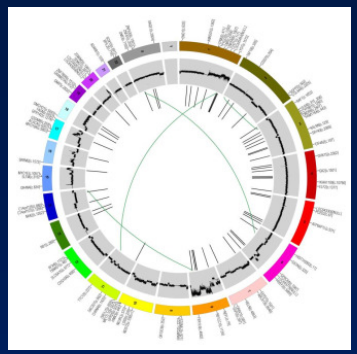
Institute of Medicine

Evidence for Clinical Utility of Molecular Diagnostics in Oncology

PEW DC Conference Center
May 24, 2012



Session I: Evidence Utilization

Guideline Development

Perspective of the American Society of Clinical Oncology

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Disclosures

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- 5UC2-CA148041-02 (NCI; Co-PI)
- 1R01HL095109-01 (NHLBI; Co-PI)
- ANC Study Group Coordinating Center (Amgen; PI)

Other Disclosures:

- Chair, ASCO Guideline Methodology Committee
- Chair, ASCO Venous Thromboembolism in Cancer Prophylaxis and Treatment Guideline
- Chair, ASCO Antiemetic Clinical Practice Guideline
- Chair, ASCO Weight-Based Chemotherapy Dosing Guideline
- Chair, ASCO Sentinel Node Biopsy Guidelines for Early-Stage Breast Cancer and Cutaneous Melanoma

Guidelines and Clinical Outcomes

"Clinicians armed with appropriate assessments and the best evidence-based practice guidelines can reduce some of the unpleasant and frequent side-effects that often accompany cancer and chemotherapy treatment, obtain the best possible clinical outcomes, and avoid unnecessary costs"

Statement from CMS, August 2005

Guideline Development

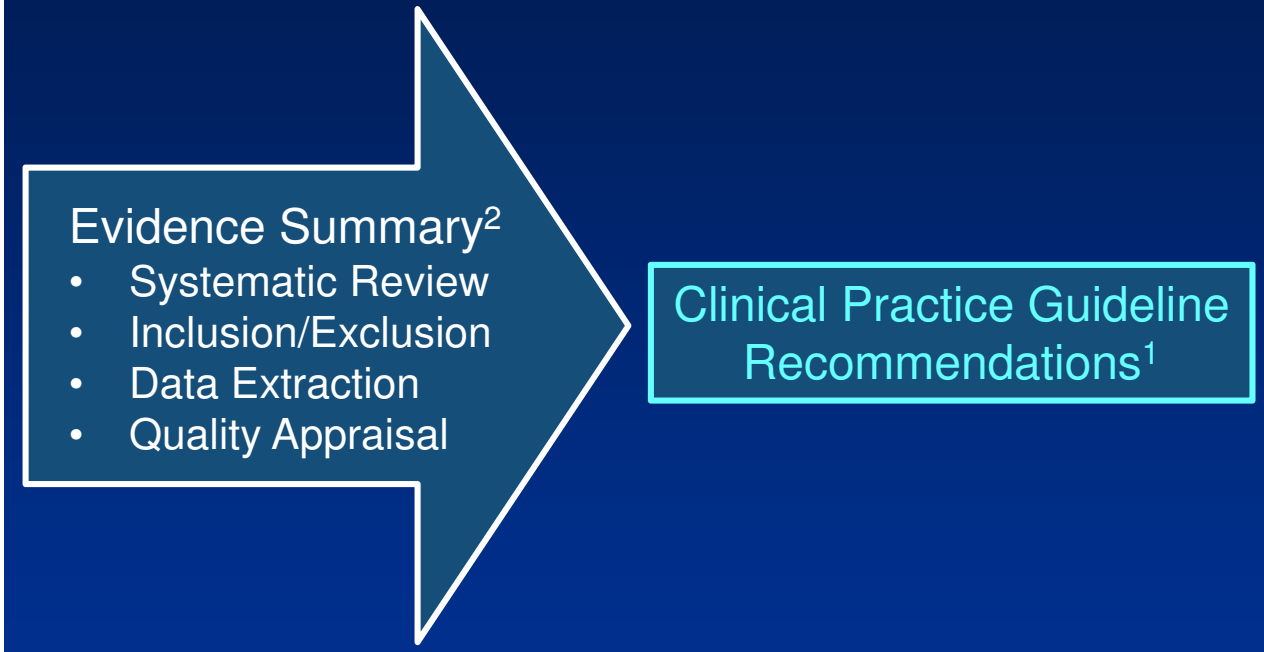
Perspective of the American Society of Clinical Oncology

Clinical Practice Guideline Recommendations[1]

[1] Clinical Practice Guidelines We Can Trust, Institute of Medicine, 2011

Guideline Development

Perspective of the American Society of Clinical Oncology

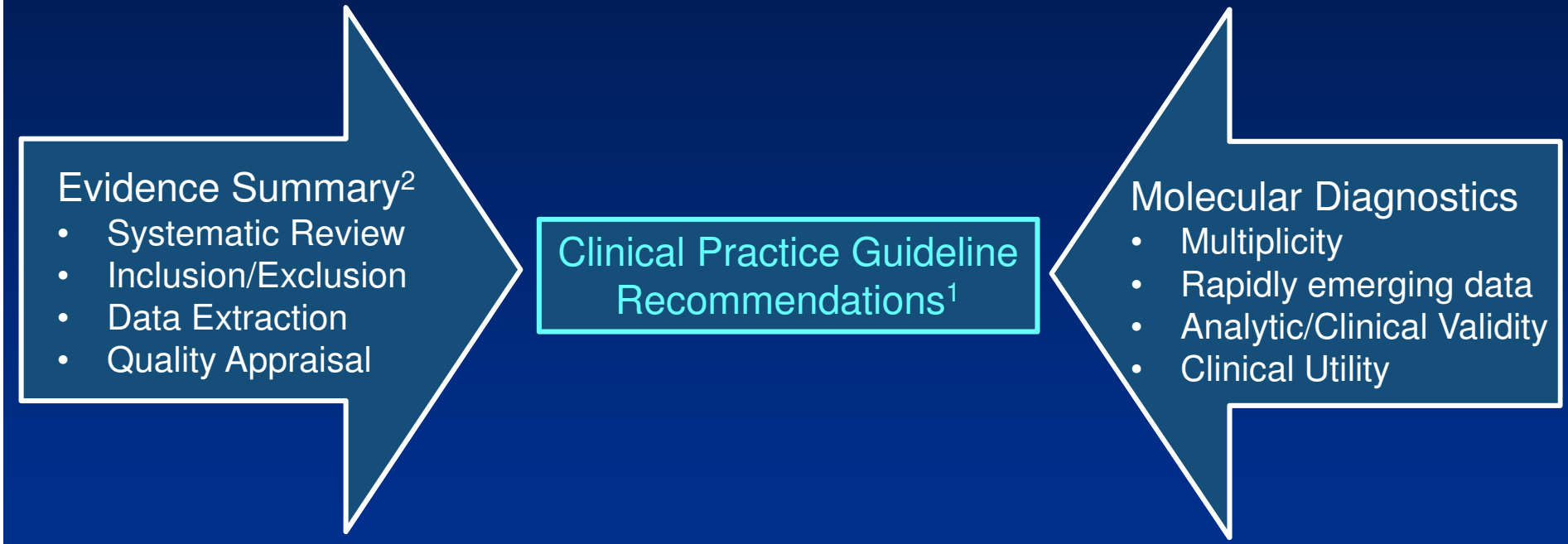


[1] Clinical Practice Guidelines We Can Trust, Institute of Medicine, 2011

[2] Finding What Works in Health Care: Standards for systematic reviews, Institute of Medicine, 2011

Guideline Development

Perspective of the American Society of Clinical Oncology



[1] Clinical Practice Guidelines We Can Trust, Institute of Medicine, 2011

[2] Finding What Works in Health Care: Standards for systematic reviews, Institute of Medicine, 2011

Guideline Development

Perspective of the American Society of Clinical Oncology

[1] Clinical Practice Guidelines We Can Trust, Institute of Medicine, 2011
[2] Finding What Works in Health Care: Standards for systematic reviews, Institute of Medicine, 2011
[3] ASCO CANCER·LINQ in development

Guideline Development

Perspective of the American Society of Clinical Oncology

1 Clinical Practice Guidelines We Can Trust, Institute of Medicine, 2011
2 Finding What Works in Health Care: Standards for systematic reviews, Institute of Medicine, 2011
3 ASCO CANCER·LINQ in development
4 ASCO Quality Oncology Practice Initiative (QOPI)
5 ASCO Pilot Rapid Systematic Review in progress
6 Point-of-care guide on regimen benefit, toxicity and costs

ASCO Guidelines: History

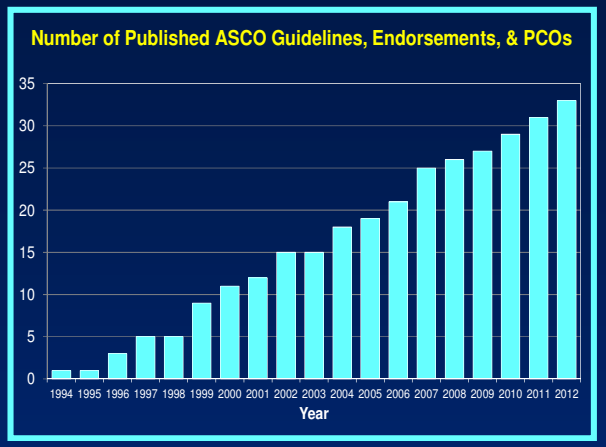
- Board of Directors votes to establish HSRC (Now CPGC) in 1993
- First ASCO guideline published in 1994
- Clinical Tools & Resources derived from guidelines added in 2005
- 3rd most important benefit after JCO and annual meeting
- Recent measures to improve guideline scope and timeliness
  - Annual systematic review updates
  - Endorsement procedure including methodology review approved in 2006
  - Collaborations with other professional organizations: CCO; CAP; SGO
  - Provisional clinical opinion (PCO) to offer more timely response to emerging data
  - Clinical evidence review (CER)
  - Consensus process based on a formal, modified Delphi technique.
- Recent measures to increased dissemination and utilization
  - Additional clinical tools and resources
  - Practice Guidelines Implementation Network (PGIN) to promulgate recommendations

Proposing a ASCO guideline topic

1. Is the burden/importance of the condition/intervention large enough to warrant guideline development?
2. Is there uncertainty or controversy about the effectiveness or safety of available clinical strategies for the condition?
3. Is there sufficient variation in practice in the management of a given condition or use of intervention?
4. Is there sufficient scientific evidence of good quality to allow development of guideline?
5. Is there potential for:
   - impact on clinical decision-making
   - impact on clinical outcomes
   - reduction in practice variation

ASCO Clinical Practice Guidelines

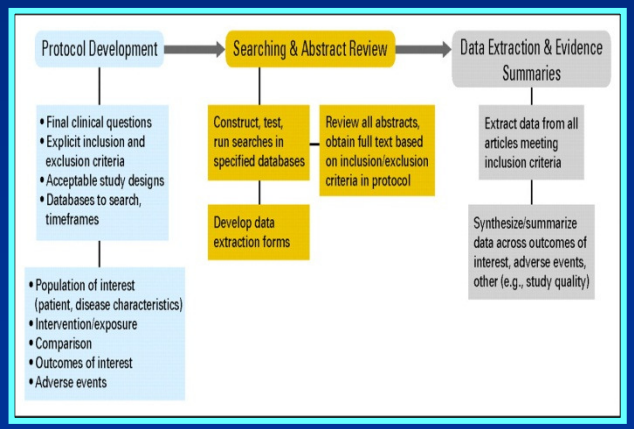
Complex Development Process



Topic selection
Appoint Steering Comm.
Define relevant questions
Multiple lit reviews

Identify Co-Chairs
Assemble panel
Manage COIs

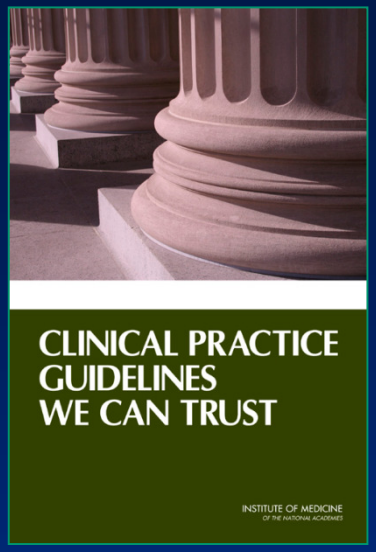
Systematic Review → Guideline Development → Dissemination



Further lit reviews
Review of evidence
Generate recs
Multiple internal and external reviews

JCO/JOP
PGIN
ASCO.org
Quality Indicators

Eight Institute of Medicine Standards



- ✓ Transparent process
- ✓ COIs managed/disclosed
- ✓ Multidisciplinary expert panels
- ✓ Based on rigorous systematic reviews
- ○ Ratings for strength of evidence and strength of recommendation
- ✓ Standardized and clear format
  - ○ Standardized and clear verbiage of recommendations
- ✓ External review
  - ○ Public comment
- ○ Updating plan

ASCO Guidelines

Clinical Tools and Resources

APPROPRIATE CHEMOTHERAPY DOSING FOR OBESE ADULT PATIENTS WITH CANCER

Clinical Practice Guideline

Search Results: QUOROM Diagram

Potentially relevant abstracts identified by electronic searching and screened for retrieval (n = 913)

Articles retrieved for full text review (n=148)

Articles excluded after full text review (n=767)

Articles that met selection criteria for data extraction (n=56)

Articles excluded after full text review (n=92)

Additional articles recommended by Panel members or identified by hand-searching (n=8 on morbidly obese, excluded) (n= 4 other papers, excluded)

