

AI IN LIVER TRANSPLANTATION: CURRENT STATUS AND FUTURE PROSPECTS

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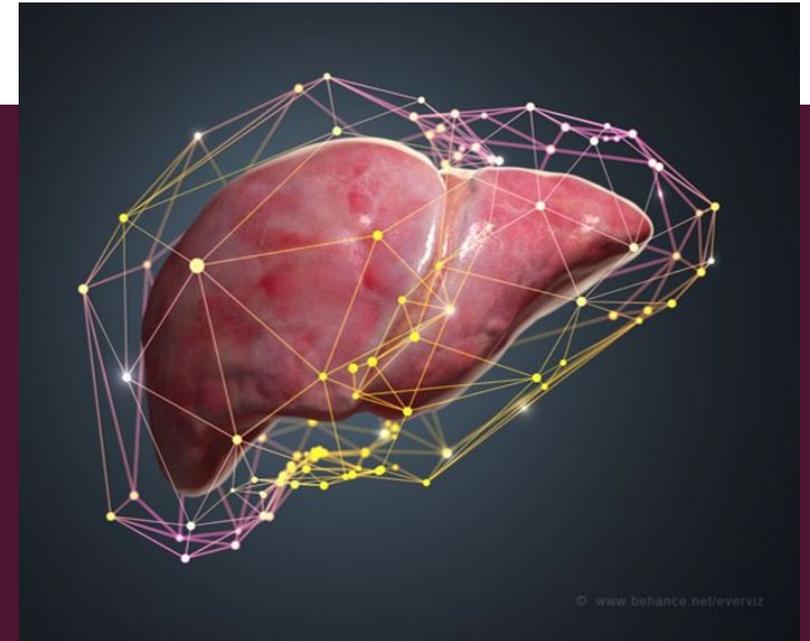
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Transplant Rounds

February 1st, 2023

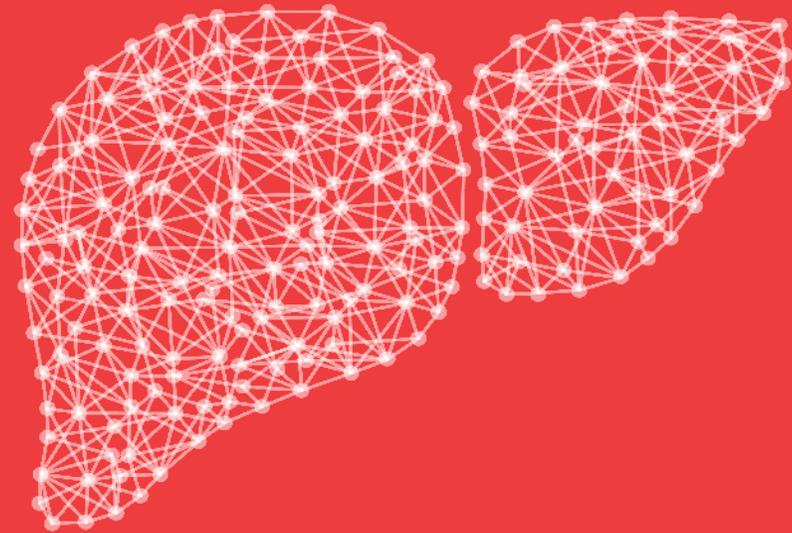


OUTLINE

- What is Machine Learning? Tools, Applications & Limitations
- Why ML in Liver Transplantation?
- Case Studies in Liver Transplantation: Pre, Post-Transplant
- How about Fine-tuning with Molecular Data?
- Steps towards Clinical Deployment!

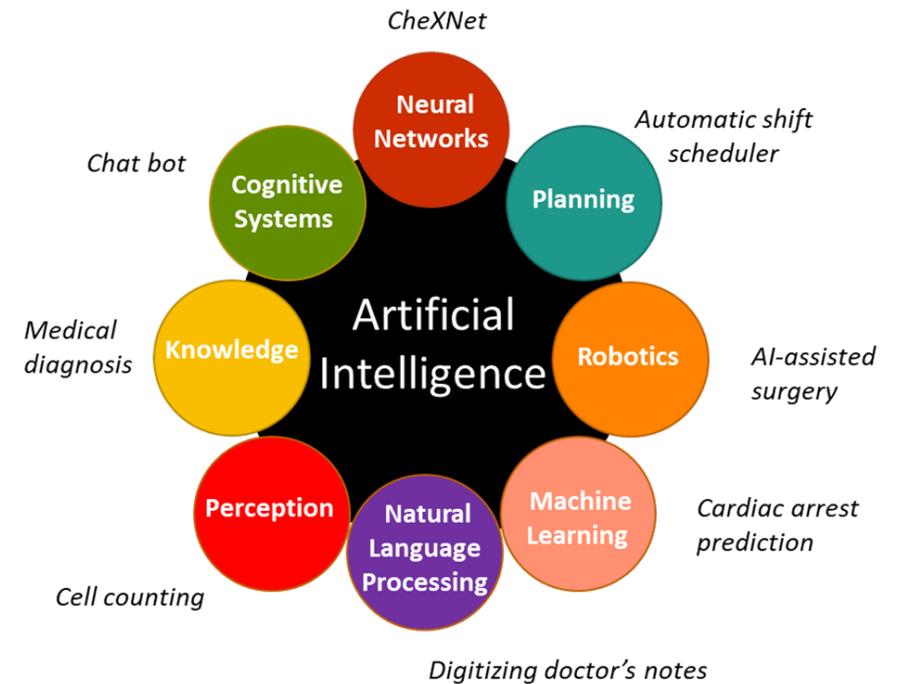


WHAT IS ARTIFICIAL INTELLIGENCE? WHAT IS MACHINE LEARNING?



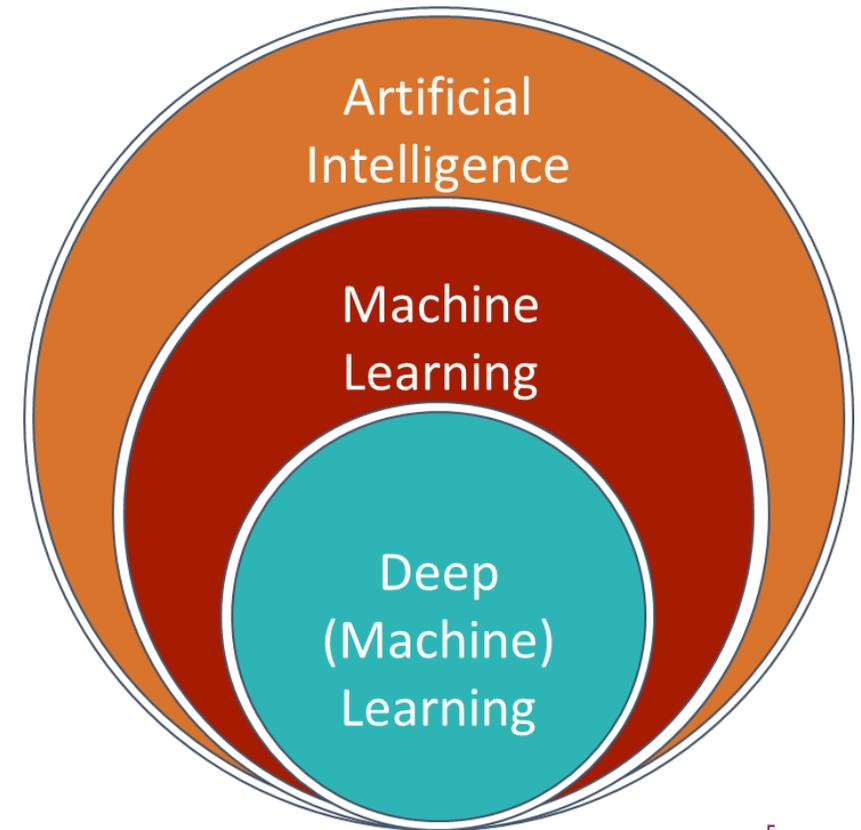
WHAT IS ARTIFICIAL INTELLIGENCE?

- Intelligence combines many traits: learning, reasoning, problem solving, etc
- **Basically Intelligence demonstrated by machines**
- Many valid definitions
 - Technology that behaves intelligently using skills associated with human intelligence
 - Systems that act rationally
 - **Computer systems that use information and “act” in a goal-directed manner**



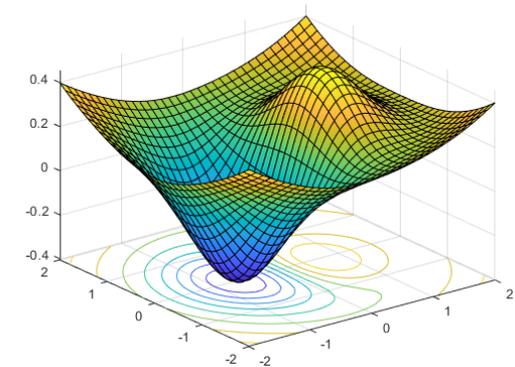
WHAT IS MACHINE LEARNING?

- When many people say “AI” they are referring to machine learning (ML)
- ML is a subset of AI
 - *Field of AI that allows software applications to become more accurate at generating predictive models without being explicitly programmed*
- Detects hidden patterns and interrelationships within large datasets
- Deep learning (DL)/Neural networks (NNs) are a type of ML algorithms

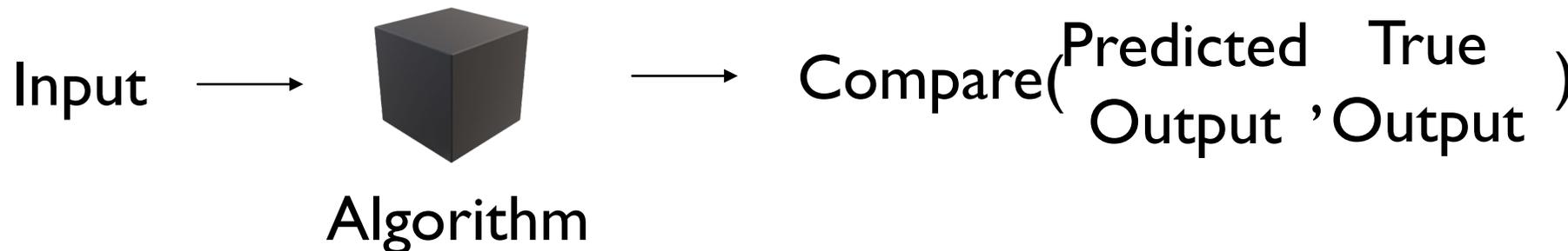


MACHINE LEARNING PIPELINE

- Collect and process **inputs**
- Choose **algorithm** that can map input to output
- Collect and process **outputs**
- **Train** (optimize) algorithm until predicted and true outputs are similar



Optimization



ML VS TRADITIONAL BIOSTATISTICS

- Standard clinical risk assessment models assume risk factor related in linear fashion to clinical outcomes
- ML can better incorporate multiple risk factors and identify more nuanced relationships between risk factors and outcomes
- ML Algorithms learn from existing data to find novel patterns

Auditable Algorithms

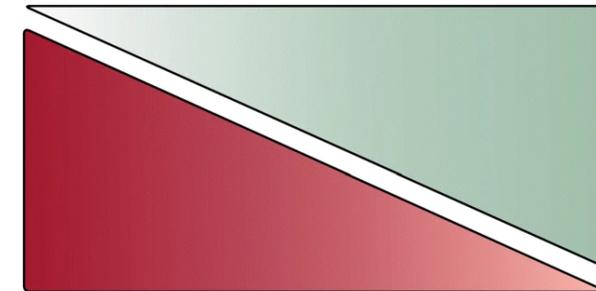
Simpler models including multiple regression and decision trees.

Linear relationships between predictors and outcomes facilitate interpretation.

Many commonalities to statistical techniques.

Computationally 'cheap' can often be run on a consumer PC.

→ Better for complex* data →



Black Boxes

Complex models including neural networks and some Support Vector Machines.

Non-linear relationships between predictors and outcomes make interpretation extremely difficult.

Share few commonalities to statistical techniques.

Computationally 'expensive', may require days of processor time to build models.

