# Oncology Clinical Pathways Colon Cancer

August 2024 - V4.2024







# **Table of Contents**

Presumptive Conditions	3
<u>Stage I</u>	4
Stage II	5
Stage III.	6
Stage IV Initial Evaluation	7
Stage IV Potentially Resectable	8
Stage IV Unresectable, pMMR First Line, Fit for Chemotherapy	9
Stage IV Unresectable, pMMR Second Line, Fit for Chemotherapy	10
Stage IV Unresectable, pMMR Third Line, Fit for Chemotherapy	11
Stage IV Unresectable, pMMR Fourth Line, Fit for Chemotherapy	
Stage IV Unresectable, dMMR	
Stage IV Unresectable, Unfit for Combination Chemotherapy	
Molecular Testing.	15
Molecular Testing Table	. 16







## **Colon Cancer – Presumptive Conditions**

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

#### Atomic Veterans – Exposure to Ionizing Radiation

• Cancer of the colon

#### Gulf War and Post 9/11 Veterans

If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if you served in the \*Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

Gastrointestinal cancer of any type

\* The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

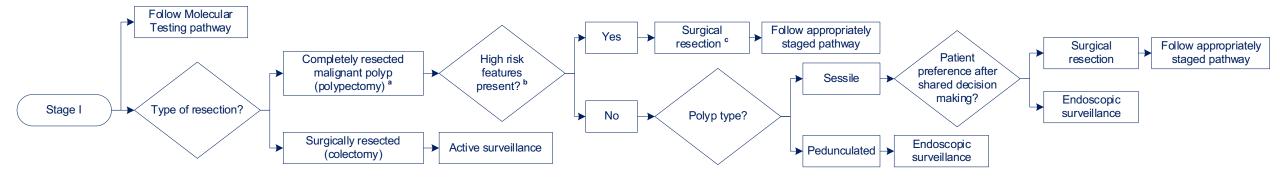
#### For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov)







## **Colon Cancer – Stage I**



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email <u>CancerClinicalTrialsNavigation@va.gov</u>.

<sup>a</sup> Resection if not a complete resection, additional endoscopic resection may be considered if feasible

<sup>b</sup> High Risk Features for Sessile Polyps includes: poor tumor differentiation, lymphovascular invasion, submucosal invasion depth >1 mm, tumor involvement of the cautery margin, tumor budding; High Risk Features for Pedunculated Polyps includes: poor tumor differentiation, lymphovascular invasion, tumor within 1 mm of the resection margin

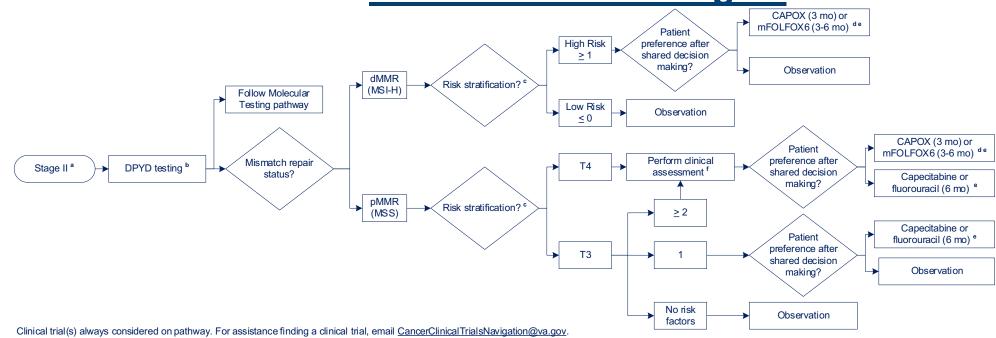
<sup>c</sup> Surgical Resection defined as a formal oncologic segmental colectomy







## **Colon Cancer – Stage II**



<sup>a</sup> Stage II determined following surgical resection, with time to initiation of chemotherapy recommended to begin 6-8 weeks following surgery; delay beyond 3 months is likely to greatly reduce the efficacy of subsequent chemotherapy and should be weighed into decision making; late initiation of chemotherapy should be evaluated on a case by case basis

