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MDS CLEARPATH: AN INTERNET-BASED EDUCATIONAL ALGORITHM FOR THE WORK-UP, DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH MYELODYSPLASTIC SYNDROMES FROM THE CANADIAN CONSORTIUM ON MDS: 2023 UPDATE

Heather A. Leitch, MD, PhD
Brian Leber, MD
Harold J. Olney, MD
April Shamy, MD

ABOUT THE AUTHORS

Heather A. Leitch, MD, PhD

Dr. Heather Leitch is a Hematologist at St. Paul's Hospital in Vancouver, Canada and Clinical Professor in the Department of Medicine at the University of British Columbia. Dr. Leitch has a clinical and research interest in transfusional iron overload in acquired anemias such as the myelodysplastic syndromes (MDS), and a longstanding interest in lymphoproliferative and other blood disorders in the setting of HIV infection. She is Director of Hematology/Oncology Research at St. Paul's Hospital, a reviewer of scientific papers for several medical journals, and an active member of the Canadian Consortium on MDS (CCMDS) and the UBC Department of Medicine Research Advisory Committee.

Affiliations: *St. Paul's Hospital and the University of British Columbia, Vancouver, British Columbia*

Brian Leber, MD

Dr. Brian Leber is a Professor of Medicine (Hematology) at McMaster University and an Attending Hematologist at the Juravinski Hosptial and Cancer Centre of Hamilton Health Sciences. He has a long-standing interest in myeloid malignancies.

Affiliations: *Juravinski Cancer Centre, Hamilton, Ontario*

Harold J. Olney, MD

Dr. Harold Olney is the Chief of the Department of Hematology-Transfusion Medicine and the Director of the malignant cytogenetics laboratory at Centre Hospitalier de l'Université de Montréal (CHUM). He is an Assistant Clinical Professor in the Department of Medicine at the University of Montreal. Dr. Olney's research Interests include myeloid diseases, lymphoproliferative syndrome, adrenal neoplasia, and Immune thrombocytopenia (ITP).

Affiliations: *Centre Hospitalier de l'Université de Montréal, Montréal, Quebec*

April Shamy, MDCM

Dr. April Shamy is an Associate Professor of Medicine at McGill University and a member of the Department of Medicine and Department of Oncology at the Jewish General Hospital. Dr. Shamy is a graduate of McGill University Medical School. She completed her Internal Medicine Residency and Hematology Fellowship at McGill University before training in Malignant Hematology at the University of Texas MD Anderson Cancer Centre. She manages a large clinical practice of patients with hematologic cancers and is actively involved in clinical research. She is an active member of the Canadian Consortium on Myelodysplastic Syndromes (CCMDS) and the Groupe des Maladies Plasmocytaires du Quebec (GMPQ). Dr. Shamy is the Medical Director of the Hematology-Oncology-Internal Medicine Ward at the JGH and is very involved in teaching within the McGill Medical School Curriculum and in the Internal Medicine and Hematology Residency Programs.

Affiliations: *Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montréal, Quebec*

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ABSTRACT

Background

Myelodysplastic Syndrome (MDS) treatments reduce transfusion dependence, delay progression to acute leukemia, and may improve survival. The Canadian Consortium on MDS (CCMDS) developed the MDS ClearPath, a comprehensive tool for the diagnosis, work-up and management of MDS of any risk category at any point during a patient's disease course.

Methods

The draft ClearPath algorithm was revised by 60 Canadian hematologists, finalized by consensus of the Steering Committee and went live in 2013. The update went online in January 2023.

Results

An approach to the diagnosis and management of MDS is provided. Appropriate investigations are detailed, current scoring systems are included as is a prognostic calculator, and an IPSS-M calculator link is included.

Treatments (erythropoiesis-stimulating agents; lenalidomide; hypomethylating agents; immunosuppressive therapy; supportive care [transfusions; antibiotics; bleeding prevention; iron chelation]; investigational agents; links to clinical trial websites) are detailed, including dosing/administration; monitoring; dose adjustments; expected response; side effect management; and provincial reimbursement.

Added were details on luspatercept, decitabine and decitabine/cedazuridine; recommendations for mutation analysis; WHO and ICC 2022 classifications; the IPSS-M and Clinical Frailty scores; familial predisposition testing; and response assessment criteria. Recommendations are made where data are lacking.

The Treatment Wizard, a series of questions specific to clinical status, leads to treatment recommendations; the self-directed mode is the overall algorithm. References with abstract links are included, and information panels included throughout.

The ClearPath in English or French is available at www.MDSClearPath.org; a (free) iPad app is being updated.

Discussion

The CCMDS presents an internet/app-based algorithm to support MDS management, with recommendations designed to assist in the standardization of MDS care.

