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HEALTH ECONOMICS (N KHERA, SECTION EDITOR)

Choosing Wisely® in Hematology: Have We Made a Difference?

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Abstract

Purpose of Review The Choosing Wisely® initiative, led by the American Board of Internal Medicine Foundation in collaboration with national professional medical societies, aims to help patients choose care that is essential, free from harm, and evidence-based. The American Society of Hematology has advocated practices specific to hematology for physicians and patients to examine carefully. Here, we summarize various barriers to adopting these practices, interventions used to improve adoption, and challenges in measuring the effectiveness of these interventions.

Recent Findings The Choosing Wisely® campaign has become an international effort with more than 20 countries worldwide having embraced it. Such widespread interest indicates that the campaign initiated an important dialog between patients and physicians about overutilization of resources. Evidence showing the positive impact of interventions on adopting these practices is accumulating, but their effect on improving clinical outcomes is uncertain.

Summary Decreasing overuse of resources is a cultural change in perspective for practitioners and patients alike. We believe that healthcare delivery is transitioning from being volume-based to value-based. As we continue to support the Choosing Wisely® campaign, we need to implement strategies to document and measure the influence of our value-based recommendations on physician practices, patient care and attitudes, and healthcare costs.

Keywords Choosing wisely · Value-based · Healthcare costs · Harms

Introduction

Choosing Wisely® is a stewardship initiative developed and led by the American Board of Internal Medicine (ABIM) Foundation in collaboration with national professional medical societies, such as the American Society of Hematology (ASH). The Choosing Wisely® campaign stemmed from a report by the Institute of Medicine published in 2012, which estimated that over 200 billion dollars is spent annually on what was deemed unnecessary medical care in the USA [1]. In the same year, the USA started its Choosing Wisely® campaign [2••, 3], followed by Canada in 2014 [4]. In 2013, ASH released its first Choosing Wisely® recommendations (Table 1), which addressed thrombophilia testing, red blood cell (RBC) transfusion practices, use of plasma for vitamin K antagonist reversal, inferior vena cava filter use, and surveillance computed tomography (CT) scans after curative-intent treatment of aggressive lymphoma [5••]. Five more items were added in ASH's second Choosing Wisely® campaign the following year [6••]. The campaign's key guiding principle is harm avoidance, but it also seeks to increase value in health care. The guidelines aim to encourage dialog among patients and physicians about the costs and benefits of medical care.

In the years since the introduction of the Choosing Wisely® campaign by the ASH, multiple institutions have attempted to implement systematic methods to trigger discussions with patients about the value of tests, procedures, or treatments. We summarize below barriers to adopting these recommendations, interventions that have been used to improve adoption and challenges in measuring the effectiveness of interventions and Choosing Wisely® recommendations on patient outcomes.

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Table 1 The American Society of Hematology Choosing Wisely list

10 things physicians and patients should question
1. Do not transfuse more than the minimum number of red blood cell (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, noncardiac in-patients)
2. Do not test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma, or prolonged immobility)
3. Do not use inferior vena cava (IVC) filters routinely in patients with acute venous thromboembolism (VTE)
4. Do not administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (i.e., outside of the setting of major bleeding, intracranial hemorrhage, or anticipated emergent surgery)
5. Limit surveillance computed tomography (CT) scans in asymptomatic patients following curative-intent treatment for aggressive lymphoma
6. Do not treat with an anticoagulant for more than 3 months in a patient with a first venous thromboembolism occurring in the setting of a major transient risk factor
7. Do not routinely transfuse patients with sickle cell disease (SCD) for chronic anemia or uncomplicated pain crisis without an appropriate clinical indication
8. Do not perform baseline or routine surveillance CT scans in patients with asymptomatic, early-stage chronic lymphocytic leukemia
9. Do not test or treat for suspected heparin-induced thrombocytopenia (HIT) in patients with a low pretest probability of HIT
10. Do not treat patients with immune thrombocytopenic purpura (ITP) in the absence of bleeding or a very low platelet count

Barriers to Adoption

Historically, efforts to improve care in hematology have focused more on underuse than overuse. In general, due to liability concerns, practitioners have been concerned about missing important clues when diagnosing patients. Retrospectively, it is easier to identify tests that were not performed instead of tests that were performed unnecessarily.