<sup>b</sup> Perform DPYD Testing If Not Already Performed if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

<sup>c</sup> Risk Stratification: high risk features include presence of clinical obstruction, localized tumor perforation, or poorly differentiated tumor (pMMR only), lymphovascular invasion, perineural invasion, <12 harvested lymph nodes, positive and/or close margin (<1mm in non-peritonealized margins), or high tumor budding (18/0.785 mm2)

<sup>d</sup> Oxaliplatin-Based Regimens risk of  $\geq$  Grade 3 neurotoxicity is lower with 3-month vs. 6-month; if  $\geq$  grade 2 neuropathy develops during treatment, may discontinue oxaliplatin after three months while continuing fluoropyrimidine to full course (6 months); for pMMR, the benefit of addition of oxaliplatin is unclear in patients aged > 70 due to paucity of data

e Capecitabine avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl < 30ml/min)

Clinical Assessment determine presence of renal dysfunction, comorbidities, neuropathy, limited performance status, or limited life expectancy, as they would negatively impact the decision to use adjuvant chemotherapy

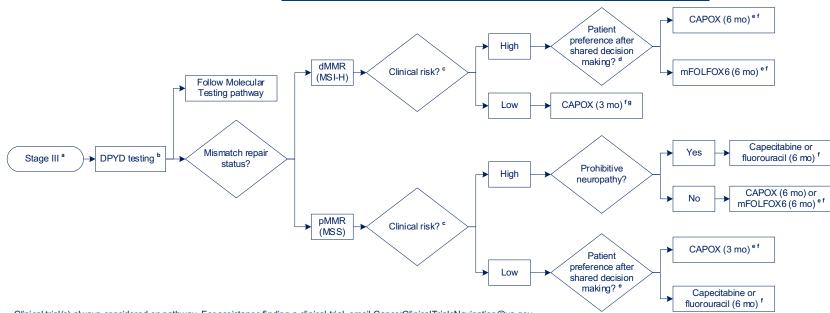
DPYD Dihydropyrimidine Dehydrogenase dMMR Mismatch Repair Deficient MMR Mismatch Repair MSI Microsatellite Instability MSS Microsatellite Stable pMMR Proficient Mismatch Repair







## **Colon Cancer – Stage III**



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

<sup>a</sup> Stage III determined following surgical resection, with time to initiation of chemotherapy recommended to begin 6-8 weeks following surgery; delay beyond 3 months is likely to greatly reduce the efficacy of subsequent chemotherapy and should be weighed into decision making; late initiation of chemotherapy should be evaluated on a case by case basis

<sup>b</sup> Perform DPYD Testing If Not Already Performed if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

<sup>2</sup> Clinical Risk defines high risk as T4 and/or N2 (≥ 4 positive nodes) and low risk as T1-3 and N1

<sup>d</sup> If Preexisting Neuropathy, single agent treatment may be an alternative for pMMR tumor, however, fluorouracil/capecitabine single agent treatment represents an inadequate option for dMMR tumors; observation may be appropriate for dMMR with significant baseline neuropathy (≥ grade 2)

<sup>e</sup> Oxaliplatin-Based Regimens risk of ≥ grade 3 neurotoxicity is lower with 3-month vs. 6-month; if > grade 2 neuropathy develops, discontinue oxaliplatin while continuing fluoropyrimidine to full course; benefit of adding oxaliplatin is unclear in patients aged > 70 due to paucity of data

Capecitabine avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl < 30ml/min)

