Some Thoughts About Getting BETTER Drugs into Practice Faster and Less Expensively

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“Prediction is very difficult especially when it is about the future”

Dan Quayle
VP, 1988-92

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“Prediction is very difficult especially when it is about the future”

Yogi Berra,
Baseball player and folk icon

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“Prediction is very difficult especially when it is about the future”

Niels Bohr,
Quantum Physicist and Nobel Laureate

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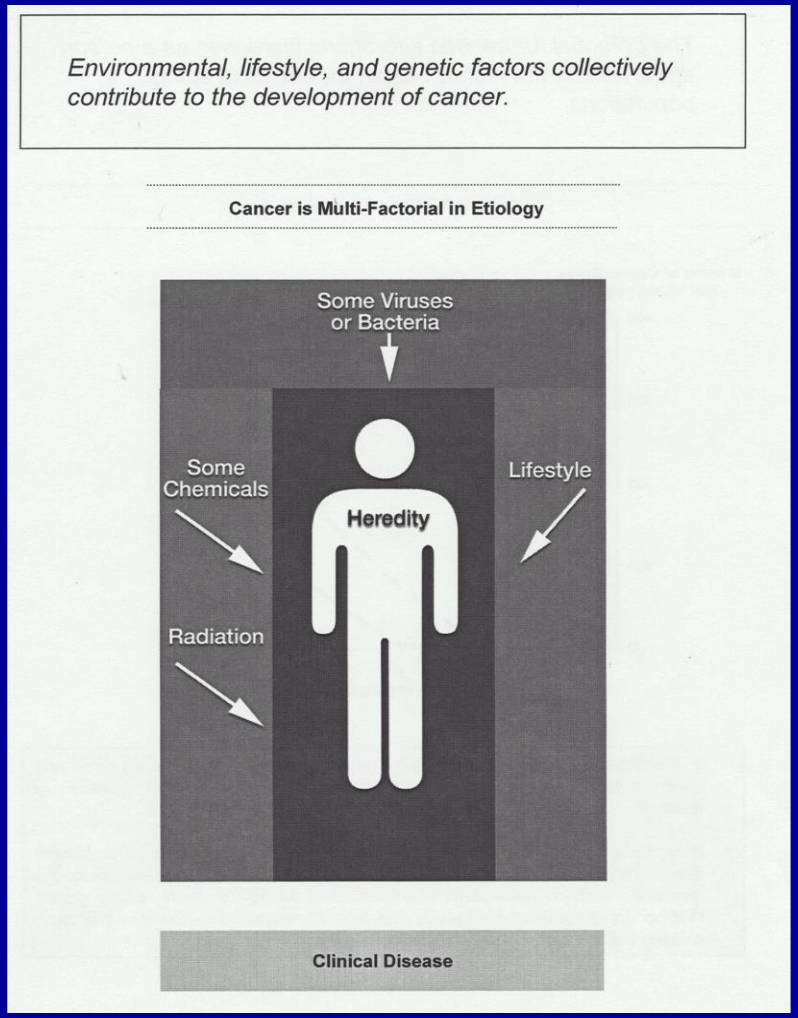
Agenda:

1. Cancer 101 Cliff Notes Version
2. Cancer Treatment in the Genome Era: How are we Doing
3. How Can We Do Better

“Cancer” is MANY Different Diseases

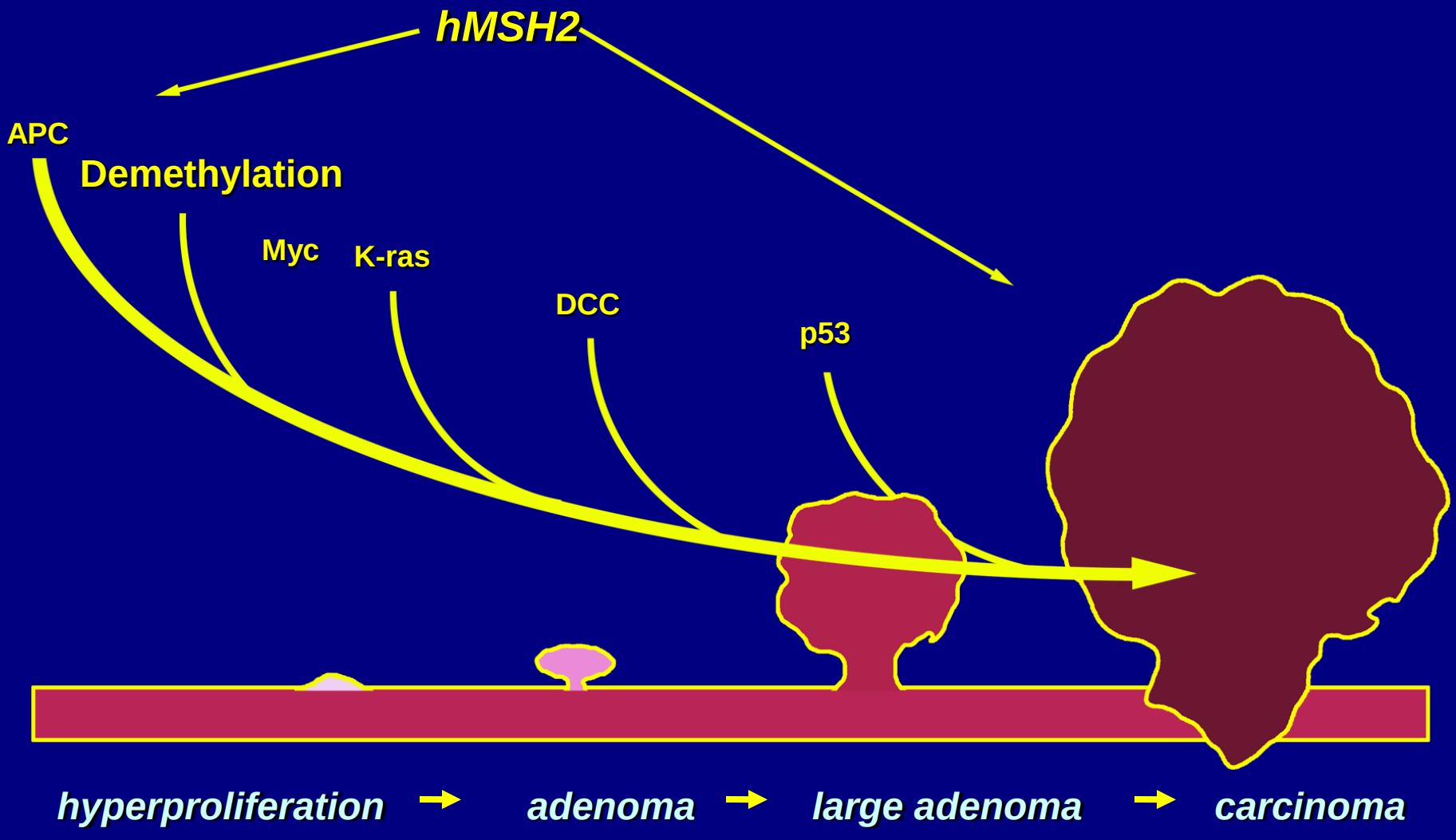
- There are hundreds of forms of cancer
- Cancers that start in the same place in different people can behave very differently
  - two different women with “breast cancer” may have very different diseases
- Cancers that appear completely unrelated may in fact be very similar

