Updating Oncology Drug Labels
Lessons from Related Efforts

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Relationships

- Employer: University of North Carolina
- Research funding: National Cancer Institute, Patient-Centered Outcomes Research Institute
- Scientific advisor: Dana Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, Sivan, CareVive, Self Care Catalysts, CMS/RTI
- Editor: JAMA
- Board of Directors: American Society of Clinical Oncology

My Perspective

- Practicing medical oncologist
- Clinical investigator
- Health services researcher

- Want best available treatments for patients
  - Need high-quality, trustworthy, updated information

Confusion Why Labels Not Updated

- To me, as an oncologist, FDA labels = definitive information about drugs
- I trust the FDA process
  - Rigorous
  - Conducted by hematologist-oncologists
  - Transparent
  - Reviewers have no financial ties to industry
  - Labels are free and publically available
- Seems strange to me that labels are locked in time
  - I want one-stop shopping for updated information

Who Currently "Updates" Drug Information?

Drug Compendia

- Defined as comprehensive listings of drugs and biologics
- Current designated compendia (as of 2008):
  - *American Hospital Formulary Service Drug Information* (*AHFS*)
  - *Clinical Pharmacology* (Elsevier)
  - *DRUGDEX* (Thompson Reuters)
  - *Lexi-Drugs (Wolters Kluwer)*
  - *NCCN Drugs & Biologics*

- Designated compendia "indications" are basis for reimbursement by CMS and private payers (federal and state legislation)

Social Security Act 1861(t)(2)(B)(ii)(I) & (II),
1993 Omnibus Budget Reconciliation Act

Key findings:

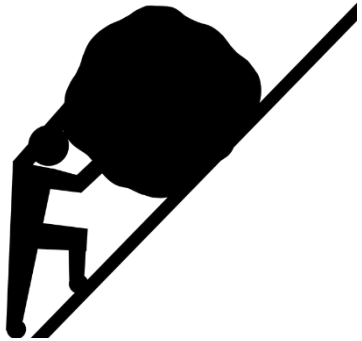
- New indications often based on low-quality or outdated evidence
- Missing key references
- Inconsistent content across different compendia
- Lack of transparent processes
- Inconsistent formatting

JAMA

JAMA 2016;316(15):1541-1542

Table. Selected Sources of Evidence Included in Compendia Listings for Off-label Use of Erlotinib

Compendium	Indication	Evidence Source Cited in Compendium	Type of Evidence	Description
Clinical Pharmacology	Head and neck	Kim ES, Kies MS, Glisson BS, et al. Final results of a phase II study of erlotinib, docetaxel and cisplatin in patients with recurrent/metastatic head and neck cancer. Presented at ASCO Annual Meeting. Chicago, IL; 2007. Abstract 6013.	Meeting abstract	Among 47 patients with recurrent or metastatic head and neck squamous cell carcinoma, combination therapy with docetaxel, cisplatin, and erlotinib, complete responses by RECIST were observed in 4 patients, partial responses in 25 patients, and 12 patients had stable disease.
DrugDex	Colorectal cancer	Hidalgo M, Siu LL, Nemunaitis J, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol*. 2001;19(13):3267-3279.	Phase 1 study	The pharmokinetics and maximum tolerated dose for erlotinib was described among 40 patients with advanced solid tumor malignancies.
DrugDex	Ovarian cancer	Ciardiello F, Tortora G. A novel approach in the treatment of cancer: targeting the epidermal growth factor receptor. *Clin Can Res*. 2001;7:2958-2970.	Review article	Description of role of EGFR inhibitors in cancer treatment and EGFR inhibitors in development
NCCN	Bone cancer (chordoma)	Singhal N, Kotasek D, Parnis FX. Response to erlotinib in a patient with treatment refractory chordoma. *Anticancer Drugs*. 2009;20:953-955.	Case report	Erlotinib-induced radiographic and symptomatic response in a patient with imatinib-refractory chordoma
NCCN	Bone cancer (chordoma)	Launay SG, Chetaille B, Medina F, et al. Efficacy of epidermal growth factor receptor targeting in advanced chordoma: case report and literature review. *BMC Cancer*. 2011;11:423.	Case report	Erlotinib-induced lesion regression in an EGFR-expressing chordoma that was imatinib-refractory
NCCN	CNS - leptomeningeal metastases	Grommes C, Oxnard GR, Kris MG, et al. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. *Neuro Oncol*. 2011;13:1364-1369.	Case series	Among 9 patients with non-small cell lung cancer metastatic to brain or leptomeninges, 6 patients had a partial response to high-dose weekly erlotinib.



