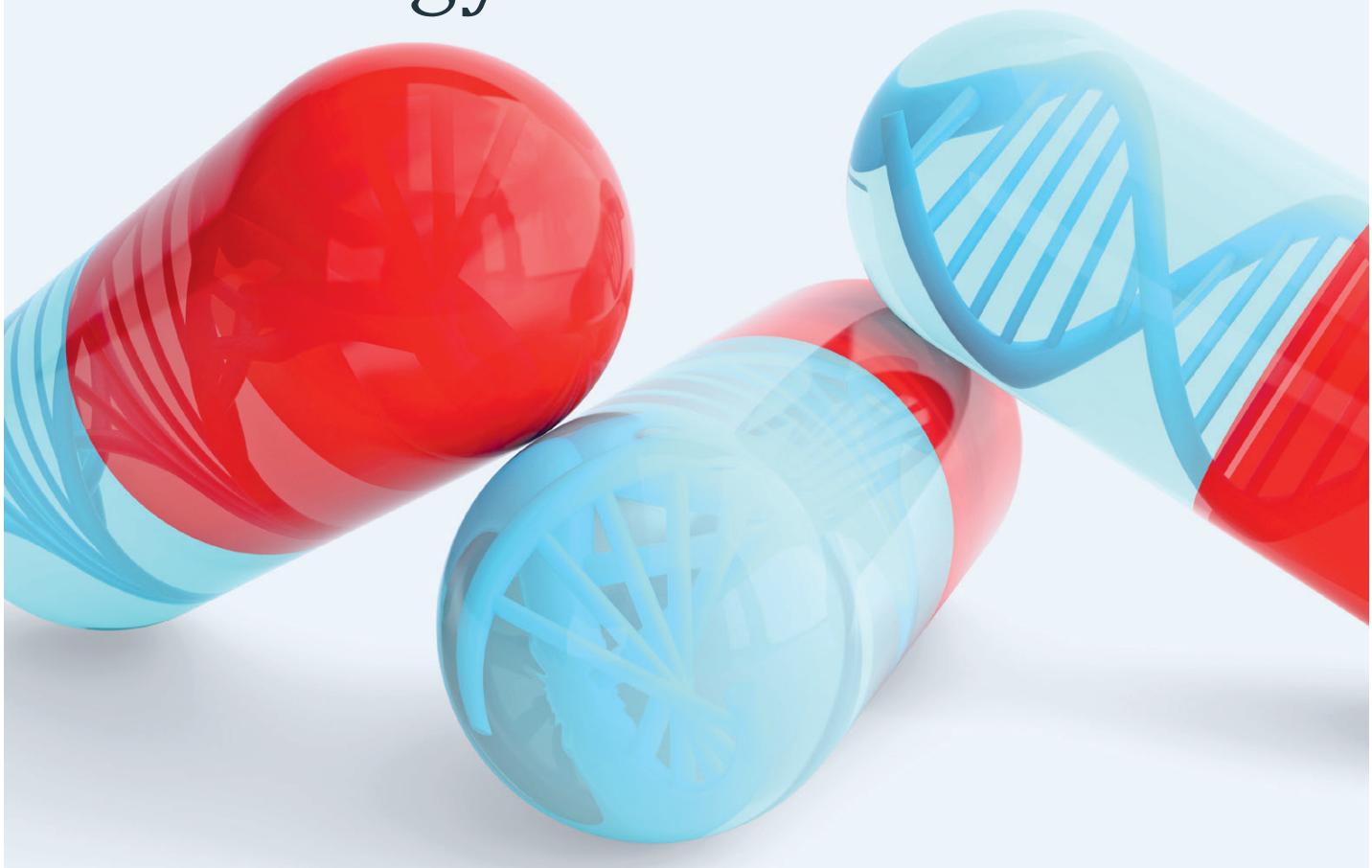
University of Basel

Faculty of Medicine

Certificate of Advanced Studies in Personalized Molecular Oncology



Universitätsspital Basel

SIB

CHUV

ADVANCED STUDIES

Detailed module program

Session 1: 2018-2019

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

- 9, 10, 23, 24 November 2018 (28h presential teaching).

Location

- Lausanne, CHUV University Hospital, room tba.

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.

Course format

- Lectures, exercises, group discussions and lab visit.

