Original Research Article

Reflex test reminders in required cancer synoptic templates decrease order entry error: An analysis of mismatch repair immunohistochemical orders to screen for Lynch syndrome

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Abstract

Background: Endometrial carcinoma (EC) is the most common extracolonic malignant neoplasm associated with Lynch syndrome (LS). LS is caused by autosomal dominant germline mutations in DNA mismatch repair (MMR) genes. Screening for LS in EC is often evaluated by loss of immunohistochemical (IHC) expression of DNA MMR enzymes MLH1, MSH2, MSH6, and PMS2 (MMR IHC). In July 2013, our clinicians asked that we screen all EC in patients ≤60 for loss of MMR IHC expression. Despite this policy, several cases were not screened or screening was delayed. We implemented an informatics-based approach to ensure that all women who met criteria would have timely screening. Subjects and Methods: Reports are created in PowerPath (Sunquest Information Systems, Tucson, AZ) with custom synoptic templates. We implemented an algorithm on March 6, 2014 requiring pathologists to address MMR IHC in patients ≤60 with EC before sign out (S/O). Pathologists must answer these questions: is patient ≤60 (yes/no), if yes, follow-up questions (IHC done previously, ordered with addendum to follow, results included in report, N/A, or not ordered), if not ordered, one must explain. We analyzed cases from July 18, 2013 to August 31, 2016 preimplementation (PreImp) and postimplementation (PostImp) that met criteria. Data analysis was performed using the standard data package included with GraphPad Prism® 7.00 (GraphPad Software, Inc., La Jolla, CA, USA). Results: There were 147 patients who met criteria (29 PreImp and 118 PostImp). IHC was ordered in a more complete and timely fashion PostImp than PreImp. PreImp, 4/29 (13.8%) cases did not get any IHC, but PostImp, only 4/118 (3.39%) were missed (P = 0.0448). Of cases with IHC ordered, 60.0% (15/25) were ordered before or at S/O PreImp versus 91.2% (104/114) PostImp (P = 0.0004). Relative to day of S/O, the mean days of order delay were longer and more variable PreImp versus PostImp (12.9 ± 40.7 vs. -0.660 ± 1.15; P = 0.0227), with the average being before S/O PostImp. Conclusion: This algorithm ensures MMR IHC ordering in women ≤60 with EC and can be applied to similar scenarios. Ancillary tests for management are increasing, especially genetic and molecular-based.

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INTRODUCTION

Endometrial carcinoma (EC) is the most common extracolonic malignant neoplasm associated with Lynch syndrome (LS),[1] which is caused by autosomal dominant germline mutations in DNA mismatch repair (MMR) genes.[2,3] Screening for LS in EC is often evaluated by loss of immunohistochemical (IHC) expression of DNA MMR enzymes MLH1, MSH2, MSH6, and PMS2 (MMR IHC).[4-6] The lifetime risk of developing EC in patients with LS is upward of 60%.[1,7] While the American Society of Clinical Oncology recommends assessment for LS in all newly diagnosed colorectal carcinomas,[8] controversy remains about universal testing for patients with EC.[9] In July 2013, our gynecological oncologists (GO) asked that we take a modified approach by screening all EC in patients ≤60 years old. Ideally, these results are available at the time of weekly GO conference (interdepartmental “tumor board”) for optimal patient management (counseling and/or referral to medical genetics). Despite agreement and implementation of this policy in pathology, several cases were not screened or screening was delayed. This led to clinician frustration and GO dissatisfaction with pathology reports, delayed turnaround time (TAT) of results, increased work to the pathology trainees and faculty in the form of addendum reports, cost to the departments and hospital, and overall poorer quality patient care. Here, we analyze the extent to which reflex test reminders in our required cancer synoptic templates ensure all women who meet criteria have timely screening.

SUBJECTS AND METHODS

Our pathology diagnostic reports are created in the PowerPath (Sunquest Information Systems, Tucson, AZ) laboratory information system (LIS) with custom synoptic templates required for cancer reporting. From March 6, 2014, we implemented a reflexive test order algorithm requiring pathologists to address MMR IHC in patients ≤60 years old with EC. Previously, from July 2013 to March 6, 2014, the responsibility of ordering MMR IHC in this patient population was left completely to the pathologist or trainee, without informatics-based intervention. Now (postimplementation [PostImp] of the algorithm), before finalizing a report in which an EC synoptic template has been entered, pathologists must answer a series of required prompts with “checkbox” selectable options [Figure 1a]. These prompts begin with: Is the patient ≤60 years old (yes/no)? If “no” is selected, the synoptic template continues without further mention of MMR IHC testing. If “yes” is selected, follow-up options related to ordering MMR IHC ensue [Figure 1b]. The aforementioned prompts are “hard stops” and if left unanswered, the report cannot be finalized (i.e., signed out [S/O]). We analyzed cases from July 18, 2013 (first applicable case after start of request from GO) to August 31, 2016 (end date of study) preimplementation (PreImp) and PostImp of the algorithm (go-live template change date March 6, 2014) that met criteria (women with EC ≤60 years old). Data methods. The burden of managing orders and results remains with the pathologist and relying on human intervention alone is ineffective. Ordering IHC before or at S/O prevents oversight and the additional work of retrospective ordering and reporting.

