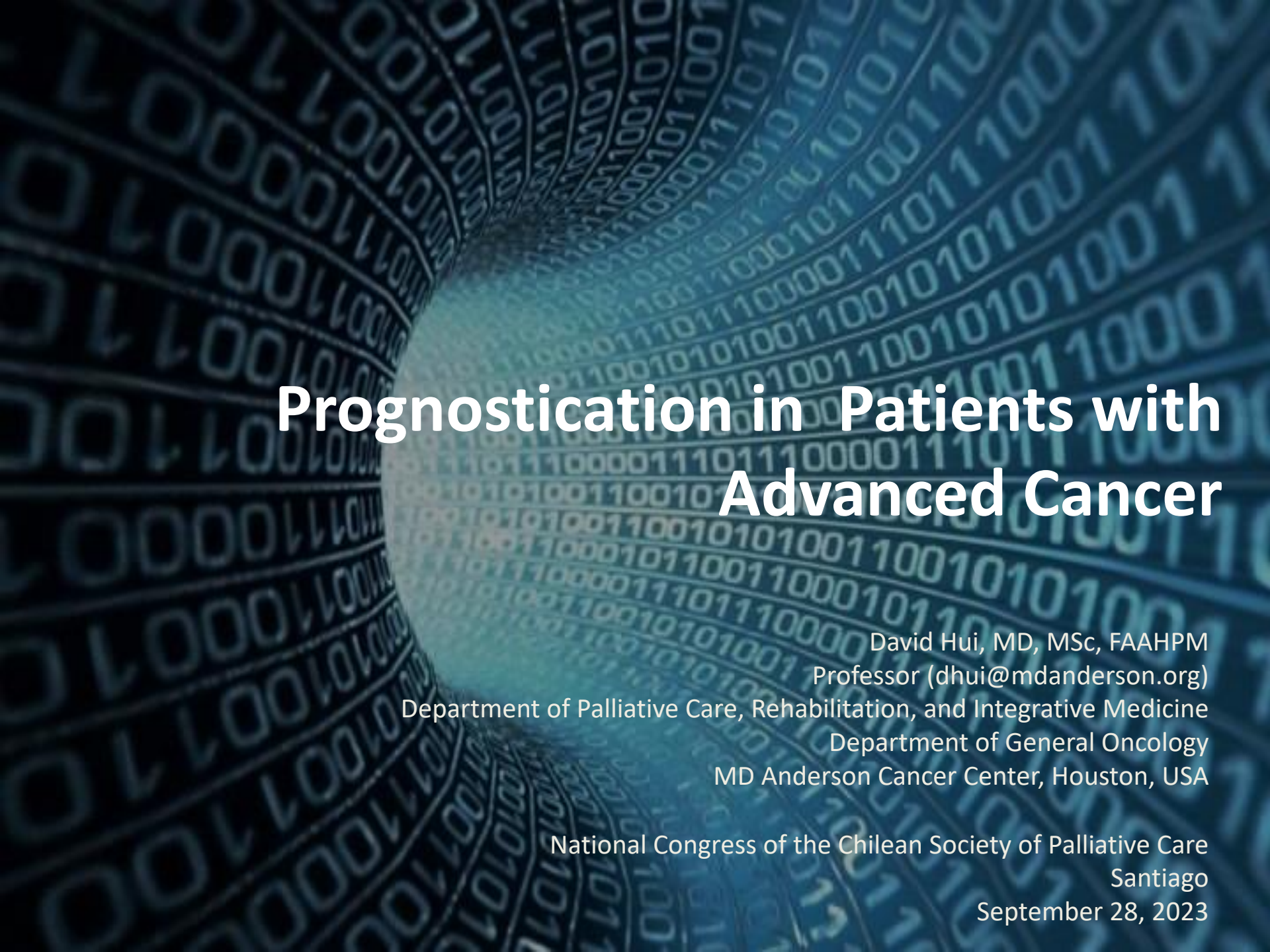


Prognostication in Patients with Advanced Cancer

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National Congress of the Chilean Society of Palliative Care
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Disclosure

- Funding sources for investigator-initiated research studies
  - National Cancer Institute
  - National Institute of Nursing Research
  - American Cancer Society
  - Andrew Sabin Family Fellowship Award
  - Sister Institution Network Fund
  - Institutional Research Grant