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

- [0h30] Introduction (Prof. Jacqueline Schoumans, CHUV)
  - Welcome
  - 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

- [1h] From DNA to proteins (Dr Fabienne Marcelli & Ilaria Scarpelli)
  - 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

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

- [2h] Precision medicine in hematological malignancies (Dr Sabine Blum FMH, 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)

- [2h] Tumor heterogeneity in hematological neoplasia (Dr Peter Valk, Erasmus MC Rotterdam)
  - Clonal evolution in myeloid leukemia
  - Clonal hematopoiesis of indeterminate potential (CHIP) mutations Genomic profiling & treatment decision

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.

- [3h] Practical demonstration of genetic methodologies and automation at the oncogenomic hematology laboratory, CHUV (demo organized by Noemie Gesson, Sandrine Bougeon, Laurence Etter & Anne Devaud)
  - Conventional karyotyping
  - FISH
  - SNP-array
  - NGS gene panels and complementary molecular tests

Day 3 – Tumor biology and hereditary genetics

- [1h30] Tumor biology of solid tumors (Prof Ivan Stamenkovic, CHUV)
  - Stem cell, microenvironment angiogenesis, inflammation

- [2h] Epigenetics in tumors: the example of neuroblastoma (Dr Nicolo Riggi, CHUV)

- [2h] Hereditary cancer in adults (Dr Benno Rothlisberger, Kantonspital Aarau)
  - 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
  - Patient demonstration

Day 4 – Molecular onco-hematology

- [2h] Genetic modifications (Dr Fabienne Marcelli & Ilaria Scarpelli)
  - 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

- [3h] Interactive workshop of genomic variant interpretation focusing on hematological malignancies (practical exercises performed individually and in small groups).

- [1h] Discussion of results of practical exercises
  - Summary and end of module.

Module 2
Molecular pathology

Dates

- 11, 12, 25, 26 January 2019 (28h presential teaching).

Location

- Basel, Basel University Hospital. Room: library of the Institute for Medical Genetics and Pathology

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

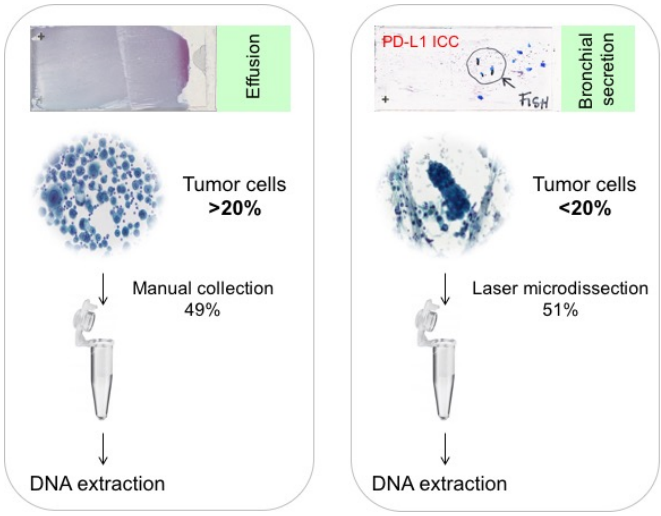
- Module 1 or equivalent knowledge.

Course format

- Lectures, exercises, group discussions and lab visit.

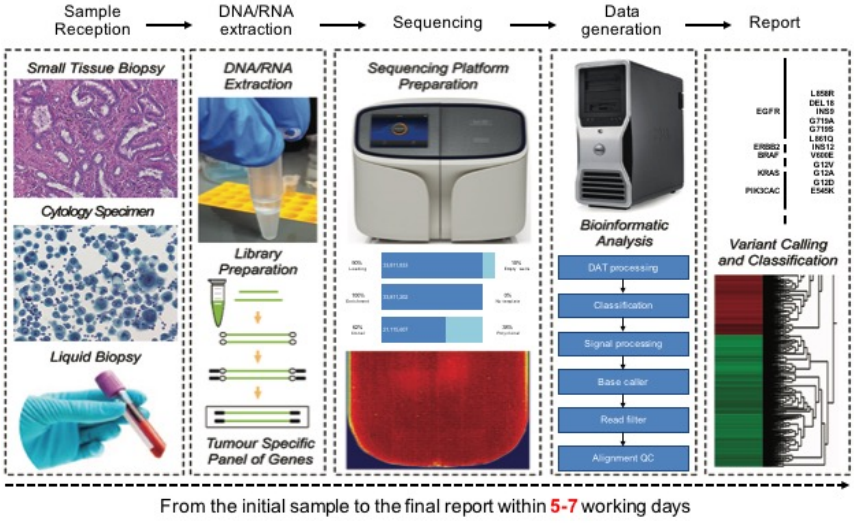
Day 1 – From the tissue to the nucleic acid: setting up a molecular profile procedure

