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PAGE Population Approach Group Europe

Modeling real-world tumor size dynamics based on electronic health records and image data in advanced melanoma patients receiving immunotherapy

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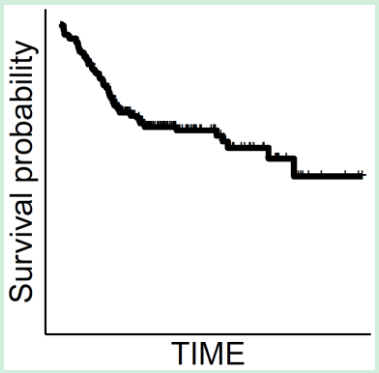
*co-first, equal contribution to the work
°co-senior

Lausanne University Hospital,
Precision Oncology Centre

The right cancer treatment to the right patient at the right dose



Immune checkpoints inhibitors (ICIs)

Precision oncology

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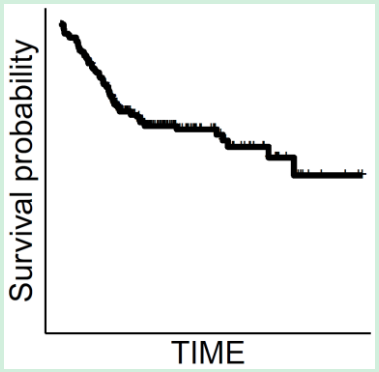

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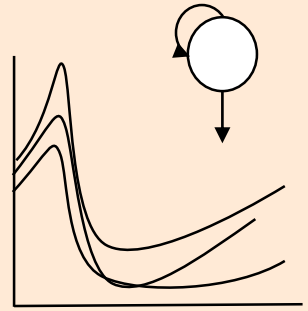
Model-informed drug development



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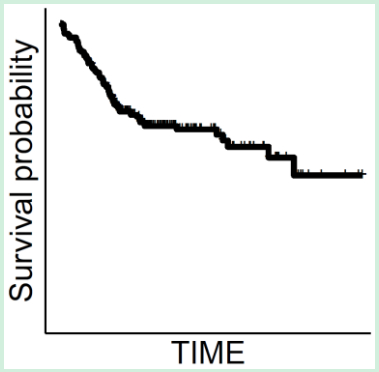

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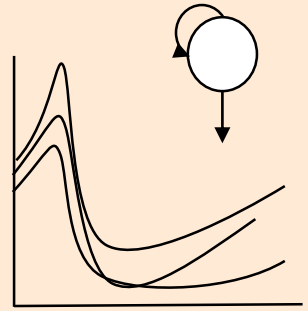

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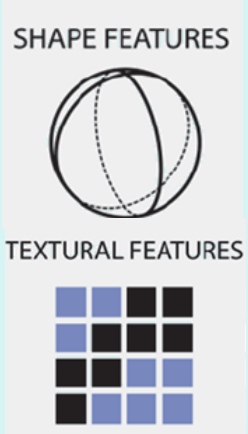
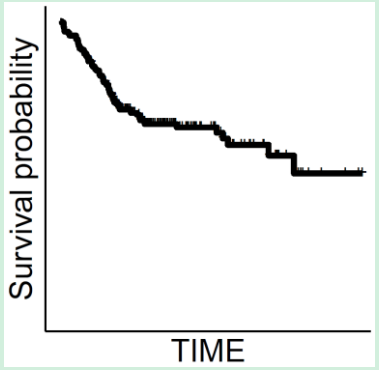


New predictive biomarkers

The right cancer treatment to the right patient at the right dose



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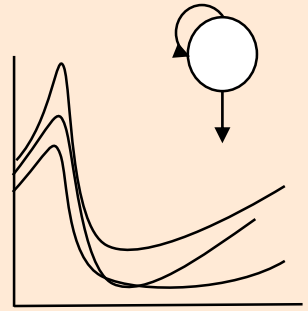

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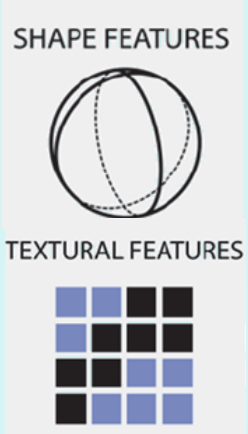
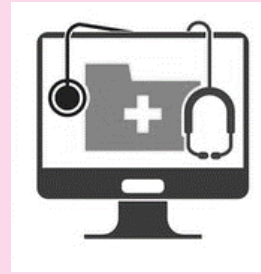


New predictive biomarkers

Real-world data (RWD)

