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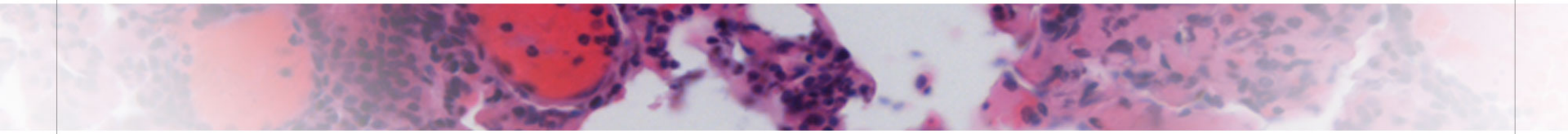


Development and Validation of the Advanced Stage Hodgkin Lymphoma (HL) International Prognostication Index (A-HIPI): A Report from the Hodgkin Lymphoma International Study for Individual Care (HoLISTIC) Consortium

Angie Mae Rodday*, Susan K. Parsons*, Jonathan W Friedberg, Andrea Gallamini, Eliza Hawkes, David Hodgson, Peter Johnson, Brian Link, Eric Mou, Kerry J. Savage, Jenica Upshaw, Pier Luigi Zinzani, Matthew Maurer, Andrew M. Evens (*co-first author)

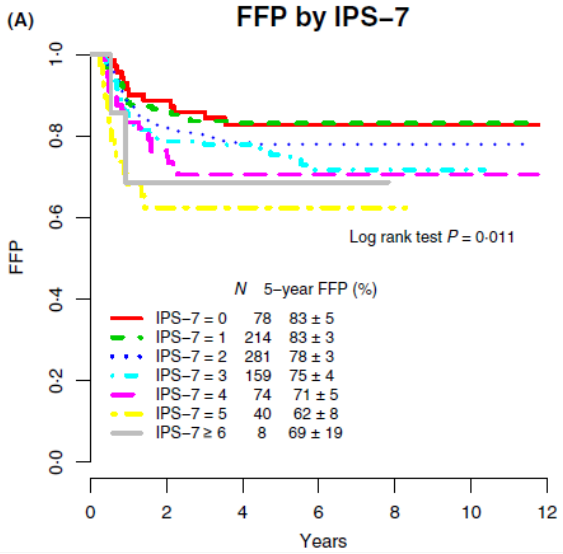
Conflict of Interest Disclosure

- I hereby declare the following potential conflicts of interest concerning my presentation:

- Consultancy and Honoraria (research or educational): Epizyme; MorphoSys; Hutchmed; Daiichi Sankyo, OncLive; Abbvie; Seattle Genetics, Pharmacyclics; and Novartis
- Research Funding: LLS, ORIEN, and NCI/NIH
- Patents and Royalties: none
- Membership on an Entity's Board of Directors or Advisory Committees: none
- Discussion of off-label drug use: checkpoint inhibitor therapy in frontline

Background

- Prognostic models based on pre-treatment factors can help identify patients with advanced stage classic Hodgkin lymphoma (cHL) who are at increased risk of relapse or death
- The International Prognostic Score (IPS7) has been a standard index in cHL for 25 years
- Performance of IPS7 diminished when analyzed in patients treated in the contemporary era
- More sophistication available in prediction model development & validation



(Hasenclever D, et al. NEJM 1998; Moccia AA et. JCO 2012; Diefenbach CS, et al. BJH 2015; Moons KGM, et al. AIM 2015)

HoLISTIC Consortium

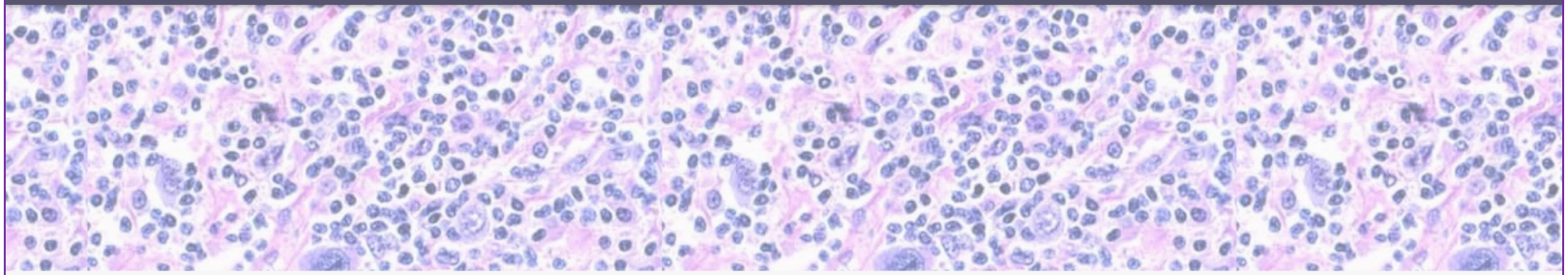
- In 2018, Drs. Parsons and Evens formed an international consortium,
  HoLISTIC (Hodgkin Lymphoma International STudy for Individual Care)
  - https://www.hodgkinconsortium.com/
- 70+ members with expertise in pediatric & adult hematology, epidemiology, imaging, biology, statistics & prediction modeling, and patient advocates
- Individual patient data on >15,000 HL patients from 16 recent, international phase III clinical trials (untreated early and advanced stage HL) and 4 major cancer registries

(Evens AM et al. EHA 2020)

www.hodgkinconsortium.com

HoLISTIC

About Research Team Contact Us Members



Hodgkin Lymphoma International Study for Individual Care

Enhancing decision support to optimize care for individual patients.

Collaboration
between worldwide investigators

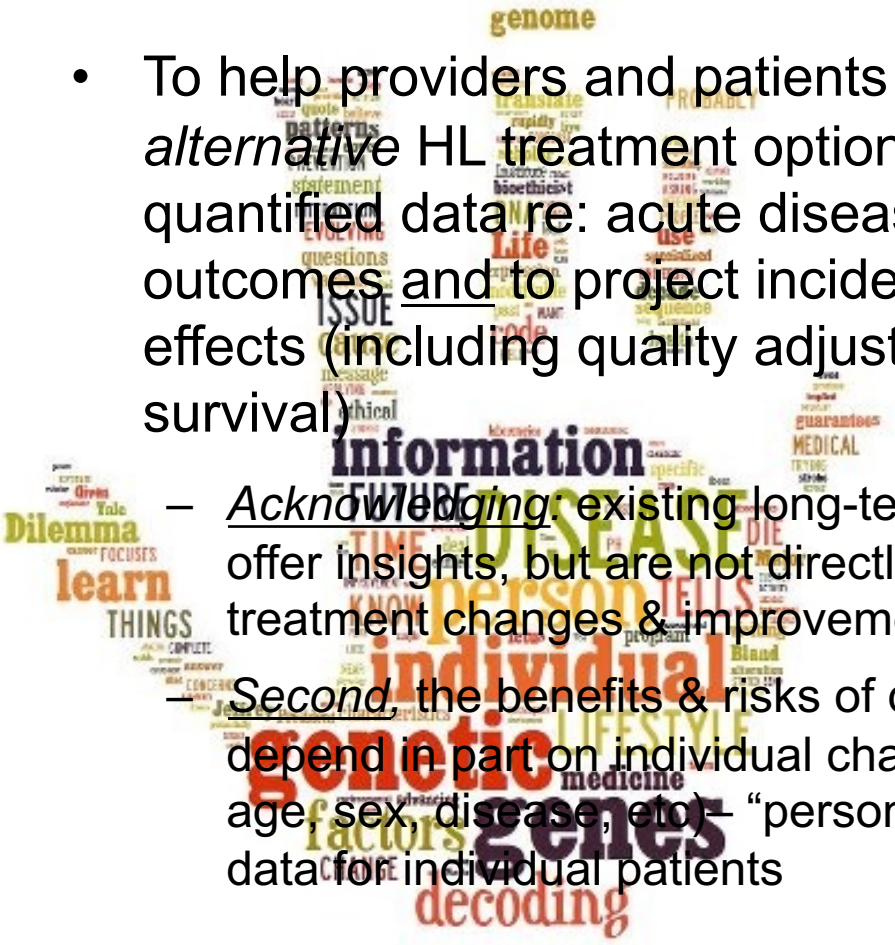
Individualization
of each person's care

Decision-Making
amongst patients, caregivers and providers

Susan Parsons, MD, MRP
Tufts Medical Center
United States

Purpose of Decision Support?