← Better for interpretation ←

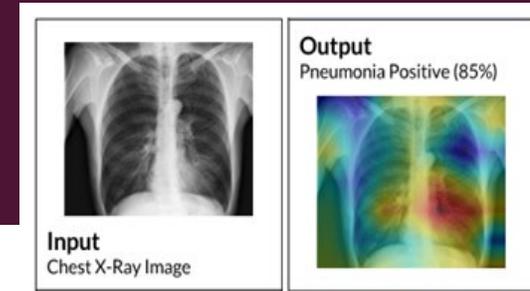
* 'Complex' data could refer to data which do not have a linear relationship with the outcome, such as a pixel in an image, the frequency of a wave in a sound bite, or movement data captured by a smart phone.

Spann A, Wang B, Goldenberg A, Bhat M. **Applying Machine Learning in Liver Disease & Transplantation: A Comprehensive Review**, Hepatology 2020

Sidney-Gibbons et al, BMC Medical Research Methodology 2019

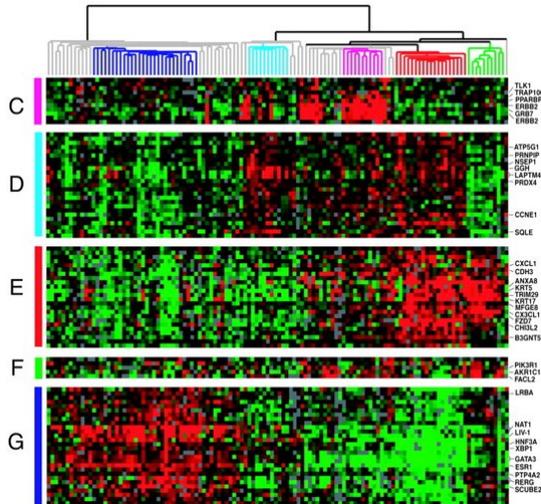
THREE MAIN PARADIGMS OF ML

- Supervised learning (*predicting labels from data*)
- Unsupervised learning (*learning representations of the data*)
- Reinforcement learning (*dynamic decision making using data*)



Predicting pneumonia from chest X-rays

Supervised Learning



Unsupervised Learning

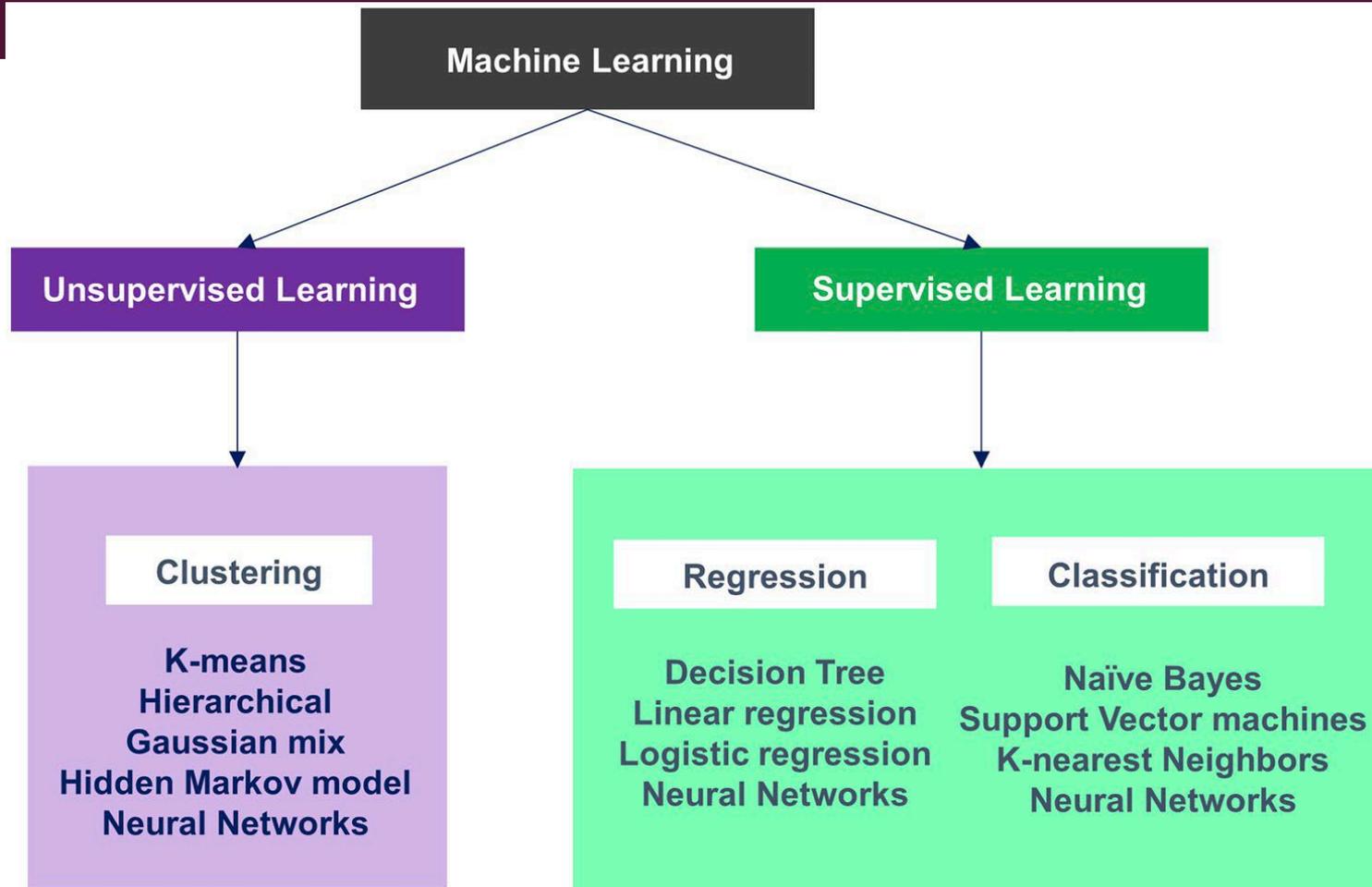
Discovering breast cancer subtypes from gene expression arrays



Reinforcement Learning

Real-time drug dosing practices to understand optimal treatment course

ML MODELS FOR SPECIFIC TASKS



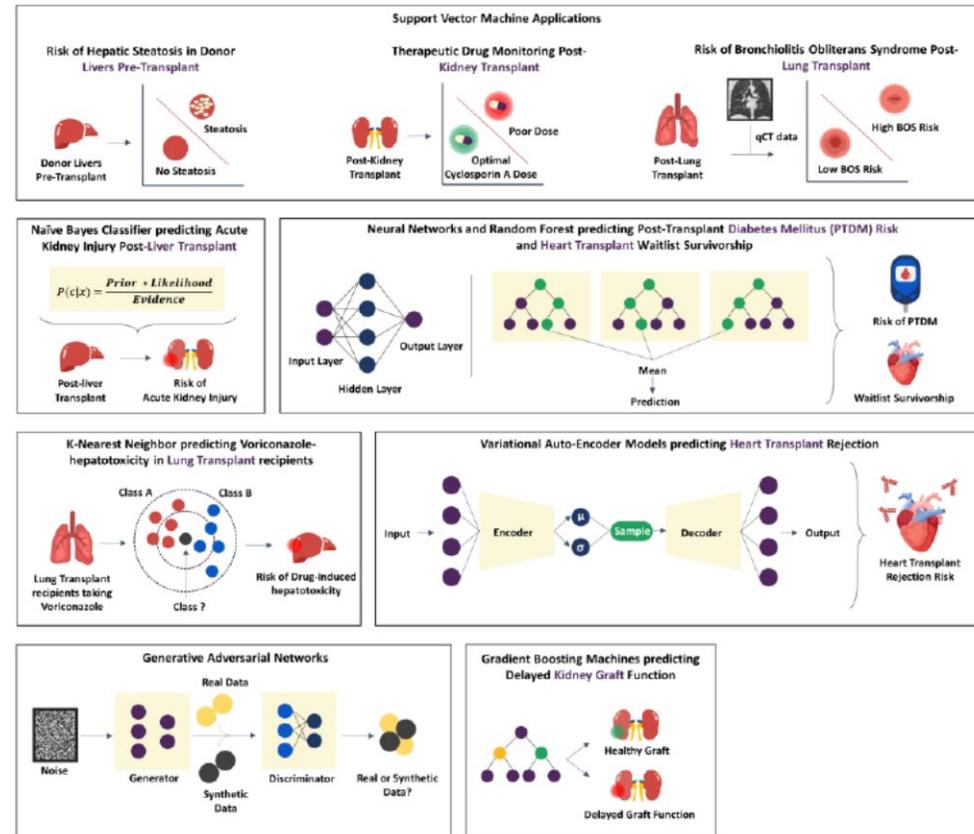


WHY ML IN TRANSPLANTATION?



WHY ML IN TRANSPLANTATION?

- Various factors affect transplant pathology & outcomes: sex, ethnicity, genetics, environmental exposures, lifestyle, BMI, diabetes, immunosuppression
- Complex, non-linear patterns in liver enzymes, liver function tests, platelets, creatinine, sodium
- Electronic health record data, imaging technologies, histology, clinical sensors, wearables, molecular data
- **Applications in Donor-recipient matching**
- **Waitlist prioritization**
- **Prediction of Outcomes**

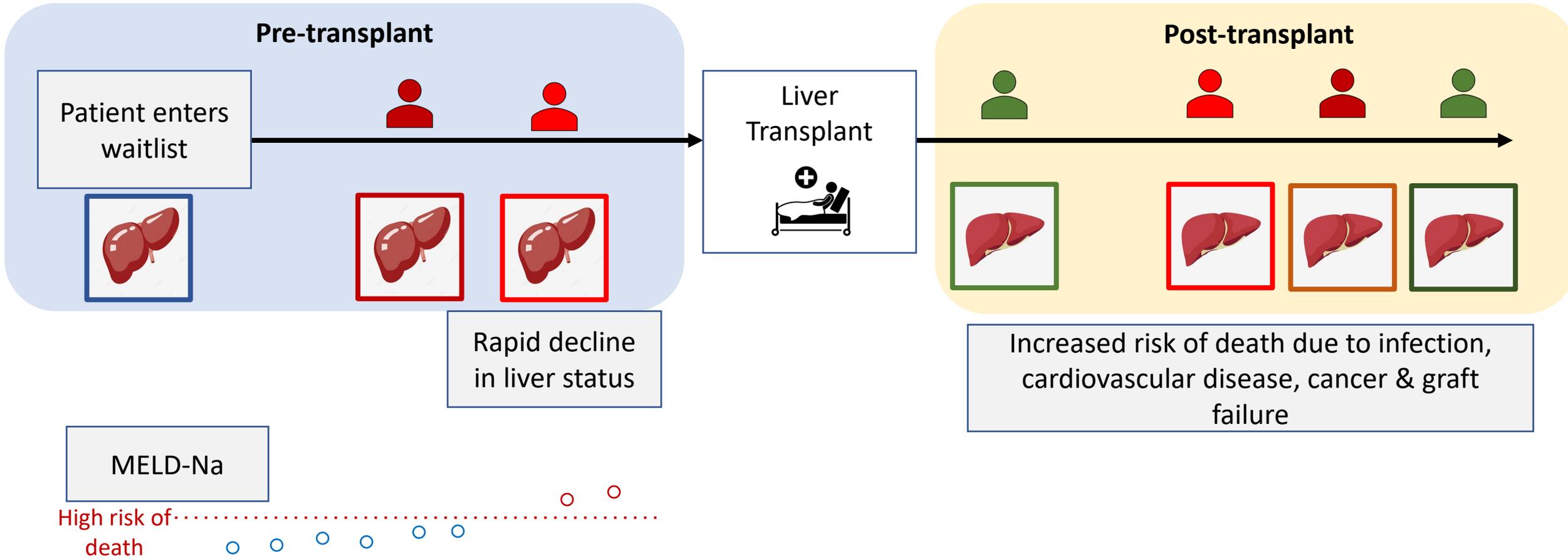


¹Spann A, Wang B, Goldenberg A, Bhat M. Applying Machine Learning in Liver Disease & Transplantation: A Comprehensive Review, Hepatology 2020

²Gotlieb N, Spann A, Wang B, Bhat M. Applying Machine Learning in Solid Organ Transplantation. NPJ Digital Medicine, 2022

