A DYNAMIC MACHINE-LEARNING BASED PREDICTION MODEL FOR SEPSIS

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Conflict of Interest

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Nasim (Zahra) Eftekhari, MSc

Have no real or apparent conflicts of interest to report
Learning Objectives

- Explain how evidence-based practice impacts technology design
- Apply a nursing evidence-based practice model to an informatics project
- Describe how to perform an evidence synthesis
- Define artificial intelligence and machine learning
- Describe how machine learning can help with clinical decision support
- Explain the methodology and design of a machine learning sepsis prediction model
About City of Hope

1. Founded in 1913
2. Comprehensive Cancer Center since 1998
3. 217 licensed beds; 40 cottages; 15 community sites
4. 2017 Visits: Inpt – 6,723; Total – 212,405
5. 224 active med staff; 1,170 RNs
6. Cancer volume statistics
   • No. 4 in California
   • No. 2 in Primary Service Area
About City of Hope

1. Over 500 clinical trials with more than 6,200 enrolled patients annually
2. Performed over 14,000 hematopoietic stem cell transplants (HSCTs)
3. Developed synthetic human insulin
4. Created the process used to make 4 top-selling cancer medications (Avastin, Rituxan, Erbitux, and Herceptin)
1-year Survival for Allogeneic HSCTs

1. One of the best post-HSCT survival rates

2. Only organization that has performed above prediction for 13 consecutive reporting years (2005-17)

<table>
<thead>
<tr>
<th>Center Code</th>
<th>Center Name</th>
<th>n</th>
<th>Survival</th>
<th>Predicted</th>
<th>95 Conf. Int.</th>
<th>Performance by report year</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>University of Nebraska Medical Center</td>
<td>174</td>
<td>70.1</td>
<td>72.6</td>
<td>66.4 - 79.0</td>
<td>0 0 0 0 0 0 0 0 0</td>
<td></td>
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<tr>
<td>73</td>
<td>Children's Hospital of Los Angeles</td>
<td>74</td>
<td>85.1</td>
<td>83.3</td>
<td>74.8 - 91.6</td>
<td>0 0 0 0 -1 -1 0 0 0</td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>VA Puget Sound Healthcare System</td>
<td>28</td>
<td>53.6</td>
<td>63.5</td>
<td>46.2 - 79.7</td>
<td>0 0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>Dana Farber Cancer Institute at Brigham and Women's Hospital - Adults</td>
<td>734</td>
<td>71.3</td>
<td>68.1</td>
<td>65.0 - 71.5</td>
<td>1 1 1 0 0 0 1 1 1 0</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>University of California - San Francisco - Pediatrics</td>
<td>98</td>
<td>87.7</td>
<td>81.1</td>
<td>73.7 - 88.4</td>
<td>0 0 0 1 1 0 0 0 0 0</td>
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<tr>
<td>77</td>
<td>Vanderbilt University</td>
<td>319</td>
<td>79.0</td>
<td>68.1</td>
<td>63.3 - 73.0</td>
<td>0 0 0 0 0 1 1 1 1 1</td>
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<tr>
<td><strong>78</strong></td>
<td>City of Hope National Medical Center</td>
<td>808</td>
<td>77.1</td>
<td>68.7</td>
<td>65.8 - 71.9</td>
<td>1 1 1 1 1 1 1 1 1 1</td>
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<tr>
<td>79</td>
<td>Cincinnati Children's Hospital Medical Center</td>
<td>201</td>
<td>83.0</td>
<td>81.7</td>
<td>76.5 - 86.7</td>
<td>0 0 0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>H Lee Moffitt Cancer Center</td>
<td>568</td>
<td>70.4</td>
<td>67.4</td>
<td>63.8 - 71.3</td>
<td>0 0 0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>81</td>
<td>MD Anderson Cancer Center</td>
<td>1061</td>
<td>63.2</td>
<td>63.9</td>
<td>61.4 - 66.9</td>
<td>0 1 1 0 0 0 0 -1 -1 -1</td>
<td></td>
</tr>
</tbody>
</table>

*Compiled by: Joycelynne M. Palmer, PhD*

Prepared by: Joycelynne M. Palmer, PhD
Hem/HCT Section, Division of Biostatistics
v2018.01.18
Evidence Based Practice

Asking is the Answer.
Evidence-based practice

What is evidence-based practice (EBP)?
Iowa Model

1. Identify issues/opportunities
2. State the question
3. Form a team
4. Research
5. Design and Pilot
6. Systemic integration
7. Disseminate results
Issues & Opportunities

