# „Next generation sequencing“ v onkologii

# „Next generation sequencing“ in oncology

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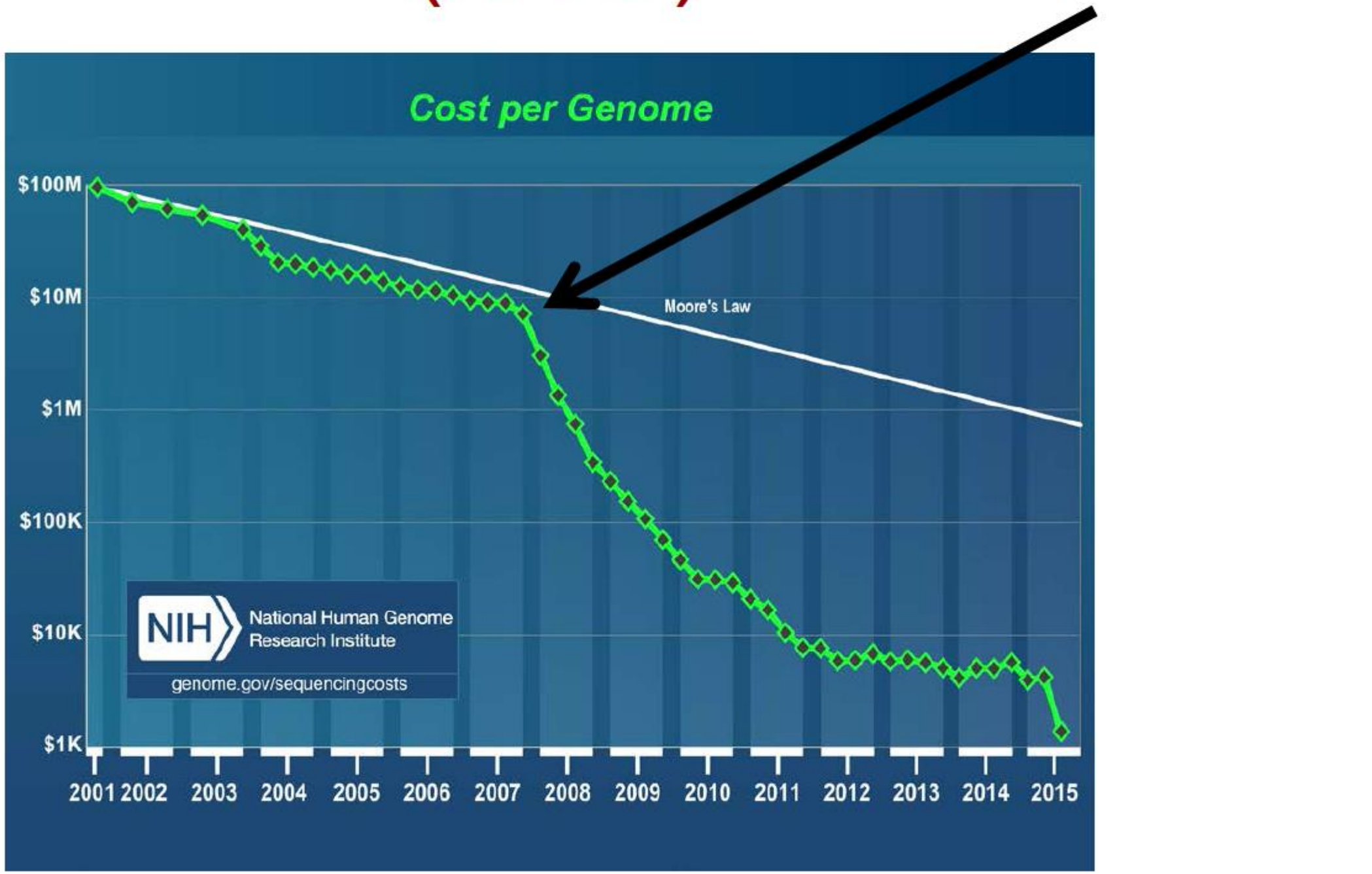
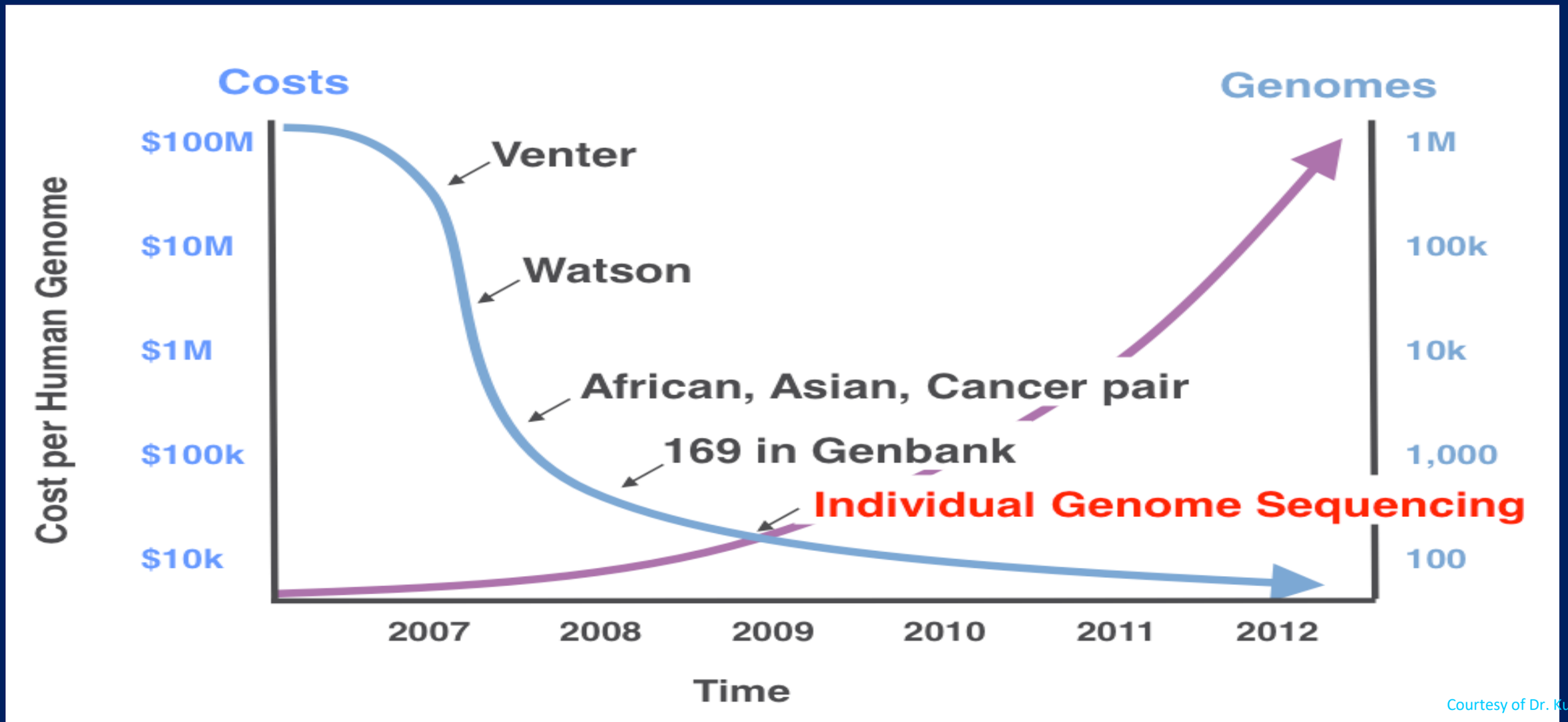
# Next Generation Sequencing (NGS)