Decreasing our overuse of resources represents a cultural change for practitioners and patients alike. Pressed by time, busy practitioners have been tempted to order various ancillary tests in an effort to be "thorough." That said, being truly "thorough" is ordering thoughtful testing when appropriate while keeping the patient's outcome front and center.

There are a few important barriers to adopting Choosing Wisely® practices (Table 2). First, making a difference in the adherence to the ASH Choosing Wisely® recommendations is dependent on practitioner education while accurately relaying the evidence underlying each recommendation. Practitioners are more likely to embrace a recommendation when they are convinced of its benefit. Evidence-based recommendations hold weight. Although electronic alerts may be useful, they frequently relay only a partial message. Furthermore, the sheer number of electronic alerts issued for various reasons such as drug-drug interactions, relative contraindications, and others in the electronic medical records (EMRs) causes alert fatigue, leading many practitioners to disregard these alerts when they are clicking through them.

Second, the campaign is based on the assumption that adherence to these practices leads to increased dialog between patients and physicians. Whether this is truly happening is not entirely clear and is difficult to measure accurately. For example, a patient with thrombocytopenia with a low-pretest probability of developing heparin-induced thrombocytopenia (HIT) will not know if the physician(s) caring for him decided not to order a HIT antibody assay. Physicians often make clinical decisions in the inpatient setting that are outside the patient's room, and the reality is that many of the thought processes behind these decisions are not always communicated to patients. In the outpatient primary care setting, evidence clearly suggests that practitioners do not have time to engage

Table 2 Barriers to adoption of Choosing Wisely recommendations

Barriers	Proposed solutions
Practitioner-related	
Familiarity	Education about the campaign
Patient request	Understand reasons behind request and engage in shared discussion
Knowledge about the evidence behind the recommendations	References for each recommendation and transparency
Skepticism towards magnitude of benefit/harm for each recommendation	Recommendations that have minimal impact on patient health and cost should not be proposed
System-related	
Concern about malpractice lawsuits	Choosing Wisely recommendations should be viewed as standard-of-care approaches
Inadequate time to engage in discussions with patients	Valuing time with patient more than performing interventions
Financial incentives to order more tests/treatments	Value-based care with a fixed, bundled payment rather than fee-for-service

patients in discussions about the pros and cons of each intervention [7].

Third, even if practitioners are educated about the evidence behind the ASH Choosing Wisely® campaign, and then decide to adopt many of the practices while engaging patients in decision-making, it is unknown if this effort will ultimately decrease cost through eliminating what is deemed unnecessary medical care in the USA. Studies looking at the change in cost of medical care in the USA after implementation of Choosing Wisely® campaign recommendations are lacking, possibly due to the relatively recent development of the campaign.

Fourth, the way healthcare is funded in the USA provides incentives for practitioners to order more tests and do more procedures since there is financial gain with each of these interventions. Economic forces drive healthcare and profit follows payment. This is especially true in the US health system with its predominant fee-for-service payment structure [8]. Adopting recommendations that minimize testing or shorten duration of treatment is a culture change. Unforeseen events also change the culture. The response to the current, unanticipated, coronavirus disease of 2019 (COVID-19) pandemic will likely change today's healthcare paradigm, at least in part. In other countries with a single-payer system, where less testing is encouraged, an argument can be made that harm avoidance has been declining prior to the Choosing Wisely® campaign. For example, in Canada, population-based health system administrative databases from Ontario were queried to try to describe the practice of surveillance imaging for diffuse large B-cell lymphoma (DLBCL) beyond 2 years of completion of therapy. The study found that the practice of surveillance imaging was prevalent (52% by 3 years of follow-up), but the cumulative incidence of scanning decreased over the study period from 62% in 2006 to 48% in 2014 ($p = < 0.001$), before Choosing Wisely Canada (CWC) was implemented [9•].

