NCCN Clinical Practice Guidelines® and Biomarker Development

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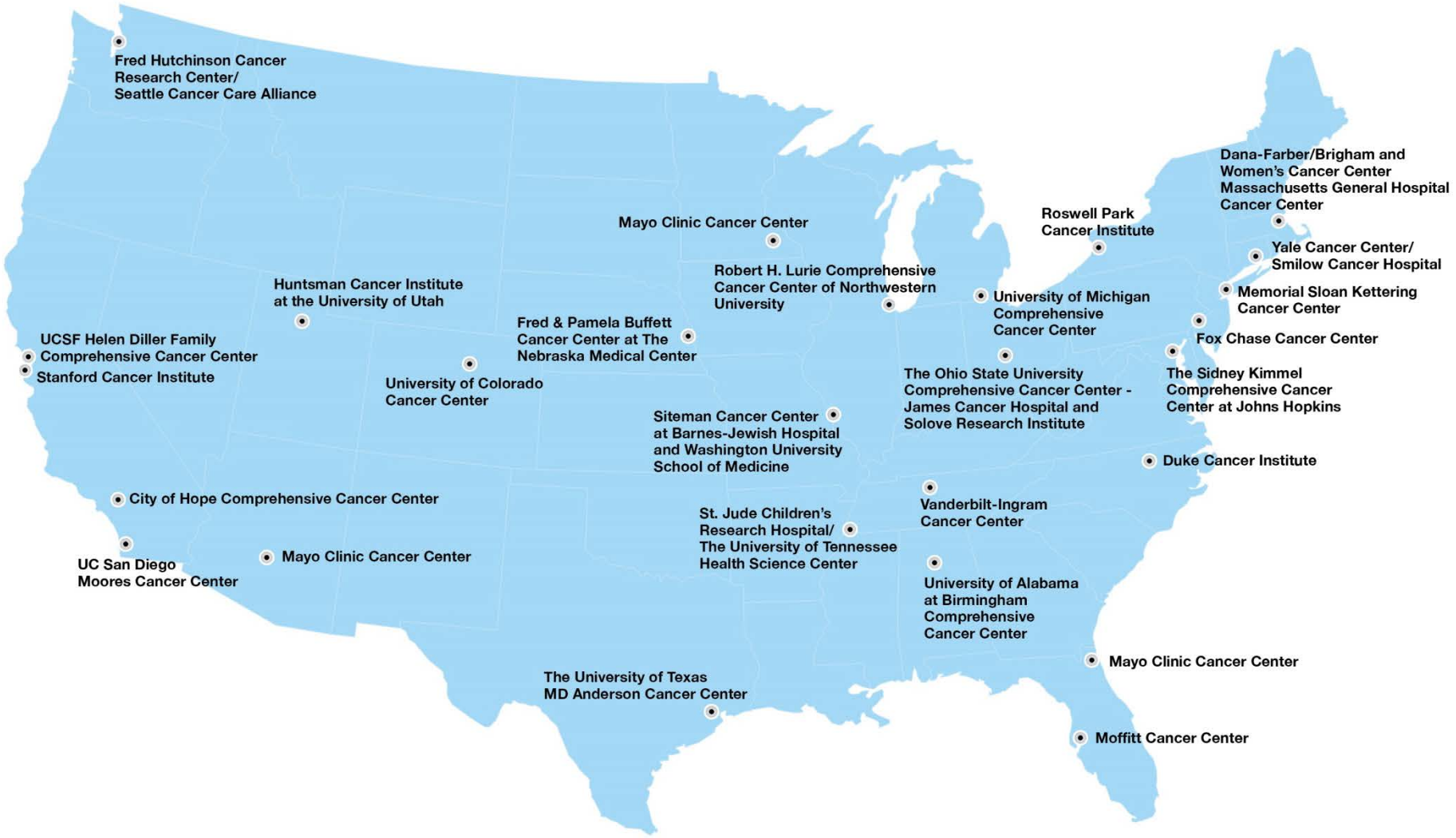
National Cancer Policy Forum Workshop 11.2014

