Diagnostically Efficient and Cost Effective Test Utilization for Hematologic Malignancies from Blood and Bone Marrow Specimens

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Disclosure

• Nothing to disclose
• No relevant financial interests
Considerations for Utilization Program Design and Implementation

• Is there an opportunity to optimize testing?
• What type of intervention is appropriate for the utilization problem that you are trying to solve?
• What are the processes that have to be modified to support the intervention?
• Have you identified all the stakeholders and engaged them in the planning and execution of the intervention?
• Have you collected data (literature and practice) to justify the intervention and ensure good medical practice?
• Do you have a strategy to gather pre- and post-intervention data to insure effectiveness of the intervention?
• Do you have strategies for audits to monitor compliance and for post-intervention review to re-adjust utilization program for practical reasons or for advances in medicine?
Is there an opportunity to optimize ancillary test utilization on bone marrow specimens obtained to assess the patient for the presence of hematologic malignancies?
“Last Week” At Mayo Clinic…

- JAK2 on both PB and BM specimens
- JAK2 exon 12 sequencing on PB in a patient with thrombocytosis (but no V617F mutation testing ordered)
- MDS FISH in a lymphoma staging bone marrow-no prior treatment
- T-cell lymphoma FISH studies in a cytopenia patient
- B-cell lymphoma FISH in a rule out MDS case
- BCR GR in PB but no flow ordered
- TCR GR in BM without flow studies
- PB flow studies in a patient with Hodgkin lymphoma
- Cytogenetic and FISH studies for the 3rd time in a follow-up MGUS patient not treated with drugs that produce Rx related MDS
- PML-RARA QRTPCR studies on PB in a patient with cytopenia (no hx of APL)
- C-MPL Exon 10 sequencing, JAK-2 V617F PCR, JAK-2 Exon 12 sequencing, KIT D816V PCR, MDS FISH on PB in a patient with neutrophilia
- Flow cytometry, cytogenetics, lymphoma FISH and PCR for Ig gene rearrangements on a morphologically positive FL staging bone marrow
Hematopathology Strategy

- Target frequently ordered, high cost, high complexity tests on bone marrow specimens for active utilization management (generalizable to any complex test)
  - Flow cytometry
  - Cytogenetics
  - FISH
  - Molecular genetics
- Use hematopathologist as “gatekeeper” to insure appropriate testing
  - Hematopathologist responsible for ultimate sign out of case
  - Hematopathologist has disease and laboratory / test performance expertise
  - Validated approach based on test utilization literature
Move from philosophy of laboratory passively performing tests to laboratory personnel collaborating with clinician to solve diagnostic/prognostic problems
Process Modification

• Physician order process for bone marrow examinations that focuses on clinical problem; not test ordering
  • Modify bone marrow order screens to make it difficult to order individual tests and to make it easy to communicate the reason for referral

• Use a single bone marrow biopsy service to collect appropriate specimens for “all possible tests” and hold in centralized location—control the specimen(s)

• Hematopathologist reviews medical record and morphology of bone marrow aspirate smears and triages held bone marrow aspirate specimens to ancillary studies based on jointly developed test guidelines/algorithms
Collaborative Process for Optimizing Test Utilization

1. Patient Evaluated
2. Differential Diagnosis Generated
3. Tests Ordered
4. Bone Marrow Biopsy
5. Specimens Await Triage
6. Morphology Review
7. Differential Diagnosis Developed
8. Guideline Consulted Test Order Refined
How do you develop test guidelines/algorithms?
Collaboration with Stakeholders

• Between laboratory divisions:
  • Laboratory Genetics
  • Hematopathology
  • Anatomic Pathology

• With clinicians
  • Expertise
  • Experience
  • Endorsement
Method For Test Guideline/Algorithm Development*

Identify opportunities
Review practice data
Review literature
Derive recommendations
Achieve consensus
Final guidelines approved
Design process
Implement
Audit
Adjust algorithms

*Method used for each disease/clinical problem
Example 1:
Development of Ancillary Test Ordering Strategy for Bone Marrow Involvement By Lymphoma in Staging Specimens
Bone marrow evaluation for lymphoma staging

• Malignant lymphoma
  • Cancer of immune system cells (lymphocytes)
  • Many types—complex classification based on morphology, phenotype and genetics
  • Diagnosed and classified on biopsies of lymph nodes, other non-nodal sites

• Bone marrow evaluation
  • Determine extent of disease (Stage/IPI)
  • Typical work up: morphology, flow cytometry, cytogenetics + FISH
  • Minimal data about utility of flow cytometry. No data about the utility of cytogenetics/FISH testing in this context.
Bone Marrow Evaluation for Lymphoma Staging—Gather Practice Data

- The traditional standard for assessing staging bone marrows for the presence of lymphoma is morphology.