- To help providers and patients assess *alternative* HL treatment options w/ objective & quantified data re: acute disease-related outcomes and to project incidence & risk of late effects (including quality adjusted long-term survival)
  - *Acknowledging*: existing long-term follow-up data offer insights, but are not directly relevant due to treatment changes & improvements over time
  - *Second*, the benefits & risks of different therapies depend in part on individual characteristics (eg, age, sex, disease, etc) – "personalizing" aggregate data for individual patients

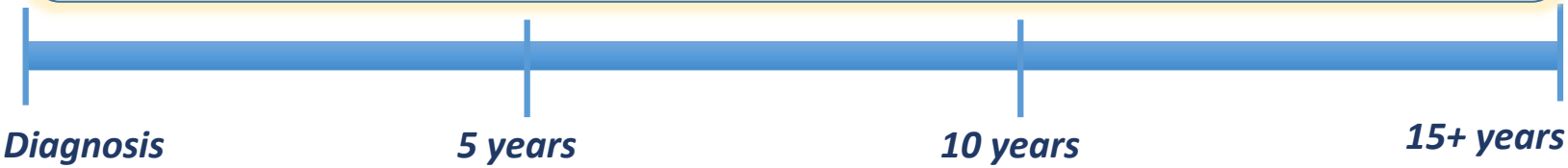


Data sources to study the continuum of care for Hodgkin lymphoma patients

Clinical Trial efficacy data (adverse event data typically stops at 1 year)

Critical Data Gaps *in post-trial morbidity, LEs, HRQL, and later outcomes & survival*

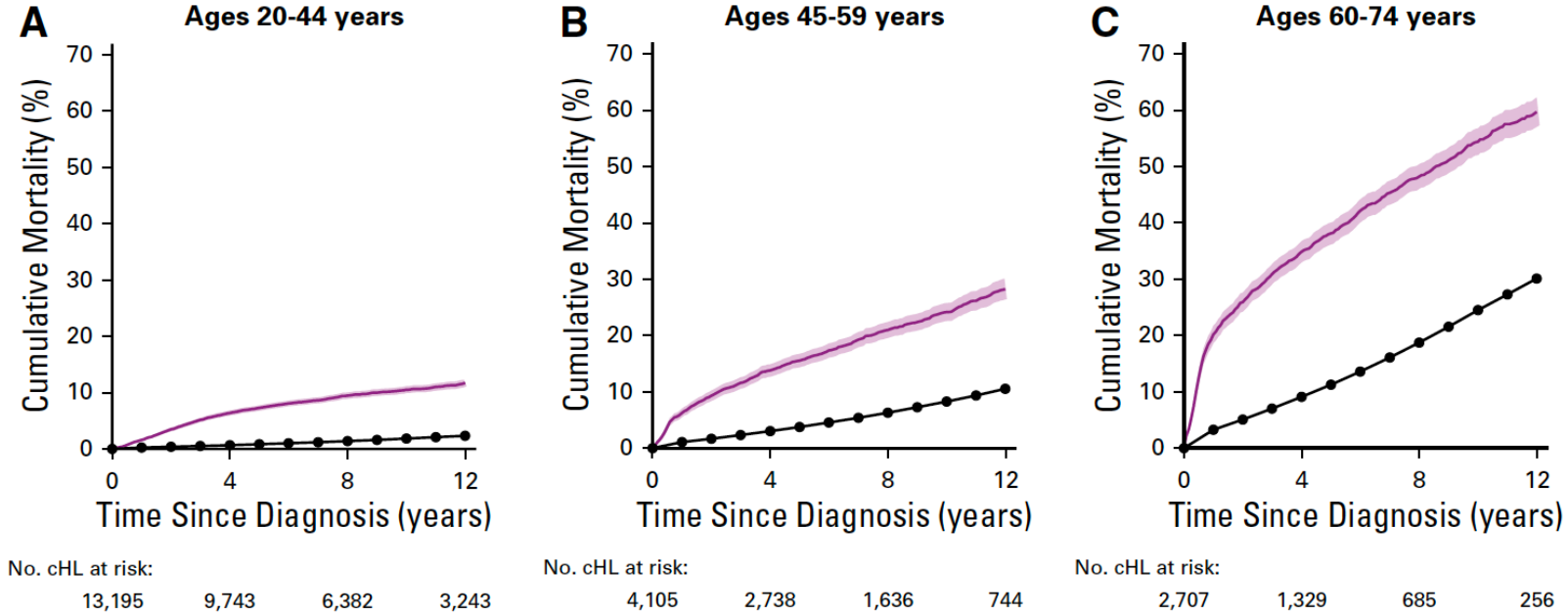
HL Registries/Cohorts & links to healthcare utilization data. Extended follow-up & detailed data of morbidities (e.g., heart disease, 2nd cancers), HRQL, and survival



- Ideal information to study morbidity and mortality across the lifelong time horizon for patients with HL are not available from a single source of data.

Adapted from Evens A and Parons S. *JCO.* 2020

Cumulative mortality: US population vs 20,007 individuals with cHL (SEER 17, 2000-2015)



EARs heart disease 60-74 yrs *SMR stage I/II 38.5; and stage III/IV 59.6*

Cumulative mortality as a result of all causes in the general population and classical Hodgkin lymphoma (cHL) population according to age group

Dores GM et al. *JCO.* 2020

HoLISTIC Timeline

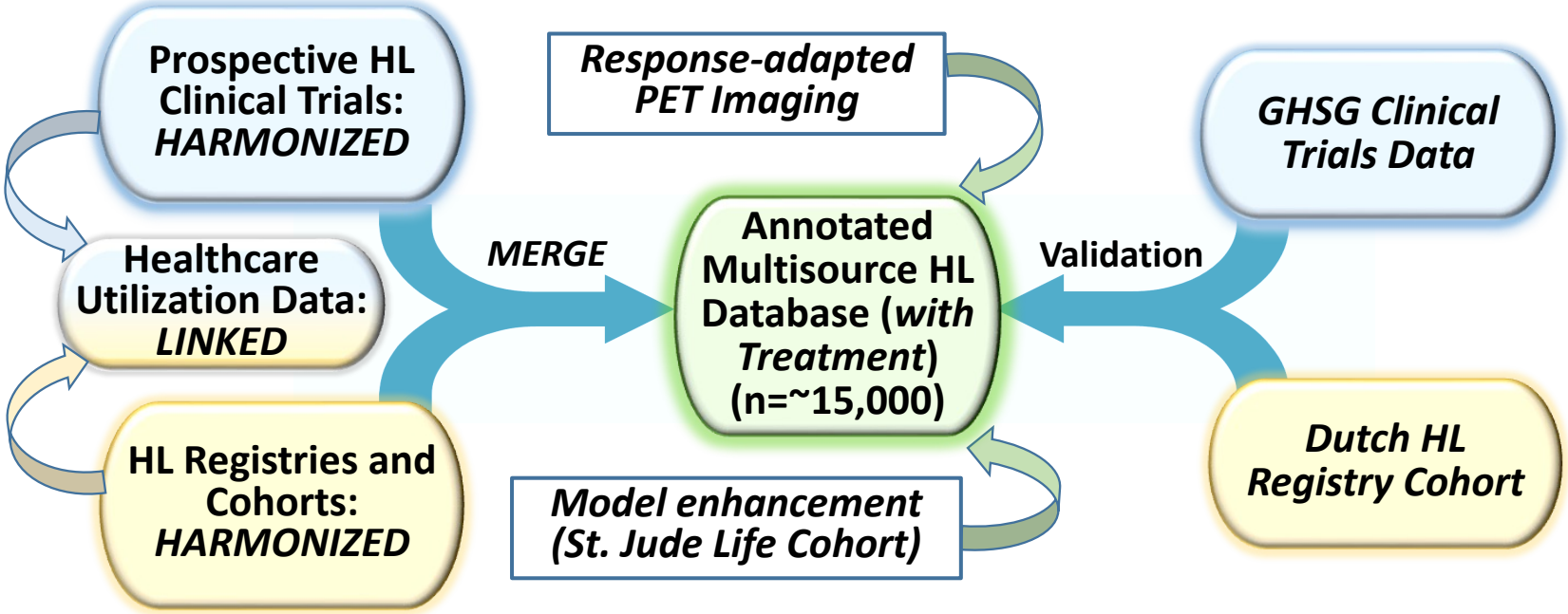
- January 2015 (Boston): idea emerges
- 2015-2017: International stakeholder engagement
- 2018: HoLISTIC officially formed
- 2018-2022: Data sharing agreements and data procurement
- 2019-2022: Common data model created with data dictionary across all sources (standardized, harmonized, and normalized)
- 2021: NCI R01 grant funded $4M
- 2022: Output: ISHL and ASH (and seminal publication)

