Translating Science to Health Care: the Use of Predictive Models in Decision Making

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Topics

• Clinical Predictive Models
• Predicting Risk
  – Acute Cardiac Ischemia
  – AMI Mortality
• Predicting Benefit from Therapy
  – Thrombolytic Therapy
  – tPA and Streptokinase
  – Time to Equipoise
• Other Models
The Netflix Prize

• Netflix offered a prize for an improved system to recommend future movie selection
  – Gave participants ratings on 18,000 movies by 500,000 customers
  – Use these to build a model to predict ratings of 3 million other ratings

• Pay $1 million to any system that would increase accuracy by 10%
  – Prize awarded 3 years later
Clinical Predictive Models

• A predictive model takes information about an individual and synthesizes it into a composite score
  – Frequently the models generate the probability of an event given patient characteristics
  – These models reduce data complexity
  – Can be used
    • to predict future events
    • to adjust for patient severity
Predictive Models

• To be useful, these tools need to
  – accurately categorize the risk of events for patients and
  – their use needs to positively impact treatment decisions and patient outcomes.
Changes in Medicine

• Technology has generated extensive information useful for clinical decision making (e.g. medical health records, tests, imaging results, etc.)
• Traditional studies have looked at average impact of treatment on the population – this ignores variability between individual subjects
• Predictive models can be used to generate patient-specific risk or benefit assessment
Acute Cardiac Ischemia (ACI)

http://www.reusableart.com
Acknowledgements

Work on these Acute Cardiac Predictive Models was done at the Center for Cardiovascular Health Services Research (CCHSR) at Tufts Medical Center

Harry P. Selker, MD, MSPH
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Cardiac Admissions (1984)

“Each year 1.5 million patients are admitted to coronary-care units (CCUs) for suspected acute ischemic heart disease; for half of these, the diagnosis is ultimately "ruled out."

“we sought to develop a diagnostic aid to help emergency room physicians reduce the number of their CCU admissions of patients without acute cardiac ischemia.”
“Original” ACI Predictive Model

- A logistic regression model was developed to predict Acute Cardiac Ischemia (ACI), n=2801
- Programmed into a hand-held calculator
- Evaluated impact in a multi-center prospective trial that included 2320 patients
  - CCU admissions of patients without ACI dropped from 44 to 33 per cent without any increase in missed diagnoses of ischemia
The ACI-TIPI (1991)

- The Acute Cardiac Ischemic Time Insensitive Predictive Model
  - Use information available at arrival at the ED to predict ACI
  - Designed for both real-time and retrospective use
ACI-TIPI: Clinical Input

- Patient's age
- Patient's gender
- The presence or absence of chest pain or pressure, or left arm pain
- Whether chest pain or equivalent symptom is the patient's most important presenting symptom
ACI-TIPI: ECG Data

- The presence or absence of pathological or significant Q waves
- The presence and degree of ST segment elevation or depression
- The presence and degree of T wave elevation or inversion

Images from the Philips ACI-TIPI Application Guide
Logistic Regression

\[ \ln(\text{odds}) = b_0 + b_1 X_1 + \ldots + b_k X_k \]

\[
\Pr(Y = 1) = \frac{1}{1 + e^{-b_0 - \sum_{i=1}^{k} b_i X_i}}
\]
Logistic Regression

\[
\ln(\text{odds}) = -3.933 + 1.231 \times \text{CPAIN} + 0.882 \times \text{SX1CP} \\
+ 0.712 \times \text{MALE} - 1.441 \times \text{AGE40} \\
+ 0.667 \times \text{AGE50} - 0.426 \times \text{MALE} \times \text{AGE50} \\
+ 0.616 \times \text{QWAVES} + 0.993 \times \text{STDEP} \\
+ 1.314 \times \text{STEL} + 1.127 \times \text{TWINV} \\
- 0.314 \times \text{TWINV} \times \text{STEL} + 1.095 \times \text{TWEL}
\]
Using the ACI-TIPI

• The ACI-TIPI has good predictive performance
  – (e.g. ROCC Area on test dataset of 0.88)
  – Very good calibration

Now “translating science to health”

• How to make the results easily used?
• Can the model impact on patient care?
Accessing the ACI-TIPI

