Predicting the unpredictable: Moving forward with Prognostication Research

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#MASCC18

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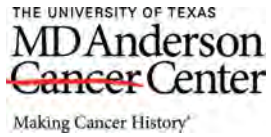
  - Insys Therapeutics
  - Teva Pharmaceutical
  - Depomed Inc

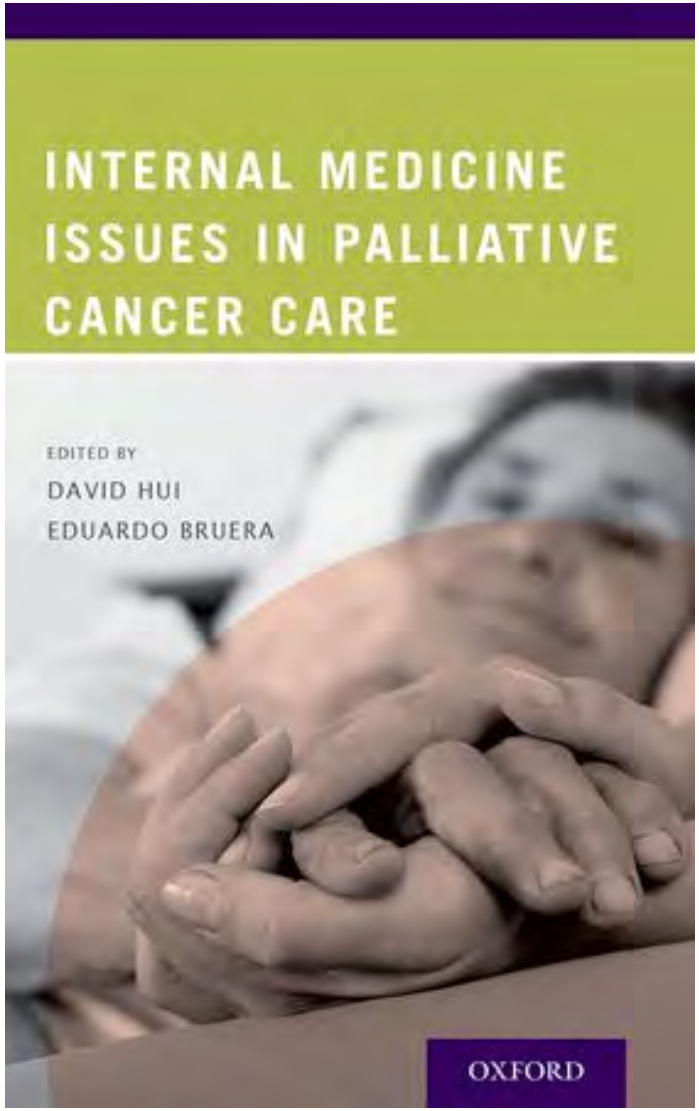


Outline

- Prognostic descriptors
- Assessing accuracy
- Prognostic website
- Machine learning

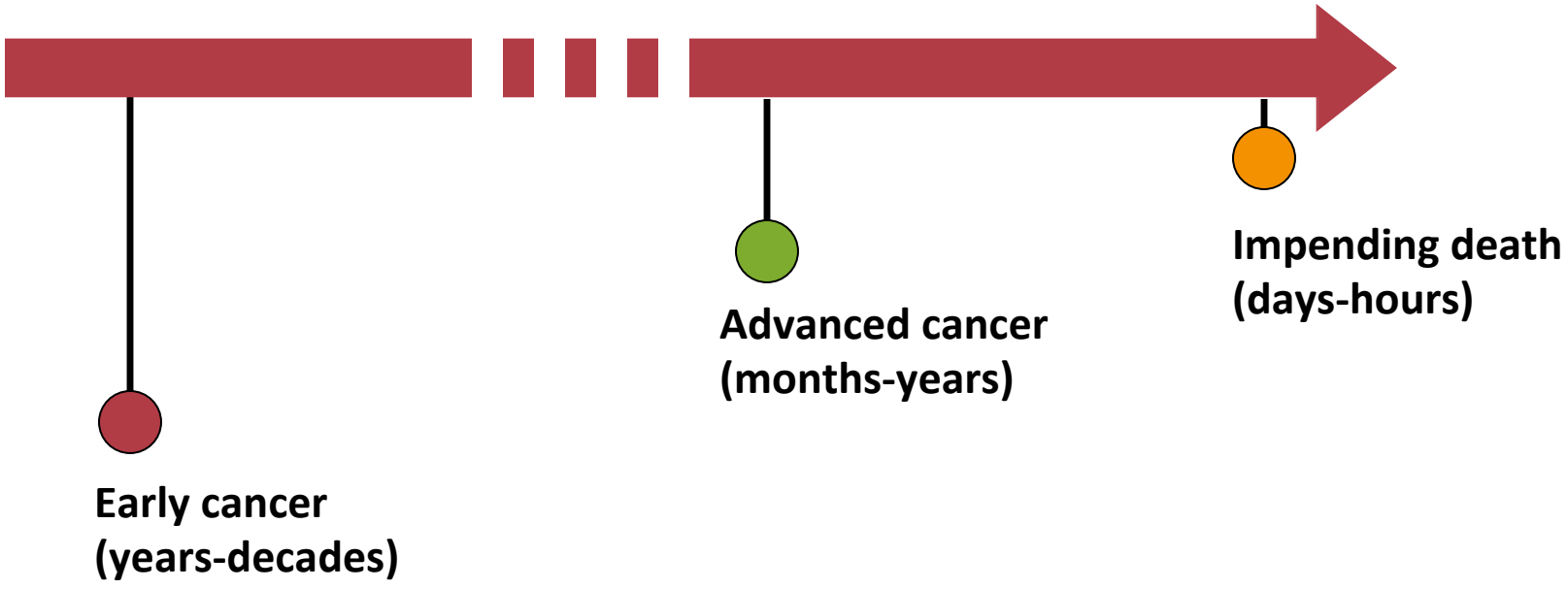
Prognosis Based Decision Making

- Management in patients with years of life expectancy
- Management in patients with months of life expectancy
- Management in patients with weeks/days of life expectancy



Disease Trajectory

Terminologies



"End of life", "terminally ill": months or less of survival

"Actively dying": days to hours of survival

Hui et al. *J Pain Symp Manage* 2013

Disease Trajectory

Literature Reporting

- How often do study authors describe the patient population adequately to tell us how far along the disease trajectory?
- How often do they use the prognostic descriptors?