("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR tumor [All Fields] OR tumour[All Fields] OR oncolog*[All Fields] OR myeloma*[All Fields] OR lymphoma*[All Fields] OR (Hodgkin*[All Fields] OR lymphoma[All Fields] OR "NHL"[All Fields] OR carcinom*[All Fields] OR adenocarcinom*[All Fields])) NOT (leukemia [All Fields]) AND (dose [All Fields] OR dosing [All Fields]) AND ("drug therapy"[Subheading] OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields])) AND ("obesity"[MeSH Terms] OR "obesity"[All Fields] OR "obese"[All Fields] OR "body weight" [All Fields] OR "body weight" [MeSH Terms] OR "overweight"[MeSH Terms] OR "overweight"[All Fields] OR "overweight"[All Fields] OR ("over"[All Fields] and "weight"[All Fields])) AND (((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR clinical trials as topic[mh] OR controlled clinical trials as topic[mh] OR randomized controlled trials as topic[mh] OR clinical trials, phase II as topic[mh] OR clinical trials, phase III as topic[mh] OR clinical trials, phase IV as topic[mh] OR clinical trial, phase II[pt] OR clinical trial, phase III[pt] OR clinical trial, phase IV[pt] OR random allocation[mh] OR "random allocation"[tiab] OR "randomly allocated"[tiab] OR double-blind method[mh] OR single-blind method[mh]) OR ((random[tiab] OR randomly[tiab] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab]) AND (clinical[tiab] OR control[tiab] OR controlled[tiab] or control groups[mh])) OR ((single[tiab] OR single-[tiab] OR double[tiab] OR double-[tiab] OR triple[tiab] OR triple-[tiab] OR multi[tiab] OR multi-[tiab] OR evaluator[tiab] OR assessor[tiab] OR interviewer[tiab]) AND (mask[tiab] OR masked[tiab] OR masking[tiab] OR blind[tiab] OR blinded[tiab] OR blinding[tiab])) OR ((placebos[mh] OR placebo[tiab] OR placebos[tiab] OR random[tiab] OR randomly[tiab] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomization[tiab]) AND (research design[mh] OR "comparative study"[tiab] OR comparative study[pt] OR evaluation studies as topic[mh:noexp] OR evaluation studies[pt] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR validation studies as topic[mh] OR follow-up studies[mh] OR "follow-up study"[tiab] OR "follow up study"[tiab] OR "follow-up studies"[tiab] OR "follow up studies"[tiab] OR prospective studies[mh] OR prospective[tiab] OR epidemiologic research design[mh] OR epidemiologic methods[mh] OR epidemiologic study characteristics as topic[mh] OR epidemiologic studies[mh] OR intervention studies[mh] OR cross-over studies[mh]))) NOT (clinical trial, phase I[pt] OR clinical trials, phase I as topic[mh]) OR ((meta-analysis[pt] OR meta-analysis as topic[mh] OR "meta-analysis"[tiab] OR "meta analysis"[tiab] OR "meta-analyses"[tiab] OR "meta analyses"[tiab] OR "meta-analyzed"[tiab] OR "meta-analysed"[tiab] OR "meta analyzed"[tiab] OR "meta analysed"[tiab] OR (meta[tiab] AND analysis[tiab]) OR (meta-[tiab] AND analysis[tiab])) OR ((critical[tiab] OR critically[tiab] OR systematic[tiab] OR systematical[tiab] OR systematically[tiab] OR evidence-based[tiab] OR "evidence based"[tiab]) AND (review[pt] OR review[tiab] OR reviews[tiab] OR reviewed[tiab] OR appraise[tiab] OR appraises[tiab] OR appraised[tiab] OR appraisal[tiab] OR assess[tiab] OR assesses[tiab] OR assessed[tiab] OR assessment[tiab] OR evaluate[tiab] OR evaluates[tiab] OR evaluated[tiab] OR evaluation[tiab] OR critique[tiab] OR critiques[tiab] OR analysis[tiab] OR analyses[tiab] OR analyzed[tiab] OR analysed[tiab])) OR ((evidence-based[tiab] OR "evidence based"[tiab]) AND (guideline[tiab] OR guidelines[tiab] OR recommendation[tiab] OR recommendations[tiab] OR consensus[mh] OR consensus[tiab] OR consensuses[tiab])) OR (review[pt] OR review literature as topic[mh] OR consensus development conference[pt] OR consensus development conference, NIH[pt] OR consensus development conferences as topic[mh] OR consensus development conferences, NIH as topic[mh] OR "consensus development"[tiab] OR health planning guidelines[mh] OR guideline[pt] OR practice guideline[pt] OR practice guidelines as topic[mh] OR "practice guideline"[tiab] OR "practice guidelines"[tiab] OR health planning guidelines[mh] OR "standard of care"[tiab] OR "evidence-based medicine"[tiab] OR "evidence based medicine"[tiab] OR "evidence-based care" OR "evidence-based practice"[tiab] OR cochrane database syst rev[ta] OR acp j club[ta] OR health technol assess[ta] OR clin evid[ta]) NOT (case reports[pt] OR case report[tiab] OR editorial[pt] OR editorial[tiab] OR letter[pt] OR newspaper article[pt])))

Dissemination: Publications

ASCO Guidelines

Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Jennifer J. Griggs, Pamela B. Mangu, Holly Anderson, Edward P. Balaban, James J. Dignam, William M. Hryniuk, Vicki A. Morrison, T. May Pini, Carolyn D. Runowicz, Gary L. Rosner, Michelle Shayne, Alex Sparreboom, Lara E. Sucheston, and Gary H. Lyman

Jennifer J. Griggs, University of Michigan, Ann Arbor, MI; Pamela B. Mangu, American Society of Clinical Oncology, Alexandria, VA; Holly Anderson, Breast Cancer Coalition of Rochester, Michelle Shayne, University of Rochester Medical Center, Rochester, Lara E. Sucheston, Roswell Park Cancer Institute, Cancer Prevention and Control, Buffalo, NY; Edward P. Balaban, University of Pittsburgh Cancer Centers Network, Pittsburgh, PA; James J. Dignam, University of Chicago, Chicago, IL; William M. Hryniuk, CarePath, Toronto, Ontario, Canada; Vicki A. Morrison, University of Minnesota Veterans Affairs Medical Center, Minneapolis, MN; T. May Pini, Medical Oncology, Houston, TX; Carolyn D. Runowicz, Florida International University, Miami, FL; Gary L. Rosner, Johns Hopkins University, Baltimore, MD; Alex Sparreboom, St Jude Children's Research Hospital, Memphis, TN; and Gary H. Lyman, Duke University and the Duke Cancer Institute, Durham, NC.

American Society of Clinical Oncology Clinical Practice Guideline Committee Approved: November 9, 2011.

Editor's note: This is the complete American Society of Clinical Oncology (ASCO) Clinical Practice Guideline on Appropriate Chemotherapy for Obese Adult Patients with Cancer, and it provides the recommendations with comprehensive discussions of the relevant literature for each. The Executive Summary of the guideline and Data Supplements with evidence tables and other tables and figures are available at www.asco.org/guidelines/wbd.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

A B S T R A C T

Purpose
To provide recommendations for appropriate cytotoxic chemotherapy dosing for obese adult patients with cancer.

Methods
The American Society of Clinical Oncology convened a Panel of experts in medical and gynecologic oncology, clinical pharmacology, pharmacokinetics and pharmacogenetics, and biostatistics and a patient representative. MEDLINE searches identified studies published in English between 1996 and 2010, and a systematic review of the literature was conducted. A majority of studies involved breast, ovarian, colon, and lung cancers. This guideline does not address dosing for novel targeted agents.

Results
Practice pattern studies demonstrate that up to 40% of obese patients receive limited chemotherapy doses that are not based on actual body weight. Concerns about toxicity or overdosing in obese patients with cancer, based on the use of actual body weight, are unfounded.

Recommendations
The Panel recommends that full weight–based cytotoxic chemotherapy doses be used to treat obese patients with cancer, particularly when the goal of treatment is cure. There is no evidence that short- or long-term toxicity is increased among obese patients receiving full weight–based doses. Most data indicate that myelosuppression is the same or less pronounced among the obese than the non-obese who are administered full weight–based doses. Clinicians should respond to all treatment-related toxicities in obese patients in the same ways they do for non-obese patients. The use of fixed-dose chemotherapy is rarely justified, but the Panel does recommend fixed dosing for a few select agents. The Panel recommends further research into the role of pharmacokinetics and pharmacogenetics to guide appropriate dosing of obese patients with cancer.

INTRODUCTION

Optimal doses of chemotherapy drugs or drug combinations are generally established through randomized controlled clinical trials (RCTs). In adult patients with cancer, drug dosing has traditionally been based on a patient's estimated body surface area (BSA).[1] Despite continuing controversy concerning the value of dose escalation and intensification schedules, there exists compelling preclinical and clinical evidence that reductions from standard dose and dose-intensity may compromise disease-free (DFS) and overall survival (OS) in the curative setting.[2-7] Furthermore, a number of authors have suggested that the optimal delivery of cancer chemotherapy should be considered an indicator of quality of care.[3,8,9] Despite studies confirming the safety and importance of full weight–based chemotherapy dosing (Data Supplement 1 at www.asco.org/guidelines/wbd), many overweight and obese patients continue to receive limited chemotherapy doses.[10-13] Many oncologists continue to use either ideal body weight or adjusted ideal body weight or to cap the BSA at, for example, 2.0 m^2 rather than use actual body weight to calculate BSA. Practice pattern studies demonstrate that up to 40% of obese patients receive limited doses that are not based on actual body weight.[10,12-17] Moreover, considerable variation in the dosing of chemotherapy in overweight and obese individuals with cancer has been documented,[3,13,14,16,18-22] suggesting considerable uncertainty among physicians about optimal dose selection. Such uncertainty likely arises from the fact that many published

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2011.39.9436
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JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Jennifer J. Griggs, Pamela B. Mangu, Holly Anderson, Edward P. Balaban, James J. Dignam, William M. Hryniuk, Vicki A. Morrison, T. May Pini, Carolyn D. Runowicz, Gary L. Rosner, Michelle Shayne, Alex Sparreboom, Lara E. Sucheston, and Gary H. Lyman

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Submitted October 7, 2011; accepted February 21, 2012; published online ahead of print at www.jco.org on April 2, 2012.

American Society of Clinical Oncology Clinical Practice Guideline Committee Approved: November 9, 2011.

Editor's note: This represents a brief summary overview of the complete new American Society of Clinical Oncology (ASCO) Clinical Practice Guideline on Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer and provides recommendations with brief discussions of the relevant literature for each. The complete guideline, which includes comprehensive discussions of the literature, methodology information, and all cited references, and Data Supplements with the evidence tables the Panel used to formulate these recommendations, are available at www.asco.org/guidelines/wbd.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

0732-183X/12/3099-1/$20.00
DOI: 10.1200/JCO.2011.39.9436

A B S T R A C T

Purpose
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Methods
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Results
Practice pattern studies demonstrate that up to 40% of obese patients receive limited chemotherapy doses that are not based on actual body weight. Concerns about toxicity or overdosing in obese patients with cancer, based on the use of actual body weight, are unfounded.

Recommendations
The Panel recommends that full weight–based cytotoxic chemotherapy doses be used to treat obese patients with cancer, particularly when the goal of treatment is cure. There is no evidence that short- or long-term toxicity is increased among obese patients receiving full weight–based doses. Most data indicate that myelosuppression is the same or less pronounced among the obese than the non-obese who are administered full weight–based doses. Clinicians should respond to all treatment-related toxicities in obese patients in the same ways they do for non-obese patients. The use of fixed-dose chemotherapy is rarely justified, but the Panel does recommend fixed dosing for a few select agents. The Panel recommends further research into the role of pharmacokinetics and pharmacogenetics to guide appropriate dosing of obese patients with cancer.

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INTRODUCTION

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ASCO GUIDELINES

Clinical Tools and Resources

Guideline Summary

Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Jennifer J. Griggs, MD, MPH, Pamela B. Mangu, MA, Sarah Temin, MSPH, and Gary H. Lyman, MD, MPH, FASCO, FRCP

University of Michigan, Ann Arbor MI; American Society of Clinical Oncology, Alexandria, VA; and Duke University, Durham, NC

More than 60% of adults in the United States have a body mass index (BMI) over 25 and are considered overweight or obese. Clinicians traditionally order chemotherapy doses based on a patient's estimated body-surface area (BSA) using formulas that were developed decades ago. Despite studies confirming the safety and importance of full weight–based chemotherapy dosing, many overweight and obese patients receive limited chemotherapy doses that are not based on actual weight. When chemotherapy doses are calculated according to actual body weight, and delivered to obese patients, they are less likely to experience toxicity and/or bone marrow suppression. Although poorer outcomes among obese patients are most likely multifactorial, systemic chemotherapy at less than full weight–based dosing and unnecessary dose reductions may partially explain the significantly higher cancer mortality rates observed in overweight and obese individuals. Underdosing of chemotherapy is of particular concern in patients with chemotherapy-responsive and potentially curable malignancies; reductions in standard chemotherapy dose intensity may increase the risk of disease recurrence and mortality.