The Root Cause of Cancer is the Impact of Environment on Genes



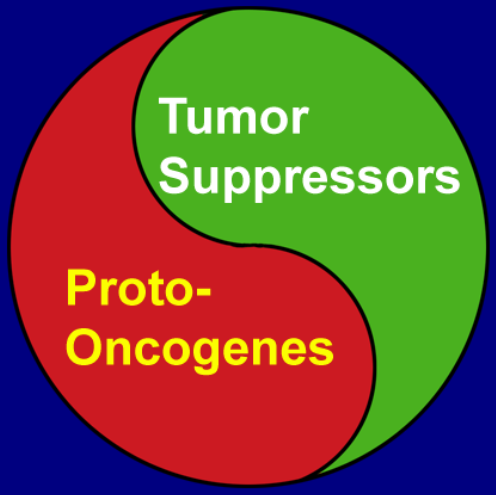
- We all inherit a greater or lesser propensity to develop particular cancers (e.g., brca)
- Environmental insults implicated as "causing cancer" have in common the ability to damage or alter (mutate) DNA (i.e., genes)
- In every cancer ever studied, one finds many mutated genes
- Altering these genes in normal cells makes them cancerous
- Cancers are caused by mutations that derange normal genes controlling cell growth, making them behave improperly
- "***Cancer happens when good genes go bad***"

