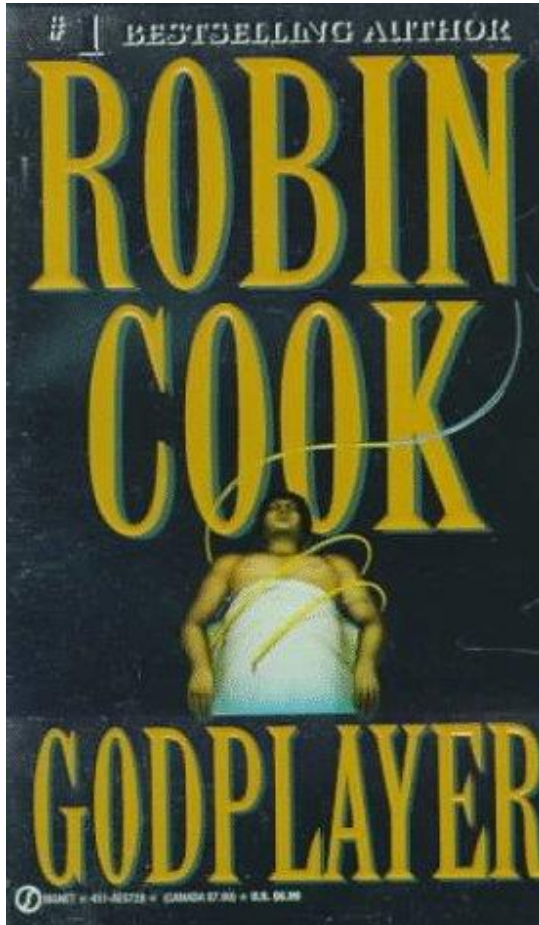# Precision Pathology
– *A new frontier*

X. Frank Zhao, MD PhD MBA

Professor & Chair

Department of Pathology

Physicians

"Surgeons know nothing but do everything.
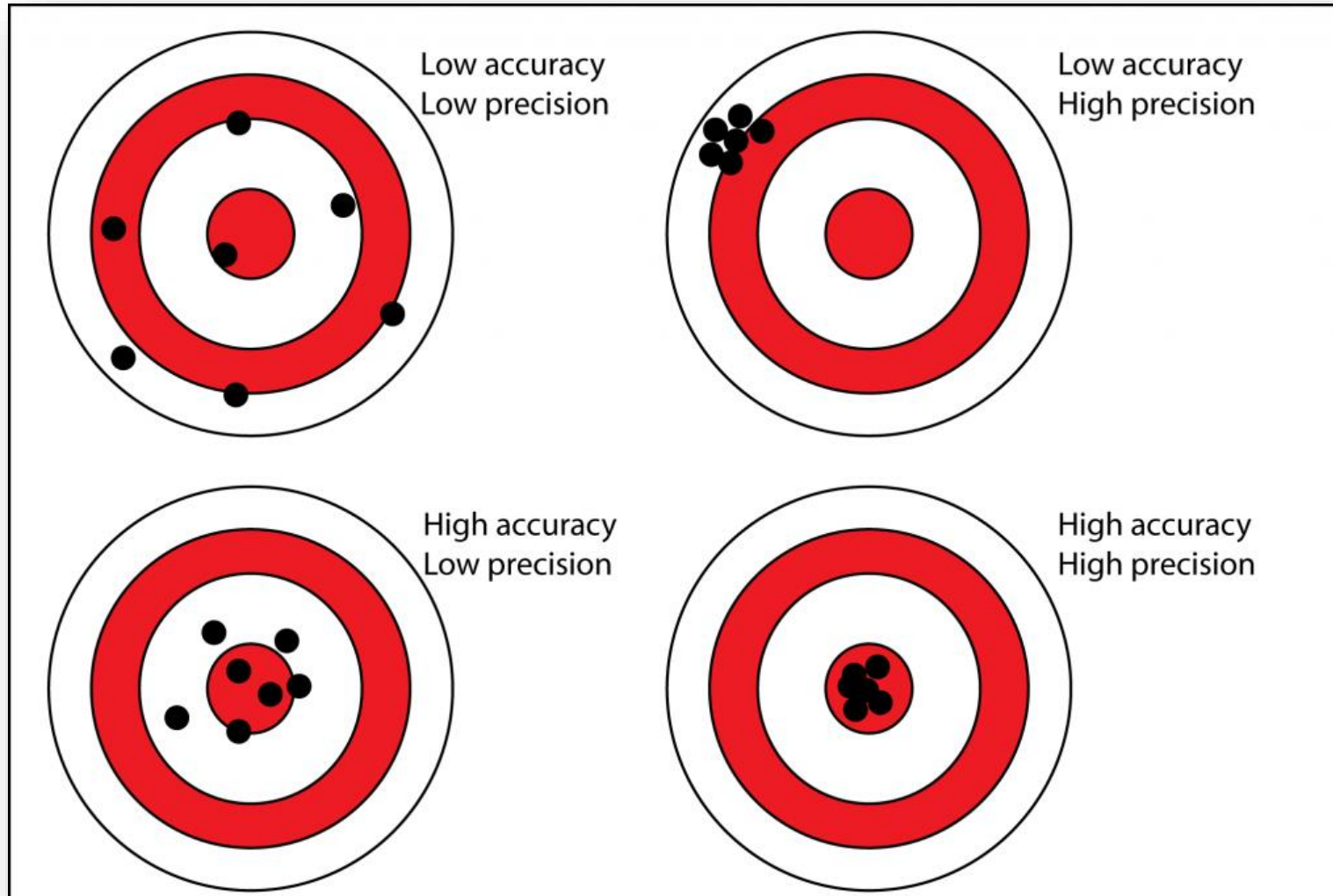
Internists know everything but do nothing.

Pathologists know everything and do everything but too late."

Cook, Robin (May 1983). Godplayer (1st ed.). Putnam Pub Group.

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The idea of precision

THE PRECISION MEDICINE INITIATIVE

"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"

- President Obama, January 30, 2015

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Precision Medicine

- Personalized medicine
- Individualized medicine

It's health care tailored to EACH individual.

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Precision medicine – why now?

- Current issues of modern medicine
  - Nonspecific toxic treatment of malignancy
  - Clinical trial based therapeutic plans
- Some targeted therapies being proved more effective
  - APL and all-*trans* retinoid acid (ATRA)
  - CML and Imatinib (Gleevec)
- Cutting-edge technologies now available
  - Next-generation sequencing (NGS), Omics and AI
  - Humanized antibodies and small molecules

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Current issues: therapy-related cancers

Ionizing Radiation - Cancers

Chemotherapy - Myelodysplasia

- Hodgkin's Disease,
- Retinoblastoma,
- Acute Lymphocytic Leukemia,
- Wilms Tumor,
- Pediatric Sarcomas,
- Upper Aerodigestive Tract Cancers,

- Breast Cancer
- Prostate Cancer
- Testicular Cancer
- Pancreas/Gastric Cancer
- Colorectal Cancer
- Endometrial/Ovarian Cancer
- Skin Cancer

Rheingold SR, Neugut AI, Meadows AT. Holland-Frei Cancer Medicine. 6th edition. Kufe, Pollock RE, Weichselbaum RR, et al., editors. Hamilton (ON): BC Decker; 2003.

Targeted therapy being proved effective

- *Some examples*:
  - Vitamin C and Scurvy
  - Insulin and Diabetes
  - APL and all-*trans* retinoic acid (ATRA)
  - CML and Imatinib (Gleevec)

Vitamin C and Scurvy

Insulin and Diabetes
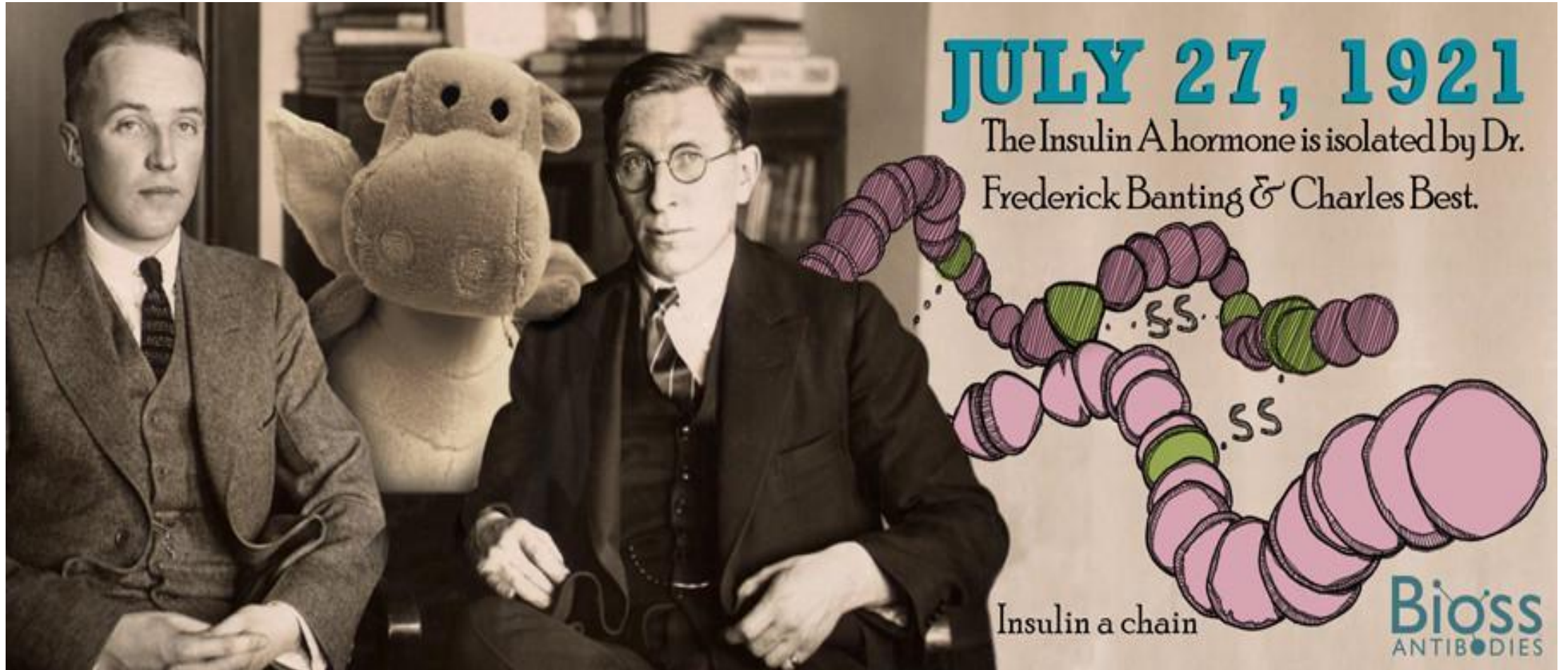
Banting House National Historic Site

Acute promyelocytic leukemia and ATRA

Wang Z-Y, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood 2008; 111: 2505–2515.
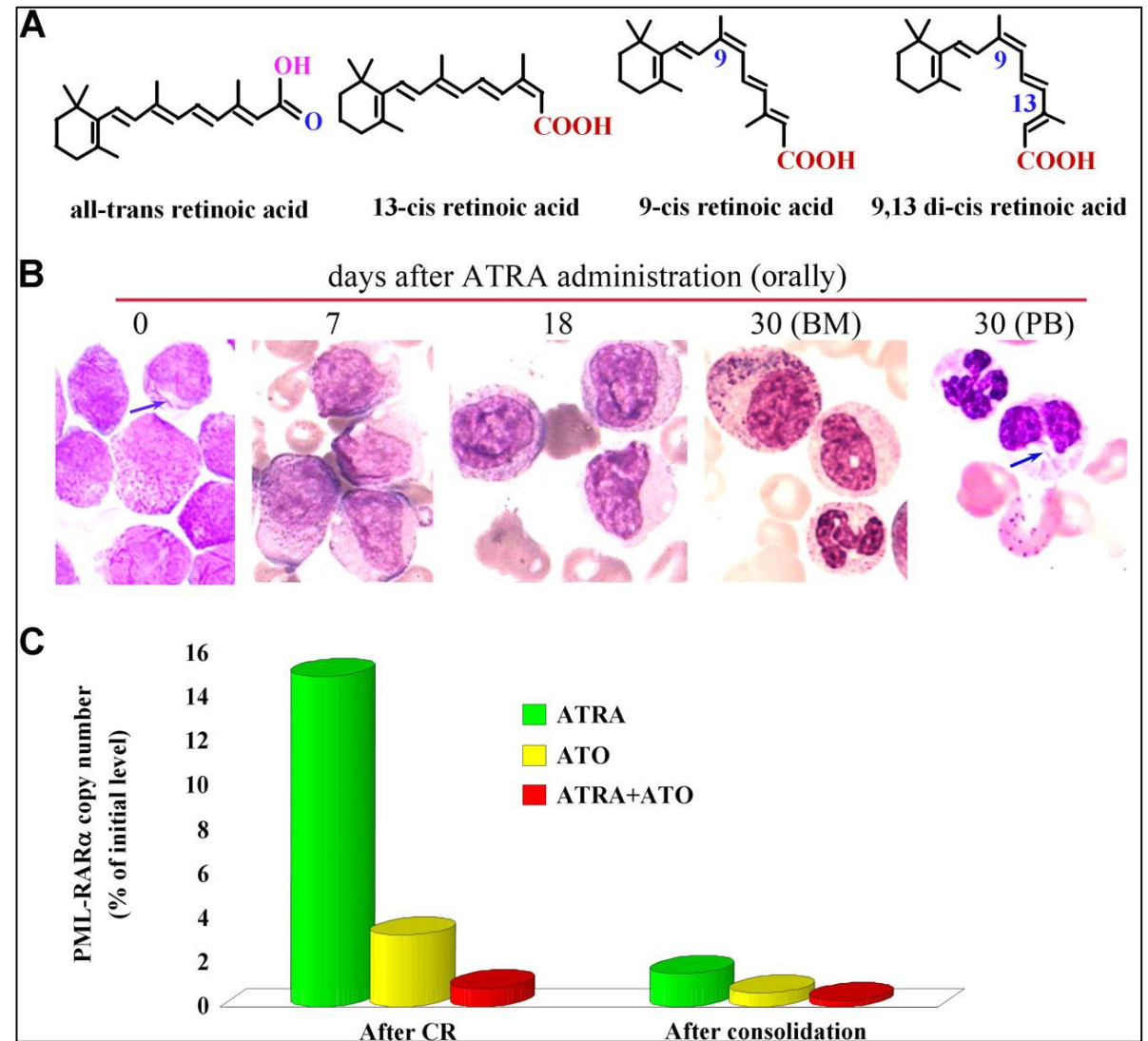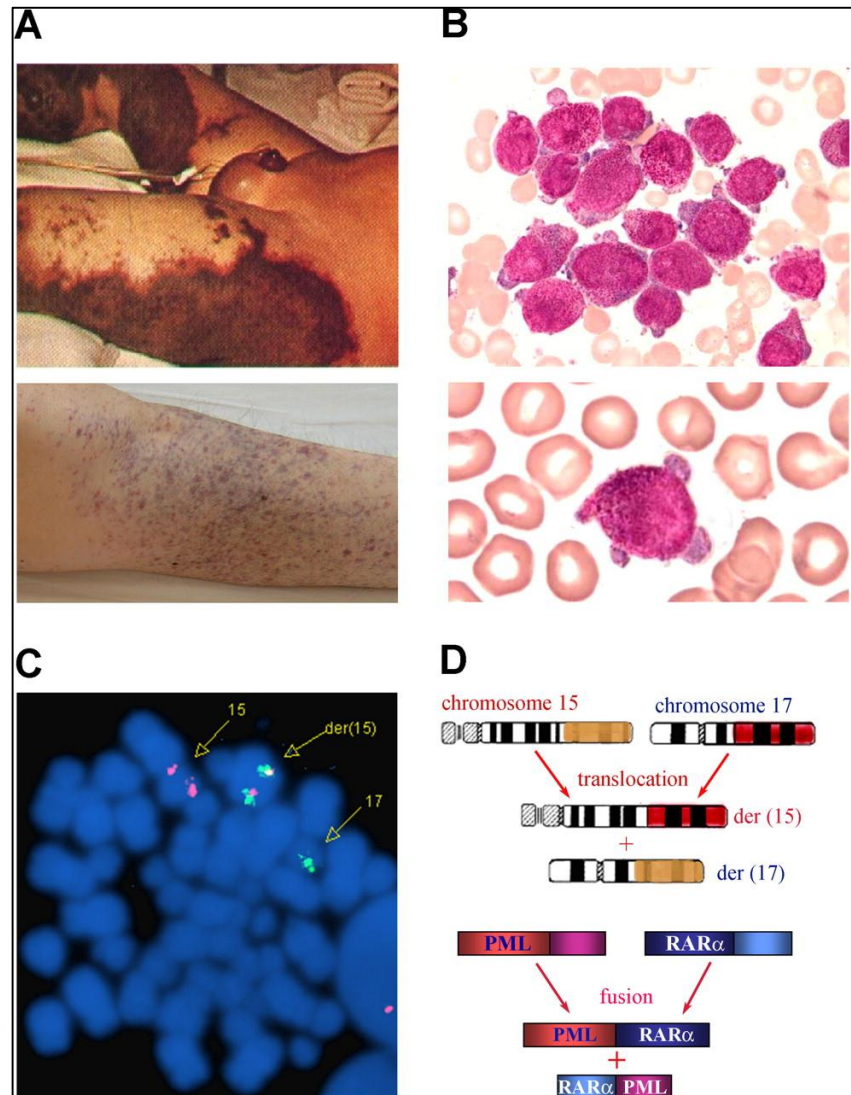
Chronic myeloid leukemia and Imatinib

