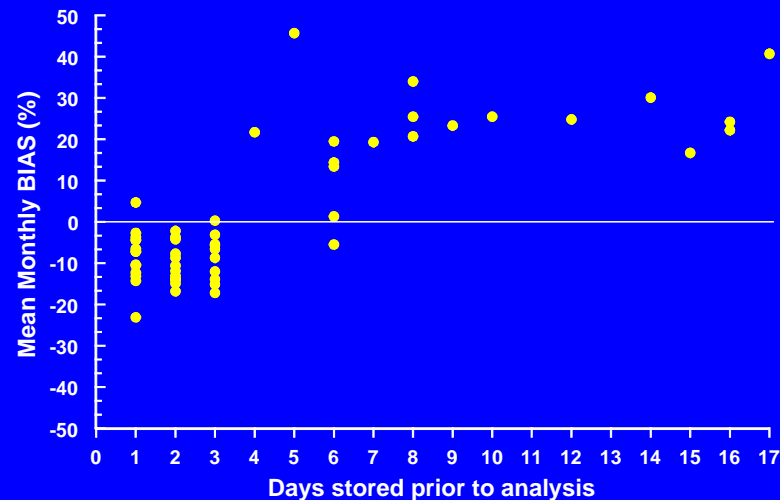
- Care and attention to detail from **when a test is first requested**
- Ready availability of a comprehensive and user-friendly **laboratory handbook**
- Good laboratory – clinician liaison and **communication**

Specimen handling

EQA observation

- Bimodal distribution of results observed for a **single** hCG method

Bias vs time to analysis



Possible explanations

- Nature and/or stability of EQA specimens?
- Different reagent lots?

