Utilization Analysis in Hematopathology

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Unique Challenges in Hematopathology

Utilization management in pathology requires the physician to consider whether a test is necessary and appropriate for the current condition of the patient. This has both medical care implications—how best to detect disease with the highest sensitivity and specificity—and fiscal implications. In an era where reimbursement is tied increasingly to bundled incidents of care or to particular quality measures, unnecessary lab costs must be avoided while adhering to the physician imperative to do no harm.

The field of neoplastic hematopathology has unique characteristics that provide fertile ground for utilization management. This field was one of the earliest to practice precision medicine, with landmark discoveries such as the BCR-ABL1 rearrangements in chronic myelogenous leukemia in 1960 by Nowell [1] and the FDA approval of imatinib in 2001 [2]. The field has remained at the forefront of precision medicine, and currently many classification categories and treatments are determined either entirely or in part by their underlying genetic lesions [3]. However, with advances in molecular techniques, the number of molecular lesions in all fields of pathology has been burgeoning, and neoplastic hematopathology has remained one of the most highly examined. As the number of molecular aberrations in hematopathology has increased, so too has the number of available tests, including now highly multiplexed assays such as next-generation sequencing panels for somatic mutations in myeloid and lymphoid neoplasms. Moreover, older tests and methodologies remain an ordering option, further complicating test selection. Therefore, testing menus have evolved over time to become increasingly diverse, using ever-more sophisticated technologies whose results require specialized training to interpret.

The wealth of testing options magnifies the risk of ordering inappropriate tests, a type of pre-analytic error, for all possible diagnoses that a clinician may be considering for a given clinical presentation. Since most testing is traditionally ordered by the direct care providers (DCPs, such as clinical hematologists or nurse practitioners), the breadth of the differential based entirely upon clinical factors at the time of ordering may be quite broad, with a correspondingly broad set of potential tests to interrogate each entity.

Hematopathology has always spanned multiple traditional specialties. This is exemplified by the historical and practical complexities of the workflow surrounding the evaluation of bone marrow specimens, which this chapter will use as a case study for utilization management. Historically in some centers, hematologists have assessed peripheral smears and aspirates (fresh cytology fluids), while pathologists reviewed bone marrow biopsies (paraffin-embedded tissues). Over time additional modalities were incorporated into the diagnosis, such as immunohistochemistry and flow cytometry. Today, cytogenetic, molecular, and genomic pathology are also utilized in diagnosis and monitoring of hematolymphoid malignancies. Since these results are produced from various laboratories within a single institution or even from several different institutions (e.g., send-out testing), multiple separate reports are generated and may be found in multiple different locations in the medical record. The turnaround times for these assays are also quite variable, ranging from hours to days or even weeks. Given this disjointed reporting, clinicians may misinterpret results or the reports may provide conflicting results on the same specimen, both examples of post-analytic errors.

The explosion of test options available to the clinician and the technical intricacies of differing testing methodologies

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K. Lewandrowski (ed.), *Utilization Management in the Clinical Laboratory and Other Ancillary Services*,
DOI 10.1007/978-3-319-34199-6_17

for the same analyte have increased the challenge in selecting and interpreting the proper test for each clinical scenario. To address these pre-analytic and post-analytic testing errors, pathologists have become increasingly integral to test selection and interpretation [4]. However, while pathologists may be the natural advocates of laboratory utilization management, they cannot succeed without strong support and collaboration from clinicians. This chapter will demonstrate one method to implement a hematopathology utilization management system for the evaluation of bone marrow biopsies.

Rules to Redesign Health Care

The fields of medicine and health care delivery have increasingly focused on systems thinking to address the issues of rising health-care costs. In 2001, the Institute of Medicine (IOM) convened a multidisciplinary group, drawing upon expertise in health care and engineering, to optimize the delivery of quality health care [5]. These quality issues focused on the misuse, overuse, and underuse of health-care resources. The goals of applied systems thinking were to improve the safety, effectiveness, efficiency, timeliness, patient-centeredness, and equity of health-care delivery.

Ten rules for the redesign of the health-care system were outlined (Table 17.1) [5]. The rules were based on some common principles, including the appropriate utilization of information technology and the optimization of human-instrument interactions, the use of standardized procedures to minimize the human factors, and the improved communications between health-care teams. This model for the reexamination of health-care processes can be applied specifically to the workflow in hematopathology. Hematopathology presents unique challenges to the ten rules of redesign.

1. *Care is based on continuous healing relationships*. In practice, there is discontinuity of patient care for patients with hematologic malignancies. Patients are often seen by a series of DCPs as they cycle between inpatient and outpatient services as per the requirements of their disease care. The pathologists that evaluate the patient specimens, particularly in larger centers, cycle between different services as well, and a single individual may not see the same patient's material over time. In addition, due to the complex physical and logistical organization of the many individuals and laboratories involved in evaluating a bone marrow, a number of different physicians may see one bone marrow specimen for separate aspirate cytology, biopsy histology, flow cytometry, karyotype, fluorescence in situ hybridization (FISH), and various molecular pathology testing platforms ranging from single target allele-specific assays to broad next-generation sequencing panels. Thus, in both direct patient care and in the laboratory, the number of individuals responsible for the care of the patient varies over time and health-care function.
2. *Care is customized according to patient needs and values*. At many institutions, a set panel of tests are ordered for a given disease type. This ignores the unique characteristics of the patient's neoplasm and disease course. For instance, certain molecular markers may be seen in a given disease, but an individual patient's neoplasm may only demonstrate a few of those variants. This is further complicated by the fact that some of these variants may be seen in only a subset of the neoplastic cells and that the techniques for following these markers to monitor residual disease may be quite varied in their analytical sensitivities. In addition, different stages of a patient's disease course may require different types of testing, such as differences in testing at diagnosis versus follow-up or pre- versus post-stem cell transplantation (SCT).
3. *The patient is the source of control*. Ideally, this is a tenet followed throughout medicine. However, when it comes to the determination of which laboratory tests are most appropriate for the patient, typically the ordering clinician acts as the patient's proxy. Therefore all testing decisions, especially if determined after the sample reaches the laboratory for reflex testing, must be with full endorsement and confidence by the patient's primary health-care provider.
4. *Knowledge is shared and information flows freely*. Since the diagnosis of numerous hematolymphoid neoplasms requires the incorporation of not only histologic findings but also clinical, molecular, genetic, and immunophenotypic data, a complete diagnosis cannot be rendered until all the data is aggregated and interpreted as a group. Data from the clinic as well as numerous laboratories within the pathology must be collectively interpreted. Making sure all the data is available for integration is paramount in hematopathology. Moreover, sharing knowledge requires assuring that the results from various tests are easily and quickly available for review by anyone on the health-care team. Collating that data in one site that is easily found and reviewed meets that expectation.
5. *Decision-making is evidence based*. If certain tests are appropriate for only a particular disease and disease state, the pathologist must ascertain the disease state with the most pretesting information possible. In addition, the clinical utility of each test for its stated purpose should also be considered. The pathologist should use published evidence where it is available. However, in many facets of hematopathology, evidence-based testing recommendations are lacking. The vast majority of the hematopathology literature is focused on diagnostic