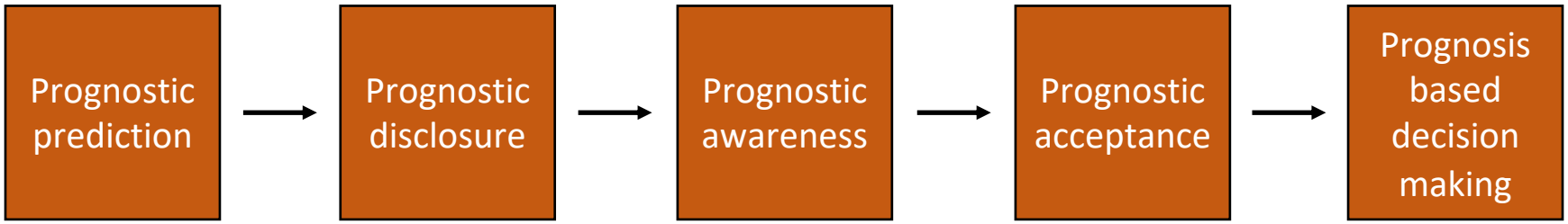
- Consultancy
  - Eton Pharmaceutical

Outline

- Clinician prediction of survival
- Prognostic factors/models
- Machine learning
- Practical approach
- Summary

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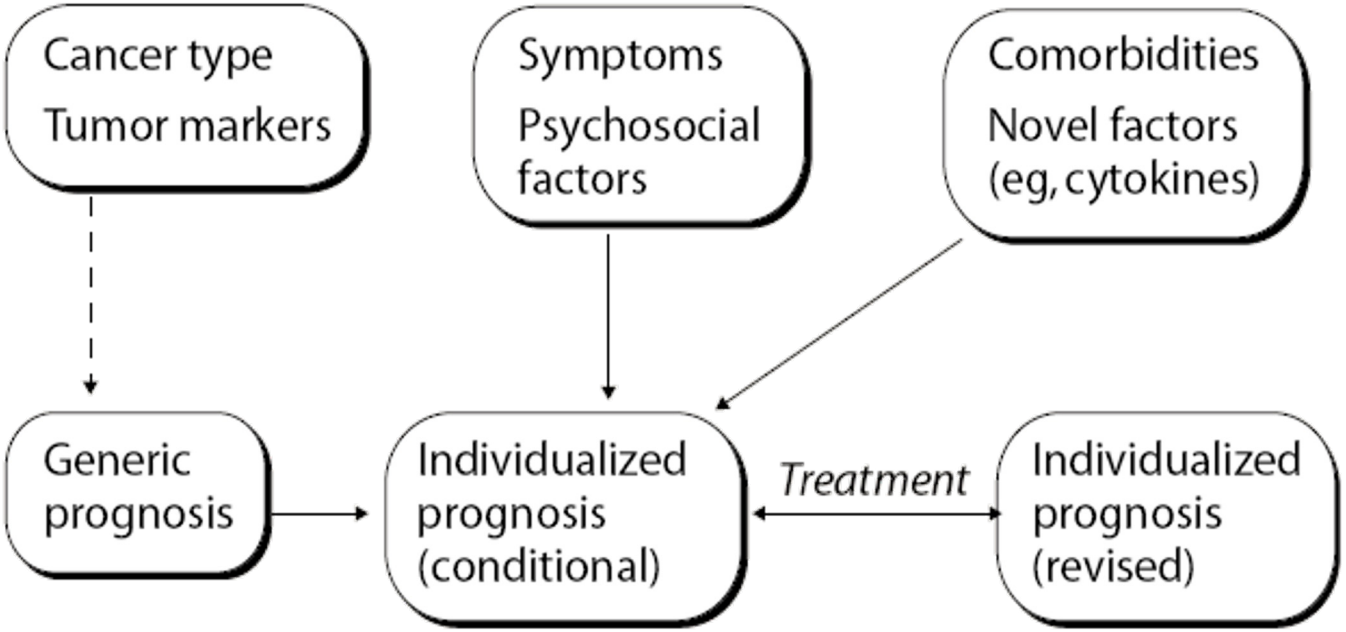
The Prognostic Continuum



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Hui et al. *Curr Treat Options Oncol* 2020

Clinician Prediction of Survival



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Mackillop *Prognostic Factors in Cancer 2nd ed.* 2001