DFCI Sarcoma



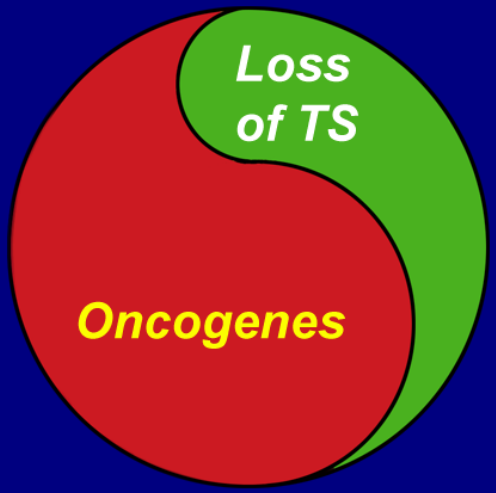
cell cycle accelerators

suppressors of apoptosis



cell cycle brakes

NORMAL CELL PROLIFERATION



NEOPLASTIC CELL PROLIFERATION

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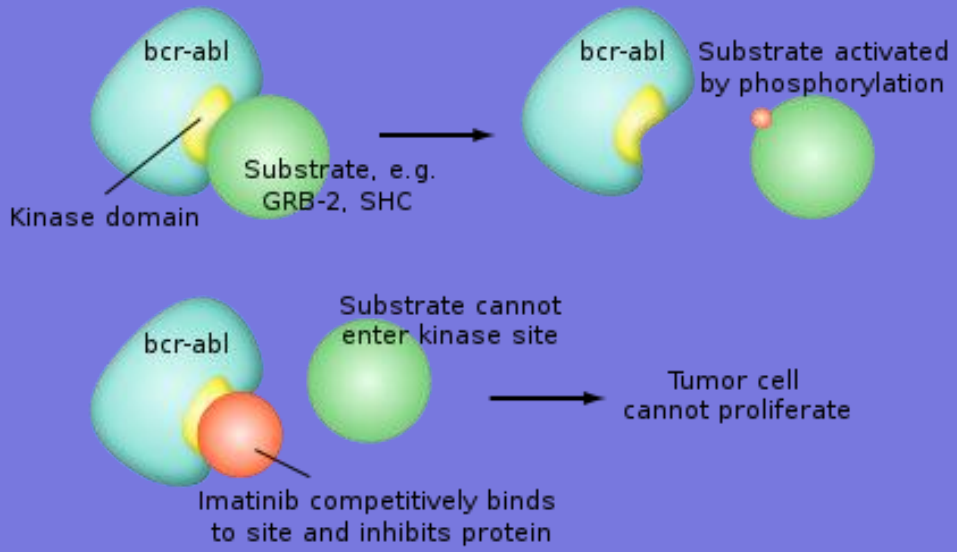
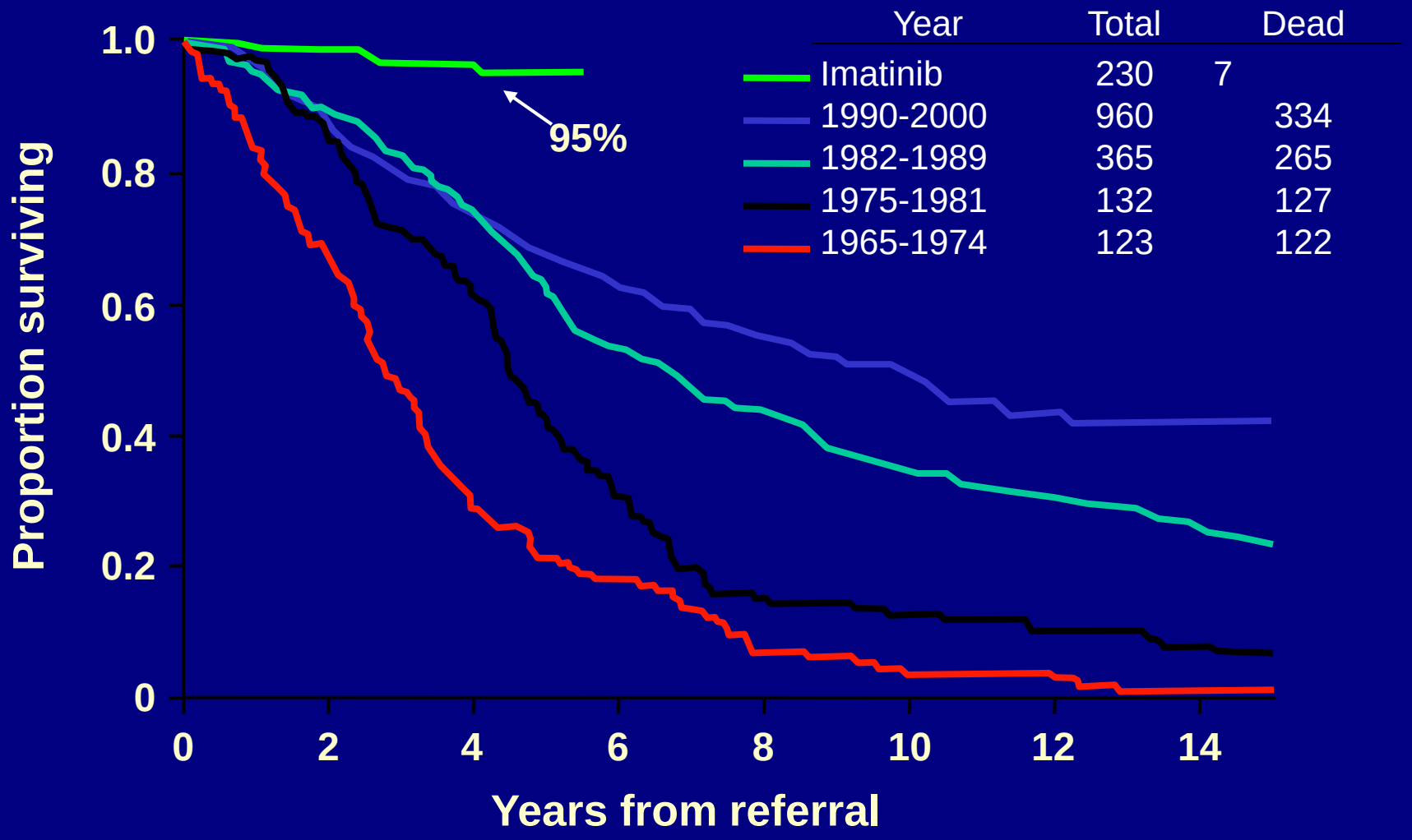
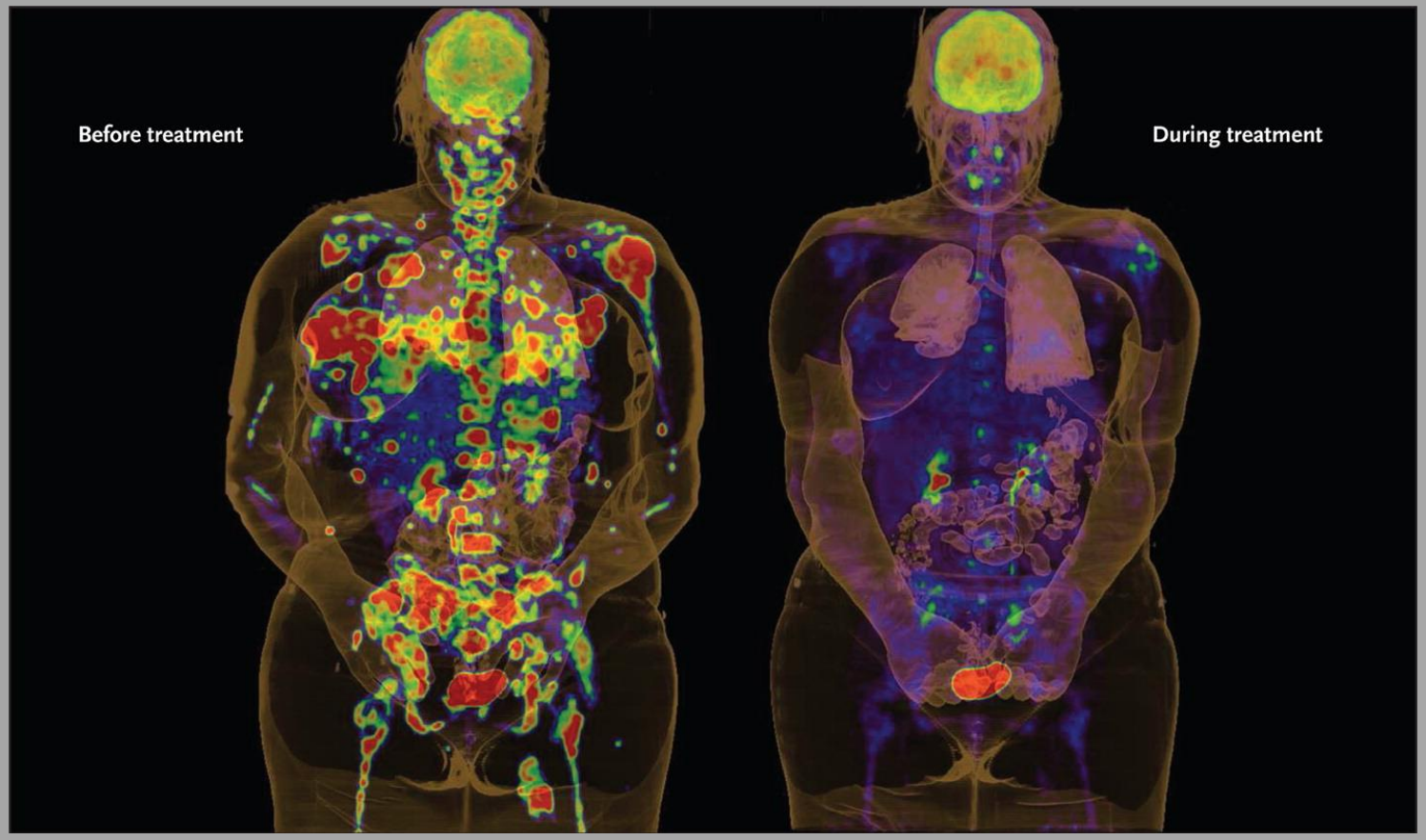
CML, bcr/abl, and Imatinib: A Paradigm Shift



