Lecture 11:

Precision Medicine and Biomarkers

- Personalized treatment era
- Success stories
- Patient impact

Introduction to Biomedical Data Science

Lecture Contents

Part 1/3:

Precision Medicine

- Conceptual framework

- Technology enablers

- Clinical applications

Personalized vs Precision Medicine

Terminology Evolution

- N-of-1 trials
- Population stratification
- Individual variability

Clinical Approaches

- Targeted therapies
- Genomic profiling
- Treatment optimization

Healthcare Economics

Precision medicine balances cost-effectiveness with improved patient outcomes through targeted interventions, reducing trial-and-error approaches and minimizing adverse drug reactions.

Pharmacogenomics (PGx)

Genetic Variant
SNPs in drug-related genes   CYP2D6*4

↓

Altered Function
Changed enzyme activity or expression level

↓

Drug Metabolism
Modified drug exposure and response

↓

Clinical Outcome
Efficacy, toxicity, or adverse reactions

↓

Dose Adjustment
Personalized dosing recommendation

PGx Variants
Genetic variations affecting drug response, metabolism, and efficacy

Drug Metabolism
CYP450 enzymes and transporter polymorphisms impact drug levels

Dosing Algorithms
Genotype-guided dosing for warfarin, clopidogrel, and more

CPIC Guidelines
Clinical Pharmacogenetics Implementation Consortium standards

Implementation Barriers: Cost, infrastructure, education, and workflow integration remain challenges for widespread PGx adoption

Cancer Genomics

STAGE 1: INITIATION

🎯 **First Driver Mutation**

Mutation provides growth advantage (e.g., TP53, KRAS)

STAGE 2: EXPANSION

📈 **Clonal Expansion**

Cell population grows, accumulates passenger mutations

STAGE 3: PROGRESSION

⚡ **Additional Drivers**

Sequential genetic changes drive tumor progression

STAGE 4: HETEROGENEITY

🌳 **Branching Evolution**

Multiple subclones emerge with distinct genetic profiles

STAGE 5: METASTASIS

🚀 **Invasive Phenotype**

Cells acquire ability to invade and colonize distant sites

🎯 **Driver Mutations**

Mutations providing selective growth advantage to cancer cells

⚪ **Passenger Mutations**

Neutral mutations accumulated during tumor evolution

🌱 **Clonal Evolution**

Tumor progression through sequential genetic changes

✖️ **Tumor Heterogeneity**

Genetic diversity within and between tumors

Tumor Profiling

NGS Panels

Next-generation sequencing for comprehensive mutation analysis

TMB Assessment

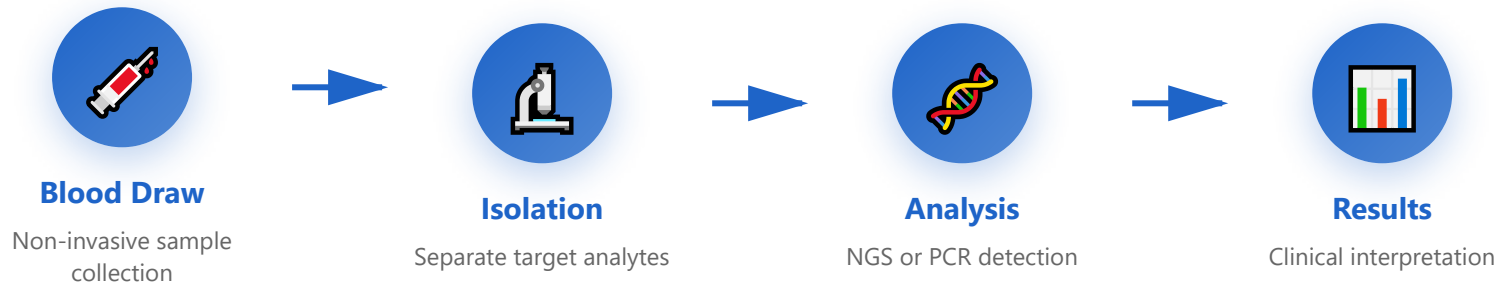Tumor Mutational Burden predicts immunotherapy response