Clinician Prediction of Survival

3 Approaches

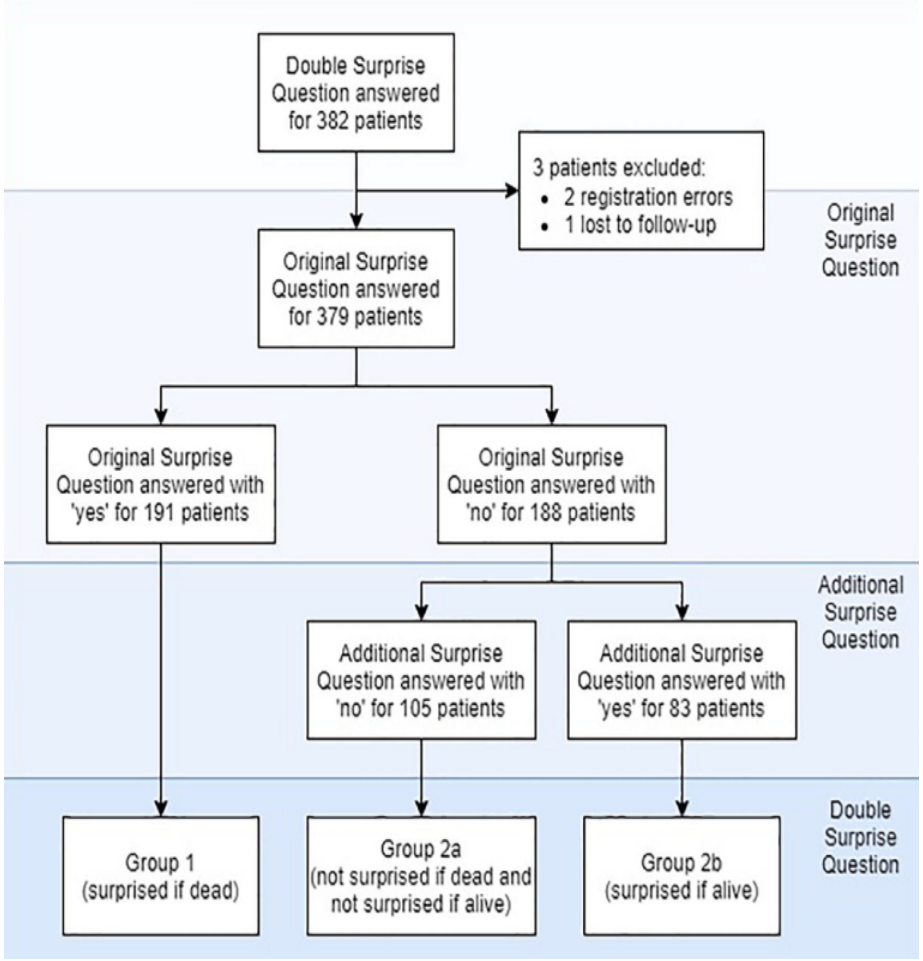
Aspects	Temporal question	Surprise question	Probabilistic question
Question	"How long will this patient live?"	Would I be surprised if this patient died in (a specific time frame)?	What is approximate probability that this patient will be alive for (a specific time frame)?
Answer	Specific time frame	Yes or no	0% to 100% (at 10% increments)
Definition of an accurate response	If estimated time frame was ±33% of actual survival	If "No" answer and patient died within specified time frame or If "Yes" answer patient remained alive by specified time frame	If answered ≤30% probability and patient died within specified time frame or If answered ≥70% probability and patient remained alive
Accuracy	20-30% if ±33% of actual survival 60-90%	65-88% (3 day to 1 year time frame)	53-91% (6 months to 24 hour time frames)
Advantages	• Simple, quick • Intuitive to understand	• Simple, quick • Intuitive to understand	• Simple, quick
Disadvantages	• Subjective • Unclear if time frame represents the average/median, maximal or minimal • May be difficult to provide a specific number (and often "wrong")	• Subjective • Time frame dependent • The threshold for "surprise" may vary by individual • Yes/No answer only	• Subjective • Time frame dependent • Probability needs to be interpreted

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Hui *Cancer Control* 2015

Double Surprise Question

- 12 medical oncologists and 379 patients
- Would I be surprised if this patient were to die within the next 12 months? No = may die
- If no to above, would I be surprised if this patient is still alive after 12 months? Yes = may die