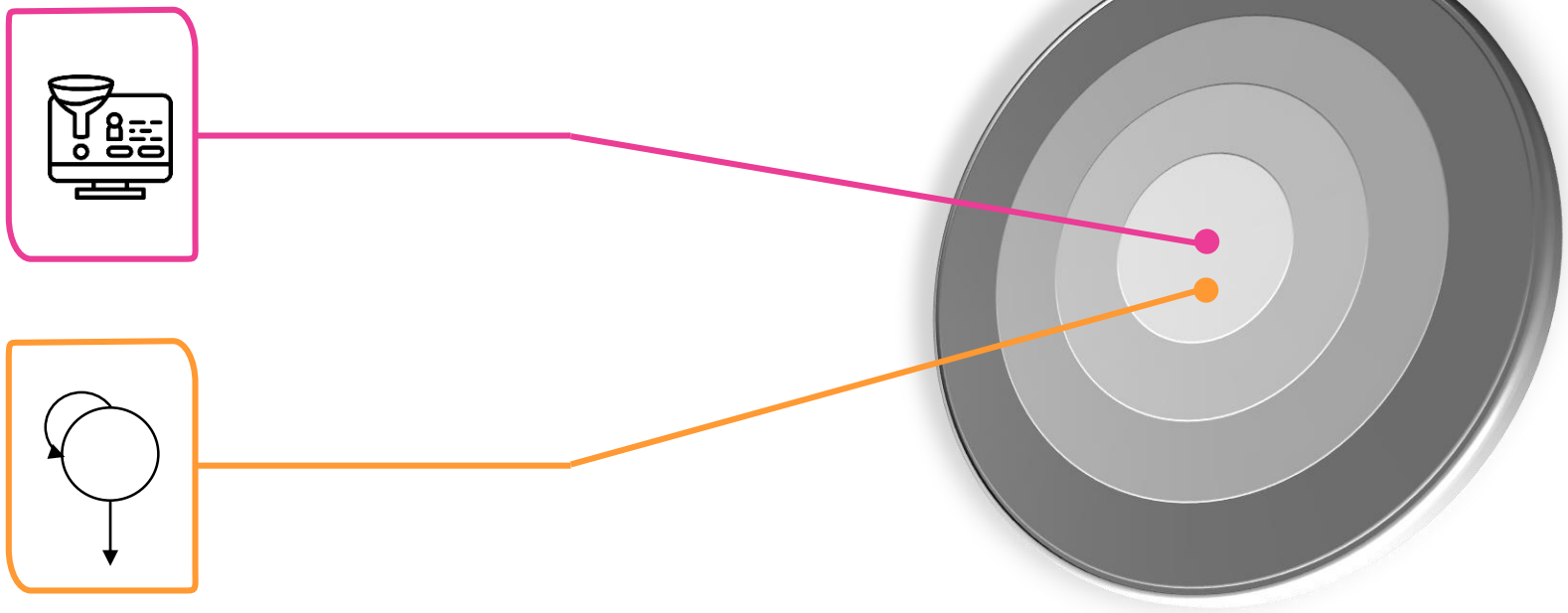


Real-World Tumor Dynamics - objectives

How can RWD inform anticancer treatment decisions?

Semi-automated pipeline for **collection and curation** of RWD[1]

Population tumor growth inhibition model in advanced cutaneous melanoma patients receiving ICIs



Data aggregation and retrospective analysis for this study have been approved by the local Ethics Committee for patients who did not refuse general informed consent.

[1]Abler D., Courlet P. Submitted.

RWD collection is challenging and requires prior data curation steps

Prospective clinical study

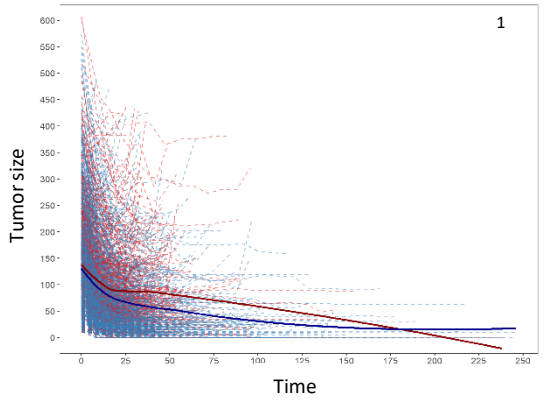
Standardized case report forms

Standardized imaging, **quantitative** grading

Study Database

Quantitative treatment & outcome data

Longitudinal modeling of tumor volume



[1]Vera-Yunca D. 2021.

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Unstructured electronic health records, free text

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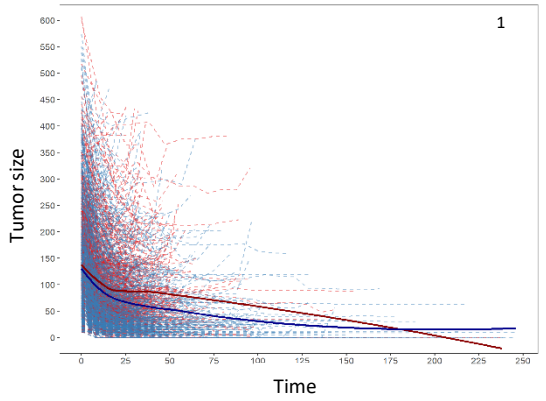

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Hospital Information Systems