- 742 original articles in palliative oncology published 2004/2009

Characteristics	*N* (%)
Actual	
Survival	247 (33)
Performance status[a]	157 (21)
Eastern Cooperative Oncology Group score	73 (10)
Karnofsky performance scale	69 (9)
WHO performance status	11 (1)
Palliative performance scale	7 (1)
Cancer stage	362 (49)
Disease trajectory[b]	273 (37)
Study setting[c]	392 (53)
No actual time-related patient characteristics reported	71 (10)
Eligibility criteria for study population	
Prognosis	104 (14)
Performance status	56 (8)
No actual characteristics or eligibility criteria reported	60 (8)
Able to classify into time-related categories[d]	378 (51)

Tayjasanant et al. *Supp Care Cancer* 2016

Disease Trajectory

Literature Reporting

Characteristics	Number of studies (%)[a]	Median survival in days (IQR)[b]
Cancer stage[c]	362 (100)	
Local	33 (9)	165 (126–354)
Locally advanced	162 (45)	148 (90–220)
Metastatic	301 (83)	132 (70–211)
Recurrent	15 (4)	144 (94–246)
Disease trajectory[c]	273 (100)	
Active cancer treatment	160 (59)	143 (84–261)
No further cancer treatment	157 (58)	77 (37–175)
Diagnosis	2 (1)	NA
Cured	2 (1)	NA
After death	39 (14)	NA
Study setting[c]	392 (100)	
Inpatient	207 (53)	58 (24–148)
Outpatient	137 (35)	122 (61–209)
Home palliative care (non-hospice)	54 (14)	75 (59–104)
Inpatient hospice	53 (14)	28 (16–71)
Home hospice care	51 (13)	37 (10–60)
Hospice day care	5 (1)	NA
ECOG performance status	157 (100)	
0	4 (3)	311 (311–311)
1	38 (24)	180 (150–245)
2	63 (40)	121 (090–186)
3	42 (27)	58 (24–84)
4	10 (6)	23 (12–47)
Time-related categories[d]	378 (100)	
7 days or less	21 (6)	3 (3–6)
>1–4 weeks	26 (7)	19 (14–24)
>1–3 months	87 (23)	61 (46–75)
>4–6 months	114 (30)	142 (115–165)
>6 months	130 (34)	266 (222–383)

Tayjasanant et al. *Supp Care Cancer* 2016

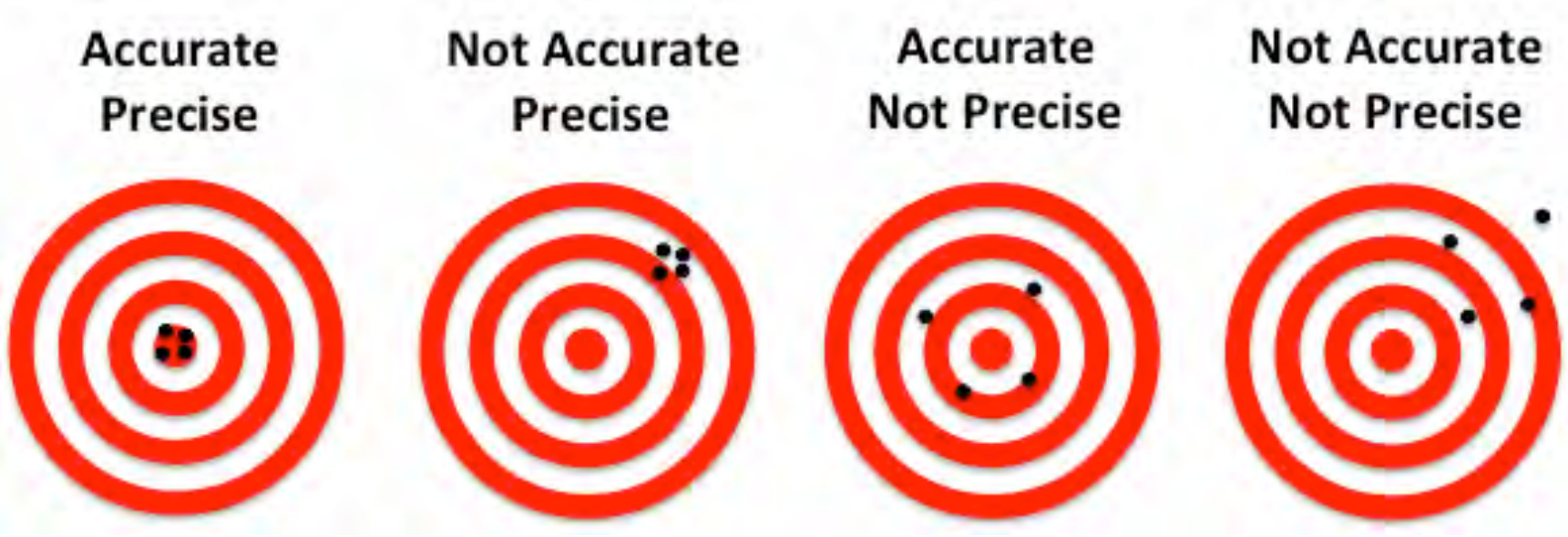
Disease Trajectory

Literature Reporting

Terminologies	Number of studies (%)[a]	Median survival in days (IQR)[b]
Advanced	123 (17)	114 (57–179)
End of life	30 (4)	63 (24–122)
Terminal	77 (10)	42 (25–84)
End stage	11 (2)	25 (14–60)
Dying	19 (3)	4 (3–16)

