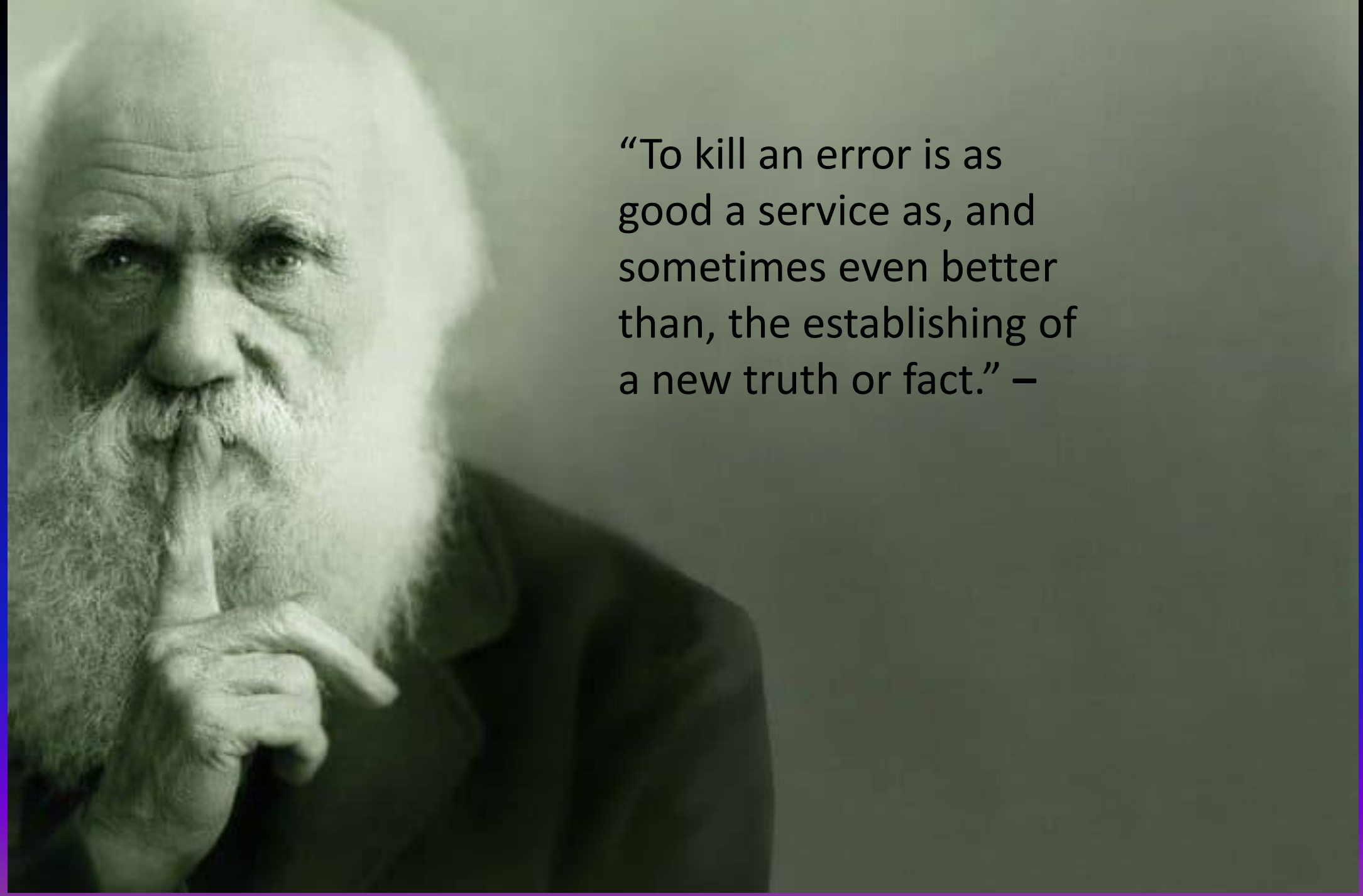
Cancer and Evolution Symposium

The Patient Perspective on Modern Cancer Therapy

Azra Raza, MD
Chan Soon-Shiong Professor of Medicine
Director MDS Center
Columbia University


“To kill an error is as good a service as, and sometimes even better than, the establishing of a new truth or fact.” –

SUMMARY 1

- Cancers diagnosed early are curable
- Cancers detected late are incurable
- Spectacular advances in cancer research
- Fore the patients, diagnosed early or late, not much has changed in 100 years

