| CERN Seminar | Virtual | 1.02.2024 |

Data Science for Precision Oncology

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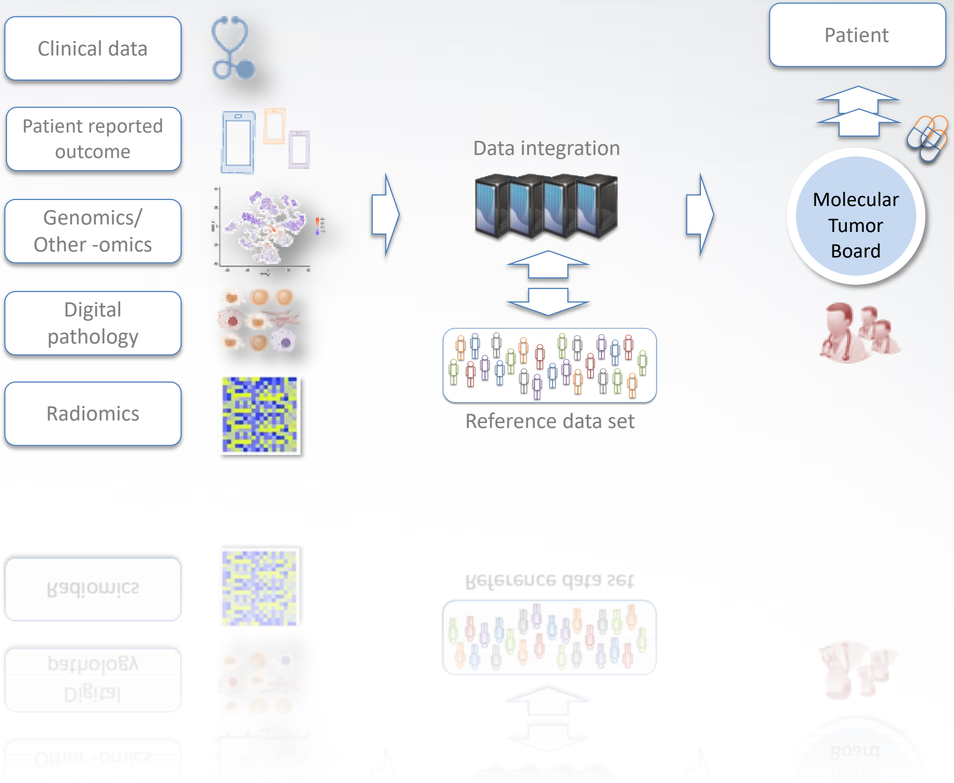
Precision oncology: from data to patients



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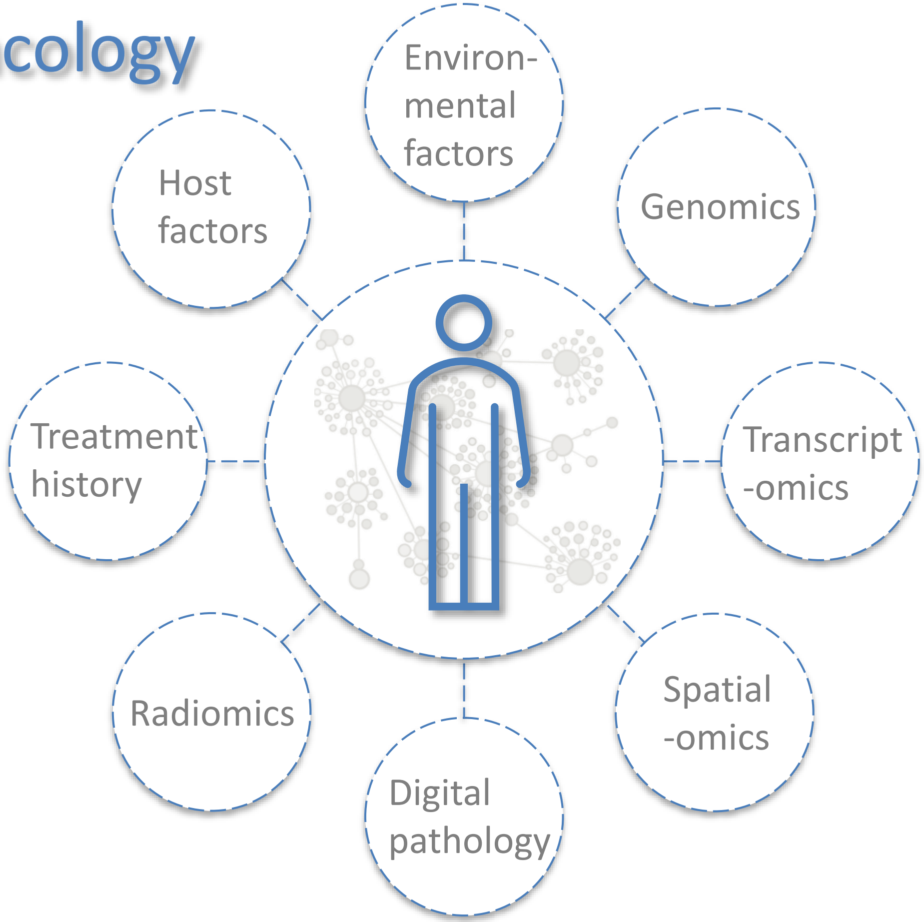
Data driven precision oncology

3 major factors are driving progress in data-driven precision oncology:

- Capacity to generate large amount of biological data (-omics and spatial -omics)
- Digitalization of the healthcare system (Electronic healthcare records)
- Methodological advances in data science for:
    - Big data (deep learning)
    - Wide data (variable selection methods)
    - Large language models



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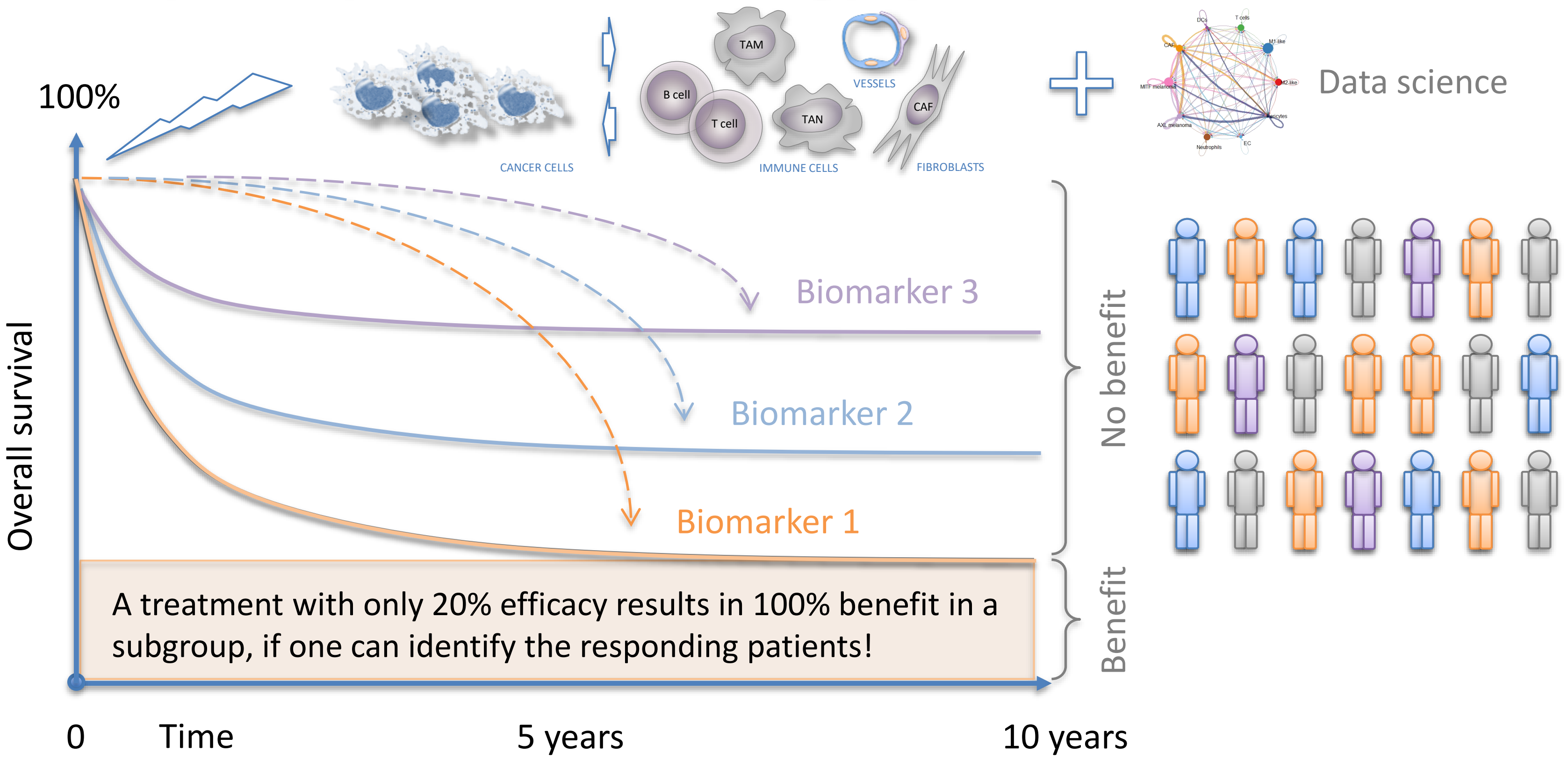
Principle of precision oncology: predictive biomarkers