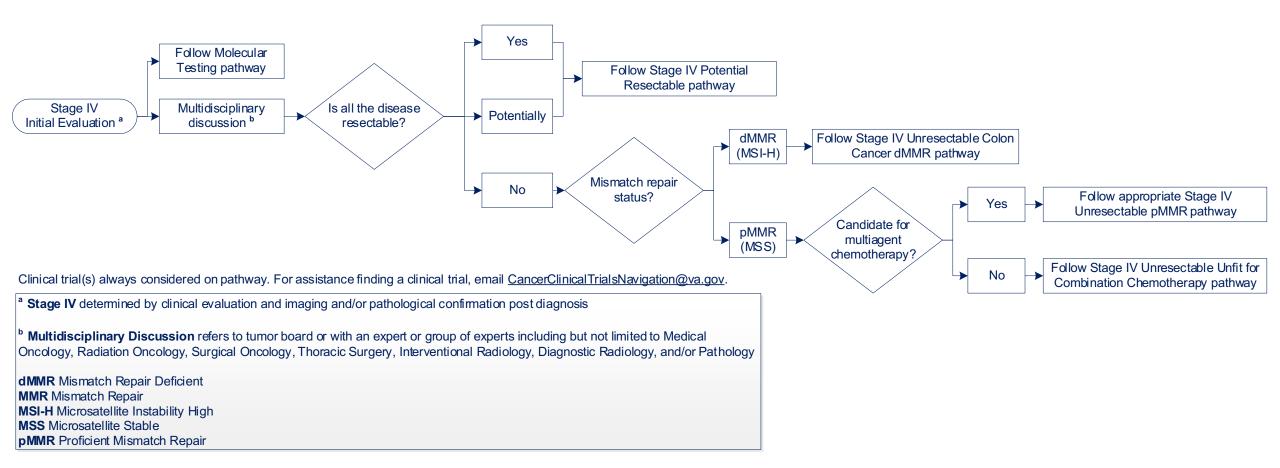
DPYD Dihydropyrimidine Dehydrogenase dMMR Mismatch Repair Deficient MMR Mismatch Repair MSI Microsatellite Instability MSI-H Microsatellite Instability High MSS Microsatellite Stable pMMR Proficient Mismatch Repair







