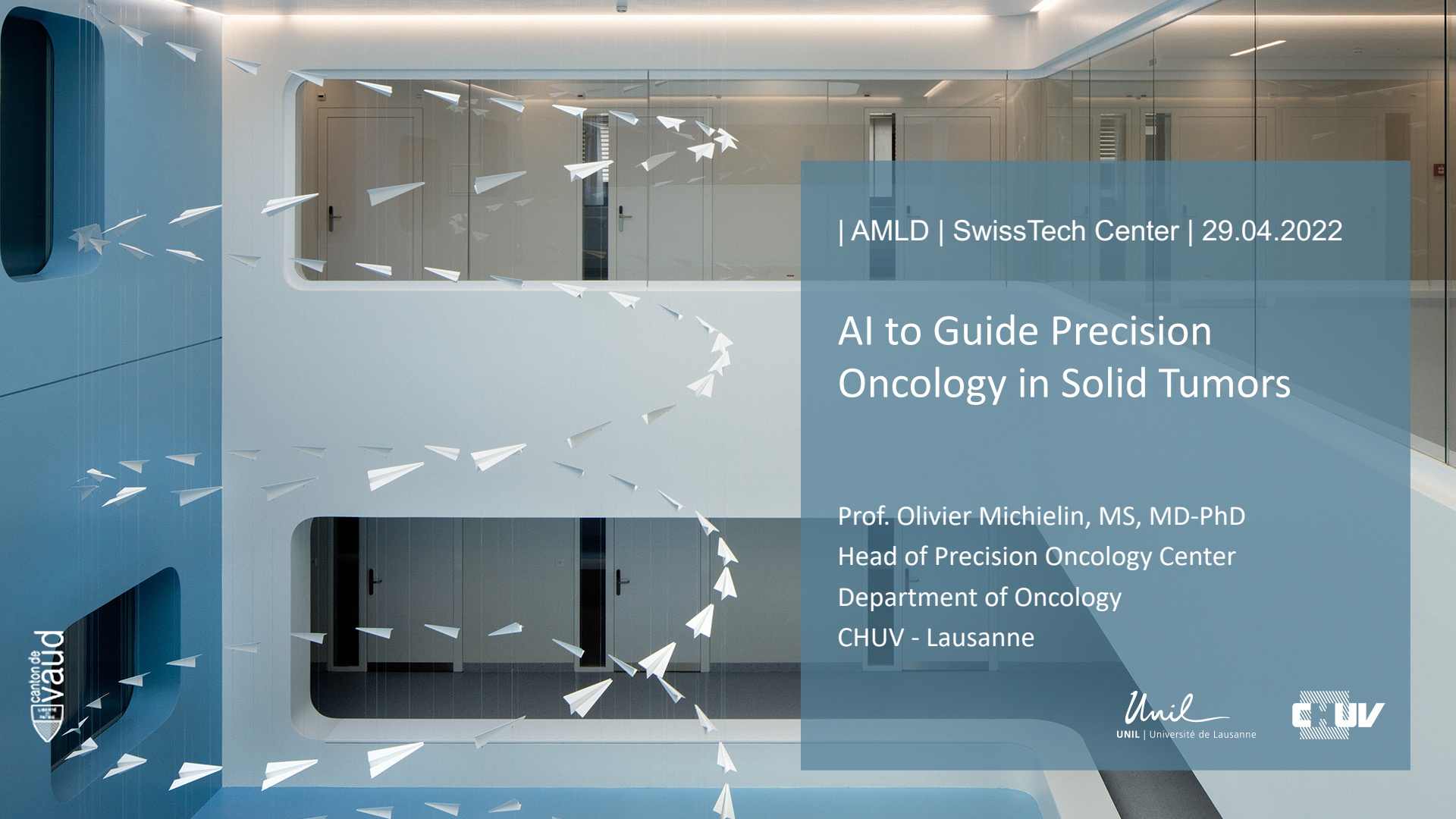

| AMLD | SwissTech Center | 29.04.2022

AI to Guide Precision Oncology in Solid Tumors

Prof. Olivier Michielin, MS, MD-PhD
Head of Precision Oncology Center
Department of Oncology
CHUV - Lausanne

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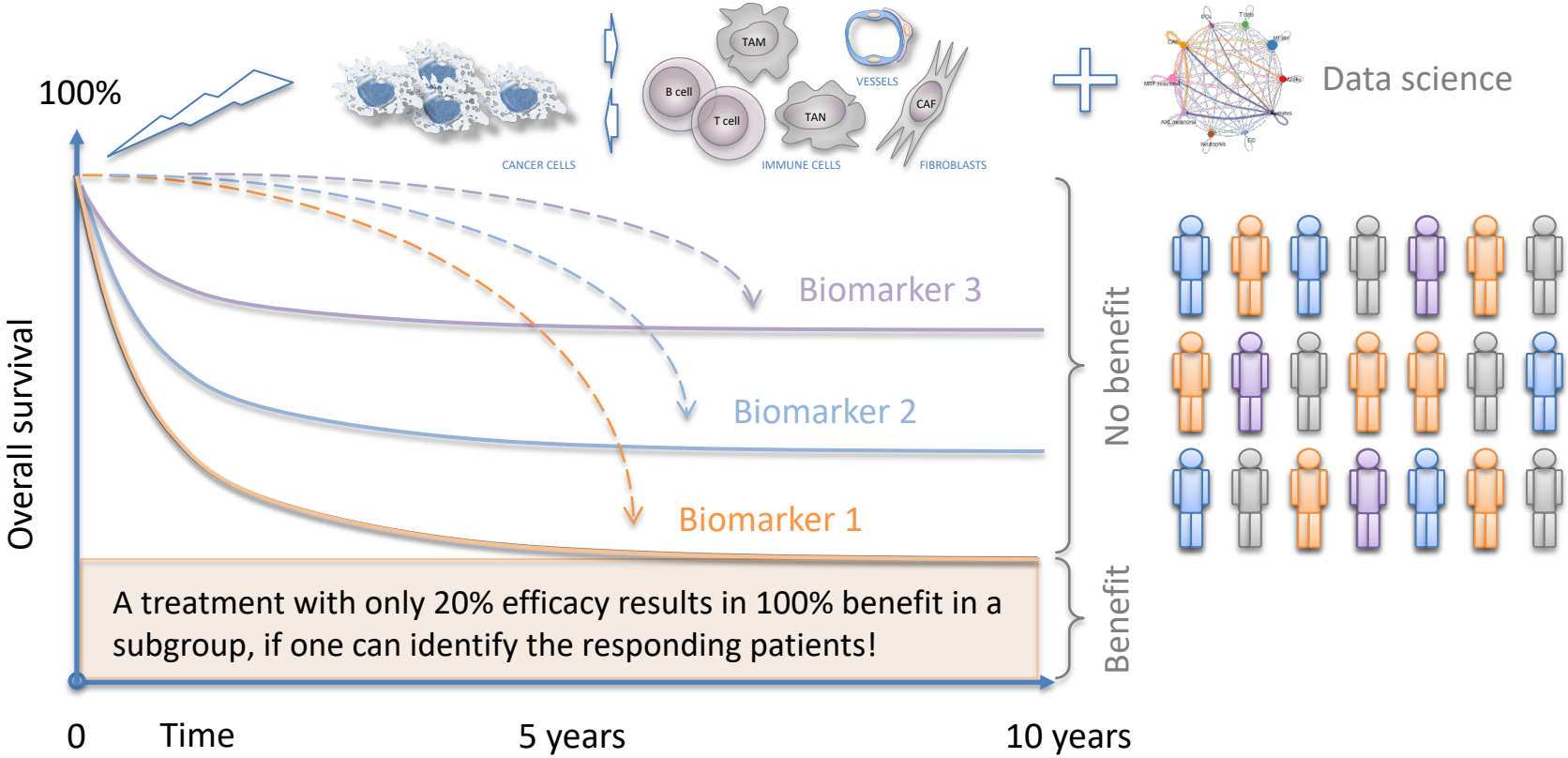
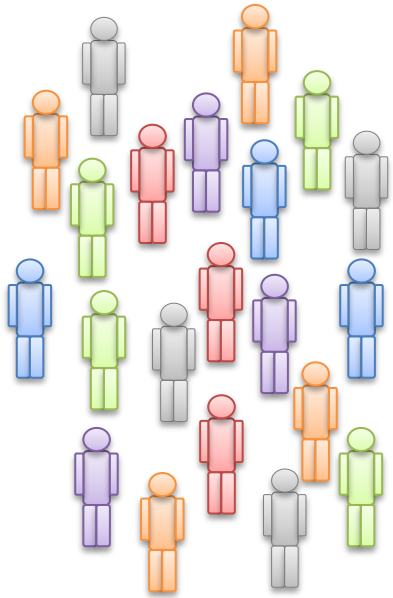
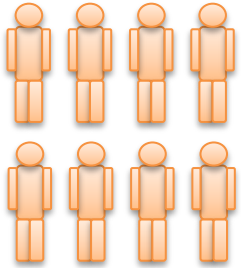
Principle of precision oncology: predictive biomarkers



Complementarity between clinical trials and real-world data:





R

Experimental treatment

Standard treatment

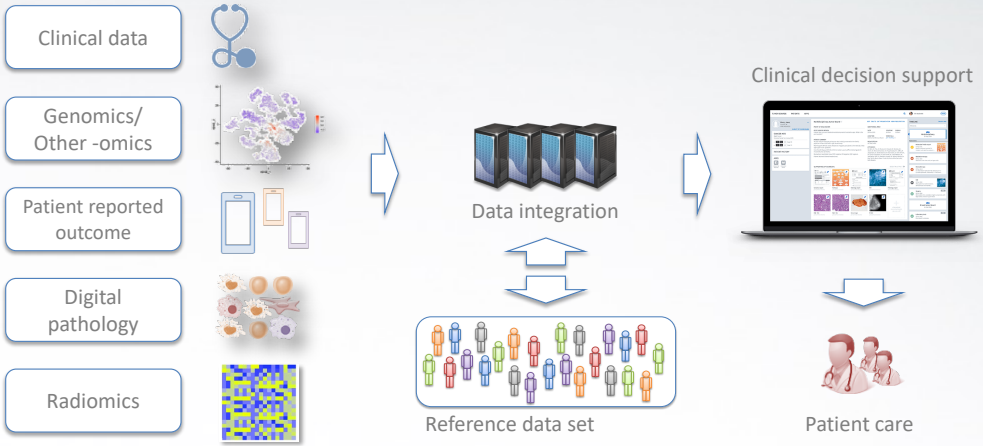
Conclusion

Patients eligible for the trial

All patients

Analysis of real-world data:
Trustworthy AI is critical

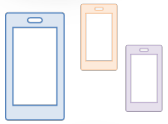
Introduction: Data types for precision oncology