Several other challenges have been discussed previously, including avoiding portraying the program as cost-cutting, which can undermine patient trust [10]. Nevertheless, when evaluating the previous comments, it is critical to remain cognizant that the Choosing Wisely® campaign is an education initiative (not an implementation campaign) hence its value cannot be fully measured based on stringent adoption of its recommendations. We foresee that adoption campaigns will be the next natural step to complement the Choosing Wisely® campaign.

Interventions to Improve Adoption

Multiple institutions have implemented methods to remind practitioners to discuss various practices recommended by the ASH Choosing Wisely® campaign. For example, thrombosis is a major risk factor in patients hospitalized for venous thromboembolism (VTE). Thrombophilia testing of adults is commonly used in that setting. However, avoiding thrombophilia testing requires educating practitioners from different departments that may be caring for a patient with a VTE, such as internal medicine, family medicine, and orthopedic surgery. A simple intervention developed at Stanford University Hospital, an electronic alert, was shown to be an effective method of reducing unnecessary thrombophilia testing in the outpatient setting. There was a small reduction in the rate of outpatient testing per month after the implementation of the electronic alert, from 36 to 31 ($p = 0.03$). In their study, Jun et al. found that adherence to the electronic alert was high in the inpatient setting, but low in the outpatient setting [11]. Interestingly, the study also found that non-hematologists were more likely than hematologists to follow the alert [11].

Internal medicine residents, arguably the most influential body of physicians that carry out many non-malignant hematology practices in the academic setting, discussed in the ASH Choosing Wisely® campaign (e.g., thrombophilia testing, plasma infusions, RBC transfusions), seemingly lacked confidence in their responses when asked about these guidelines [12]. For some recommendations, fewer than half the responders knew the correct answer (e.g., workup for heparin-induced thrombocytopenia). Having done a hematology rotation, especially a consult rotation, was more likely to lead to correctly identifying the Choosing Wisely® practice and being confident of the answer [12]. This underscores the importance of one-on-one education to improve rates of adherence to these recommendations rather than electronic alerts (Table 3).

Another electronic medical record alert was evaluated at Banner Health facilities [13]. The generated alert (Fig. 1) reminded clinicians to carefully weigh the anticipated benefits of post-treatment imaging scans against potential harms in asymptomatic patients following curative intent treatment for aggressive lymphoma (Fig. 2). An alert with a message, "limit surveillance PET or CT scans in asymptomatic patients following curative treatment for lymphoma," appeared on the EMR when ordering a scan. In the 8 months prior to implementing the reminder, the number of imaging studies was 387 for an average of 48.3 scans per month across the Banner Health system. In the 3 months since the reminder was implemented, the number of imaging studies decreased to 76 for an average of 25.3 scans per month across the Banner system. At the same time, lymphoma survivorship pamphlets were placed in the clinics to facilitate discussions between physicians and patients regarding surveillance imaging (Fig. 3). The goal was to transition efforts from relapse detection to improved survivorship. Education and reminders had an influence on practice patterns, but it is unknown whether that change is durable.

