**Submitted by:** Brian Alexander, MD
**Company:** Foundation Medicine, Inc.
**Address:** 150 Second Street, Cambridge, MA 02141
**Phone: 617-418-2200 Ext. 2256**
**Email:** balexander@foundationmedicine.com
**Date of request:** June 12, 2020
**NCCN Guidelines Panel:** Pancreatic Cancer

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Pancreatic Cancer Guidelines Panel consider the requested updates pertaining to the evaluation and management of patients with pancreatic cancer.

**Requested Update: Amend the algorithm on page PANC-1 to more clearly indicate that genomic profiling is recommended for all patients diagnosed with metastatic disease ("*Genomic profiling of tumor tissue recommended ~~as clinically indicated~~*").**

**Requested Update: Amend footnote (g) on pages PANC-1, PANC-6 ,PANC-7, PANC-8, PANC-9, and PANC-10 to clearly indicate that the Tumor/somatic profiling recommendation is inclusive of larger NGS-based panels (>50 genes) and/or comprehensive genomic profiling, ("*Tumor/somatic ~~gene~~ genomic profiling, via large validated NGS-based panels (>50 genes) and/or comprehensive genomic profiling, is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for actionable somatic findings including, but not limited to: fusions (ALK, NRG1, NTRK, ROS1), mutations and/or copy number changes (BRAF, BRCA1/2 & other HRR genes, HER2, KRAS, PALB2), and mismatch repair (MMR) deficiency (detected by tumor IHC PCR, or NGS). Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible*.")**

**Rationale:**

Comprehensive genomic profiling (CGP) can efficiently detect both somatic and germline mutations in individual genes (e.g. *BRCA1*, *BRCA2*, other homologous recombination repair (HRR) genes, MMR genes, *PALB2*, *ATM, BRAF*, *KRAS*, etc.), copy number changes (eg. *BRCA1/2* deletion, *HER2* amplification, etc.) and fusions (eg. *NTRK*, *ALK*, *NRG1*, *ROS1*) and MSI-H status using a single sample[1]. This would allow conservation of tissue while obtaining as much information as possible to inform the use of currently available biomarker driven therapies, immunotherapy, and define/refine clinical trial options, as well as to potentially inform the need for confirmatory germline testing for the patient and their family members when appropriate. Clearly defining "tumor/somatic profiling" of being inclusive of large validated NGS-based panels (>50 genes) and/or CGP would increase access to this type of testing to pancreatic cancer patients. Traditionally, PDAC patients have been treated similarly and with no attention to their genomic makeup (a "one size fits all" approach), but there is now accumulating evidence that subpopulations of patients with wild-type KRAS, homologous recombination repair (HRR) deficiency or MSI-high status can derive substantial clinical benefit from targeted treatments. Because these tumors are highly heterogeneous due to the diverse class of genes that are altered in KRAS wild-type and homologous recombination deficient (HRD) tumors, validated NGS-based panels (>50 genes) would be required to adequately capture the spectrum of alterations and confer the greatest benefit to patients.

- In a study of 640 pancreatic cancer patients from the Know Your Tumor (KYT) program[2] who underwent next-generation sequencing (99% CGP testing), "highly actionable" alterations were identified in 27%. Alterations were determined to be highly actionable if they might modify treatment options that affect a drug target (off-label or clinical trial). These highly actionable alterations included those identified in the following genes: BRCA1, BRCA2, PALB2, ATM, CHEK1/2, FANCA/C/G, STK11, AKT1/2/3, TSC1/2, CDK4/6, FGFR1/2/4, HER2, RET, NTRK1, NTRK3, BRAF, ALK, and ROS1. Of the 156 patients who began new treatments after receiving a CGP report, 126 (81%) chose treatment options presented in the report. The types of treatments chosen by the 126 patients utilizing the report were: standard of care (80 of 126, 63%), off-label molecular targeted (20 of 126, 16%), and clinical trials (26 of 126, 21%). Pancreatic cancer clinical trial enrollment historically has been less than 5 % of patients[3]. Patients receiving genomically-matched therapy vs those receiving non-genomically matched therapy had a median PFS of 4.1 months vs 1.9 months (HR 0.47; P=0.03).

