



Universität Augsburg  
Fakultät für Angewandte  
Informatik

# Towards a Modular Knowledge and Data Driven Molecular Tumor Board (MoMoTuBo)

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# Agenda

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**1** Introduction and Definition of an MTB

**2** Digitalization of MTBs

**3** Junior Research Group MoMoTuBo

**4** Workflow and Future Plans



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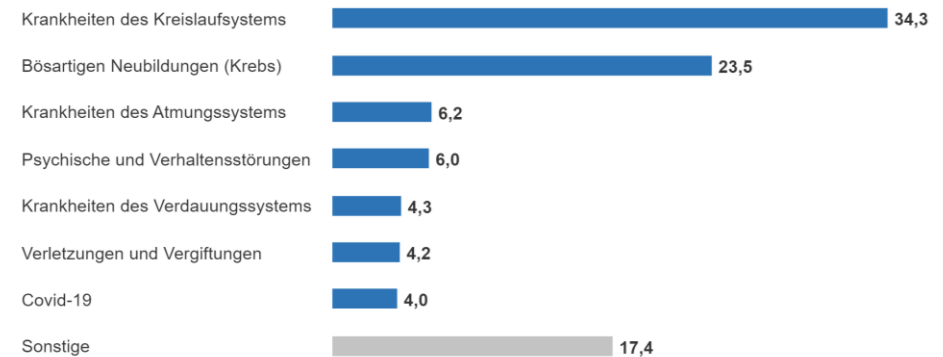
# Introduction

## Motivation

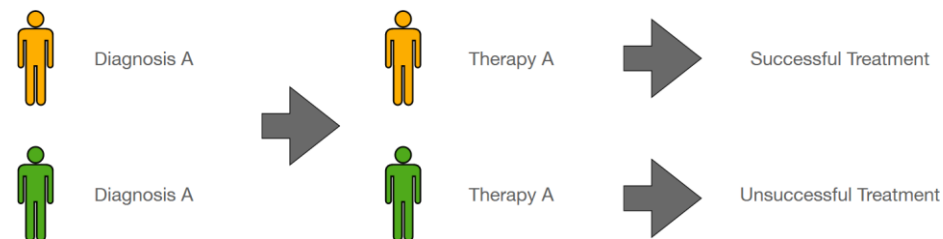
- **Cancer:**
  - one of the most common causes of death in Germany and worldwide
  - high numbers of cancer patients → improving the treatment of cancer is becoming increasingly relevant
  - better understanding tumor biology, disease etiology, risk stratification, and pathways to novel treatments
- **Problem:** the task of matching tumor alterations with approved or experimental therapies depends on the expertise of individual centers or clinics
- **Solution:** MTBs to facilitate the decision-making process

Todesursachen nach Krankheitsarten 2020

in %



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# Definition of an MTB

## What is an MTB?

- Meeting of experts from various clinical fields to collectively discuss challenging, individual cancer patient cases
- Individuals with wide-range expertise (e.g. molecular pathologists, genetic counselors, pharmacists, oncologists etc.)
- Assist in providing accurate and timely clinical interpretations of complex genomic results for each patient within an institutional or hospital network
- Recommendations derived from multidisciplinary discussions
  - Specific molecular modifications
  - Features of a patient (Performance, Status, Comorbidities)
  - Written reports including patient identification, report content, and interpretation of results