There is a crisis in Oncology

FDA Approves Opdivo® (nivolumab) for Advanced Esophageal Squamous Cell Carcinoma (ESCC)

The median OS better by 2.5 months for *Opdivo* compared to docetaxel or paclitaxel

Cost for the patient: $100,000

BMS CORPORATE FINANCIAL NEWS: WEDNESDAY, JUNE 10, 2020 7:52 PM EDT
https://www.vox.com/science-and-health/2018/10/1/17923720/immunotherapy-cancer-cost

FDA Approves Selinexor for Relapsed or Refractory DLBCL

- Overall response rate of 29%, and 13% CR
- Median response 3 months
- $22,000 per month
- David Steensma (Dana Farber) called it “ridiculous to charge $22,000 per month for such a marginal drug”
- Vincent Rajkumar (Mayo Clinic) went further “It's laughable to think **selinexor** is worth $22,000”

ASCO POST: 6/22/2020 4:16:00 PM

- In 1977, I was treating AML with 7+3
- In 2020, I am treating AML with 7+3
- New form of liposomal 7+3 that improves survival by 3.8 months
- The cost: ~$40,000 versus ~$4,300
- What if I had AML today?
- I would take 7+3

Liyna Anwar

- Parents came from Pakistan to LA
- Liyna born and raised in LA
- Coveted job at LA Times at 28
- At 29, diagnosed with AML
- 7+3
- Allo-transplant
- Haplo-transplant from her brother
- Relapsed in 6 months
- A second haplo-transplant
- The most painful death possible on March 26, 2020 (*NYT April 13, 2020*)

We failed Liyna

“So death by leukemia is a local and not an express. Same run, a few more stops. But that’s medicine. The art of prolonging disease”

…Peter De Vries, 1961

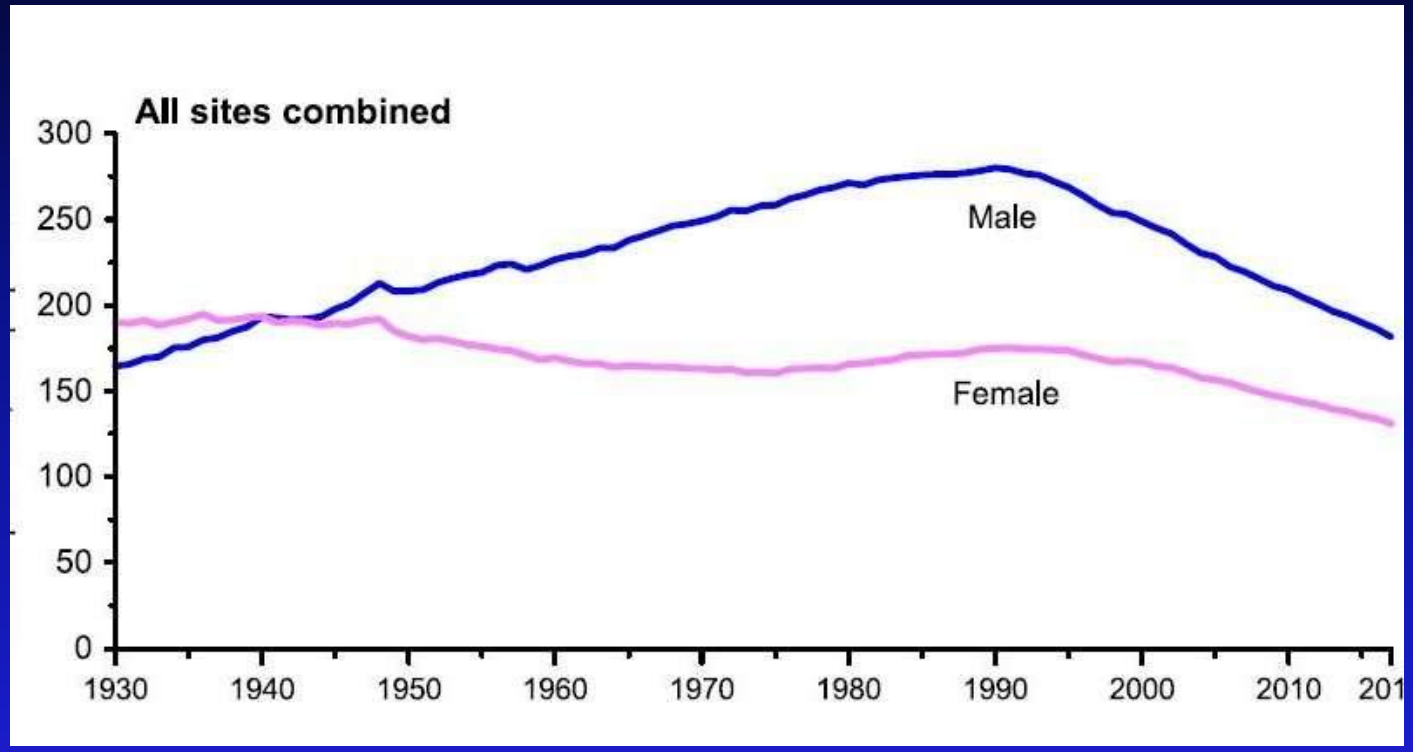
- Between 2002-2014, 72 new anti-cancer drugs were introduced
- They prolonged survival by 2.1 months compared to the older existing drugs
- Two-thirds of cancer drugs approved in the last two decades have shown zero improvement in survival
- FDA approving therapies under pressure from patients, advocacy groups, societies