- [0h30] Introduction: short presentation of the Institute of Pathology in Basel;
- [1h] Overview of the pathologist's checklist for tissue morphology analysis;
- [1h] Different type of samples (tissue biopsies, resections, blood, etc.) and how to handle them;



Examples of routinely use samples in Molecular Pathology – Quagliata's Team

- [1h] Overview about the different techniques used in molecular pathology (e.g. FISH, IHC);
- [1h30] Focusing on Genomics: when and what to extract, principles of nucleic acids handling from tissue samples;
- [1h] What qualifies for sequencing? QC steps for nucleic acids - definitions and examples;
- [1h] Step-by-step to perform sequencing: how to prepare a library and to generate sequencing data – from time management to required expertise.
- [1h] Group discussion and case analysis;



Internal pipeline of the NGS workflow at the Institute of Pathology in Basel – Quagliata's Team

Day 2 – Biomarker testing in molecular pathology

- [1h] Different types of biomarkers and their use: diagnostic vs. predictive (companion diagnostics) vs. prognostic;
- [0h30] Use of genomic biomarkers;
- [1h] Definition of gene panels to identify clinically relevant genomic alterations;
- [1h] Targeted vs. Exome vs. Whole-Genome sequencing;
- [1h] Clinical usage of biomarker data;
- [0h30] Future perspectives in genomic medicine and beyond (digital pathology, other omics…);
- [1h] Group discussion and case analysis;

Day 3 – Molecular pathology organization, data QC and standards for laboratory accreditations

- [1h30] Laboratory accreditation (ISO certification, Robin tests, general QC);
- [2h] Organization of a laboratory molecular unit;
- [1h] QC of molecular diagnostics: from IHC to genomics;
- [1h] Principles of genomic data analysis;
- [1h30] Group discussion and QC on use cases;

Day 4 – Medical Report generation, interpretation of results and data usage

- [1h] Morpho-molecular diagnosis;
- [1h] How are variants classified (pathogenicity, actionability)? What is considered clinically relevant?
- [1h] What do you find in a molecular pathology report?
- [1h] Guidelines for molecular profile reporting;
- [1h] Interpretation of a molecular profile;
- [0h30] What happens to the generated data and medical report?
- [1h30] Group discussion and case analysis;

Module 3
Clinical bioinformatics

Dates

- 22, 23 March; 5, 6 April 2019 (28h presential teaching).

Location

- Lausanne, University of Lausanne, room tba.

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.

Course format

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

Day 1 – Somatic and germline variant calling

- [1h] Introduction and general overview
  - Participants introduce themselves.
  - Very short presentation of the SIB Swiss Institute of Bioinformatics.
  - Reminder of the clinical genomics workflow based on NGS data
  - What can be expected from gene panels?
  - Overview of the bioinformatics analysis pipeline of NGS data.

- [1h30] Pre-processing and quality control
  - Base calling (Illumina vs. Ion Torrent), Phred score, FASTQ file
  - Demultiplexing and adapter trimming
  - Overall and well/cluster quality check (per technology).
  - Read quality-based filtering
  - HANDS-ON: Reads pre-processing.

- [1h30] Sequence alignment
  - General principles of pair-wise sequence alignment (nucleic acid, protein)
  - HANDS-ON: Map fragments of different lengths, to understand limitations of short reads and very long reads (processing time, quality depending on the technology...)
  - *De novo* vs. reference genome alignment: conceptual difference.

- [1h30] Read mapping:
  - Reference genome
  - Read length, single-end vs. paired-end vs. mate-pair reads
  - General properties of mappers
  - Mapping quality score, alignment score
  - Alignment file formats (SAM, BAM)
  - HANDS-ON: Mapping

- [1h30] Sequencing depth, genome and gene coverage, variant frequency:
  - Definitions and examples from WGS, WES, gene panels.
  - Sequencing depth and variant frequency.
  - DISCUSSION: average sequencing depth required to identify a variant with a certain frequency *p* (if WGS, WES or gene panel)?