RWD Curation

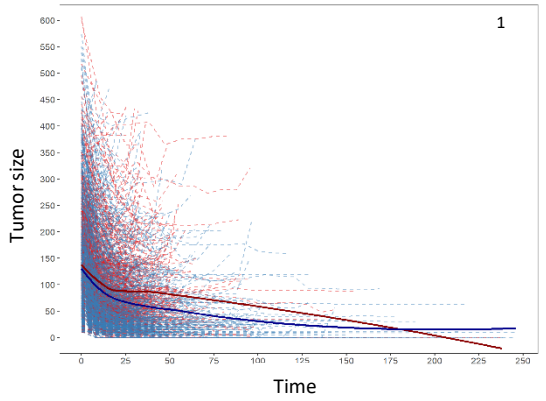
Clinical data

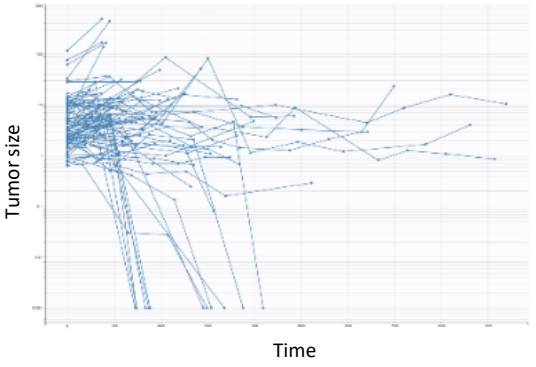
Image data

Quality assurance

Quantitative treatment & outcome data

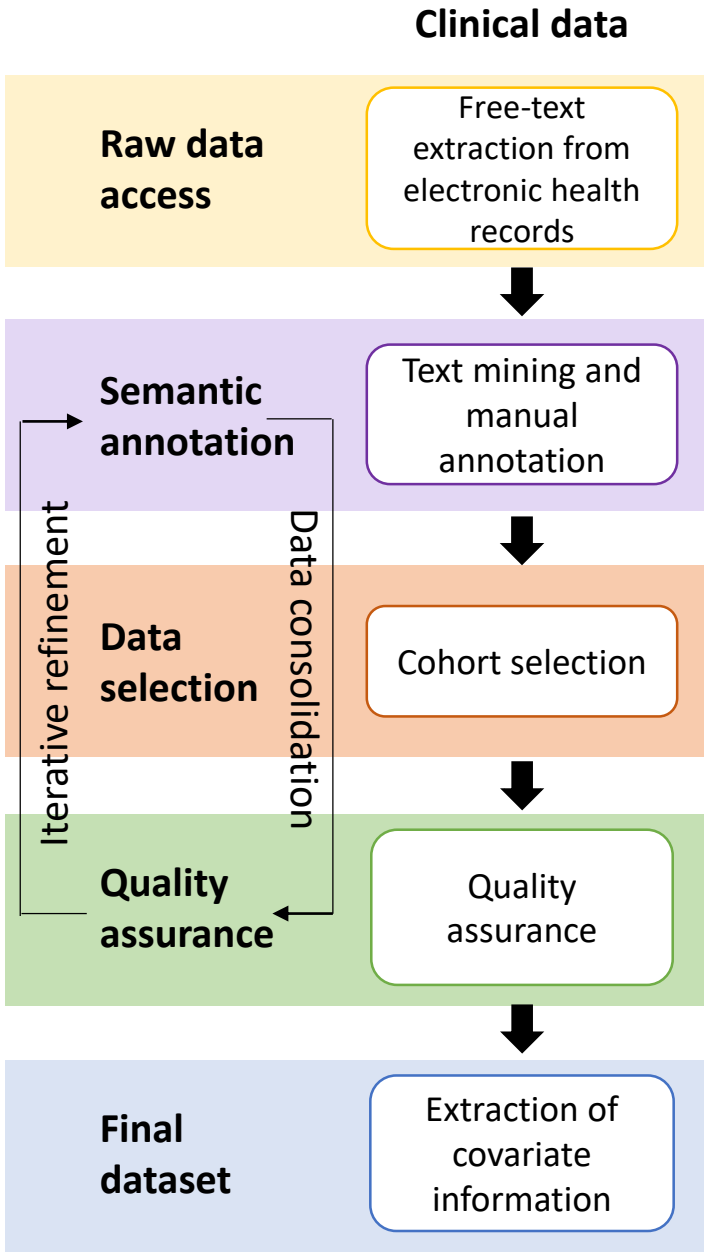
Longitudinal modeling of tumor volume



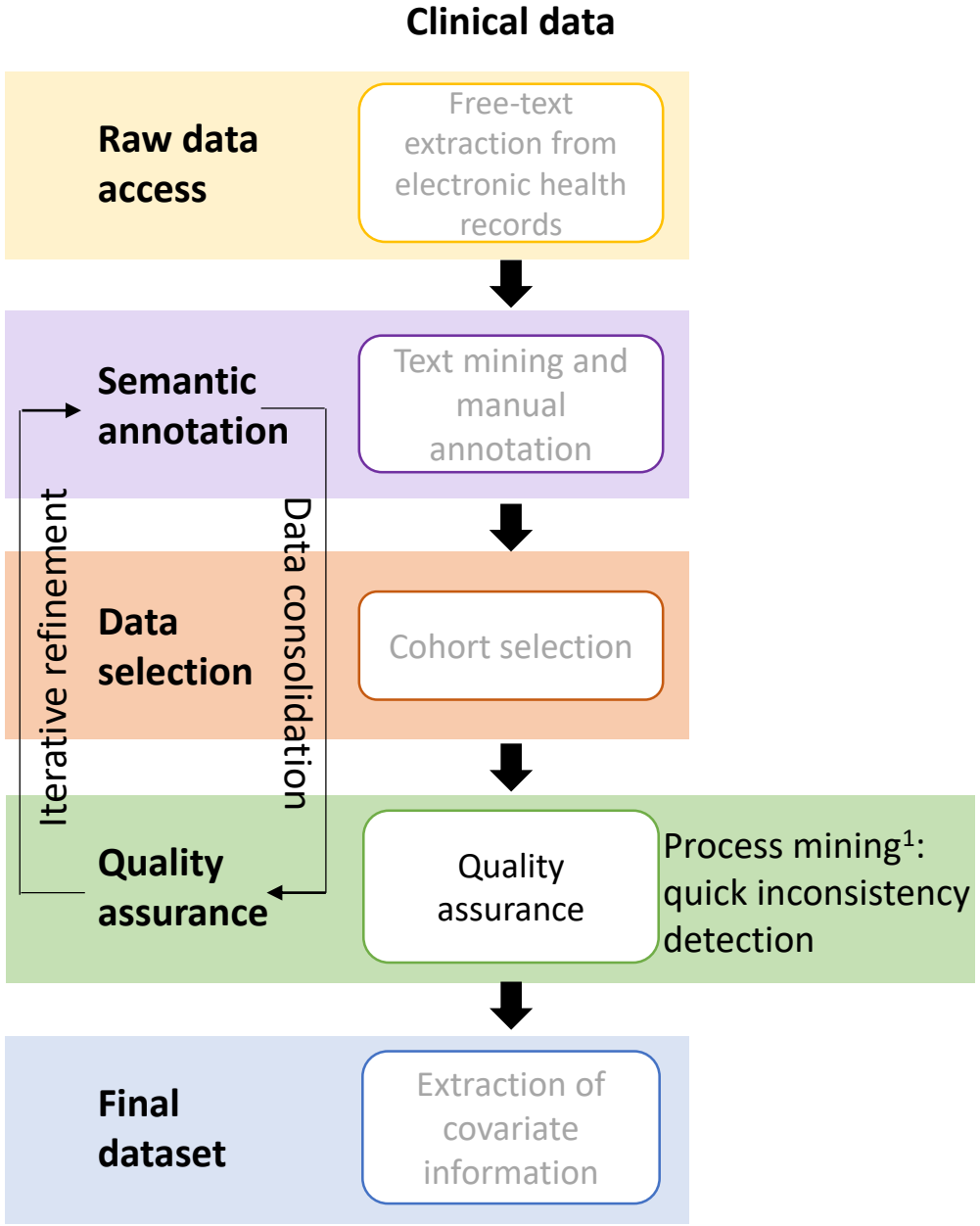


[1]Vera-Yunca D. 2021.