# Genomic Technology
# Breathtaking Progress Unparalleled in Human History

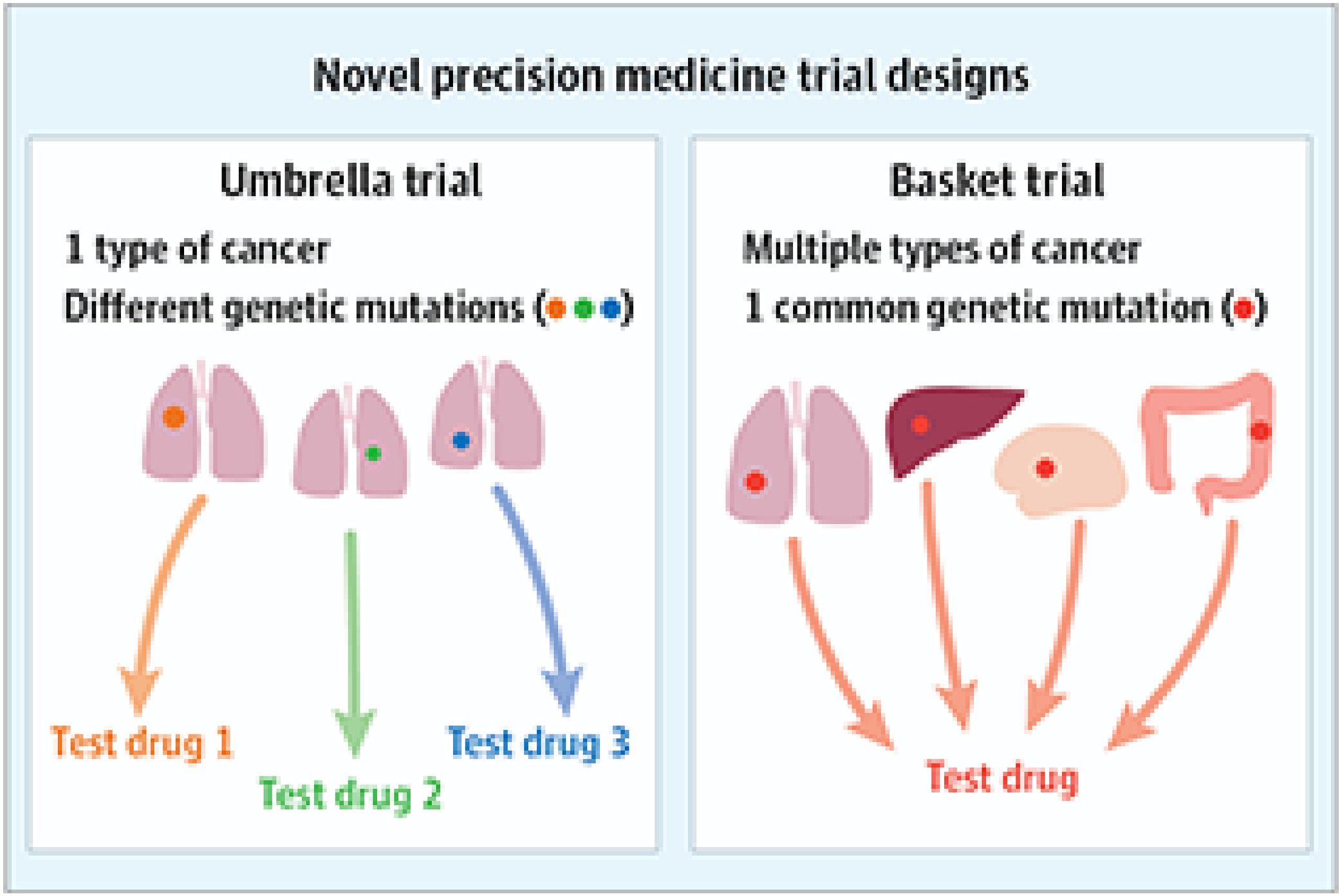
QUICKER, SMALLER, CHEAPER

| Genome sequenced (publication year) | HGP (2003) | Venter (2007) | Watson (2008) | Current (2015) |
|---|---|---|---|---|
| Time taken (start to finish) | 13 years | 4 years | 4.5 months | ~1 days |
| Number of scientists listed as authors | > 2,800 | 31 | 27 | |
| Cost of sequencing (start to finish) | $2.7 billion | $100 million | < $1.5 million | ~$1000 |
| Coverage | 8–10 × | 7.5 × | 7.4 × | 30-50X |
| Number of institutes involved | 16 | 5 | 2 | |
| Number of countries involved | 6 | 3 | 1 | |




