Clinical Chemistry 54:11
1935–1939 (2008)

Preamble

National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for the Use of Tumor Markers

Eleftherios P. Diamandis,[1,2] Barry R. Hoffman,[1,2] and Catharine M. Sturgeon[3*]

The National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines for Use of Tumor Markers are intended to encourage more appropriate use of tumor marker tests by primary care physicians, hospital physicians and surgeons, specialist oncologists, and other health professionals. This introduction accompanies the e-publication of 2 reports summarizing NACB Quality Requirements for use of tumor markers in clinical practice *(1)* and NACB Guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers *(2)*. Two further reports will follow, summarizing the NACB Guidelines for use of tumor markers in liver, pancreatic, gastric, bladder, and cervical cancers and the NACB Guidelines for use of tumor markers in parathyroid, thyroid, neuroendocrine and lung cancers, monoclonal gammopathies, and melanoma.

Background to the NACB Tumor-Marker Guidelines

Here we report the updating and extension of practice guidelines first proposed in 2002 *(3)*. Undertaken under the direction of a steering committee appointed by the NACB (Table 1), this process involved consideration of 16 specific cancer sites, together with quality requirements for well-established tumor markers and tumor markers being developed by use of new technologies (Table 2). With its wide scope, this project is one of the most comprehensive and complex of its type to date. The draft guidelines were posted on the NACB website in July 2005 and were presented as an EduTrak at the 2005 Joint AACC/IFCC Annual meeting in Orlando, Florida. Informed comment was also actively sought from individuals, organizations, and other interested parties.

NACB Tumor-Marker Guideline Development Group

Nineteen subcommittees developed draft guidelines (Table 2). Subcommittee members included individuals with extensive expertise in the science, technology, and clinical practice of tumor markers in academia, hospitals, and/or industry. In guidelines in which expert opinion is incorporated as part of the recommendations, bias, including conflict of interest, may intrude *(4)*. Members of the in vitro diagnostic industry were deliberately included in the subcommittee membership to obtain a representative cross-section of experts and perspectives in the field. The disciplines of all authors are provided in a Supplemental Table attached to each paper (see Supplemental Table 1 in the Data Supplement that accompanies the online version of this preamble at http://www.clinchem.org/content/vol54/issue11), together with statements of conflicts of interest, declared according to NACB requirements. This major undertaking has involved significant input from approximately 100 scientists and clinicians from more than 10 countries and with diverse backgrounds.

Methodological Approach

Extensive literature is available on the preparation *(5, 6)* and evaluation *(7)* of practice guidelines. Many experts have emphasized the importance of a good evidence base in developing such guidelines *(5, 8)* and the challenges of their effective implementation *(9–11)*. Good methodology during guideline development is highly desirable, although it has recently been noted that good reporting of methodological quality does not necessarily lead to more valid recommendations or vice versa *(12)*.

A recent assessment of 9 clinical oncology practice guidelines has demonstrated significant heterogeneity in the development, structure, potential users, and endpoints of these guidelines, which the authors of the

[1] Department of Pathology and Laboratory Medicine, Mount Sinai Hospital; [2] Department of Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Canada; [3] Department of Clinical Biochemistry, Royal Infirmary of Edinburgh, Edinburgh, UK.
* Address correspondence to this author at: Department of Clinical Biochemistry, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK. Fax 44-131-242-6882; e-mail c.sturgeon@ed.ac.uk.
Received February 17, 2008; accepted August 27, 2008.
Previously published online at DOI: 10.1373/clinchem.2008.105494

Table 1. Steering committee for NACB Laboratory Medicine Practice Guidelines on Use of Tumor Markers in clinical practice.

Eleftherios P. Diamandis	Chair
Catharine M. Sturgeon	Vice-Chair & Coordinator
Barry R. Hoffman	Vice-Chair
Daniel W. Chan	Member
Herbert A. Fritsche	Member
Nils Brünner	Member
Martin Fleisher	Member
Michael J. Duffy	Member
Nadia Harbeck	Member
Daniel F. Hayes	Member
Farooq Ghani	Member

assessment concluded was not detrimental but rather was necessary to meet divergent demands *(13)*. No available guidelines are likely to be perfect in all situations—all have limitations, some of which the NACB Guidelines presented here undoubtedly share. Characteristics identified as critical to the effectiveness of practice guidelines, however, are a clear definition of purpose and intended audience (i.e., for the NACB Tumor-Marker Guidelines, to encourage more appropriate use of tumor markers by health professionals), adherence to methodological standards, and systematic evaluation (audit) of the clinical impact of the guidelines following their introduction *(13)*.