Effect of Imatininib on Survival in CML



BRAF Inhibitor Shrinks Metastatic Melanoma

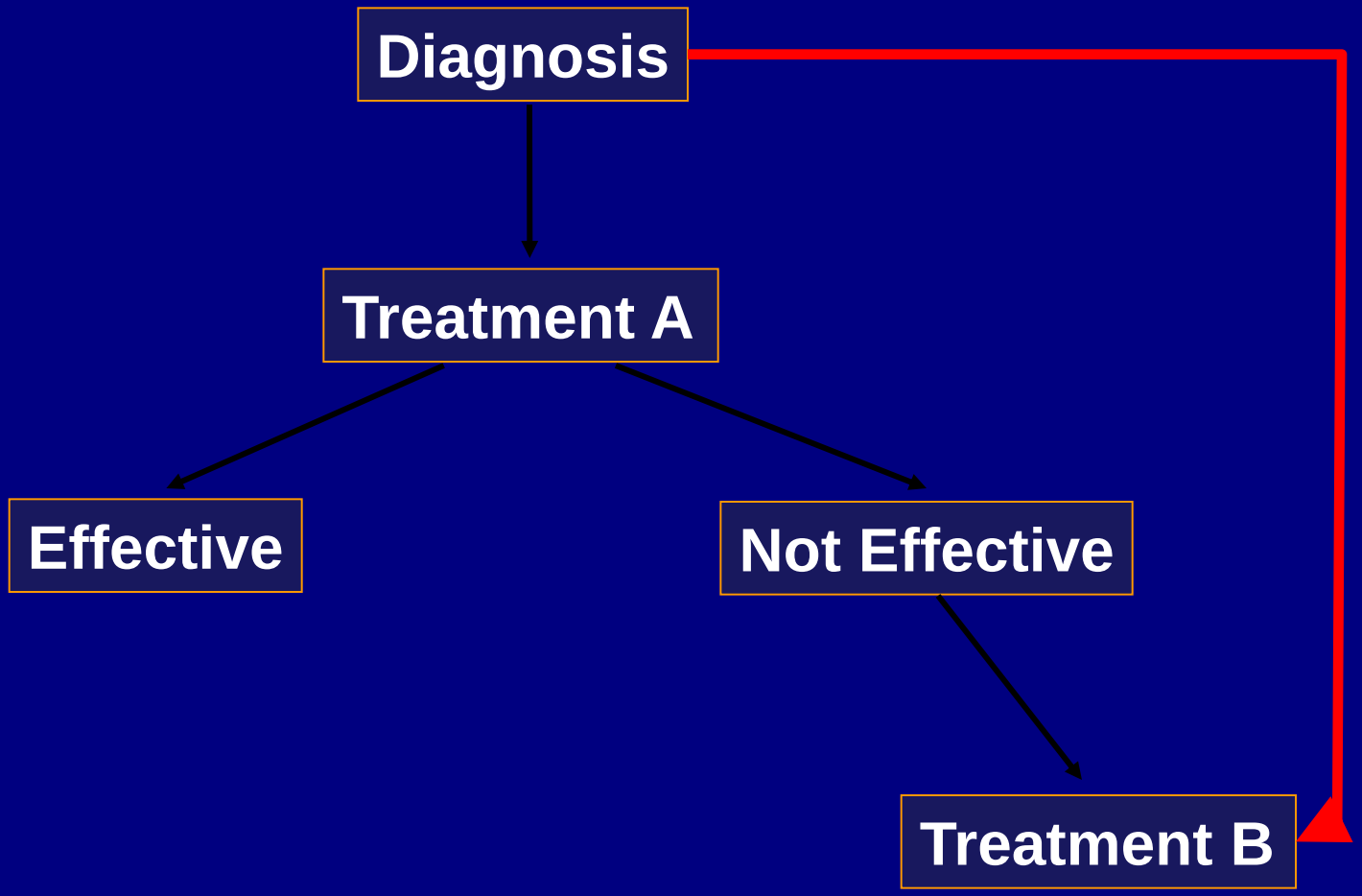


McDermott U et al. N Engl J Med 2011;364:340-350.

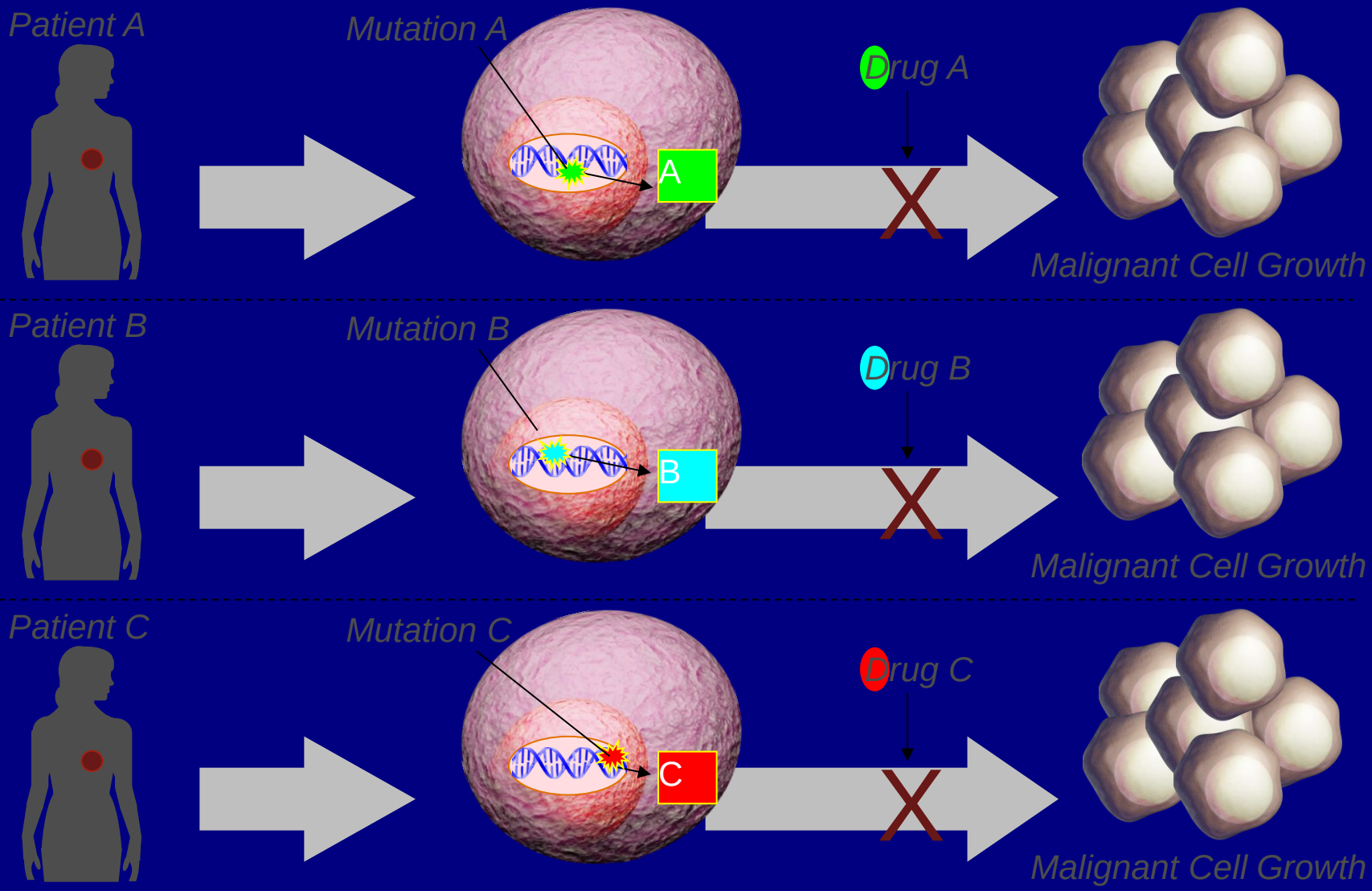
BRAF Inhibitor Prolongs Survival in Patients with Metastatic Melanoma

