Background: Bladder cancer remains a significant health problem, and a major cost to the health care system. While the majority of cases of bladder cancer are non-muscle invasive and are treated by cystoscopic resection, for those with muscle-invasive disease, therapy consists of either a radical cystectomy or radiation therapy. Even with definitive treatment, the mortality from muscle-invasive bladder cancer and metastatic disease remains high. Despite numerous clinical trials, treatment options for advanced bladder cancer have not improved, demonstrating the need for predictive models. Patient derived models (PDMs) are a powerful tool to study preclinical responses, however the benefits of each model have not been compared in head-to-head when models are derived from the same surgical specimen. Models of bladder cancer are needed to improve the preclinical testing of novel therapeutics and to predict response to therapy.

Methods: Surgical specimens (n=48) were implanted in hosts and were classified as no growth, some growth, or established lines. The PDMs representing xenografts (PDX), organoids (PDO), and spheroids (PDS) were characterized pathologically and molecularly by RNA sequencing. The universal molecular subtype and model-specific gene signatures were determined in order to compare PDMs to each other and their matching surgical specimen. Differential gene expression between the PDMs and surgical specimens were determined. PDMs and surgical specimens were clustered using the Euclidian distance analysis to test model fidelity.

Results: PDX models were established from 9/48 specimens. Overall, the molecular profiles of PDXs were the most similar to their matching patient specimen than the PDO and PDS from that patient. Likewise, each model was more similar to its matching patient sample than surgical samples and models from another patient. It is interesting to note that only Basal/Squamous (Ba/Sq) or Luminal Papillary (LumP) tumors established PDX models.

Conclusion: Surgical specimens had the most differentially expressed genes reflecting loss of immune and stromal compartments in PDMs. Moreover, PDMs upregulated a clear, patient-specific bladder cancer signal. Surgical specimens with the Ba/Sq molecular subtype are the most likely to form PDX models, alternative strategies to have models represent the other molecular subtypes are needed to provide models representing all subtypes of the disease.