## **Colon Cancer – Stage IV Initial Evaluation**

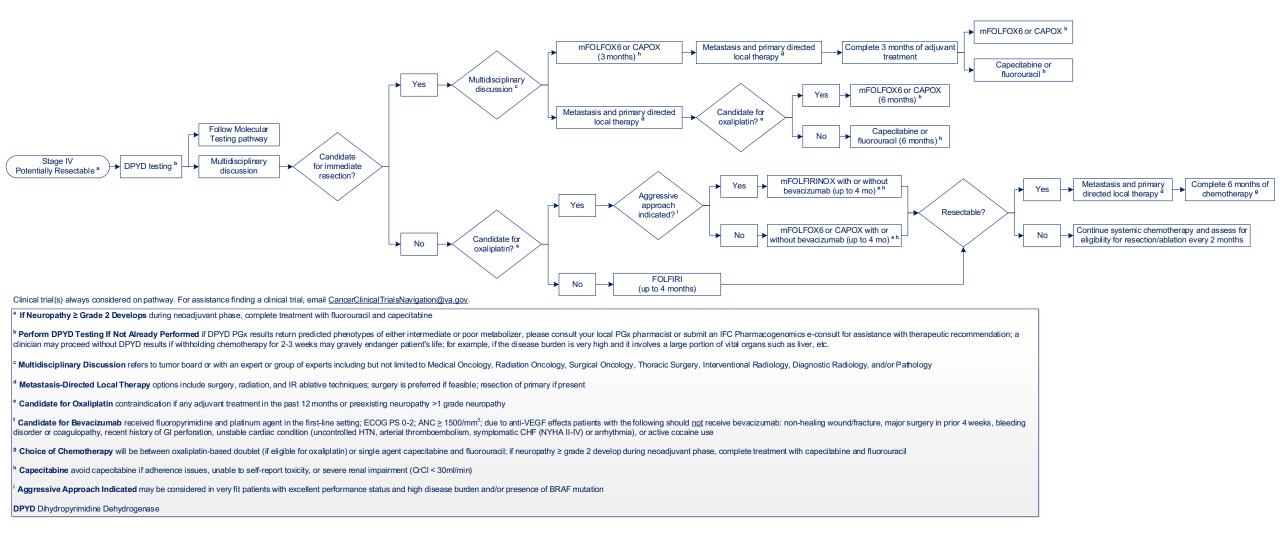








## **Colon Cancer – Stage IV Potentially Resectable**

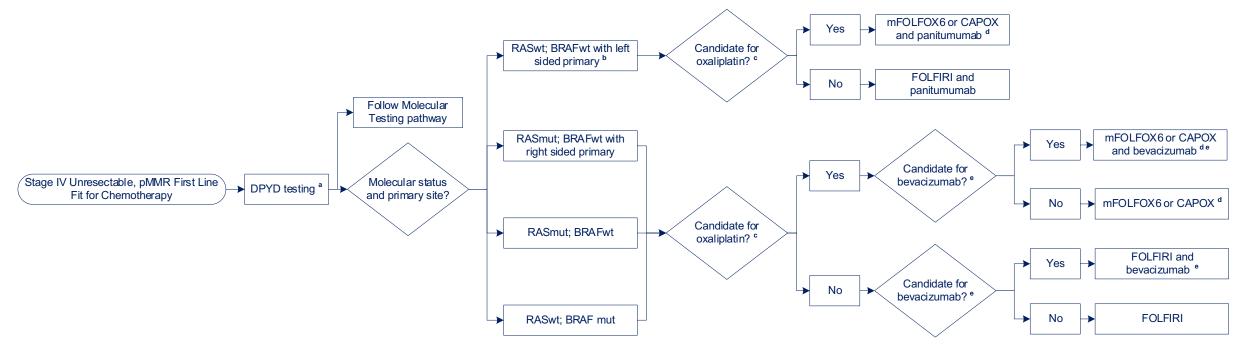








## Colon Cancer – Stage IV Unresectable, pMMR First Line Fit for Chemotherapy



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

<sup>a</sup> Perform DPYD Testing If Not Already Performed if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

<sup>2</sup> Left Sided Primary is defined as primary originating in splenic flexure and colon distal to that

<sup>c</sup> Candidate for Oxaliplatin contraindication if any adjuvant treatment in the past 12 months or preexisting neuropathy >1 grade neuropathy; patient preference to avoid neuropathy

<sup>d</sup> Capecitabine avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl <30 ml/min)

<sup>e</sup> Candidate for Bevacizumab received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC ≥ 1500/mm<sup>3</sup>; due to anti-VEGF effects patients with the following should <u>not</u> receive bevacizumab: non-healing wound/fracture, major surgery in prior 4 weeks, bleeding disorder or coagulopathy, recent history of GI perforation, unstable cardiac condition (uncontrolled HTN, arterial thrombœmbolism, symptomatic CHF (NYHA II-IV) or arrhythmia), or active cocaine use

DPYD Dihydropyrimidine Dehydrogenase mut mutation pMMR Proficient Mismatch Repair wt wild type

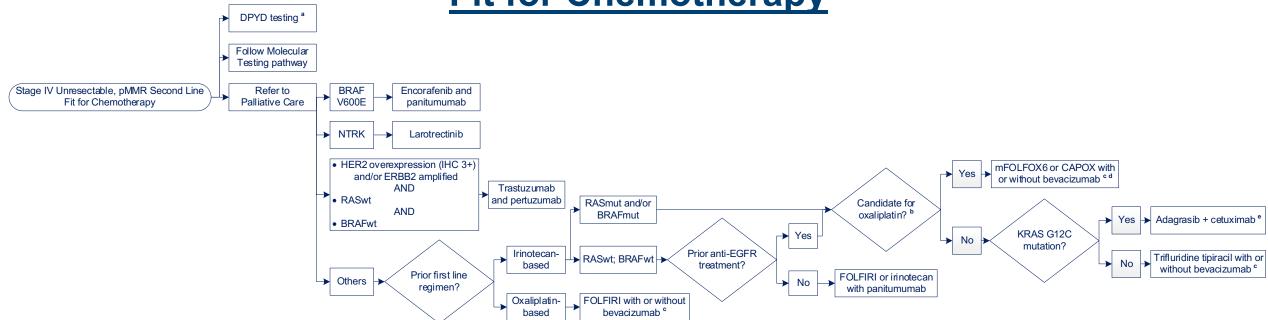






# Colon Cancer – Stage IV Unresectable, pMMR Second Line

### **Fit for Chemotherapy**



#### Clinical trial (s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

<sup>a</sup> Perform DPYD Testing If Not Already Performed if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