MSI Status

Microsatellite Instability as biomarker for treatment selection

HRD Testing

Homologous Recombination Deficiency guides PARP inhibitor use

PD-L1 Expression: Key biomarker for immune checkpoint inhibitor therapy eligibility

Liquid Biopsy

Blood Draw
Non-invasive sample collection

Isolation
Separate target analytes

Analysis
NGS or PCR detection

Results
Clinical interpretation

ctDNA Detection
Circulating tumor DNA analysis from blood samples

CTCs Analysis
Circulating Tumor Cells isolation and characterization

Exosomes
Extracellular vesicles carrying tumor-derived molecules

Early Detection
Non-invasive screening for cancer presence

Monitoring Response: Real-time treatment efficacy assessment through serial sampling

Companion Diagnostics

FDA Co-development
Simultaneous drug and diagnostic test development

Test Validation
Analytical and clinical validation requirements

Labeling Requirements
Regulatory guidelines for test-drug pairing

Market Examples
HER2 testing, EGFR mutations, ALK rearrangements

Future Trends: Multi-gene panels and liquid biopsy-based companion diagnostics

Part 2/3:

Biomarker Discovery

- Discovery strategies

- Validation frameworks

- Statistical considerations

Types of Biomarkers

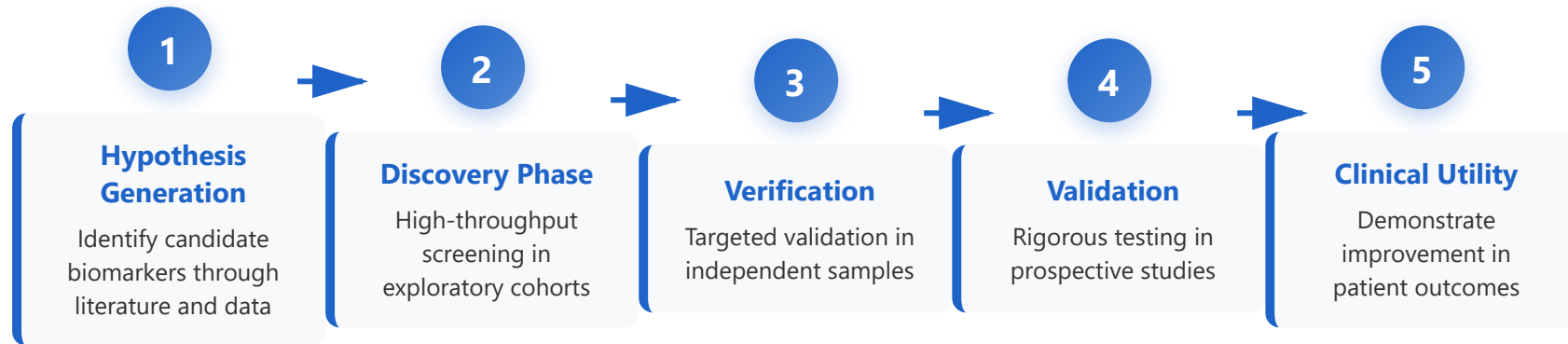|	
Diagnostic	Identify presence or absence of disease
Prognostic	Predict disease outcome independent of treatment
Predictive	Forecast response to specific therapy
Pharmacodynamic	Measure biological response to treatment
Safety	Detect potential adverse effects or toxicity

Each biomarker type serves distinct clinical purposes in precision medicine workflows

Discovery Pipeline

1

Hypothesis Generation

Identify candidate biomarkers through literature and data

2

Discovery Phase

High-throughput screening in exploratory cohorts

3

Verification

Targeted validation in independent samples

4

Validation

Rigorous testing in prospective studies

5

Clinical Utility

Demonstrate improvement in patient outcomes

⚠️ Attrition rate is high - most candidates fail before reaching clinical implementation