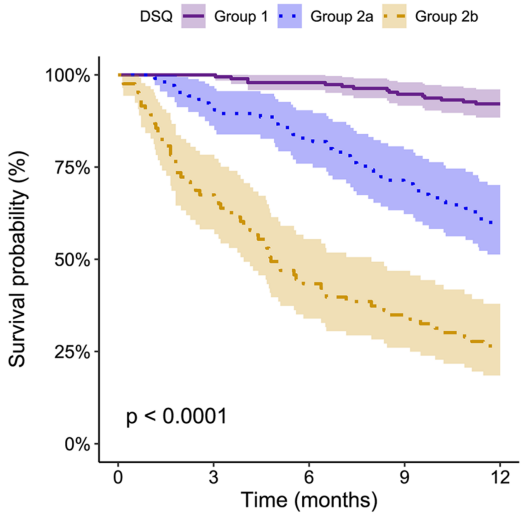


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Ermers *Palliat Med* 2021

Double Surprise Question

		Deceased *N*	Alive *N*	Total *N*	Sensitivity,[a] % (95% CI)	Specificity,[b] % (95% CI)	PPV,[c] % (95% CI)	NPV,[d] % (95% CI)
SQ1	No	103	85	188	87.3 (79.9–92.7)	67.7 (61.6–73.3)	54.8 (47.4–62.0)	92.1 (87.4–95.5)
	Yes	15	176	191			No	
	Total	118	261	379				
SQ2[e]	Yes	61	22	83	59.2 (49.1–68.8)	74.1 (63.5–83.0)	73.5 (62.7–82.6)	60.0 (50.0–69.4)
	No	42	63	105				
	Total	103	85	188				
DSQ	Predicted death	61	22	83	51.7 (42.3–61.0)	91.6 (87.5–94.6)	73.5 (62.7–82.6)	80.7 (75.8–85.1)
	Predicted alive	57	239	296			No/yes	
	Total	118	261	379				



- Double surprise has lower sensitivity but higher specificity than single surprise
- 74% of double surprise patients (no/yes) died in 1 year vs. 55% in single surprise (no)
- Limitations: overall survival not known (appears >1 year), stage unclear

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Ermers *Palliat Med* 2021

Clinician Prediction of Survival

- Overall accuracy 60-85%, but varies significantly by
  - The patient population
  - The time frame of prognostication
  - The clinician/profession
  - And maybe the question



- Your prediction for an individual patient may or may not be correct – but how would you know (until it is too late)?
  - No clinician is 100% correct
  - Some clinicians have higher accuracy

Outline

- Clinician prediction of survival
- Prognostic factors/models
- Machine learning
- Practical approach
- Summary

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Prognostication 101

- Clinical factors
  - Decreased performance status
  - Dyspnea
  - Dysphagia/cachexia/anorexia syndrome
  - Delirium

- Laboratory markers
  - Elevated CRP or ESR
  - Leukocytosis
  - Lymphopenia
  - Thrombocytosis
  - Elevated LDH
  - Hypoalbuminemia

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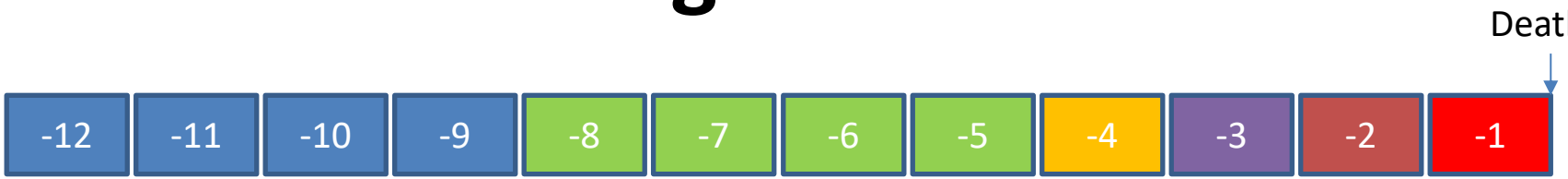
Overview of Prognostic Models

	Weeks to Days of life expectancy										Months of life expectancy		
Characteristics	**PPS**	**PaP**	**D-PaP**	**PPI**	**PPI-ECOG**	**OPS**	**PiPS-A14**	**PiPS-A56**	**PiPS-B14**	**PiPS-B56**	**GPS**	**BPN**	**PPT**
Number of variables	1	6	7	5	5	7	10	10	12	12	2	5	4
Clinical variables													
Sex												●	
Performance status	PPS	KPS	KPS	PPS	ECOG	ECOG	ECOG	ECOG	ECOG			KPS	KPS
Delirium			●	●	●		●	●	●				
Dyspnea		●	●	●	●	●	●						
Anorexia		●	●	●	●	●	●	●	●				
Weight loss								●					
Dysphagia							●						
Edema				●	●								
Tiredness										●			
Global health score							●	●	●	●			
Pulse rate							●	●	●	●			
Clinician prediction		●	●										
Disease variables													
Breast cancer								●					
Male genital cancer								●		●			
Distant metastases							●	●	●			●	●
Liver metastases							●	●					
Bone metastases							●		●				
Laboratory variables													
Leukocyte		●	●			●			●	●		●	
Neutrophils										●			
Lymphocytes		●	●							●			
Platelets									●	●			
C-reactive protein									●	●	●		
Albumin										●	●	●	●
Others						Cr, Bili, LDH			Urea, ALT	Urea, ALP			LDH

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Hui et al. *Curr Opin Supp Palliat Care* 2019

Overview of Prognostic Models



Glasgow Prognostic Score (GPS)
Barretos Prognostic Nomogram (BPN)
PRONOPALL Prognostic Tool (PPT)