Introduction

Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cells disorders characterized by ineffective hematopoiesis leading to peripheral blood cytopenias and an increased risk of progression to acute myeloid leukemia (AML). The International Prognostic Scoring System (IPSS) and newer scores predict survival and AML risk.[1-7] Predisposing factors are unknown in over 80% of patients; however, MDS is increased in older patients—the median age of onset is in the 70s[8]—and in males. Secondary causes include prior cytotoxic chemotherapy, radiation, exposure to chemicals, and immunosuppressive medications. Some patients may have a familial predisposition; however most MDS are primary and sporadic. In low-risk patients, over 80% die of MDS-related causes.[9] The age-related life expectancy in the Canadian population is: at 65 years of age, a Canadian can expect another 18.8 years of life and at 75 years, another 11.8 years.[10] In contrast, in low IPSS risk MDS, at age 60 years, a patient can expect only another 4.8 years of life, and at 70, only 3.9 years, with the life expectancy decreasing with increasing risk score. In high IPSS risk patients, the life expectancy at age 60 and 70 years is 0.5 and 0.4 years, respectively.[1] Similarly, the time to 25% evolution to AML for low and high IPSS risk MDS is 9.4, and only 0.2 years, respectively.[1] Red blood cell (RBC) transfusion-dependent MDS patients have inferior outcomes; this is recognized in the World Health Organization (WHO) based Prognostic Scoring system or WPSS. Nearly 40% of low and 80% of high IPSS risk MDS patients are RBC transfusion-dependent.[2,11,12]) Factors to take into account when making treatment decisions in MDS include predictive factors for outcome such as risk scores but also the degree of cytopenias; number of blasts and specific karyotype; pattern of somatic mutations; pace of progression; and patient-related factors such as age, comorbidities, and distance from the treatment centre.[13] MDS, then, is a serious condition with an increased risk of AML, transfusion dependence and shortened survival. The MDS ClearPath algorithm was developed to provide a comprehensive tool for the work-up, diagnosis and management of MDS for Canadian hematologists, to develop a unified and evidence-based approach to decision points, and to identify areas where data is lacking. The MDS ClearPath was initially activated online in 2013 and was most recently updated in 2016. Since then, newer information has become available to further refine diagnosis, prognosis, predictions for and assessment of clinical response, and a limited number of new treatments are available. With these advances in mind, we updated the MDS ClearPath algorithm in 2023 and herein discuss information currently available within the algorithm.

Methods

The MDS ClearPath was developed and approved by a Steering Committee of four, with input from 60 collaborating Canadian hematologists. The Steering Committee developed a draft version of the algorithm in August 2011, which was discussed at a national meeting in October 2011. Input was then obtained from 60 Canadian hematologists through a series of nine regional meetings. In March 2013, a review was conducted at a national meeting, and final points were incorporated by the Steering Committee through a series of conference calls which were completed in September 2013, at which point the website went live and the iPad app became available for download. The 2016 and 2023 updates were implemented by Steering Committee input and consensus.

Results

The algorithm provides a step-by-step approach to the work- up diagnosis, and management of all risk groups of MDS. Diagnostic investigations are detailed. Newly added in 2022-23 were information on predisposing conditions such as clonal hematopoiesis of indeterminate potential (CHIP), clonal cytopenia of undetermined significance (CCUS) and idiopathic cytopenia of undetermined significance (ICUS); recommendations for somatic mutation analysis; the WHO and International Consensus Criteria (ICC) 2022 classifications; and recommendations on testing for familial predisposition syndromes.[6, 14-16] A prognostic calculator for most scoring systems is included, and newly added is the Clinical Frailty Score (CFS) and the molecular IPSS (IPSS-M) scoring system with a link included to the specific IPSS-M calculator.[6,7] Data on therapies [growth factors including erythropoiesis stimulating agents (ESA)]; lenalidomide; azacitidine; immunosuppressive therapy (IST); investigational agents; and clinical trials with links to clinical trial websites, and supportive care: transfusions, antibiotics, bleeding prevention, iron chelation) is provided. Included is information on likelihood of achieving response; dosing/administration; monitoring; response assessment criteria; dose adjustments; side effect management, provincial reimbursement, and loss of response. Therapies added were details on luspatercept, decitabine and decitabine/cedazuridine (DEC/C). Where data are lacking, expert recommendations were incorporated. The MDS Clear Path can be navigated via two distinct routes. The Treatment Wizard guides the user through a series of questions specific to the patient's clinical status, resulting in a treatment recommendation. In the Self-Directed mode, the user can enter the algorithm at any point (**Figure 1**). References are provided with a link from the references to the PubMed abstract for the article. The algorithm is available in English or French at www.MDSClearPath.org and a free iPad app that can be downloaded from the website or the Apple app store is being updated and will be available in late 2023. Over 250 information panels are included in the MDS ClearPath. An example case demonstrating how to navigate the ClearPath follows.

Example Case

A 74-year-old woman is referred for anemia. She is otherwise well and has not required transfusions. However, she is fatigued and short of breath on exertion. Her hemoglobin is 95 G/L with a mean corpuscular volume MCV of 116 fL, neutrophils 1.7×10^9/L and platelets 84×10^9/L. The blood smear shows dysplastic changes. Serum B12, thyroid stimulating hormone (TSH), ferritin,

