An Oncology Strategy for IMI

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Strategic Themes of the Oncology SGG

The mission and vison of the SGG Oncology is to define projects that will aspire to effectively double the following parameters by 2025

"5 Doubles"

- Progression-Free Survival / Overall Survival

- Number of patients able to access innovative personalized medicines

- Speed of drug development

- Treatment tolerability

- Cost effectiveness in cancer drug development

SGG Oncology Priorities - Integrated Dynamic Personalized Cancer Care - IDPCC

Beyond patient stratification

- gathering large amounts of longitudinal diagnostic and treatment information
- how the function of these networks are altered by treatment, and how cells adapt to pharmacological treatment, including resistance mechanisms vs. escape for checkpoint.

Context specificity - MutOmics

- No two tumours behave the same, even after stratifying samples based on genotype and pre-selecting those that could reasonably be presumed similar
- systematically explore and predict contextual dependencies will require complex studies to test different drugs in different context and different indications

Immune Oncology – Tumor microenvironment

- Further advances can be fostered via a multi-pronged approach to continue to develop next generation IO and targeted monotherapies to augment our current treatment arsenal, and define IO
- Targeted or even IO – IO treatment combinations or sequencing of therapy that may show broad efficacy in previously challenging to treat tumour conditions

Cell Free DNA – Liquid Biopsy

- cfDNA assessment could also allow to overcome the challenges of tumour heterogeneity both spatial and temporal as well as triggered by treatment pressure.

The Era of Big Data – HARMONY, THE BIG 5, Prostate Initiative

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Projects

HARMONY

- Development of an outcomes-focused platform to empower policy makers and clinicians to optimize care for patients with hematologic malignancies

MutOmics

- Identify the interdependencies of tumor mutations, stromal factor, extracellular matrix and gene expressions in order to identify responder populations differently.

The "Big 5", Prostate Cancer Initiative

- RWE (Real world evidence) is a key factor to improve cancer outcome and establish meaningful endpoints, treatment sequences and toxicities.
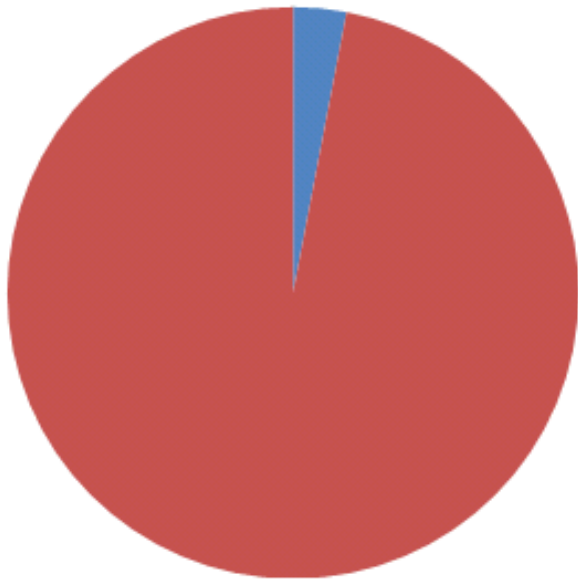
Tumor microenvironment

- Profiling specifically designed to deeply interrogate tumor microenvironment and patient immune system over time

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Clinical Trial data vs. Real World Evidence

Clinical Trials
3% -5%

Cancer Patients in daily clinical practice 97%

- 3%-5% of all cancer patients are in clinical trials
  - Stringent inclusion / exclusion criteria
  - Highly structured and organized towards submissions
  - Treatments assessed are limited by trial design
  - Focused on countries where participating sites are located
- 95% of patients do not participate in clinical trials
  - Data in health care systems, governmental registries, patient advocacy groups
  - Contain information on all cancer treatment paths actually used in patients across different countries / regions / ethnicities
  - May allow better understanding of drug efficacies
    - Estimate of effect of controls / comparators
  - May allow better understand the physician best practices across the EU
  - Present a huge potential opportunity to community

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Innovation by Real World Evidence

1. Identify and form an industry, government, academic, payer / provider, patient advocacy collaboration to evaluate health outcomes and value of cancer therapies

2. Generate a standard set of outcomes, clinical endpoints and patient centric value measures for the select set of solid tumors of interest

3. Initial identification of data types and sources which will comprise database tool

4. Generation of harmonized data standards, robust quality metrics and a set of data cleaning tools that will facilitate the upload and curation of data into the database

5. Build suite of data visualization and analytical tools to provide initial analysis of the data in the system. Provide platform upon which additional tools may be generated

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Value in Cancer Care is shifting

From Right Drug for the right Patient....... To......

Right Living

Increased Screening

Longer life span without cancer
Less end of life costs

Right Care

Disease Mgmt
Right Drug Usages

Longer survival
Reduced mortality
Reduced intervention

Right Value

Real World Evidence / Big Data

Prevention of AEs
Pricing leverage

Right Innovation

Technology meets Patients

New drugs / better regimens
Improved clinical trial efficiency
Improved access

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Key Trends in Oncology

|	
Smaller, stratified patient populations, complex treatment paradigms	1.5x higher growth rate in low incidence tumors, 50% PIII with CDx Treatment paradigms with sequential subpopulations
Accelerated innovation and product life cycles	Less than 20% exclusive targets in pipeline Product life cycles from 5+ years to 1-2
Increased role of combinations and collaborations	External Innovation drives significant growth ~ 50% of PD(L)-1 trials in combinations
Value shifts, big data and novel access models	Big data allowing more nuanced value capture Real World Evidence brings Innovation to Life
Wave of new technologies and innovation	Next wave of innovation (CAR-T, mRNA, CRISPR) Wearables, Clinical Trial as N=1, 10 ? Increased opportunities for personalization

Science and technology are continually evolving

Science

Complexity

2004   2014   Future

Classification of lung adenocarcinoma
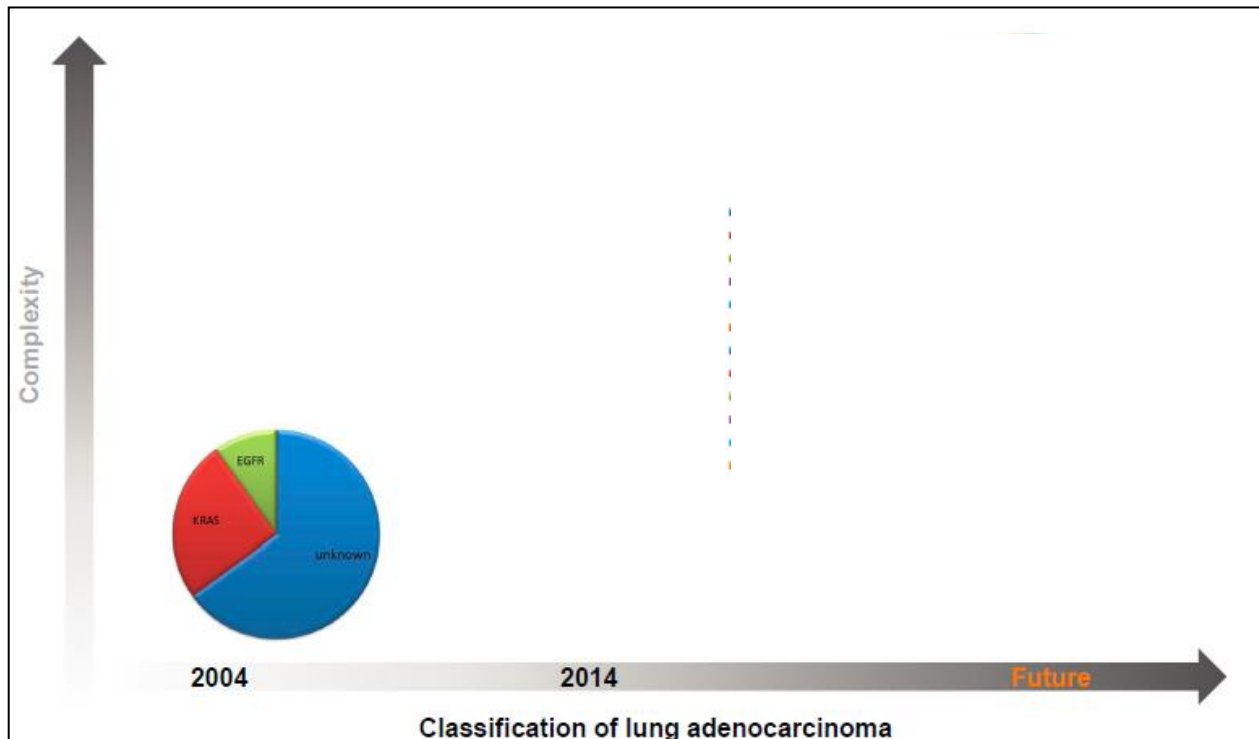
⇒ **due to continual evolving technologies, understanding of molecular disease complexity is increasing**

Technology

- **Sanger sequencing**
- **Sequenom (hot-spot mutations)**
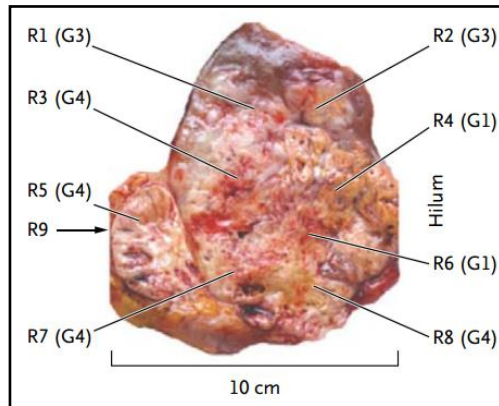- **Gene microarray**
- **Protein array**