- Take home messages
  - Significant deficiencies in reporting of time-related patient characteristics in the palliative oncology literature
  - Major impact on generalizability of findings
  - Essential to adequately describe patient population
    - Overall survival is ideal
    - Disease stage, performance status , study setting
  - Minimize prognostic descriptors (e.g. end-of-life) or define them when used

Tayjasanant et al. *Supp Care Cancer* 2016


Accurate
Precise
Not Accurate
Precise
Accurate
Not Precise
Not Accurate
Not Precise

Accuracy of Common Prognostic Tools

- Temporal Question
  - Margin of error 20% (Christakis et al. *BMJ* 2000)
  - AUC 58% (Hui et al. *EJC* 2016)
- Surprise Question
  - AUC 77%-83% (Downar et al. *CMAJ* 2017)
  - C-index 74% (White et al. *BMC Med* 2017)
- Probabilistic Question
  - Confidence 53-96% (Hui et al. *Oncologist* 2011)
- Palliative Prognostic Score
  - C-index 72% (Maltoni et al. *Oncologist* 2012)
  - AUC 70-83% (Baba et al. EJC 2015)
- Palliative Prognostic Index
  - C-index 62% (Maltoni et al. *Oncologist* 2012)
  - AUC 69-79% (Baba et al. *EJC* 2015)

Thought Experiment

- Would you be surprised if the panelists died in 1 day?
- Would you be surprised if the panelists died in 1 month?
- Would you be surprised if the panelists died in 1 year?
- Would you be surprised if the panelists died in 10 years?
- Would you be surprised if the panelists died in 100 years?

Thought Experiment

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- Would you be surprised if the panelists died in 1 month?
- Would you be surprised if the panelists died in 1 year?
- Would you be surprised if the panelists died in 10 years?
- Would you be surprised if the panelists died in 100 years?

Probabilistic Question

- Eight palliative care physicians and 20 nurses completed prognosis forms on admission for 151 consecutive APCU patients
- Temporal approach
  - What is the approximate survival for this patient? (days)
- Probabilistic approach
  - What is the approximate probability that this patient will be alive for

≥24 hours?	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
≥48 hours?	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
≥1 week?	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
≥2 weeks?	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
≥1 month?	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
≥3 months?	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
≥6 months?	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

- Actual survival data collected from Vital Statistics Database

Hui et al. *Oncologist* 2011

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≥3 months?	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
≥6 months?	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

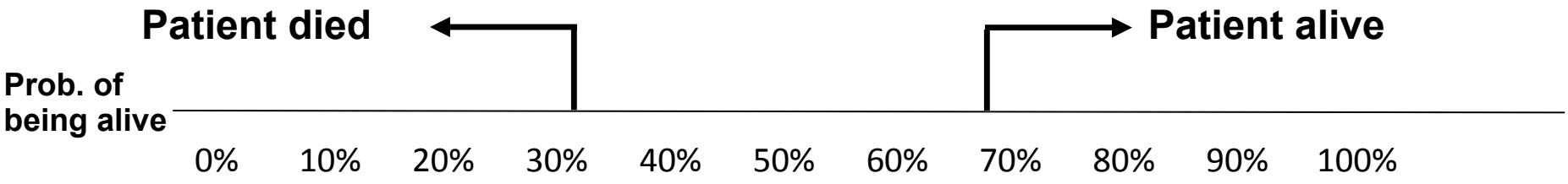
- Actual survival data collected from Vital Statistics Database

Hui et al. *Oncologist* 2011

Probabilistic Question

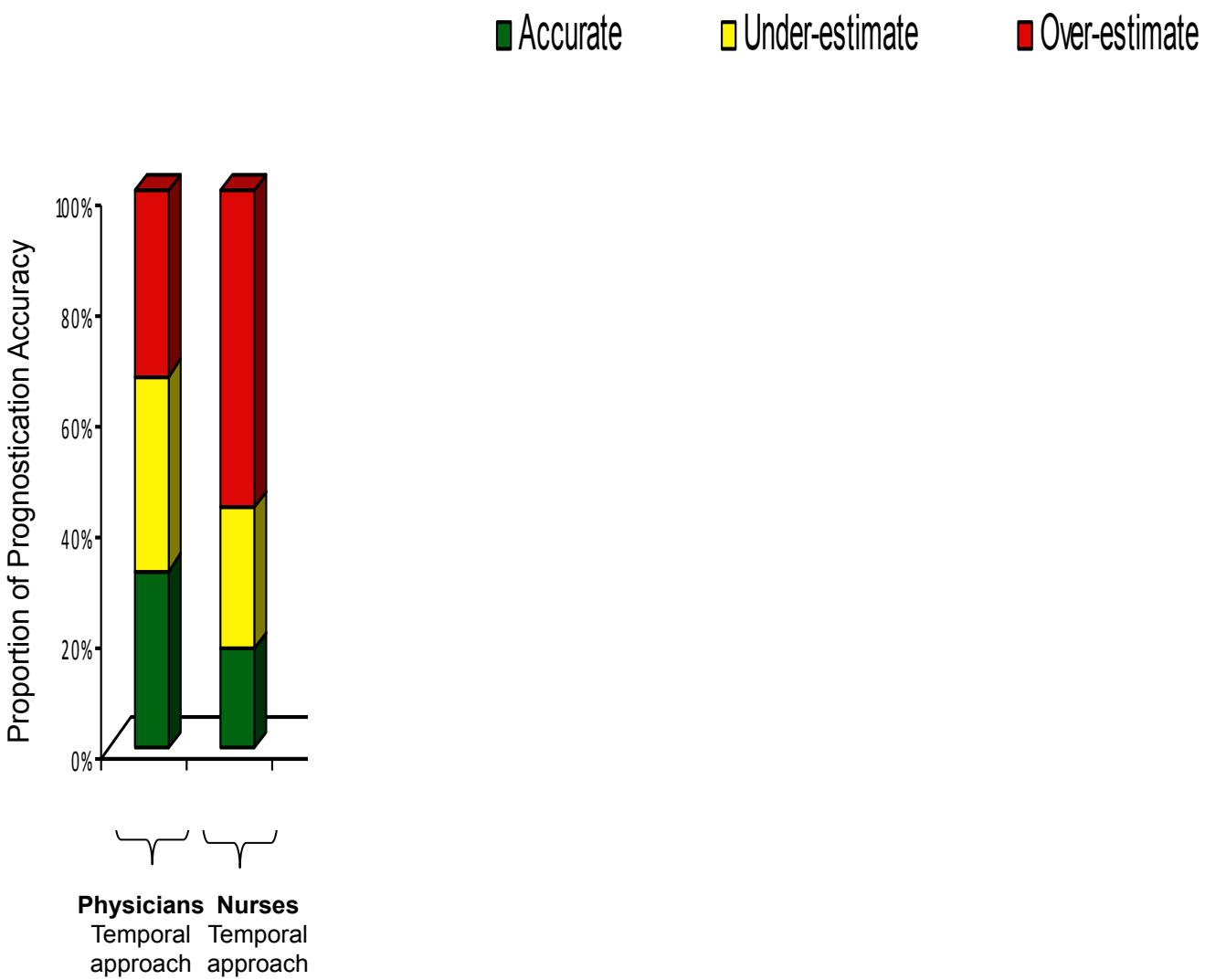
- Temporal approach
  - Considered accurate if ±33.3% of actual survival
  - Considered inaccurate if >1.333 or <0.667 of actual survival