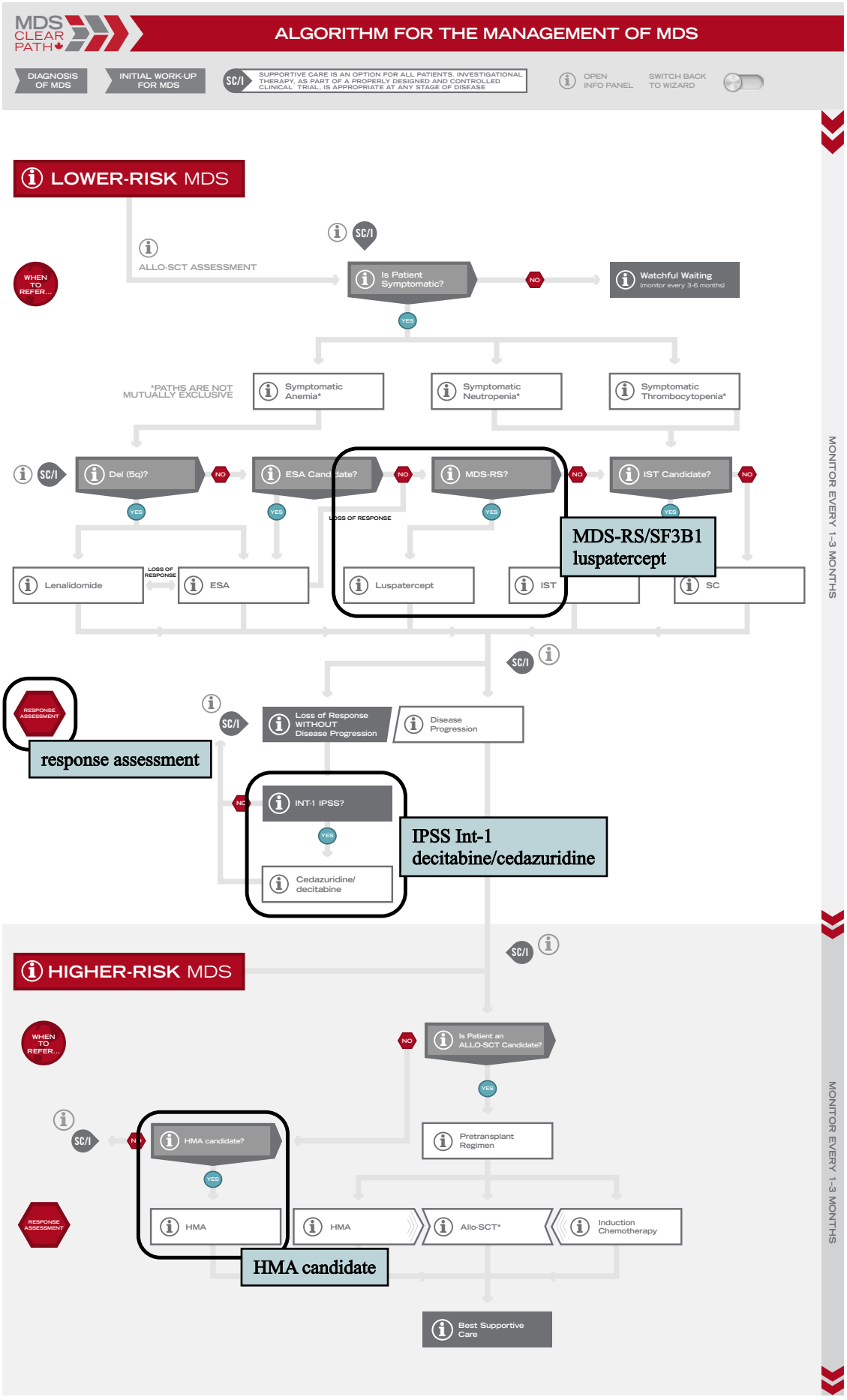

Figure 1. The MDS ClearPath Self-Directed Mode (overall algorithm). Modifications made for the 2023 update are indicated.

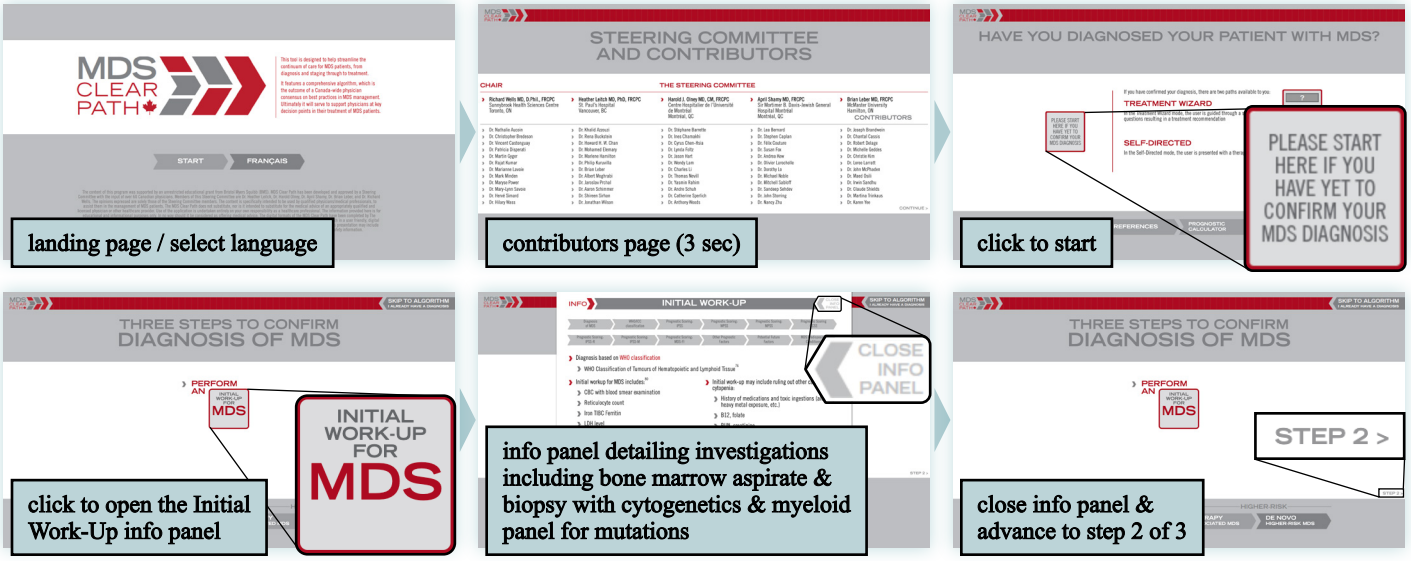

Figure 2. Navigation of the MDS ClearPath; a case-based approach. Shown are the website landing page, contributors page, and the initial work-up for MDS information panel (step 1 of "Three Steps to Confirm Diagnosis of MDS").