Lessons from the Compendia

- The process of searching, analyzing, evaluating, and contextualizing evidence at the necessary level of sophistication is laborious and requires substantial methodological and clinical knowledge; likely difficult to recruit and retain qualified personnel in medical publishing
- Without clear criteria for evaluating evidence, inconsistencies ensue
- Finding appropriate domain expertise without ties to industry (conflicts of interest) is close to impossible outside of government

JAMA Oncology | Brief Report

August 25, 2016

Financial Relationships With Industry Among National Comprehensive Cancer Network Guideline Authors

- 84% of compendia authors received general payments from industry (consulting, meals, lodging)

Positive Attributes of Compendia

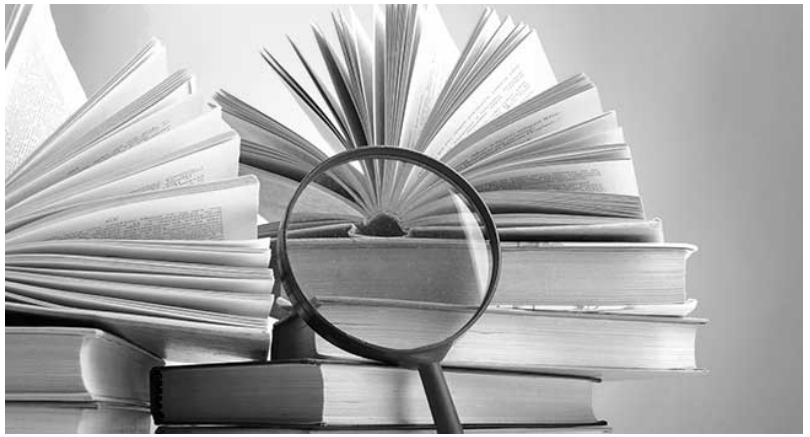
- Consider combination regimens, multimodality therapy, subpopulations
- Capture some updated information and clinical thinking
- Provide information in generally digestible format

Ideal Future Approach – My Opinion

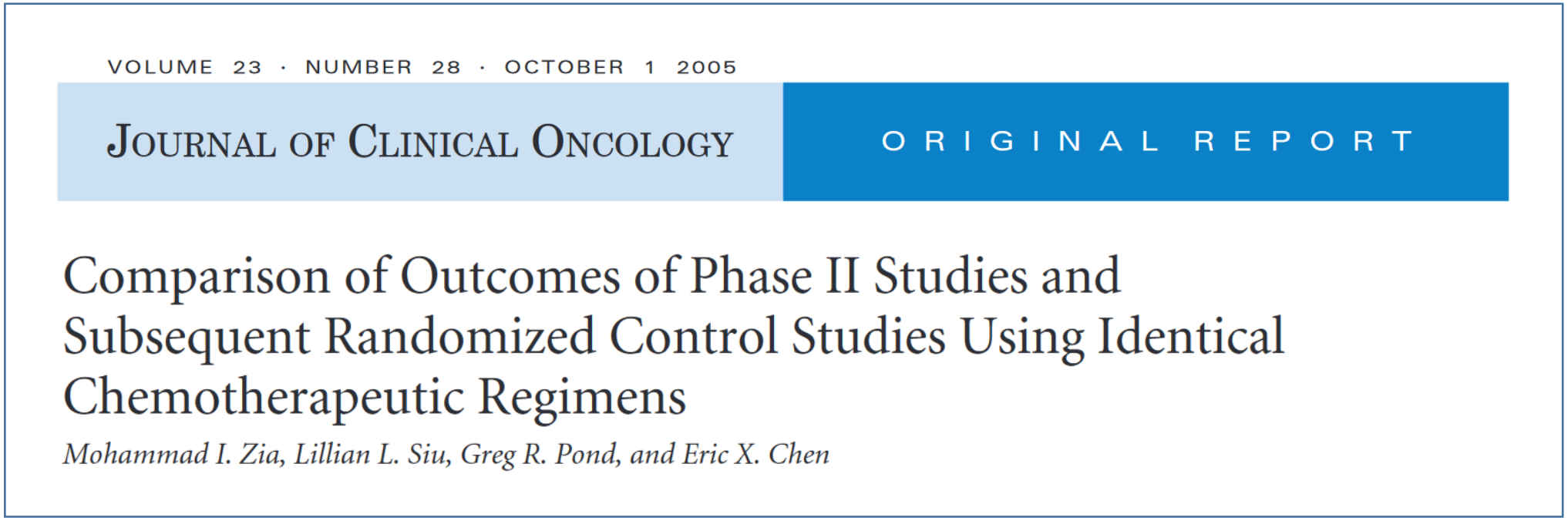
- The FDA will evaluate evidence and initiate update process for all labels
  - Scheduled regular updates
  - Process for immediate update if key new data
- Discontinue compendia legislative designation

