I respectfully request the NCCN Panel for Head/Neck Cancer review the enclosed data for inclusion in
the initial diagnostic evaluation of patients preparing to receive treatment with a fluoropyrimidine (e.g.
capecitabine, fluorouracil 5-FU).

Specific Changes: Revise the guidelines to recommend pre-screening of patients using a “functional”
test that measures the dihydrouracil/uracil ratio to identify individuals with impaired dihydropyrimidine
dehydrogenase (DPD) activity for whom the fluoropyrimidine dosage should be reduced to avoid severe
toxic reactions; treatments should also rely upon pharmacokinetic follow-up to indicate more precisely
recommended dosage levels.

FDA Clearance: not applicable

Rationale: Patients with impaired DPD activity (due to genetic and non-genetic factors) are unable to
metabolize the fluoropyrimidine and therefore are at risk of severe toxic reaction; pre-screening
patients will improve patient care, treatment efficacy, and significantly reduce grade 3 and 4 toxic
reactions and fatalities (instances of severe toxicity range from 10-40%).

The following articles are submitted to support this proposed change: These studies show that severe
reactions are far from rare (estimated 500-1000 fatalities/year in the US) and demonstrate that pre-
treatment screening and dose management of fluoropyrimidine can effectively reduce the incidence of
severe toxic and fatal reactions. (Note: fluoropyrimidines are used also in the treatment of breast, and
colorectal cancers).

Caudle, KE; Diasio, RB; et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for
Dihydropyrimidine Dehydrogenase Genotype and Fluorouracil Dosing, Clinical Pharmacology &
Therapeutics, (29 August 2013), doi:10.1038/clpt.2013.172. This study reports 10-40% of patients with
5-FU suffer severe and sometimes life threatening toxic reactions and recommends starting dosage at
50%, in order to minimize toxicities, followed by an assessment of the patient’s tolerance before
increasing dose levels.

Zhu, Andrew; Puchalski, Thomas; et al. Dihydropyrimidine Dehydrogenase and Thymidylate Synthase
Polymorphisms and Their Association with 5-Fluorouracil/Leucovorin Chemotherapy in Colorectal
Cancer, Clinical Colorectal Cancer, 2004 (Vol 3, No. 4): 225-234. This paper indicates that toxicity is not a
rare condition: 15-20% suffer grade 3, 3-10% grade 4 toxic reactions to 5-FU treatment; between 500-1000 US patients die annually due to 5-FU toxicity.

Ciccolini, Joseph; Mercier, Cedric; et al. Routine Dihydropyrimidine Dehydrogenase Testing for Anticipating 5-Fluorouracil-Related Severe Toxicities: Hype or Hope?, Clinical Colorectal Cancer, 2010 (Vol 9, No. 4): 224-228. This study indicates non-genetic factors may lower DPD levels and put patients at risk; it reports that functional techniques (uracil/dihydrouracil plasma tests and uracil breath tests) are available to identify patients who have a limited ability to metabolize 5-FU; and it asserts that pre-screening and dose tailoring systemically improved clinical outcomes of 5-FU patients.

Piper, Margaret; Aronson, Naomi; et al. Pharmacogenetic Testing to Predict Serious Toxicity From 5-Fluorouracil (5-FU) for Patients Administered 5-FU-Based Chemotherapy for Cancer, Technology Evaluation Center, Assessment Program Vol 24, No. 13, Aug 2010. This study reports 30% of patients receiving this treatment regimen suffer severe toxic reactions; genetic testing has poor predictive value.

Saif, M. Wasif, et al. Pharmacokinetically Guided Dose Adjustment of 5-Fluorouracil: A Rational Approach to Improving Therapeutic Outcomes, Journal National Cancer Institute, 2009, 101: 1543-1552. The authors offer that dose management may lead to substantial costs savings and better patient outcomes.

Gamelin, Erick, et al. Individual Fluorouracil Dose Adjustment Based on Pharmacokinetic Follow-up Compared With Conventional Dosage: Results of a Multi-Center Randomized Trial of Patients With Metastatic Colorectal Cancer, Journal of Clinical Oncology, 2008, 26: 2099-2105. This study found that plasma-level measurements of 5-FU is the optimal means of minimizing toxicity while ensuring the proper dose intensity; it also offered that this practice can be easily integrated into clinical practice.