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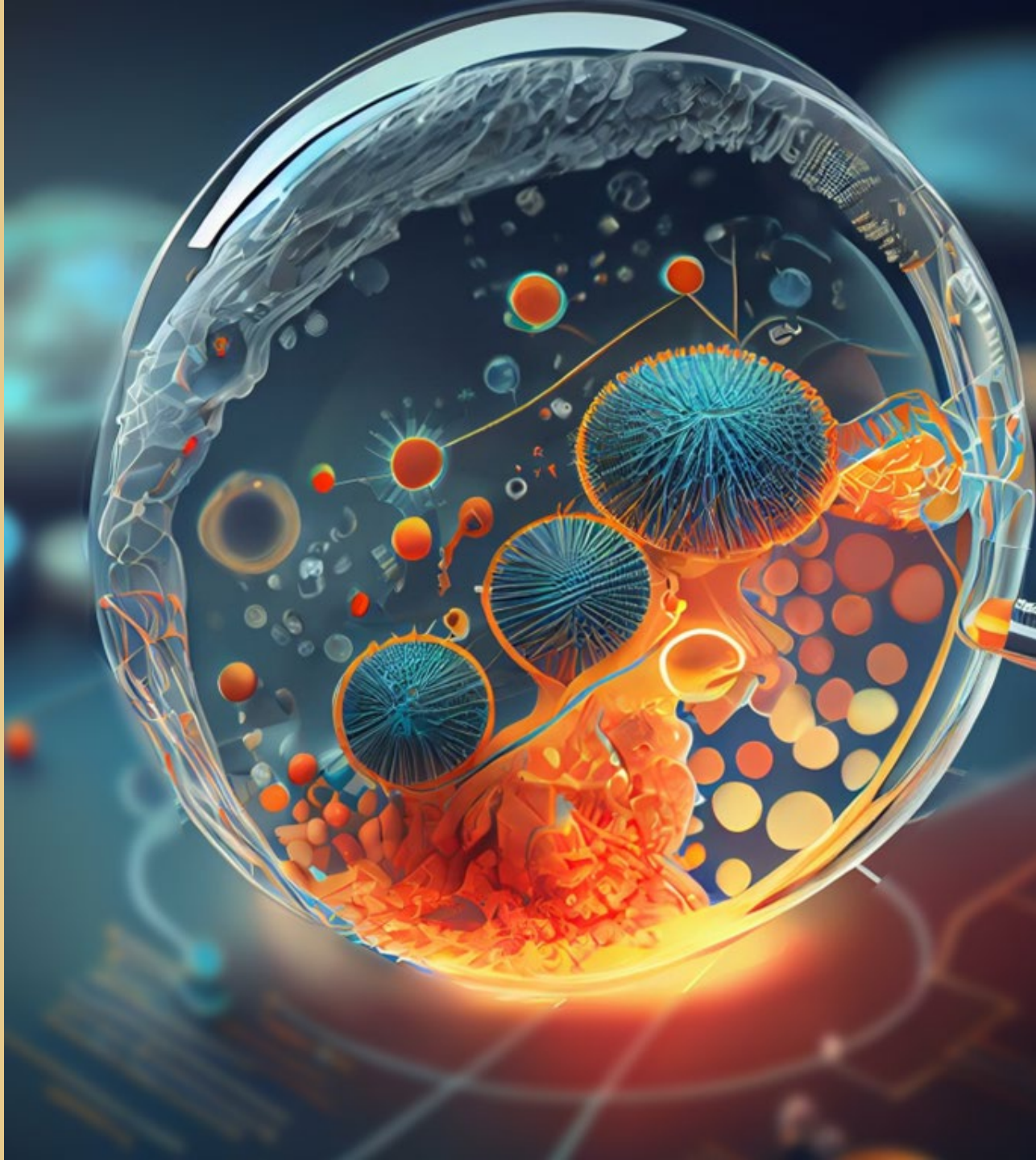
Optimizing specimen handling for precision medicine applications