HoLISTIC Multi-Source Data

- 16 Clinical Studies: US NCI cooperative groups (i.e., SWOG, ECOG, COG), Canada (CCTG), United Kingdom (UK), the EORTC, LYSA (France), FIL (Italy): *N=11,579 pts*
- 4 Large HL Registries: Princess Margaret, BC Cancer, Australia, Iowa/Mayo SPORE, etc; *N=4,275 HL pts*
- Large community oncology practice (Kaiser, n=620 pts)
- *Validation cohorts: St Jude LIFE, Dutch, GHSG (N=20,000+)*
- *Patient advocate groups: LLS, LRF, Lymphoma Coalition*

Evens AM et al. EHA. 2020

Harnessing Multisource Data for Individualized Decision Support



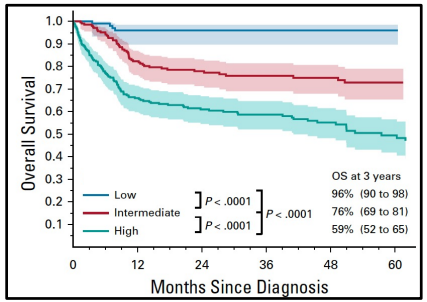
Data sets in **BLUE** harness granular acute 3-5 year data, especially involving HL outcomes; data sets in **YELLOW** are enriched with later non-HL events >5-10 years post-therapy.

Abbreviations: HL, Hodgkin lymphoma; PET, positron emission tomography; GHSG, German Hodgkin Study Group.

Modeling Multi-Source Data: Specific Aims

Sp. Aim #1: Predictive modeling

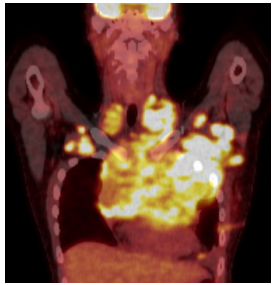
Merge >12,000 multi-source IPD to create, validate, and calibrate a pre-treatment prediction model of HL survival



Sp. Aim #2: Multi-state modeling

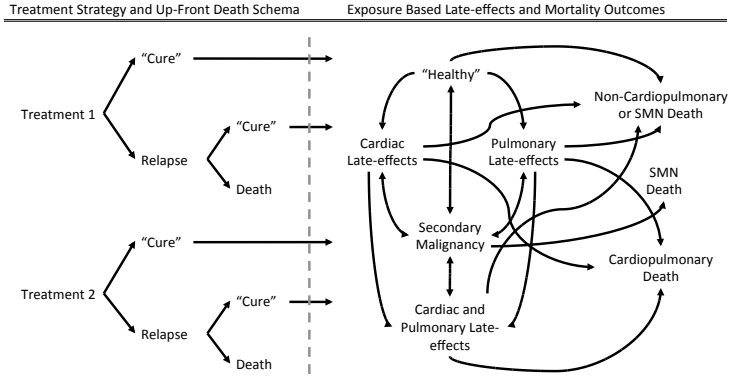
Estimate the impact of alternative treatments & response-adapted imaging on HL survival (5-year)

Key treatment differences (chemotherapy regimens & number of cycles) and use of radiation



Sp. Aim #3: Simulation modeling

Establish simulation models of late effects & long-term non-HL outcomes based on cumulative therapy exposures & key patient factors



NCI R01262265-01A1 (Parsons/Evens, MPI)

Aim

- Develop and validate a modern pre-treatment model to predict progression free survival (PFS) and overall survival (OS) at 5 years in adult patients with newly-diagnosed advanced stage cHL

A-HIPI Population & Data

- Population
  - Adults aged 18 to 65 years
  - Newly diagnosed with stage IIB, III, or IV cHL
- Model development: 4,022 patients from 8 advanced staged cHL trials conducted from 1996 to 2014
  - HD9601, HD2000, UK Stanford V, ECOG2496, SWOG0816, RATHL; HD0801, HD0607
- Model validation: 1,431 patients from 4 cHL cancer registries diagnosed from 1996-2019
  - BC Cancer, Princess Margaret Cancer Centre, Iowa/Mayo SPORE, Australia
  - Treated with curative intent & not treated on a trial above

Outcomes & Potential Predictors

- Outcomes
  - 5-year PFS defined as progression, relapse, or death from any cause
  - 5-year OS defined as death from any cause
- Potential pre-treatment predictors
  - Sex and age at diagnosis
  - Stage, B symptoms, histology, and bulk
  - White blood cell count, absolute lymphocyte count, hemoglobin, albumin, and erythrocyte sedimentation rate
  - Linearity of continuous predictors assessed
  - Multiple imputation used for missing data

Model Development & Validation

- Built separate *Cox models* for 5-year PFS and OS using *backward elimination* ($p<0.05$) to select predictors
- *Discrimination* assessed using Harrell's c-statistic
- *Calibration* assessed by comparing observed and predicted 5-year outcomes by decile of predicted probability
- *Internal validation* to obtain shrinkage factors to reduce overfitting
- *Internal-external validation* using leave-one-out cross-validation on trials in development cohort to assess heterogeneity in performance
- Discrimination & calibration of model in external validation cohort assessed (discrimination/calibration of IPS7 in external validation cohort)
- All vis-à-vis TRIPOD recommendations & checklist

(Steyerberg EW, et al. EHJ 2014; Moons KGM, et al. AIM 2015; Steyerberg EW, et al. JCE 2016; Van Calster B et al., BMC Medicine 2019)

Rigorous Predictive Modeling: TRIPOD

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	5c	D;V	Give details of treatments received, if relevant.	6
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6-7
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	7
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	Supplement, page 2
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7 and Supplement
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	7-8 and Supplement
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7-8 and Supplement
	10c	V	For validation, describe how the predictions were calculated.	8 and Supplement
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8 and Supplement
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	6
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8-9 and Figure S1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 1
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	8
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Tables S4 and S5
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Supplement page 5
	15b	D	Explain how to the use the prediction model.	10
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	10
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	N/A
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	14
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	13-14
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	14
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	14
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	10, 16
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	15

- TRIPOD Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
- **DISCRIMINATION:** how well a model differentiates those at higher risk of having an event from those at lower risk
- **CALIBRATION:** informs clinicians how similar the predicted outcome is to the *true/observed outcome* in external groups of patients (the accuracy of *absolute risk* estimates, or the ability of a model to accurately predict outcomes in other cohorts)

Moons KGM, et al. AIM 2015; Steyerberg EW, et al. EHJ 2014
Steyerberg EW, et al. JCE 2016; Alba AC, et al. JAMA. 2017; 318:1377-1384