But ONLY in patients whose tumors have the BRAF mutation

INDIVIDUALIZING PATIENT TREATMENT



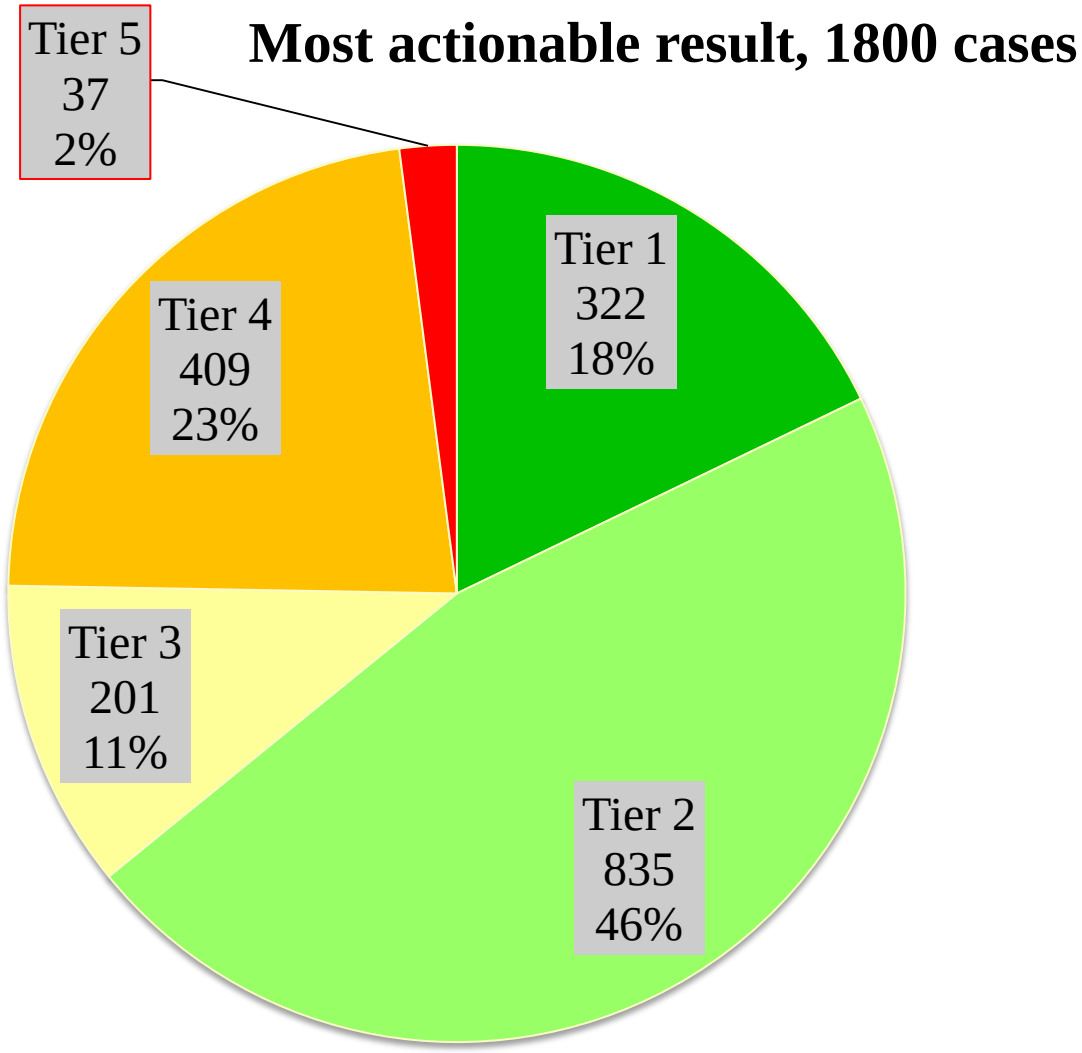
Targeted Treatments Require Knowledge of the Mutation – Personalized Medicine



Targeted therapies Report Card

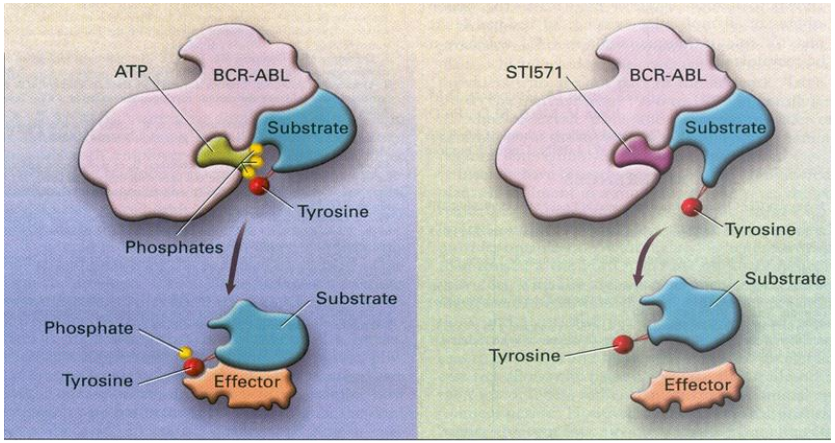
- Dramatic Responses in selected subsets of patients – small percentage
  - (Responses usually correlate with molecular phenotyping)
- Responses usually short lived – many resistance mechanisms identified
- Long term survival improved at best in a subset of the subset of patients
- ("Idiosyncrasies" persist despite genotyping)
- Results in patients taught that it's a lot more complicated inside a tumor than it seemed