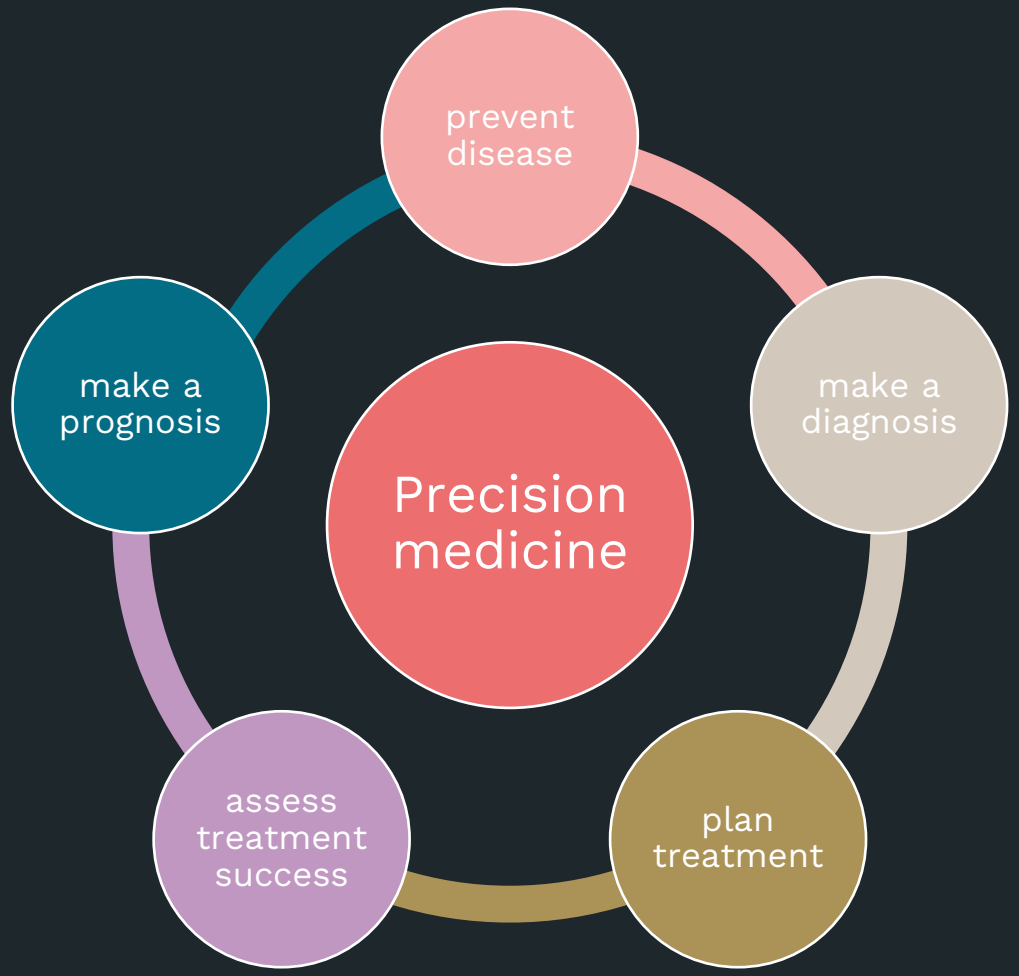
27.09.24 Tea Pemovska, PhD

MEDICAL UNIVERSITY OF VIENNA

I have no disclosures

Contents

A form of medicine that uses information about person's genes or proteins

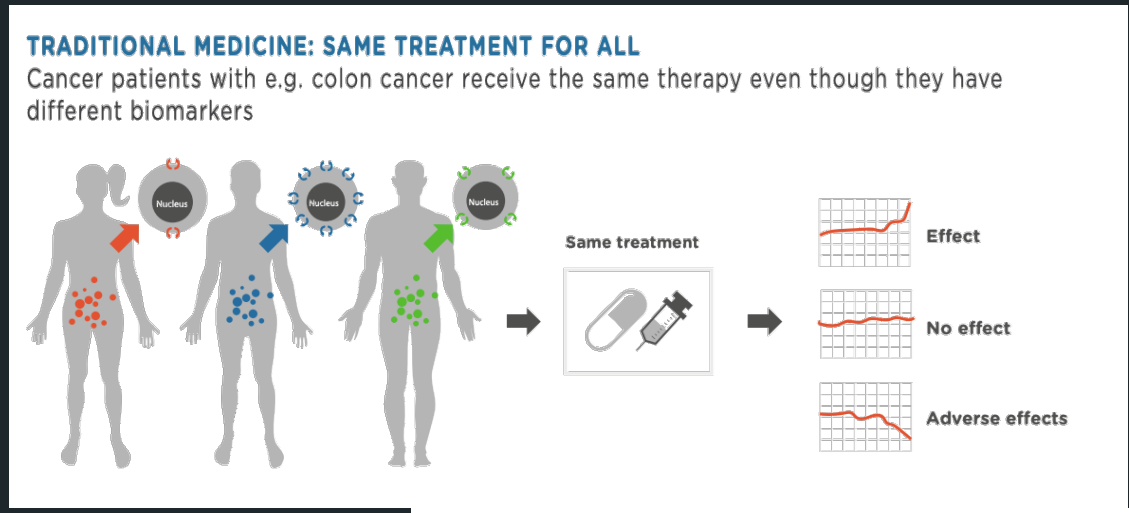


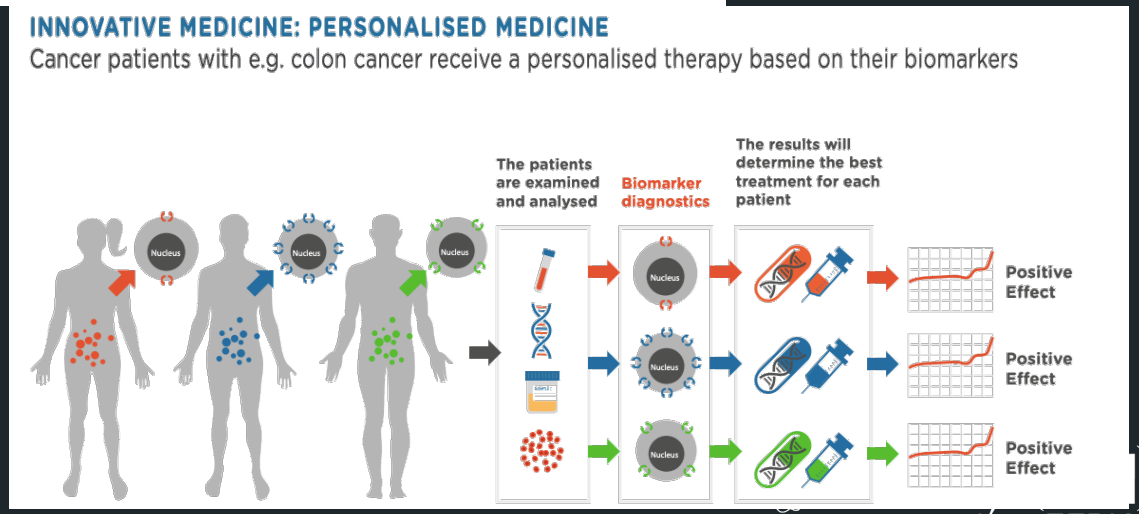
- nowadays common practice to collect and store numerous different biological samples
  - healthy donors and patients
    - biobanks
      - collection, processing, preservation, and storage
      - assuring high-quality samples and data
      - ethical and legal compliance
      - transparent and efficient access procedures
- *insight into the molecular mechanisms underlying individual diseases*
  - can only be obtained from investigation of human biological samples

Why precision medicine?

Personalized therapy can reduce healthcare costs in the long run

- by reducing
  - ineffective treatments
  - side effects
  - low quality of life
  - hospitalizations





EFPIA

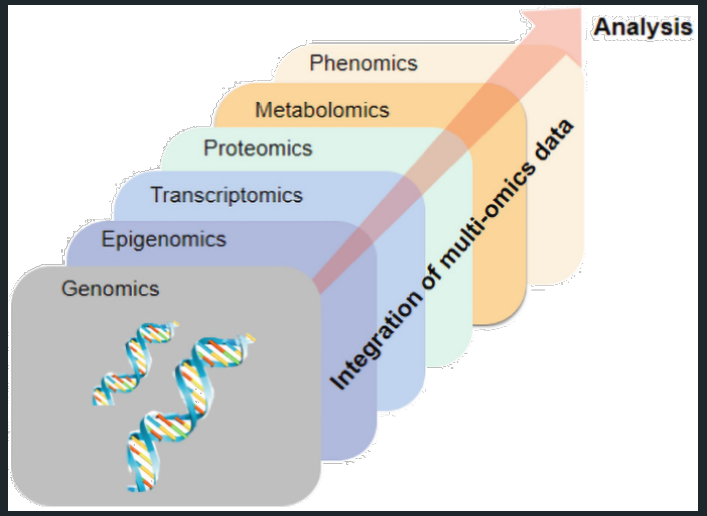
Rapid advances in molecular technology

Yielded clinical-grade tests

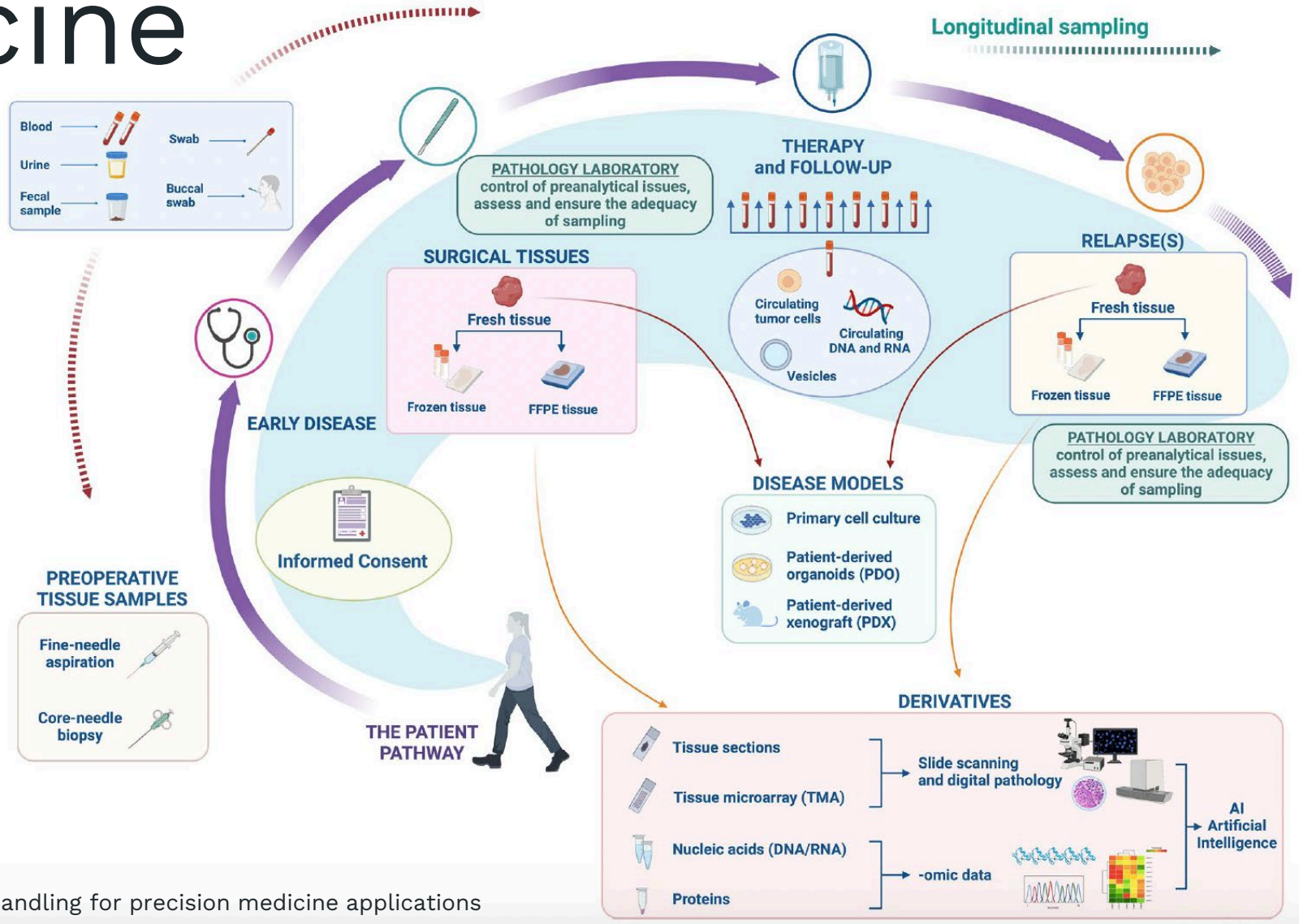
- permit deep interrogation of tumor biology
- identification of complex and unique molecular features
- provide personalized treatment to patients

Precision medicine

- exploited next-generation sequencing
- customization of patient therapy
- successfully transformed the outlook for several fatal cancers
- **Enabled a revolution in clinical trial design**



Role of biobanks in personalized medicine



Annaratone et al, Virchows Archiv 2021

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Sample collection and preservation

1

Patient Consent and Information

Obtaining informed consent from patients is paramount. Patients must understand the purpose of sample collection, the potential risks and benefits, and the use of their data. Clear communication and detailed documentation are essential.

2

Appropriate Collection Methods

Proper collection methods are crucial to minimize contamination and maintain sample integrity. Standardized procedures, trained personnel, and appropriate collection tools should be employed to ensure consistent and accurate sample collection.

3

Preservation and Storage

Preserving and storing samples correctly is vital for maintaining their quality and stability over time. This involves using appropriate storage conditions, including temperature, humidity, and light exposure, to prevent degradation and ensure reliable analysis.

Functional precision medicine (FPM) in oncology

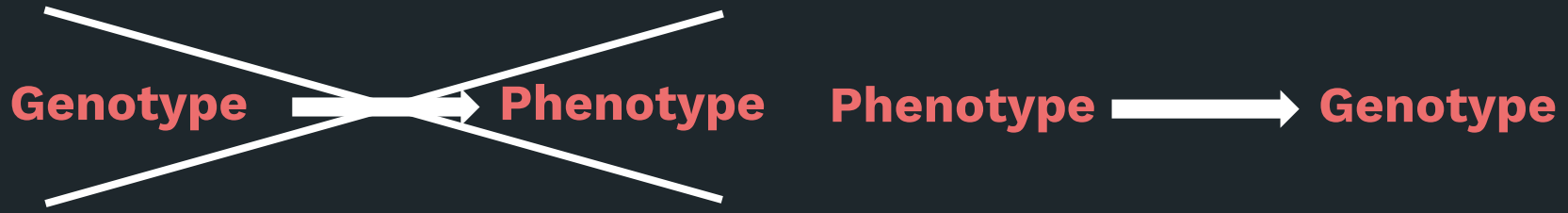
Patient's tumor cells are directly perturbed with drugs

- generates dynamic, functional data
  - encompassing key vulnerabilities and dependencies
  - agnostic with respect to disease mechanisms
  - rely on direct measurements of cellular functions

"put drugs on cancer cells and see if they work"

Help us to read the cancer genome

- functional profiles can link to genetic alteration patterns



- potential for immediate translation of results, personalized treatment recommendation