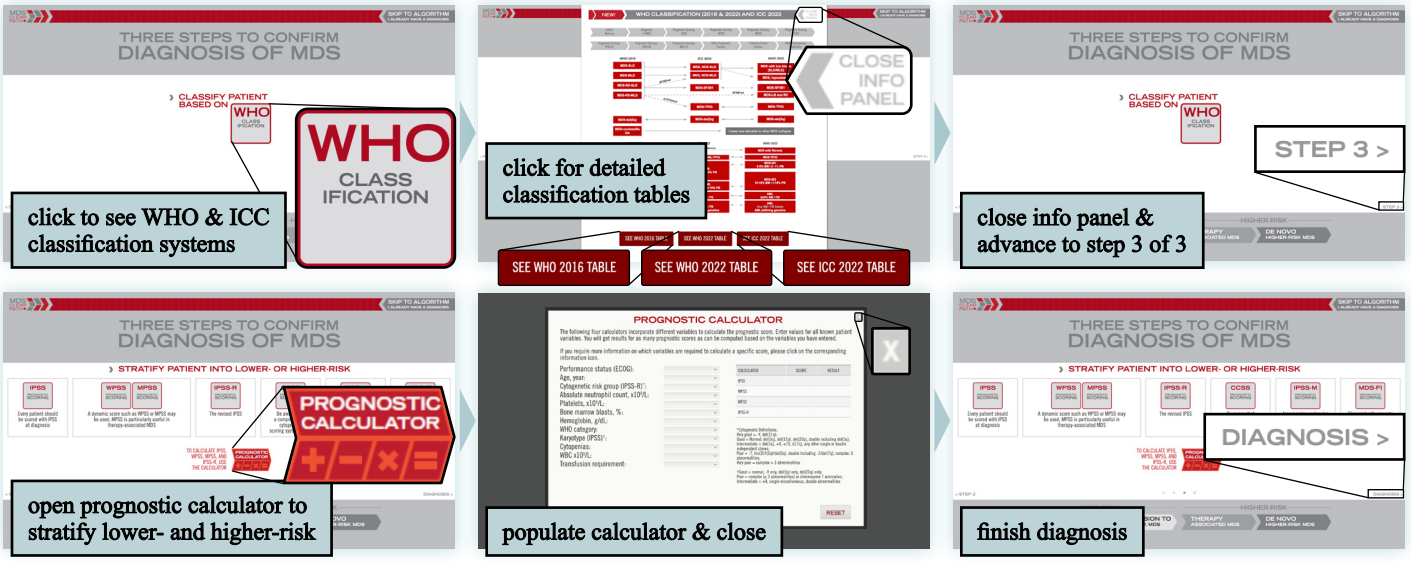

Figure 3. Navigation of the MDS ClearPath, a case-based approach. Shown are the World Health Organization (WHO) and International Consensus Criteria (ICC) classifications (the prognostic scores included) and the prognostic calculator.

renal profile, and serum protein electrophoresis are normal. At this point, for a summary of the additional investigations needed, the user can turn to the MDS ClearPath. Entering the algorithm takes the user to a panel entitled "Have you diagnosed your patient with MDS?" If the user then clicks on the button "Please start here if you have yet to confirm your MDS diagnosis," the next panel that appears is "Three steps to confirm diagnosis of MDS". Clicking on the button indicated by "Perform an initial work-up for MDS" directs the user to a list of investigations that should be conducted, including a bone marrow aspirate and biopsy with mandatory cytogenetic analysis, and a recommendation to send marrow for a myeloid panel for evaluation of somatic mutations, as well as additional blood work to rule out other conditions. Each chevron at the top of this (and each) panel, links to related topics with details on each. In this case the question is diagnosis of MDS; included are prognostic scoring system IPSS, WPSS, MPSS (MD Anderson prognostic scoring system); CCSS (comprehensive cytogenetic scoring system); and IPSS-R (IPSS-revised). Newly added are the CFS and IPSS-M.[1-7] Details on navigating these steps are shown in **Figure 2**. Step 2 of "Three Steps to Confirm Diagnosis" is "Classify patient based on the WHO classification," with a link to information on the WHO 2016 classification of MDS. Newly added are the WHO and ICC 2022 classification systems, with comparisons between classification systems.[14,15,17]

The patient's bone marrow aspirate and biopsy show trilineage dysplasia, 2% blasts, 15% ring sideroblasts, and an SF3B1 mutation; the WHO 2022 classification is MDS with low blasts and SF3B1 mutation, whereas the WHO 2016 classification is MDS with multilineage dysplasia and ring sideroblasts (MDS-MLD-RS). Cytogenetic analysis reveals a del(20q). Her erythropoietin level is 174 mIU/mL.

