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Experience of Myeloproliferative Neoplasms Guidelines in the United Kingdom: Perspective and International Context

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The hematology community in the United Kingdom has an established process for identifying the need for a guideline and then producing and disseminating it. The British Committee for Standards in Haematology (BCSH) was formed in 1964, with the first published guideline in 1984. The resultant library of documents includes guidelines on aspects of laboratory practice, from areas such as blood transfusion to highly complex clinical management. These guidelines are published in peer-reviewed journals but are also available via a Web-based platform with free access (<http://www.bcsghguidelines.com>). This article discusses the process and history of the production of these guidelines, with particular reference to those for myeloproliferative neoplasms (MPNs).

The BCSH Guideline Process

Although formed in 1964, after various negotiations, the BCSH became a subcommittee of the British Society for Haematology (BSH) in 1976. BCSH has been producing guidance for hematologists since the first guideline was published in 1984. The guidelines were initially focused on laboratory practice guidelines, but subsequently moved into areas of clinical practice. The primary aim of the BCSH guideline process is to provide hematologists with up-to-date advice on the diagnosis and treatment of hematologic disease.

The BCSH process or methodology for guideline production has evolved over the years. Laboratory guidelines were mainly methodologically based, but clinical guidelines review literature, and access and grade evidence using a standardized process.

Currently, 4 BCSH task forces review general hematology, hemostasis and thrombosis, blood transfusion, and hematology-oncology, covering the main areas of hematology practice. Guidelines are produced in 3 different formats. First, evidence-based guidance is produced using a standardized process of conducting systematic reviews, following a primary systematic review of the evidence. Second, evidence-based guidance referencing other previously published evidence-based guidelines (eg, international guidelines) are produced through systematic review. Third, guidance and recommendations are used in areas in which less robust evidence is available but for which a degree of consensus is likely to benefit patient care.

BCSH guideline writing groups are composed of appropriate experts (consultants or senior healthcare scientists in practice in the United Kingdom), a member of the relevant task force, and representatives of relevant professional and patient bodies. The writing group members are approved by the task force. After formation of the writing group, databases are searched with appropriate keywords, search period, and inclusion and exclusion criteria. All references are sourced and evaluated by the group and recommendations are formulated. An audit tool is attached to each guideline to assess adherence to the guidance. The GRADE nomenclature is currently in use for evaluating evidence and assessing the strength of recommendations.¹

When complete, guidelines are reviewed by both the relevant task force and then by "sounding boards," which are composed of practicing hematologists and provide peer review. When the final guideline is agreed, it is posted on the Web site. The goal is then to publish in a peer-reviewed journal, usually the *British Journal of Haematology*.

The ideas and viewpoints expressed in this commentary are those of the author and do not necessarily represent any policy, position, or program of NCCN.

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BCSH MPN Guidelines

In 2005, the first BCSH guideline in MPNs was published. The BCSH MPN guidelines are all evidence-based guidelines formulated after primary review of the evidence when available. When evidence is not available, expert opinion is agreed. A summary of the current MPN guidelines and their content is shown in Table 1, at the end of this article. This and all subsequent guidelines in MPNs were developed by various groupings of MPN-interested hematologists working in the Myeloproliferative Disorders Study Group, which became an official subgroup of the National Cancer Research Institute (NCRI) in 2006. Experts from other areas were invited as required.

The first guideline was a comprehensive discussion of the diagnosis, investigation, and management of polycythemia/erythrocytosis. It covered the diagnostic processes for the investigation of erythrocytosis in detail. The guideline group included expert hematologists and experts from other disciplines, including respiratory medicine and pediatric cardiology. The management of polycythemia vera (PV) was included with review of all randomised clinical trials, and then recommendations on treatment and cytoreductive therapies were formulated. Management of thrombotic and hemorrhagic complications, pruritus, and pregnancy in PV was also considered. The guideline document then formulated the recommended management of other types of erythrocytosis, apparent erythrocytosis, idiopathic erythrocytosis, high oxygen affinity hemoglobins hypoxic pulmonary disease, cyanotic congenital heart disease, and post-renal transplant erythrocytosis.² As such, this guideline presented advice for a large spectrum of clinical conditions associated with an erythrocytosis.

Soon after the initial publication of this guideline, the acquired JAK2 mutation was discovered in many patients with MPN.³ This finding had major implications on the diagnostic pathway in PV, and this evidence was evaluated and new diagnostic criteria formulated. This was published as an amendment in 2007; the Web site is structured so that amendments are always linked with the original guideline.⁴

After this, BCSH undertook thrombocytosis guidelines, and in 2010 published a guideline for the investigation and management of adults and children presenting with a thrombocytosis.⁵ This covered all aspects of the diagnostic pathway with differential diagnosis. In the management of essential thrombocythemia (ET) prognosis, risk stratification and thrombotic risk were considered. All therapies were reviewed, and treatment-specific recommendations made. Management of the specific circumstances, such as during pregnancy, post-ET myelofibrosis (MF), leukemia transformation, in children, splanchnic vein thrombosis, and surgery, were considered.