weisses blut (white blood) = leukemia
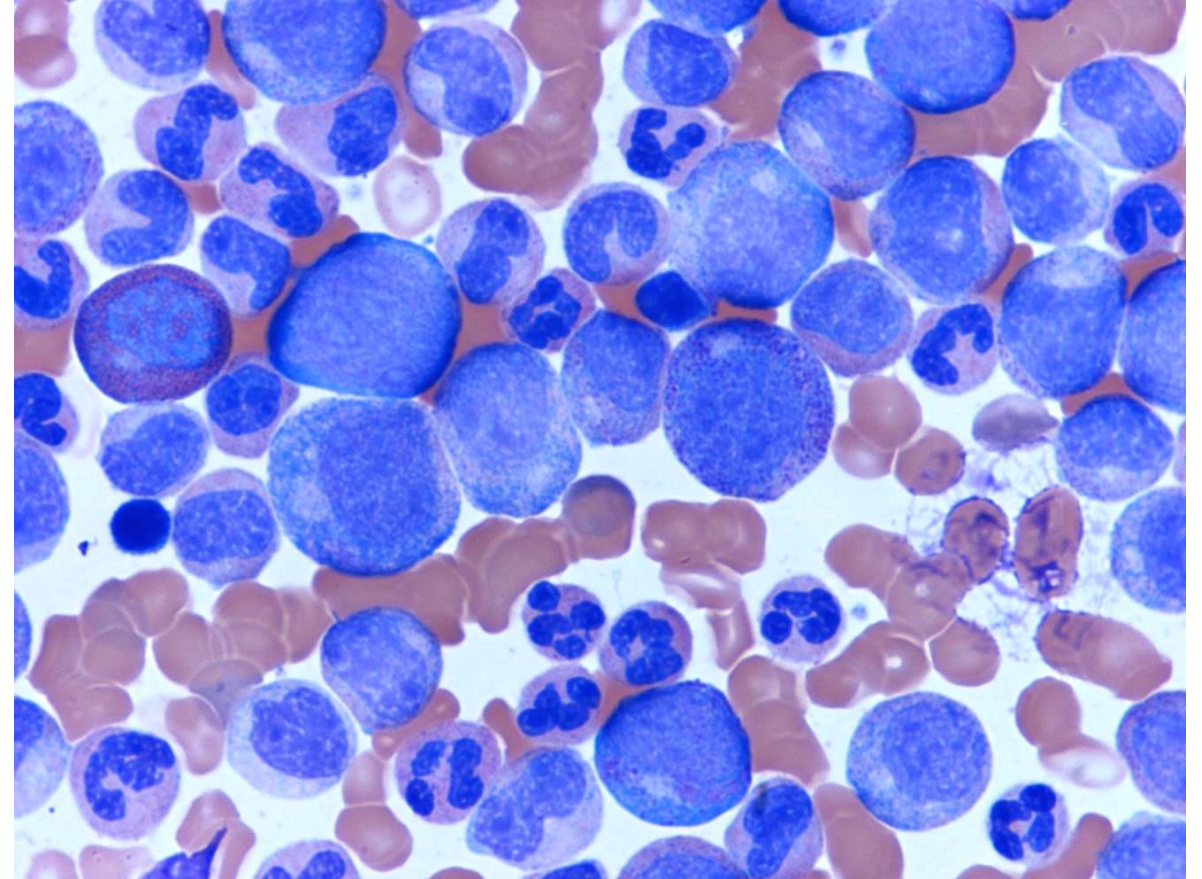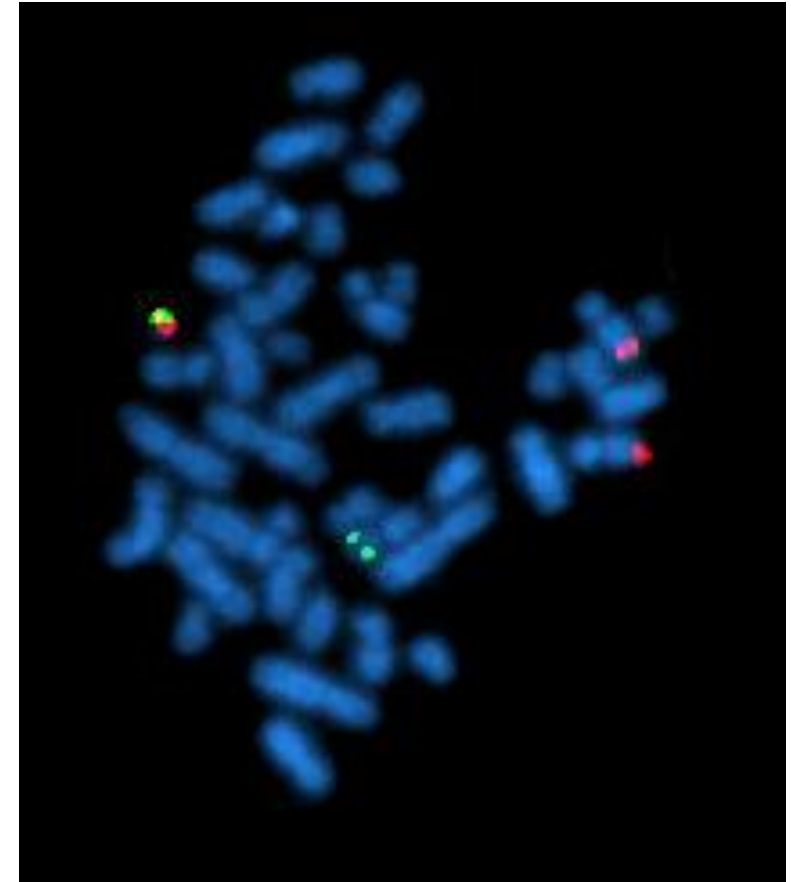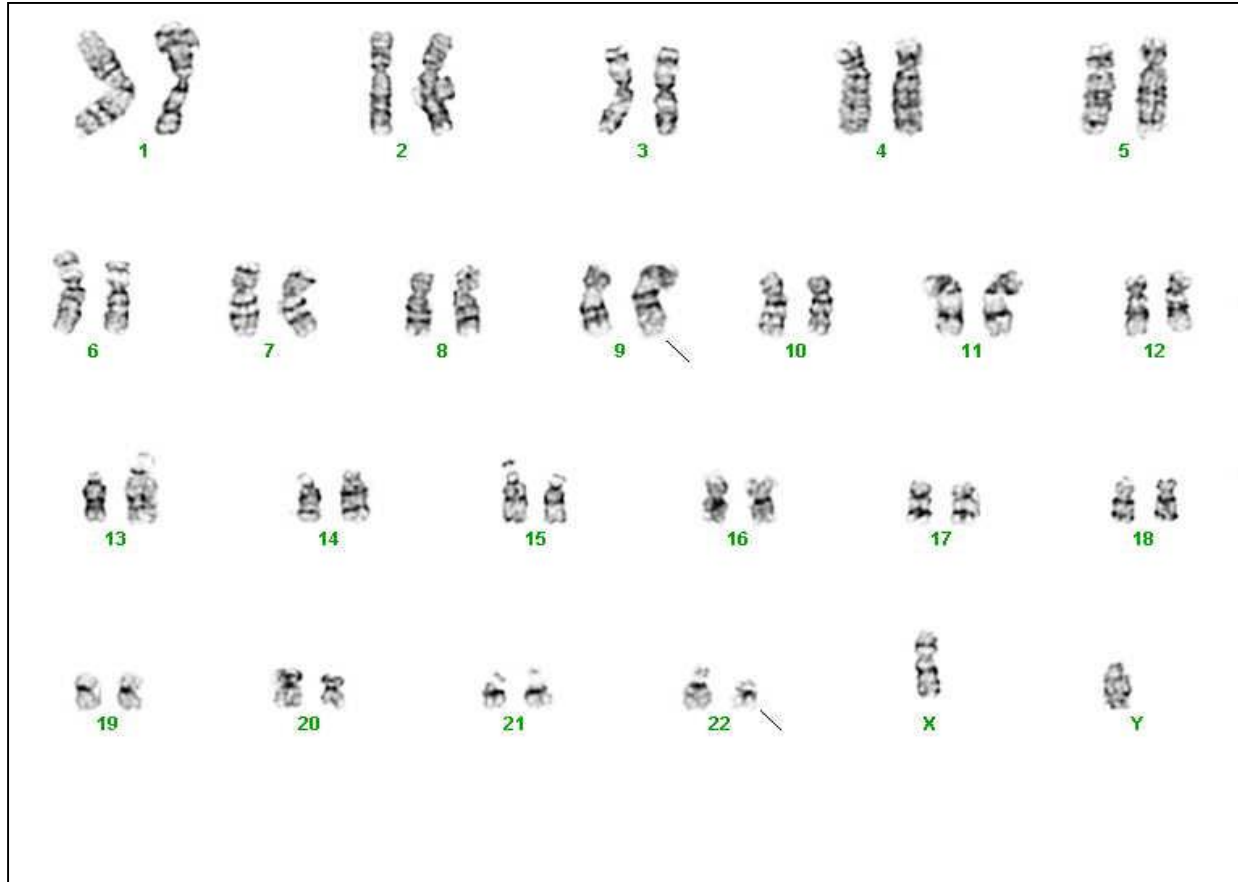
Chronic myeloid leukemia and Imatinib

# Chronic myeloid leukemia and Imatinib
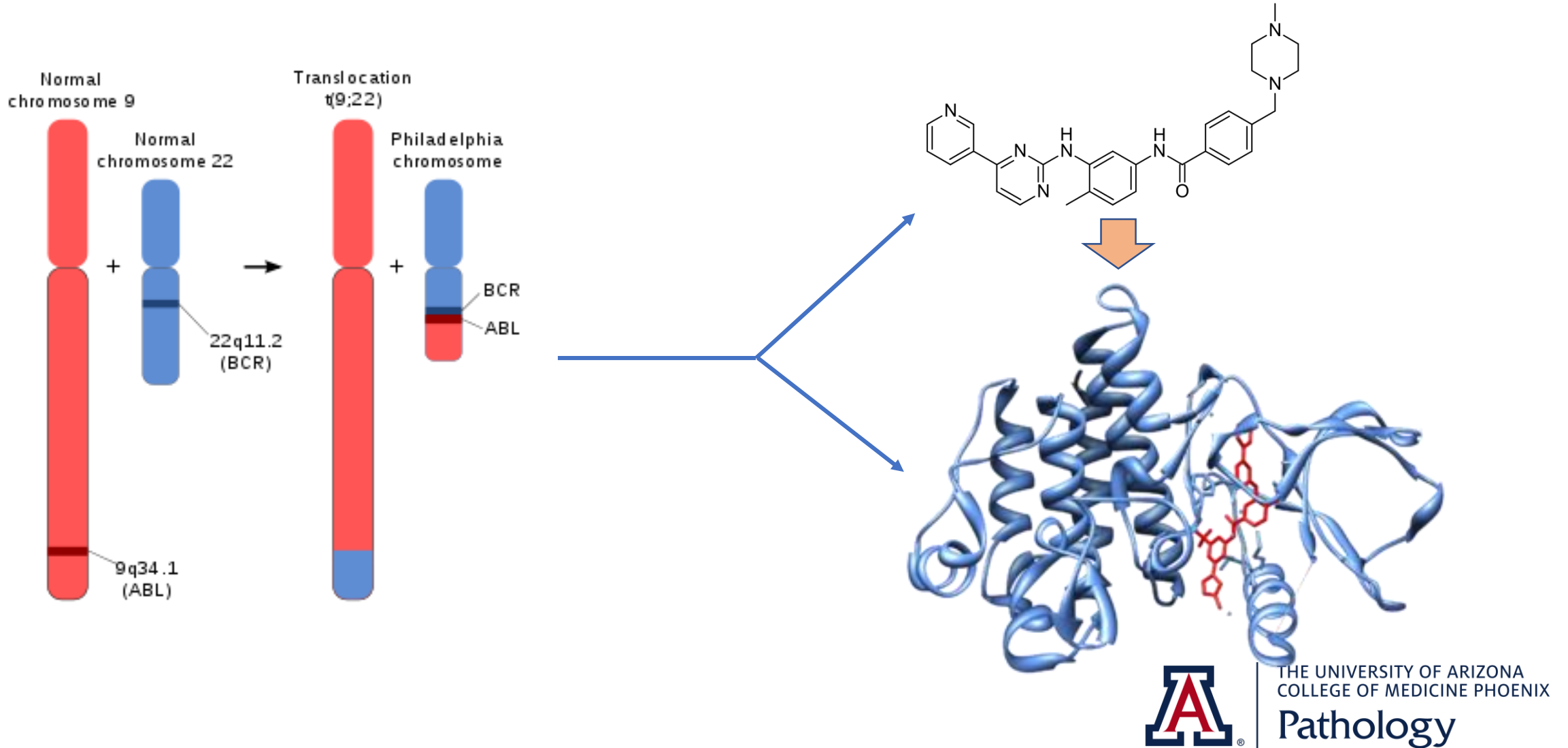
Cutting-edge tools of clinical laboratories