# Definition of an MTB

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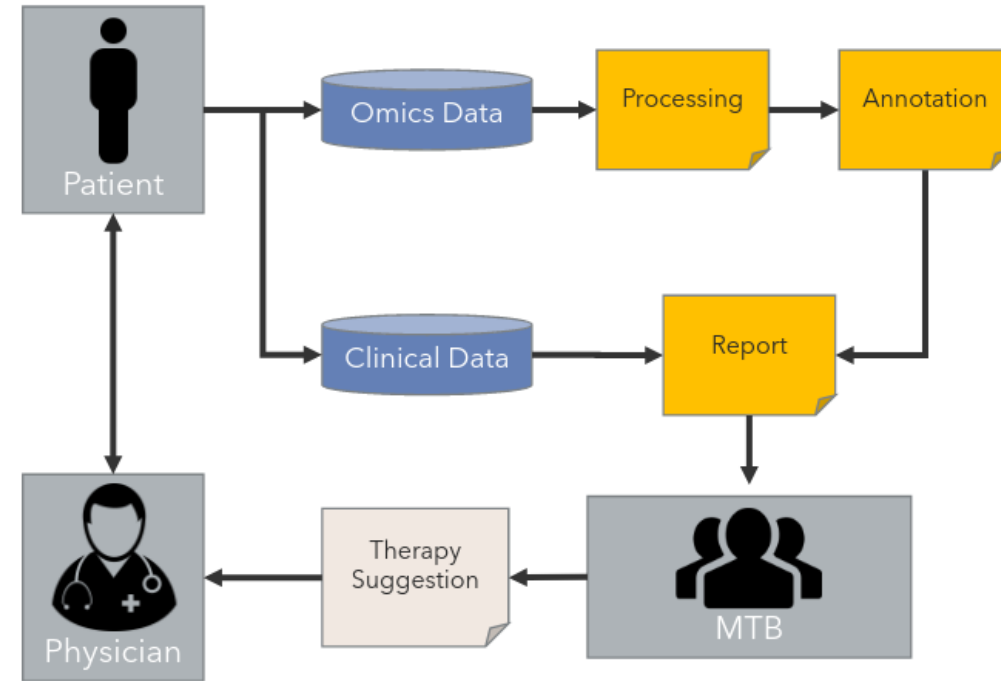
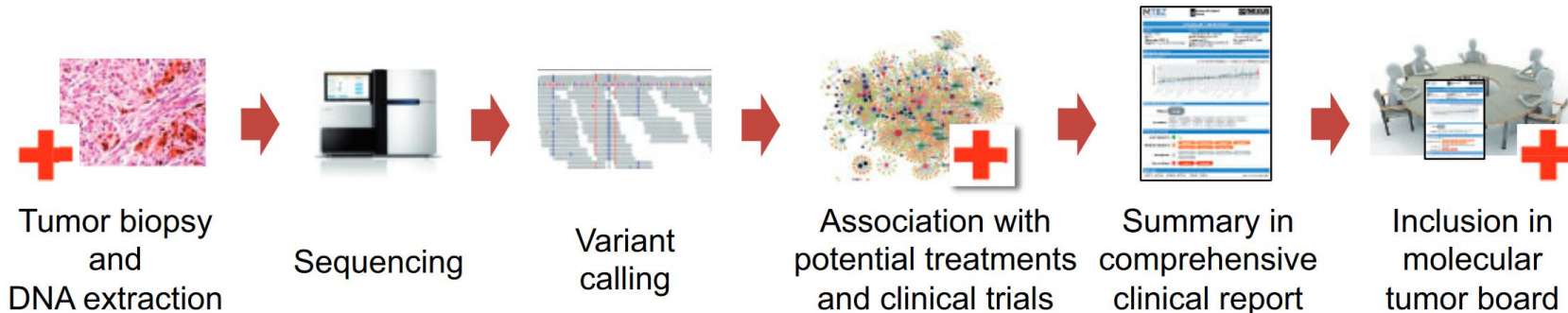
## Goals of an MTB

- Identify all potential therapeutic strategies based on genetic analysis for patients who do not respond to standard-of-care systemic therapies
- Recognition of molecular drivers of carcinogenesis & identification of actionable therapeutic targets from somatic variants of the respective tumor
- Educational tool in teaching hospitals/university clinics
- Clarification of conflicting interpretations of clinical variants
- Use of molecular data (genome, transcriptome), suggest novel therapeutic options, derived from multidisciplinary discussions

