histology in distinguishing ET from PMF, but marrow histology, although distinctive, is not always diagnostic for any of the MPDs.[2] Furthermore, isolated thrombocytosis is not a disease per se but, like myelofibrosis, it is only a disease manifestation that must be assessed in the context of both the patient and time. It takes approximately 8 years for isolated thrombocytosis to evolve into a PMF phenotype,[3] and this is also true for its evolution to PV. Viewed from this perspective, the authors cannot be sure of the correct diagnosis of the patient illustrated in their Figure 2. However, considering that clonal dominance is least common in ET as is *JAK2* V617F homozygosity, whereas both are most common in PMF,[4] a high circulating $CD34^+$ cell concentration or a high *JAK2* V617F allelic burden, when present, should separate ET from PMF, but this was not discussed. With respect to PV, the distinction is even easier, yet Beer et al err by assuming that *JAK2* V617–positive thrombocytosis patients with "normal iron stores/MCV" cannot have PV, which is incorrect,[2] and then they err again: conflating the venous hematocrit with the total body hematocrit derived by isotope dilution, they remarkably assert, "However, in the presence of a normal hematocrit and normal iron stores, the clinical significance of a raised red cell mass is unclear, and so we do not measure the red cell mass in our ET patients."[1p1475] This conceptual error, that the hematocrit is an accurate reflection of the red cell mass in the MPD, has been repeatedly discredited[5] and has no place in modern medical practice. Indeed, because 64% of *JAK2* V617–positive ET patients had an elevated red cell mass but a normal hematocrit,[6] and because venous thrombosis is more common in PV than in ET, this conceptual error has important therapeutic implications. The authors also misinterpret the PT-1 study: hydroxyurea was only more effective than anagrelide in preventing transient ischemic attacks because it is a nitric oxide donor, but not arterial thrombosis, and was markedly less effective for preventing venous thrombosis; others have made similar observations. Finally, given that life span is normal in ET, whereas hydroxyurea is at best palliative, it is unclear how the authors can dismiss an established body of evidence identifying hydroxyurea as leukemogenic in the MPD (reviewed in Spivak[7]) when discussing its use.

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Response

Essential thrombocythemia: seeing the wood for the trees

We thank Dr Spivak and Dr Silver for their interest in our review.[1] We completely agree that diagnostic accuracy is important and that isolated thrombocytosis is not a disease entity. However, we disagree with the remainder of their comments, which fall into 3 categories: the relationship of ET to PMF, the relationship of ET to PV, and the appropriate use of hydroxyurea therapy.

With regard to the relationship between ET and PMF, Drs Spivak and Silver suggest that, in a patient presenting with isolated thrombocytosis, CD34 count, *JAK2* V617F homozygosity, and mutant allele burden should be used routinely to distinguish these disorders. We feel this would be inappropriate because these tests are neither standardized nor widely available, show considerable overlap between MPN subtypes, and are of unproven prognostic utility. In our article, we outline a pragmatic approach to diagnosis that is widely applicable, while acknowledging that future improvements in molecular diagnosis will likely further illuminate the many gray areas. In Figure 2 we describe a patient who presented with an isolated thrombocytosis and markedly increased bone marrow reticulin, but no other features of PMF. Importantly, such patients are common (15%-20% of ET patients), cannot be classified as having either ET or PMF according to WHO criteria,[2] and, because they have a relatively good prognosis, are best managed as ET. We also cite several lines of evidence supporting the concept that PMF represents presentation in accelerated phase of a previously undiagnosed MPN, usually ET.

Concerning the relationship of ET to PV, Drs Spivak and Silver are simply wrong when they state that we assume "JAK2 V617F–positive thrombocytosis patients with 'normal iron stores/MCV' cannot have PV." Instead, we clearly explain that "there are inherent problems in the use of continuous variables, such as hemoglobin, hematocrit, or red cell mass, to make this binary distinction [ie, between ET and PV], because the group of patients with borderline values will inevitably include both disorders."[1p1475] They are wrong again when they state that we conflate "the venous hematocrit with the total body hematocrit derived by isotope dilution." Instead, we clearly state, "We recognize that, unless markedly elevated, hematocrit does not accurately predict a raised red cell mass."[1p1475] When considering how to manage a patient with a normal hematocrit but a raised red cell mass, it is important to remember that clinical trials of PV have never included this subgroup of patients. It is therefore correct for us to assert that "in the presence of a normal hematocrit and normal iron stores, the clinical significance of a raised red cell mass is unclear."[1p1475] Drs Spivak and Silver do not reveal whether they propose measurement

of red cell mass in all patients diagnosed with ET, or indeed how an abnormal result should influence therapy. In the absence of informative clinical studies we take a pragmatic approach and base a diagnosis of PV on the presence of a *JAK2* mutation and a raised hematocrit (with or without supporting features such a low serum erythropoietin), an approach consistent with both WHO and BCSH guidelines,[3,4] and we do not measure red cell mass in our ET patients.

