Supplemental Table legends:

Table S1. A. Patient-derived organoid cohort. Information on patients described in this study from which *bona fide* PDAC organoids were derived as well as the hN cohort. Gender, age, treatment status and tumor stage are indicated as well as the completion stage of each organoid in the precision medicine pipeline. **B. PDAC Core Gene Distribution**. The presence and allele frequencies of genetic alterations in the four most commonly mutated genes in PDAC. **C. PDAC Core Gene Summary.** A summary of the presence of compound genetic alterations in the four most commonly mutated genes in PDAC. **D. PDAC Core Gene Overlap.** The concordance between genetic alterations in the four most commonly mutated genes in PDAC were examined using WGS on matched patient and PDO specimens.

Table S2. Patient-derived organoid pathway analysis using gene set enrichment analyses with a FDR cutoff of 0.15. Pathway enrichment is shown following comparison of PDAC relative to hN organoid cultures as well as comparing the NMF C1 and NMF C2 clusters. Hallmarks and KEGG pathway gene sets are used for both up and down comparisons. POS refers to pathways that are enriched in the first comparator (e.g. Cancer or C1) while NEG refers to the pathways enriched in the second comparator (e.g. Normal or C2). **A.** Cancer versus Normal, POS, Hallmarks. **B.** Cancer versus Normal, NEG, Hallmarks. **C.** Cancer versus Normal, POS, KEGG. **D.** Cancer versus Normal, NEG, KEGG. **E.** C1 versus C2, POS, Hallmarks. **F.** C1 versus C2, NEG, Hallmarks. **G.** C1 versus C2, POS, KEGG. **H.** C1 versus C2, NEG, KEGG.

Table S3. Gene lists used to classify the PDOs into subtypes. A. Basal-like/Classical gene sets used to define these subtypes in PDOs. **B.** The C1/C2 gene sets derived by NMF and used to identify these subtypes in the PDOs.

Table S4. Patient-derived organoid pharmacotyping analyses. A. The AUC values for each PDO following treatment with chemotherapeutic agents. Red indicates a resistant PDO therapeutic profile (top 34% AUC) while Blue indicates a sensitive PDO therapeutic profile (lowest 33% AUC). **B.** The AUC values for each PDO following treatment with targeted agents. Blue indicates the most sensitive PDOs (10% most sensitive). **C.** PDOs insensitive to any chemotherapeutic agents (resistance is in red), and including the response of the that PDO to targeted agents. Blue indicates sensitive to targeted agent (10% most sensitive PDOs).

Table S5. PDO-derived chemo-sensitivity genes. Lists of genes whose expression changes are correlated with AUC. Gemcitabine (**A**), Paclitaxel (**B**), SN-38 (**C**), 5-FU (**D**) and Oxaliplatin (**E**) signatures. Rho values are shown for each gene. Positive Rho values indicate association with higher AUC (less sensitive) while negative values indicate correlation with lower AUC (more sensitive). The chemo-sensitivity signatures used in Figures 6, 7, S10, S11, and S12 were based upon genes whose expression increased with decreased AUC (negative rho).