³Bhat M, Rabindranath M, Sordid-Chara B, Simonetto D. In Press, Journal of Hepatology 2023

OPPORTUNITY FOR AI IN LIVER TRANSPLANT



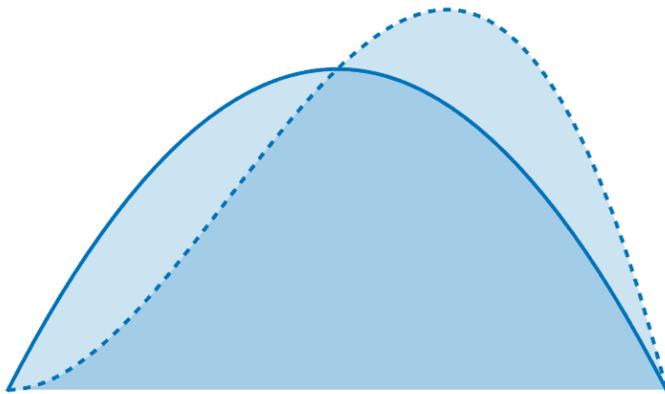


CASE STUDIES IN LIVER TRANSPLANTATION

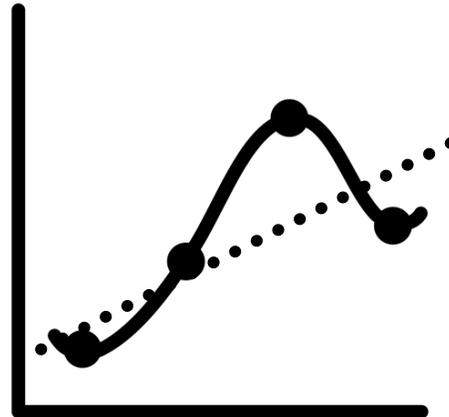


MELD NA

$$\text{MELD-Na} = \text{MELD} + 1.32 \times (137 - \text{Na}) - [0.033 \times \text{MELD} \times (137 - \text{Na})]$$
$$\text{MELD} = 3.78 \times \ln[\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$$



Shift in Underlying Patient Cohort

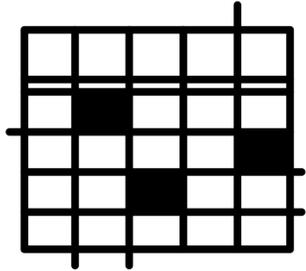


Linear Functional Form



Disadvantages Female Patients
(Locke et al., 2020;
Karnam R et al, JAMA Surgery, 2021)

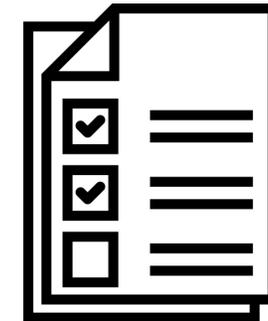
AI METHOD: DYNAMELD



121,647 Patients Listed
for Transplant in U.S.
Between 2002 and 2021



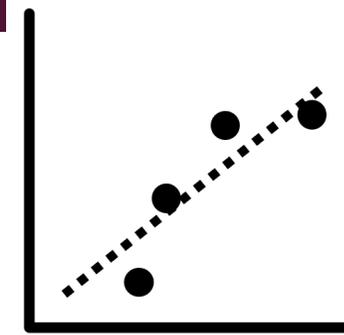
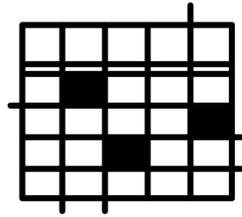
Adult Patients with
Decompensated
Cirrhosis



342 Static and Time-
Varying Features per
Patient

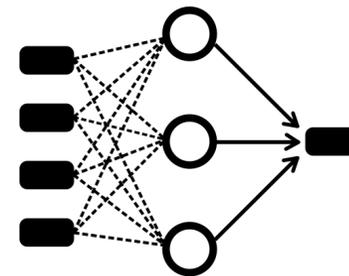
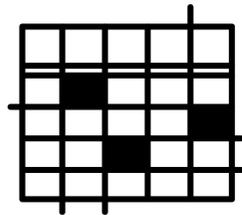
DYNAMELD

CoxPH:
(Linear Survival Analysis)



Patient Risk Score

DeepSurv:
(Nonlinear Survival Analysis)

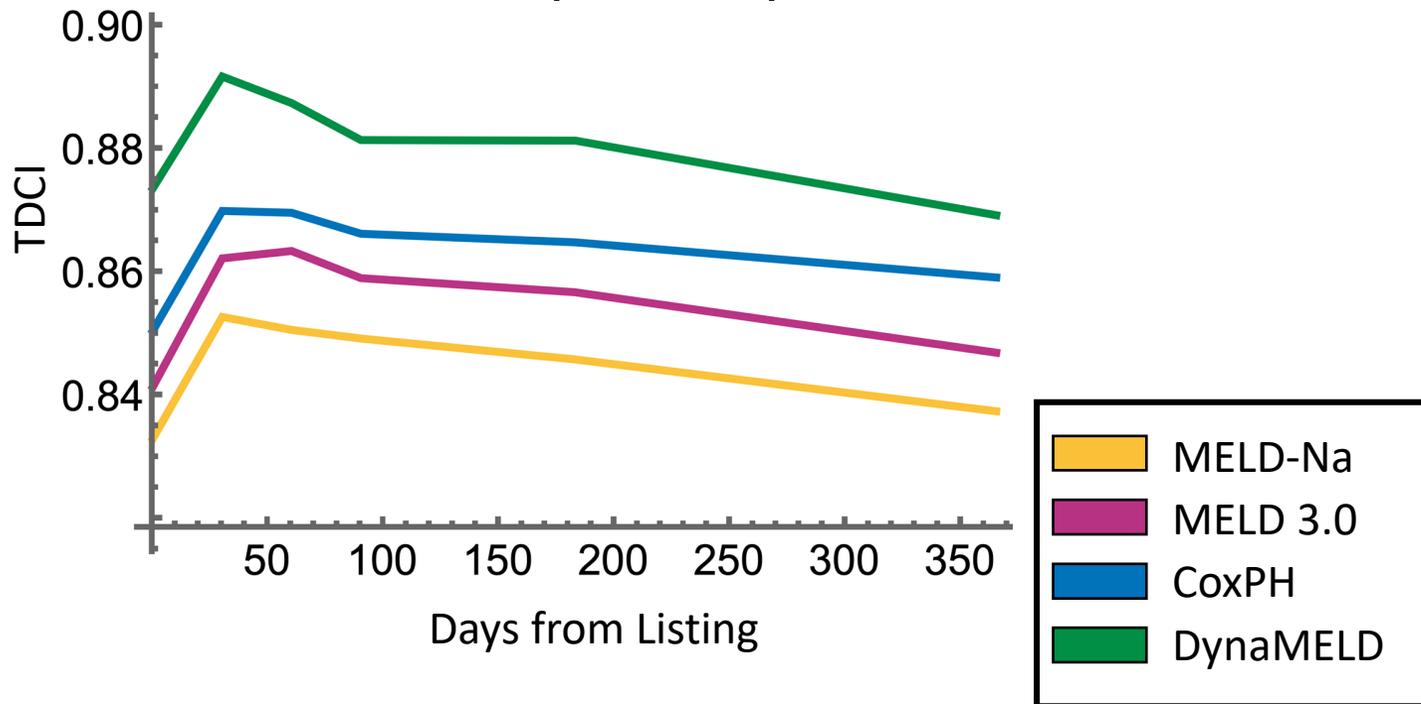


Patient Risk Score

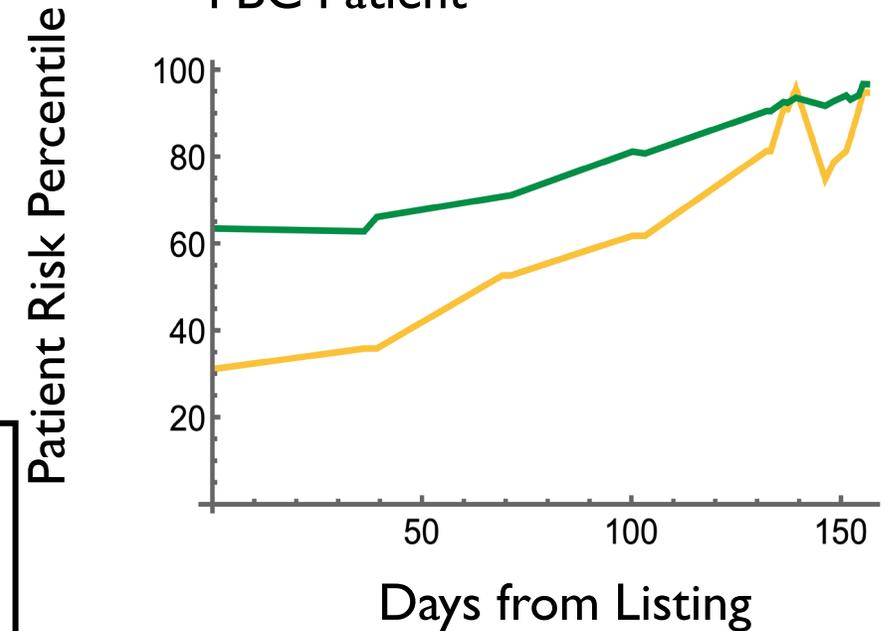
DynaMELD: **DeepSurv** model, but modified to add covariates to each patient/time-point instance that correspond to ***rate-of-change of time varying covariates***

DynaMELD: AUC of 0.92 vs MELD Na AUC of 0.85

Time-Dependent Concordance Index(TDCI), 90-Day-Mortality



Risk Percentile, 54y/o Female PBC Patient



Initial MELD-Na Score: **17**
Died after **156** Days Waitlisted

Significance testing: At listing, $TDCI_{MELD-Na} < TDCI_{DynaMELD}$, ($p = 9.7e^{-55}$)

LIVSIM: SIMULATING ALLOCATION OUTCOMES

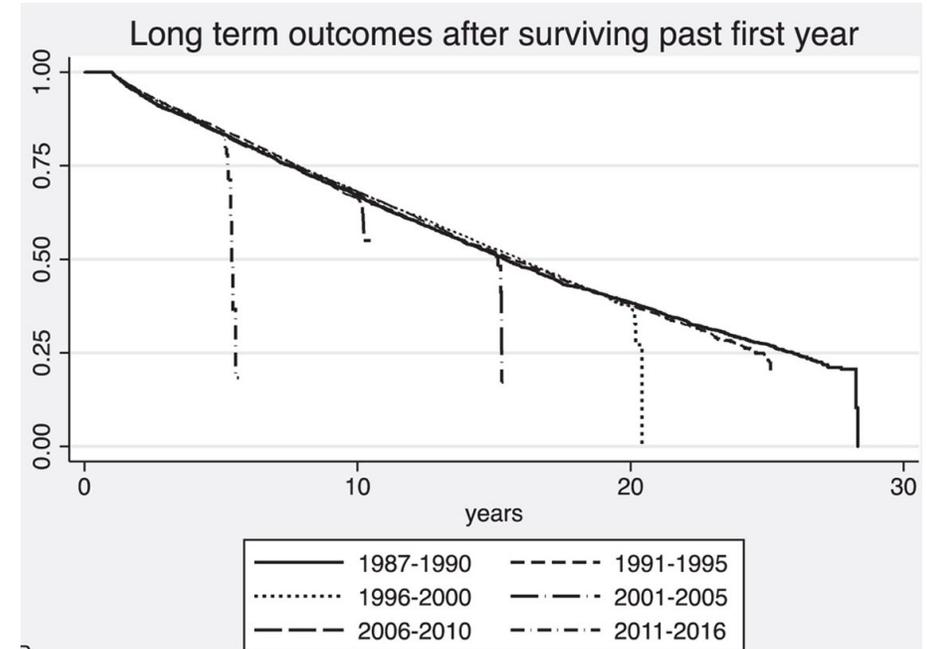
Dataset: Cohort of 16,210 (9339 M, 6871 F) patients listed since the introduction of the MELD-Na.