Good risk:
Many months of life expectancy

Intermediate risk:
Several months of life expectancy

Poor risk:
Few months of life expectancy

Palliative Performance Scale (PPS)
Palliative Prognostic Score (PaP)
Palliative Prognostic Index (PPI)
Objective Prognostic Score (OPS)
Prognosis in Palliative Care Study (PiPS)

Good risk: months of life expectancy

Intermediate risk: weeks of life expectancy

Poor risk: days of life expectancy

Overall accuracy of models:

- C-index/AUC: 60-85%

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Hui et al. *Curr Opin Supp Palliat Care* 2019

https://www.predictsurvival.com

Estimating Prognosis in Advanced Cancer Patients Using Multiple Prognostic Models

This website gives prognostic data based on the Palliative Prognostic Score (PaP along with the Delirium-PaP), Palliative Prognostic Index (PPI), Performance Status-Based Palliative Prognostic Index (PS-PPI), Palliative Performance Scale (PPS) and various Performance Status Scales (KPS, PPS, and ECOG) in patients with advanced cancer.

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

	Select If Available:		Required For:
Palliative Performance Scale (PPS)	40%		PPS, PPI
Karnofsky Performance Status (KPS)	50%		KPS, PaP, D-PaP
ECOG	3		ECOG, PS-PPI
Edema	No		PPI, PS-PPI
Oral Intake[1]	Reduced but more than		PPI, PS-PPI
Dyspnea[2]	Yes		PPI, PS-PPI, PaP, D-PaP
Delirium[3]	No		PPI, PS-PPI, D-PaP
Anorexia[4]	Yes		PaP, D-PaP
Total WBC (cell/cc)[5]	Normal (4,800-8,500)		PaP, D-PaP
Lymphocyte Percentage[5]	Low (12.0-19.9%)		PaP, D-PaP
Your Prediction of Survival	30	days	PaP, D-PaP
	Prognosticate!		

For convenience, here is a reference to look up the PPS, KPS, and ECOG of a patient.

Notes:

1. In the PPI, oral intake is considered normal if a patient is on total parenteral nutrition (TPN) for a bowel obstruction.
2. In the PPI dyspnea was positive if it was at present at rest. For the PaP & D-PaP, it was positive if it was present at the time of scoring, which for this calculator is assumed to be at rest as well.
3. 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.
4. This is the *clinical symptom* of anorexia (ie, lack of appetite), not to be confused with cachxia or weight loss.
5. In the PaP and D-PaP models, scoring for for low WBCs or high lymphocytes was not reported. In practice we input low WBCs or high lymphocyte counts as "normal".

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https://www.predictsurvival.com

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):	10.5/17.5	25 to 35 days	Predicts *weeks* of survival
Palliative Prognostic Score with Delirium (D-PaP):	10.5/19.5	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):	50%	49 to 86.1 days	Predicts *weeks to months* of survival
ECOG Performance Status:	3	55 days	Predicts *weeks* of survival

Your Estimate: 30 days

The inputs you gave were: ECOG: 3, KPS: 50, Edema: no, Lymphocyte: 12.0-19.9%, PPS: 40, WBC: greater than 11,000, Oral Intake: reduced but more than mouthfuls, Delirium: none, Anorexia: yes, 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.
- It is important to note that prognostic estimates can differ significantly in the same patient based on the clinical scenario in which they are being evaluated. In the more detailed results below, papers have been divided by patient location or scenario if it was specified, which may give more accurate information.

Outline

- Clinician prediction of survival
- Prognostic factors/models
- Machine learning
- Practical approach
- Summary

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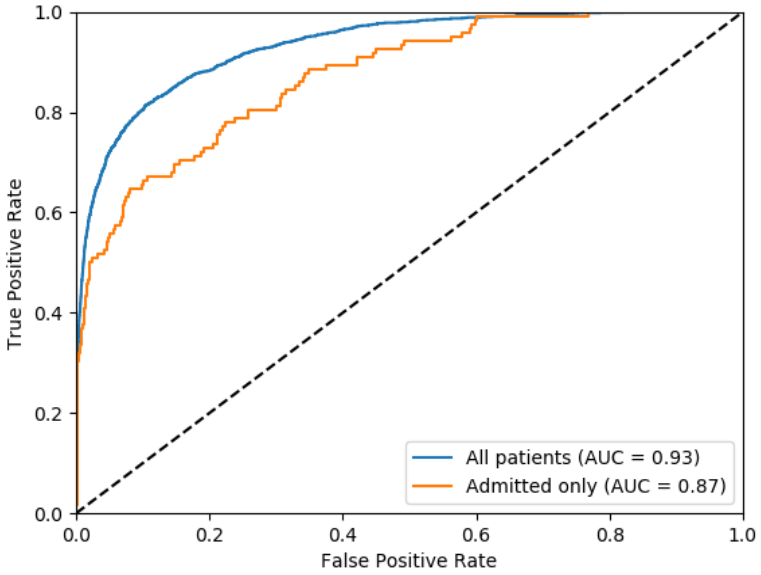


"I HAVEN'T USED A CRYSTAL BALL IN YEARS."