A relatively informal methodological approach was adopted, and subcommittee chairs were allowed considerable latitude. Consequently some reports are longer and more detailed than others. Although some of the diversity evident in the guidelines presented here undoubtedly reflects the predilection and idiosyncrasy of individual subcommittees, much of it arises from the different numbers of tumor markers described for each specific cancer as well as the variable maturity of clinical validation and currently available evidence for these markers. It is therefore not realistic to expect to achieve consistency of approach across the spectrum of cancers examined.

The subcommittees were, however, asked to follow a recommended structure (online Supplemental Table 2) when developing and formulating the guidelines and to consider each of the major potential clinical applications of tumor markers (screening/early detection, diagnosis, prognosis, treatment monitoring, and surveillance) to achieve a reasonably homogeneous presentation across cancer types. Subcommittees were also strongly encouraged to undertake as thorough a review of the literature as feasible, with particular attention given to reviews (including systematic reviews), prospective randomized trials that included the use of markers, and existing guidelines.

An important feature of the process was that each subcommittee was asked to compare its guidelines with those of other groups and to present these comparisons in tabular form, elaborating on any differences and also providing estimates of both the level of evidence *(9)* and the strength or grade of recommendation *(14)* (Table 3) ascribable to each NACB recommendation. The level of evidence and strength or grade of recommendation, respectively, reflect the strength of published evidence supporting the recommendations made and the degree of consensus within the guideline development group, and the tables relating to individual malignancies provide a convenient summary of the relevant NACB Guidelines. When consensus could not be achieved within a subcommittee, an explanation is provided along with descriptions of and reasons for the conflicting views.

The final result is a set of practice guidelines that follow a reasonably homogeneous style and approach. The strength and type of evidence underlying each recommendation is clearly stated, together with an estimate of the confidence with which each recommendation has been made, so the reader can readily discern which recommendations are based on incontrovertible clinical evidence and which are based on the expert consensus of committee members.

Review and Refinement of the NACB Tumor-Marker Guidelines

Subcommittee chairs reviewed and responded to suggestions and corrections received following posting of the guidelines on the NACB website and other publicity. Comments received, and action taken in response to them, are presented in a supplement accompanying the relevant paper (see the online Data Supplement).

These NACB Guidelines will inevitably require updating, refinement, and modification in the future, as knowledge and understanding of tumor markers and their biological roles increases. As suggested in the very helpful AGREE (Appraisal of Guidelines Research and Evaluation) document *(7)*, and reflecting work in progress for a number of tumor markers, when the guidelines are next updated it may be possible to include some estimate of the cost-effectiveness of tumor marker use, to take account of patients' views (psychological aspects of tumor marker use having only been touched on in the present guidelines), and to report on audit studies of their effectiveness. For this purpose it would be desirable to use a consultation form similar to that developed by the Scottish Intercollegiate Guideline Network [see, e.g., *(15)*].

Table 2. Subjects and subcommittee members for NACB Laboratory Medicine Practice Guidelines on Use of Tumor Markers in clinical practice.