- Next generation sequencing (NGS)
- Omics:
  - Genomics
  - Transcriptomics
  - Proteomics
  - Kinomics
  - Metabolomics
- Biosensors
- Artificial intelligence (AI): deep thinking and machine learning
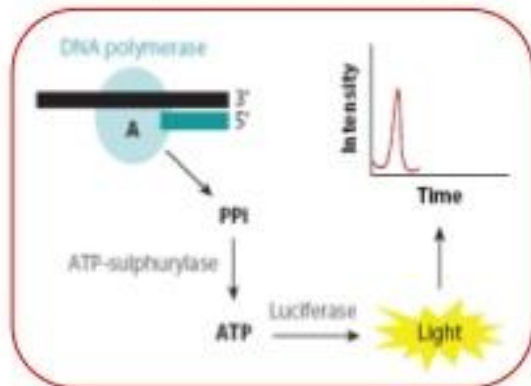- Humanized antibodies and small molecules

Next-generation DNA sequencing

1 Library preparation
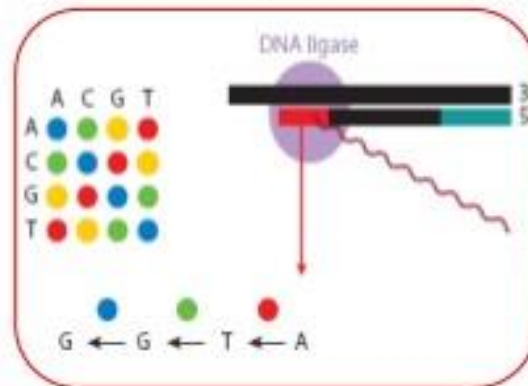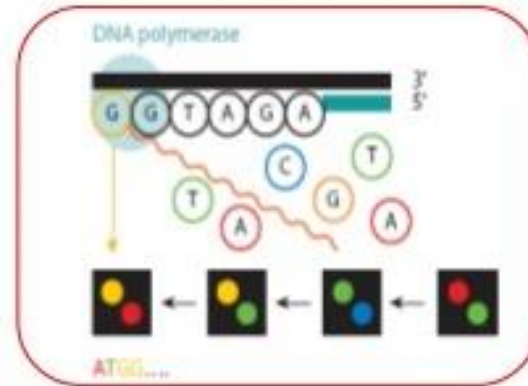2 Clonal amplification
3 Cyclic array sequencing

DNA fragmentation and in vitro adaptor ligation

emulsion PCR

bridge PCR
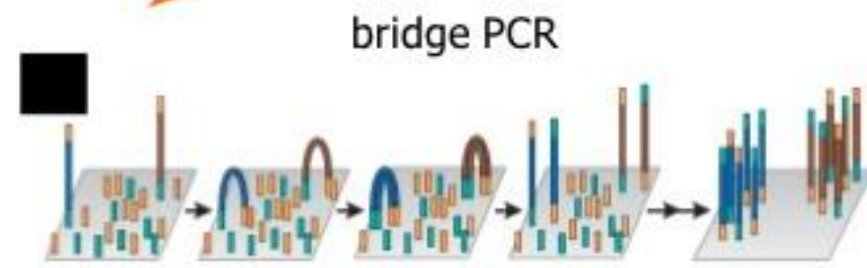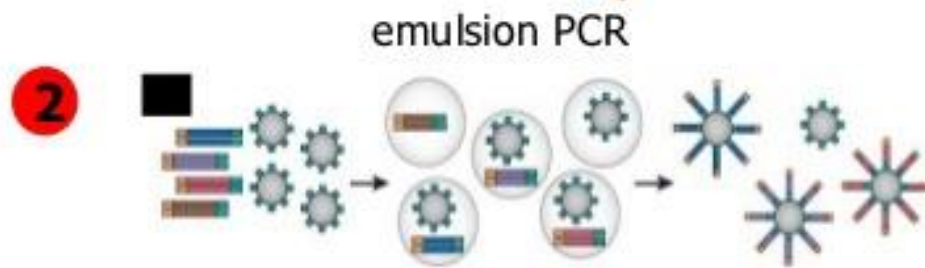
Pyrosequencing

Sequencing-by-ligation

Sequencing-by-synthesis

454 sequencing
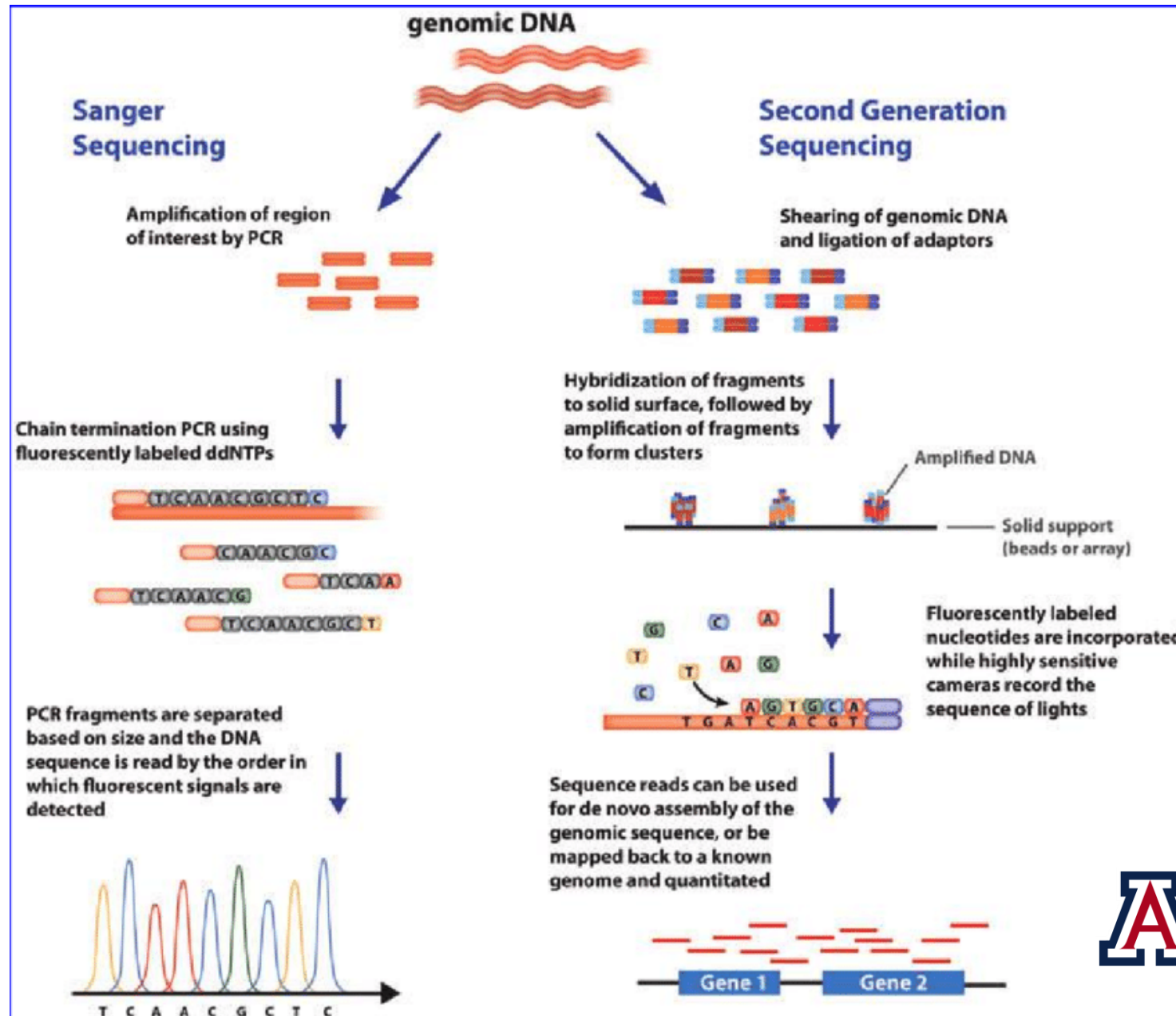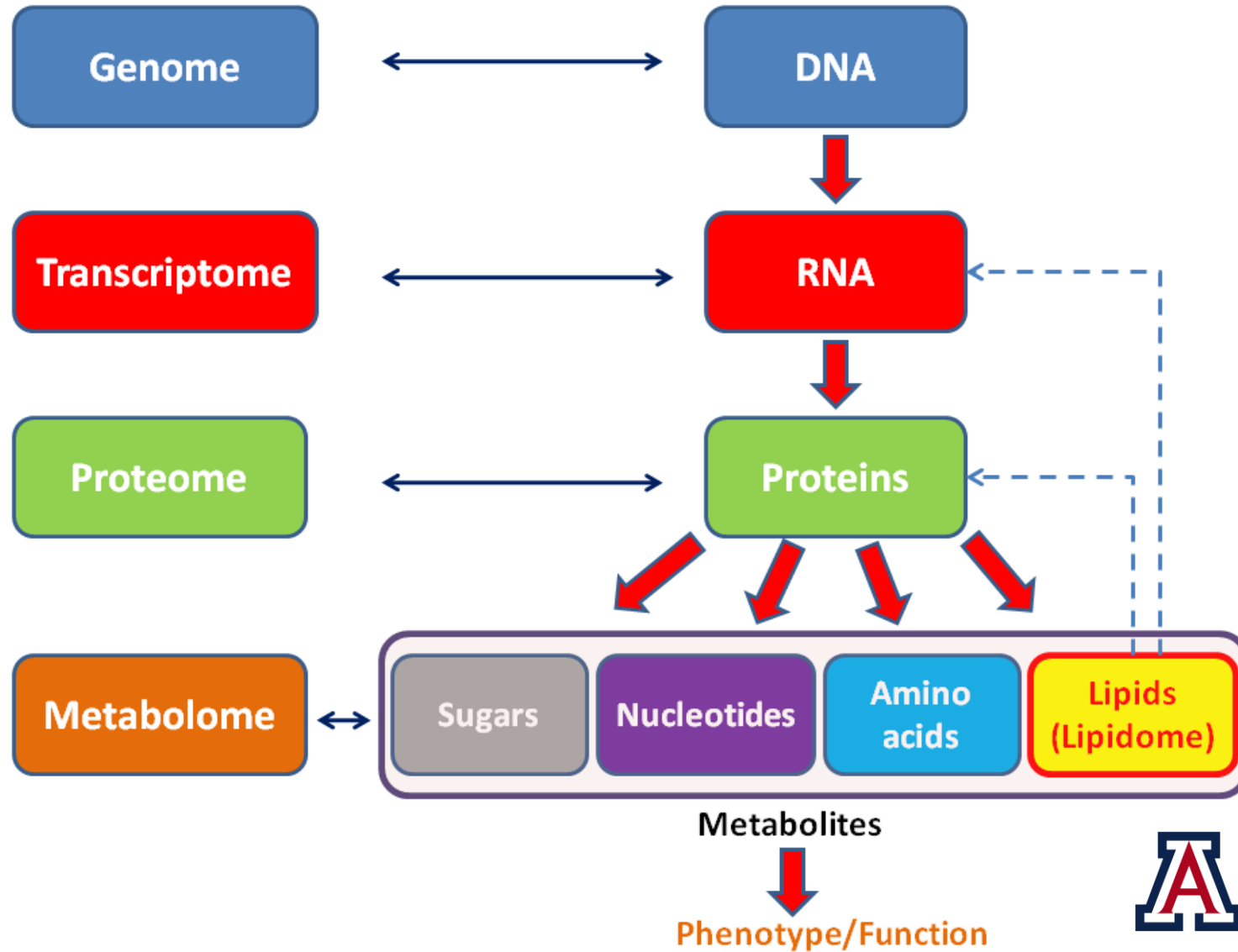
SOLiD platform

Solexa technology

Next generation sequencing
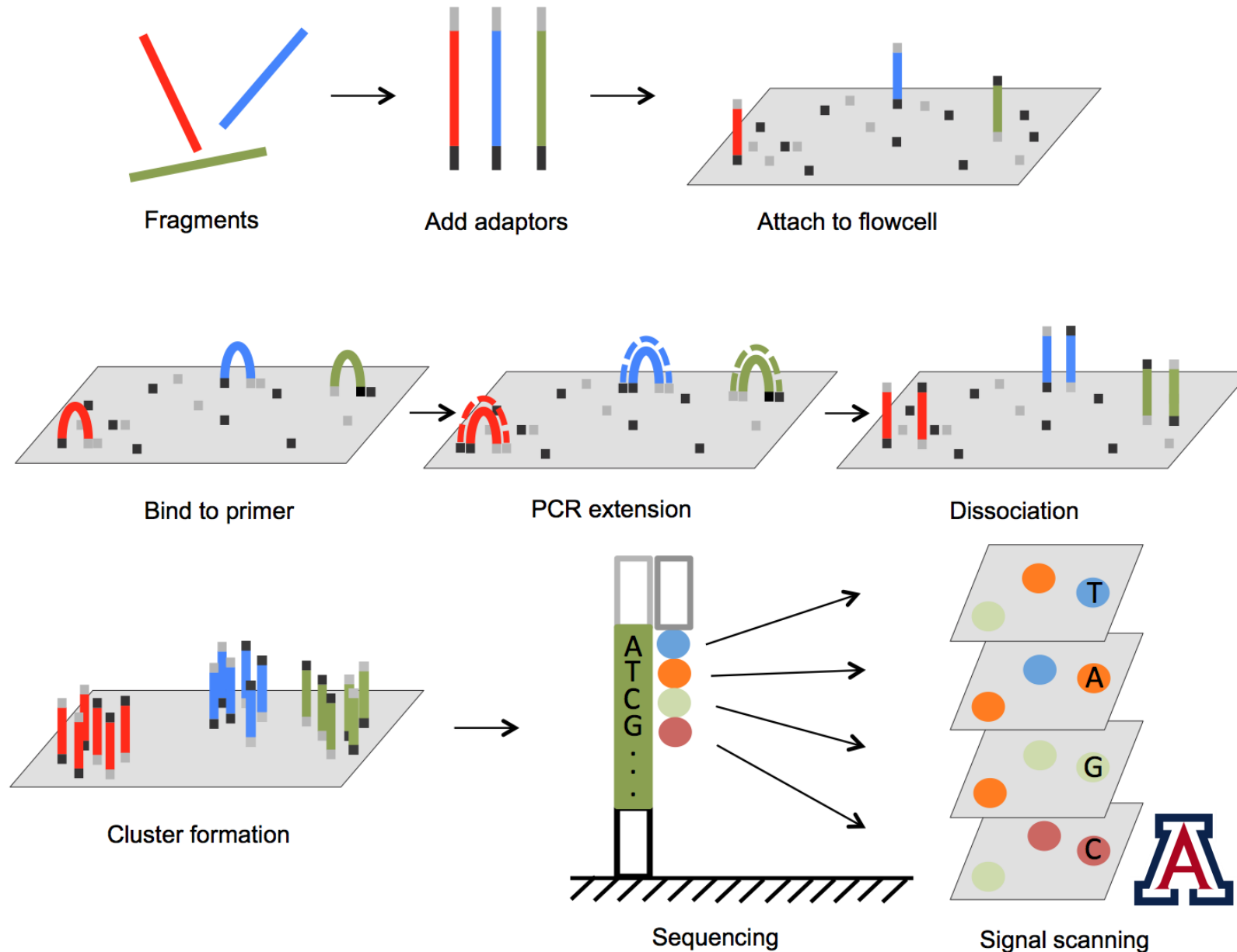
Difference between Sanger sequencing and NGS