Table 3 Choosing wisely champions from the American Society of Hematology

Lead	Year	Topic	Study methods and interventions
Ravi Sarode	2016	Thrombophilia testing	Local guidelines developed, education program, implemented guidelines in EHR via a series of cascading questions that providers must answer before ordering tests
Javier Munoz	2016	Imaging in lymphoma	Described in this manuscript
Maria Juarez	2016	Single-unit transfusion	Institutional clinical practice recommendation, EHR workflow change, educational campaign
Marc Zumberg	2017	Indications for blood products	Local guidelines, automatic alert that prompts the clinician to indicate the reason for the order. These are reviewed by the pharmacy director or blood bank medical directors then approved or denied per institutional guidelines
Matthew Scheff	2017	Individualized pain plans in sickle cell anemia	Multi-disciplinary team that used a "Plan-Do-Study-Act" (PDSA) format to add an individualized pain plan (IPP) document to EHR and create IPPs for the highest resource users. The team then measured the presence of an IPP, adherence to the IPP, and time to first and second opiate dose administration
Yulia Lin	2017	Iron deficiency anemia	Education session created an algorithm on IDA management and implemented a toolkit for emergency department physicians. Made intravenous iron more readily available in the emergency department, improved access to a transfusion specialist for guidance and presented on the topic at rounds
Prakash Vishnu	2018	Restrictive transfusion program	Weekly didactic sessions, pamphlets, and verbal instruction for 2 months to clinicians, hematology trainees, and nurses educating about transfusing one unit of red blood cells instead of two for eligible patients
Ming Lim	2018	Heparin-induced thrombocytopenia	Developed an anticoagulation and bleeding management service team to be alerted on a daily basis for patients suspected of having HIT. Centralized hospital-wide protocol that coordinated testing and treatment of patients suspected to have HIT
Adam Binder	2018	Antibiotic use in neutropenic fever	Institutional algorithm developed to guide prescriptions related to febrile neutropenia and conducted recurring educational initiatives emphasizing criteria for appropriate vancomycin initiation based on well-established guidelines

A study that aimed to increase the use of IV iron instead of packed red blood cell (pRBC) transfusions for patients with iron deficiency anemia presenting to the Emergency Department (ED) incorporated multiple interventions to facilitate adopting the use of IV iron instead of pRBC [14]. These interventions included an education session presenting the rationale, introducing IV ferumoxytol, which can be infused over 15 min, developing an algorithm for the ED, and access to a transfusion medicine specialist for guidance when needed. The end result led to 50% increase in the utilization of what was considered appropriate pRBC transfusions, with a corresponding increase in IV ferumoxytol use for patients who, before the interventions, would have otherwise received pRBC transfusions [14].

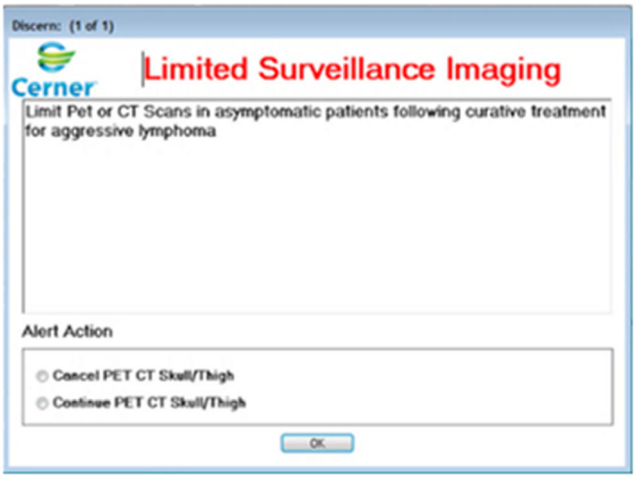


Fig. 1 Electronic medical record alert

The interventions seemed to improve recognition and education about the evidence for these recommendations, thereby improving adherence. Adherence, however, depends upon whether the interventions are adopted by institutions beyond the study period. Evidence supporting the premise that improved recognition and knowledge of recommendations leads to increased adoption and adherence in the long run is lacking. Needless to say, the Choosing Wisely® campaign has successfully been able to set the stage for individuals, institutions, and government to develop subsequent implementation strategies and policies that can lead to sustained changes in practice.