- **IHC**
- **FISH**
- **RT-PCR**
- **Flow cytometry**

- **NGS**
- **Digital PCR**
- **Multiplex IHC**
- **Nanostring**

- **ctDNA (non-invasive)**

9

▪ Pao & Girard. Lancet Oncol 2011; Johnson, et al. ASCO 2013
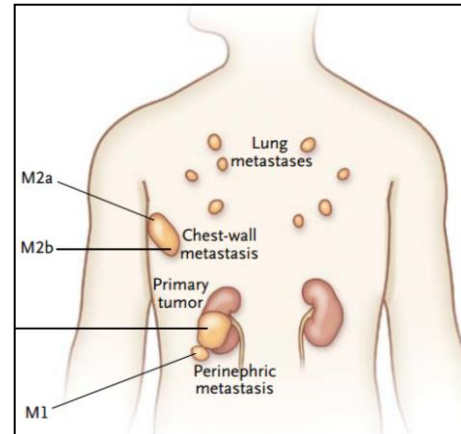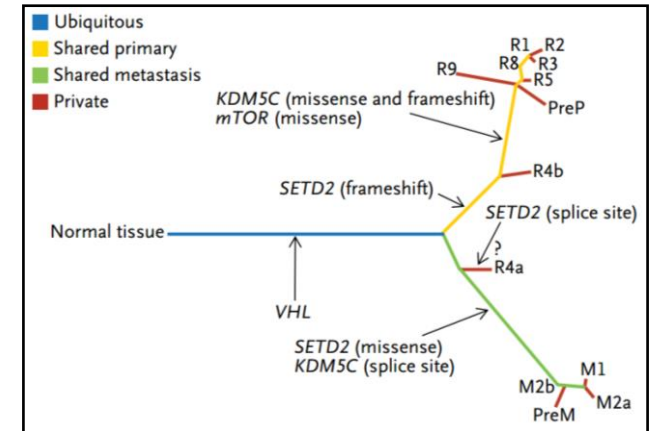
Cancer is a Dynamic Disease

Spatial and temporal heterogeneity play a critical role to identify appropriate treatment
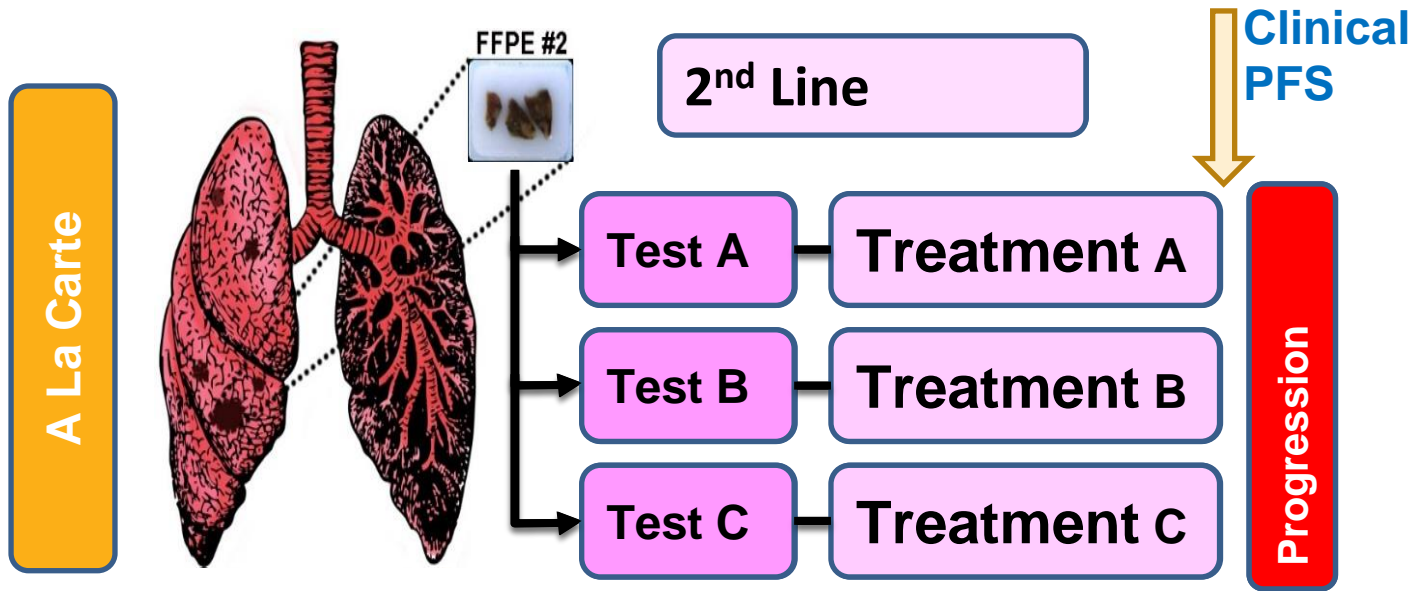

Intralesion

Interlesion

Temporal

- By understanding each dimension of tumor heterogeneity, we are able to better understand the genetic makeup of the tumor

- Provides opportunity to enroll/treat patients dynamically into clinical trials and to characterize their disease biology

- Provides a contemporaneous view during therapy of driver mutation changes in the tumor, which may justify a new course of treatment for the patient
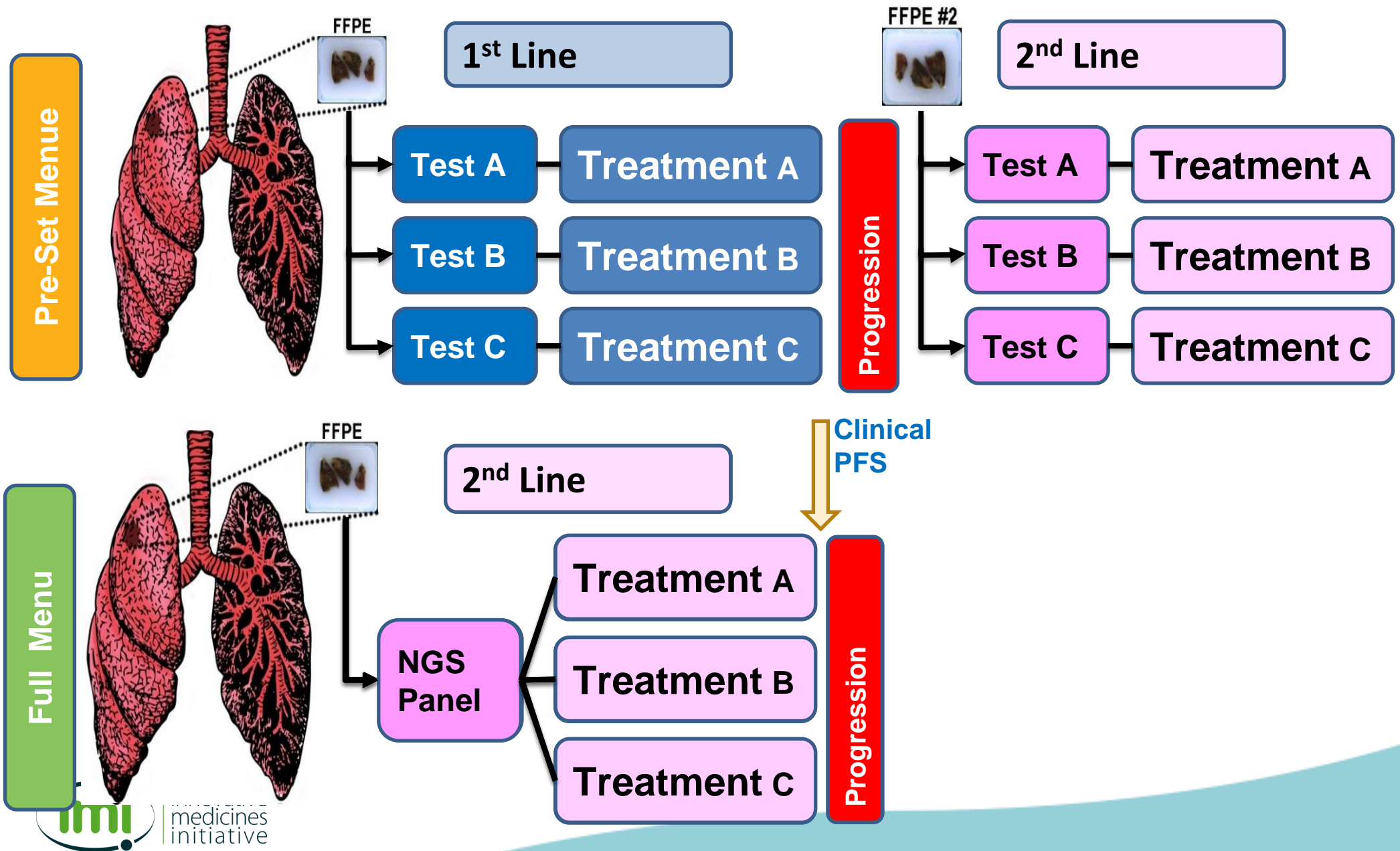
Gerlinger M, *et al. New Engl J Med.* 2012;366;883–892.