Table 17.1 The ten rules of redesign of health-care systems [5] and the unique challenges presented in hematopathology

Ten rules for redesign	Hematopathology-specific issues
1. Care is based on continuous healing relationships	• Patients cycle between inpatient and outpatient encounters • Patients cycle between multiple direct care providers • Patients specimens are handled by multiple different laboratories within pathology
2. Care is customized according to patient needs and values	• Typical testing panels do not take into account the unique molecular features of the patient's disease • Typical testing panels do not take into account the stage of the disease course
3. The patient is the source of control	• Testing decisions should be with full endorsement and confidence of the patient and the patient's proxy (typically the direct care provider)
4. Knowledge is shared and information flows freely	• Communication is required between the laboratory and the direct care providers • Communication is also required between the different laboratories within pathology, since diagnostic criteria in hematopathology include integration of multiple testing modalities
5. Decision-making is evidence based	• Evidence-based data is lacking for many stages if disease (particularly at times of routine follow-up), relying upon expert opinion in many cases
6. Safety is a system property	• Without uniform testing practices, tests may be overutilized or underutilized • Without uniform reporting, incomplete reports may jeopardize care
7. Transparency is necessary	• It is difficult to track what testing has been performed, especially when the list of tests ordered may vary from care provider to care provider and from patient encounter to encounter • Results of testing may appear in a multitude of different reports which may be found in various locations in the medical record
8. Needs are anticipated	• Unexpected findings in the marrow study that the direct care provider could not have anticipated may be identified that could affect testing decisions
9. Waste is continuously decreased	• Without tracking testing practices, there is no way to continuously improve the quality of care
10. Cooperation among clinicians is a priority	• In order for consensus practice decisions to be made, the direct care providers and all laboratorians/pathologists need to be working with a common harmonious goal of patient care, with complete understanding of what tests need to be performed and which portions of the decision-making process lie with which parties

recommendations, rather than disease monitoring, limiting the base of evidence for many testing practices to "best practices."

6. *Safety is a system property*. Safety concerns that may arise even with quality pathology review lie in the "human factor." These include both the underutilization of necessary testing and the overutilization of unnecessary testing. In addition, pathology reports may provide an avenue for omitted or misrepresented data. These latter issues may be especially true with pathologists who do not routinely see hematopathology cases.
7. *Transparency is necessary*. In practice, it is often a challenge both for pathologists and DCPs to know what tests have been ordered and what the status of those tests may be. Further complicating this issue, testing that impacts hematopathology may be the product of multiple different laboratories with different turnaround times and different reporting locations within the medical record.
8. *Needs are anticipated*. Although DCPs know in detail the clinical status of their patients, it is impossible for them to know the cellular content of their patients' bone marrows, necessitating a microscopic analysis of the tissue. Therefore, it is correspondingly difficult for a DCP to anticipate the appropriate testing prior to the morphologic review of the marrow. DCPs therefore either cast a broad net through testing, some of which may not be relevant to the patient's disease state, or run the risk of omitting the critical test appropriate for the marrow findings. Both impact the quality of cost-effective medicine.
9. *Waste is continuously decreased*. Without tracking testing practice, there is no way to identify potential areas for waste elimination. In most hematopathology practices, there is no ongoing record of testing activities, precluding iterative quality improvement. In addition, hematopathology is a rapidly evolving field, with increasing emphasis upon new molecular markers of disease and a concomitant rapid evolution of testing practices. This scenario is ripe for potentially wasteful testing if too much flexibility is allowed in ordering practices and for the omission of new clinically validated markers if ordering restrictions are too strict.
10. *Cooperation among clinicians is a priority*. The clinicians on the front line of direct patient care as well as the clinicians in the laboratories must make a cohesive team for optimal patient care. There must be a harmonious understanding of the clinical value of each test. In addition, there must be agreement on which practitioner is best positioned to provide the various facets of patient information required to make educated testing decisions. In addition, informaticians need to work closely with both groups to ensure that the information technologies meet the needs of each individual group and provide the communication tools required for the groups to work together.

Diagnostic Management Team Approach to Hematopathology

At Vanderbilt University Medical Center (VUMC), three groups—pathologists/laboratorians (including those involved in hematopathology, immunopathology, cytogenetics, and molecular diagnostics), DCPs (hematologists and hematology nurse practitioners), and biomedical informaticians—comprise the core of the diagnostic management team (DMT) in hematopathology. The DMT was developed as a way to incorporate all ten of the IOM rules of health-care system redesign to create a cohesive and transparent team approach to patient care.

A key mission of the DMT is to maximize the pretesting information available to guide appropriate testing practices. In conventional practice, the primary patient care team (hematologists and hematology nurse practitioners) typically orders tests prior to morphologic review of the specimen. However, since morphologic data can markedly modify the differential diagnosis and thereby significantly influence test selection, a pathologist-driven testing model may refine the selection of tests in many cases. The DMT combines information about the clinical scenario with the morphologic and immunophenotypic findings of the marrow study prior to making testing decisions. The combination of all this information determines the assignment of a clinicomorphologic decision point (CMDP) for testing. A CMDP is essentially the patient's disease, and the point in therapy (new diagnosis, relapse, remission, etc.) at which the current patient encounters occurs. In all clinical testing, the positive predictive value of a test is maximized by increasing the prevalence of disease. In the case of bone marrow-associated testing, knowing the true clinical and morphologic disease status prior to testing increases the value of any appropriate testing.

This DMT approach involved creating teams of DCPs and laboratorians that together decided upon the appropriate testing practices surrounding each disease category at each CMDP within the neoplastic hematopathology. The development and maintenance of these mutually agreed-upon standard ordering protocols (SOPs) represent one of the main activities of the DMT (Fig. 17.1). This allows the pathologist to order agreed-upon sets of tests after integrating both the clinical information provided by the electronic medical record and the DCP with the actual marrow findings, whether those findings be diagnostic/overt or for residual disease testing.