With these issues in mind, ASCO recently published a new clinical practice guideline on appropriate chemotherapy dosing for obese adult patients with cancer, in *Journal of Clinical Oncology*. The guideline is based on a systematic search and review

THE BOTTOM LIN

**Appropriate Chemotherapy Dosing for Obese Adult Patients Wit
Clinical Practice Guideline**

Intervention
- Recommendations for appropriate chemotherapy dosing for obese adult

Target Audience
- Medical oncologists, pharmacists, oncology nurses

Key Recommendations
- Panel recommends that full weight- based chemotherapy doses be used i particularly when the goal of treatment is cure.
- Clinicians should respond to all treatment-related toxicities in obese pati patients.
- If a dose reduction is used in response to toxicity, consideration should b subsequent cycles, especially if a possible cause for the toxicity (eg, impai no evidence to support the need for greater dose reductions for obese pat
- The use of fixed-dose cytotoxic chemotherapy is rarely justified (except f

Methods
- Systematic review of medical literature and analysis of the medical literat

Additional Information
- The recommendations, clinical questions, and a brief summary of the lit publication (http://jco.ascopubs.org/content/early/2012/05/27/JCO.2011.3
- The full guideline, with comprehensive discussions of the literature, meth tools and resources, can be found at www.asco.org/guidelines/wbd.
- A commentary by Gary H. Lyman is available at http://jop.ascopubs.org/

Journal of Oncology Practice Publish Ahead of Print, published on May 8, 2012 as doi:10.1200/JOP.2012.000623

Commentary

Weight-Based Chemotherapy Dosing in Obese Patients With Cancer: Back to the Future

By Gary H. Lyman, MD, MPH, FASCO, FRCP(Edin)

See accompanying article at jco.ascopubs.org/content/early/recent, doi: 10.1200/JCO.2012.42.8375

Early in the history of modern cancer chemotherapy, preclinical and clinical studies demonstrated that both treatment efficacy and toxicity were associated with a clear dose-response relationship. In experimental tumor-bearing animals, the dose-response relationship is steep for most chemotherapeutic agents, with the steepness of the curve related to specific tumor sensitivity to a particular drug.[1] In fact, for highly sensitive tumors, the dose-response curve is very steep and generally linear.[1] Schabel[2] and Skipper[3] demonstrated in animal tumor models that a reduction in chemotherapy dose of as little as 20% may virtually eliminate an otherwise high complete remission rate and reduce cure rates by as much as 50%.[2,3] Goldie and Coldman[4,5] demonstrated that higher chemotherapy doses reduce the likelihood of resistant malignant clones emerging in tumors. At the same time, Norton and Simon developed mathematical models suggesting that shortening the interval between chemotherapy doses would reduce the opportunity for tumor regrowth and the emergence of drug resistance.[6,7] Prior to the study of new

experience myelosuppression while receiving chemotherapy may subsequently experience improved disease-free and overall survival.[11,12] Although data from prospective randomized controlled trials are less abundant, deliberate randomization to different dose-intensity schedules in early-stage breast cancer has demonstrated a significant association with disease-free and overall survival.[13-15] Although the shape or slope of the dose-response curve varies between cancer types, abundant evidence that patients who receive chemotherapy experience improved survival compared with untreated controls confirms a dose-response relationship between a dose intensity of 0 (untreated patients) and the dose intensity delivered in the trials.[16-18] Extending the theoretical and experimental evidence in favor of shortened dosing intervals with standard doses (dose dense), several clinical trials have demonstrated improved disease-free and overall survival compared with standard dosing and schedule.[19-23]

Therefore, considerable data support the importance of maintaining the chemotherapy dose and schedule used in the definitive clinical trials upon which a treatment indication is based, especially in responsive malignancies treated in the curative setting. Nevertheless, practice pattern surveys have demonstrated that frequent major reductions in chemotherapy dose intensity occur in clinical practice throughout the United States and in other countries.[24-27] These studies have also demonstrated considerable variation and apparent uncertainty in the appropriate dosing of chemotherapy in obese cancer patients with cancer, resulting in dose modification, including the use of an idealized body weight or the capping of the total dose. Such arbitrary dose adjustments are major factors associated with reduced chemotherapy dose intensity received by obese patients with cancer.[26,28] (Figure 1) Most of the reduction in dose intensity associated with obesity is evident from the start of therapy (planned), with no increase in dose reductions associated with toxicity that were planned at the start of treatment. At the same time, studies have demonstrated that obese patients being treated with curative intent have a significantly greater risk of mortality.[29] In a retrospective analysis of the Cancer and Leukemia Group B 8541 trial, Rosner et al found that obese women with early-stage breast cancer who received full-dose-intensity adjuvant chemotherapy experienced no excess toxicity or worse outcome than similarly dosed healthy-weight patients, whereas women who received reduced doses of chemotherapy had a worse failure-free survival.[30] In addition, pharmacokinetic studies have demonstrated that chemotherapy dose calculations should generally be based on actual rather than ideal body

Journal of Oncology Practice Publish Ahead of Print, pub

ASCO Guidelines

Clinical Tools and Resources

APPROPRIATE CHEMOTHERAPY DOSING FOR OBESE ADULT PATIENTS WITH CANCER

Clinical Practice Guideline

ASCO GUIDELINES

Clinical Tools and Resources

Advice for Overweight or Obese Patients and Caregivers

- Physicians will prescribe the right amount of chemotherapy based on a patient's actual weight, but if obese patients or caregivers inquire about dosing, a discussion about the evidence supporting weight-based dosing is appropriate.
- Physicians may have to explain to overweight or obese patients and caregivers that higher doses of chemotherapy are needed to be effective.
- Suboptimal treatment could result if chemotherapy dosing is not weight-based.
- It is important to reassure obese patients that toxicity from the appropriate dose of chemotherapy is not expected to be greater.
- Adverse effects will be monitored closely.
- Patients should be warned that costs may be higher.

Abbreviations
AUC, area under the curve; BMI, Body Mass index; BSA, body surface area; Ht, height; Wt, weight

Source
Griggs JJ, Mangu PB, Anderson H, Balaban EP, Dignam JJ, Hryniuk WM, Morrison VA, Pini TM, Runowicz CD, Rosner GL, Shayne M, Sparreboom A, Sucheston LE, and Lyman GH. American Society of Clinical Oncology (ASCO) Guideline on Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer. *J Clin Oncology*, Published online April 2, 2-12: doi Available at www.asco.org/guidelines/wbd

Disclaimer
This resource is a practice tool for physicians based on an ASCO® practice guideline. The practice guideline and this tool are not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This tool does not recommend any particular product or course of medical treatment. Use of the practice guideline and this resource is voluntary. The full practice guideline and additional information are available at http://www.asco.org/guidelines.

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GUIDELINES Pocketcard

ASCO
American Society of Clinical Oncology
Making a world of difference in cancer care

Weight-Based Chemotherapy

Obese Adult Patients

Consultant:
xxxxxx

2012

Key Points
Diagnosis and Assessment
Calculation Tools for BSA and BMI
Advice for Overweight or Obese Patients

GuidelineCentral.com™

Key Points

- Reductions from an actual weight-based chemotherapy dose and/or reducing … promise disease-free and overall survival in the …
- …ing an adult obese patient with cancer based on the …ht are unfounded.
- … demonstrate that up to 40% of obese patients receive …ot based on actual body weight.
- …ue to use either ideal body weight or adjusted ideal …e BSA at, for example, 2.0 m² rather than use actual …e body surface area (BSA).
- …ese patients continue to receive limited chemotherapy …
- …e same or less pronounced among the obese than the …n full weight-based doses.
- …ond to all treatment-related toxicities in obese patients …o for non-obese patients.
- …c studies have clearly demonstrated that actual …veight should be used in dose calculations for …ts in patients with cancer who are obese.

…mendations

- …when selecting cytotoxic chemotherapy doses (both IV …obesity status, and use full weight-based doses because …s may result in poorer disease-free and overall survival …
- …hemotherapy dosing for morbidly obese patients with …n the goal of treatment is cure, subject to appropriate …omorbid conditions.
- …the same guidelines for dose reduction, regardless of …tients, depending on the type and severity of toxicity, …s, and whether the treatment intention is cure or …
- …ler fixed dosing only with select cytotoxic agents …ycin).
  …*neurotoxicity concerns, vincristine is capped at a maximum dose …rt of the CHOP* [cyclophosphamide, hydroxydoxorubicin …e (Oncovin), prednisone] and CVP [cyclophosphamide, …rednisone] *regimens.*
- …y of the standard formulas.
- …ng recommendations are based on a evidence-based …atic review of the literature, including randomized …rational studies, and pharmacokinetic studies.
- …d agents is not addressed in the guideline.

Calculation Tools for BSA and BMI

- Chemotherapy is usually dosed by square meter of body surface area (BSA). BSA has been chosen rather than body weight as the basis for calculation for two reasons. First, BSA has been demonstrated to provide a more accurate comparison of activity and toxicity for certain drugs. Second, BSA can be more closely correlated with cardiac output, which determines the blood flow to the liver and kidneys, thus influencing drug elimination.
- Average values of BSA– 1.9 m² for a man and 1.6 m² for a woman.
- For adults, a BMI of 25.0 to 29.9 is considered overweight and a BMI of 30.0 or higher is considered obese.

BSA Calculation Resources

BSA Formula Name	BSA Formula	BSA Calculation Tool
Chemotherapy is usually dosed by square meter of body surface area (BSA). BSA has been chosen rather than body weight as the basis for calculation for two reasons. First, BSA has been demonstrated to provide a more accurate comparison of activity and toxicity for certain drugs. Second, BSA can be more closely correlated with cardiac output, which determines the blood flow to the liver and kidneys, thus influencing drug elimination.		
Calvert	Total Dose (mg) = (target AUC) X (GFR + 25)	Scan to use the online Carboplatin Dose Calculator https://hccapps.unsc.edu/hemonc/carboplatin_dose_calculator.htm
DuBois and DuBois	$BSA(m^2) = Wt(kg)^{0.425} \times Ht(cm)^{0.725} \times 0.007184$	Scan to use the online European Society for Medical Oncology calculator http://www.esmo.org/fileadmin/practice/bodymass.php
Gehan and George	$BSA(m^2) = Wt(kg)^{0.51456} \times Ht(cm)^{0.42246} \times 0.0235$	
Haycock, et al.	$BSA(m^2) = Wt(kg)^{0.5378} \times Ht(cm)^{0.3964} \times 0.024265$	
Mosteller (Adults and Children)	$BSA(m^2) = \sqrt{\frac{Ht(in) \times Wt(lb)}{3131}}$ $BSA(m^2) = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$	Scan to use the online MedCalc calculator http://www.medcalc.com/body.html
BMI Calculations	$BMI = \frac{mass\ (kg)}{(height\ (m))^2}$ $BMI = \frac{mass\ (lb) \times 703}{(height\ (in))^2}$	Scan to use the online BMI calculator http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator.bmi_calculator.html/

ASCO GUIDELINES

Clinical Tools and Resources

5 Things to Remember About Patients with Cancer Who Are Obe

1. Many obese patients are under-dosed, which compromises the efficacy of cyt chance for cure.
2. Obese patients should receive weight-based doses.
3. There is no evidence that toxicity will increase with weight-based dosing for p
4. It is ok to talk to patients about obesity and appropriate dosing. It is possible monitoring and managing toxicities.
5. There are a few select agents* that are given in a capped dose and some ther agents, where the data are insufficient to recommend weight-based doses.

Frequently Asked Questions

Q. I've always capped the dose, perhaps because of toxicity concerns. Really – you dose now?

A. Many clinicians are reluctant to prescribe weight-based doses, in fact, studies shov better overall survival. Patients may need extra time and reassurance if they questior Randomized controlled trials (RCTs), observational studies, and pharmacokinetic studies do not support dose capping.

Clinicians are often reluctant to discuss obesity with cancer patients. It can be difficult to reassure patients that increased doses of cytotoxic chemotherapy (IV or oral) do not usually mean increased toxicity.

Empiric decreases from pharmacokinetic findings in drug dose for obese patients do not support dose capping for any agent.

*It is acceptable to cap the dose for some agents, e.g., a maximum dose of 2.0 mg of vincristine when used as part of the CHOP [cyclophosphamide, hydroxydoxorubicin (doxorubicin), vincristine, prednisone)] and CVP [cyclophosphamide, vincristine, prednisone) regimens.

There are insufficient data for addressing dosing for overweight and obese patients receiving targeted therapies.

Appropriate Chemotherapy Dosing For Obese Adult Patients With Cancer: ASCO Clinical Practice Guideline

ASCO Guidelines

Clinical Tools and Resources

Calculation Tools for Body Surface Area (BSA) And Body Mass Index (BMI)

Carboplatin Calculation Resource

Formula Name	Formula
Calvert	Total Dose (mg) = (target AUC) X (GFR + 25)

BSA Calculation Resources

Formula Name	Formula
Chemotherapy is usually dosed by square meter of body surface area (BSA). BSA has been chosen rather than body weight as the basis for calculation for two reasons. First, BSA has been demonstrated to provide a more accurate comparison of activity and toxicity for certain drugs. Second, BSA can be more closely correlated with cardiac output, which determines the blood flow to the liver and kidneys, thus influencing drug elimination.	
Boyd	$BSA\ (m^2) = 0.0003207 \times Ht(cm)^{0.3} \times weight(g)^{(0.7285 - (0.0188 \times LOG_{10}\ weight(g)))}$
DuBois and DuBois	$BSA(m^2) = Wt(kg)^{0.425} \times Ht(cm)^{0.725} \times 0.007184$
Gehan and George	$BSA(m^2) = Wt(kg)^{0.51456} \times Ht(cm)^{0.42246} \times 0.0235$
Haycock, et al.	$BSA(m^2) = Wt(kg)^{0.5378} \times Ht(cm)^{0.3964} \times 0.024265$
Mosteller (Adults and Children)	$BSA(m^2) = SQR\ RT((Ht(cm) \times Wt(kg))/3600)$ or

Types of Biomarker Prognostic and Predictive Studies

1. Phase I: Exploratory Association Studies (derivation)
2. Phase II: Confirmatory Association Studies (validation)
3. Phase III: Comparative Effectiveness Studies
   a. Randomized: guided vs. unguided controls
   b. Nonrandomized: guided vs. unguided concurrent controls
   c. Nonrandomized: guided vs. historical controls

Altman and Lyman, *Breast Cancer Res Treat*, 1998

Levels of Evidence

Level	Definition
I	Prospective, Marker Primary Objective, Well-powered trial or meta-analysis
II	Prospective, Marker Secondary Objective
	MOST BIOMARKER STUDIES
III	Retrospective, Outcomes, Multivariate Analysis
IV	Retrospective, Outcomes, Univariate
V	Retrospective, Correlation with Other Marker No Outcomes

