NCCN Clinical Practice Guidelines® Development Process

Robert W. Carlson, M.D.
CEO, National Comprehensive Cancer Network
Professor of Medicine, Emeritus
Stanford University
Adjunct Professor of Medical Oncology
Fox Chase Cancer Center
Quality Health Care

Quality of health care is the degree to which health services for individuals and populations increase the likelihood of desired outcomes and are consistent with current professional knowledge.

Institute of Medicine, 1990
Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.

Institute of Medicine, 1990
Rationale for Guidelines

• Evidence evaluated and recommendations made by experts
• Objective, explicit decision making process
• Minimize variation in care
• Provide standard of care for quality of care assessment
• Payers can assess appropriateness of care
• Educational instruments
Characteristics of high quality guideline development process

- Explicit process
- Evidence-based when possible
- Level of evidence identified for each recommendation
- Multidisciplinary panel
- Expert panelists
- Conflicts of interest managed
- Updated frequently
- Logical and follow though processes of users
- Supporting documentation provided
Continuum of disease and patient care

Evidence-based guideline

Evidence-based consensus guideline

- High-level evidence exists
- Gaps in evidence filled with expert consensus
- Standard for clinical care and policy in oncology in United States
- 48 multidisciplinary panels with 25-30 experts per panel
- Estimated 21,000+ hours volunteered by Guidelines Panel Members in 2013
- 59 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with 163 algorithms updated continuously
- Widely available free of charge on the Internet
- Basis for insurance coverage policy and quality evaluation
NCCN Process: Identification of Discussion Items

• Staff literature search for clinical trials reports
• NCCN institutional review
• Panel member review
• Patient advocacy review
• Pharmaceutical industry and payor requests
• Community oncology requests
• Individual recommendations
Panel Member Responsibilities

- Manage institutional reviews of guidelines
- Prepare for and participate in panel meetings
- Review draft guidelines
- Participate in development of derivative products
- Respond to availability polls
- Complete COI disclosures semi-annually
  - Clinical trials participation disclosed but not counted against $$ thresholds
  - Limits for panel participation: $20,000 from one source, $50,000 aggregate from all sources
  - Panel member, spouse, domestic partner, dependents

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Providing Data to NCCN Panels

• Institutional Review: Each panel member is responsible for submitting guideline to the disease team at his/her institution

• Submissions from community sites, industry, payers, and the advocacy community:
  – Data submitted to the NCCN (not to individual panel members)
  – Quality of data very important

• Panels review and interpret the data using their expert judgment
Annual Meeting and Update Process

PRE-MEETING
• Identification of new issues
  - Panel chair and members, institutional review, staff, industry, others
• Assignment of issue to specific panelist(s) in advance
• Agenda is circulated in advance of the meeting

AT MEETING
• Disclosure of conflicts of interest
• Formal presentation of evidence by panelist(s) and recommendation
• Discussion by panel
• Decision regarding potential modification

POST-MEETING
• Generation of modified Guideline and supporting documentation
• Dissemination of Guideline
Guidelines Update Process

- Institutional Review, including relevant supporting data
- Outside Submissions

- Panel Meeting/teleconference
- NCCN Staff Review and Update
- Panel Chair Review
- Panel Review

- FDA Approval
- Significant scientific publication or presentation

Monitoring and Review of literature

Concurrent development and production of Discussion, Compendium and Chemotherapy Order Templates
- NCCN Categories of Evidence
  - 1, 2A, 2B, 3

- Quality of evidence
  - Meta analysis/systematic review, RCTs, non-RCTs, clinical experience

- Extent of evidence
  - Extensive, less extensive, little, clinical experience

- Consistency of evidence
  - Highly consistent, single trial, variable data
Categories of Evidence and Consensus

• **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus ($\geq 85\%$) that the intervention is appropriate.

• **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus ($\geq 85\%$) that the intervention is appropriate.

• **Category 2B:** Based upon lower-level evidence, there is NCCN consensus (50-85%) that the intervention is appropriate.

