



Molecular Tumor Genetic Testing

Adult Oncology – Solid Tumors

Clinical Practice Guideline

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UK Healthcare Molecular Tumor Board Executive Committee (11/21/2017)

Release Date: 11/21/2017

Next Review Date: 11/21/2019

Executive Summary

Guideline Overview

This guideline contains recommendations for the indications for genetic testing of oncology tumors, and is heavily influenced by recommendations released by the National Comprehensive Cancer Network (NCCN) as well as local expert opinion.

Key Practice Recommendations

1. It is recommended that patients with cancer gene mutation panel testing be referred to the Molecular Tumor Board. (*Level A Recommendation*)
2. Patients with new diagnosis or first recurrence breast cancer (*NCCN Evidence Category 2A*), metastatic colorectal cancer (*NCCN Evidence Category 2A*), new non-small cell lung cancer (*NCCN Evidence Category 1*), recurrent or metastatic melanoma (*NCCN Evidence Category 2A*), new diagnosis or refractory to first and second line therapies including platinum-resistant thyroid cancer (*NCCN Evidence Category 2B*), recurrent or metastatic thyroid cancer (*NCCN Evidence Category 1*) recurrent or advanced uterine cancer (*NCCN Evidence Category 2B*), or glioma CNS tumors (*NCCN Evidence Category 2A*) should be tested using a broad cancer gene mutation panel.
3. Genomic testing using a cancer gene mutation panel may be considered in all other patients with solid tumors who have refractory cancer or lack adequate treatment options. (*Level C Recommendation*)
4. Genomic testing using a cancer gene mutation panel may be considered in rare tumors or refractory tumors in which extensive evidence is unavailable. (*Level C Recommendation*)

Companion Documents

[cBioPortal Website](#)

[OncoKB Website](#)

Pertinent UK Health Policies and Procedures

None

Patient Resources

[My Cancer Genome](#)

1. Scope

- 1.1. Disease/Condition(s): Solid Tumors, Cancer
- 1.2. Clinical Specialty: Medical Oncology, Laboratory
- 1.3. Intended Users: Oncologists, Referring Oncologists
- 1.4. CPG Objective(s): To outline evidence-based recommendations for molecular tumor diagnostic testing in patients with cancer which will support treatment decision-making using somatic test results
- 1.5. Target population: Adult patients 18 years or older with solid tumor cancer.
- 1.6. Interventions and Practices Considered: Molecular genetic testing
- 1.7. Guideline Metrics:
 1. Percentage of patients with panel testing who are referred to the Molecular Tumor Board.
 2. Number of patients with breast cancer, colorectal cancer, non-small cell lung cancer, melanoma, ovarian or uterine cancer, thyroid cancer or CNS tumors tested upon initial diagnosis or with advancing disease using a cancer gene mutation panel.
 3. Progression free survival of patients referred to UK MTB for treatment compared to patients who have not been referred
 4. Progression free survival ratio of patients treated with targeted therapy based on the recommendation by the UK MTB. The ratio will be calculated by the individual patient's progression free survival on current targeted therapy divided by the progression free survival on the regimen on which disease progression was experienced.

2. Methodology

2.1. Methods Used to Collect/Select the Evidence:

Electronic database searches (i.e., PUBMED) were conducted by the workgroup members to collect evidence for review. Expert opinion, clinical experience, and regard for patient safety/experience were also considered during discussions of the evidence.

2.2. Methods Used to Assess the Quality and Strength of Evidence:

Internally developed recommendations during the workgroup meetings were evaluated using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence to establish evidence grades for each individual piece of literature and/or recommendation.¹

2.3. Rating Scheme for the Strength of the Evidence:

See [Appendix A](#) for the evidence-rating scheme used within this document.

2.4. Methods Used to Formulate the Recommendations:

The interdisciplinary workgroup members agreed to adopt recommendations developed by external organizations, and arrived at a consensus through discussion of the literature evidence and expert/institutional experiences. Recommendations developed by external organizations, such as the National Cancer Center Network (NCCN), maintained the evidence grades assigned within the original document and were adopted for use. The workgroup subsequently accepted the Strength of Recommendation Taxonomy (SORT) express the strength of the practice recommendations.²

2.5. Rating Scheme for the Strength of the Recommendations:

See [Appendix A](#) for the recommendation rating schemes used within this document.

3. Introduction

Advances in technology have enabled routine molecular testing of tumors, which may provide guidance in treatment decisions for some of the most common and deadly malignancies. This guideline provides recommendations for genetic testing in common cancer types and education on the Molecular Tumor Board.