# Definition of an MTB

## MTB Workflow

- Wide range of methods and techniques in the field of genomics to identify characteristic modifications in cancer
  - Targeted multigene NGS
  - Whole exome and RNA sequencing
  - Array comparative genomic hybridization
  - Whole-genome sequencing
  - mRNA



# Definition of an MTB

## Examples of MTBs in Germany

- Interd. TC weekly
  - DKTK / TREAT-20+ / CCC Charité
- 14 interd. TC weekly
  - Advanced and rare Tumors
  - UMG / MHH / AOK
- 16 interd. TC weekly
  - Complex findings, rare tumors or unusual clinical courses
  - Panel or exome sequencing
  - UCT Precision Oncology Program
  - OncoNeT Rhein Main
- Interd. TC weekly
  - State-of-the-art molecular pathology methods
  - Off-label application procedure
- 22 interd. TC weekly
  - Guideline therapy not effective
  - Off-label recommendations
  - 53% patients with recommendations
- Interd. TC weekly
  - Next-generation sequencing
  - UKA / CCCA, 29 Clinics and Institutes







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# Digitalization of MTBs

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## Digital MTB Platforms

- Online forum for collaborative governance, provenance, and information sharing among experts outside a hospital or hospital network
- Results of molecular analyses for potential biomarkers and ranking of biomarkers using pre-defined levels of evidence
- Integration of publicly available databases and establishment of an internal database

# Digitalization of MTBs

## MTB Knowledgebases

Resource Name	Primary Institute	VICC Member <sup>a</sup>	Cancer Focused <sup>b</sup>	Therapeutic Evidence	Predisposing Evidence	Diagnostic Evidence	Prognostic Evidence	Variant Emphasis	Data Access	Web Address
BRCA Exchange	GA4GH	X	X		X			Germline	Free	<a href="http://brcaexchange.org/">http://brcaexchange.org/</a>
CanDL	Ohio State University/ James Cancer Hospital	X	X	X				Somatic	Free	<a href="https://candl.osu.edu/">https://candl.osu.edu/</a>
CGI	Institute for Research in Biomedicine, Barcelona, Spain	X	X	X				Somatic	Free for noncommercial/ research use	<a href="https://www.cancergenomeinterpreter.org/home">https://www.cancergenomeinterpreter.org/home</a>
ClinGen Knowledge Base	ClinGen				X			Germline	Free	<a href="https://www.clinicalgenome.org/resources-tools/">https://www.clinicalgenome.org/resources-tools/</a>
CIVIC	Washington University School of Medicine	X	X	X	X	X	X	Majority somatic	Free	<a href="https://civicdb.org">https://civicdb.org</a>
ClinVar	National Center for Biotechnology Information			X	X			All variants	Free	<a href="http://www.ncbi.nlm.nih.gov/clinvar/">http://www.ncbi.nlm.nih.gov/clinvar/</a>
COSMIC Drug Resistance Curation	Wellcome Trust Sanger Institute		X	X				Somatic	Free for noncommercial/ research use	<a href="http://cancer.sanger.ac.uk/cosmic/drug_resistance">http://cancer.sanger.ac.uk/cosmic/drug_resistance</a>
Gene Drug Knowledge Database	Synapse	X	X	X		X	X	Somatic	Free	<a href="https://www.synapse.org/#!/Synapse:syn2370773/wiki/62707">https://www.synapse.org/#!/Synapse:syn2370773/wiki/62707</a>
JAX CKB	The Jackson Laboratory	X	X	X	X	X	X	Somatic	Partial content free for noncommercial/ research use	<a href="https://ckb.jax.org/">https://ckb.jax.org/</a>
My Cancer Genome	Vanderbilt University		X	X		X	X	Somatic	Free for noncommercial/ research use	<a href="https://www.mycancergenome.org/">https://www.mycancergenome.org/</a>
OncoKB	Memorial Sloan Kettering Cancer Center	X	X	X				Somatic	Free for noncommercial/ research use	<a href="http://oncokb.org/">http://oncokb.org/</a>
Personalized Cancer Therapy Database	The University of Texas MD Anderson Cancer Center		X	X	X	X	X	Somatic	Free for noncommercial/ research use	<a href="https://pct.mdanderson.org/#/home">https://pct.mdanderson.org/#/home</a>
PharmGKB	Stanford University			X				Germline	Free	<a href="https://www.pharmgkb.org/">https://www.pharmgkb.org/</a>
PMKB	Weill Cornell Medical College	X	X	X	X	X	X	Somatic	Free	<a href="https://pmkb.weill.cornell.edu/">https://pmkb.weill.cornell.edu/</a>
HGMD	Institute of Medical Genetics in Cardiff				X			Germline	Partial content free for noncommercial/ research use	<a href="http://www.hgmd.cf.ac.uk">http://www.hgmd.cf.ac.uk</a>