Courtesy of Dr. Kurzrock

# REMEMBER THIS!




JAMA Oncology: doi:10.1001/jamaoncol.2016.5299

# Meta Analysis of 32,149 Patients in Phase II Clinical Trials

- **Non-personalized targeted arms led to poorer outcomes than cytotoxics arms**

(**All P<0.0001, except P=0.048 for OS meta-analysis).**

**Worst outcome**

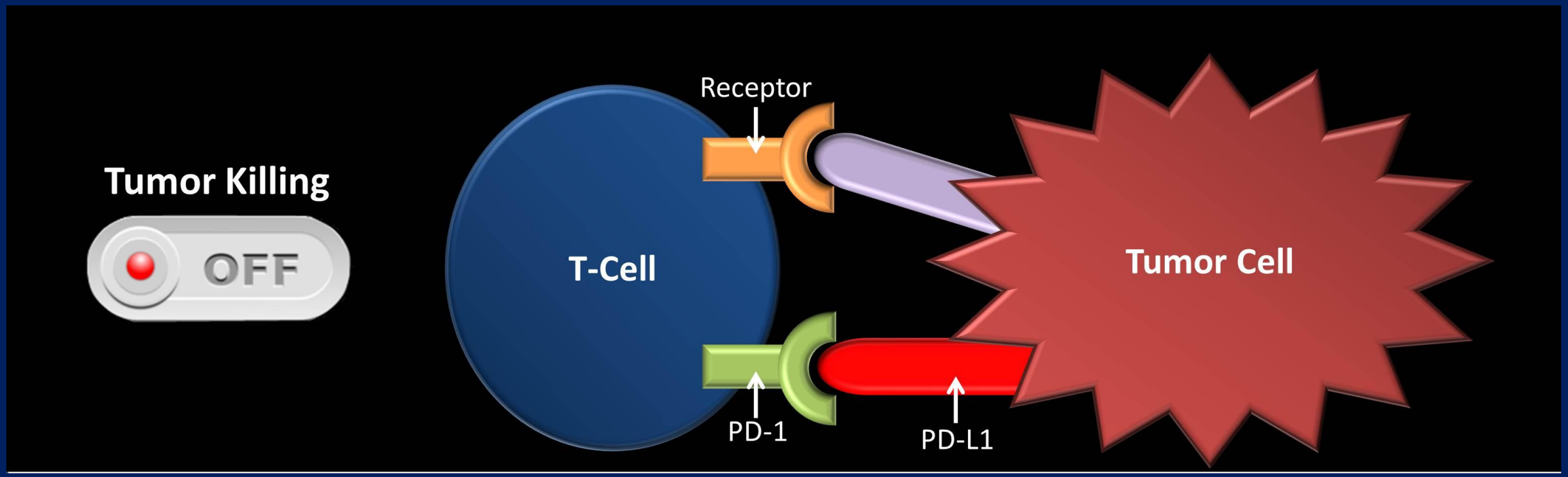
**Best outcome**

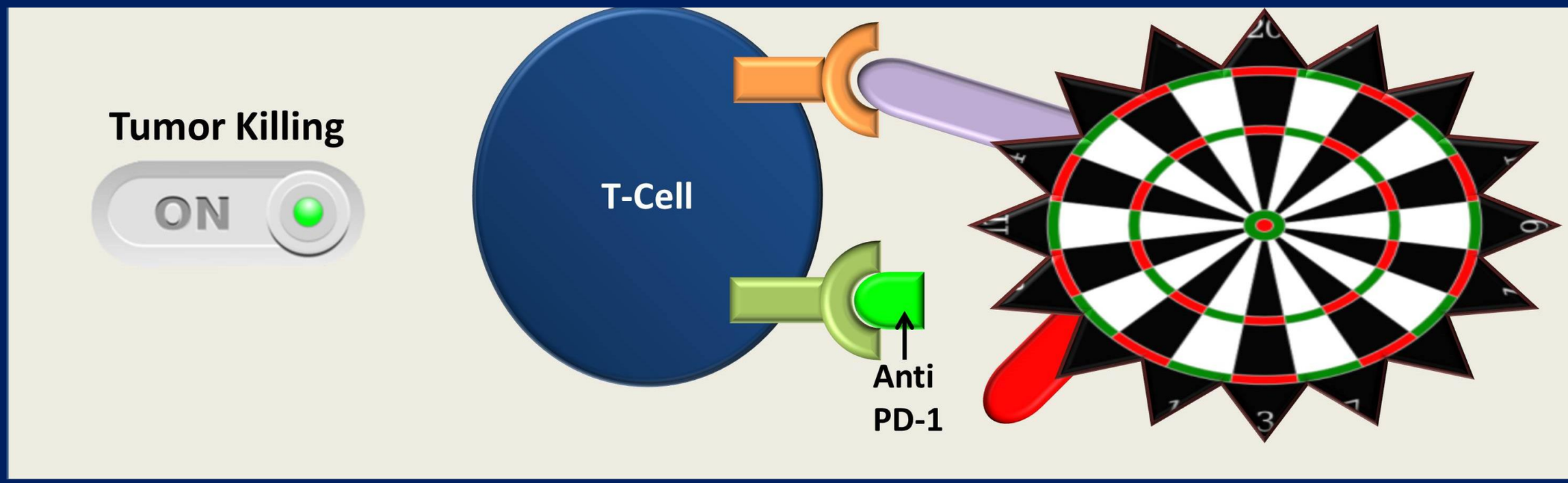
| | POOLED Analysis | | | Meta-analysis | | |
|---|---|---|---|---|---|---|
| ARMS type | R Rate (%) | PFS (Mos) | OS (Mos) | RR (%) | PFS (Mos) | OS (Mos) |
| Non-personalized targeted | 4 | 2.6 | 8.7 | 7.5 | 2.5 | 8.3 |
| Cytotoxic | 12 | 3.3 | 9.4 | 16.1 | 3.3 | 9.3 |
| Personalized targeted | 30 | 6.9 | 15.9 | 31.3 | 6.1 | 13.7 |