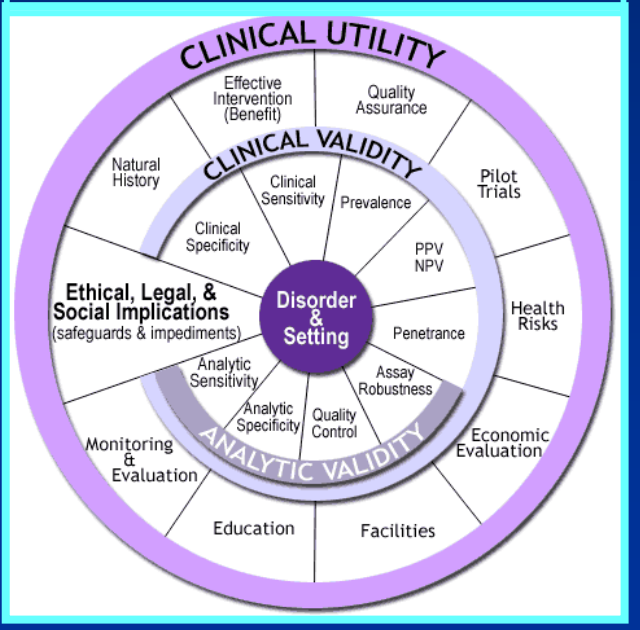
Hayes, et al; *JNCI* 88:1456, 1996

Personalized Medicine in Cancer Diagnosis and Treatment

Biomarkers and Cancer Treatment

- Source studies
  - RCTs or large prospective cohorts
  - Appropriate control groups
  - Clinically relevant endpoints of efficacy and safety
  - Biomarker results available on most patients
- Analytic validity
  - Biomarker importance biologically plausible
  - Good assay performance characteristics
  - Measurement blinded to study outcomes
- Clinical validity
  - Biomarker subgroups & planned analysis prespecified
  - Adequate power
  - Adjust for known prognostic/predictive factors
  - Drug-biomarker interaction
- Clinical Utility
  - Reclassification
  - Decision impact
  - Impact on outcomes (Benefit and Harm)
  - Improved value compared to standard of care

Analytical Validity	Ability of the test to yield consistent results
Clinical Validity	Ability to predict outcome
Clinical Utility	
Risk classification	Percentage of patients reclassified based on test
Therapeutic choice	Percentage of patients where treatment altered
Patient outcome	Effect on outcomes, eg, LE, AEs, quality of life
Economic Validity	Cost benefit and cost-effectiveness



American Society of Clinical Oncology

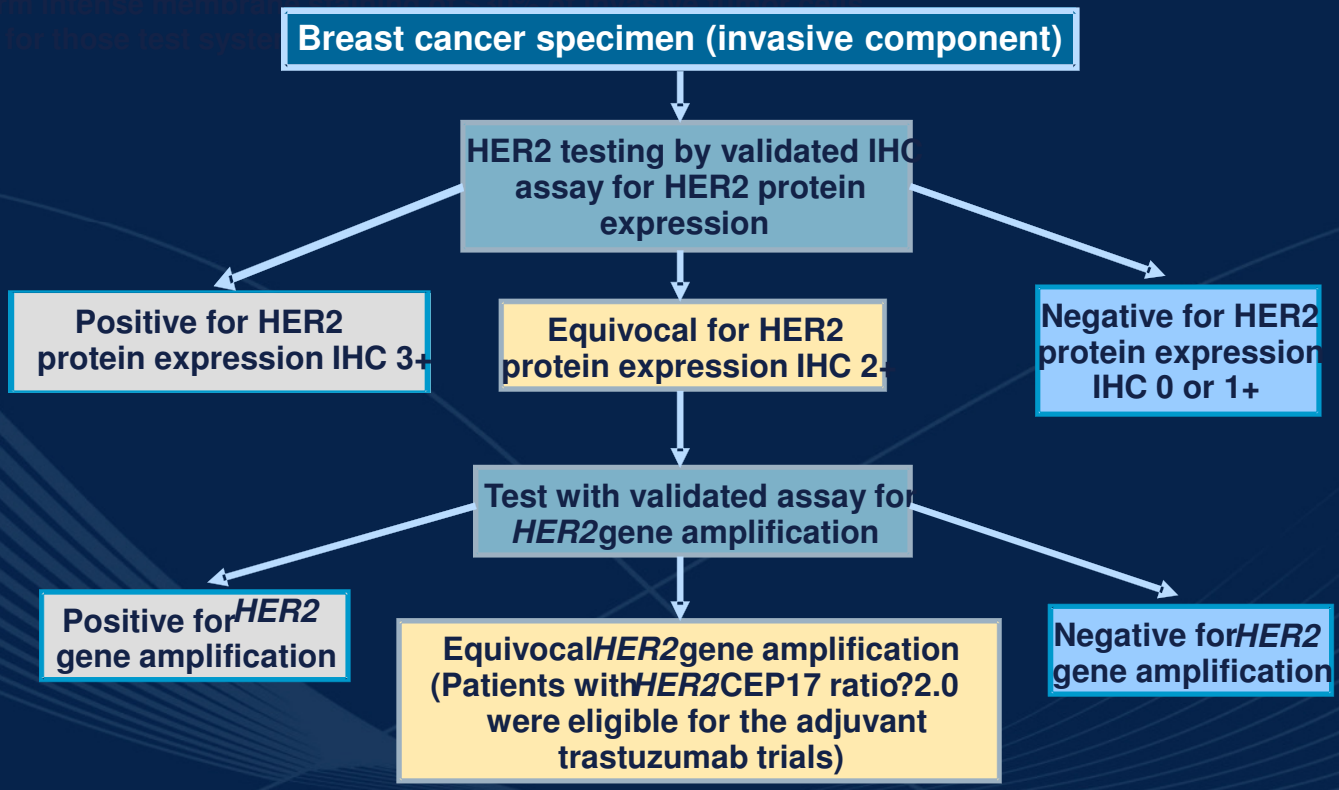
Making a world of difference in cancer care

Guideline Recommendations for HER2 Testing in Breast Cancer ASCO/College of American Pathologists Practice Guideline Recommendations

Result Category	IHC Score HER2 Protein Expression	FISH Score *HER2* Gene Amplification
Positive	3+**	*HER2*/CEP 17 ratio >2.2, or Average *HER2* gene copy number >6 §
Equivocal	2+	*HER2*/CEP 17 ratio of 1.8 – 2.2, or Average *HER2* gene copy number 4 – 6 §
Negative	0 – 1+	*HER2*/CEP 17 ratio <1.8, or Average *HER2* gene copy number <4 §

** Defined as uniform intense membrane staining of [illegible]

§ Signals/nucleus for those test systems [illegible]



American Society of Clinical Oncology

Making a world of difference in cancer care

American Society of Clinical Oncology (ASCO)/ College of American Pathologists (CAP) Guideline Recommendations for Immunohistochemical Testing of Estrogen/Progesterone Receptors in Breast Cancer

ASCO Guidelines for Tumor Markers in Patients with Breast Cancer

	Not Recommended	Recommended
CA 15-3, CA 27.29 (Circulating)	Screening, diagnosis, staging, prognosis, or surveillance. Using alone for monitoring.	For monitoring patients with metastatic disease during active therapy, in conjunction with diagnostic imaging, history, and physical exam.
CEA (Circulating)	Screening, diagnosis, staging, prognosis, or surveillance. Using alone for monitoring.	For monitoring patients with metastatic disease during active therapy, conjunction with diagnostic imaging, history, and physical exam.
ER (tissue), PgR (tissue)	For women with DCIS who are candidates for hormonal therapy.	For diagnosis, treatment planning – on every primary invasive breast cancer and on metastatic lesions if would influence treatment planning.
DNA Flow Cytometry-based proliferation (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Ki67, Cyclin D, Cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
HER2 (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring. Should not be used to withhold or select one specific type of endocrine treatment. Not to Guide use of adjuvant taxane treatment.	For t may anthr
Circulating Extracellular Domain of HER2	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
P53 (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Cathepsin D (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
uPA and PAI-1 (tissue)	Screening, diagnosis, staging, surveillance, or monitoring.	To determine prognosis. For treatment planning. To guide use of CMF-based adjuvant chemotherapy.
Cyclin E Fragments (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Proteomic Analysis (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Multiparameter Gene Expression Analysis (tissue)	Screening, diagnosis, staging, surveillance, or monitoring. Not for prediction of hormonal therapies other than tamoxifen or other chemotherapy regimens.	Oncotype™ for prognosis for patients with node-negative, ER positive breast cancer who will receive tamoxifen. Guiding use of adjuvant tamoxifen and adjuvant chemotherapy (specifically CMF).
Multiparameter Gene Expression Analysis, (tissue) other	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Bone Marrow Micrometastases	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Circulating tumor cell assays	Screening, diagnosis, staging, prognosis, surveillance, predicting or monitoring.	

ASCO Guidelines for Tumor Markers in Patients with Breast Cancer

Diagnosis State	Recommended	Not Recommended
Newly Diagnosed Primary Invasive	ER/PgR test, HER2 test	
Newly Diagnosed Metastatic Invasive	ER/PgR test, HER2 test, CA 15-3 and CA 27.29	Using CA 15-3 and CA 27.29 alone; Using CEA alone
Newly Diagnosed Primary Invasive LN -and either ER and/or PgR +	Onco*type* DX™, uPA and PAI-1 test	Other multiparameter gene expression assays
Newly Diagnosed Primary Invasive Node - and ER and PgR -	uPA and PAI-1 test	
Recurrent Primary Invasive	HER2 test	ER/PgR test; Oncotype Dx; uPA and PAI-test
DCIS	n/a	ER/PgR test

ASCO Guidelines for Tumor Markers in Patients with Breast Cancer

Breast Cancer Tumor Marker Recommendations

– ER, PgR +	Select Endocrine Therapy
– HER2 +	Select Trastuzumab/Lapitinib
– UPA/PAI -1	Avoid Chemo if ER+/Node neg
– Oncotype DX -	Avoid Chemo if ER+/Node neg

Why Are the Guidelines So Conservative?

– Recommend only those markers for which results would change clinical decisions

– Evidence-based

– Lack of Level of Evidence I or II studies

Harris L., et al. *J Clin Oncol*. 2007

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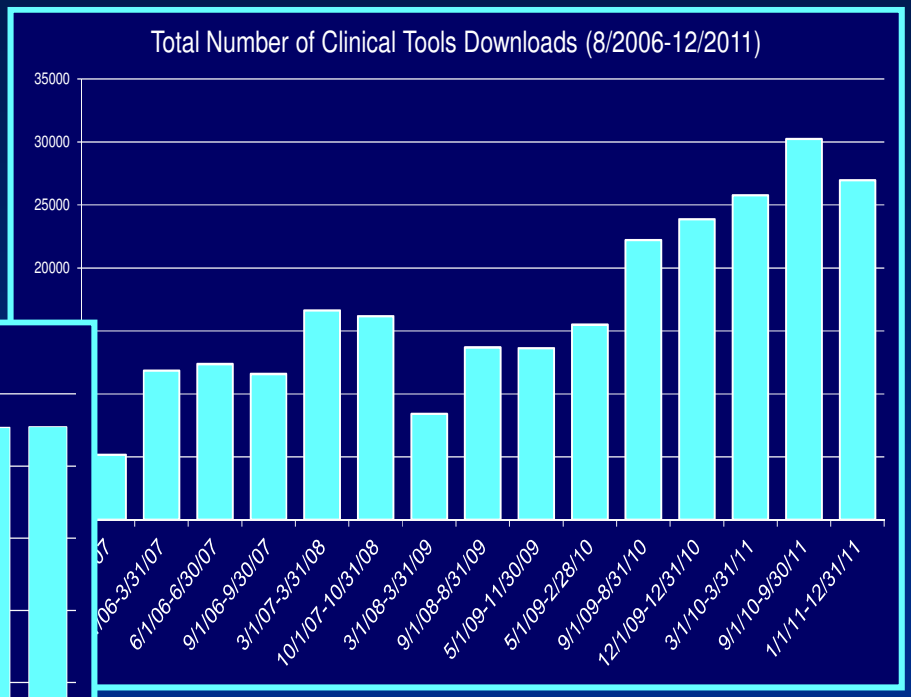
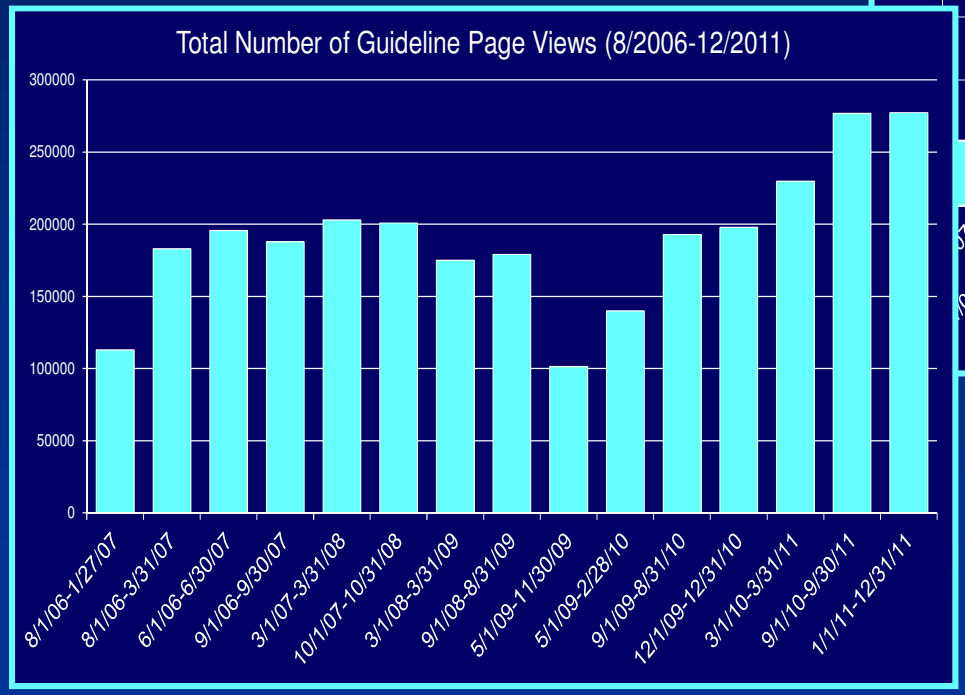
Measuring ASCO Guideline Access and Utilization
ASCO.org Statistics

