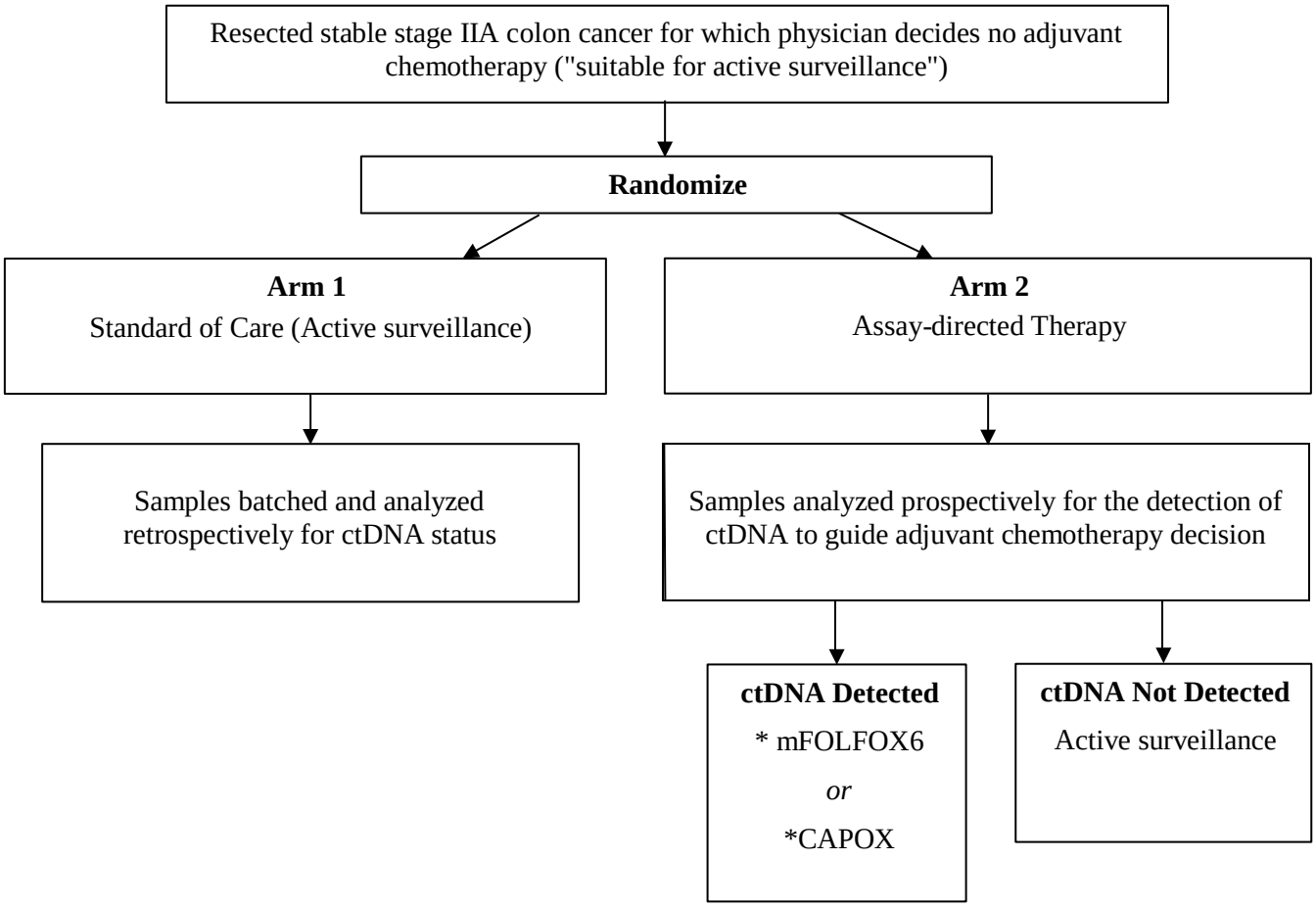
Figure 1. NRG-GI005 Schema



***Acceptable regimens for Arm 2 patients with "ctDNA detected" are:**

- mFOLFOX6: oxaliplatin 85 mg/m^2 IV Day 1 + leucovorin 400 mg/m^2 IV Day 1 + 5-fluorouracil (5-FU) 400 mg/m^2 IV bolus Day 1 followed by 5-FU 2400 mg/m^2 continuous infusion over 46 hours every 2 weeks for twelve cycles

  or

- CAPOX: Oxaliplatin 130 mg/m^2 IV over 2 hours on day 1 + capecitabine 1000 mg/m^2 PO BID on days 1-14 every 3 weeks for eight cycles

3.0 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Clinical Coordinating Department (CCD).

Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of mFOLFOX6 or CAPOX, when deciding if a patient is an appropriate candidate for this trial.

Submission of blood samples for ctDNA analysis, archived resected primary tumor tissue (FFPE), and uninvolved margin of resection (normal tissue) is **required for all patients**. In addition, all patients will be asked to consent to the submission of optional blood and tumor tissue samples for future research.

Investigators should check with their site Pathology department regarding release of tissue before approaching patients about participation in the trial.

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.

