ETH zürich

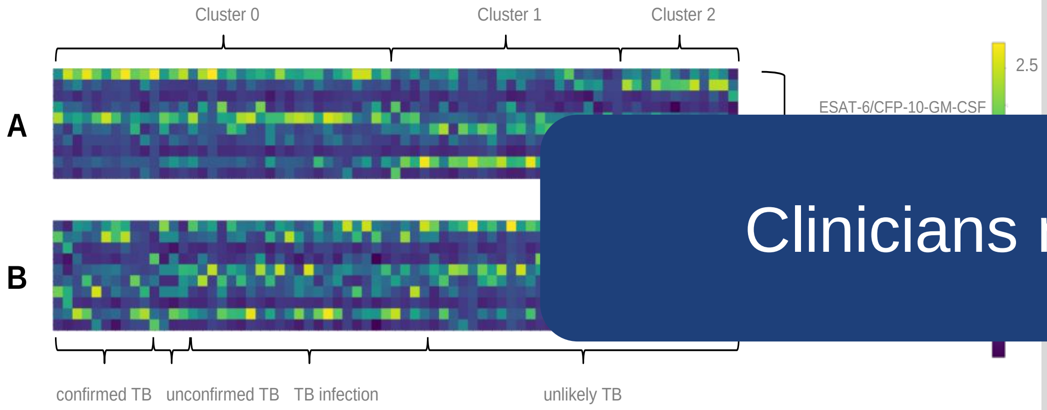
D-INFK

Clinical Research and Machine Learning: Bridging the Gap

Prof. Julia Vogt
Medical Data Science Group
Department of Computer Science
ETH Zurich

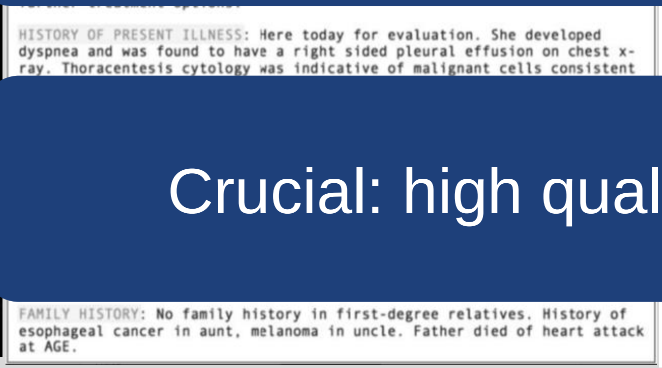
medical
data
science

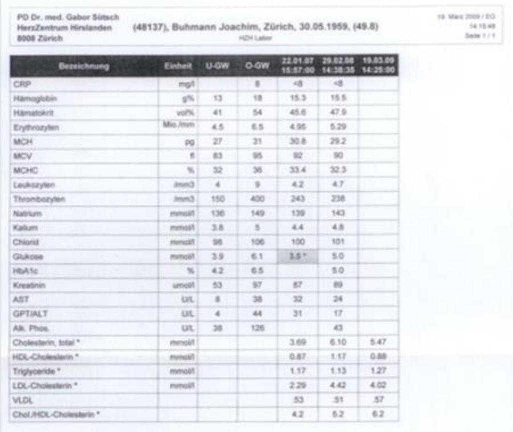
Need for Machine Learning in Medicine



Clinicians need support!

Develop new ML methods and tools





PD Dr. med. Gabor Sütsch
HerzZentrum Hirslanden
8008 Zürich

(48137), Buhmann Joachim, Zürich, 30.05.1959, (49.8)

HZH Labor

Bezeichnung	Einheit	U-GW	O-GW	22.01.07 15:57:00	29.02.08 14:38:35	19.03.09 14:25:00
CRP	mg/l		8	<8	<8	
Hämoglobin	g%	13	18	15.3	15.5	
Hämatokrit	vol%	41	54	45.6	47.9	
Erythrozyten	Mio./mm	4.5	6.5	4.96	5.29	
MCH	pg	27	31	30.8	29.2	
MCV	fl	83	95	92	90	
MCHC	%	32	36	33.4	32.3	
Leukozyten	/mm3	4	9	4.2	4.7	
Thrombozyten	/mm3	150	400	243	238	
Natrium	mmol/l	136	149	139	143	
Kalium	mmol/l	3.8	5	4.4	4.8	
Chlorid	mmol/l	98	106	100	101	
Glukose	mmol/l	3.9	6.1	3.8 *	5.0	
HbA1c	%	4.2	6.5		5.0	
Kreatinin	umol/l	53	97	87	89	
AST	U/L	8	38	32	24	
GPT/ALT	U/L	4	44	31	17	
Alk. Phos.	U/L	38	126		43	
Cholesterin, total *	mmol/l			3.69	6.10	5.47
HDL-Cholesterin *	mmol/l			0.87	1.17	0.88
Triglyceride *	mmol/l			1.17	1.13	1.27
LDL-Cholesterin *	mmol/l			2.29	4.42	4.02
VLDL				.53	.51	.57
Chol./HDL-Cholesterin *				4.2	5.2	6.2

Crucial: high quality data!

High Level Goal of our Research

Improve patient care with machine learning

The Need for Interdisciplinary Collaborations

Machine Learning Researcher

Computer Scientists

Mathematicians

Physicists

Clinicians

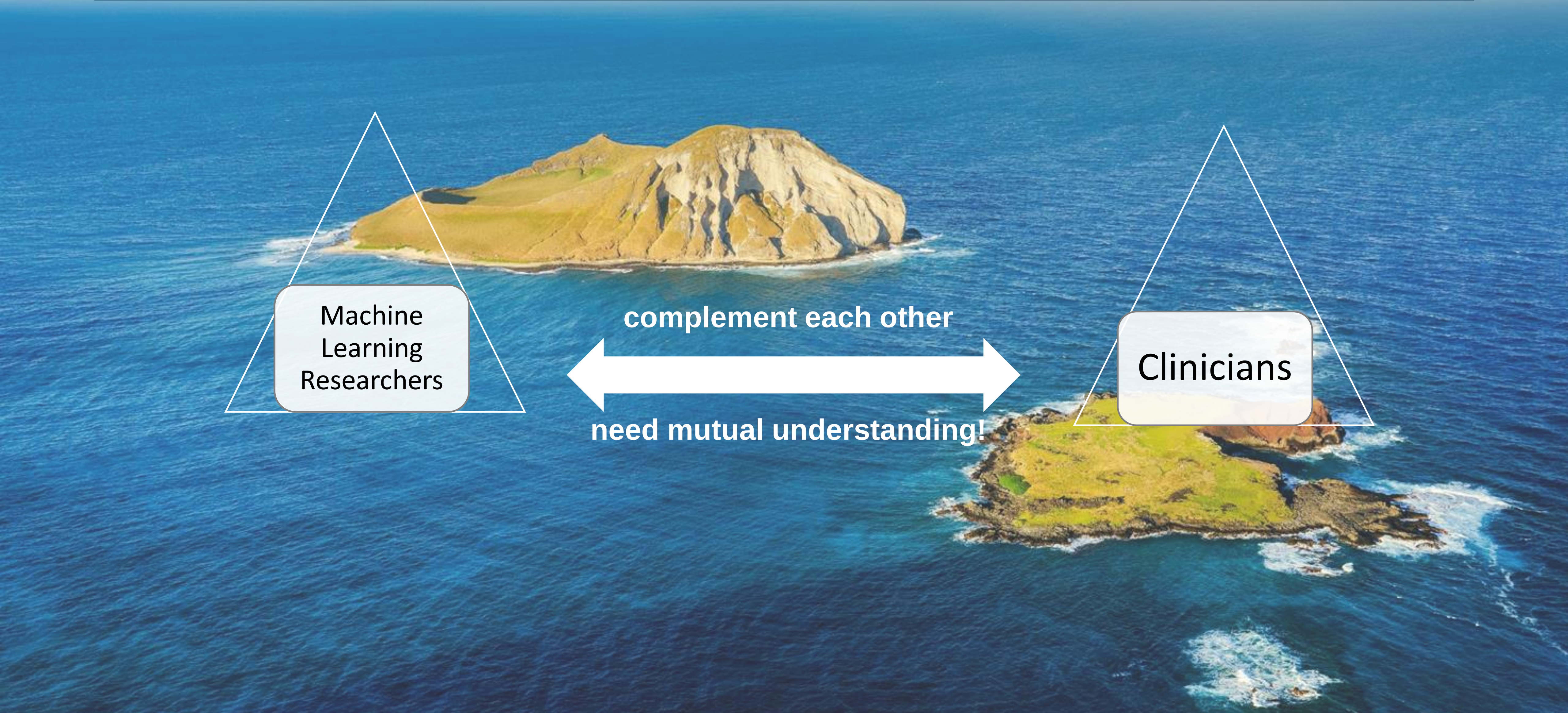
Physicians

Biologist

→ methods not applicable to real clinical problems

→ models might overfit, or might not fulfill underlying statistical assumptions

Bridging the Gap



Bridging the Gap

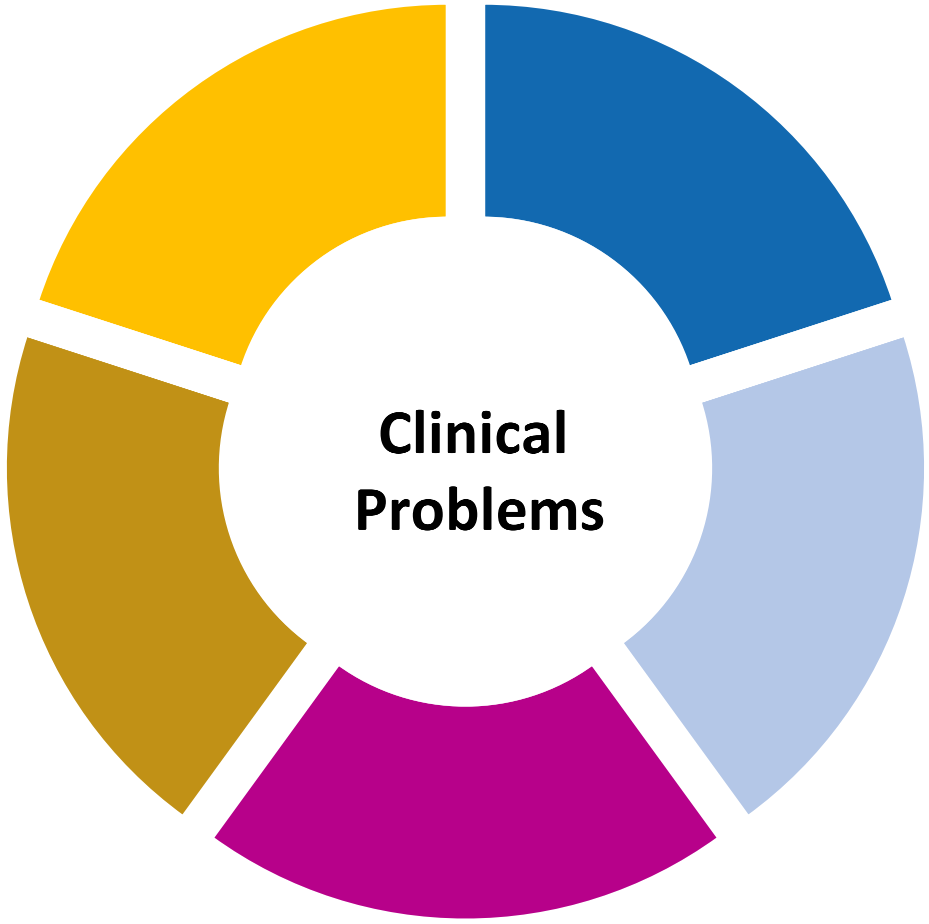
Translational barrier:

State-of-the-art ML techniques are stalled at the research paper level and are not implemented into daily clinical practice

Transparency!