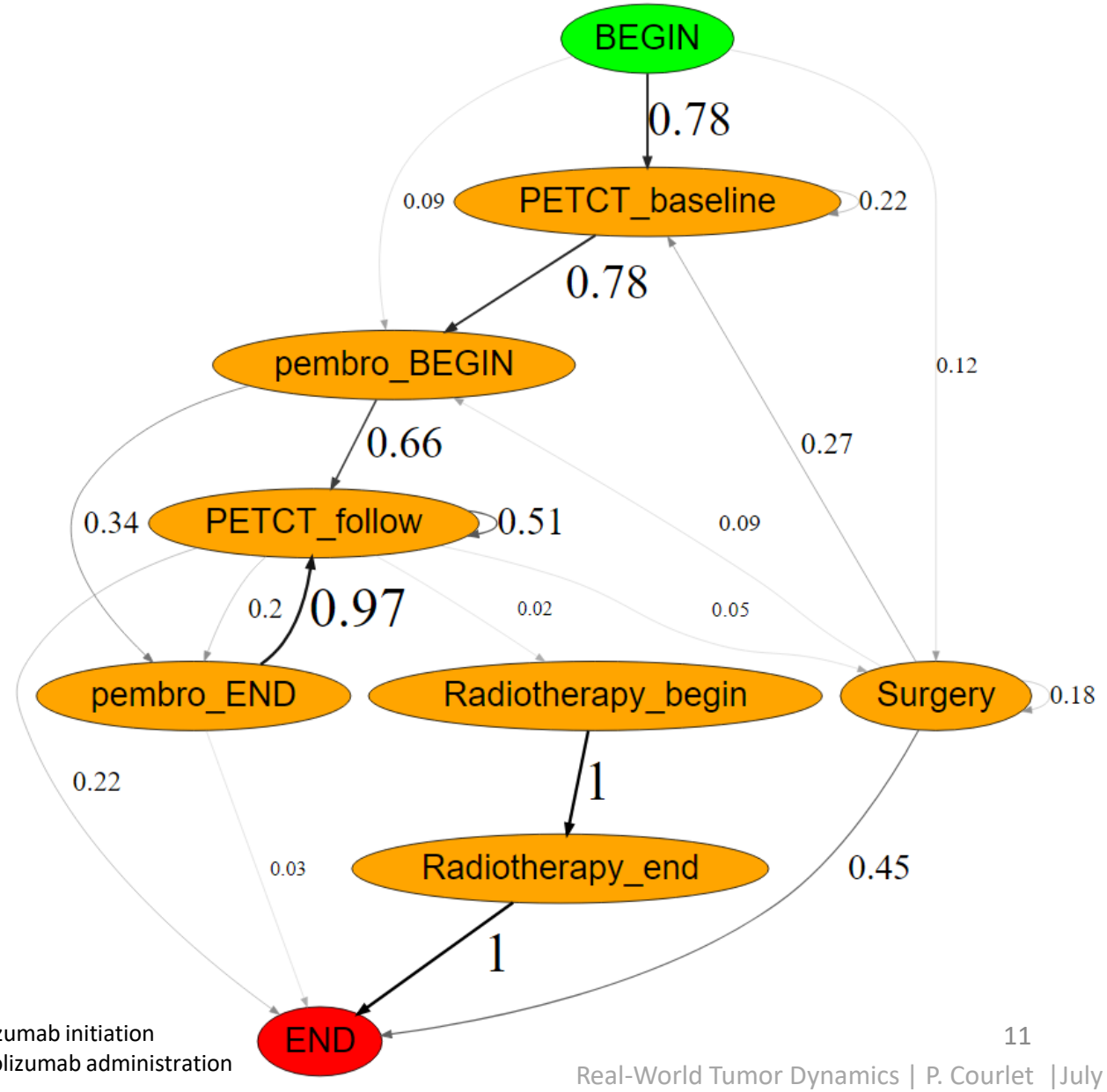
Clinical data were extracted from electronic health records, annotated and assessed for quality



Process mining was employed as quality assurance step to validate the extracted data



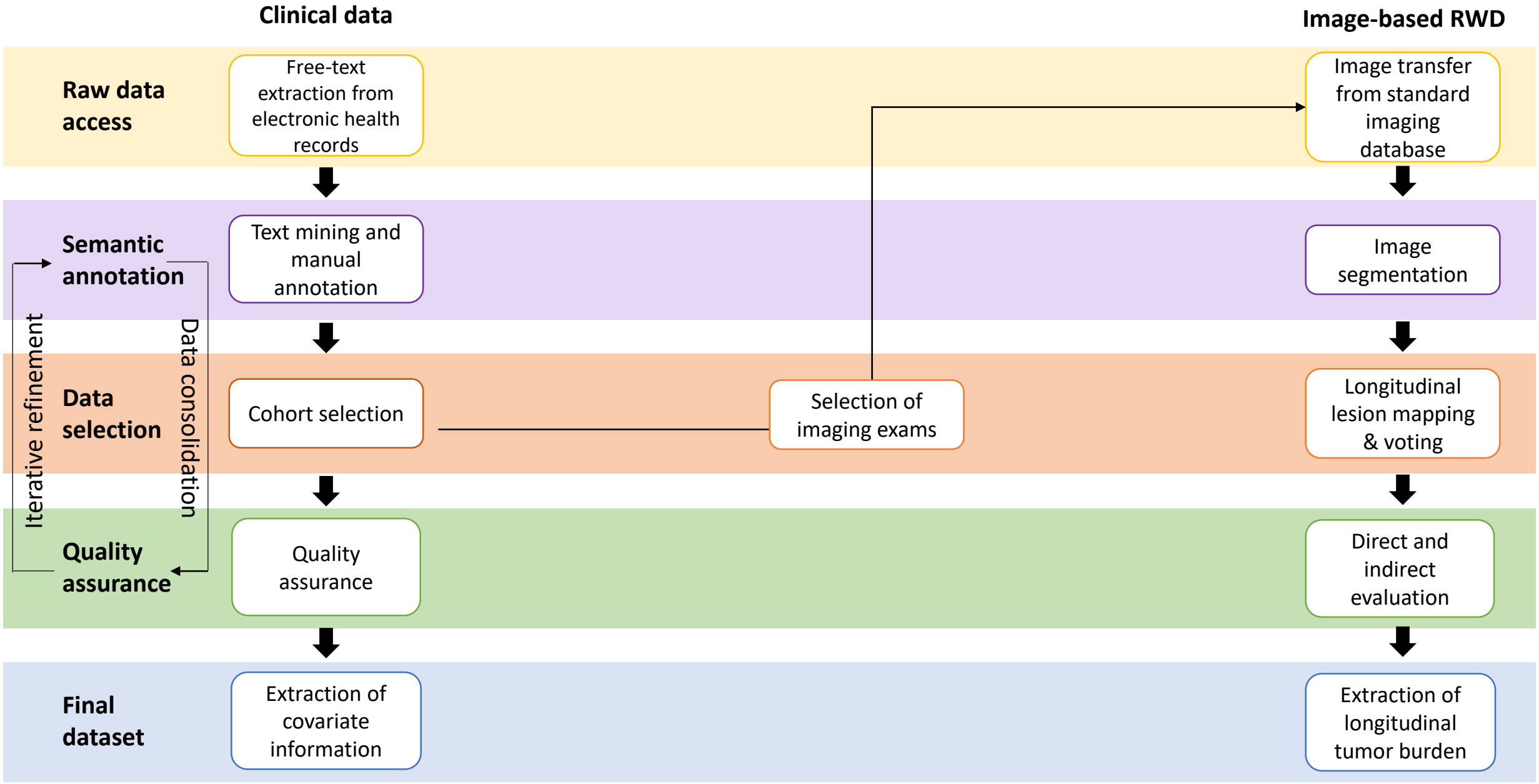
Example of patients workflow



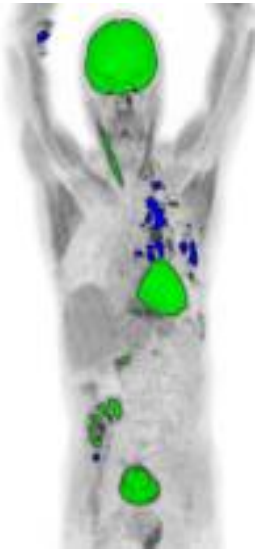
pembro_BEGIN: pembrolizumab initiation
pembro_END: last pembrolizumab administration

[1]Gatta R. 2017.