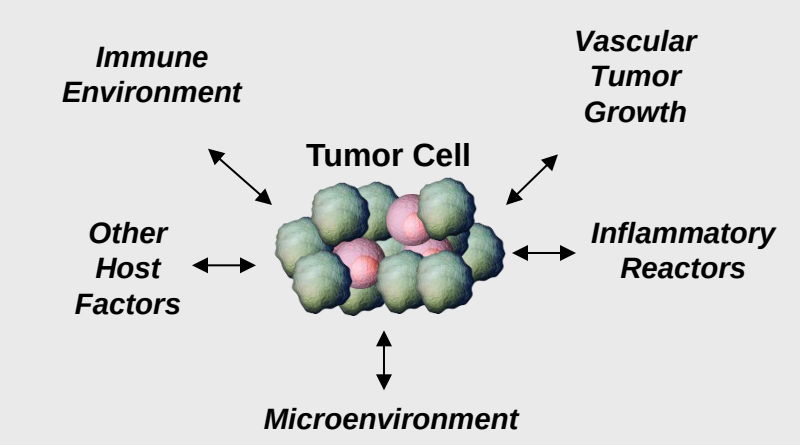
Actionable OncoPanel Results



Cancer science is undergoing a major transformation

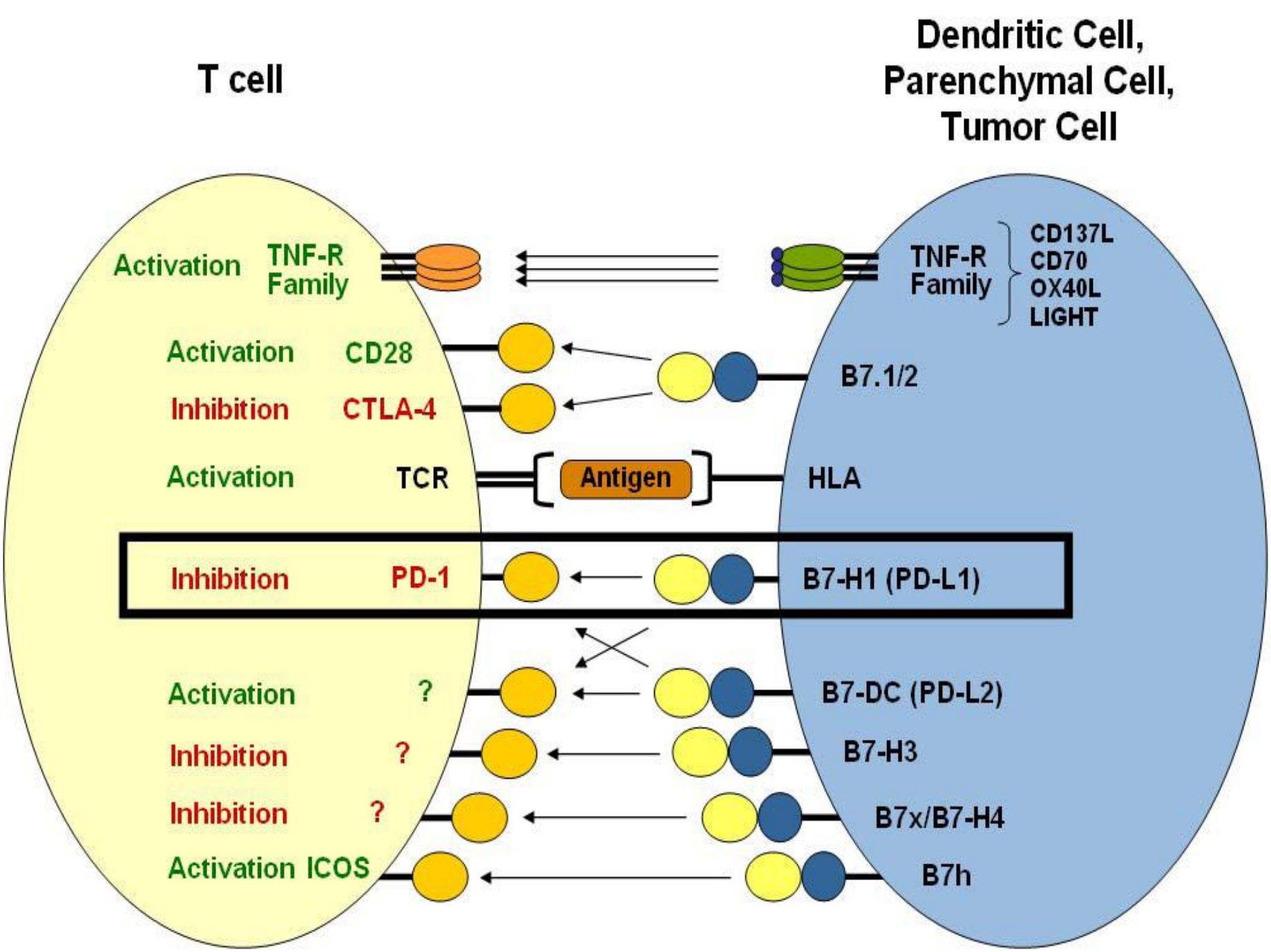
Pathologic Genome Anatomy → **Genomic & Epigenomic PathoPhysiology**