NCCN Member Institutions



Clinical Practice Guidelines

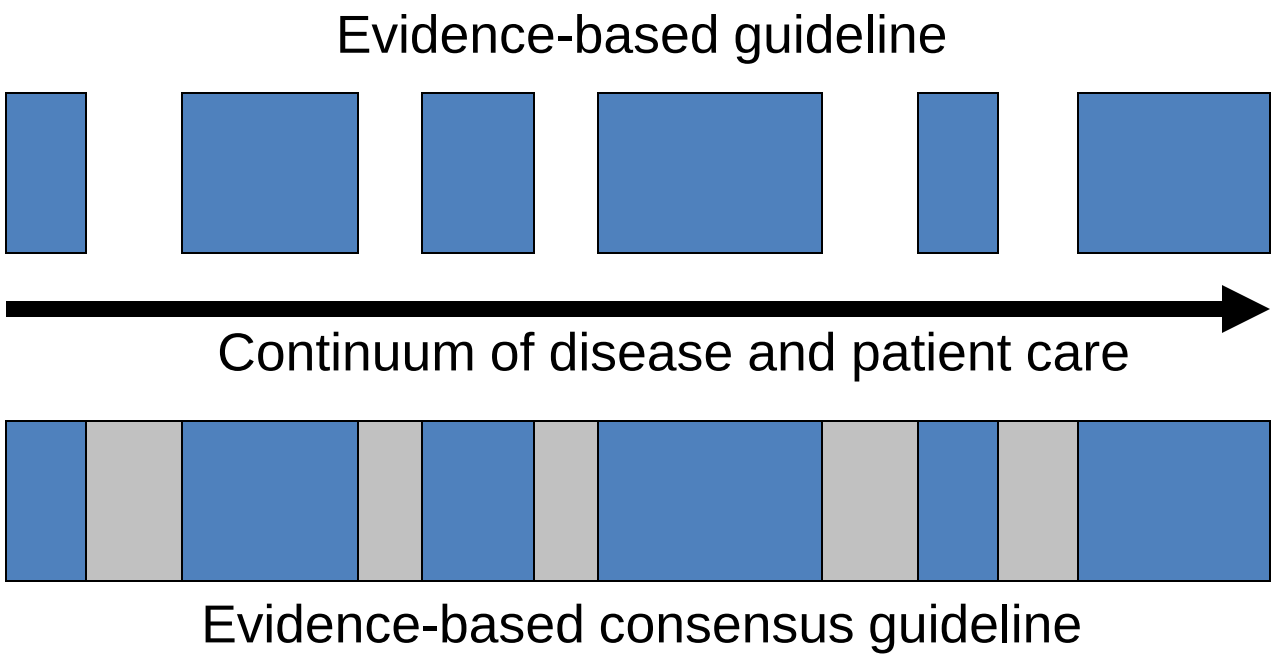
Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.

Institute of Medicine, 1990

Rationale for Guidelines

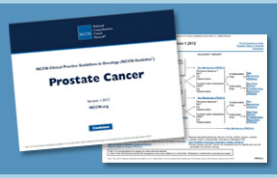
- Evidence evaluated and recommendations made by experts
- Objective, explicit decision making process
- Minimize variation in care
- Provide standard of care for quality of care assessment
- Payers can assess appropriateness of care
- Educational instruments