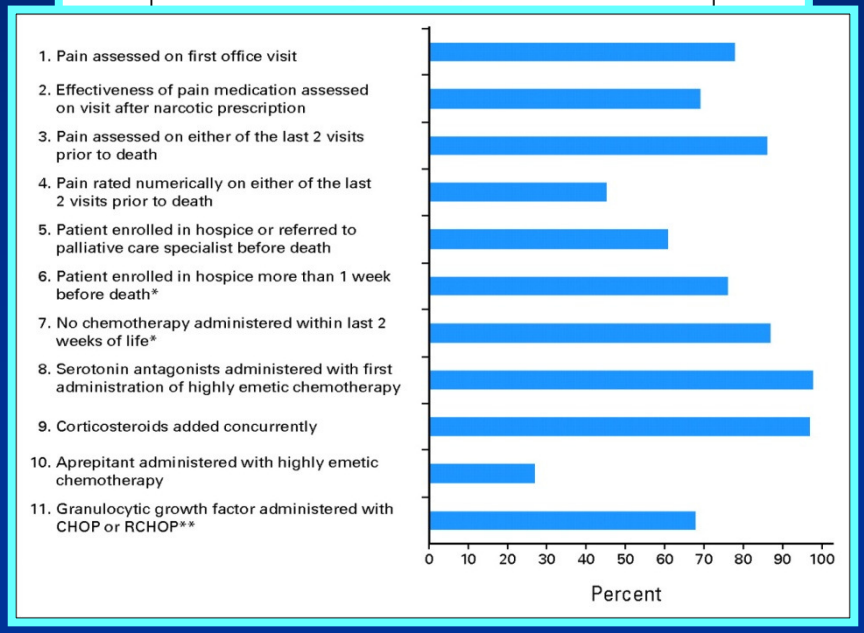




Measuring the Impact of Guidelines

Quality Oncology Practice Initiative (QOPI)

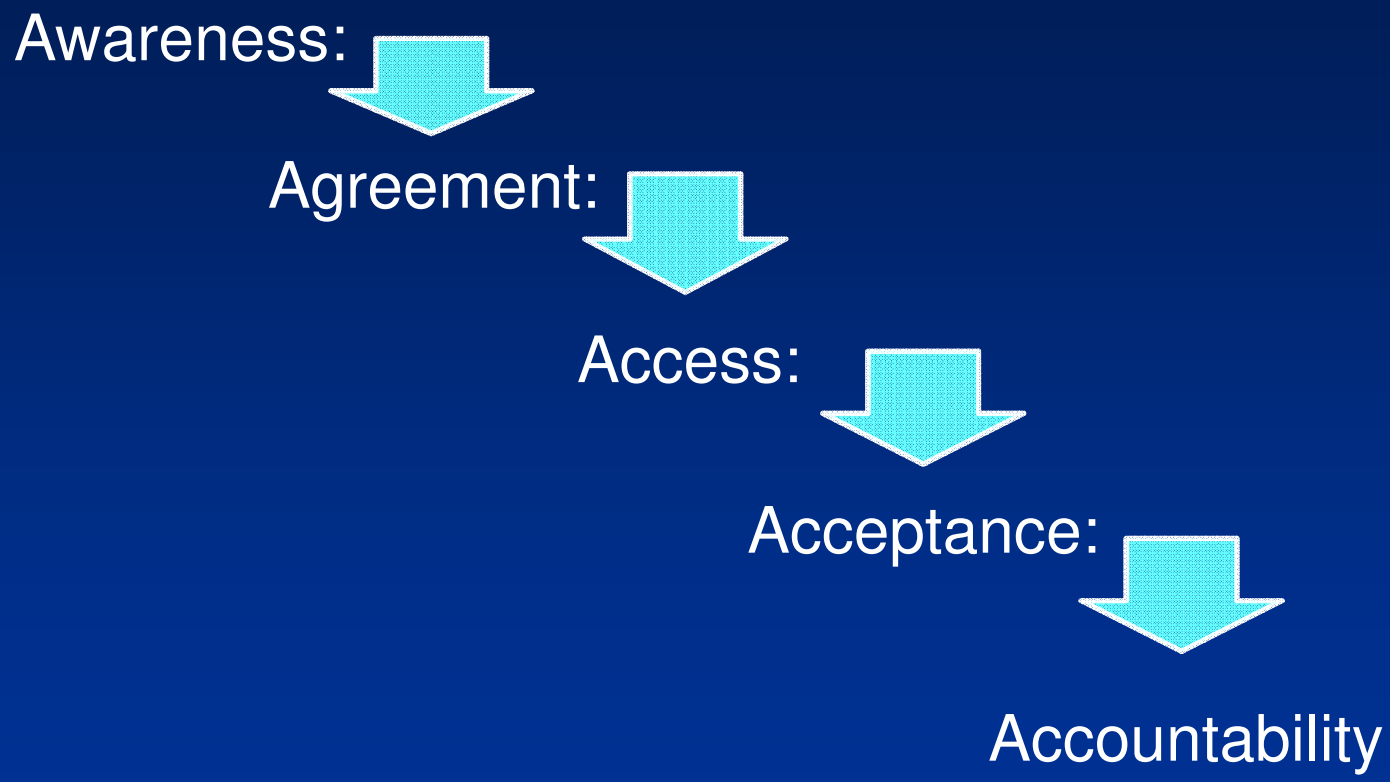
- Quality of care measures identified with all new ASCO Guidelines
- Measures offered to QOPI library of quality of care tools
- Integration of measures in QOPI data collection to evaluate sites and benchmark compliance over time.
- Pilot: QOPI provides a “rapid and objective measurement of practice quality that allows comparisons among practices and over time”



Neuss MN, et al. *J Clin Oncol.* 2005;23:6233-6239.

Practice Guideline Barriers Remain

Awareness, Agreement, Access, Acceptance, Accountability



Cabana MD, et al. JAMA Oct 20 , 1999; 282:1458-1465.

ASCO CANCER·LINQ™
Learning Intelligence Network for Quality

ASCO Vision: Rapid Learning Oncology Care System

PATIENT DATA
- Patient reported information

PROVIDER DATA
- Electronic health record
- Practice management system

PATIENT KNOWLEDGE
- Individualized education and decision support
- Real time symptom management
- Treatment plans and summaries
- Treatment calendars
- Social support

Central Knowledge Base

PROVIDER KNOWLEDGE
- Next-generation QOPI participation and benchmarking reports
- Clinical guidance/decision support tools
- Meet quality reporting requirements
- Patient treatment plan and treatment summary
- Patient identification for clinical research
- Information exchange with other providers

RESEARCHER DATA
- New evidence
- Guidelines/guidance

RESEARCHER KNOWLEDGE
- Comparative effectiveness research
- Health outcomes studies
- Population health studies
- Clinical trial development
- Evidence generation

ASCO CANCER LINQ™
Learning Intelligence Network for Quality

ASCO'S ONCOLOGY
RLS

RLS Knowledge Generation

- Phase IV Studies/Monitoring
- REMS
- Appropriate Use Studies
- Test Quality Measures and Guidelines
- Health Outcomes Studies
- Population Health / Epidemiology Research
- Comparative Effectiveness Research
- Clinical Trials
- Endless other research generation

Cost Estimates Associated with VTE Prophylaxis and Treatment

Management	Drug	Regimens[1]	Estimated Weekly Cost	Estimated 6 month Cost
Prophylaxis				
Hospitalized Medical or Surgical Cancer Patients[4]	Unfractionated Heparin	5000 U q 8 h[2]	$12.08	**$313.95**
	Dalteparin (Fragmin ®)	5000 U daily	$152.40	**$3,962.50**
	Enoxaparin (Lovenox ®)	40 mg daily	$154.59	**$4,019.29**
	Fondaparinux (Arixtra ®)	2.5 mg daily	$199.92	**$5,197.92**
Treatment				
Initial[5]				
	Dalteparin (Fragmin ®)	100 U/kg q 12 hr	$426.73	**n/a**
		200 U/kg daily[7]	$426.73	**n/a**
	Enoxaparin (Lovenox ®)	1 mg/kg q 12 hr	$541.06	**n/a**
		1.5 mg/kg daily[7]	$405.79	**n/a**
	Heparin	80 U/kg IV bolus, then 18 U/kg/hr IV [adjust level based on PTT[8]]	$24.99	**n/a**
	Fondaparinux (Arixtra ®)	<50 kg, 2.5 mg daily	$199.92	**n/a**
		50-100 kg, 5 mg daily	$399.84	**n/a**
		>100 kg, 7.5 mg daily	$599.76	**n/a**
	Tinzaparin (Innohep ®)	175 U/kg daily	$198.17	**n/a**
Long Term[9]				
	Dalteparin (Fragmin ®)	200 U/kg daily for 1 m; then 150 U/kg daily	$334.12	**$8,687.04**
	Warfarin	**5-10 mg po daily; adjust dose to INR 2-3**	**$4.43**	**$115.15**

Lyman GH et al: J Clin Oncol 2007; 25:5490-5505

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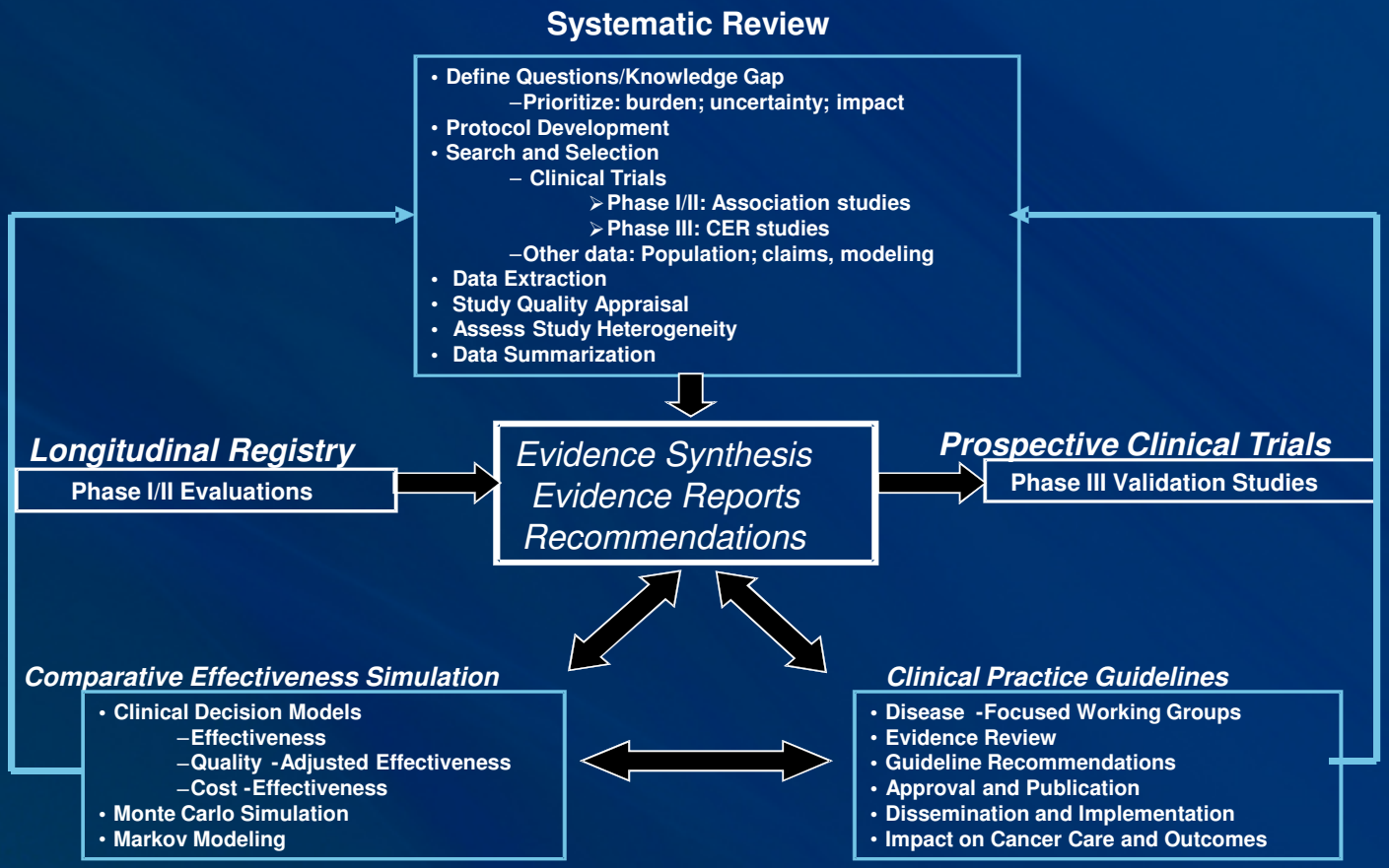
Programs in Clinical Effectiveness of Cancer Pharmacogenomics