Abbreviation: CanDL, Cancer Driver Log; CGI, Cancer Genome Interpreter; CIVIC, Clinical Interpretation of Variants in Cancer; CKB, JAX Clinical Knowledgebase; COSMIC, Catalogue of Somatic Mutations in Cancer; GA4GH, Global Alliance for Genomics and Health; HGMD, The Human Gene Mutation Database; PharmGKB, Pharmacogenomics Knowledgebase; PMKB, Precision Medicine Knowledgebase; VICC, Variant Interpretation for Cancer Consortium.

<sup>a</sup>VICC members are collaborating knowledgebases in the design and analysis of standards for representing interpretation knowledge.

<sup>b</sup>Cancer focused indicates that the knowledgebase primarily or exclusively describes interpretations of cancers.



Shruti Rao, Beth Pitel, Alex H. Wagner, Simina M. Boca, Matthew McCoy, Ian King, Samir Gupta, Ben Ho Park, Jeremy L. Warner, James Chen, Peter K. Rogan, Debyani Chakravarty, Malachi Griffith, Obi L. Griffith, and Subha Madhavan  
 JCO Clinical Cancer Informatics 2020 :4, 602-613

# Digitalization of MTBs

## Existing Software Solutions



Available as an Open-Source-Software

- Offers functions like data integration, analysis and visualization.
- Integrates data from various fields, including genomics, transcriptomics and proteomics
- Offers an intuitive user interface that enables fast and efficient data analysis



Connects data from different sources in a central platform

- Integrates data from various fields, including genomics, transcriptomics and proteomics and clinical data.
- Offers functions like data identification, integration, analysis and administration.
- Enables fast and efficient analysis of big data sets.



# Digitalization of MTBs

## Existing Software Solutions



### MTB Report

A tool to support the decision making in an MTB

- Comparison of biomarkers and other patient omics data with a variety of available databases.
- Genomic input data is matched with databases specialized in biomarkers for cancer prediction.
- MTB most relevant results in the form of a summary report
- Various tabular data formats supported (TXT, CSV, XLSX)



### Molecular Tumor Board Portal

Public MTBP analysis pipeline

- Usage of a combination of internal and publicly available resources to annotate variants.
- Functional analysis: sources of evidence (variants with well-reported effects, biological assumptions, and computational metrics)
- Predictive analysis: specific knowledge bases for curating cancer biomarkers (diagnosis, prognosis, and drug response)

# Digitalization of MTBs

## Existing Software Solutions



### Free open-source solution

- Integration of data from multiple sources, including reference genomes and genome databases
- Possibility of more complete analysis
- Adaptability by researchers to meet individual needs



### Annotation of tumor alterations on different evidence levels

- Freely available via an API or a Web-Interface
- Identification of tumor alterations driving diseases which may be actionable
- Inventory from special resources with 5314 validated mutations, including cancer-predisposing variants
- Interpretation of cancer genomes to recognise tumor alterations