Patient Selection Today
From **Pre-Set Menu**

FFPE #2

A La Carte

2nd Line

Clinical PFS

Test A — **Treatment A**

Test B — **Treatment B**
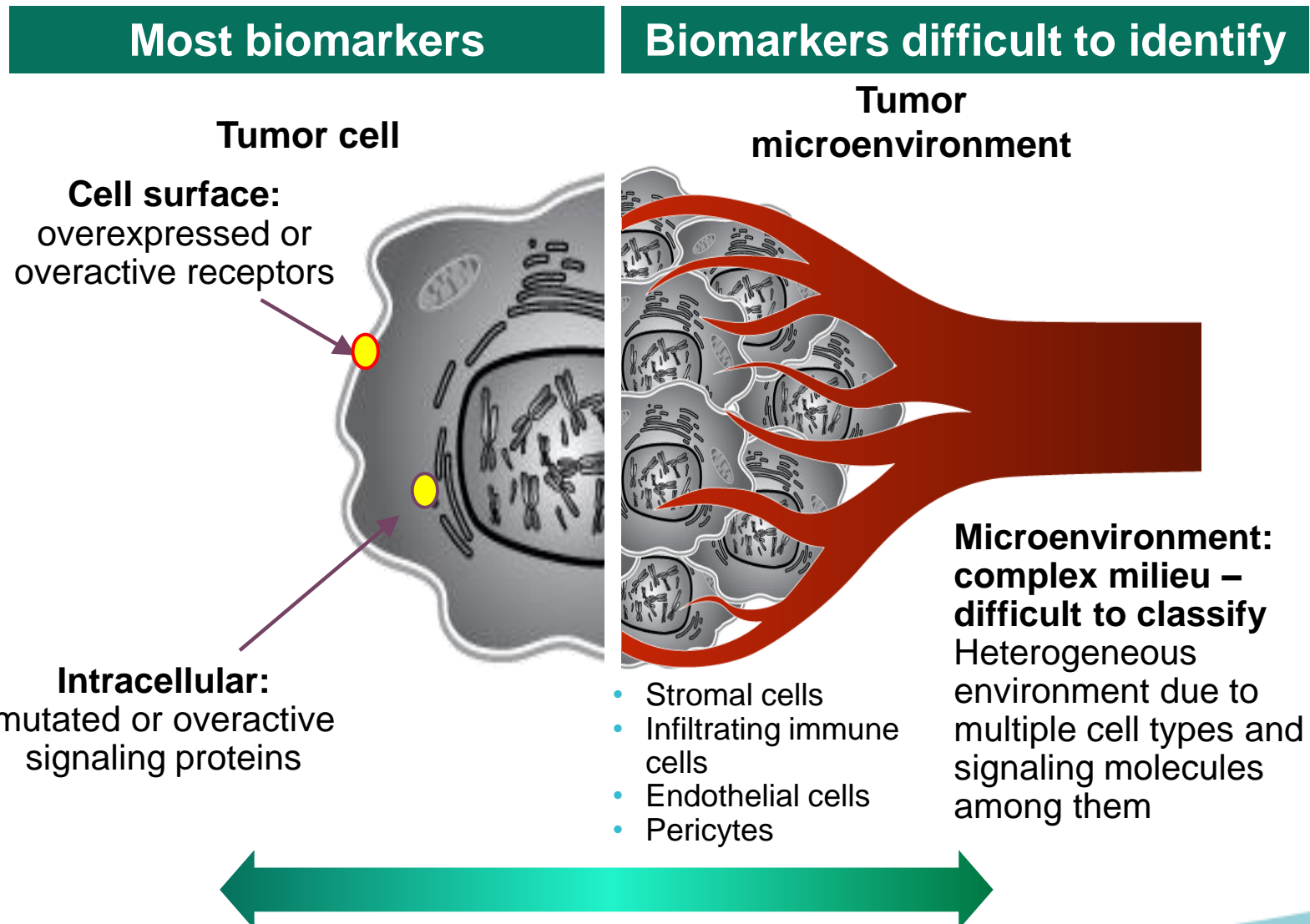
Test C — **Treatment C**

Progression

Patient Selection Today
*From Pre-Set Menu to **Full Menu Selection***

Biomarker challenges by complexity of cancer biology[1-3]

Most biomarkers	Biomarkers difficult to identify

Tumor cell

Cell surface:
overexpressed or overactive receptors

Intracellular:
mutated or overactive signaling proteins

Tumor microenvironment

Microenvironment: complex milieu – difficult to classify
Heterogeneous environment due to multiple cell types and signaling molecules among them

- Stromal cells
- Infiltrating immune cells
- Endothelial cells
- Pericytes

1. Sawyers CL. *Nature* 2008;452:548–52. 2. Kulasingam V, Diamandis EP. *Nat Clin Pract Oncol* 2008;5:588–99. 3. Joyce JA, Pollard JW. *Nat Rev Cancer* 2009;9:239–52. Cell illustrations adapted from The Cancer Genome Atlas (TCGA). The National Cancer Institute. http://cancergenome.nih.gov/media/images.asp. Accessed July 18, 2007.

Heterogeneity in Real Life

Mix of textures, tastes, color
=
Mutation, Expression, Protein

Differentiated textures, tastes, color =
Mutation, Expression, Protein

Contextual Dependency

Google translate accuracy is 57.7% and the tool was best at translating Western European languages (74% accuracy) and worst at African languages (45% accuracy) ([Patil S, Davies P. BMJ 2014;349:g7392](#))
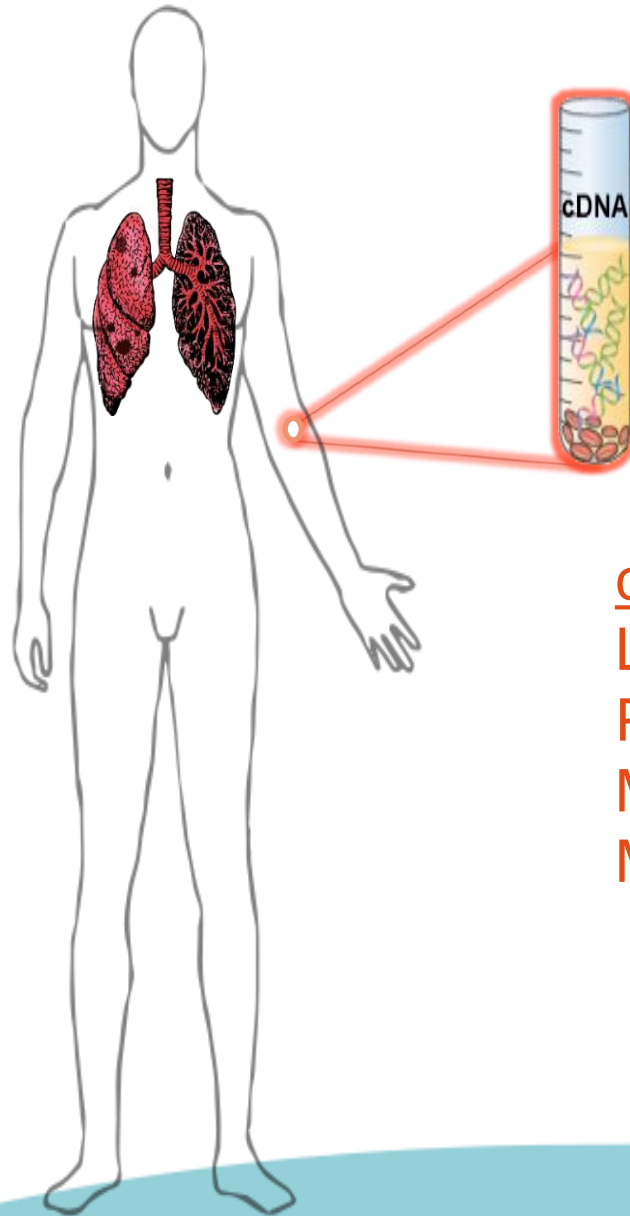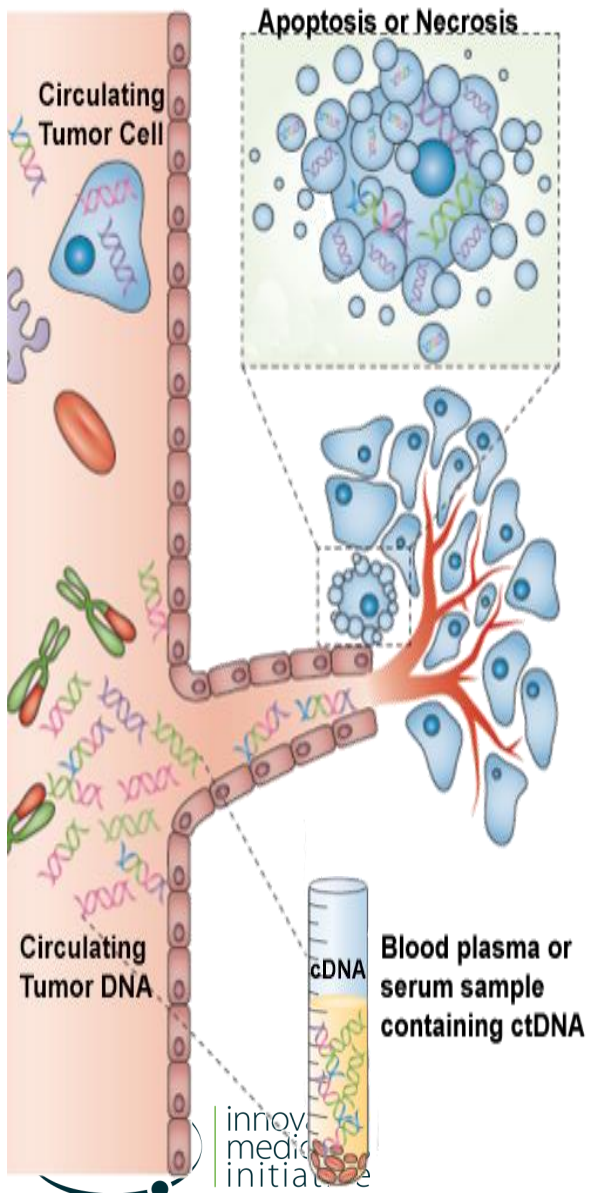
Book:

- I read a book

- Book me a flight

- Book him

Point:

- The pencil has a sharp point

- It is not polite to point at people

- You have a point

Patient Selection Tomorrow
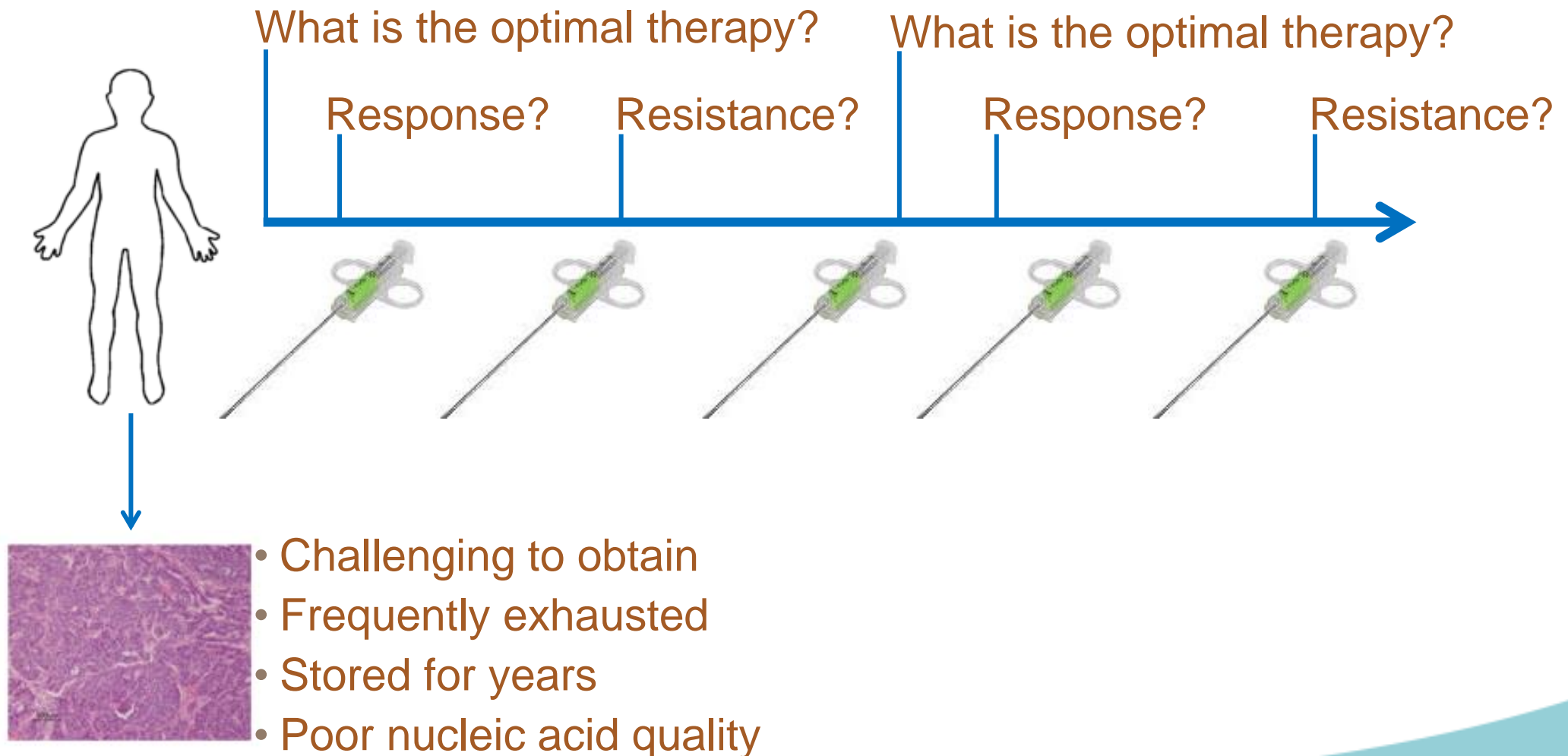## From A La Carte to *Full Menu Sampling*

ctDNA:
Liquid Biopsy
Pharmacodynamics
Molecular Resistance
MRD

Non-invasive enabling of personalized medicine

Understanding individual tumor genetics to tailor therapies
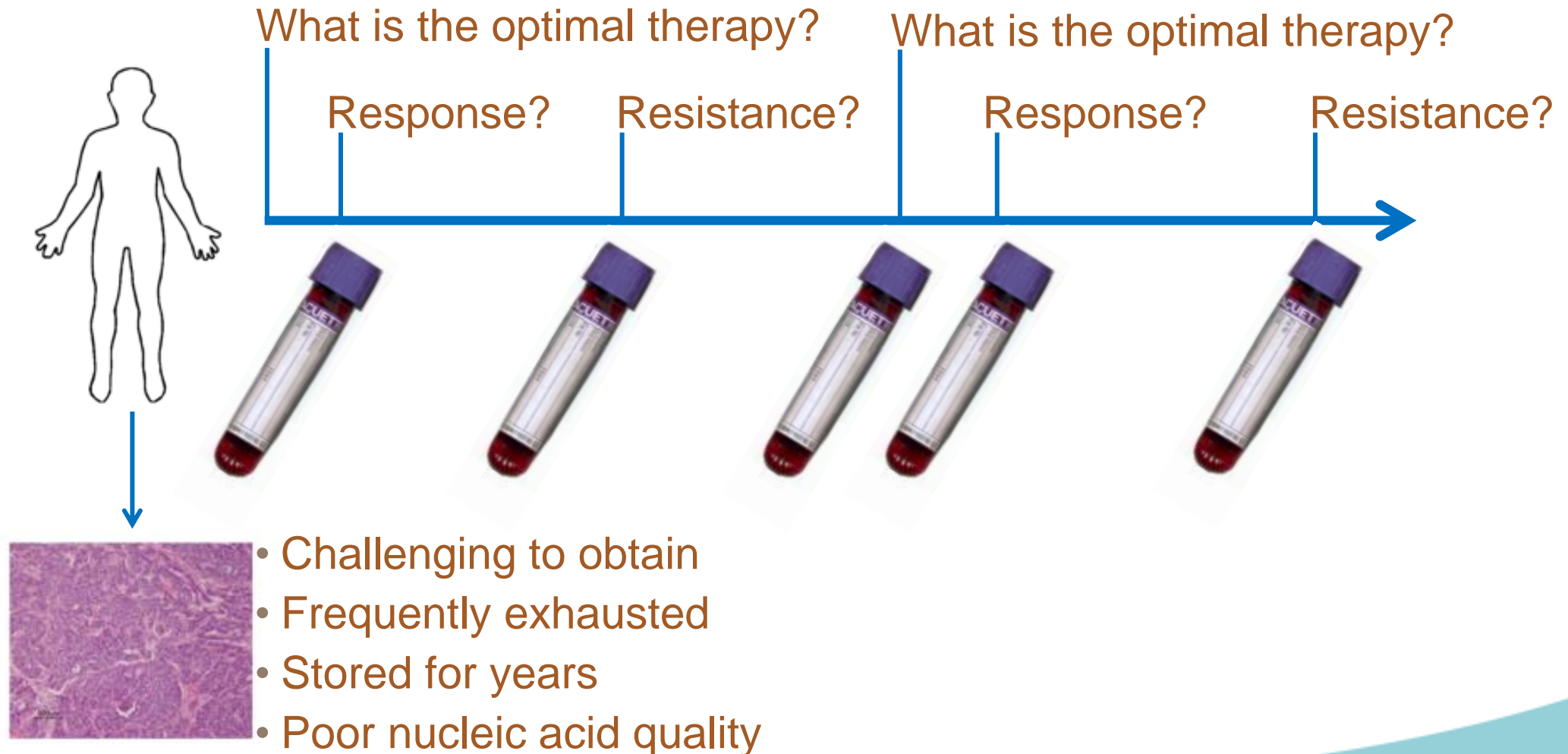
Patient sample collection and clinical decision making

What is the optimal therapy?   What is the optimal therapy?

Response?   Resistance?   Response?   Resistance?

- Challenging to obtain
- Frequently exhausted
- Stored for years
- Poor nucleic acid quality

Non-invasive enabling of personalized medicine

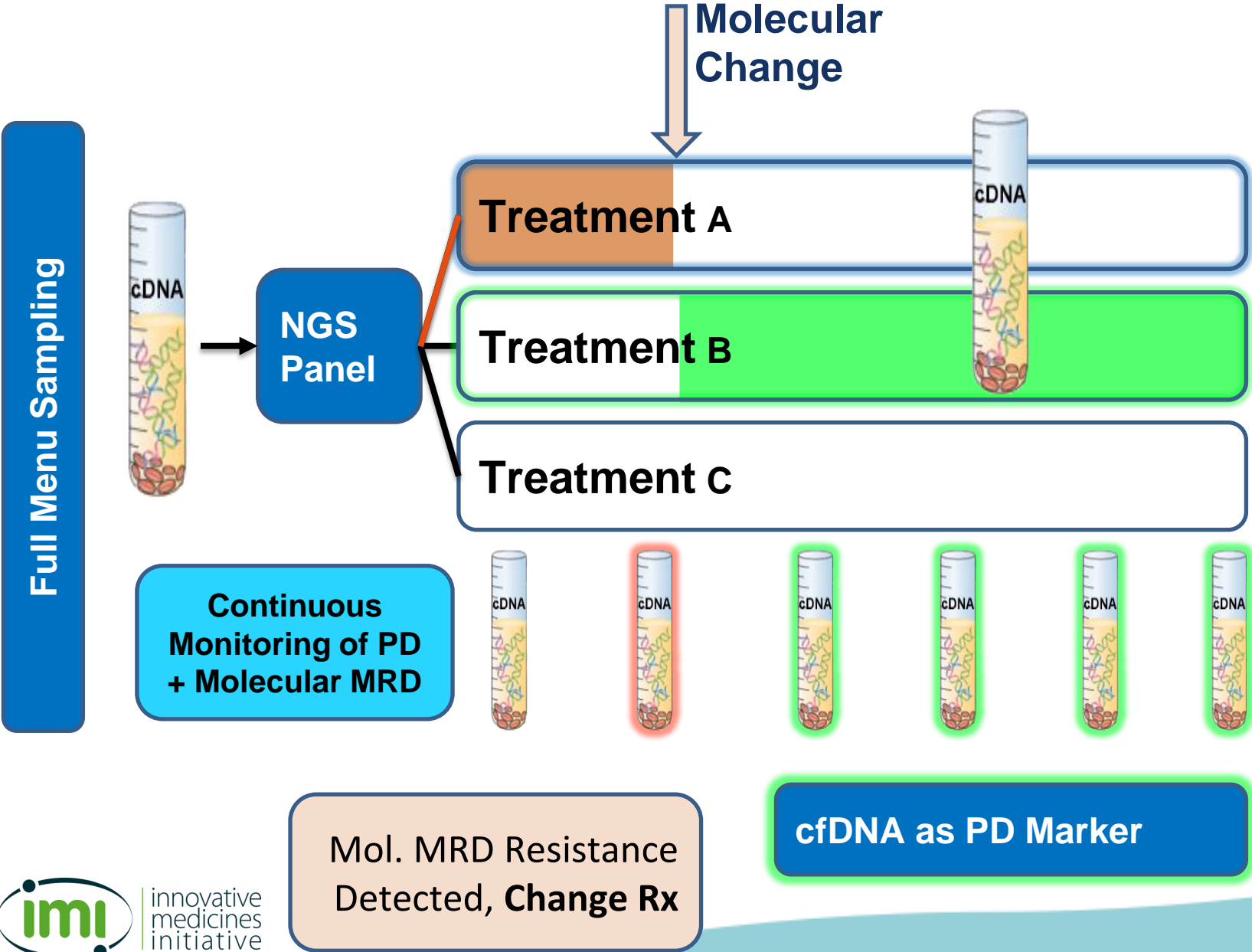*Understanding individual tumor genetics to tailor therapies*