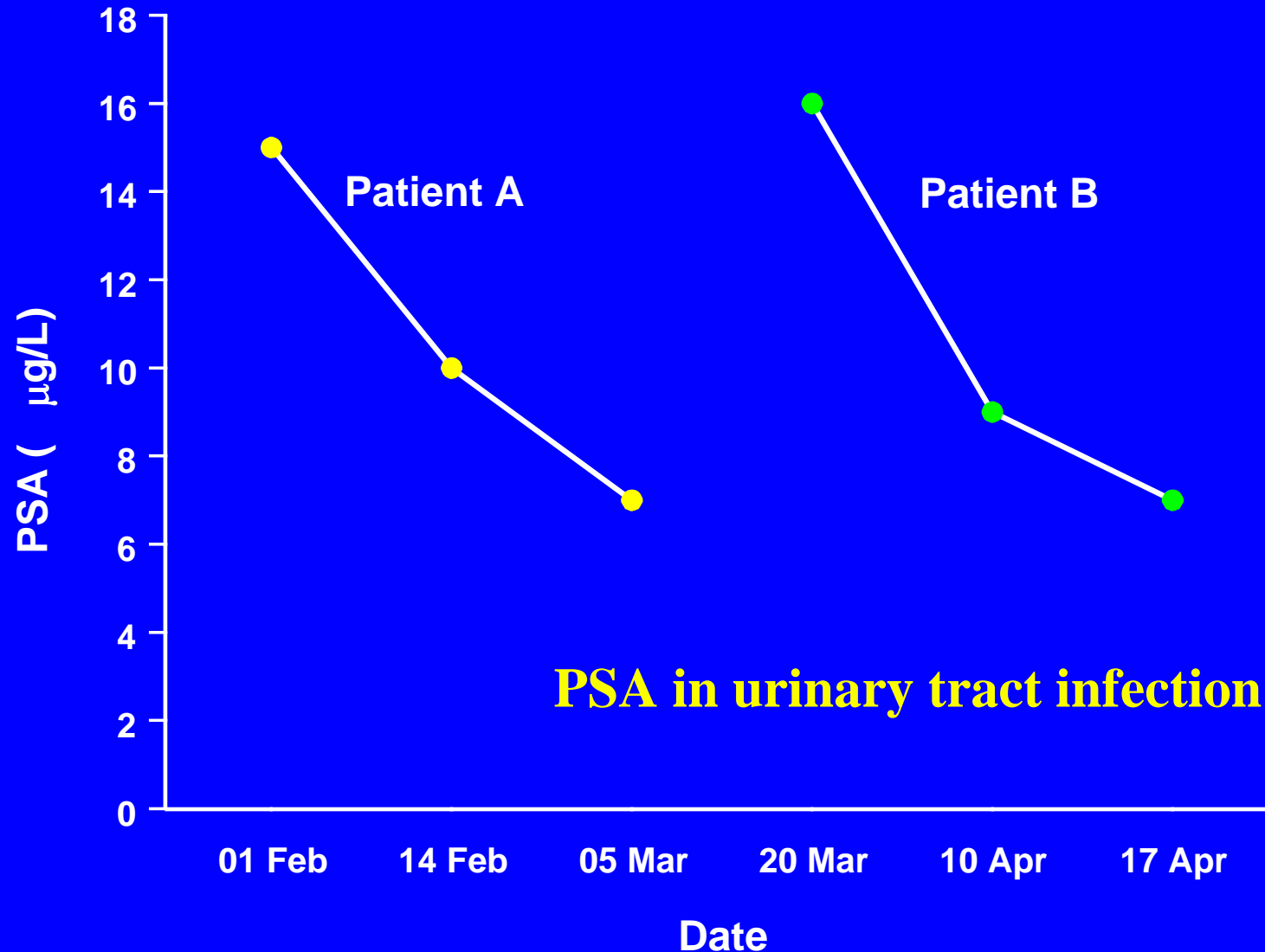
Actual explanation

- Antibody-related problem

Corrective action

- **Users** → Follow specimen storage instructions!
- **Manufacturer** → Change kit antibody

Specimen timing



Summary: Pre-analytics

- **It is absolutely essential that attention is paid to pre-analytical factors – both specimen-related and patient-related.**
- **These considerations are of critical importance in the early investigation of new technologies – e.g. proteomics.**

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Analytical requirements

- **Between-method comparability of results**
- **Appropriate Internal Quality Control (IQC) provision**
- **Minimal lot-to-lot variation & reagent stability over time**
- **Protocol for method changes**
- **Awareness of clinically relevant interferences & protocols to detect these**
- **Assays for hCG detecting both intact hCG & its beta-subunit**

IQC provision

- **Assessment of reproducibility –**
 - **Intra-assay variation <5%;**
 - **Inter-assay variation <10%.**
 - **Achievable for most analytes.**
- **Specimens closely resembling patient sera.**
 - **52% of labs use only controls from the supplier of the kit**
- **Specimens of clinically relevant concentrations.**
 - **Concentrations used vary.**
- **Established criteria for assay acceptance**
 - **Procedures vary markedly.**

Stability of results over time

One sample of the same low concentration pool (~3 ng/mL CEA) issued in each of six consecutive months. Individual CVs calculated for each lab and the mean of these CVs determined for each method.

Method	n	Mean CV (%)	Range (%)
Abbott Architect	20	6.8	0.2-11.7
Bayer Centaur	42	10.0	3.1-28.4
Roche ElecSys	42	6.5	0.0-15.9
DPC Immulite	40	9.0	2.9-22.0

Awareness of interferences

Analytical interferences

- Awareness of vulnerability of method used to interference from
 - Cross-reacting molecules
 - High dose “hooking”
 - Carry-over
 - Heterophilic Abs / HAMA
- Investigation of results not in accord with the clinical picture by
 - Performing dilution checks
 - Adding non-immune sera
 - Using blocking tubes
 - Testing in second method
- Maintaining communication with clinical users of the lab service!!!

