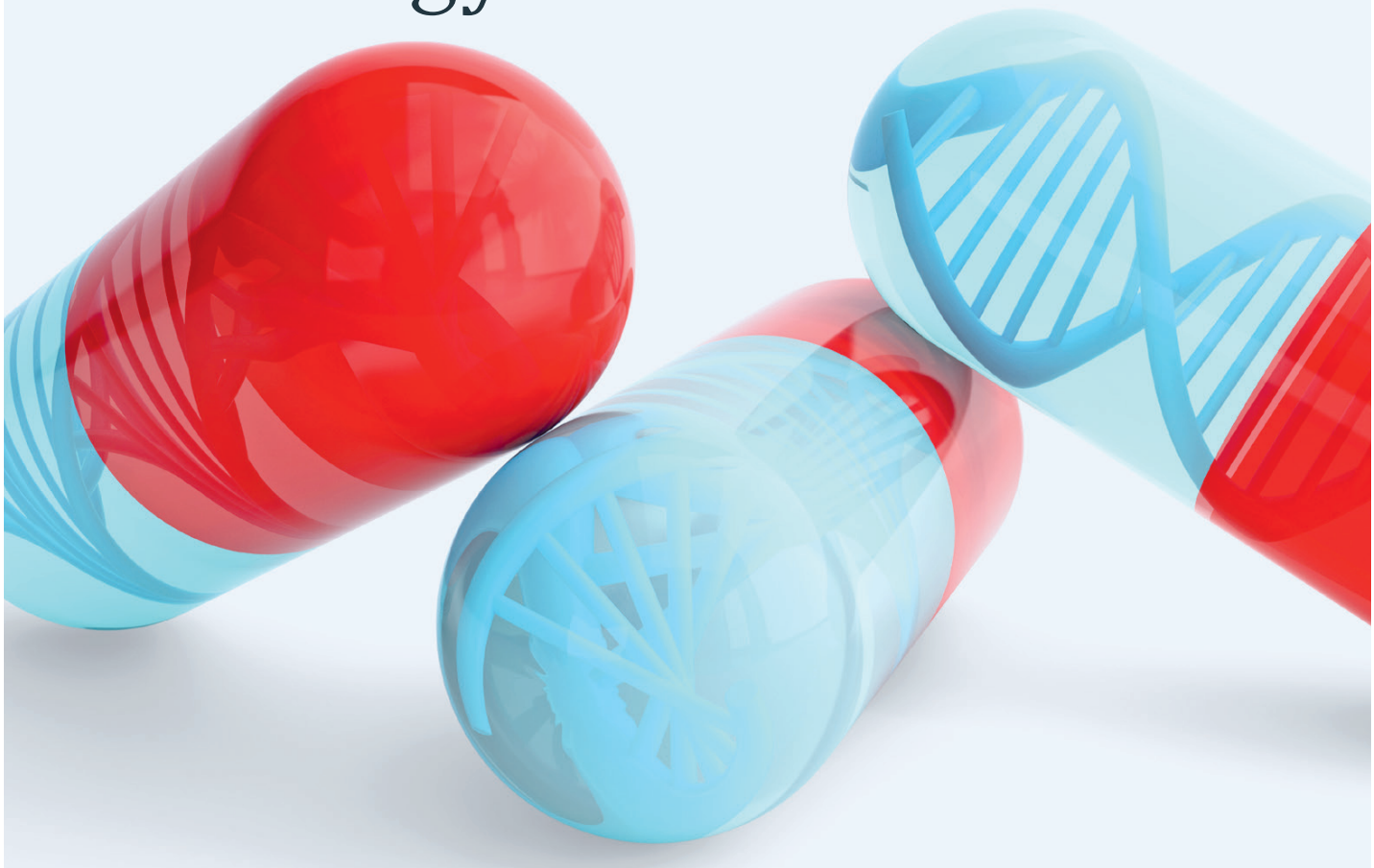
University of Basel

Faculty of Medicine

Certificate of Advanced Studies in Personalized Molecular Oncology



Universitätsspital Basel

SIB

CHUV

ADVANCED STUDIES

Detailed module program

Edition 3: 2021-2022

Document version 2 – 15 March 2021

CAS Personalized Molecular Oncology | 10 ECTS | Duration: approx. 10 months		
	Module title	Module coordination
Module 1	Tumor biology and genetics	CHUV Cancer Genetic
Module 2	Molecular pathology	USB Pathology
Module 3	Clinical bioinformatics	SIB Clinical Bioinformatics
Module 4	Clinical oncology	USB Oncology
Mini-thesis	Planned in small groups	Program Board

Module 1
Tumor biology & genetics

Dates

- 5, 6; 19, 20 November 2021 (28h presential teaching).