Schwaederle……Kurzrock, JCO, 2015

Courtesy of Dr. Kurzrock

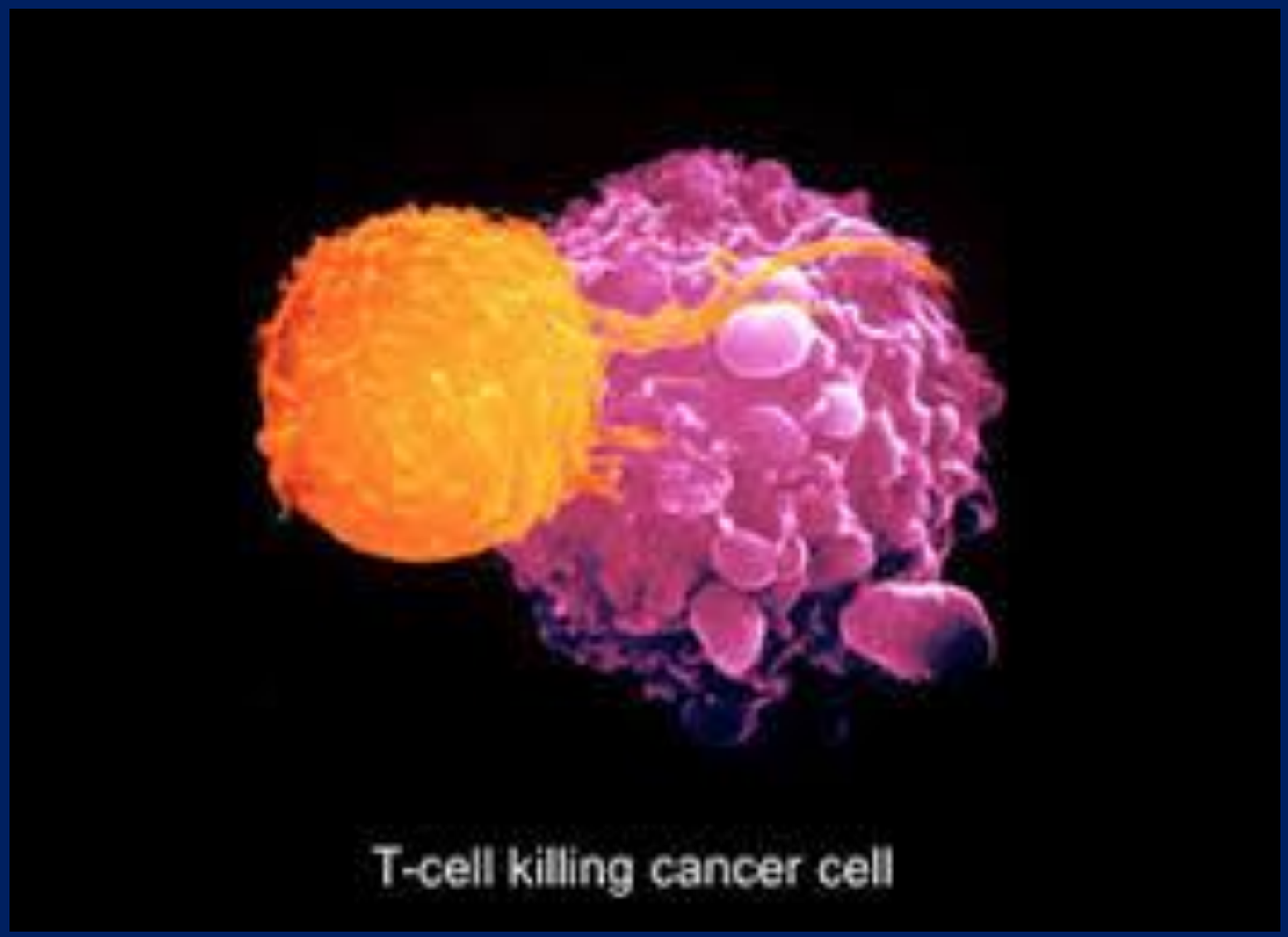
# Checkpoint inhibitors



# Harnessing the Immune System

**The immune system is the bringing the fight to the same level**



# Bridging

## Genomics and Immunotherapy

### **Mutanome-Directed Immunotherapy**

The more mutated the tumor,
the better the response to immunotherapy

- 4% response rate for low mutational burden
- 26% response rate for intermediate
- 45% response rate for high
- 67% response rate for very high mutational burden

Courtesy of Dr. Kurzrock

**FDA Approves pembrolizumab (anti-PD1) for solid tumors based on MSI-H**
(microsatellite instability high)

May 23, 2017

- Tissue agnostic approval
- Approval based on genomic marker
- Approval based on retrospective data

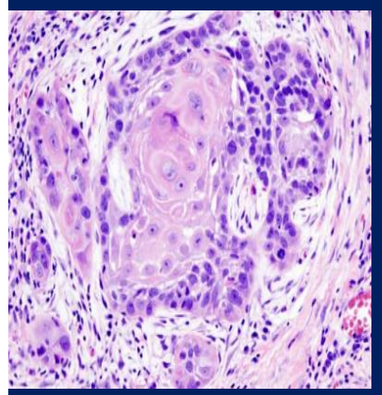
Courtesy of Dr. Kurzrock

# Molecular Tumor Board

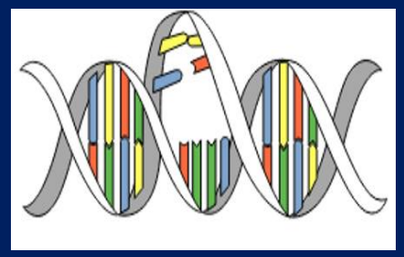
- Multidisciplinary discussion of patients
- Molecular profiling (clinical-grade)  (N ~ 8000)
- Targeted, tailored treatment recommendations

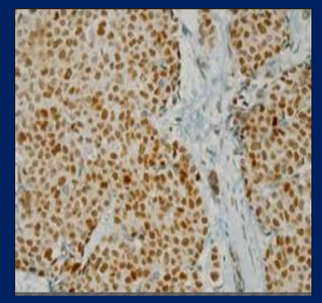
Courtesy of Dr. Kurzrock

# Comprehensive Profiling



Tumor





**PREDICT/ IPREDICT Clinical Trial**

**Comprehensive molecular profiling:**

- Next-Generation DNA Sequencing
- Protein analysis
- Immune signature analysis
- Liquid biopsy (cancer DNA detection from blood )