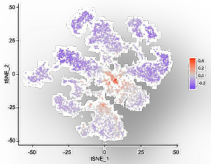
Precision oncology: integrating multiple data streams

Clinical data

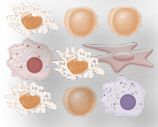
Patient reported outcome



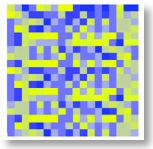
Genomics/ Other -omics



Digital pathology



Radiomics

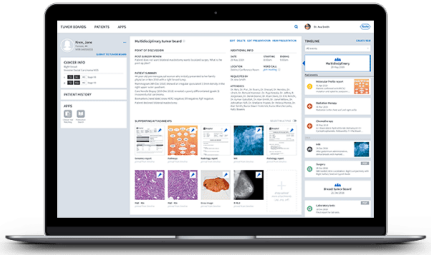


Trustworthy AI

Data integration

Reference data set

Clinical decision support



Patient care

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SPHN Swiss Personalized Health Network

Swiss general consent

Information about the use of health-related data and samples for research purposes

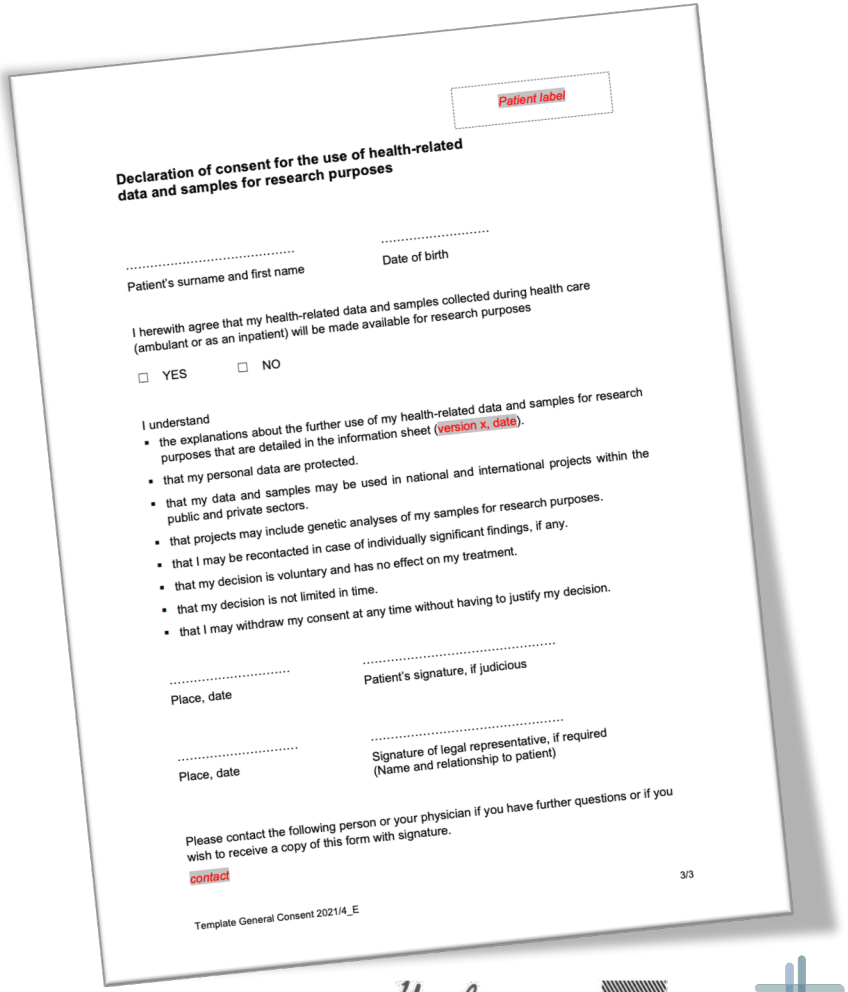
Dear Patient,

Our ability to diagnose and treat diseases has progressed significantly in recent decades. These advances are the result of long-standing medical research in which doctors, scientists and patients of several generations have actively participated. An important part of this research relies on patients' health-related data from medical history, such as results of laboratory analyses, therapy information or genetic predispositions. Any biological material collected during the hospital stay that is no longer needed for the treatment is also extremely valuable for research. These leftover samples can be, for example, blood, urine or tissue samples.

This leaflet explains how patients can contribute to medical progress and provides information in terms of data protection and associated rights. Thank you for your interest and attention.

How can you contribute to research?

By signing the declaration of consent with «Yes», you are making your clinical data and leftover samples available for research purposes. Data and samples include those that have been collected and will be collected during your hospital stay. Your consent is voluntary. It remains valid indefinitely or until withdrawn. You are entitled to withdraw your consent at any time without having to justify your decision. After withdrawal, your data and samples will not be available for new projects. Your decision has no effect on your medical treatment.



Patient label

Declaration of consent for the use of health-related data and samples for research purposes

....
Patient's surname and first name Date of birth

I herewith agree that my health-related data and samples collected during health care (ambulant or as an inpatient) will be made available for research purposes

☐ YES ☐ NO

I understand
- the explanations about the further use of my health-related data and samples for research purposes that are detailed in the information sheet (version x, date).
- that my personal data are protected.
- that my data and samples may be used in national and international projects within the public and private sectors.
- that projects may include genetic analyses of my samples for research purposes.
- that I may be recontacted in case of individually significant findings, if any.
- that my decision is voluntary and has no effect on my treatment.
- that my decision is not limited in time.
- that I may withdraw my consent at any time without having to justify my decision.

....
Place, date Patient's signature, if judicious

....
Place, date Signature of legal representative, if required (Name and relationship to patient)

Please contact the following person or your physician if you have further questions or if you wish to receive a copy of this form with signature.

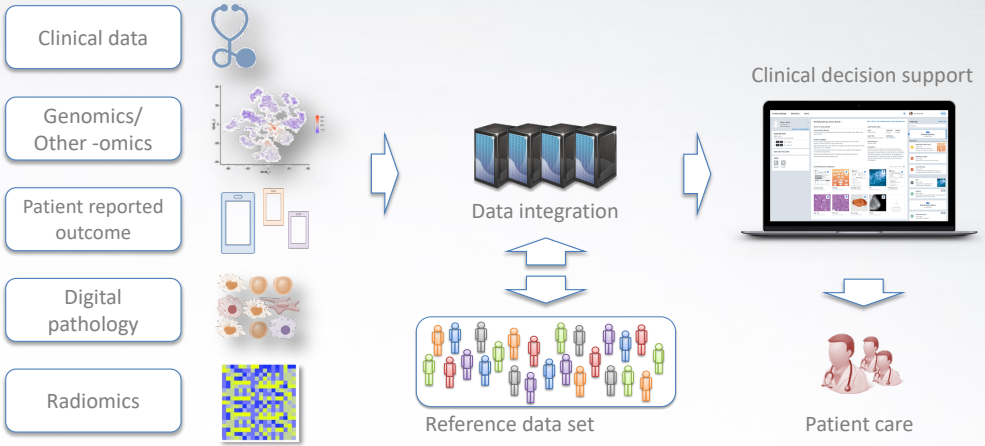
contact

3/3

Template General Consent 2021/4_E

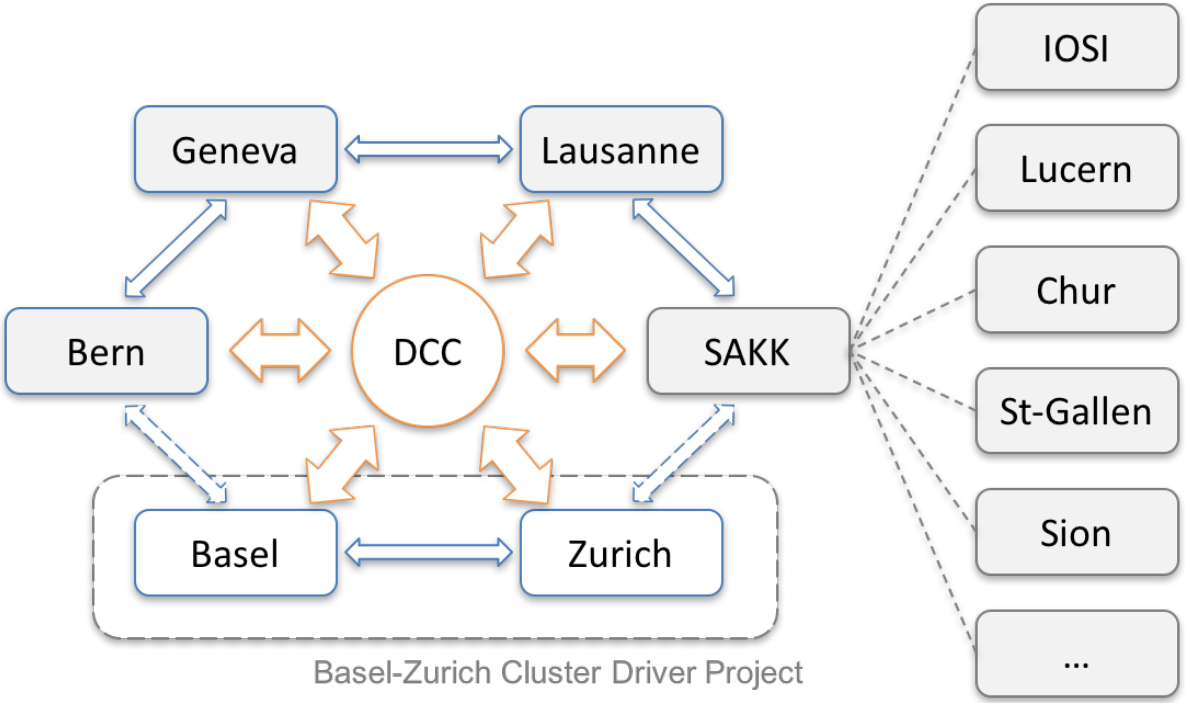
Swiss AI programs rely on common general consent
https://swissethics.ch/en/documents/generalkonsent