- Earlier model could be programmed into a calculator to generate probability of ACI

\[
P(Y = 1| X) = \frac{1}{1 + e^{-(b_0 + \sum b_i x_i)}}
\]

- ACI-TIPI programmed directly into the electrocardiograph machine

http://www.hpmuseum.org
ACI-TIPI ECG

“Predictive instruments to aid in confident decision making for your patient and your environment, such as the Philips ACI-TIPI predictive instrument for acute cardiac ischemia and the Philips TPI for Thrombolysis” - http://www.healthcare.philips.com
Advantages of Using the ECG

• Does not require any substantial effort by physicians to use
• Is incorporated into standard practice routines
• Can utilize directly data from the ECG (and thus may be more specific than patient reported data)
② ACI-TIPI: RCT

- Impact of the use of the ACI-TIPI tested in a controlled clinical trial at 10 EDs
  - Predictions presented on alternating months
  - N=10,689 subjects
  - Showed a shift towards sending subjects without ACI less to CCU and more home at hospitals with relatively low capacity telemetry beds.
AMI Mortality

• Create a logistic regression model to predict acute mortality
  – Severity adjustor

• Developed on 4,099 subjects (from original predictive model dataset)
  ROCC area = 0.82

• Model Accuracy tested on 1,372 subjects
  ROCC area = 0.85
Predicted Models for Events

• These models
  – identify individuals, based on presenting characteristics, who are at higher or lower risk for medical events
  – may be used to assist in decision-making or for risk adjustment
Predicting Benefit: Thrombolytic Therapy (1997)
Patient-Specific Benefit

• Heterogeneity of Treatment Effects (HTE)
  – Frequently there is considerable variation in risk for clinical outcomes (even in RCTs)
  – Treatment risks and potential benefit may differ across patient subgroups

Thrombolytic Therapy

- Clinical trials have shown significant average benefit in mortality and myocardial salvage of early use of thrombolytic therapy (TT) if given early
- The use of TT carries some risk of thrombolytic stroke
Benefit of Thrombolytic Therapy

• Can we identify patients most likely to benefit from the use of TT?
  – High reduction in mortality
  – Lower risk of stroke

• Data gathered from 13 clinical trials and registries

• Divided into development (n=3263) and test (n=1648) datasets
Thrombolytic Predictions

- Regression models developed, to predict with and without thrombolytic therapy,
  1) 30 day mortality
  2) 1-year mortality
  3) Cardiac arrest
- Regression models to predict with the use of thrombolytic therapy
  4) Thrombolysis-related intracranial hemorrhage
  5) Major bleed
The TPI ECG

1223246
11/15/1995
57 years
Male

JOHN DOE

76 kg

Time since acute ischemic symptom:
Hx: Diabetes, Hypertension

BP: 156/88
2 Hrs (120 Min)

Rate: 60
PR: 130
QRSD: 94
QT: 351
Qtc: 351

TPI PREDICTED OUTCOMES:

Acute Anterior MI; ST >= 0.1mV in 4 of V1-4; Abnormal Qs in 4 Lead(s)

>> MD NOTE: Use predictions ONLY if MD-diagnosed acute MI with 0.1mV ST elev <<

THROMBOLYTIC PREDICTIVE INSTRUMENT (TPI)

30-Day Mortality
One-Year Mortality
Cardiac Arrest Probability Within 48 Hrs
Thrombolysis-Related Intracranial Hemorrhage
Thrombolysis-Related Other Major Bleed

--AXIS--
P: 51
QRS: -36
T: 57

MD NOTE: Consider above in context of patient contraindications to thrombolysis.

PRELIMINARY-MD MUST REVIEW
30 Day Mortality

- Patient age
- History of diabetes
- Heart rate
- Initial systolic blood pressure (by AMI location)
- ECG (size of infarct, Q-waves, RBBB, AMI location)
Interaction Terms

• Use of TT and time from symptom onset
  – As onset time increases the benefit of TT decreases

• Use of TT and time from onset to treatment (incorporates ECG earliness measure)
  – As time to treatment increases the benefit of TT lessens
TPI Clinical Trial

• Prospective trial of the impact of the use of the electrocardiograph-based TPI at 28 hospitals
  – 1237 randomized subjects analyzed
  – No overall impact, although a slight increase in the use of TT was seen in patients with inferior AMIs randomized to the ECG
THROMBOLYSIS PREDICTIVE INSTRUMENT


Assignees: Univ. of Washington New England Medical Center Hospitals, Inc., Seattle, Wash.; Duke University, Durham, N.C.