• **Category 3:** Based upon any level of evidence, there is major NCCN disagreement (at least 3 institutions on each side) that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.
Poonacha T K, Go R S JCO 2011;29:186-191
Citations Across Guidelines
Preliminary Data

In general:

• More references:
  – Large complicated guidelines
  – Large number of patient cohorts
  – High priority cancers

• Fewer references
  – Lower incidence
  – Few innovations
  – Fewer effective interventions
Minimization of Bias

- Large number of panel members
- Multidisciplinary (e.g., med onc, radiation, surgery, nursing, others) membership
- Geographic diversity
- Different philosophical views represented
- Institutional review
- External review and input: submissions, conferences/symposia, international
- Formal declaration of potential conflicts: verbal/written
NCCN Clinical Practice Guidelines
Multidisciplinary Panels

- Medical oncology
- Surgery/Surgical oncology
- Radiation oncology
- Hematology/Hematology oncology
- Bone Marrow Transplantation
- Urology
- Neurology/neuro-oncology
- Gynecologic oncology
- Otolaryngology
- Orthopedics/orthopedic oncology
- Pathology
- Dermatology
- Internal medicine
- Gastroenterology
- Endocrinology
- Diagnostic Radiology
- Interventional Radiology

- Nursing
- Cancer genetics
- Psychiatry, psychology
- Pulmonary medicine
- Pharmacology/Pharmacy
- Infectious diseases
- Allergy/immunology
- Anesthesiology
- Cardiology
- Geriatric medicine
- Epidemiology
- Patient advocacy
- Palliative, Pain management
- Pastoral care
- Oncology social work

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Conflict of Interest Disclosure

• No industry or any other interest group funds are used to support panel meetings
• No industry representatives allowed at meetings
• Individual panel members disclose conflicts of interest at semi-annually
• Financial conflicts of interest published for individuals on NCCN.org
• Members are excused from deliberations when degree of conflict warrants
• Members with substantial COI are excluded from panels
Identification and Disclosure of Relationships with External Entities

NCCN has added individual electronic disclosures for each of the NCCN Guidelines Panels and NCCN Oncology Research Program (ORP) Scientific Committees. This will be expanded this year to include levels of financial compensation.

- NCCN Guidelines Panels
- NCCN Staff

NCCN Guidelines Panels
- Acute Lymphoblastic Leukemia Panel
- Acute Myeloid Leukemia Panel
- Adolescent and Young Adult Oncology Panel
- Adult Cancer Pain Panel
- Anemias Panel
- Bladder/Penis Cancers Panel
- Bone Cancer Panel
- Breast Cancer Panel
- Breast Cancer Risk Reduction Panel
- Breast Cancer Screening and Diagnosis Panel
- Cancer- and Chemotherapy-Induced Anemia Panel
- Cancer-Related Fatigue Panel
- Central Nervous System Cancers Panel
- Cervical/Uterine Cancers Panel
- Chronic Myelogenous Leukemia Panel
- Colon/Rectal/Airway Cancers Panel
- Colorectal Cancer Screening Panel
- Distress Management Panel
- Esophageal/Gastric Cancers Panel
- Genetic/Familial High-Risk Assessment: Breast and Ovarian Panel
### Panel Member Disclosures

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support/Data Safety Monitoring Board</th>
<th>Advisory Board, Speaker’s Bureau, Expert Witness, or Consultant</th>
<th>Patent Equity, or Royalty</th>
<th>Other</th>
<th>Date Completed</th>
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<td>N.O. Abusaid, MD</td>
<td>None</td>
<td>None</td>
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<td>4/17/2014</td>
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<td>S. M. Apet, MD, MS</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4/18/2014</td>
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<tr>
<td>S. Posada, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>K. M. Cho, MD</td>
<td>None</td>
<td>None</td>
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<tr>
<td>C. Chu, MD</td>
<td>Azava; Cancer Care, Inc.</td>
<td>None</td>
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<tr>
<td>D. Cohn, MD</td>
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<td>AstraZeneca Pharmaceuticals LP; Novartis Pharmaceuticals</td>
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<td>None</td>
<td>None</td>
<td>None</td>
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– Requests for changes in recommendations for drugs and biologics to a guideline are available to the public for a period of not less than 5 years
– A listing of all evidence reviewed or considered
– A listing of all individuals who have substantively participated in the review
– Minutes and voting records of meetings for the review and disposition
– Direct or indirect financial relationships that exist between individuals or the spouse or minor child of individuals who have substantively participated
Submission Request to the NCCN Guidelines Panels

These documents will open in a new browser window.