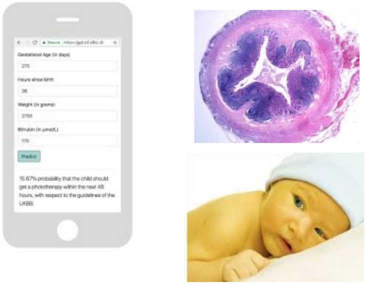
Decision Support Tools!

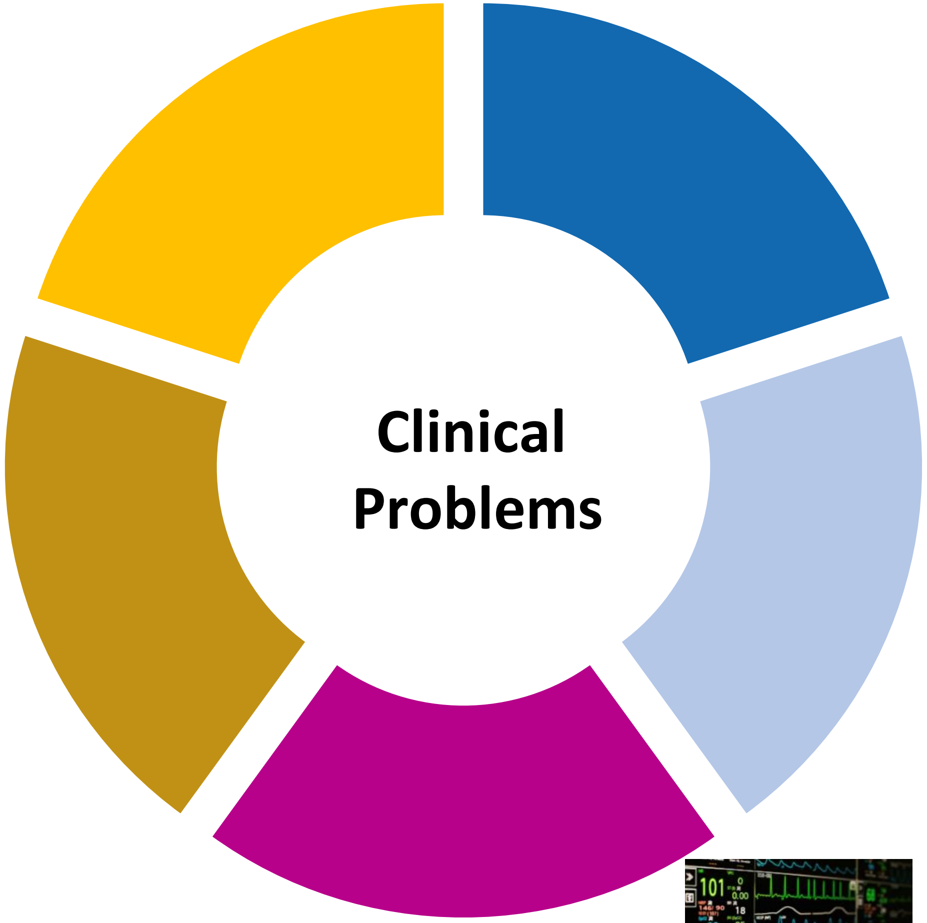
Overview of the Group’s Machine Learning Research



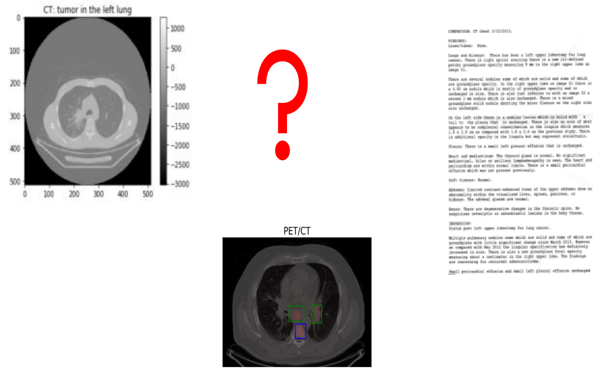
Overview of the Group’s Machine Learning Research

Decision Support Tools

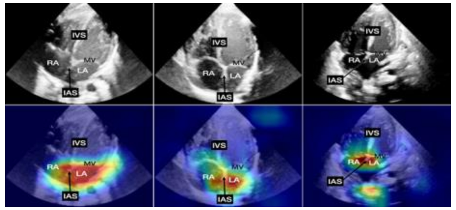




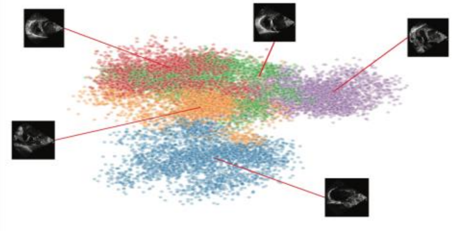
Multimodal Data Integration



Transparent Methods

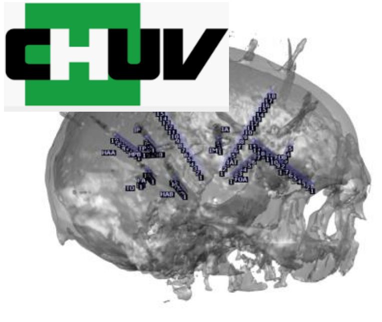


Structure Detection



Time-Varying Data

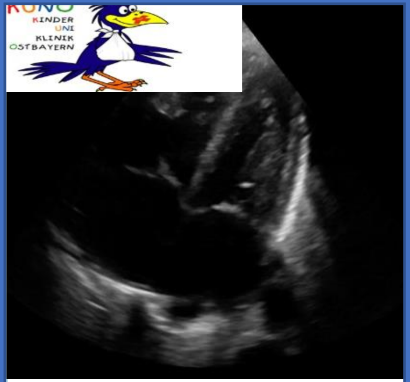
Examples of Clinical Projects



Epilepsy

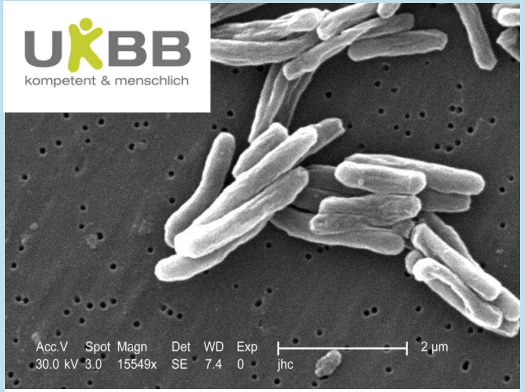
Sepsis (Blood Poisoning)

Appendicitis

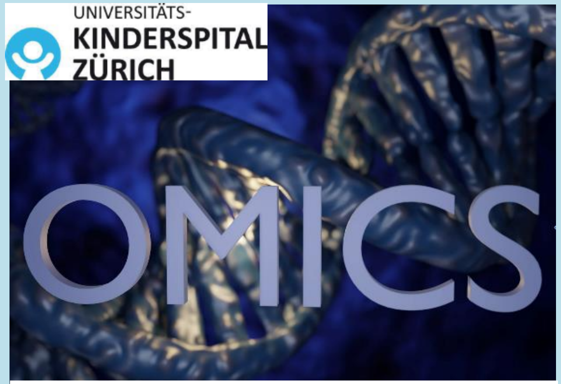


Heart-Defects

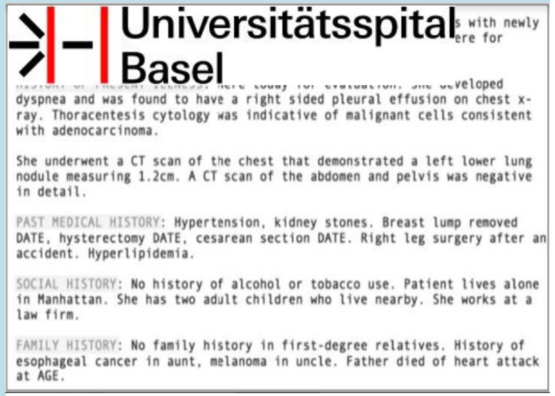
Severe Jaundice



Tuberculosis



Rare Diseases



dyspnea and was found to have a right sided pleural effusion on chest x-ray. Thoracentesis cytology was indicative of malignant cells consistent with adenocarcinoma.

She underwent a CT scan of the chest that demonstrated a left lower lung nodule measuring 1.2cm. A CT scan of the abdomen and pelvis was negative in detail.

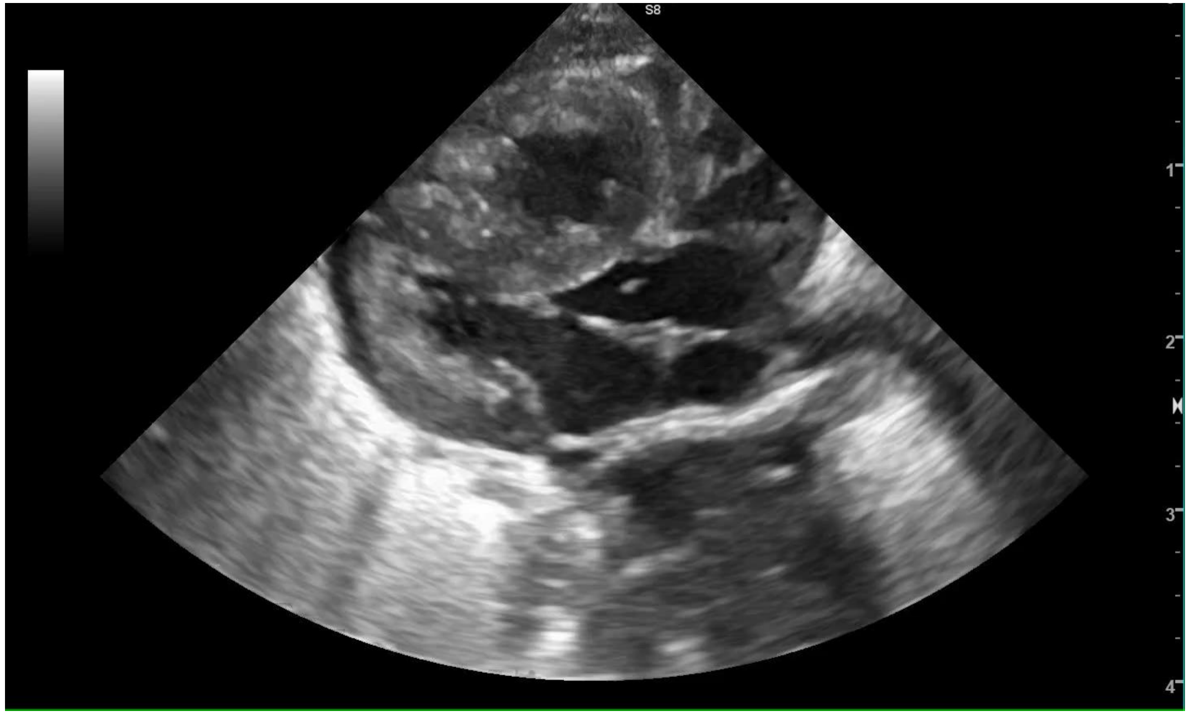
PAST MEDICAL HISTORY: Hypertension, kidney stones. Breast lump removed DATE, hysterectomy DATE, cesarean section DATE. Right leg surgery after an accident. Hyperlipidemia.

SOCIAL HISTORY: No history of alcohol or tobacco use. Patient lives alone in Manhattan. She has two adult children who live nearby. She works at a law firm.

