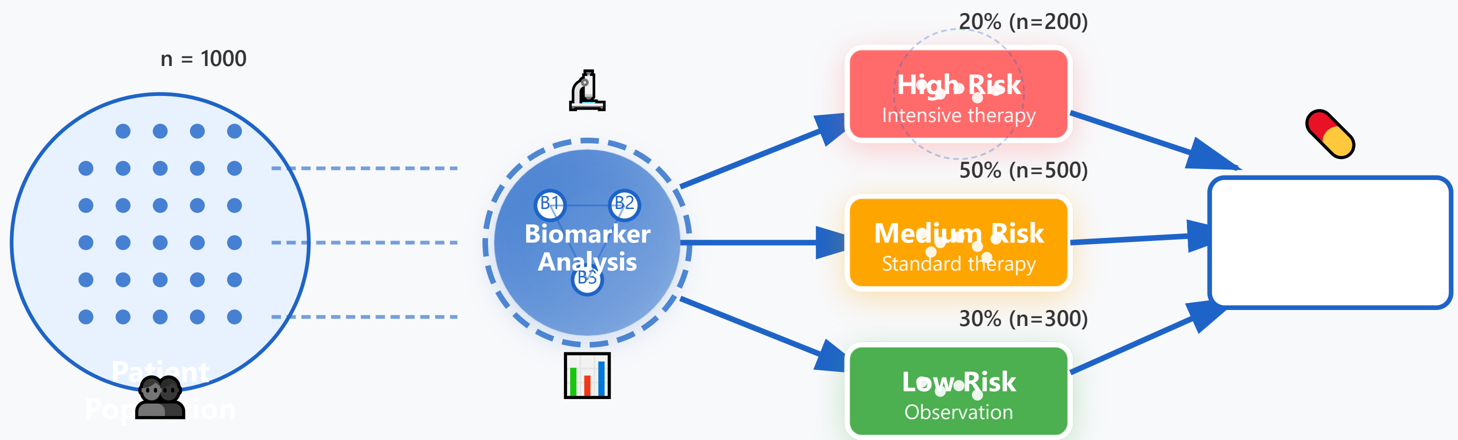
Patient Stratification



🎯 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

Adaptive Designs: Trial designs that evolve based on accumulating biomarker data

1. Subgroup Identification 🎯

🔍 What is Subgroup Identification?

Subgroup identification is the process of discovering and defining distinct patient populations within a larger heterogeneous cohort based on shared biological, clinical, or molecular characteristics. This approach recognizes that patients with the same diagnosis may have fundamentally different disease mechanisms requiring tailored therapeutic approaches.

Core Principle: Not all patients with the same disease label respond identically to treatment. By identifying molecular and phenotypic subtypes, we can optimize therapeutic strategies for each subgroup.

🎯 Key Objectives

- Discover biologically distinct patient subpopulations
- Identify predictive biomarkers for treatment response
- Enable precision medicine approaches
- Improve clinical trial efficiency and success rates