Statistical Methods

Feature Selection   LASSO, elastic net, random forests for variable selection

Multiple Testing   FDR correction and permutation-based adjustments
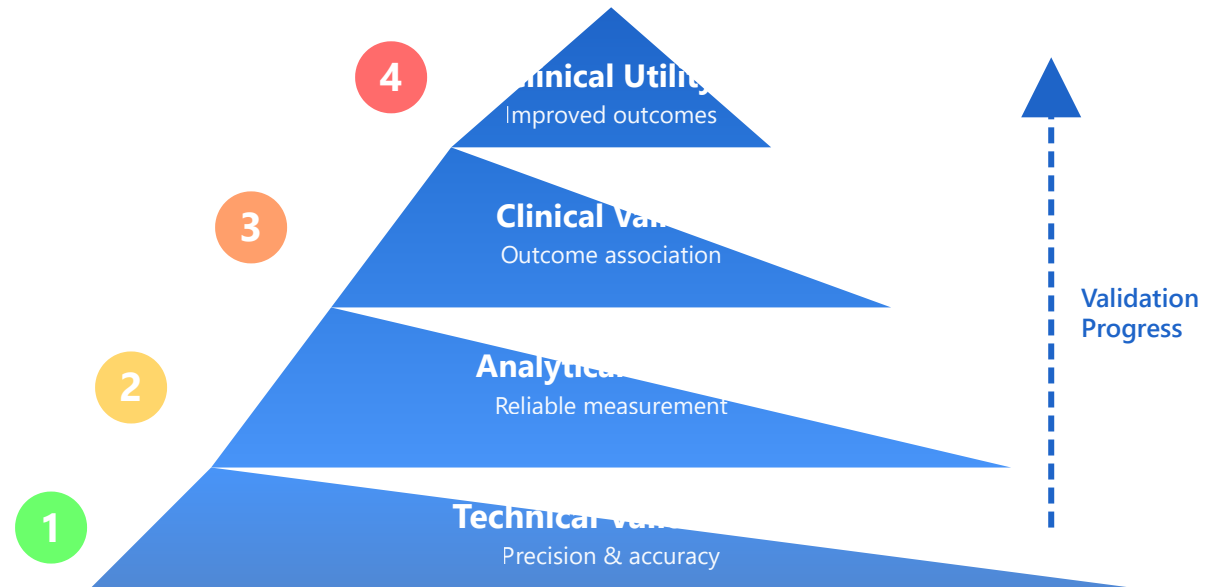
Cross-validation   K-fold CV and nested CV prevent overfitting

Bootstrap CI   Confidence intervals through resampling methods

Power Analysis: Essential for determining adequate sample size and detecting true effects