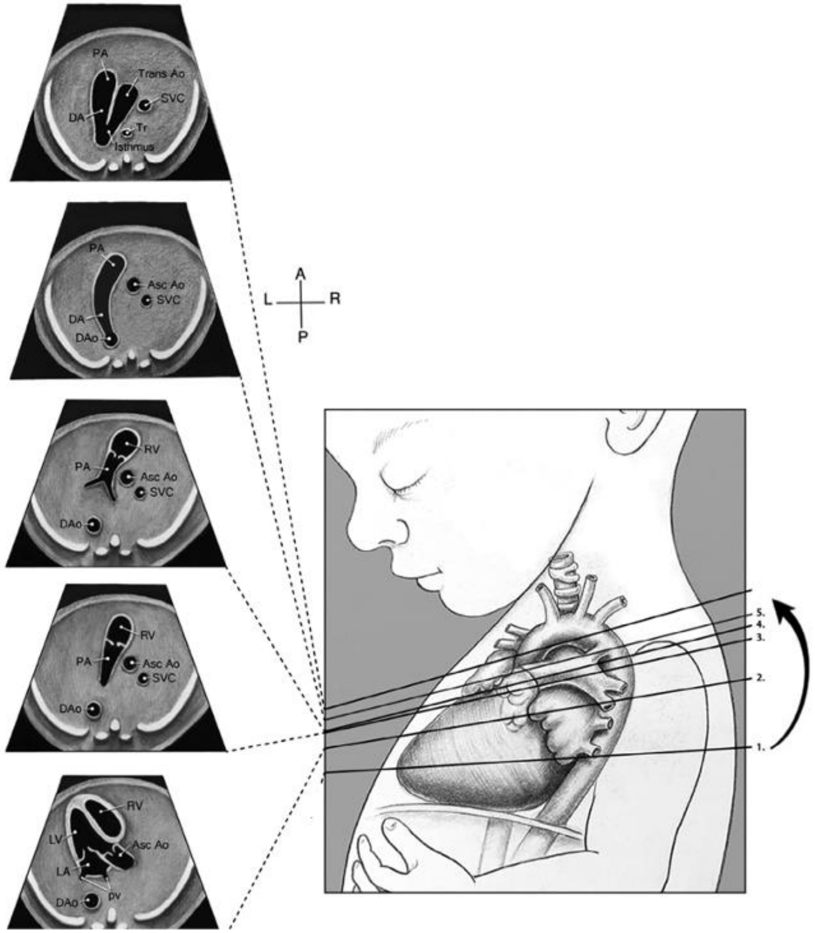
FAMILY HISTORY: No family history in first-degree relatives. History of esophageal cancer in aunt, melanoma in uncle. Father died of heart attack at AGE.

Electronic Health Records

Example 1: Detecting Heart Defects in Newborns



Heart Echo Data Set (5 different views)



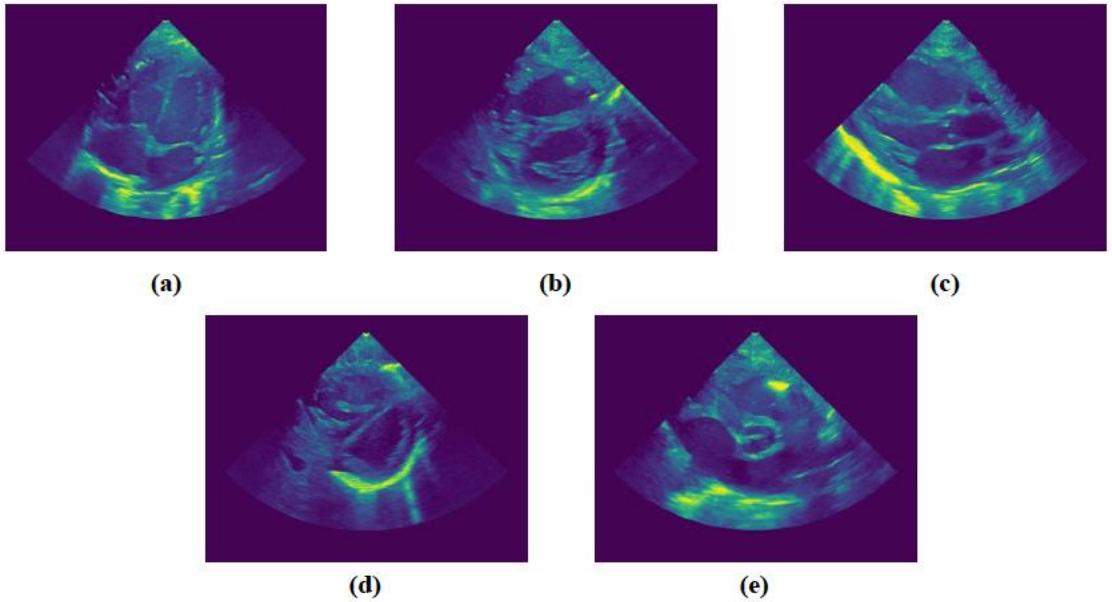
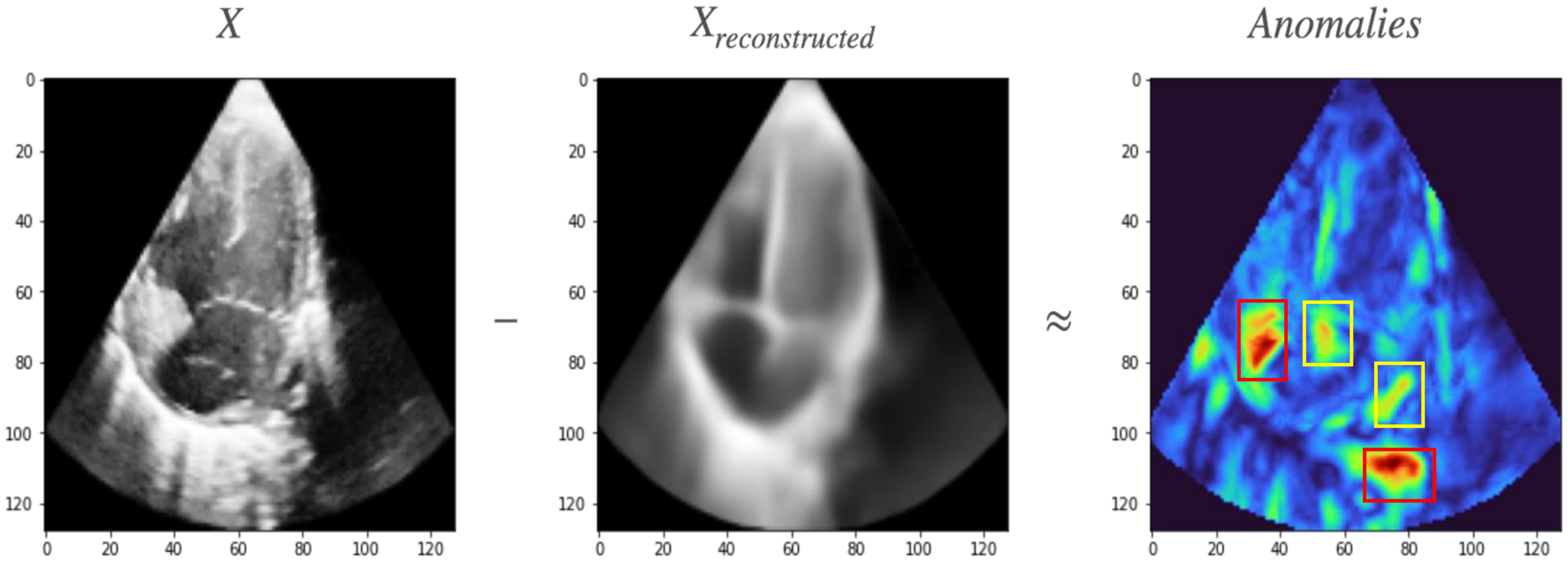


Image: obgynkey.com

Anomaly Detection

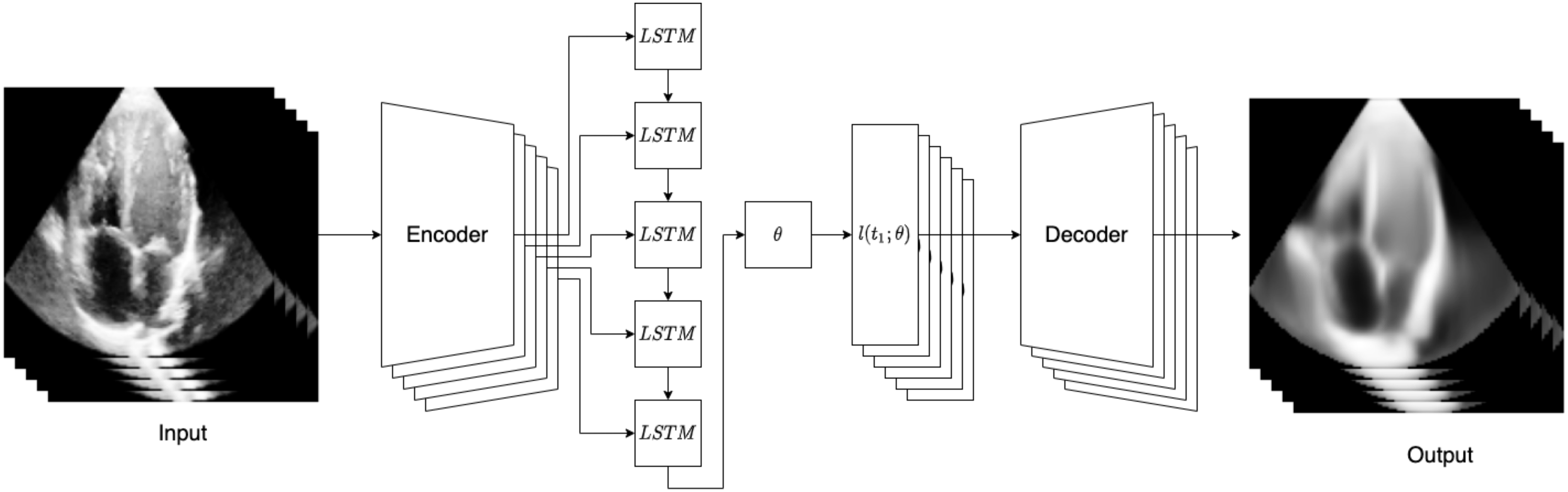


Ultrasound image

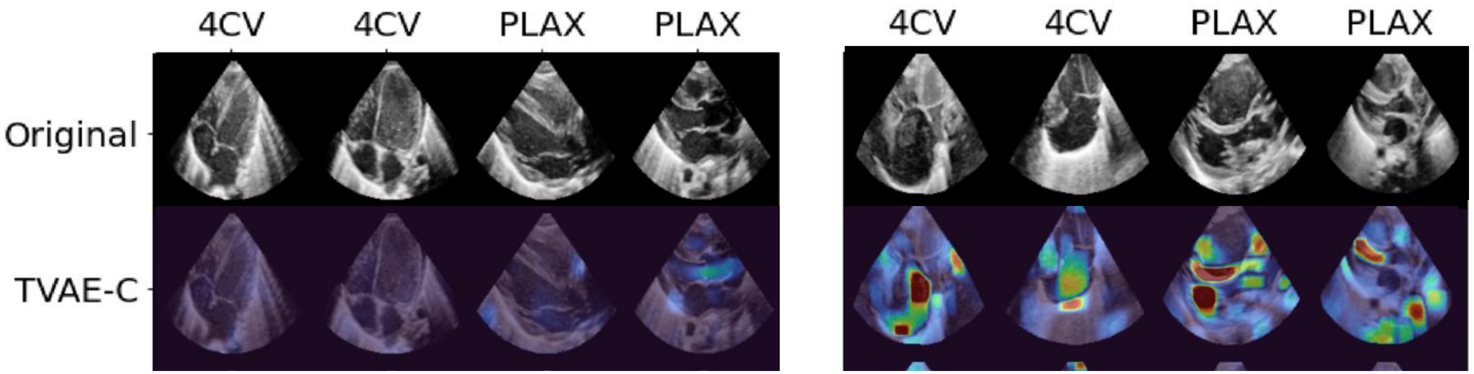
Reconstructed healthy heart

Visualization of the differences

Latent Trajectory Model



Interpretability



Proceedings of Machine Learning Research 182:1–22, 2022 Machine Learning for Healthcare