Issues

1. Risk
2. Occurrence
3. Mortality

Opportunities

1. Population specific algorithm
2. Lead time
3. Early treatment

“My team has created a very innovative solution, but we’re still looking for a problem to go with it.”
Literature Review

Google Scholar

1. Publication year: After 2017
2. Systematic review
   – Key term: sepsis machine learning systematic

PubMed

1. Publication year: 2013 – 2018
2. Randomized Controlled Trials and Cohort Studies
   – Key terms: machine learning sepsis & sepsis prediction
Evidence Appraisal Tool

### JHNEBP Evidence Rating Scale

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Experimental study/randomized controlled trial (RCT) or meta analysis of RCT</td>
</tr>
<tr>
<td>II</td>
<td>Quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Non-experimental study, qualitative study, or meta-synthesis.</td>
</tr>
<tr>
<td>IV</td>
<td>Opinion of nationally recognized experts based on research evidence or expert consensus panel (systematic review, clinical practice guidelines)</td>
</tr>
<tr>
<td>V</td>
<td>Opinion of individual expert based on non-research evidence. (Includes case studies; literature review; organizational experience e.g., quality improvement and financial data; clinical expertise, or personal experience)</td>
</tr>
</tbody>
</table>

### Quality of the Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Research</th>
<th>Summative Reviews</th>
<th>Organizational</th>
<th>Expert Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>consistent results with sufficient sample size, adequate control, and definitive conclusions; consistent recommendations based on extensive literature review that includes thoughtful reference to scientific evidence.</td>
<td>well-defined, reproducible search strategies; consistent results with sufficient numbers of well defined studies; criteria-based evaluation of overall scientific strength and quality of included studies; definitive conclusions.</td>
<td>well-defined methods using a rigorous approach; consistent results with sufficient sample size; use of reliable and valid measures.</td>
</tr>
<tr>
<td>B</td>
<td>Good</td>
<td>reasonably consistent results, sufficient sample size, some control, with fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence.</td>
<td>reasonably thorough and appropriate search; reasonably consistent results with sufficient numbers of well defined studies; evaluation of strengths and limitations of included studies; fairly definitive conclusions.</td>
<td>Well-defined methods; reasonably consistent results with sufficient numbers; use of reliable and valid measures; reasonably consistent recommendations.</td>
</tr>
<tr>
<td>C</td>
<td>Low quality or major flaws</td>
<td>little evidence with inconsistent results, insufficient sample size, conclusions cannot be drawn.</td>
<td>undefined, poorly defined, or limited search strategies; insufficient evidence with inconsistent results; conclusions cannot be drawn.</td>
<td>Undefined, or poorly defined methods; insufficient sample size; inconsistent results; undefined, poorly defined or measures that lack adequate reliability or validity.</td>
</tr>
</tbody>
</table>

*A study rated an A would be of high quality, whereas a study rated a C would have major flaws that raise serious questions about the believability of the findings and should be automatically eliminated from consideration.*

Evidence Synthesis – Commonalities

1. Retrospective analysis
2. Publically available data sets
3. Population
4. 1-hr carry forward computation
5. Supervised learning
6. Lead time
7. EBP comparison
8. Institutional Review Board\textsuperscript{7}
Evidence Synthesis - Gaps in Evidence

1. ICD-9/10
2. Generalizability
3. 1-hour carry forward computation
4. Censoring effect
5. Prospective validation
6. Lead time
7. Treatment recommendations
## Feature Identification