Key words: Algorithm, endometrial carcinoma, hard stop, Lynch syndrome, mismatch repair enzymes, order entry error, synoptic templates
that included worksheet responses and IHC ordering information were extracted from PowerPath for all cases in which an EC synoptic template was chosen during this period. Data analysis was performed using GraphPad Prism® 7.00 (GraphPad Software, Inc., La Jolla, CA, USA).

RESULTS

For the 147 patients who met study criteria (29 PreImp and 118 PostImp), we analyzed the frequency with which MMR IHC was ordered and the timeliness of ordering [Table 1]. PreImp, 4/29 (13.8%) cases never had MMR IHC ordered, whereas PostImp, only 4/118 (3.39%) cases failed to have IHC ordered (P = 0.0448) [Figure 2a]. Moreover, the content of the reports suggested different reasons for failure to order IHC. PreImp, none of the reports had an indication that IHC would be ordered (suggesting failure to remember to place the order) while PostImp, all 4 reports indicated that IHC would be performed (suggesting failure to follow through on intended ordering).

Timeliness of ordering was assessed by the fraction of cases with IHC ordered at or before S/O and by the average delay for ordering relative to the day of S/O. Of PreImp cases with MMR IHC ordered, only 15/25 (60.0%) orders were placed before or at S/O versus 104/114 (91.2%) orders for PostImp cases (P = 0.0004) [Figure 2b]. Before the synoptic worksheet change, IHC orders were often delayed by weeks to months so that the average delay for all PreImp cases was 12.9 ± 40.7 days, with marked variability [Table 1 and Figure 3]. In contrast, after the change, only 1/114 (0.88%) of cases had IHC ordered more than 1 day after S/O. On average, IHC orders for PostImp cases were 0.660 ± 1.15 days before S/O (P = 0.023). Collectively, these results indicate that completeness and timeliness of ordering improved markedly following the worksheet change.

DISCUSSION

Reflex testing algorithms that pathologists are expected to execute on cancer specimens are increasing in number and complexity. For example, a study conducted by the United Health (2012) estimates the average annual spending

![Figure 2](image-url)  
*Figure 2: (a) Cases with mismatch repair immunohistochemistry ordered or not ordered preimplementation versus postimplementation of algorithm. Preimplementation, 4/29 (13.8%) cases did not get any mismatch repair immunohistochemistry, but postimplementation, only 4/118 (3.39%) cases were missed (P = 0.0448). (b) Cases with mismatch repair immunohistochemistry ordered relative to sign out (day 0) preimplementation versus postimplementation of algorithm. Of cases with mismatch repair immunohistochemistry ordered, 15/25 (60.0%) were ordered before or at sign out preimplementation versus 104/114 (91.2%) postimplementation (P = 0.0004)*

![Figure 3](image-url)  
*Figure 3: Days before (negative), at (zero), or after (positive) sign out mismatch repair immunohistochemistry was ordered preimplementation versus postimplementation of algorithm. Relative to day of sign out, the mean days of order delay were longer preimplementation versus postimplementation (12.9 ± 40.7 versus -0.660 ± 1.15; P = 0.0227), with the average being before sign out postimplementation. No cases postimplementation were ordered more than 5 days post sign out (dashed lined) indicating results will be available during a 7-day post sign out window while cared for by gynecological oncologists. Preimplementation, 5 cases were ordered more than 5 days post sign out, which included 8, 34, 36, 57, and 195 days*

| Date range (Template change 3/6/14) | Total cases (N) | Cases (n) | IHC ordered (%) | IHC not ordered (%) | Avg days IHC ordered after S/O |
|------------------------------------|----------------|-----------|-----------------|---------------------|-----------------------------|
|                                    |                | Before or at S/O |                  | After S/O          | Mean SD SEM 95% CI          |
| 7/18/13 ≤ PreImp < 3/6/14          | 29             | 15 (51.7 of n; 60.0 of ordered) | 10 (34.5 of n; 40.0 of ordered) | 4 (13.8 of n) | 12.9 40.7 8.13 −3.86-29.7 |
| 3/6/14 ≤ PostImp ≤ 8/31/16         | 118            | 104 (88.1 of n; 91.2 of ordered) | 10 (8.47 of n; 8.77 of ordered) | 4 (3.39 of n) | −0.660 1.15 0.112 −0.883-0.438 |