Evidence-based Consensus Allows Comprehensive Guidelines



High-level evidence exists

Gaps in evidence filled with expert consensus

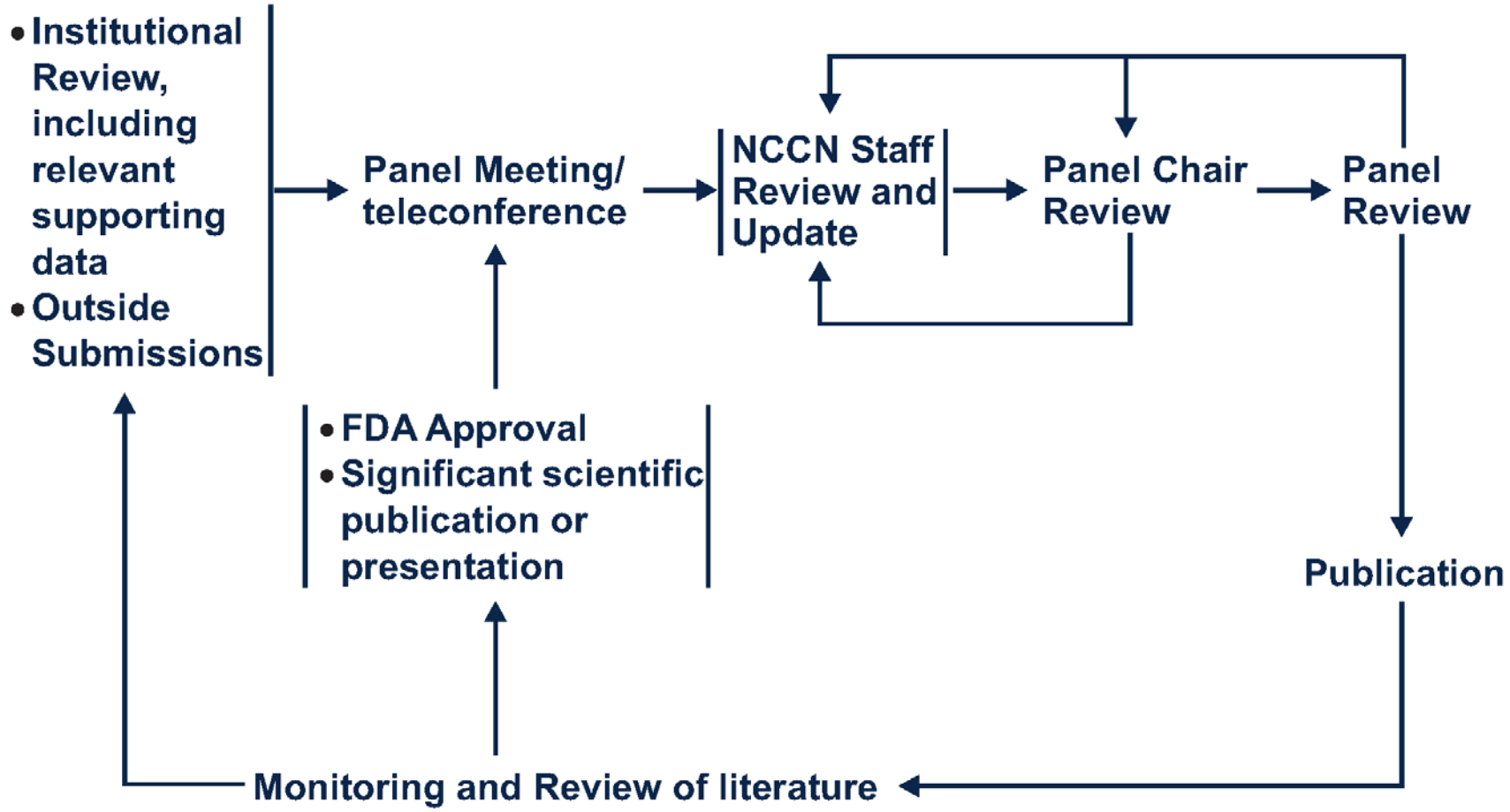


NCCN Guidelines®

- Standard for clinical care and policy in oncology in United States
- 48 multidisciplinary panels with 25-30 experts per panel
- Estimated 20,000+ 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 National Comprehensive Cancer Network®

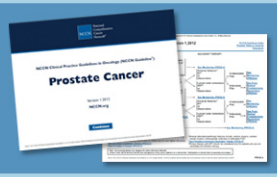
Guidelines Update Process



Concurrent development and production of Discussion, Compendium and Chemotherapy Order Templates

Critical Analysis of Data

- NCCN Categories of Evidence
  - 1, 2A, 2B, 3
- Quality of evidence
  - Meta analysis/systematic review, RCTs, nonRCTs, clinical experience
- Extent of evidence
  - Extensive, less extensive, little, clinical experience
- Consistency of evidence
  - Highly consistent, single trial, variable data