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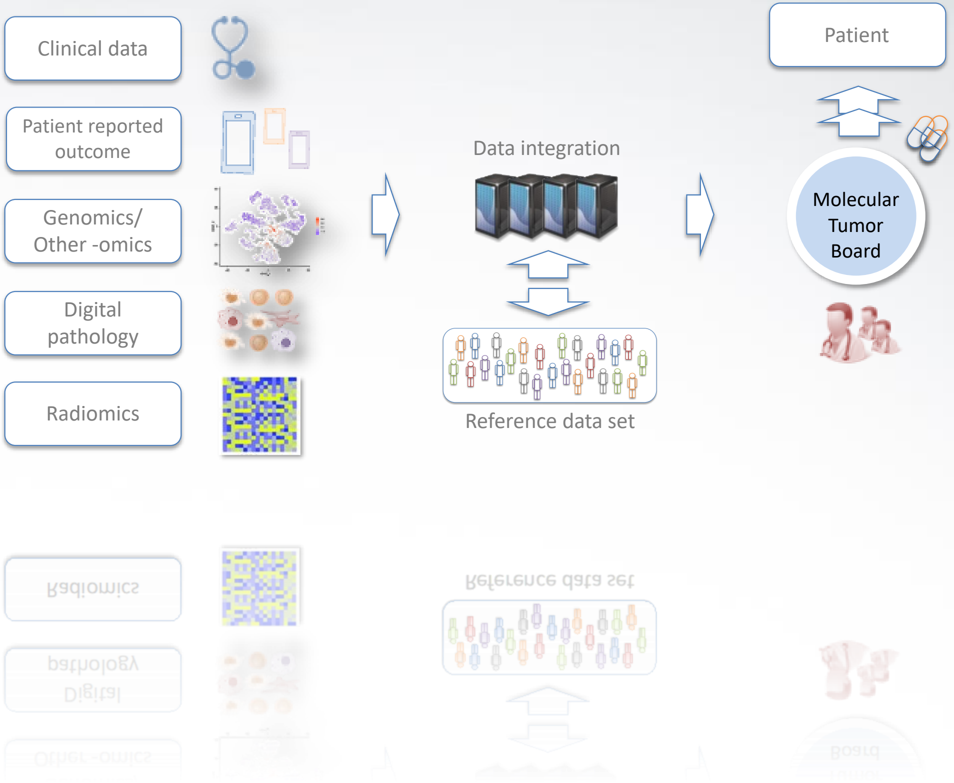
Introduction: Data types for precision oncology



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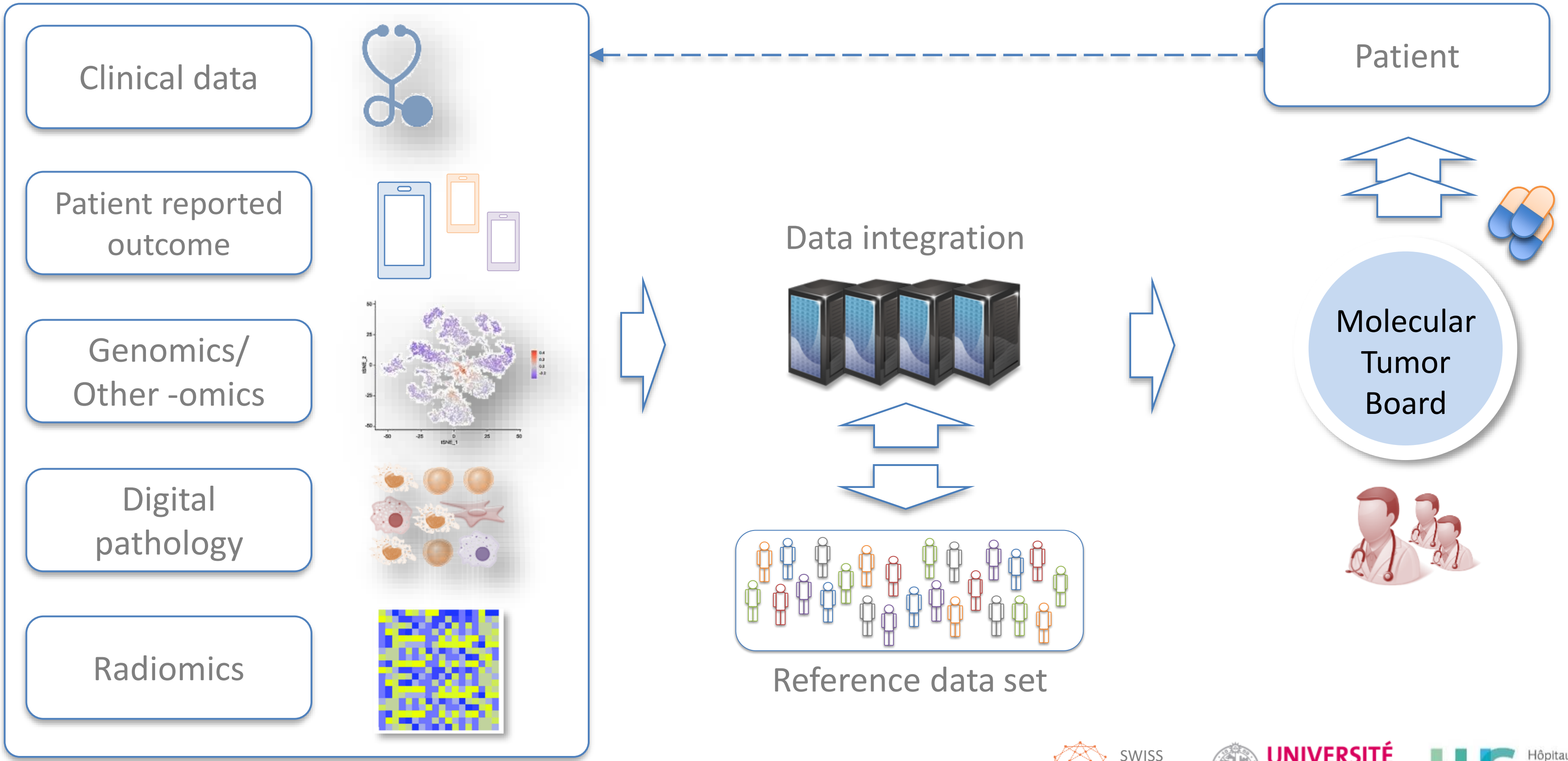
Precision oncology: integrating multiple data streams