Patient sample collection and clinical decision making

What is the optimal therapy? What is the optimal therapy?

Response? Resistance? Response? Resistance?

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Patient Selection Tomorrow
*From A Set Menu to **Full Menu Analysis***

NGS based cfDNA Pan Cancer Assay

600 gene assay to characterize cell-free DNA
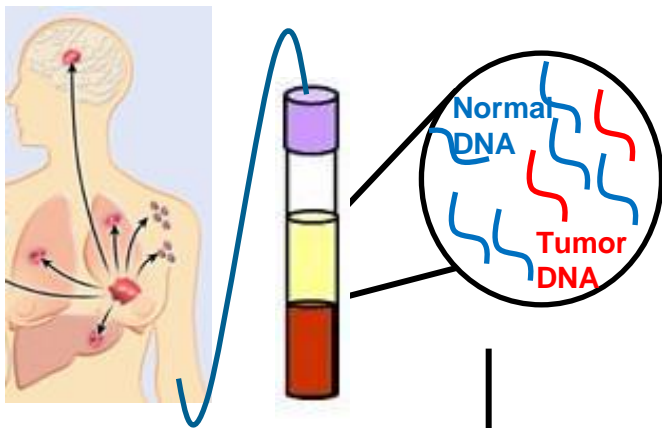
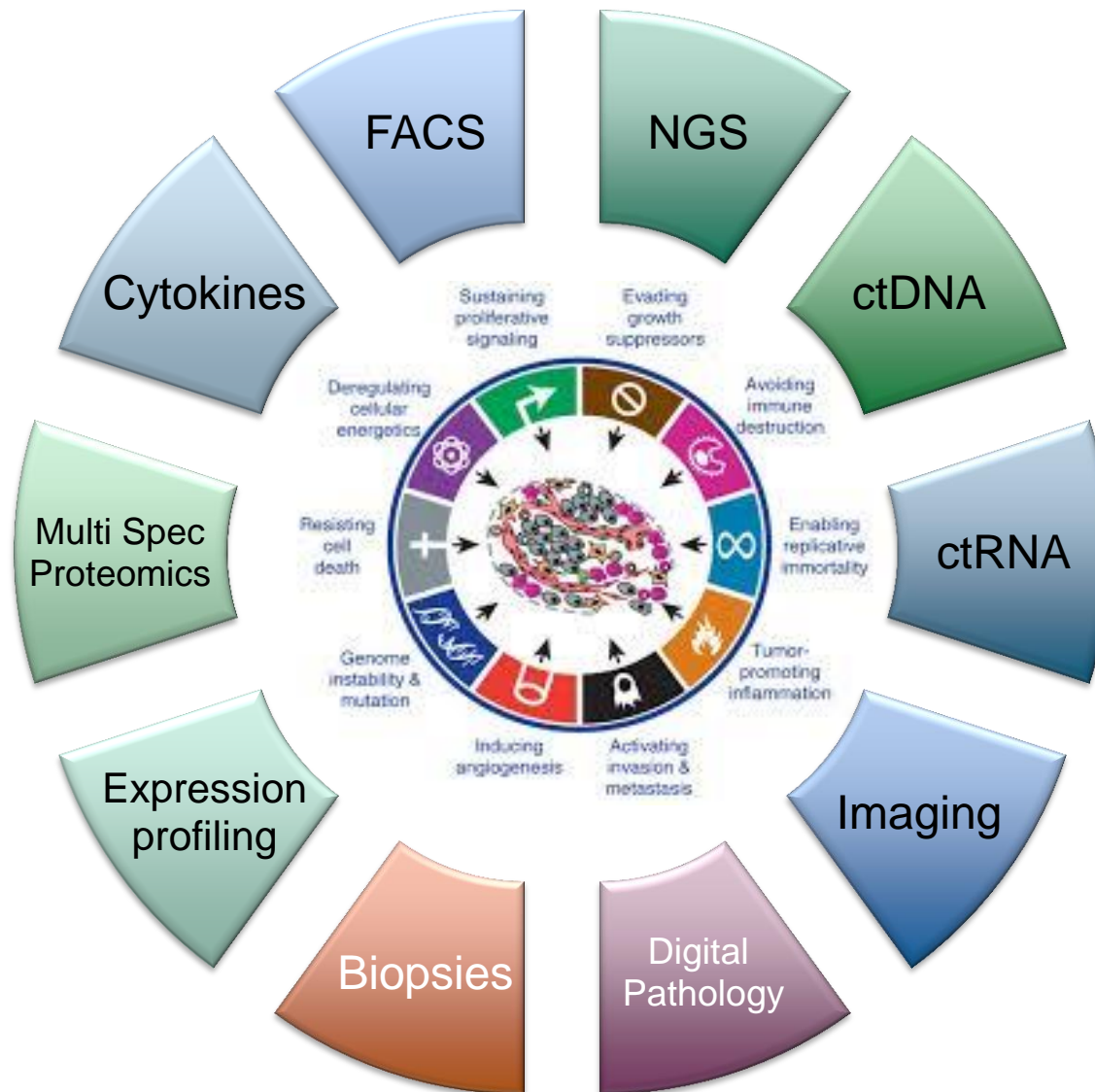| PanCancer Panel	Genes
Curated cancer genes	139
Copy number alterations	195
Signaling pathways	251
Translocation Loci	56
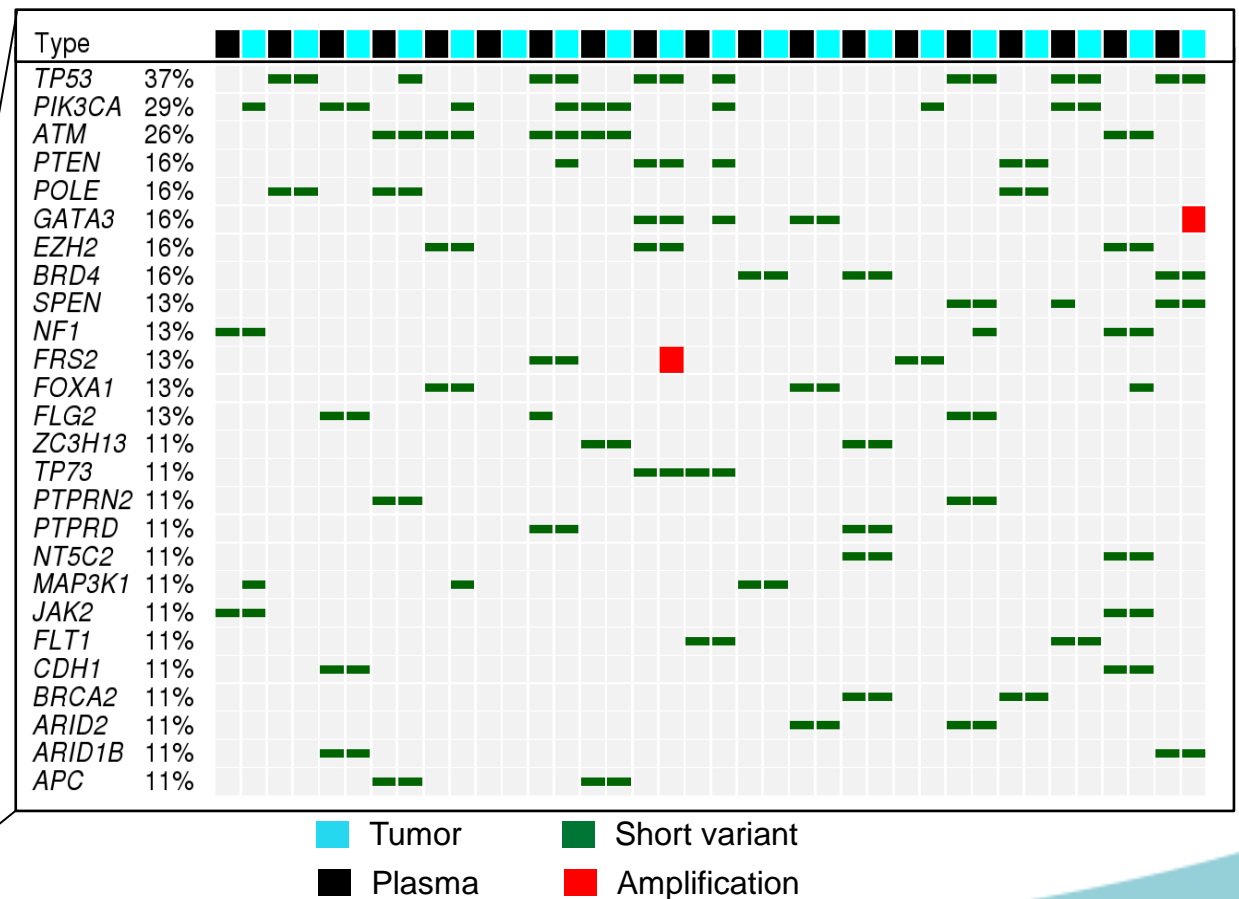
Cancer is a Multidimensional Disease
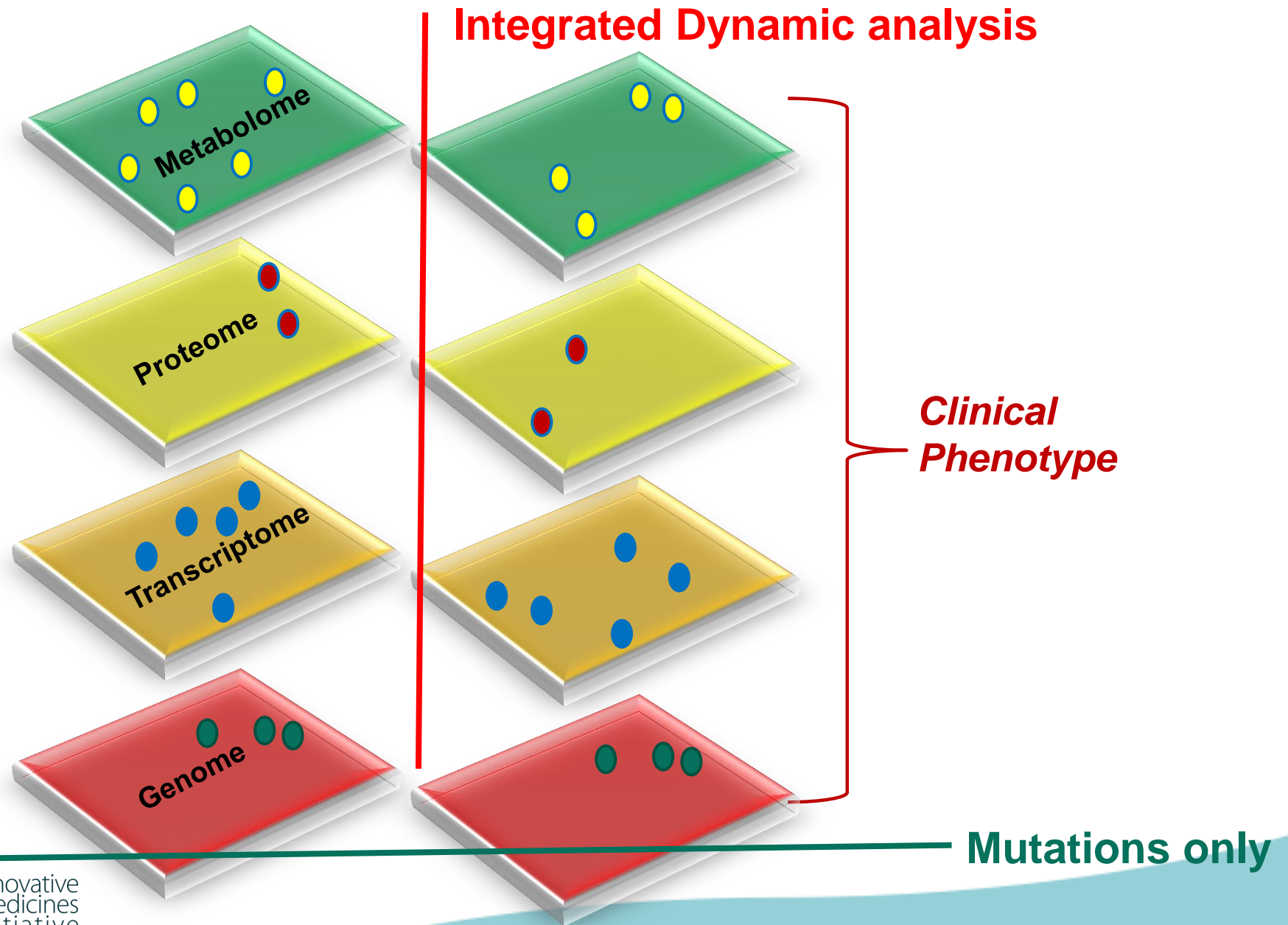
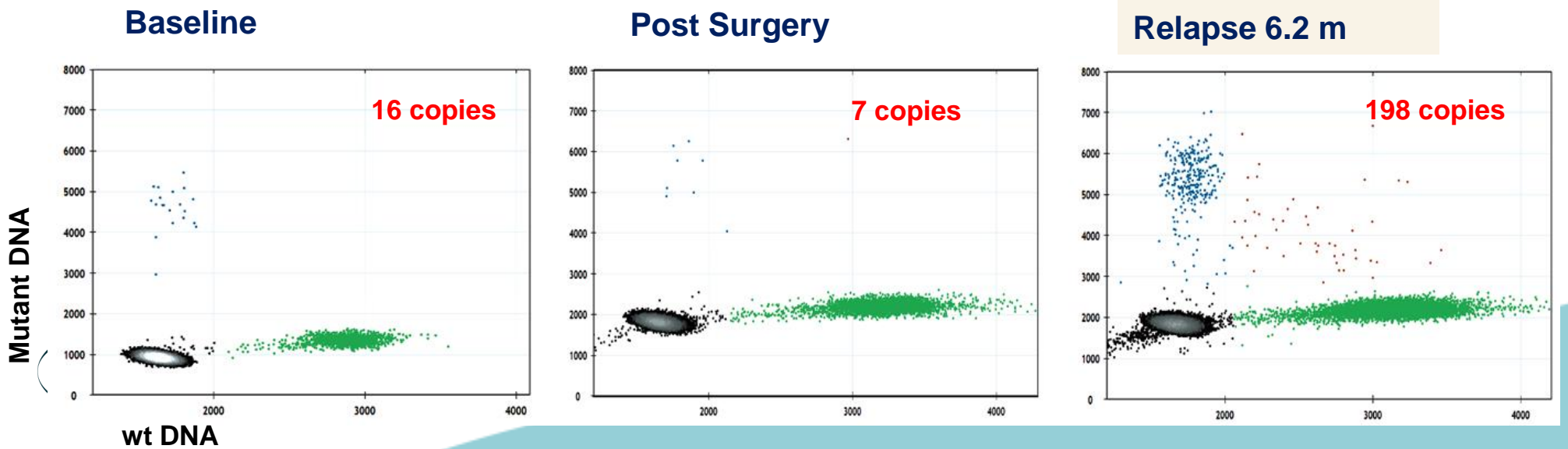# Next wave of Innovation in Oncology – Hallmarks of cancer technology