Acute Lymphoblastic Leukemia Panel

- Portaserm - Submitted by Ariad Pharmaceuticals on 12/1/2012
- Portaserm - Submitted by Ariad Pharmaceuticals on 1/15/2014

Breast Cancer Panel

- Devagrumab - Submitted by Genentech on 6/25/2010
- Estirbul - Submitted by Sial on 11/17/2010
- Danusumab - Submitted by Amgen on 1/31/2010
- Zaleplon - Submitted by Novartis Pharmaceuticals Corporation on 5/6/2011
- Everolimus - Submitted by Novartis Pharmaceuticals Corporation on 10/10/2011
- Pertuzumab - Submitted by Genentech on 5/1/2012
- Ado-Trastuzumab Emtansine - Submitted by Genentech on 2/22/2013

Cervical/Urinary Cancers Panel

- Tamoxifen - Submitted by Sarcoma Unit Royal Marsden Hospital, United Kingdom on 5/15/2012

Chronic Myelogenous Leukemia Panel

- Nilotinib - Submitted by Novartis Pharmaceuticals Corporation on 5/7/2010
- Bosutinib - Submitted by Pfizer Oncology on 9/4/2012
- Dasatinib - Submitted by Ariad Pharmaceuticals on 12/21/2012
- Dasatinib - Submitted by Ariad Pharmaceuticals on 1/10/2014

Colon/Rectal/Anal Cancers Panel

- Bevacizumab - Submitted by Genentech on 6/8/2010
- Cotuzamab - Submitted by Buhl/Myers Squibb on 9/1/2011
- Capedocetin (Ivuconazole) - Submitted by Genentech on 6/7/2011
Dissemination of Guidelines

• Algorithms always published with supporting documentation (manuscript)
• Available free of charge via internet (www.nccn.org)
• Released on flash drives
• Published in JNCCN periodically
• Have been translated into multiple languages, including Japanese, Chinese, Spanish
• Selectively available in patient-oriented versions.
Unique Visitors to NCCN.org

- 2006: 1,039,078
- 2007: 1,383,298
- 2008: 1,636,536
- 2009: 1,273,131
- 2010: 1,468,925
- 2011: 1,717,940
- 2012: 2,035,620
- 2013: 2,558,805

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Guideline Downloads
More Than 25 Million Downloads Since 2006
2013 Top 10 Guideline Views

- Breast: 480,017
- NHL: 292,335
- NSCLC: 286,816
- Colon: 285,792
- Head and Neck: 207,059
- Prostate: 165,607
- Rectal: 129,235
- Gastric: 118,195
- Esophageal: 116,461
- Melanoma: 114,216
Virtual Library of NCCN Guidelines®

Access the Complete Library, including International Editions and Translations
On December 13, 2013, NCCN launched the Virtual Library of NCCN Guidelines® Free App formatted for iPhone and Android Smartphone in addition to the already existing tablet applications, which was launched in September, 2012.

**More Than One Million Guideline Downloads***

*Via mobile device since the App was launched in September, 2012*
## TOP TEN COUNTRIES: 2013

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<th>Country</th>
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<td>Japan</td>
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<td>Brazil</td>
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<td>India</td>
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<td>South Korea</td>
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<td>Mexico</td>
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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Guideline Value Leveraged for Derivative Products

- NCCN Drugs and Biologics Compendium®
- NCCN Biomarkers Compendium®
- Licensed to multiple IT organizations for use in computer-based systems
- NCCN Guidelines for Patients®
• Based directly on NCCN Guidelines
• 228 agents used in cancer care
• NCCN Compendium lists both FDA-approved uses and appropriate uses beyond the FDA-approved label
• Recognized as an authoritative reference for oncology coverage policy
• Used by health care professionals to determine coverage of drugs
NCCN Guidelines® & Clinical Resources

NCCN Drugs & Biologics Compendium (NCCN Compendium®)

Click here to subscribe to the NCCN Compendium®

Based directly on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), the NCCN Drugs & Biologics Compendium (NCCN Compendium®) contains authoritative, scientifically derived information designed to support decision-making about the appropriate use of drugs and biologics in patients with cancer.