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FPM is not a new concept

Chemosensitivity testing began more than 50 years ago

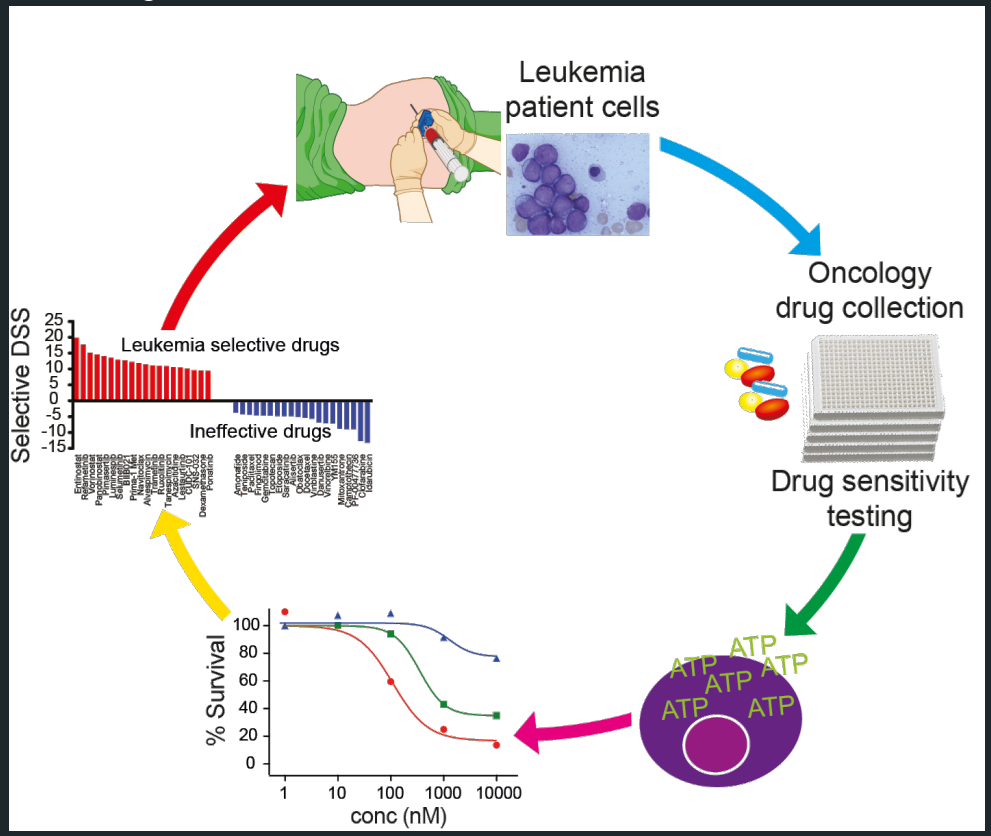
- most curative cytotoxic regimens used today derived from these crude assays

Two editorials in NEJM in 1983 and position papers by ASCO cast doubt on the utility

- personalizing cancer care
  - lack of tumor cells surviving culture conditions
  - unsophisticated culture conditions
  - uninformative assays
  - drug armamentarium relatively small
  - lack of prospective data demonstrating utility

Restored interest in the last decade

- increased in biological knowledge
- available technology
- number of drugs available



Challenges of FPM

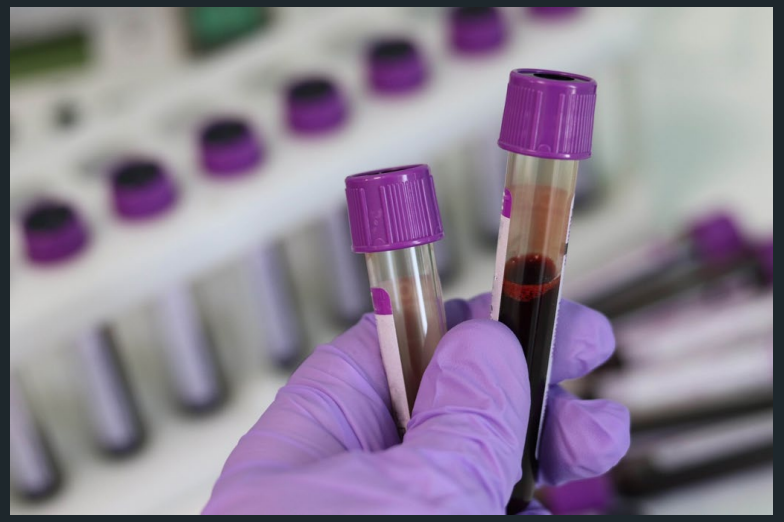
- Requirement of viable tissue
- Requirement of sufficient tumor cell yields
  - highly suitable for hematological cancers
- Limit the presence of unfavorable areas (e.g., necrosis, fibrosis, blood clots)
- Adapting routine sample handling in hospitals
  - preserve viability
  - sample integrity
  - still enable standard diagnostic procedures
- Proper specimen sampling
  - capturing specimen heterogeneity
  - avoidance of selection bias (overly or underly abundant cell populations)

Session scope and objectives

to understand best practices in shipping, storage, and quality control of patient specimens

importance of quality control in ensuring specimen integrity and reliability of results

Biospecimens



- Materials obtained from the human body
  - used to diagnose and analyze disease (e.g., cancer)
  - tissue
  - blood
  - plasma
  - other biological fluids
- *High-quality biospecimens are defined as those whose biology most closely resembles the biology of the biospecimen prior to its removal from the human research participant*
- Once the biospecimen is collected (and sometimes before its removal)
  - the biospecimen may begin to take on new characteristics
    - changes to the biospecimen's environment
    - that may occur during a surgical or collection procedure
    - ➢ inaccurate determinations of molecular and physical biospecimen characteristics

Lifecycle of biospecimens

- The life cycle stages of biosamples can vary
  - type of sample
  - intended use
  - critical
    - maintaining their integrity
    - quality
    - usefulness for future research

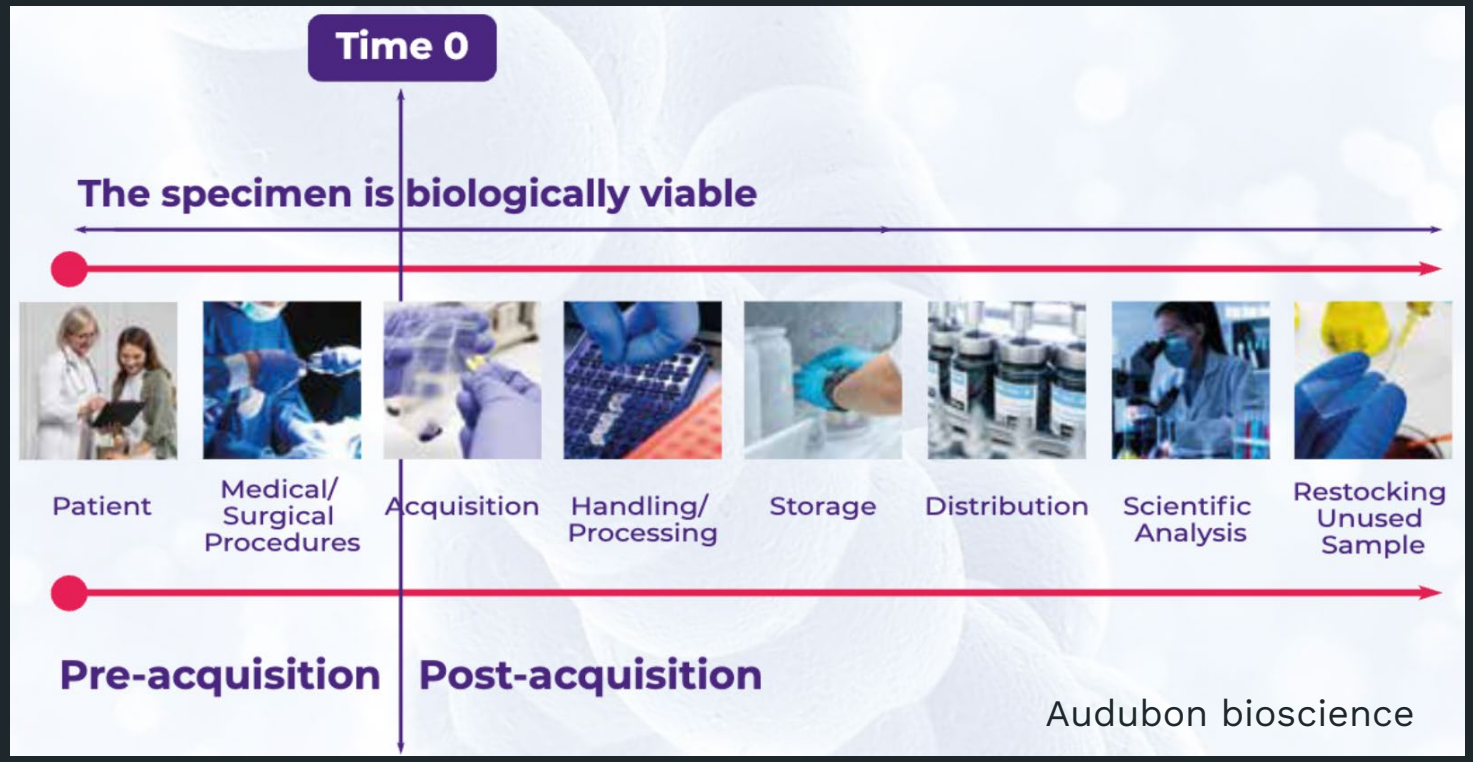


Table I. The life cycle steps of biosamples for personalized medicine.