Secured data sharing: SPHN-SPO & MedCO



The Swiss Personalized Oncology (SPHN Driver): SPO

All data are handled accoring to FAIR principles: Findable, Accessible, Interoperable, Reusable



Swiss Personalized Oncology

CHUV

HUG Hôpitaux Universitaires Genève

Universitätsspital Basel

SAKK

INSELSPITAL UNIVERSITÄTSSPITAL BERN HOPITAL UNIVERSITAIRE DE BERNE BERN UNIVERSITY HOSPITAL

USZ Universitäts Spital Zürich

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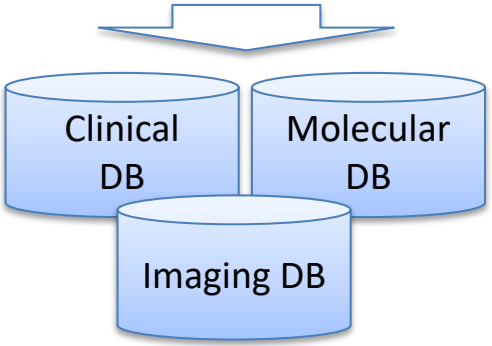
SPHN Swiss Personalized Health Network

Data strategy for SPO/SPHN: Minimal Data Set (MDS)

- Each hospital is adapting the cancer patient's information flow to generate the MDS automatically, insuring the sustainability of the SPO program

Electronic Patient Reccord



#	Group	Data Category	Required Single Data Point
1	DEMOGRAPHIC	Demographic	Year of birth
2			Gender
3	1st DIAGNOSIS	Classification	First date of diagnosis (Biopsy or Main Tumor)
4			CIM 10
5			ICD-O3 / Morphology
6			ICD-O3 / Topography
7			Free text diagnosis
8		Staging	TNM classification
9			TNM Version
10			Stage
11			Staging system
12			Grade
13			Grading system
14	TREATMENT	Therapy	Type of treatment
15			Date of treatment
16			Treatment specification
17	RESPONSE	Outcome	Method of assessment
18			Date of assessment
19			Results from the assessment (RECIST 1.1)
20			Updated stage
21			Staging system
22	SURVIVAL	PFS	Follow-up event
23			Date of follow-up event
24		OS	Date of event
25			Event type

SPHN Swiss Personalized Health Network

Local infrastructure @
Hospital X: heterogeneous

Interoperable MDS @
Hospital X: fully interoperable

Mutualisation via
SPO/SPHN

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SPO Driver Project: complex governance

Required Agreements for the SPO project:

- Ethic protocol
- Consortium Agreement (CA), including also:
  - Data Transfer and Use Agreement (DTUA)
  - Data Transfer and Processing Agreement (DTPA)
  - Material Transfer Agreement (MTA)

Are there solutions to facilitate such lenghly process?

TUNE INSIGHT & SPO: Federated analytics platform for research and molecular tumor board

Q1: How many adult cancer patients consenting on reuse of routine data for research with diagnosis of a malignancy on or after 1st January 2015, mutations in BRAF gene and under anti-PD-1 are there?

Explore

Analysis

Q2: Among these patients, what is the overall survival for patients with and without a mutation on position 600 of the BRAF gene?

Universitätsspital Basel
TUNE INSIGHT

USZ Universitäts Spital Zürich
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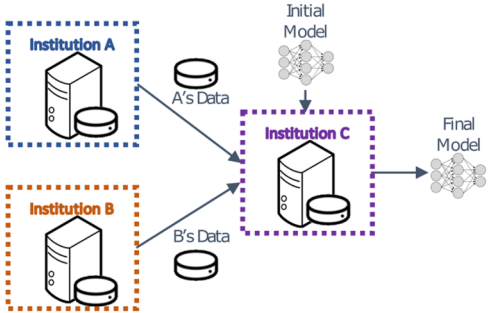
Swiss Personalized Oncology

Main approaches for data collaborations

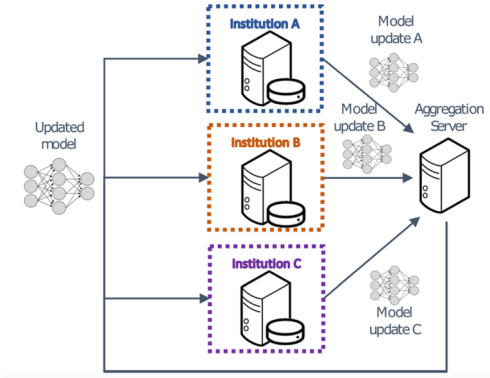
(a) Centralized approach



Figures taken from (Sheller et al. Nature Sci. Reports 2020)

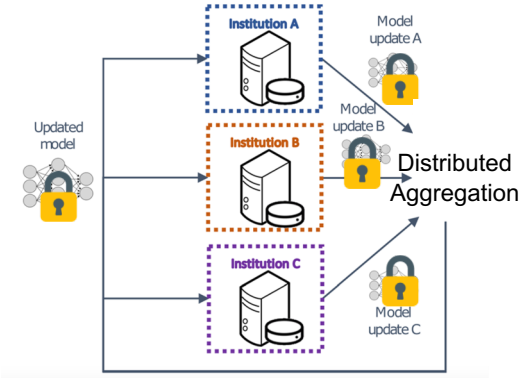
- *Transfer raw, de-identified data to a central database and do all computations there*
- *Single point of failure at the central database*
- ***Individual sites lose control over their data***
- ***Not always feasible across jurisdictions***

(b) Federated Learning (FL)



- *"Send the algorithm to the data"*
- ***Still need to trust aggregation server***
- ***Vulnerable to re-identification and reconstruction attacks****

(c) Secure and distributed approach TUNE INSIGHT



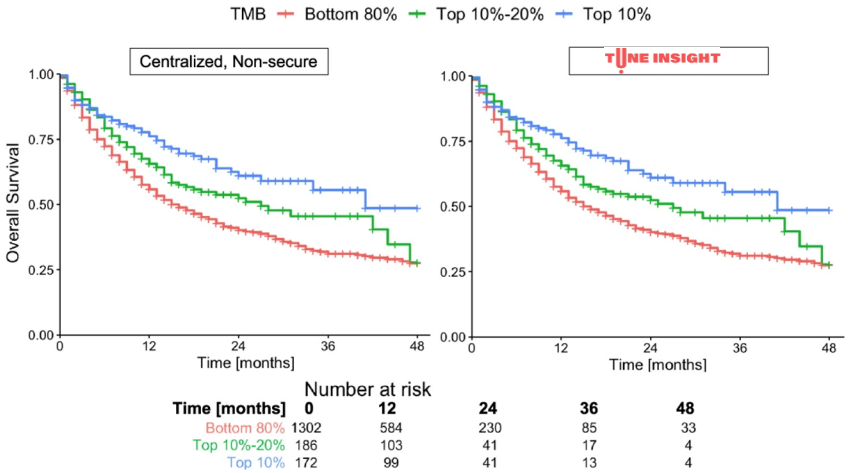
- *"Send the algorithm to the data"*
- *Local output is encrypted*
- ***Operations are performed under encryption (Multiparty Homomorphic Encryption - MHE)***
- ***No more need to trust third parties!***

*Some recent works on attacks to Federated Learning:

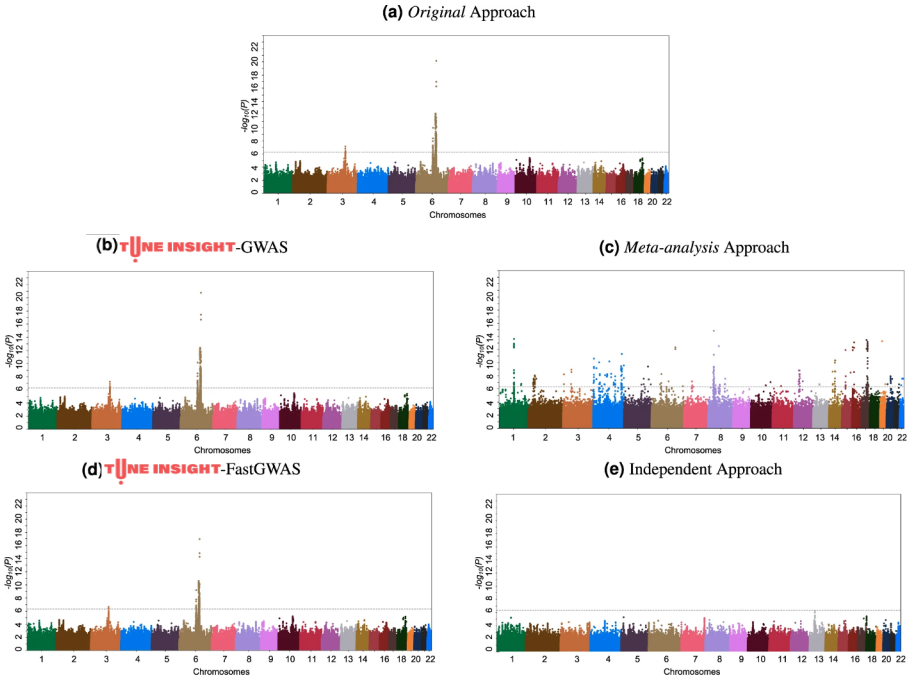
B. Hitaj, G. Ateniese, and F. Perez-Cruz. Deep models under the GAN: Information leakage from collaborative deep learning. In ACM CCS, 2017.
Z. Wang, M. Song, Z. Zhang, Y. Song, Q. Wang, and H. Qi. Beyond inferring class representatives: User-level privacy leakage from federated learning. In IEEE INFOCOM, 2019.
L. Zhu, Z. Liu, and S. Han. Deep leakage from gradients. In NIPS. 2019.
L. Melis, C. Song, E. De Cristofaro, and V. Shmatikov. Exploiting unintended feature leakage in collaborative learning. In IEEE S&P, 2019
M. Nasr, R. Shokri, and A. Houmansadr. Comprehensive privacy analysis of deep learning: Passive and active white-box inference attacks against centralized and federated learning. In IEEE S&P, 2019