Omics

Metabolomics
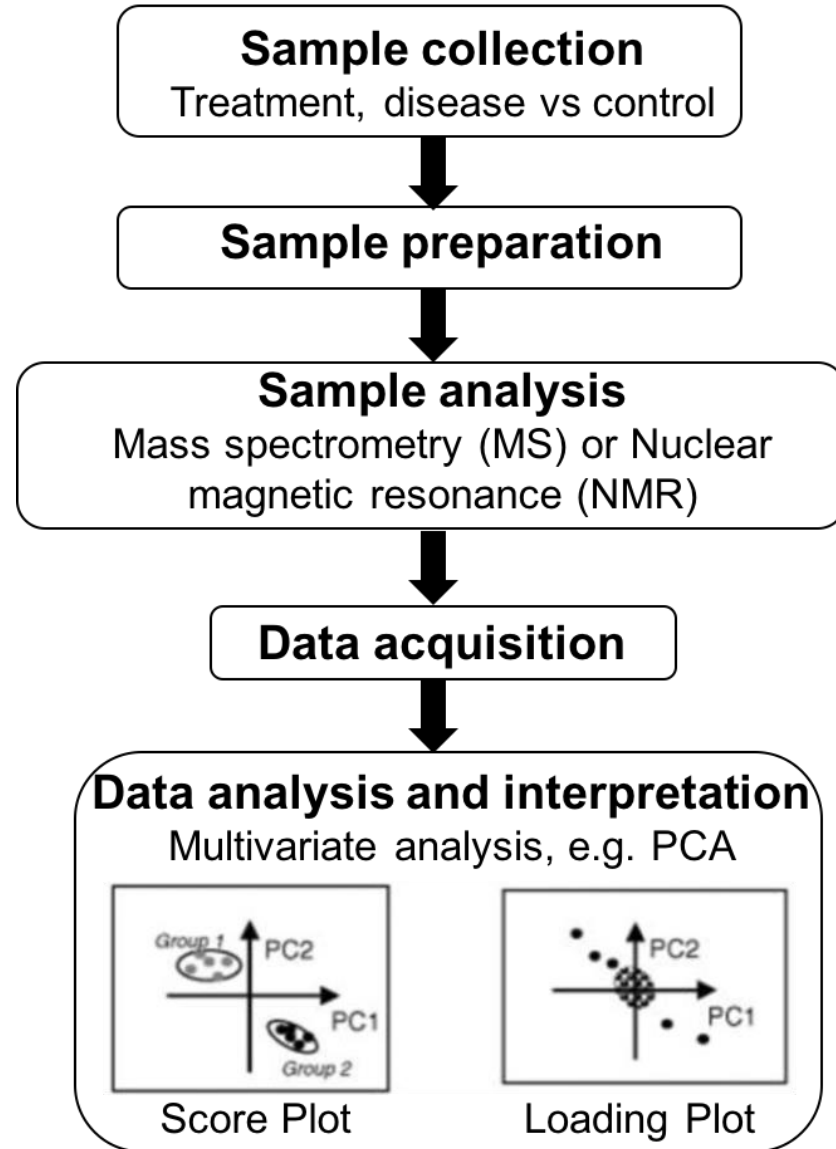
Metabolomics

Biosensors

Elements of a Biosensor

Samples:
- Cell Cultures
- Human Samples (Blood, Urine, Saliva)
- Food Samples
- Environmental Samples (Air, Water, Soil, Vegitation)

Transducers:
- a) Bioreceptor(s): Nucleic Acids, Cells, Antibodies, Enzymes
- b) Electrical Interface(s): FET Devices, Nanowire Array, Nanoparticles, Electrodes

Electronic System:
- c) Signal Amplifier
- d) Signal Processor
- e) Display
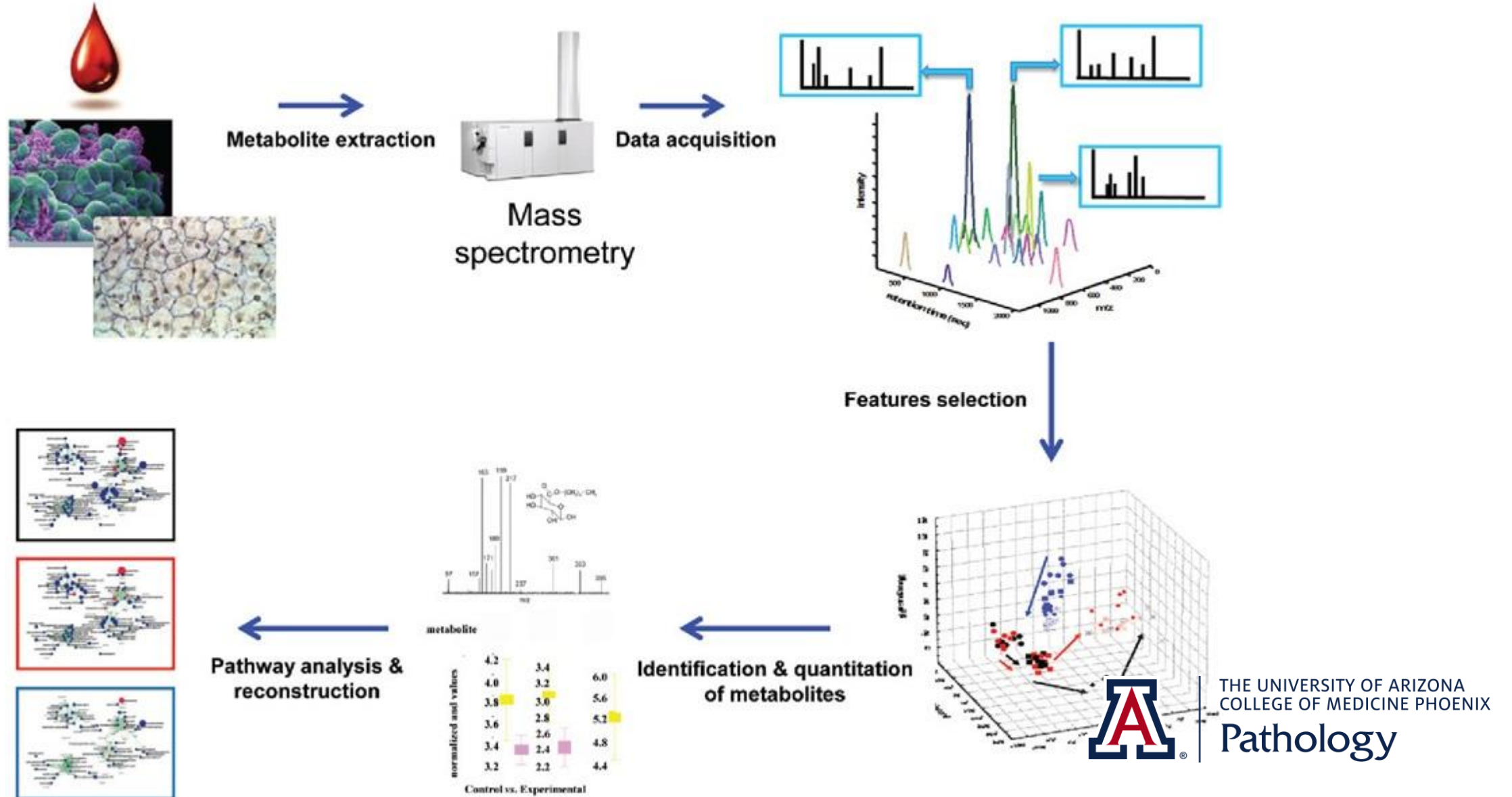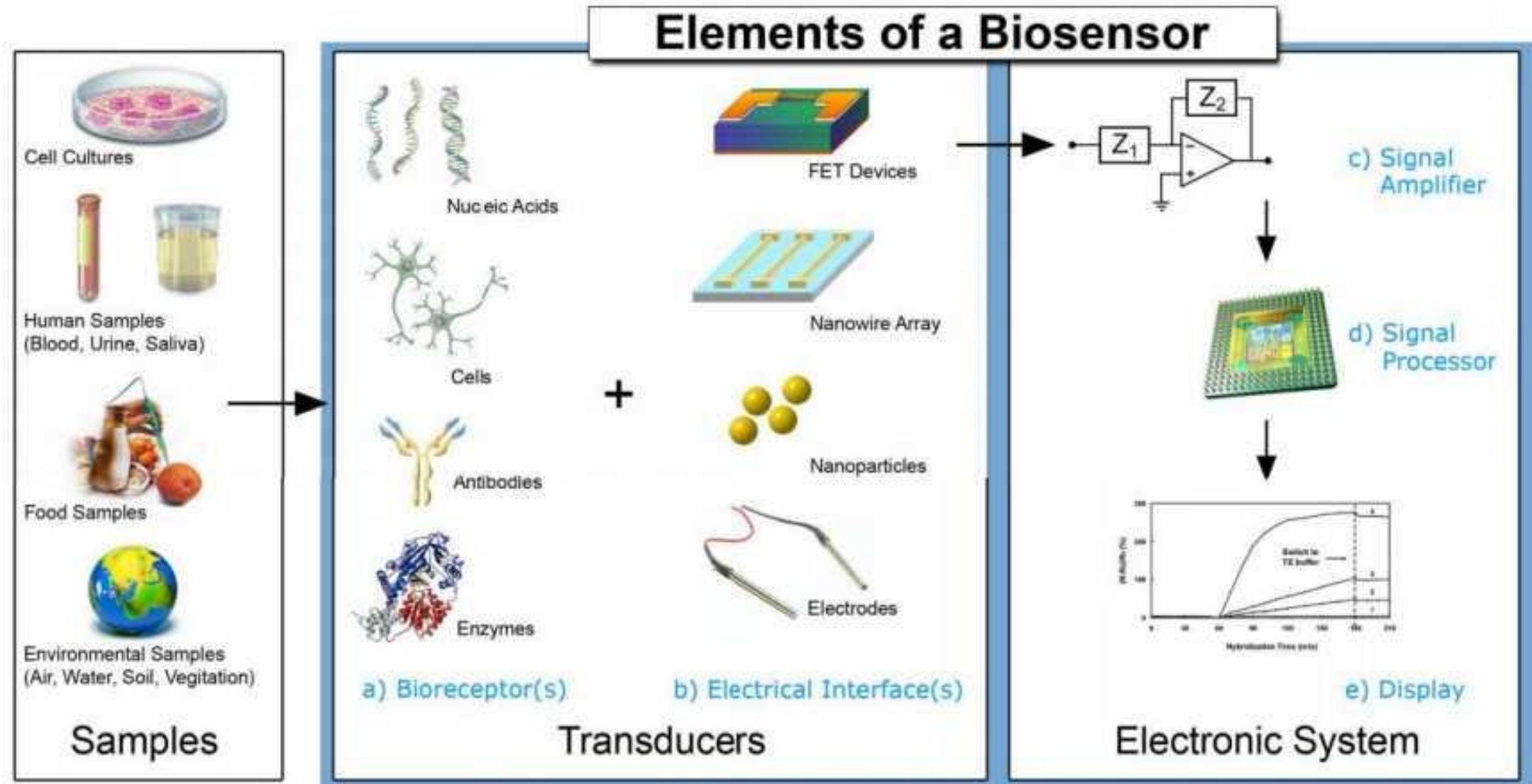
Magnetic nanoparticle biosensor
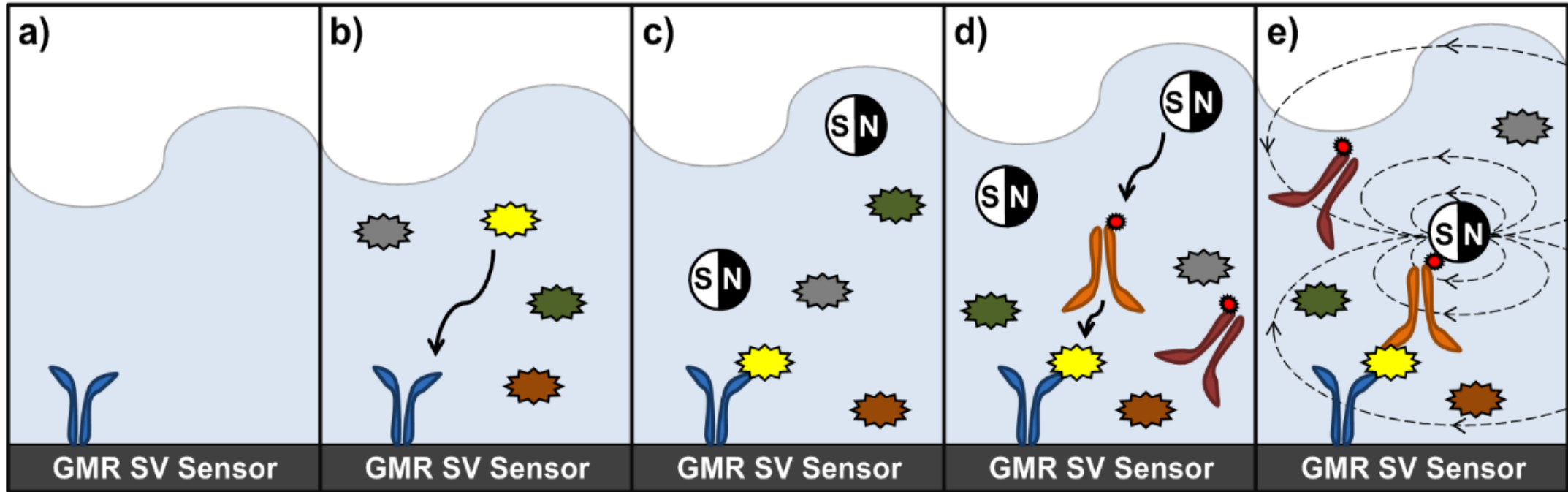
Sequence of steps for the auto-assembly of magnetic immunoassay