- Do flow cytometry, conventional cytogenetics, FISH and/or molecular genetics add sensitivity or specificity for lymphoma detection in staging bone marrows?

- Method generalizable to address the question:
  - The traditional standard for the diagnosis of disease X is simple and low cost test A
  - Do complex/expensive/new tests B, C, D, etc. add clinically relevant diagnostic sensitivity or specificity for diagnosing disease X over and above test A?
Conclusions Following Data Review

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Intervention</th>
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<tbody>
<tr>
<td><strong>Flow cytometry</strong>*</td>
<td>Cancel/do not perform routine flow cytometry</td>
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<tr>
<td>does not add sensitivity or</td>
<td></td>
</tr>
<tr>
<td>specificity over morphology</td>
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<td>*Inappropriate as screening</td>
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<tr>
<td>and pathology review</td>
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*Inappropriate as screening modalities; use only to solve pathology problems posed by clinical history and pathology review
Example 2:
Development of an Algorithm for Optimal Testing for Myeloproliferative Neoplasms
Principles for Algorithm Development

• Algorithms…
  • are useful to resolve differential diagnoses that involve clinically or pathologically similar, but distinct diseases
  • rely on sequential application of a series of tests the results of which progressively converge on a single diagnosis
• Start by clearly defining the entities that must be distinguished from one another
• Know their diagnostic criteria
• Know the diagnostic sensitivity and specificity of the tests that support the diagnoses
• Sequence the tests by…
  • The frequency of the diseases in the ddx
  • The diagnostic sensitivity and specificity of the tests
Myeloproliferative Neoplasm: A Diagnostic Approach to Bone Marrow Evaluation

Clinical suspicion of myeloproliferative neoplasm

Bone marrow testing begins with:
- 70016 / Hematopathology Consultation, Wet Tissue
- BM / Chromosome Analysis, Hematologic Disorders, Bone Marrow
- JAK2M / JAK2 V617F Mutation Detection, Bone marrow
- BADX / BCR/ABL, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Qualitative, Diagnostic Assay
- OR MDCR / BCR/ABL, Translocation 9:22, FISH (D-FISH)

Negative for BCR/ABL

Bone marrow morphology: MPN?

NO

Erythrocytosis?

YES

Negative for JAK2 V617F Mutation

Complete blood count (CBC)
EPO / Erythropoietin (EPO), Serum

REVP / Erythrocytosis Evaluation

PV possible

JAKXX / JAK2 Exon 12 and Other Non-V617F Mutation Detection, Bone Marrow

POSITIVE

NEGATIVE

PV

NO

EQUIVOCAL

Positive or Equivocal for JAK2 V617F Mutation

Complete blood count (CBC)
Clinical findings
Bone marrow features
EPO / Erythropoietin (EPO), Serum
CALR / CALR Mutation Analysis, Myeloproliferative Neoplasm (MPN)

POSITIVE

NEGATIVE

MPLM / MPL Exon 10 Mutation Detection, Bone Marrow

POSITIVE

NEGATIVE

ET
PMF
MPN, not otherwise specified (ET or PMF)

LEGEND

PV: Polycythemia vera
ET: Essential thrombocythemia
PMF: Primary myelofibrosis
MPN: Myeloproliferative neoplasm

05/2014
Progress

• Complete
  • Lymphoma staging bone marrows
  • Chronic lymphocytic leukemia diagnosis, prognosis and follow up
  • Chronic myeloid leukemia diagnosis and follow up
  • Evaluation of myeloproliferative neoplasms
  • Evaluation and diagnosis of eosinophilia/mast cell disorders
  • Evaluation of myelodysplastic syndromes
  • Acute myeloid leukemia
  • Acute promyelocytic leukemia diagnosis and follow up

• In progress
  • Reassessment of plasma cell algorithms
  • Acute lymphoblastic leukemia diagnosis and follow up
Time to Audit
Algorithm and Guideline Impact on Test Ordering in Hematopathology: 2013