Since the Choosing Wisely® campaign introduced evidence-based recommendations demonstrating that omitting a test or treatment in the appropriate setting is not associated with adverse outcomes, it appears that omission might, in fact, reduce harm, both physical and financial. Consequently, the Choosing Wisely® campaign gained enormous momentum both nationally and internationally for other countries to

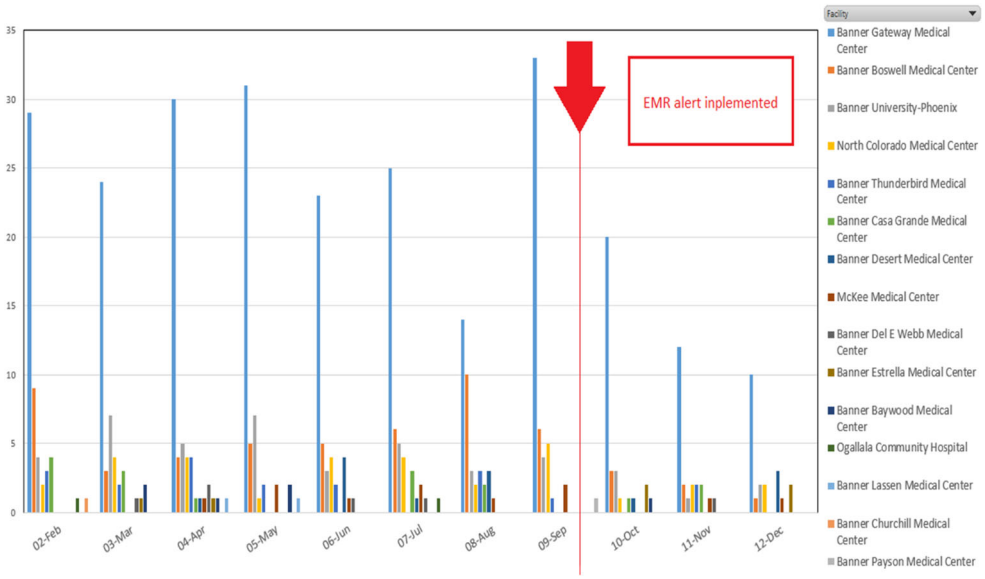
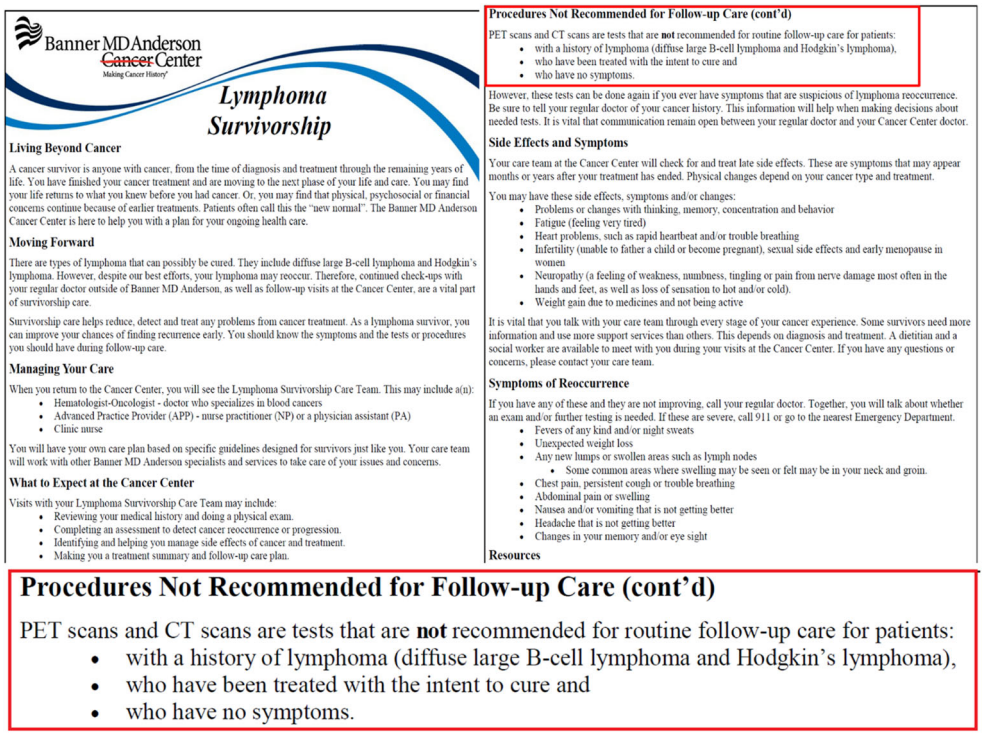


