EPAteam – *Localita' Ciocco Lucca*

Le sfide del trapianto di fegato nel 2023

14-15 Aprile 2023

Machine learning nel trapianto di fegato

Patrizia Burra

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Applying Machine Learning in Liver Disease and Transplantation

Machine learning utilizes artificial intelligence to generate predictive models efficiently and more effectively than convenventional methods through detection of hidden patterns within large data sets.

- Predicting modeling in NAFLD, PSC, Viral hepatitis, HCC
- Screening and selection of liver transplant recipients
- Prediction of post transplant survival and complications

Ashley Spann, Angeline Yasodhara, Justin Kang, Kymberly Watt, Bo Wang, Anna Goldenberg, Mamatha Bhat
Hepatology 2020

Application of machine learning in liver transplantation

- Machine learning has been increasingly applied in the health-care and liver transplant setting.
- The demand for liver transplantation continues to expand on an international scale, and with advanced aging and complex comorbidities, many challenges throughout the transplantation decision-making process must be better addressed.
- There exist massive datasets with hidden, non-linear relationships between demographic, clinical, laboratory, genetic, and imaging parameters that conventional methods fail to capitalize on when reviewing their predictive potential.

Jason Tran · Divya Sharma· Neta Gotlieb · Wei Xu · Mamatha Bhat
Hepatology International 2022

Application of machine learning in liver transplantation

Pre-transplant challenges

Addressing efficacies of liver segmentation

Hepatic steatosis assessment

Graft allocation

Post-transplant applications

Predicting patient survival

Graft rejection

Graft failure

Post-operative morbidity risk

Jason Tran · Divya Sharma· Neta Gotlieb · Wei Xu · Mamatha Bhat
Hepatology International 2022

Machine learning techniques: disadvantages

(1) the requirement of adequate preprocessing of input data

(2) tuning of the parameters

(3) overfitting challenges whereby models mistakenly adopt noise from the training set

(4) poorer performances with variability in missing datasets

(5) imbalances between cases and controls

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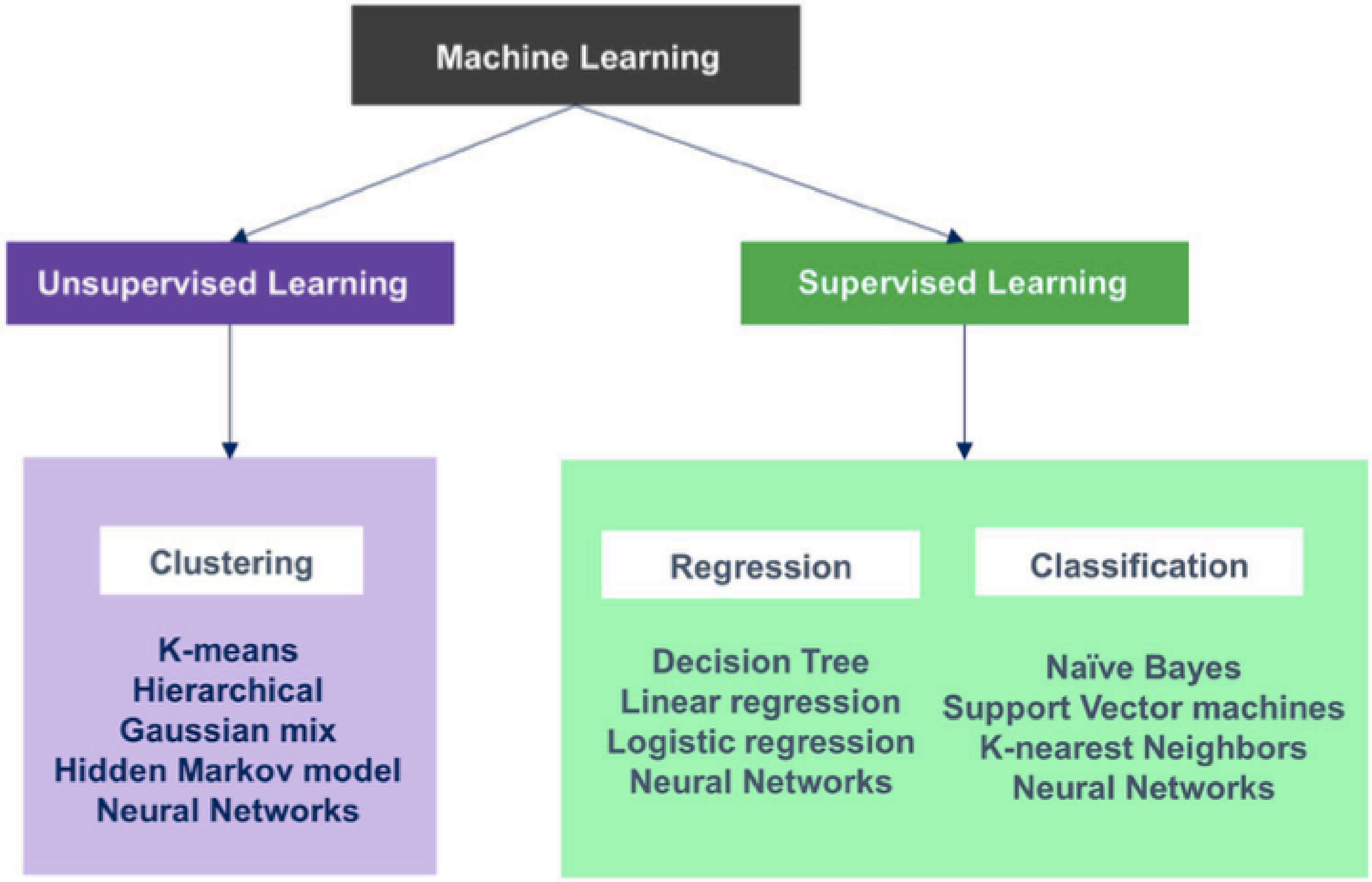
Machine learning classification

classification of ML captures unsupervised learning, supervised learning, and reinforcement learning. Supervised learning encompasses regression and classification subtypes that offer task-driven computational power for predictive use while the relevant unsupervised learning subtype includes clustering that offer data-driven power to adequately group datasets



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Machine learning main approaches

(1) Artificial neural networks

automatically learn from high-dimensional data

detect non-linear relationships between the input and the output

have been efficient in studies where prognosis depends on complex variables pertaining to the donor or recipient

require large data to train and estimate their parameters accurately.