<table>
<thead>
<tr>
<th>Domain</th>
<th>Feature</th>
<th>Reference</th>
<th>HSCT Complication</th>
<th>HSCT Comp Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant Type</td>
<td>Autologous</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant Type</td>
<td>Allogeneic</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>AMS</td>
<td>6, 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditioning</td>
<td>Conditioning Intensity</td>
<td>Dr. Nakamura/Dadwal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>WBC &gt; 12,000 cells/mm³</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>WBC &lt; 4,000 cells/mm³</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>PaO₂/FiO₂ &lt; 300 mmHg</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>PaO₂/FiO₂ &lt; 250 mmHg in the absence of pneumonia as infection source</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>INR &gt; 1.5 or aPTT &gt; 60 secs</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Platelets &lt; 100,000/µL</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Creatinine &gt; 0.5mg/dL</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Creatinine &gt; 2mg/dL</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Hyperglycemia</td>
<td>1, 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Lactate &gt; 1 mmol/L</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Lactate &gt; 4 mmol/L</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>Temp &gt; 38.3 degrees Celsius</td>
<td>10</td>
<td>Engraftment Syndrome</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neutropenic Fever</td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>Temp &lt; 36 degrees Celsius</td>
<td>6, 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>&gt; 20 breaths/min</td>
<td>2, 10</td>
<td>SCVS</td>
<td>6</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>&gt; 90 beats/min or more than 2 SD above normal value for age</td>
<td>10</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Nursing observation</td>
<td>AMS, restlessness, irritability, inappropriate euphoria</td>
<td>6</td>
<td>ICP, Hyperkalemia, Cardiac Tamponade</td>
<td>6</td>
</tr>
<tr>
<td>Nursing observation</td>
<td>Lethargy, confusion</td>
<td>6</td>
<td>Hypercalcemia, Hyperkalemia, TLS</td>
<td>6</td>
</tr>
<tr>
<td>Problems</td>
<td>Medical history (co-morbidities)</td>
<td>Dr. Nakamura/Dadwal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Model Inclusion

<table>
<thead>
<tr>
<th>676 HSCT Visits*</th>
</tr>
</thead>
<tbody>
<tr>
<td>91 Septic (13.5%)</td>
</tr>
<tr>
<td>431 Autologous (64%)</td>
</tr>
</tbody>
</table>

**Age range: (18-79) with median 57**

### Features

<table>
<thead>
<tr>
<th>Transplant and Disease Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>HCTCI</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

### Vital Signs

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2 Delivery</td>
<td>SPO2</td>
</tr>
<tr>
<td>Weight</td>
<td>Temperature</td>
</tr>
</tbody>
</table>

### Lab Values

<table>
<thead>
<tr>
<th>Calcium</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>WBC</td>
</tr>
<tr>
<td>Platelet</td>
<td>Lymphocyte</td>
</tr>
</tbody>
</table>

### Demographics

| Age | Gender | Race |

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* Date range Jan 1, 2015 – Dec 1, 2017
Proposed Solution – Machine Learning

**ARTIFICIAL INTELLIGENCE**
Artificial Intelligence captures the imagination of the world.

**MACHINE LEARNING**
Machine learning starts to gain traction.

- **1950s**
  - Turing Test Devised

- **1960s**
  - ELIZA (1964 - 1966)

- **1970s**
  - Edward Shortliffe writes MYCIN, an Expert or Rule based System, to classify blood disease

- **1980s**
  -

- **1990s**

- **2000s**

- **2010s**
  - AlphaGo defeats Go champion Lee Sedol (2016)

**DEEP LEARNING**
Deep learning catapults the industry.

Image Link
Healthcare is One of the Least Technologically Advanced Industries!
Artificial Intelligence in Healthcare, Yes or No?

"I'm a human being," Kasparov said at the time, "When I see something that is well beyond my understanding, I'm afraid.

"I LOST MY FIGHTING SPIRIT."
What is the Problem with AI?

1. Are we opening Pandora’s box?
2. Draw the line between AI hype and AI hope
3. “Narrow AI” in contrast to “general AI”
4. Don’t call AI by name, call it by what it does and does not do

*IT’S NOT ARTIFICIAL INTELLIGENCE*
Top 4 Machine Learning Use Cases for Healthcare

1. Imaging analytics and pathology
2. Natural language processing (NLP)
3. Cybersecurity
4. *Clinical Decision Support And Predictive Analytics*
How Does the Machine Learn about Sepsis?
Design

1. Ensemble of 4 Machine Learning Algorithms
2. Every hour after HSCT and as new data becomes available, a risk score generated by the algorithms
3. A final risk index is calculated based on the sum of all scores
4. If the risk index is higher than a certain threshold for 8 consecutive hours, the patient is flagged as high risk
Results – MEWS & MLA

1. MEWS AUC 0.68 (true positive 73% & false positive 49%)

2. MLA set a same true positive as MEWS had a false positive rate of 14%

AUC on the training set: 0.9

- True positive rate in training: 82%
- False positive rate in training: 22%

AUC on the validation set: 0.86

- True positive rate in validation: 78%
- False positive rate in validation: 20%
What’s Next?

1. Validation on real-time data
2. Dissemination of results
3. Interventional IRB
4. Notification process
5. Communication & training plan
Questions


