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LETTER TO THE EDITOR

Neutrophilia and the *JAK2* V617F Mutation

Stephen E. Langabeer[1] · **Karl Haslam**[1]

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To the Editor:

The *JAK2* V617F mutation is the most commonly observed driver mutation in the myeloproliferative neoplasms (MPN), present in greater than 95% of polycythaemia vera patients and in 50–60% of patients with essential thrombocythemia and primary myelofibrosis. This mutation is also present in a smaller but significant proportion of patients with myelodysplastic/myeloproliferative syndromes. The diagnosis of MPN is multifactorial and is dependent upon haematological parameters, clinical presentation, bone marrow morphological features, and increasingly, the underlying molecular genetic signature [1]. While there exists an abundance of literature concerning how to detect the *JAK2* V617F and other MPN-associated mutations, there remains a lack of evidence as to which patients not fulfilling the major diagnostic criteria should be screened for this mutation. One of the most frequently observed reasons for *JAK2* V617F mutation analysis is the presence of a neutrophilia, either isolated or in association with other haematological features. Given that neutrophilia is one of the most commonly observed haematological abnormalities (causes include infection, inflammation, malignancy, trauma, certain drugs, growth factors, haemorrhage and splenectomy) and the previously documented increase and referral centre variation in *JAK2* V617F mutation testing [2], the value of molecular diagnostic screening for this mutation in patients presenting with neutrophilia was assessed.

An audit was performed on all diagnostic *JAK2* V617F requests between January 2006 and June 2016 inclusive, received at a molecular diagnostic centre. Of 13,615 requests, clinical details were provided with 7603 (55.8%) and of which 951 included details of a neutrophilia. Of these latter requests, 482 had neutrophilia as the only detail provided whereas 469 had neutrophilia noted in conjunction with one or more additional features noted as thrombocytosis (n = 327), raised haemoglobin or haematocrit or red cell count (n = 65), splenomegaly or hepatosplenomegaly (n = 36), anaemia (n = 22), basophilia (n = 18), monocytosis (n = 12), eosinophilia (n = 10), lymphocytosis (n = 10), thrombocytopenia (n = 9), constitutional symptoms (n = 7), deep vein thrombosis or pulmonary embolism or myocardial infarction (n = 5), leukoerythroblastic blood picture (n = 3), splanchnic vein thrombosis (n = 3), and lymphadenopathy (n = 2). The *JAK2* V617F was detected in 188 (40.1%) of patients with neutrophilia plus another documented feature but in only four (0.8%) of those patients with a reported isolated neutrophilia. Confirmation of other undocumented presenting features in these four patients was sought but was unobtainable.

Neutrophilia remains a specified indication for *JAK2* V617F mutation analysis in some diagnostic guidelines despite lack of supporting evidence [3]. The above observation in patients with an isolated neutrophilia suggests that investigation for *JAK2* V617F is not routinely indicated in the absence of other clinical or laboratory features of an MPN. It is acknowledged that absence of clinical details accompanying a request does not necessarily signify absence of that presenting feature and that isolated neutrophilia, in exceptional cases, can be the presenting aspect of an MPN. Long-term, follow up studies have concluded that while chronic neutrophilia can morphologically resemble chronic myeloid leukaemia (CML), the neutrophilia is highly unlikely to develop into a clinically recognizable MPN [4] and that screening for the *BCR-ABL1* fusion gene, the molecular hallmark of CML, in patients with neutrophilia is correlated with the co-existence of a basophilia [5]. We agree that the practice of

✉ Stephen E. Langabeer
slangabeer@stjames.ie

[1] Cancer Molecular Diagnostics, Central Pathology Laboratory, St. James's Hospital, Dublin Dublin 8, Ireland

en bloc screening for the *JAK2* V617F mutation is scientifically irrational and economically irresponsible [6] and propose a more considered selection of tests for the investigation of neutrophilia.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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