Step	Role	Reference
Collection	Biosamples are collected from donors or patients through various methods, such as biopsy, blood draw, or saliva swab, in a sterile and consistent manner to avoid contamination or degradation	[4,19,26]
Processing	Processed to extract specific components or prepare them for analysis; separating cells from tissues, isolating DNA or RNA, or freezing the samples for long-term storage.	[4,26]
Storage	Can be stored for various periods (ranging from a few hours to several decades). Proper storage conditions are critical to ensure sample integrity and avoid degradation or contamination. Depending on the sample type and storage duration, different storage methods, such as refrigeration, freezing, or cryopreservation, may be used	[4,19,26]
Analysis	Biosamples are typically analyzed to answer research questions or diagnose medical conditions. This may involve various techniques, such as microscopy, genomics, proteomics, or metabolomics, depending on the specific research question and sample type are some specific requirements related to quality control for samples.	[4,9,26]
Disposal/ Restocking	Once the analysis is complete, biosamples may be disposed of in a proper and ethical manner. This may involve autoclaving, incineration, or chemical treatment, depending on the sample type and any associated hazards.	[4,9,26]

Policiuc et al, Med Pharm Rep 2023

The use of human biospecimens for personalized medicine in oncology

- Use of high-quality samples
  - strict ethical
  - procedural guidelines
- Standardized protocols is paramount
  - consistent processing of samples across different studies
  - same equipment, reagents, and procedures
    - minimize variability
    - increase reproducibility
- Speed of processing also important
  - prevent degradation
  - maintain the integrity of biological molecules (e.g., DNA, RNA, proteins)
- Quality control measures
  - quantity
  - quality
  - free from contamination
  - other factors affecting reproducibility

Specimen integrity

- dependent on accurate pre-analytical processes
  - patient preparation
  - specimen collection
  - handling
  - transportation
  - processing
  - analysis
  - storage
- Improper collection and handling
  - erroneous results
  - compromise data translatability
  - care of the patient

Processing variability

Factors affecting the biospecimens during the processing steps

- Type of processing method used
- Time between collection and processing
- Conditions during processing
  - Can also lead to changes in the biospecimen composition
    - impacting the accuracy and reproducibility of data generated
- Post-analytical processing
  - factors affecting data generated after the biospecimens have been analyzed
    - data analysis methods
    - data interpretation
  - lead to differences in the results obtained
    - impacting the reproducibility of data generated

Preanalytical variables

Patient-Related factors

Individual factors like age, gender, diet, medications, and overall health status can influence the composition and integrity of specimens. Understanding these factors helps in interpreting results accurately.

Time of Day and Collection Procedure

The time of day can affect certain biomarkers, such as hormones. The method of collection, whether it involves fasting or specific protocols, can also impact specimen integrity.

Transportation and Handling

How specimens are transported and handled during transit can influence their quality. Timely transportation, proper temperature control, and adherence to established protocols are essential.

Specimen collection

1 Appropriate Collection Techniques

Using the correct tools and procedures for collecting specimens is critical. For example, using sterile needles and tubes for blood collection minimizes contamination risks, while tissue biopsies should be performed with precision to avoid damage.

2 Timely Processing

Specimens should be processed as soon as possible after collection to minimize degradation. This involves steps like centrifugation for blood samples or immediate fixation for tissue samples. The delay in processing can lead to changes in cellular structure and composition.

3 Proper Labeling and Storage

Accurate labeling of specimens is crucial to prevent mix-ups and ensure traceability. Proper storage conditions, such as refrigeration or freezing, are essential to maintain specimen integrity over time.

4 Environmental Factors

Exposure to extreme temperatures, humidity, or light can negatively impact specimens. Proper packaging and transport conditions should be implemented to protect them from environmental fluctuations.

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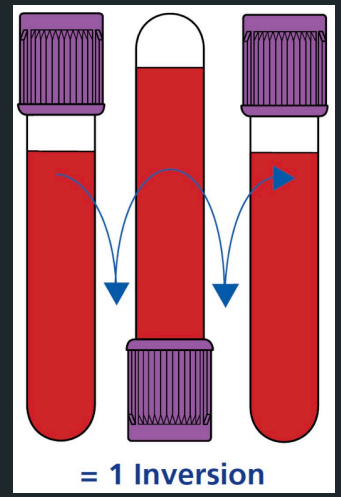
Specimen collection

Patient results are only as good as the specimen collected

- Requirements for collection and handling must be followed
- Critical that adequate volumes are collected
- Avoid the use of expired collection tubes
- Collect in the correct order of draw (blood samples)
  - inverted gently to ensure proper mixing of additive or anticoagulant
    - prevent contamination with anticoagulants and inaccurate results
- Tissue samples – histologically reviewed by histopathologist
- Specimen labeling
  - unique identifiers
- Preservation method
  - as quick as possible
  - suited for expected and unforeseen future use
  - preventing confounders influencing molecular stability and degradation



Specimen Preservation and Storage

1

Fixation

For tissue specimens, fixation is often used to preserve cellular structure and prevent degradation. Common fixatives include formalin, alcohol, or special solutions depending on the type of tissue.

2

Freezing

Freezing is used for preserving samples at very low temperatures, often using liquid nitrogen or ultra-low freezers. This helps to slow down or stop biological processes and maintain the integrity of specimens for extended periods.

3

Storage Conditions

Specimens are stored in specific conditions based on their type and intended use. These conditions include appropriate temperatures, humidity levels, and light exposure, all crucial for maintaining their integrity.

4

Long-Term Stability

Long-term storage strategies for specimens, such as cryopreservation or lyophilization (freeze-drying), aim to preserve their integrity and maintain their suitability for future analysis.

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Biospecimen storage

- Storage in a stabilized state
- Avoiding freeze-thaw cycles
- Appropriate storage temperature
  - biospecimen type
  - downstream application
  - length of storage
  - use of appropriate storage containers for storage temperature
- Optimal volume
  - prevent sample loss
  - minimize costs
  - collection
  - storage
  - retrieval

screw-cap cryovials may be used for long-term, low-temperature storage

glass vials or vials with popup tops are unsuitable for long-term storage

snap-frozen biospecimens should be wrapped in aluminum foil or placed in commercial storage containers to minimize desiccation

formalin-fixed, paraffin-embedded tissue should be stored as a block and not sliced until analysis is imminent

slide-mounted cut sections must undergo thorough dehydration and processing prior to storage

Specimen Handling

- Every attempt to optimize specimen handling
  - ⬇ minimize molecular changes from processing activities
    - e.g., cold ischemia time
    - temperature
    - processing time
    - size and volume of biospecimen
    - number of aliquots
    - rate at which samples are cooled to storage temperature
    - avoiding freeze-thaw cycles

The quality of assays can be impacted by inconsistent sample handling

Contamination and degradation

Biological Contamination

From bacteria, fungi, or viruses can alter specimen integrity. Sterile techniques and proper handling are essential to minimize these risks.

Chemical Contamination

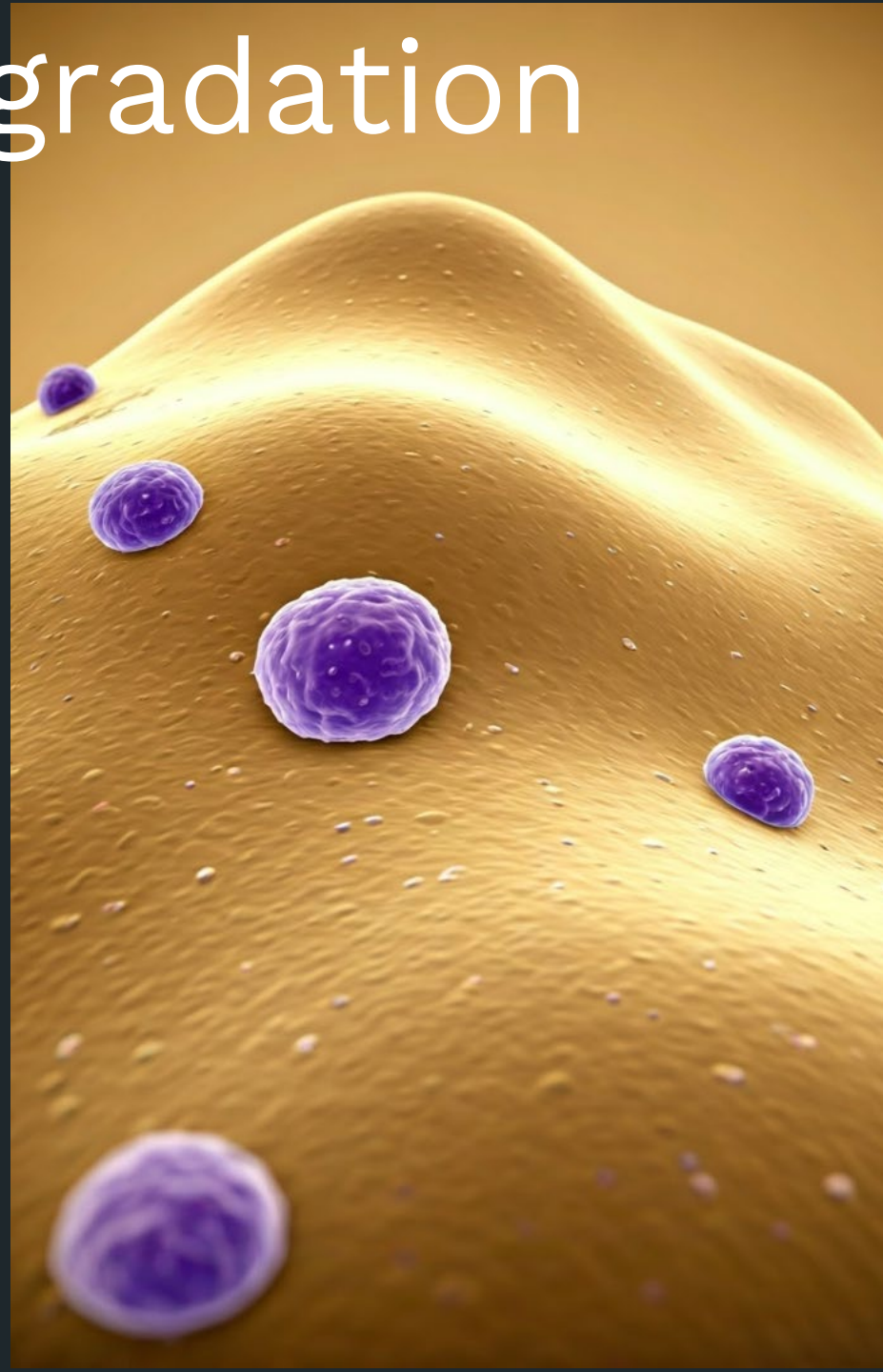
Exposure to chemicals, such as cleaning agents or solvents, can damage specimens. Avoiding cross-contamination is crucial.