Location

- Lausanne, CHUV University Hospital.

Main topics

- Basic cytogenetics and molecular genetics
- Hereditary vs. acquired genetics
- Genetic recombination, DNA damage and repair
- Solid tumors and hematological malignancies
- Genetic predisposition to cancer
- Diagnostic genetic testing
- Tumor cell proliferation
- Clonal evolution & tumor heterogeneity

Learning objectives for participants

- Describe the mechanisms yielding to genetic variation, and be familiar with the various types of genetic variants.
- Distinguish hereditary genetic anomalies from acquired genetic anomalies.
- Discuss the advantages and limitations of different genetic laboratory methodologies for diagnostic testing.
- Demonstrate how to interpret non-hotspot mutations using public databases and taking into account overall genomic aberrations and clonal evolution.
- Be aware of ethical implications of incidental genetic findings.

Prerequisites to attend the module

- Basic notions of biology.

Module coordinator

- Prof. Jacqueline Schoumans (CHUV)

Course format

- Lectures, exercises, group discussions and lab visit.

Day 1 – Cell biology and tumor genetics focusing on hematological malignancies

- [0h45] Welcome
  - Introduction to the CAS (Dr Aitana Lebrand, SIB)
  - Introduction to module 1 (Prof. Jacqueline Schoumans, CHUV)
    - All participants introduce themselves and their background
    - Brief introduction of clinical utility of somatic genetic testing with overview of organization of laboratories performing genetic testing at the CHUV

- [0h45] From DNA to proteins (Dr Fabienne Marcelli & Ilaria Scarpelli, CHUV)
  - DNA structure: chromosomes, nucleotides, genes, introns, exons, regulatory elements
  - From DNA to proteins: transcription, translation, post-translational modifications
  - Roles of proteins in cells (regulatory/signaling networks), importance of 3D structure

- [1h] Introduction to hematological neoplasia (Dr Sabine Blum, CHUV)

- [1h15] Precision medicine in hematological malignancies (Dr Sabine Blum, CHUV)
  - History of first targeted therapy (precision medicine) in chronic myeloid leukemia (CML)
  - Development of Tyrosine kinase inhibitors (TKI)
  - Acquired resistant mutations
  - Monitoring of treatment response by Minimal Residual Disease measurements (MRD)

- [1h15] Clonal evolution and tumor heterogeneity in hematological neoplasia (Dr Joop Jansen, Radboud UMC, The Netherlands)
  - Clonal evolution in myeloid leukemia
  - Clonal hematopoiesis of indeterminate potential (CHIP) mutations
  - Genomic profiling & treatment decision

- [2h] Usefulness of cytogenetics in hematological neoplasia (Dr Valerie Parlier, CHUV)
  - Confirmation and WHO classification of disease
  - Prognostication with scoring systems and risk stratification
  - Interactive interpretive exercises with chromosome anomalies

Day 2 – Diagnostic applications of tumor genetics focusing on hematological malignancies

- [2h] Tumor genetics in the lab (Prof Jacqueline Schoumans, CHUV)
    - Hereditary cancer genetics vs. acquired genetics
    - Meiosis, mitosis, genetic mechanisms (e.g DNA repair, homologous recombination, double hit chromothripsis)
    - Solid tumor vs. hematology
    - Brief overview of laboratory technologies and their capabilities and limitations for detecting genetic aberrations in cancer such as insertions, inversions, translocations, fusions, copy number variants, polyploidy, mutations.
    - Testing strategies and interpretation of results in a diagnostic setting
    - Incidental findings

- [1h30] Practical exercises concerning genetic testing strategies and interpretation of results will be solved in small groups and discussed at the end of the session in the entire group (Prof. Jacqueline Schoumans, CHUV).