Magnetic nanoparticle biosensor assay
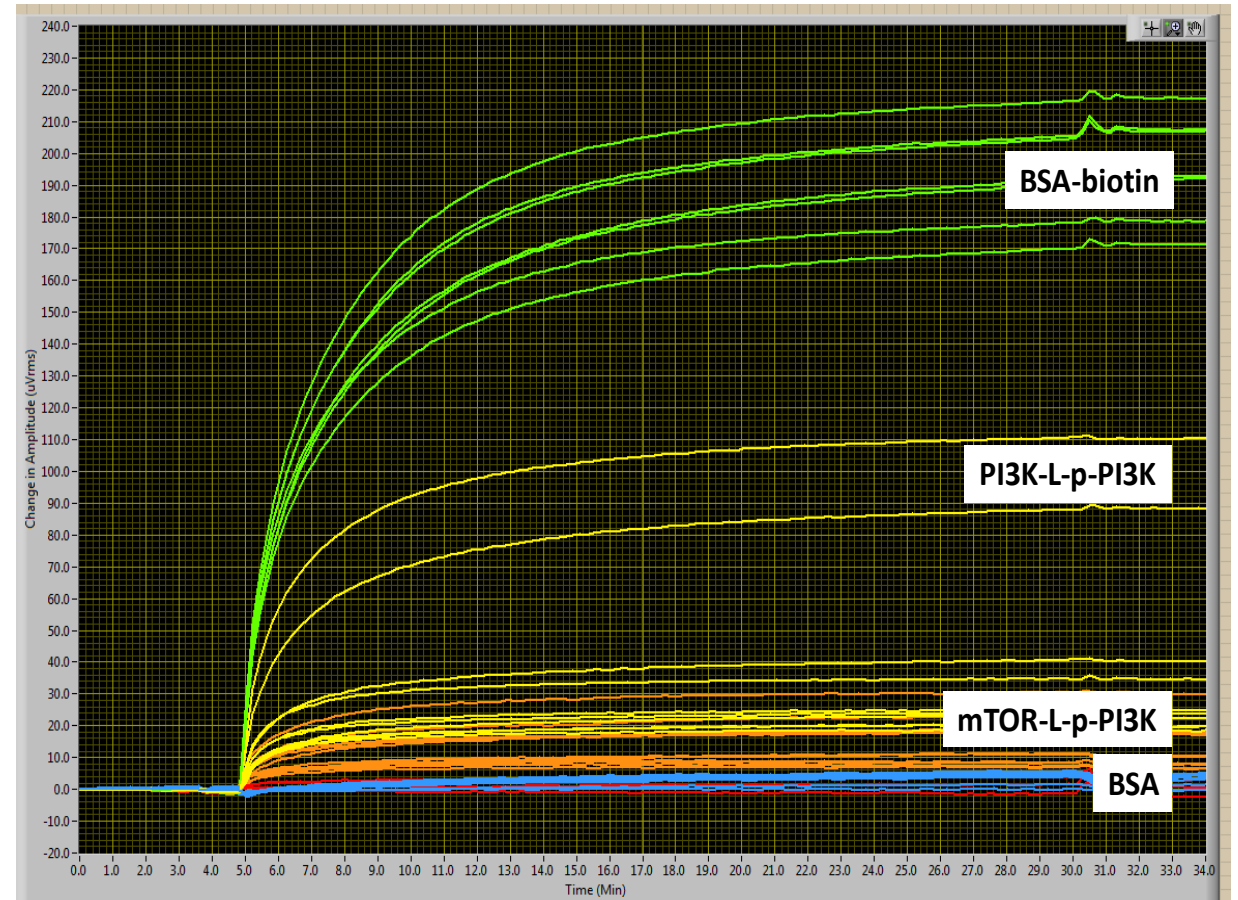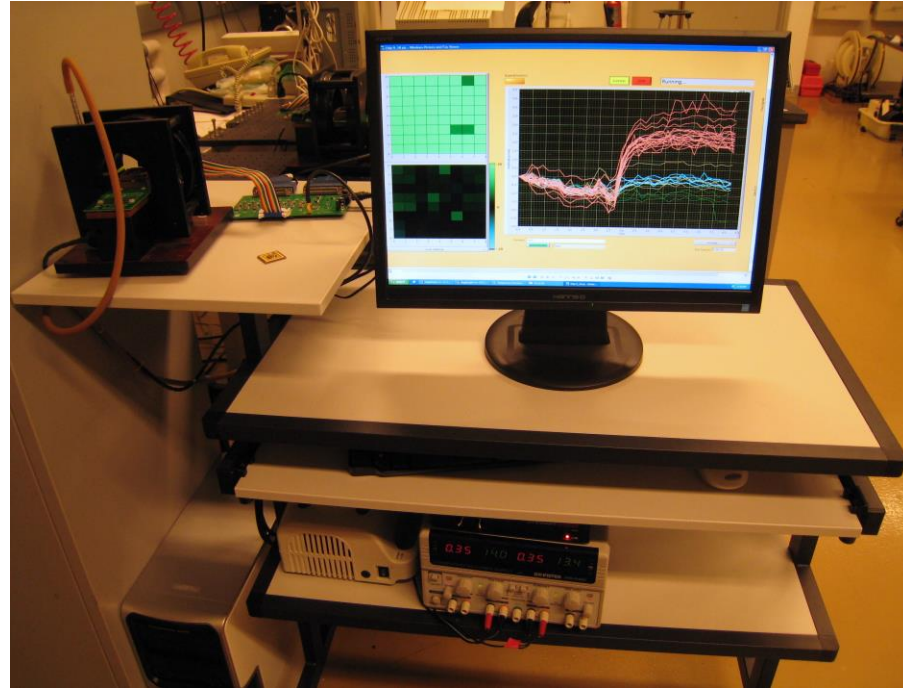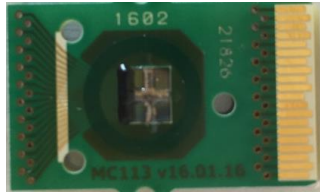
AI concept

Deep thinking and machine learning
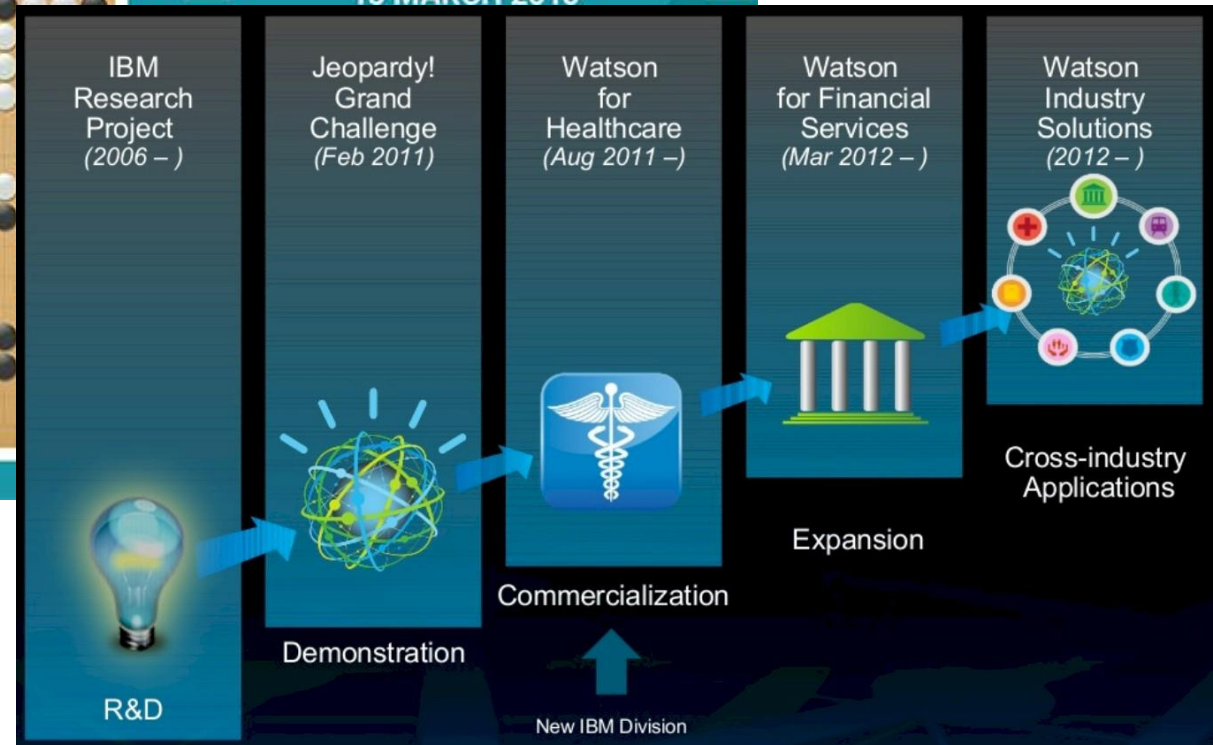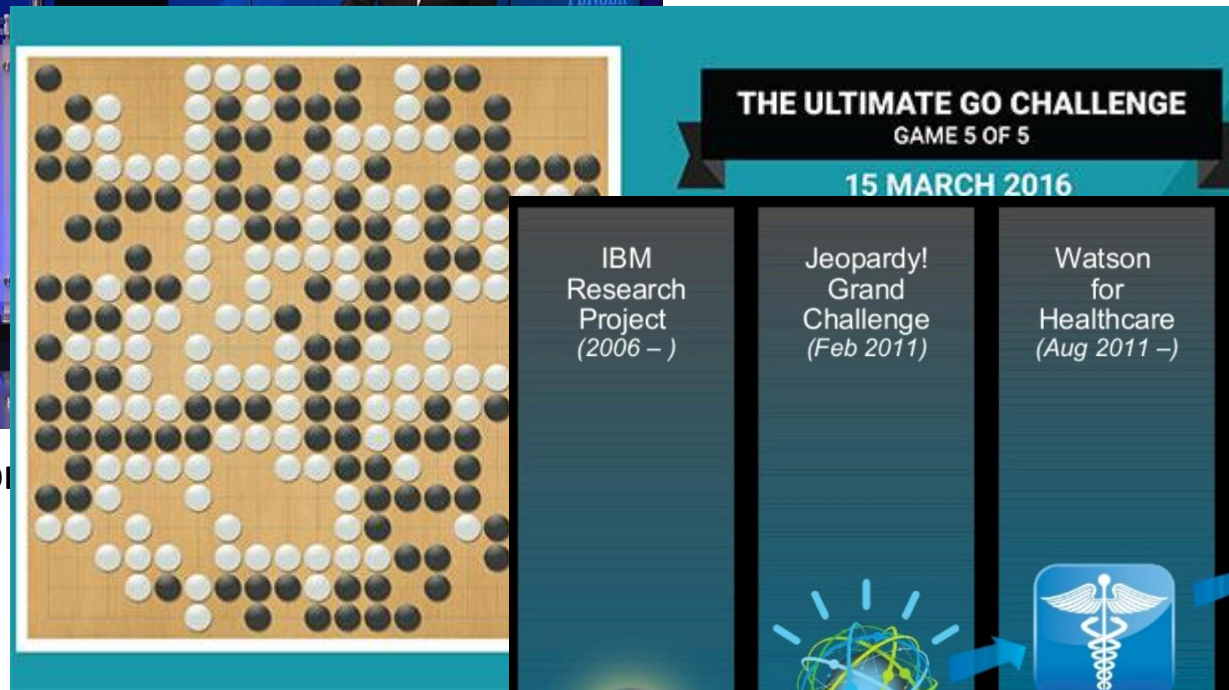
AI in action in Pathology

Stumpe M, Peng L. Assisting pathologists in detecting cancer with deep learning. *Google AI Blog*. Friday, March 3, 2017

Precision Pathology

- Unlike traditional pathology, which applies pattern recognition, precision pathology employs cutting-edge techniques to identify the etiological factors of a disease and optimize treatment by focusing on the therapeutic targets.
  - It provides molecular targets in the disease for specific therapy.
  - It provides molecular evidence in the patient for optimal clinical outcome.

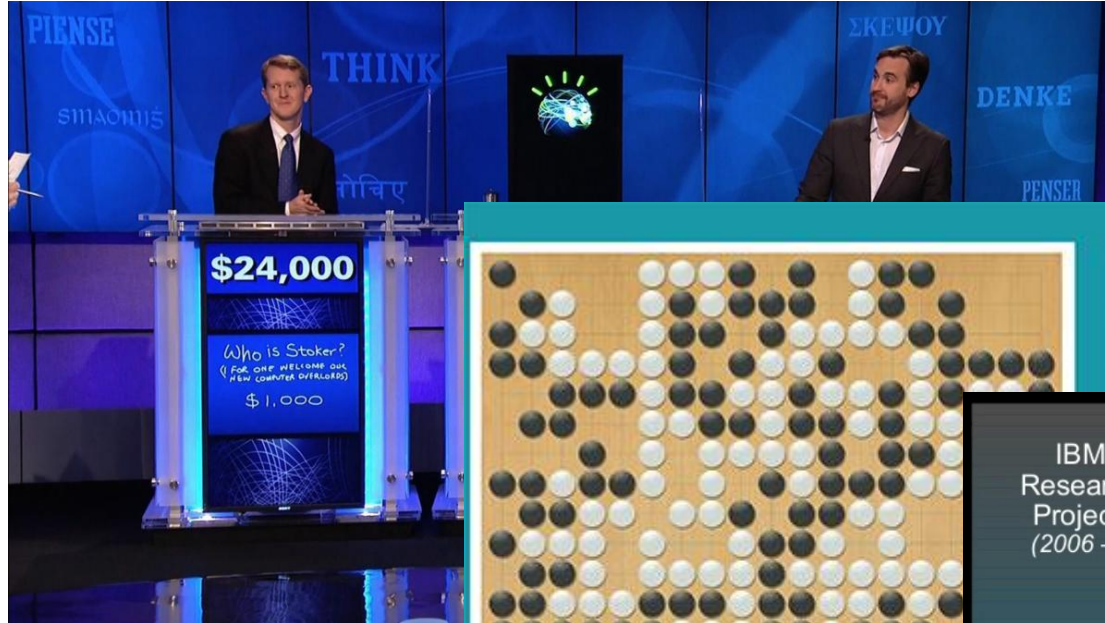- Zhao XF. Precision pathology: a new frontier. *Hematopath*. 2018; 3: 24-25.