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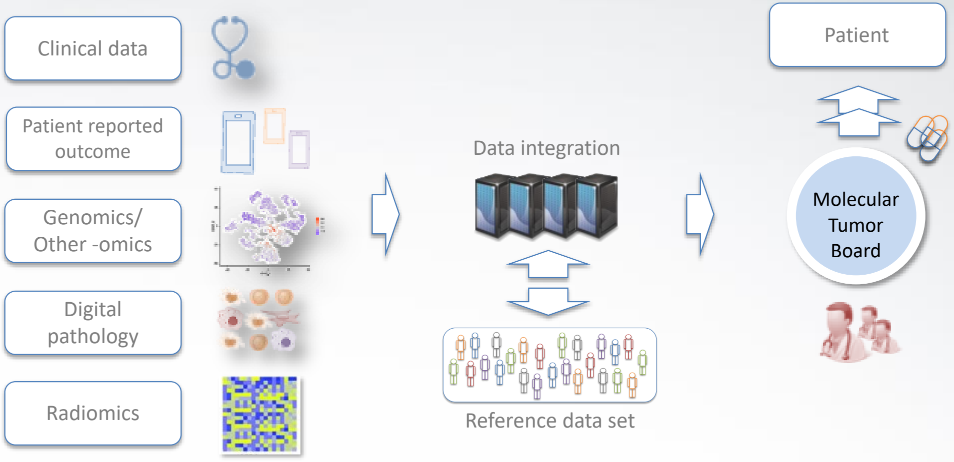
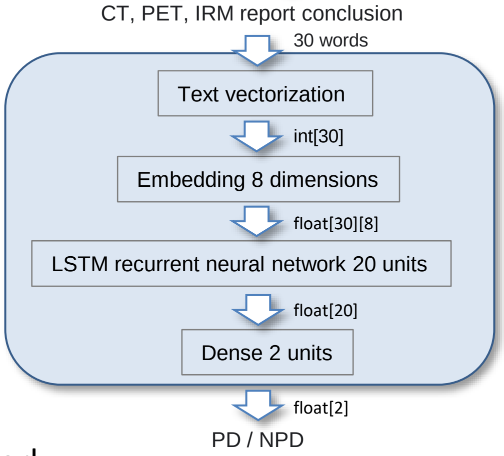
Precision oncology: exploiting clinical data



Example of NLP project: predicting disease progression

- Radiology reports are in unstructured text
- Real-world PFS calculation requires manual annotation to capture first progression event
- Machine learning can help analyzing large retrospective or prospective cohorts

Implemented in TensorFlow - 42202 parameters

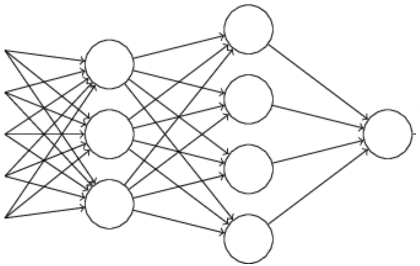


Radiology report

Conclusion text

L'examen PET-CT de ce jour montre une légère progression métabolique avec stabilité morphologique d'une adénopathie latéro-trachéale gauche en dessous de la crosse aortique.
Stabilité morpho-métabolique de l'adénopathie hypermétabolique visualisée à hauteur du trajet des vaisseaux iliaques externes gauches et de l'adénopathie inguinale gauche. Absence de nouvelle lésion hypermétabolique suspecte sur le reste des structures examinées.

Neural network

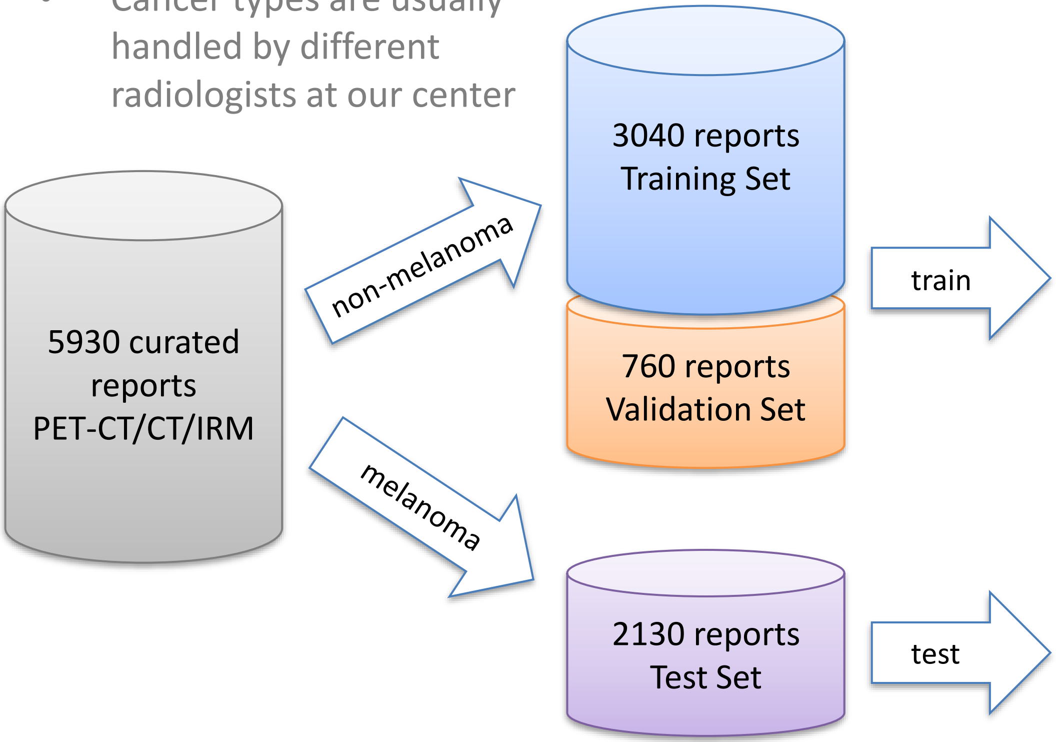


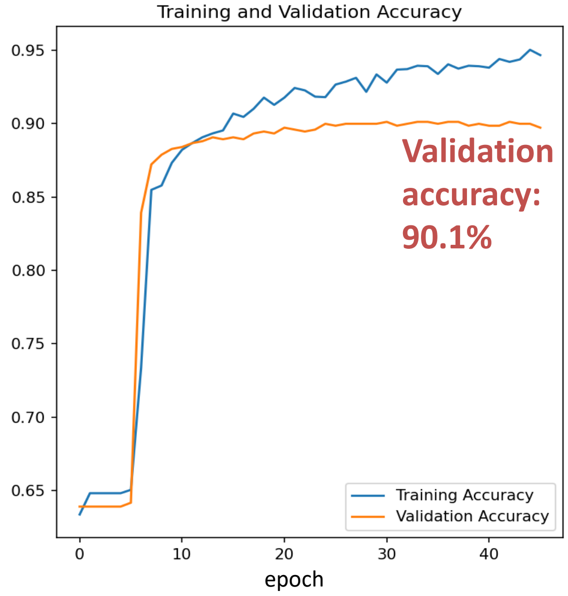
Progressive Disease (PD)

Non-Progressive Disease (NPD)

Testing transferability to unseen cancer type (melanoma)

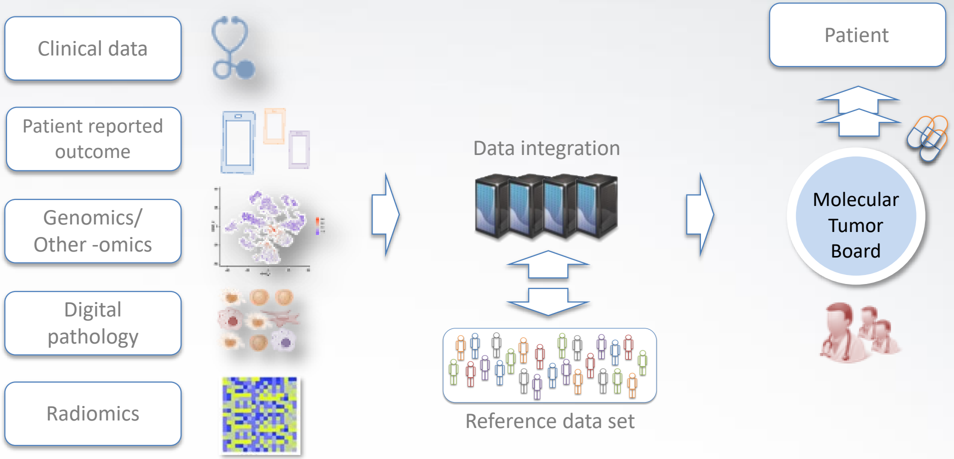
- Cancer types are usually handled by different radiologists at our center