- [3h] Practical demonstration of genetic methodologies and automation at the oncogenomic hematology laboratory, CHUV (demo organized by Isabel Pinto, Christina Botoucharova, Sandrine Bougeon & Anne-Laure Chanson, CHUV)
    - Conventional karyotyping
    - FISH
    - SNP-array
    - NGS gene panels and complementary molecular tests

- [0h45] Questions & Answers, wrap-up of the day

Day 3 – Tumor biology and hereditary genetics

- [1h30] Tumor biology of solid tumors (Dr Nicolo Riggi, CHUV)
    - Stem cell, microenvironment angiogenesis, inflammation

- [1h15] Epigenetics in tumors (Dr Nicolo Riggi, CHUV)

- [2h] Hereditary cancer in adults (Dr Benno Rothlisberger, Genetica AG)
    - Hereditary breast cancer, identification, genetic counseling, ethical aspects

- [2h30] Hereditary cancer in children (Dr Raffaele Renella, CHUV)
    - Predisposition to cancer by inherited genomic instability
    - Example of Fanconi anemia and acute myeloid leukemia
    -

Day 4 – Molecular onco-hematology

- [2h] Genetic modifications (Dr Fabienne Marcelli & Ilaria Scarpelli, CHUV)
    - Quick reminder of DNA to proteins
    - Definition of genomics (whole genome, whole exome, panel), transcriptomics, proteomics, metabolomics
    - Definitions of allele, genotype, haplotype, phenotype
    - Types of mutations: SNVs, SNPs, insertions, deletions,
    - Frequency of mutation in a tumor (VAF) and in population (MAF)
    - Effect of the mutations: synonymous, non-synonymous mutations; nonsense, missense mutations; frameshifts.
    - Impact of the mutations: variant of uncertain significance, benign variant vs. pathogenic prediction, variant databases

- [4h] Interactive workshop of genomic variant interpretation focusing on hematological malignancies (practical exercises performed individually and in small groups) (Drs Fabienne Marcelli & Ilaria Scarpelli, CHUV).

- [0h30] Introduction to Moodle and online exam system (Dr Aitana Lebrand, SIB)

Module 2
Molecular pathology

Dates

- 21, 22 January; 11, 12 February 2022 (28h presential teaching).

Location

- Basel, Basel University Hospital.

Main topics

- Sample classification and preparation
- Principles of nucleic acids extraction
- Sequencing platforms and setup
- Understanding gene panels
- Internal / external quality controls
- Laboratory accreditation
- Reporting clinically relevant genomic variants
- Interpreting a molecular profile

Learning objectives for participants

- Gain knowledge about the different types of specimens (e.g. tissue biopsy, cytology, resections, blood samples).
- Get an overview about the currently used technological platforms in molecular diagnostics (comparison with the research setting).
- Get familiar with all the steps that lead from sample collection to final molecular report generation along with all possible bottlenecks.
- Algorithms for appropriate gene panel selection.
- Understand the basics (procedures and rules) of an accredited clinical laboratory, including internal and external quality controls.
- Get familiar with the most common clinically relevant variants along with their interpretation and classification system.

Prerequisites to attend the module

- Module 1 or equivalent knowledge.

Module coordinators

- PD Dr. Christian Ruiz (USB), Dr. Salvatore Piscuoglio (USB), PD Dr. Matthias Matter (USB)

Course format

- Lectures, exercises, group discussions and lab visit.

Day 1 – General Introduction into Pathology and Molecular Pathology

- [0h30] Welcome and Introduction to the Institute of Pathology in Basel (PD Dr. Christian Ruiz, USB, Prof. Dr. Luigi Terracciano, USB)
- [0h30] Different types of samples and requirements for molecular analysis (PD Dr. Christian Ruiz, USB)
- [1h] Introduction into general pathology: general concepts of neoplasia (PD Dr. Matthias Matter, USB)
- [1h] Overview of the techniques used in molecular pathology (PD Dr. Matthias Matter, USB)
- [1h] Lab visits:
    - I: General pathology laboratory (30 min) (PD Dr. Christian Ruiz, USB, Prof. Dr. Alexandar Tzankov, USB)
    - II: Molecular pathology (30 min) (PD Dr. Michel Bihl, USB, Dr. Philip Jermann, USB)
- [0h45] Different types of biomarkers: diagnostic, prognostic and predictive (Prof. Dr. Luigi Terracciano, USB)
- [1h30] Practical/Hands-on microscope: real-life cases of clinical pathology (PD Dr. Matthias Matter, USB, Prof. Dr. Luigi Tornillo, GILAB AG)
- [0h30] Wrap up of the day, questions & answers

Day 2 – Intro into genomics; Tumor specific molecular pathology; Accreditation; Molecular Pathology: Analysis of different tumor types