Validation Strategies

4 Technical Utility
Improved outcomes

3 Clinical Validation
Outcome association

2 Analytical Validation
Reliable measurement

1 Technical Validation
Precision & accuracy

Validation Progress

Technical
Assay precision, accuracy, and reproducibility in controlled settings

Analytical
Reliable and accurate measurement of biomarker across conditions

Clinical
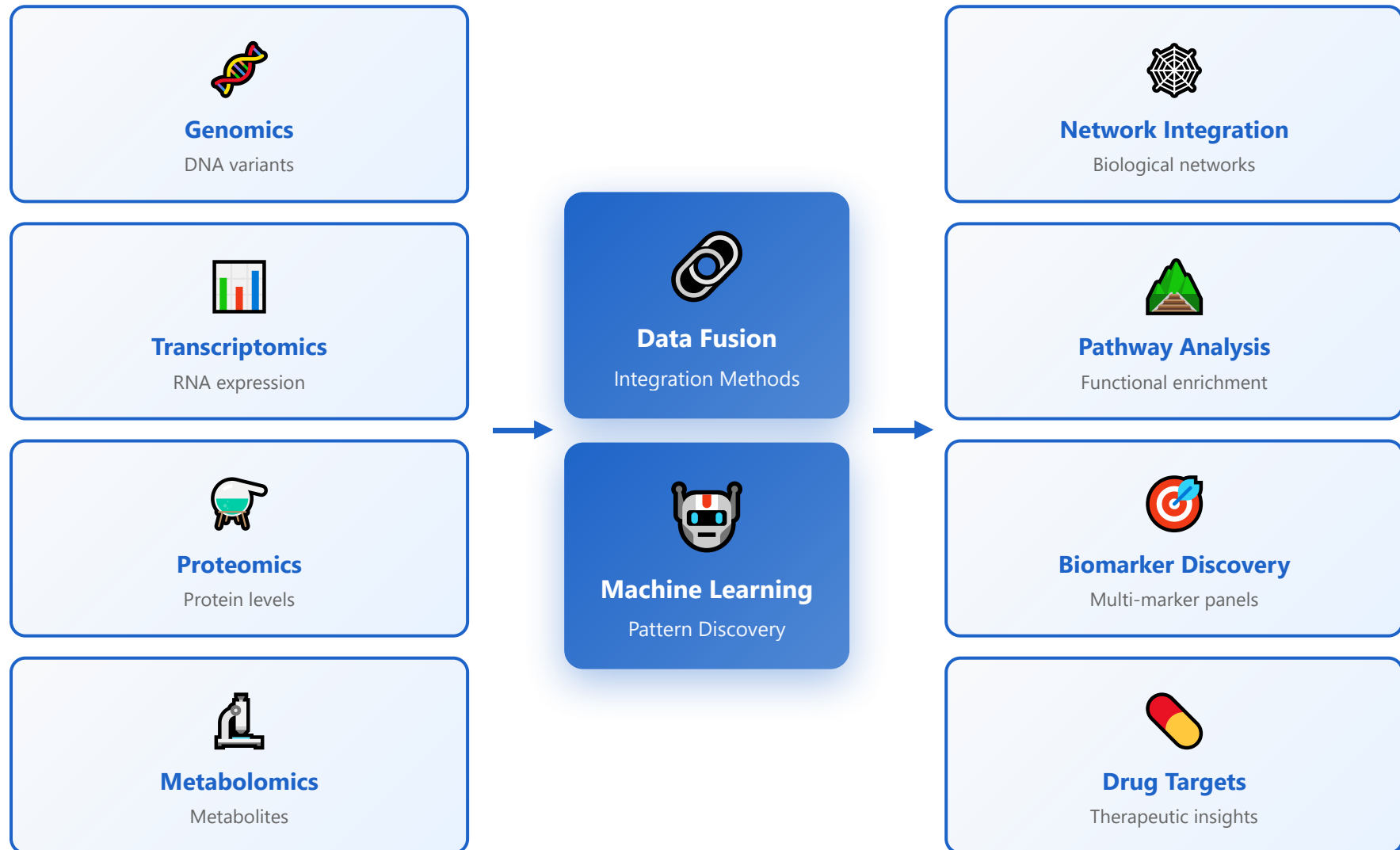Performance and association with outcome in patient population
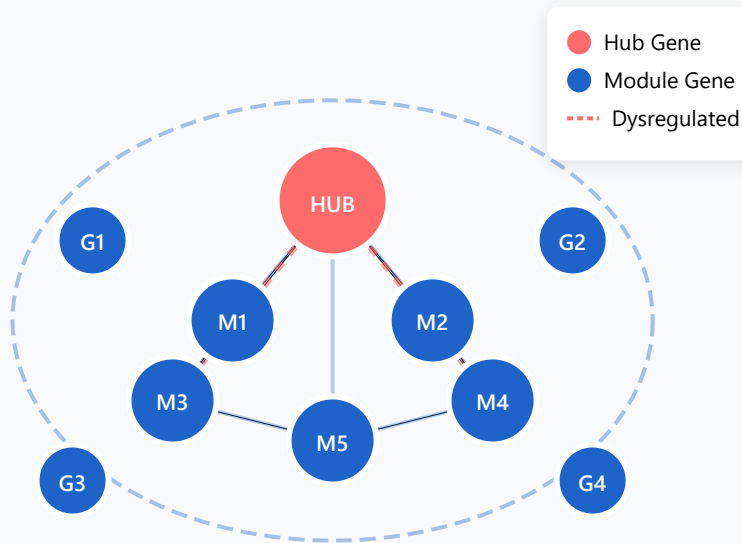
Utility
Improves decision-making and patient outcomes in practice

