Lack of National Consensus for the Molecular Investigation of Myeloproliferative Neoplasms: Part 2

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Dear Editor,

The diagnosis of a myeloproliferative neoplasm (MPN) requires consideration of clinical, haematological and bone marrow histo-morphological features. The description of the first MPN-specific molecular abnormality in 2005, the \textit{JAK2 V617F} mutation, revolutionised the molecular diagnosis of these diseases. As this mutation is present in nearly all patients with polycythaemia vera and half of those with essential thrombocythaemia (ET) and primary myelofibrosis (PMF), assessment of this mutation was rapidly incorporated into classification systems. Subsequent genome sequencing studies of MPN identified recurrent mutations of the \textit{CALR} gene in 2013. \textit{CALR} mutations occur in up to 80\% of \textit{JAK2 V617-negative} ET and PMF cases and are almost mutually exclusive from the \textit{JAK2 V617F} mutation. This information compels the inclusion of \textit{CALR} mutation analysis into the MPN diagnostic algorithm after exclusion of the \textit{JAK2 V617F} as evident in the most recent 2016 World Health Organization classification of myeloid malignancies.\footnote{1} Given the previously documented centre-to-centre and clinician-to-clinician variation in ordering \textit{JAK2 V617F} analysis,\footnote{2} an audit was instigated to assess whether this deviation persisted in requesting the more recently described \textit{CALR} mutations.

Prospective, diagnostic \textit{CALR} requests on adults from a facility for haematological malignancy molecular diagnostics received in the four and a half years between January 2014 and June 2018 inclusive were included in the audit. \textit{CALR} requests were analysed according to the requesting centre, all of which were hospital Haematology departments. Centres were excluded if the number of requests was ten or more in the audit period to eliminate those with smaller practices that would not routinely request \textit{CALR} mutation analysis. The methodology for detecting mutations was unchanged throughout the audit period. A total of 1050 requests were received from 19 centres with the “hit-rate” calculated as the percentage of \textit{CALR} positive cases divided by the overall number of requests. The median number of requests from all centres was 35 (range 10-188) with a median “hit-rate” of 14.4\%. Conspicuously, a wide range in the individual centre “hit-rate” was evident, ranging from 4.8\% (successful in less than 1 in 20 requests) to 28.6\% (successful in more than 1 in 4 requests).

Evidently, indications for \textit{CALR} mutation screening vary from haematology centre to centre implying a continued lack of national consensus approach to testing. That the “hit-rate” is less than that of 19.2\%
previously reported for the more common JAK2 V617F mutation is indeed confounding. Several reasons may be responsible with unfamiliarity with testing algorithms likely to be largely responsible. CALR mutation analysis is only indicated in those patients with suspected ET or PMF with strong evidence emerging that testing is not warranted in patients presenting with an erythrocytosis, even those with a low serum erythropoietin, nor in patients with a first or recurrent thrombosis. Findings are to be disseminated to all centres with further audits scheduled to reassess requesting patterns. This audit highlights certain impediments in implementing rapidly evolving, molecular diagnostic guidelines and emphasizes the need for continual education and adoption of a consensus approach for the molecular investigation of MPN, particularly in the context of defined laboratory resources.

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**References**