(2) Logistic regression

uses a logistic function to predict dependent variables from independent variables

benefits from limited hyperparameters in its modeling but is unable to capture non-linear relationships

application is popular in liver transplant studies when there are limited variables, and the relative contribution of each variable to the outcome is the focus, owing to its simplistic interpretability

(3) Least absolute shrinkage and selection operator (LASSO) regression

regularized linear regression that avoids overfitting and encourages simple, sparse models

is preferred in studies that focus on variable selection to ideanalyze the role of certain important features during prediction

in cases where two predictors are highly correlated, it leads to arbitrary selection.

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Machine learning main approaches

(4) Support vector machines

identify a hyperplane in a high-dimensional feature space that creates clear boundaries to distinctly classify the subjects of different classes during prediction

is data driven and model free, in contrast to regression techniques which depend on pre-determined models to predict the outcome

is robust to overfitting and yield better predictions, but struggle when scaling to large datasets

(5) Random forests

are flexible and accurate in estimating non-linear relationships by taking majority vote of decision trees on different samples for classification

are widely popular in liver transplant studies with large datasets and multivariable interactions

but are challenging to interpret

(6) Gradient boosting

utilizes decision trees for prediction

aims to minimize the overall prediction error

performance is robust when the datasets contain correlated features from the donor and recipient

though it requires tuning of many hyperparameters which results in slower development

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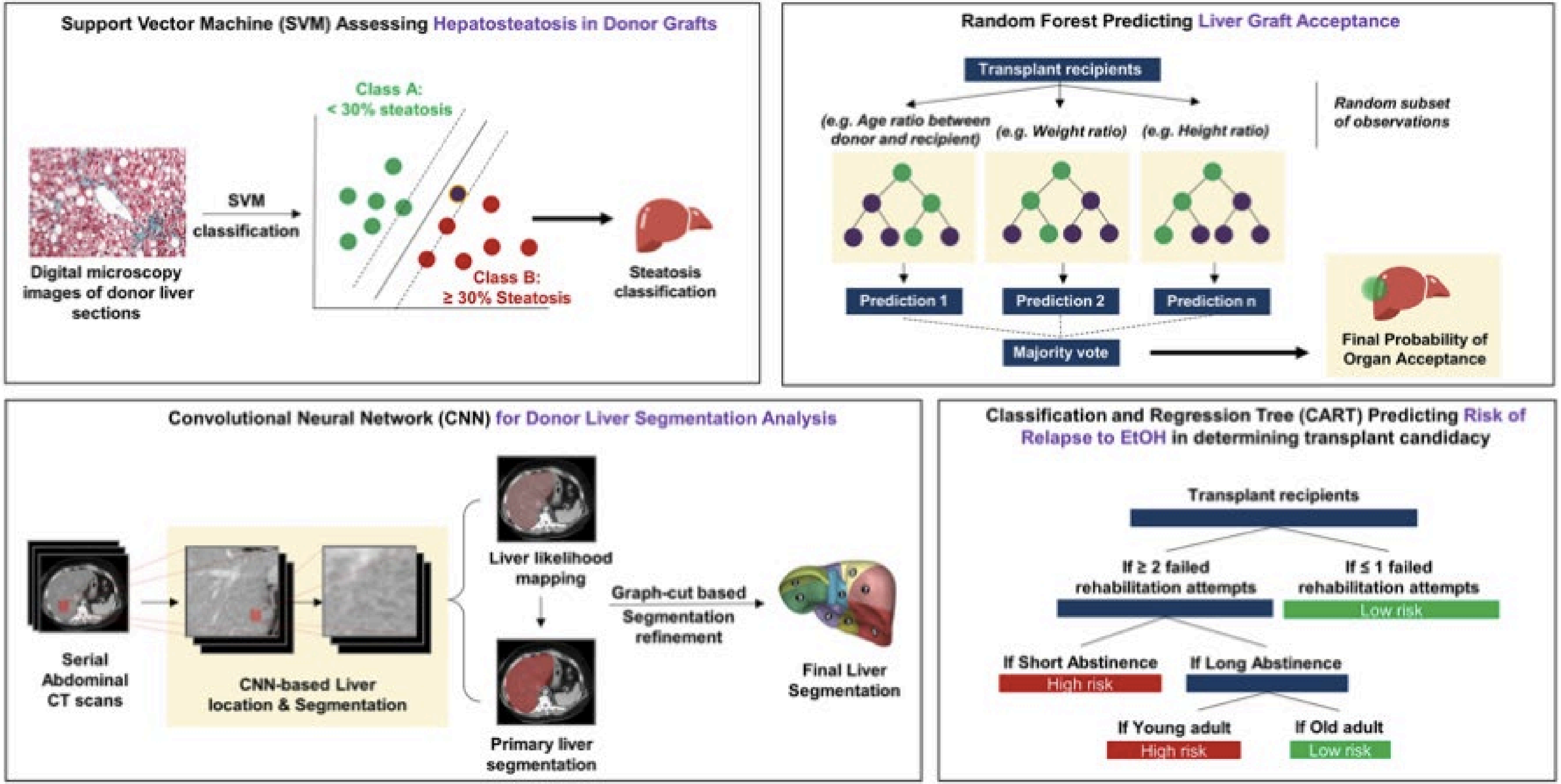
Summary of machine learning applications in the pre-liver transplantation setting