Clinical Utility: Biomarker must improve decision-making and patient outcomes in practice

Multi-omics Integration

Genomics
DNA variants

Transcriptomics
RNA expression

Proteomics
Protein levels

Metabolomics
Metabolites

Data Fusion
Integration Methods

Machine Learning
Pattern Discovery

Network Integration
Biological networks

Pathway Analysis
Functional enrichment

Biomarker Discovery
Multi-marker panels

Drug Targets
Therapeutic insights

Network Biomarkers

Hub Gene
Module Gene
Dysregulated

HUB
G1
G2
M1
M2
M3
M4
M5
G3
G4

Module Identification
Detect functional gene/protein modules

Hub Genes
Central nodes in biological networks

Edge Biomarkers
Dysregulated interactions between molecules

Dynamic Networks
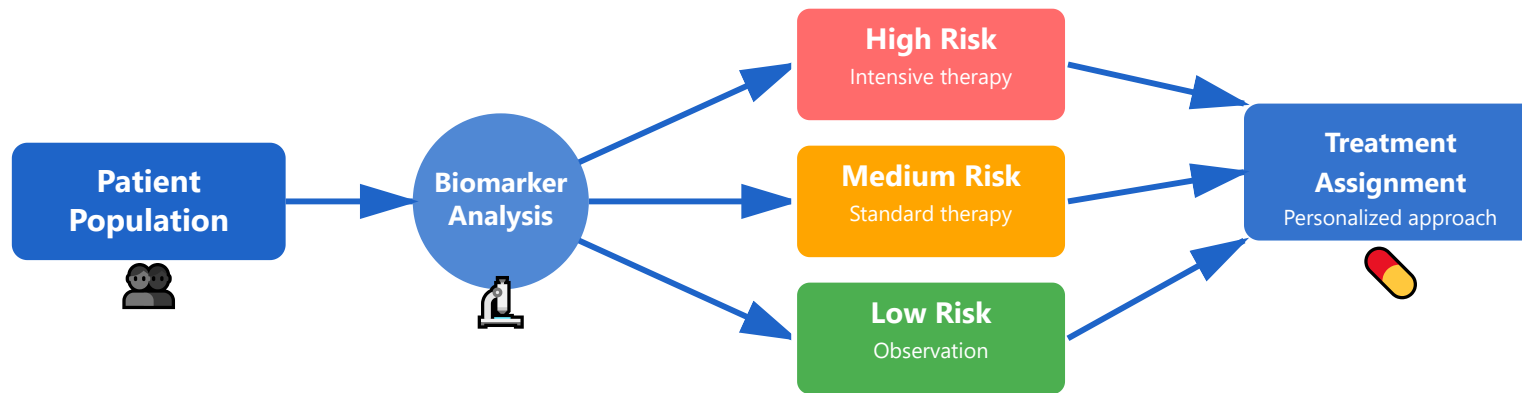Time-varying network states

Robustness Analysis: Network biomarkers often more stable than individual markers

Part 3/3:

Clinical Translation

- Implementation strategies
- Real-world evidence
- Healthcare integration

Patient Stratification

Patient Population

Biomarker Analysis

High Risk
Intensive therapy

Medium Risk
Standard therapy

Low Risk
Observation

Treatment Assignment
Personalized approach

🎯 **Subgroup Identification**

Clustering and classification to define patient groups

📊 **Risk Groups**

Stratify patients by disease risk or prognosis

💊 **Treatment Assignment**

Match therapies to molecular profiles

✨ **Enrichment Strategies**

Select patients likely to benefit from intervention

Treatment Selection

Decision Algorithms

Computational tools for treatment recommendations

Combination Therapies

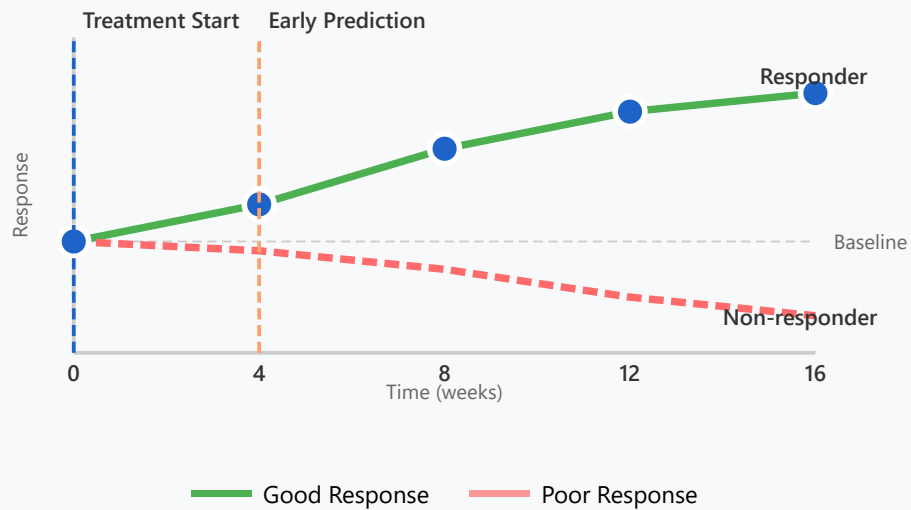Biomarker-guided multi-drug regimens

Sequential Treatments

Treatment sequencing based on molecular changes

Resistance Mechanisms

Anticipate and overcome therapy resistance

Cost-effectiveness: Balance improved outcomes with healthcare resource utilization

Response Prediction

Response

Treatment Start   Early Prediction

Responder

Baseline

Non-responder

0   4   8   12   16
Time (weeks)

━━━ Good Response   ┅┅┅ Poor Response

⚡ Early Indicators

Biomarkers predicting response before clinical signs

🎯 Surrogate Endpoints

Intermediate markers replacing clinical outcomes
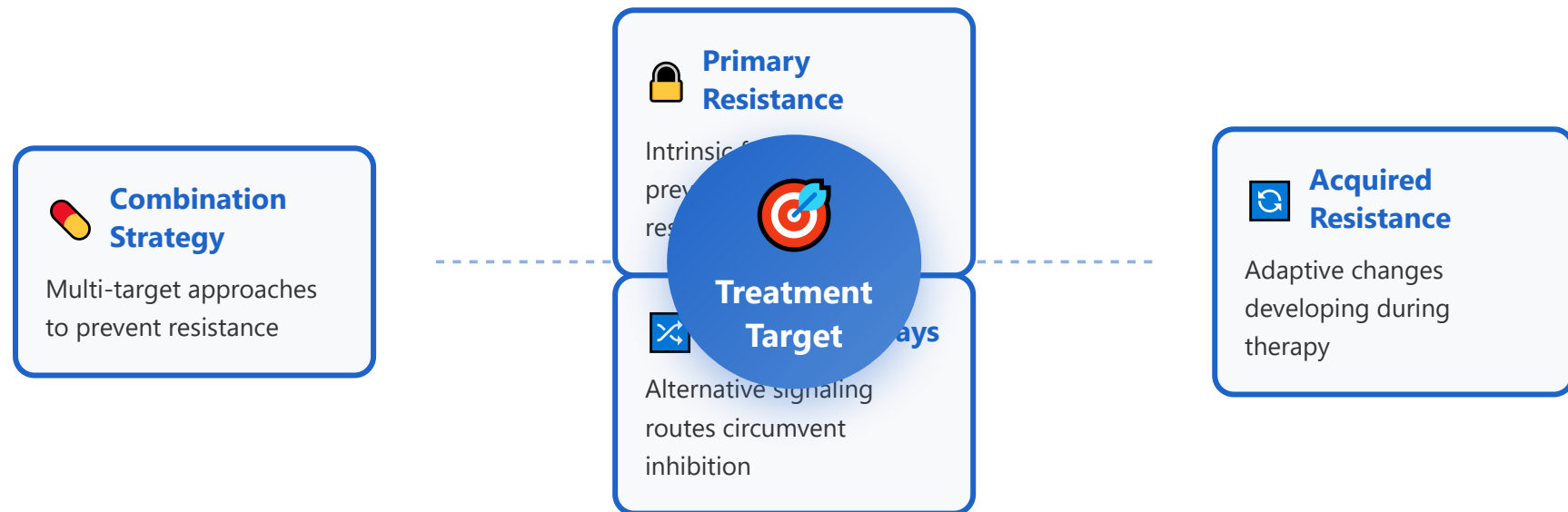
📷 Imaging Biomarkers