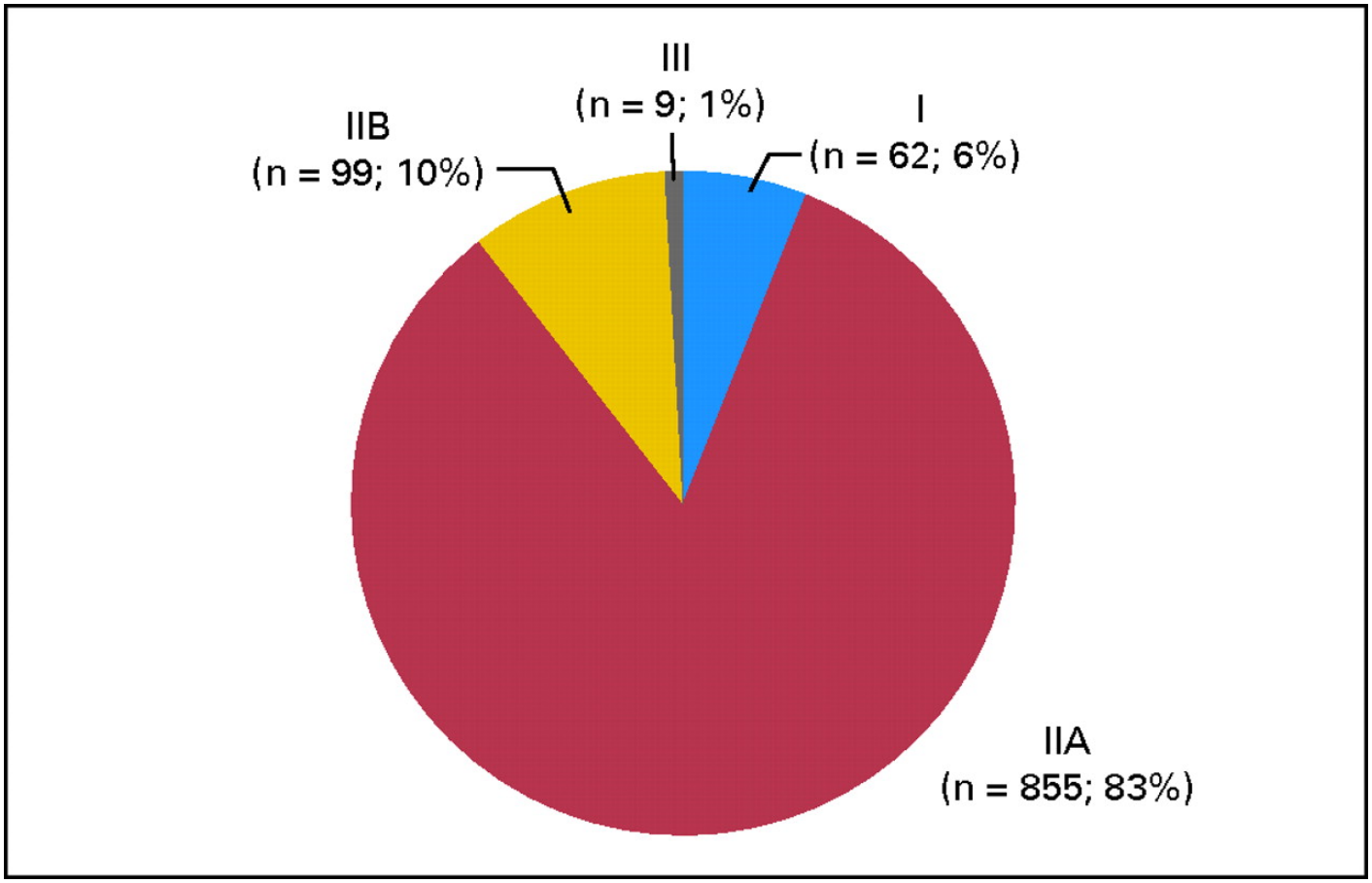


Categories of Evidence and Consensus

- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus (≥85%) that the intervention is appropriate.
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus (≥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.