Degradation Over Time

Even under optimal storage conditions, biological specimens undergo natural degradation processes involving enzyme activity, oxidation, or the breakdown of cellular structures.

DNA Degradation

DNA is particularly susceptible to degradation, especially in the presence of enzymes like DNases. Proper handling and storage are essential to minimize DNA breakdown.



Automation and standardization

Automated Sample Processing

Automated systems can significantly improve efficiency, consistency, and accuracy in sample handling. Robotic systems can perform tasks such as sample extraction, preparation, and analysis, reducing manual error and increasing throughput.

Standardized Protocols

Implementing standardized protocols for sample handling ensures consistency across different laboratories and research groups. This reduces variability and enhances the reproducibility of results.

Data Integration

Integrating data from different sources, such as sample tracking systems, laboratory instruments, and clinical databases, can provide a comprehensive view of the entire sample lifecycle, enhancing data analysis and interpretation.

Specimen Transport

1

Chain of Custody

Establishing a chain of custody is crucial for maintaining sample traceability and ensuring sample integrity. This involves meticulously documenting the handling and movement of samples from collection to analysis, ensuring accountability and preventing misidentification.

2

Transport Conditions

Maintaining appropriate temperature and humidity controls during transport is crucial for preserving sample quality. Specialized containers, cold-chain systems, and tracking devices are used to ensure samples remain stable and viable.

3

Sample Identification and Labeling

Accurate sample identification and labeling are essential for preventing misidentification and ensuring correct data association. Clear, legible labels with unique identifiers should be attached to each sample throughout the handling process.

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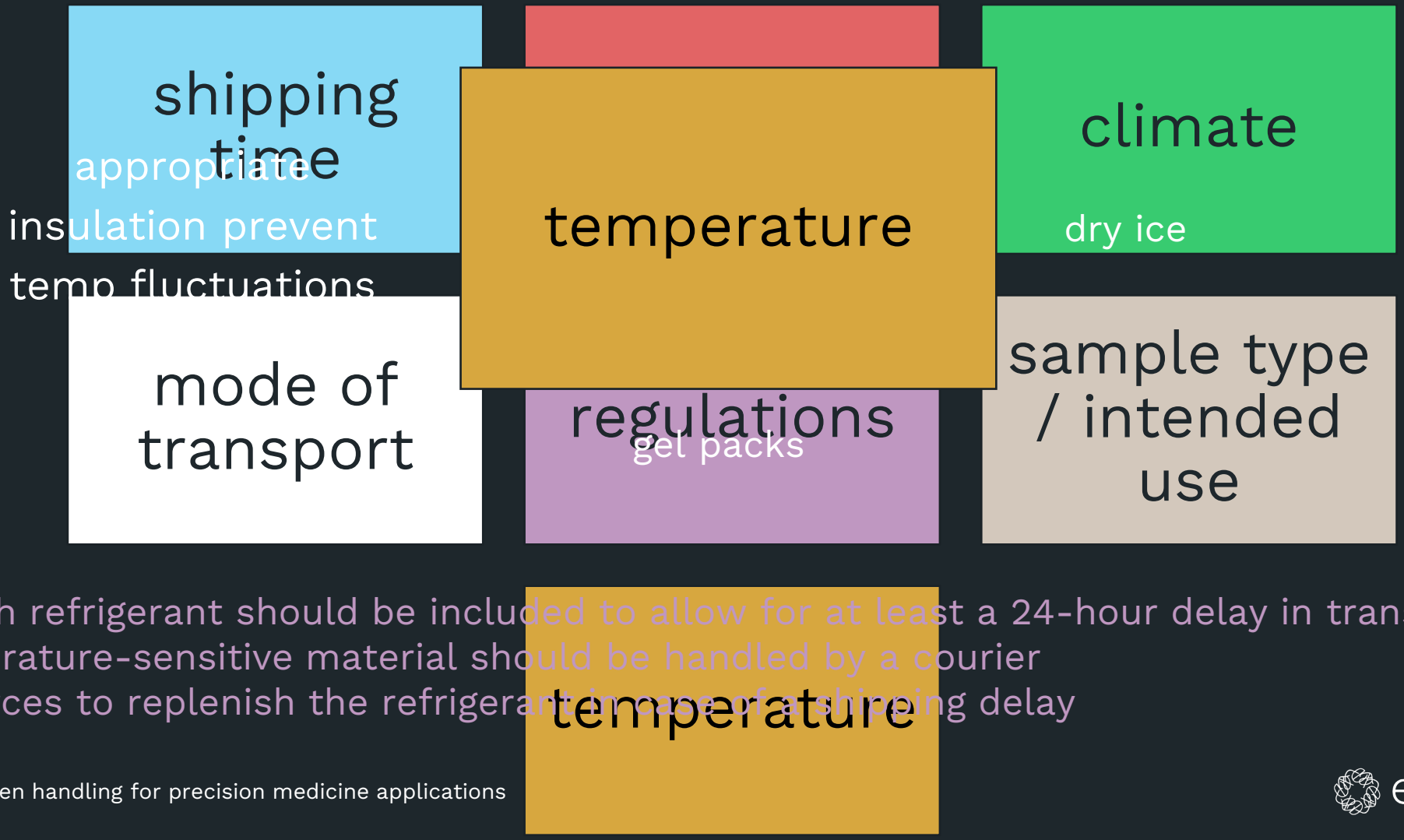
Key considerations – sample shipment



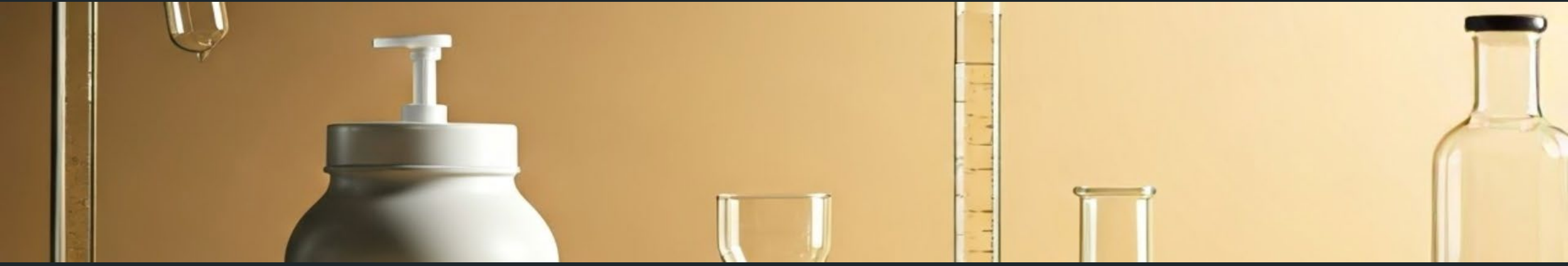
- enough refrigerant should be included to allow for at least a 24-hour delay in transport
- temperature-sensitive material should be handled by a courier
- resources to replenish the refrigerant in case of a shipping delay

Packaging

- **Primary Container:**
  - Use leak-proof, sterile containers for collecting blood or bone marrow samples. Ensure that the container is securely closed.
- **Secondary Container:**
  - Place the primary container in a secondary, leak-proof container with enough absorbent material to contain any potential leaks.
- **Tertiary Packaging:**
  - Use a rigid, puncture-resistant outer container for added protection. This is often a foam or insulated box to maintain temperature control.
- **Cushioning:**
  - Ensure that the samples are well-cushioned to prevent movement and breakage during transit.

Analytical factors

- Introducing pre-analytical variables
  - differences in the performance of a particular assay
- To minimize errors
  - Use of validated assays, where possible
  - Use of SOPs by well-trained staff
  - Lot uniformity of reagents
  - Inclusion of appropriate type and number of quality control (reference) samples
  - Randomization, when possible
  - Standardized methods for documenting and interpreting test results



Impact of Specimen Integrity on Precision Medicine

Accurate Diagnosis

Degraded or contaminated specimens can lead to inaccurate diagnostic results, potentially delaying or misdirecting treatment.

Personalized Treatment Selection

Reliable information from specimens is crucial for choosing the most effective and targeted therapies for individual patients.

Scientific Research

Maintaining specimen integrity ensures the validity and reliability of research findings, impacting the advancement of precision medicine and therapeutic strategies.

Improved Patient Outcomes

By ensuring accurate and reliable data from specimens, precision medicine aims to optimize treatment outcomes, reduce adverse effects, and improve patient well-being.

Challenges and Future Directions

1 Sample Heterogeneity

Biological samples exhibit considerable variability, presenting challenges for standardization and analysis. Developments in biobanking and sample characterization are needed to address this heterogeneity.

