Precision Medicine and Pragmatic Trials: Friends or Foes?

Spencer Phillips Hey

Program On Regulation, Therapeutics, And Law (PORTAL)
Division of Pharmacoepidemiology and Pharmacoeconomics
Brigham and Women’s Hospital

Center for Bioethics
Harvard Medical School
Funding:

- Program on Regulation, Therapeutics, and Law (PORTAL)
- The Laura and John Arnold Foundation
- PACEOMICS
“Ensure that the right treatment is delivered to the right patient at the right time, every time.”
Medicine of the present: one treatment fits all

Cancer patients with e.g. colon cancer

Therapy

Effect  No effect  Adverse effects

Medicine of the future: more personalized diagnostics

Cancer patients with e.g. colon cancer

Blood, DNA, urine and tissue analysis

Biomarker diagnostics

Therapy

Effect

A circular diagram with the following sections:

- **Eligibility**: Who is selected to participate in the trial?
- **Recruitment**: How are participants recruited into the trial?
- **Setting**: Where is the trial being done?
- **Organisation**: What expertise and resources are needed to deliver the intervention?
- **Primary outcome**: How relevant is it to participants?
- **Follow-up**: How closely are participants followed-up?
- **Primary analysis**: To what extent are all data included?
- **Flexibility: adherence**: What measures are in place to make sure participants adhere to the intervention?
- **Flexibility: delivery**: How should the intervention be delivered?

Source: BMJ 2015; 350:h2147
A New Initiative on Precision Medicine
Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

“Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

— President Barack Obama, State of the Union Address, January 20, 2015

President Obama has long expressed a strong conviction that science offers great potential for improving health. Now, the President has announced a research initiative that aims to accelerate progress toward a new era of precision medicine (www.whitehouse.gov/precisionmedicine). We believe that the time is right for this visionary initiative, and the National Institutes of Health (NIH) and other partners will work to achieve this vision.

The concept of precision medicine — prevention and treatment strategies that take individual variability into account — is not new1; blood typing, for instance, has been used to guide blood transfusions for more than a century. But the prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases (such as the human genome sequence), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large sets of data. What is needed now is a broad research program to encourage creative approaches to precision medicine, test them rigorously, and ultimately use them to build the evidence base needed to guide clinical practice.

The proposed initiative has two main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease. Both components are now within our reach because of advances in basic research, including molecular biology, genomics, and bioinformatics. Furthermore, the initiative taps into converging trends of increased connectivity, through social media and mobile devices, and Americans’ growing desire to be active partners in medical research.

Oncology is the clear choice for enhancing the near-term impact of precision medicine. Can-
Americans are keen to take part in a national precision medicine program
A New Initiative on Precision Medicine

STAT

Americans are keen to take part in a national precision medicine program

OPINION | BARACK OBAMA

Medicine’s next step

A breast cancer patient received a trial medication treatment in San Francisco in 2005.

By Barack Obama | JULY 07, 2016
Reporting of prognostic studies of tumour markers: a review of published articles in relation to REMARK guidelines

S Mallett, A Timmer, W Sauerbrei and DG Altman

1Centre for Statistics in Medicine, University of Oxford, Oxford, UK; 2Institute of Epidemiology, Helmholtz Zentrum München, German Research Centre for Environmental Health, München, Germany; 3German Cancer Center, Institute of Medical Biometry and Medical Informatics, University Medical Center Freiburg, Freiburg, Germany; 4Institute of Medical Biometry and Medical Informatics, University Medical Center Freiburg, Freiburg, Germany

BACKGROUND: Poor reporting compromises the reliability and clinical value of prognostic tumour marker studies. We review articles to assess the reporting of patients and events using REMARK guidelines, at the time of guideline publication.

METHODS: We sampled 50 prognostic tumour marker studies from higher impact cancer journals between 2006 and 2007. The inclusion criteria were cancer; focus on single biological tumour marker; survival analysis; multivariable analysis; and not gene array or proteomic data. Articles were assessed for the REMARK profile and other REMARK guideline items. We propose a reporting aid, the REMARK profile, motivated by the CONSORT flowchart.

RESULTS: In 50 studies assessed for the REMARK profile, the number of eligible patients (56% of articles), excluded patients (54%) and patients in analyses (98%) was reported. Only 50% of articles reported the number of outcome events. In multivariable analyses, 94% and 30% of articles reported patient and event numbers for all variables. Of the studies, 66% used archival samples, indicating a potentially biased patient selection. Only 36% of studies reported clearly defined outcomes.

CONCLUSIONS: Good reporting is critical for the interpretability and clinical applicability of prognostic studies. Current reporting of key information, such as the number of outcome events in all patients and subgroups, is poor. Use of the REMARK profile would greatly improve reporting and enhance prognostic research.