# Digitalization of MTBs

## Existing Software Solutions

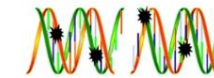


### Personal Cancer Genome Reporter

Standalone open-source software package for the annotation of somatic variants

- Integration of a comprehensive set of knowledge resources on tumor biology and therapeutic biomarkers, both at the gene and variant levels
- Extension of basic variant annotations from the Variant Effect Predictor (VEP) to include oncologically relevant annotations
- Creation of a multi-level report to support interpretation of individual cancer genomes in a clinical setting
- Creation of interactive HTML reports intended for clinical implementation

### CancerVar



Precise analysis of cancer variants

- Identification and classification of genetic alterations in cancer cells using advanced statistical methods and machine learning
- Better diagnosis, treatment and personalized therapeutic approaches for cancer patients
- Delivery of full details of variants through the web server (all automatically generated criteria, most supporting evidence, and predictive scores for clinical significance)
- Ability to manually adjust criteria and reinterpret based on prior knowledge or experience



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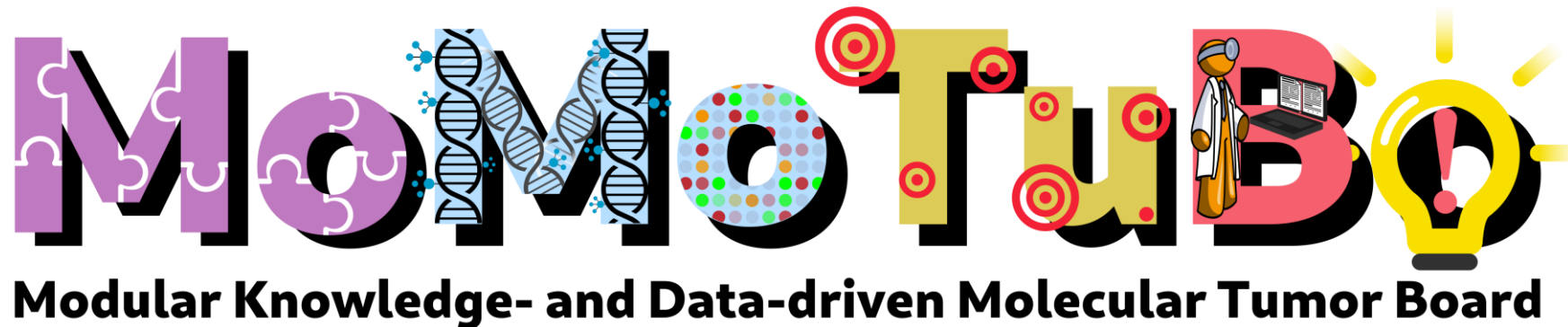


# MoMoTuBo



## Introduction

- **Modular Knowledge and Data-driven Molecular Tumor Board**
- A junior group (2021 – present) of the DIFUTURE Consortium
- Fields: Bioinformatics and Medical informatics