Fig. 2 Imaging trends in patients with lymphoma since February 2015 to January 2016

develop their own Choosing Wisely® campaigns. The Choosing Wisely® campaign in hematology published its first set of recommendations in 2015, highlighting slightly different practices than those of the ASH campaign. These included avoiding intravenous immunoglobulin (IVIG) use for asymptomatic immune thrombocytopenia, not bridging warfarin in low-risk patients undergoing invasive procedures, not performing thrombophilia testing in the workup of early pregnancy loss, avoiding the use of fine-needle aspiration in the diagnosis of lymphoma, and not transfusing RBC for an arbitrary hemoglobin threshold [15].

Challenges in Measuring Impact

The Choosing Wisely® campaign celebrated its fifth anniversary in 2017 and published a report of the progress seen following efforts instituted by the American Board of Internal Medicine. The campaign has become an international effort, with more than 20 countries worldwide having embraced it. The central message of avoiding harm and reducing overuse associated with unnecessary care has resonated with many practitioners. The uptake indicates that the campaign has started an important dialog between patients and physicians


Banner MD Anderson Cancer Center
Making Cancer History®

Lymphoma Survivorship

Living Beyond Cancer

A cancer survivor is anyone with cancer, from the time of diagnosis and treatment through the remaining years of life. You have finished your cancer treatment and are moving to the next phase of your life and care. You may find your life returns to what you knew before you had cancer. Or, you may find that physical, psychosocial or financial concerns continue because of earlier treatments. Patients often call this the "new normal". The Banner MD Anderson Cancer Center is here to help you with a plan for your ongoing health care.

Moving Forward

There are types of lymphoma that can possibly be cured. They include diffuse large B-cell lymphoma and Hodgkin's lymphoma. However, despite our best efforts, your lymphoma may reoccur. Therefore, continued check-ups with your regular doctor outside of Banner MD Anderson, as well as follow-up visits at the Cancer Center, are a vital part of survivorship care.

Survivorship care helps reduce, detect and treat any problems from cancer treatment. As a lymphoma survivor, you can improve your chances of finding recurrence early. You should know the symptoms and the tests or procedures you should have during follow-up care.

Managing Your Care

When you return to the Cancer Center, you will see the Lymphoma Survivorship Care Team. This may include a(n):

- Hematologist-Oncologist - doctor who specializes in blood cancers
- Advanced Practice Provider (APP) - nurse practitioner (NP) or a physician assistant (PA)
- Clinic nurse

You will have your own care plan based on specific guidelines designed for survivors just like you. Your care team will work with other Banner MD Anderson specialists and services to take care of your issues and concerns.

What to Expect at the Cancer Center

Visits with your Lymphoma Survivorship Care Team may include:

- Reviewing your medical history and doing a physical exam.
- Completing an assessment to detect cancer reoccurrence or progression.
- Identifying and helping you manage side effects of cancer and treatment.
- Making you a treatment summary and follow-up care plan.

Procedures Not Recommended for Follow-up Care (cont'd)

PET scans and CT scans are tests that are **not** recommended for routine follow-up care for patients:

- with a history of lymphoma (diffuse large B-cell lymphoma and Hodgkin's lymphoma),
- who have been treated with the intent to cure and
- who have no symptoms.