In the context of hydroxyurea, Drs Spivak and Silver claim that we have misinterpreted the results of the PT-1 trial. This is incorrect. We state that "Hydroxycarbamide (also known as hydroxyurea) is the only cytoreductive agent proven to reduce thrombotic events in a randomized controlled trial"[1p1477] and feel it would be inappropriate to ignore carefully documented transient ischemic attacks given the considerable evidence that they are harbingers of completed strokes.[5] Last, Drs Spivak and Silver claim we dismiss evidence that hydroxyurea is leukemogenic. Once again this is wrong. After weighing up the strength of the published evidence and citing multiple papers supporting both sides of this debate, we conclude "At this time it is unclear whether single agent hydroxycarbamide is leukemogenic; however, any increased risk is likely to be small and should be balanced against the reduction in thrombotic complications."[1p1478]

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To the editor:

NOD2/CARD15 gene polymorphisms affect outcome in pediatric allogeneic stem cell transplantation

Distinct polymorphisms of *NOD2/CARD15* (rs2066844 [SNP08], rs2066845 [SNP12], and rs2066847 [SNP13]) have influence on the incidence of Crohn disease (CD), a chronic inflammatory disorder of the gastrointestinal tract. Similar symptoms of CD and GVHD after allogeneic stem cell transplantation (allo-SCT) inspired Holler and coworkers to initiate a study that actually showed association of these polymorphisms and transplantation outcome.[1] Subsequently some groups confirmed unfavorable association,[2-5] whereas others did not.[6-10] Because the impact of *NOD2/CARD15* on SCT is still debatable, we initiated a retrospective multicenter study in pediatric patients (median age 9.8 years [0.2-21 years]) who received allo-SCT. The study was approved by the Goethe-University ethics committee (no. 294/05) and informed consent was obtained according to the Declaration of Helsinki. Genetic variants were analyzed in 567 donor-recipient pairs transplanted between 1996 and 2008. Of these, 446 were HLA-matched and 121 were mismatched. Primary diagnosis comprised hematologic malignancies (n = 472), nonhematologic malignancies (n = 23), and nonmalignant diseases (n = 72). We found polymorphisms in 74 donors (13.1%) and in 70 recipients (12.3%). In 29 (5.1%) cases, both donor and recipient were coincidental variant. The observed genotype frequencies were consistent with the Hardy-Weinberg equilibrium. End points considered in the analysis were overall survival (OS), relapse of disease (REL), treatment-related mortality (TRM), acute GVDH (grades II-IV; II-IV) and chronic GVHD (within day 365). The probability of OS was obtained by the Kaplan-Meier method and cumulative incidences with competing events of TRM, REL, and GVHD according to Kalbfleisch and Prentice using the "survival" and "cmprsk" packages for R 2.9.2 software (www.r-project.org). Differences were tested with the log-rank or the Gray test, respectively. Multivariate analyses were performed using Cox proportional hazard regression analyses of SPSS 15.0, the incidences of categorical parameters were calculated by the Pearson χ^2 or the Fisher exact test, and parametric variables were tested by ANOVA or the unpaired *t* test. The median observation period was 18 months (0.5-119.4 months) and pOS was 61.1% (56.9-65.5%). Clinical risk factors associated with transplantation outcome were diagnoses, stem cell source, HLA match or mismatch, severe acute GVHD, second transplantation, in vivo T-cell reduction, donor leukocyte infusion administration, and type of gastrointestinal decontamination, as revealed by univariate analysis ($P < .05$). Initial analysis comparing wild-type with variant transplantations did not indicate any association of nod2 variants with adverse outcome. Moreover, coincidental polymorphisms were associated even with favorable outcome, which could be explained by familial aggregation preferably in matched related