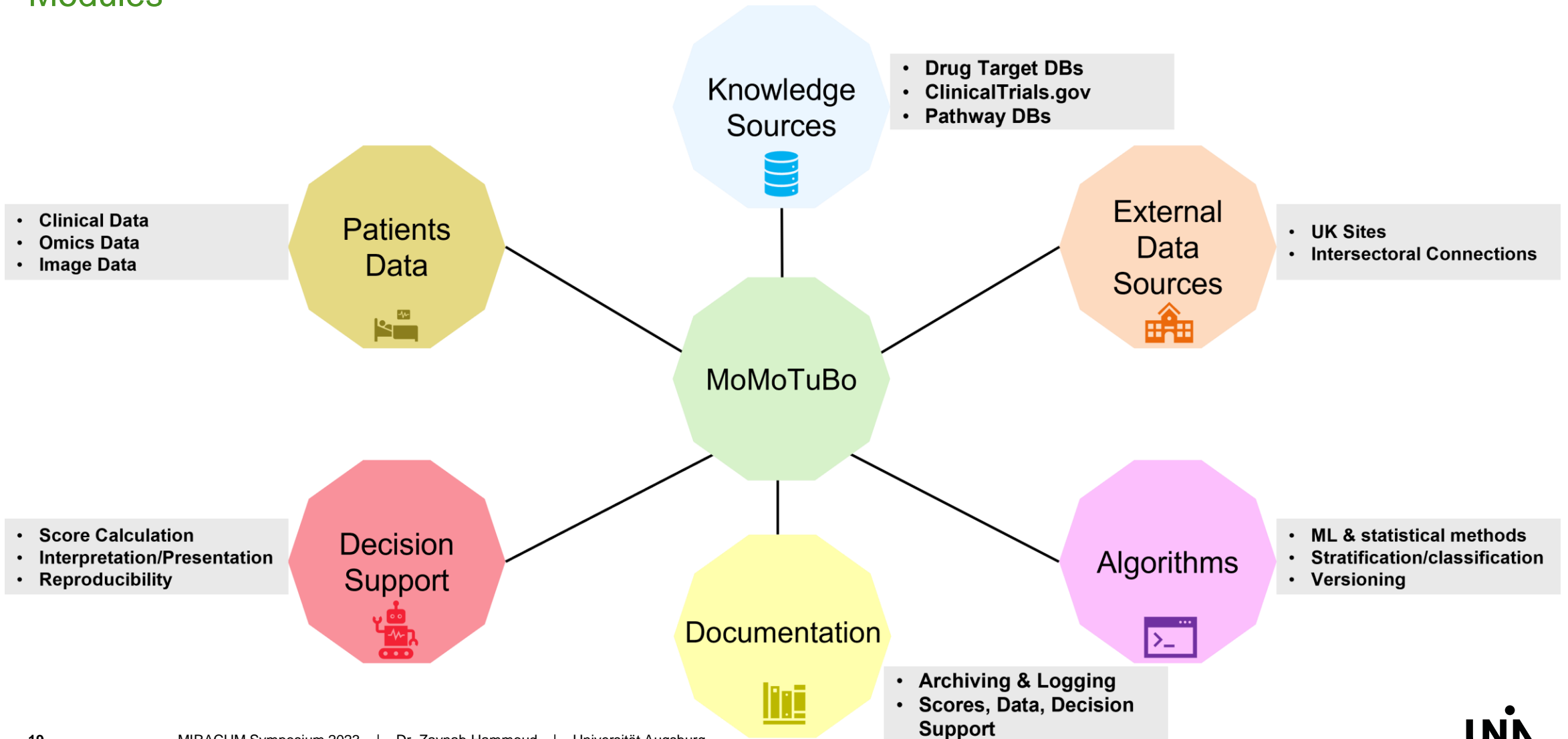


# MoMoTuBo

## Goals

- Conceptualization of a modular MTB
  - Reproducibility, documentation and update mechanisms along the process
- A concept for the connection to the systems of clinical routine and research data
- An improvement and (partial) automation of data integration and comprehensive reprocessing involving external knowledge
- The development of machine learning methods for learning from similar cases (patients like me)
  - Usage of unstructured knowledge (doctors' reports, publications)
  - Complex signatures, if applicable, across multiple levels of data that can predict treatment response or resistance to treatment.
  - the realization of \*continuous learning\* in clinical practice
- Implementation of a prototype and an open-source software for a modular platform to support MTBs