Recommendations by Category



Poonacha T K , Go R S JCO 2011;29:186-191

NCCN Biomarkers Compendium™

Launched December 1, 2012

- Good uptake by providers
- To ensure access to appropriate testing as recommended by NCCN Guidelines
  - All testing recommendations are derived directly from NCCN guidelines, with additional information to help users find relevant records
  - Tests used to screen, diagnose, monitor, or provide predictive or prognostic information are included in the compendium
  - Testing recommendations are updated to correspond with Guideline updates, often multiple times per year as data evolve
  - Tests needed for clinical decision making are included and those used for research purposes only typically are not

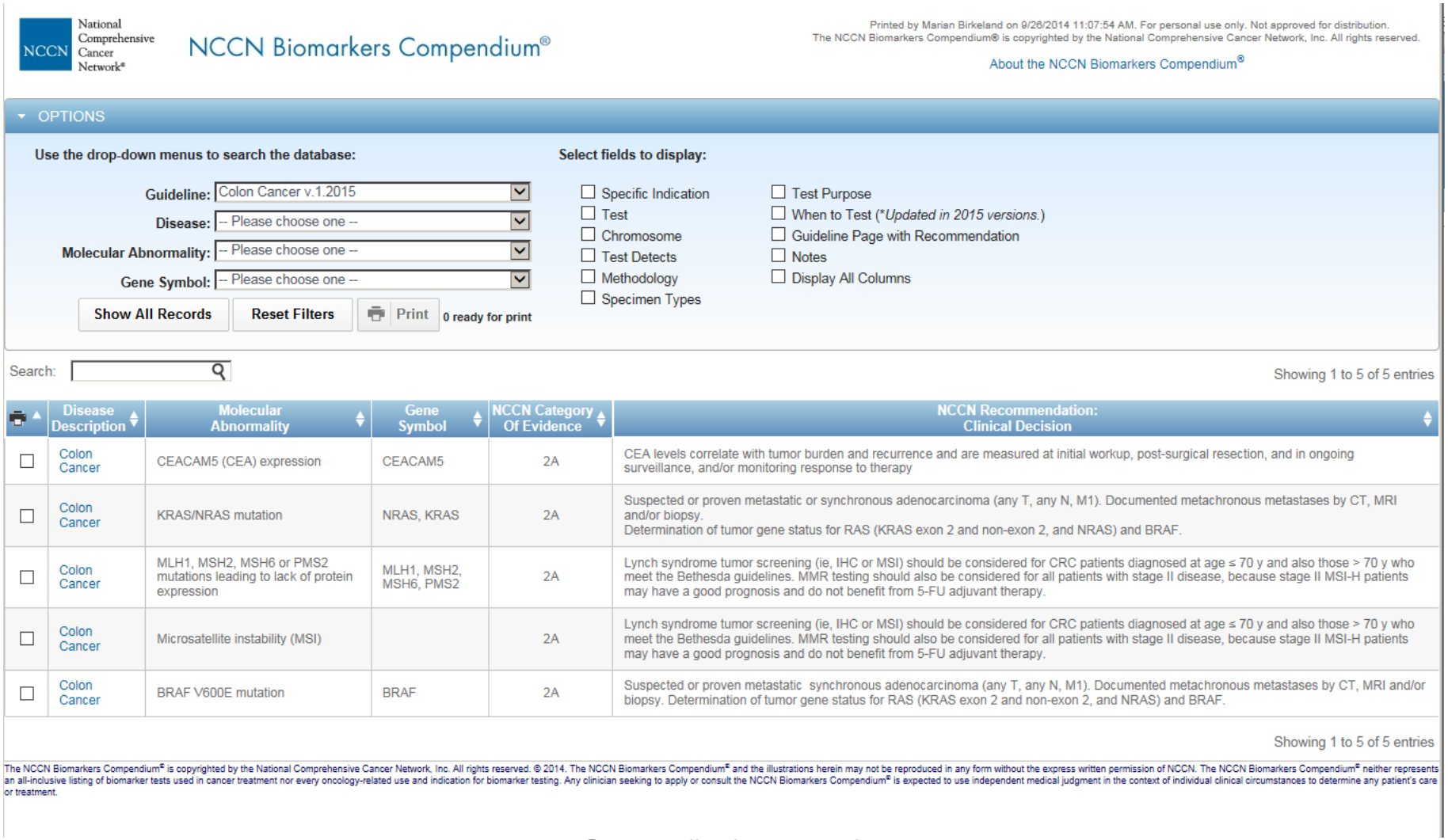
What do we consider to be a 'biomarker'?