- [1h] Variant calling:
  - General principles for calling SNVs and indels
  - Somatic vs. germline: what's the difference?
  - From single variants to haplotypes
  - Phasing (trio analyses)
  - VCF, BED formats
  - Calling CNAs, SVs: specific challenges

Day 2 – Variant quality control and annotation

- [3h] QC at the variant-level:
  - Common measures and thresholds (local coverage, base quality, strand bias, allele frequency)
  - DISCUSSION: Example case
  - HANDS-ON: identification of technical artifacts

- [3h] Variant annotation
    - Annotation using literature and databases: essentials and extras (somatic and germline, SVIP)
    - From variant to gene, assessing functional impact
        - Reminder of variant effects on the protein (missense, nonsense, frameshift, splicing region, importance of where they occur in the protein sequence, literature validation)
        - Existing tools and when *not* to use them (VEP, SnpEff vs. PolyPhen, SIFT)
    - Genes, transcripts and HGVS nomenclature
    - HANDS-ON: Annotation using bioinformatics tools
    - Pairing samples: how it can help distinguish somatic vs. germline variants (tumor/normal), follow patients longitudinally, follow primary vs. metastasis…
    - DISCUSSION: Beyond gene panels: WES and WGS challenges

Day 3 – What else? Molecular modeling, risks, neo-epitopes, RNA-seq and IT

- [2h] Molecular modeling: predicting the impact of variants on proteins
    - HANDS-ON: Impact of mutations on proteins 3D structure

- [2h] Risks and probabilities for the interpretation of genetic results

- [1h] Personalized cancer immunotherapy: predicting neo-epitopes

- [1h] RNA-seq for biomarker identification

- [2h] Hardware, security and privacy
    - Computing – HPC, cloud.
    - Architecture: where to compute and store data.
    - Structuring data for sharing and re-use
    - Querying resources – what is an API, a beacon?
    - Data privacy and security
    - DISCUSSION: implementing technical solutions for ethical use of omics data for diagnosis and clinical research – SVIP study case.

Day 4 – Artificial intelligence basics and applications in clinical bioinformatics

- [2h] Machine learning
    - Machine learning basics (models, features, training, cross-validation, metrics), limitations and challenges
    - DISCUSSION: use cases.

- [3h] First steps into digital pathology
    - Basic principles of image analysis
    - Segmentation and feature extraction
    - HANDS-ON: automated image analysis.

- [1h] Invited talk on integrative -omics for personalized medicine (towards systems medicine) and other perspectives.

Module 4
Clinical oncology

Dates

- 10, 11, 24, 25 May 2019 (28h presential teaching).

Location

- Basel, Basel University Hospital, room tba.

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 or equivalent knowledge.

Course format

- Lectures, exercises and group discussions.

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

- [1h] Cancer statistics and epidemiology
- [1h] Familiar cancer, cancer genetics
- [2h] Basic concepts of cancer therapy:
    - Surgery, radiation therapy, systemic therapy
    - Adjuvant, neoadjuvant, palliative
    - Markers for systemic therapy: prognostic, predictive
    - Definitions: OS, PFS, ORR, etc.

- [1h] Pharmacology and antitumoral agents

- [2h] Tumor biology: from molecular biology of cancer to targets for anti-cancer drugs
    - 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

Day 2 – Tumor Immunology, Genomic Reports, Response Prediction

- [2h] Tumor immunology: how to get an immune response against cancer
    - 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?
    - 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
    - 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?
    - 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 (breast, lung).

- [2h] Current clinical standard: Interpreting predictive markers (both genomics and others) in the big four: part 2 (colorectal and prostate).

- [1h] Does big data play a role in oncology?
    - What is big data?
    - How do we get access to big data?
    - How can big data inform drug development and individual therapy decision (in trial setting and in clinical routine)?

- [2h] Overview: drug development in oncology
    - 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

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

- [1h] What impact does therapy prediction have on drug development?
    - Co-development of biomarkers
    - FDA vs EMA approach (companion-diagnostics vs open source tests)
    - Impact on attrition rate

- [1h] Reimbursement: how to get a drug after your test predicts utility
    - DISCUSSION: assurance of equal treatment for all patients (“off-label” use)

- [2h] Beyond genetics in therapy prediction
    - Proteomics
    - Single cell phenotyping
    - Machine-based learning

- [1h] Algorithm trials: how to transform data in a robust prediction

- [2h] Point of care: decisions at the molecular tumor board
    - How can a molecular board improve care for cancer patients?
    - HANDS ON: simulate molecular board

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