Simulation Results:

Model Class	Pre-Transplant Mortality	Pre-Transplant Mortality (Women)
MELD-Na	1,282 (7.9%)	550 (8.1%)
MELD 3.0	1,249 (7.7%)	553 (8.2%)
DynaMELD	1,119 (6.9%)	468 (6.9%)

POST-TRANSPLANT

- Median survival of LT recipients 20 years less than Canadian life expectancy*
- Existing comorbidities, lifelong immunosuppression
- Compromised by heightened incidence of cancer, cardiometabolic disease, and infection
- Care of LT recipients based on limited evidence
- **How can we change this and turn Transplant into a Cure?**



Rana A, et al, Annals of Surgery 2019

Bera C, et al, 2023



Predicting mortality due to long-term complications after LT

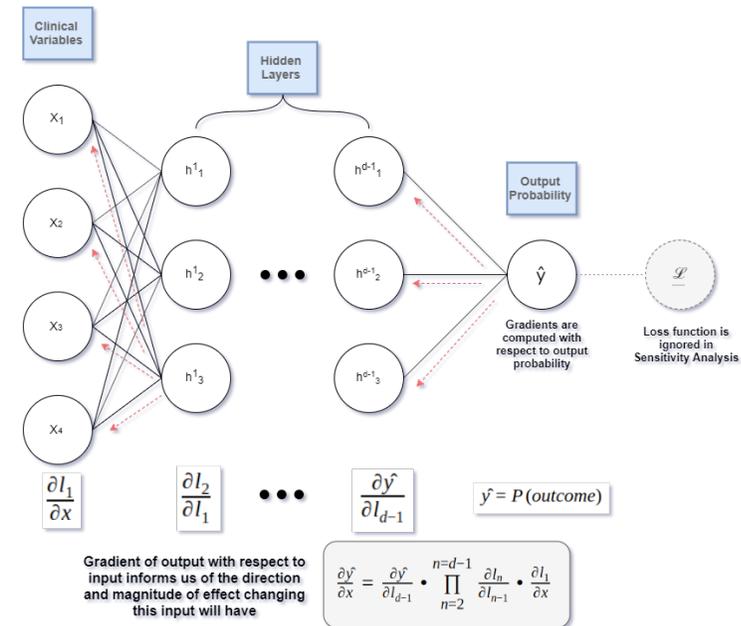
Long-term mortality risk stratification of liver transplant recipients: real-time application of deep learning algorithms on longitudinal data

Osvald Nitski, Amirhossein Azhie*, Fakhar Ali Qazi-Arisar, Xueqi Wang, Shihao Ma, Leslie Lilly, Kymberly D Watt, Josh Levitsky, Sumeet K Asrani, Douglas S Lee, Barry B Rubin, Mamatha Bhat†, Bo Wang†*



PREDICTING MORTALITY DUE TO LONG-TERM COMPLICATIONS AFTER LT

- Evaluated various Deep ML algorithms to predict mortality
- Incorporate **longitudinal** data
- Classify patients into **major** risk categories
- Make a more **'personalized'** risk calculator for managing long term transplant care that can be used at each follow up



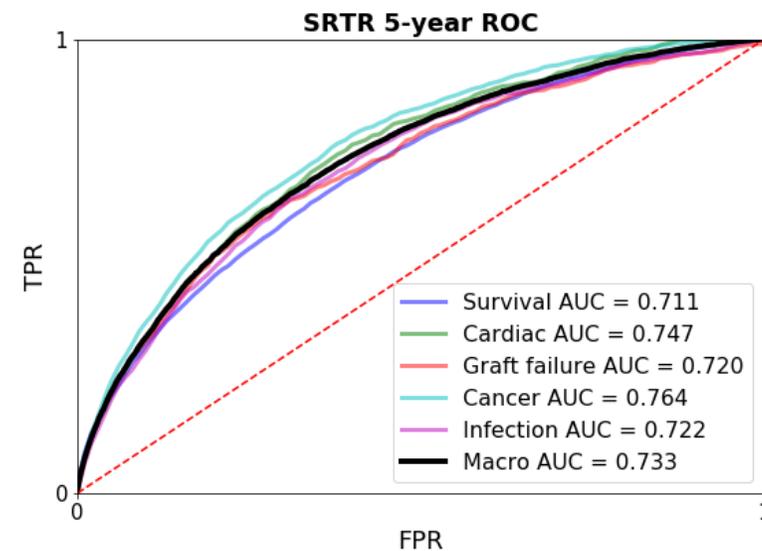
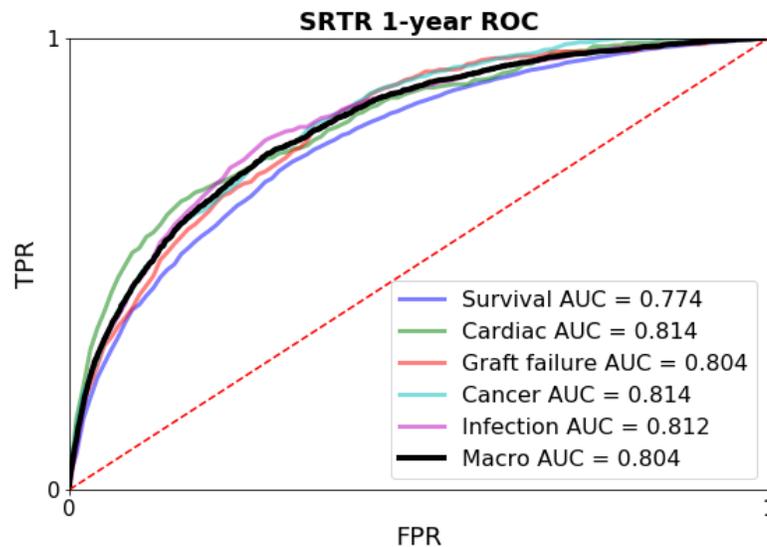
- **65,732** U.S. liver transplant recipients between 2002-2014
- **Annual** follow-ups
- **267** clinical variables used
- **5 outcomes** predicted
 - ▣ Survival
 - ▣ Death by Graft Failure
 - ▣ Death by Infection
 - ▣ Death by Cardiac event
 - ▣ Death by Cancer
- **1 year & 5 year** outlooks predicted



SCIENTIFIC
REGISTRY OF
TRANSPLANT
RECIPIENTS

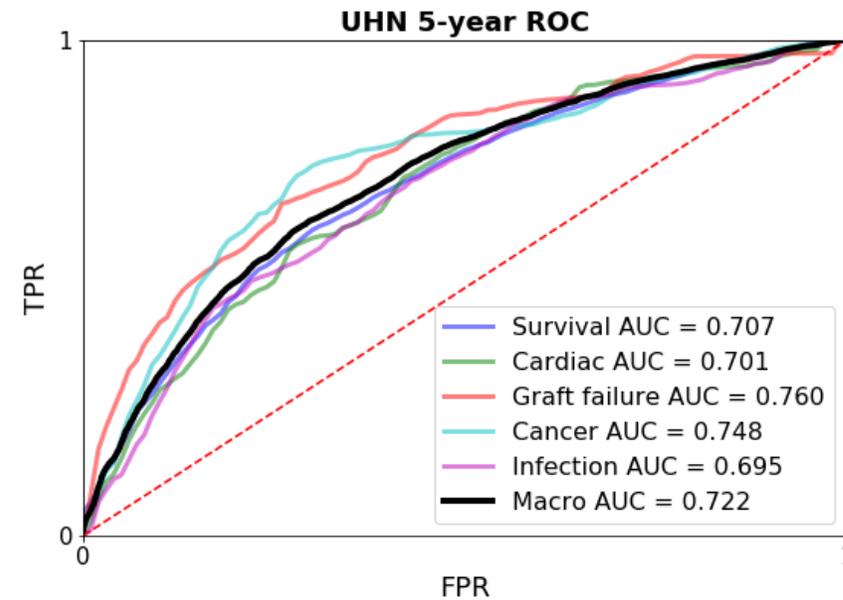
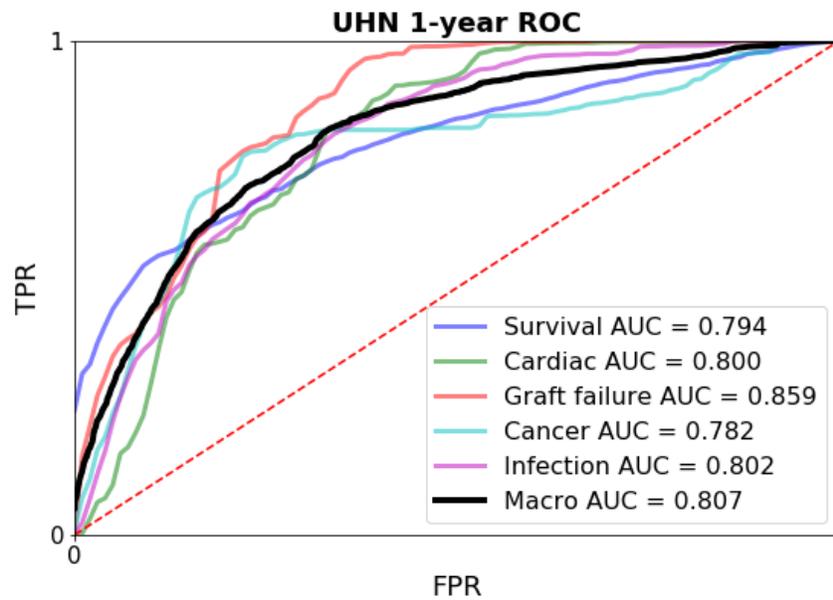
SRTR Test Set Performance (AUROC)

- Best performing model is Transformer



- **Logistic Regression AUC is 0.714 (1 year) and 0.648 (5 year)**

UHN Cross-Validation



RANKED FEATURES

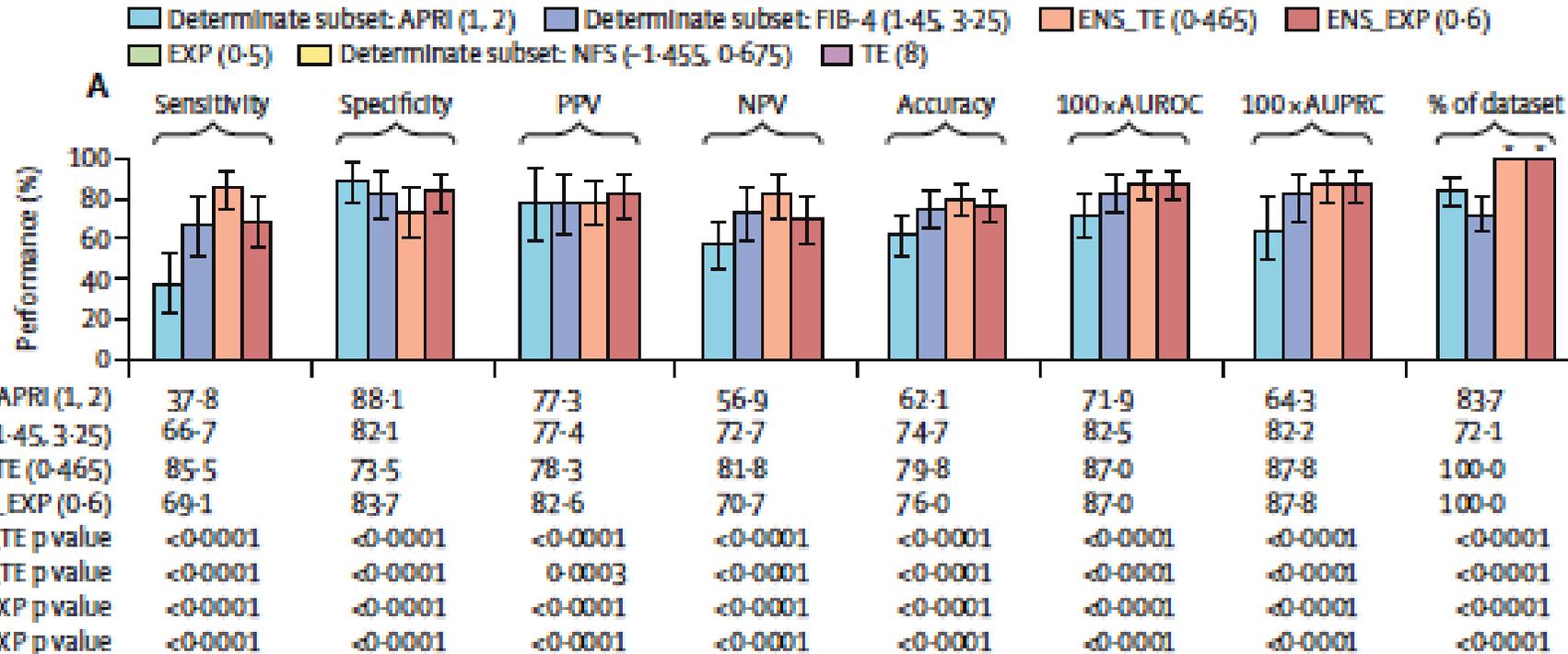
Top 10 in SRTR

Time since transplant
Donor Age
Candidate Age
Recipient Age at Transplant
Number of hospitalizations after LT
Candidate last serum Sodium
Serum Total Bilirubin (at follow up)
Serum Alkaline Phosphatase (at follow up)
Number of rejection episodes after LT
Serum SGOT (AST) at follow up