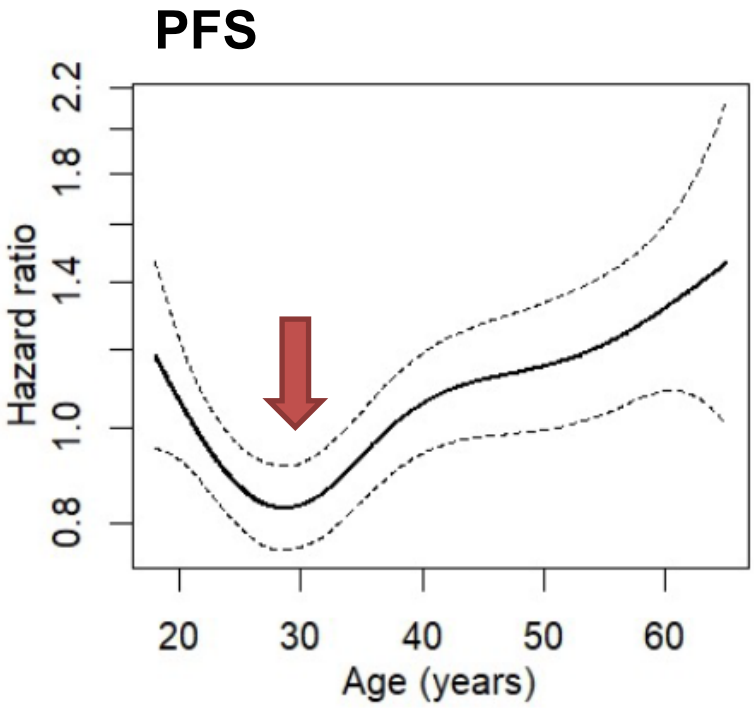
Characteristics of A-HIPI cohorts

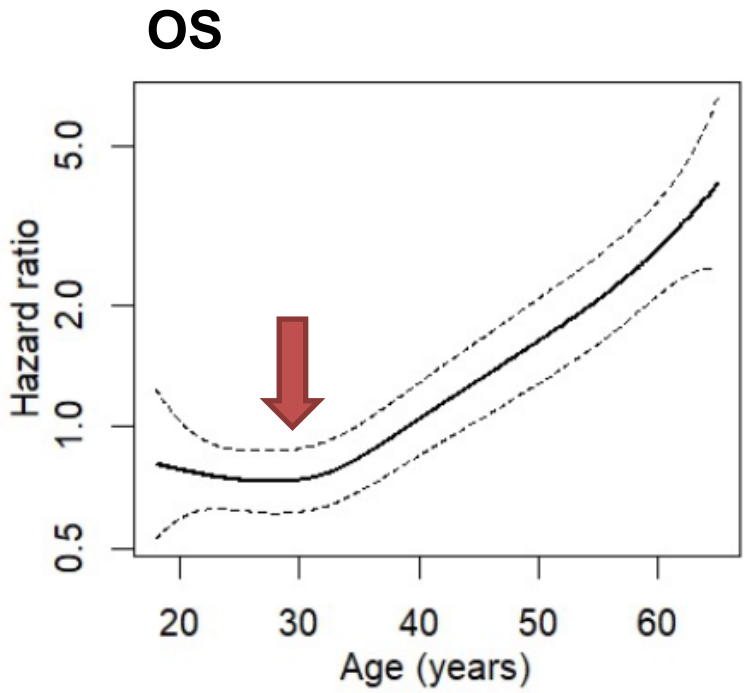
	Development (N=4022)
Age (years), mean (SD)	35 (12)
Female sex	45%
Stage	
Stage IIB	28%
Stage III	39%
Stage IV	34%
Bulk	35%
Hemoglobin (g/dL), mean (SD)	12 (2)
Albumin (g/dL), mean (SD)	3.7 (0.6)
Lymphocyte count (10^3/uL), mean (SD)	1.5 (0.7)
5-year PFS (KM)	77%
5-year OS (KM)	92%

Characteristics of A-HIPI cohorts

	Development (N=4022)	Validation (N=1431)
Age (years), mean (SD)	35 (12)	36 (13)
Female sex	45%	44%
Stage		
Stage IIB	28%	38%
Stage III	39%	30%
Stage IV	34%	33%
Bulk	35%	30%
Hemoglobin (g/dL), mean (SD)	12 (2)	12 (2)
Albumin (g/dL), mean (SD)	3.7 (0.6)	3.7 (0.6)
Lymphocyte count (10^3/uL), mean (SD)	1.5 (0.7)	
5-year PFS (KM)	77%	78%
5-year OS (KM)	92%	91%

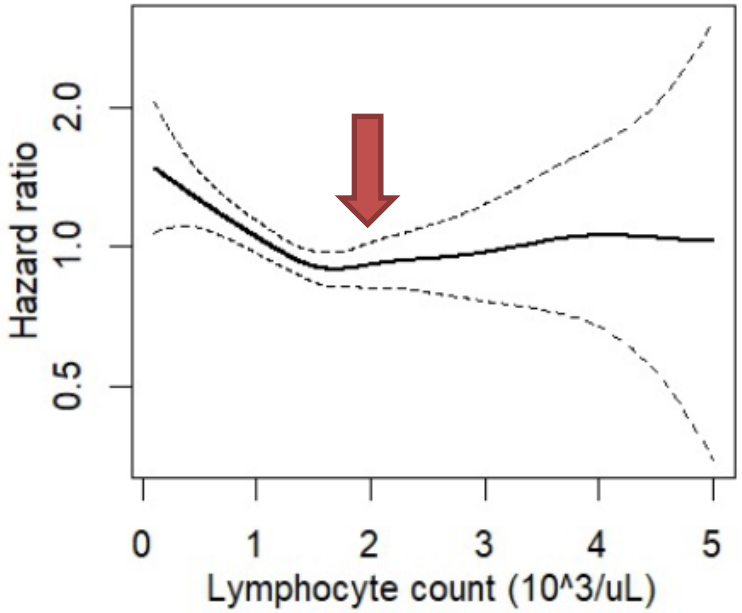
Non-linear relationship for age



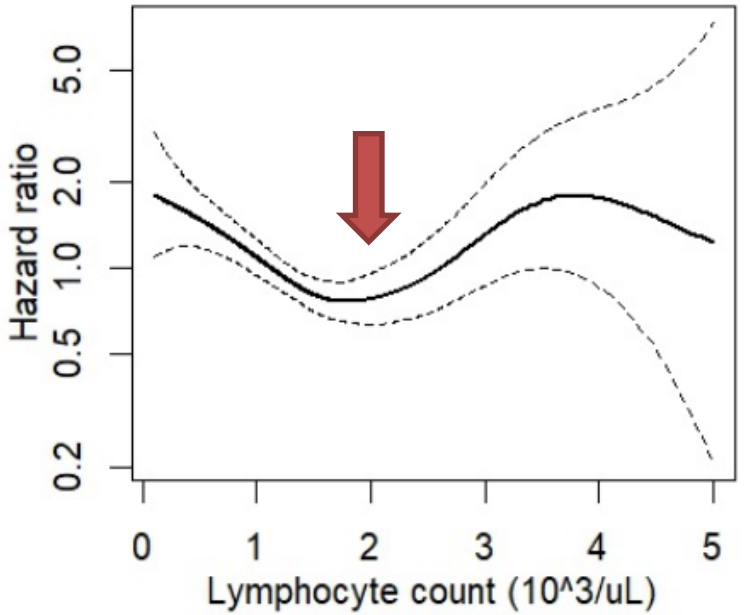


Non-linear relationship for lymphocyte count

PFS



OS



A-HIPI model parameters for 5-year PFS

	5-year PFS HR (95% CI)
Age (years)	
Linear effect in 18 to 30 years	0.97 (0.95, 1.00)
Linear effect in >30 years	1.02 (1.01, 1.02)
Female	--
Stage	
Stage IIB	
Stage III	1.23 (1.03, 1.48)
Stage IV	1.53 (1.27, 1.83)
Bulk	--
Hemoglobin (g/dL)	--
Albumin (g/dL)	0.74 (0.66, 0.82)
Lymphocyte count (10^3/mm^3)	
Linear effect in .1 to 2	0.75 (0.65, 0.87)
Linear effect in 2 to 5	1.21 (0.96, 1.52)

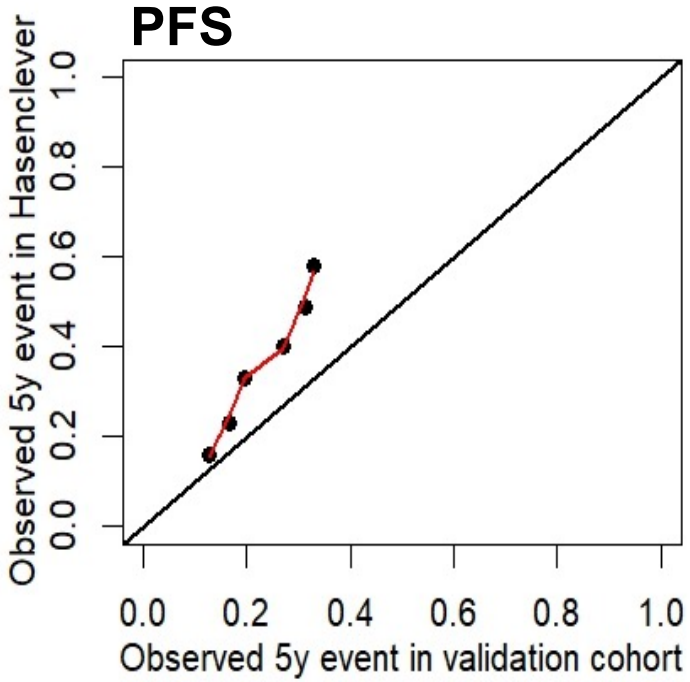
A-HIPI model parameters for 5-year PFS & OS