Images-related data were then retrieved and analyzed



PET/CT imaging data were segmented by employing Deep learning methods



3D-segmentations of metabolically active regions-of-interest (ROI)

benign

(physiologically expected)

malignant

(presence of metabolically active cancer cells)

- Artefacts (*e.g.* catheters)

- No lesions correspondence across time

Image-based RWD

Image transfer from standard imaging database

PARS[1,2] software

Image segmentation

Longitudinal lesion mapping & voting

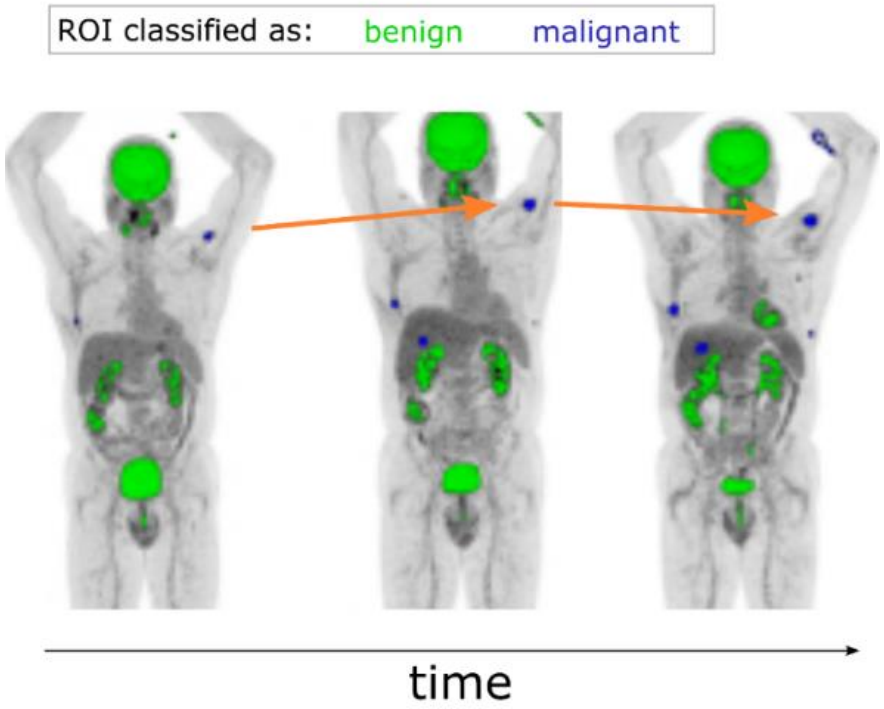
Direct and indirect evaluation

Extraction of longitudinal tumor burden

[1]Sibille L. 2020. [2]Capobianco N. 2021.

PARS: PET-Assisted Reporting System, Siemens Medical Solutions USA

Trajectories of individual tumor lesions were reconstructed through automated longitudinal mapping and majority voting of the status



- Same location → *same* tumor lesion
- Malignancy status assigned to the entire lesion trajectory

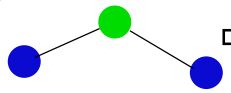


Image-based RWD

Image transfer from standard imaging database

Image segmentation

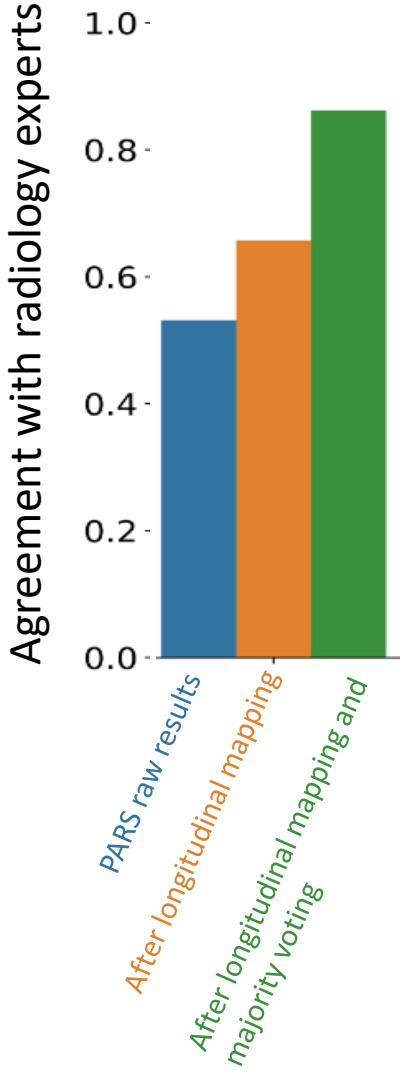
Corresponding lesions across time and classification