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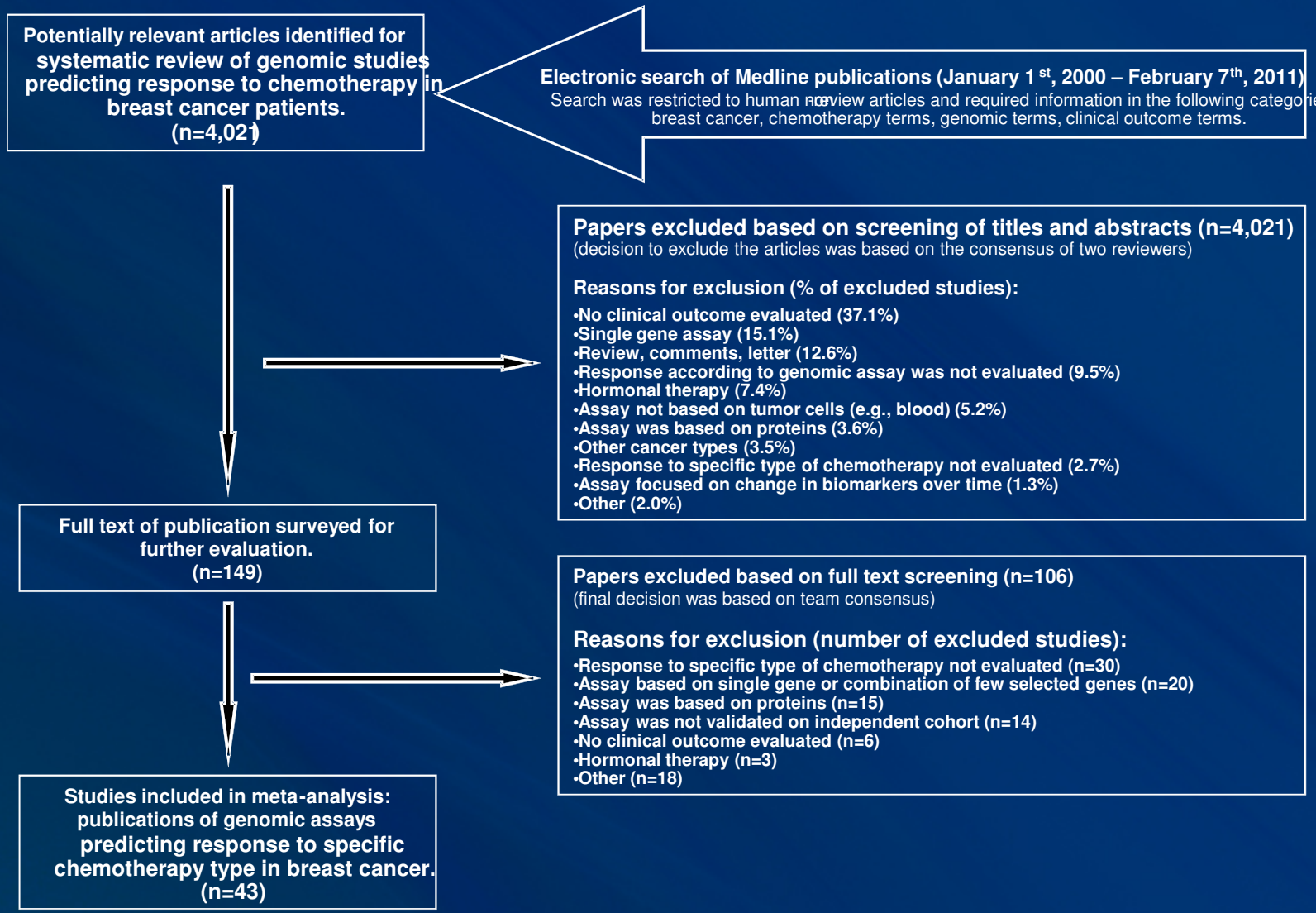
QUOROM Diagram



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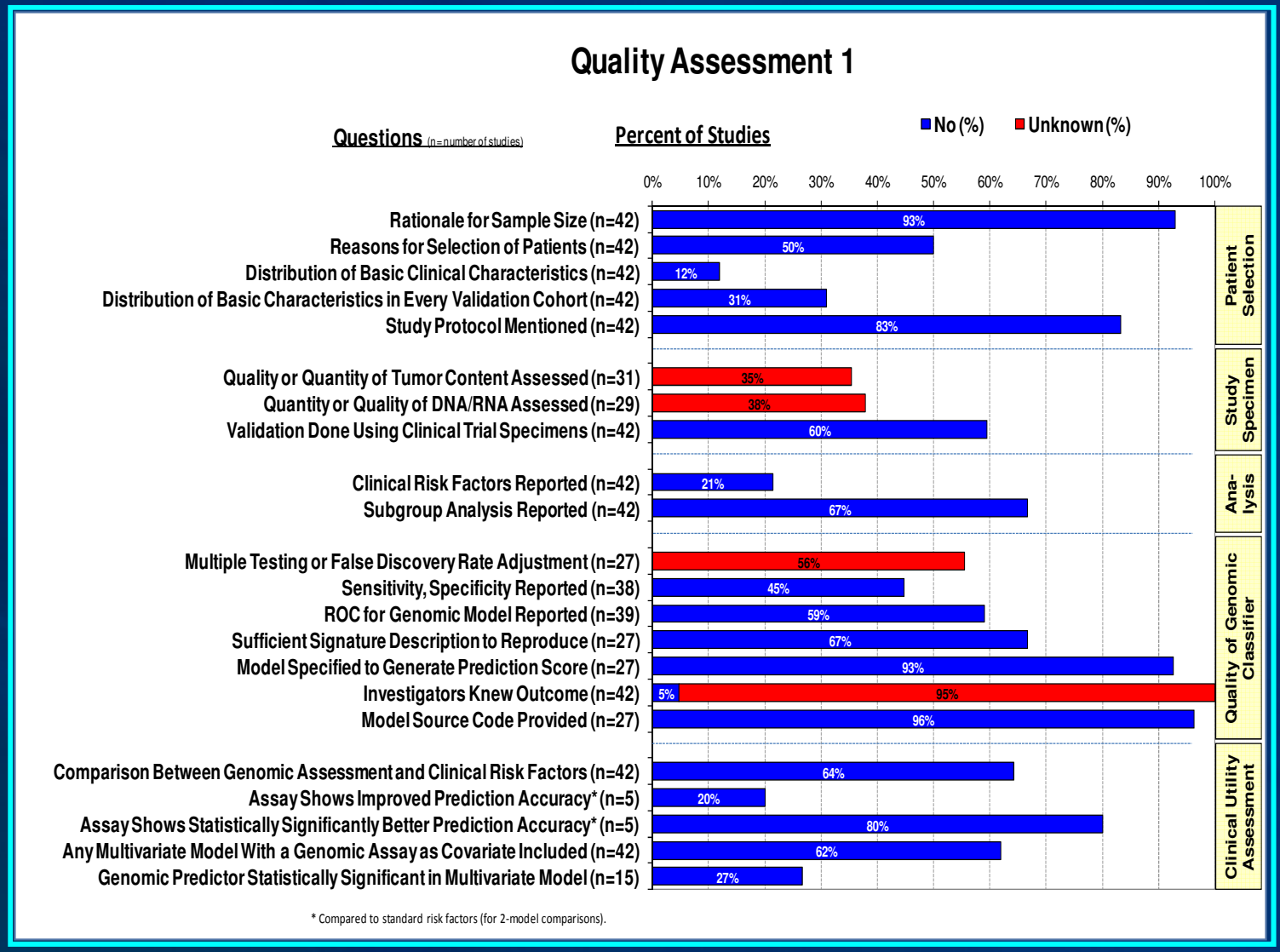

Kuderer NM et al; ASCO 2011

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Quality Appraisal of Multigene Assay Response Prediction Assays

Quality Scoring Based on 22 study parameters

Quality Domains Considered

- Patient selection criteria
- Specimen quality
- Analysis
- Classifier derivation and validation
- Clinical utility

Kuderer NM et al; ASCO 2011

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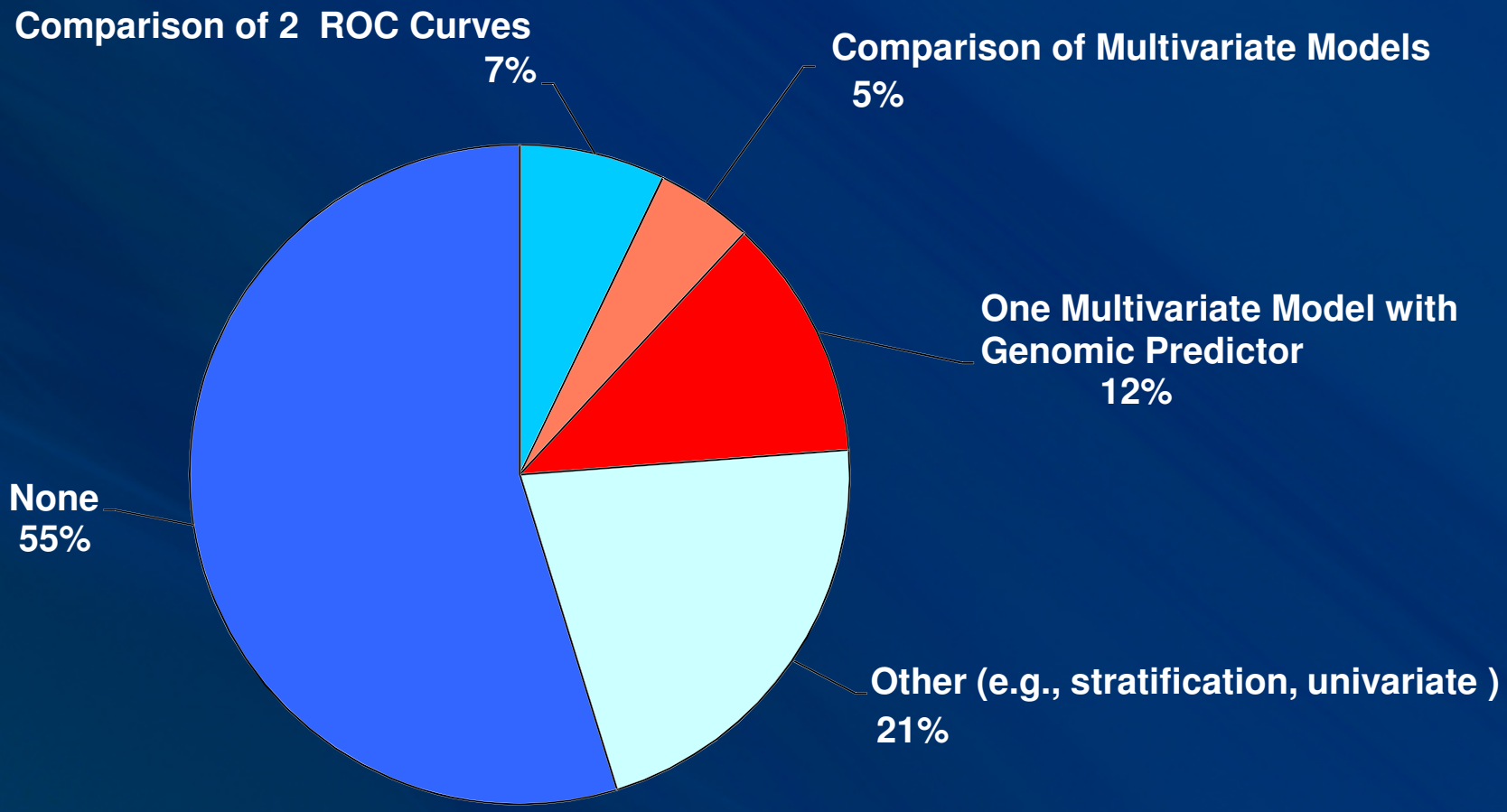
Clinical Validity of the Genomic Classifiers

Statistical Methods Utilized



Kuderer NM et al; ASCO 2011

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Multigene Prediction Signatures in Patients with ESBC

Study Characteristics (N=33)

Multigene Prediction Signatures in Patients with ESBC Study Characteristics

Response Prediction Assay Performance in the Neoadjuvant Setting (N=33)

STUDY	COHORT	DESIGN	SOURCE	STUDY	REGIMEN TYPE	RESPONSE	VALIDATIO
de Ronde (2010) Breas: Cancer Res Treat	NKI-191	Intrinsic	NKI	cohort	AC CD PTC FEC. AT	pCR	EX
Straver (2010) Breas: Cancer Res Treat	NKI-167	MammaPrint	NKI	clirical :rials	AC AC-CD/AD. PTC	pCR	EX
Baselga (2009) JCO	Ixabepilone-trt	10-gene PLR	Ixabepilone-Baselga	clirical :rial	Ixabepilone	pCR	SSM
Liedtke (2009) JCO	MDA (HER2 norm)	GGI	MDA	See Hess 2006	T-FAC	pCR/RCB-1	EX
Lin (2009) Breast Can res treat	Basal-like	Easal type (lin)	MDA-UW	prospective clinical trial	ET T-FAC	pCR	IIS
Parker (2009) JCO	MDA133	FAM50 Intrinsic ROR	MDA	cohort	T-FAC	pCR	EX
Vegran (2009) British Journal of Cancer	TAXHER01 GETNAC1-Val	Vegran-28	Centre Georges Fran _leclerc	phase I clinca trials'	TH or TCH	pCR	IIS
Williams (2009) Cancer Res	MDA133	COXEN	MDA	cohort	T-FAC	pCR	EX
Zemburisu (2009) Int. of Oncology	Japan-Sapporo-Val	classification score	Tokyo, Japar	cohort	docetaxel	PR	SSM
Chang (2006) Breast Cancer Res Treat	Baylor-72	Oncotype DX	Baylor College+ Mount Vernon	cohort	Docetaxel	clinical CR	EX
Julka (2006) British Journal of Cancer	India Gem+Cox->Gem +Cis	Intrinsic	phase II study	Phase II trial	Gem+Dox Gem+Cis	pCR	EX
Natowicz (2006) BVC Bioinformatics	MDA-147	CLDA30-bioinformative	MDA	cohort	T-FAC	pCR	IIS
Salter (2006) PLoS One	MDA133	Duke-T/FAC	MDA	cohort	T-FAC	pCR	EX
Esteva (2007) Breast cancer research	Buzdar-HER2-	CLDA30	MDA	part RTS, part cohort	T/FEC	pCR	EX
Ikeda (2007) Anticancer Research	JAP Doc/6-DF	JAP Doc/6-DF	JAP Doc/6DF	cohort	Docetaxel/5-DFUR	path response	SSM
Lee (2007) PNAS	Baylor-24 Docetaxe	Coxen-Docetaxel	Baylor College+ Mount Vernon	cohort study	Docetaxel	Response	EX
Peintinger (2007) Clin Cancer Res	MDA133(n=61+23)	CLDA30	MDA	cohort	T-FAC	pCR	IIS
Rody (2007) The Breas:	GEPARTRIC-50	Intrinsic	GEPARTRIO trial	clirical :rial GEPARTRIC	TAC TAC->VK	pCR	EX
Hess (2006) JCO	MDA133(n=51)	CLDA30	MDA	cohort	T-FAC	pCR	IIS
Thuerigen (2006) JCO	GEDoc	Thuerger-512	Heidelberg	clirical :rial	GEDoc	pCR	IIS
Iwao-Kozumi (2005) JCO	Jap-Doce-Val	Jap-Doce	Jap-Doce	cohort study	Docetaxel	CR or PR	IIS
Modlich (2005) J Translational Medicine	Dusseldorf-83	k-NN	City Hospital Dusseldorf	cohort	EC	pCR	IIS
Rouzier (2005) Clin Cancer Res	MDA133(n=82)	Intrinsic	MDA	cohort	T-FAC	pCR	EX
Ayers (2004) JCO	MDA42-Val	Ayer-74	MDA	cohort	T/FAC	pCR	IIS
Ocutent (2011) Clinical Cancer Research	MDACC/MAQC-142	39-gene p53 status	MDA	cohort study	T/FAC	pCR	EX
Naoi (2011) Cancer	Osaka-PFEC	GGI	Osaka University	cohort study	P-FEC	pCR	EX
Ertel (2011) Cell Cycle	MDA133ER+	RE-loss signature	MDA cohort ' ER+ as in Ertel	cohort	FAC	pCR	EX
Rodriguez (2010) Breat Can Res. Treat	BCM2-Baylor Triple negative	DNA repair signature	Baylor College of Medicine	cohort study	AC	pCR	EX
Tabchy (2010) Clin Cancer Res	MDA-RCT TFAC	CLDA30	MDA TFAC RCT	RCT	T/FAC	pCR	EX