**“MATCH” the therapy based on the profiling.**
**Personalized/Precision Medicine approach.**

Courtesy of Dr. Kurzrock

## Liquid Biopsy Program

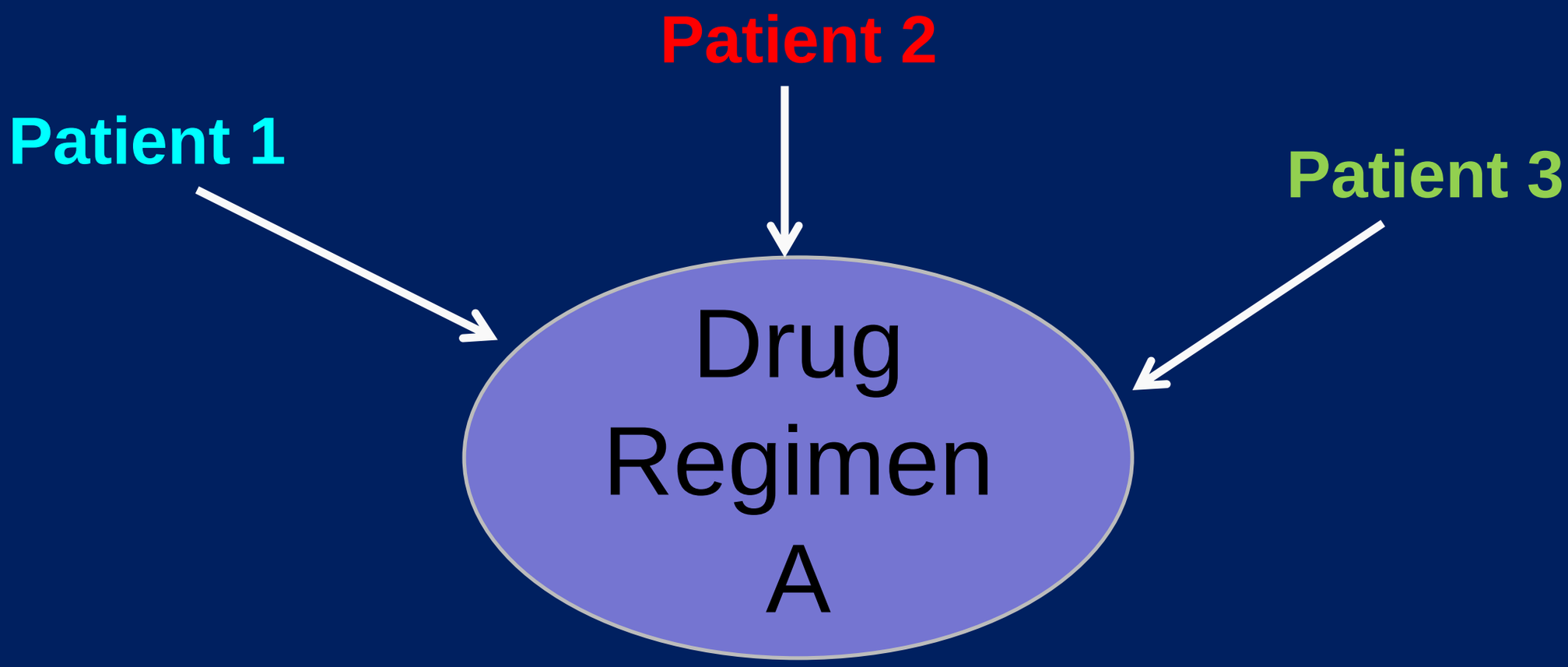
Doing genomics on DNA from a small tube of blood or from urine

