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# IMPROVED CRITERIA FOR CLINICAL, LABORATORY, MOLECULAR AND PATHOLOGIC (2018 CLMP) DIAGNOSIS AND STAGING OF PREFIBROTIC JAK2, CALR AND MPL MUTATED MYELOPROLIFERATIVE NEOPLASMS

**Jan Jacques Michiels[1], Yonggoo Kim, Myungshin Kim[2,3],Vasily Shuveav[4], Francisca Valster[5], Vincent Potters[5], Zwi Berneman[6], Alain Gadisseur[6], Wilfried Schroyens[6], Mihaela Andreescu[7], Adrian Trifa[8, 9] and Hendrik De Raeve[10]**

[1]Goodheart Institute in Nature Medicine, Bloodcoagulation, Phlebology & Vascular Medicine Science Center Rotterdam, Netherlands
[2]The Catholic University of Korea, Seoul, Korea
[3]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea
[4] Russian Research Institute of Hematology and Transfusiology, Saint-Petersburg, Russia
[5]Bravis Hospital, Bergen op Zoom, The Netherlands
[6]University Hospital Antwerp, Edegem, Belgium
[7] Colentina Clinical Hospital, Bucharest, Romania
[8]Luliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[9]Ion Chiricuta Oncology Institute, Cluj-Napoca, Romania
[10]OLV Hospital Aalst, Belgium
[11]University Hospital Brussels, Belgium

**The broad spectrum of JAK2 V617F mutated trilinear myeloproliferative neoplasms (MPN) include essential thrombocythemia (ET), prodromal polycythemia vera (PV), erythrocythemic PV, classical PV, masked PV and PV complicated by splenomegaly and myelofibrosis (MF). ET heterozygous for the JAK2V617F mutation is associated with low MPN disease burden and normal life expectancy. JAK2V617F mutation load increases from less than 50% in prodromal and early stage PV to above 50% up to 100% in combined heterozygous/homozygous or homozygous JAK2V617F mutated PV, advanced PV and progressive myelofibrosis (MF). Pretreatment bone marrow morphology and cellularity distinguish JAK2V617F mutated trilinear MPN from calreticulin (CALR) and MPL mutated MPN. The morphology of clustered large pleomorphic megakaryocytes with hyperlobulated nuclei are similar in JAK2V67F ET and PV patients. CALR mutated thrombocythemia shows bone marrow characteristics of normocellular megakaryocytic (M) proliferation and subsequent dual megakaryocytic granulocytic (MG) myeloproliferation, first described in the 1990s as primary megakaryocytic granulocytic myeloproliferation (PMGM) without features of PV in blood and bone marrow. MPL515 mutated thrombocythemia is featured by monolinear proliferation of large to giant megakaryocytes with hyperlobulated staghorn like nuclei. Natural history and life expectancy relate to the degree of splenomegaly, myelofibrosis,**

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constitutional symptoms and increased allele burden in JAK2V617F trilinear MPN and MPL515 thrombocythemia but CALR thrombocythemia runs a more favourable course during life-long follow-up. The acquisition of epigenetic mutations at increasing age predicts unfavorable outcome in JAK2, CALR and MPL mutated MPN. Low dose aspirin in ET and phlebotomy on top of aspirin in PV is mandatory to prevent platelet-mediated microvascular circulation disturbances. Pegylated interferon is the first line myeloreductive treatment option in prodromal and early stage JAK2V617F mutated PV and in CALR and MPL mutated thrombocythemia to postpone or obviate the targeted use of hydroxyurea and ruxolitinib as long as possible.

goodheartcenter@outlook.com

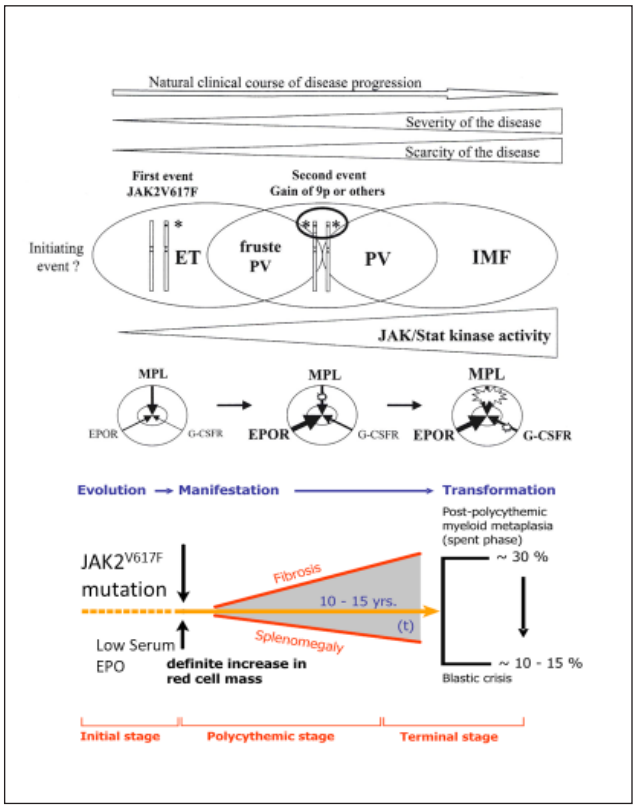


**Figure:-**The Constantinescu, Michiels and Vainchenker classificationof JAK2V617F mutated trilinear myeloproliferative neoplasms ET, PV and MF