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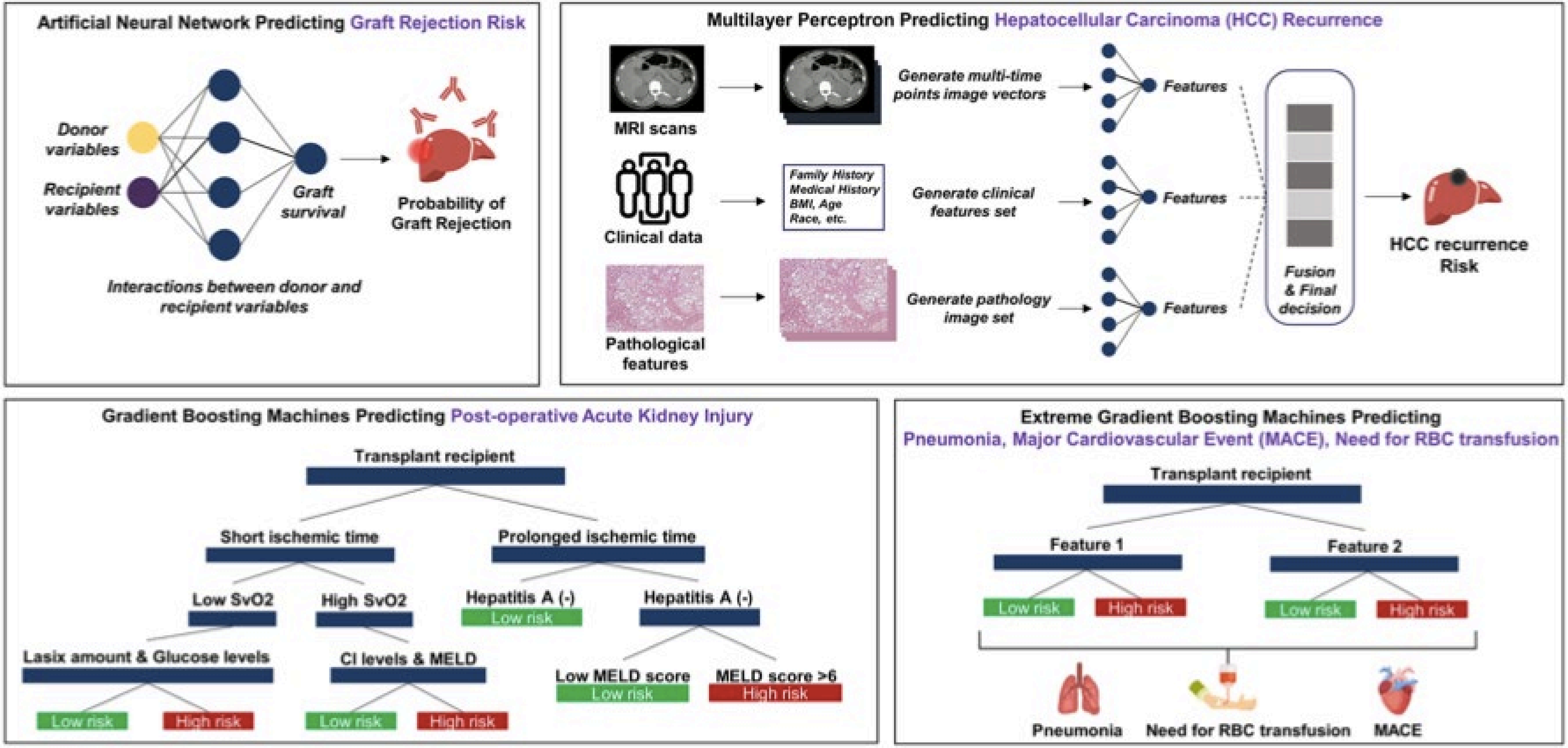
Summary of machine learning applications in the post-liver transplantation setting



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LEOPARD: a European project

Liver Electronic Offering Platform with Artificial intelligence-based Devices

Horizon Europe HLTH 2022 Tool 12 01 two-stage: Computational models for new patient stratification strategies

Budget: 6M euros

Courtesy of Professor Christophe Duvoux, Chair of the Leopard project

Limitations of current liver donor allocation systems and the impact of newer indications for liver transplantation

Patrizia Burra[1,*,a], Didier Samuel[2,a], Vinay Sundaram[3,a], Christophe Duvoux[4,a], Henrik Petrowsky[5,a], Norah Terrault[6,a], Rajiv Jalan[7,a]

By general agreement, MELD-based allocation systems should eagerly be revisited and refined, considering several emerging opportunities.

Journal of Hepatology 2021

Predictors of mortality in decompensated cirrhotics

New predictors of mortality
independent of MELD
HR ≥ 2

Clinical variables
Encephalopathy
Ascitis, sepsis
Frailty
Sarcopenia…

Biomarkers
CRP, Vit D, Ferritine
Copeptine
NGAL/cystatin
VW Ag
Lactate…

OMICs signatures
Transcriptomic (miRNA)
Metabolomic

New composite MELD scores

MELD Na, MELD 3.0
MELD sarcopenia
MELD frailty…

New mathematical models

CLIF C scores
-CLIF C organ failure
- CLIF C ACLF
- CLIF C AD

A room
- To test new available mathematical models
- To design new models
Integrating new predictors
In the setting of liver transplantation

Burra P et al; J Hepatol, 2021

Predictors in HCC patients

New HCC predictors

A room for developing specific models of drop-out in HCC patients

- Response to bridging therapies
- 18 FDG PET
- **AI-based/radiomics signatures**
- Predictive OMICs signatures: Tumor biology
  - Hepatopredict/Ophiomics
  - Microvascular invasion (mi RNA)
- Liquid Biopsy approach to explore

Courtesy of Professor Christophe Duvoux, Chair of the Leopard project

Strategical Opportunities

Horizon Europe HLTH 2022 Tool 12 01 two-stage
Computational models for new patient stratification strategies

- Proposing new computational stratification tools to improve patients outcomes
- Tools should unlock the potential of new AI-based approaches and be evidenced-based, robust and validated in the real-life
- Early interaction with health authorities are encouraged for adoption and extended impact
- Projects should be based on multidisciplinary approaches
- Networking and joint initiatives with ongoing European projects is strongly encouraged