Recommendations were also made for management of reactive thrombocytosis and myelodysplastic/MPN overlap disorders. After this publication, 2 further articles were published, clarifying the diagnostic process. First, the process was clarified to note that BCR-ABL1 testing should be performed in all patients to ensure a diagnosis of chronic myeloid leukemia was excluded.⁶ The second development was because of the discovery of new mutations. In the process of evaluating a patient for ET, acquired mutations in the *CALR* gene supported the clonal nature of the disorder.⁷ This development was incorporated into the diagnostic criteria.⁸

The group then specifically considered MF and developed a guideline for its diagnosis and management. This also considered the diagnostic pathway and all the management options, including myelosuppressive therapy and bone marrow transplantation. Specific clinical situations, including splenomegaly and extramedullary hematopoiesis, anemia, and the management of constitutional symptoms were evaluated. Management options for blast crisis, pregnancy, and MF in childhood were also included.⁹ This guideline was published in 2012. Trials of JAK inhibitors were underway at that time and were mentioned in the guideline, but

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the trials had not yet been published. Once they were published, a modification was published to include them along with modified management advice.¹⁰

A comprehensive guideline for the detection of JAK2 V617F and other mutations covering laboratory practice, including sample issues and laboratory methodology, and assay validation was also prepared and published.¹¹ Currently, guidelines for the investigation and management of eosinophilia and a second set of guidelines for the management of mast cell disorders are in preparation.

Thus, over almost 10 years, guidelines for the diagnosis and management of all aspects of MPN have been prepared and published, primarily aimed at hematology practice in the United Kingdom.

Guideline Use in Healthcare

In a digital world, doctors have instant Internet access in their working environment, either by desktop computer or handheld device. The BCSH guidelines are freely available via the BSH Web site, and clinicians in the United Kingdom consult the guidelines frequently via the Internet and often in real time as part of a consultation. This is evidenced by the fact that the BSH guidelines Web site has almost 500,000 page views per year from the United Kingdom. Although this figure includes all guidelines, the MPN guidelines are among those frequently visited. In 2015, the MF and erythrocytosis guidelines were both among the top 10 guidelines visited in the year, despite the fact that the erythrocytosis guideline dates back 10 years.

In 2014, in conjunction with the *British Journal of Haematology*, an app was created. Activity via the app reached a maximum of 9,000 downloads per month in 2015 before starting to decline. In view of the costs of maintaining apps, this program is not being continued.

The guidelines are all published in peer-reviewed journals, mainly—and, in the case of the MPN guidelines, exclusively—in the *British Journal of Haematology*. This journal has universal open access, and the guidelines are frequently accessed and downloaded in the United Kingdom and beyond from the journal site. The investigation and management of thrombocytosis in adults and children has been one of the most frequently cited and downloaded articles from the journal.

The MPN and other BCSH guidelines are used not only in day-to-day clinical practice but also in other situations. For example, guidelines are used as a basis for education, both for trainees and for ongoing professional development. They are also accessed by patients and representatives of the pharmaceutical industry. Furthermore, currently guidelines are also produced with an associated tool that facilitates audit and standardization of practice.

Finally, the guidelines are used in the National Institute for Health and Care Excellence (NICE) processes, at least in part to inform standard practices in the United Kingdom. This not only relates to drug reimbursement—a practical example of which is the approval of the JAK1/2 inhibitor ruxolitinib—but also may relate to approval of funding for specific tests (eg, implementation of and funding for molecular tests).

International Practice Patterns

Although BCSH guidelines are written primarily for practice in the United Kingdom and are written in the context of the National Health Service, they are consulted worldwide. The pattern of downloads of BCSH guidelines for the past 12 months show use from Ireland (27,085), the United States (13,597), India (16,311), Sri Lanka (15,770), Australia (11,553), Saudi Arabia (9,088), Malaysia (8,901), Pakistan (9,138), Italy (11,124), and others (149,880), and the MPN guidelines have doubtless

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contributed greatly to this activity. For example, at the time of writing, the modified BCSH guidelines for MF incorporate the use of ruxolitinib and were the first widely internationally available MPN guidelines to do so.

Other guidelines do exist for MPN practice, including the new NCCN Clinical Guidelines in Oncology (NCCN Guidelines). At writing, the most widely used are those from the European LeukemiaNet (ELN)¹² and the European Society for Medical Oncology.¹³ These 3 are the only other guidelines in the public domain to recommend the JAK inhibitor ruxolitinib. The BCSH guidelines (and frequently the NCCN Guidelines), unlike the ESMO guidelines, for example, suggest practical measures for starting, monitoring, and stopping therapy, all of which are important for rare conditions when clinicians may have little experience with using newer agents.