- Probabilistic approach
  - Considered accurate if
    - Patient alive and clinician indicated ≥70% survival
    - Patient died and clinician indicated ≤30% survival
  - Considered inaccurate if
    - Patient alive and clinician indicated <70% survival
    - Patient died and clinician indicated >30% survival
    - Clinician indicated 40-60% chance of survival



Probabilistic Question

Accuracy of Temporal and Probabilistic CPS



Hui et al. *Oncologist* 2011

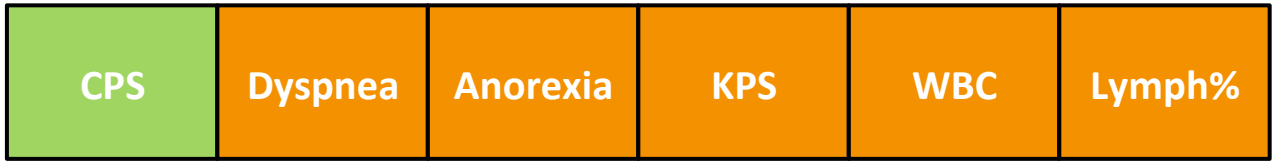
What Determines Accuracy?

- From this study
  - How we ask the question matters!
  - The time frame of prognostication matters!
  - The profession matters!
  - How we evaluate accuracy matters!

- More considerations
  - The study population (median survival matters)

CPS vs. PaP Score

- PaP score = CPS + 5 other variables



- Is PaP score more accurate than CPS?

- Does CPS help increase the accuracy of PaP score?

Hui et al. *Eur J Cancer* 2016

CPS vs. PaP Score

- 216 patients seen by inpatient palliative care consultation team
- Median survival 109 days

Predictor	Concordance index (95% CI)	AUC for 30 day survival (95% CI)	AUC for 100 day survival (95% CI)
Raw-CPS	0.58 (0.47, 0.68)	0.58 (0.47, 0.68)	0.62 (0.54, 0.70)
PaP-total score	0.64 (0.54, 0.74)	0.73 (0.64, 0.82)	0.68 (0.60, 0.76)

Conclusion: PaP better than CPS

- 204 patients seen by inpatient palliative care unit
- Median survival 10 days

Predictor	C-index (95% CI)	AUC for 30 day survival (95% CI)	AUC for 14 day survival (95% CI)	AUC for 7 day survival (95% CI)
CPS-raw	0.75 (0.71, 0.79)	0.85 (0.78, 0.92)	0.78 (0.71,0.85)	0.81 (0.75,0.88)
PaP score	0.70 (0.66, 0.74)	0.82 (0.73, 0.91)	0.75 (0.67,0.83)	0.75 (0.68,0.81)

Conclusion: PaP not better than CPS

Hui et al. *Eur J Cancer* 2016

Summary so far…

- Many factors affect accuracy
  - Patient population and setting
  - Professional characteristics (CPS)
  - Time frame of prediction
  - Prognostic tool and comparator

- Some tools are better for some time frames
  - Don’t use PaP score in stage I cancer

- Others may be more general
  - Performance status

Assessing Accuracy

- Common metrics
  - Margin of error
  - Concordance index
  - Area under the ROC curve
  - 2x2 tables (sensitivity/specificity)
  - Brier score (probabilistic)
  - Investigator-defined

- Additional impact
  - Net reclassification index
  - Integrated discrimination improvement

Hui et al. *Eur J Cancer* 2016; Hui *Cancer Control* 2015

$\langle \phi_n | \phi_m \rangle = \langle \phi_n | \int dx\, |x\rangle\langle x| \phi_k \rangle$

$\phi_n(x) = \langle x | \phi_n \rangle \quad \phi_n^*(x) = \langle \phi_n | x \rangle$

$\langle \phi_n | \phi_n \rangle = \int_{-L/2}^{+L/2} dx\, |\phi_n(x)|^2 = \int_{-L/2}^{+L/2} dx \frac{1}{L} = L \cdot \frac{1}{L} = 1$

$\langle \phi_n | \phi_{n'} \rangle = \langle \phi_n | \int dx\, |x\rangle\langle x| \phi_{n'} \rangle$