## Modules





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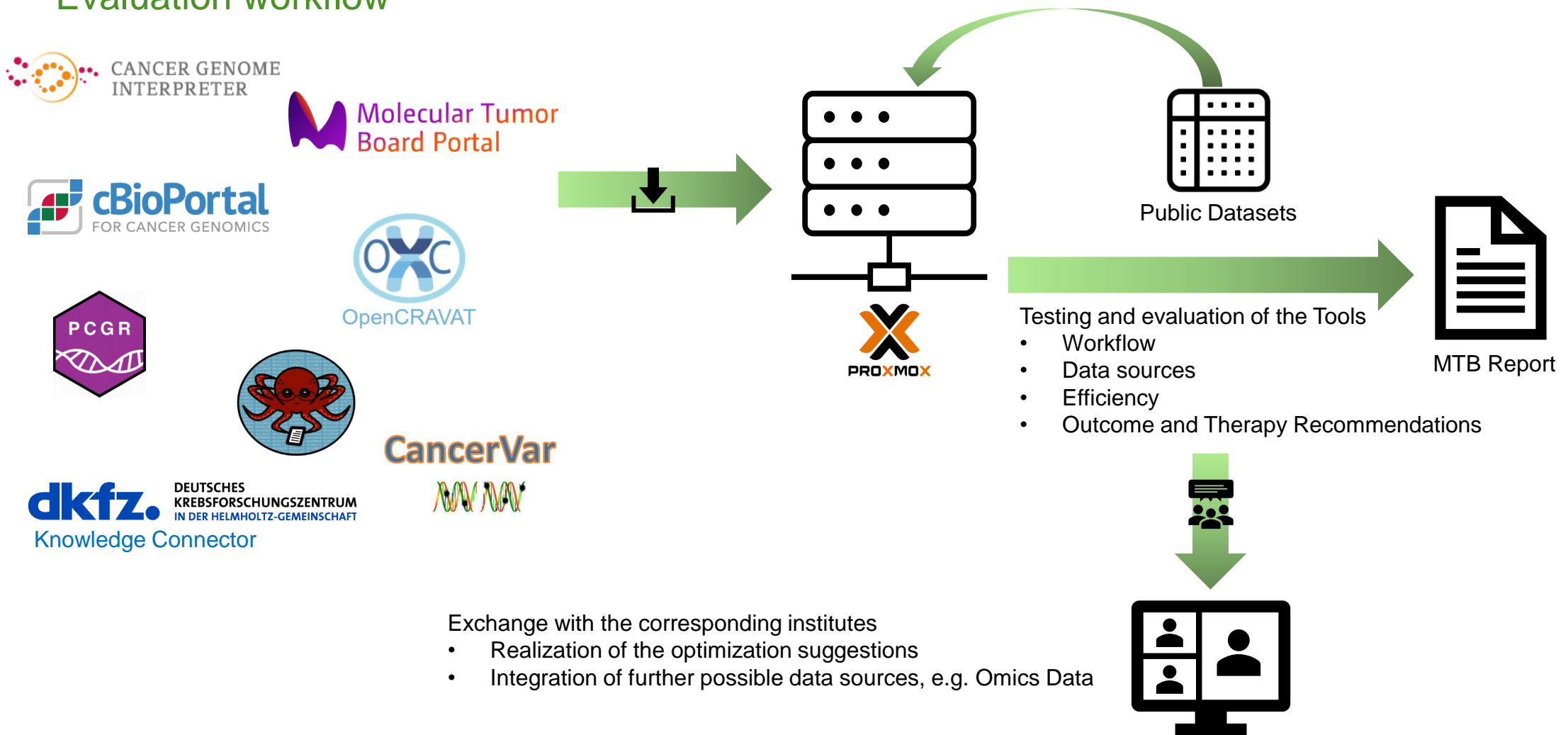
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# Workflow and Future Plans

## Evaluation workflow





# Workflow and Future Plans

## Conclusion

- MTB: Identify potential therapeutic strategies based on genetic analysis for patients who do not respond to standard systematic therapies
- Goals of the Digitalization:
  - better knowledge management
  - better analysis infrastrukture
  - better communication
- Existing Tools:
  - Different implementation and structure
  - Different workflows
  - Research software rather than a productive solution
- MoMoTuBo: Essential is the Conceptualization:
  - How are MTBs structured?
  - What are the software requirements?
  - How to take reproducibility and change management into consideration?

Thank you for your attention !!



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