- [1h] Introduction into Genomics & NGS (Dr. Philip Jermann, USB)
- [1h] NGS panels for genomic analyses, BRCAness, TMB, genomic biomarkers (Dr. Philip Jermann, USB)
- [0h45] Molecular Pathology of Soft Tissue Tumors (PD Dr. Sylvia Höller, USB)
- [0h45] Molecular Pathology of Breast Cancer (PD Dr. Simone Münst, USB)
- [0h45] Laboratory Accreditation (Prof. Dr. Alexandar Tzankov, USB)
- [0h45] Molecular Pathology of the Lung (PD Dr. Spasenija Savic, USB)
- [0h45] Molecular Pathology of Gastrointestinal Tumors (Prof. Dr. Nicola Normanno, Istituto Nazionale Tumori IRCCS, Italy)

- [1h] QC in Molecular Pathology (Prof. Dr. Nicola Normanno, Istituto Nazionale Tumori IRCCS, Italy)

- [0h45] Molecular Pathology of Urothelial Carcinomas (Dr. Tatjana Vlajnic, USB)

Day 3 – New cutting-edge Technologies in Molecular Pathology

- [1h] Advances in liquid biopsies (CTCs) (Prof. Dr. Nicola Aceto, DBM, University of Basel)

- [1h] Special Metabolomics (Prof. Dr. Theodor Alexandrov, EMBL, Heidelberg)

- [1h] Organoids for diagnostics (PD Dr. Marianna Kruithof-de-Julio, DBMR, University of Berne)

- [1h] Digital Pathology (Prof. Dr. Viktor Kölzer, University Hospital Zurich)

- [1h] Single cell sequencing (Dr. Guglielmo Roma, Novartis)

- [0h45] Methylome Analysis (Dr. Jürgen Hench, USB)

- [1h] Cell-Free DNA (Dr. Philip Jermann, USB)

Day 4 – Results, Data Interpretation, data usage, etc.

- [0h45] Guidelines for diagnostic reporting (PD Dr. Matthias Matter, USB)

- [1h] How are variants classified? What is considered clinically significant? (Dr. Charlotte Ng, DBMR University of Berne, Dr. Salvatore Piscuoglio, USB)

- [1h] Computational Analysis (Dr. Charlotte Ng, DBMR University of Berne)

- [1h] Analysis of real-life cases using –omics technologies (Dr. Salvatore Piscuoglio, USB)

- [1h] Analysis of real-life diagnostics (Prof. Dr. Tom McKee, HUG)

- [0h45] Nanopore Sequencing (Dr. Jürgen Hench, USB)

- [1h] Data handling and IT regulations (Dr. Thierry Sengstag, University of Basel, sciCORE)

- [0h30] Wrap up of the day, questions & answers

Module 3
Clinical bioinformatics

Dates

- 18, 19 March; 1, 2 April 2022 (28h presential teaching).

Location

- Lausanne, University of Lausanne.

Main topics

- Data pre-processing
- Read mapping
- Variant calling
- Quality control
- Variant annotation
- Hardware, security, privacy
- Artificial intelligence (AI) basics
- AI current and future applications

Learning objectives for participants

- Communicate efficiently with bioinformaticians.
- Describe a bioinformatics analysis pipeline to call mutations from NGS data.
- Perform quality control at the run, read and variant levels.
- Use off-the-shelf bioinformatics tools to annotate and support the interpretation of variants.
- Consider hardware, security and privacy issues when managing omics data.
- Understand how artificial intelligence contributes to and will further impact personalized oncology.

Prerequisites to attend the module

- Modules 1 and 2, or equivalent knowledge.

Module coordinators

- Dr. Aitana Lebrand (SIB), Valérie Barbié (SIB)

Course format

- Lectures, hands-on, exercises and group discussions.