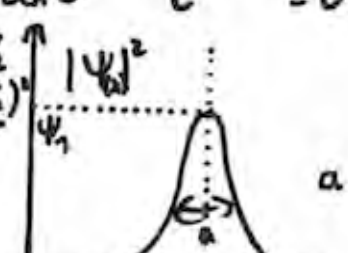
$\langle \phi_n | \phi_{n'} \rangle = \int_{-L/2}^{+L/2} dx\, \phi_n^*(x) \cdot \phi_{n'}(x)$

$\langle \phi_n | \phi_{n'} \rangle = \frac{1}{L} \int dx\, e^{-ikx} e^{ik'x} \stackrel{!}{=} 0 ; k \neq k'$

$|\psi(x)|^2 = |\psi_0|^2 e^{-\frac{(\vec{x}-\vec{x}_0)^2}{2a^2}}$

$\int_{-\infty}^{+\infty} dx\, e^{-Ax^2} = \sqrt{\frac{\pi}{A}}$

$A = \frac{1}{2a^2} \Rightarrow |\psi_0| = \frac{1}{(2\pi a^2)^{3/4}}$



$a \approx 10^{-10} m$

$\psi_a - \psi_b = 0, 2\pi \ldots \Rightarrow e^{i\psi_a} = e^{i\psi_b}$

$\{|R\rangle, |L\rangle\}$

$\psi_n(x) = \frac{1}{\sqrt{2L}} e^{i\varphi_0} \left(e^{i(\frac{2\pi}{L}n + k_0)x} + e^{-i(\frac{2\pi}{L}n + k_0)x} \right) = \frac{2}{\sqrt{2L}} e^{i\varphi_0} \cos\left[\left(\frac{2\pi}{L}n + k_0\right)x \right]$; $\psi_n(x = \pm L/2) = 0$

$\Rightarrow \left(\frac{2\pi}{L}n + k_0\right)\frac{L}{2} = \frac{\pi}{2}(2\ell - 1), \ell = 1, 2 \ldots \Rightarrow k_0 = -\frac{\pi}{L}$

$\psi_n(x) = \sqrt{\frac{2}{L}} \cos\left[\frac{\pi}{L}(2n-1)x\right]$; $\varphi_a - \varphi_b = \pi$; $\psi_n(x) = \sqrt{\frac{2}{L}} \sin\left[\frac{2\pi}{L}nx\right]$

$\hat{H}\psi_{ns}(x) = -\frac{\hbar^2}{2m}\partial x^2 \psi_{ns}(x) = \frac{\hbar^2}{2m}\left(\frac{\pi}{L}[2n-1]\right)^2 \psi_{ns}(x)$

$E_{ns} = \frac{\hbar^2}{2m}\frac{\pi^2}{L^2}(2n-1)^2$, $n = 1, 2 \ldots$; $\hat{H}\psi_{nA}(x) = \frac{\hbar^2}{2m}\left(\frac{2\pi}{L}n\right)$

$\hat{H}\psi_a = -\frac{\hbar^2}{2m}\partial x^2 \psi_a(x) = \frac{\hbar^2}{2m}\frac{1}{2a^2}\psi_a(x) - \frac{\hbar^2}{2m}\frac{1}{4a^4}(x-x_0)^2\psi_a(x)$

$= -\frac{\hbar^2}{2m}\left(-\frac{1}{2a^2} + \left(\frac{1}{2a^2}(x-x_0)\right)^2\right) e^{-\frac{(x-x_0)^2}{4a^2}} \psi$; $V(x) = \frac{\hbar^2}{2m}\frac{1}{4a^4}(x-x_0)^2$

$\hat{H} \to \hat{H} = -\frac{\hbar^2}{2m}\partial x^2 + V(\hat{x})$; $\hat{H}\psi_a = \frac{\hbar^2}{2m}\frac{1}{2a^2}\psi_a = E_a\psi_a$

$V(x) = \frac{1}{2}m\omega^2(x-x_0)^2 \to m\omega^2 = \frac{\hbar^2}{m4a^4} \Rightarrow \boxed{\omega = \frac{\hbar}{2ma}}$

$E_a = \frac{\hbar^2}{2m}\frac{1}{2a}$

$[\hat{p}, \hat{x}] = \frac{\hbar}{i}$; $\hat{p} = \frac{\hbar}{i}\partial x$ / $\hat{H} = \frac{\hat{p}^2}{2m} + \frac{1}{2}m\omega^2\hat{x}^2$

1. $a^2 + b^2 = (a+ib)(a-ib)$; $a, b \in \mathbb{R}$; 2 $(a\hat{p} \mp ib\hat{x})(a\hat{p} - ib\hat{x})$, $a, b \in \mathbb{R}$

$= a^2\hat{p}^2 + iba\hat{x}\hat{p} - iab\hat{p}\hat{x} + b^2\hat{x}^2 = a^2\hat{p}^2 + b^2\hat{x}^2 - bai$

$\hat{H} = (a\hat{p} + ib\hat{x})(a\hat{p} - ib\hat{x}) = bai$; $a^2 = \frac{1}{2m}$; $b^2 = \frac{1}{2}m\omega^2$

Def: $c^+ \frac{1}{\sqrt{\hbar\omega}}(a\hat{p} + ib\hat{x})$; $c^- = \frac{1}{\sqrt{\hbar\omega}}(a\hat{p} - ib\hat{x}) \Rightarrow \hat{H} = \hbar\omega c^+ c + \frac{1}{2}\hbar\omega$

$\left\{ \begin{pmatrix} \omega & z \\ -\bar{z} & \bar{\omega} \end{pmatrix} \middle| \omega, z \in \mathbb{C} \right\}$ $\{\pm 1\}$ $iSU(2) \cong S^3$ $A \to \omega \bar{A} \omega^{-1}$