4. Recommendations

4.1. Major Recommendations

4.1.1. Molecular Tumor Board Review

It is recommended that patients with cancer gene mutation panel testing are referred to the Molecular Tumor Board. (*Level A Recommendation*) Regional affiliates or outreach facilities may consider submitting cases to the Molecular Tumor Board based upon a discussion of the risks and benefits with their patients. (*Level C Recommendation*)

4.1.2. Test Type

Cancer gene mutation panel test results must be available prior to case presentation at the Molecular Tumor Board. (*Level A Recommendation*) Benefits to ordering a panel over sequential individual tests include increasing efficiency (e.g., cost effective) and improving patient care (e.g., avoiding lengthy turnaround time for sequential test results and exhaustion of tissue which requires the patient to undergo an additional biopsy). When using a multi-gene panel clinically actionable mutations that drive treatment decisions are more likely to be identified with the first test ordered. In addition, markers with promising utility may be identified which may direct additional lines of therapy or clinical trial participation; clinical trials are routinely recommended as standard management for many patients with cancer. (*NCCN Evidence Category 2A*) Similarly, all individual genetic markers recommended in this document are available through the comprehensive solid tumor panel and other laboratory tests offered by UK.

4.1.3. When to Test

Patients with new diagnosis or first recurrence breast cancer (*NCCN Evidence Category 2A*), metastatic colorectal cancer (*NCCN Evidence Category 2A*), new non-small cell lung cancer (*NCCN Evidence Category 1*), recurrent or metastatic melanoma (*NCCN Evidence Category 2A*), new diagnosis or refractory to first and second line therapies including platinum-resistant thyroid cancer (*NCCN Evidence*

Category 2B), recurrent or metastatic thyroid cancer (*NCCN Evidence Category 1*), recurrent or advanced uterine cancer (*NCCN Evidence Category 2B*), or glioma CNS tumors (*NCCN Evidence Category 2A*) should be tested using a broad cancer gene mutation panel.

- 4.1.4. Rationale for Comprehensive Profiling in Common Cancer Types
Determining each patient’s mutation status allows clinicians to make better therapy selection decisions, including eligibility for clinical trials. The following recommendations for genetic testing by cancer type are not exhaustive, but function to provide guidance related to the mutations in common cancer types. This listing will be continuously updated to reflect evolving evidence in this field.

4.2. Recommendations Based on Tumor Type

4.2.1. Breast Cancer

Along with estrogen receptor (ER) and progesterone receptor (PR), the determination of human epidermal growth factor 2 (HER2) tumor status is recommended for all newly diagnosed invasive breast cancers and for first recurrences of breast cancer whenever possible.^{3,4} (*NCCN Evidence Category 2A*) Mismatch repair deficiencies have been identified in a number of tumor types, providing another target for drug therapy.^{5,6} Although breast cancer is not typically identified as an MMR deficient tumor, up to 2% of breast cancers have identified as such.⁷

Due to the growing list of emerging targeted agents for genetic alterations within breast cancer, broad molecular profiling is recommended. (*Level 2 Evidence, Level A Recommendation*) The additional mutations listed in the table below have shown promising utility in guiding therapy selection.⁸⁻¹⁴ (*Level 5 Evidence, Level C recommendation*)

Table 1. Genetic Mutations in Breast Cancer

AKT1	ERBB2 (HER2)	MMR
AR	FGFR1	PR
CDH1	FGFR2	PTEN
ER (ESR1)	PIK3CA	TP53

4.2.2. Colorectal Cancer

All patients with metastatic colorectal cancer should have their tumor tissue genotyped for RAS mutations (KRAS and NRAS) and BRAF mutations.^{3,15,16} (*NCCN Evidence Category 2A*) Testing may be performed on the primary colorectal cancers and/or the metastasis.¹⁶ (*NCCN Evidence Category 2A*) Somatic MMR defects have been reported in 19-52% of colorectal cancer tumors.^{17,18} Identification of patients with mismatch repair mutations is imperative to identify patients at risk for Lynch syndrome and assist with prognostication.^{15,16} (*NCCN Evidence Category 2A*) The TP53 gene mutation has been

found to be associated with higher disease staging, high rate of reoccurrence, and higher mortality.¹⁹

Due to the growing list of emerging targeted agents for genetic alterations within colorectal cancer, broad molecular profiling is recommended. (*Level 2 Evidence, Level A Recommendation*) The additional mutations listed in the table below have shown promising utility in guiding therapy selection.^{8,20,21} (*Level 5 Evidence, Level C recommendation*)