Integrated Dynamic Personalized Cancer Treatment
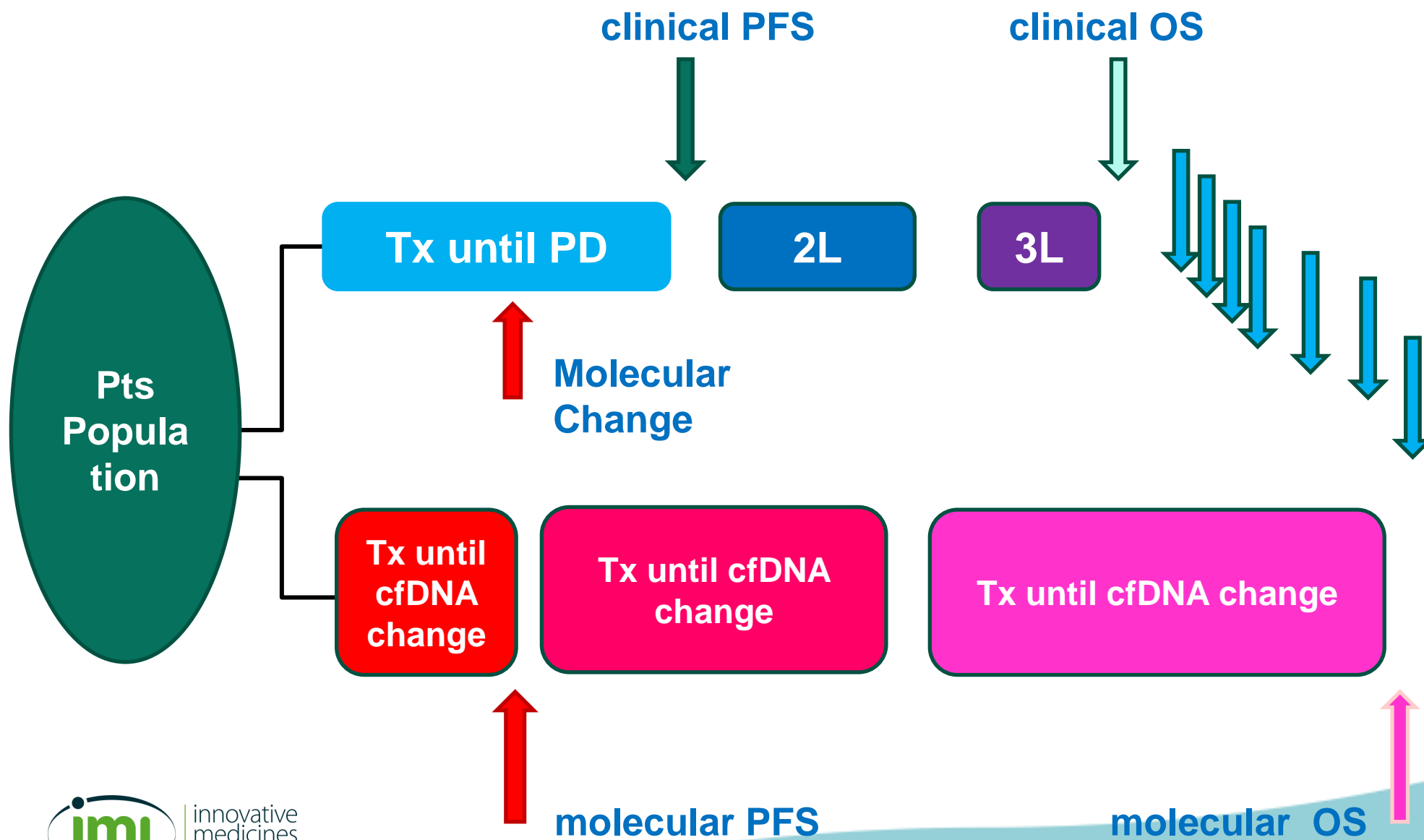
The Future is here...