Anomaly Detection in Echocardiograms with Dynamic Variational Trajectory Models

Alain Ryser[1], Laura Manduchi[1], Fabian Laumer[1], Holger Michel[2], Sven Wellmann[2], and Julia E. Vogt[1]

[1]Department of Computer Science, ETH Zurich
[2]Department of Neonatology, University Children's Hospital Regensburg (KUNO), University of Regensburg, Germany

Example 2: Pulmonary Hypertension (PH) in Newborns

PH in newborns is a **rare heart condition**

- Contributes to morbidity and mortality
- Pulmonary Artery Pressure (PAP) ≥ 25 mmHG
  - Determined by Right Heart Catherisation

Manual assessment using **echocardiography (ECHO)**

- Early detection important for treatment
- But assessment is time consuming

View1 View2

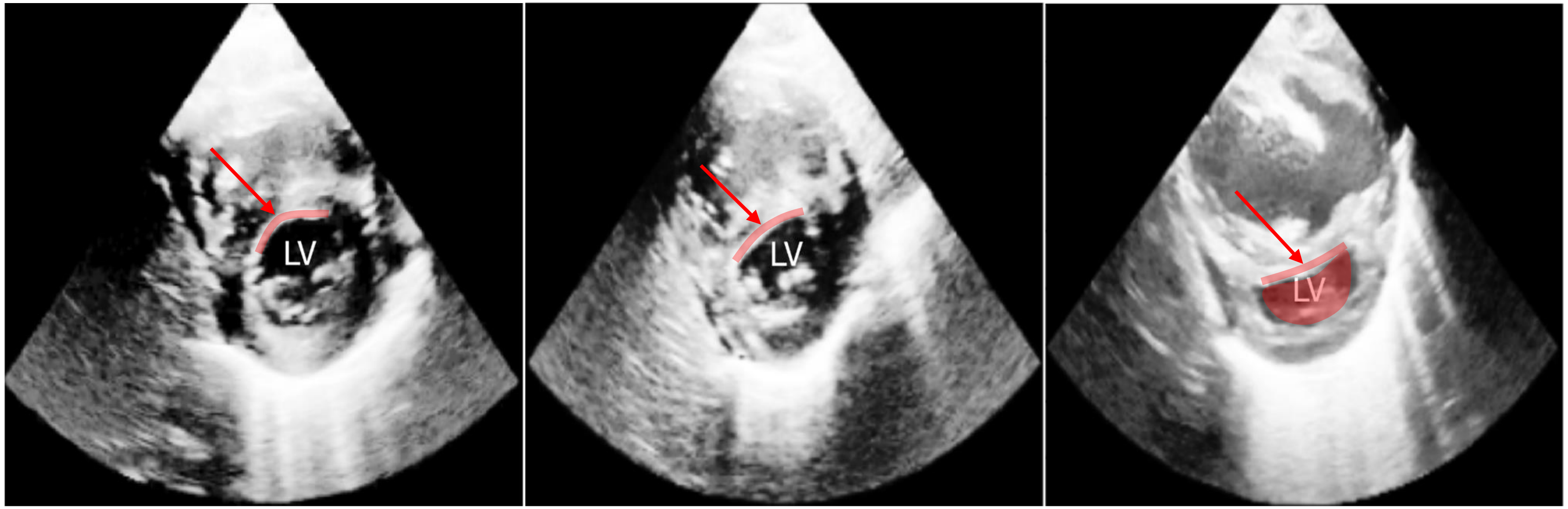
Few methods for automatic PH prediction*:

- Only for the **adult** population
- Do not predict PH **severity**
- Not **interpretable** or **explainable**

*J. Zhang, et al. Fully automated echocardiogram interpretation in clinical practice: Feasibility and diagnostic accuracy. 2018.
A. Leha, et al. A machine learning approach for the prediction of pulmonary hypertension. October 2019.

Pulmonary Hypertension in Newborns from ECHOs

No PH | Mild PH | Severe PH



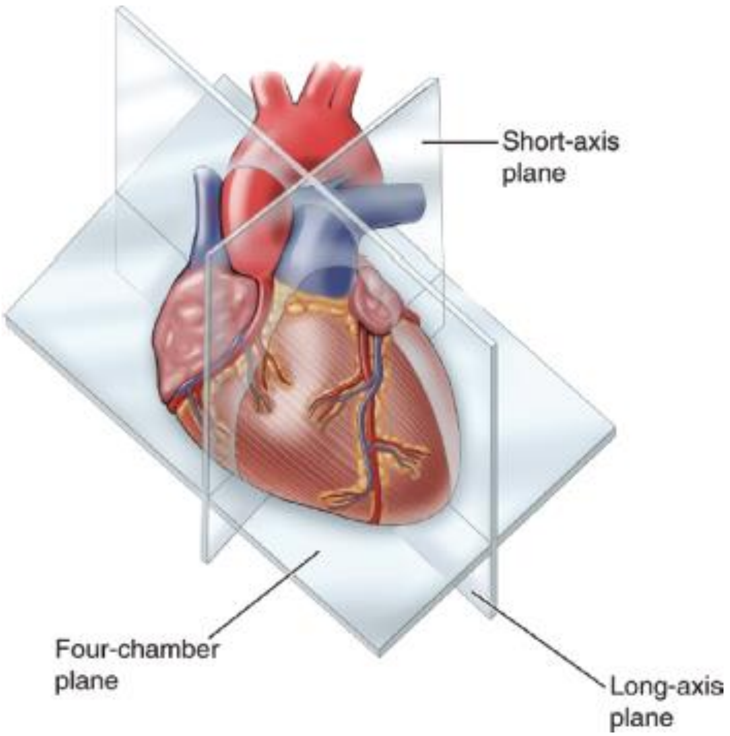
Pulmonary Hypertension (PH) in Newborns

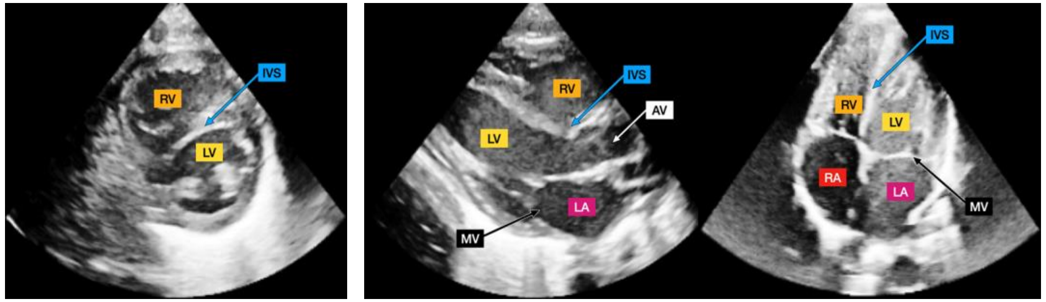
Aim: create a robust and **explainable** automatic approach for the detection of **PH** and its **severity** in newborns, using **echocardiography**.

Echocardiography Dataset

ECHO from approx. 200 newborns from 5 views

- 3 parasternal short axis views (PSAX):
  - **PSAX-P**, PSAX-S, PSAX-A
- Parasternal long axis view (**PLAX**)
- Apical four chamber view (**A4C**)