Day 1 – Somatic and germline variant calling

- [0h45] Introduction and general overview (Dr. Aitana Lebrand, SIB)
- [1h45] Pre-processing and quality control (Dr. Aitana Lebrand, SIB)
    - HANDS-ON: Reads pre-processing.
- [1h] Sequence alignment and read mapping (Dr. Aitana Lebrand, SIB)
- [1h30] Bioinformatics for RNA-seq (Dr. Geoffrey Fucile, Unibas)
    - Read counting and differential expression analysis, GO enrichment, pathway analysis
- [1h30] HANDS-ON: Exploring BAM files (Dr. Yann Christinat, HUG/SIB; Dr. Aitana Lebrand, SIB)
- [0h30] Sequencing depth, genome and gene coverage, variant frequency (Dr. Aitana Lebrand, SIB)
- [1h] Variant calling (Dr. Edoardo Missiaglia, CHUV)

Day 2 – Variant quality control and annotation

I. QC at the variant-level

- [0h30] Example case (Dr. Yann Christinat, HUG/SIB).
- [1h15] HANDS-ON: Technical artifacts (Dr. Yann Christinat, HUG/SIB)
- [0h30] Copy number variants (CNVs) and other structural variants (SVs) (Dr. Yann Christinat, HUG/SIB)
- [0h30] HANDS-ON on SVs in IGV (Dr. Yann Christinat, HUG/SIB)

II. Variant annotation

- [0h45] Effect and functional impact (Dr. Aitana Lebrand, SIB)
- [2h] HANDS-ON (Dr. Yann Christinat, HUG/SIB)
    - Genes, transcripts and HGVS nomenclature.
    - Spotting germline variants and assessing clonality.
    - Annotation using bioinformatics tools.
- [0h30] DISCUSSION: Beyond gene panels (Dr. Yann Christinat, HUG/SIB; Dr. Aitana Lebrand, SIB)

Day 3 – What next?

- [2h] Risks and probabilities for the interpretation of genetic results (PD Dr. Frédéric Schütz, UNIL/SIB)

- [2h30] Molecular modeling: predicting the impact of variants on proteins (Prof. Dr. Vincent Zoete, UNIL/CHUV/SIB)
    - HANDS-ON: Impact of mutations on proteins 3D structure

- [1h30] Computational Cancer Pharmacogenomics (Dr. Michael Menden, Helmholtz München)

- [1h30] Personalized cancer immunotherapy: predicting neo-epitopes (Prof. Dr. David Gfeller, UNIL/CHUV/SIB)

Day 4 – Artificial intelligence basics and applications in clinical bioinformatics

- [2h15] Introduction to image analysis (Dr. Andrew Janowczyk, CHUV/UNIL/SIB)
    - HANDS-ON: features extraction (manual and automated)

- [1h15] Machine learning basics (Dr. Aitana Lebrand, SIB)

- [1h15] HANDS-ON: predicting diagnosis from the extracted features (Dr. Andrew Janowczyk, CHUV/UNIL/SIB)

- [1h45] All you need is IT: a study case on all that's hidden (Florent Tassy & Valérie Barbié, SIB)
    - Computing and data storage – HPC, cloud.
    - Structuring data for sharing and re-use

Module 4
Clinical oncology

Dates

- 20, 21 May; 10, 11 June 2022 (28h presential teaching).

Location

- Basel, Basel University Hospital.

Main topics

- Tumor Physiology
- Tumor Immunology
- Cancer Statistics and Epidemiology
- Prognostic and Predictive Markers
- Targeted Therapies in Clinical Oncology
- Risks / probabilities for the interpretation of genetic results and counseling
- Clinical Trials in Molecular Oncology
- Molecular Tumor Board

Learning objectives for participants

- Describe main intracellular signaling pathways in solid tumors and molecular aberrations hampering this signaling.
- Get detailed knowledge of immunological mechanisms and how these may be used to optimize therapeutic approaches.
- Get a basic understanding of the principles underlying the design and analysis of clinical trials in oncology.
- Understand the importance of predictive markers in molecular oncology.
- Get familiar with the most frequent molecular aberrations in solid tumors and routinely used targeted therapies.
- Learn about genetic counseling and its implications for patients and families.

Prerequisites to attend the module

- Modules 1, 2, 3 or equivalent knowledge.

Module coordinators

- PD Dr. Dr. Sacha Rothschild (USB), PD Dr. Dr. Andreas Wicki (USZ)

Course format

- Lectures, exercises and group discussions.

Day 1 – Tumor Biology, Epidemiology and Basic Concepts of Cancer Therapy

- [1h] Welcome. Cancer statistics and epidemiology (PD Dr. Dr. Sacha Rothschild, USB)

- [1h] Familiar cancer, cancer genetics (Prof. Karl Heinimann, USB)

- [2h] Basic concepts of cancer therapy: (PD Dr. Dr. Sacha Rothschild, USB)
    - Surgery, radiation therapy, systemic therapy
    - Adjuvant, neoadjuvant, palliative
    - Markers for systemic therapy: prognostic, predictive
    - Definitions: OS, PFS, ORR, etc.