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Machine Learning

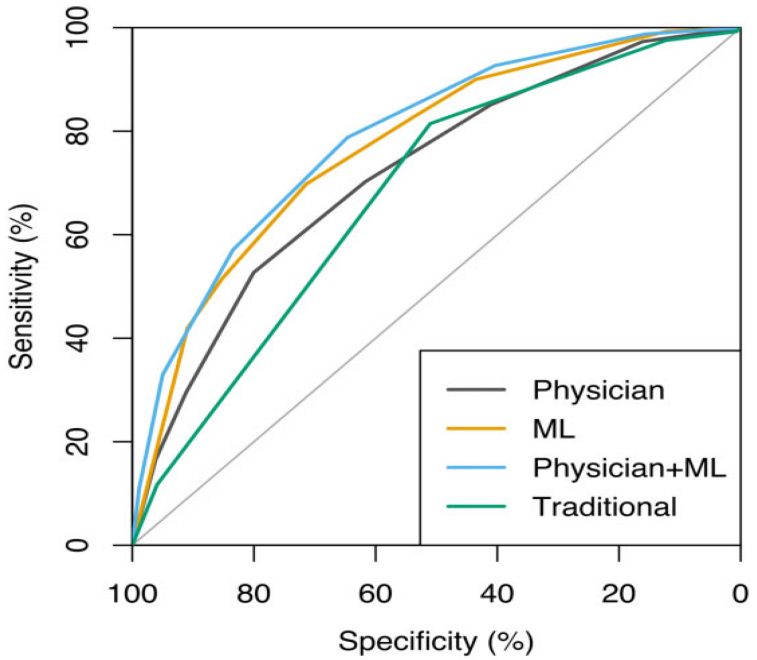
- Predict 3-12 month mortality (yes/no)
- Patient population
  - Outpatient and inpatient
  - Agnostic to disease type, stage, severity
- Features
  - 13,654 features
  - ICD 9 diagnostic and billing codes, Current RxNorm Prescription codes, encounters
- Deep neural network
  - Supervised model
  - 13654 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)
AUPRC score 0.69 (0.65 on admitted pts)
Brier score 0.042

Avati et al. *IEEE* 2017

Machine Learning



- Training set 14,600 metastatic cancer patients
- Directly compared radiation oncologists' prediction to machine learning
- Also include separate cohort of patients with ECOG prediction
- Median survival 11.7 months

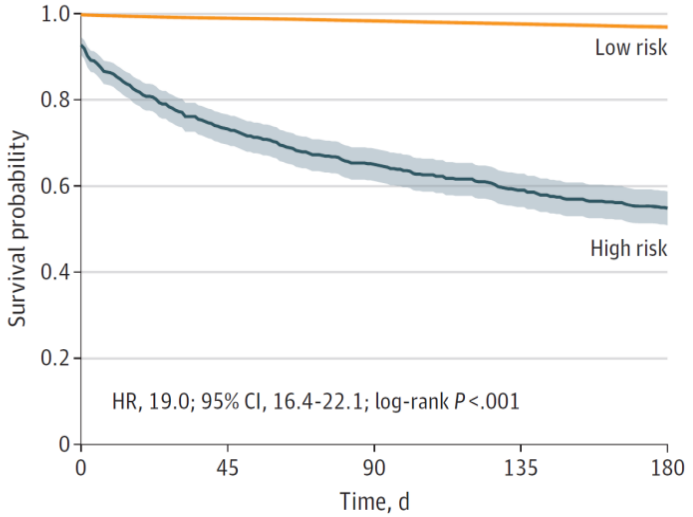
- AUROC 1-year survival
- Machine learning 0.77 (0.73–0.81)
- Physician 0.72 (95% CI 0.63–0.81)
- ECOG only 0.68 (0.65–0.71)

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Gensheimer et al. *JAMIA* 2020

Machine Learning

- Gradient-boosted model included 559 structured HER features to predict 6 month mortality (Parikh JAMA Netw Open 2019)
- Validation cohort included 24,582 cancer patients in oncology practices (University of Pennsylvania Health System)
- 24% had stage IV cancer