Test accuracy on melanoma: 89.7%

Precision oncology: Real-world versus trial data



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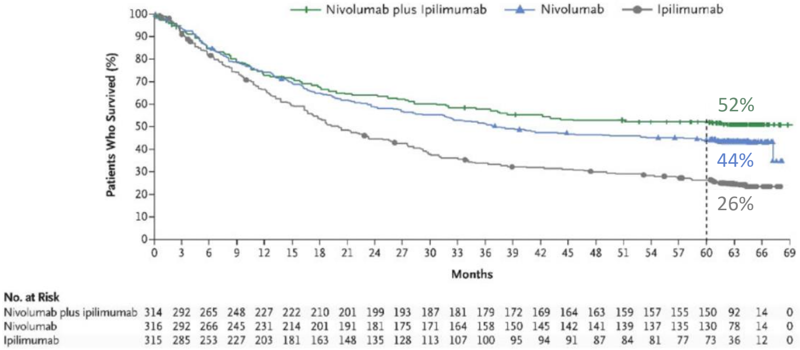
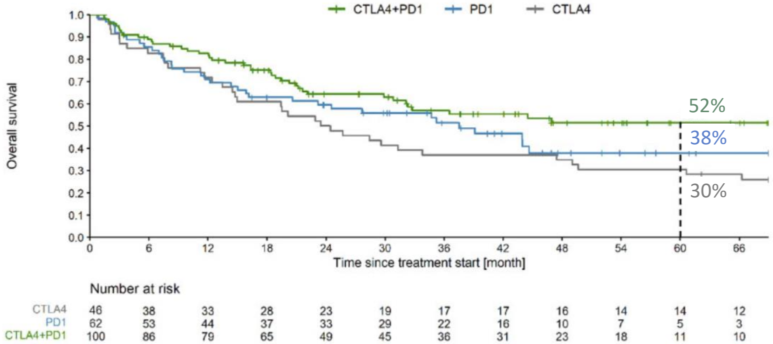
Clinical data: real-world data vs Checkmate-067 – 1st line

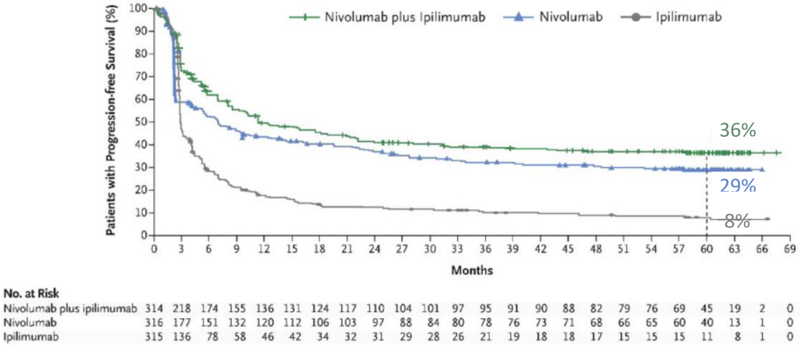
A CM-067 OS[1]



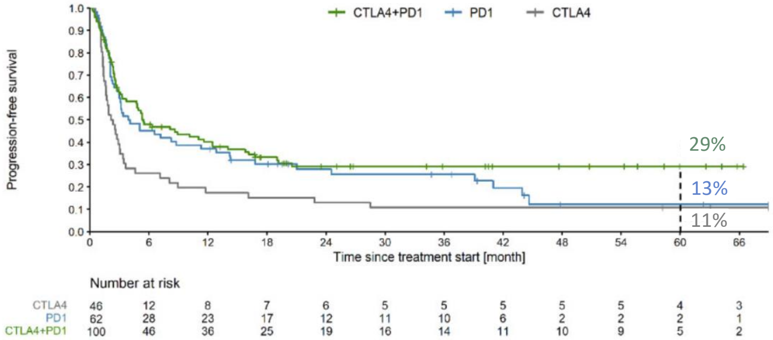
B RWD OS[2]



C CM-067 PFS[1]



D RWD PFS[2]



[1]Larkin, NEJM 2019; [2]Wicky, *Frontiers* 2023

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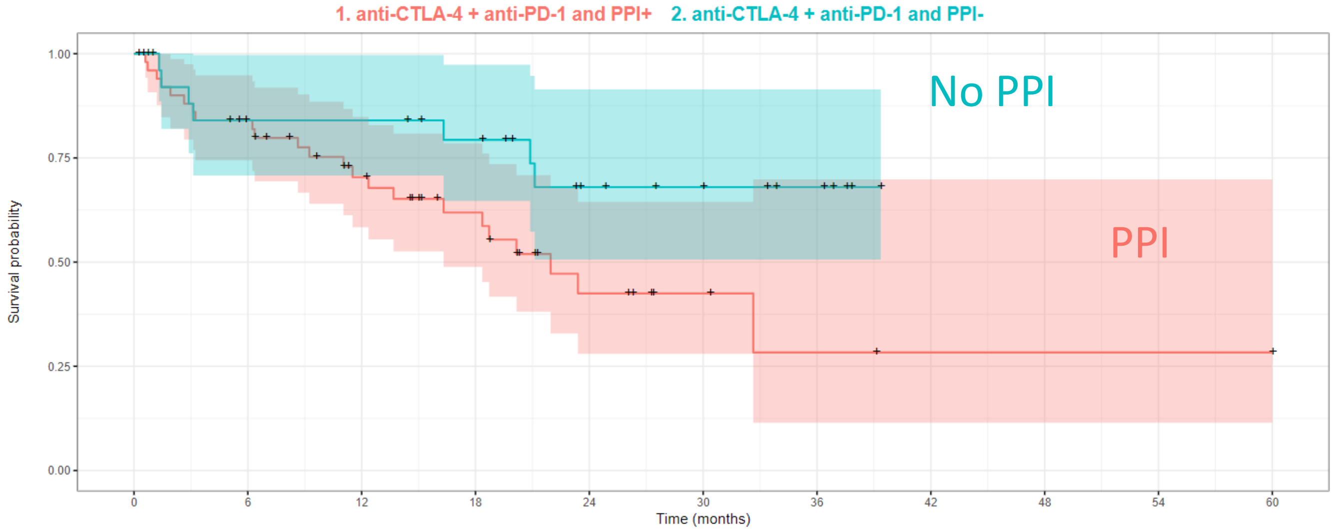
Impact of co-medications in the real-world setting

PPI:
Proton
Pump
Inhibitors



Number at risk (number of events)

	0	6	12	18	24	30	36	42	48	54	60
cohort=1	51 (0)	40 (8)	28 (14)	19 (17)	9 (22)	4 (22)	2 (23)	1 (23)	1 (23)	1 (23)	1 (23)
cohort=2	28 (0)	20 (4)	20 (4)	17 (5)	10 (7)	8 (7)	5 (7)	0 (7)	0 (7)	0 (7)	0 (7)

Log-rank p-value (KM)	0.047
Hazard ratio	0.43
95% CI on hazard ratio	0.18 - 1.01
Log-rank p-value (Cox)	0.04
Wald p-values (Cox)	0.054