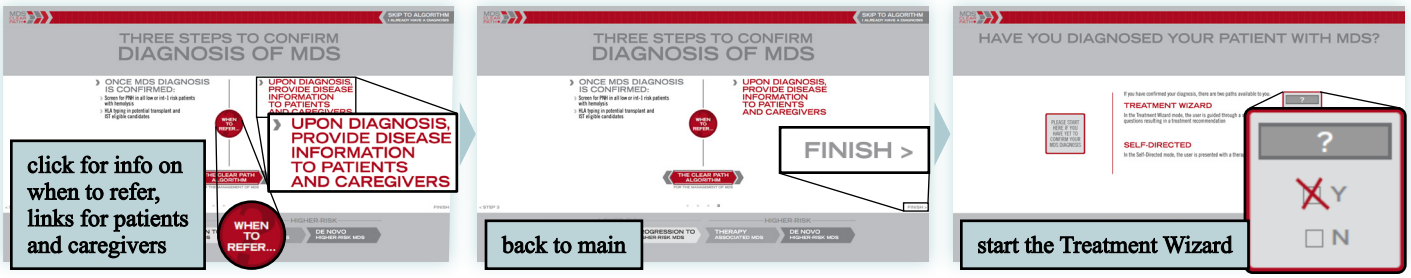

Figure 4. Navigation of the MDS ClearPath, a case-based approach. Shown are information on when to refer to a centre with expertise and ancillary tests on MDS diagnosis, information to give to patients and caregivers, and entry into the Treatment Wizard.

The next question is: What is her risk category? Proceeding to Step 3 in "Confirm diagnosis" directs the user to links to the prognostic scoring systems and a direct link to the calculator for several prognostic scoring systems; including the link to the IPSS-M web calculator. Clicking on "IPSS Prognostic Scoring" directs the user to details of this score, with links to survival curves and AML evolution. Clicking on "IPSS calculator" directs the user to the list of factors required to determine risk scores. Entering her Eastern Cooperative Oncology Group (ECOG) performance status;[18] age; cytogenetic risk; neutrophils; platelets; bone marrow blasts; hemoglobin; and WHO category, the IPSS-R appears as very low risk. If the user proceeds to enter the IPSS karyotype and number of cytopenias, the IPSS appears as intermediate-1. Entering the white blood cell count and red blood cell (RBC) transfusion requirement, the WPSS and MPSS appear as low and intermediate-1, respectively **(Figure 3)**. Moving on to the IPSS-M web calculator and inputting her data, the IPSS-M score is -0.86 or low risk. Clicking on "Diagnosis" directs the user to a panel with a reminder that once the MDS diagnosis is confirmed, all lower risk patients with hemolysis should be screened for paroxysmal nocturnal hemoglobinuria (PNH),[19] and human leucocyte antigen (HLA) typing should be done in potential candidates for hematopoietic stem cell transplantation (SCT) and IST.[20]

Information on MDS should be given to all patients and caregivers, with links to MDS patient groups and foundations; information is provided on when to refer to an MDS specialist (**Figure 4**). Clicking on "Finish" directs the user back to the initial panel, with links to either the overall algorithm or the Treatment Wizard. Clicking on the Treatment Wizard directs the user to the question: Does your patient have lower- or higher-risk MDS? This panel contains information on what constitutes lower- or higher-risk. Clicking on "Lower-risk" directs the user to a reminder to assess for allogeneic SCT in all lower-risk patients, with a link to a list of SCT eligibility criteria. This in turn links to information on pre-SCT regimens; SCT efficacy; safety; donor availability; and SCT eligibility in higher-risk patients.[21,22] Selecting "Assessment complete" directs the user to a panel entitled "Is your patient symptomatic?" **(Figure 5)**. Clicking on "Yes," the user arrives at a panel asking whether or not the patient has symptomatic anemia, neutropenia, or thrombocytopenia, with information panels on each. The information panel on symptomatic anemia discusses that hemoglobin thresholds for symptoms may vary from patient to patient, with links to RBC transfusion thresholds, which in turn links to RBC transfusion complications; iron chelation therapy (ICT), ICT safety, efficacy, adverse event management, and provincial reimbursement.[23-27] For more information on iron overload diagnosis, work-up and management, and discussion of mechanisms of iron toxicity and clinical endpoints impacted, the algorithm has a link to a separate web-based algorithm, the MDS Iron Road.[28] This website discusses in detail pre-clinical and clinical evidence regarding the effects of iron overload in MDS, and similarly makes treatment recommendations. In the ClearPath, clicking on reimbursement directs the user to a map of Canada and, if connected to the internet, clicking on the province of interest takes the user to the website detailing reimbursement in that province. Similarly, the information panels on neutropenia and thrombocytopenia discuss means to decrease the risk of infection and bleeding, respectively. If the patient is not symptomatic, the Treatment Wizard recommends a watch-and-wait approach, with information on frequency and details of monitoring. Going back to symptomatic anemia, the next question is whether or not the patient has deletion of chromosome 5q [del(5q)] (with "Yes" linking to detailed information on treatment with lenalidomide).[29-32] The current patient does not; therefore, the next question is whether or not she is a candidate for IST (with "Yes" linking to detailed information on this therapy).[20,33-37] Choosing "No" directs the user to the question of whether or not she is a candidate for an ESA with an information panel on what the criteria are for predicting response to ESA.[38-40] If "Yes" is chosen, she is an ESA candidate and the treatment recommendation is ESA. This panel includes detailed information on this subject including dosing and monitoring; safety; efficacy; reimbursement; the addition of granulocyte colony-stimulating factor (G-CSF), and G-CSF dosing in combination with ESA[41-47] (**Figure 6**). If the user returns to the self-directed mode at this point, the program will highlight the path taken through the algorithm, which can then be reset for the next clinical situation.