PSAX-P PLAX A4C

Label	Ratio
Healthy	65%
Mild	16%
Moderate to Severe	19%

Methods - Overview

Data Processing

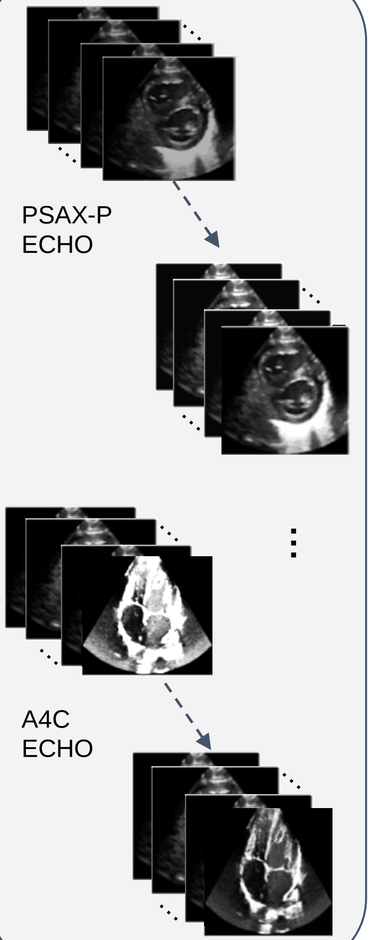
Classification

Explainability

19

Methods - Overview

Data Processing

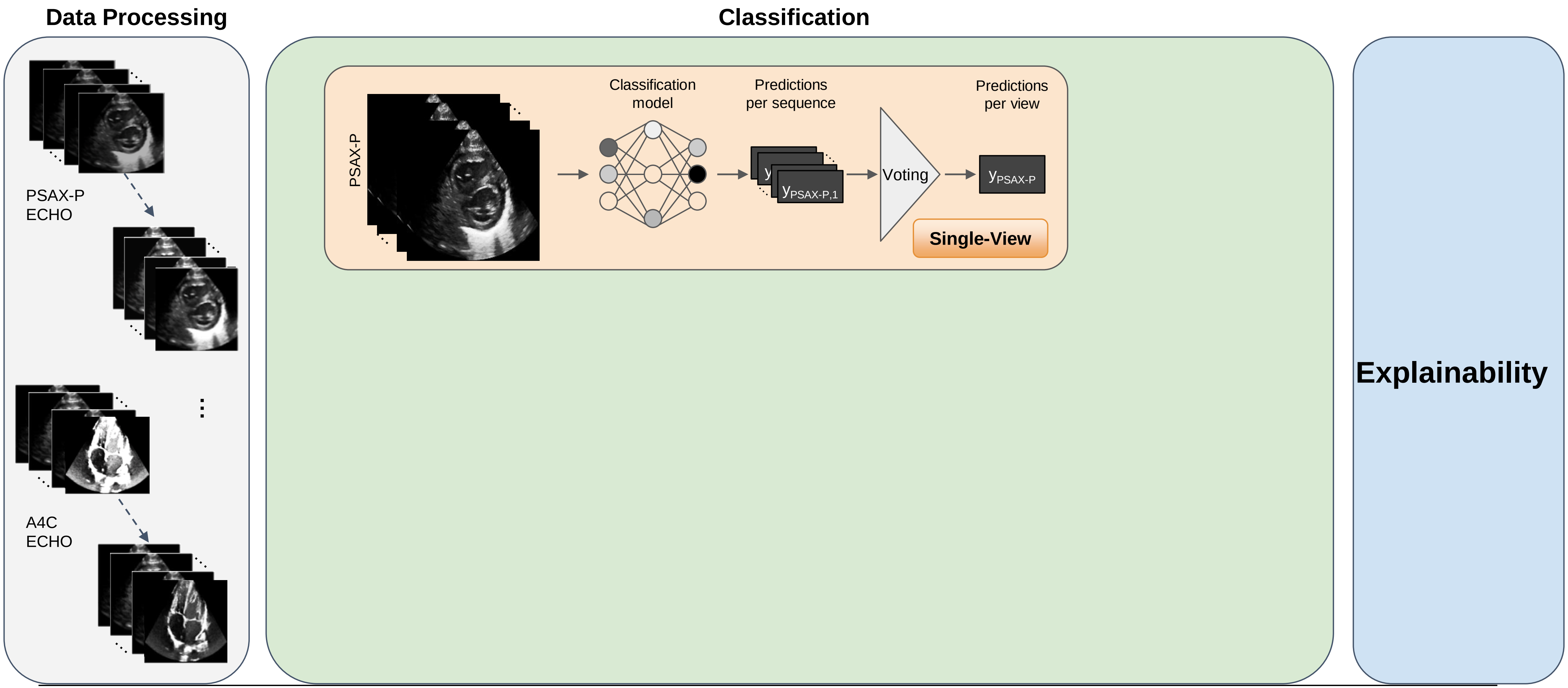


Classification

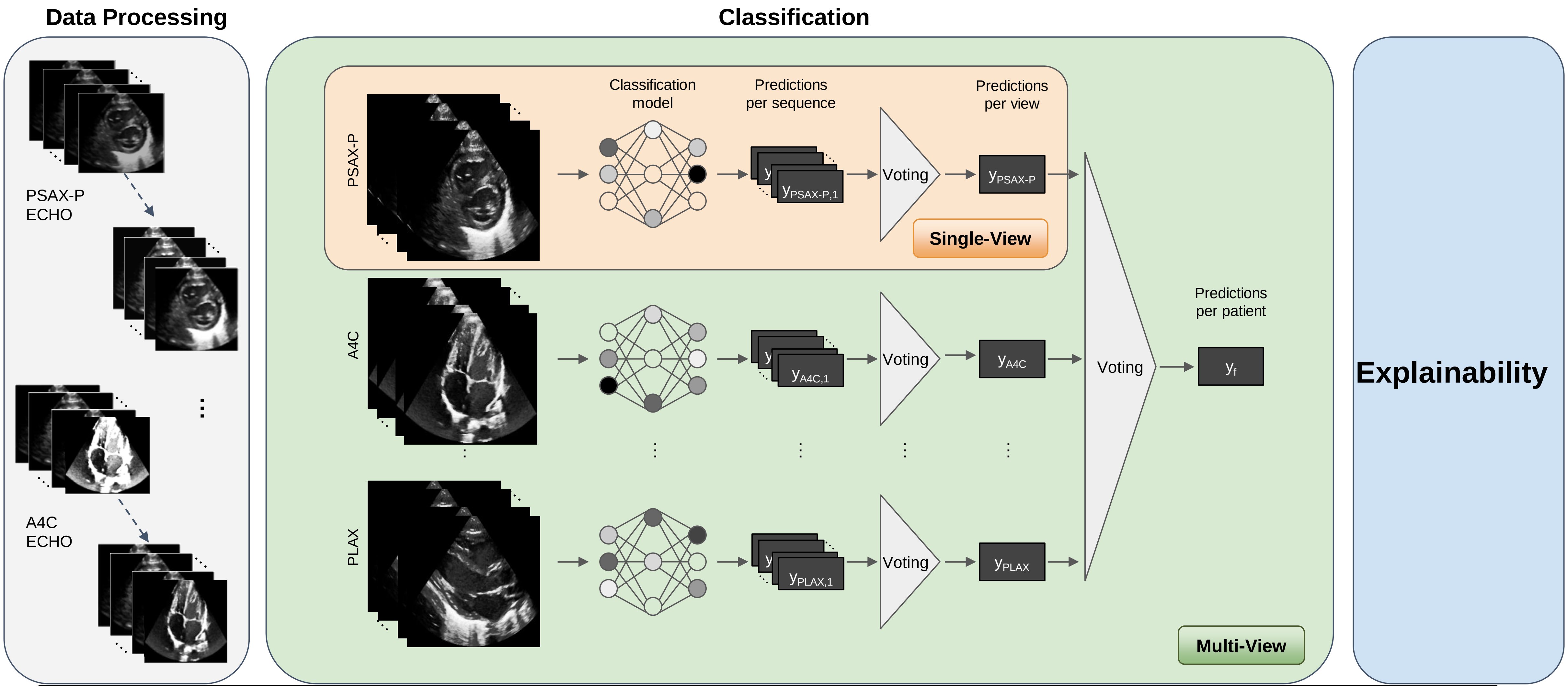
Explainability

20

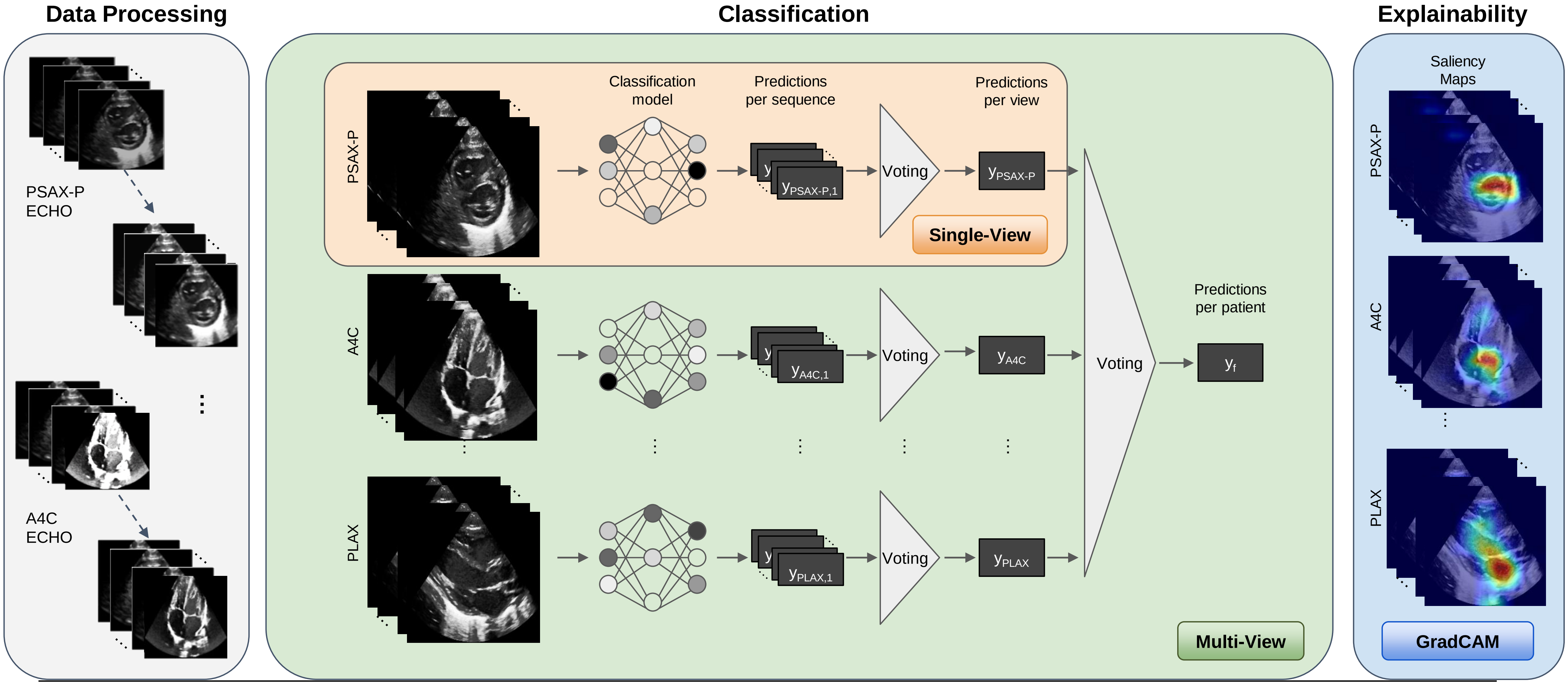
Methods - Overview



Methods - Overview



Methods - Overview



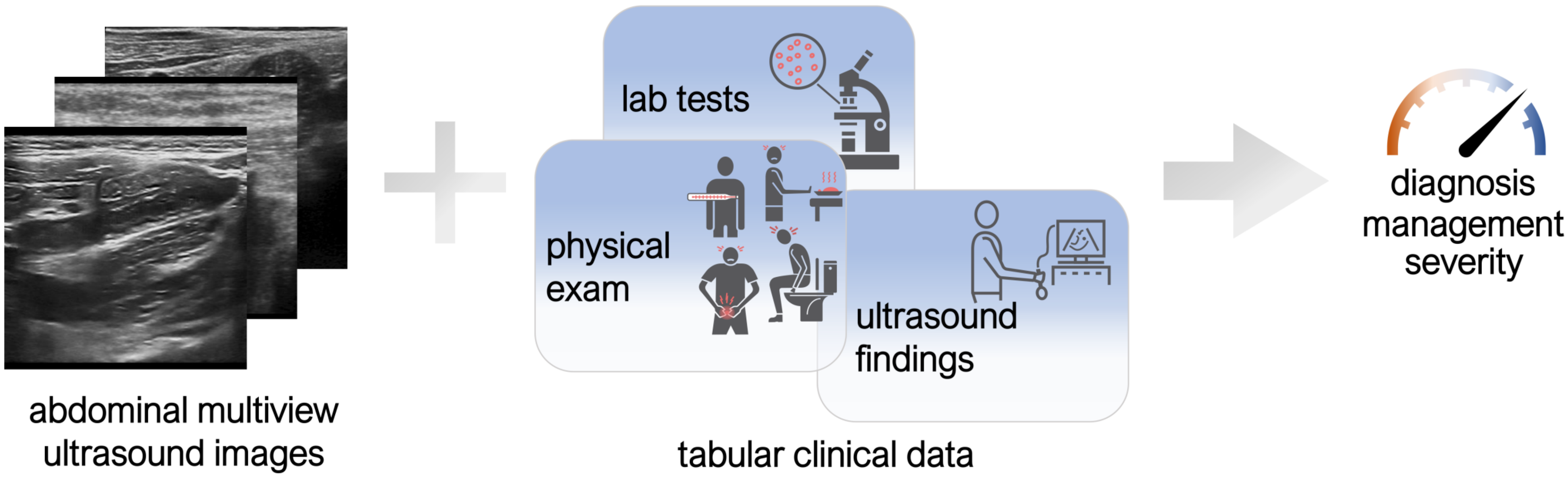
Interpretable Prediction of Pulmonary Hypertension in Newborns Using Echocardiograms

Hanna Ragnarsdottir[1], Laura Manduchi[1], Holger Michel[2], Fabian Laumer[1], Sven Wellmann[2], Ece Ozkan[1(✉)], and Julia E. Vogt[1]

[1] Department of Computer Science, ETH Zürich, Zürich, Switzerland
ece.oezkanelsen@inf.ethz.ch

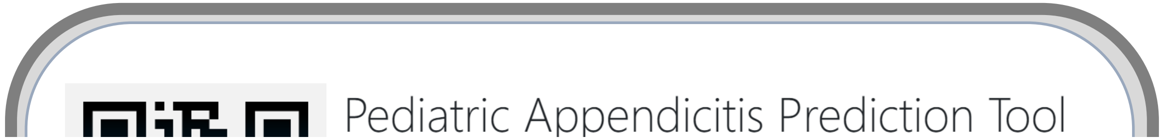
[2] Department of Neonatology, University Children's Hospital Regensburg (KUNO), Regensburg, Germany