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Impact of co-medications in the clinical trial setting

cancers

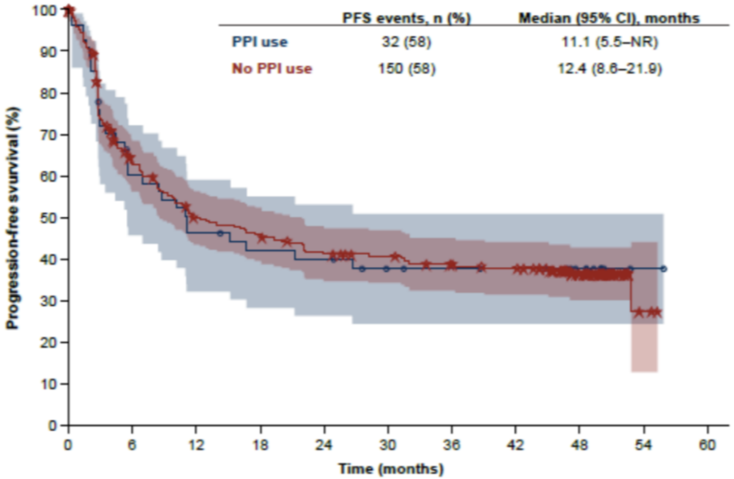
MDPI

Article

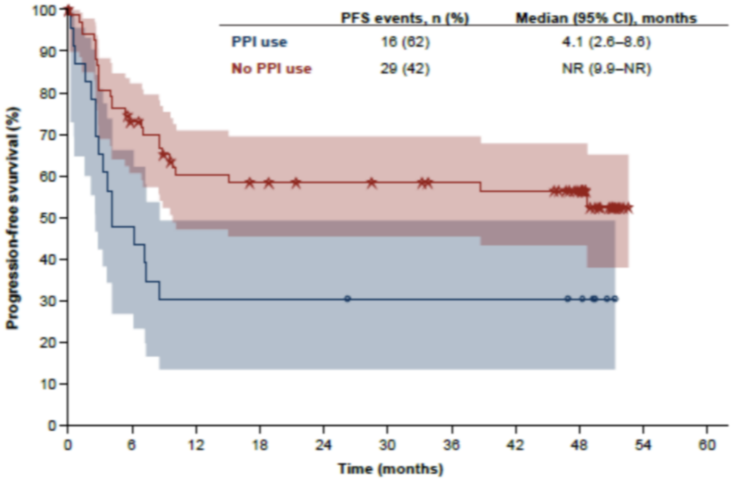
Proton Pump Inhibitor Use and Efficacy of Nivolumab and Ipilimumab in Advanced Melanoma

Krisztian Homicsko [1,*], Reinhard Dummer [2], Christoph Hoeller [3], Jedd D. Wolchok [4,5,6], F. Stephen Hodi [7], James Larkin [8], Paolo A. Ascierto [9], Victoria Atkinson [10,11], Caroline Robert [12,13], Michael A. Postow [5,14], Sandra Re [15], David Paulucci [15], Darin Dobler [15] and Olivier Michielin [16]

C. CheckMate 067, nivolumab plus ipilimumab



D. CheckMate 069, nivolumab plus ipilimumab



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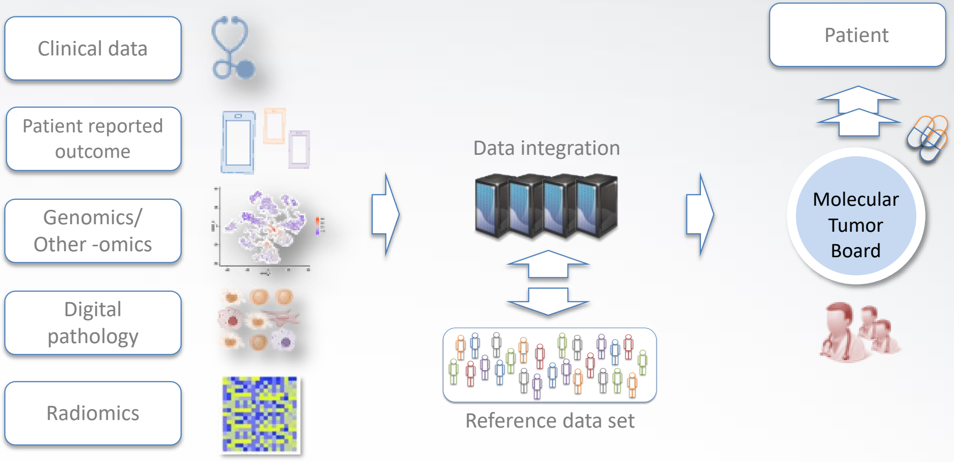
Precision oncology: exploiting image data



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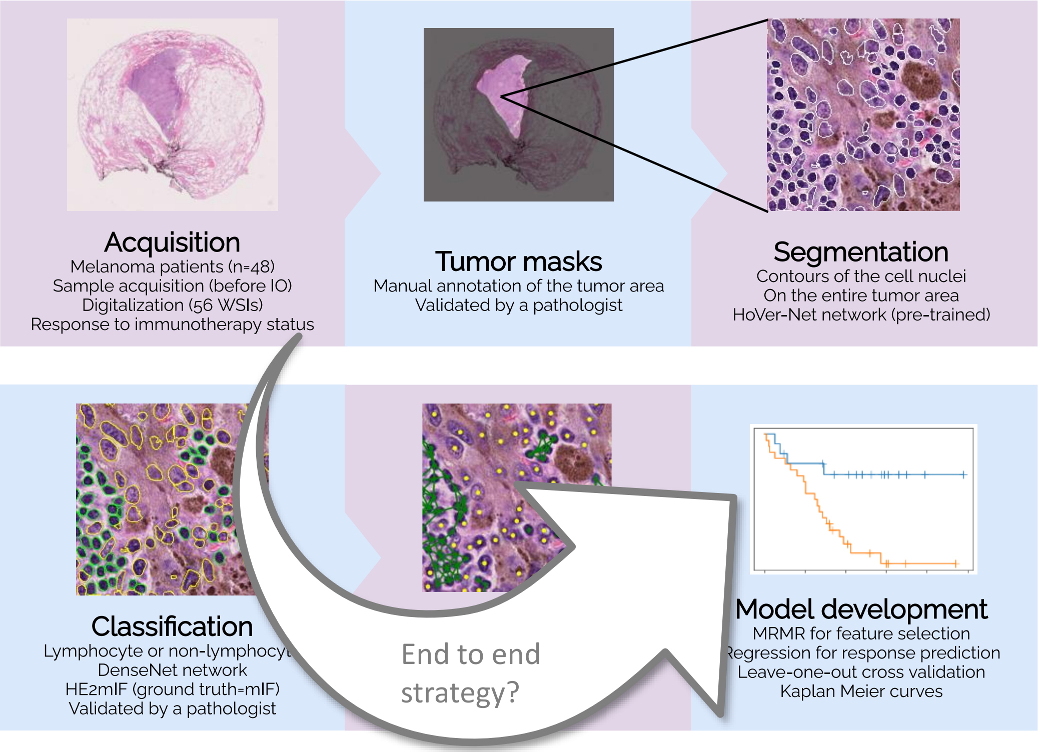
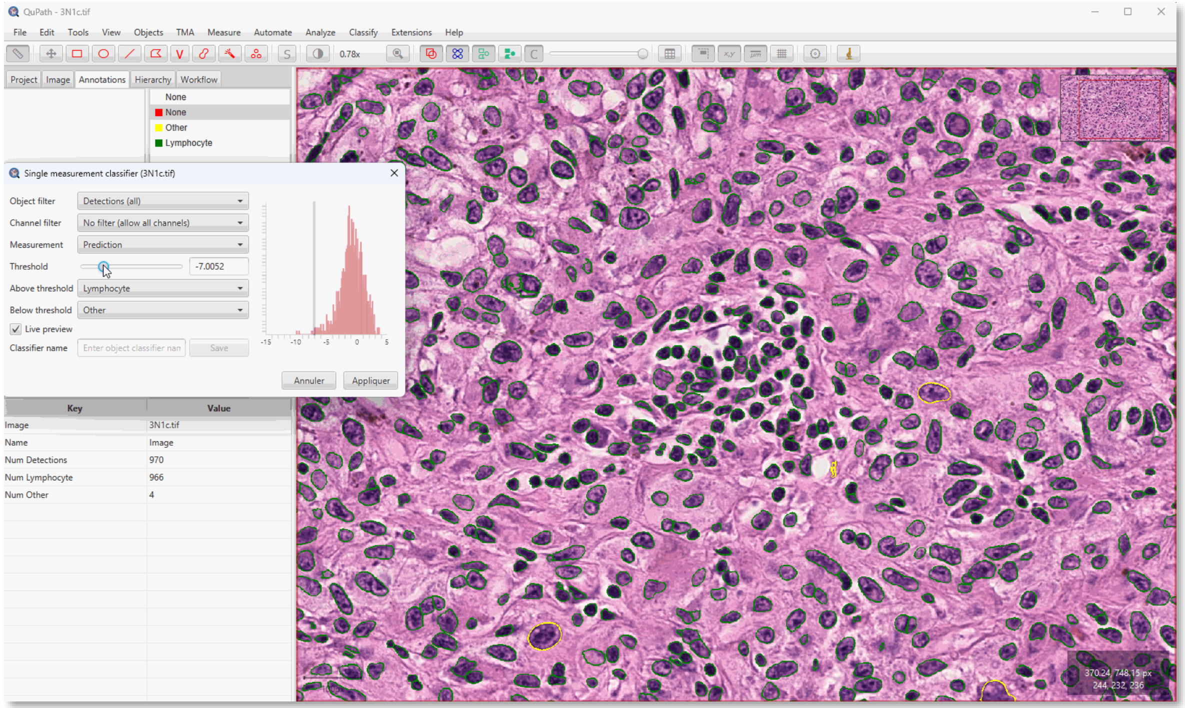
Digital pathology-based IO predictive biomarker: overview