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U.S. Cl. ................. 128/606; 128/702
Field of Search ............ 128/695, 696, 702, 703, 128/704, 705

References Cited
U.S. PATENT DOCUMENTS
4,457,315 7/1984 Bennish .................. 128/704
4,664,125 5/1987 Pinto .................. 128/695

Patent Number: 4,998,535
Date of Patent: Mar. 12, 1991

4,680,708 7/1987 Ambos et al. ................. 364/417
4,754,762 7/1988 Stuchl .................. 128/696

OTHER PUBLICATIONS

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ABSTRACT
An instrument for predicting the benefit of using thrombolytic therapy to treat a patient with a heart condition including a first input port for receiving inputs derived from electrocardiograph measurements of the patient's condition, and a processor for computing an estimate of said benefit based upon the electrocardiograph-derived inputs.
Predicting Benefit: tPA and Streptokinase

Acknowledgements
David Kent, Tufts University
tPA and Streptokinase

• Using data on 24,146 patients in the GUSTO trial we created a model to predict outcomes
  – GUSTO trial compared tPA and Streptokinase for patients with AMI
  – Model based on the independently-derived TPI model
Benefit from tPA

- Most of the benefit of the use of tPA was in a small proportion of patients with high mortality risk and short time to presentation. (D Kent, Am J Med. 2002)
• “The size of the circles reflects the relative size of the trials. The slope of the (bold) regression line is 0.56 and the x-axis intercept is 2.0%, indicating that populations at mortality risks below this level are unlikely to demonstrate benefit for angioplasty over thrombolytic therapy and may show harm.”
Predicting Benefit

• These models provide a predicted benefit between treatments (comparative effectiveness research)
  – Predictions can be used to assist in decision making for treatment
Comparison of Mortality Benefit of Immediate Thrombolytic Therapy Versus Delayed Primary Angioplasty for Acute Myocardial Infarction

David M. Kent, MD, MS, Robin Ruthazer, MPH, John L. Griffith, PhD, Joni R. Beshansky, RN, MPH, Cindy L. Grines, MD, Thomas Aversano, MD, Thomas W. Concannon, PhD, Robert J. Zalenski, MD, Harry P. Selker, MD, MSPH

Received 21 September 2006; received in revised form 21 December 2006; accepted 21 December 2006.
• Combined data from multiple studies on patients with STEMI (ST elevation AMI) treated with TT or primary percutaneous coronary intervention (PCI) (n=2781)
  – Started with the TPI mortality predictions (TT)
  – Added model for predicting mortality for patients receiving PCI
PCI-TPI Model

• Expectation is that mortality benefit from use of PCI will vary between patients based on their individual risk
  – Benefit greater for patients at highest risk
• Impact of PCI treatment is also dependent on the time duration to treatment
  – Longer delay to treatment would decrease benefit
PCI-TPI Model

- Includes patient age, baseline risk (from TPI model), time from ECG to reperfusion
- Also interactions of treatment with baseline risk and with time from ECG to treatment
Time to Equipoise

• If you can start TT within 30 minutes, how long can you delay treatment with PCI and still have some benefit in reduction in mortality?

• Solve equations to get a “Time to Mathematical Equipoise” (TIME) for any given patient
Mortality Risk by Time

Circumstance 1: PCI at 90 min vs. TT at 30 min:

PCI predicted to be better than TT 34% of the time and have no benefit (0.8<RR<1.2) the remaining 66% of the time.
Mortality Risk by Time

Circumstance 2: PCI at 120 min vs. TT at 30 min:

No predicted benefit of either treatment 100% of the time.
Mortality Risk by Time

Circumstance 3: PCI at 180 min vs. TT at 15 min:

TT predicted to be better than PCI 20% of the time, worse than PCI <1% of the time, and have no benefit 79% of the time.
Application of TIME