<sup>b</sup> Candidate for Oxaliplatin contraindication if disease progression within 12 months of adjuvant treatment or preexisting neuropathy >1 grade neuropathy

<sup>c</sup> Candidate for Bevacizumab ECOG PS 0-2; ANC ≥ 1500/mm<sup>3</sup>; due to anti-VEGF effects patients with the following should <u>not</u> receive bevacizumab: non-healing wound/fracture, major surgery in prior 4 weeks, bleeding disorder or coagulopathy, recent history of GI perforation, unstable cardiac condition (uncontrolled HTN, arterial thrombœmbolism, symptomatic CHF (NYHA II-IV) or arrhythmia), or active cocaine use

<sup>d</sup> Capecitabine avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl <30 ml/min)

e Cetuximab in high-risk regions, cetuximab can be substituted by panitumumab; no prior use of KRAS G12C inhibitor

DPYD Dihydropyrimidine Dehydrogenase EGFR Epidermal Growth Factor Receptor mut Mutation NTRK Neurotrophic Tyrosine Receptor Kinase pMMR Proficient Mismatch Repair wt Wild Type

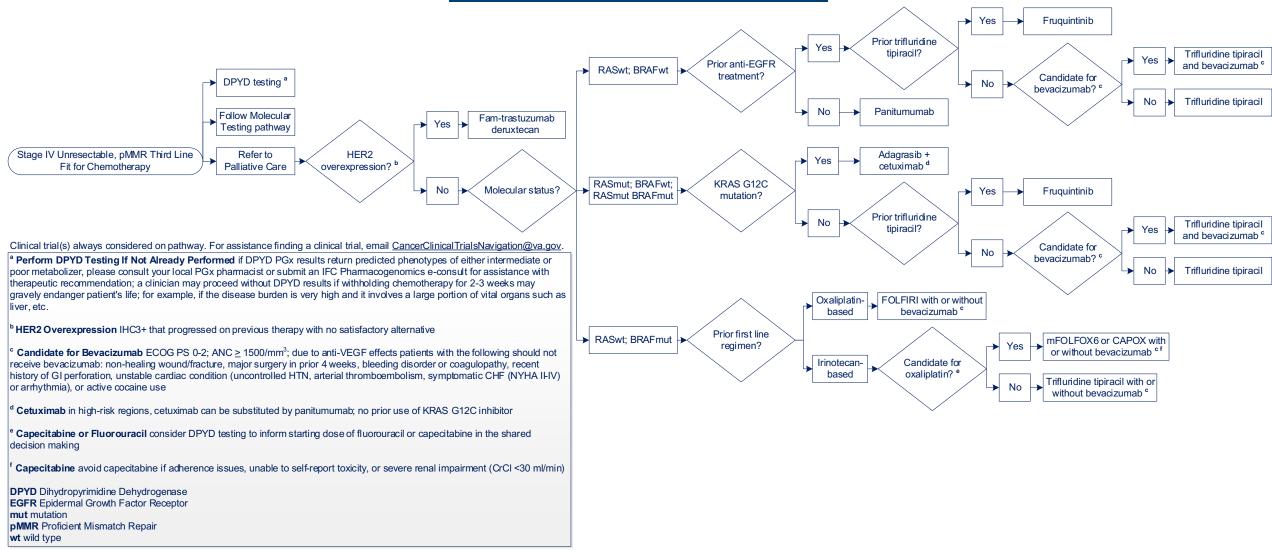






# Colon Cancer – Stage IV Unresectable, pMMR Third Line

## **Fit for Chemotherapy**

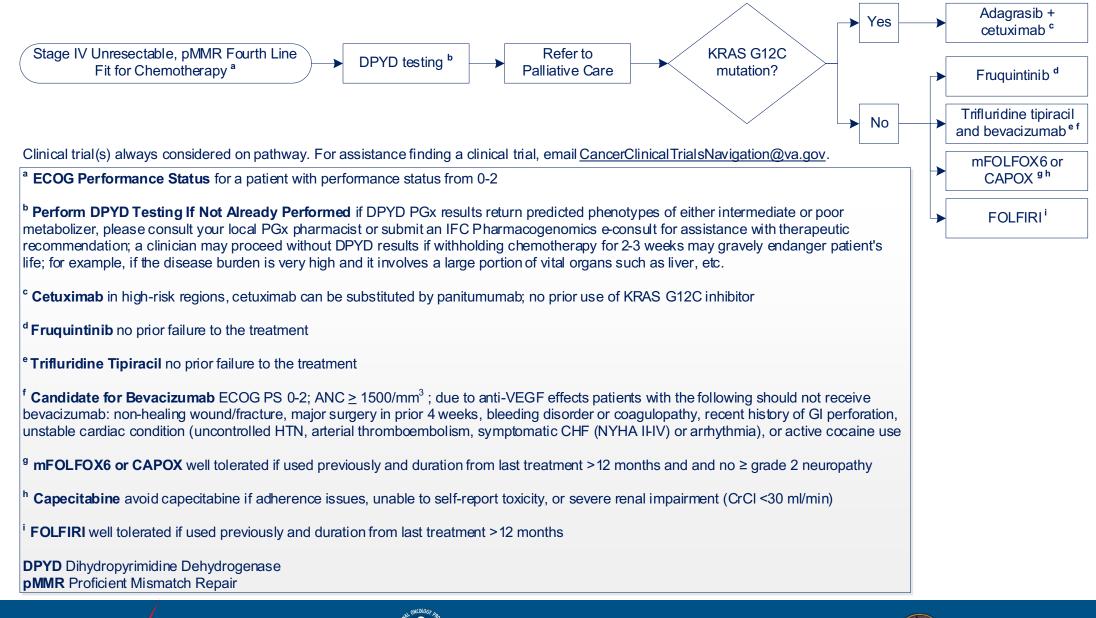








## Colon Cancer – Stage IV Unresectable, pMMR Fourth Line Fit for Chemotherapy









## Colon Cancer – Stage IV Unresectable dMMR



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

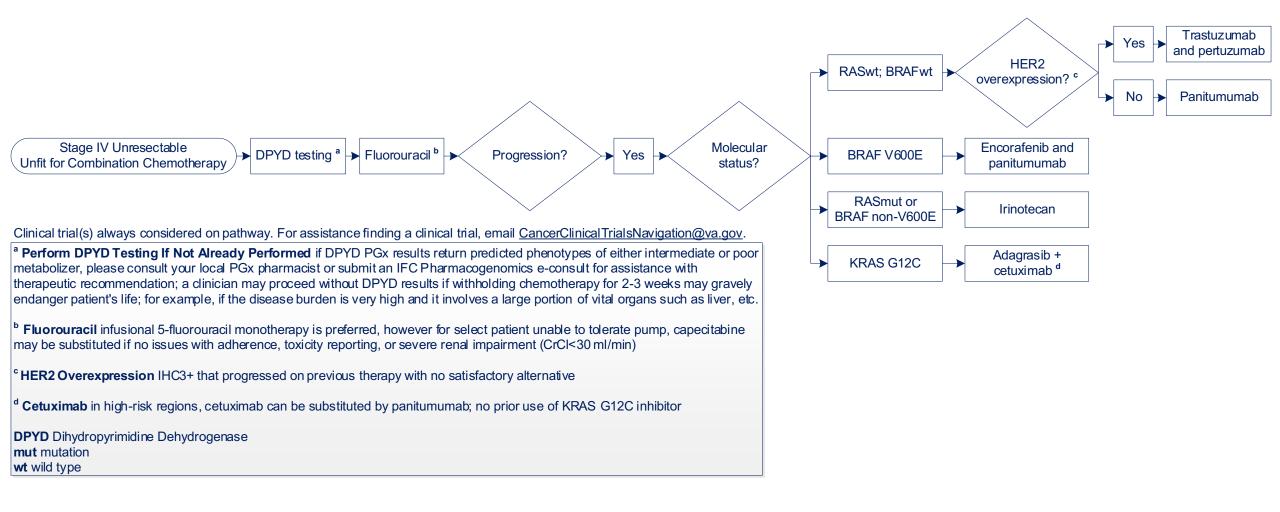
**dMMR** Mismatch Repair Deficient **pMMR** Proficient Mismatch Repair







