CANCER GENETICS®

Empowering Personalized Cancer Treatment

CRC COMPLETE

CRC Complete™

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the U.S. with 140,000 new cases per year and the third leading cause of cancer death in both men and women with 50,000 deaths per year. In 2012, there were ~1.2 million Americans living with a history of CRC. The risk of CRC increases with age as 90% of new CRC cases and 93% of deaths occur in people over the age of 50.

Lynch Syndrome is an inherited disorder that increases the risk of CRC and increases the risk of developing the disease at a younger age. Approximately 3-5% of CRCs are caused by Lynch Syndrome.

CGI's CRC Complete™ Program assists in determining the best personalized course of action for the patient by predicting overall prognosis and treatment response. CRC Complete™ also risk stratifies patients for likelyhood of developing Lynch Syndrome leading to earlier CRC screening and diagnosis for those identified as high risk.

Empowering Personalized Medicine

Clinicians have long known that patients respond differently to treatment. Genomics is now helping them in apprehending each patient's unique genetic make-up and the probable outcome of their disease. Testing patients for specific biomarkers can provide insight into diagnosis, prognosis, and the patient's likelihood of responding to certain treatments.

Tests being offered in the Complete℠ Programs include biomarkers that rely on various methodologies and that have diagnostic and prognostic significance for each patient.

List of CRC Complete™ Tests

Physicians can order tests individually or allow CGI pathologists and directors to determine a panel evaluation as determined necessary.

IHC

Histological Evaluation

The Histological evaluation is used for diagnosis. Markers include CK7, CK20, and CDX-2. The CDX-2 protein is expressed in primary and metastatic CRCs. CK7 and CK20 expression distinguishes pulmonary ovarian and breast cancers from colon cancers.

p53

p53 analysis by IHC is used for the prognosis of CRC. p53 expression indicates aggressive disease and is associated with poor prognosis and shorter overall survival.

Microsatellite Instability (MSI) Testing

Tumors from individuals with Lynch Syndrome demonstrate microsatellite instability (MSI). Lynch Syndrome is a hereditary cancer syndrome associated with germline mutations in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. MMR protein expression testing utilizes IHC to identify tumors with loss of protein expression for these mismatch repair genes. Deletions within the EPCAM gene has also been associated with Lynch Syndrome.

MSI testing and MMR protein expression testing are interpreted together to subtype the tumor into two distinct phenotypes: MSI-H and MSS/MSI-L. MSI-H is the primary phenotype observed in tumors from patients with Lynch Syndrome and is associated with a significantly better prognosis compared to those with MSS/MSI-L.

BRAF

BRAF IHC analysis can help to distinguish between a sporadic and germline etiology when absence of MLH1/PMS2 is observed in tumors being tested for MMR protein expression.

Molecular Diagnostics

KRAS Mutation Analysis

KRAS mutations occur in 40% of CRC cases and are predominantly in codons 12 and 13. Mutations of the KRAS gene are associated with poor prognosis and resistance to anti-EGFR therapies.

BRAF Mutation Analysis

BRAF mutations in CRC are associated with poor prognosis and decreased responsiveness to anti-EGFR therapy in patients with no KRAS mutation. Mutations of the BRAF gene are most common in codons 600 and 464-469, and occur in 5%-22% of CRC cases.

PIK3CA Mutation Analysis

PIK3CA mutations predict resistance to anti-EGFR therapies and an increased risk of local recurrences in rectal cancer.

NRAS Mutation Analysis

NRAS mutations predict resistance to anti-EGFR therapies.

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Work Up for CRC Complete™

Histological Evaluation

CK7, CK20, CDX-2 → Colon Primary

Mutation Analysis

Molecular

KRAS Mutation
- (+) → Resistance to Anti-EGFR Antibodies
- (−) → BRAF Mutation
  - (+) → Resistance
  - (−) → NRAS Mutation
    - (+) → Lack of Response
  - (−) → PIK3CA Mutation
    - (+) → Resistance, ↑ Risk of Local Recurrences in Rectal Cancer

IHC

p53 (IHC) → Poor Prognosis, Shorter Overall Survival

MSI Testing

Tumor Testing for MMR Protein Expression (IHC)

- Loss of MLH1/PMS2 → BRAF (IHC)
  - (+) → Sporadic Cancer
  - (−) → MSI
    - ≥2 → MSI-H → Germline testing for MLH1, PMS2 mutation
- Loss of MSH2/MSH6 → MSI
  - ≥2 → MSI-H → Germline testing for MSH2, MSH6 mutation
- No Loss
  - No Known LS Risk → Stop
  - (+) for LS Risk → MSI
    - ≥2 → MSI-H → Germline testing for MLH1, MSH2, MSH6, PMS2 & EPCAM mutation
    - <2 → MSS or MSI-L Sporadic Cancer

This work up is intended as a guide for the comprehensive suite of diagnostic tests included in CRC Complete™ to diagnose and monitor CRCs. Physicians can order tests individually or allow CGI pathologists and directors to determine a panel evaluation as determined necessary. Tests offered through CGI's Complete™ Programs are also available via Digital Pathology.

Specimen Requirements

	Test	TAT (Mon.-Fri.)	Tissue	Shipping Requirements
IHC	Histological Evaluation	1-2 days	FFPE block/H&E slide	Room temperature
IHC	p53	2-4 days	FFPE block or Ten 4-5 µm thick FFPE sections on positively coated slides	Room temperature
IHC	MSI Testing	5-7 days		
IHC	BRAF	2-4 days		
MDX	KRAS Mutation	5-7 days	FFPE block or 3-5 sections at 10 µm thickness containing at least 20% of tumor cells on regular unstained slides with H&E slides	Room temperature
MDX	BRAF Mutation			
MDX	PIK3CA Mutation	7-10 days		
MDX	NRAS Mutation			
CRC Complete™ Panel		10 - 15 days	FFPE block or 3-5 sections at 10 µm thickness containing at least 20% of tumor cells on regular unstained slides with H&E slides	Room temperature

FFPE: formalin-fixed paraffin-embedded

CGI Laboratory Licensure

CAP (Laboratory #: 7191582, AU-ID: 1434060), CLIA (Certificate #: 31D1038733), New Jersey (CLIS ID #: 0002299), New York State (PFI: 8192), Pennsylvania (031978), Florida (800018142), Maryland (1395), California (COS 800558).

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