2 Data Security and Privacy

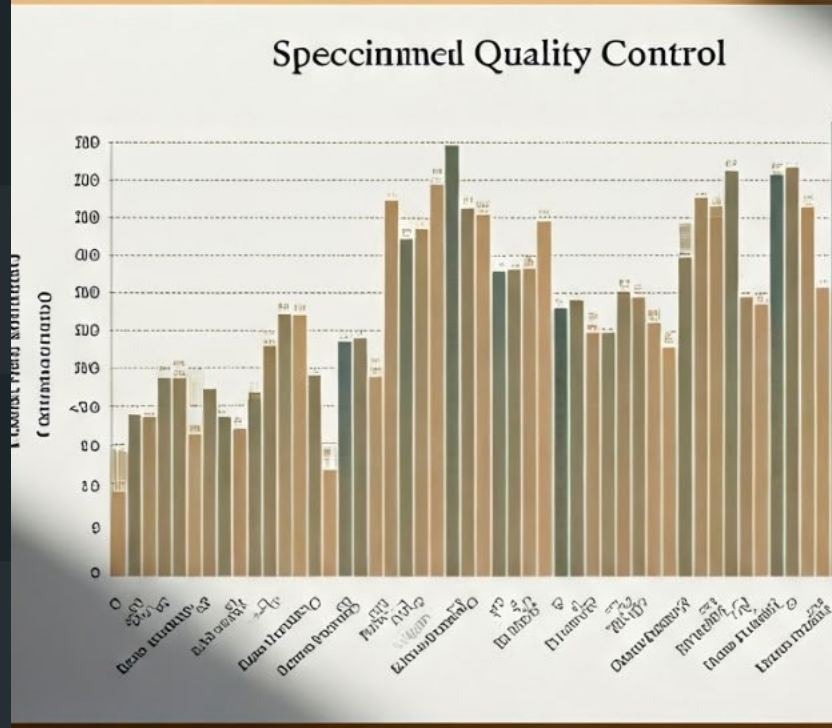
Protecting sensitive patient information is critical. Robust data security measures and ethical guidelines are essential to ensure responsible use and prevent unauthorized access to patient data.

3 Emerging Technologies

Advances in technologies such as liquid biopsies, microfluidic devices, and artificial intelligence are transforming specimen handling. These innovations offer potential for increased efficiency, precision, and personalized medicine.

Quality Control and Assurance

Control Measures	Purpose
Specimen Identification and Tracking	Ensure accurate labeling and traceability throughout the process.
Temperature Monitoring	Maintain optimal storage and transport conditions.
Visual Inspection	Identify any visible signs of degradation or contamination.
Analytical Validation	Verify the accuracy and reliability of analytical techniques.
Audits and Reviews	Assess compliance with established protocols and identify areas for improvement.



Conclussion

Maintaining specimen integrity is a critical aspect of precision medicine, ensuring accurate and reliable data for diagnosis, prognosis, and treatment selection. By understanding the factors that can affect specimen quality, implementing appropriate procedures, and utilizing emerging technologies, we can enhance the accuracy and effectiveness of precision medicine, ultimately improving patient outcomes and advancing personalized healthcare.

Case studies

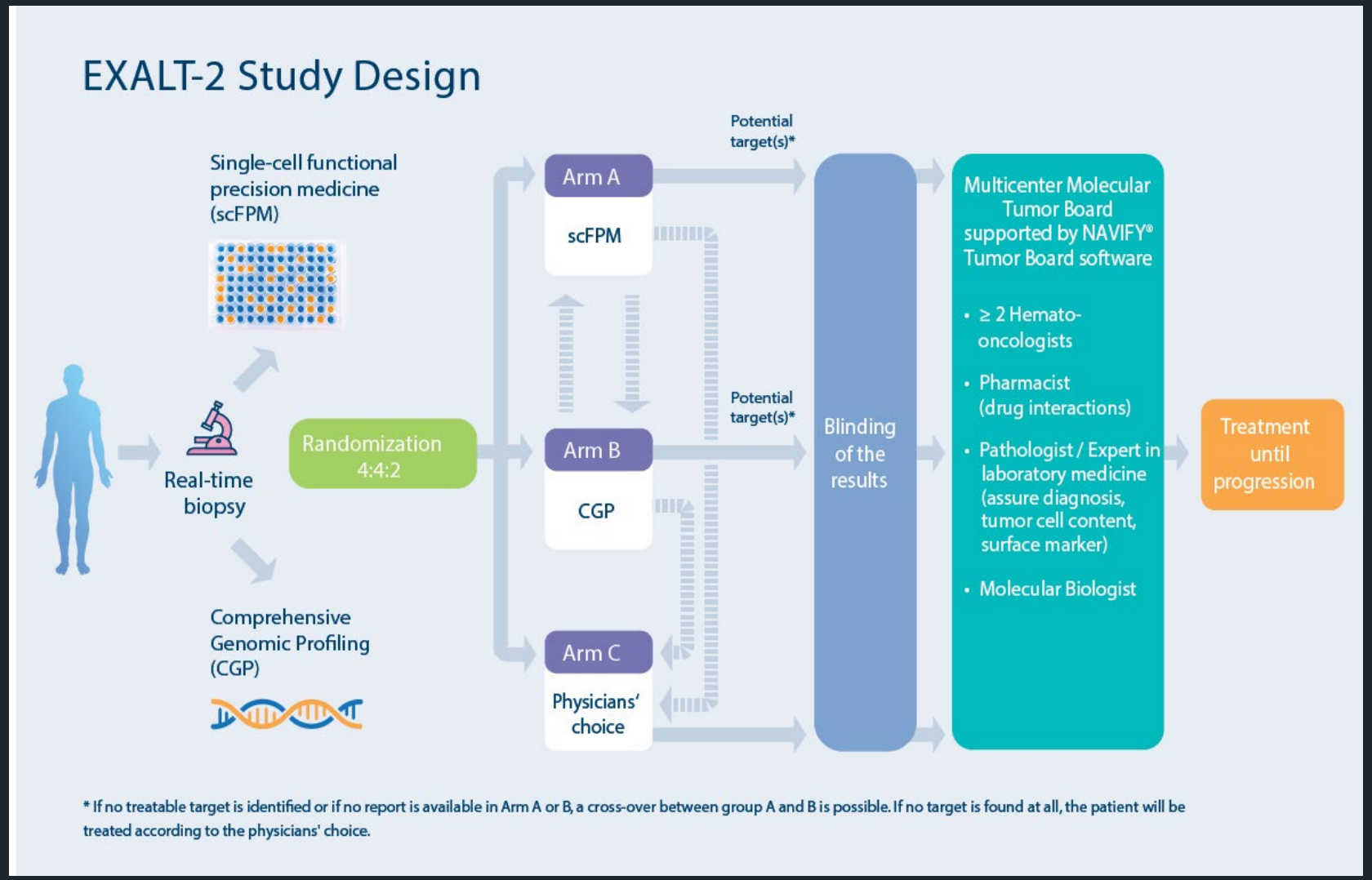
Cancer Treatment

Personalized cancer treatments based on tumor genomic and functional profiling have led to significant improvements in patient outcomes, showcasing the power of precision medicine.

- EXALT-2 study sample handling procedures
- Alice Soragni’s organoid generation from solid tumor biopsies

EXALT 2.0

Comprehensive genomic profiling and next generation drug screening for patients with aggressive haematological malignancies: next generation personalized hematology



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Medical University Salzburg

Start Q2 2020

Sponsor MUW, Roche

PI Staber, Kazianka

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Protocol overview – Eligibility criteria

Inclusion	Exclusion
r/r aggressive hematological malignancy	2nd malignancy*
≥ 2 prior lines of therapy**	participation in another clinical trial
response to previous therapy < 1 year	pregnancy
ECOG ≤ 2	ECOG > 2
antitumor therapy medically feasible	Hodgkin's lymphoma
real-time biopsy feasible	age < 18 years

* diagnosed < 1 year prior to study inclusion (except for localized squamous cell carcinoma and basal cell carcinoma of the skin; ** or 1 prior therapy and no standard of care available

Protocol overview – Efficacy endpoints

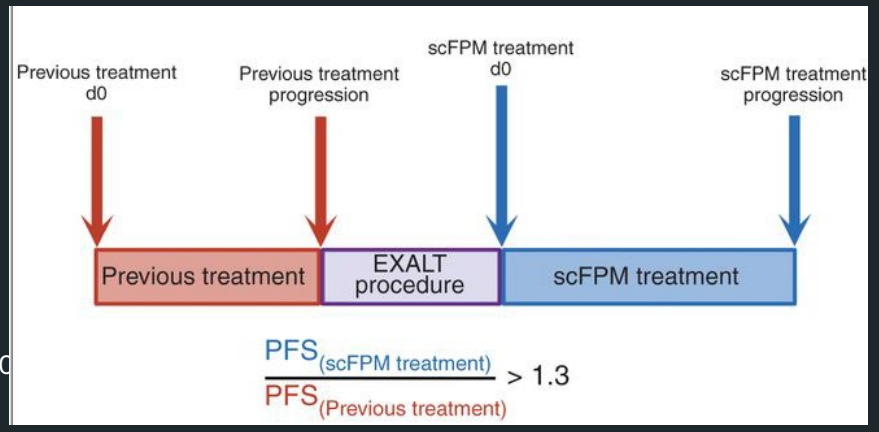
Individual PFS benefit

PFS ratio (PFS on A or B or C / PFS of most prior therapy) ≥ 1.3

Average Ratio of PFS on A or B or C treatment

Overall response rate (ORR)

Number of treatable targets



Overall survival (OS)