- Goal: develop a predictive image-based digital pathology biomarker for IO therapy response in metastatic melanoma
- Quantify local tumor-infiltrating lymphocyte microenvironment via features extracted from H&E pathology images
- Go beyond what is visually possible to reproducibly quantify
- Application in precision medicine: identify optimal patient treatment plan based on retrospective cohort evaluation
- H&E is available for most patients
- HUG pathology is digitalizing more than 1000 slides per day (Prof. Laura Rubbia-Brandt, Prof. Doron Merkler)



Digital pathology: Fine tunning

- Fine tuning of the HE2mIF model to combat domain shift
- Raw lymphocyte prediction scores imported into QuPath
- Selection of the best classification thresholds for each slide by collaborating pathologist Dr Amanda Seipel at HUG, Service of Pathology (Prof. Laura Rubbia-Brandt)



Visualization with different classification thresholds on a ROI in QuPath (lymphocytes in green, other cells in yellow)

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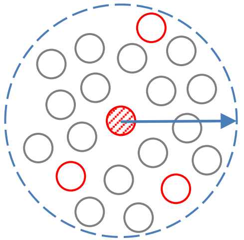
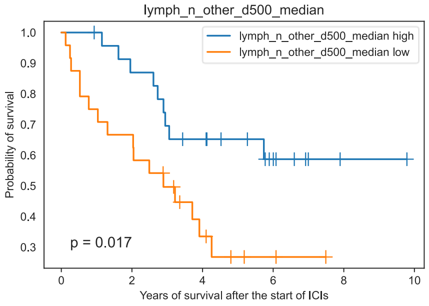
Example of abstract features (I)

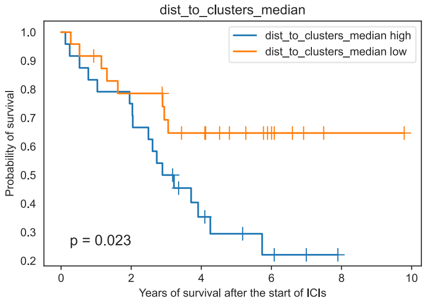
- We can much better stratify patients with sophisticated higher-order features, available only via computational pathology
- Multiple features are promising, 2 examples:
  - Median number of non-lymphocyte cells within 500 pixels of each lymphocyte (lymph_notherd500_median)
  - Median distance between each non-lymphocyte cell to the nearest lymphocyte cluster (dist_to_clusters_median)



- Importantly: neither of these features are visually discernable in routine practice and require computer aided approaches!



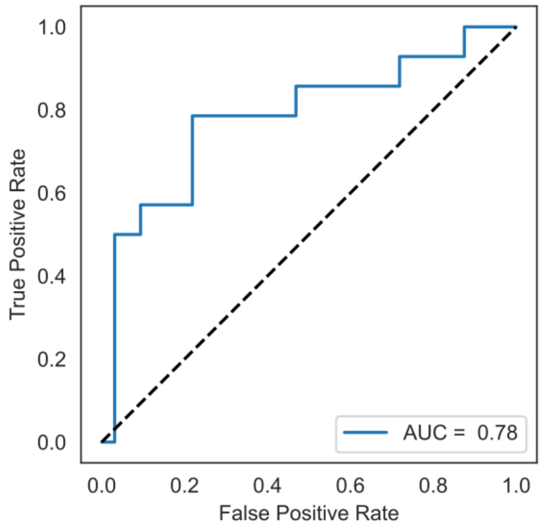
	0	2	4	6	8	10
lymph_n_other_d500_median high						
At risk	24	20	14	7	1	0
Censored	0	1	2	8	14	15
Events	0	3	8	9	9	9
lymph_n_other_d500_median low						
At risk	24	16	6	2	0	0
Censored	0	0	3	6	8	8
Events	0	8	15	16	16	16



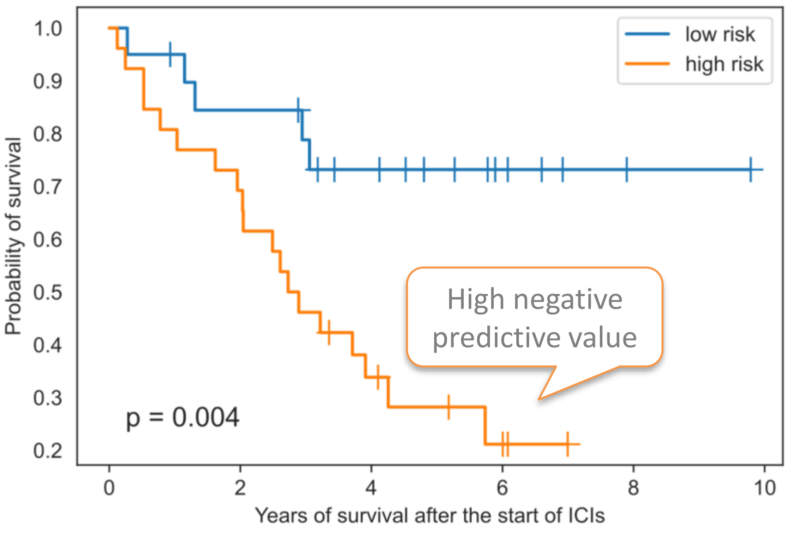
	0	2	4	6	8	10
dist_to_clusters_median high						
At risk	24	18	7	3	0	0
Censored	0	0	2	4	7	7
Events	0	6	15	17	17	17
dist_to_clusters_median low						
At risk	24	18	13	6	1	0
Censored	0	1	3	10	15	16
Events	0	5	8	8	8	8

Digital pathology: combining features using MRMR

- Leave-one-out cross-validation
- Maximum relevance minimum redundancy (MRMR) for selection of 6 features
- Logistic regression to predict response
- Encouraging results with an AUC of 0.78



ROC curve and AUC for 6 feature-response classifier



Kaplan Meier curve with model assigned risk score: high risk (prediction = no response) vs low risk (prediction = response))

Unpublished – do not post

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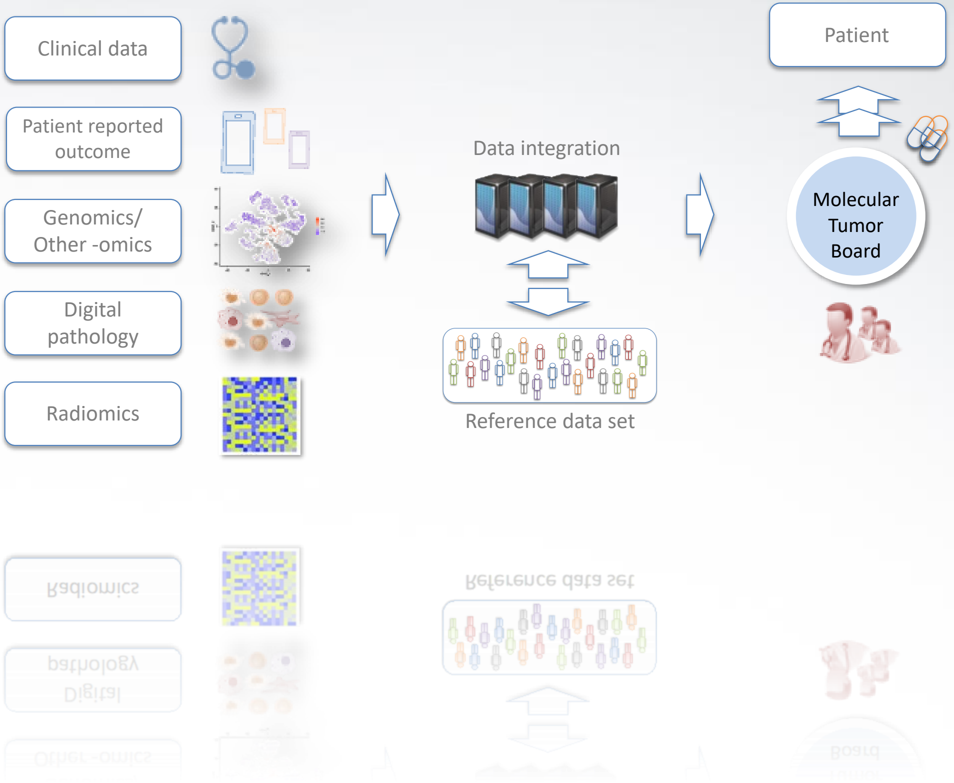
Precision oncology: molecular tumor board