Subject	Chairs and Committee Members
NACB Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Clinical Practice: Quality Requirements	
NACB Guidelines on quality requirements for the use of tumor markers	Catharine Sturgeon [Chair], Soo-Ling Ch'ng, Elizabeth Hammond, Daniel F. Hayes, György Sölétormos
NACB Guidelines on the use of microarrays in cancer diagnostics	E.P. Diamandis [Chair], Manfred Schmitt, Da-elene van der Merwe
NACB Guidelines on the use of MALDI-TOF mass spectrometry profiling to diagnose cancer	Daniel W. Chan [Chair], Eleftherios P. Diamandis, Lance A. Liotta, Emanuel F. Petricoin, Oliver J. Semmes, Da-elene van der Merwe
NACB Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Clinical Practice: Testicular, Prostate, Colorectal, Breast, and Ovarian Cancer	
NACB Guidelines for the use of tumor markers in testicular cancer	Ulf-Håkan Stenman [Chair], George J. Bosl, Rolf Lamerz, Leendert H. Looijenga
NACB Guidelines for the use of tumor markers in prostate cancer	Hans Lilja [Chair], Richard Babaian, Barry Dowell, George Klee, Harry Rittenhouse, Axel Semjonow, Paul Sibley, Lori Sokoll, Carsten Stephan
NACB Guidelines for the use of tumor markers in colorectal cancer	Nils Brünner [Chair], Michael J. Duffy, Caj Haglund, Mads Holten-Anderson, Hans J Nielsen
NACB Guidelines for the use of tumor markers in breast cancer	Michael J. Duffy [Chair], Francesco J. Esteva, Nadia Harbeck, Daniel F. Hayes, Rafael Molina
NACB Guidelines for the use of tumor markers in ovarian cancer	Daniel W. Chan [Chair], Robert C. Bast Jr, Ie-Ming Shih, Lori J. Sokoll, György Sölétormos
NACB Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Clinical Practice: Liver Cancer, Pancreatic Ductal Adenocarcinoma, Gastric Cancer, Bladder Cancer, Cervical Cancer, and Lung Cancer	
NACB Guidelines for the use of tumor markers in liver cancer	Rolf Lamerz [Chair], Peter Hayes, Ralf-Thorsten Hoffmann, Florian Löhe, Yasushi Shiratori, Kazuhisa Taketa
NACB Guidelines for the use of tumor markers in pancreatic ductal adenocarcinoma	Michael Goggins [Chair], Marcia I. Canto, Ralph H. Hruban, Jens Koopmann, Dawei Yang
NACB Guidelines for the use of tumor markers in gastric cancer	Johannes M.G. Bonfrer [Chair], Johanna Louhimo
NACB Guidelines for the use of tumor markers in bladder cancer	Herbert A. Fritsche [Chair], Barton Grossman, Seth P. Lerner, Ihor Sawczuk
NACB Guidelines for the use of tumor markers in cervical cancer	Katja N. Gaarenstroom [Chair], Johannes M.G. Bonfrer
NACB Guidelines for the use of tumor markers in lung cancer	Petra Stieber [Chair], Rudolf Hatz, Stefan Holdenrieder, Rafael Molina, Marius Nap, Joachim von Pawel, Andreas Schalhorn, Joachim Schneider, Ken Yamaguchi
NACB Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Clinical Practice: Parathyroid Gland Adenomas and Carcinomas, Differentiated Epithelial Thyroid Carcinoma, Neoplasms of the Dispersed Neuroendocrine System, Monoclonal Gammopathies, and Malignant Melanoma	
NACB Guidelines for the use of tumor markers in parathyroid gland adenomas and carcinomas	Frank H. Wians [Chair], Fiemu Nwariaku, Alan T. Remaley, William H. Snyder, Lori J. Sokoll, Jiaxi Wu
NACB Guidelines for the use of tumor markers in differential epithelial thyroid carcinoma	Kenneth B. Ain [Chair], Ronald J. Whitley
NACB Guidelines for the use of tumor markers in neoplasms of the dispersed neuroendocrine system	Shereen Ezzat [Chair], Sylvia L. Asa, Steven J. Lamberts, Kjell E. Oberg, Daniel T. O'Connor, Laurent Taupenot
NACB Guidelines for the use of tumor markers in monoclonal gammopathies	Martin Fleisher [Chair], Raymond L. Comenzo, Seema Gupta, Barry R. Hoffman
NACB Guidelines for the use of tumor markers in malignant melanoma	Rishab K. Gupta [Chair], Alistair J. Cochran, Eddy C. Hsueh, Donald L. Morton, Steven D. Trocha

IMPLEMENTATION OF THE NACB TUMOR-MARKER GUIDELINES

Adoption of these guidelines is voluntary; some recommendations may not be appropriate in all settings (e.g., clinical trials), and for effective implementation guidelines may require translation and/or other modification in some settings. There is good evidence that "lo-

Table 3. Levels of evidence and strength of recommendations used to grade the NACB Guidelines for tumor markers [adapted from Hayes et al. *(9)* and Atkins et al. *(14)*].

Assessment	Criteria
Level of evidence *(9)*	
I	Evidence from a single, high-powered, prospective, controlled study that is specifically designed to test marker, or evidence from a metaanalysis, pooled analysis, or overview of level II or III studies.
II	Evidence from a study in which marker data are determined in relationship to a prospective therapeutic trial that is performed to test therapeutic hypothesis but not specifically designed to test marker utility.
III	Evidence from large prospective studies.
IV	Evidence from small retrospective studies.
V	Evidence from small pilot studies.
Expert opinion	Formal consensus of subcommittee members.
Strength of recommendation *(14)*	
High (A)	Further research is very unlikely to change the panel's confidence in the estimate of effect.
Moderate (B)	Further research is likely to have an important impact on the panel's confidence in the estimate of effect and is likely to change the estimate.
Low (C)	Further research is very likely to have an important effect on the panel's confidence in the estimate of effect and is likely to change the estimate.
Very low (D)	Any estimate of effect is very uncertain.

cally owned" guidelines are much more likely to be successfully adopted in routine clinical practice *(6)*. Additionally, carefully designed audit studies would be highly desirable before and after introduction of the guidelines *(13)*.