Lyman GH et al; AACR-SABCS 2011

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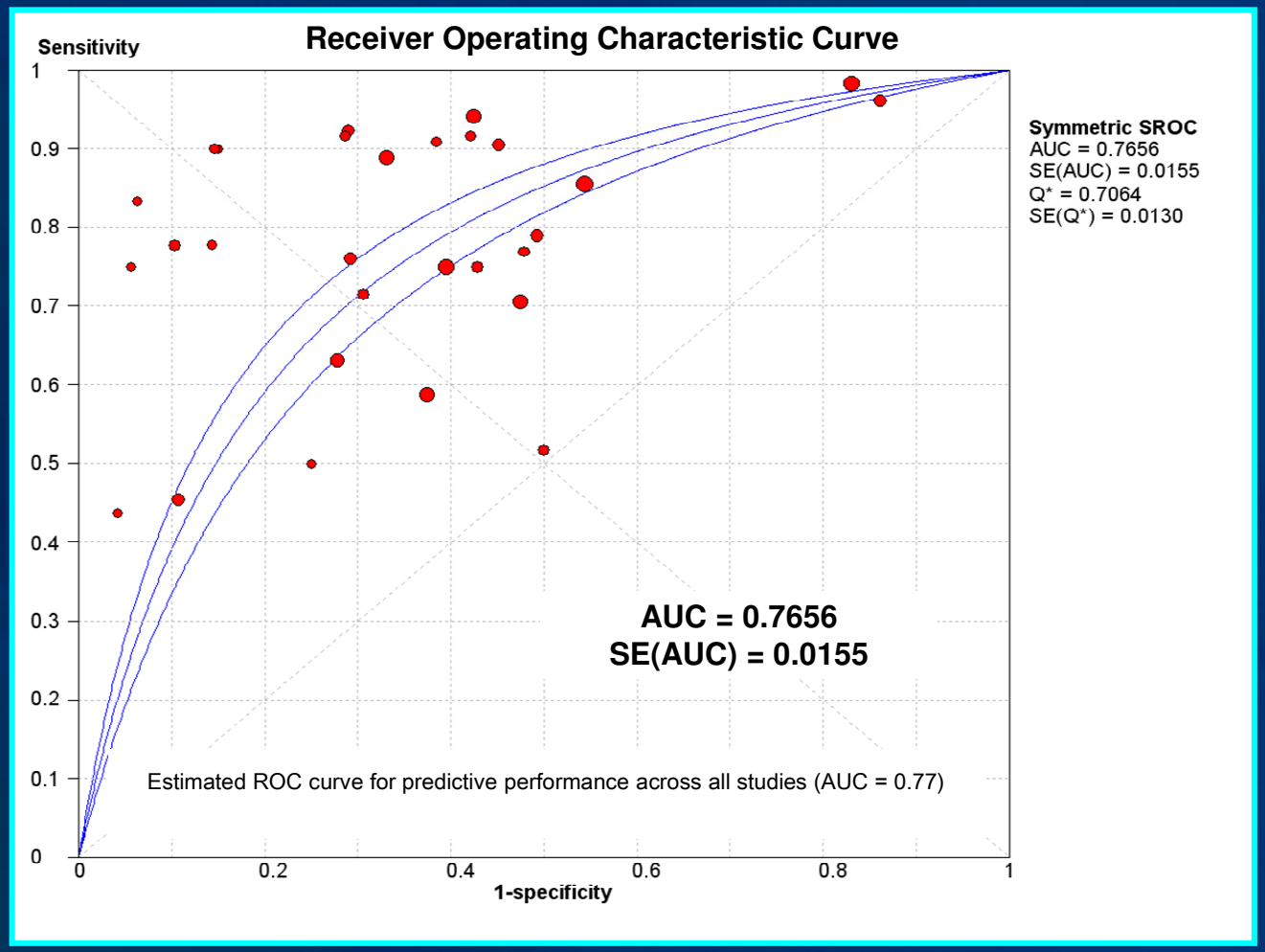
Multigene Prediction Signatures in Patients with ESBC

Response Prediction Assay Performance in the Neoadjuvant Setting (N=33)



Lyman GH et al; AACR-SABCS 2011

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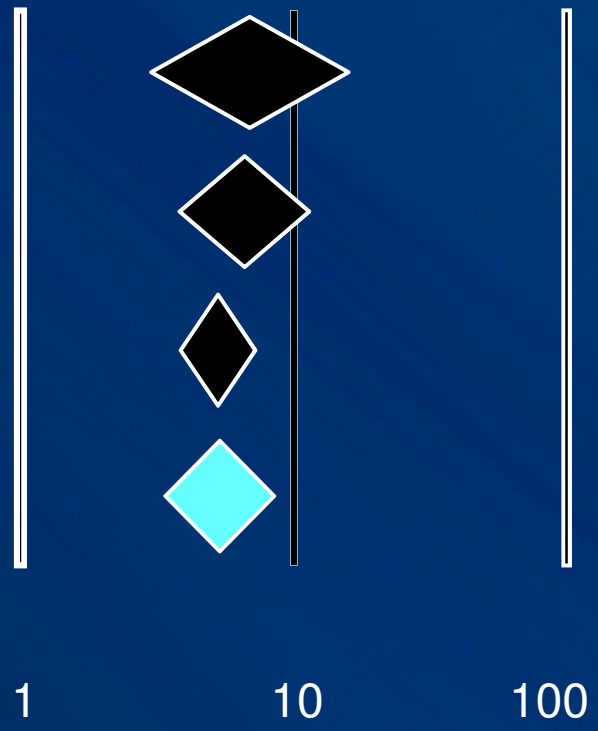
Method of Genomic Classifier Development

Study Design	Statistics for each study			Diagnostic Odds Ratio [95% CI]
	MH OR	[95% CLs]	p-Value	
Intrinsic	6.935	3.019	15.933 <.0001	
Prognostic	6.609	3.816	11.446 <.0001	
Response	5.313	3.877	7.280 <.0001	
Overall	5.788	4.462	7.509 <.0001	



$P_{interaction}$=.103

Lyman GH et al; AACR-SABCS 2011

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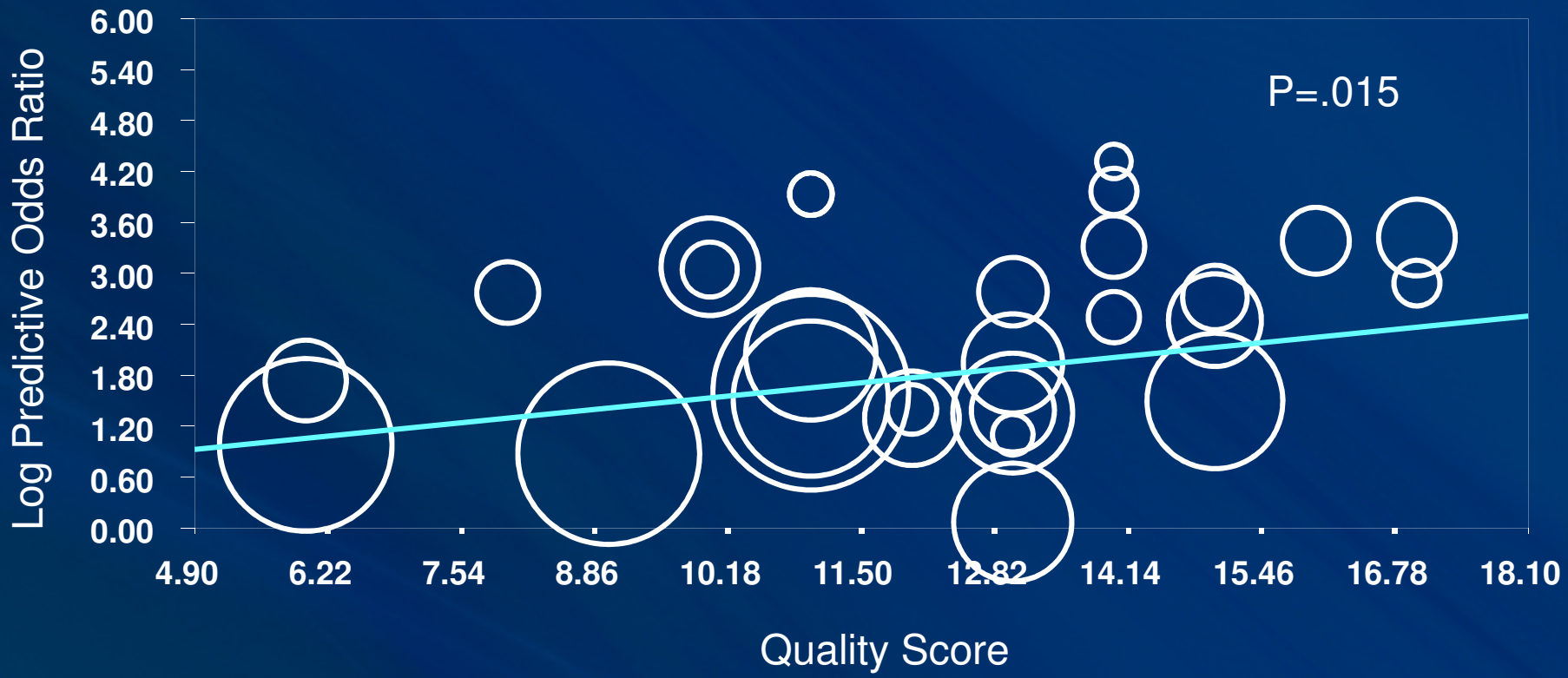
Regression of Quality Score on Predictive Odds Ratio



Lyman GH et al; AACR-SABCS 2011

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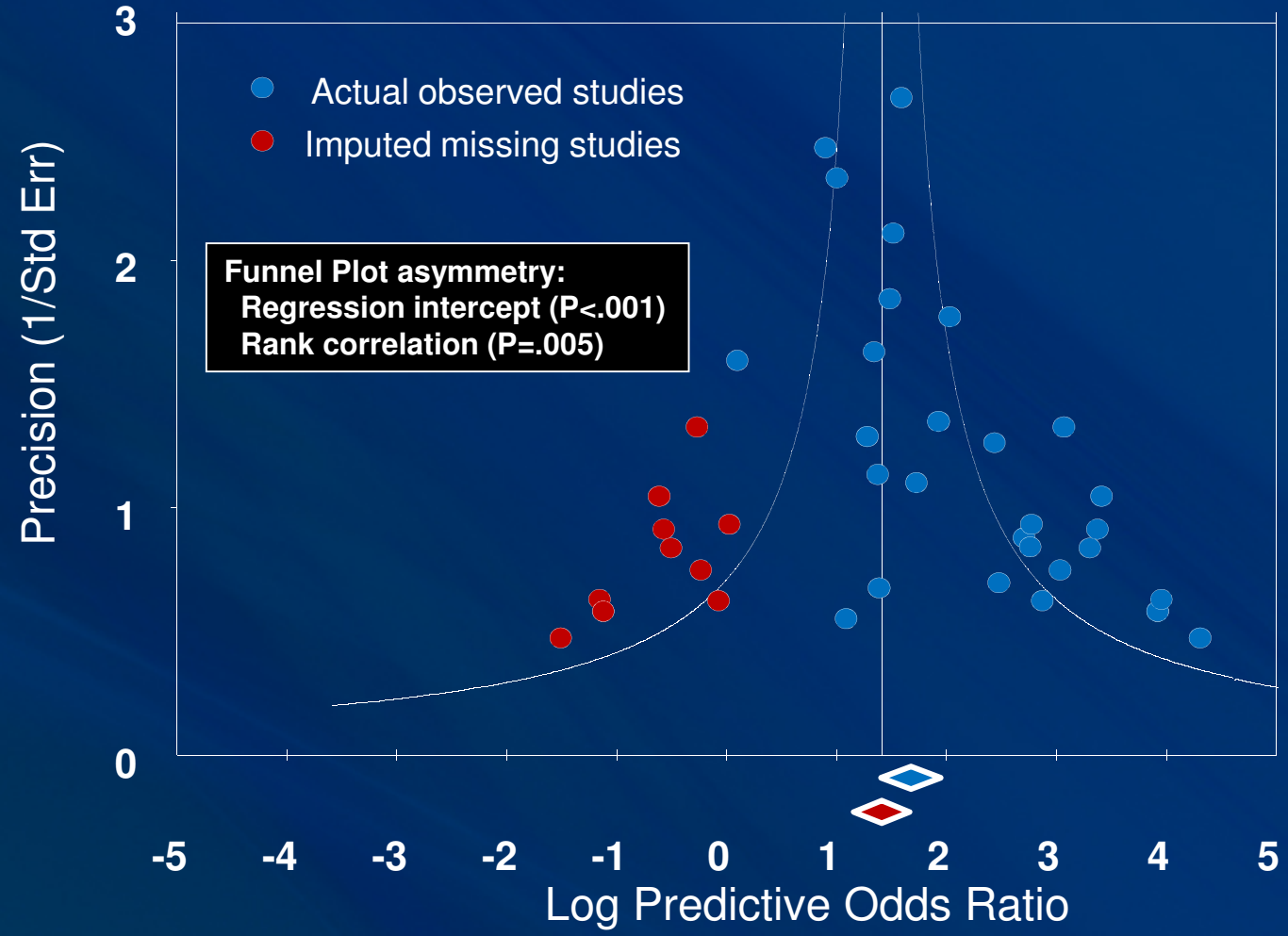
Funnel Plot of Precision by Log Predictive Odds Ratio