Successful bridging to HSCT for eligible patients

Time to result

informed consent signed

biopsy taken

availability of results

randomization

board decision

start of treatment

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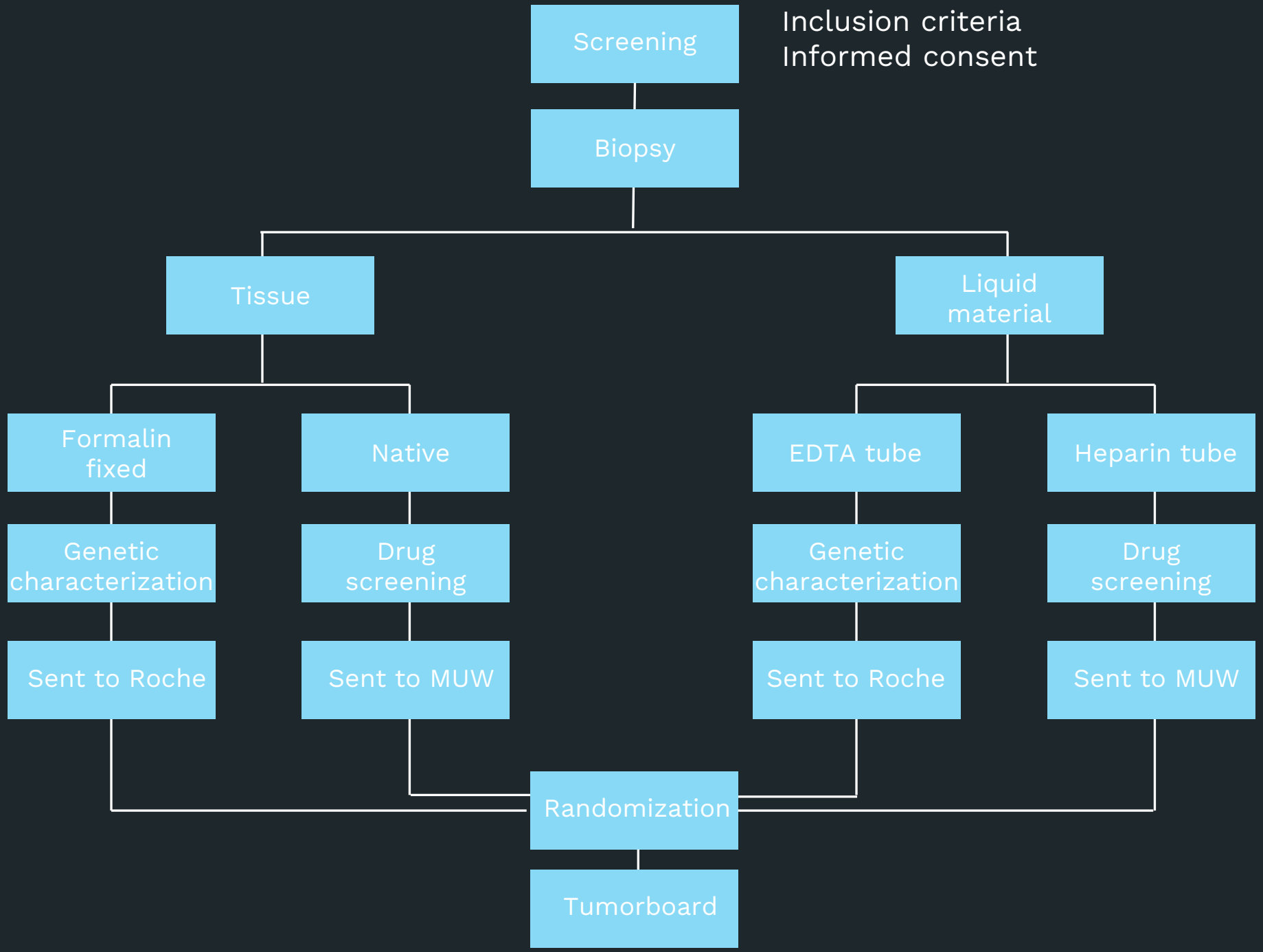
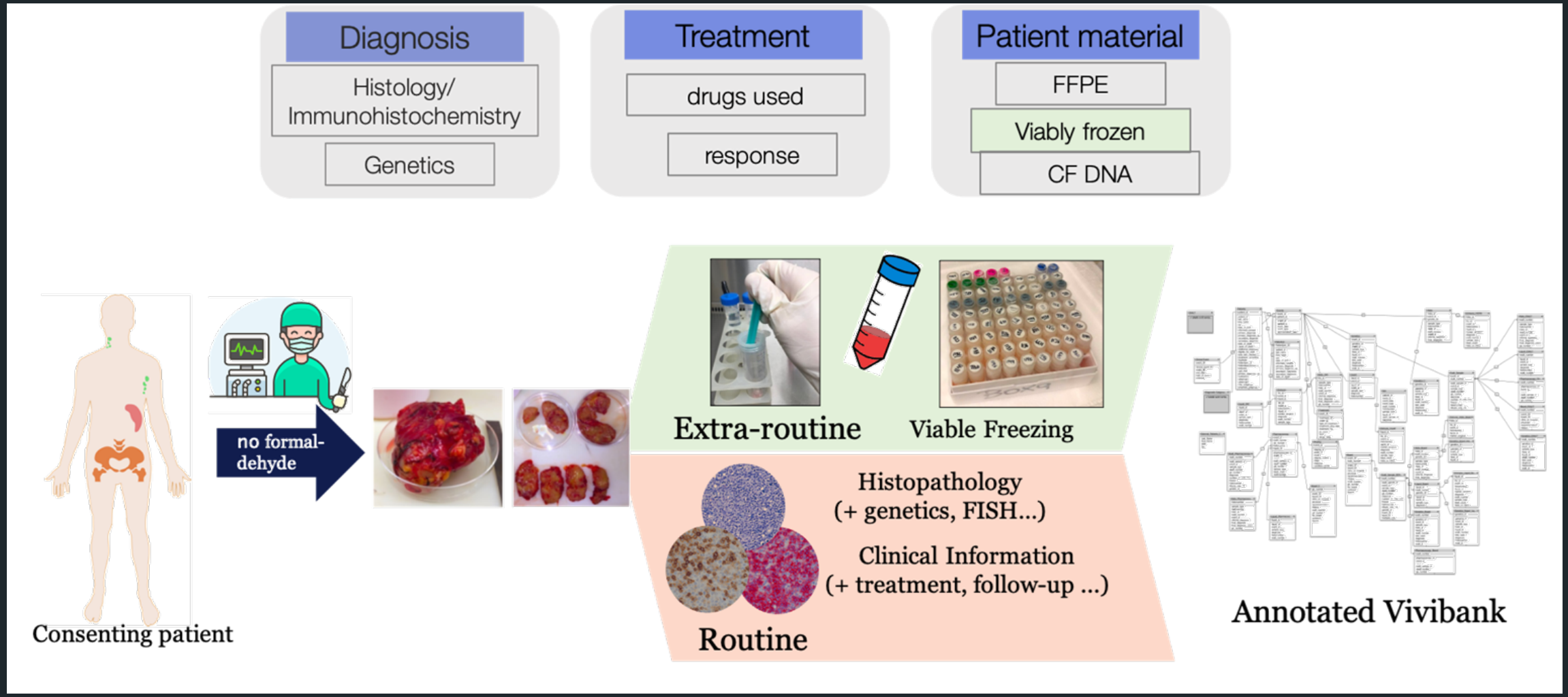

Screening
Inclusion criteria
Informed consent
Biopsy
Tissue
Liquid material
Formalin fixed
Native
EDTA tube
Heparin tube
Genetic characterization
Drug screening
Genetic characterization
Drug screening
Sent to Roche
Sent to MUW
Sent to Roche
Sent to MUW
Randomization
Tumorboard

Vivi-bank

Collaboration with Institute of Pathology



FOUNDATIONONE®HEME

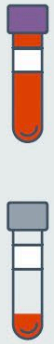
Specimen Instructions

Fresh Specimens (Peripheral Whole Blood or Bone Marrow Aspirate)

Lesional tissue should constitute >20% of nucleated elements for optimal analysis.

PERIPHERAL WHOLE BLOOD

- ☐ **1** Fill the EDTA (lavender-top) tube with blood (for submission, not for waste).
- ☐ **2** Collect 2.5mL blood in the PAXgene Blood RNA Tube (see separate instruction sheet for additional details).
  - a. Ensure that tube is at room temperature.
  - b. Always ensure that the PAXgene tube is the last tube drawn in the phlebotomy procedure.
- ☐ **3** Confirm that both the EDTA and PAXgene tubes are labelled with the specimen type (e.g., PB = peripheral blood), date of collection, and two unique patient identifiers (labels included in kit).
- ☐ **4** Ship BOTH tubes at ambient temperature, confirming expedited / overnight shipping with courier to guarantee next day delivery (see shipping instructions below for further details).



BONE MARROW ASPIRATE

- ☐ **1** Collect 2.5 mL bone marrow aspirate in one EDTA (lavender-top) tube.
- ☐ **2** Confirm tube is labelled with the specimen type (e.g., BMA = bone marrow aspirate), date of collection, and two unique patient identifiers (labels included in kit).
- ☐ **3** Ship at ambient temperature, confirming expedited / overnight shipping with courier to guarantee next day delivery (see shipping instructions below for further details).

FOUNDATIONONE®HEME

Specimen Instructions

Fresh Specimens (Peripheral Whole Blood or Bone Marrow Aspirate)

Additional Submission Requirements

1. Peripheral blood and bone marrow aspirate must be received the day after collection for optimal analysis, as sensitivity of detection may degrade with time. Please ensure specimens are shipped from Monday through Thursday, at ambient temperature, confirming expedited/overnight shipping with courier to guarantee next day delivery. Specimens shipped on Friday can only be received before 14.00 CET on Saturday.
2. Neoplastic/lesional cells must constitute at least 20% of nucleated cellular elements (tumour content will be determined based upon cytomorphologic review in conjunction with other supporting laboratory results when appropriate).
3. Specimens should NOT be frozen prior to submission.
4. Please submit concurrent or recent laboratory test results (e.g., CBC/differential, flow cytometry results, final bone marrow pathology report) if available.