The patient wishes to avoid transfusion and is given a trial of erythropoietin (EPO) at 40,000 units per week for 6 weeks. Her hemoglobin remains suboptimal at 88 g/L. She is dose-escalated to EPO 60,000 units weekly, and her hemoglobin improves to 109 g/L, with resolution of symptoms. She maintains stable counts on EPO for 12 months, then she loses her response. A repeat bone marrow aspirate and biopsy is unchanged. She requires

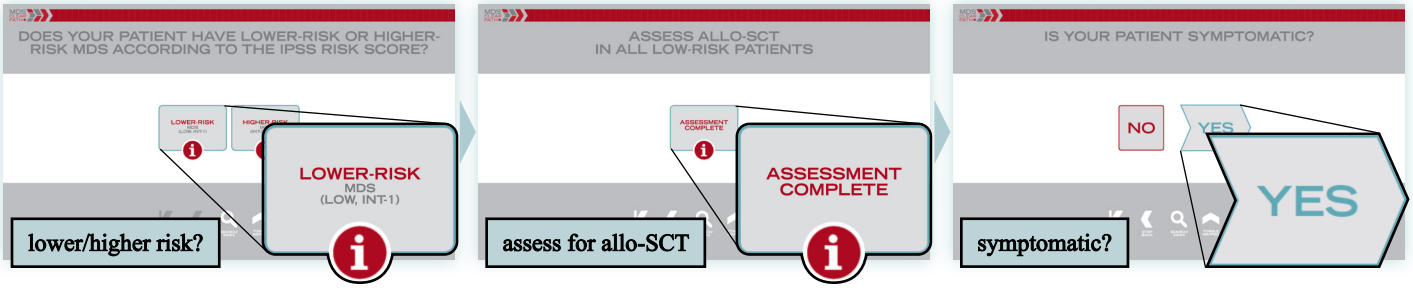

Figure 5. Navigation of the MDS ClearPath, a case-based approach (Treatment Wizard). Shown are selection of risk group, assessment for allogeneic stem cell transplantation where appropriate, and determination of whether the patient is symptomatic.

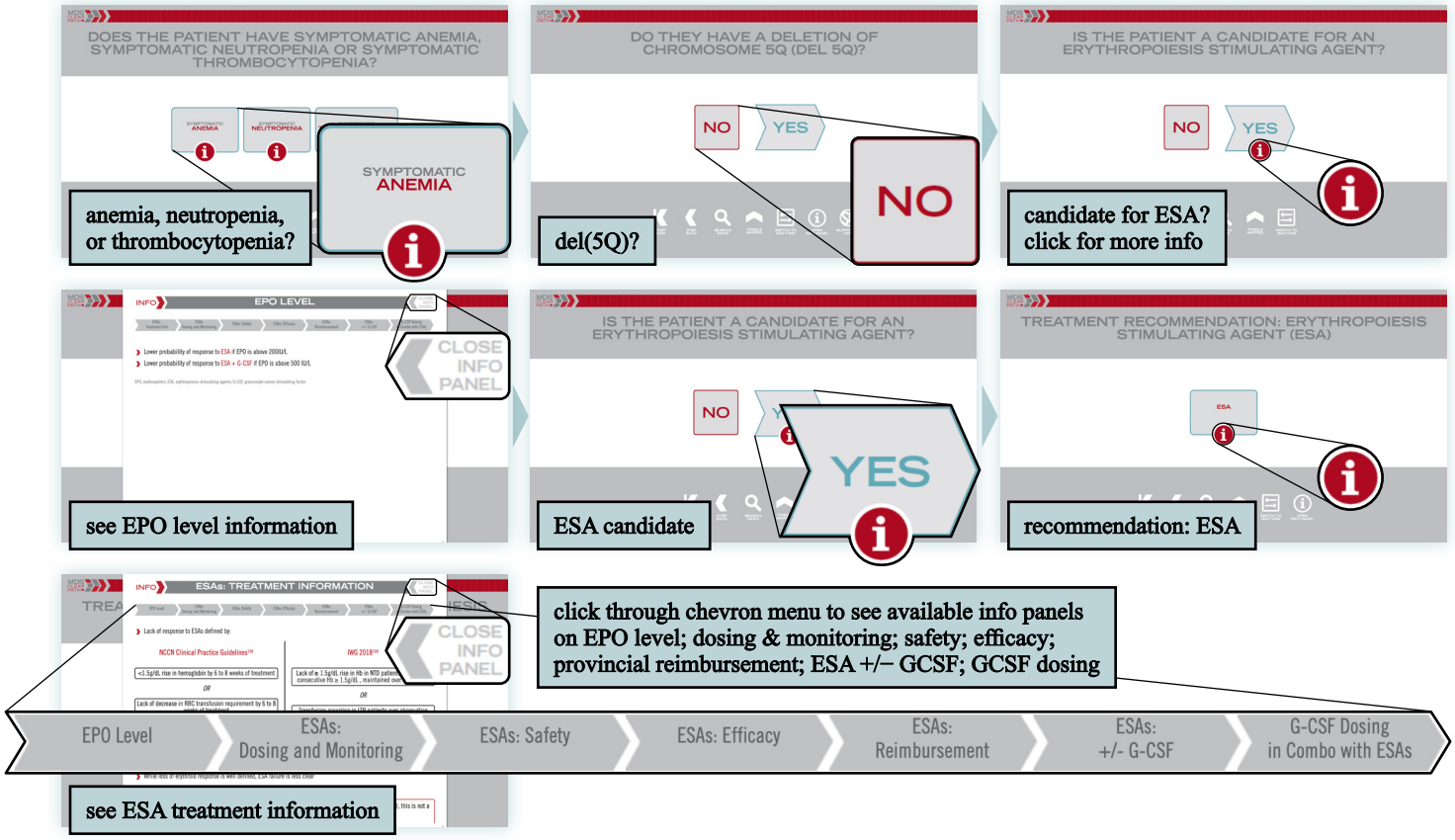

Figure 6. Navigation of the MDS ClearPath, a case-based approach. Shown are determination of cytopenias causing symptoms, ruling in or out whether the MDS is del(5q), determination whether the patient is a candidate for ESA, information on predicted response by erythropoietin (EPO) level, treatment recommendation for ESA, and ESA treatment information details.