Radiological features predicting treatment response

🧬 ctDNA Dynamics

Circulating DNA changes track treatment efficacy

Resistance Prediction: Anticipate resistance before clinical progression occurs

Resistance Mechanisms

Combination Strategy

Multi-target approaches to prevent resistance

Primary Resistance

Intrinsic f...
prev...
res...

Treatment Target

Alternative signaling routes circumvent inhibition

Acquired Resistance

Adaptive changes developing during therapy

Monitoring Approaches: Serial biopsies and liquid biopsy track resistance evolution

Clinical Trial Design

Basket Trials
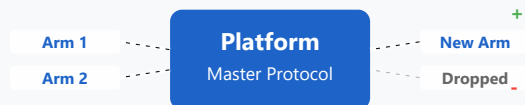Multiple tumor types with same molecular alteration

Lung — Melanoma — BRAF — Colon — Thyroid

Umbrella Trials
Single disease with multiple biomarker-driven arms

NSCLC → EGFR+ — ALK+ — KRAS+

Platform Trials
Perpetual trials adding/dropping arms dynamically

Arm 1 — Arm 2 — Platform (Master Protocol) — New Arm + — Dropped −

Biomarker-stratified
Randomization based on biomarker status

Patients — Test — Positive → Drug A — Negative → Drug B

Master Protocols: Efficient frameworks for precision oncology trials

Regulatory Approval

Biomarker Qualification

FDA/EMA process to approve biomarkers

Context of Use

Specific intended application of biomarker

Evidence Requirements

Standards for analytical and clinical validation

Global Harmonization

Align biomarker standards across regions

Expedited Pathways: Breakthrough designations accelerate biomarker-drug approval

Cost-effectiveness

QALY Analysis

Quality-Adjusted Life Years in economic evaluation

Budget Impact

Healthcare system financial implications

Value Frameworks

ASCO, ESMO, NCCN value assessment tools

Reimbursement

Insurance coverage and payment models

Access Issues: Balance innovation with affordability and equitable distribution

Implementation Barriers

Technical Challenges

Assay complexity and standardization needs

Clinical Workflow

Integration into existing healthcare systems

Education Needs

Training clinicians in precision medicine

Infrastructure

Lab capabilities and IT systems requirements

Equity Concerns: Ensure access across socioeconomic and geographic boundaries

🎯 Precision Medicine Success Stories

HER2+ Breast Cancer

Trastuzumab (Herceptin)

First companion diagnostic: **HER2 testing** identifies patients who benefit from targeted therapy. Dramatically improved survival in HER2+ patients.

CML Treatment Revolution

Imatinib (Gleevec)

Targeting **BCR-ABL fusion** transformed CML from fatal to manageable chronic disease. 5-year survival >90%.