No tissue biopsy

**~2000 patient samples**

Courtesy of Dr. Kurzrock

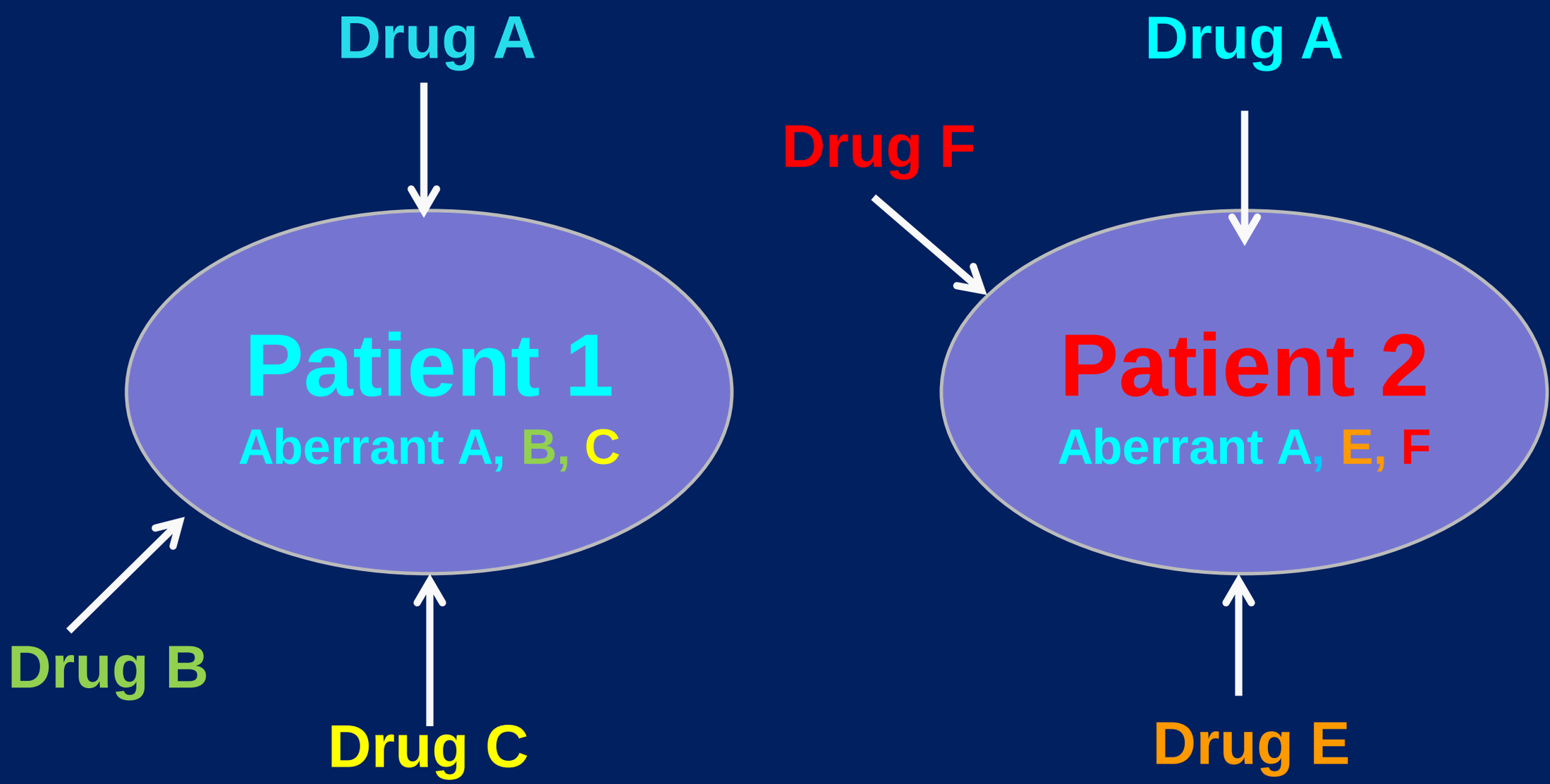
# Drug-Centric Trial (Traditional)




**Strategy**: Find common feature between patients (e.g. type of cancer or type of molecular aberration) and place all on same drugs