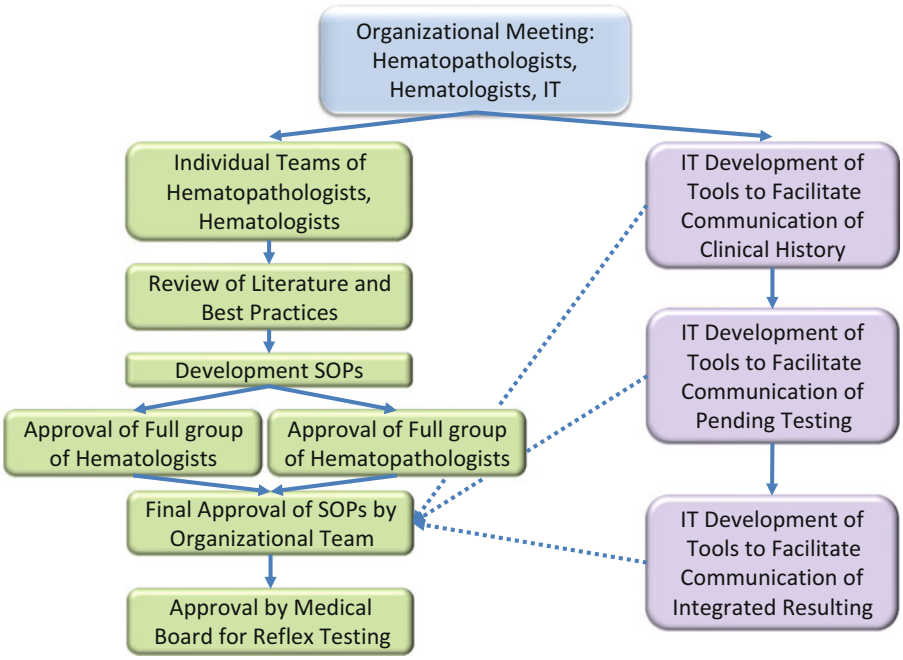

Fig. 17.1 Schematic of the parallel development of the standard ordering protocols (SOPs) and information technology (IT) tools for the DMT

In order to enhance the communication between the patients, the DCPs, and the pathologists and pathology laboratories, the DMT developed a number of informatics tools (see Sect. 3.2 below). These included online ordering forms and clinical history flow sheets to facilitate communication of the clinical history to the laboratories. To enable communication on which tests were ordered on a given bone marrow specimen as well as the status of those tests, dashboards displaying testing status were created in the electronic medical record (EMR) rather than the laboratory information system (LIS) so that it would be accessible to all parties. Finally, the DMT group designed new synoptic or structured morphologic reports, as well as comprehensive reports. The latter compile in a single place all the results associated with a single bone marrow specimen and synthesize an overarching interpretation. These informatics tools represent the second activity of the DMT (Fig. 17.1). Through these means, all members of the clinical care teams can be reassured that the testing appropriate for the patient is being performed while minimizing unnecessary testing.

Development of the SOPs

The development of disease-specific SOPs is a fundamental building block for the DMT. These SOPs are applied to each disease, taking into account both the stage of therapy and the pathologist's initial morphologic review of the bone marrow specimens. The implementation of the SOPs allows for an agreed-upon set of tests to be ordered by the pathologist rather than the DCP using the shared knowledge of the patient's disease, the patient's stage of therapy, and the pathologist's initial review of morphology (CMDPs). Ancillary testing practices for each disease category must be extensively researched by teams of collaborating hematologists and pathologists.

At VUMC, the DMT focused initially on optimizing the testing for bone marrow biopsies, since the operational workflow for these specimens was the most uniform. In the first iteration, seven teams were formed, each dedicated to one of seven most common disease categories for which bone marrow biopsies are ordered. SOPs were generated for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) together, bone marrow failure syndromes, myeloproliferative neoplasms, lymphoma, plasma cell neoplasms, and acute lymphoblastic leukemia/lymphoma (B and T, considered separately). These disease entities represent approximately 95 % of all adult bone marrow cases at VUMC. Subsequent iterations of this process have redefined these categories, as some disease entities proved to be best handled by the SOPs in their own specialized categories. However, it should be noted that each institution should examine its own case distribution and testing practices to form these teams in an institution-appropriate manner.

The teams identified all relevant evidence-based recommendations for the utilization of any given test at given stages of a disease course. Published literature and guidelines for testing in certain disease categories formed the basis of these SOPs. Recommendations are available through the National Comprehensive Cancer Network (NCCN), bone marrow transplantation or clinical trial requirements, and various professional societies with dedicated educational

Fig. 17.2 Levels of evidence. Levels 1–3 contain compiled data, while levels 4–6 represent primary data. Level 7 represents expert opinion that may be based on best clinical practice and experience, but does not rely upon validated data (adapted from the EBM Pyramid and EBM page Generator, © 2006 Trustees of Dartmouth College and Yale University)

missions such as the College of American Pathologists (CAP), the Association for Molecular Pathology (AMP), and the American Society for Clinical Pathology (ASCP). In addition, validation documentation on the clinical utility of tests is required for accreditation agencies such as the College of American Pathologists (CAP), Clinical Laboratory Improvement Amendments (CLIA), Joint Commission in Accreditation of Healthcare Organizations (JCAHO), individual state accreditation programs, and potentially the US Food and Drug Administration (FDA). These recommendations are considered level 1 and level 2 evidence, considered the best forms of evidence in the hierarchy of evidence-based medicine (see Fig. 17.2), and formed a minimal base for testing standardization.

However, there is a paucity of medical literature with strong evidence-based data or published guidelines for many lab tests at particular CMDPs. While much of the literature is devoted to appropriate studies to be performed at diagnosis or relapse, the literature on testing when there is no morphologic evidence of disease, including bone marrow biopsies for therapy monitoring and pre- and post-stem cell transplantation (SCT), is often less clear. Moreover, much of the literature is focused on proving that a particular test shows clinical validity, rather than demonstrating superior clinical utility over alternative tests (as an extreme example, leukocyte alkaline phosphatase staining score does detect chronic myeloid leukemia, but qPCR is preferred). The SOP teams, therefore, also included recommendations based upon best clinical practice and mutually agreed upon community standards. However, these latter represent simply expert opinion, considered the lowest level of evidence (Fig. 17.2, level 7).

Interestingly, every SOP team at VUMC independently came to very similar conclusions about how to define relevant CMDPs. Since there were relatively well-defined recommendations on testing at initial diagnosis and moderately defined support for testing practices at relapse, these two CMDPs were created. In later iterations, persistent disease (i.e., multiple encounters with continued disease) became a CMDP as well. All of these were collectively grouped together as "overt disease" categories. A "no overt disease" CMDP might include multiple encounters during routine follow-up of the treated patient with testing focused on minimal residual disease detection with possible inclusion of specific testing required related to the pre- or post-SCT setting. Within this basic framework, individual adaptations were required for certain disease types with additional distinct CMDPs. For instance, negative staging bone marrows for lymphoma were separated from bone marrows with overt involvement by lymphoma. In addition, the other CMDPs were then segregated by whether or not lymphomatous involvement was ever present in the marrow.