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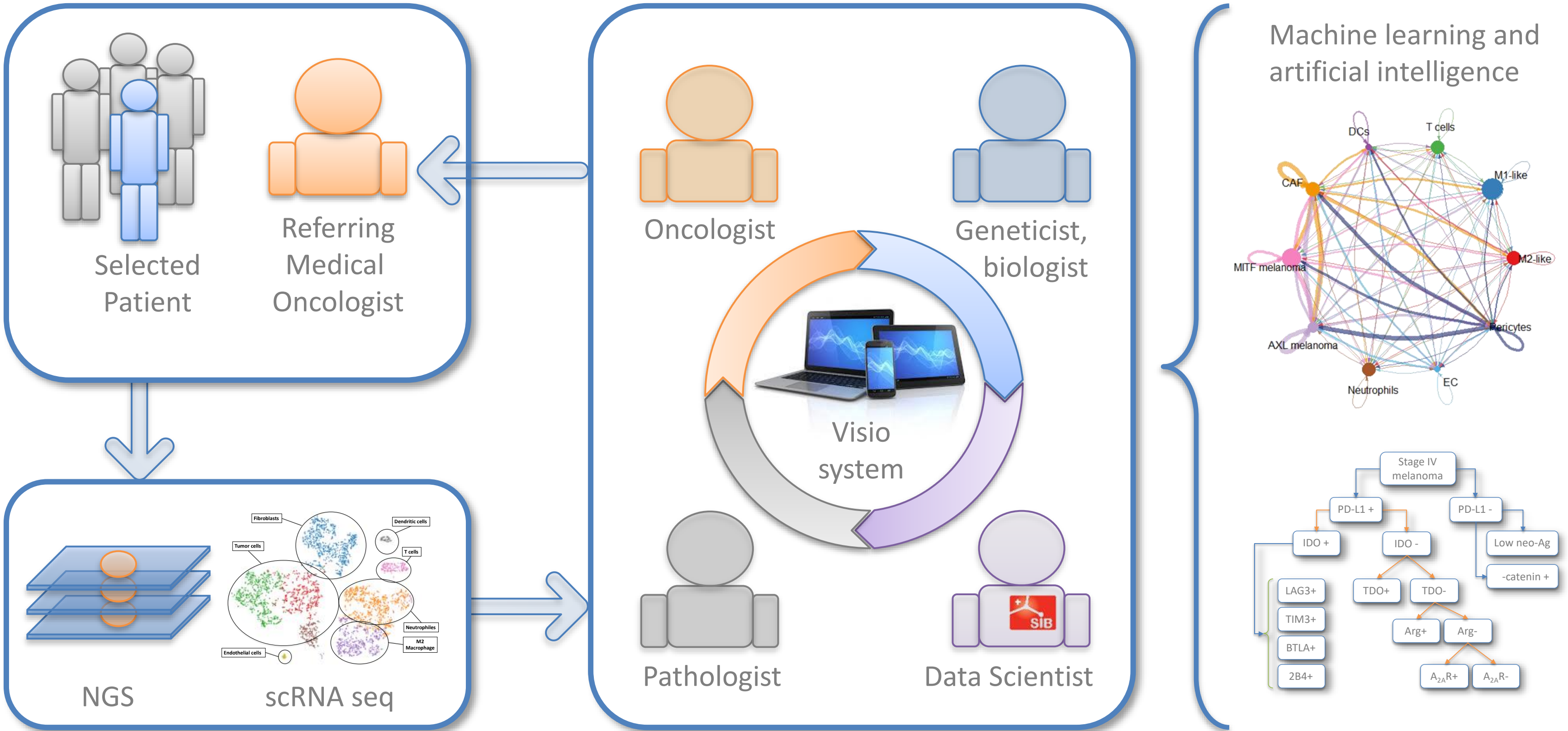
Molecular tumor-board and AI



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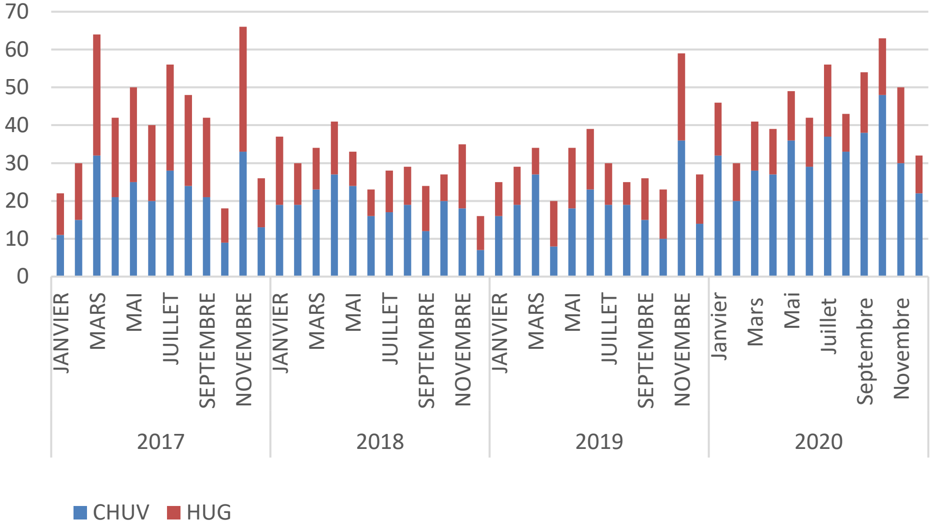
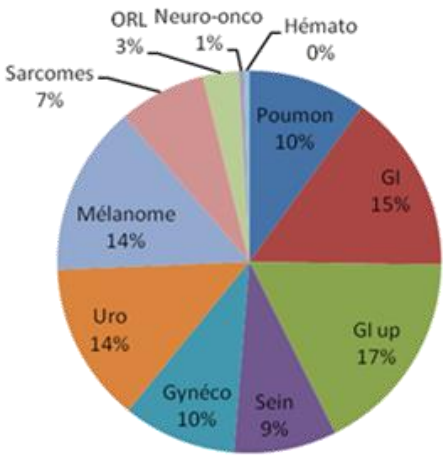
Molecular Tumor Board: Activity

- All comer training data set!



	Patients presented since 01/2017
HUG + CHUV	3000+



Proposed treatment options	
Off Label	46%
Clinical Trials	45%
No proposition	8%
Genetic counseling	6%

- Around 400 cases per year from > 50 medical oncologists referring cases on a regular basis
- As a comparison, the MTB from Curie (Paris) sees around 250 cases per year

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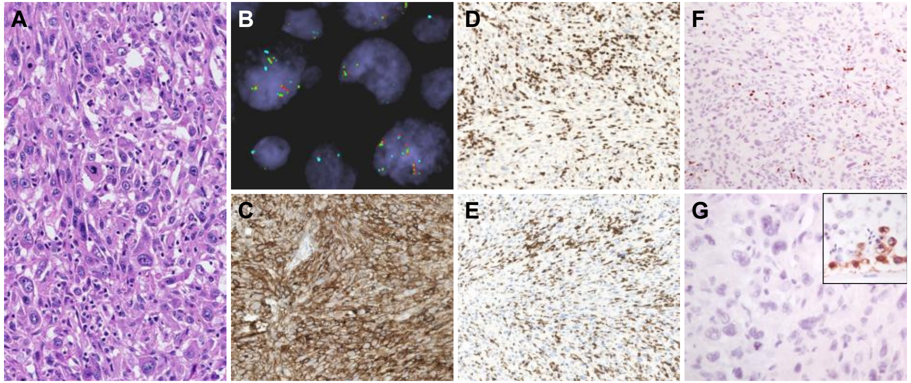
Molecular Tumor Board: example of clinical outcome