Top 10 in UHN

Donor age
MELD score
Patient carried over from pediatric to adult LT clinic
Sirolimus trough level
Cyclosporine 2 hours post-dose level
Hepatocellular carcinoma (primary indication for LT)
Recipient age at transplant
Graft Failure
Recurrent HCC
Tacrolimus trough level

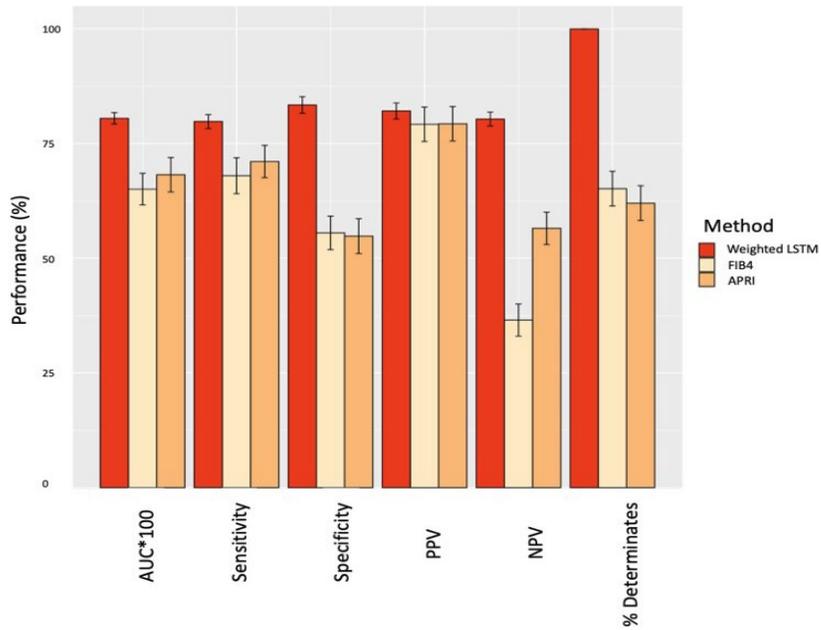
EFFECTIVE DETECTION OF ADVANCED FIBROSIS WITH ENSEMBLE ML



THE LANCET
Digital Health

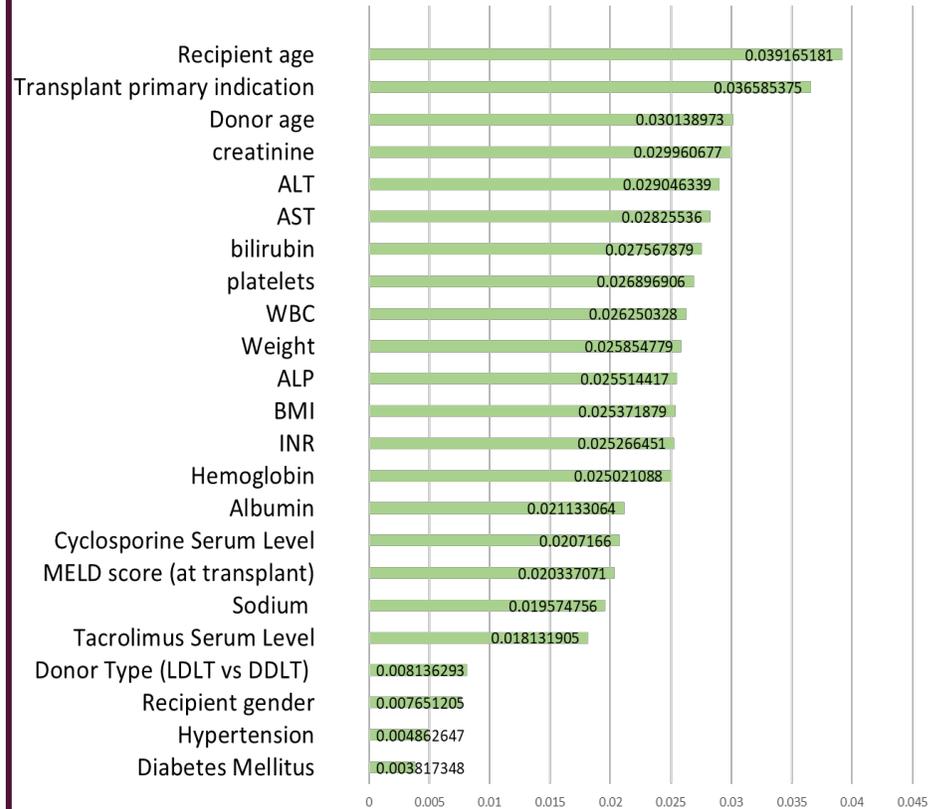
Development and validation of an ensemble machine learning framework for detection of all-cause advanced hepatic fibrosis: a retrospective cohort study

Deep Learning Framework for Dynamic Diagnosis of Graft Fibrosis after Liver Transplantation using Longitudinal Data



Parameters	Weighted LSTM	FIB4	APRI
AUC	0.798 [0.790, 0.810]	0.650 [0.636, 0.663]	0.682 [0.671, 0.694]
Sensitivity	0.788	0.68	0.711
Specificity	0.814	0.555	0.548
Positive predictive value	0.821	0.792	0.793
Negative predictive value	0.803	0.365	0.565
% Determinates	100	65.17	62.01

Top Ranked Features

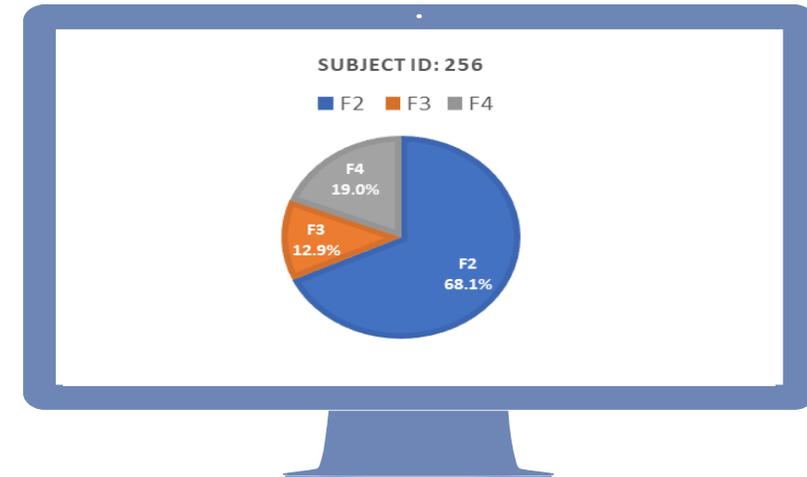
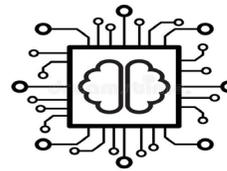


Azhie A*, Sharma D*, Xu W, Bhat M,
Lancet digital health, 2023

WHAT WOULD A CLINICIAN SEE?

Input variables for 1 sample patient at 279 days after transplant

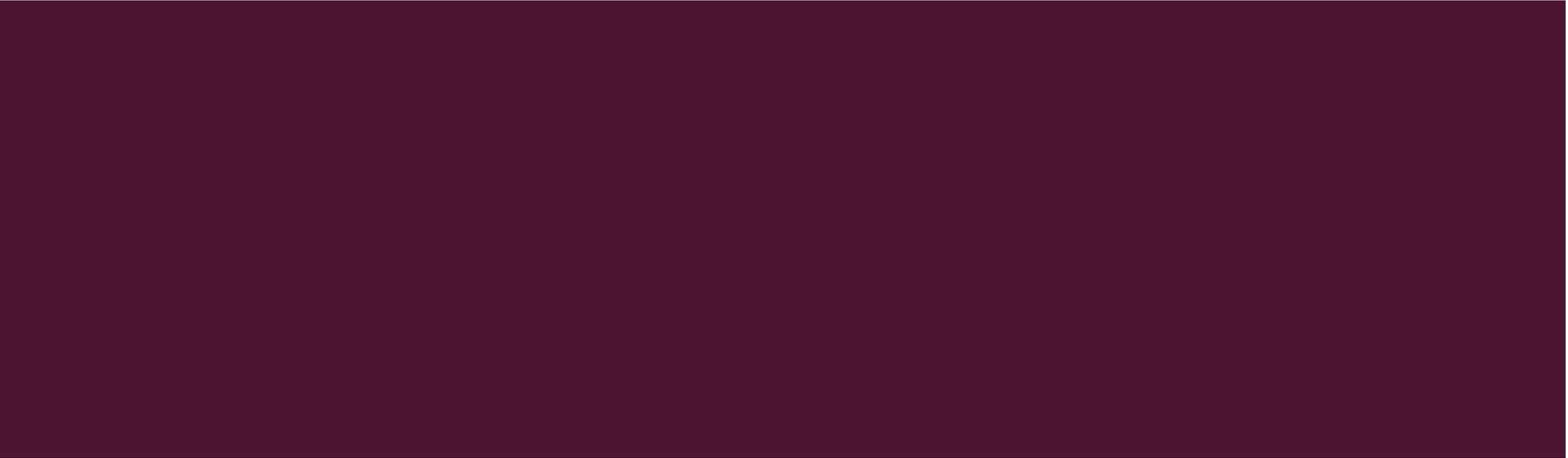
Variables	Subject ID 256	
Timepoint	Transplant	Liver biopsy
Days after transplant	-----	279
Fibrosis stage (biopsy)	-----	F2
Recipient gender	Female	Female
Recipient age	47.93	-----
WBC	2	1.2
Platelets	30	43
Creatinine	20	132
INR	1.36	1.44
Albumin	33	31
Sodium	134	142
TACROLIMUS	-----	18.2
Cyclosporine	-----	-----
Sirolimus	-----	-----
Hemoglobin	78	86
Total bilirubin	18	93
AST	63	44
ALT	50	37
ALP	22	106
MELD	12	12
Donor age	63	-----
Transplant primary indication	Hepatitis C	Hepatitis C
Donor Type	DDLT	DDLT
Weight(kg)	53.6	55.5
BMI	22.02	22.80
Diabetes mellitus (Y/N)	0	0
Hypertension (Y/N)	0	0
Dyslipidemia (Y/N)	0	0



This patient is at high risk of F2 fibrosis at this follow up visit
→ May benefit from more strict management