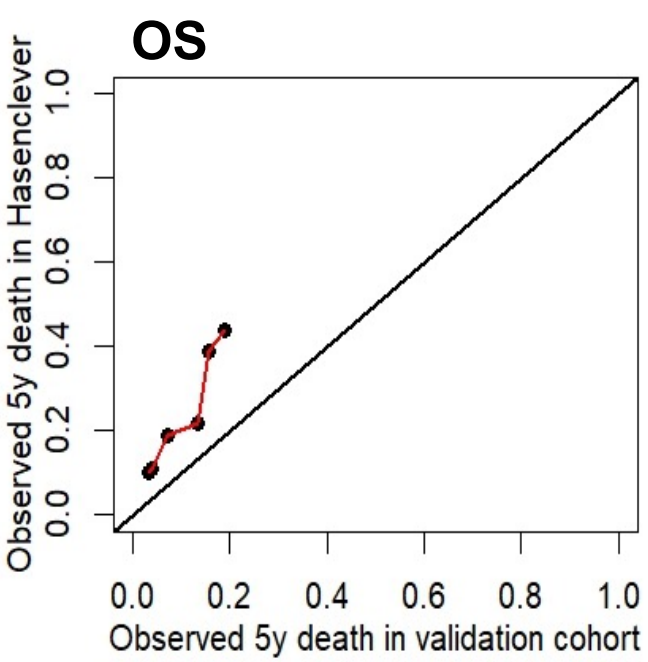
	5-year PFS HR (95% CI)	5-year OS HR (95% CI)
Age (years)		
Linear effect in 18 to 30 years	0.97 (0.95, 1.00)	0.98 (0.94, 1.02)
Linear effect in >30 years	1.02 (1.01, 1.02)	1.05 (1.04, 1.07)
Female	--	0.78 (0.61, 1.00)
Stage		
Stage IIB		
Stage III	1.23 (1.03, 1.48)	
Stage IV	1.53 (1.27, 1.83)	1.33 (1.04, 1.70)
Bulk	--	1.37 (1.05, 1.78)
Hemoglobin (g/dL)	--	0.88 (0.81, 0.96)
Albumin (g/dL)	0.74 (0.66, 0.82)	0.67 (0.53, 0.84)
Lymphocyte count (10^3/mm^3)		
Linear effect in .1 to 2	0.75 (0.65, 0.87)	0.61 (0.46, 0.80)
Linear effect in 2 to 5	1.21 (0.96, 1.52)	1.49 (0.99, 2.22)

A-HIPI model discrimination for 5-year PFS & OS

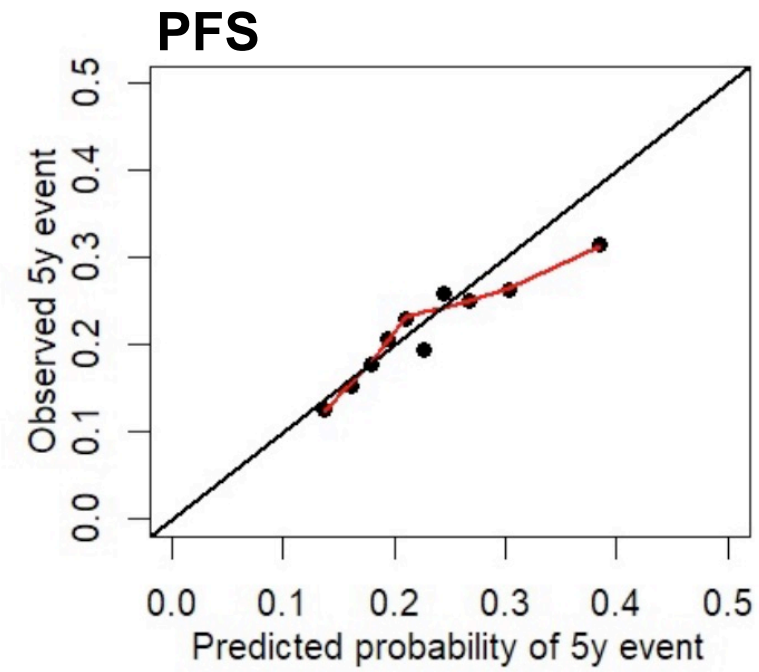
C-statistic	5-year PFS	5-year OS
Development cohort	0.605	0.732
Development cohort: optimism corrected	0.595	0.717
Validation cohort	0.590	0.730
IPS7, validation cohort	0.597	0.692
IPS3, validation cohort	0.579	0.657

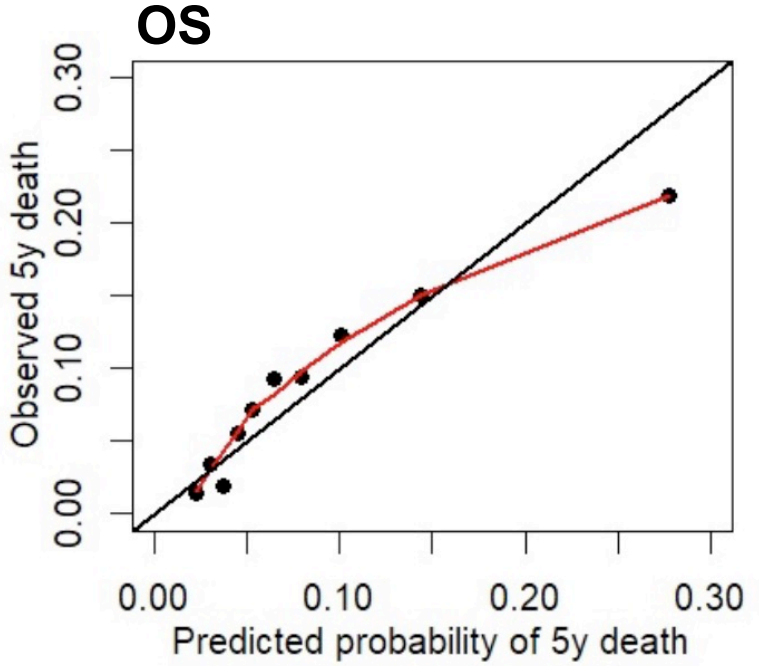
Calibration of IPS7 in validation cohort