Longitudinal lesion mapping & voting

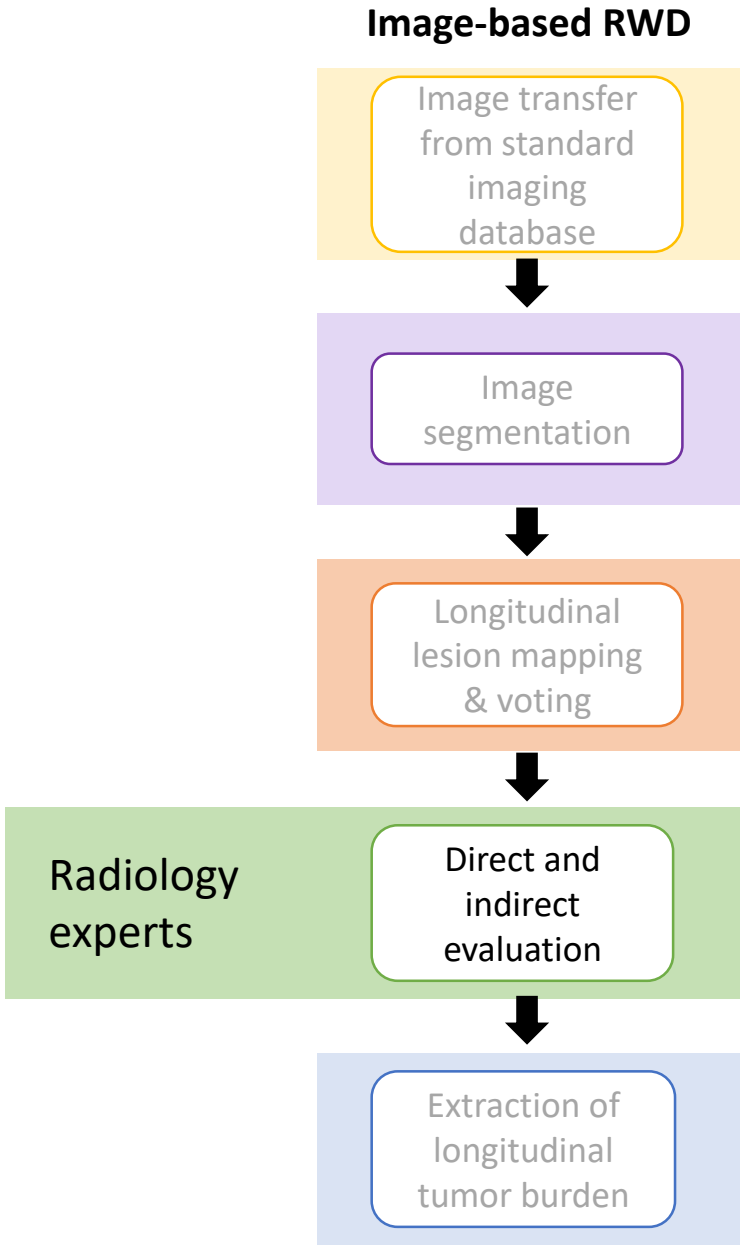
Direct and indirect evaluation

Extraction of longitudinal tumor burden

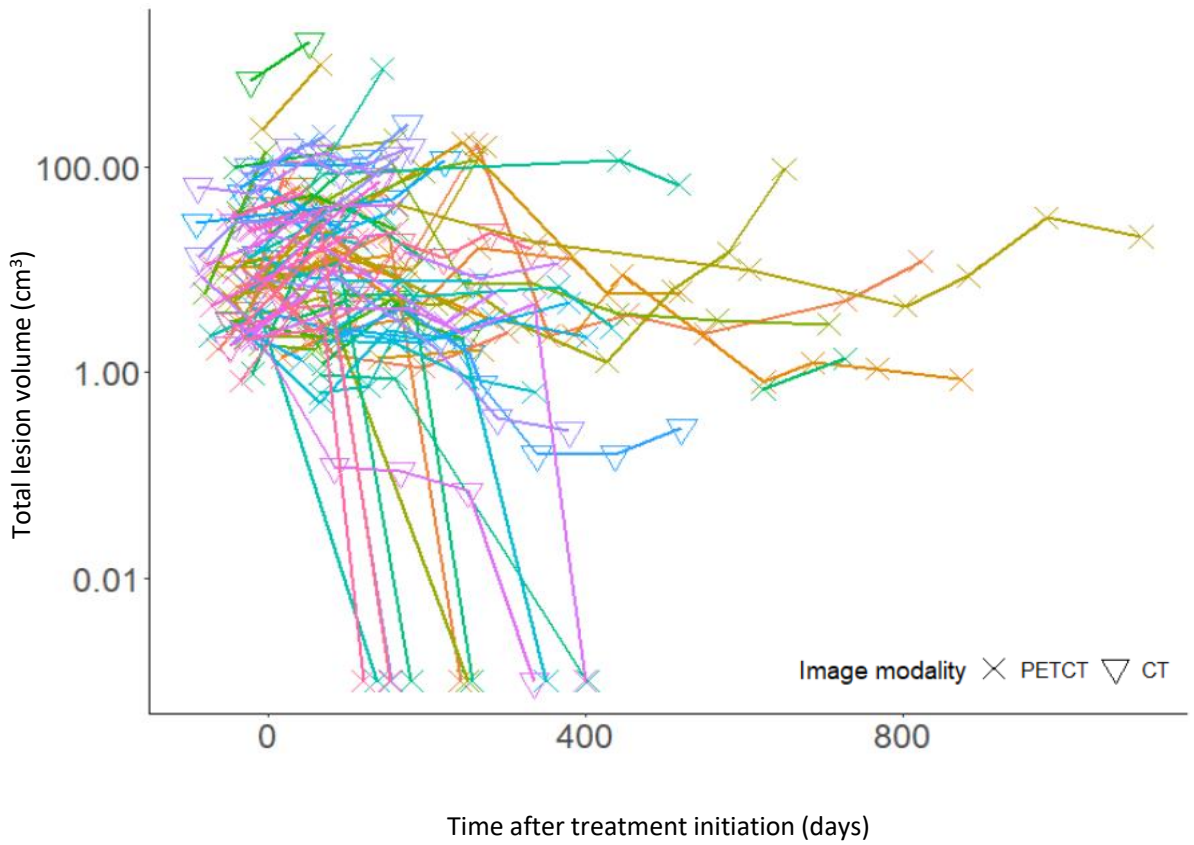
Our methods greatly improved data quality



Improvement in the consistency of image-derived data compared to isolated segmentation results.



Tumor profiles over time were derived from 91 melanoma patients receiving ICIs



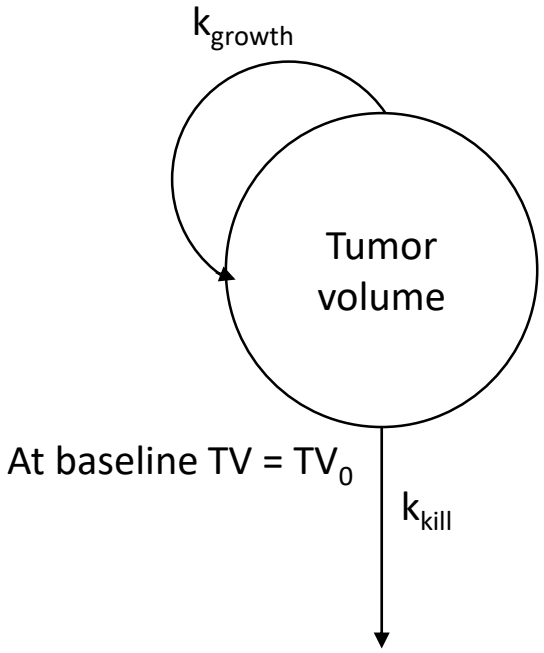
Treatments
- Ipilimumab
- Nivolumab
- Pembrolizumab

Image-based RWD

- Image transfer from standard imaging database
- Image segmentation
- Longitudinal lesion mapping & voting
- Direct and indirect evaluation

Real-world tumor dynamics ← Extraction of longitudinal tumor burden

A model describing longitudinal tumor volumes was developed by assessing different system- and treatment-related assumptions