There are two general paradigms that have been explored for these SOPs (Fig. 17.3). The first creates a two-dimensional array of diseases by CMDPs with the appropriate testing panel designated for each point in the array (Fig. 17.3a). While this array is quite intuitive, it does not take into account the elements of data that contribute to the decision of which CMDP is relevant, and testing options within each point of the array may vary depending upon the patient's prior testing results. Therefore, for clarity and ease of automation, a decision tree model may be more helpful, with branching logic for each key question in the assignment of the correct CMDP (Fig. 17.3b). While some of the questions require clinical and historical input, others require morphologic assessment, and these contributions are clearly discriminated in the decision tree model.

Several guiding principles were applied to the determination of appropriate testing for any given disease at any given CMDP (Table 17.2). Within the overt disease category, tests should be ordered at initial diagnosis if they demonstrate clinical utility for diagnosis, prognosis, therapy, or future disease monitoring. At relapse, however, only therapeutic or future disease monitoring concerns are most salient, as diagnosis is already established, and most disease is already considered poor prognosis at that time. Although some additional prognostic information may still be helpful moving forward, these are most relevant in the context of informing future therapy from the time of relapse (such as acquisition of a mutation that would indicate a need for transplantation or refractoriness to certain therapies). Finally, in cases of morphologically persistent disease, testing should be ordered

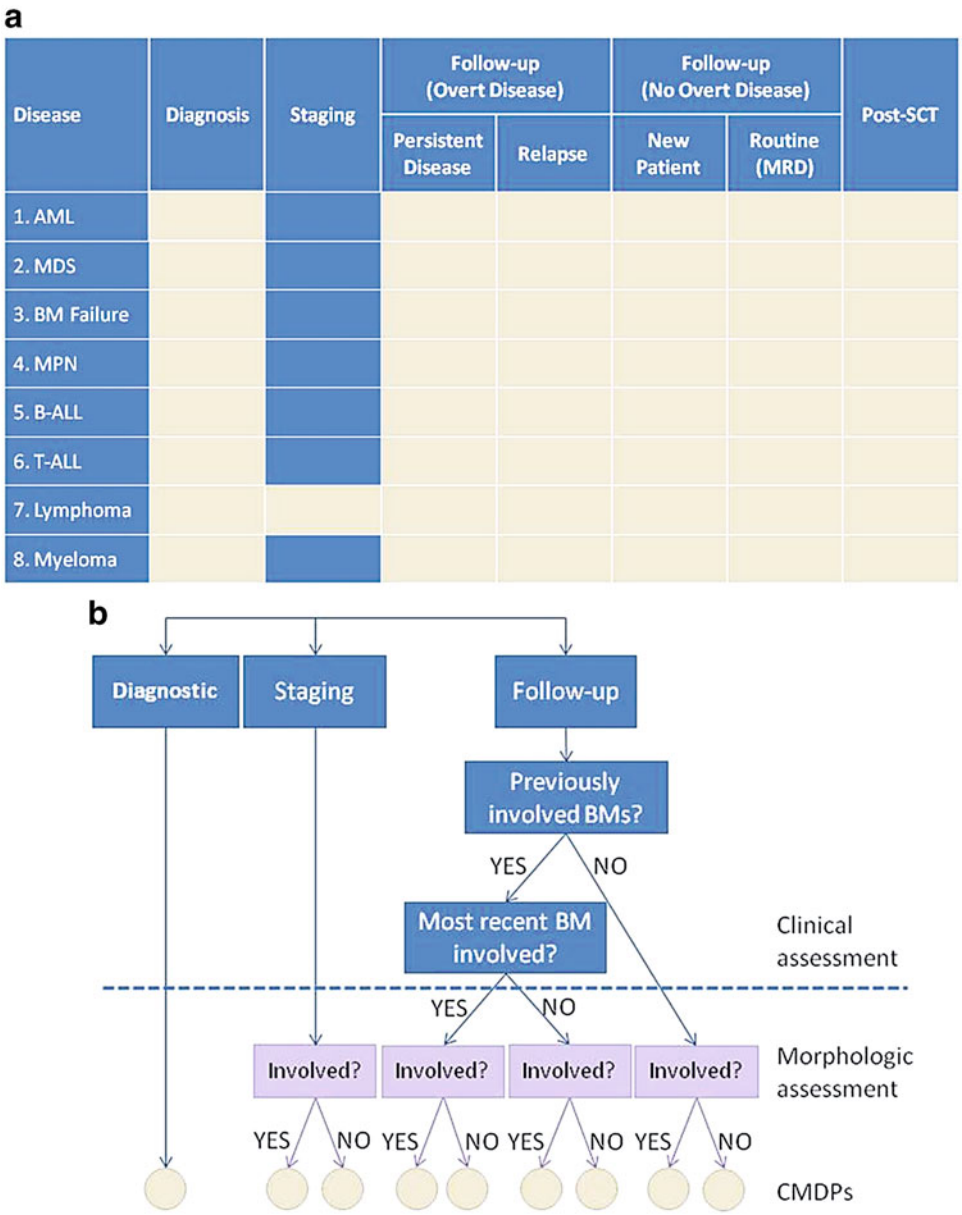

Fig. 17.3 (**a**) Example of a two-dimensional array of hematopoietic malignancies and clinicomorphologic decision points (CMDPs in *gold*). (**b**) Example of a decision tree for the determination of clinicomorphologic decision points (CMDPs in *gold*) with clearer separation of the pre-procedure input information (clinical assessment, *blue*) and the morphologic assessment (*lavender*)

Table 17.2 Purpose of testing for key clinicomorphologic decision points

		Purpose of testing				
	Time point	Diagnosis	Prognosis	Therapy	Routine residual disease monitoring	Chimerism monitoring
Overt disease	Diagnosis	+	+	+	+	
	Relapse			+	+	If applicable[a]
	Persistent Dz			±		If applicable[a]
No overt disease	Routine follow-up				+	If applicable[a]

[a]If applicable = after allogeneic stem cell transplantation

only if there is some clinical reason to suspect a change in mutational status that would affect therapy decisions. Tests at follow-up time points with no overt disease should be ordered only if they (1) were positive in the most recent marrow with overt disease, (2) are sufficiently sensitive for residual disease detection (i.e., better analytical sensitivity than morphologic and routine immunophenotypic studies), and (3) represent the most analytically sensitive testing modality (if there is more than one modality of testing).