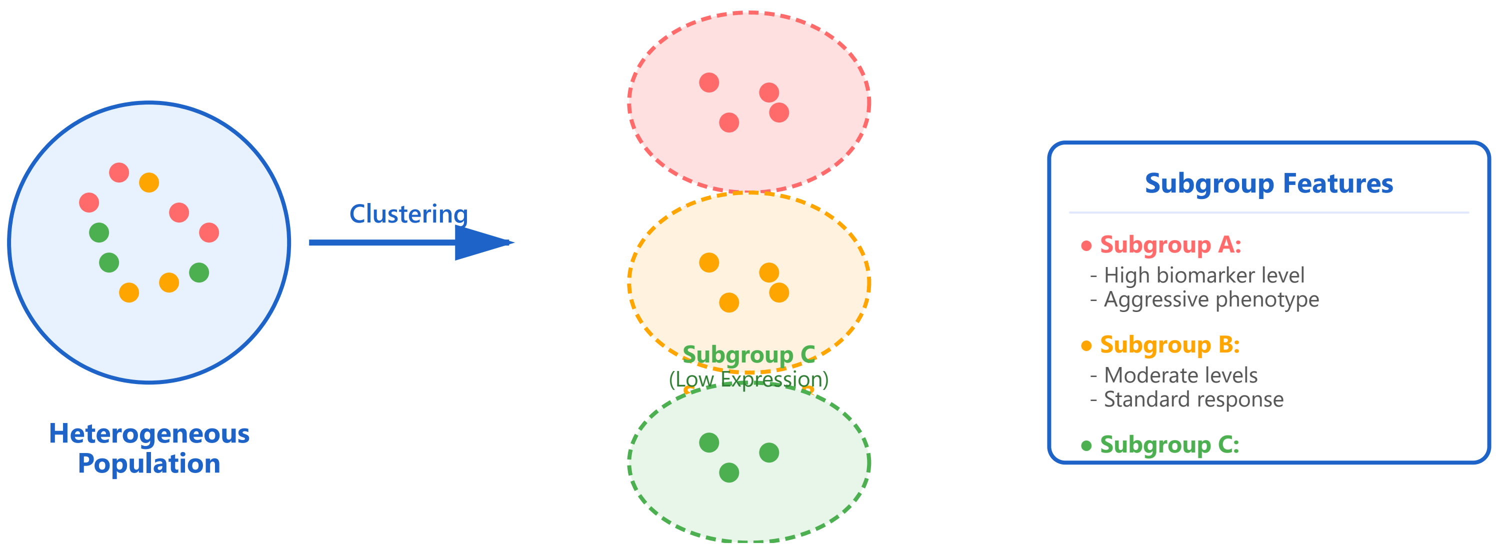


Figure 1: Transformation of heterogeneous patient population into distinct molecular subgroups

🧬 Unsupervised Clustering

Methods: K-means, hierarchical clustering, consensus clustering
Data: Gene expression, genomic mutations, multi-omics profiles
Output: Natural groupings without predefined labels

🎯 Supervised Classification

Methods: Random forests, SVM, neural networks
Data: Labeled training data with known outcomes
Output: Predictive models for subgroup assignment

📊 Pathway Analysis

Methods: GSEA, pathway enrichment, network analysis
Data: Gene sets, signaling pathways, biological networks
Output: Mechanistically distinct subgroups

🔬 Biomarker-Driven

Methods: Threshold-based stratification, composite scores
Data: Specific biomarkers (e.g., HER2, EGFR, PD-L1)
Output: Clinically actionable subgroups

💡 Clinical Example: Breast Cancer Molecular Subtypes

- **Luminal A:** ER+/PR+, HER2-, low Ki-67 → Excellent prognosis, hormone therapy responsive
- **Luminal B:** ER+/PR+/-, HER2+/-, high Ki-67 → Intermediate prognosis, may need chemotherapy

- **HER2-enriched:** ER-, PR-, HER2+ → Responds to anti-HER2 targeted therapy (trastuzumab)
- **Triple-negative/Basal-like:** ER-, PR-, HER2- → Aggressive, requires chemotherapy

2. Risk Groups 📊

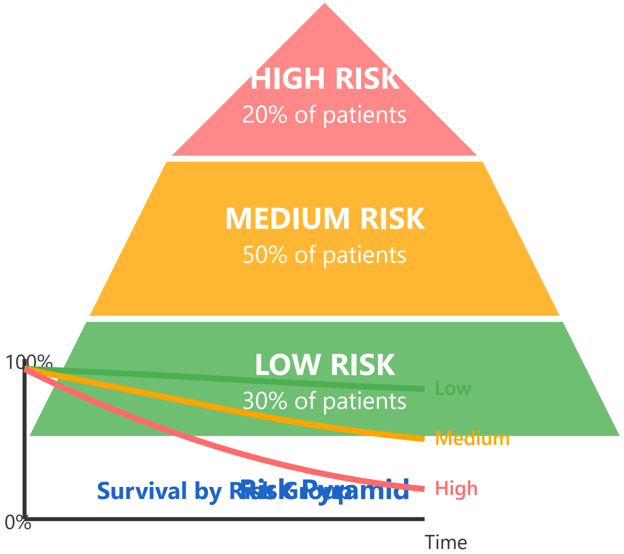
⚖️ What are Risk Groups?

Risk stratification is the systematic classification of patients into categories based on their probability of experiencing adverse outcomes, disease progression, or treatment complications. This approach enables clinicians to match the intensity of intervention to the level of risk, avoiding both under-treatment and over-treatment.