Results: Privacy-Preserving Federated Analytics for Precision Medicine

Survival analysis



GWAS



D. Froelicher, J.R. Troncoso-Pastoriza, et al. "Truly privacy-preserving federated analytics for precision medicine with multiparty homomorphic encryption", Nat Commun 12, 5910 (2021). https://doi.org/10.1038/s41467-021-25972-y

Legal and ethical implication of homomorphic encryption

Revolutionizing Medical Data Sharing Using Advanced Privacy-Enhancing Technologies: Technical, Legal, and Ethical Synthesis

James Scheibner[1,2], BComp, LLB, PhD; Jean Louis Raisaro[3,4], BSc, MSc, PhD; Juan Ramón Troncoso-Pastoriza[5], BSc, MSc, MPhil, PhD; Marcello Ienca[1], BA, MA, MSc, PhD; Jacques Fellay[3,6,7], MD, PhD; Effy Vayena[1], BA, MSc, PhD; Jean-Pierre Hubaux[5], Dr-Eng

[1]Health Ethics and Policy Laboratory, Department of Health Sciences and Technology, Eidgenössische Technische Hochschule Zürich, Zürich, Switzerland

[2]College of Business, Government and Law, Flinders University, Adelaide, Australia

[3]Precision Medicine Unit, Lausanne University Hospital, Lausanne, Switzerland

[4]Data Science Group, Lausanne University Hospital, Lausanne, Switzerland

[5]Laboratory for Data Security, School of Computer and Communication Sciences, École polytechnique fédérale de Lausanne, Lausanne, Switzerland

[6]School of Life Sciences, École polytechnique fédérale de Lausanne, Lausanne, Switzerland

[7]Host-Pathogen Genomics Laboratory, Swiss Institute of Bioinformatics, Lausanne, Switzerland

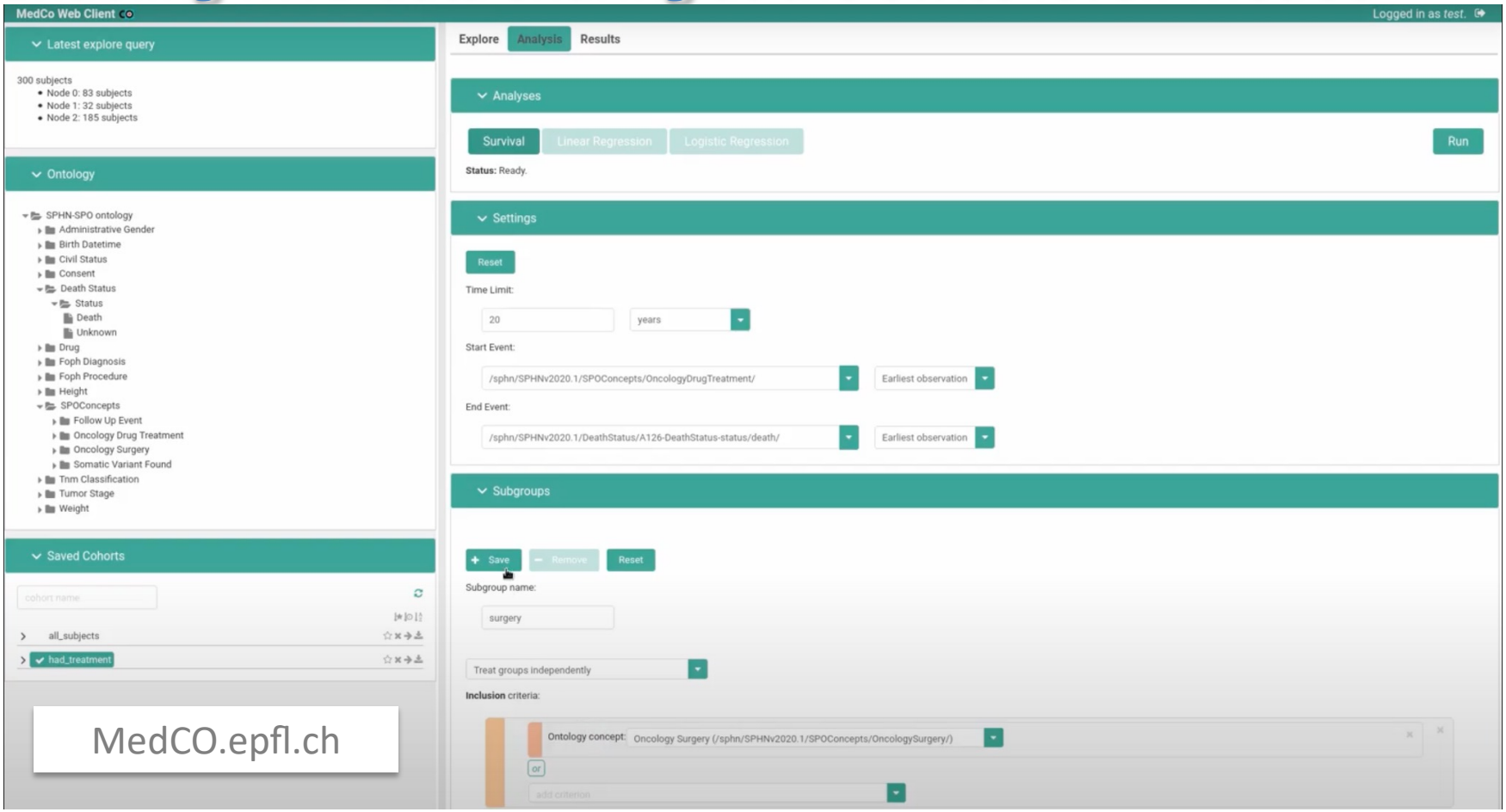
Abstract

Multisite medical data sharing is critical in modern clinical practice and medical research. The challenge is to conduct data sharing that preserves individual privacy and data utility. The shortcomings of traditional privacy-enhancing technologies mean that institutions rely upon bespoke data sharing contracts. The lengthy process and administration induced by these contracts increases the inefficiency of data sharing and may disincentivize important clinical treatment and medical research. This paper provides a synthesis between 2 novel advanced privacy-enhancing technologies—homomorphic encryption and secure multiparty computation (defined together as multiparty homomorphic encryption). These privacy-enhancing technologies provide a mathematical guarantee of privacy, with multiparty homomorphic encryption providing a performance advantage over separately using homomorphic encryption or secure multiparty computation. We argue multiparty homomorphic encryption fulfills legal requirements for medical data sharing under the European Union's General Data Protection Regulation which has set a global benchmark for data protection. Specifically, the data processed and shared using multiparty homomorphic encryption can be considered anonymized data. We explain how multiparty homomorphic encryption can reduce the reliance upon customized contractual measures between institutions. The proposed approach can accelerate the pace of medical research while offering additional incentives for health care and research institutes to employ common data interoperability standards.

(J Med Internet Res 2021;23(2):e25120) doi: 10.2196/25120

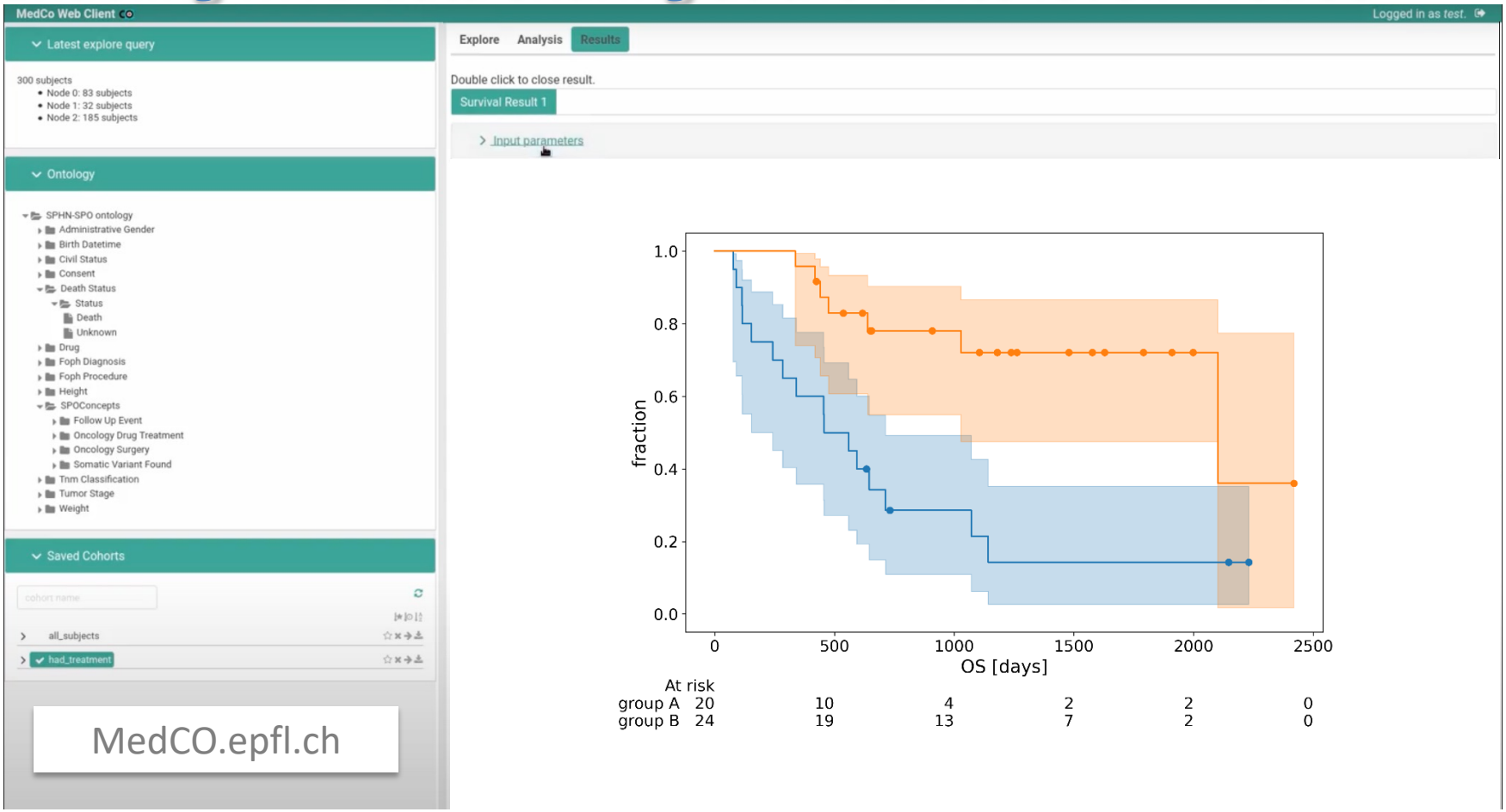
- Homomorphic encryption provides added security, but could also change the legal and ethical constraints to exchange data
- Legal: simplified DTUA procedure as data are considered anonymous
- Ethical: simplified ethics approval as data are considered anonymous
- MedCO is currently being investigated in a pilot project within the SPHN SPO consortium
- Tune Insight will provide the support and know-how to deploy and maintain MedCO in all involved insitutions