RBC transfusions. The next panel of the Treatment Wizard discusses loss of response without or with disease progression, with a link to the International Working Group (IWG) criteria for response and loss of response, and a list of clinical and laboratory criteria that could indicate MDS progression.[48-49] The next recommendation is to assess RS/SF3B1 status, which she has; therefore, the treatment recommendation is luspatercept, with detailed information on all aspects of treatment with this agent included as discussed for ESA **(Figure 7)**.

After another 12 months, the patient is now 76 years old. A routine CBC shows a hemoglobin of 70 G/L, absolute neutrophil count of 0.5×10^9/L and platelet count of 21×10^9/L. A repeat bone marrow aspirate and biopsy shows 14% blasts with poor risk cytogenetics. The ECOG performance status is 2. Proceeding to "Progression to higher-risk MDS," the Treatment Wizard asks the user "Is the patient a candidate for SCT (for higher-risk MDS patients)?" The answer for this patient is "No". The next question is "Is the patient an HMA (hypomethylating agent) candidate?" Clicking on "Yes" directs the user to information on azacitidine, decitabine, and DEC/C including treatment information; the azacitidine prognostic scoring system; safety; efficacy; provincial reimbursement; adverse event management; duration of treatment; and loss of response.[50-58] Proceeding to treatment information directs the user to dosing and monitoring with links to the other topics.

The patient receives two cycles of an HMA and her hemoglobin is 64 G/L with white blood cells of 1.1×10^9/L and platelets of 9×10^9/L. Should the HMA be continued? Consulting the panel on duration of therapy, 91% of initial

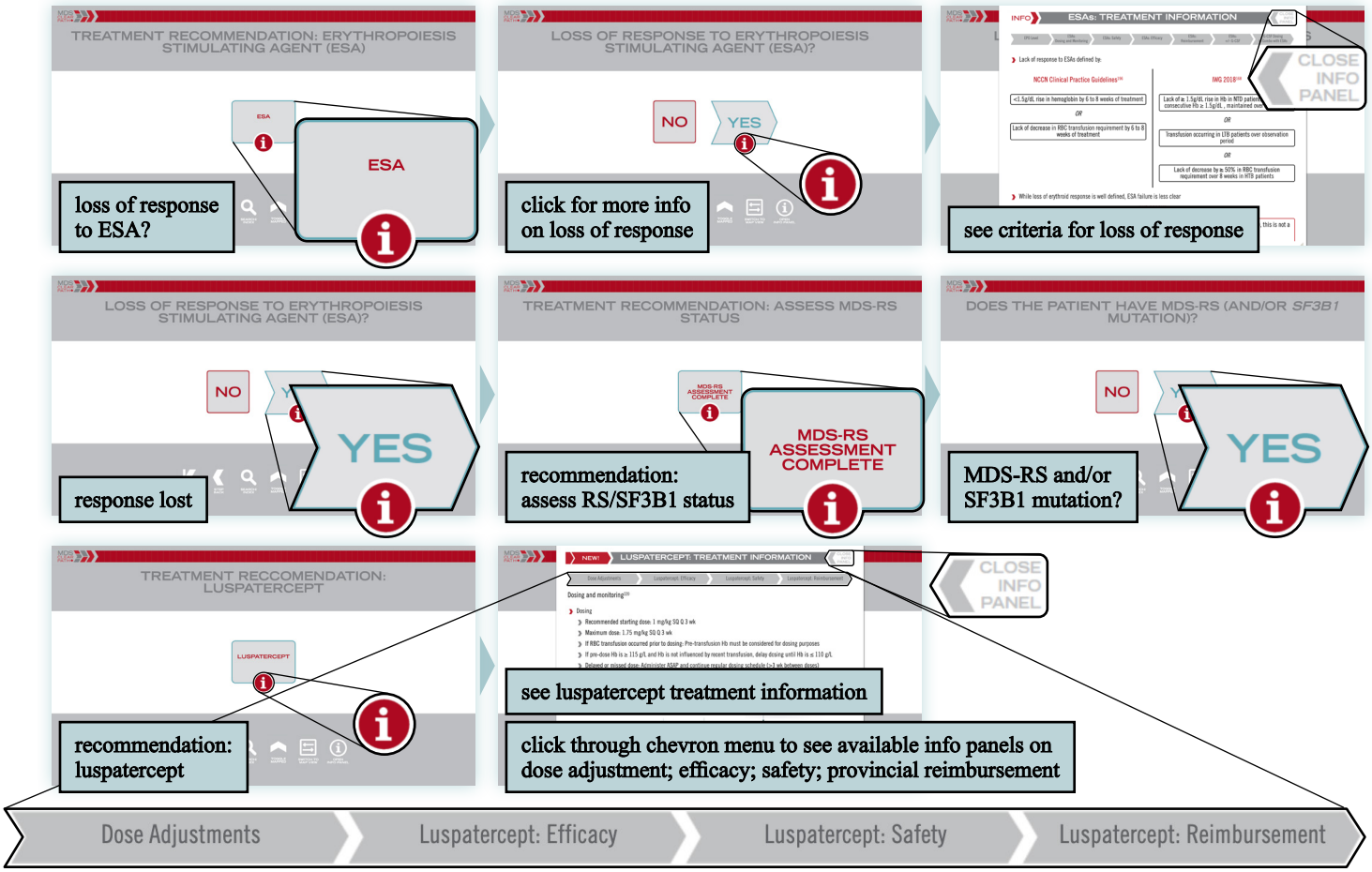

Figure 7. Navigation of the MDS ClearPath, a case-based approach. Shown are criteria for loss of response, recommendation to assess for ring sideroblast (RS)/SF3B1 mutation status, treatment recommendation for luspatercept, and luspatercept treatment information details.