<table>
<thead>
<tr>
<th>Assay</th>
<th># tests canceled</th>
<th>Cost Savings (via EXACT)</th>
<th>Assay</th>
<th># tests canceled</th>
<th>Cost Savings (via EXACT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomes</td>
<td>595</td>
<td>286427.05</td>
<td>Imatinib FISH</td>
<td>13</td>
<td>8192.34</td>
</tr>
<tr>
<td>BCR-ABL FISH</td>
<td>65</td>
<td>18056.35</td>
<td>CHIC2 FISH</td>
<td>1</td>
<td>313.49</td>
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<tr>
<td>PCPD FISH</td>
<td>331</td>
<td>174284.74</td>
<td>B-GR*</td>
<td>8</td>
<td>5649.33</td>
</tr>
<tr>
<td>CLL FISH</td>
<td>9</td>
<td>6176.43</td>
<td>T-GR*</td>
<td>35</td>
<td>24713.89</td>
</tr>
<tr>
<td>B-lymphoma FISH</td>
<td>12</td>
<td>8235.24</td>
<td>JAK2 V617F*</td>
<td>98</td>
<td>49784.00</td>
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<tr>
<td>T-lymphoma FISH</td>
<td>23</td>
<td>15784.21</td>
<td>JAK2 exon 12*</td>
<td>32</td>
<td>11744.00</td>
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<tr>
<td>MDS FISH</td>
<td>65</td>
<td>41601.30</td>
<td>MPL exon 10*</td>
<td>8</td>
<td>3920.00</td>
</tr>
<tr>
<td>AML FISH</td>
<td>50</td>
<td>54439.50</td>
<td>KIT*</td>
<td>26</td>
<td>17810.00</td>
</tr>
<tr>
<td>ALL FISH</td>
<td>19</td>
<td>13101.64</td>
<td>CSF Flow studies*</td>
<td>254</td>
<td>82296.00</td>
</tr>
</tbody>
</table>

2013 summary: 1462 tests canceled; cost savings = $822,529.51

* EXACT Cost data not available; costs based on previous WLR estimates
## Chromosome Analysis – Utilization Review

<table>
<thead>
<tr>
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<th>Original</th>
<th>Post-Utilization Implementation</th>
</tr>
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<tbody>
<tr>
<td>% of total BMs</td>
<td>Abnormalities per 100 BM</td>
<td>% of total BMs</td>
</tr>
<tr>
<td><strong>Mayo Rochester</strong></td>
<td>51%</td>
<td>20</td>
</tr>
<tr>
<td><strong>Hospital C</strong></td>
<td>95%</td>
<td>21</td>
</tr>
</tbody>
</table>

$600,000 annual cost savings
Optum Labs – What is it?

- A research alliance between Optum (a subsidiary of UnitedHealth Group), a technology and health services business, and Mayo.
- Optum brings analytical tools and data on nearly 100 million UnitedHealth Group patients, including claims, laboratory values and demographic information.
- Mayo Clinic brings clinical data on more than 3 million patients and patient-focused research expertise.
- Launched in January 2013.
- Optum Labs was created to facilitate combining information and ideas to improve the delivery and quality of care. It’s the largest data-combining effort of its type.
- All data is kept in a secure environment and, in accordance with HIPAA regulations, no personally identifiable information is being shared.
If generalized to the national practice what impact would implementation of Mayo guidelines/algorithms have?

- Bone Marrow Project: Assessment of flow cytometry and chromosome test order patterns following bone marrow biopsy and/or aspiration
- Use Optum labs “national” data to estimate frequency and cost of flow cytometry and cytogenetic testing on bone marrow samples
- Compare to frequency and cost of flow cytometry and cytogenetics testing using implemented Mayo guidelines and algorithms
If generalized to the national practice what impact would implementation of Mayo guidelines/algorithms have?

Preliminary Results:

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Test Pathway</th>
<th>Impact of Guideline</th>
<th>Cost Savings Per Case</th>
<th>$ Impact per 100,000 lives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who underwent bone marrow biopsy</td>
<td>Flow cytometry and cytogenetics</td>
<td>Reduction in cost of testing per case</td>
<td>$1214.00</td>
<td>$267,162.00</td>
</tr>
</tbody>
</table>

UnitedHealth insures 30 million “lives” translates to $80 million savings across the insured population ($0.22 PMPM)
Conclusions

• You can easily find opportunities for optimizing test utilization by reviewing your practice.

• Think like a clinician—understand the clinical problem and how testing supports the practice.

• Orient your utilization management strategy around the clinical problem.

• Learn test performance data (analytical sensitivity, diagnostic sensitivity/specificity) in the context in which the test is used.

• Mine data from your practice to determine test performance and utilization patterns.
Conclusions

• Use a utilization management intervention that matches the problem you are trying to solve
  • Hard stop cancel of unnecessary tests that do not add diagnostic/prognostic value (lymphoma staging example)
  • Use algorithms to resolve differential diagnostic problem (myeloproliferative neoplasm example)

• Collaborate across laboratories Clinical problem solving requires coordination between laboratories—communicate, develop/share common processes for common problems, support each other

• Communication/true collaboration with clinician groups
  • Involve clinicians in developing guidelines/algorithms
  • Set laboratory utilization expectations
  • Audit, communicate, educate, modify as practice changes
Conclusions

• The outcomes of a successful test utilization strategy include:
  • More efficient and effective patient care
  • Cost savings to laboratory/institution

• If generally applied across an insured population test utilization management can potentially result in very large positive financial consequences for payers

• Don’t expect perfection or 100% applicability
  • Biology doesn’t work this way
  • Neither does human behavior

• You will learn a lot of medicine!!!
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Questions?
Discussion