JAMA Otolaryngol Head Neck Surg. 2014;140(12):1225-1236

- We are boasting of God-like technology, cutting and pasting DNA

- Yet, the treatment for cancer remains Paleolithic

The age adjusted mortality in 2020 is the same as in 1930



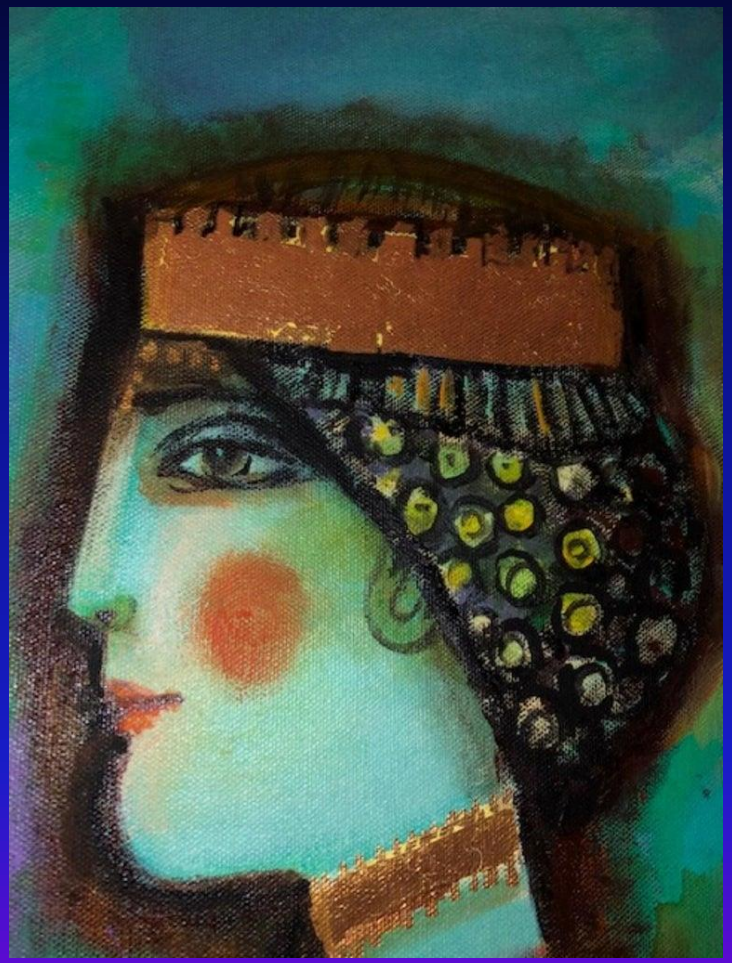
The 1% annual decline in parallels the rise and fall in smoking

American Cancer Society
https://medicalxpress.com/news/2020-01-cancer-mortality-steady-decline-driven.html

- Curing 68% cancers today
- Slash-poison-burn
- A quarter of a trillion dollars on research?