At VUMC, the full committee of hematologists and pathologists, including representatives from molecular pathology and cytogenetics laboratories, reviewed and approved the recommendations from each disease-specific team prior to implementation. Each of the seven disease categories underwent a similar development process with multiple rounds of evidence-based discussion, group presentations, and revisions. Because the implementation of SOPs also easily allows for iterative refinement of the SOPs themselves, the DMT chose to implement initially an overly inclusive set of tests with the promise of subsequent improvement by recursive data analysis (see section Iterative Rapid Learning System (Quality Improvement)).

The utility of SOPs is multifactorial, directly addressing many of the IOM rules (Table 17.1). The assignment of CMDPs is critical to customizing care to the true clinical stage of the patient's disease course (rule #2)—truly personalized medicine. In addition, the CMDPs are designed to take into account the individual molecular features of the patient's neoplasm as well (rule #2). The use of SOPs effectively extends empowerment to the pathologists to act directly on the patient's behalf, becoming the surrogate for patient-centered control of their clinical care (rule #3). This can only be achieved through the mutual agreement and collaboration of patients with their DCPs and the DCPs with the laboratorians (rule #10). The testing decisions of each CMDP are evidence based wherever possible (rule #5). Safety is addressed by the uniformity of the testing algorithms to minimize overutilization and minimize underutilization (rule #6). Finally, the ability of the SOPs to readily adapt to unexpected findings the marrow addresses also addressed rule #8. Therefore, the use of SOPs remakes clinical hematopathology practice according to IOM recommended standards.

Development of Informatics Tools

Informatics tools, although not essential to the DMT, can greatly optimize the workflow and information transfer processes while simultaneously minimizing error. These tools facilitate and document the initial communication of clinical history from the clinician to the pathologist (online ordering forms), the interrogation of the patient medical record by the pathologist (clinical flow sheets), the communication from the pathologist to the clinical team of which ancillary tests are being ordered for the patient and the tracking of the status of those studies (dashboards of pending tests), the standardization of the report output (synoptic or structured reporting), and the communication of different laboratory findings to the clinical team as individual reports as well as in an aggregated form with a comprehensive interpretation (comprehensive reports). In the process of implementing the DMT, development of these tools ideally may proceed in parallel to the development of the SOPs, as the precise requirements and structure of these tools will often be informed by the needs of the DMT participants (Fig. 17.1).

Online Ordering Forms The utilization of electronic ordering forms provides a measure of quality control to the ordering process by mandating the type of patient information required to provide adequate clinical context to the pathologist, addressing IOM rules on knowledge sharing and cooperation (rules #4 and 10, respectively). The benefit of specialized ordering forms is that the DMT process may depend on different information than is usually provided in the context of a pathology interpretation. Because the SOP depends on both determining the current state of disease and a detailed knowledge of the patient's diagnostic and testing history, required data should include information about the diagnosis and the previous genetic and molecular aberrations that characterize the patient's disease. In addition, critical information about the state of the patient's disease, including current treatment (particularly those modalities that may affect the results or interpretation of ancillary testing, such as cytotoxic chemotherapy, targeted inhibitors, or growth factors), and relevant details of any SCT, such as type (reduced intensity or myeloablative) and date of transplant, should be included. Finally, the form should include mention of any clinical concerns about the status of the patient, e.g., whether this is a routine follow-up marrow, or if the patient has recently dropping counts or displays failure of count recovery after chemotherapy. Including this data ensures that the pathologist customizes test ordering for that particular patient (rule #2). The form also allows the clinical team to mandate specific tests regardless of the morphologic findings, based upon their clinical concern or clinical trial requirements. This encourages continued empowerment of the DCPs to represent their patients where certain testing needs are not clear from the clinical history (rule #3). For the pathologist, this context allows them to understand the context of specific testing ordered outside of the confines of the SOP and perhaps guide or suggest additional or more appropriate testing once the CMDP has been determined.

Clinical Flow Sheets Clinical flow sheets in the EMR may be used as a way to visualize the important longitudinal information about a patient's entire hematopathologic history quickly and succinctly, rather than in multiple documents in

	2/1/2015	2/15/2015	2/29/2015	5/1/2015	8/1/2015	11/1/2015	12/1/2015
Comprehensive Diagnosis	Acute myeloid leukemia (47% blasts) with NPM1 and FLT3-ITD mutations	Low level involvement by acute myeloid leukemia by cytogenetic and molecular studies	1) Complete remission marrow 2) No morphologic, immunophenotypic, cytogenetic or molecular evidence of leukemia 3) ANC = 3.89, PLT = 390	1) Complete remission marrow 2) No morphologic, immunophenotypic, cytogenetic or molecular evidence of leukemia 3) ANC = 4.21, PLT = 415	1) Complete remission marrow 2) No morphologic, immunophenotypic, cytogenetic or molecular evidence of leukemia 3) ANC = 3.59, PLT = 387	1) Complete remission marrow 2) No morphologic, immunophenotypic, cytogenetic or molecular evidence of leukemia 3) Fully engrafted marrow (0% Recipient DNA) 4) ANC = 5.32, PLT = 323	1) Recurrent acute myeloid leukemia (24% blasts), NPM1+, FLT3-ITD+ 2) Incompletely engrafted marrow (12% Recipient DNA)
Cytogenetics	46,XY,del(9)(q13q22)[12]/46,XY[8]	46,XY,del(9)(q13q22)[2]/46,XY[7]	46,XY[20]	46,XY[20]	46,XY[20]	//46,XX[20]	46,XY,del(9)(q13q22)[5]//46,XX[15]
FISH	Normal for the tested MDS and AML panels						
NPM	Detected	Detected	Not Detected	Not Detected	Not Detected	Not Detected	Detected
NPM Allelic Ratio	0.73	0.07					0.18
FLT3-ITD	Detected	Detected	Not Detected	Not Detected	Not Detected	Not Detected	Detected
FLT3-ITD Allelic Ratio	0.12	0.03					0.19
CEBPA	Not Detected						
C-KIT	Not Detected						
Chimerism						0% Recipient	12% Recipient
WBC	24.3	0.1	10.6	8.6	8.2	9.5	10.2
ANC	0.4	0	3.89	4.21	3.59	5.32	1.2
Hgb	10.5	8.4	11.2	12.4	11.9	11.7	6.8
PLT	46	20	390	415	387	323	107

Fig. 17.4 Example of a patient flow sheet. Clinical pathology encounters are listed in chronological order across the top, while different testing results are listed along the Y axis. Of note, the list of tests included on the flow sheet is flexible and may change as testing modalities evolve

multiple locations. Given the frequent discontinuity of clinical care in hematology (*vide supra*), a shared timeline display can provide continuity to the entire team (rule #1). By tying the flow sheet to the EMR rather than to a disconnected database, the information displayed is guaranteed to remain up to date as relevant clinical information is added, and pathologists and DCPs have access to the same pool of information. Moreover, at the time of the morphologic review of the current specimen, the pathology team can easily supplement the clinical data from the electronic ordering form as needed, which is particularly important in complicated cases or patients with a history of multiple previous tests. By its very design, this system promotes transparency of clinical care (rules #4 and 7) (Fig. 17.4).