Example 3: Pediatric Appendicitis



Predictive Models for Tabular Data

gnosis/management/severity using tabular data:



frontiers in Pediatrics

Using Machine Learning to Predict the Diagnosis, Management and Severity of Pediatric Appendicitis

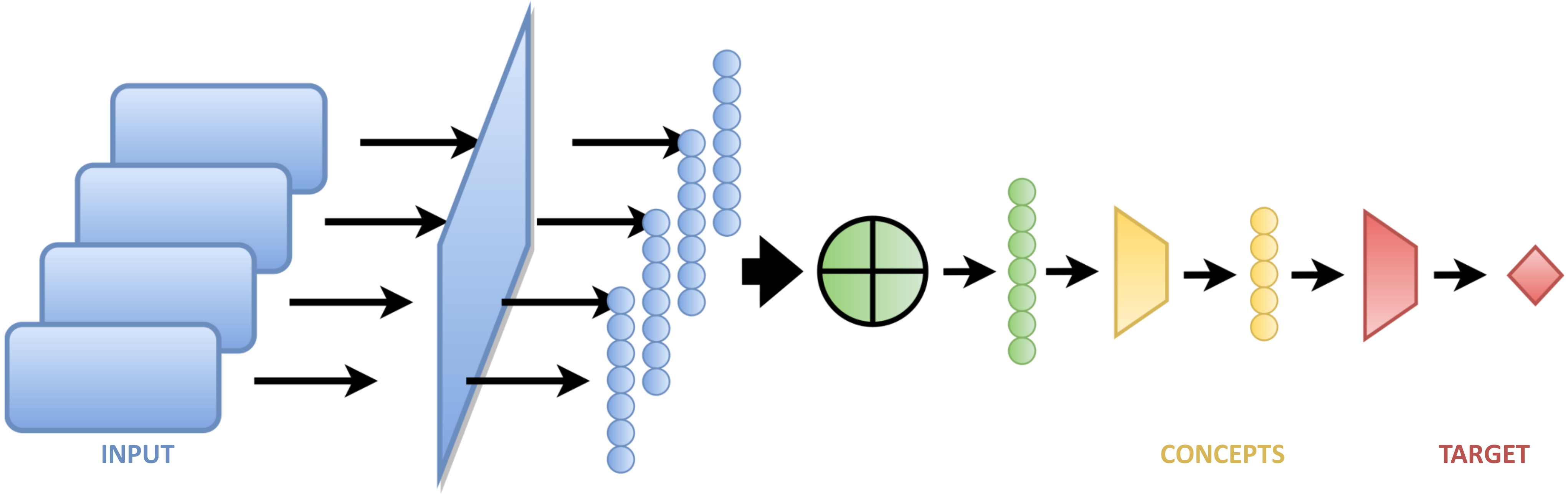
Ricards Marcinkevics[1†], Patricia Reis Wolfertstetter[2†], Sven Wellmann[3], Christian Knorr[2‡] and Julia E. Vogt[1‡]*

Interpretable Ultrasonography-based Models

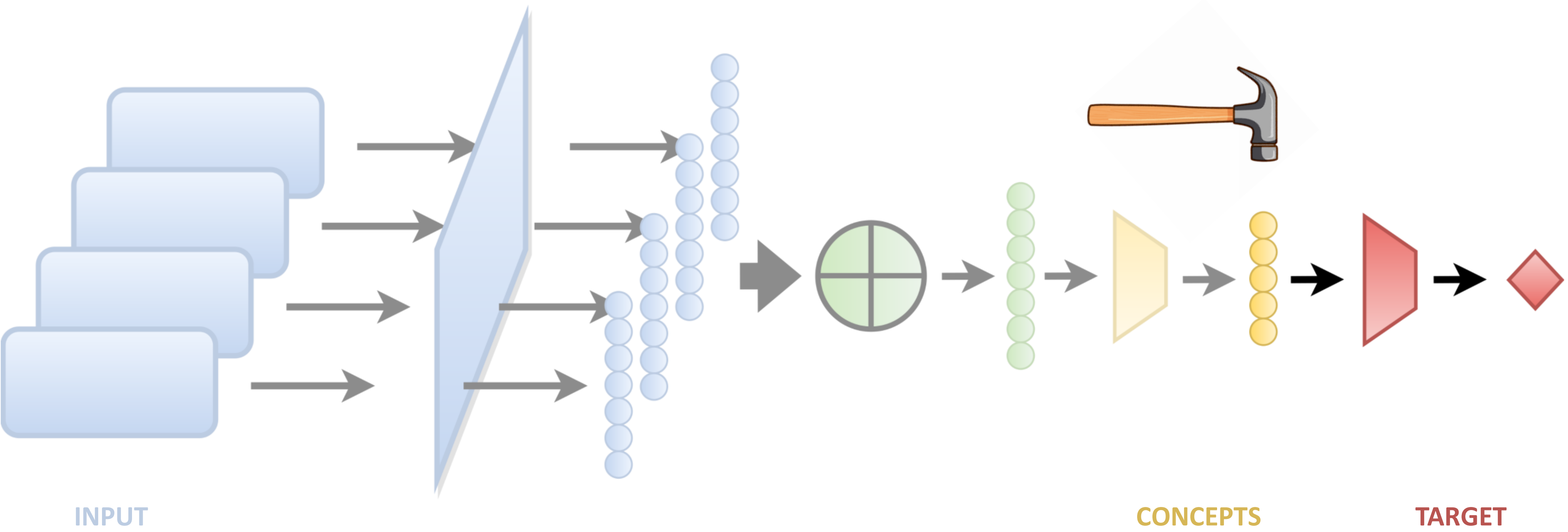
Approach: Concept-based Classification:

We build on concept bottleneck models to devise an interpretable and powerful predictive model

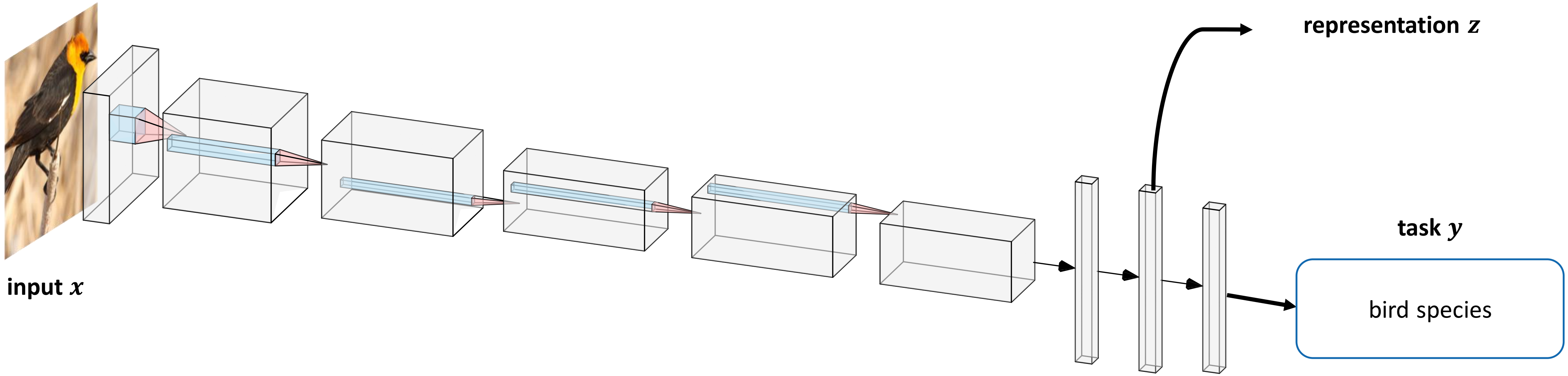
First, human-understandable concepts are predicted, then, the target variable:



Interpretable Ultrasonography-based Models

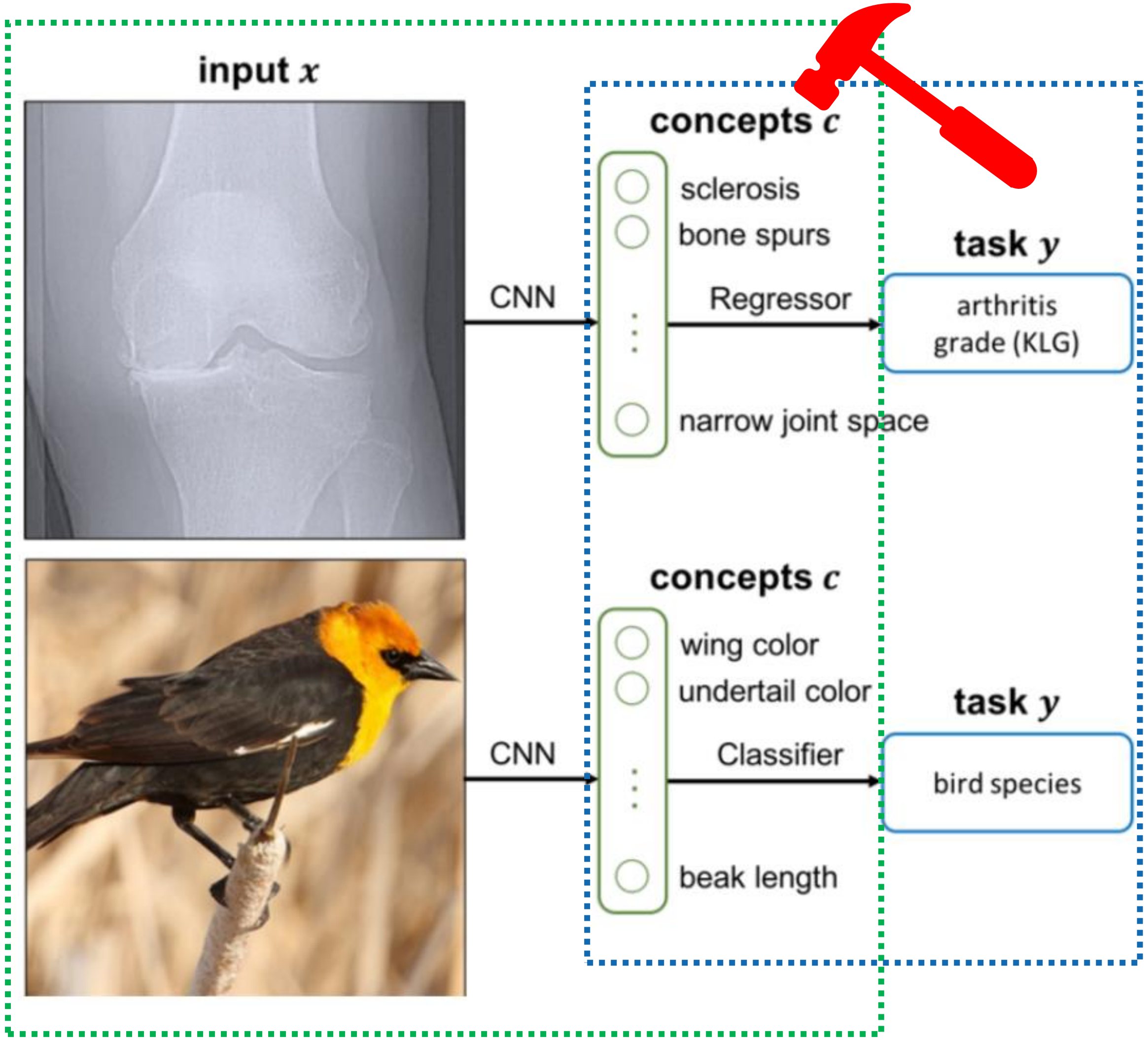


Concept Bottleneck Models: Motivation



- Consider a classical end-to-end deep learning pipeline…
- Representations learned by deep networks are often unintelligible
  - not regularized
  - entangled
  - non-trivial for a user to interact with and 'steer' the model's predictions
- Can we introduce an intermediate layer that is human-understandable?