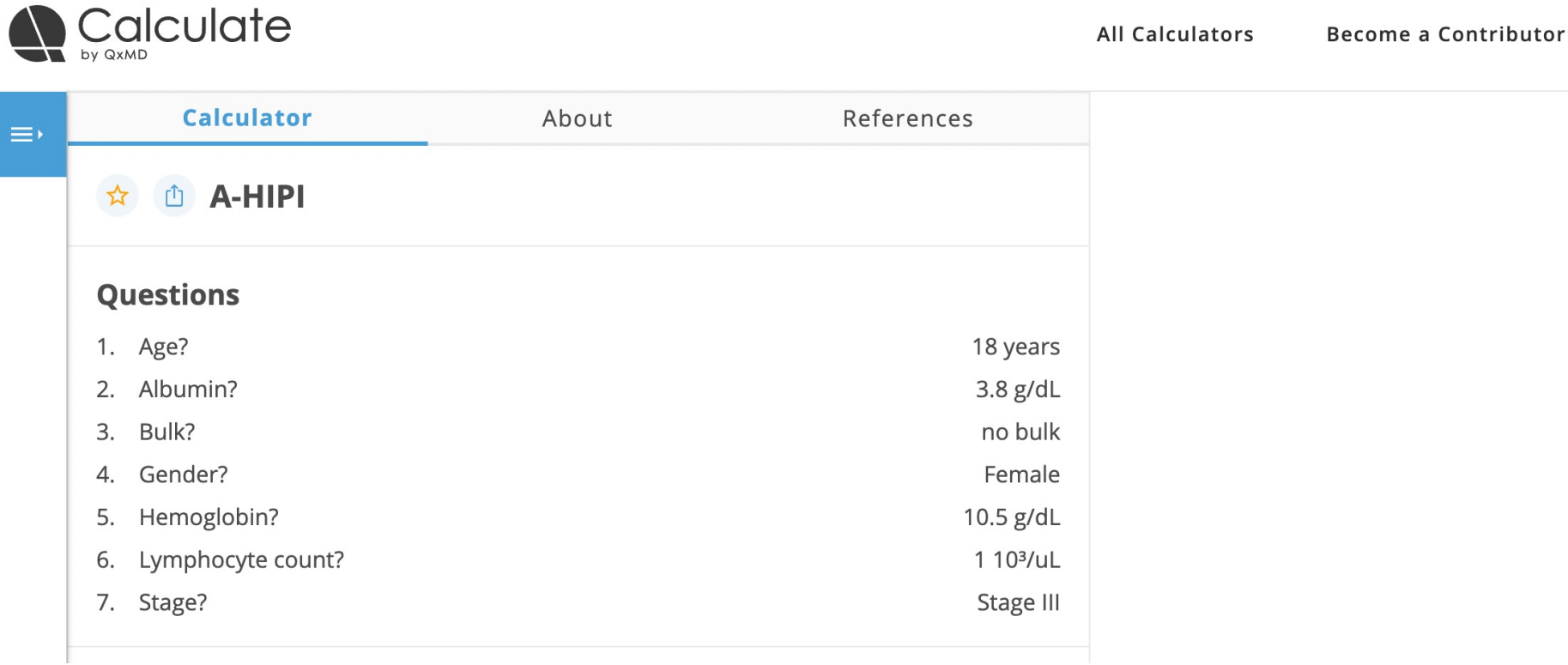
A-HIPI model calibration in validation cohort





(Van Calster B. et al., BMC Medicine 2019)

Online calculator for point-of-care use (QxMD)



Conclusion & Next Steps

- We identified novel non-linear relationships between age and lymphocyte count and patient outcomes
- A-HIPI model discrimination was similar for PFS and better for OS than IPS7
- A-HIPI model calibration was superior for PFS and OS than IPS7
- Future studies will:
  - Incorporate post-baseline factors (e.g., interim imaging, variable treatment, etc) and biology to improve prediction of individualized outcomes
  - Estimate risk of post-acute & late effects (based on patient & treatment factors)
  - Conduct similar analyses in early stage cHL and relapsed/refractory disease
  - Examine HRQL, cost of care, and biology

Journal of Clinical Oncology®

The Advanced-Stage Hodgkin Lymphoma International Prognostic Index (A-HIPI): Development and Validation of a Clinical Prediction Model from the HoLISTIC Consortium

ascopubs.org/doi/full/10.1200/JCO.22.02473

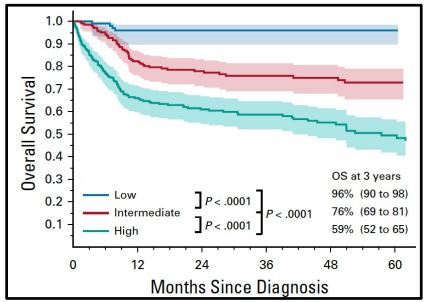
SCAN ME

American Society of Hematology

Modeling Multi-Source Data: Specific Aims

Sp. Aim #1: Predictive modeling

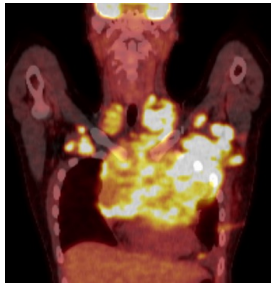
Merge >12,000 multi-source IPD to create, validate, and calibrate a pre-treatment prediction model of HL survival



Sp. Aim #2: Multi-state modeling

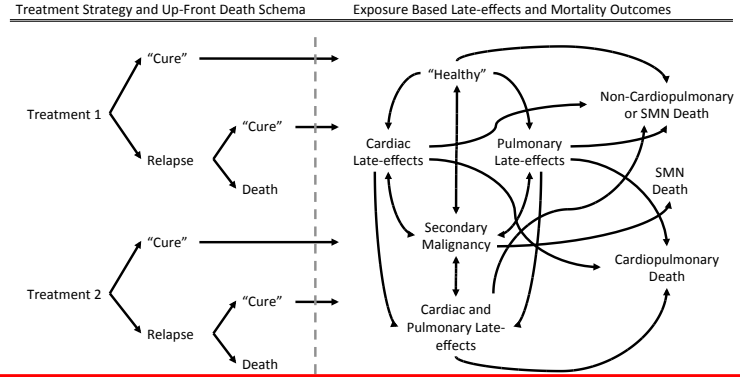
Estimate the impact of alternative treatments & response-adapted imaging on HL survival (5-year)

Key treatment differences (chemotherapy regimens & number of cycles) and use of radiation



Sp. Aim #3: Simulation modeling

Establish simulation models of late effects & long-term non-HL outcomes based on cumulative therapy exposures & key patient factors



NCI R01262265-01A1 (Parsons/Evens, MPI)

Early-stage Hodgkin lymphoma (ESHL) in the modern era: simulation modeling to delineate long-term patient outcomes

- Considered contemporary (post-2000) randomized clinical trials comparing RT-based CMT vs chemotherapy alone for untreated ESHL with favorable features (Nachman 2002; Meyer 2005; Raemaekers 2014; Radford 2015; Andre 2017)
- Detailed computer simulation model to project disease natural history for pediatric & adult ESHL pts treated with chemotherapy alone or combined modality therapy
  - Model consisted of a series of health states: (i) at risk for relapse; (ii) relapse; (iii) cured without relapse; (iv) cured with relapse; (v) cured with late effects; and (vi) dead

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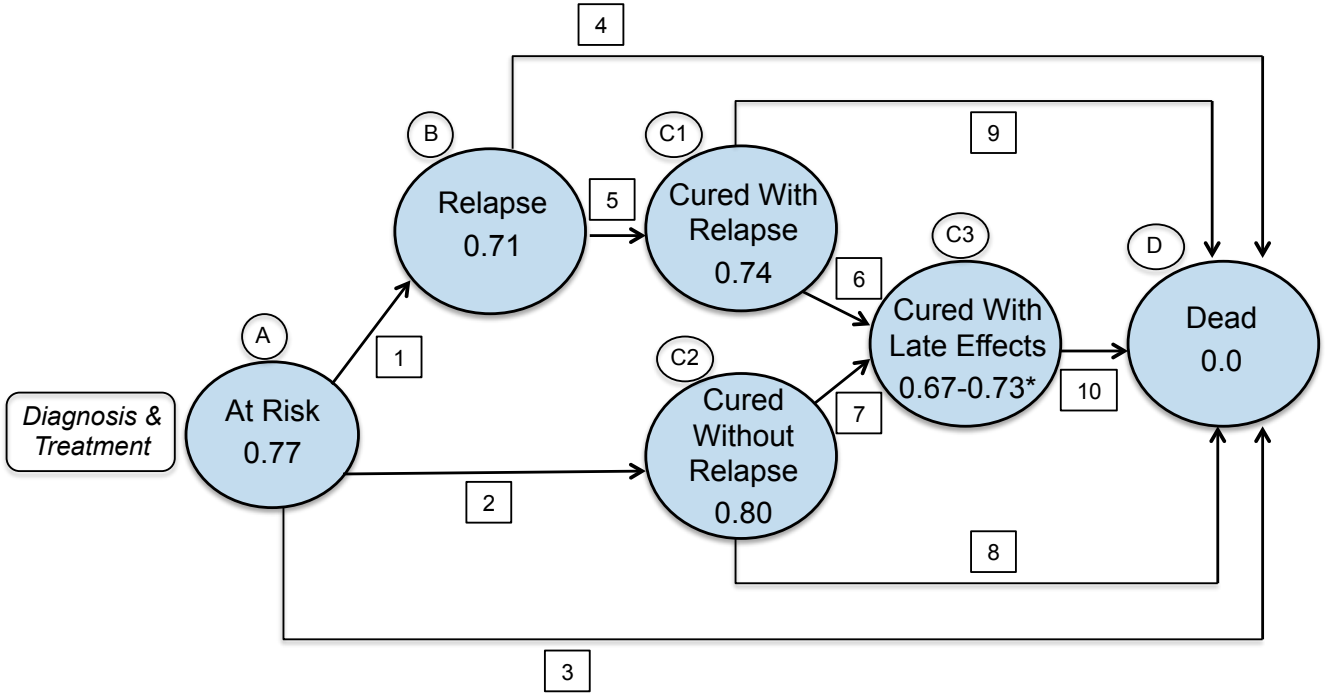
Multistate models to estimate transition probabilities