3.1.2 Age ≥ 18 years at diagnosis.

3.1.3 ECOG Performance Status of 0 or 1 (see Appendix A).

3.1.4 Histologically/pathologically confirmed stage IIA adenocarcinoma of the colon (T3, N0, M0) with at least 12 lymph nodes examined at the time of surgical resection.

3.1.5 Appropriate for active surveillance (i.e., no adjuvant chemotherapy) at the discretion of and as documented by the evaluating oncologist based on current practice patterns.

3.1.6 The distal extent of the tumor must be ≥12 cm from the anal verge on pre-surgical endoscopy (i.e., excluding rectal adenocarcinomas warranting treatment with chemoradiation). If the patient did not undergo a pre-surgical endoscopy, then the distal extent of the tumor must be ≥12 cm from the anal verge as determined by surgical examination or pre-operative imaging.

3.1.7 The patient must have had an en bloc complete gross resection of tumor (curative resection) as definitive surgical cancer treatment within 14 to 60 days of study randomization. Patients who have had a two-stage surgical procedure to first provide a decompressive colostomy and then, in a later procedure, to have the definitive surgical resection, are eligible.

3.1.8 Availability and provision of adequate surgical tumor tissue for molecular diagnostics and confirmatory profiling.

3.1.9 Adequate hematologic function within 28 days before randomization defined as follows:

- Absolute neutrophil count (ANC) must be ≥ 1200/mm^3;
- Platelet count must be ≥ 100,000/mm^3; and
- Hemoglobin must be ≥ 9 g/dL.

3.1.10 Adequate hepatic function within 28 days before randomization defined as follows:

- total bilirubin must be ≤ ULN (upper limit of normal) for the lab unless the patient has a chronic grade 1 bilirubin elevation due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; *and*
- alkaline phosphatase must be < 2.5 x ULN for the lab; *and*
- AST and ALT must be < 1.5 x ULN for the lab.

3.1.11 Adequate renal function within 28 days before randomization defined as serum creatinine ≤ 1.5 x ULN for the lab ***or*** measured or calculated creatinine clearance ≥ 50 mL/min using the Cockroft-Gault formula for patients with creatinine levels > 1.5 x ULN for the lab.

For Women

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For Men

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

3.1.12 Pregnancy test (urine or serum according to institutional standard) done within 14 days before randomization must be negative (for women of childbearing potential only).

3.1.13 Patients receiving a coumarin-derivative anticoagulant must agree to weekly monitoring of INR if they are randomized to Arm 2 and receive capecitabine.

3.2 Ineligibility Criteria

Patients with one or more of the following conditions are NOT eligible for this study.

3.2.1 Colon cancer histology other than adenocarcinoma (i.e., neuroendocrine carcinoma, sarcoma, lymphoma, squamous cell carcinoma, etc.).

3.2.2 Pathologic, clinical, or radiologic evidence of metastatic disease. This includes isolated, distant, or non-contiguous intra-abdominal metastases, even if resected (including the presence of satellite nodules constituting N1c disease in the absence of lymph node involvement).

3.2.3 Tumor-related bowel perforation.

3.2.4 History of prior invasive colon malignancy, regardless of disease-free interval.

3.2.5 History of organ transplantation.

3.2.6 Any prior systemic chemotherapy, targeted therapy, or immunotherapy; or radiation therapy administered as treatment for colorectal cancer (e.g., primary rectal adenocarcinomas for which treatment with neoadjuvant chemoradiation is warranted are not permitted).

3.2.7 Other invasive malignancy within 5 years before randomization. Exceptions are colonic polyps, non-melanoma skin cancer or carcinoma-in-situ of the cervix.

3.2.8 Synchronous primary rectal and/ or colon cancers.

3.2.9 Antineoplastic therapy (e.g., chemotherapy, targeted therapy, or immunotherapy) within 5 years before randomization. (For the purposes of this study, hormonal therapy is not considered chemotherapy.)

3.2.10 Uncontrolled cardiac disease, in the opinion of the treating medical oncologist, that would preclude the use of any of the drugs included in the GI005 treatment regimen. This includes but is not limited to:

- Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling temporary pacemaker.
- Ventricular tachycardia or supraventricular tachycardia that requires treatment with Class Ia antiarrhythmic drugs (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic drug (e.g., sotalol, amiodarone, dofetilide). Use of other antiarrhythmic drugs is permitted.

- Second- or third-degree atrioventricular (AV) block unless treated with a permanent pacemaker.
- Complete left bundle branch block (LBBB) unless treated with a permanent pacemaker

3.2.11 Sensory or motor neuropathy ≥ grade 2, according to CTCAE v5.0.

3.2.12 Active seizure disorder uncontrolled by medication.

3.2.13 Active or chronic infection requiring systemic therapy.

3.2.14 Known homozygous DPD (dihydropyrimidine dehydrogenase) deficiency.

3.2.15 Pregnancy or lactation at the time of randomization.

3.2.16 Co-morbid illnesses or other concurrent disease that, in the judgement of the clinician obtaining informed consent, would make the patient inappropriate for entry into this study (i.e., unable to tolerate 6 months of combination chemotherapy or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens or prevent required follow-up).