## **Colon Cancer – Stage IV Unresectable Unfit for Combination Chemotherapy**

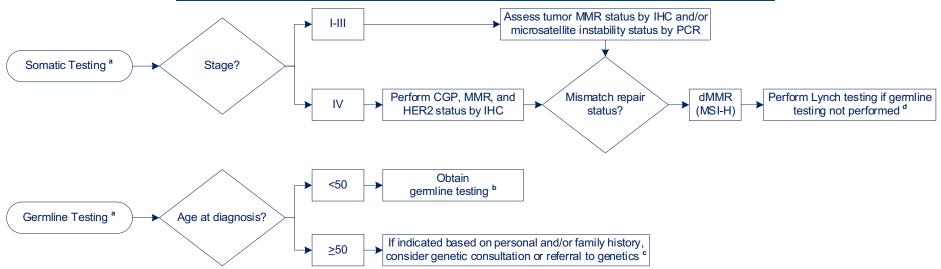








## **Colon Cancer – Molecular Testing**



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email<u>CancerClinicalTrialsNavigation@va.gov</u>.

<sup>a</sup> Molecular Testing perform for pathologically confirmed cancer

<sup>b</sup> Germline Testing an appropriate germline testing panel should include at minimum the following genes: APC; AXIN2; BMPR1A; CHEK2; EPCAM; GALNT12; GREM1; MLH1; MLH3; MSH2; MSH3; MSH6; MUTYH; NTHL1; PMS2; POLD1; POLE; PTEN; RNF43; SMAD4; STK11; and TP53

<sup>c</sup> **Personal and Family History** consider germline testing if significant personal and/or family history of multiple polyps, other Lynch syndrome or other hereditary cancer syndromeassociated cancers (e.g., colorectal, endometrial, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome), or pathogenic or likely pathogenic variant in a gene associated with known hereditary cancer syndrome is present in the patient or a family member

<sup>d</sup> Lynch Testing the diagnostic Lynch genetic testing algorithm depends on the pattern of MLH1, MSH2, MSH6, and PMS2 expression by IHC; diagnostic Lynch genetic testing should be performed if there is loss of MSH2, MSH6, MSH2/MSH6, or PMS2 expression by IHC; if there is loss of MLH1 expression by IHC, *MLH1* promoter hypermethylation testing should be performed; *MLH1* hypermethylation suggests somatic mutation, but diagnostic Lynch genetic testing should be performed if *MLH1* is unmethylated in the context of MLH1 loss by IHC; a diagnostic Lynch genetic testing genes: *EPCAM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* 

CGP Comprehensive Genomic Profiling dMMR Mismatch Repair Deficient IHC Immunohistochemistry MMR Mismatch Repair MSI-H Microsatellite Instability High PCR Polymerase Chain Reaction