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© 2010 Cancer Research UK

Keywords: prognostic; REMARK; survival analysis; tumour marker; reporting guideline
Pragmatic issues in biomarker evaluation for targeted therapies in cancer

Armand de Gramont, Sarah Watson, Lee M. Ellis, Jordi Rodón, Josep Tabernero, Aimery de Gramont and Stanley R. Hamilton

Abstract | Predictive biomarkers are becoming increasingly important tools in drug development and clinical research. The importance of using both guidelines for specimen acquisition and analytical methods for biomarker measurements that are standardized has become recognized widely as an important issue, which must be addressed in order to provide high-quality, validated assays. Herein, we review the major challenges in biomarker validation processes, including pre-analytical (sample-related), analytical, and post-analytical (data-related) aspects of assay development. Recommendations for improving biomarker assay development and method validation are proposed to facilitate the use of predictive biomarkers in clinical trials and the practice of oncology.


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Perspective

Improving Validation Practices in “Omics” Research

John P. A. Ioannidis¹ and Muin J. Khoury²

“Omics” research poses acute challenges regarding how to enhance validation practices and eventually the utility of this rich information. Several strategies may be useful, including routine replication, public data and protocol availability, funding incentives, reproducibility rewards or penalties, and targeted repeatability checks.

Keywords: prognostic, REMARK; survival
Analytical and clinical evaluation of biomarkers assays: When are biomarkers ready for prime time?

Gene A Pennello

Improving Validation Practices in “Omics” Research

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Inconsistency in large pharmacogenomic studies

Two large-scale pharmacogenomic studies were published recently in this journal. Genetic data are well correlated between studies, however, the measured drug response data are highly discordant. Although the source of inconsistency remains uncertain, it has potential implications for using these outcome measures to assess gene-drug associations or select potential anticancer drugs on the basis of their reported results.

Keywords: Prognostic, Reproducible, surp

John P. A. Ioannidis1 and Munir I. Khoury2

Clinical Trials 2013; 10: 666–676

DOI: 10.1002/etc.1281

Pragmatic issues for targeted trials

Benjamin Haber-Kaufman, Nehme El Hachem, Nidal Paul Richan, Andrew C. In, Andrew H. Peck, Hugo W. L. Aerts, and John Quackenbush. 5, 4

We propose a reporting aid for this kind of analysis and not gene array.

10.1002/etc.1281

Correction above may apply to previous version.

We propose a reporting aid for this kind of analysis and not gene array.
Focus: Biomarkers and Biospecimens

Analytic Variability in Immunohistochemistry

Biomarker Studies

Vassano K. Anagnostou, Allison W. Walsh, Jennifer M. Giltinan, Summar Siddiqui, Camil Llaca, Mark Gustavson, Konstantinos N. Syrigos, Jill L. Reller, and David L. Rimm

Abstract

Background: Despite the widespread use of immunohistochemistry (IHC), there are no standardization guidelines that control for antibody probe variability. Here we describe the effect of variable antibody reagents in the assessment of cancer-related biomarkers by IHC.

Methods: Estrogen receptor (ER), epidermal growth factor receptor (EGFR) 1, and human epidermal growth factor receptor 3 (HER3) were evaluated by quantitative immunofluorescence. Correlations between ER clones 1D5, SP1, F8, and ER60c, and EGFR monoclonal 31G7, 2-18C9, H11, and 15F8, and polyclonal 2232 antibodies were assessed in 642 breast cancer patients. HER3 was measured by RTJ1, RTJ2, SCP1, MZ297, RB-9211, and C-47 antibodies in 42 lung cancer patients. Survival analysis was done with the use of multiple cutoff points to reveal any prognostic classification.

Results: All ER antibodies were tightly correlated (Pearson’s r² = 0.94; 0.96; P < 0.0001) and western blotting confirmed their specificity in MCF-7 and BT474 cells. All EGFR antibodies but 2232 yielded specific results in western blotting; however, only 31G7 and 2-18C9 were strongly associated (Pearson’s r² = 0.61; P < 0.0001). HER3 staining was nonspecific and nonreproducible. High EGFR-expressing patients had a worse prognosis when EGFR was measured with H11 or 31G7 (log rank P = 0.015 and P = 0.00). There was no statistically significant correlation between survival and EGFR detected by 2-18C9, 15F8, or polyclonal 2232 antibodies.

Conclusions: Antibody validation is a critical analytic factor that regulates IHC readings in biomarker studies. Evaluation of IHC proficiency and quality control are key components toward IHC standardization.

Impact: This work highlights the importance of IHC standardization and could result in the improvement of clinically relevant IHC protocols. Cancer Epidemiol Biomarkers Prev; 19(4): 982–91. ©2010 AACR.
Uses and Abuses of Tumor Markers in the Diagnosis, Monitoring, and Treatment of Primary and Metastatic Breast Cancer

N. Lynn Henry, Daniel F. Hayes

Department of Internal Medicine, Breast Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan, USA

Key Words: Tumor marker • Her-2/neu • Breast cancer • Estrogen receptor • Prognostic factor • Predictive factor

Abstract

Background: Despite the widespread use of immunohistochemistry (IHC), there are no standardization guidelines that control for antibody probe variability. Here we describe the effect of variable antibody reagents in the assessment of cancer-related biomarkers by IHC.