Synoptic or Structured Reporting Structured reporting, most often implemented in the context of pathologic reports in the style of the CAP-recommended synoptic reports, is a vital part of the DMT process for at least two distinct reasons. First, it enforces uniformity in the information that is included in the report. This ensures that the report meets not only the quality requirements mandated by external accrediting agencies such as JCAHO or the CAP but also the needs of the DMT process, by documenting the determination of the CMDP at the level of detail necessary for proper implementation of the SOP. With a properly designed structured report, a wide variety of pathologists can create reports without jeopardizing the ability of any given report to feed into the DMT process for future encounters with that patient. Because information is provided in the same location every time, structured reporting promotes communication between clinical care teams (rule #4) and provides structure to minimize the risk of inadvertent omission of critical information (rule #6). Structured reporting may also be designed to ensure transparent documentation of any pending ancillary testing, an important element of communication with the clinical care teams as well as within the laboratory (rule #7). A beneficial by-product of this uniformity, particularly in academic medical institutions, is that the structured report can serve as a useful didactic model for teaching trainees or practicing pathologists unfamiliar with the DMT system.

Second, structured reporting greatly simplifies the process of parsing the report into discrete data elements for storage in a database, which is a vital part of the iterative nature of optimizing the DMT (rule #9). This is an area

MRN	Patient Name	DOB	Age	Gender	Specimen Date	Order Form	Pathology Report	Karyotype	FISH	Molecular	Comprehensive Report
12345678	A,B	01/01/1934	81	F	2015-01-01						
23456789	B,C	01/01/1935	80	M	2015-01-01						
34567890	C,D	01/01/1936	79	F	2015-01-01						
45678901	D,E	01/01/1937	78	F	2015-01-01						
56789012	E,F	01/01/1938	77	M	2015-01-01						
67890123	F,G	01/01/1939	76	F	2015-01-01						
78901234	G,H	01/01/1940	75	M	2015-01-01						
89012345	H,I	01/01/1941	74	F	2015-01-01						

Fig. 17.5 Example of a pending list which reflects the status of testing. The *green* color indicates that a final report is available. *Red* indicates that a result or report is pending. *Yellow* indicates that some tests within that category have been resulted and some are still pending (e.g., multiple molecular tests have been requested and only some are complete). Panels can be created on demand, according to the needs of the creator; for a pathologist, it might represent all the bone marrows reviewed on any given period of time on service. For a direct care provider, it might represent their clinic or inpatient team list

where traditional synoptic reporting in the style encouraged by the CAP falls short and where more specialized tools provide a powerful opportunity. Rather than a "fill-in-the-blank" style synoptic report, where the contents of the data fields can be recorded but do not necessarily conform to predefined values, custom data structures can be developed that allow very detailed parsing and storage of data elements, with minimal user input necessary.

Pending Lists These electronic tools allow clinicians and laboratorians alike to have real-time access to the status of all pending testing, another important element in communication between health-care teams (rule #4) (Fig. 17.5). While pending tests may be readily identifiable within the laboratory information systems (LIS) of most laboratories, the DCPs typically do not have access to the LIS. By embedding the pending lists in the EMR, it is accessible to all participants in the DMT process (rule #7). Additionally, by collecting the pending lists for a set of patients in one place (Fig. 17.5), it is easier for the pathologist to manage the process of creating and updating comprehensive reports in a timely manner. Pending lists may also be useful to the laboratories as an additional quality control measure of turnaround times, a CAP requirement.

Comprehensive Interpretation Finally, informatics tools can be designed to facilitate the creation of comprehensive reports that bring all the available data—clinical, morphologic, immunohistochemical, flow cytometric, cytogenetic, FISH, and molecular—in one place to create a final summative diagnosis (Fig. 17.6), enabling clear communication of all the data to all clinical teams (rule #4). A final diagnosis at all stages of disease in hematopathology is dependent upon the incorporation of critical ancillary testing data, in particular molecular genetic diagnostic or prognostic categories and various molecular and flow cytometric measures of residual disease. To serve this purpose, the comprehensive diagnosis tool is created to be flexible and incorporate multiple modalities of clinical and laboratory evidence, as indicated by the CMDP of the patient (rules 2 and 5).

Iterative Rapid Learning System (Quality Improvement)

An important feature of the DMT is the ability to utilize accumulated data through the DMT process to guide further refinements of the SOPs such that waste is continuously

Comprehensive Diagnosis	Acute myeloid leukemia (47% blasts) with myelomonocytic differentiation, positive for NPM1 and FLT3-ITD mutations
Clinical History	73-year old male with new onset cytopenias and circulating blasts.
Morphologic Diagnosis	Hypercellular marrow (80-90% cellularity) with decreased trilineage hematopoeisis; involved by acute myeloid leukemia (47% blasts) with myelomonocytic differentiation
Flow Cytometry	Increased myeloblasts Gating on blasts (47% of total cells) identified on CD45/side scatter histograms, immature cells have the following immunophenotype: CD2 (negative), CD4 (heterogeneous dim), CD7 (dim), CD11b (partial moderate), CD13 (dim), CD14 (negative), CD15 (dim), CD16 (negative), CD19 (negative), CD33 (bright), CD34 (partial moderate), CD45 (dim), CD56 (partial dim), CD64 (moderate), CD117 (partial moderate), HLA-DR (bright), MPO (partial moderate)
Karyotype	Abnormal male karyotype 46,XY,del(9)(q13q22)[12]/46,XY[8]
FISH	Normal for the tested MDS and AML panels nuc ish 8q22(RUNX1T1x2),21q22(RUNX1x2)[200] nuc ish 15q22-24(PMLx2),17q21(RARAx2)[200] nuc ish 16q22(CBFBx2)[200] nuc ish 11q23(KMT2Ax2)[200] nuc ish 5q15.2(D5S23,D5S721x2),5q31(EGR1x2)[200] nuc ish 7cen(D7Z1x2),7q31(D7S486x2)[200] nuc ish 8cen(D8Z2x2)[200] nuc ish 20q12(D20S108x2)[200]
Molecular Studies	**NPM1 mutation** Detected 0.73 **FLT3-ITD mutation** Detected 0.12 **CEBPA mutation** Not Detected **c-KIT mutation** Not Detected