- The Cox PH assumption of non-informative censoring is violated when there are competing events or risks that prevent the occurrence of an event of interest (e.g., death prevents the occurrence of relapse)
  - Intermediate, non-fatal events that influence the risk of a future event can also undermine this assumption (e.g., relapse changes the risk of death)
- Multi-state models make it possible to estimate transition rates from an initial state, to different transient states, and to a final, absorbing state (e.g., death), while also accounting for

Health State Transition Diagram



Circles represent individual health states; value within each circle is the *utility weight* (or health-related quality of life impact) of that health state; arrows represent *transition pathways* b/t states (*represents range of utility weight values categorized on severe or non-severe LEs)

Prototype of Simulated Disease Progression Model

- For each treatment, estimated quality-adjusted life expectancy (QALYs), survival in years, with each year scaled by a utility preference weight corresponding to that year's health state
  - health state utility preference weights range from 0 to 1, with a weight of zero for the 'Dead' state, and a weight of 10 for the (hypothetical) state of 'perfect health'
- Analyzed 35-year late effect probabilities following 10-year latency (w/ sensitivity analyses)

Linendoll N et al, Health and Quality of Life Outcomes. 2016

Simulation Modeling to Predict Long-Term Patient Outcomes: Early-Stage Hodgkin Lymphoma in the Modern Era

- *Case examples*
  - Case #1: 25 yo M favorable ESHL (stage IA right cervical and supraclavicular)
  - Case #2: 25 yo F unfavorable ESHL (stage IIA mediastinal, hilar, and b/l axillary disease)
  - 3-year PFS 91%-97% with LEs range from 30-45-90% (sex, use of CMT vs CA and relapse vs not)
- Case #1: CMT superior to CA in quality-adjusted discounted survival (0.074 QALYs) and unadjusted survival (0.016 life years)
- Case #2: CMT inferior to CA in quality-adjusted discounted survival (-1.161 QALYs) and unadjusted survival (-5.137 life years)

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HoLISTIC Outputs

- Modern, granular, individualized prediction models (pre-treatment and post-treatment factors) with acute, post-acute & late effects (e.g., specific cardiovascular/arterial and cancer risks, etc)
  - Based on individual patient/disease factors and varied treatment options
  - Newly-diagnosed advanced stage, early stage, relapsed/refractory
- Future options
  - Cost of care
  - Incorporation of biology (e.g., tumor factors, genetic risk (e.g., SNPs) of late effects); and HRQL
  - Integration of patient preferences

Opportunities!

- Additional clinical trial and registry data integration
- Working Groups (advanced, early-stage, relapsed/refractory, elderly, imaging, late effects, etc)
- HoLISTIC Consortium governance/charter with finalized executive & voting committee (and policies and procedures)
  - Day-to-day management of consortium
- Conversion of consortium to “open membership”
  - Related data management (and cloud) & statistical support, etc
- Collaboration with industry?
- A resource for new extramural funding & other analyses


GRAZIE!
#LetsBeatHodgkinLymphomaTogether

ADDITIONAL MATERIAL

Range of lab values

- Plausible lab values were defined as:
  - 1-6 for albumin (g/dL)
  - ≥1 for erythrocyte sedimentation rate (mm/hr)
  - 5 to 16.5 for hemoglobin (g/dL)
  - 0.1 to 5.0 for lymphocyte count (10^3/µL)
  - 0.1 to 5.0 for white blood cell counts (10^3/µL)

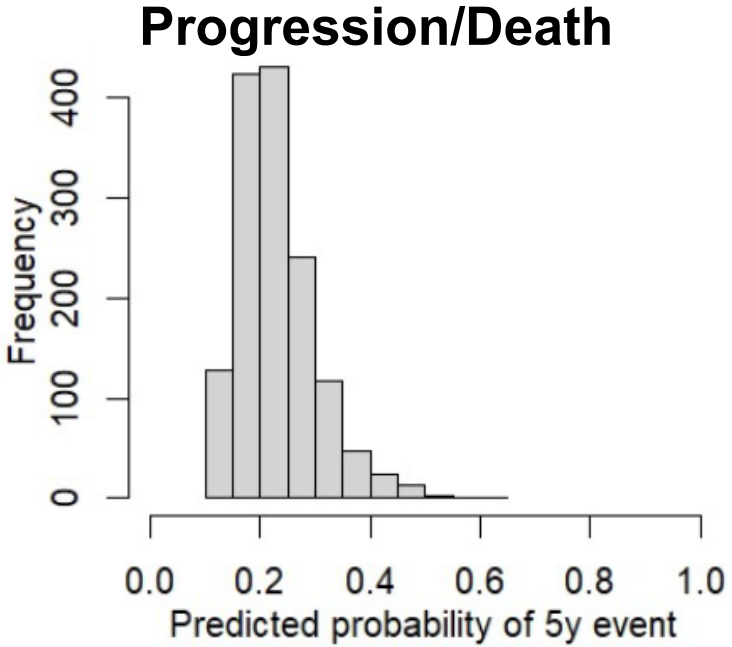
Study Sample - extra

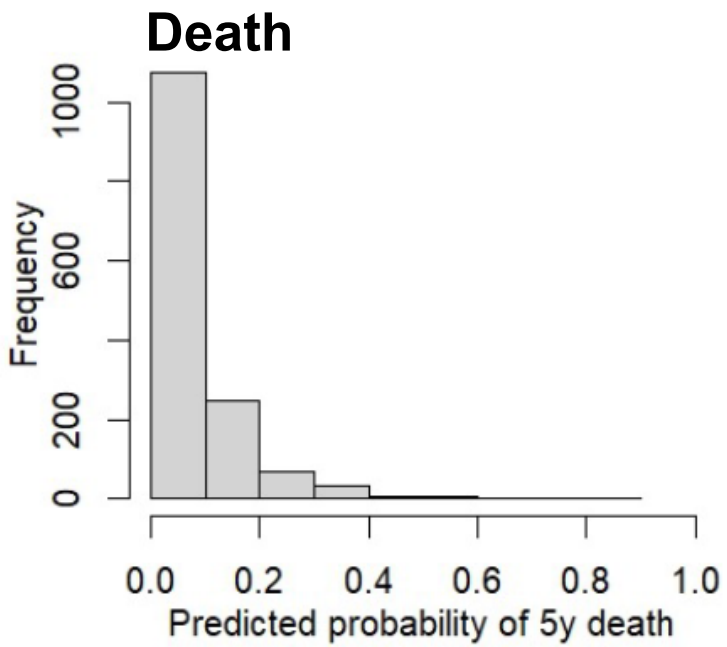
	Development (N=4022)	Validation (N=1431)
Categorical age (years), n (%)		
18 to 30	1618 (40.2%)	613 (42.8%)
>30	2404 (59.8%)	818 (57.2%)
Histology, n (%)		
Lymphocyte depleted	46 (1.1%)	7 (0.5%)
Lymphocyte rich	102 (2.5%)	22 (1.5%)
Mixed cellularity	521 (13.0%)	85 (5.9%)
Nodular sclerosis	2986 (74.2%)	1023 (71.5%)
NOS	367 (9.1%)	294 (20.6%)
B symptoms, n (%)	2938 (73.1%)	1104 (77.1%)
WBC count (10^3/uL), mean (SD)	10.7 (5.3)	10.8 (5.2)
Categorical lymphocyte count (10^3/uL), n (%)		
0.1 to 2	3183 (79.1%)	1160 (81.0%)
2 to 5	839 (20.9%)	271 (19.0%)
ESR (mm/hour), mean (SD)	59.0 (35.7)	52.8 (35.6)
Follow-up time (months), median (q1, q3)	60.0 (36.0, 60.0)	74 (31, 131.5)