Enabling MTB data sharing at the Swiss level: MedCO



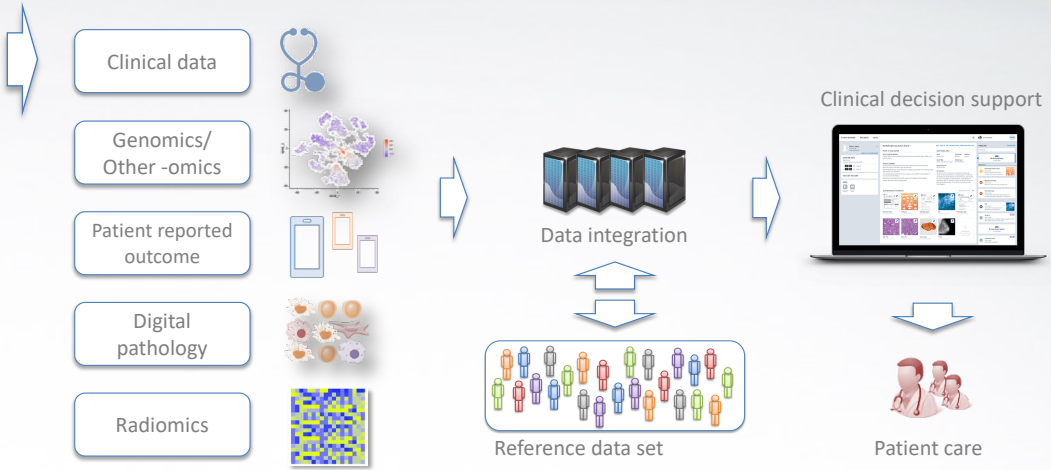
MedCO.epfl.ch

Enabling MTB data sharing at the Swiss level: MedCO



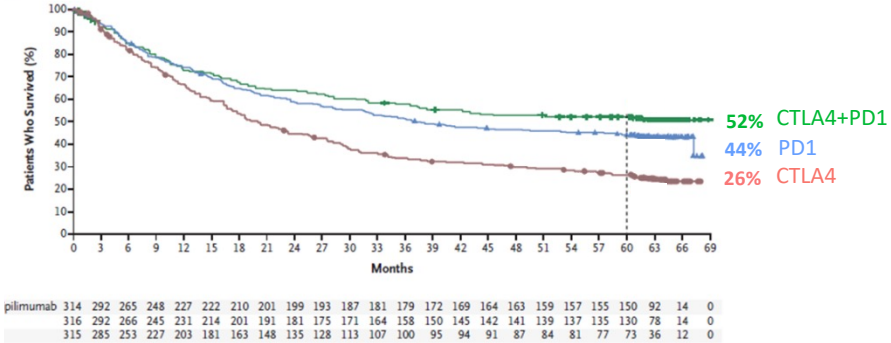
MedCO.epfl.ch

Precision oncology: example of use - clinical data



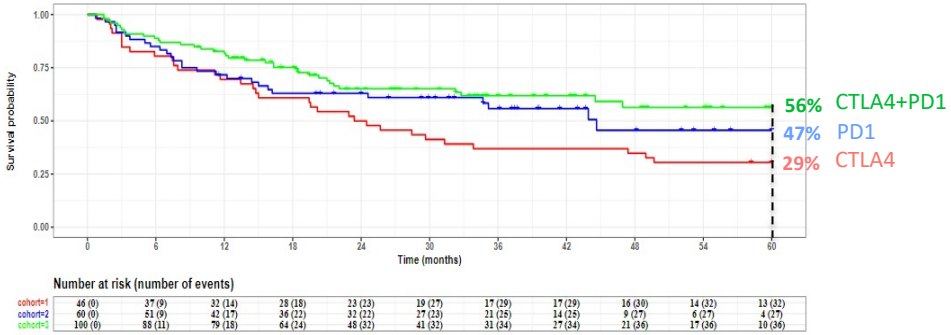
Process mining: CHUV data vs Checkmate-067 – 1st line

OS-Checkmate 067



pilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

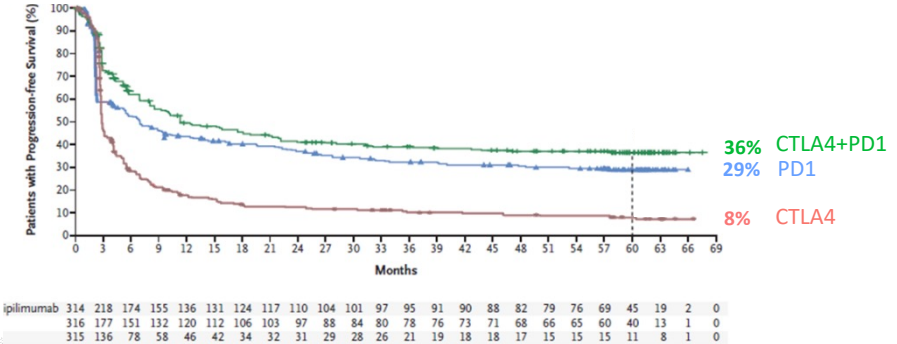
OS-SPO Real World Data



Number at risk (number of events)

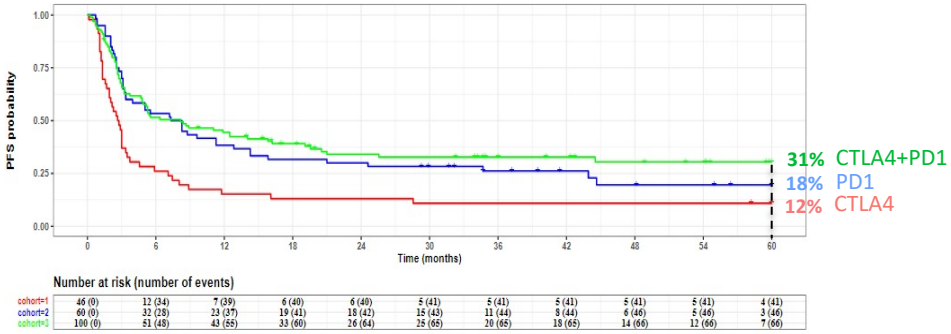
cohort=1	46 (0)	37 (9)	32 (14)	28 (18)	23 (23)	19 (27)	17 (29)	17 (29)	16 (30)	14 (32)	13 (32)
cohort=2	60 (0)	51 (9)	42 (17)	36 (22)	32 (22)	27 (23)	21 (25)	14 (25)	9 (27)	6 (27)	4 (27)
cohort=3	100 (0)	88 (11)	79 (18)	64 (24)	48 (32)	41 (32)	31 (34)	27 (34)	21 (36)	17 (36)	10 (36)

PFS-Checkmate 067



ipilimumab	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	17	15	15	15	11	8	1	0