Fig. 17.6 Example of a comprehensive report that incorporates in one place a summary of all the results obtained on a single bone marrow study, tied together by an interpretive summary that includes all the data. Ideally the results from all other reports would be automatically merged (autopopulated) into the comprehensive report to minimize transcription error and time. The type of data included can range from binary values (detected/not detected) to complex text strings like flow immunophenotype to panels of testing such as the results of next-generation sequencing

decreased (rule #9). In many ways, this follows the PDSA (plan-do-study-act) model of quality improvement that allows rapid cycle improvement for improving processes or implementing changes (Fig. 17.7) [6]. After implementation of the DMT, test utilization and results are monitored carefully and studied, so that further actions may be taken. In the case of the hematopathology DMT, data on the clinical utility of the results of certain tests are monitored to determine if their utilization is warranted. This is particularly critical when published data regarding the clinical validity of certain tests at specific CMDPs are lacking. This iterative process enables each institution to study the efficacy of their own testing practices in their clinical/institutional environment and, based upon that data, to determine if tests may be removed from the SOPs. In essence, each institution can create its own cohort studies in support of their testing practices (Fig. 17.2, level 5 evidence). In addition, the continuously evolving nature of the SOPs also easily permits the addition of tests as literature provides evidence for their utility or as new molecular genetic aberrations become known.

Test Utilization Analysis: Outcomes and Impact of the DMT

To measure the outcome of the DMT implementation, our group established four criteria of success. If successful, (1) our clinician colleagues would express confidence in the system, (2) the system would be more efficient, (3) there would be improved test utilization and performance, and (4) the testing guidelines would evolve as evidence for best practices accumulates. These outcomes were detailed by Seegmiller et al. [7].

Clinician confidence was measured in two ways. First, the 34 DCPs that interacted with the DMT service were sur-

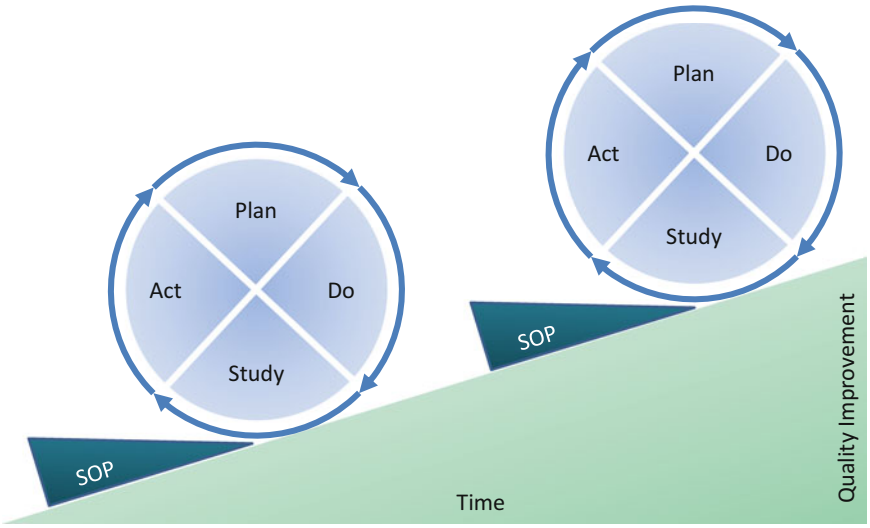

Fig. 17.7 Long-term quality improvement with the DMT. With each iteration of the SOPs, new data is acquired about testing practices and results. This data is in turn used to plan and implement the next iteration with successive improvement in the quality of testing practices over time. In addition, this iterative process enables the flexible incorporation over time of additional biomarkers as they are demonstrated to have clinical utility (adapted from https://en.wikipedia.org/wiki/PDCA#/media/File:PDCA_Process.png)

veyed 11 months after the initiation of the DMT to evaluate their experience. This survey showed that a majority (73 %) of the clinicians were aware of the option to have pathologists order the tests and were familiar with the SOPs on which these decisions were made. In addition, most DCPs expressed trust that the pathologists (81 %) and the SOPs (86 %) would make correct testing decisions for their patients. One of the major concerns expressed during DMT development was that clinicians might be hesitant to cede decision-making authority over test selection for their patients. However, after experiencing the DMT approach, the vast majority of DCPs (91 %) indicated that they preferred this approach to one in which they had primary responsibility for testing decisions.

Perhaps the best indicator of clinician confidence is their voluntary utilization of the DMT. There is an opt-out provision in the DMT that allows clinicians to order tests themselves outside of the SOPs. During the first few weeks of DMT implementation, a majority of clinicians continued to order tests in this manner. However, as familiarity and experience with the DMT increased, that percentage rapidly fell. Ten weeks post-implementation, the DMT process was utilized voluntarily in greater than 80 % of bone marrow biopsies.

Efficiency was also measured in the clinician survey. When asked, a vast majority of clinicians indicated that both the DMT reflex testing system (86 %) and the comprehensive reports (63 %) reduced the time spent in ordering bone marrow tests and reviewing the results. Clinicians estimated that with these two activities, the DMT saved approximately 10 min each time a patient had a bone marrow biopsy.

Test utilization was clearly improved as a result of DMT implementation (Fig. 17.8). To measure utilization, bone marrow cytogenetic and molecular tests were categorized as concordant (i.e., recommended by the SOPs for a patient with a specific hematologic neoplasm, at a particular stage of therapy), discordant (i.e., not recommended by the SOPs), or omitted (i.e., recommended by the SOP, but not ordered). A retrospective analysis showed that prior to the DMT, more than one-third of tests were discordant and that there were frequent test omissions (Fig. 17.8a). Improved test utilization would be reflected by a decrease in discordant and omitted tests. Indeed, in the first 12 months following implementation of the DMT, there was a 69 % decrease in discordant tests (Fig. 17.8b) and an 88 % decrease in omitted tests (Fig. 17.8c), leading to an overall 15 % decrease in total tests. These combined effects reduced by 18 % ($442 per marrow) the average cost of bone marrow testing to payers. This reduction in waste is an important component of IOM rule #9.