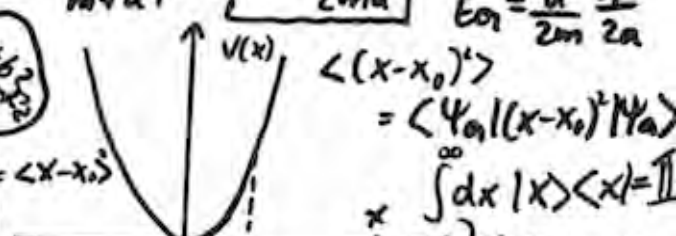
$\omega = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}$ $\sigma_1 = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}$, $\sigma_2 = \begin{pmatrix} 0 & -i \\ i & 0 \end{pmatrix}$; $\sigma_3 = \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}$ $S_i = \frac{\hbar}{2}\sigma_i$; $i \in [1,2,3]$

$\|\psi\| = \sqrt{\langle\psi|\psi\rangle}$

$\rho = \hbar\frac{2\pi}{\lambda}$

$t_n = \frac{\hbar}{2\pi}$

$\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$



$\langle (x-x_0)^2 \rangle = \langle \psi_a | (x-x_0)^2 | \psi_a \rangle$

$= \int_{-\infty}^{\infty} dx\, |x\rangle\langle x| = \mathbb{1}$

$\psi_a^*(x) \langle k | x \rangle$

$= \int_{-\infty}^{\infty} dx\, \psi_n^*(x)(x-x_0)^2 |x\rangle = x|x\rangle$

$= \int_{-\infty}^{\infty} dx\, \psi_n^*(x)(x-x_0)^2 \psi_a(x) = \int_{-\infty}^{\infty} dx (x-x_n)^2 \psi$

If Prognostic Models Can Help, Why We Are Not Using Them?

- There are too many scores. Which one is best?
- I cannot remember all the variables in each score
- Calculation is cumbersome
- How to interpret the score?

John Maxwell, MD

https://www.predictsurvival.com

Estimating Prognosis in Advanced Cancer Patients Using Multiple Prognostic Models

This website gives prognostic data based on published studies using the Palliative Prognostic Score (PaP), Palliative Prognostic Score with Delirium (D-PaP), Palliative Prognostic Index (PPI), Performance Status-Based Palliative Prognostic Index (PS-PPI), and several Performance Status/Scales (KPS, PPS, and ECOG) in patients with advanced cancer. If this is your first time visiting, here is an introduction to the website

Intended only for patients with a survival of six months or less. Data is most valid in the one to three month range.

Enter as many variables as possible and this prognostic calculator will provide survival data based on published studies.

	Enter as Much as You Can:	Required For:
How Long do You Think the Patient Will Live?	60 days	PaP, D-PaP
Palliative Performance Scale (PPS) Help?	40%	PPS, PPI
Karnofsky Performance Status (KPS) Help?	40%	KPS, PaP, D-PaP
ECOG Performance Status Help?	3	ECOG, PS-PPI
Edema	No	PPI, PS-PPI
Oral Intake	Reduced but more than mc	PPI, PS-PPI
Dyspnea at Rest	Yes	PPI, PS-PPI, PaP, D-PaP
Delirium[1]	No	PPI, PS-PPI, D-PaP
Anorexia[2]	Yes	PaP, D-PaP
Total WBC (cell/cc)	Greater than 11,000	PaP, D-PaP
Lymphocyte Percentage	Less than 11.9%	PaP, D-PaP

Prognosticate!

Notes:

1. In the PPI delirium is counted as absent if it is due to a single medication. The D-PaP study makes no such allowance for medication induced delirium, hence there are three options.
2. This is the *clinical symptom* of anorexia (ie, lack of appetite), not to be confused with cachexia or weight loss.

Disclaimer: Please keep in mind the information given on this website represents survival estimates only – it is important to use clinical judgement to interpret the results accordingly. *Do not use this information without the input of a healthcare provider.*

https://www.predictsurvival.com

Summary Results, Scroll Down for More Detailed Results by Location and Publication

Keep in mind these outputs represent survival estimates only – use clinical judgement to interpret the results accordingly.