MSI-High Cancers

Pembrolizumab (Keytruda)

First tissue-agnostic approval based on **MSI biomarker**. Immunotherapy success across multiple cancer types.

Melanoma Breakthrough

BRAF Inhibitors

BRAF V600E mutation testing enables combination therapy. Median survival improved from 9 to 25+ months.

CAR-T Cell Therapy

Tisagenlecleucel (Kymriah)

💡 Key Lessons

• Strong biomarker-target link
• Rigorous validation studies
• Drug-diagnostic co-development

CD19+ B-cell targeting in leukemia/lymphoma. Complete remission in 80%+ of refractory patients.

🚀 Future Directions in Precision Medicine

🔬 Single-cell Biomarkers
Tumor heterogeneity analysis at single-cell resolution for personalized therapy

📱 Digital Biomarkers
Wearables and mobile health monitoring for continuous patient assessment

🤖 AI-discovered Biomarkers
Machine learning identifies novel patterns invisible to traditional analysis

🧬 Combination Panels
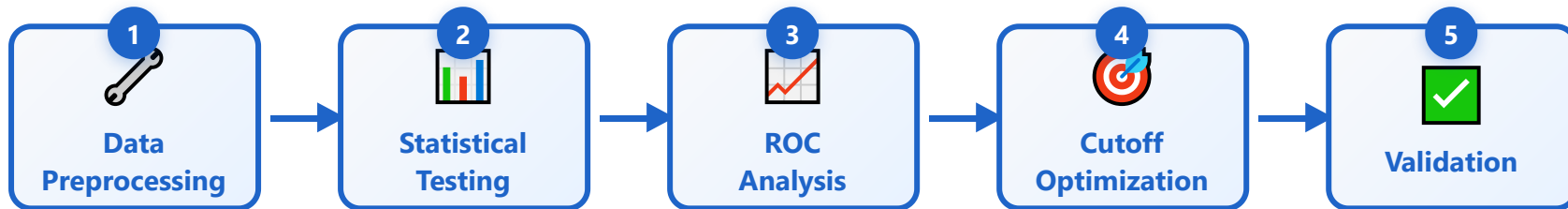Multi-biomarker signatures improve accuracy and clinical utility

Dynamic Monitoring

Real-time tracking of disease evolution and treatment response

Vision: Seamless integration of multi-modal biomarkers into routine clinical care

💻 Hands-on: Biomarker Analysis Pipeline

1 Data Preprocessing	→	2 Statistical Testing	→	3 ROC Analysis	→	4 Cutoff Optimization	→	5 Validation

🔑 Key Steps

▸ Normalize and quality control data

▸ Feature selection with LASSO/elastic net

▸ Statistical comparison (t-test, ANOVA)

▸ Multiple testing correction (FDR, Bonferroni)

📏 Performance Metrics

▸ AUC-ROC for discrimination ability

▸ Sensitivity, specificity, PPV, NPV

▸ Cross-validation for robustness

▸ Independent cohort validation

💻 Hands-on: Patient Stratification Methods

📊 Clustering Methods

K-means, hierarchical clustering, and consensus clustering to identify patient subgroups based on molecular profiles

📈 Risk Score Development

Cox regression and machine learning models to create prognostic scores for treatment decisions

⏱ Survival Analysis

Kaplan-Meier curves, log-rank tests, and Cox proportional hazards models for outcome prediction

🔄 Treatment Interaction

Subgroup analysis to identify biomarker-treatment interactions and optimal therapy assignment

📉 Visualization

✅ Cross-validation

Heatmaps, forest plots, and interactive dashboards for communicating stratification results

Internal validation with bootstrap and external validation in independent cohorts

🛠️ Tools & Packages

scikit-learn	lifelines	survminer
ComplexHeatmap	ggplot2	plotly

Thank You

🎯 **Precision Health**

🛡️ **Prevention Focus**

🌍 **Global Implementation**

🤝 **Equitable Access**

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