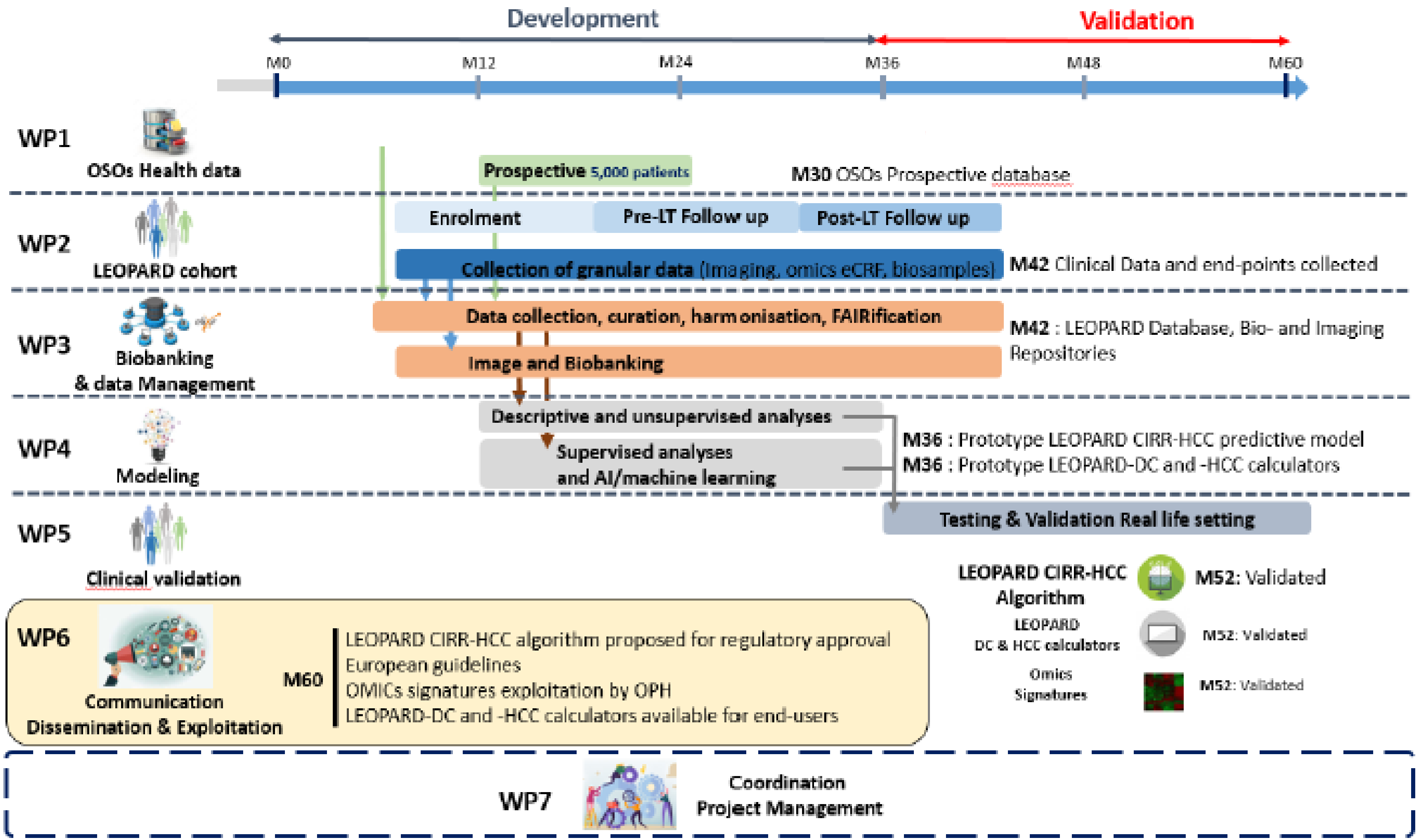
Courtesy of Professor Christophe Duvoux, Chair of the Leopard project

The LEOPARD project

- **Primary aims:** in partnership with key European Organ Sharing Organizations
  - Building on the above-described opportunities, to design new multimodal AI-based predictive models of drop out/mortality in HCC and DC LT candidates, superior to MELD-based models, to improve stratification and patients outcome on the waitlist
  - To validate these models in external cohorts to achieve robust evidence
  - To integrate these models in a single algorithmic solution, proposed OSOs for integration in new offering schemes
- **Final aim:**
  - Reduction of mortality on the waitlist, considering Spain & Italy as benchmark: 8-10%, without hampering post LT outcomes
  - Improving equity of access to LT across Europe