Methods: Estrogen receptor (ER), epidermal growth factor receptor (EGFR) 1, and human epidermal growth factor receptor 3 (HER3) were evaluated by quantitative immunofluorescence. Correlations between ER clones 1D5, SP1, F80, and ER66c, and EGFR monoclonal 31G7, 2-18C9, H11, and 15F8, and polyclonal 2232 antibodies were assessed in 642 breast cancer patients. HER3 was measured by RTJ1, RTJ2, SCG1, M7297, RB-9211, and C-47 antibodies in 42 lung cancer patients. Survival analysis was done with the use of multiple cutoff points to reveal any prognostic classification.

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Practices in
Pragmatic issues for targeted treatment

Inconsistent biomarker studies

Benjamin Haibe-Kains & John Quackenbush

Two large-scale comprehensive studies that compare biomarkers across institutions and studies remains underexplored. In addition, there is a need to understand the potential biases and limitations of different biomarker platforms.

TUMOR-BIOMARKER DIAGNOSTICS

Breaking a Vicious Cycle

Daniel F. Hayes,1* Jeff Allen,2 Carolyn Compton,3 Gary Gustavsen,4 Debra G. B. Leonard,5 Robert McCormack,6 Lee Newcomer,7 Kristin Pothier,4 David Ransohoff,8 Richard L. Schilsky,9 Ellen Sigal,2 Sheila E. Taube,10 Sean R. Tunis11

Despite prodigious advances in tumor biology research, few tumor-biomarker tests have been adopted as standard clinical practice. This lack of reliable tests stems from a vicious cycle of undervaluation, resulting from inconsistent regulatory standards and reimbursement, as well as insufficient investment in research and development, scrutiny of biomarker publications by journals, and evidence of analytical validity and clinical utility. We offer recommendations designed to serve as a roadmap to break this vicious cycle and call for a national dialogue, as changes in regulation, reimbursement, investment, peer review, and guidelines development require the participation of all stakeholders.

Conclusions: Antibody validation is a critical analytic factor that regulates IHC readings in biomarker studies. Evaluation of IHC proficiency and quality control are key components toward IHC standardization.

Impact: This work highlights the importance of IHC standardization and could result in the improvement of clinically relevant IHC protocols. Cancer Epidemiol Biomark Prev; 19(10): 982–91. ©2010 AACR.
OMICS-based personalized oncology: if it is worth doing, it is worth doing well!

Daniel F Hayes
Failing to adequately test the driving biological theories
Therapy
- Agents
- Dosage
- Schedule

Population
- Condition
- Age
- History

benefit
Therapy
- Agents
- Dosage
- Schedule

Biomarker
- Mutation
- Protein
- mRNA

Assay
- Specimen
- Reagents
- Cut-off

Population
- Condition
- Age
- History

predict
benefit
classify
detect
Population with Condition

Study Sample

Group A
Experimental Therapy

Group B
Control Therapy

Compare Clinical Outcomes
Population with Condition

Study Sample

Biomarker Diagnostic

Group M+

Experimental Therapy

Group M-

Experimental Therapy

Control Therapy

Compare Clinical Outcomes
Example: BRAF inhibitors as PM for metastatic melanoma

- BRAF encodes a protein involved in cell signaling and cell growth
- First identified in 2002, BRAF mutations can be found in nearly half of all metastatic melanoma specimens, with mutations at codon V600 being the most common
- Two BRAF inhibitors approved: Vemurfenib (2011) and dabrafenib (2013)
Methods:

- Searched PubMed, Embase for all trials or retrospective studies reporting BRAF-mutation stratified outcomes
- Extracted published reports for biomarker ensemble components, methodological quality, and association between BRAF-mutation status and (a) ORR, (b) PFS, (c) OS
- Descriptive analysis
Results:

- 16 study reports in final analysis
- Only 1 study showed a significant association between BRAF-mutation and prolonged overall survival
- Generally low adherence with methodological reporting guidelines
- No replication, no apparent standardization or consensus on assay method
- No published study examining BRAF-status and BRAF-inhibitor therapy
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Ethical Implications

- Lack of adequate testing/validation → worse patient outcomes
- Participant burdens insufficiently redeemed by wasteful or inefficient research programs
- Mismatch between hype and reality of precision medicine undermines patient/participant trust in the healthcare and research enterprises
Recommendations

- Both the theory underlying the biomarker and the theory underlying the assay need to be adequately tested before approval.
- PM trials should allocate participants contrary to biological hypotheses.
- Novel mechanisms for coordinating replication and validation efforts are needed.
Conclusions:

- PM trials will involve additional diagnostic components that are unlikely to be used in practice.
- But robust knowledge of the causal system—explanatory understanding furnished by PM—can improve our decision-making.
- Deconstruction of the explanatory/pragmatic dichotomy?
- PM and pragmatic trials should be understood as complimentary approaches.
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thank you

◊

shey@bwh.harvard.edu