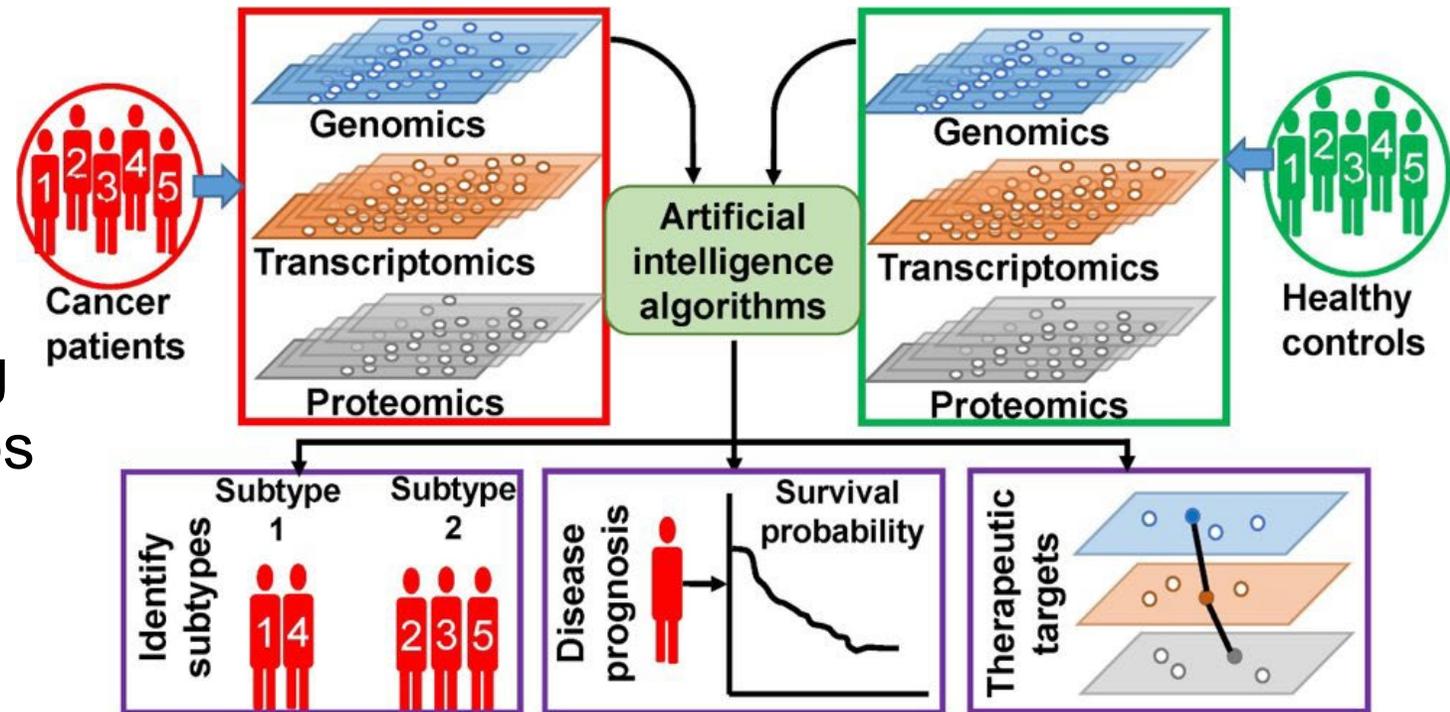


HOW ABOUT FINE-TUNING PREDICTIONS WITH MOLECULAR DATA?



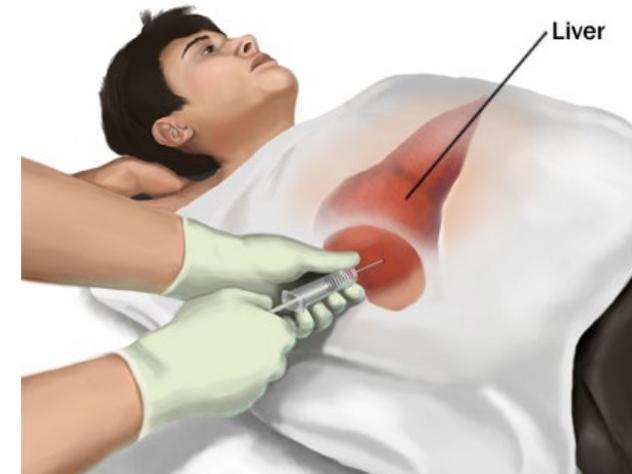
INTEGRATION OF MULTI-OMICS & CLINICAL DATA

- **Supervised:** for Prognostic prediction
- **Unsupervised:** for Clustering into patient disease subgroups



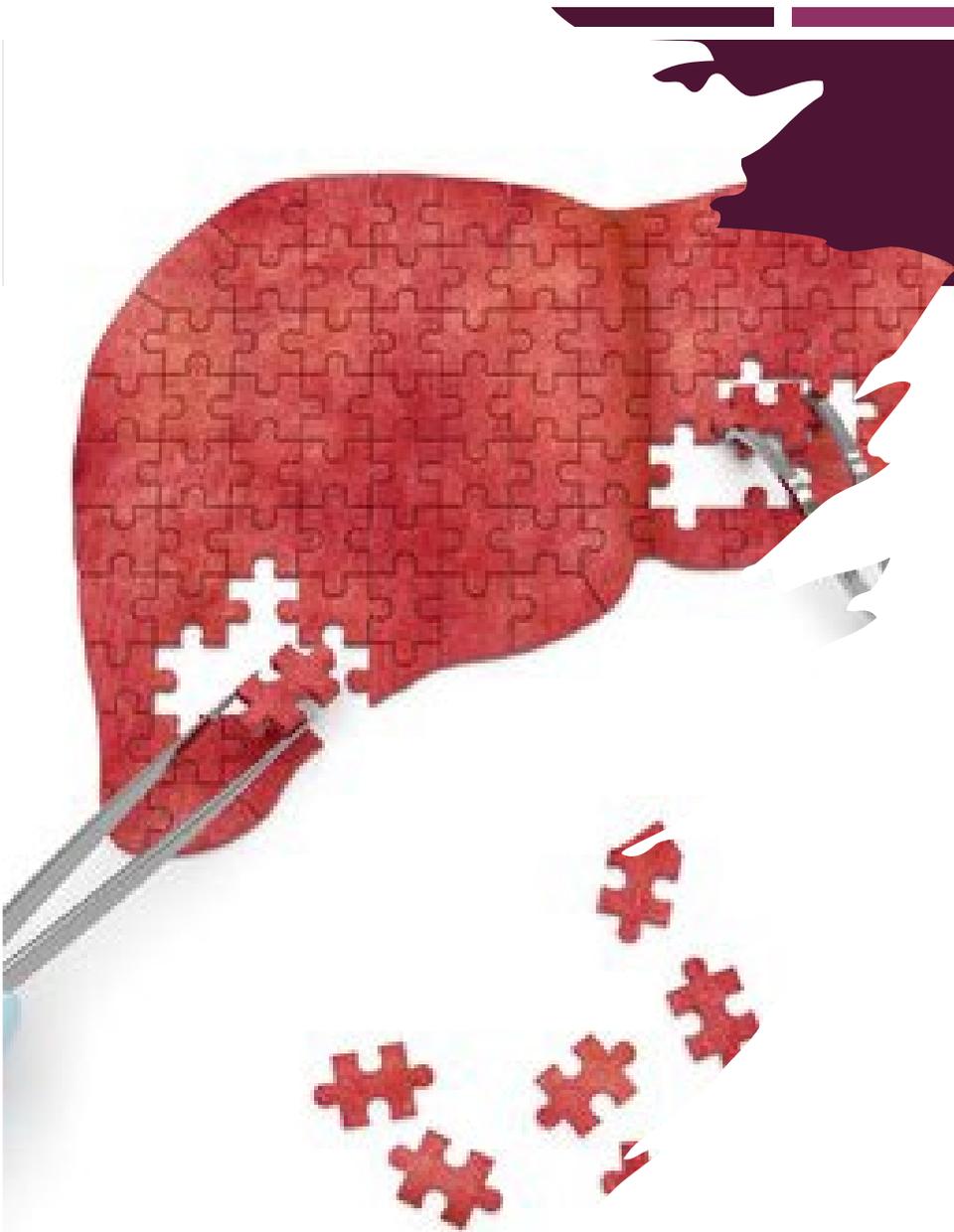
LIVER GRAFT INJURY IN OVER 50%

- 25% of post-LT mortality is due to graft failure
- Over 50% of LT will have increased Liver enzymes
- Rejection, NASH, viral, biliary
- Ultrasound with Doppler followed by
- Liver biopsy as gold standard for diagnosis
- **BUT Invasive (multiple risks)**
- Often Delayed



DIAGNOSTIC PUZZLE

- Physician has a hunch based on patient profile and test patterns
- Example:
- Young LT recipient
- Elevated LEs (100-200 range)
- ALT>AST and elevated ALP while tapering IS
- Most likely to be Acute rejection



HOWEVER, PUZZLE MAY FALL APART!

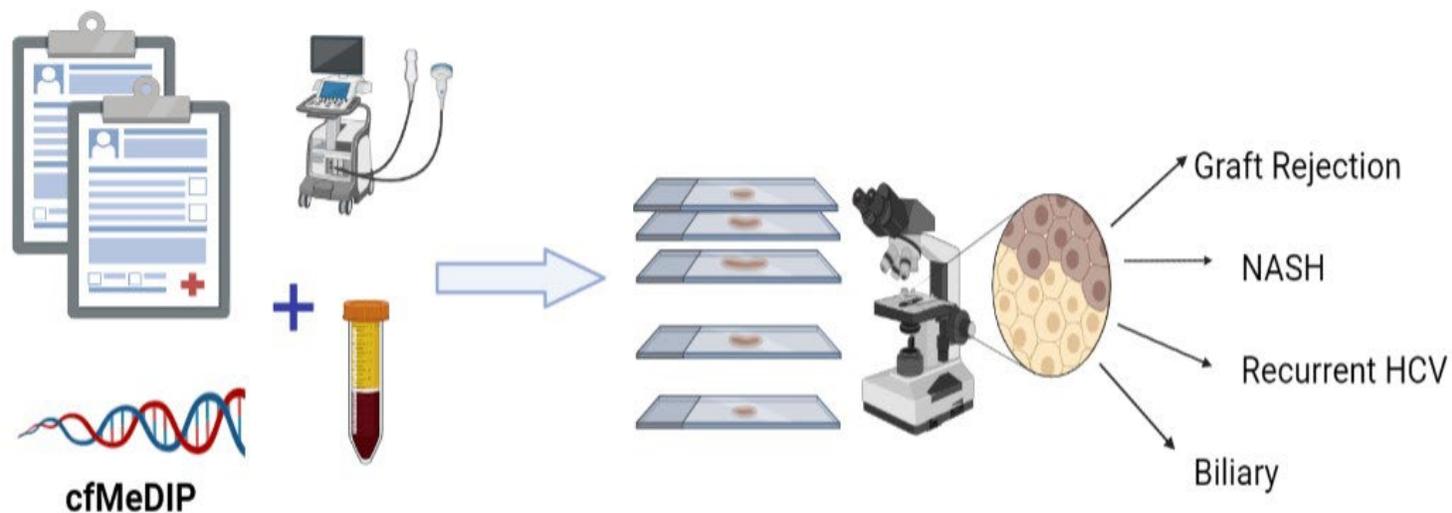
- Biopsy not readily available
- Treatment empirically initiated before biopsy
- Inappropriate therapy may be administered,
i.e. steroids when it is a viral infection
=>Unsafe, risk of adverse outcomes

**ALGORITHMIC DECISION SUPPORT
NEEDED!**



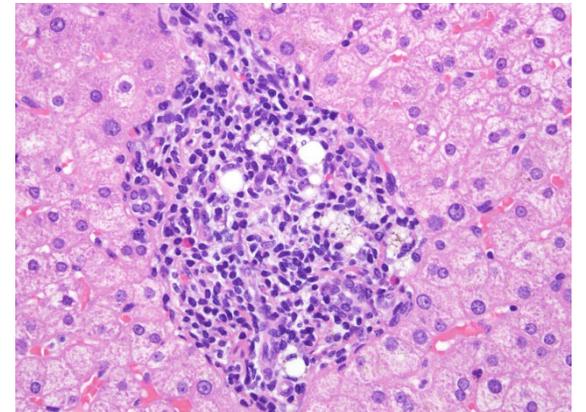
OBJECTIVE:

- **Develop a Machine Learning Algorithm** trained on Clinical, Laboratory, and Radiomic data to identify graft pathology
- Methylation patterns on circulating dd-cfDNA to further refine



STUDY POPULATION

- Over 7,000 liver graft biopsies performed at UHN 1987-2020
- **Longitudinal Clinical, Laboratory, and Radiomic features on ultrasound** over the week preceding biopsy
- Recipients divided based on histologic diagnosis:
 - Graft rejection
 - NASH
 - Recurrent HCV
 - Biliary complications