- Any measurable diagnostic indicator that is used to assess the risk or presence of disease (Gutman & Kessler Nat Rev Cancer(2006) 6:565)
- Tests that measure changes in **genes or gene products** and which are used for diagnosis, screening, monitoring, surveillance, or for providing predictive or prognostic information are included in the NCCN Biomarkers Compendium

Types of biomarkers in current Guidelines

- Risk assessment (BRCA-1/BRCA-2)
- Screening (PSA for prostate)
- Diagnosis (BCR/ABL in CML)
- Prognosis (serum LDH levels are a part of the international prognostic index for Follicular Lymphoma)
- Prediction (HER2 status in breast)
- Risk of toxicity (TPMT gene polymorphisms in ALL patients being treated with 6MP)
- Monitoring/Surveillance (CEA levels in colorectal cancer)

Biomarkers Compendium Website: Tests recommended for Colon Cancer



National Comprehensive Cancer Network®

NCCN Biomarkers Compendium®

About the NCCN Biomarkers Compendium®

OPTIONS

Use the drop-down menus to search the database:

Guideline: Colon Cancer v.1.2015
Disease: -- Please choose one --
Molecular Abnormality: -- Please choose one --
Gene Symbol: -- Please choose one --

Show All Records | Reset Filters | Print | 0 ready for print

Select fields to display:

- ☐ Specific Indication
- ☐ Test
- ☐ Chromosome
- ☐ Test Detects
- ☐ Methodology
- ☐ Specimen Types
- ☐ Test Purpose
- ☐ When to Test (*Updated in 2015 versions.*)
- ☐ Guideline Page with Recommendation
- ☐ Notes
- ☐ Display All Columns

Search:

Showing 1 to 5 of 5 entries

Disease Description	Molecular Abnormality	Gene Symbol	NCCN Category Of Evidence	NCCN Recommendation: Clinical Decision
Colon Cancer	CEACAM5 (CEA) expression	CEACAM5	2A	CEA levels correlate with tumor burden and recurrence and are measured at initial workup, post-surgical resection, and in ongoing surveillance, and/or monitoring response to therapy
Colon Cancer	KRAS/NRAS mutation	NRAS, KRAS	2A	Suspected or proven metastatic or synchronous adenocarcinoma (any T, any N, M1). Documented metachronous metastases by CT, MRI and/or biopsy. Determination of tumor gene status for RAS (KRAS exon 2 and non-exon 2, and NRAS) and BRAF.
Colon Cancer	MLH1, MSH2, MSH6 or PMS2 mutations leading to lack of protein expression	MLH1, MSH2, MSH6, PMS2	2A	Lynch syndrome tumor screening (ie, IHC or MSI) should be considered for CRC patients diagnosed at age ≤ 70 y and also those > 70 y who meet the Bethesda guidelines. MMR testing should also be considered for all patients with stage II disease, because stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.
Colon Cancer	Microsatellite instability (MSI)		2A	Lynch syndrome tumor screening (ie, IHC or MSI) should be considered for CRC patients diagnosed at age ≤ 70 y and also those > 70 y who meet the Bethesda guidelines. MMR testing should also be considered for all patients with stage II disease, because stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.
Colon Cancer	BRAF V600E mutation	BRAF	2A	Suspected or proven metastatic synchronous adenocarcinoma (any T, any N, M1). Documented metachronous metastases by CT, MRI and/or biopsy. Determination of tumor gene status for RAS (KRAS exon 2 and non-exon 2, and NRAS) and BRAF.