However, these tests can be done again if you ever have symptoms that are suspicious of lymphoma reoccurrence. Be sure to tell your regular doctor of your cancer history. This information will help when making decisions about needed tests. It is vital that communication remain open between your regular doctor and your Cancer Center doctor.

Side Effects and Symptoms

Your care team at the Cancer Center will check for and treat late side effects. These are symptoms that may appear months or years after your treatment has ended. Physical changes depend on your cancer type and treatment.

You may have these side effects, symptoms and/or changes:

- Problems or changes with thinking, memory, concentration and behavior
- Fatigue (feeling very tired)
- Heart problems, such as rapid heartbeat and/or trouble breathing
- Infertility (unable to father a child or become pregnant), sexual side effects and early menopause in women
- Neuropathy (a feeling of weakness, numbness, tingling or pain from nerve damage most often in the hands and feet, as well as loss of sensation to hot and/or cold).
- Weight gain due to medicines and not being active

It is vital that you talk with your care team through every stage of your cancer experience. Some survivors need more information and use more support services than others. This depends on diagnosis and treatment. A dietitian and a social worker are available to meet with you during your visits at the Cancer Center. If you have any questions or concerns, please contact your care team.

Symptoms of Reoccurrence

If you have any of these and they are not improving, call your regular doctor. Together, you will talk about whether an exam and/or further testing is needed. If these are severe, call 911 or go to the nearest Emergency Department.

- Fevers of any kind and/or night sweats
- Unexpected weight loss
- Any new lumps or swollen areas such as lymph nodes
  - Some common areas where swelling may be seen or felt may be in your neck and groin.
- Chest pain, persistent cough or trouble breathing
- Abdominal pain or swelling
- Nausea and/or vomiting that is not getting better
- Headache that is not getting better
- Changes in your memory and/or eye sight

Resources

Procedures Not Recommended for Follow-up Care (cont'd)

PET scans and CT scans are tests that are **not** recommended for routine follow-up care for patients:

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- who have no symptoms.

Fig. 3 Lymphoma survivorship pamphlets were placed on the clinics to facilitate discussions between physicians and patients regarding surveillance imaging

about overutilization of specific resources. However, evidence reporting a positive effect on clinical outcomes is necessary to strengthen the argument in support of future endeavors [16•].

Measuring a difference in adherence rates beyond a single institution can be difficult in the US healthcare system given its fragmented nature. Multi-institutional initiatives are lacking and it is unclear if educational campaigns by themselves achieve fostering and encouraging dialog between patients and physicians. When looking at other Choosing Wisely® initiatives by other societies, the results are mixed. A retrospective analysis of claims data for members of Anthem-affiliated commercial health plans looking at seven "low-value" services showed only two services modestly declined over a 3-year span with an absolute difference of 1%–2% [17•].

On the Critical Care front, a six-question survey assessed whether Choosing Wisely® recommendations had been implemented in the ICU setting; only 50% reported familiarity with the campaign and had implemented some of the recommendations through various methods, including institutional guidelines (65%) or EMR orders (55%) [18]. Administrative data from Ontario assessed the impact of Choosing Wisely in Urology and found no evidence of a significant change in three practice patterns [19]. In Oncology, cancer registry records for women diagnosed with breast cancer before and after the launch of the Choosing Wisely campaign were used to examine patterns of surveillance advanced imaging and serum tumor marker testing. There was a slight decrease in the use of advanced imaging (odds ratio of 0.68; 95% CI, 0.52–0.89), but no change in the prevalence of serum tumor marker testing [20]. Another study showed a small but steady decline in low-value breast cancer care since 2010 (before the launch of the Choosing Wisely campaign) that did not seem to accelerate after the launch of the campaign [21].