What Evidence Should Be Reviewed by FDA?

1. Indications/Usage
   - For new indications:
     - Prospective studies meeting **similar standards for "substantial evidence" as initial labels**
     - Include studies of combination/multimodality regimen data
     - Q: Should FDA review of **individual patient data** be required? *Yes, whenever possible*.
     - Q: Should observational data/RWE or syntheses of underpowered trials be acceptable? *No*.
   - For refining existing indications
     - Population subgroup and biomarker data



What about Phase II Trials?



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

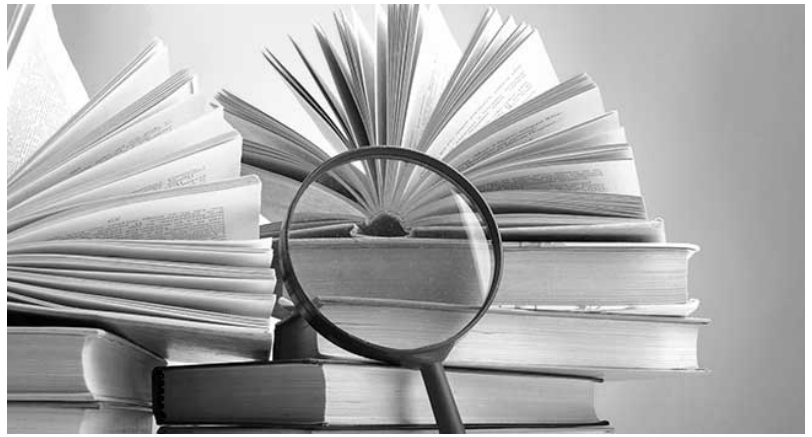
Comparison of Outcomes of Phase II Studies and Subsequent Randomized Control Studies Using Identical Chemotherapeutic Regimens

Mohammad I. Zia, Lillian L. Siu, Greg R. Pond, and Eric X. Chen

- The vast majority of phase III trials using regimens based on phase II regimens are *negative* with substantially *lower response rates* than the prior phase II findings

What Other Evidence Should Be Reviewed by FDA?

2. Dosage/Administration and Safety
   - Surveillance, observational studies/registries/RWE, KOL input
3. Patient Experience
   - Patient-reported outcome/QOL studies, registries



What Expertise is Required?

- Literature searches and quality rating
  - Trained systematic reviewers with clinical orientation
    (model used by ASCO and Cancer Care Ontario for clinical practice guidelines)