The NCCN Compendium® is recognized by public and private insurers alike, including, but not limited to the Centers for Medicare and Medicaid Services (CMS) and UnitedHealthcare as an authoritative reference for oncology coverage policy. Managed care medical directors, pharmacy benefits directors, and other health care professionals also reference the NCCN Compendium when making decisions that impact patient access to appropriate therapy. The users identified are based upon evaluation of evidence from scientific literature integrated with expert judgment in an evidence-based process. Indicated uses are categorized in a systematic approach that describes the type of evidence available for and the degree of consensus underlying each recommendation. All recommendations (at all category levels) in the NCCN Compendium constitute appropriate, medically-necessary care. The NCCN Compendium lists both FDA-approved uses and appropriate uses beyond the FDA-approved label.

The NCCN Drugs & Biologics Compendium (NCCN Compendium®) is copyrighted by the NCCN. All rights reserved. NCCN content may not be reproduced in any form for any purpose without the express written permission of the NCCN. Permissions Requests Section

Search The Compendium
NCCN Compendium Chapters for Treatment of Cancer by Site
NCCN Compendium Chapters for Detection, Prevention, & Risk Reduction of Cancer
NCCN Compendium Chapters for Supportive Care

Table of Contents

Browse by Generic Name:

Search by Generic name:  

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<table>
<thead>
<tr>
<th>NCCN Disease Indication</th>
<th>Agent</th>
<th>Trade Name(s)</th>
<th>Pharmacologic Class</th>
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<th>ICD-O Code</th>
<th>NCCN Recommendations Use</th>
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<tr>
<td>MEL - Mantle Cell Lymphoma</td>
<td>Ibritumomab tiuxetan</td>
<td>Zevalin</td>
<td>Antimyeloma monoclonal antibodies and anti-CD-20 monoclonal antibodies</td>
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NCCN Templates®

- Helps clinicians administer regimens and agents in the NCCN Guidelines and Compendium safely and effectively
- References NCCN Guidelines and relevant studies
- Includes emetic risk and FN risk from NCCN Guidelines, monitoring and cautions etc
- NCCN currently has 1041 posted templates
- NCCN is developing electronic-facing interface

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Launched December 1, 2012

• Goal: To ensure access to appropriate testing as recommended by NCCN Guidelines
• Identify the utility of a biomarker to screen, diagnose, monitor, or provide predictive or prognostic information
• Use broad definition
• Identify biomarkers that affect treatment decisions and can divide patients into clinically relevant subgroups
• Consider the biologic activity not the specific test
• Widespread availability of reliable testing
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<tr>
<th>Test Detects</th>
<th>Number of Recommendations</th>
<th>Number of unique entities (gene symbols, rearrangements, translocations, etc)</th>
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<td>Translocation</td>
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<td>Mutation</td>
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<td>Chromosome deletion, abnormality, trisomy, inversion, complex alteration, etc.(^1)</td>
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<tr>
<td>Gene rearrangements</td>
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<td>Disease Description</td>
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NCCN Informatics Collaborations

- Active Health
- Advocate Healthcare
- CareCore National, LLC
- Computer Sciences Corporation
- Corporate Care Management
- DK Pierce & Associates, Inc.
- DNA Direct
- Epocrates
- eviti
- Equicare Health
- Genospace
- Hines
- IBM Watson
- Interlink
- inVentiv
- Ion
- Magellan Health
- McKesson Health Solutions
- McKesson Specialty Health
- New Century Health
- Oncology Analytics
- On Q Health
- Optum
- Patients with Power
- Prime Therapeutics
- Presence Health
- Rush University Medical Center
- Skyscape
- UnitedHealthCare
- Zynx Health Inc.

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### 2013 Total Page Views on NCCN.org/.com

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Total Page Views = 2,639,545
NCCN Process: Identification of Discussion Items

- Staff literature search for clinical trials reports
- NCCN institutional review
- Panel member review
- Patient advocacy review
- Pharmaceutical industry and payor requests
- Community oncology requests
- Individual recommendations

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NCCN Guidelines®

- Evidence-based consensus process for development
- Multidisciplinary panels
- Multiple sources of input of information to be considered
- Conflicts of interest tightly managed
- Make recommendations across the continuum of care
- Continuously updated
- Define the standard of cancer care and coverage within the USA
- Basis of multiple NCCN programs and initiatives