- **We've had some spectacular but limited success in using genomics to direct and develop better cancer therapies**

- **The future depends on how we figure out how to put massive amounts of genomic information into a functional and pathophysiological context that illuminates behavior of cancer cells *and the tissues they form* and use the insights gained to provide meaningful clues for better therapy**


T cell
Dendritic Cell,
Parenchymal Cell,
Tumor Cell
Activation
TNF-R
Family
TNF-R
Family
CD137L
CD70
OX40L
LIGHT
Activation
CD28
B7.1/2
Inhibition
CTLA-4
Activation
TCR
Antigen
HLA
Inhibition
PD-1
B7-H1 (PD-L1)
Activation
?
B7-DC (PD-L2)
Inhibition
?
B7-H3
Inhibition
?
B7x/B7-H4
Activation
ICOS
B7h

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Cancer Treatment in the 21st Century: Individualized Medicine

- Patients have their tumors analyzed for genetic abnormalities
  - Given only the drugs specific for their abnormalities
  - Given the only vaccines specific for their abnormalities
- Scientific and technological advances make this vision realizable but practically difficult

Doing Better: Better Drugs

- Accelerate Disease Oriented Basic Research
- Better Cell and Animal Models – PDX, Organoids, etc.
- Better Pre-Clinical Validation in Patients
- Better Clinical Trial End Points – Biomarker Based

Doing Better: Administrative and Bureacratic Efficiency

- Continue FDA Innovations
- Streamline Industry/ Academic/ Government/ Contracting
- Adaptive Trial Design

Doing Better: Better Information Management

- Sharing Big Data Across Centers – Disease Fragmentation – Genie, Orien, etc.
- Better Security to Deal with HIPAA
- Reduce/Remove Proprietary Barriers _ “PreCompetitive Space” to Facilitate Multi Agent Testing, Kepp or Dump Targets, etc.

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What Next – some bets on the 5-10 year horizon

Some form of genomic/gene expression profiling will be standard of care

Clinical trials will change profoundly – “bucket trials”, larger and larger Phase I trials with expansion cohorts

Metastasis and resistance will be increasingly targeted

“Personalized” immunotherapy will be a game changer

So will “tumor control” (vs tumor killing) strategies

Clinical care and clinical research will continue to converge – N of 1 trials will become the norm

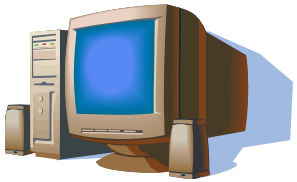
The interface between “industry” and academia will become increasingly broad based, longitudinal and iterative.

A ”technology gap” will increase the challenge of reducing disparities

Outcomes will improve but in unpredicted ways

Like Technology, Our World Is Changing and Converging…

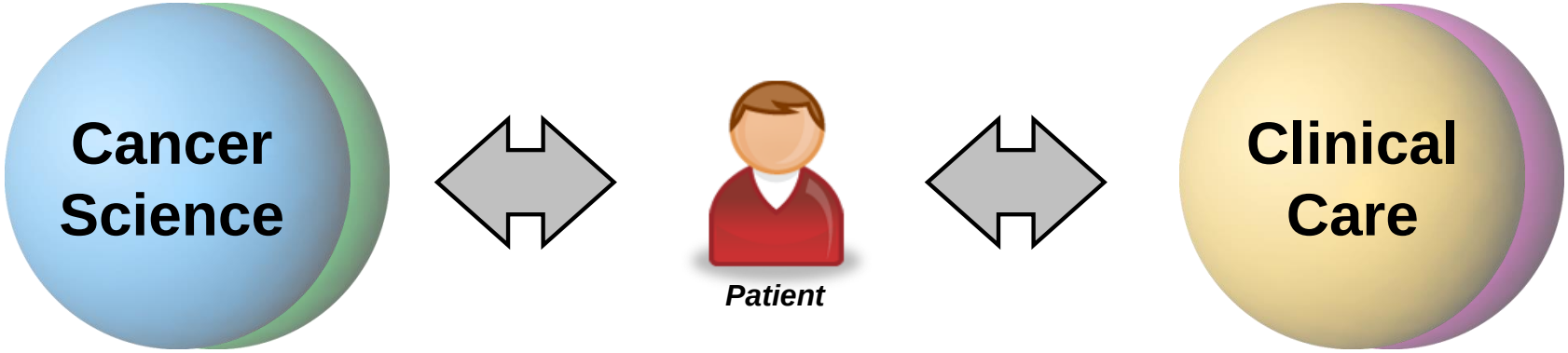
Our World in 2003



Our World Today

A Paradigm Shift in Cancer Research and Care

WHERE WE WERE: Linear Continuum



WHERE WE'RE GOING: Network