Table 1: Data preimplementation versus postimplementation of algorithm with included descriptive statistics
per member on molecular and genetic tests increased by about 14% between 2008 and 2010 across their healthcare plans, primarily due to increased utilization. Moreover, test algorithms are often conditional, meaning that the testing should only be performed on populations defined by multiple factors, such as tumor type, age, and other factors. This presents a substantial burden for pathologists to remember testing criteria and to order appropriate testing. Relying on memory and human processes alone to ensure timely and efficient ordering (preanalytical) and reporting (postanalytical) of ancillary tests in specific patient populations is error-prone, with most errors occurring in the pre- and post-analytical phase. One large study conducted by Valenstein and Meier on behalf of the College of American Pathologists (CAP) across 660 institutions revealed approximately 5% of outpatient test requisitions had associated computer entry order (preanalytical) errors. They identified four institutional factors most associated with increased error rates which included: Orders verbally communicated to the laboratory, no requirement to compare tests requested versus tests ordered/entered into computer, failure to monitor the accuracy of order entry on a regular basis, and higher percentage of occupied beds (i.e., busier hospital).

Our current study shows that a simple intervention of adding obligatory reminders to an existing routine process (synoptic worksheets) results in dramatic improvements in the completeness and timeliness of test ordering. Yet, there are still imperfections, represented by the 4 cases PostImp where IHC was never ordered despite assertions in the report that the testing would be done. These cases likely represent miscommunication between the attending pathologist and trainee with regard to responsibility for MMR IHC ordering or a failure to save the initiated order in the LIS at S/O. The root cause associated with this error involves all four of the CAP identified categories discussed above. (1) Attending asking trainee to order MMR IHC (verbal order). (2) No follow-up after S/O to ensure MMR IHC was ordered, saved, and reported (test requested versus test order/entered). (3) No routine review of MMR IHC in patients younger than or equal to 60 years old (failure to monitor order accuracy). (4) Working at a busy academic hospital (busy S/O service). We believe the continued reliance on voluntary human actions is responsible for the residual defects. Additional technological enhancements of the worksheets and integration with the LIS, such as automated ordering of tests based on responses in the synoptic worksheet would likely make the IHC ordering process even more robust.

Users of prepackaged LIS software are generally limited by the capabilities of their LIS unless they have access to custom programming resources and the rights to make modifications. However, flexible and extensible synoptic reporting tools are available to most pathology groups, either through built-in capabilities of their LIS or through third party add-ons. Once a flexible synoptic reporting tool is available, it is trivial to implement internal prompts and obtain the workflow benefits such as we have described. Certainly, approaches like these are needed to successfully navigate the ever-changing landscape of ancillary test ordering. It is also a clear example of why synoptic cancer checklists need to be flexible to allow for additional content to meet the local or evolving needs of practicing pathologists.

The outcome we experienced of IHC testing being ordered before or at S/O 91% of the time PostImp had salubrious benefits for overall patient management. With a TAT for MMR IHC of 48 h, MMR IHC results are either pending or available at weekly GO conference and are generally in the medical record before discharge. At our institution which serves as the major referral center for the majority of the Pacific Northwest (Washington, Wyoming, Alaska, Montana, Idaho), the ability to refer patients to medical genetics before a flight home saves cost and simplifies follow-up care logistics. If one considers a 7-day period post-S/O reasonable to follow-up ancillary study results and patient management (consultation and/or referral), all our GO patients with IHC ordered PostImp had results available in this window. Finally, because of the improved completeness of ordering, improved efficiency of reporting, and less additional work of retrospective ordering and reporting, our GO clinicians have voiced increased satisfaction PostImp, an important qualitative improvement.

CONCLUSION

Laboratory test order entry errors delay diagnostic reports, consume resources, and cause clinician inconvenience and dissatisfaction. Modifying worksheets to include algorithmic reminders improves MMR IHC ordering in women ≤60 years old with EC and can be easily applied to similar scenarios in both large academic and small private practices. These types of novel approaches are required to manage the increased burden of ancillary testing as relying on voluntary action alone is insufficient. Pathologists and laboratory professionals must continue to be creative to ensure appropriate clinical testing in a timely manner. Our study emphasizes the power of placing reflex order instructions in required synoptic templates and the potential for greater effectiveness for using worksheet choices to automate reflex orders.

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Conflicts of Interest
There are no conflicts of interest.
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