Core Principle: Different patients have different baseline risks and prognoses. By accurately stratifying risk, we can optimize resource allocation, intensify treatment for high-risk patients, and spare low-risk patients from unnecessary toxicity.

📈 Risk Stratification Goals

- Predict disease-free survival and overall survival
- Estimate probability of recurrence or metastasis
- Guide treatment intensity decisions
- Inform surveillance and monitoring strategies
- Enable personalized prognostic counseling



Risk Stratification Factors

📋 Clinical Factors

- Age, performance status
- Disease stage, tumor size
- Comorbidities, prior treatment

🧬 Molecular Factors

- Genetic mutations (TP53, KRAS)
- Gene expression signatures
- Chromosomal abnormalities

🔬 Laboratory Markers

- Tumor markers (PSA, CEA, CA-125)
- Inflammatory markers (CRP, LDH)

Figure 2: Risk stratification pyramid and corresponding survival outcomes

📐 Scoring Systems

Examples: APACHE, GRACE, CHA_2DS_2-VASc
Approach: Weighted sum of clinical variables
Advantage: Simple, interpretable, widely validated

🎯 Nomograms

Examples: Memorial Sloan Kettering nomograms
Approach: Graphical regression models
Advantage: Individualized risk prediction

🧬 Molecular Signatures

Examples: Oncotype DX, MammaPrint, Decipher
Approach: Multi-gene expression panels
Advantage: Biological insight, high accuracy

🤖 Machine Learning Models

Methods: Cox regression, random survival forests, deep learning
Approach: Integrate complex multi-dimensional data
Advantage: Handle non-linear relationships

💡 Clinical Example: Prostate Cancer Risk Stratification (D'Amico Classification)

- **Low Risk:** PSA ≤10 ng/mL AND Gleason score ≤6 AND stage T1c-T2a
  → Treatment: Active surveillance or focal therapy
- **Intermediate Risk:** PSA 10-20 ng/mL OR Gleason score 7 OR stage T2b
  → Treatment: Radiation + short-term hormone therapy OR surgery
- **High Risk:** PSA >20 ng/mL OR Gleason score 8-10 OR stage ≥T2c
  → Treatment: Radiation + long-term hormone therapy + chemotherapy

3. Treatment Assignment 💊

🎯 What is Treatment Assignment?

Treatment assignment is the precision medicine approach of matching specific therapeutic interventions to individual patients or patient subgroups based on their unique molecular, genetic, and clinical profiles. This strategy moves beyond one-size-fits-all protocols to deliver personalized treatment plans that maximize efficacy while minimizing toxicity.

Core Principle: The right treatment for the right patient at the right time. By matching therapies to the underlying molecular drivers of disease, we can dramatically improve response rates and reduce unnecessary adverse effects from ineffective treatments.

🎯 Treatment Selection Objectives

- Match targeted therapies to actionable biomarkers
- Predict treatment response and toxicity

- Optimize drug-target engagement
- Avoid treatments likely to be ineffective
- Sequence therapies based on resistance mechanisms