responses (to azacitidine) occurred by cycle 6, with 100% occurring by cycle 12. Following the initial response, 48% of responders had further improvement. Therefore, a minimum of six months of treatment is recommended unless there is clear disease progression or unacceptable toxicity. Response should be assessed following six cycles and in patients with stable disease or greater, treatment should be continued until progression or intolerance.[59] Following six cycles of HMA, the patient is transfusion-independent with a hemoglobin of 110 G/L, neutrophils of 0.9×10^9/L and a normal platelet count. Her bone marrow assessment of response shows 4% blasts. How long should HMA be continued? Per the previous panel: for patients with stable disease or greater, treatment is continued until progression or intolerance.

Following 13 cycles of HMA, the patient continues to manage well. A repeat bone marrow biopsy shows 4% blasts. The question here is, how often should this patient be monitored? In the treatment information the following recommendation is made: "Day 1 of each cycle: CBC and differential; serum creatinine; electrolytes; GGT; alkaline phosphatase; AST; ALT; LDH; and bilirubin (total and direct). Bone marrow assessment should be performed at six and 12 months, and again when progression or toxicity is suspected. The treatment information suggests dose adjustments of HMA for hematological toxicity.

It is suggested that the first six months of HMA be viewed as similar to induction chemotherapy, and that initially, worsened cytopenias should be expected. Links to guidelines for the management of non-hematological adverse events of injectional azacitidine are provided. Once the patient loses response, the Treatment Wizard directs the user to a choice between investigational therapy, with a link to clinical trials sites such as clinicaltrials.gov,[60] the National Cancer Institute of Canada, The Leukemia and Lymphoma Society, the United States National Institute of Health clinical trials site and others, and supportive/palliative care, with detailed information on this type of management provided.[61,62]

In the Treatment Wizard mode, the buttons at the bottom of the screen allow the user to start over, step back to the previous screen, search the algorithm by term of interest, switch to the Self-Directed mode, toggle the map to view both the algorithm and Wizard in the same screen; open an information panel, and obtain information on supportive care. In the overall algorithm Self-Directed mode, the MDS ClearPath icon returns to the home screen, the references are linked to the PubMed abstracts and, if supported by the user's software, to the entire article online, information panels are provided throughout, and there is a button for switching back to the Wizard.

Figure 8. MDS ClearPath metrics as of April 14, 2023.

Figure 8 illustrates metrics on use of the MDS ClearPath to April 2023; the website has been accessed in 120 countries with 16,101 sessions, 289,621 page views and 10,476 users, and the app has been downloaded in 34 countries.

Discussion

The MDS ClearPath was developed through a collaboration of Canadian hematologists. It is a user-friendly internet/app-based algorithm to support healthcare providers in the work-up, diagnosis and management of MDS. Recommendations from the algorithm should help to standardize an approach to the diagnosis, work-up and management of MDS, and to provide evidence-based care for MDS patients.

Content of the ClearPath will be updated as advances are made in MDS. A 2016 update added information on MDS/myeloproliferative neoplasm overlap syndromes and their management; work-up and management of autoimmune phenomena in MDS; incorporation of molecular information into MDS care; and an ability to access the reference of interest from the panel of interest rather than having to consult the complete reference list. The 2023 update added updated classification systems including the WHO and ICC 2022 classification systems, with comparisons between these and the WHO 2016 classifications. Also added were new prognostic scores, the Clinical Frailty Score and the IPSS-M. Refined prognostic scores for predicting response to ESA were added, along with updated definitions of response criteria and loss of response. Full information was added on luspatercept for MDS-RS/SF3B1 including mechanism of action; results of clinical trials; dosing; dose adjustments; side effect management; and provincial reimbursement criteria. Information was added on decitabine and DEC/C as above for higher risk MDS, and IPSS intermediate-1 risk and higher, respectively. Now that DEC/C is available in Canada, the algorithm and Treatment Wizard refer to HMA (if the patient is a candidate for HMA) rather than azacitidine, and then links to the specific HMA's. Updated information on promising newer therapies that are not yet approved or funded, for lower and higher risk MDS has been added. A link outside the algorithm to a separate algorithm for the work-up diagnosis and management of tranfusional iron overload in MDS is provided, termed the MDS Iron Road. The Iron Road algorithm discusses preclinical and clinical evidence for mechanisms of iron toxicity and strategies to mitigate this toxicity, given that options for reducing transfusion requirement in MDS, while improved from the time of the original MDS ClearPath in 2013, remain somewhat limited.[28]

The MDS ClearPath provides a mechanism by which to obtain important information informing management recommendations available in a single location, in a user-friendly manner. Statistics on access to the ClearPath via website logins and app downloads speak to the convenience and practicality of this information format, which is likely to remain popular through the current iteration and future updates.

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Correspondence

Dr. Heather A. Leitch
Email: hleitch@pacifichematology.ca

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MDS CLEARPATH: AN INTERNET-BASED EDUCATIONAL ALGORITHM FOR THE WORK-UP, DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH MYELODYSPLASTIC SYNDROMES FROM THE CANADIAN CONSORTIUM ON MDS: 2023 UPDATE

Heather A. Leitch, MD, PhD
Brian Leber, MD
Harold J. Olney, MD
April Shamy, MD