Trans-catheter aortic valve replacement (TAVR) is a non-invasive procedure to treat severe aortic valve disease in patients at high-risk for open heart surgical aortic valve replacement (SAVR). Due to its non-invasive nature, TAVR has a strong appeal to become standard of care even in lower risk patients. Currently, major complications from TAVR include para-valvular leaks (PVLs), coronary ostium obstruction, and thrombo-embolism. From a biomechanics standpoint most valve related adverse outcomes may be attributed to the manner in which the TAV interacts with individual patient’s calcified aortic valve as well as the aortic root system. If the patient already has a degenerated bioprosthetic valve, then the interaction between the TAV and the calcified or degenerated bioprosthetic valve can dictate performance, durability, and adverse outcomes. Our lab is focused on building a precision medicine approach that not only aims to understand how patient-specific anatomic parameters impact the outcomes of different TAVs but also develop a new framework to help improve guidelines for valve selection and valve positioning individualized for every patient. Our framework utilizes multi-modal approaches starting with high-resolution patient imaging, clinical history, in-vitro 3D printing, particle image velocimetry, computational fluid dynamics modeling, and finite element structural modeling. This framework is illustrated through case examples illustrating the complex interactions between TAVs such as the Edwards Sapien, and Medtronic Corevalve Evolut interacting with patient specific Bicuspid, Tricuspid aortic roots or degenerated bioprosthetic valves with severe calcification and tissue ingrowth. Results paint a complex and rich interaction between the TAV and patient specific factors governing hemodynamic performance, sinus flow washout characteristics, para-valvular leakage, and coronary obstruction. Over the long term, as TAVR becomes standard of care even for lower risk patients, this research aims to bring precision medicine guidelines including computational modeling based planning to not only maximize the therapeutic impact of TAVR but also unravel new heart valve design principles to engineer future prosthetic heart valves.