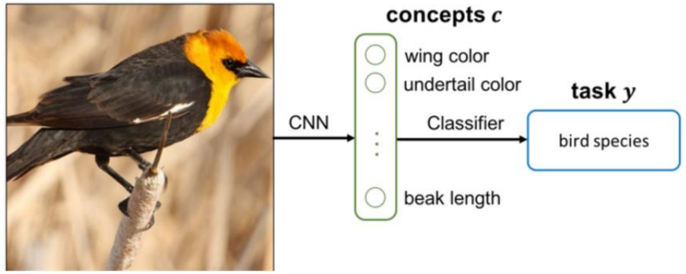
Concept Bottleneck Models: Idea



Concept bottleneck models (CBMs):

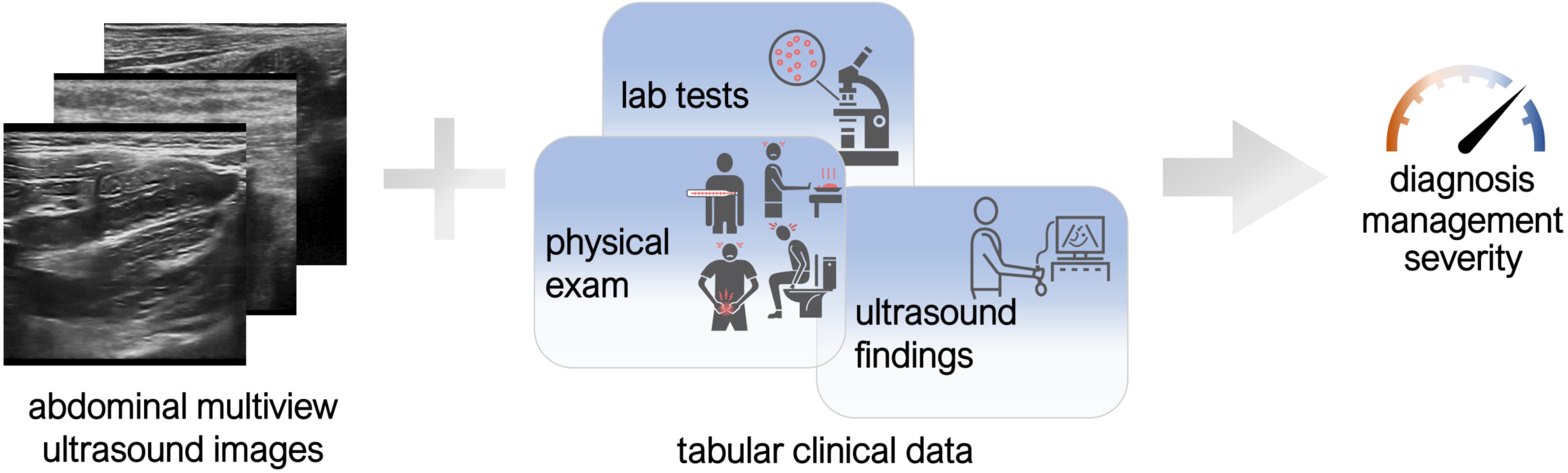
- given an input $\boldsymbol{x}$, first, predict human-understandable concepts $\boldsymbol{c}$
- then, predict target $\boldsymbol{y}$ based *only* on $\boldsymbol{c}$, i.e. $\boldsymbol{c}$ is a bottleneck
- at test time: a human expert can intervene on the predicted $\boldsymbol{c}$ to change the model's output

Concept Bottleneck Models: Interventions



At test time, a user can edit the model's concept predictions $\hat{c}$ to affect $\hat{y}$. This is an intervention!

Example: Pediatric Appendicitis



Concepts for Pediatric Appendicitis

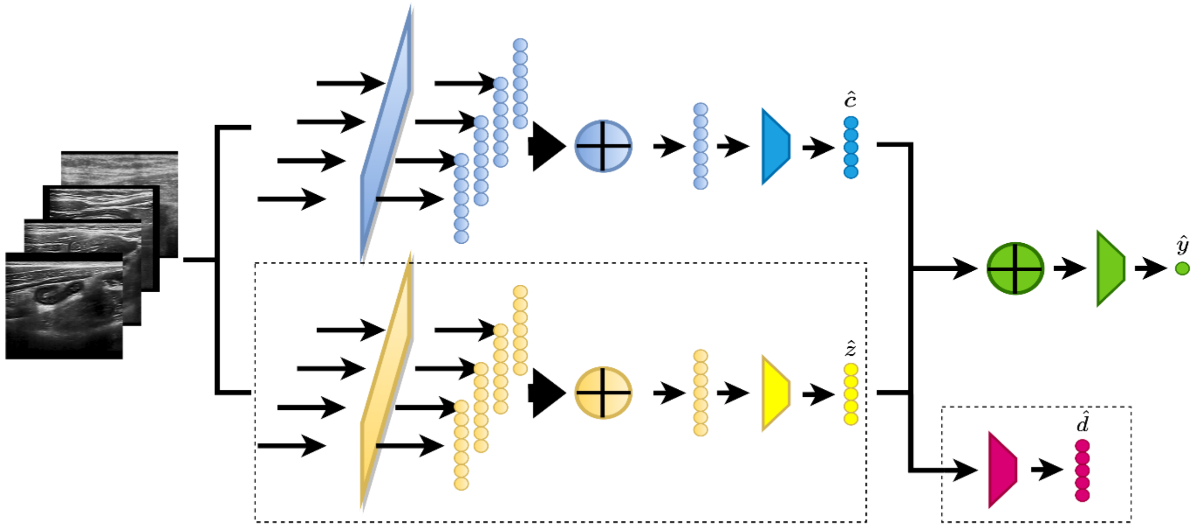
	Name	Description	Pos., %
c_1	Visibility of the appendix	visibility of the vermiform appendix during the examination	76
c_2	Free intraperitoneal fluid	free fluids in the abdomen	43
c_3	Appendix layer structure	characterization of the appendix layers, e.g. irregular in case of an increasing inflammation	14
c_4	Target sign	axial image of the appendix with the fluid-filled center surrounded by echogenic mucosa and submucosa and hypoechoic muscularis	13
c_5	Surrounding tissue reaction	inflammation signs in tissue surrounding the appendix	33
c_6	Pathological lymph nodes	enlarged and inflamed intra-abdominal lymph nodes	21
c_7	Thickening of the bowel wall	edema of the intestinal wall, $>$ 2–3 mm	8
c_8	Coprostasis	fecal impaction in the colon	6
c_9	Meteorism	accumulation of gas in the intestine	15

MVCBM Extended

Challenge: often, a set of observed concepts is incomplete, *e.g. due to the cost of measurement or lack of domain knowledge*

→ in this case, there exists a clear performance-interpretability tradeoff

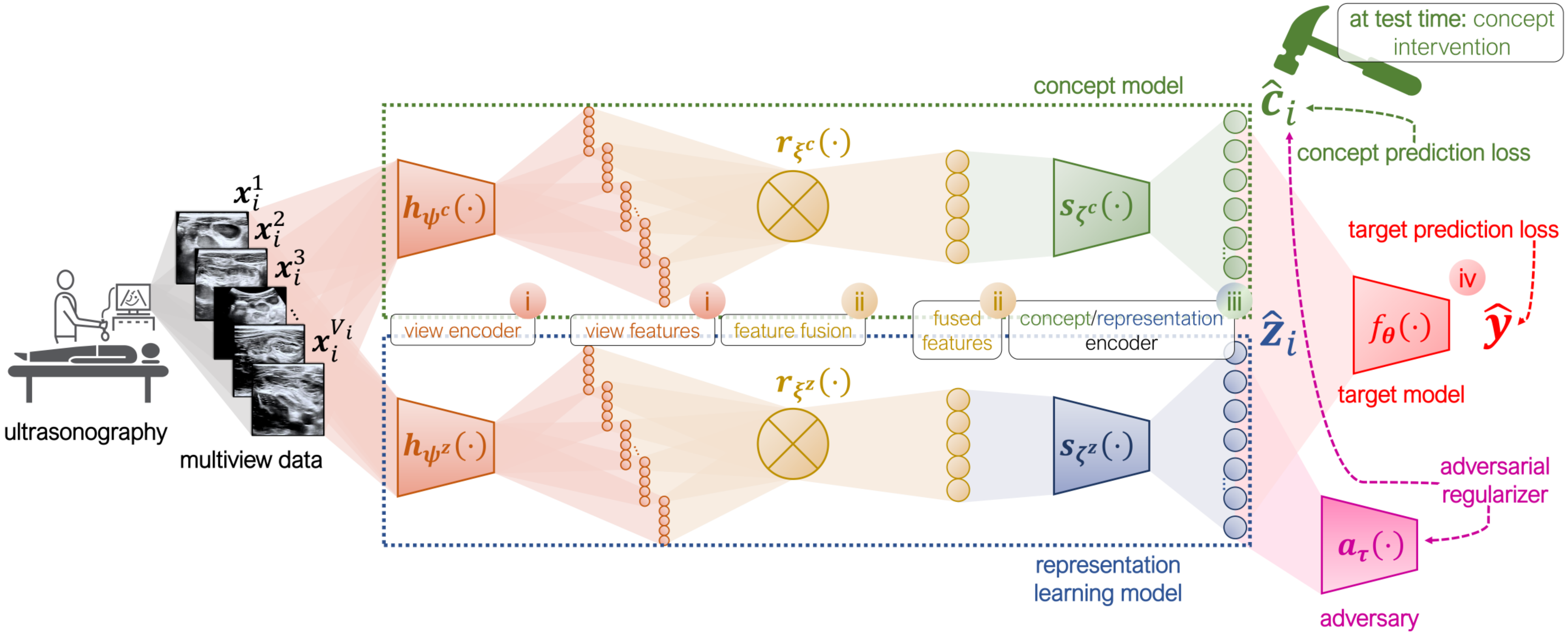
Can we resolve this tradeoff?



unsupervised encoder

adversary:
$\hat{C} \perp\!\!\!\perp \hat{Z} \mid Y$

Interpretable Ultrasonography-based Models



Diagnosis Prediction

Model	AUROC	AUPR
Random	0.50	0.75
Radiomics + RF	0.63±0.01	0.82±0.01
Single-view Black Box	0.70±0.07	0.88±0.04
Single-view Concept-based	0.64±0.06	0.84±0.04
Multiview Black Box	0.76±0.04	0.91±0.02
Multiview Concept-based	0.73±0.03	0.89±0.01
Multiview Concept-based Semi-supervised	0.80±0.03	0.92±0.02

Prediction Tool: https://papt.inf.ethz.ch

F

Interpretable and Intervenable Ultrasonography-based Machine Learning Models for Pediatric Appendicitis

Ričards Marcinkevičs [†,1], **Patricia Reis Wolfertstetter** [†,2], **Ugne Klimiene** [†,1], **Ece Ozkan** [3], **Kieran Chin-Cheong** [1], **Alyssia Paschke** [4], **Julia Zerres** [4], **Markus Denzinger** [2], **David Niederberger** [1], **Sven Wellmann** [4,5], **Christian Knorr** [‡,2], **Julia E. Vogt** [‡,1]

Outlook: SwissPedHealth

Expertise in pediatrics, rare diseases and omics, epidemiology, governance, PPI, computer science and engineering to improve children's health care.