Tumor growth model:
Exponential tumor growth with a rate constant retrieved from literature[1]

Treatment effect (no PK data):
- KPD model[2]
- Drug dose
- Treatment ON/OFF

Log-kill hypothesis:
- One killing rate/drug
- $k_{kill,nivolumab} = k_{kill,pembrolizumab}$[3]
- $k_{kill,nivolumab} = k_{kill,pembrolizumab} = k_{kill,ipilimumab}$

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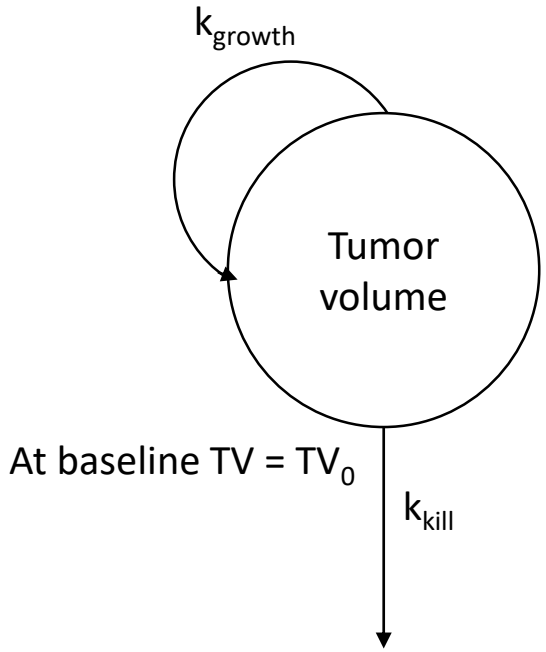

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- $k_{kill,nivolumab} = k_{kill,pembrolizumab} = k_{kill,ipilimumab}$ Principle of parsimony

OFF treatment: $dTV/dt = k_{growth} \times TV$
ON treatment: $dTV/dt = k_{growth} \times TV - k_{kill} \times TV$

Similar performances when comparing simple and more complex models (precision, BIC, GOF, VPCs) → Model simplification

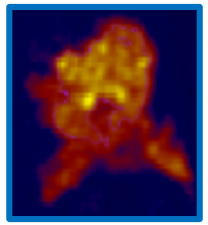
[1]Chatterjee MS. 2017. [2]Jacqmin P. 2007. [3]Fessas P. 2017.

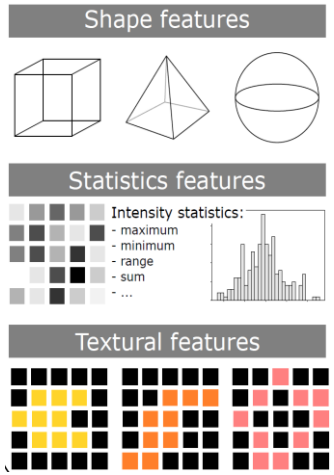
Multi-dimensional covariate assessment enabled by machine learning approaches

16 clinical covariates
(demographics, disease status, lab values, genomics)

Radiomics features

Quantitative description of imaging ROI





>100 features per lesion & timepoint

~230 features per patient

Standard PMX covariate assessment[1,2]

[1]Prague M. 2022. [2]Ayral G. 2021.

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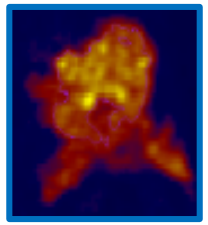

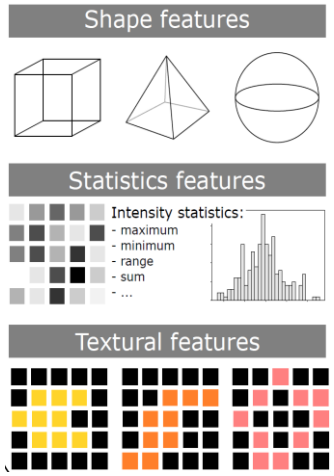

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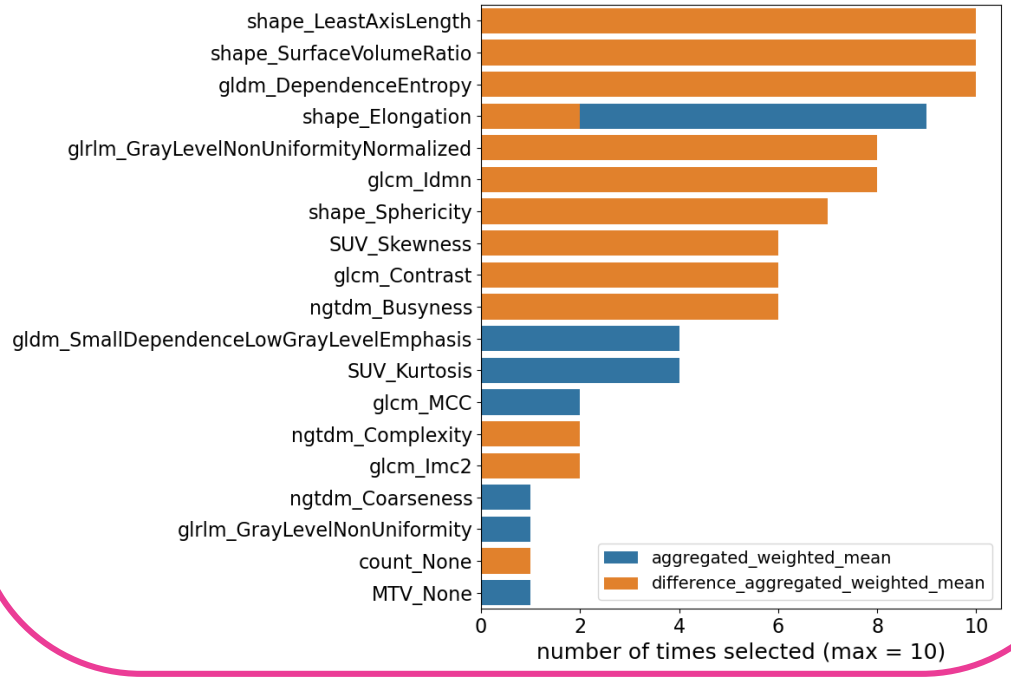
ML-based radiomics feature pre-selection[3]