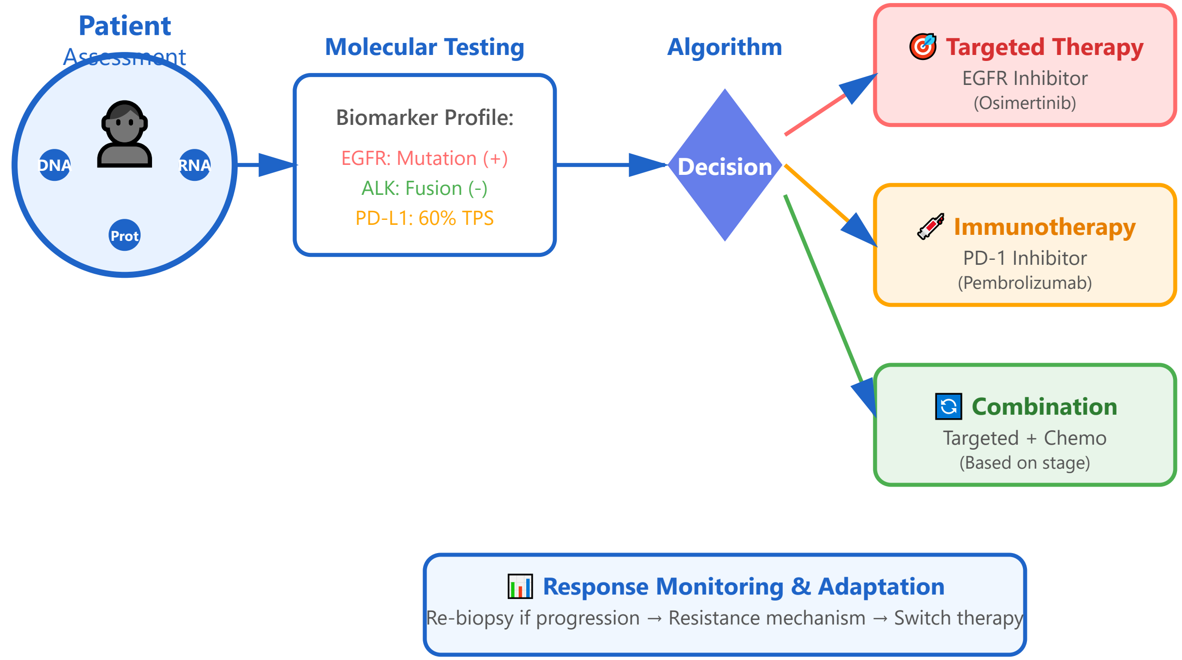


Figure 3: Biomarker-driven treatment assignment workflow

🧬 Genomic Matching

Approach: Identify actionable mutations

Examples: EGFR mutations → EGFR-TKIs, BRAF V600E → BRAF inhibitors

Tools: Next-generation sequencing, liquid biopsy

🎯 Protein Biomarkers

Approach: Target overexpressed proteins

Examples: HER2+ → Trastuzumab, PD-L1+ → Immunotherapy

Tools: IHC, flow cytometry, mass spectrometry

📊 Expression Signatures

🔬 Functional Testing

Approach: Multi-gene predictive models
Examples: Oncotype DX for chemotherapy benefit
Tools: Gene expression profiling, RNA-seq

Approach: Test drug sensitivity ex vivo
Examples: Organoid drug screening, PDX models
Tools: 3D culture systems, patient-derived models

💡 Clinical Example: Non-Small Cell Lung Cancer (NSCLC) Treatment Assignment

- **EGFR Mutation Positive:** First-line osimertinib (3rd generation EGFR-TKI)
  → Response rate: 80%, PFS: 18 months vs 10 months with chemotherapy
- **ALK Rearrangement Positive:** First-line alectinib (ALK inhibitor)
  → Superior CNS penetration, PFS: 34 months vs 11 months with chemotherapy
- **PD-L1 ≥50%, No Driver Mutations:** First-line pembrolizumab (PD-1 inhibitor)
  → OS benefit: 20 months vs 12 months with chemotherapy
- **No Actionable Alterations:** Platinum-based chemotherapy ± immunotherapy
  → Standard approach when targeted options not available

4. Enrichment Strategies ✨

🔍 What are Enrichment Strategies?

Enrichment strategies in clinical trials involve the selective recruitment of patients who are most likely to benefit from an investigational therapy, thereby increasing the probability of detecting a true treatment effect. This approach maximizes trial efficiency by focusing resources on responsive populations while protecting patients unlikely to benefit from unnecessary exposure to experimental treatments.

Core Principle: Not every patient will benefit equally from an intervention. By enriching trial populations with biomarker-selected patients who have the highest likelihood of response, we can reduce sample sizes, shorten trial duration, and increase the probability of regulatory success.