Regarding future initiatives, a randomized study evaluating the quality of interventions needed to improve adherence may provide the most robust data in support of some interventions over others. For example, a multi-institutional study may be designed to randomize patients to care involving a series of interventions that include quarterly educational sessions for practitioners including discussion of pros and cons of intervention (test arm) or a single educational session followed by an electronic alert for practitioners (control arm). The aim would be to analyze which intervention arm would lead to improved adherence to an intervention and patient satisfaction. Corollary studies would include practitioner attitudes towards each intervention arm. The analysis of such data would shed light on attitudes of practitioners and patients towards each intervention arm, as well as the effectiveness of each intervention arm in improving adherence and patient outcomes.

Early indicators of long-term adoption of the recommendations are not conclusive. Some of the reasons for this include lack of reporting on long-term impact beyond the study period for a given intervention. Moreover, interventions that are not adopted at an institutional level may not be sustainable. Alternatively, multicenter, regional, or national collaborative registry studies may be appropriate to measure adherence to an intervention and qualitatively evaluate reasons why certain recommendations were not followed on a case-by-case basis (e.g., clinical circumstances and family history that prompted thrombophilia testing). That said, it is important to mention again that the Choosing Wisely® campaign is primarily an education and awareness initiative instead of a standalone implementation initiative per se. Education is the first step for change; nevertheless, education does not bring change on its own. Since its inception in 2016, ASH has chosen three Choosing Wisely® Champions per year which is a testament that the campaign has inspired a generation of physicians and that the impact of the recommendations can be measured [13].

To answer the question regarding whether or not the Choosing Wisely® Campaign has made a difference, the answer is a resolute yes. The campaign has succeeded in raising awareness regarding overutilization, educating regarding harm-reducing maneuvers, and has remained relevant throughout the years. Furthermore, there are pediatric-focused and non-ASH recommendations currently available recognizing the benefits of collaboration between medical societies, thus, the Choosing Wisely® campaign has proven to be an ever-expanding education tool. Certainly, there are challenges at hand but the Choosing Wisely® campaign has been a critical steppingstone that has resonated through various medical societies and transpired to educate practitioners.

The relevance of the Choosing Wisely® campaign is clearly further accentuated in the context of the COVID-19 pandemic as unnecessary tests could potentially harm patients and practitioners alike in the outpatient and inpatient settings. It goes without saying that we should avoid bringing a patient from home to an overwhelmed healthcare system, with potential unintended exposure to COVID-19 while in the hospital, for an unnecessary test. Furthermore, ordering unnecessary tests in a patient hospitalized with confirmed COVID19 exposes technicians, nurses, and practitioners to potentially acquire the disease themselves.

Although the Choosing Wisely® campaign has begun to change the discussion about how we can improve the practice of medicine to focus on what it truly necessary, there remain barriers to implementation and uptake [22]. The COVID-19 pandemic will likely have a long-lasting effect in medicine beyond just transforming healthcare through telemedicine. Today more than ever, administrators and practitioners will have to proactively lead the way with cost-saving evidence-based recommendations that will reduce patient harm and also allow us to emerge from this pandemic with a viable financial stance. We envision that a change in healthcare delivery from volume-based to value-based incentives will refocus the aims of our healthcare system. As we continue to embrace the

Choosing Wisely® campaign, we need to implement strategies to document and measure the influence of our value-based recommendations on physician practices, patient care, and healthcare costs.

Compliance with Ethical Standards

Conflict of Interest TH has no conflicts of interest. JM has the following disclosures. Consulting: Pharmacyclics, Bayer, Gilead/Kite Pharma, Pfizer, Janssen, Juno/Celgene, BMS, Kyowa, Alexion, Beigene, Fosunkite, Innovent, Seattle Genetics, and Beigene. Research funding: Kite Pharma, Celgene, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, and Millennium. Honoraria: Kyowa and Seattle Genetics. Speaker's bureau: Gilead/Kite Pharma, Kyowa, Bayer, Pharmacyclics/Janssen, Seattle Genetics, Acrotech, Beigene, Verastem, AstraZeneca, Celgene, and Genentech/Abbvie.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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