THE MYELOPROLIFERATIVE NEOPLASMS: *ACQUIRED GENETICS AND A SURPRISE*

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The myeloproliferative neoplasms (MPNs) are a related group of seven marrow disorders characterized by clonal hematopoiesis, driven by acquired genetic changes, with a variable tendency to evolve towards frank leukemia. The primary characteristic is overproduction of one or more myeloid blood cell lineages, with symptoms of the disorders related not only to the expansion of the various blood cell types, but to their dysfunction. With the discovery of the Ph1 chromosome in 1960 in virtually all patients with chronic myelogenous leukemia, and its genetic characterization in 1984, additional chromosomal mutations were discovered in each of the MPNs, most notably in 2005, when an acquired, activating mutation of the JAK2 kinase was discovered in patients with polycythemia vera, essential thrombocythemia and primary myelofibrosis. Occasional patients were also found to possess congenital, MPN-predisposing mutations, and as their diseases advanced, secondary acquired genetic mutations. About 10 years ago, based on very large whole genome or exome sequencing of healthy populations (who served as controls for genome wide association studies), a fraction of individuals with normal blood counts and no symptoms were found to possess clonal hematopoiesis, driven by mutations in many of the same genes found in patients with MPNs, myelodysplastic syndromes, and frank leukemia. This form of clonal hematopoiesis was dubbed CHIP (clonal hematopoiesis of indeterminant potential). The frequency of CHIP was found to be age related, with as many as 15% of healthy octogenarians displaying clonal blood cells of from 2-20%. Follow-up or look back studies of such individuals revealed an approximate 10-fold increase in the likelihood of such individuals developing acute leukemia over the subsequent decades, but the surprising finding was a 2-4-fold increased risk of developing cardiovascular disease (CVD; myocardial infarction, stroke, peripheral vascular disease), even when controlled for CVD risk factors. The molecular explanation for these events are under intense study and will be discussed.