These recommendations, which, to facilitate their dissemination, are being published in electronic form in a widely read journal, should encourage more optimal use of tumor-marker tests by clinical and laboratory staff, thereby better informing medical decisions directed toward improved clinical outcome and/or quality of life for increasing numbers of cancer patients.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures of Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: None declared.
Stock Ownership: None declared.
Honoraria: C. Sturgeon is the recipient of speaker expenses and/or honoraria from Abbott Diagnostics, Bayer Diagnostics, Beckman Coulter Diagnostics, Becton Dickinson Diagnostics, DAKO, DPC, Roche Diagnostics, Tosoh Biosciences, and Wallac Oy.
Research Funding: None declared.
Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

Acknowledgments: We thank the numerous scientists and clinicians who have contributed to this undertaking, Hassima Omar Ali for her excellent assistance, David Bruns and Nader Rifai for agreeing to consider publishing these guidelines in *Clinical Chemistry*, and of course the National Academy of Clinical Biochemistry and the American Association of Clinical Chemistry for their much appreciated support and encouragement.

References

1. Sturgeon CM, Hoffman BR, Chan DW, Ch'ng SL, Hammond E, Hayes DF, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Clinical Practice: Quality Requirements. Clin Chem 2008;54:e1–10.

2. Sturgeon CM, Duffy MJ, Stenman U-H, Lilja HJ, Brunner N, Chan DW, et al. National Academy of Clinical Biochemistry Laboratory Medicine

Practice Guidelines for use of tumor markers in testicular, prostate, colorectal, breast and ovarian cancers. Clin Chem Forthcoming 2008;54.

3. Fleisher M, Dnistrian A, Sturgeon C, Lamerz R, Witliff J. Practice guidelines and recommendations for use of tumor markers in the clinic. In: Diamandis EP, Fritsche HA, Lilja H, Chan DW, Schwartz MK, eds. Tumor markers: physiology, pathobiology, technology and clinical applications. Washington (DC): AACC Press; 2002. p 33–63.
4. Detsky AS. Sources of bias for authors of clinical practice guidelines. Can Med Assoc J 2006;175: 1033, 1035.
5. Oosterhuis WP, Bruns DE, Watine J, Sandberg S, Horvath AR. Evidence-based guidelines in laboratory medicine: principles and methods. Clin Chem 2004;50:806–18.
6. Sturgeon C. Practice guidelines for tumor marker use in the clinic. Clin Chem 2002;48:1151–9.
7. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12:18–23.
8. Price CP, Christenson RH, editors. Evidence-based laboratory medicine: principles, practice and outcomes. 2nd ed. Washington (DC): AACC Press; 2007. 545 p.
9. Hayes DF, Bast RC, Desch CE, Fritsche H Jr, Kemeny NE, Jessup JM, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst 1996; 88:1456–66.
10. Hayes DF. Prognostic and predictive factors for breast cancer: translating technology to oncology. J Clin Oncol 2005;23:1596–7.
11. Yamauchi H, Stearns V, Hayes DF. When is a tumor marker ready for prime time? A case study of c-erbB-2 as a predictive factor in breast cancer. J Clin Oncol 2001;19:2334–56.
12. Watine J, Friedberg B, Nagy E, Onody R, Oosterhuis W, Bunting PS, et al. Conflict between guideline methodologic quality and recommendation validity: a potential problem for practitioners. Clin Chem 2006;52:65–72.
13. Pentheroudakis G, Stahel R, Hansen H, Pavlidis N. Heterogeneity in cancer guidelines: should we eradicate or tolerate? Ann Oncol Forthcoming [Epub ahead of print 2008 Jul 28].
14. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328:1490.
15. Scottish Intercollegiate Guidelines Network (SIGN). Management of adult testicular germ cell tumours. http://www.sign.ac.uk/pdf/sign28.pdf (Accessed October 2007). SIGN publication no. 28; 1998.