- [2h] Tumor biology: from molecular biology of cancer to targets for anti-cancer drugs (Dr. Nicola Miglino, KSBL)
    - What are the hallmarks of cancer (Weinstein/Hanahan)?
    - What hallmarks are druggable?
    - Clinical data for drugs targeting hallmarks of cancer
    - Clinical data for markers of benefit in targeted therapies
    - Mechanisms of resistance to targeted therapies

- [1h] Questions & Answers, wrap-up of the day

Day 2 – Tumor Immunology, Genomic Reports, Response Prediction

- [2h] Tumor immunology: how to get an immune response against cancer (PD Dr. Dr. Heinz Läubli, USB)
    - What mechanisms prevent the immune system to attack cancer cells?
    - How can we overcome silencing of the immune system?
    - What are druggable targets for immuno-oncology?
    - Clinical data for drugs targeting the immune system
    - Clinical data for markers of benefit in immune therapies

- [1h] Overview: what markers can predict outcome of therapies? (PD Dr. Dr. Andreas Wicki, KSBL)
    - Clinical parameters
    - Radiology parameters
    - Histology
    - Immunohistochemistry
    - FISH
    - Comparative genomic hybridization
    - Sequencing of DNA, RNA (genomics, transcriptomics)
    - Others

- [2h] Using genetic markers to predict therapy in cancer patients (PD Dr. Dr. Andreas Wicki, KSBL)
    - Bulk sequencing vs single cell sequencing
    - Tissue vs liquid biopsy
    - Targeted/amplicon-based sequencing vs whole exome/genome
    - Issue of interpretation
    - Service providers in Switzerland
    - Clinically relevant turn-around time
    - Integration of genetic data in clinical routine
    - DISCUSSION: ethical issues with genetic data (germline vs tumor DNA)

- [2h] How do you read a genomic report as a clinician? (PD Dr. Dr. Sacha Rothschild, USB)
    - Basics: sources of information, databases
    - Tips and tricks
    - HANDS-ON: interpret bulk DNA sequencing report

Day 3 – Clinical Oncology, Drug Development in Oncology

- [2h] Current clinical standard: Interpreting predictive markers (both genomics and others) in the big four: part 1 (colorectal and urogenital) (PD Dr. Arnoud Templeton, Claraspital Basel / PD Dr. Dr. Andreas Wicki, KSBL)

- [2h] Current clinical standard: Interpreting predictive markers (both genomics and others) in the big four: part 2 (breast and lung) (PD Dr. Marcus Vetter, USB / PD Dr. Dr. Sacha Rothschild, USB)

- [1h30] Point of care: decisions at the molecular tumor board (PD Dr. Dr. Sacha Rothschild, USB / PD Dr. Dr. Andreas Wicki, KSBL
    - How can a molecular board improve care for cancer patients?
    - HANDS ON: simulate molecular board

- [0h30] CAS mini-thesis: presentation of topics and general explanations (Dr. Aitana Lebrand, SIB)

- [2h] Overview: drug development in oncology (PD Dr. Dr. Andreas Wicki, KSBL)
    - Preclinical
    - Early phase
    - Late phase and approval
    - Post marketing studies
    - Attrition rate
    - Clinical trial protocol, role of ethical committees and Swissmedic, informed consent
    - Primary endpoints vs secondary endpoints vs exploratory endpoints

    - Relevance of endpoints in clinical trials: OS, PFS, TTP, ORR, etc.
    - How to interpret a clinical trial
    - HANDS-ON: detailed analysis of current clinical trial protocols

- [1h30] Questions & Answers, wrap-up of the day

Day 4 – Predictive Biomarkers in Clinical Trials, Molecular Tumor Board

- [1h] Reimbursement: how to get a drug after your test predicts utility (PD Dr. Dr. Sacha Rothschild, USB)
    - DISCUSSION: assurance of equal treatment for all patients ("off-label" use)

- [2h] Beyond genetics in therapy prediction (PD Dr. Dr. Andreas Wicki, KSBL)
    - Proteomics
    - Single cell phenotyping
    - Machine-based learning

- [1h] Algorithm trials: how to transform data in a robust prediction (PD Dr. Dr. Andreas Wicki, KSBL)

- [0h30] Questions & Answers, wrap-up of the day

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