Courtesy of Professor Christophe Duvoux, Chair of the Leopard project

LEOPARD Work Packages

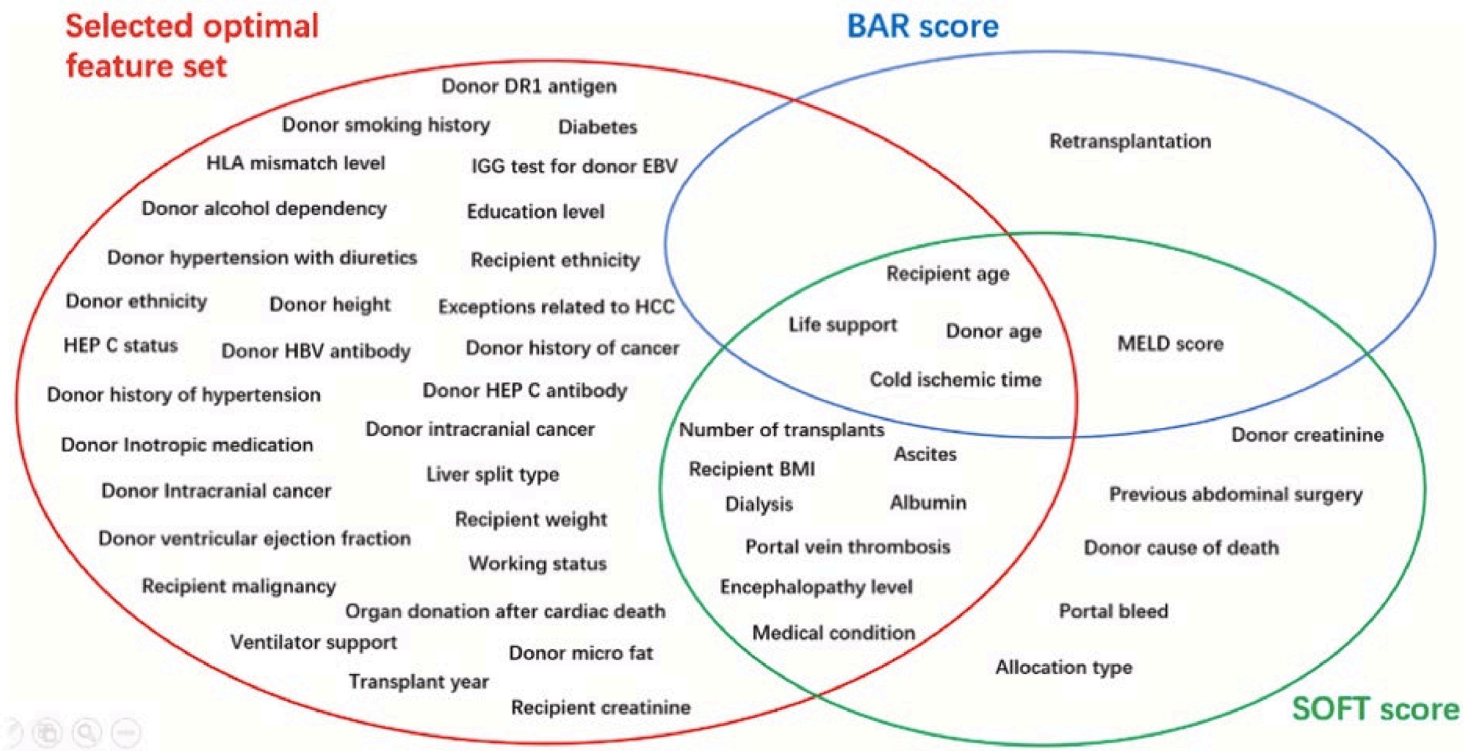


Courtesy of Professor Christophe Duvoux, Chair of the Leopard project

Interpretable prediction of mortality in liver transplant recipients based on machine learning

- Existing risk scoring models, such as the Balance of Risk (BAR) score and the Survival Outcomes Following Liver Transplantation (SOFT) score, do not predict the mortality of post-liver transplantation with sufficient accuracy.
- The optimal feature set for the prediction of the mortality was selected by a wrapper method based on binary particle swarm optimization (BPSO).
- Seven machine learning models were applied to predict mortality over different time windows.
- The best-performing model was used to predict mortality through a comprehensive comparison and evaluation.

Venn diagram of selected feature set and clinical features used for BAR score and SOFT score.



Xiao Zhang, Ricard Gavaldà, Jaume Baixeries
Computers in Biology and Medicine 2022

Interpretable prediction of mortality in liver transplant recipients based on machine learning

- The feature set selected by BPSO outperformed both the feature set in the existing risk score model (BAR score, SOFT score) and the feature set processed by principal component analysis.

- The best-performing model, was found to improve the AUC values for mortality prediction by:
  - 6.7% at 3 months
  - 11.6% at 3 years
  - 17.4% at 10 years

  compared to the SOFT score

Xiao Zhang, Ricard Gavaldà, Jaume Baixeries
Computers in Biology and Medicine 2022

Prediction of waitlist drop out in liver transplant candidates based on machine learning

- Accurate prediction of outcome among liver transplant candidates with HCC remains challenging.
- A prediction model for waitlist dropout among liver transplant candidates with HCC.
- The study included 18,920 adult liver transplant candidates in the U.S. listed with a diagnosis of HCC.
- The primary outcomes were 3-, 6-, and 12-month waitlist dropout

Allison Kwong| Bilal Hameed | Shareef Syed | Ryan Ho | Hossein Mard | Sahar Arshad | Isaac Ho | Tashfeen Suleman | Francis Yao | Neil Mehta
Cancer Medicine 2022

Prediction of waitlist drop out in liver transplant candidates based on machine learning

- Using 1,181 unique variables, the random forest model and Spearman's correlation analyses converged on 12 predictive features involving 5 variables, including:
  – AFP (maximum and average)
  – largest tumor size (minimum, average, and most recent)
  – bilirubin (minimum and average)
  – INR (minimum and average)
  – ascites (maximum, average, and most recent).
- The final Cox proportional hazards model had a concordance statistic of 0.74 in the validation set.
- **An online calculator was created for clinical use and can be found at: http://hccli vercalc.cloudmedxhealth.com/.**
- A simple, interpretable 5-variable model predicted 3-, 6-, and 12-month waitlist dropout among patients with HCC, which can be used to appropriately prioritize patients with HCC.

Allison Kwong| Bilal Hameed | Shareef Syed | Ryan Ho | Hossein Mard | Sahar Arshad | Isaac Ho | Tashfeen Suleman | Francis Yao | Neil Mehta
Cancer Medicine 2022

Interpretable prediction of mortality in liver transplant recipients based on machine learning

Machine Learning Algorithm Improves the Prediction of Transplant Hepatic Artery Stenosis or Occlusion

A Single-Center Study

Keith Feldman, PhD,† Justin Baraboo, MSc,‡ Deeyendal Dinakarpandian, PhD,§ and Sherwin S. Chan, MD, PhD‖¶*

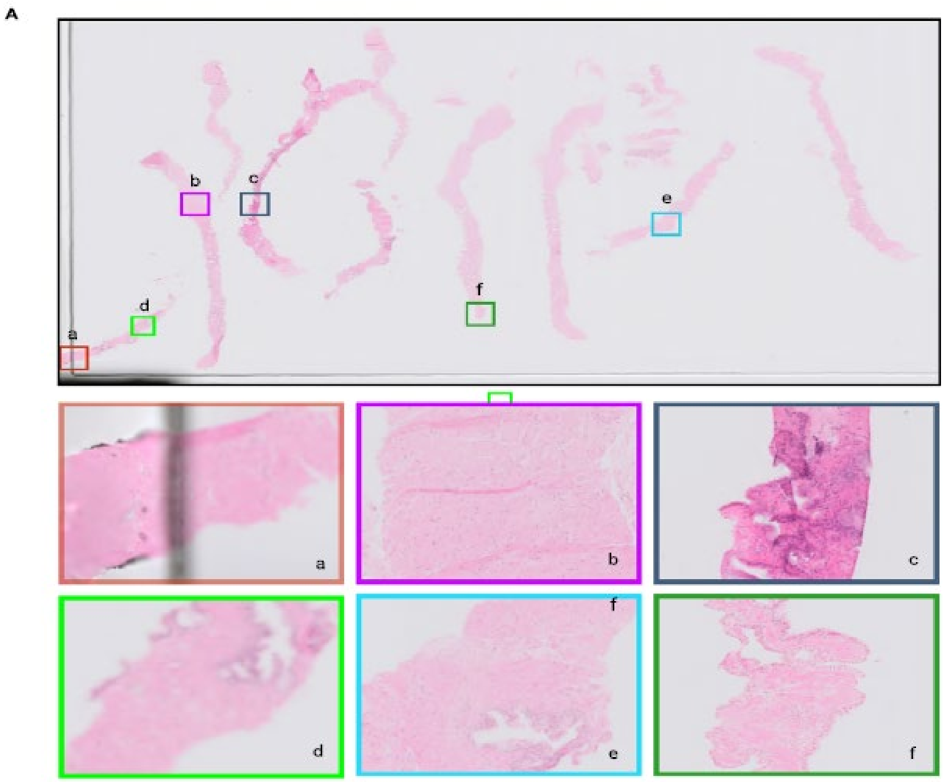
Ultrasound Quarterly 2022

Development and validation of a practical machine learning model to predict sepsis after liver transplantation