Model parameters

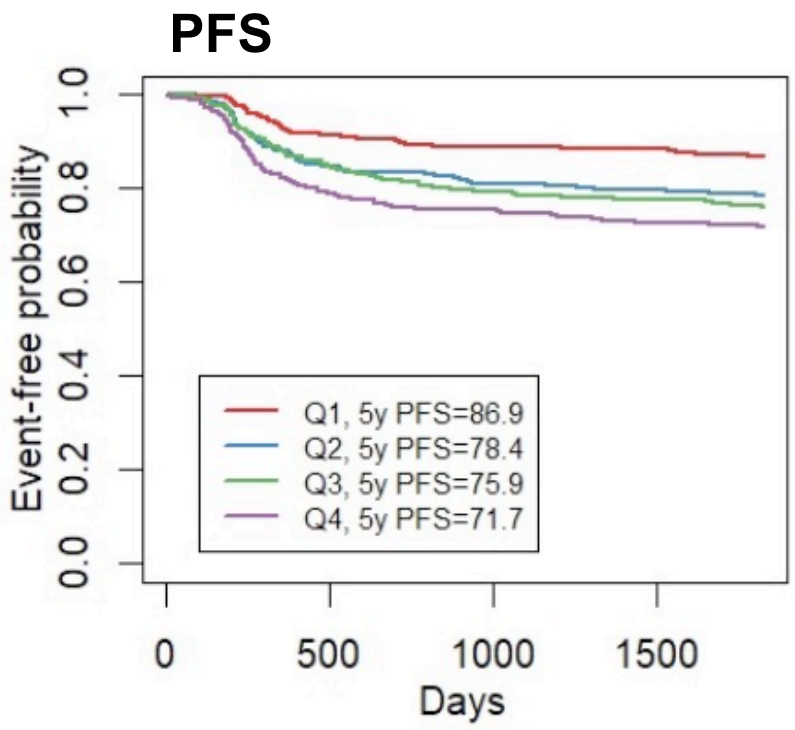
	5-year PFS*			5-year OS*		
	Beta coefficient	HR (95% CI)	Optimism-corrected beta coefficient	Beta coefficient	HR (95% CI)	Optimism-corrected beta coefficient
Age (years)						
Linear effect in 18 to 30 years	-0.026	0.97 (0.95, 1.00)	-0.024	-0.022	0.98 (0.94, 1.02)	-0.020
Linear effect in >30 years†	0.016	1.02 (1.01, 1.02)	0.014	0.049	1.05 (1.04, 1.07)	0.046
Female				-0.251	0.78 (0.61, 1.00)	-0.234
Stage^						
Stage IIB						
Stage III	0.207	1.23 (1.03, 1.48)	0.184			
Stage IV	0.423	1.53 (1.27, 1.83)	0.377	0.285	1.33 (1.04, 1.70)	0.266
Any bulk				0.312	1.37 (1.05, 1.78)	
Lymphocyte count (/mm^3)						
Linear effect in .1 to 2	-0.287	0.75 (0.65, 0.87)	-0.255	-0.497	0.61 (0.46, 0.80)	-0.463
Linear effect in 2 to 5†	0.188	1.21 (0.96, 1.52)	0.167	0.396	1.49 (0.99, 2.22)	0.369
Hemoglobin (g/dL)				-0.124	0.88 (0.81, 0.96)	-0.116
Albumin (g/dL)	-0.307	0.74 (0.66, 0.82)	-0.274	-0.406	0.67 (0.53, 0.84)	-0.379

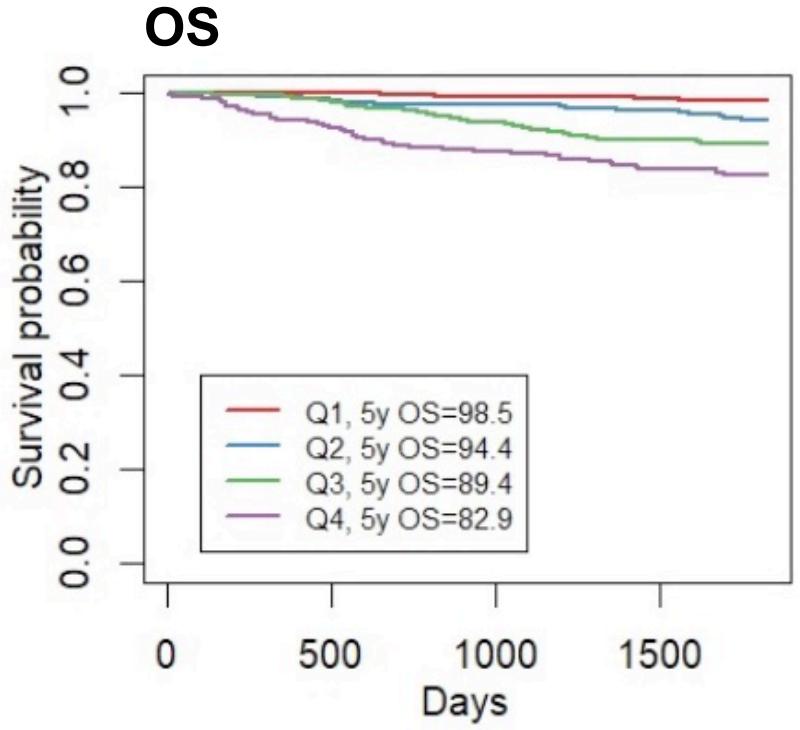
Distribution of predicted probability of outcomes





KM estimators for PFS & OS by quartile





Internal-External Validation

- Internal-external validation using leave-one-out cross-validation on development cohort to assess heterogeneity in performance
  - Each clinical trial was left out ‘one at a time’ to account for between-trial heterogeneity (e.g., use of baseline imaging & staging, definitions of bulk, treatment regimen)
- Results: C-statistics in the omitted trial ranged from 0.54 to 0.65 for PFS and 0.61 to 0.77 for OS

Internal-external validation of A-HIPI Model

- 5-year PFS
  - C-statistics in remaining trials: 0.59 to 0.61
  - C-statistics in the omitted trial: 0.54 to 0.65
- 5-year OS
  - C-statistics in remaining trials: 0.71 to 0.74
  - C-statistics in the omitted trial: 0.61 to 0.77

Internal-external validation of A-HIPI Model

	5-year PFS C-statistic		5-year OS C-statistic	
Trial omitted	Remaining trials	Omitted trial	Remaining trials	Omitted trial
ECOG2496	0.6055	0.584	0.7094	0.721
SWOG0816	0.6064	0.571	0.7291	0.749
HD2000	0.6103	0.547	0.7403	0.642
HD9601	0.6019	0.610	0.7373	0.700
HD0607	0.5949	0.647	0.7137	0.768
HD0801	0.6076	0.577	0.7318	0.702
Stanford V	0.6044	0.543	0.7378	0.613
RATHL	0.6134	0.584	0.7268	0.728

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Table II. Sensitivity analyses and model results.

	Late effect probabilities*				Proportion of late effects severe		Results				CMT advantage	
	C1: with relapse		C2: no relapse				LY	LY	QALY	QALY	LY	QALY
Patient	Chemo	CMT	Chemo	CMT	Chemo	CMT	Chemo	CMT	Chemo	CMT	Delta	Delta
1·0	0·45	0·45	0·30	0·45	0·20	0·20	50·37	50·58	19·10	19·21	0·21	0·11
1·1					**0·10**	**0·10**	50·61	50·97	19·12	19·26	0·35	0·14
1·2					**0·05**	**0·05**	50·73	51·16	19·14	19·29	0·43	0·15
2·0	0·45	**0·90**	0·30	**0·90**	0·20	0·20	50·40	49·48	19·11	18·73	−0·92	−0·37
2·1					0·20	**0·40**	50·37	47·65	19·10	18·49	−2·71	−0·61
2·2					0·20	**0·60**	50·37	45·78	19·10	18·24	−4·59	−0·86
2·3					0·20	**0·80**	50·37	43·82	19·07	17·97	−6·54	−1·10

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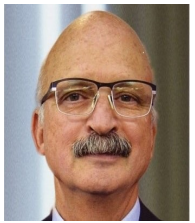

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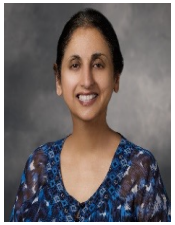

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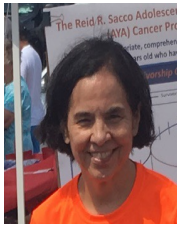

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