Showing 1 to 5 of 5 entries

HER2 (ERBB2): Testing recommended across diseases

OPTIONS

Use the drop-down menus to search the database:

Guideline: -- Please choose one --
Disease: -- Please choose one --
Molecular Abnormality: -- Please choose one --
Gene Symbol: ERBB2

Show All Records | Reset Filters | Print | 0 ready for print

Select fields to display:

- ☐ Specific Indication
- ☐ Test
- ☐ Chromosome
- ☐ Test Detects
- ☐ Methodology
- ☐ Specimen Types
- ☐ Test Purpose
- ☐ When to Test (*Updated in 2015 versions.)
- ☑ Guideline Page with Recommendation
- ☐ Notes
- ☐ Display All Columns

Search:

First | Previous | 1 | 2 | Next | Last — Showing 1 to 10 of 13 entries

Disease Description	Molecular Abnormality	Gene Symbol	NCCN Category Of Evidence	NCCN Recommendation: Clinical Decision	Guideline Page with Test Recommendation
Gastric Cancer	ERBB2 (HER2-neu) gene amplification	ERBB2	2A	For patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach or esophagogastric junction for whom trastuzumab therapy is being considered, assessment for tumor HER2-neu overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization method is recommended.	• GAST-1 • GAST-6 • GAST-B 3 of 4
Gastric Cancer	ERBB2 (HER2-neu) gene amplification	ERBB2	2A	For patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach or esophagogastric junction for whom trastuzumab therapy is being considered, assessment for tumor HER2-neu overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization method is recommended.	• GAST-1 • GAST-6 • GAST-B 3 of 4
Esophageal and Esophagogastric Junction Cancers	ERBB2 (HER2) gene amplification	ERBB2	2A	For patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the esophagus or esophagogastric junction for whom trastuzumab therapy is being considered, assessment for tumor HER2-neu overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization methods is recommended	• ESOPH-1 • ESOPH-16 • ESOPH-17 • ESOPH-B 3 of 4
Esophageal and Esophagogastric Junction Cancers	ERBB2 (HER2-neu) gene amplification	ERBB2	2A	For patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the esophagus or esophagogastric junction for whom trastuzumab therapy is being considered, assessment for tumor HER2-neu overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization methods is recommended	• ESOPH-1 • ESOPH-16 • ESOPH-17 • ESOPH-B 3 of 4
Breast Cancer - Invasive	ERBB2 (HER2) gene amplification	ERBB2	1	Workup for Stage I (T1, N0, M0) or Stage IIA (T0, N1, M0; T1, N1, M0; T2, N0, M0) or Stage IIB (T2, N1, M0; T3, N0, M0) or Stage IIIA (T3, N1, M0): Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status.	• BINV-1 • BINV-A • BINV-K
Breast Cancer - Invasive	ERBB2 (HER2) protein overexpression	ERBB2	1	Workup for Stage I (T1, N0, M0) or Stage IIA (T0, N1, M0; T1, N1, M0; T2, N0, M0) or Stage IIB (T2, N1, M0; T3, N0, M0) or Stage IIIA (T3, N1, M0): Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status.	• BINV-1 • BINV-A • BINV-K
Breast Cancer - Invasive	ERBB2 (HER2) gene amplification	ERBB2	1	Preoperative Chemotherapy Guideline. Clinical stage: Stage IIA: T2, N0, M0; Stage IIB: T2, N1, M0; T3, N0, M0; Stage IIIA: T3, N1, M0; and fulfills criteria for breast-conserving surgery except for tumor size. Workup: Determination of tumor ER/PR status and HER2 status.	• BINV-10 • BINV-A
Breast Cancer - Invasive	ERBB2 (HER2) protein overexpression	ERBB2	1	Preoperative Chemotherapy Guideline. Clinical stage: Stage IIA: T2, N0, M0; Stage IIB: T2, N1, M0; T3, N0, M0; Stage IIIA: T3, N1, M0; and fulfills criteria for breast-conserving surgery except for tumor size. Workup: Determination of tumor ER/PR status and HER2 status.	• BINV-10 • BINV-A
Breast Cancer - Invasive	ERBB2 (HER2) gene amplification	ERBB2	1	Locally Advanced Invasive Breast Cancer (non-inflammatory). Clinical stage: Stage IIIA: T0, N2, M0; T1, N2, M0; T2, N2, M0; T3, N2, M0; Stage IIIB: T4, N0, M0; T4, N1, M0; T4, N2, M0; Stage IIIC: Any T, N3, M0. Workup: Determination of tumor ER/PR status and HER2 status.	• BINV-14 • BINV-A
Breast Cancer - Invasive	ERBB2 (HER2) protein overexpression	ERBB2	1	Locally Advanced Invasive Breast Cancer (non-inflammatory). Clinical stage: Stage IIIA: T0, N2, M0; T1, N2, M0; T2, N2, M0; T3, N2, M0; Stage IIIB: T4, N0, M0; T4, N1, M0; T4, N2, M0; Stage IIIC: Any T, N3, M0. Workup: Determination of tumor ER/PR status and HER2 status.	• BINV-14 • BINV-A