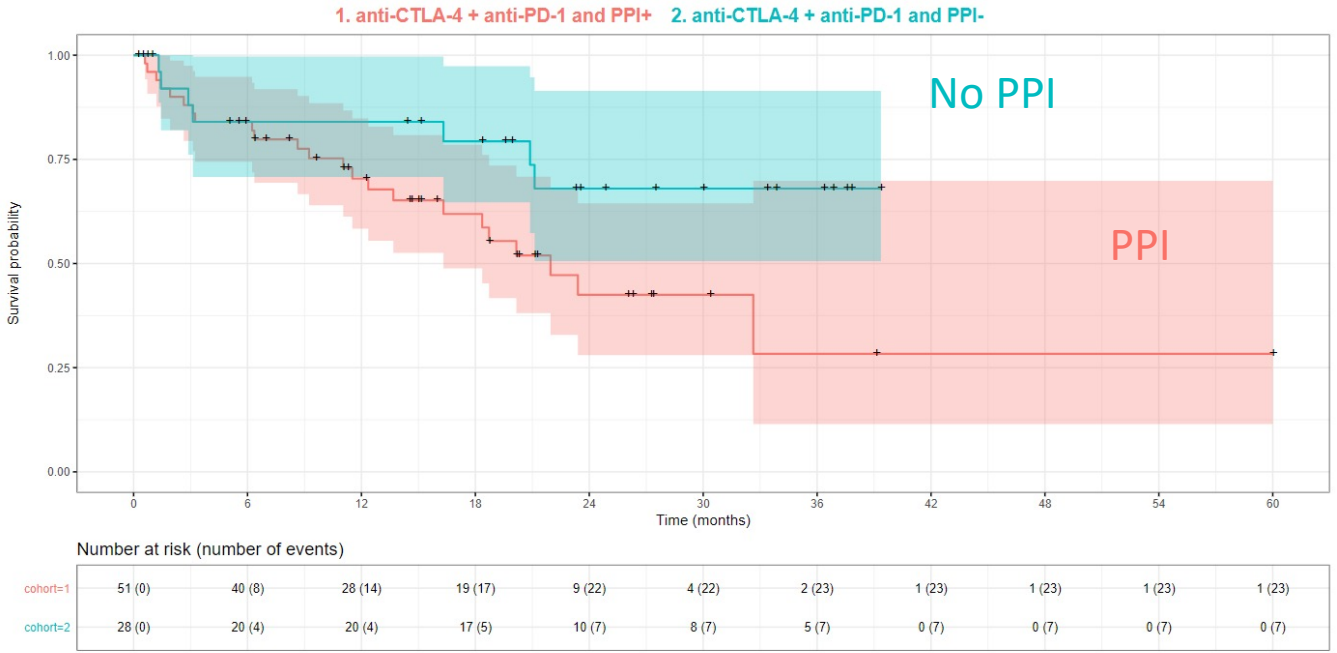
PFS-SPO Real World Data



Number at risk (number of events)

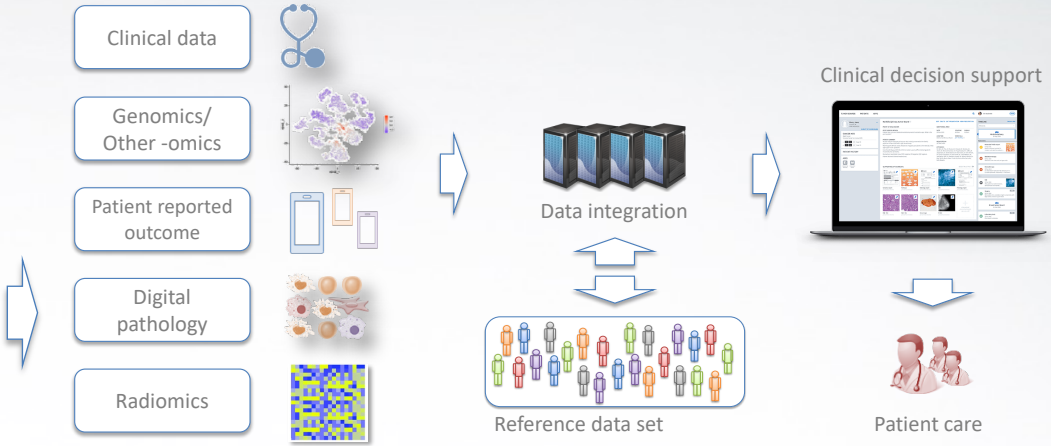
cohort=1	46 (0)	12 (34)	7 (39)	6 (40)	6 (40)	5 (41)	5 (41)	5 (41)	5 (41)	5 (41)	4 (41)
cohort=2	60 (0)	32 (28)	23 (37)	19 (41)	18 (42)	15 (43)	11 (44)	8 (44)	6 (46)	5 (46)	3 (46)
cohort=3	100 (0)	51 (48)	43 (55)	33 (60)	26 (64)	26 (65)	20 (65)	18 (65)	14 (66)	12 (66)	7 (66)

Looking at the impact of other factors: co-medications



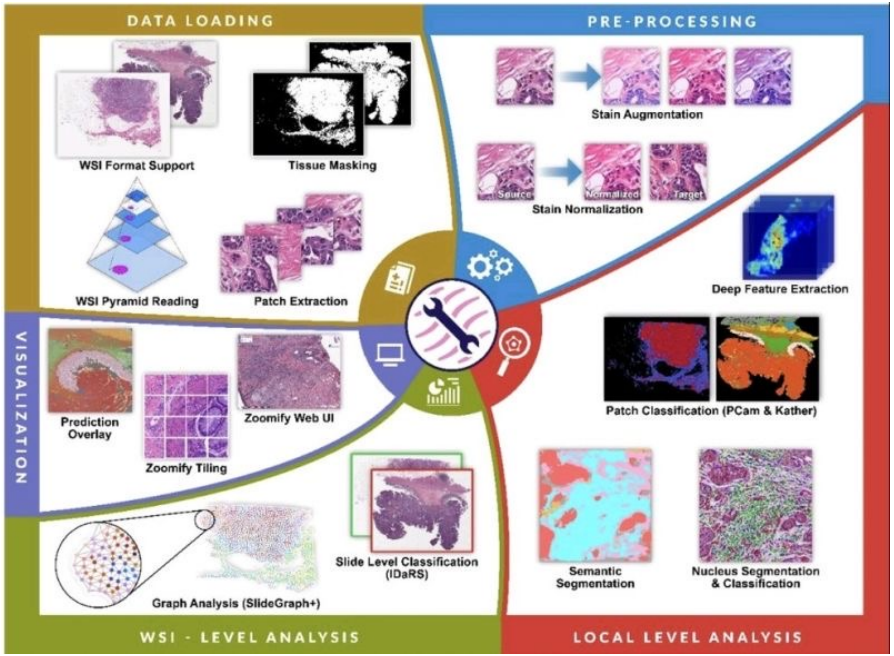
Log-rank p-value (KM)	0.047
Hazard ratio	0.43
95% CI on hazard ratio	0.18 - 1.01
Log-rank p-value (Cox)	0.04
Wald p-values (Cox)	0.054

Precision oncology: example of use - image data



Digital pathology: application to precision oncology

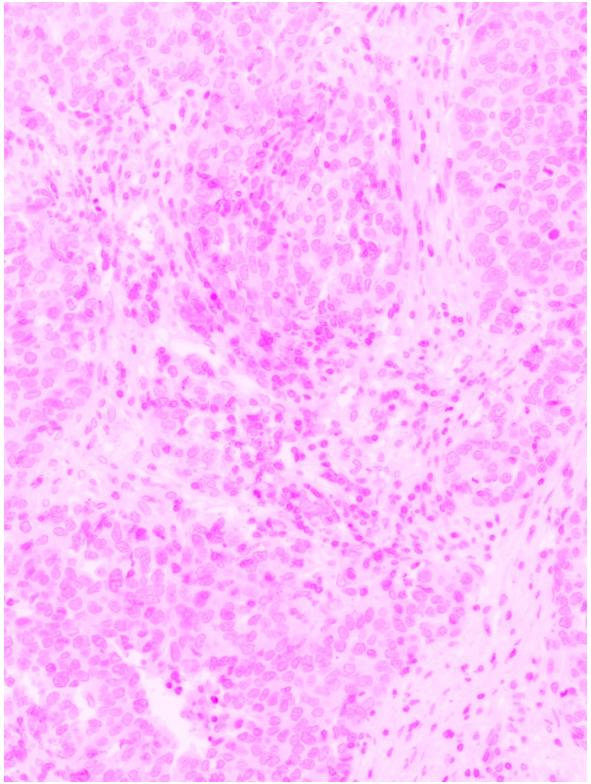
- Digital pathology is a rapidly emerging field at the crossing between pathology and data science
- Deep learning allows unprecedented image analysis that can now be applied to pathology slides (H&E, mIF, mIHC, …)
- Digital pathology can be used by
  - Pathologists to quantify and standardize pathology reports
  - Oncologists to derive predictive biomarkers
- As digital pathology can work on all sorts of stainings, including H&E, large retrospective datasets can be analyzed



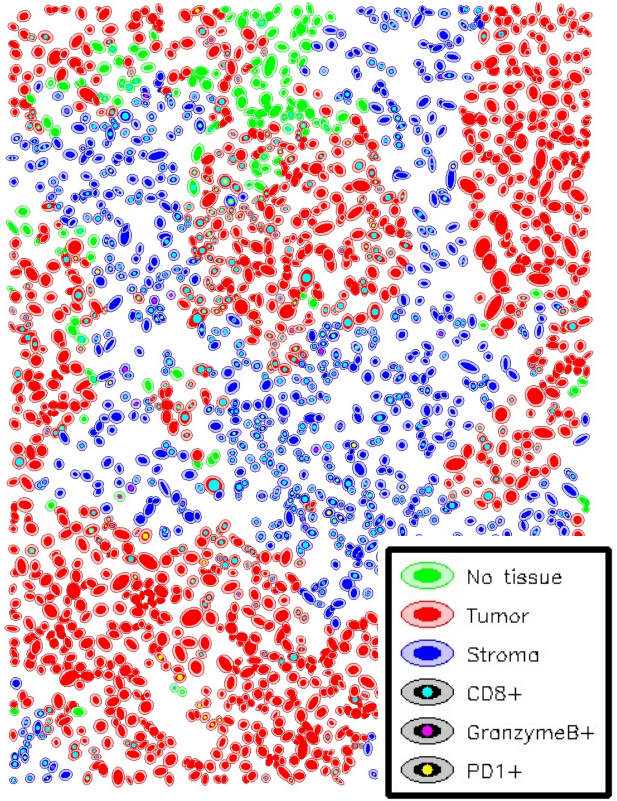
Pocock & al, BioRxiv, https://doi.org/10.1101/2021.12.23.474029;