Variable	Prognostic index	
	ECOG (n = 6225)	Elixhauser (n = 24 582)
Baseline classifier AUC (95% CI)	0.72 (0.70-0.75)	0.69 (0.68-0.71)
ΔAUC (95% CI) between ML algorithm and baseline classifier	0.17 (0.14-0.19)	0.20 (0.18-0.21)
Baseline classifier PPV, No.	0.27	0.10
ΔPPV between ML algorithm and baseline classifier, No.	0.18	0.36
NRI (95% CI) from enhanced vs baseline classifier	0.09 (0.04-0.14)	0.23 (0.20-0.27)

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Manz et al. *JAMA Oncol* 2020

Machine Learning

Variable	AUC (95% CI)	AUPRC	Scaled Brier score	PPV	NPV	Sensitivity	Specificity	No.	Rate	
									Mortality	Alert
Overall	0.89 (0.88-0.90)	0.34	0.29	0.45	0.97	0.27	0.99	24 582	0.04	0.025
Practice site[a]										
Included in algorithm training										
Yes	0.89 (0.88-0.90)	0.37	0.29	0.47	0.97	0.29	0.98	18 927	0.05	0.03
No	0.86 (0.83-0.88)	0.22	0.26	0.36	0.98	0.17	0.99	5655	0.03	0.01
Practice site										
Tertiary academic	0.89 (0.87-0.90)	0.37	0.31	0.45	0.97	0.31	0.98	10 658	0.05	0.03
Breast	0.96 (0.94-0.98)	0.49	0.38	0.57	0.99	0.41	0.99	1862	0.03	0.02
Gastrointestinal	0.85 (0.81-0.88)	0.38	0.32	0.39	0.92	0.29	0.95	1193	0.10	0.08
Thoracic	0.82 (0.77-0.86)	0.38	0.32	0.42	0.93	0.34	0.95	1060	0.09	0.08
Genitourinary	0.88 (0.80-0.94)	0.33	0.43	0.39	0.98	0.36	0.98	1048	0.04	0.03
Gynecologic	0.91 (0.87-0.95)	0.24	0.25	0.50	0.99	0.25	1.00	1049	0.02	0.01
Leukemia	0.85 (0.79-0.90)	0.39	0.27	0.50	0.96	0.33	0.98	1062	0.07	0.04
Lymphoma	0.91 (0.85-0.95)	0.29	0.14	0.50	0.97	0.16	1.00	1259	0.04	0.01
Melanoma	0.90 (0.84-0.95)	0.35	0.20	0.25	0.95	0.09	0.98	403	0.06	0.02
Myeloma	0.91 (0.85-0.96)	0.44	0.26	0.62	0.98	0.32	0.99	1179	0.04	0.02
Neuro-oncology	0.74 (0.64-0.83)	0.14	0.21	0.11	0.94	0.05	0.98	355	0.06	0.03
General oncology	0.89 (0.87-0.90)	0.31	0.27	0.45	0.97	0.24	0.99	13 924	0.04	0.02

- High specificity = low false positive rate
- Moderate sensitivity = moderate false negative rate

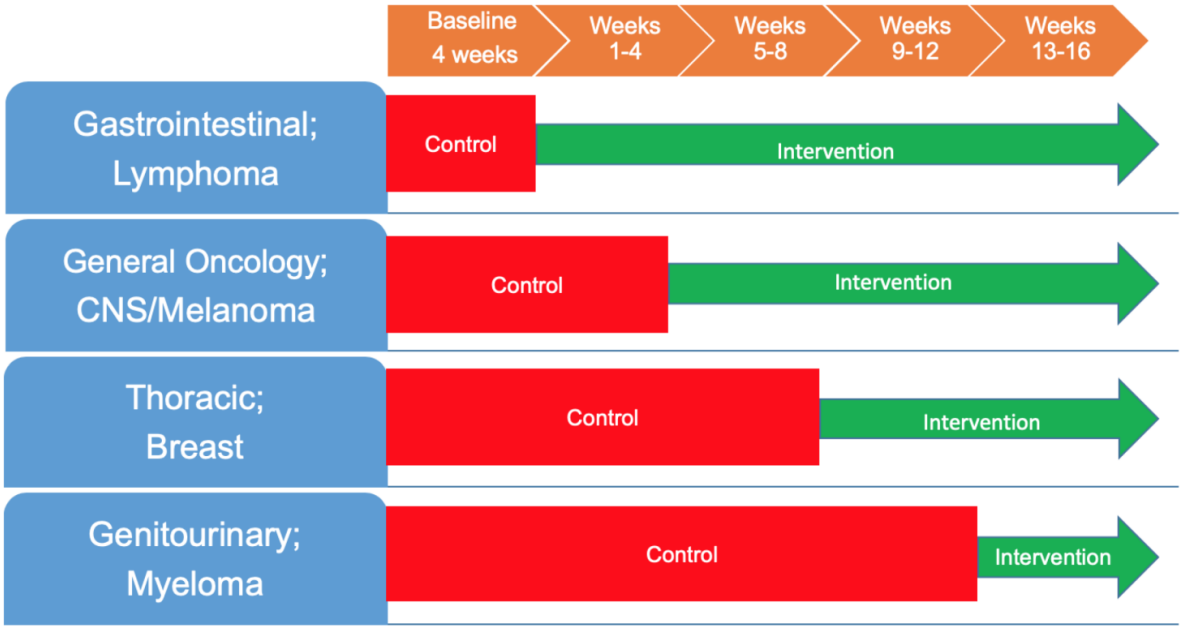
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Manz et al. *JAMA Oncol* 2020