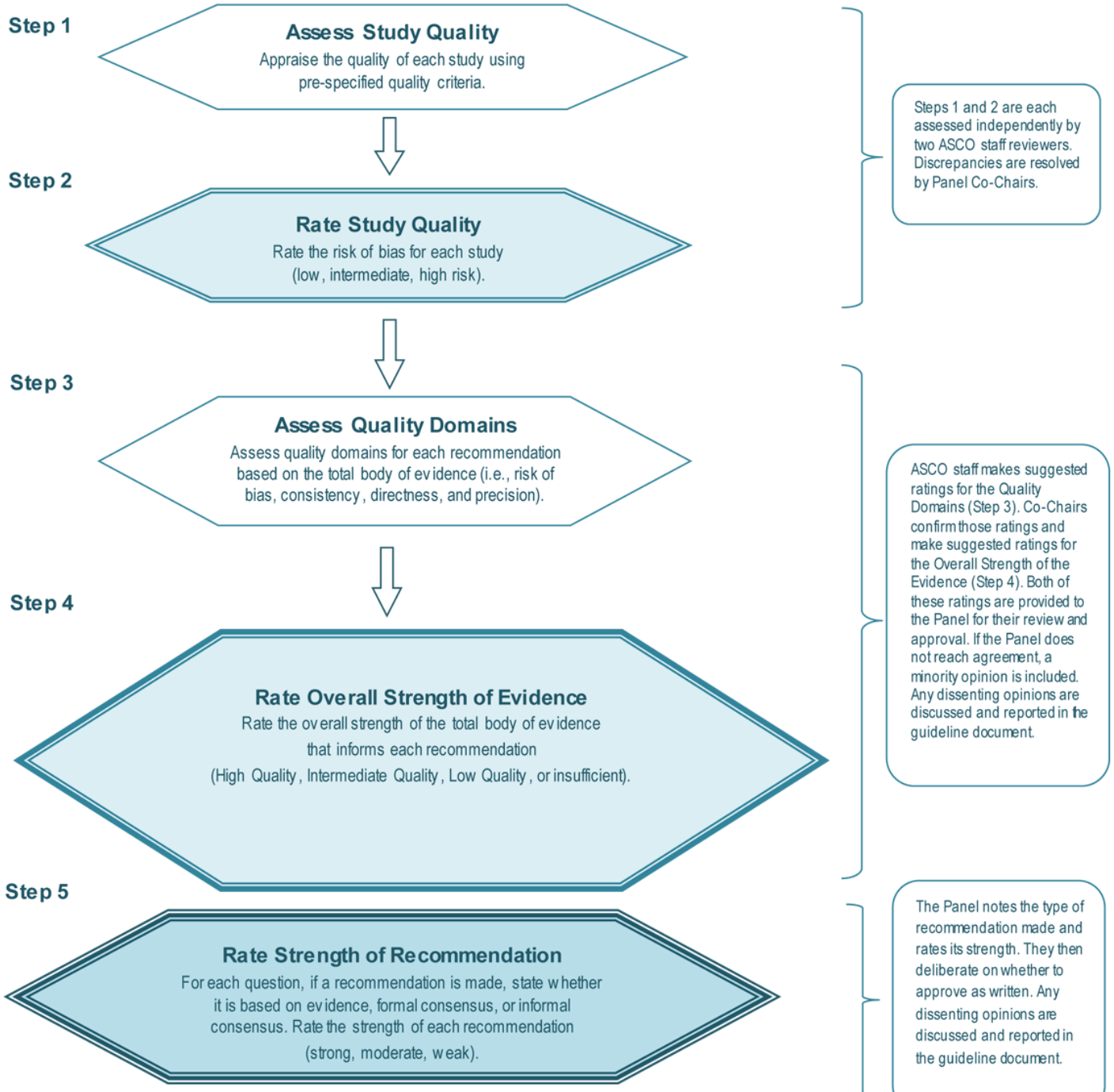
- Evaluation
  - Reviewers similar to current processes for new applications/supplements
  - Consultation with professional organization(s) and/or KOLs

Lessons from ASCO/CCO Clinical Practice Guidelines

- Model for staffing and process
  - Professional systematic reviewers (on staff)
  - Panel with expert knowledge
  - Frequent interactions between systematic reviewers with panel
  - Administrative coordinator curates procedures

- Framing of guidelines differs from labels
  - Based around clinical questions, not specific drugs
  - Rely on publications - **individual patient level data not reviewed**
  - Criteria for evaluating quality of evidence and strength of recommendation

ASCO Evidence Rating Approach



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Conclusion

Goals of future approach

- Provide consistent source of information throughout drug lifecycle to ensure patient safety
- Maintain standard of evidence between new labels and updates
- Avoid real or perceived COIs

Thank You

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