- An updated analysis of pancreatic cancer patients in the KYT program was recently published and included outcomes for n=677 patients[6]. Those patients with actionable alterations who received a matched therapy (n=46) had significantly longer median overall survival (mOS) than patients who received unmatched therapies (n=143; 2.58 years [95% CI 2.39 to not reached] vs 1.51 years [1.33-1.87]; HR 0.42 [95% CI 0.26-0.68], p=0.0004). The report concluded that while about 25% of patients have actionable alterations, currently less than 5% are able to receive treatment because of barriers that include aggressiveness of PDAC, logistic and financial issues. However, most importantly, patients receiving matched therapy lived at least a year longer than the corresponding non-matched population.

- Another analysis of the KYT program evaluated 820 pancreatic cancer patients with molecular testing results (>97% CGP testing) who had adequate longitudinal outcomes and treatment history data[5]. Patients with a somatic or germline pathogenic

mutation in the homologous recombination DNA-damage response (HR-DDRm) pathway (including BRCA1/2, PALB2, ATM, ATR, ATRX, BAP1, BARD1, BRIP1, CHEK1/2, RAD50/51/51B, FANCA/C/D2/E/F/G/L) who had a history of platinum-treated disease had significantly longer median OS versus patients without an HR-DDR pathogenic mutation (2.37 years v 1.45 years, respectively). No difference was identified in the platinum naïve patients.

- In 2019 Singhi et al. published results of CGP testing on 3594 pancreatic ductal adenocarcinomas[7]. Overall 17% (n=611) of tumors analyzed had alterations considered to be therapeutically relevant, defined as linked to a currently available approved therapy or clinical trial. This included genomic alterations that are potentially targetable with kinase inhibitors in the *RAS* wild-type setting, including alterations in *BRAF*, *EGFR*, *ERBB2 (HER2)*, *ERBB3 (HER3), ERBB4*, *MET*, *ALK*, *RET*, *NTRK1*, *FGFR3*, *RAF1*, *MAP3K13*, *MAP3K1*, *MAP3K6*, *MAP2K1 (MEK1)*, *MAP2K4*, *FGFR1*, *FGFR3*, and *FGFR4;* predictive biomarkers for treatment identified in the BRCA-FANC pathway that may be targeted with platinum-based regimens or PARP inhibition, such as alterations in B*RCA2*, *BRCA1*, *ATM*, *CHEK2*, *PALB2*, *FANCF*, *RAD54L, FANCC*, *MRE11A*, *FANCG*, *RAD51C, RAD51L3*, *FANCL*, *FANCM*, *FANCA*, *FANCD2*, *RAD50*, *FANCI*, *RAD51*, *XRCC3*, *ERCC4*, *FANCE*, *CHEK1*, *BARD1*, B*RIP1*, and *ATR;* and an MSI or TMB high phenotype which may predict response to immunotherapies.

- CGP testing on tumor samples from 262 patients with PDAC identified a homologous recombination gene mutation (HRm) in any one of 17 HR genes in 19% (n=50)[4]. While the majority of HRms were germline in origin (15%), somatic HRms were identified in 4% of cases. Importantly, regardless of germline or somatic origin, HR gene alterations were associated with superior PFS in advanced PDAC patients subjected to first line platinum treatment (HR 0.44; p<0.01). Biallelic HRm showed enriched benefit of platinum treatment, independent of germline versus somatic origin. The authors conclude that determining the HRD status is ideally needed at the time of diagnosis to optimize survival and refine treatment selection in advanced PDAC.