Chaojin Chen[a*], Bingcheng Chen[a*], Jing Yang[a*], Xiaoyue Li[a], Xiaorong Peng[a], Yawei Feng[a], Rongchang Guo[b], Fengyuan Zou[b], Shaoli Zhou[a] and Ziqing Hei[a]

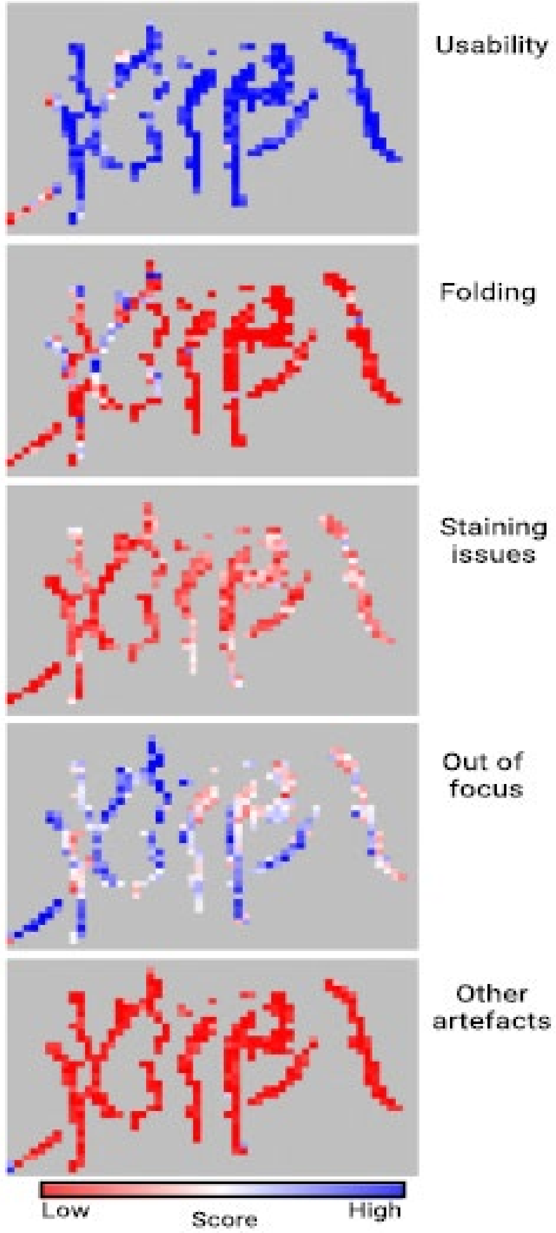
Annals of Medicine 2023

Automated quality assessment of digitised histology cohorts by artificial intelligence



- Glass slides are digitised for the development and validation of artificial intelligence tools.
- Trained and validated a multi-task deep neural network to automate the process of quality control of a large cohort of cases.
- To demonstrate its wider potential utility, the pipeline was applied to the original cohort for comparison.
- The model indicates comparable predicted usability of images from the cohorts assessed.

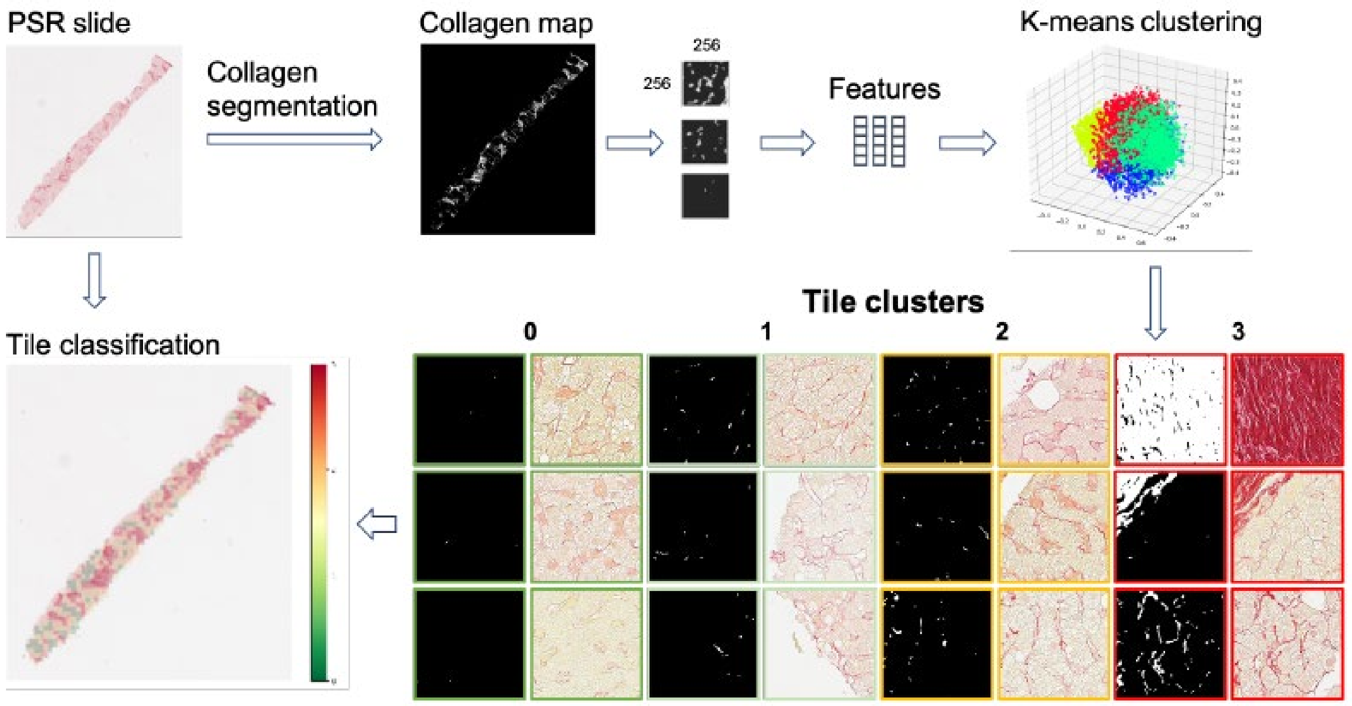
Artificial intelligence can be used to automate the process of quality control of large retrospective cohorts to maximise their utility for research.