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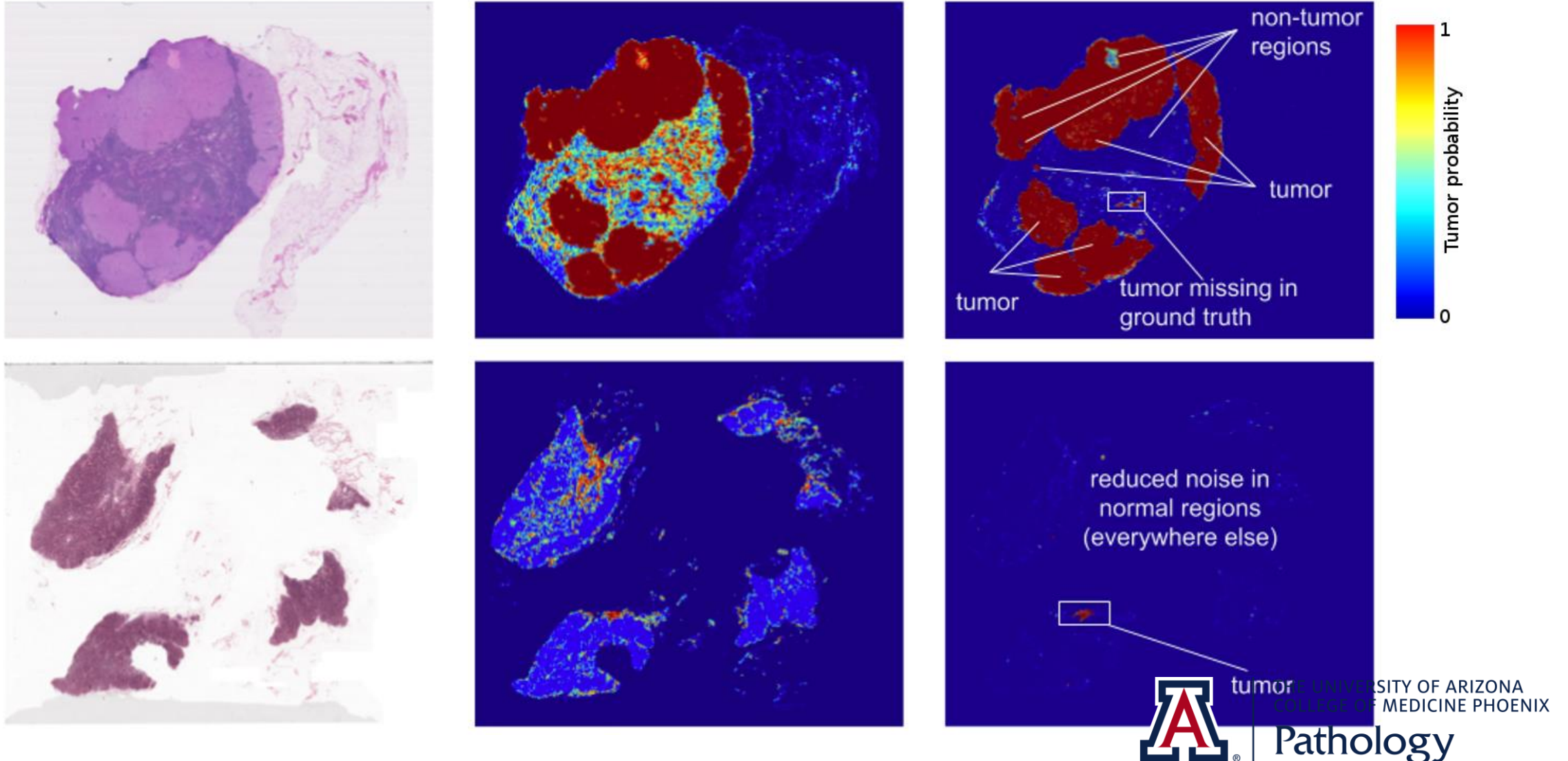# The concept of precision pathology

- It is a deep-thinking approach to define a pathological condition with a panel of molecular changes at DNA, RNA, protein and metabolite levels.

- Precision pathologists identify therapeutic targets in a unique biological ecosystem based on the NGS and Omics to design the optimal therapeutic plan.

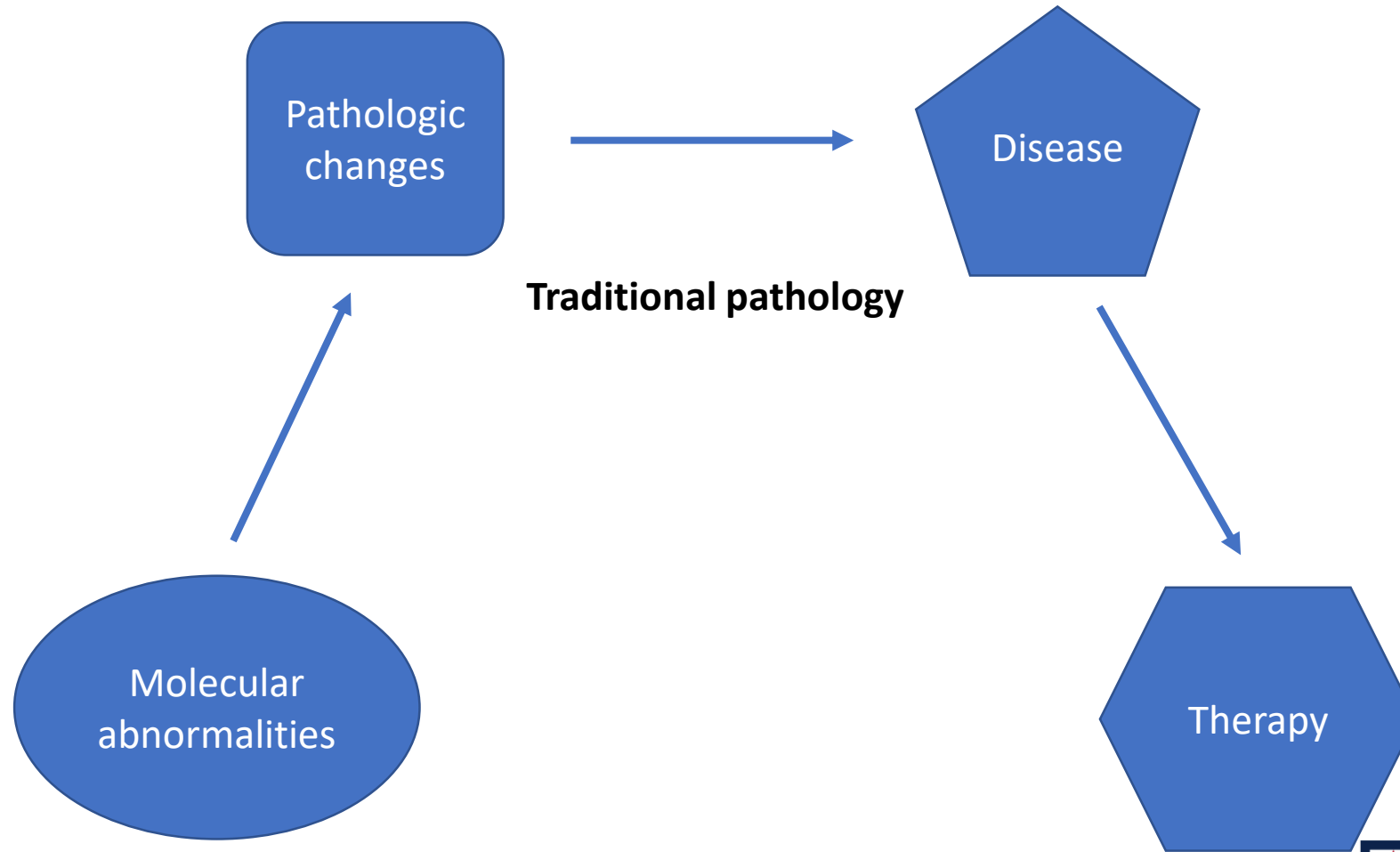# Molecular Pathology vs. Precision Pathology

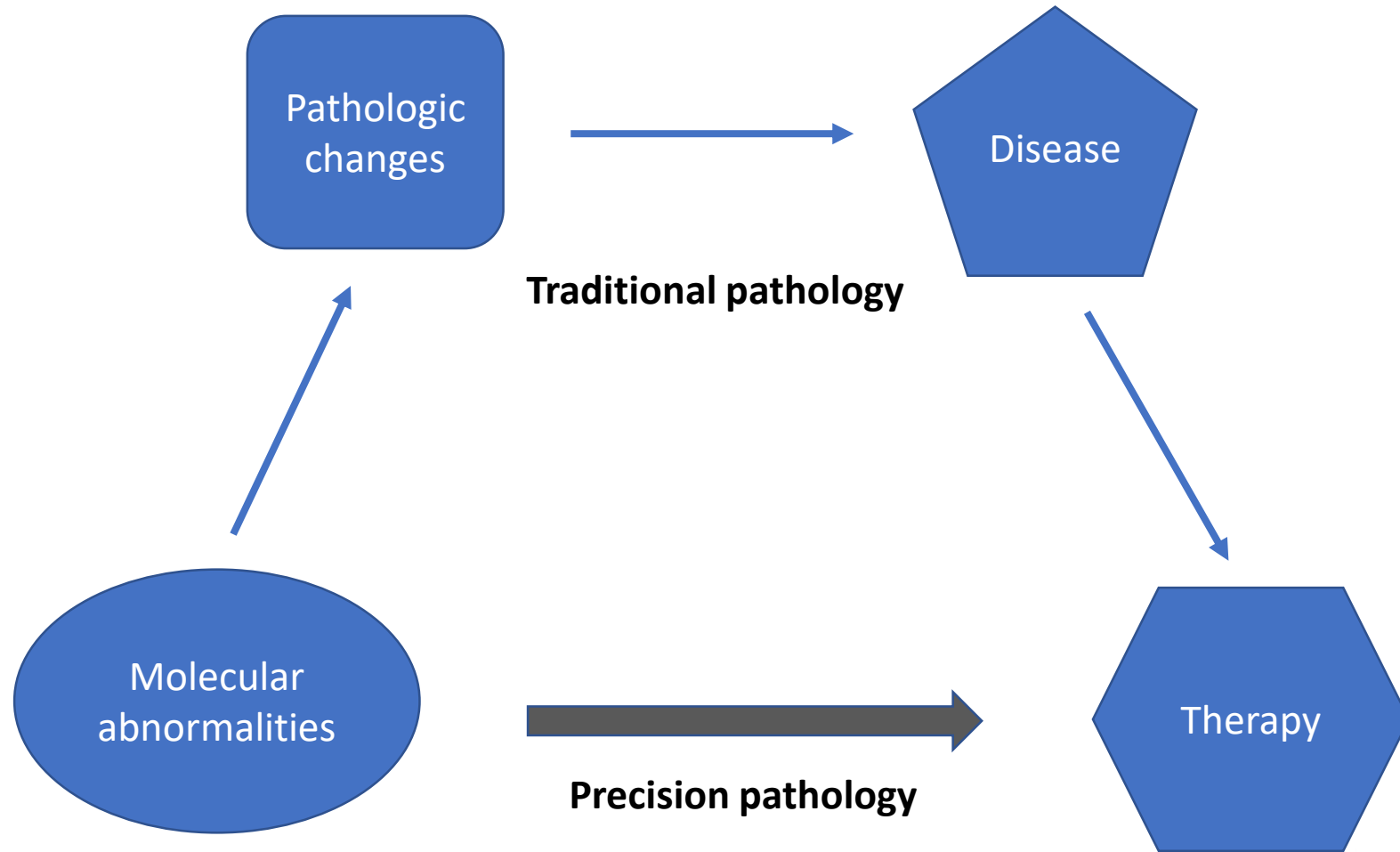- Although both are utilizing molecular techniques, but the former focuses on <u>diagnosis</u> and the latter focuses on <u>therapy</u>.
  - Molecular pathology provides supporting evidence for the diagnosis of diseases.
  - Precision pathology provides therapeutic targets and pharmacomics for optimally managing patients.

More steps and more likely errors...

Yes…

Traditional Pathology vs. Precision Pathology
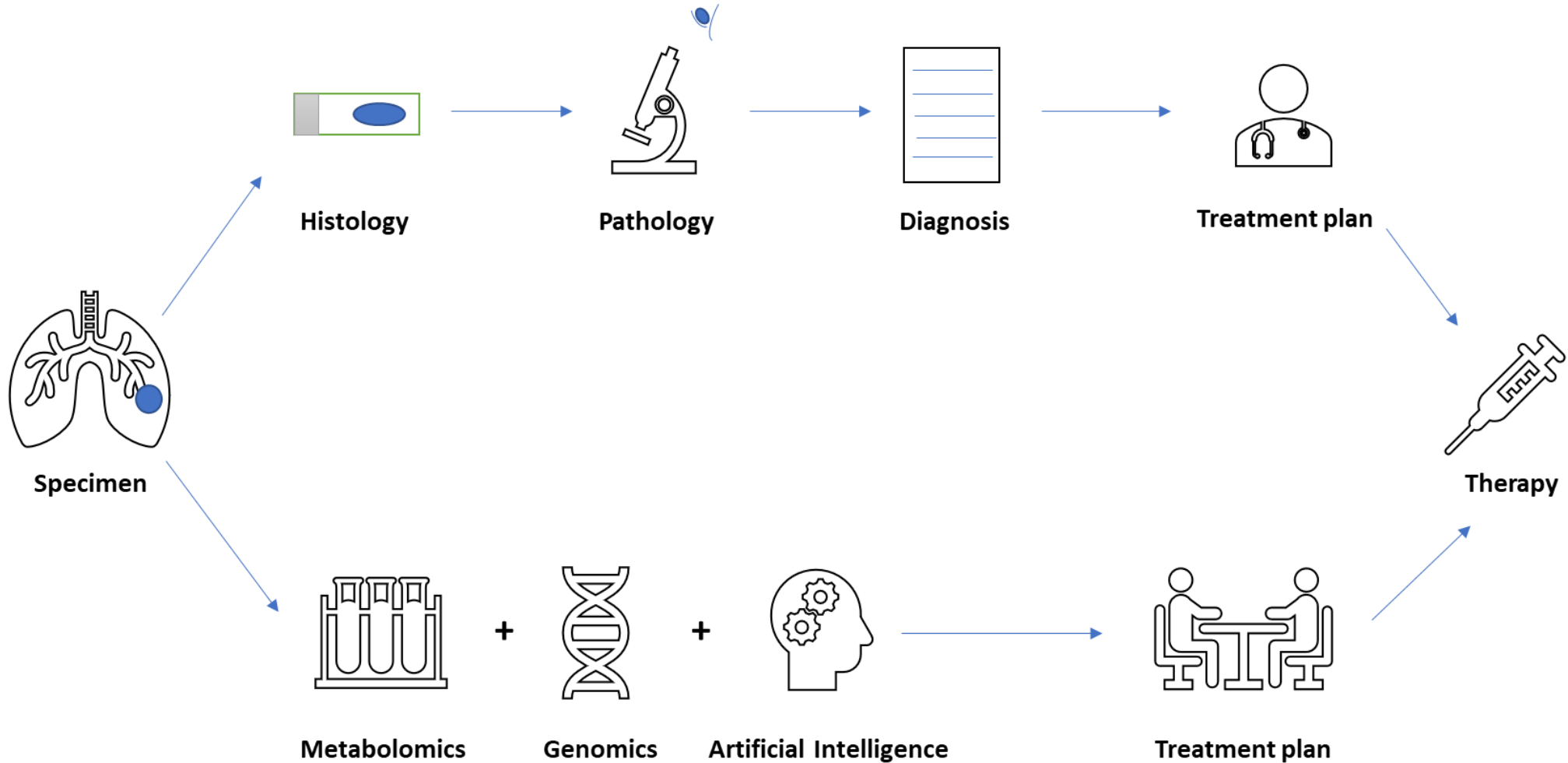
Impacts on medical education

- Medical training:
  - Changes in pathology, pharmacology, oncology, and therapeutics

- Residency training:
  - Shifting from recognizing different pathological entities to identifying the molecular changes for each pathological conditions

