The increasing ability to generate vast data from a patient's tumor and germline DNA at the point-of-care has required the development of a scientific discipline to harness this information avalanche for clinical and translational purposes: clinical computational oncology. This field, defined by the development and application of algorithms that analyze and interpret multi-omic data directly from patients to tackle scientific questions grounded in clinical care, has catalyzed new discoveries that directly impact precision cancer medicine strategies in many ways. This includes 1) prospective identification of patient-specific genomic features linked to therapeutic actions to guide individualized care, 2) definition of genomic mediators of response to existing and emerging cancer therapies, and 3) discovery of clinical tumor evolution mechanisms in multiple therapeutic resistance scenarios. In this presentation, we will present new advances in each of these areas of ongoing research, spanning multiple cancer types and clinical contexts. Broadly, the initiation and development of clinical computational oncology has significantly accelerated translational and clinical oncology discovery, whereby bioinformatics methodologies driven by clinically grounded investigators are leveraged specifically for clinical use at the point of care. Future efforts that expand this science across cancers and populations will inform their utility for precision cancer medicine.