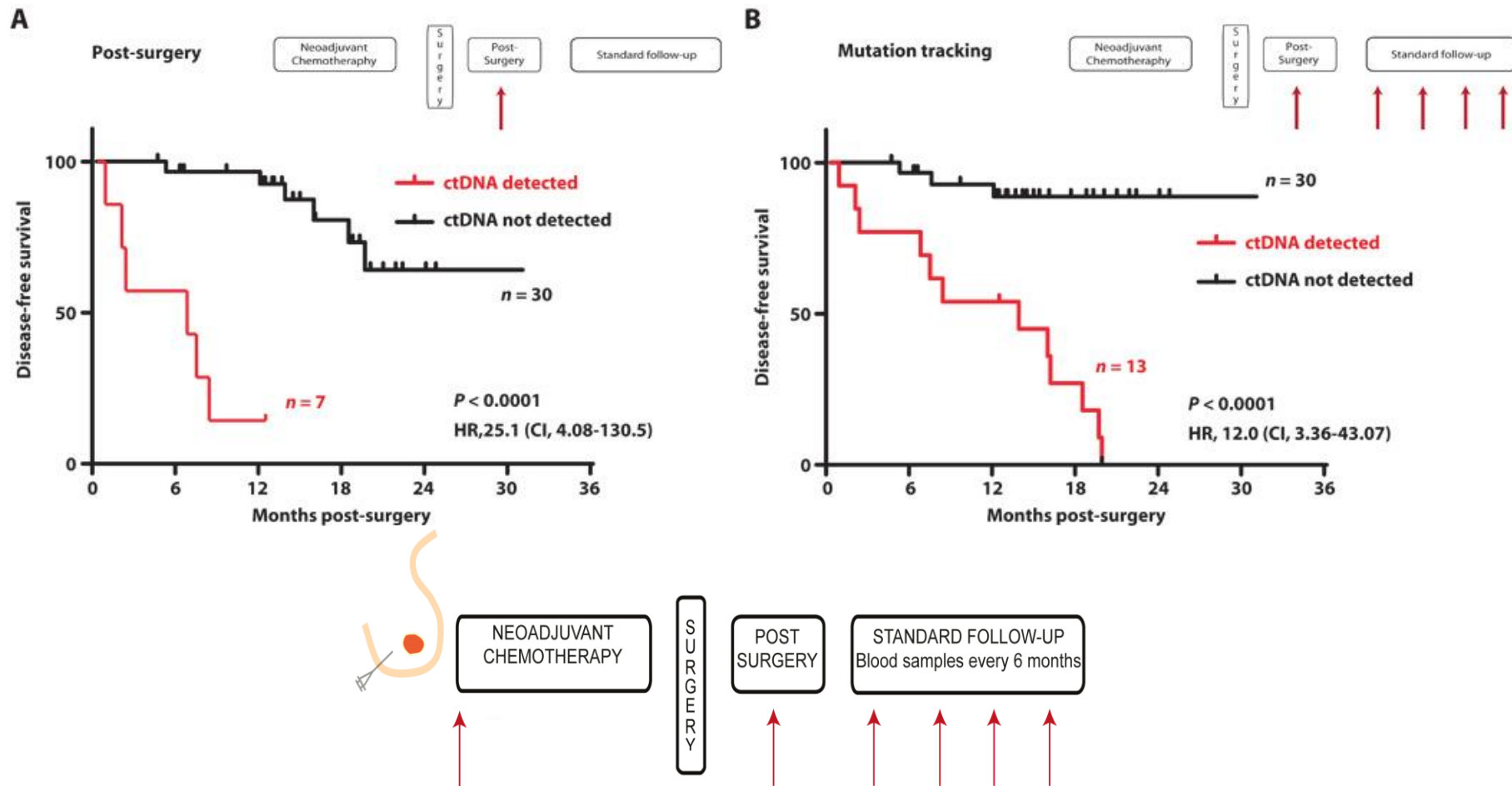Nick Turner ASCO 2014

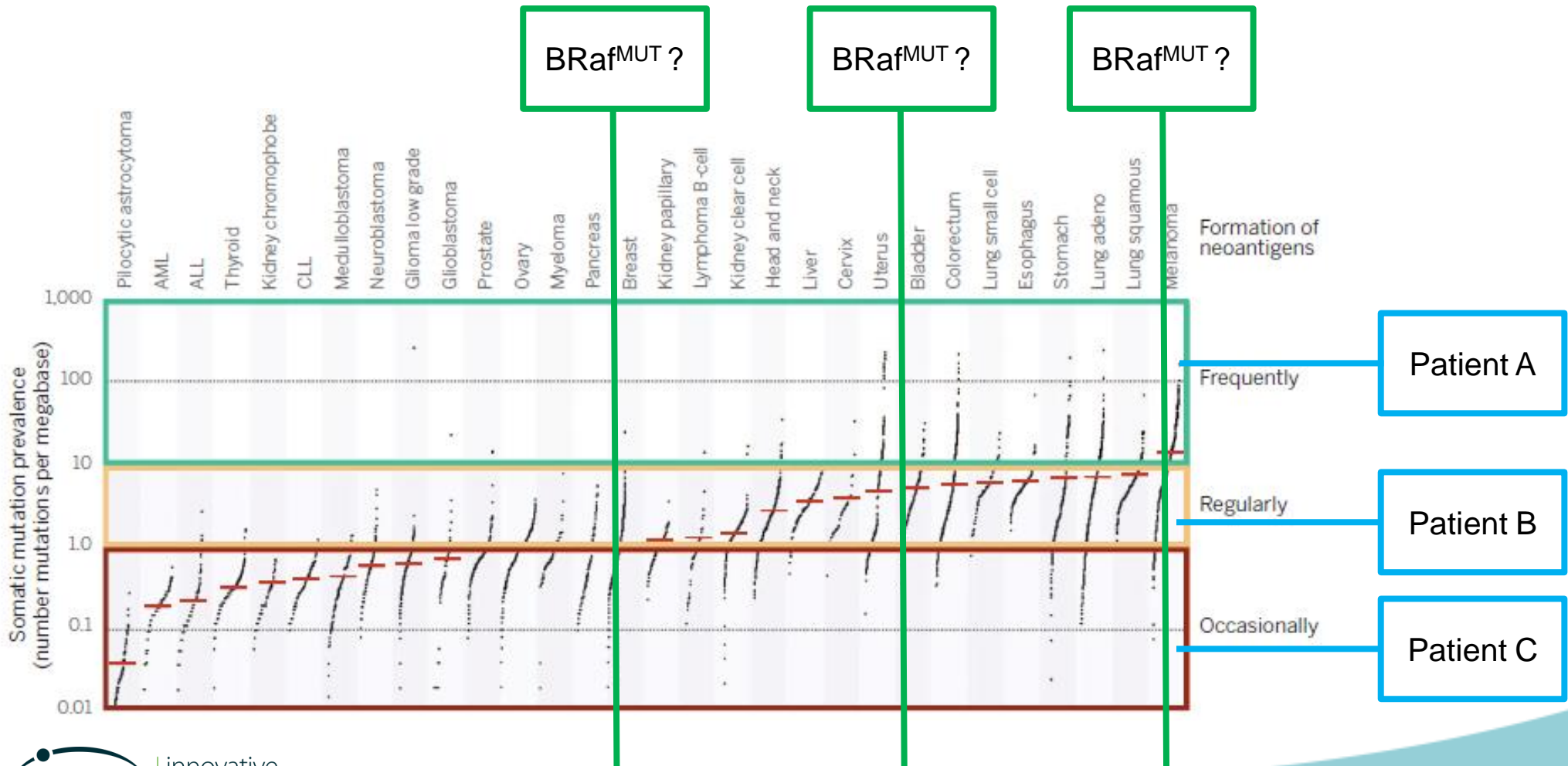# ctDNA may predict Disease Recurrence in early BCa

Mutation tracking in serial plasma samples predicts early relapse

Garcia-Murillas I, et al. *Sci Transl Med*. 2015;7:302ra133.

cfDNA and Immunomodulatory Agents

Mutation load and neo-antigens

Limitations of today's treatment paradigm
Example for lung treatment

Linear treatment of cancer based on a predefined protocol that does not account for changing molecular biology of the tumor

Diagnosis	Staging & treatment	Palliative care

Biopsy & diagnosis
1

Disease progression (as confirmed by medical imaging)

EGFR
ALK+
BRAF
...