Changing Process

Although the BCSH guideline process has been highly beneficial and successful, it is being revised and improved. The scope of searches, with comprehensive inclusion and exclusion criteria for articles, is being planned. In these, medical writers help perform searches after clear questions have been formulated. NICE has a process for the accreditation of guidelines, and BCSH is working toward implementation of processes to gain NICE accreditation.

Under the revised system, a new guideline on the diagnosis and management of PV is planned. This involves reviewing the evidence from trials of new agents in the past 10 years and formulating evidence-based management advice. Review of the evidence for diagnosis and management of secondary erythrocytosis will also be reviewed in the near future. Guidelines for eosinophilia and mastocytosis are in progress.

Conclusions

The well-established BCSH process for producing guidelines has evolved since its inception in 1987. The MPN guidelines include 3 existing guidelines for the common Philadelphia-negative diseases: ET, PV, and MF. These guidelines are reviewed and updated, if necessary, at least every 3 years—sooner if required due to new findings (eg, the *CALR* mutation) or new therapies (eg, the JAK inhibitor ruxolitinib). These are produced using a highly rigorous technique and are peer reviewed through the BCSH task forces, a sounding board, and then before publication in an academic journal. The benefits of such guidelines include education, standardization of practice, tools for auditing practice, and, on occasion, facilitating reimbursement of novel tests or therapies.

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Table 1. Summary of the Current British Committee for Standards in Haematology MPN Guidelines

Guideline	Subjects Covered	Main Recommendation
Diagnosis, investigation, and management of polycythemia/erythrocytosis	Management of PV Pregnancy and PV Apparent erythrocytosis Idiopathic erythrocytosis High oxygen affinity hemoglobins Hypoxic pulmonary disease Cyanotic congenital heart disease Postrenal transplant erythrocytosis	<u>Management of PV</u> Venesection to maintain the HCT to <0.45 Aspirin , 75 mg/d unless it is contraindicated Cytoreduction should be considered if: poor tolerance of venesection, symptomatic or progressive splenomegaly, or other evidence of disease progression (eg, weight loss, night sweats, thrombocytosis) Choice of cytoreductive therapy , if indicated: <ul style="list-style-type: none">• Age <40 y: first-line interferon, second-line hydroxycarbamide or anagrelide• Age 40–75 y: first-line hydroxycarbamide, second-line interferon or anagrelide• Age >75 y: first-line hydroxycarbamide, second-line 32P or intermittent low-dose busulphan
Investigation and management of thrombocytosis	Diagnostic process Risk stratification Management of ET Management of special circumstances Management of thrombocytosis in MDS/MPN disorders Management of reactive thrombocytosis	<u>Management of ET</u> All patients: start aspirin unless contraindicated High-risk patients: hydroxycarbamide plus aspirin first -line; interferon-alfa option in younger patients Low- and intermediate-risk patients: aspirin and aggressively manage cardiovascular risk factors
Diagnosis and management of MF	Diagnosis Molecular investigation Prognosis Treatment of splenomegaly and extramedullary hematopoiesis Treatment of anemia Management of constitutional symptoms Myelosuppressive therapy Bone marrow transplantation Blast phase Pregnancy and childhood MF	<u>Recommendations for management of splenomegaly</u> First-line JAK inhibition <u>Recommendations for anemia</u> Identify cause, consider EPO if levels <125IU/L or danazol or thalidomide or corticosteroids <u>Recommendations for myelosuppressive therapy in MF</u> Hydroxycarbamide: first-line choice, anagrelide with caution, interferon-alfa in early-phase disease <u>For symptoms</u> Consider JAK inhibitor is refractory to standard therapy
Detection of <i>JAK2</i> V617F and other relevant mutations	Sample Assay Interpretation Validation of assay <i>JAK2</i> exon 12 mutations <i>MPL</i> exon 10 mutations <i>BCR-ABL1</i> assessment	<pre>graph TD A[Suspected PV, ET, or PMF] --> B[JAK2 V617F] B -- Positive --> C[MPN confirmed
Final diagnosis
according to blood
count, bone
marrow, and
clinical features] B -- Negative --> D[Erythrocytosis] B -- Negative --> E[Thrombocytosis] B -- Negative --> F[Suspected PMF] C --> D C --> E C --> F D --> G[JAK2 exon 12] E --> H[MPL exon 10
BCR-ABL1] F --> I[MPL exon 10
BCR-ABL1]</pre>

Abbreviations: ET, essential thrombocythemia; EPO, erythropoietin; HCT, hematocrit; MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasms; PMF, primary myelofibrosis; PV, polycythemia vera.

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