### **Colon Cancer – Molecular Testing Table**

Eligibility	Test Category	Test Туре	Recommended Vendors	NPOP Coverage	Specimen Type	
Stage HII	IHC*	Mismatch repair (MMR) protein expression by IHC: MLH1, MSH2, MSH6, and PMS2.	Local VA or locally contracted vendor	No	Tumor Tissue	
	PCR*	Microsatellite instability (MSI) status by PCR.	Regional VA Testing Center (GLA)	Yes	Tumor Tissue and Normal Tissue or Blood	
	IHC	Consider BRAF V600E IHC if MLH1 or PMS2 expression is lost by IHC, or if MSHH and IHC not performed. Mutated suggests somatic mutation. Unmutated calls for Methylation testing.	Local VA or locally contracted vendor	No	Tumor Tissue	
	Molecular Testing	Consider <i>BRAF</i> V600E mutation testing if MLH1 or PMS2 expression is lost by IHC, or if MSIH and IHC not performed. Mutated suggests somatic mutation. Unmutated calls for Methylation testing.	Local VA or locally contracted vendor	No	Tumor Tissue	
	Methylation Testing	<i>MLH1</i> promoter hypermethylation testing (in the setting of loss of MLH1 or PMS2 expression by IHC). Hypermethylation suggests somatic mutation. Unmethylated calls for Germline Lynch testing.	Local VA or locally contracted vendor	No	Tumor Tissue	
	Germline NGS***	If full germline testing not performed, perform Germline Lynch testing if: 1) MSH2 or MSH6 loss by IHC or 2) MLH1 or PMS2 loss by IHC and <i>MLH1</i> unmethylated or 3) MSI-H without IHC testing AND <i>BRAF</i> unmutated AND <i>MLH1</i> unmethylated	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood	
Stage IV	Somatic NGS	CGP using both DNA and RNA based methodology	Tempus Foundation Medicine	Yes Yes	Tumor Tissue*****, Blood	
	IHC	HER2	Local VA or locally contracted vendor	No	Tumor Tissue	
	FISH	Reflex to HER2 FISH if 2+ on IHC	Local VA or locally contracted vendor	No	Tumor Tissue	
	IHC**	Mismatch repair (MMR) protein expression by IHC: MLH1, MSH2, MSH6, and PMS2.	Tempus	Yes (When ordered with CGP)	Tumor Tissue	
	PCR**	Consider microsatellite instability (MSI) status by PCR if MSI by CGP is not performed or equivocal.	Regional VA Testing Center (GLA)	Yes	Tumor Tissue and Normal Tissue or Blood	
	Methylation Testing	<i>MLH1</i> promoter hypermethylation testing (in the setting of loss of MLH1 or PMS2 expression by IHC). Hypermethylation suggests somatic mutation. Unmethylated calls for Lynch testing.	Local VA or locally contracted vendor	No	Tumor Tissue	
	Germline NGS***	If full germline testing not performed, perform Germline Lynch testing if: 1) MSH2 or MSH6 loss by IHC or 2) MLH1 or PMS2 loss by IHC and <i>MLH1</i> unmethylated or 3) MSI-H without IHC testing AND <i>BRAF</i> unmutated AND <i>MLH1</i> unmethylated	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood	
Diagnosis Below the Age of 50	Germline NGS****	Full Germline Testing	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood	
Personal and/or Family History of Multiple Polyps, Other Lynch Syndrome or Other Hereditary Cancer Syndrome Associated Cancers, or Pathogenic or Likely Pathogenic Variant in a Gene Associated with Known Hereditary Cancer Syndrome is Present in the Patient or a Family Member	Germline NGS****	Full Germline Testing	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood	
* For Stage Hill, either MMR or MSI or Both can be performed						
** For Stage IV, Both MMR and MSI should be performed; If MSI cannot be determined by CGP, then MSI by PCR can be performed						
** Germline Lynch testing should include at n	ninimum the followir	ng genes: EPCAM (deletion), MLH1, MSH2, MSH6, PMS2, POLE, and POLD1				
**** VA Common Hereditary POC panel or Equivalent Germline Test; Full Germline testing should include at minimum the following genes: APC; AXIN2; BMPR1A; CHEK2; EPCAM; GALNT12; GREM1; MLH1; MLH3; MSH2; MSH3; MSH6; MUTYH; NTHL1; PMS2;						
		genetic online ordering, refer to CCGS page for further details	· · · · · · · · · · · · · · · · · · ·			
****Tissue preferred, but liquid acceptable if	tissue insufficient					