🎯 Enrichment Strategy Goals

- Increase statistical power to detect treatment effects
- Reduce sample size requirements and trial costs
- Improve patient safety by avoiding futile treatments
- Accelerate drug development timelines
- Enable biomarker-driven drug approvals

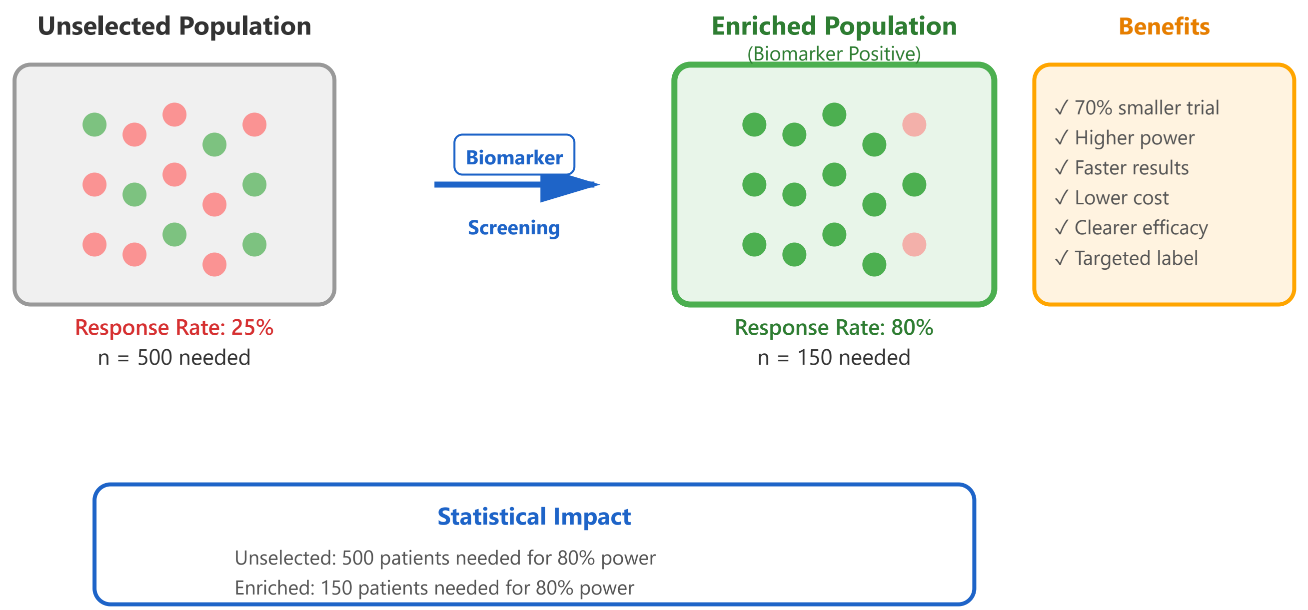


Figure 4: Comparison of unselected vs biomarker-enriched clinical trial populations

🎯 Prognostic Enrichment

Goal: Select patients at high risk of events
Rationale: Increases event rates, reduces follow-up time
Example: High-risk cardiovascular patients for prevention trials

🧬 Predictive Enrichment

Goal: Select patients likely to respond to therapy
Rationale: Increases treatment effect size
Example: HER2+ breast cancer for anti-HER2 therapy

📊 Pharmacodynamic Enrichment

Goal: Ensure target engagement in study population
Rationale: Confirms mechanism of action
Example: Demonstrating pathway inhibition in dose-finding

🔬 Adaptive Enrichment

Goal: Modify enrollment during trial based on interim data
Rationale: Optimize enrollment in real-time
Example: Focus on biomarker+ subgroup if showing benefit

💡 Clinical Example: Vemurafenib Development for Melanoma

- **Traditional Approach (hypothetical):** All metastatic melanoma patients
  → BRAF V600E prevalence: ~50%, Response rate in unselected: 24%
  → Would require ~600 patients for adequate power
- **Enrichment Strategy (actual):** Only BRAF V600E-positive patients enrolled
  → Response rate in enriched population: 48% (doubled)
  → Required only 132 patients in Phase II trial
  → Received FDA breakthrough therapy designation
- **Outcome:** Dramatic acceleration of development timeline
  → Approval within 4 years of Phase I initiation
  → Clear indication: BRAF V600E-positive metastatic melanoma
  → Companion diagnostic (cobas® BRAF mutation test) approved simultaneously

⚖️ Considerations for Enrichment

- **Biomarker validation:** Ensure robust analytical and clinical validity
- **Prevalence:** Balance enrichment benefit vs screening burden
- **Label implications:** Restricted indication may limit market but ensure appropriate use
- **Health equity:** Ensure biomarker testing is accessible to all populations

- **Companion diagnostics:** Develop and validate alongside therapeutic