Maryam Haghighat & Jens Rittscher Nature Portfolio 2022

Early detection of liver fibrosis using graph convolutional networks

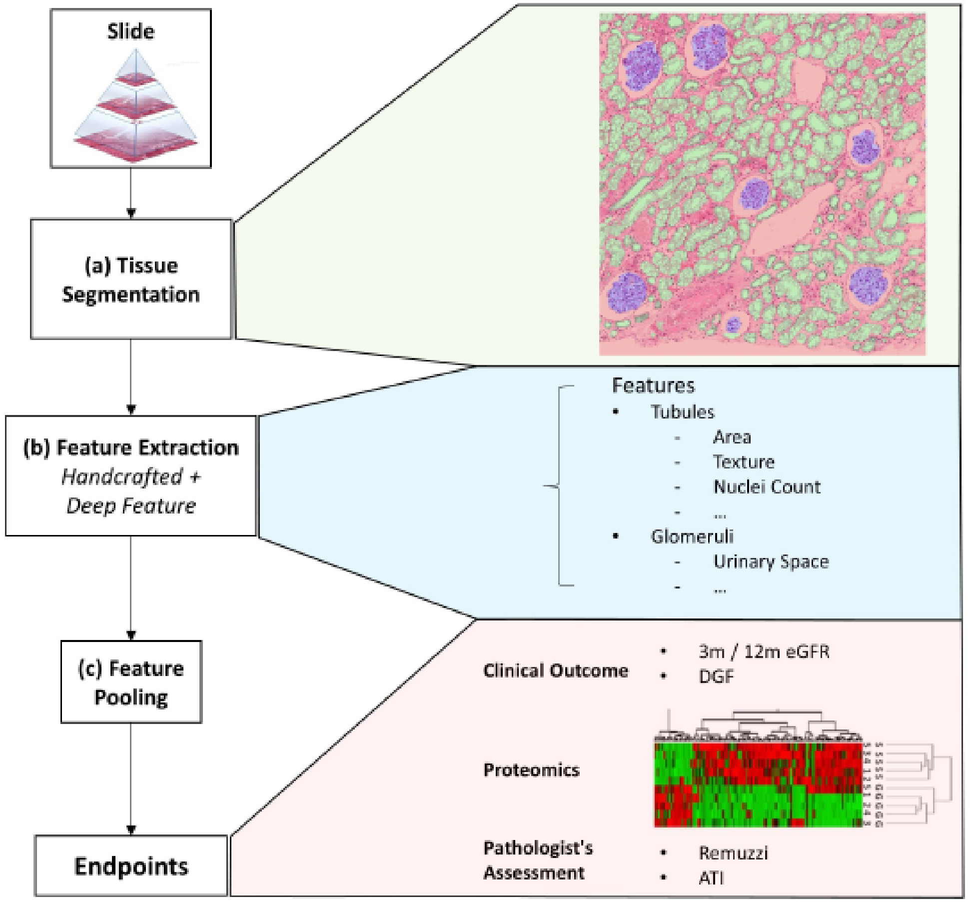
- A **quantitative analysis of fibrosis** patterns will improve diagnostic quality.
- Deep learning to identify **elementary fibrosis patterns**.
- Graphical model is utilised to model **the spatial organisation** of the fibrosis patterns.
- This approach **correlates well** with established clinical grading.



Four clusters of collagen tiles have been identified, each representing a different level of collagen content.

Wojciechowska et al 2021

Predicting Clinical Endpoints and Visual Changes with Quality-Weighted Tissue-based Renal Histological Features



Using a soft attention model to predict several slide-level labels:

1) delayed graft function
2) acute tubular injury
3) *Remuzzi* grade components.

Tam et al Medical Image Analysis 2022

PNRR - DARE
Digital lifelong prevention

Task 4.4 Bringing Medicine Digitalization into the Italian Solid Organ Transplant Network

Responsible:
Patrizia Burra (burra@unipd.it, Gastroenterology and Multivisceral Transplant Unit, Department od Surgery, Oncology and Gastroenterolgy – (DISCOG) – Padua University Hospital)

Working group:
Albino Eccher, Pathology, Verona University Hospital
Lucrezia Furian, Kidney-Pancreas Transplant Unit, DISCOG Padua University Hospital
Alberto Zanetto, Gastroenterology, DISCOG Padua University Hospital