Print record feature: BRAF mutation in melanoma

National Comprehensive Cancer Network®

NCCN Biomarkers Compendium®

Disease Description:	Melanoma
Specific Indication:	Advanced or metastatic melanoma
Molecular Abnormality:	BRAF V600 mutation
Test:	BRAF V600 mutation
Chromosome:	7q34
Gene Symbol:	BRAF
Test Detects:	Mutation
Methodology:	Molecular analysis
NCCN Category of Evidence:	1
Specimen Types:	FFPE tumor tissue
NCCN Recommendation - Clinical Decision:	Systemic therapy options for advanced or metastatic melanoma; Vemurafenib, dabrafenib, and trametinib are recommended only for patients with V600 mutation of the *BRAF* gene documented by an FDA approved or Clinical Laboratory Improvement Amendments (CLIA) -approved facility.
Test Purpose:	Predictive
When to Test:	
Guideline Page with Test Recommendation:	ME-E 1 of 4
Notes:	Single-agent trametinib is not indicated for the treatment of patients who have experienced progression of disease on prior BRAF inhibitor therapy. Single-agent trametinib can be used for the treatment of *BRAF*-mutated melanoma in patients who are intolerant to single-agent BRAF inhibitors.

Guideline: Melanoma v.3.2014, as of 3/3/2014 1:34:47 PM NCCN Reference ID: 2678

Criteria for Clinical Usefulness

- Data demonstrating that the biomarker affects treatment decisions
- Evidence that the biomarker can divide patients into clinically relevant subgroups
- Widespread availability of reliable testing
  - NCCN specifies which biomarker(s) should be assayed and when but does not specify how to do so
  - With few exceptions specific test or kit is not identified

NCCN Biomarkers Compendium™

Test Detects	Number of Recommendations	Number of unique entities (gene symbols, rearrangements, translocations, etc
Protein/Protein Expression (includes flow/IHC)	558	112
Translocation	105	64
Mutation	87	36
Chromosome deletion, abnormality, trisomy, inversion, complex alteration, etc.[1]	50	
Gene rearrangements	40	10

NCCN Biomarkers Compendium™

Tests Used for Predictive/Targeted Therapy Selection Purposes

Test	Guideline or Disease
ALK Rearrangement	Non-Small Cell Lung Cancer
BRAF mutation	Non-Small Cell Lung Cancer, Melanoma, Colon Cancer, Rectal Cancer
EGFR mutation	Non-Small Cell Lung Cancer
• ERBB2 amplification/overexpression	Breast Cancer, Esophageal and Esophagogastric Junction Cancers, Gastric Cancer
ESR1 expression	Breast Cancer
KRAS mutation	Colon Cancer, Rectal Cancer, Non-Small Cell Lung Cancer
MGMT promoter methylation	Central Nervous System Cancers: Anaplastic glioma/glioblastoma
MLH1, MSH2, MSH6, PMS2 expression and/or mutation, MSI testing	Colon Cancer, Rectal Cancer
PGR expression	Breast Cancer
ROS1 rearrangement	Non-Small Cell Lung Cancer
21 gene PCR expression assay	Breast Cancer
KIT mutation	Soft Tissue Sarcoma: GIST
PDGFRA mutation	Soft Tissue Sarcoma: GIST
ABL1 mutation	Ph+ ALL, CML

NCCN Concerns

- Ensure access to tests that
  - Influence treatment decisions for standard of care management
  - Determine whether entry criteria for biomarker-driven clinical trials are met
- Reduce confusion among providers about which tests will be reimbursed. Assist payers in understanding which tests they are being asked to pay by ensuring a rich collection of codes
- With the proliferation of tests, ensure an industry standard approach to ordering and interpreting results of tests—including across different platforms