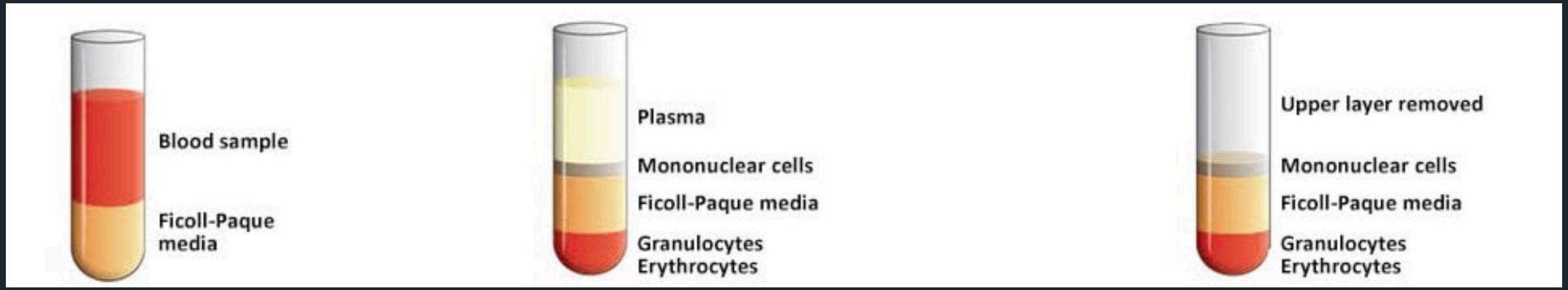
Extracted Nucleic Acid Submission Requirements

NUCLEIC ACID TYPE	SUBMISSION FORMAT	CONCENTRATION*	VOLUME	SHIPPING INSTRUCTIONS
DNA	Nuclease-free water	Picogreen: ≥3.5 ng/µl UV: ≥10 ng/µl	≥60 µl	Ship overnight, frozen on dry ice
RNA	Nuclease-free water	Ribogreen: ≥20 ng/µl	≥30 µl	Ship overnight, frozen on dry ice

* Please specify concentration on requisition form.

PB/BM sample preparation for drug screening application

- Combine PB/BM from at least two heparin tubes
- Perform Ficoll-density gradient mononuclear cell isolation
- Centrifugation 300 g for 30 min at RT (brake should be turned off)
- Draw off the upper layer containing plasma and platelets using a sterile pipette, leaving the mononuclear cell layer undisturbed at the interface
- Transfer the mononuclear cell fraction to a clean tube & wash with PBS



FOUNDATIONONE®HEME

Specimen Instructions

FFPE Specimens (Block or Slides)

DO NOT USE strong acids (e.g. hydrochloric acid, sulfuric acid, picric acid) as these destroy nucleic acid. When decalcification is required, the use of EDTA is recommended.

☐ **SAMPLE TYPE**

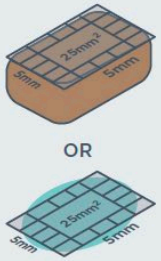
1 **FFPE BLOCK OR 16 UNSTAINED SLIDES (+ 1 H&E SLIDE)**

Tissue should be formalin-fixed and embedded into a paraffin block. Use standard fixation methods with 10% neutral-buffered formalin. DO NOT use other fixatives (AZF, B5, Bouin's, Holland's). If sending slides, send 16 unstained slides (charged and unbaked, with tissue cut at a 5 micron thickness), plus 1 H&E slide.

☐ **SURFACE AREA**

2 **OPTIMUM: 5 × 5 mm²**

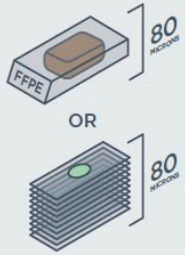
Tissue should have a surface area of at least 25 mm² (5 x 5 mm², 2.5 x 10 mm²).



☐ **SURFACE VOLUME**

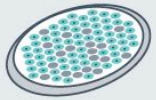
3 **OPTIMUM: 2 mm³**

Optimal sample volume can be achieved by sending optimal tissue surface area (25 mm²) at a depth of ≥80 microns. For suboptimal tissue surface area, additional depth is required.



☐ **NUCLEATED CELLULARITY**

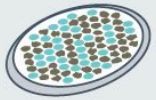
4 DNA is extracted from nucleated cells. Samples with low nucleated cellularity (e.g., those with abundant mature erythrocytes, lesional cells that contain excessive cytoplasm, or tissue with extensive associated fibrosis) may require greater tissue volume to yield sufficient DNA at extraction.



☐ **TUMOR CONTENT**

5 **MINIMUM: ≥20%**

If the ratio of nucleated malignant to nucleated non-malignant cells is too low, sensitivity of detection of certain classes of alterations is reduced. High tumor content is preferable.

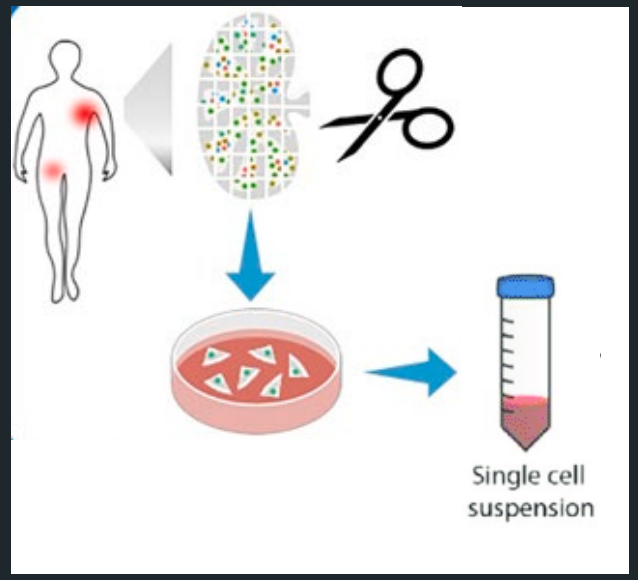


Note for liver specimens: Higher tumor content may be required because hepatocyte nuclei have twice the DNA content of other somatic nuclei.

Note: All cytologic and histologic specimens will be reviewed internally by a pathologist, and a determination of sample adequacy will be made. Additional or alternate material may be requested for optimal analysis.

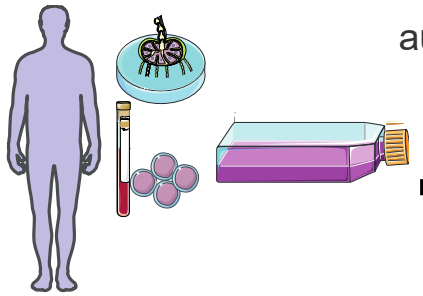
Tissue sample handling for drug screening application

- Place tissue in a Petri dish and cover completely with PBS
- Cut tissue into small pieces (≥0.5 cm) with a scalpel
- Place tea strainer on an Erlenmeyer flask
- Place 3-4 pieces of chopped tissue into the sieve and push them through with a plunger (5mL syringe)
  - rinse with PBS
  - repeat until all tissue has been processed
- Filter the suspension through a 70µm cell strainer
- Centrifuge 100g for 10min at RM
- Resuspend pellet in warm media
- Filter the suspension once more
- Count cells and aliquot
- If extra cells freeze @ -80℃ using Mr. Frosty



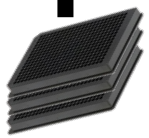
if shipping from other sites ship frozen cells on dry ice avoiding shipment on Fridays

Ex-vivo drug testing platform MUW

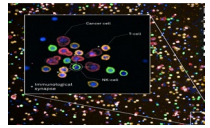


Leukemia / Lymphoma patient cells

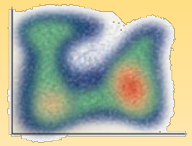
MultiFlo™ FX
automated multi-mode reagent dispenser



Acoustic compound transfer

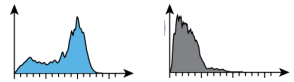


Automated imaging

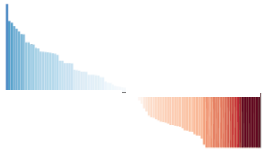


iQue3
Automated high throughput flow cytometer

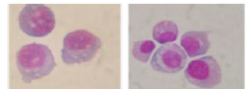
Quantification of marker surface expression



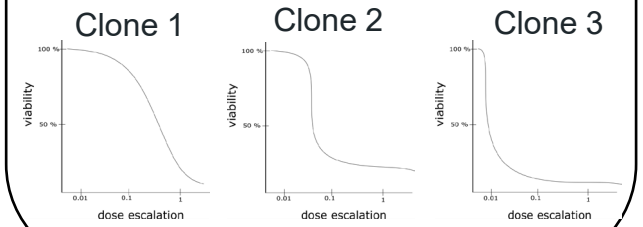
Cancer selective killing



Cell Differentiation



Clonal drug response tracking



eha Sf(PM)

Discussion points

Strategies for dealing with unforeseen delays or damaged shipments

Ensuring sample viability for cutting-edge tests

Importance of backup plans for specimen storage in case of equipment failures

Future trends in specimen handling

Can you share a case study or example where proper or improper handling significantly impacted specimen integrity?

What are the most common pitfalls in specimen handling, and what proactive steps can be taken to avoid them?

How can organizations prepare backup plans for specimen storage in the event of equipment failure or power outages?

What role does staff training play in mitigating risks related to specimen handling and shipping?