Example for tumor growth rate constant

baseline

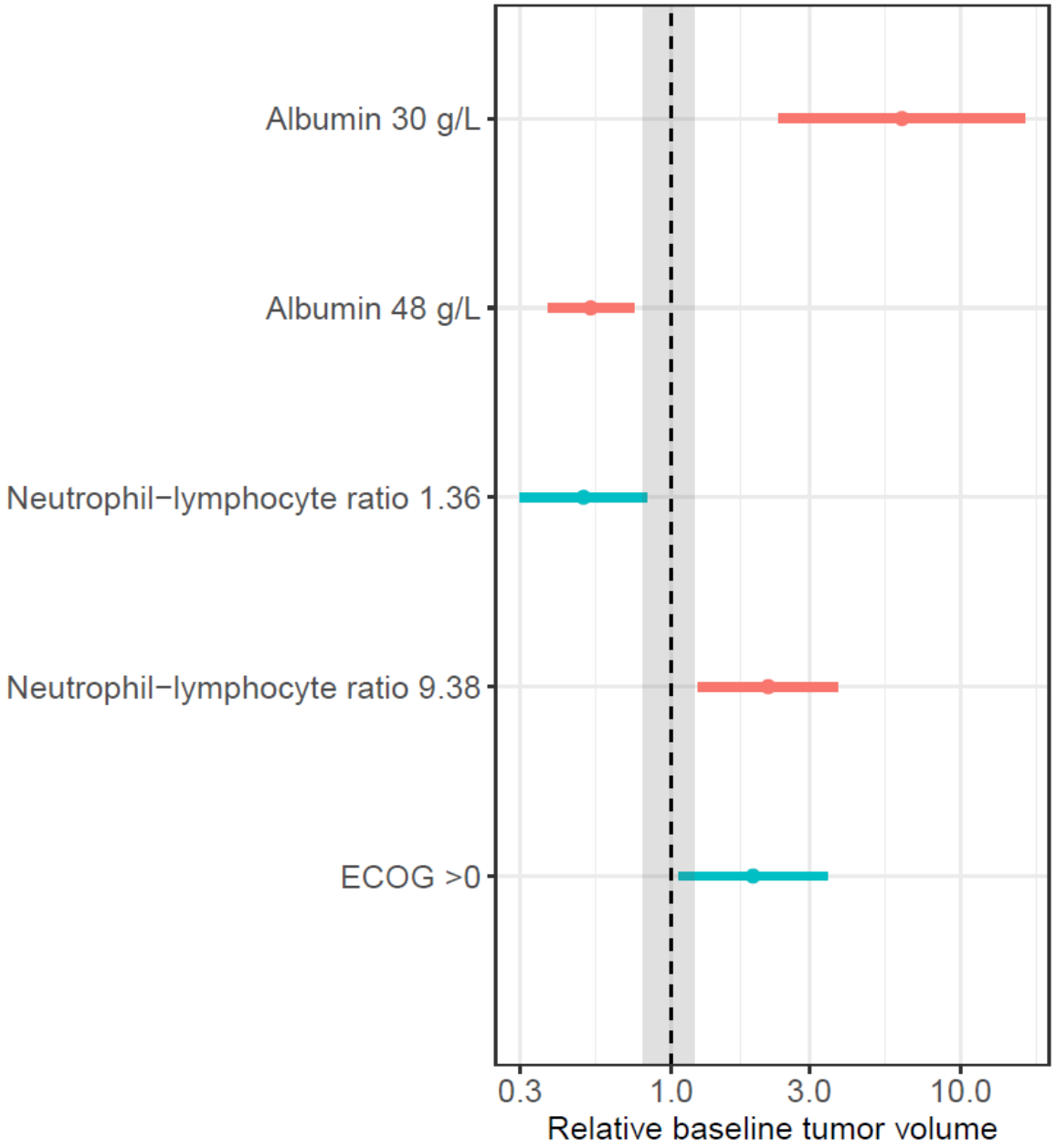
1st follow-up - baseline



Standard PMX covariate assessment[1,2]

[1]Prague M. 2022. [2]Ayral G. 2021. [3]Terranova N. 2021.

Clinically relevant covariate effects were identified on baseline tumor volume



Influence of factors related to cachexia, inflammation and advanced disease identified on TV_0

24% of variability on TV_0 explained by covariates

Potential effect of NRAS mutation on k_{growth}

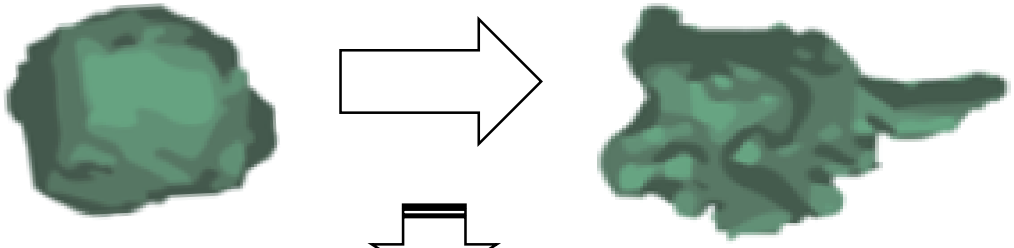
Some radiomics features were significantly associated with model parameters

k_{growth}

Delta Shape Elongation

Baseline image

1^{st} follow-up image

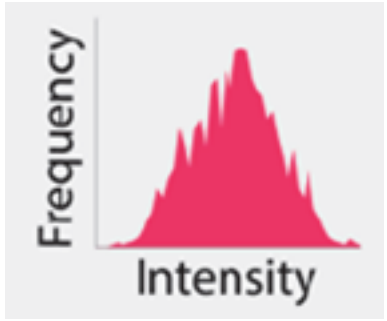


Higher k_{growth}

TV_0

Gray Level Non Uniformity

Homogeneity



Lower TV_0

Preliminary results (38 patients)

Multiple imputation

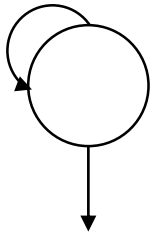
Clinical relevance

Conclusion: Real-world tumor dynamics data collected using our newly developed semi-automated pipeline were successfully described by a TGI model

Semi automated pipeline

Data quality supports population-based analyses

Easily applicable to other cancer subtypes and therapies



Modeling and multi-dimensional covariates

Tumor dynamics successfully described in our RW population

Identification of sources of variability

Multi-dimensional analysis of clinical and image-based RWD has the potential to advance precision oncology towards more individualized treatment solutions

Acknowledgments

Clinical Research Data Warehouse
Precision Oncology Centre
Department of Nuclear Medicine and Molecular Imaging
Department of Diagnostic and Interventional Radiology

Lisa Benincosa , Translational Medicine
Karthik Venkatakrishnan , Quantitative Pharmacology

Federico Amato, Swiss Data Science Centre

Siemens team

Thank you for your attention!