Over the last 10 years there have been significant advances in understanding the molecular mechanisms underlying the myeloproliferative neoplasms (MPN). The identification of the JAK2 V617F gene mutation has had a wide ranging impact on clinical care, leading to changes in how we make a MPN diagnosis and determine prognosis. Ruxolitinib, a JAK1/2 inhibitor was developed as a targeted therapy for MPN and is commercially available for the treatment of myelofibrosis and polycythemia vera. Other JAK inhibitors continue in development. More recently, the CALR mutation was identified in most MPN patients who do not have the JAK2 mutation. Work is ongoing to further characterize the cellular role of CALR and the clinical impact of the mutation. Patients with myelofibrosis can carry additional mutations including EZH2, ASXL1, SRSF2 and IDH1/2 which are prognostically significant. Next generation sequencing can be used to for patient mutation profiling, however cost of testing remains a barrier to integration into routine clinical care.