Automated feature extraction: machine learning/network analysis

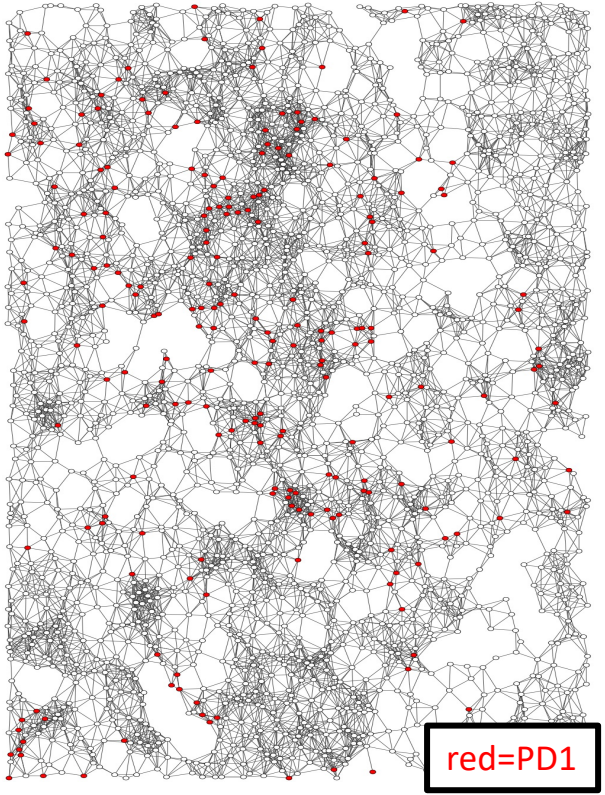
H&E slide



Phenotyping



Network abstraction



Courtesy : Sylvie Rusakiewicz

SDSC project iLearn, with Pascal Frossard, Dorina Thanou and collaborators - EPFL

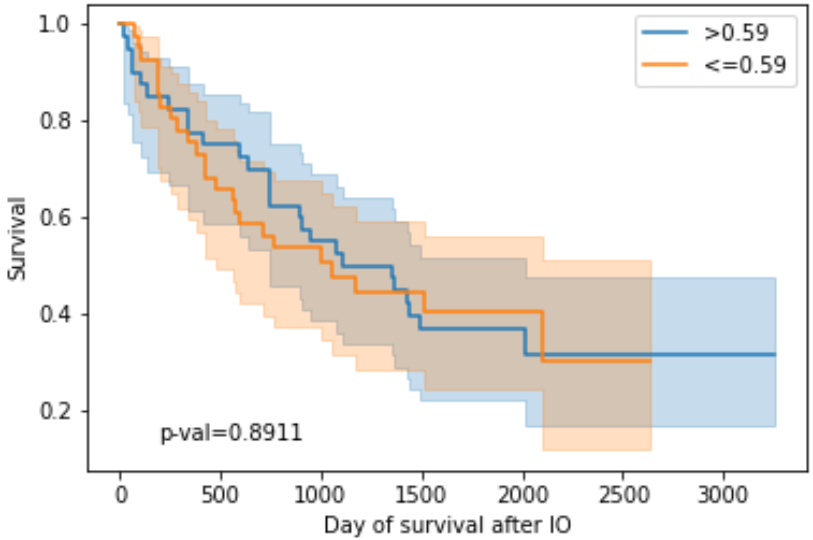
Using digital pathology to build a predictive biomarker[1]

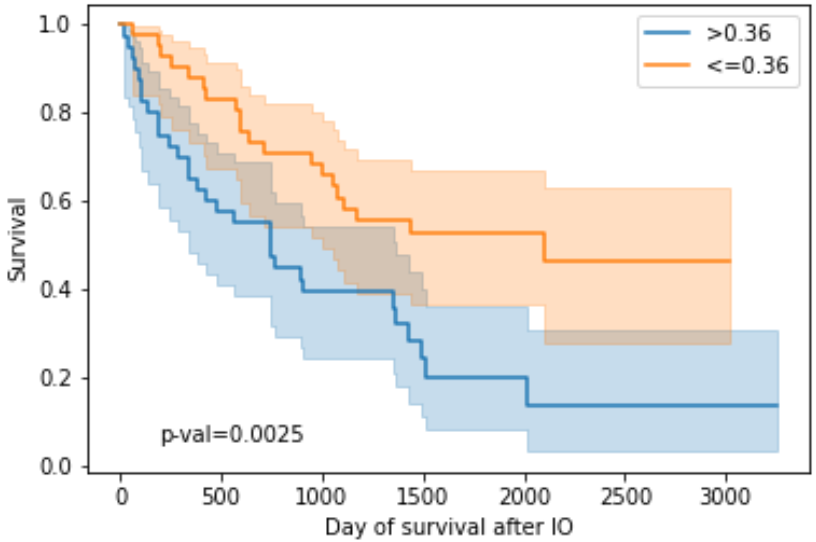
High average lymphocyte density

Low average lymphocyte density

Network based Feature 178 low

Network based Feature 178 high

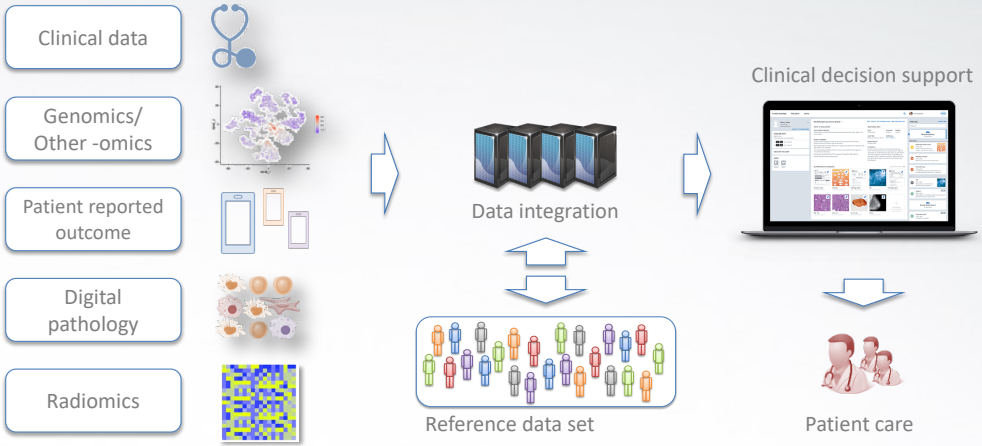




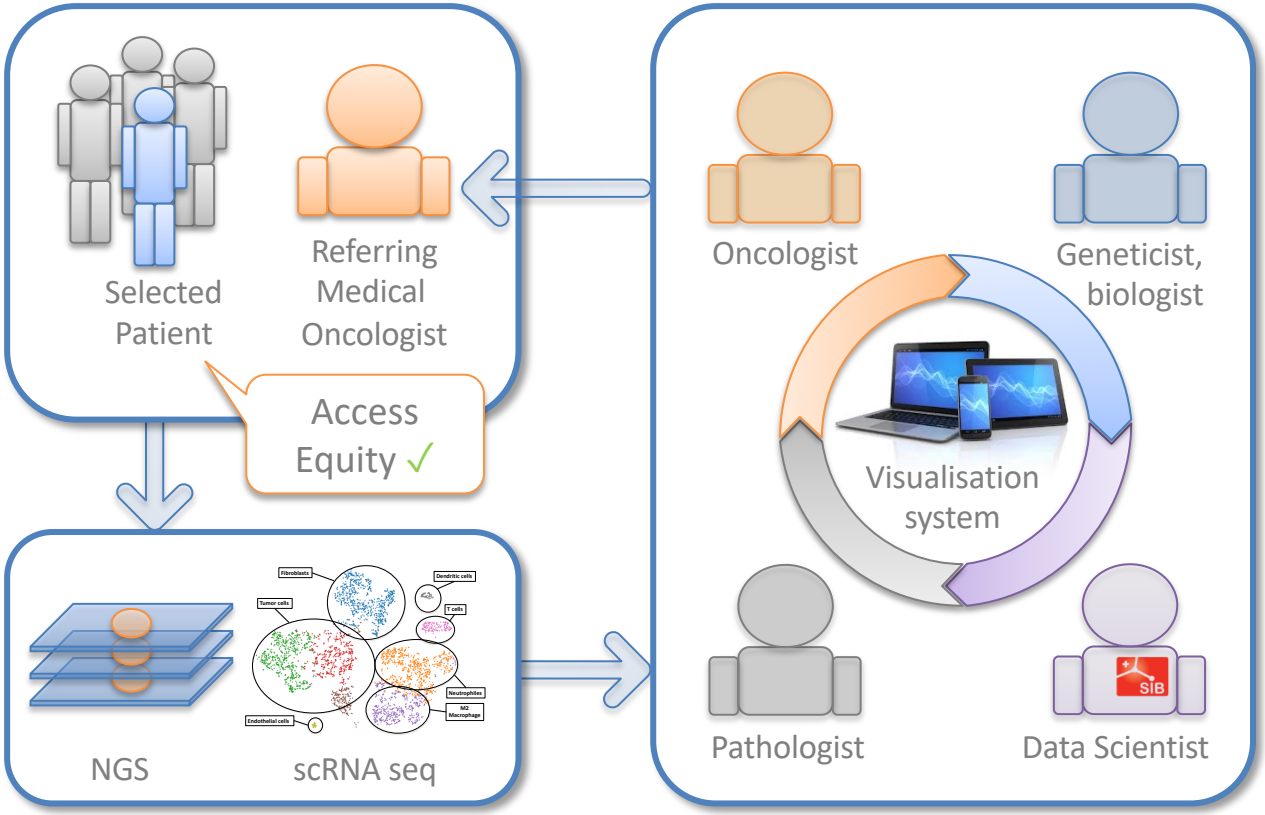
SDSC project iLearn, with Pascal Frossard, Dorina Thanou and collaborators - EPFL