Machine Learning with Nudges

Stepped Wedge Randomized Trial

78 clinicians, 14,607 patients, outpatient oncology encounters



Intervention

- Weekly emails to oncology clinicians with SIC performance feedback (# of SIC notes and peer comparisons)
- A list of up to 6 high-risk patients (≥10% predicted risk of 180-day
- mortality) the next week based on machine learning algorithm
- Opt-out SIC reminder prompts to clinicians on appointment day
- Control: usual care with weekly emails of cumulative SIC performance

Outcomes

1. Change in SIC rate among all patient encounters
2. Changes in rates of (1) SICs among high-risk patients and (2) ACPs for the overall sample and for the high-risk subgroup

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Manz et al. *JAMA Oncol* 2020

Machine Learning with Nudges

Stepped Wedge Randomized Trial

Table 2. Adjusted Changes in Serious Illness Conversations and in Advanced Care Planning

Conversation	No./total No. (%) of encounters		Adjusted difference for intervention relative to control, percentage points (95% CI)[a]	*P* value
	Control	Intervention		
Serious illness encounters				
All patients	155/12 170 (1.3)	632/13 889 (4.6)	3.3 (2.3-4.5)	<.001
High-risk patients	77/2125 (3.6)	304/1999 (15.2)	11.6 (8.2-15.5)	<.001
Advanced care planning encounters				
All patients	231/12 170 (1.9)	680/13 889 (4.9)	3.0 (2.1-4.1)	.001
High-risk patients	124/2125 (5.8)	350/1999 (17.5)	11.7 (8.4-15.7)	<.001

"The electronic medical record had an ACP section in which Advance care planning notes were documented. Any note documented in this section was classified as an ACP. The subset of notes that included a preformatted SIC template was classified as an SIC. Thus, ACPs encompassed both SIC and non-SIC documentation about treatment goals and wishes."

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Manz et al. *JAMA Oncol* 2020

Unique Challenges

- Generalizability
  - Training set patient population
  - Training set variables

- Electronic health record
  - Different platforms (siloed)
  - Applying algorithm (all variables available?)
  - Integration into user interface

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Outline

- Clinician prediction of survival
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The Hurricane is coming!



It’s time to “Hunker Down”!



Navigating Prognostic Uncertainty

- It is OK not to be certain
- Communicate in time frames
  - Days, weeks, months,
  - Days to weeks, weeks to months, months to years
- In addition to survival, prediction of treatment response, adverse effects, and function
- Artificial intelligence will augment, not replace, clinicians

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Supporting Decision Making

Clinical Triggers

- Advance care planning
  - Manz et al. JAMA Oncol 2020
- Goals of care discussions
  - Hui et al. J Clin Oncol 2023
- Specialist palliative care referral
  - Avati et al. IEEE 2017
  - Hui et al. Lancet Oncol 2017

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Summary

- Prognostic approaches
  - Clinician prediction of survival—temporal question, surprise question,
  - Prognostic models—PPI, PaP, PiPS, OPS
  - Machine learning

- Prognostication is, by definition, filled with uncertainty
  - Embrace uncertainty
  - Trigger clinical actions
  - Empower patients to plan head

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  - Dr. Yvonne Heung
  - Dr. Rida Khan
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  - Dr. Kevin Madden
  - Dr. Varsha Pawate
  - Dr. Akhila Reddy
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  - Julia Herskovits
  - Diane Lablue
  - Anna McCall
  - Jessica Miles
  - Joann Nguyen
  - Tam Ta
  - Sally Xu
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  - Thoracic Rad Onc (Dr. Zhongxing Liao, Dr. Michael O'Reilly, Dr. Saumil Gandhi)
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  - Hospital Medicine (Dr. Marina George, Dr. Cerena Leung)
  - Ethics (Dr. Nico Nortje)
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