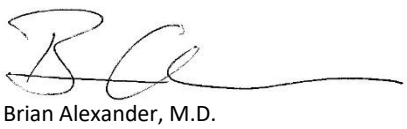
- In 2018, Aguirre et al. in a proof-of-principle study performed CGP testing on 71 metastatic PDAC biopsy samples and identified therapeutically relevant genomic alterations in 48% (34/71) of patients[8]. HR repair genes such as BRCA1/2, RAD51C and PALB2 were found to be altered in 14% (10/71), making these patients candidates for PARP inhibitor therapy. Furthermore, a total of 44% (31/71) exhibited alterations in DDR genes (BRCA1/2, PALB2, ATM, CHEK2, BLM, FANCA, FANCL, RAD50), which might confer enhanced sensitivity to platinum chemotherapy. Significantly, 7/71 patients harbored wild-type KRAS, and this population included BRAF alterations, a ROS1 fusion and FGFR amplification. One patient with BRAF mutation responded to off-label treatment with MEK1/2 inhibitor trametinib. Taken together, 30% (21/71) of patients experienced a change in clinical management as a consequence of CGP.

- **Clinical Trials**

  Numerous promising therapeutic approaches are based upon genomic characterization of tumors and therefore many clinical trials require specified genomic alterations for patient enrollment, including trials offered by the NCI (MATCH NCT02465060) and ASCO (TAPUR NCT02693535). Consistent with the NCCN® recommendation to provide patients with opportunities to participate in therapeutic clinical trials, comprehensive genomic profiling assays like FoundationOne® CDx, can potentially match more patients to targeted therapies in clinical trials based on detected alterations. Foundation Medicine is an approved testing platform for both NCI-MATCH and ASCO TAPUR and is accelerating accrual to these transformative trials using the combination of CGP and clinical trial matching capabilities.

Thank you for your review of this submission.

Sincerely,



Brian Alexander, M.D.
Chief Medical Officer
Foundation Medicine

**References**


1. FDA Label: Foundation Medicine Inc. FoundationOne® CDx Technical Information as of 6/12/20 found at https://assets.ctfassets.net/vhribv12lmne/6Rt6csmCPuaguuqmgi2iY8/26c3601c30e0d64c4f7e908543b8d62a/P170019.S015.Label.Technical_Info.FINAL.pdf (pdf attached)
2. Pishvaian MJ, Bender RJ, Halverson D, et al. Molecular Profiling of Patients with Pancreatic Cancer: Initial Results from the Know Your Tumor Initiative. *Clin Cancer Res.* 2018;24(20):5018-5027.
3. Hoos WA, James PM, Rahib L, Talley AW, Fleshman JM, Matrisian LM. Pancreatic cancer clinical trials and accrual in the United States. J Clin Oncol 2013;31:3432–8.
4. Park W, Chen J, Chou JF, et al. Genomic Methods Identify Homologous Recombination Deficiency in Pancreas Adenocarcinoma and Optimize Treatment Selection [published online ahead of print, 2020 May 22]. *Clin Cancer Res*. 2020;10.1158/1078-0432.
5. Pishvaian MJ, Blais EM, Brody JR, et al. Outcomes in Patients with Pancreatic Adenocarcinoma with Genetic Mutations in DNA Damage Response Pathways: Results from the Know Your Tumor Program. DOI: 10.1200/PO.19.0015 *JCO Precision Oncology*-published online October 23, 2019
6. Pishvaian MJ, Blais EM, Brody JR, et al. Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial [published correction appears in Lancet Oncol. 2020 Apr;21(4):e182]. *Lancet Oncol*. 2020;21(4):508-518.
7. Singhi AD, George B, Greenbowe JR, et al. Real-Time Targeted Genome Profile Analysis of Pancreatic Ductal Adenocarcinomas Identifies Genetic Alterations That Might Be Targeted With Existing Drugs or Used as Biomarkers. *Gastroenterology*. 2019;156(8):2242-2253.e4.
8. Aguirre AJ, Nowak JA, Camarda ND, et al. Real-time Genomic Characterization of Advanced Pancreatic Cancer to Enable Precision Medicine. *Cancer Discov*. 2018;8(9):1096-1111.