1st line (ALK inhibitor)

2nd line (ALK inhibitor)

3rd line (chemo)

Medical imaging and staging

Aggressive progression of disease results in **compression of later line treatments**

Stratification of patients based on initial biopsy

Initiation of treatment based on a **treatment protocols**

Subsequent lines of treatments are based on disease progression, as measured by **number of tumor locations, tumor size, invasiveness**

Understanding which tumor subtypes/clones are present would allow targeted treatment & potentially increased treatment options

Disconnect from what actually happens:
Tumor continues to evolve, resist / tolerate treatment

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1. Including clinical examination, histopathology

IDPCC may transform cancer care

From line treatment to precision medicine

Treatment of cancer according to IDPCC

| Diagnosis | Staging & treatment | Palliative care |

Biopsy & diagnosis

Real time response of treatment according to molecular evolution of the tumor

Targeted agent + a standard chemotherapy

Targeted therapy

Targeted therapy

Chemo

Chemo

IDPCC (liquid biopsy) & imaging

IDPCC may progress PSF and improve quality of life

Stratification based on **molecular markers or signatures**

Personalized treatment tailored to a patient's tumor

Continuous monitoring over the course of the treatment, using liquid biopsy - treatment decisions made in real time based on **how tumor evolves on a molecular level**

Connected with what actually happens:
Appropriate treatment selected to target resistant or tolerate clonal populations

imi
innovative
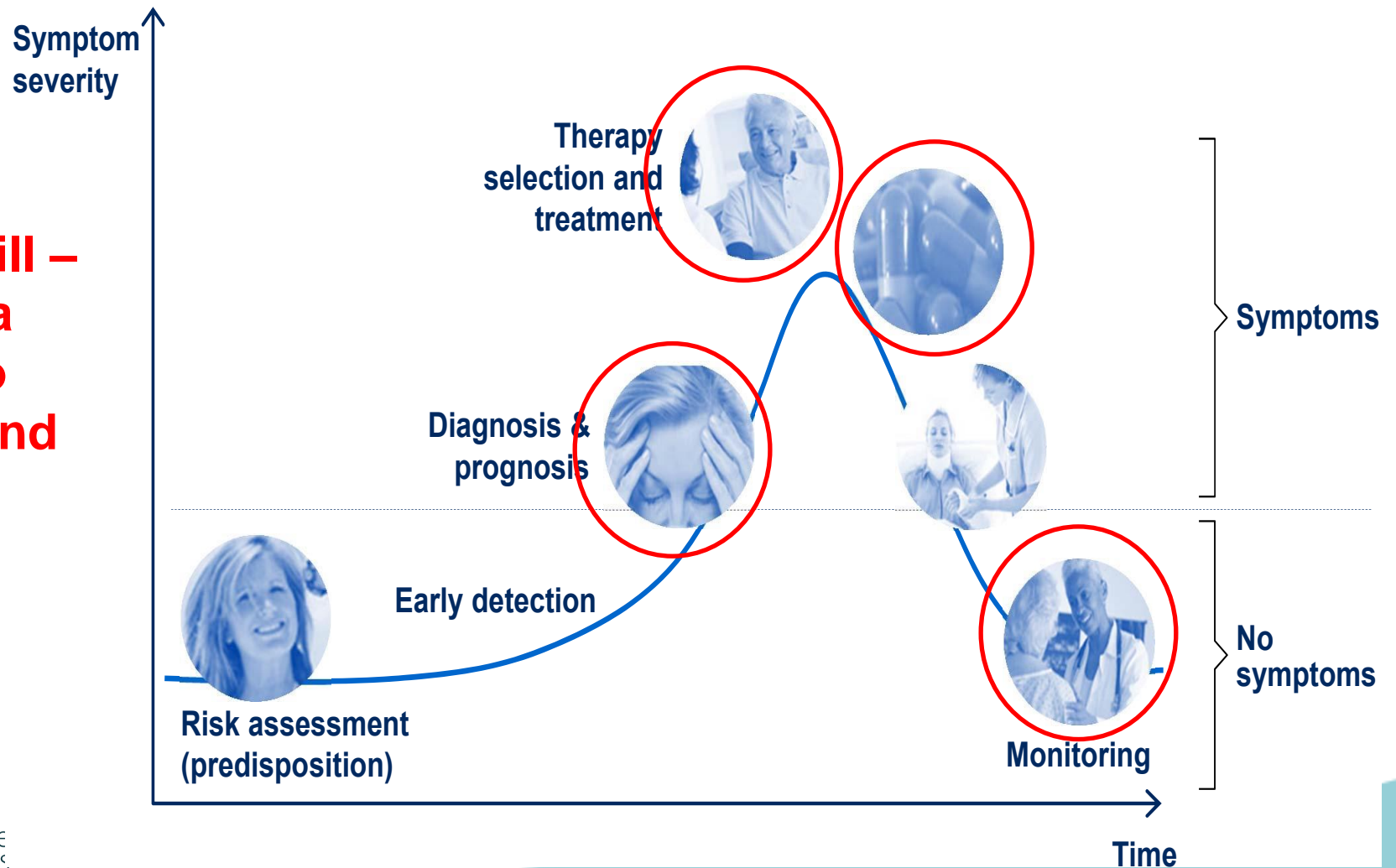medicines
initiative

IDPCC – Game Changer in Disease Management

Personalized medicine: Medical care tailored to the individual based on that individual's unique characteristics or unique characteristics of the disease itself

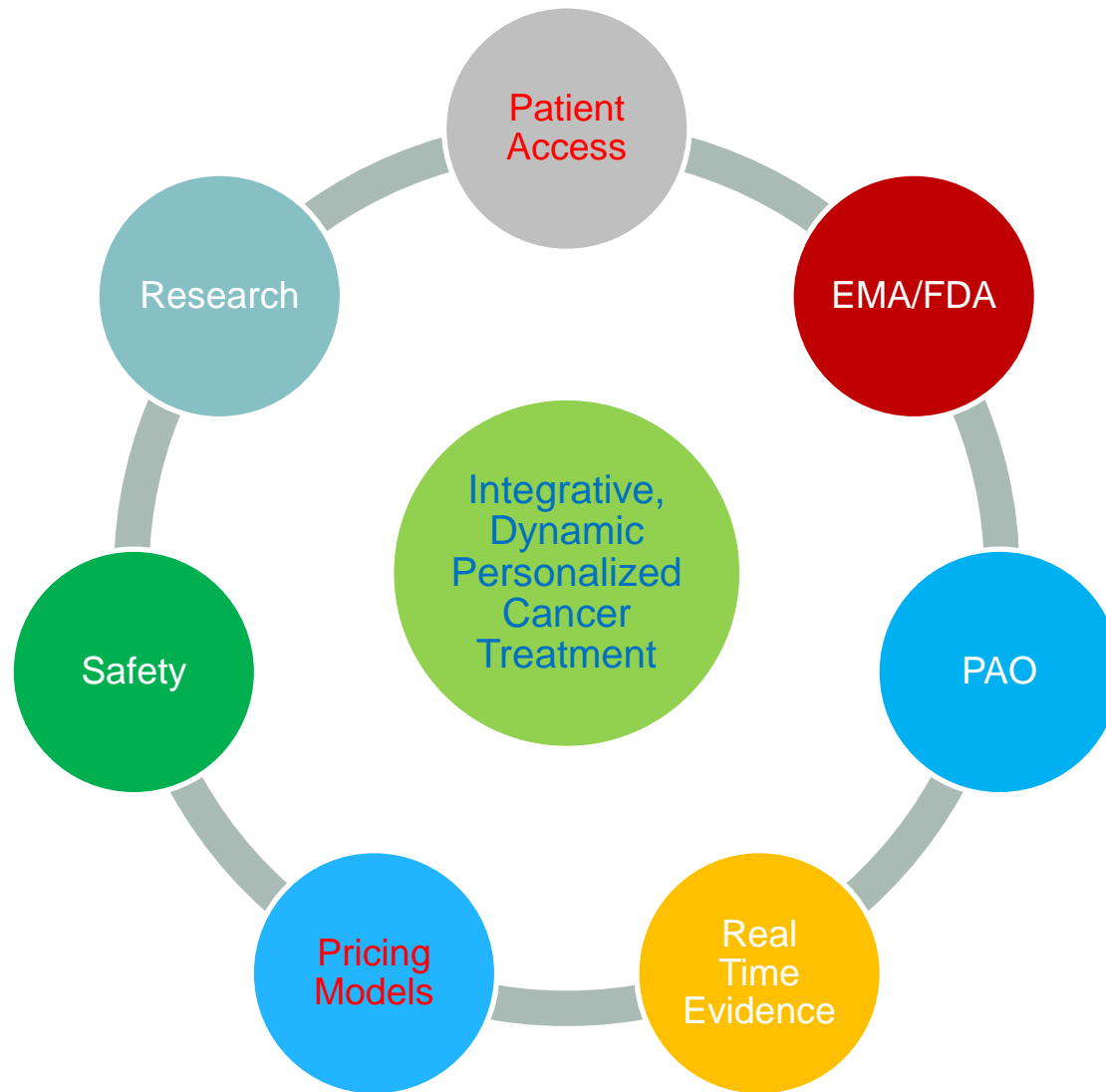**Beyond the Pill – Providing a Solution to Physicians and Patients**

Symptom severity

Therapy selection and treatment

Diagnosis & prognosis

Early detection

Risk assessment (predisposition)

Monitoring

Symptoms

No symptoms

Time

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The Silos are for Farms, not for Pharma

Fostering Collaboration and Exchange

Gap Check

What do we need to focus on to complete our strategy, reach our goal and demonstrate the impact on cancer patient and society?

IDPCC is the corner stone of success, more is needed to take it from research to patient and transform it to "Real Time Oncology"