Up to 40% of patients with intermediate-risk prostate cancer will fail radical prostatectomy or precision image-guided radiotherapy (IGRT). Additional genetic prognosticators are needed to triage these patients towards intensified combination therapy with novel targeted therapies to improve both local and systemic control rates. To address these questions, we are performing genomic analyses (for mutations and copy number alterations (CNAs) using comparative genomic hybridization and whole genome sequencing) of tumour DNA derived from frozen needle biopsies of 126 men with intermediate-risk disease who underwent image-guided radiotherapy (IGRT) to a mean dose of 76.4 Gy or men undergoing radical prostatectomy. Patients whose tumors had CNAs in both Pten and c-Myc, NKX3.1 and StAR/HSD17B2 had significantly increased genetic instability (recurrent genome alteration; PGA). We demonstrate that c-Myc gain alone, or combined c-Myc gain and PTEN loss, were increasingly prognostic for relapse on multivariable analyses (hazard ratios (HR) of 2.58/p=0.005 and 3.21/p=0.0004; respectively). Other loci were also prognostic for biochemical disease-free relapse (STAR: HR=2.84, 95% CI: 1.44-5.61, p=0.00269; HSD17B2: HR=1.97, 95% CI: 1.06-3.64, p=0.031 and NKX3.1 haploinsufficiency was associated with bRFR when tested alone (HR=3.05, 95% CI:1.46-6.39, p=0.0030) or when combined with c-Myc gain (HR=3.88, 95% CI:1.78-8.49, p=0.00067). All aCGH hits were also positive for outcome on multivariable analyses in prostate cancer surgery patients. Finally, a novel genetics-based signature has been developed that is independently prognostic. Our multidisciplinary group has also shown that both increased genetic instability and intra-glandular hypoxia predicts for poor outcome in intermediate risk prostate cancer. Additionally, when paired with information from hypoxia measurement in the same patients, a combination of genetic and hypoxic biomarkers is more prognostic that either alone. Our data from primary human specimens suggest that triaging patients by the use of personalized genetics may allow for better use of systemic therapies to target sub-clinical metastases or locally recurrent disease. The development and utility of such genetics-based tests and use within novel clinical trials with curative intent will be discussed. This personalized approach will improve clinical outcome in more than 20,000 patients worldwide who currently fail precision radiotherapy and surgery despite having localized disease.