ML RESULTS

Category	Sensitivity	Specificity	PPV	NPV	AUC
Acute Cellular Rejection	0.8139	0.7366	0.6449	0.8707	0.7752
Alloimmune hepatitis	0.8923	0.9325	0.8021	0.9598	0.9123
Biliary complications	0.9024	0.9112	0.8263	0.9153	0.9021
Vascular Congestion	0.8823	0.9254	0.8155	0.9221	0.9054
Recurrent HCV	0.8630	0.7427	0.7143	0.8791	0.8028
NASH	0.8766	0.8923	0.8119	0.9234	0.9003
Averaged AUC over all the classes : 0.866					

Performance of ANN in detecting different graft pathologies as well as the overall AUC

Comparison of ANN with other ML algorithms and logistic regression

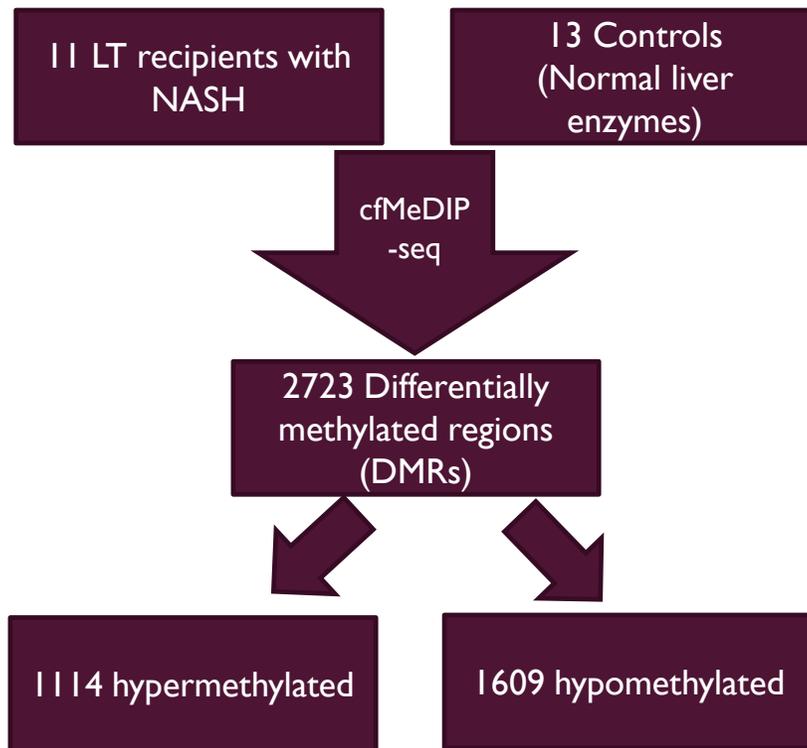
Methods	Primary diagnosis AUC, [95% CI]
Neural Network (ANN- Best performing model)	0.866 [0.844, 0.891]
Random Forest (RF)	0.823, [0.812, 0.839]
Logistic Regression	0.767, [0.626, 0.796]
Lasso Regression	0.783, [0.769, 0.802]
Ridge Regression	0.781, [0.771, 0.811]

Top Predictive Variables for Graft Pathologies (Using ANN)

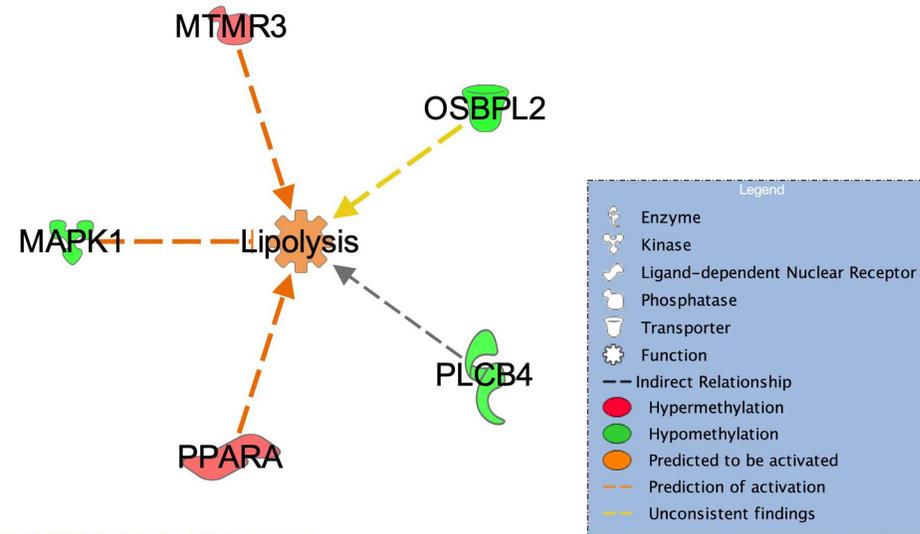
Top 10 Predictive Variables	Acute cellular Rejection	Alloimmune Hepatitis	Biliary Complications	Congestion	Recurrent HCV	NASH
1	ALT	Recipient Age	ALP	ALP	ALP	Hgb
2	ALP	Cyclosporine serum level	Total Bilirubin	Platelets	Total Bilirubin	ALP
3	Hgb	AST	Recipient Age	Total Bilirubin	Hgb	Recipient Age
4	WBC	Hgb	ALT	Recipient Age	WBC	ALT
5	Recipient Age	Platelets	WBC	ALT	Recipient Age	Creatinine
6	Total Bilirubin	Donor age	Hgb	Cyclosporine Serum level	ALT	AST
7	Creatinine	Total Bilirubin	AST	AST	Creatinine	Platelets
8	AST	Tacrolimus Serum level	Platelets	Donor Age	Albumin	Cyclosporine Serum level
9	Albumin	WBC	Creatinine	WBC	AST	Albumin

CFMEDIP-SEQ: DNA METHYLATION PATTERNS ON CIRCULATING DNA

- ddcfDNA tells us there is graft injury, but **not the cause**
- Methylation patterns on cfDNA could help



Lipid metabolism with lipolysis function particularly upregulated in LT recipients with NASH versus Controls

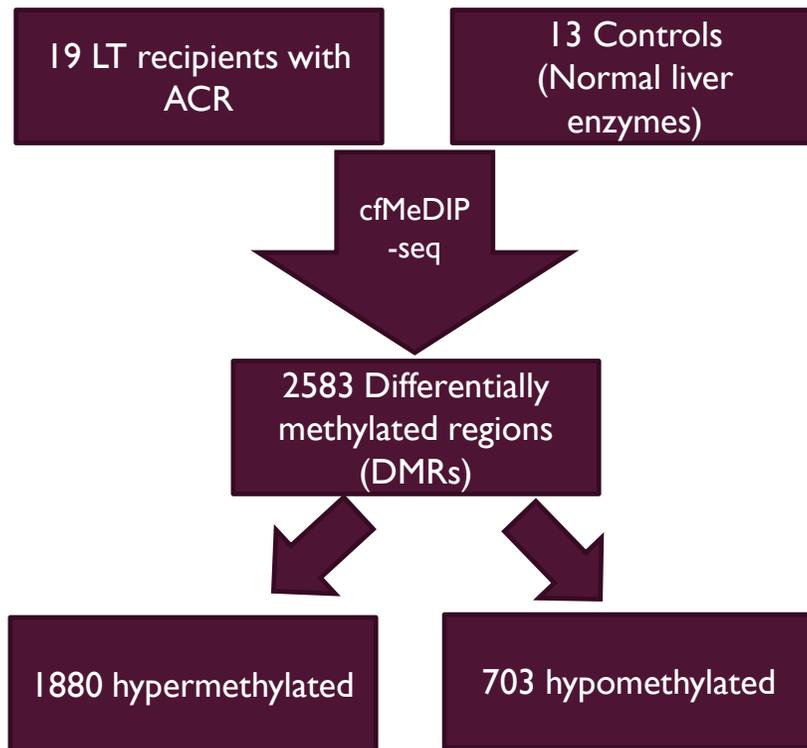


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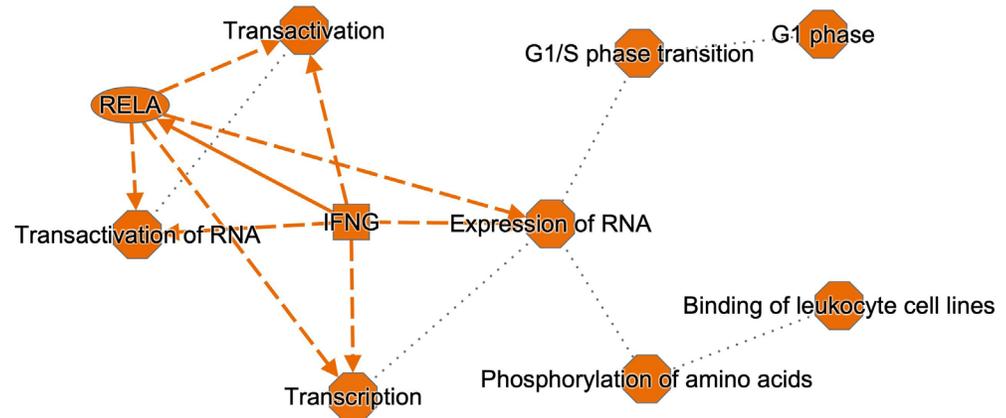
cfMeDIP-seq assay: Shen R, D. De Carvalho, Nature 2018

METHYLATION PATTERNS SPECIFIC FOR REJECTION

- Methylation patterns on cfDNA could distinguish ACR patients from Controls



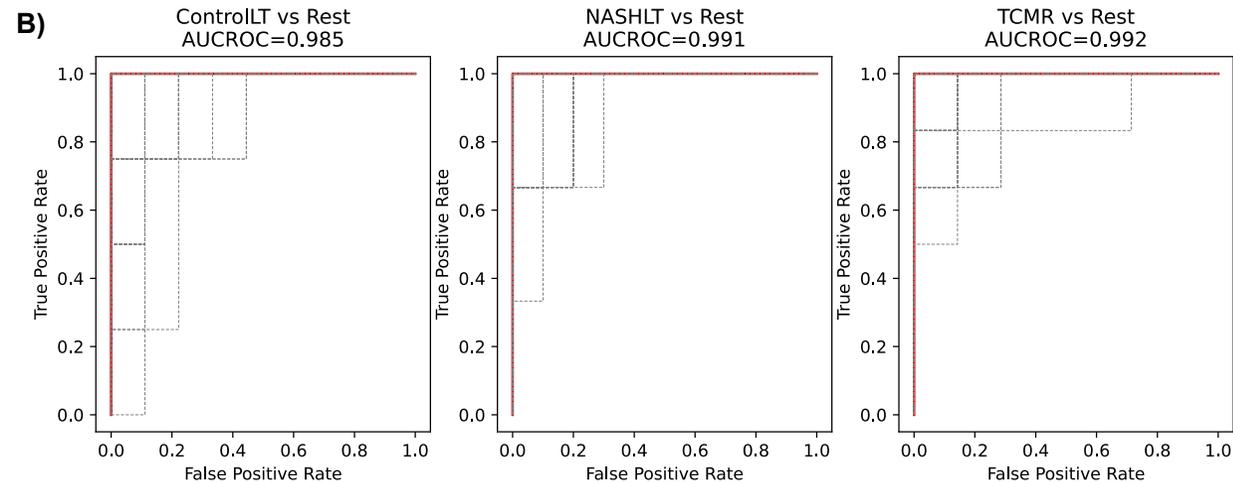
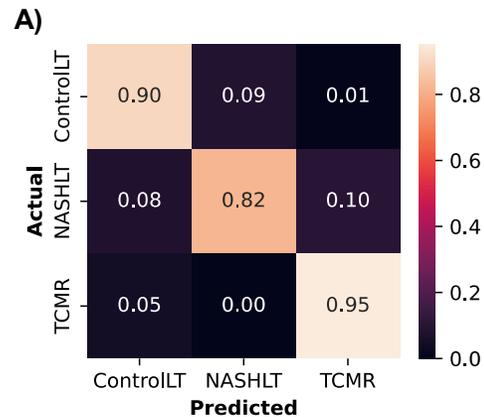
- Platelet derived graft factors (PDGFs) pathway is activated in LT recipients with ACR versus Controls
- ACR triggers activation of several processes:



INTEGRATIVE ML TOOL TO CLASSIFY LIVER PATHOLOGY: COMBINED CLINICAL VARIABLES + CFMEDIP-SEQ

Model	Multiclass Logistic Regression with L2 regularization Models were trained with class weights to deal with class imbalances
Features	Methylation enrichment levels of top 1000 differentially methylated regions (DMRs) + Clinical and Laboratory Variables
Samples	43 patients; NASH-LT (n=11), Acute Rejection (n=19), Control LTRs (n=13)

Results from 101 stratified bootstrapped models, each with a different 70-30 train-test split



Results suggest that the DMRs computed from cfMeDIP-seq are biologically relevant non-invasive diagnostic markers of graft pathology.