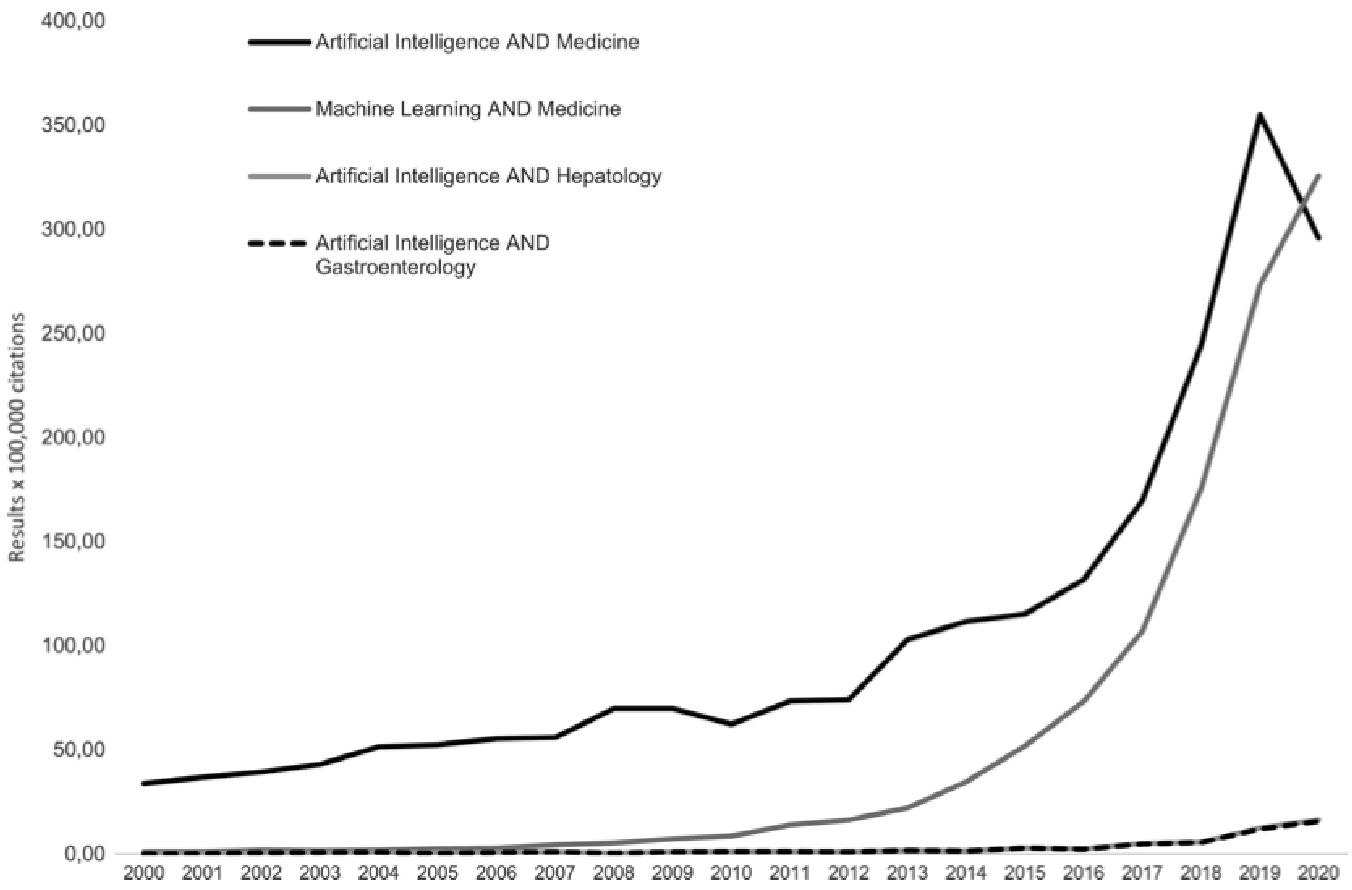
Other keypersons:
Angelo Paolo Dei Tos, Pathology, Padua University Hospital
Massimo Cardillo, Director of the National Transplant Center, Rome, Giuseppe Feltrin, Coordinator of the Regional Transplant Center of Veneto Region
Umberto Cillo-Chief Liver Transplant, Gino Gerosa-Chief Heart Transplant, Federico Rea-Chief Lung Transplant, Paolo Rigotti-Chief Kidney-Pancreas Transplant Units, Padua University Hospital

External scientific consultation: Professor of Engineering Science, Jens Rittscher from Oxford University.

REVIEW

Machine learning in liver transplantation: a tool for some unsolved questions?

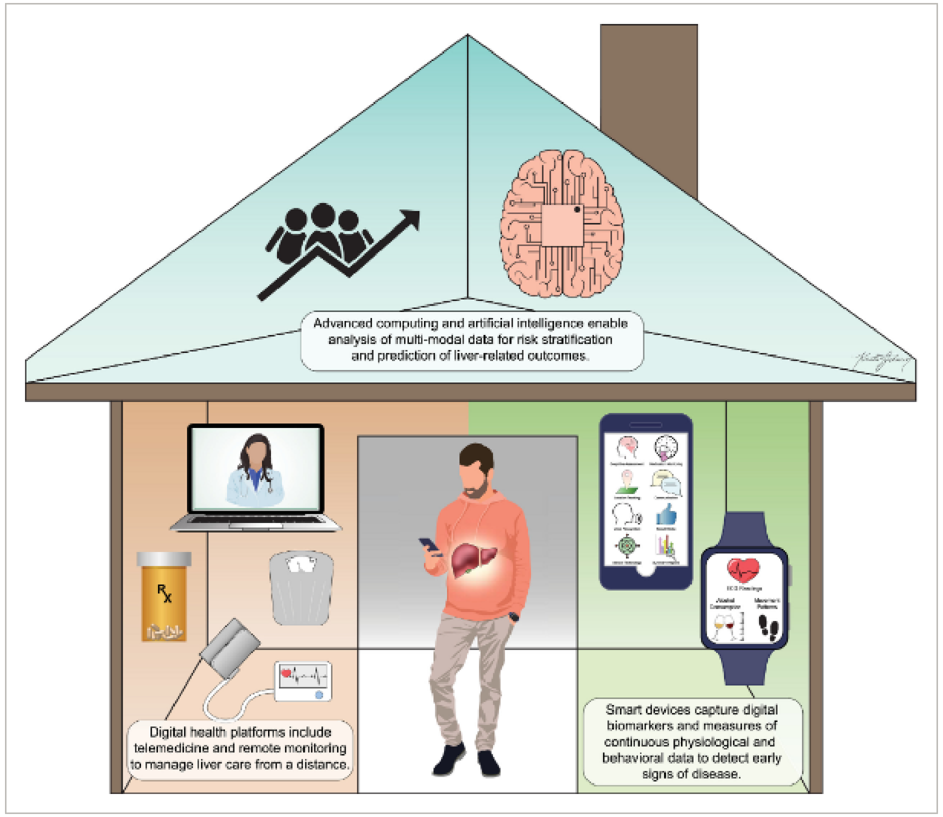
Alberto Ferrarese[1], Giuseppe Sartori[2], Graziella Orrù[3], Anna Chiara Frigo[4], Filippo Pelizzaro[1], Patrizia Burra[1] & Marco Senzolo[1]



Trend of citations on PubMed regarding artificial intelligence and machine learning applied in medicine, gastroenterology and hepatology between 2000 and 2020.

The digital transformation of health care defines an innovative model of care delivery for patients with liver disease

- The unique transformation underway in the care of patients with liver disease.
- Digital transformation of diagnostics, prediction and clinical decision-making, and management.



Confirm validity of new technologies.

Confirm usability and acceptability of digital solutions.

Ensure equity and inclusivity of vulnerable populations.

Wu, Hepatology 2022

Take home messages

Machine learning produces powerful predictive models that exploit data to continually self-adapt and improve analytical accuracy.

Benefits

Drawbacks

Obstacles for implementation into clinical practice