How to hit the target?
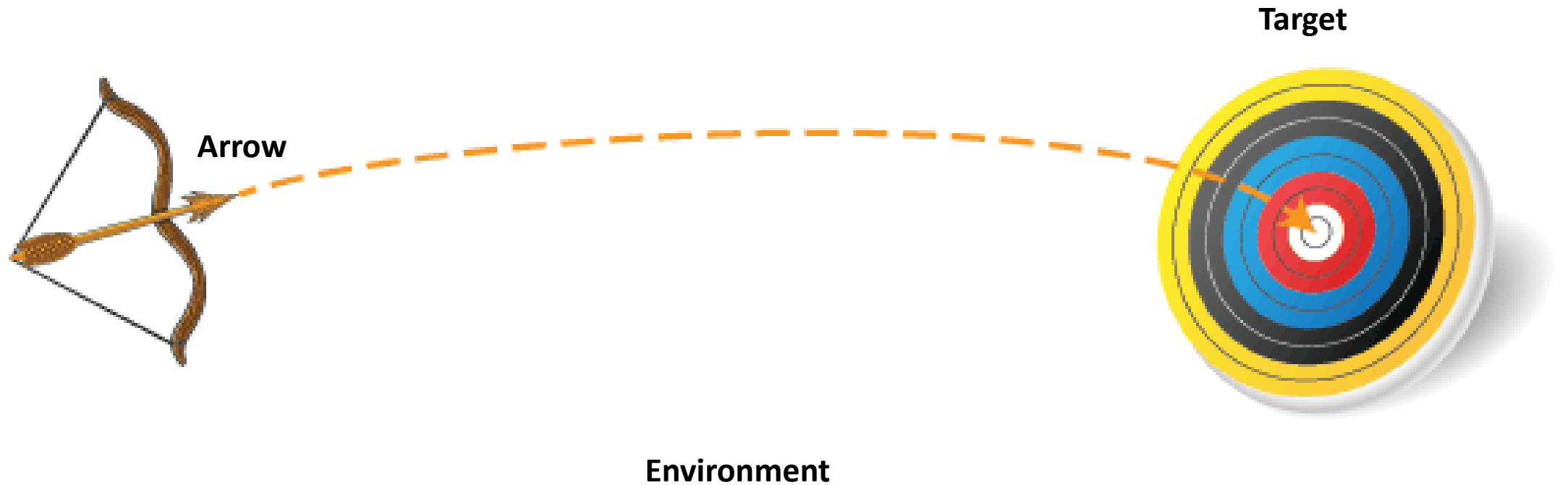
Target

Arrow

Environment

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Molecular basis of precision pathology

- Cancer "Driver" genes (targets)

Driver vs. Rider

- Driver genes – Oncogenes, mutated tumor suppressor genes:
  - Oncogenes: ABL1, BRAF, cyclin D1, EGFR/Her-2, KRAS, PIK3CA, RARA
  - Tumor suppressors: APC, PTEN, p53, RB

- Rider genes – Tissue specific genes and reactive genes
  - Tissue specific: cytokeratin, CD3, CD7, CD13, CD20
  - Reactive: ILs, cytokines, chemokines

- The strategy is to target the "Driver".

Molecular basis of precision pathology

- Cancer "Driver" genes (targets)
- Node theory – key joints of signal transduction network (targets)

Node Theory
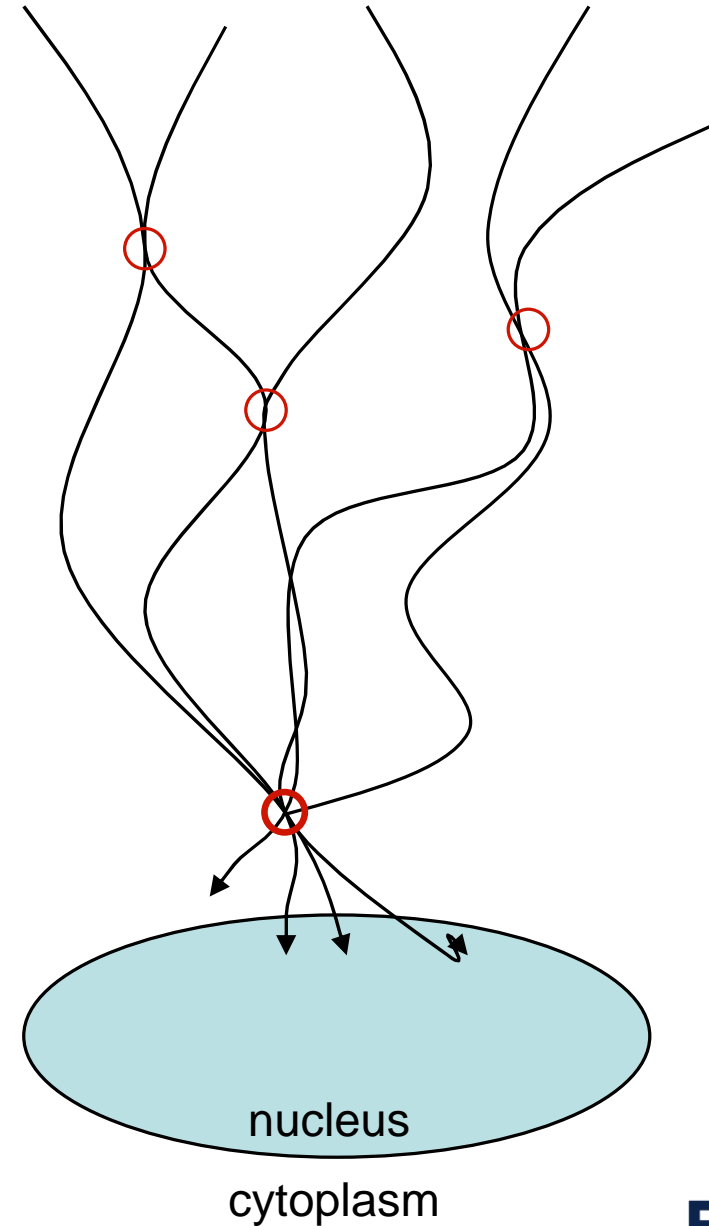
Zhao XF & Gartenhaus RB. *Expert Opin Ther Targets.* 2009; 13: 1085-1093.

nucleus

cytoplasm

Signal transduction network in a cell
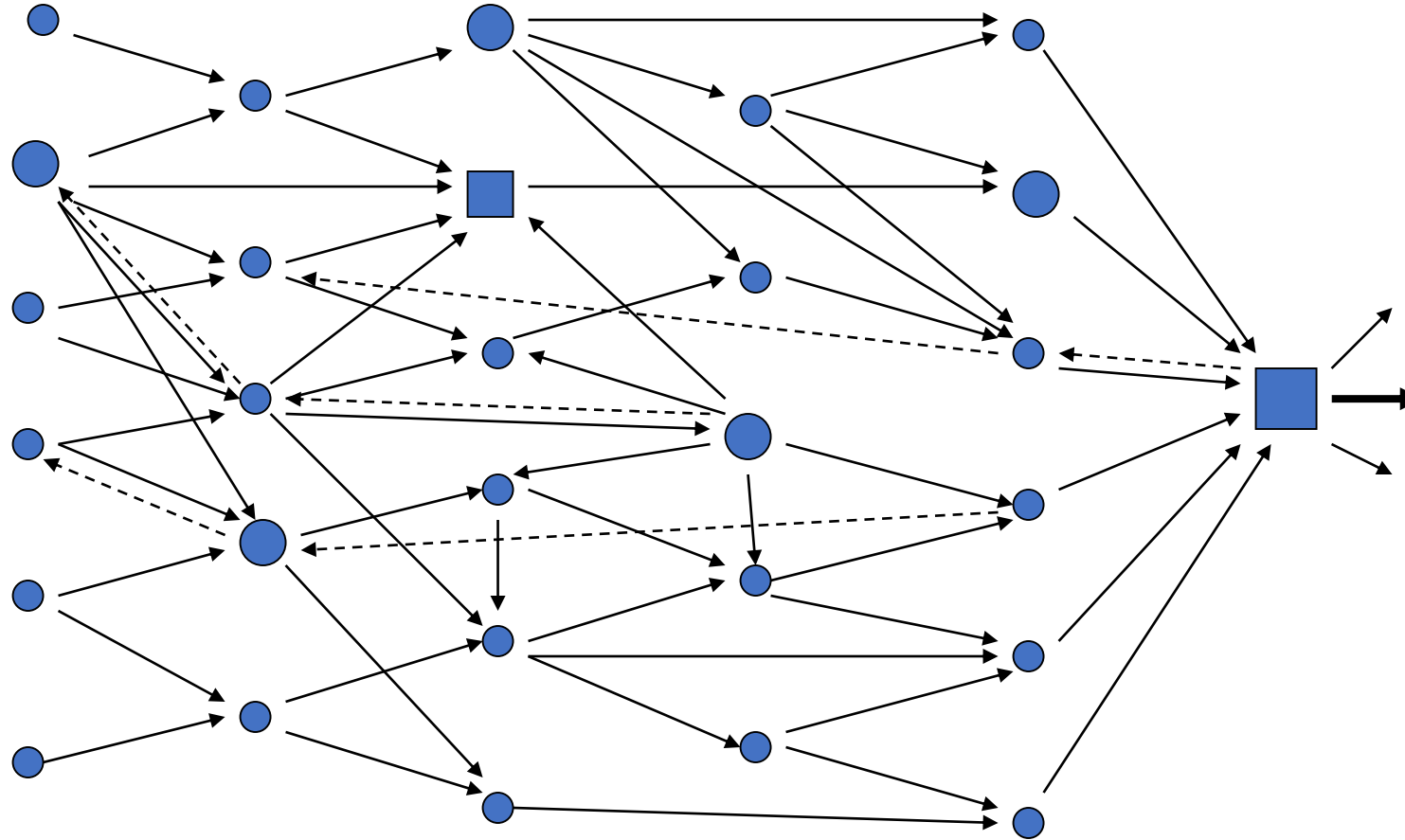
Connecting nodes - key players in the network
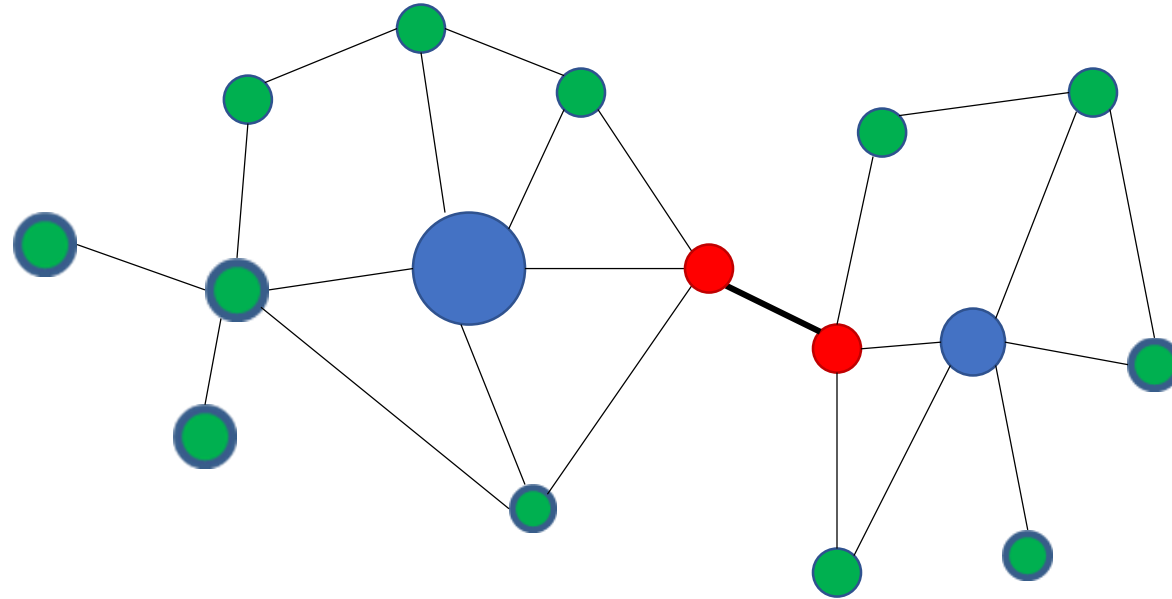
Structural "hole" – the shunt of signals
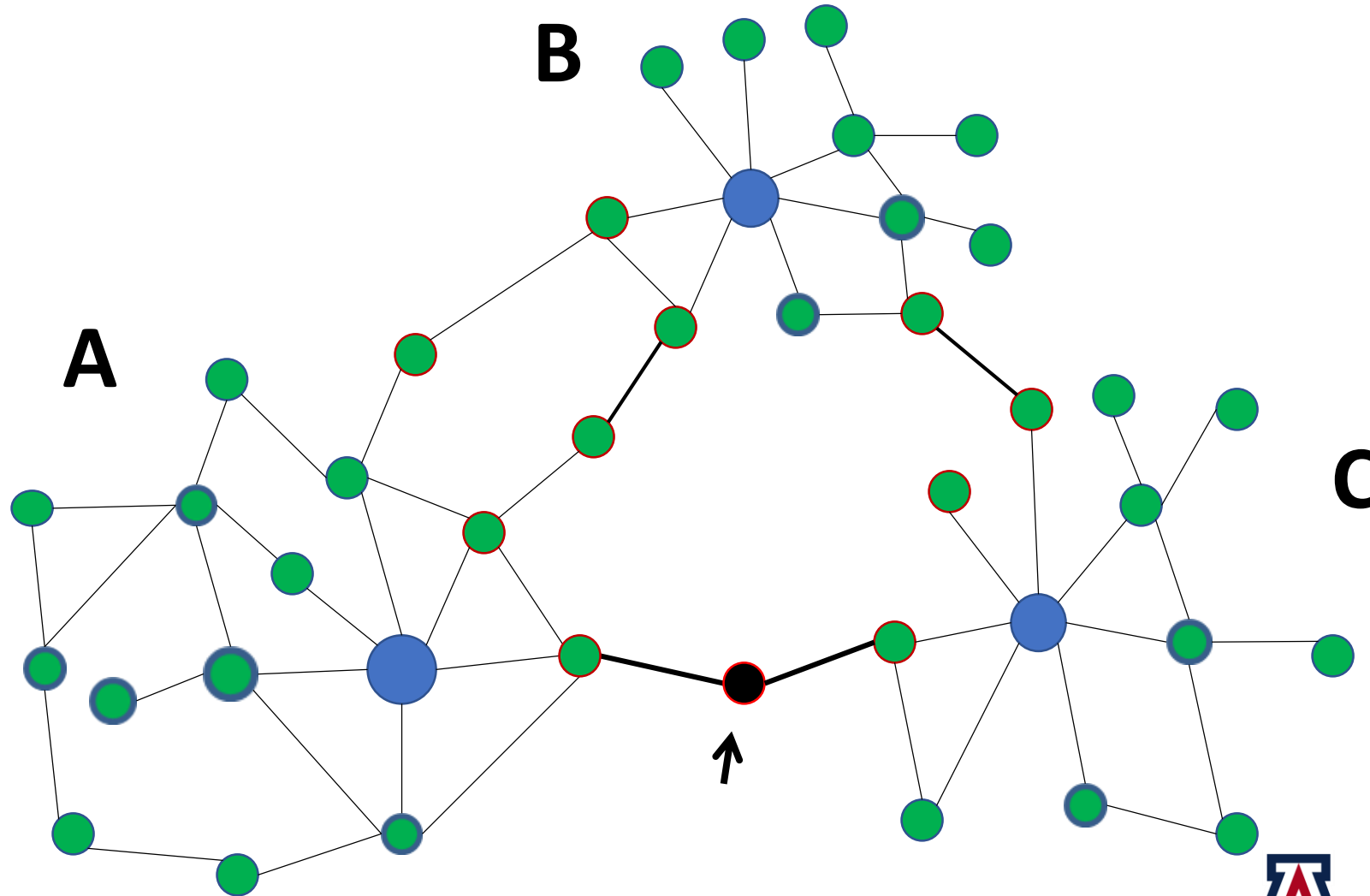
BCR-ABL1
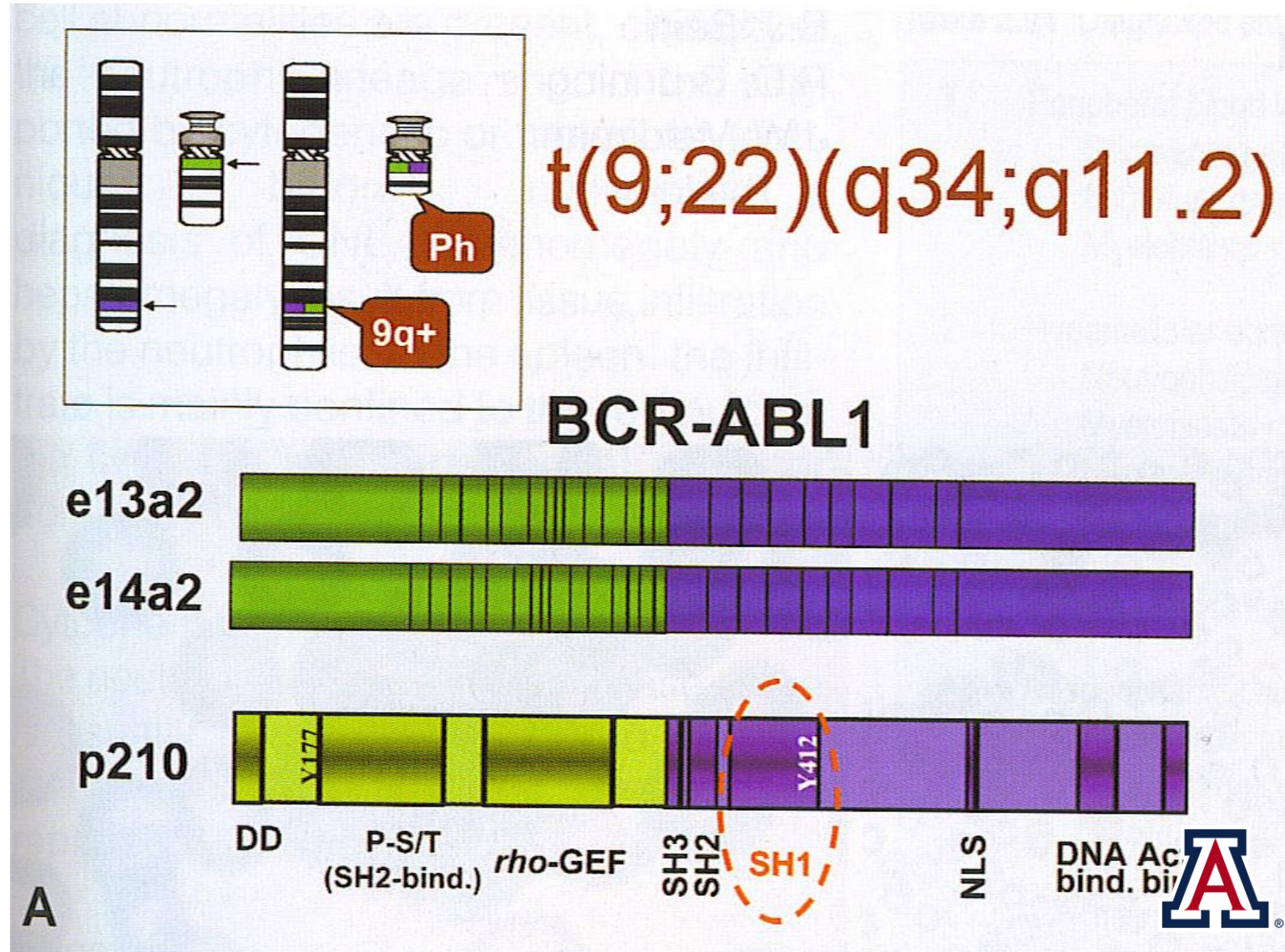
BCR-ABL1