Worst case example

22 year old – irregular bleeding

hCG ~250 U/L



Chemotherapy for 4 months



hCG still raised



Hysterectomy

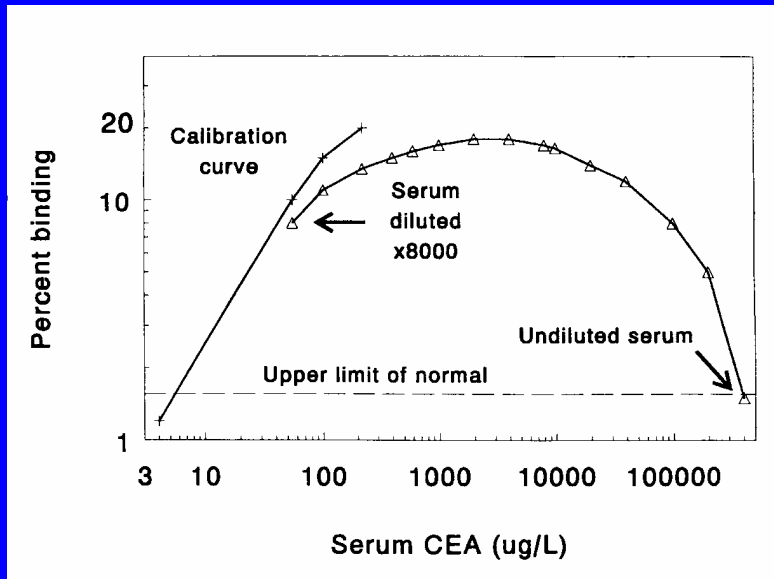


hCG still raised



Lung biopsy

High dose hook effect



Added hCG: 720,000 U/L*

Lab A 6,965 U/L

Lab B 500,395 U/L

Lab C 7,327 U/L

Lab D >10,000 U/L

Lab E 6,938 U/L

- Most likely for tumour markers as wide physiological range.
- Risk decreased by two-step assays, kinetic measurements, or assaying at two dilutions.
- Lab protocol desirable.

- Recognizing high dose hook particularly important for tumors that are potentially **rapidly fatal but curable**, e.g. choriocarcinoma.

**Dr Simon Packer (Scipac) kindly gifted the hCG used to prepare these UK NEQAS samples.*

Summary: Methodology

- **Greater use of IQC material from independent sources and objective criteria for run rejection desirable.**
- **Little information available about how method changes are managed.**
- **Some labs take steps to ensure minimal changes of reagent lot - but some do not.**
- **Greater awareness of possible interferences and assessment of their frequency desirable.**

Post-analytical quality

Factual requirements

- **Clinical information from the requesting doctor**
- **Availability of appropriate reference ranges**
- **Interpretation criteria for immunohistochemical tests**
- **Knowledge of what constitutes a clinically relevant change**
- **Defined protocol when changing methods**
- **Objective audit of tumour marker utility**

Reporting requirements

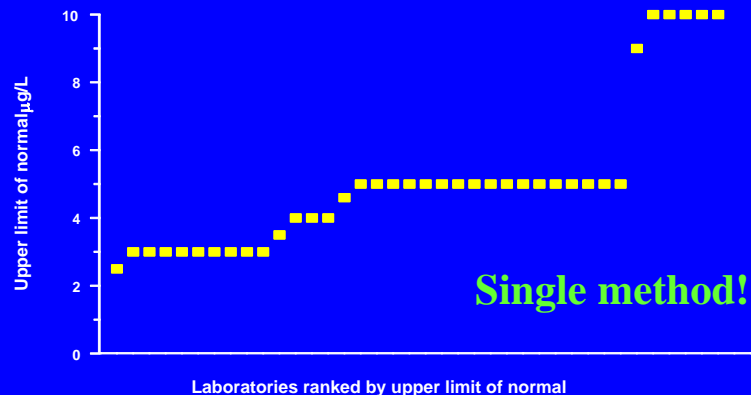
- **Provision of fully cumulated results – to show trends**
- **Method used indicated on the report**
- **Advice about appropriate frequency of monitoring**
- **Advice about need for confirmatory specimens – always to confirm increases**
- **Good communication between the laboratory and clinical users of the service!!**

Present practice

Most labs quote an upper limit / normal “cut-off” value.

About 40% of UK labs provide cumulative reports.

CEA



Summary: Post-analytics

- **Provision of fuller information to clinicians when reporting results would be desirable.**
- **Improved consensus regarding reference intervals and decision points required.**
- **What constitutes a clinically relevant change should be established for each tumour marker.**

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Conclusions

- **Guidelines may already have encouraged**
 - More appropriate test requesting
 - Awareness of requirements and limitations of these tests
 - More cumulative reporting and interpretative advice
- **Maximizing the impact of guidelines requires**
 - Their promotion at local, regional and national levels
 - Careful audit post-implementation to assess progress

www.nacb.org