Courtesy of Dr. Kurzrock

# Patient-Centric Trial (N-of-One)

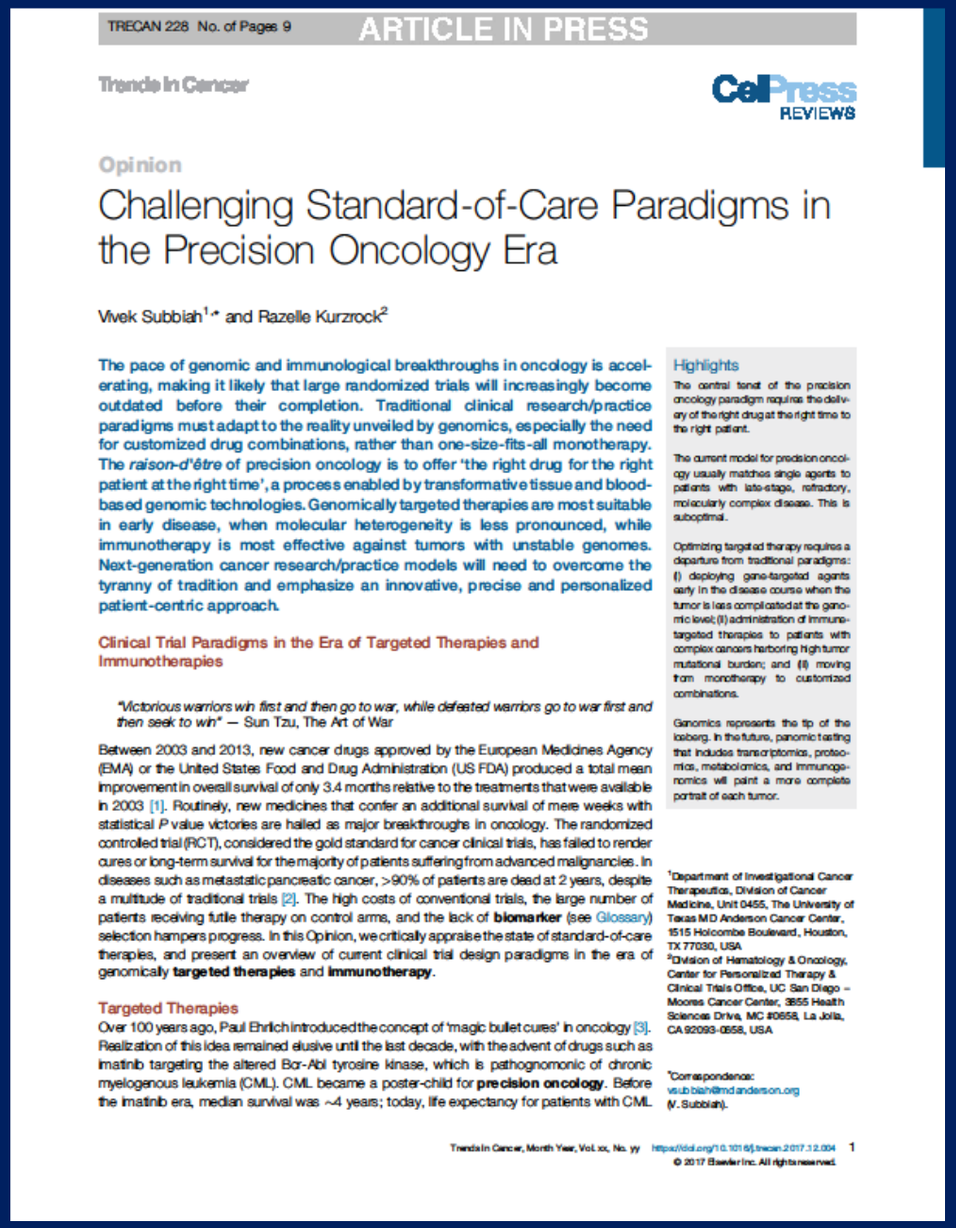



**Strategy**: Molecular matching for each patient with customized therapy combination

Courtesy of Dr. Kurzrock

# READ THIS PAPER

.it is well-written and easy to read:





Trends in Cancer

CellPress REVIEWS

Opinion

## Challenging Standard-of-Care Paradigms in the Precision Oncology Era

Vivek Subbiah[1,*] and Razelle Kurzrock[2]

**The pace of genomic and immunological breakthroughs in oncology is accelerating, making it likely that large randomized trials will increasingly become outdated before their completion. Traditional clinical research/practice paradigms must adapt to the reality unveiled by genomics, especially the need for customized drug combinations, rather than one-size-fits-all monotherapy. The *raison-d'être* of precision oncology is to offer 'the right drug for the right patient at the right time', a process enabled by transformative tissue and blood-based genomic technologies. Genomically targeted therapies are most suitable in early disease, when molecular heterogeneity is less pronounced, while immunotherapy is most effective against tumors with unstable genomes. Next-generation cancer research/practice models will need to overcome the tyranny of tradition and emphasize an innovative, precise and personalized patient-centric approach.**

Highlights

The central tenet of the precision oncology paradigm requires the delivery of the right drug at the right time to the right patient.

The current model for precision oncology usually matches single agents to patients with late-stage, refractory, molecularly complex disease. This is suboptimal.

Optimizing targeted therapy requires a departure from traditional paradigms: (i) deploying gene-targeted agents early in the disease course when the tumor is less complicated at the genomic level; (ii) administration of immune-targeted therapies to patients with complex cancers harboring high tumor mutational burden; and (iii) moving from monotherapy to customized combinations.

Genomics represents the tip of the iceberg. In the future, panomic testing that includes transcriptomics, proteomics, metabolomics, and immunogenomics will paint a more complete portrait of each tumor.

### Clinical Trial Paradigms in the Era of Targeted Therapies and Immunotherapies

*"Victorious warriors win first and then go to war, while defeated warriors go to war first and then seek to win"* — Sun Tzu, The Art of War

Between 2003 and 2013, new cancer drugs approved by the European Medicines Agency (EMA) or the United States Food and Drug Administration (US FDA) produced a total mean improvement in overall survival of only 3.4 months relative to the treatments that were available in 2003 [1]. Routinely, new medicines that confer an additional survival of mere weeks with statistical *P* value victories are hailed as major breakthroughs in oncology. The randomized controlled trial (RCT), considered the gold standard for cancer clinical trials, has failed to render cures or long-term survival for the majority of patients suffering from advanced malignancies. In diseases such as metastatic pancreatic cancer, >90% of patients are dead at 2 years, despite a multitude of traditional trials [2]. The high costs of conventional trials, the large number of patients receiving futile therapy on control arms, and the lack of **biomarker** (see Glossary) selection hampers progress. In this Opinion, we critically appraise the state of standard-of-care therapies, and present an overview of current clinical trial design paradigms in the era of genomically **targeted therapies** and **immunotherapy**.

### Targeted Therapies

Over 100 years ago, Paul Ehrlich introduced the concept of 'magic bullet cures' in oncology [3]. Realization of this idea remained elusive until the last decade, with the advent of drugs such as imatinib targeting the altered Bcr-Abl tyrosine kinase, which is pathognomonic of chronic myelogenous leukemia (CML). CML became a poster-child for **precision oncology**. Before the imatinib era, median survival was ~4 years; today, life expectancy for patients with CML

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5822744/

# THANK YOU
# for your attention


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