Molecular basis of precision pathology

- Cancer "Driver" genes (targets)
- Node theory – key joints of signal transduction network (targets)
- Small molecules specifically targeting the "driver genes" and the "nodes" (arrows)

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Drugs for precision therapeutics

- EGFR inhibitors:
  - gefitinib   small molecule   reversible
  - erlotinib   small molecule   reversible
  - lapatinib   small molecule   reversible
  - canertinib   small molecule   irreversible
  - Neratinib   small molecule   irreversible
  - osimertinib   small molecule   irreversible
  - cetuximab   humanized antibody
  - necitumumab   humanized antibody
  - panitumumab   humanized antibody

- BCR-ABL1 inhibitor – imatinib

- mTOR inhibitor – Rapamycin

- BRAF inhibitor – vemurafenib (Zelboraf), dabrafenib (Tafinlar), and encorafenib (Braftovi)
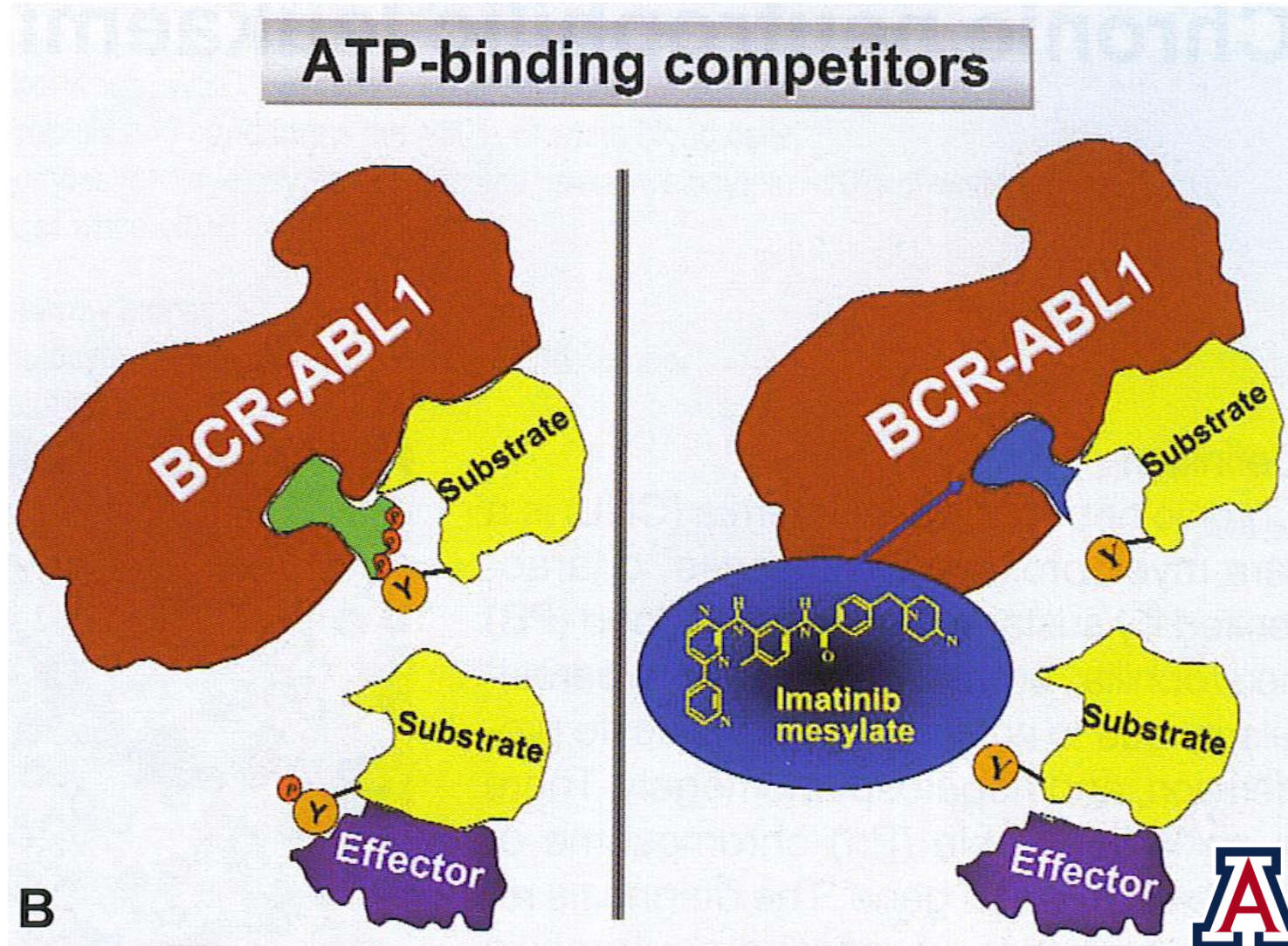
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Molecular basis of precision pathology

- Cancer "Driver" genes (targets)
- Node theory – key joints of signal transduction network (targets)
- Small molecules specifically targeting the "driver genes" and the "nodes" (arrows)
- Individual unique metabolism that affects drug effects and toxicities (environment: distance, wind, visibility, etc.)
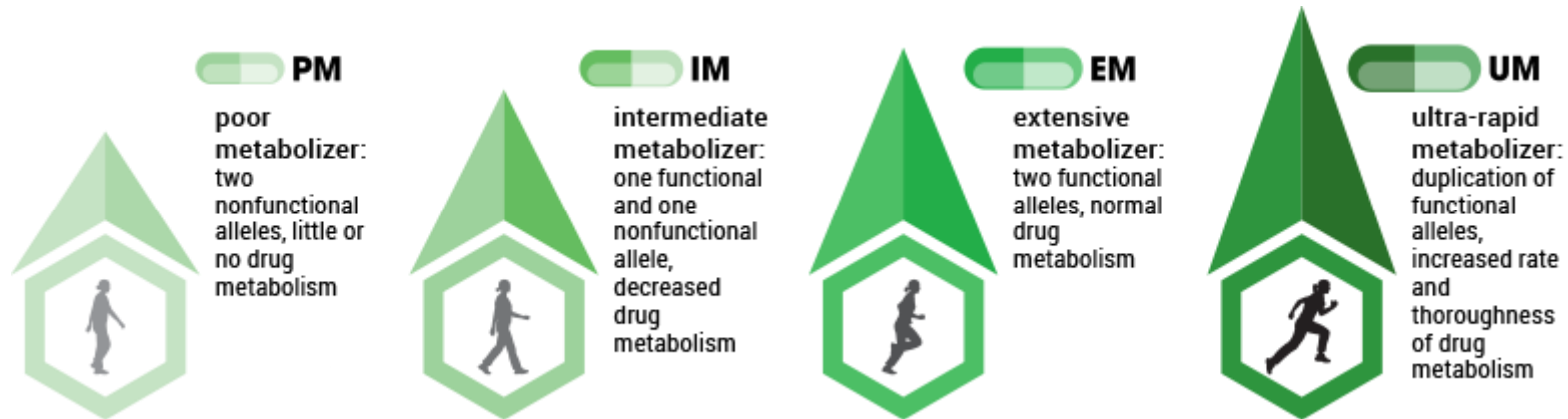
Pharmacomics

- Pharmacogenomics:
  - P450 family: CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4, and CYP3A5

PM poor metabolizer: two nonfunctional alleles, little or no drug metabolism

IM intermediate metabolizer: one functional and one nonfunctional allele, decreased drug metabolism

EM extensive metabolizer: two functional alleles, normal drug metabolism

UM ultra-rapid metabolizer: duplication of functional alleles, increased rate and thoroughness of drug metabolism

- Pharmacoproteomics:
  - Drug-binding proteins: CBG, SHBG
  - Drug receptors
- Pharmacometabolomics:

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Future Healthcare Team
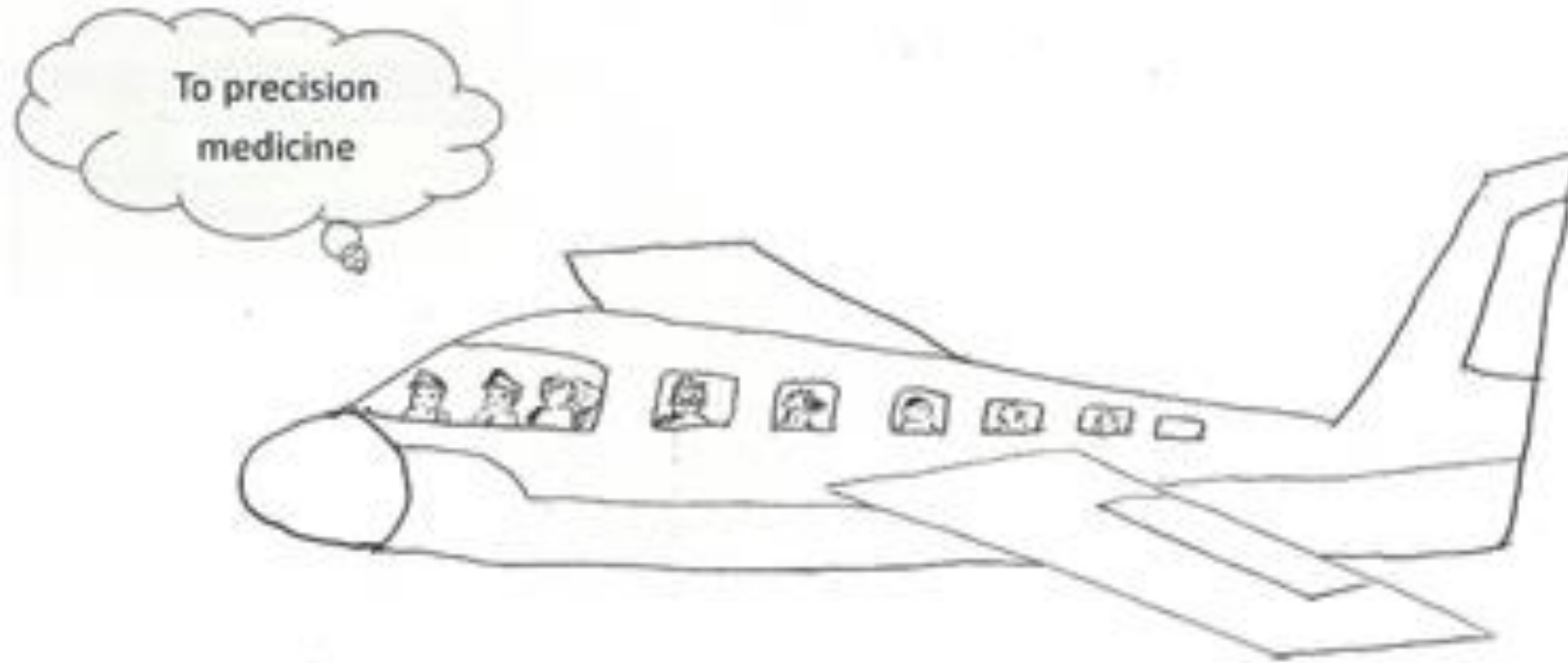
reimagine
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It's all here

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