[1]120 melanoma cohort prior to PD-1 based therapy

Precision oncology and AI: access equity

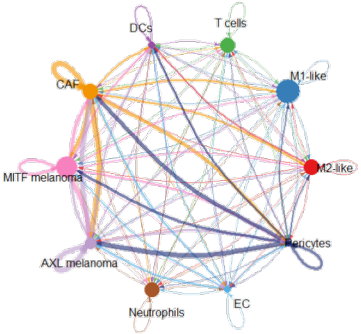


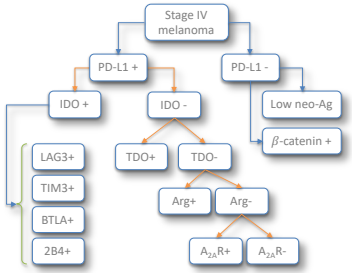
Molecular tumor-board and AI



Performance
Equity ✓

Machine learning and artificial intelligence





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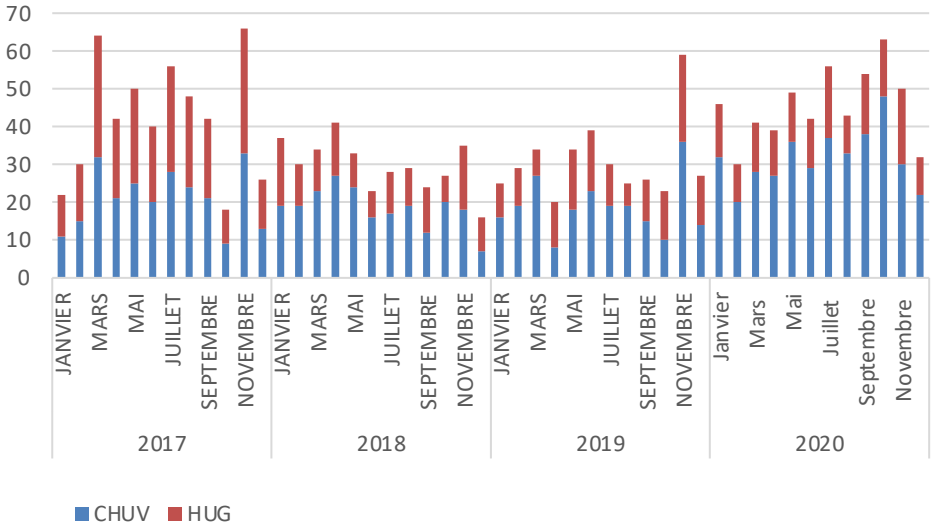
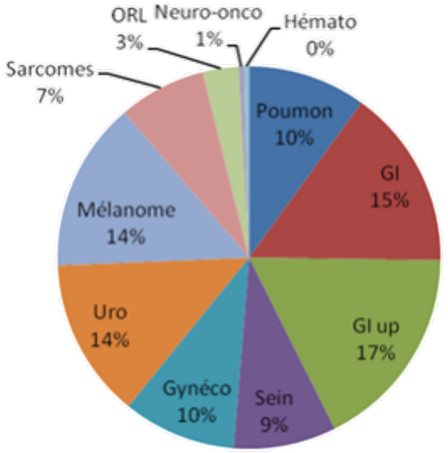
Molecular Tumor Board: Activity

- All comer training data set!





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

	Patients presented since 01/2017
HUG + CHUV	2000+

- 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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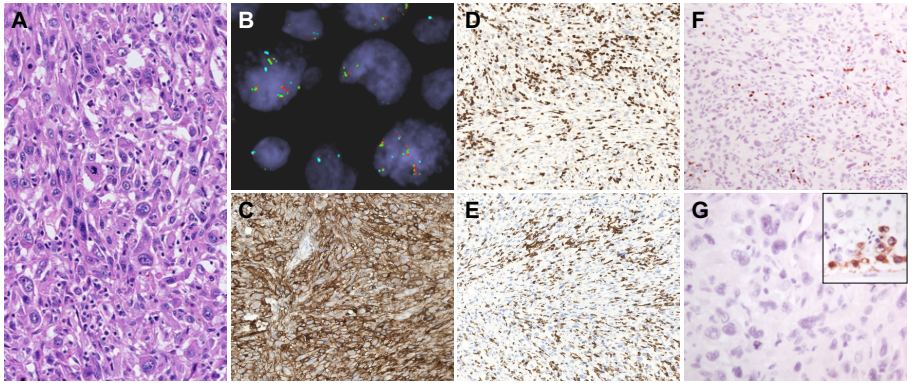
Molecular Tumor Board: example of clinical outcome

- 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 (Dr. Bohanes)



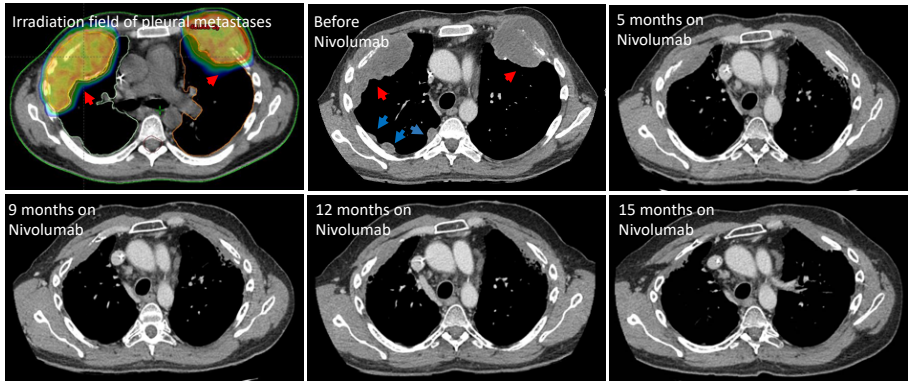
Deep response to anti-PD-1 therapy of metastatic neurofibromatosis type 1-associated malignant peripheral nerve sheath tumor with *CD274/PD-L1* amplification

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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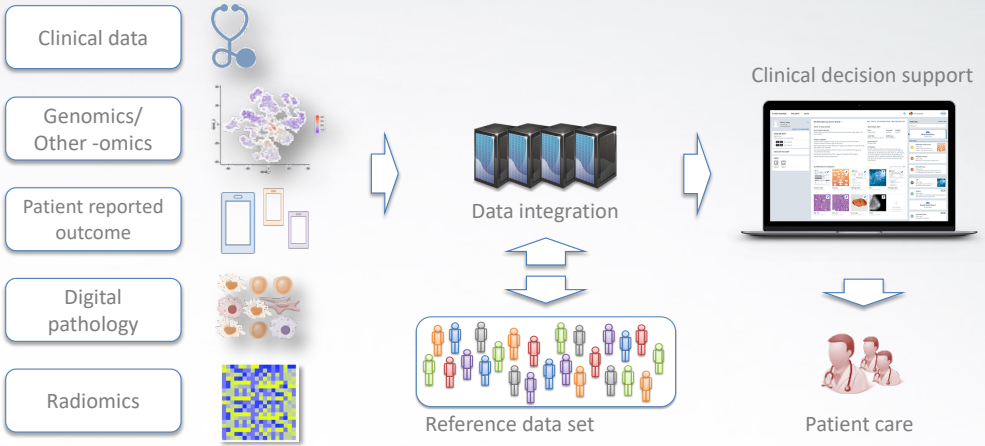
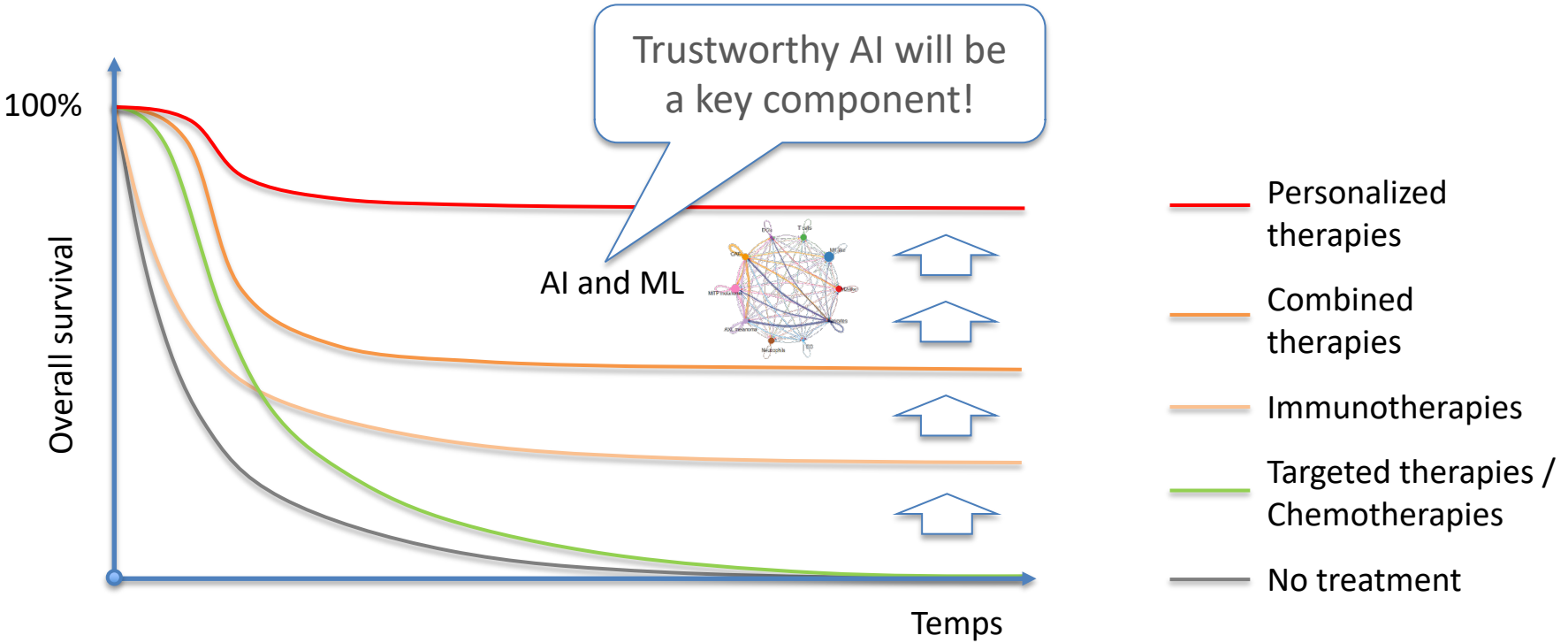
Conclusion and Outlook



Expected benefit from personalized strategies



Adapted from A. Ribas, *WCM* 2013


| AMLD | SwissTech Center | 29.04.2022
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