• In RCT randomization to different treatments can only occur when there is no clear evidence of the superiority of one of the treatments (“equipoise”)

• Use the PCI-TPI to explore when randomization for TT/PCI could be done.
Other Applications of Predictive Models

Shared Decision Making
“The overall objective of this study is to assess whether the development of a risk prediction model for advanced colorectal neoplasia is a feasible and valid strategy for facilitating effective SDM [Shared Decision Making] and improving the cost-effectiveness of screening colonoscopy.”
Renal Supportive Care

Shared Decision Making and Renal Supportive Care

Principal Investigator
Lewis Mitchel Cohen, MD

Organization
Baystate Medical Center

Funding Announcement
Communication and Dissemination Research
Patient-Centered Outcomes Research (PCOR) helps people and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options. This research answers patient-centered questions such as:

1. “Given my personal characteristics, conditions and preferences, what should I expect will happen to me?”
2. “What are my options and what are the potential benefits and harms of those options?”
3. “What can I do to improve the outcomes that are most important to me?”
4. “How can clinicians and the care delivery systems they work in help me make the best decisions about my health and healthcare?”

http://www.pcori.org/research-we-support/pcor/
End of Life Decision Making

“It is tragic that we now can predict which individuals are most likely to die within the next 6 months, and yet dialysis staff rarely sit down with them and their loved ones to discuss the situation. They die without completing advance directives, appointing healthcare proxies, or knowing they have the right to stop dialysis. They die in intensive care units, hospitals, and nursing homes, and are never given the opportunity to discuss the possibility of receiving hospice services and dying at home surrounded by friends and loved ones.”
“Results: In a Cox multivariate analysis of the derivation cohort, five variables were independently associated with early mortality: Older age (hazard ratio [HR] for a 10-yr increase 1.36; 95% confidence interval [CI] 1.17 to 1.57), dementia (HR 2.24; 95% CI 1.11 to 4.48), peripheral vascular disease (HR 1.88; 95% CI 1.24 to 2.84), decreased albumin (HR for a 1-U increase 0.27; 95% CI 0.15 to 0.50), and SQ (HR 2.71; 95% CI 1.76 to 4.17). Area under the curve for the resulting prognostic model predictions of 6-mo mortality were 0.87 (95% CI 0.82 to 0.92) in the derivation cohort and 0.80 (95% CI 0.73 to 0.88) in the validation cohort.”
SDM-RSC Intervention

• Multi-modal intervention utilizing…
  – Face-to-face prognosis encounter
  – Intervention by social worker(s)
  – Hospice outreach
• Nephrologists and social workers involved in the study will undergo training to administer intervention
Study Aims

• To determine whether SDM-RSC impacts the use of hospice services, location of death, and EOL planning.
• To determine the effect of SDM-RSC on quality of life/death and caregiver satisfaction with patient care in the last week of life.
Ongoing Research

Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE)
Keith A A Fox, Omar H Dabbous, Robert J Goldberg, Karen S Pieper, Kim A Eagle, Frans Van de Werf, Álvaro Avezzù, Shaun G Goodman, Marcus D Flather, Frederick A Anderson Jr, Christopher B Granger, for the GRACE Investigators

Molecular Med TRI-CON 2014
February 9-14, 2014
Moscone North Convention Center
San Francisco, CA

Predictive Preclinical Models in Oncology
Cambridge Healthtech Institute’s Second Annual
February 10-12, 2014 | Moscone North Convention Center | San Francisco, CA

The selection of appropriate animal models based on similarity to human biology carries considerable potential to ensure a higher predictability of preclinical results. Innovative ex vivo models are equally important for minimizing the odds of preclinical errors. This conference is designed to highlight the cutting edge in vitro and in vivo preclinical models that allow researchers to more effectively evaluate novel cancer therapeutics, as well as to identify predictive biomarkers in early stages of drug development. Case studies and solutions for increasing the predictability of preclinical cancer studies will be presented.
In the Future

• How can we
  – assess the impact of predictive models without costly and time consuming clinical trials?
  – incorporate uncertainty in modeling predictions?
  – Continue to include patient and individual preferences in decision making?