❑ Models achieved relatively good classification for Control LT and Acute Rejection (with **94% and 98% TPR** (recall/sensitivity) respectively)

DASHBOARD EXAMPLES



DATA

PREDICTIONS

Emily Johnson



Age: 54	DOB: 01-Jun-1969	Status: Outpatient
Transplants: LIV: DD: 17-NOV-2017	Duct: Duct-to-duct	Dx: Primary biliary cholangitis
Primary care: Mamatha Bhat	Primary coord: G. Yarranton	Phone: H: (123) 456-3213 W: (314) 159-2223
Allergies: 0	Alerts: OHIP	TGLN ID: 8222575

Filter by Date Display Columns

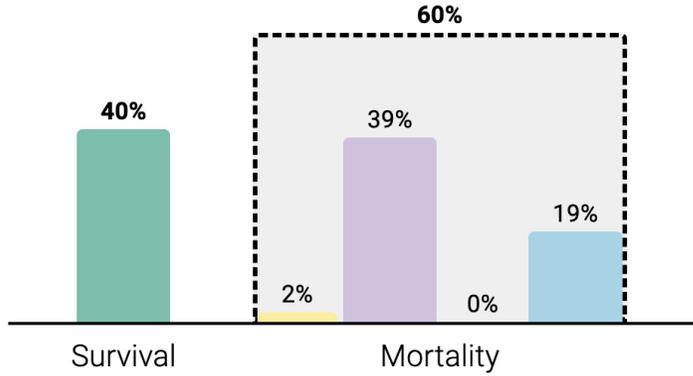
Search

Date	<input type="checkbox"/> Weight	<input type="checkbox"/> MELD	<input type="checkbox"/> Hemoglobin (Hgb)	<input type="checkbox"/> White Blood Cell (WBC)	<input type="checkbox"/> Platelets (PLT)	<input type="checkbox"/> International Normalized Ratio (INR)	P
2022-05-01	77.7						
2022-03-21		9	134	3.2	151	0.9	
2022-02-08		8	135	4.4	164	0.8	
2022-01-09		11	119	3.5	143	0.9	
2021-11-12		7	128	3.1	143	0.9	
2021-11-02	70.5						
2021-10-28		6	129	3.9	144	0.9	28
2021-10-14		7	132	3.5	165	0.9	

DATA

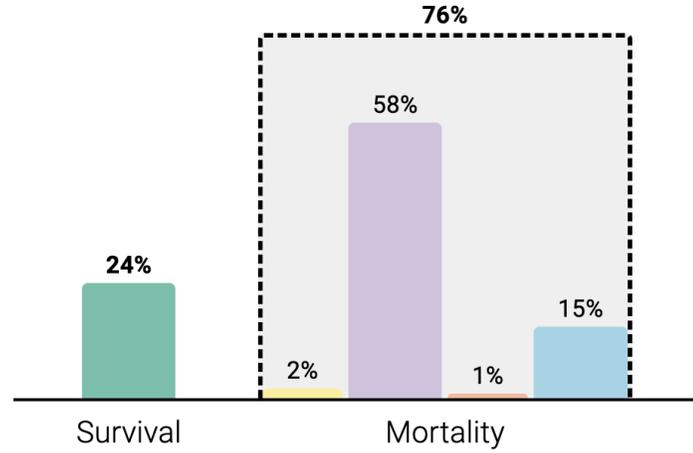
PREDICTIONS

Predictions After 1 Year



EDIT DATA

Predictions After 5 Years



LOAD

SAVE

- Cancer
- Cardiac Events
- Graft Failure
- Infection
- Mortality

Feature importance for: Survival ⓘ

1 Year

Outcome probability: 40 Baseline: 86

Increasing Probability



Decreasing Probability



Data

Results

Imp. rank ▾	Patient Data ▾	Value ▾	Add ▾
1	Donor age	54	+
2	MELD score	21 pts	+
3	Patient transferred from paediatric...	Yes	+
4	Sirolimus trough level	2 ng/mL	+
5	Ciclosporin 2-h post-dose level	712.7 n...	+
6	Hepatocellular carcinoma as a pri...	No	+
7	Recipient age at transplantation	24	+
8	Graft failure	No	+
9	Recurrent hepatocellular carcinoma	No	+
10	Tacrolimus trough level	4 ng/mL	+
11	HCV-induced cirrhosis as a prima...	No	+
12	Primary sclerosing cholangitis as ...	Yes	+
13	Donor type	Living	+
14	MELD-Na score	20 pts	+
15	Time since liver transplantation	3 mo.	+
16	Diabetes (at follow-up)	No	+
17	NASH cirrhosis as a primary indicat...	No	+

Interventions

Reset All

Run

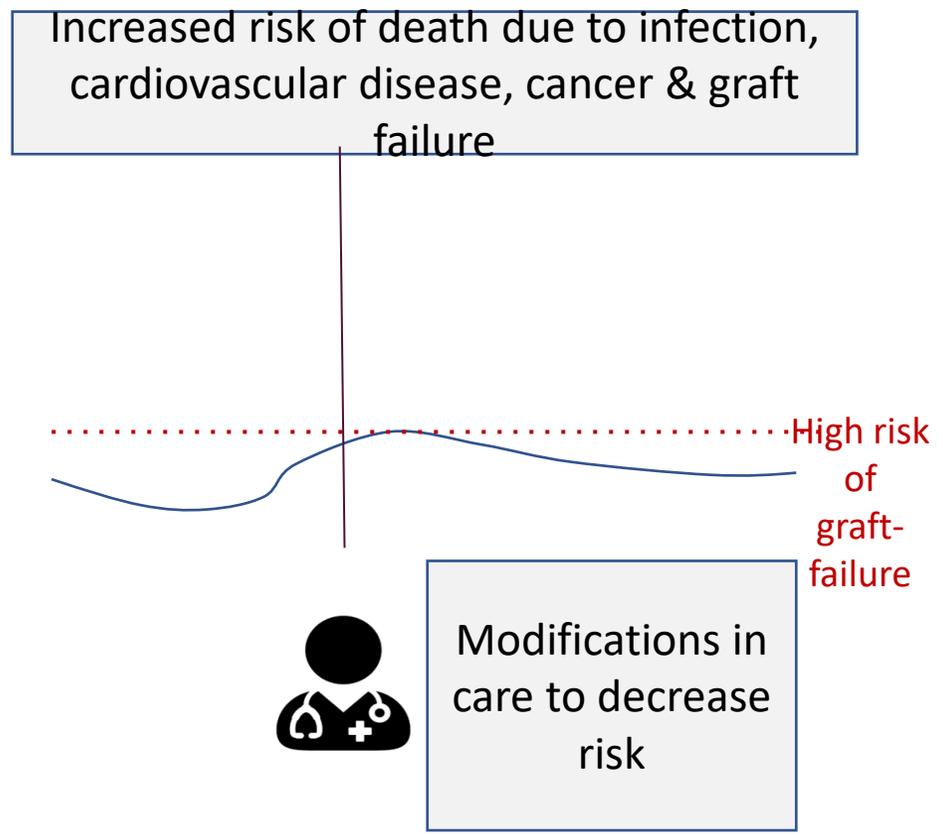
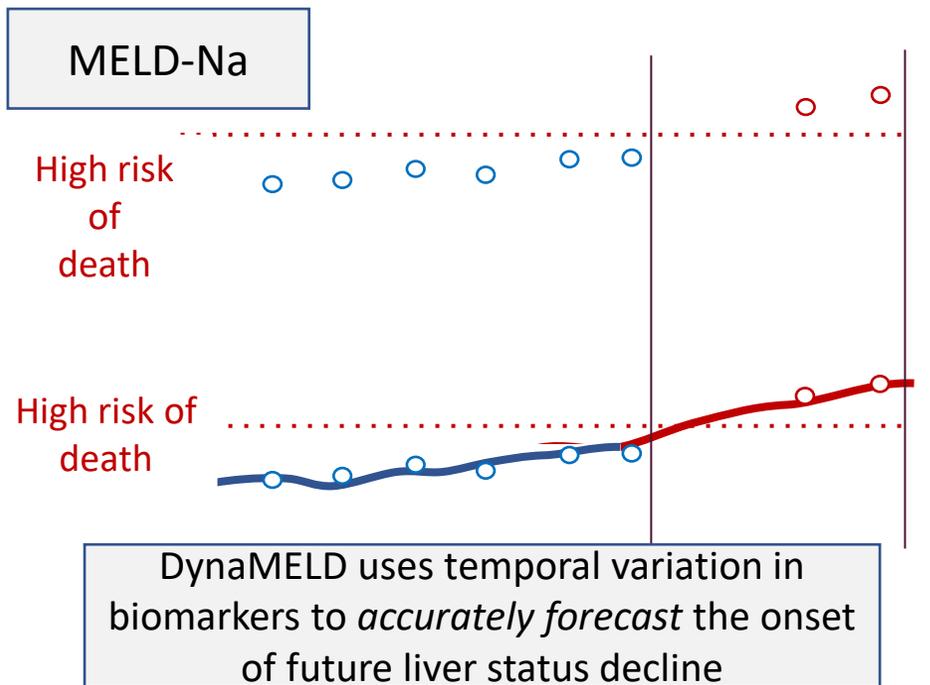
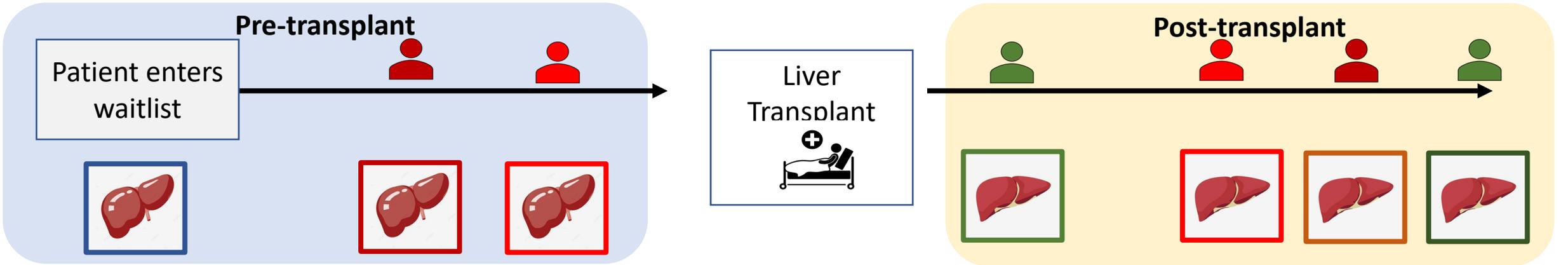
DYNACOMP DEPLOYMENT GOALS

- Integrate DynaCOMP into LT clinic to Optimize Patient Outcomes
- **SHAPley values** to obtain modifiable ranked features
- Evaluate impact by **patient outcomes** and number of relevant referrals made by physicians supported by AI tool
- Evaluate **patient comfort** with AI-guided care in clinic
- Conduct **qualitative interviews** of physicians and refine dashboards to prepare for deployment beyond UHN

CURRENT STATE

- **Endorsement from UHN Ajmera Center: Transplant AI Initiative**
- QA/QI approval for deployment of ML model
- AI-LTP front end fully designed and validated with clinicians
 - ML models were validated by UHN DATA ML Engineers
- Direct access to Epic (new) and OTTR (historic) data established
- National efforts through CDTRP

Vision for the Future of AI in Liver Transplantation



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- Gang Zheng (MBP, Princess Margaret)
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[HTTP://BHATLAB.CA](http://bhatlab.ca)