Table 2. Genetic Mutations in Colorectal Cancer

AKT1	PIK3CA
BRAF	PTEN
KRAS	SMAD4
MMR	TP53
NRAS	

4.2.3. Lung Cancer

All patients with recurrent or metastatic non-small cell lung cancer (NSCLC) should be tested for ALK and ROS1 gene rearrangements, PD-L1 expression, BRAF and EGFR mutations.^{3,22-24} (*NCCN Evidence Category 1*) Patients with microsatellite instability-high (MSI-H) tumors or mismatch repair (MMR) deficiency have been associated with high PD-LI expression and may benefit from FDA-approved targeted therapy.^{23,25} EGFR and ALK testing in early stage disease (stage I, II, or III) is encouraged, especially in participation in clinical trial.^{23,25,26} Testing in early stage disease allows for the availability of molecular information if recurrence should occur.²⁷ It is not recommended that KRAS mutation be used as a sole determinant of EGFR tyrosine kinase inhibitor therapy selection.²⁷

Due to the growing list of emerging targeted agents for genetic alterations within NSCLC, broad molecular profiling is recommended.²⁴ (*Level 2 Evidence, Level A Recommendation*) Some of the genetic alterations with the strongest evidence are MET amplification, MET exon 14 skipping mutation, and RET rearrangements.²⁴ (*NCCN Evidence Category 2A*) In addition, other disease-relevant genes providing information on available targeted agents include HER2 mutations.²⁴ (*NCCN Evidence Category 2B*) The additional mutations listed in the table below have shown promising utility in guiding therapy selection.²⁸⁻³⁴ (*Level 5 Evidence, Level C recommendation*)

Table 3. Genetic Mutations in NSCLC

ALK	DDR2	MMR
AKT1	EGFR	NRAS
BRAF	ERBB2 (HER2)	NTRK1
CCND1	FGFR1	PIK3CA
CCND2	KRAS	PTEN
CCND3	MAP2K1 (MEK1)	RET
CDK4	MET	ROS1

4.2.4. Melanoma

All patients with recurrent or advanced melanoma should be tested for BRAF mutation status.³⁵⁻³⁷ (*Level 1 Evidence, Level A Recommendation*) Targeted therapy significantly improves overall survival in previously untreated patients with metastatic melanoma with BRAF V600E or V600K mutations.³⁶ Melanomas that arise on mucosal, acral, or chronic sun damaged skin should be assessed for KIT mutations.³⁸ (*Level 2 evidence, Level A Recommendation*) All patients with recurrent or advanced melanoma being considered for routine treatment or clinical trials should receive mutational analysis.³⁷ (*NCCN Evidence Category 2A*) Patients with microsatellite instability-high (MSI-H) tumors or mismatch repair (MMR) deficiency have been associated with high PD-L1 expression and may benefit from targeted therapy.^{25,39}

Due to the growing list of emerging targeted agents and arsenal of FDA-approved therapies for genetic alterations within melanoma, broad molecular profiling is recommended in advanced or recurrent disease. (*Level 2 Evidence, Level A Recommendation*) The additional mutations listed in the table below have shown promising utility in guiding therapy selection.⁴⁰⁻⁴³ (*Level 5 Evidence, Level C recommendation*)

Table 4. Genetic Mutations in Melanoma

BRAF	MAP2K1 (MEK1)
CTNNB1	MMR
GNA11	NF1
GNAQ	NRAS
KIT	

4.2.5. Ovarian and Uterine Cancer

Gynecological cancers have low rates of actionable mutations when compared to other solid tumors. However, the molecular profiling of these tumors is opening the gateway for investigations of molecular targets with available drug agents. Endometrial cancer targets include PIK3 and PTEN.⁴⁴ Mutations in TP53 and PIK3CA have been found in uterine and ovarian cancers alike.^{45,46} Germline BRCA mutations have been described in ovarian cancer and may be predictive to response of targeted therapies; therefore mutational analysis should be considered in advanced stage or recurrent disease.^{47,48} (*NCCN Evidence Category 2B*) Patients with microsatellite instability-high (MSI-H) tumors or mismatch repair (MMR) deficiency in endometrial, cervical, uterine, and other female genital tract tumors have been associated with high PD-L1 expression and may benefit from FDA-approved targeted therapy.^{5,23,25} All patients with endometrial tumors under 60 years of age should be tested for mismatch repair deficiency.⁴⁹ Molecular pathway treatment decisions would benefit those with ovarian cancer with refractory disease to first and second line therapies or those resistant to platinum based therapies.⁴⁸ (*NCCN Evidence Category 2B*) Uterine cancer molecular analysis may be beneficial in advanced or recurrent disease.⁵⁰ (*NCCN Evidence Category 2B*)