Accompanying any reduction in utilization is the concern that the changes go too far and that at least some of the reduction comes at the cost of essential laboratory information that may impact patient care. To address this concern, we used test results (positive or negative) as a rough surrogate measure of test utility, with the assumption that positive test results provide more important clinical information than negative test results. While it is recognized that some negative test results are highly significant, this measure is still a valid first approximation for test utility. Reviewing 18 months of test results from before and after DMT implementation, we found that a significantly higher fraction of concordant tests generated positive results compared with discordant tests (27 vs. 4 %). Furthermore, the majority of positive discordant tests were unlikely to have clinical impact (i.e., they were redundant with other recommended testing or they were transient changes/false-positive results). Accordingly, there was a significant increase in the fraction of positive results after DMT implementation

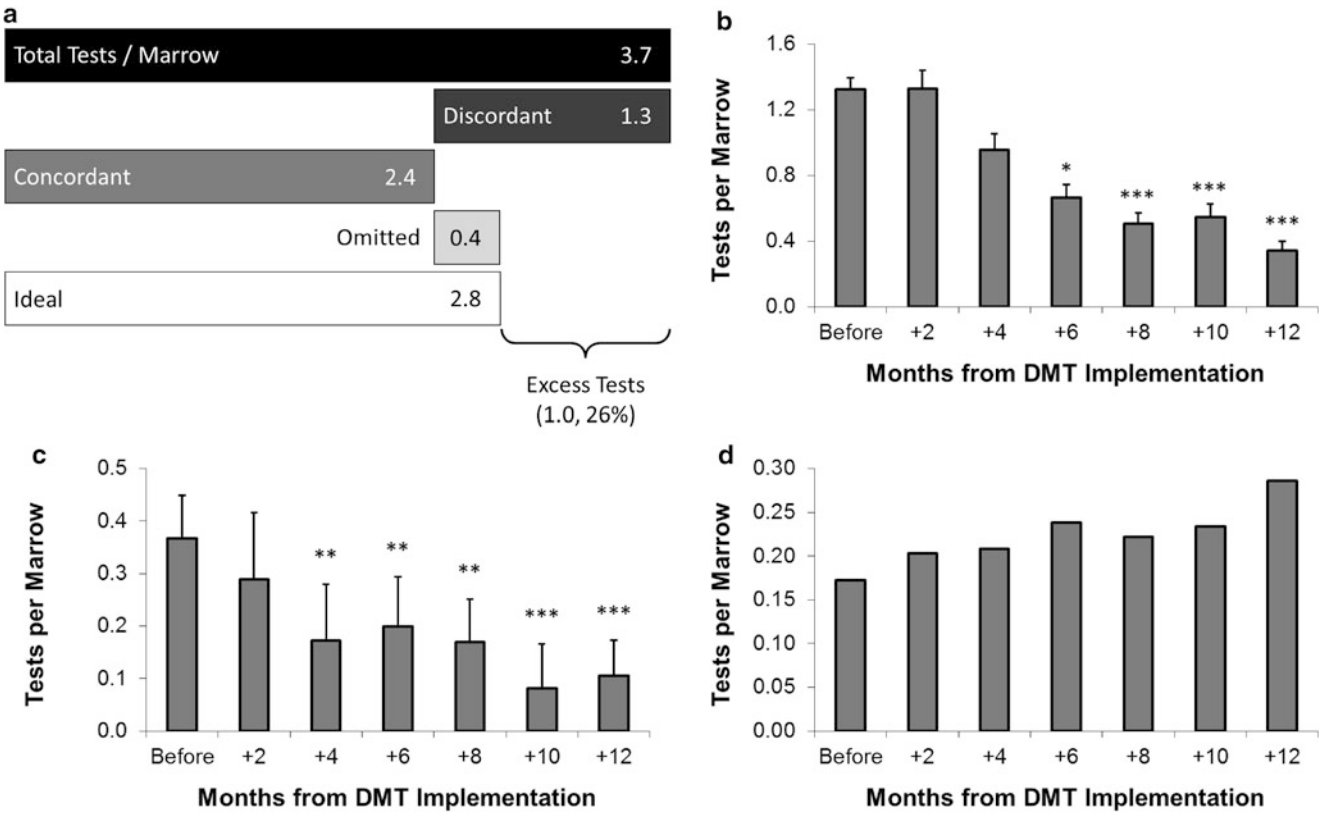

Fig. 17.8 Change in testing practices after institution of the DMT. (**a**) Summary of the average number of tests per marrow study (3.7) prior to the institution of the DMT with the number of tests that would have been deemed discordant to the SOP (overutilization, 1.3), the number of tests that would have been concordant to the SOP (2.4), and the number of tests that should have been ordered according to the SOP but were not (underutilization, 0.4). (**b**) Longitudinal graph of the number of discordant tests before and after the implementation of the DMT in bimonthly increments. (**c**) Longitudinal graph of the number of omitted tests before and after the implementation of the DMT in bimonthly increments. (**d**) The fraction of tests that were determined to be positive on the bone marrow studies as a surrogate for the increased positive predictive value of the testing

(Fig. 17.8d). As the DMT changes the pretest probability of a positive test, one can surmise that these improvements would improve test performance, particularly positive predictive value.

The last measure of success is the ability of the DMT system to evolve over time. This is important for two reasons. First, the initial SOPs were constructed using incomplete information. As discussed above, for many testing decisions, there was little or no published evidence, no practice guidelines, nor other consensus documents available to guide decisions. Second, with technological advances, there is a continual increase in the list of possible testing options, and a decision support tool must always stay current with test menus. In the DMT, we addressed this through continual data collection and analysis, allowing us to generate evidence that could be used to regularly refine the SOPs. Through this cycle of SOP creation, data collection, analysis, and refinement, the DMT acted as a rapid learning system, a recognized approach to successful health-care innovation [8, 9].

One example of this rapid-cycle revision is fluorescence in situ hybridization (FISH) testing for myelodysplastic syndrome (MDS). The original SOP recommended a complete MDS FISH panel be performed on every bone marrow from patients with suspected MDS. The subsequent study indicated that routine karyotype testing was adequate to assess the cytogenetic status of patients, and the results of FISH testing were redundant and no more sensitive in most cases [10]. Subsequent elimination of FISH testing in patients with an adequate quality karyotype (i.e., 20 metaphases) resulted in further decreases in total testing with improved test performance. This evidence-based revision of SOPs based upon internally collected data on our testing practices allowed us to replace decisions that were based on expert opinion alone (level 7 evidence in Fig. 17.2 above) with more reliable cohort study data (level 5 evidence).

Generating data such as these, the DMT groups revised the SOPs to reflect experience using the DMT protocol over the first year and to take into account new evidence

obtained by observing test result and utilization patterns. In most cases, these revisions reduced tests in particular diseases and at particular CMDPs where results were rarely if ever positive. There were, however, occasional situations for which the data indicated that application of the SOPs excluded tests that may sometimes generate clinically important data. These tests were added back to the new SOPs. Data analysis over the subsequent year indicated a further decrease in total tests and associated costs and additional increase in rate of positive tests (unpublished data).

These outcomes illustrate the impact of the DMT process on bone marrow testing at Vanderbilt. Through this program, we were able to reduce wasteful testing with its associated costs, while improving test performance, with the full support of the ordering clinicians. We improved communication of ongoing cases and provided a more comprehensive diagnosis for each patient biopsy. We think that this process can serve as a template for utilization management in other areas of complex pathology testing. Importantly, while what we present here is a solution for Vanderbilt hematopathology, each site must customize its approach to development and implementation of a utilization management system.

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