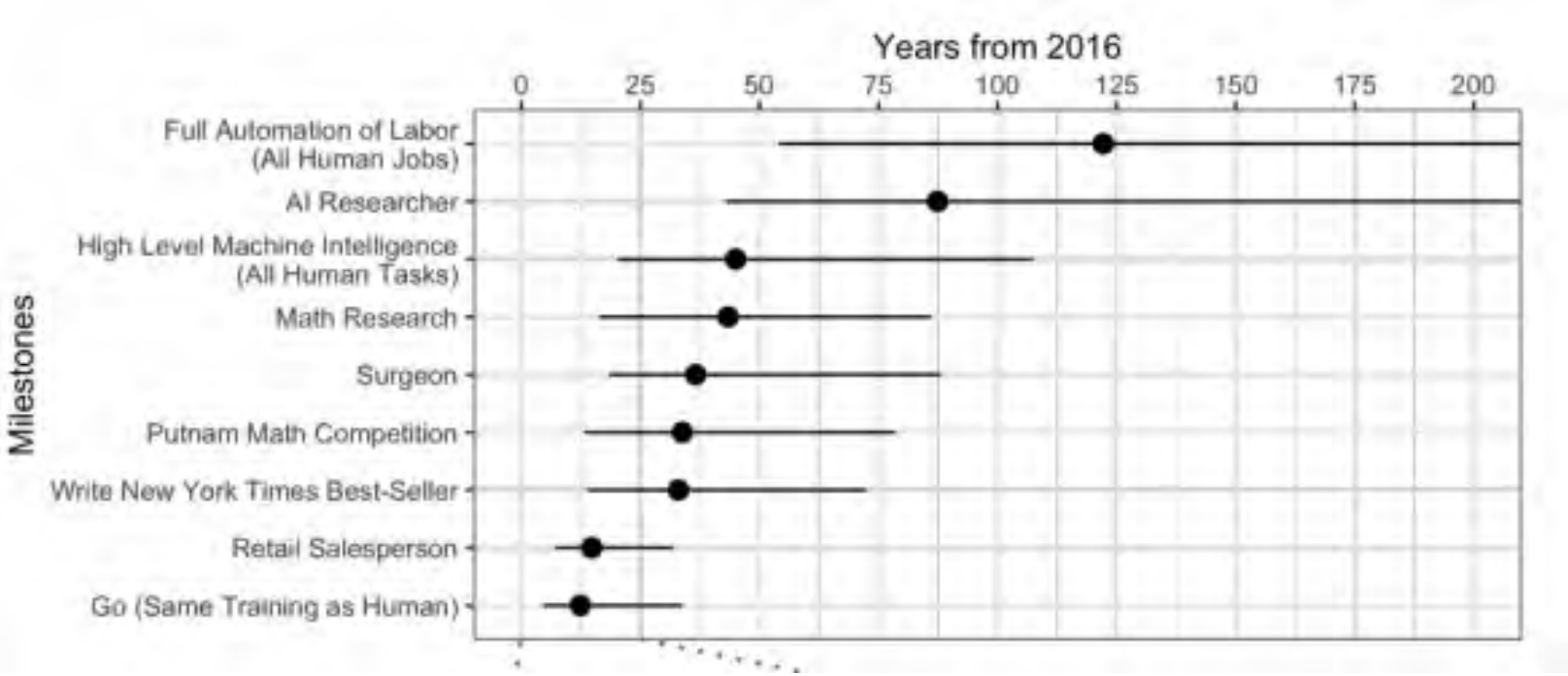
Model	Score	Median Survival	Communicating with Patients and Families
Palliative Prognostice Index (PPI):	8.5/15	12 to 25 days	Predicts *weeks* of survival
Performance Status-Based Palliative Prognostic Index (PS-PPI):	10.0/15	15 to 20 days	Predicts *weeks* of survival
Palliative Prognostic Score (PaP):	8.5/17.5	25 to 35 days	Predicts *weeks* of survival
Palliative Prognostic Score with Delirium (D-PaP):	8.5/19.5	23 to 30 days	Predicts *weeks* of survival
Palliative Performance Scale (PPS):	40%	24 to 51 days	Predicts *weeks* of survival
Karnofsky Performance Status (KPS):	40%	49 to 49.8 days	Predicts *weeks* of survival
ECOG Performance Status:	3	55 days	Predicts *weeks* of survival
Your Estimate:	---	---	60 days

The inputs you gave were: ECOG: 3, KPS: 40, Edema: absent, Lymphocyte: Less than 11.9%, PPS: 40, WBC: Greater than 11,000, Oral Intake: reduced, Delirium: none, Anorexia: present, Dyspnea: present.

Summary Result Notes:

- Median survival ranges are taken from the original validation studies for the models as well as select large validation studies (except for ECOG and PS-PPI, which each use one study currently).
- The 'Communicating with Patients and Families' column gives summary prognostic information based on the following definitions: 'days' of expected survival is 10 days or less, 'weeks' is 11 to 60 days, and months includes 61 days and greater.
- Prognostic estimates can differ significantly for the same patient input depending on the clinical scenario in which they are being evaluated. In the detailed results below, papers have been divided by patient location or scenario if available, which may give more accurate information.

experts predict when artificial intelligence will exceed human performance

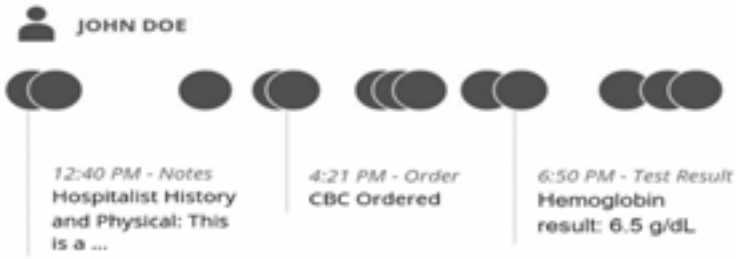


MIT Technology Review 2017

Machine Learning

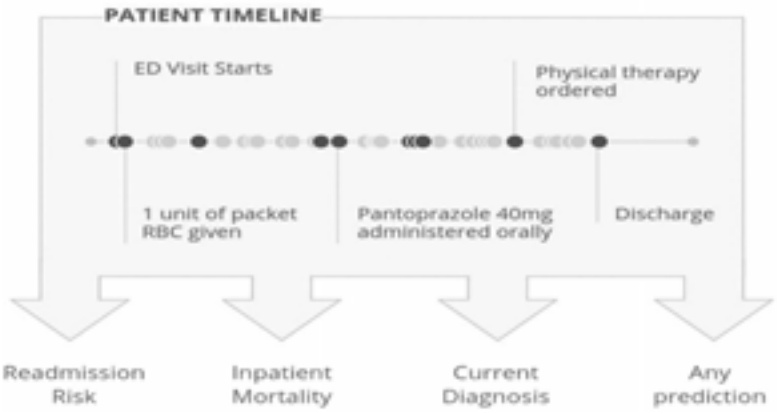
1

Health systems collect and store electronic health records in various formats in databases.



2

All available data for each patient is converted to events recorded in containers based on the Fast Healthcare Interoperability Resource (FHIR) specification.