- Personalization focusses strongly on immuno-oncology
- Example of molecular tumor board case:
  - MPNST with PD-L1 amplification presenting a near CR on PD-1 blockade[1]
  - Patient followed in the private sector



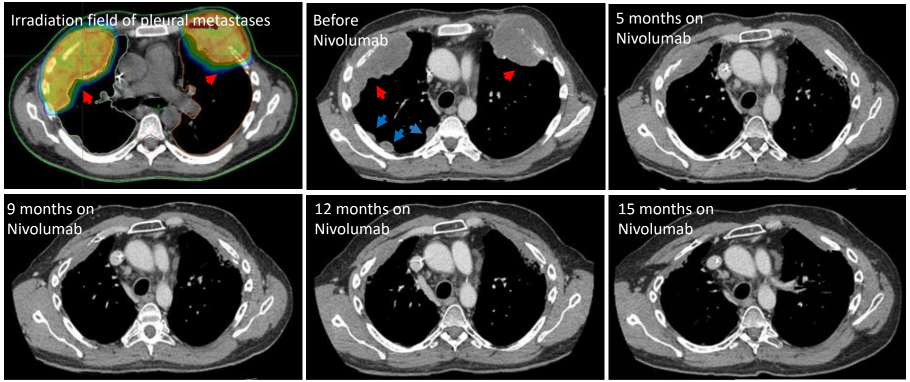
Deep response to anti-PD-1 therapy of metastatic neurofibromatosis type 1-associated malignant peripheral nerve sheath tumor with *CD274/PD-L1* amplification

Berna C. Özdemir[1,2], Pierre Bohanes[3], Bettina Bisig[4], Edoardo Missiaglia[4], Petros Tsantoulis[5], George Coukos[1,6,7], Michael Montemurro[1], Krisztian Homicsko[1,6,7], Olivier Michielin[1,6,7]

PD-L1

COPY NUMBER VARIATIONS (CNV) *

REGION	GENES	TYPE OF VARIATION	ESTIMATED COPY NUMBER PER CELL
9p24-p23	*JAK2, CD274, PTPRD*	Amplification	≥5
9p22-p21	*CDKN2A, CDKN2B, FANCG*	Deletion	1
9q	All genes in the region	Amplification	≥5
11q	All genes in the region	Amplification	≥5



[1]Ozdemir, *JCO PO* 2019

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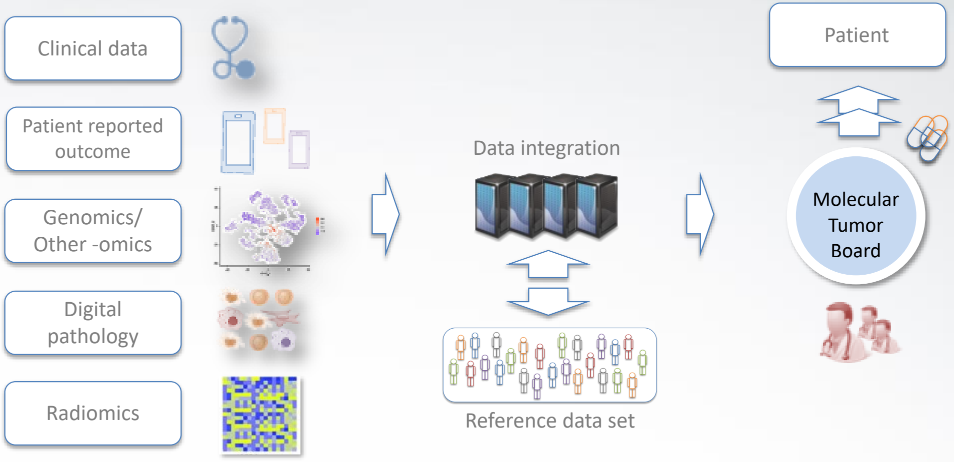
Conclusion and Outlook



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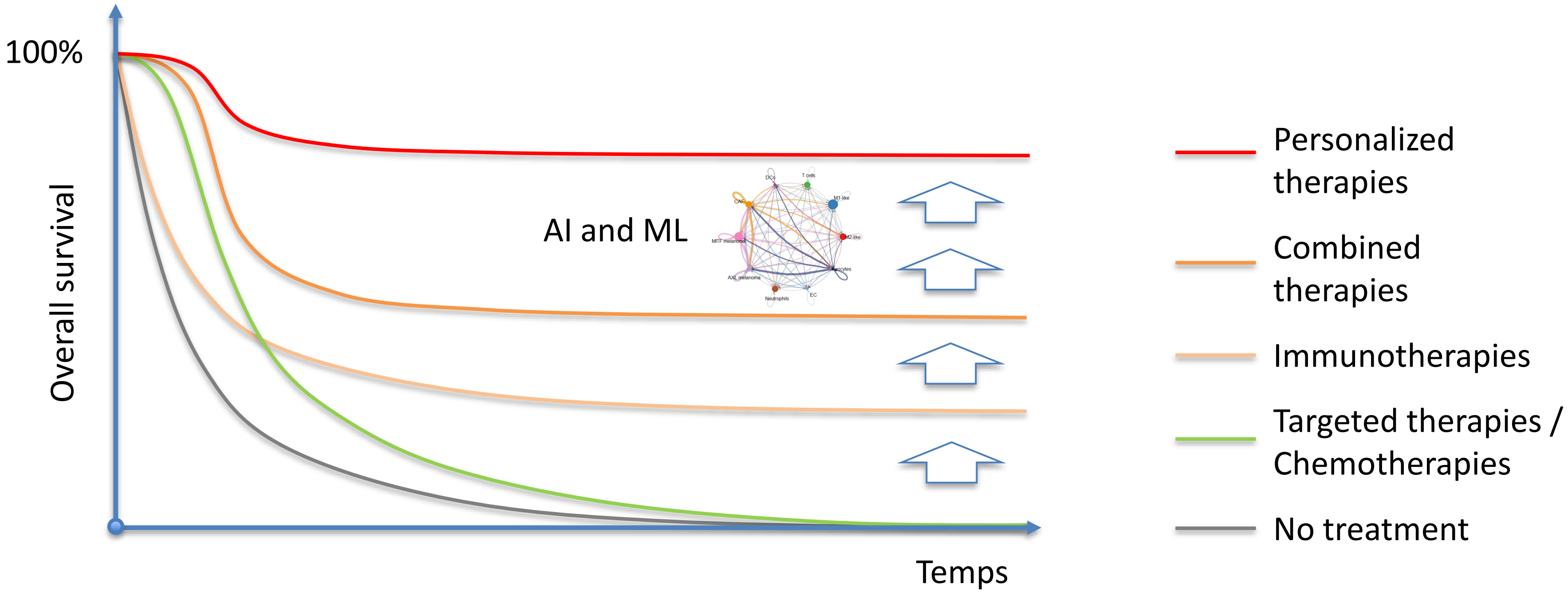
Expected benefit from personalized strategies



Adapted from A. Ribas, *WCM* 2013

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Key partners: it takes a village…

- **HUG:**
  - Andrew Janowczyk
  - Jonatan Bonjour
  - Petros Liakopoulos
  - Daniel Abler
  - Petros Tsantoulis
  - Timothée Olivier
  - Pierre Chapuis
  - Alfredo Addeo
  - Laura Rubbia-Brandt
  - Doron Merkler
  - Amanda Seipel
  - Valentina Garibotto
- **EPFL:**
  - Pascal Frossard, Dorina Thanou
  - Elisa Oricchio and ISREC

Andrew Janowczyk

Jonatan Bonjour

Petros Liakopoulos

Laura Rubbia

- **CHUV/UNIL:**
  - Michel Cuendet
  - Sylvain Pradervand
  - Alexandre Wicky
  - Jennifer Veillard
  - Marian Caikovski
  - Nicolas Freundler
  - Christine Sempoux
  - John Prior
  - Clarisse Dromain
  - Giovanni Ciriello
  - Susan Gasser
  - George Coukos
- **UNIGE:**
  - Mikael Pittet - CRTOH

Michel Cuendet

Alexandre Wicky

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