Main applicants

- Schlapbach, Luregn
- Vogt, Julia

SPHN co-applicants

- Kuehni, Claudia
- Bielicki, Julia
- Posfay-Barbe, Klara
- Baumgartner, Matthias
- Latzin, Philipp
- Giannoni, Eric

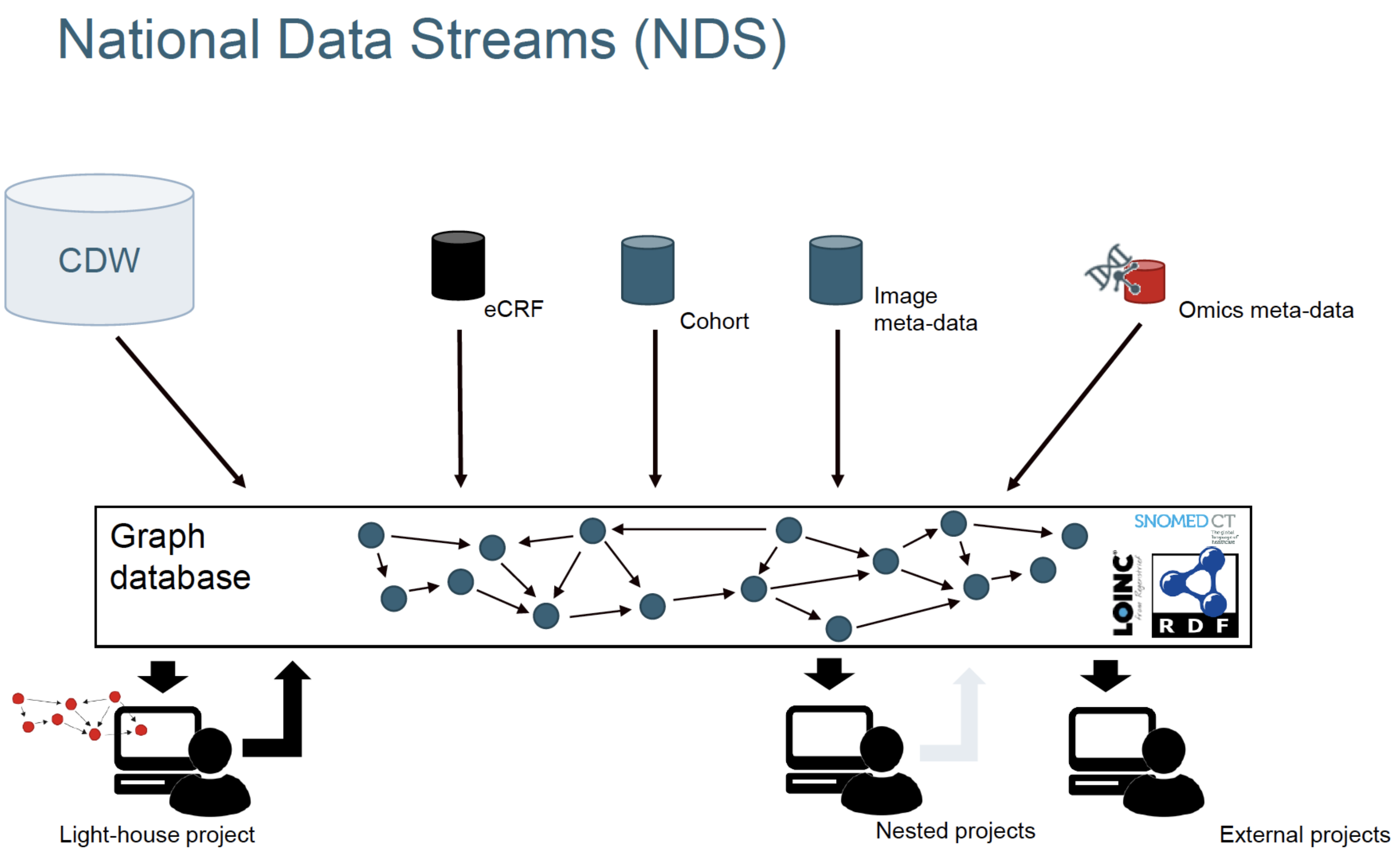
PHRT co-applicants

- Fellay, Jacques
- Borgwardt, Karsten
- Vayena, Effy

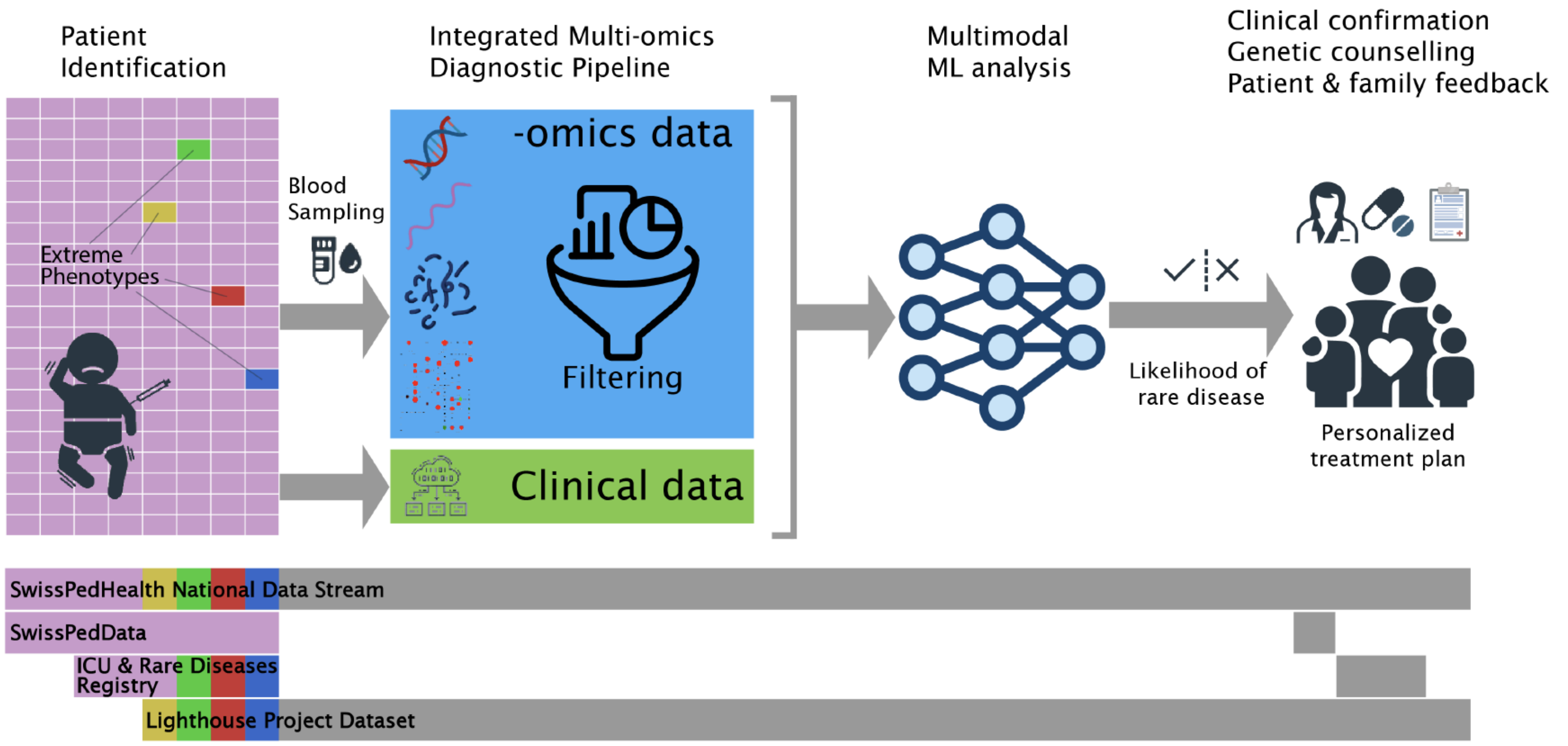
Associated applicants

- Ormond, Kelly
- Stocker, Martin
- Lauener Roger
- Schulzke, Sven
- Froese, Sean
- Goetze, Sandra
- Pedrioli, Patrick
- Pachlopnik Schmid, Jana
- Zamboni, Nicola
- Rauch, Anita
- Spycher, Ben
- Forrest, Christopher

Build a National Data Stream



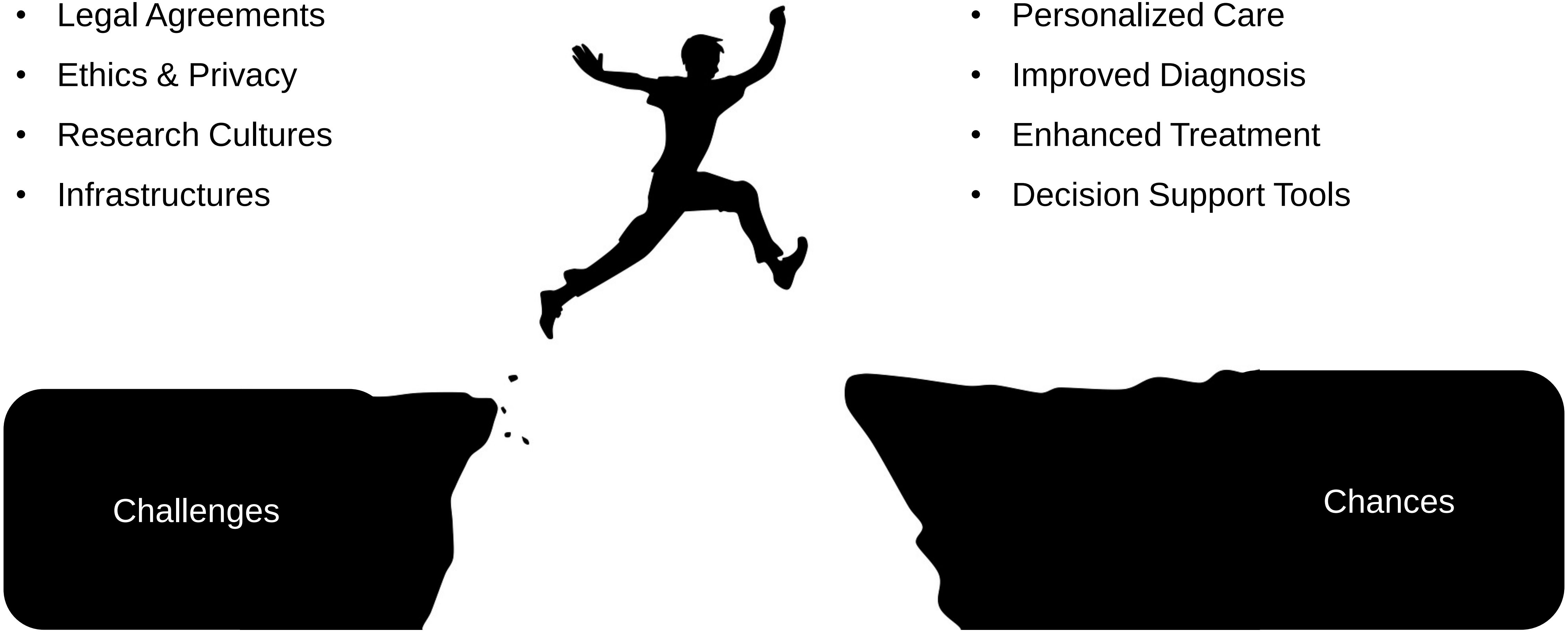
Lighthouse: Detecting Rare Diseases in Children



Bridging the Gap: Challenges and Chances

- Data Access & Availability
- Legal Agreements
- Ethics & Privacy
- Research Cultures
- Infrastructures

- Early Prediction/ Intervention
- Personalized Care
- Improved Diagnosis
- Enhanced Treatment
- Decision Support Tools



Machine Learning and Medicine: A Challenging Symbiosis

Develop novel machine learning methods and decision support tools

MACHINE LEARNING

medical data science

MEDICINE

Aim: improved patient care