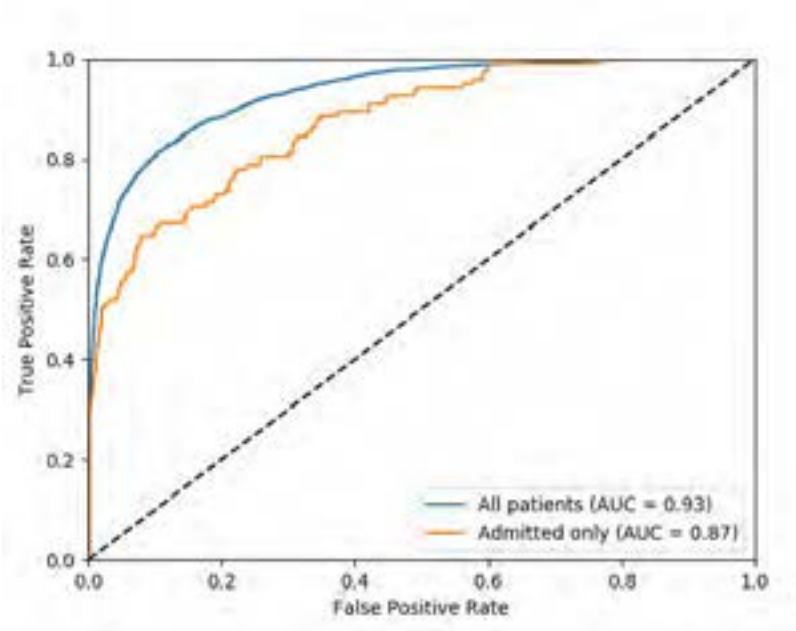
3

The FHIR resources are placed in temporal order, depicting all events recorded in the EHR (i.e. timeline). The deep learning model uses this full history to make each prediction.

Rajkomar et al. *Digital Medicine* 2018

Machine Learning

- Predict 3-12 month mortality (yes/no)
- Patient population
  - Outpatient and inpatient
  - Agnostic to disease type, stage, severity
- Features
  - 13,654 features
  - ICD 9 diagnostic and billing codes, Current procedural terminology codes, RxNorm Prescription codes, encounters
- Deep neural network
  - Supervised model
  - 13654 dimensions
  - 18 hidden layers
- Sample split (8:1:1)
  - Training 177,011
  - Validation 22,139
  - Testing 22,134

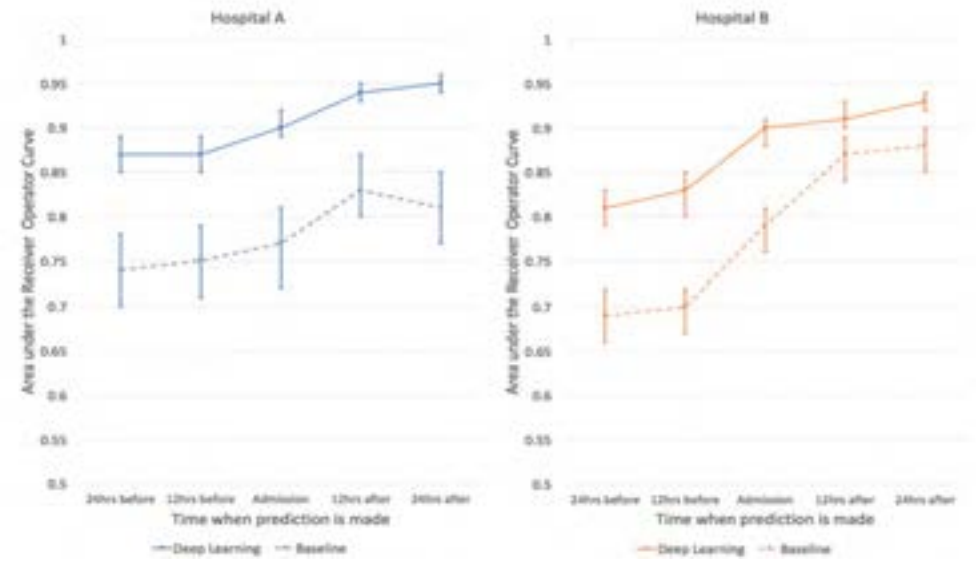


AUC 0.93 (0.87 for admitted pts)
AP score 0.69 (0.65 on admitted pts)
Brier score 0.042

Avati et al. *IEEE* 2017

Machine Learning

- Predict various outcomes for hospitalized patients
- Patient population
  - 216,221 inpatients (at least 24 h adm)
  - Fast Healthcare Interoperability Resources (FIHR) format
- Features
  - ICD-9 codes (14,025), medications, nursing flowsheets, and clinical notes
- Three deep neural networks
  - Recurrent neural networks (long short-term memory (LSTM)
  - Attention based TANN
  - Boosted time-based decision stumps
- Sample split (8:1:1)



AUC
Inhospital mortality 0.93-0.94
30 day unplanned admission 075-0.76
Prolonged stay 0.85-0.86

Rajkomar et al. *Digital Medicine* 2018

Dawn of the Machines

- Requires big data
  - Electronic health records
  - Tens/hundreds of thousands of patients
  - Appropriate format
- Variables
  - Pre-defined
  - Manual selection
  - Machine selection
- Many different computing models
  - Deep neural network (DNN)
  - Multilayer perception (MLP)
  - Naïve Bayes (NB)
  - Random Forest (RF)
  - Vector machines
  - Elastic-net logistic regression
- Refinements
  - Natural language processing
  - Cognitive learning
  - Real time longitudinal predictions
- Many different disciplines
  - Biostatistics
  - Computer scientist
  - Prognostication scientists
  - Clinicians
- Generalizability of model


Google DeepMind
Challenge Match
ALPHAGO
00:45:23
LEE SEDOL
00:43:04


humans are still required (at least for now)
Predictions
•CPS
•Tools
•Calculators
•AI-EHR
Disclosures
•Communication techniques
•Pt preferences
•Uncertainty
Decisions
•Decision aids
•Preferences
•Implementation
Outcomes
•Treatment decisions
•Quality of end-of-life care

Summary

- Moving the field forward
  - Standardize reporting of patient population
  - Standardize methods to assess accuracy
- Computers can help humans
  - Prognostic websites
  - Machine learning
- Other fertile areas of research
  - Prognostic disclosure
  - Prognostic based decision making
  - Prognostic outcomes