Due to the growing list of emerging targeted agents for genetic alterations within ovarian and uterine cancer, broad molecular profiling is recommended. (*Level 2 Evidence, Level A Recommendation*) The table below lists additional mutations have been identified in

both ovarian and uterine cancer and may assist in guiding therapy selection.^{45,46} (Level 5 Evidence, Level C recommendation)

Table 5. Genetic Mutations in Ovarian and Uterine Cancers

Ovarian		Uterine	
BRCA1	KRAS	ARID1A	PIK3CA
BRCA2	MYC	FBXW7	PTEN
CCNE1	NF1	LRP1B	RB1
CDKN2A	PIK3CA	MMR	TP53
CDKN2B	TP53		

4.2.6. Thyroid Cancer

Molecular diagnostic testing can be done to assist in management decisions on cytologically indeterminate thyroid nodules.⁵¹ (NCCN Evidence Category 2B) Both point mutations (BRAF and N/K/H-RAS) and rearrangements (RET/PTC and PAX8/PPAR γ) are commonly associated with thyroid cancer.^{51,52} Due to the high propensity for germline mutations, patients with recurrent or metastatic medullary carcinoma should be tested for RET proto-oncogene and MEN 2⁴⁴ (NCCN Evidence Category 2A).

Due to the growing list of emerging targeted agents for genetic alterations within thyroid cancer, broad molecular profiling is recommended. (Level 3 Evidence, Level B Recommendation) The mutations and rearrangements listed in the table below have shown promising utility in guiding therapy selection.⁵³ (Level 5 Evidence, Level C recommendation)

Table 6. Genetic Mutations in Thyroid Cancer

BRAF	PTEN
HRAS	RET/PTC
KRAS	PAX8/PPAR γ
NRAS	TP53
PIK3CA	

4.2.7. Tumors of the Central Nervous System

Gliomas are the most common tumors of the central nervous system (CNS). Astrocytoma, oligodendroglioma, and mixed oligoastrocytoma are the major histologic types of human gliomas; histologic differentiation among these tumors can be difficult. It has been shown that specific genetic alterations, such as deletions of the short arm of chromosome 1(1p) and long arm of chromosome 19 (19q), methylation of the MGMT (O[6]-methylguanine-DNA methyltransferase) promoter and certain mutations in the IDH1 and IDH2 (nicotinamide adenine dinucleotide phosphate (NADP)-dependent isocitrate dehydrogenases 1 and 2) genes are highly associated with specific morphologic types of gliomas.⁵²⁻⁵⁶ (NCCN Evidence Category 2A) In addition, specific genetic alterations seem to predict prognosis (survival), as well as response to specific chemotherapeutic and radiotherapeutic regimens, irrespective of tumor morphology.^{54,56-58} (Level 3 Evidence, Level A recommendation)

Table 7. Genetic Mutations in CNS Tumors

<p>1p 19q co-deletions MGMT promoter methylation IDH1/IDH2 mutations</p>
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6. UK HealthCare Implementation

6.1. Potential Benefits:

Following these guidelines should lead to standardized tumor genotyping by providers. The results from appropriate molecular testing can aid in the selection of optimal treatment regimens, which may result in improved cancer patient outcomes.

6.2. Potential Harms: None identified.

6.3. Dissemination Plan/Tools:

Education will be provided as a webinar available to UK affiliates and UK Healthcare faculty and staff as well as a live educational symposium planned for April 2018.

6.4. Implementation Plan/Tools:

1. Guideline will be housed on Molecular Tumor Board Website and linked to this website through other webpages such a Pathology and Laboratory Services, and UK HealthCare Careweb.
2. Release of the guideline will be advertised through the Molecular Tumor Board correspondence and through other electronic communications portals with the affiliates.

7. Disclaimer

Clinical Practice Guidelines (CPG) are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This CPG outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

8. Appendix A. Rating Schemes for the Strength of Evidence and Recommendations

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Level 1	Level 2	Level 3	Level 4	Level 5
Is this diagnostic or monitoring test accurate?	Systemic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross section studies with consistently applied reference standard blinding	Non-consecutive studies, or studies without consistently applied reference studies	Case-control studies, or poor or non-independent reference standard	Mechanism-based reasoning
Is this test worthwhile?	Systemic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study	Case-series, case-control, or historically controlled studies	Mechanism-based reasoning

SORT Rating for Recommendations

Level of Strength Recommendation	Definition
A	Recommendation based on consistent and good-quality evidence
B	Recommendation based on inconsistent or limited-quality evidence
C	Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening

National Comprehensive Cancer Network (NCCN) Categories of Evidence and Consensus

Category	
1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.