Adjusted POR: 4.09 [95% CI: 3.18 – 5.28]

Lyman GH et al; AACR-SABCS 2011

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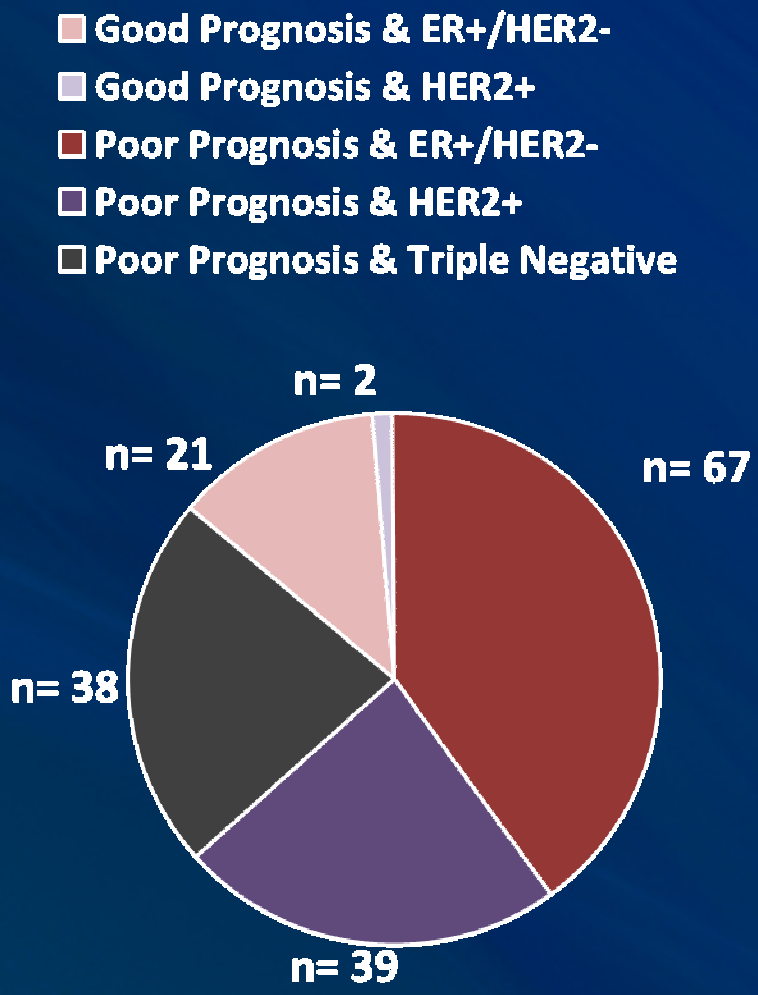

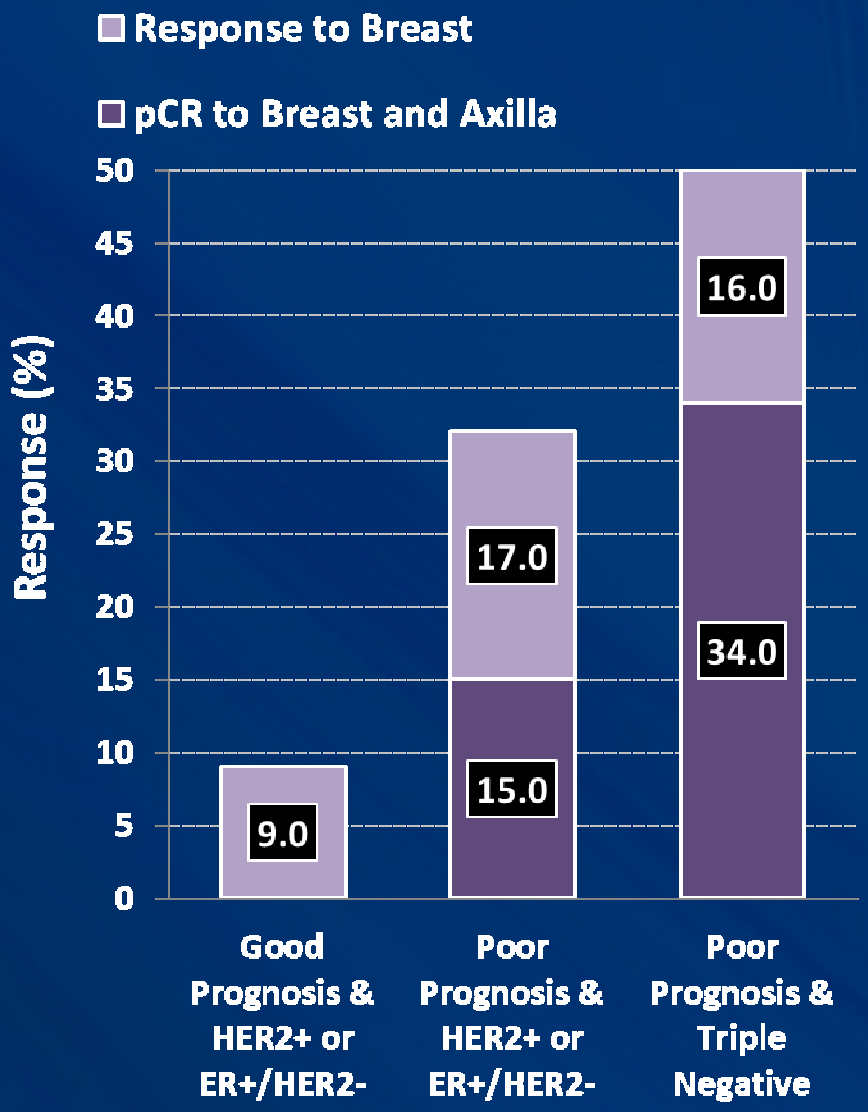

Culakova E et al; AACR-SABCS 2011

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Multigene Prediction Signatures Conclusions

- A compelling need exists for greater methodologic rigor and standardization of reporting.
- Analytic and clinical validity of genomic response prediction assays should be evaluated in patient cohorts independent of those utilized for signature development.
- The clinical utility of these assays must then be further assessed ideally in comparative effectiveness studies compared to common utilized clinical and laboratory measures.

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Personalized Medicine and Cancer Supportive Care

Where do we go from here?

- Innovative clinical trial designs
- Better data capture of treatment-related complications in pivotal RCTs and post approval.
- Strongly encourage routine tumor and blood sample collection for concurrent or future biomarker development and validation in pivotal trials of new targeted therapies
- Go beyond clinical validity to studies of clinical utility to demonstrate meaningful balance of effectiveness and toxicity compared to conventional strategies
- Reach consensus of stakeholders on the appropriate value of diagnostic, treatment and prevention strategies.

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Targeted Therapies and Predictive Biomarkers

Recommendations for Co-Development

1. Source studies should be well designed, large, RCTs with appropriate control groups and clinically relevant endpoints of efficacy and safety.
2. Biomarker should be based on a biologically plausible rationale, have good test performance and reproducibility.
3. Biomarker results should be available on a majority of subjects with a detailed accounting of the reasons for unavailable samples or results.
4. Biomarker subgroups and the planned analysis prespecified.
5. Adequate power to establish with confidence any differential treatment effect in subgroups based on the biomarker.
6. Biomarker measurement should be blinded to the treatment group assignment and study outcomes.
7. Appropriate adjustment for multiple testing.
8. Formal testing of any drug-biomarker interaction.
9. Results adjusted for all known prognostic and predictive factors.
10. Consistent findings on biomarker observed in at least two large trials

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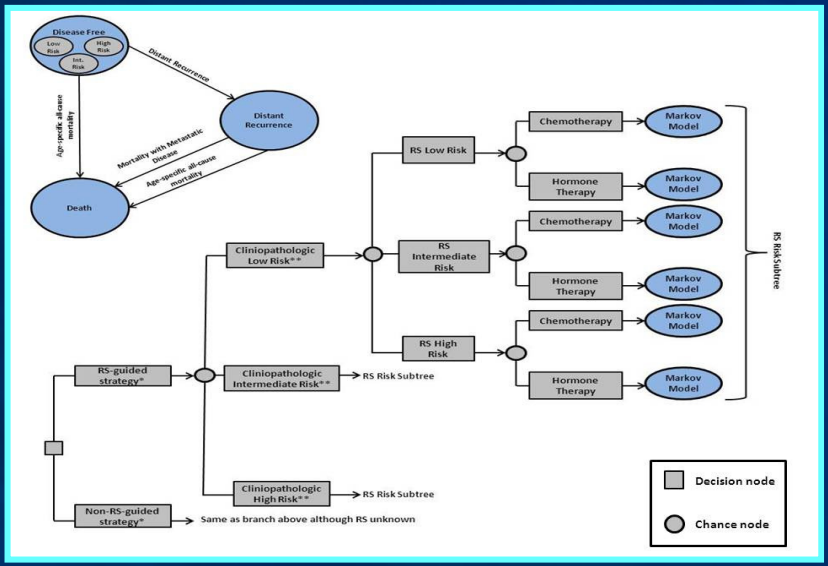
Cost-Effectiveness of Oncotype DX in the Setting of Multifactorial Decision Making for Chemotherapy in Early-Stage Breast Cancer*

Shelby D. Reed, PhD; Michaela A. Dinan, PhD[1]; Kevin A. Schulman, MD; Gary H. Lyman, MD



Health state utilities	Mean (SE)
Chemotherapy in the first year	0.48 (0.06)[4]
Hormonal therapy	0.68 (0.06)[4]
Remission	0.68 (0.06)[4]
Distant recurrence	0.42 (0.06)[4]
Direct medical costs, $	**Mean (SE)**
21-Gene Recurrence Score Assay	4075
Chemotherapy, first year	16,947 (1655)[5]
Hormonal therapy, annually for 5 years	105
Monitoring and follow-up during remission, annually for up to 10 years	1,108 (61)[6]
Distant recurrence, one-time cost	17,478 (2,444)[7]
Indirect costs, $	**Mean**
Absence from work attributable to chemotherapy	12,686[3]
Patient time during last year of life with metastatic breast cancer	3,902[8]

% of women by risk group		RS Assay Risk Group[1,2]		
Clinicopathologic risk group	All	Low	Intermediate	High
Low	53%	0.61	0.24	0.15
Intermediate	19%	0.46	0.19	0.35
High	29%	0.34	0.21	0.45
% Adjuvant Chemotherapy		**RS Assay Risk Group[1,2]**		
Clinicopathologic risk group	All	Low	Intermediate	High
Low	0	0.05	0.10	1.0
Intermediate or High	1.0	0.25	0.62	1.0

* ASCO 2012; Chicago IL

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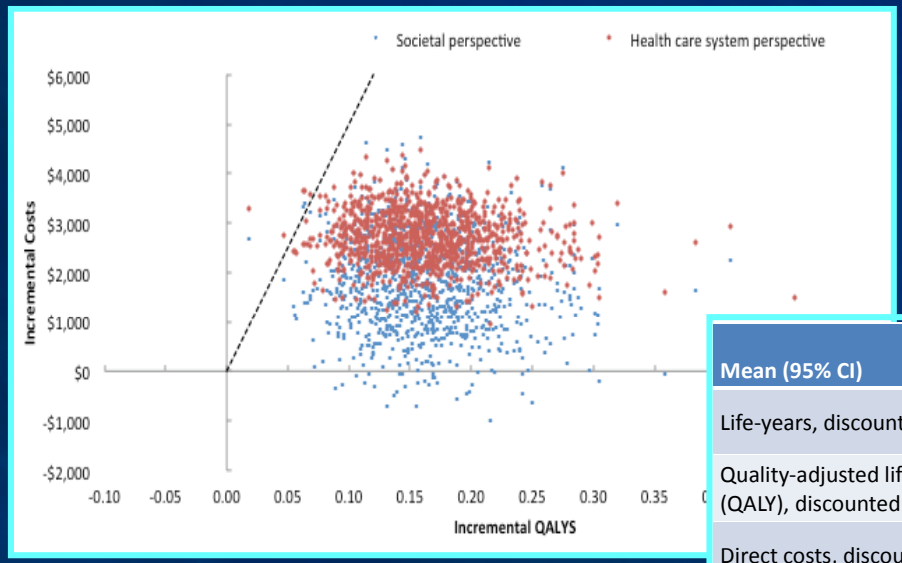

Mean (95% CI)	RS-Guided Strategy	Non-RS-Guided Strategy	Difference
Life-years, discounted	15.02 (14.66 to 15.24)	14.82 (14.46 to 15.07)	0.19 (0.09 to 0.32)
Quality-adjusted life-years (QALY), discounted	10.09 (8.24 to 11.79)	9.93 (8.12 to 11.60)	0.16 (.08 to 0.28)
Direct costs, discounted	$21,090 (19,306 to 23,139)	$18,398 (16535 to 20,448)	$2692 (1546 to 3821)
Indirect costs, discounted	$5307 (4615 to 6178)	$6257 (5794 to 6745)	$-950 (-1732 to -111)
Total costs, discounted	$26,397 (24,073 to 28,957)	$24,656 (22,599 to 26,887)	$1741 (-85 to 37100
ICER, health care system perspective	**$16,677/QALY ($7613 to $27,219)**		
ICER, societal perspective	**$10,788/QALY ($6840 to $28,912)**		

* ASCO 2012; Chicago IL