Queen Atossa

550 BC to 475 BC



Slashing then and slashing now

Mustard gas – from the Great War to frontline chemotherapy

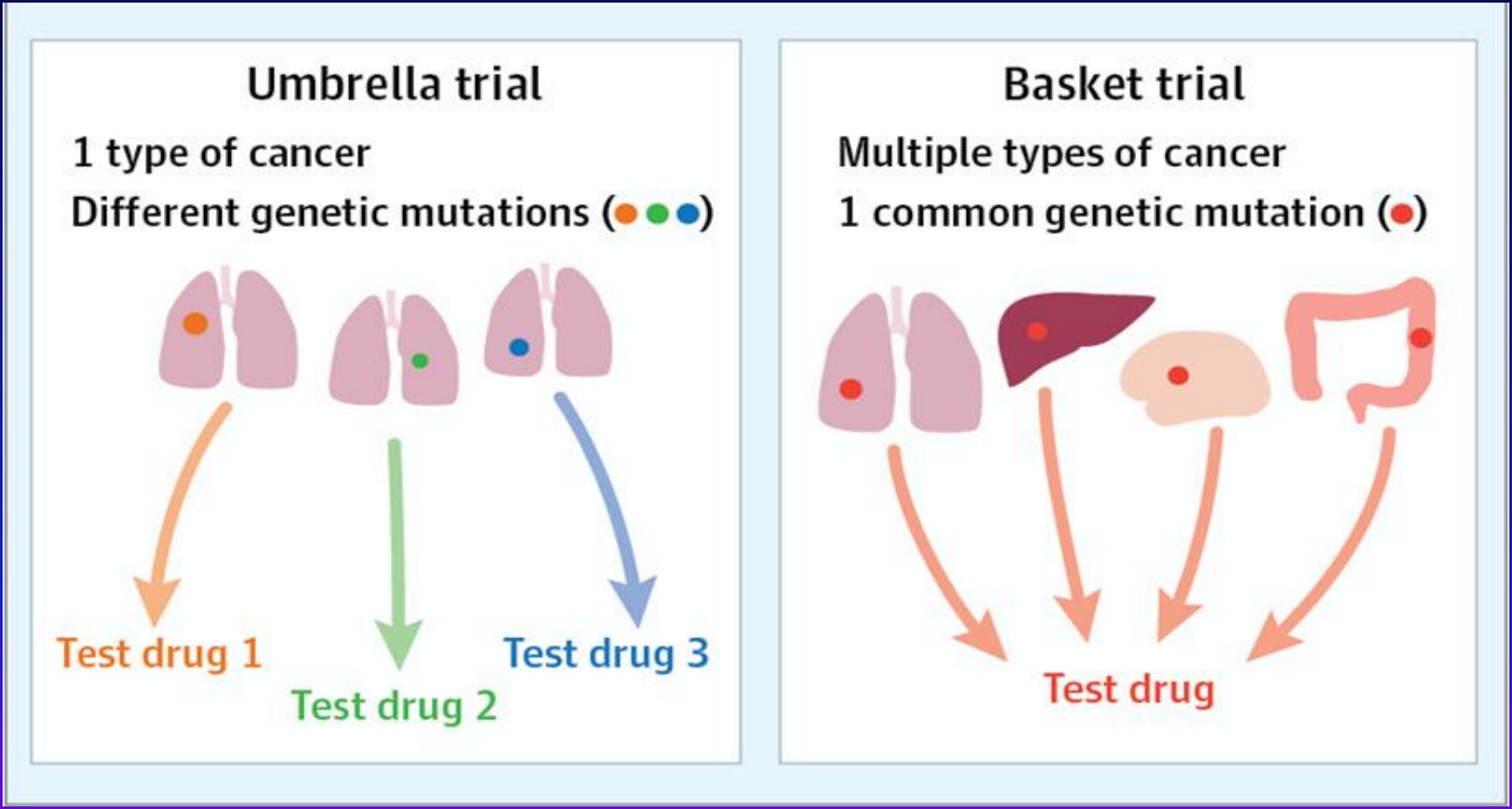
How well are new experimental drugs performing?

- 95% experimental trials fail today
- 5% that succeed should have failed

The Precision-Oncology Initiative

- Use genetic testing
- Identify a mutation
- Administer drugs that target the mutation

Novel Precision Medicine Trial Designs



JAMA Oncol. 2017;3(3):423. doi:10.1001/jamaoncol.2016.5299

Being matched is not proof of benefit

- Only around 30% respond
- The median progression-free survival is just 5.7 months
- A few are super-responders

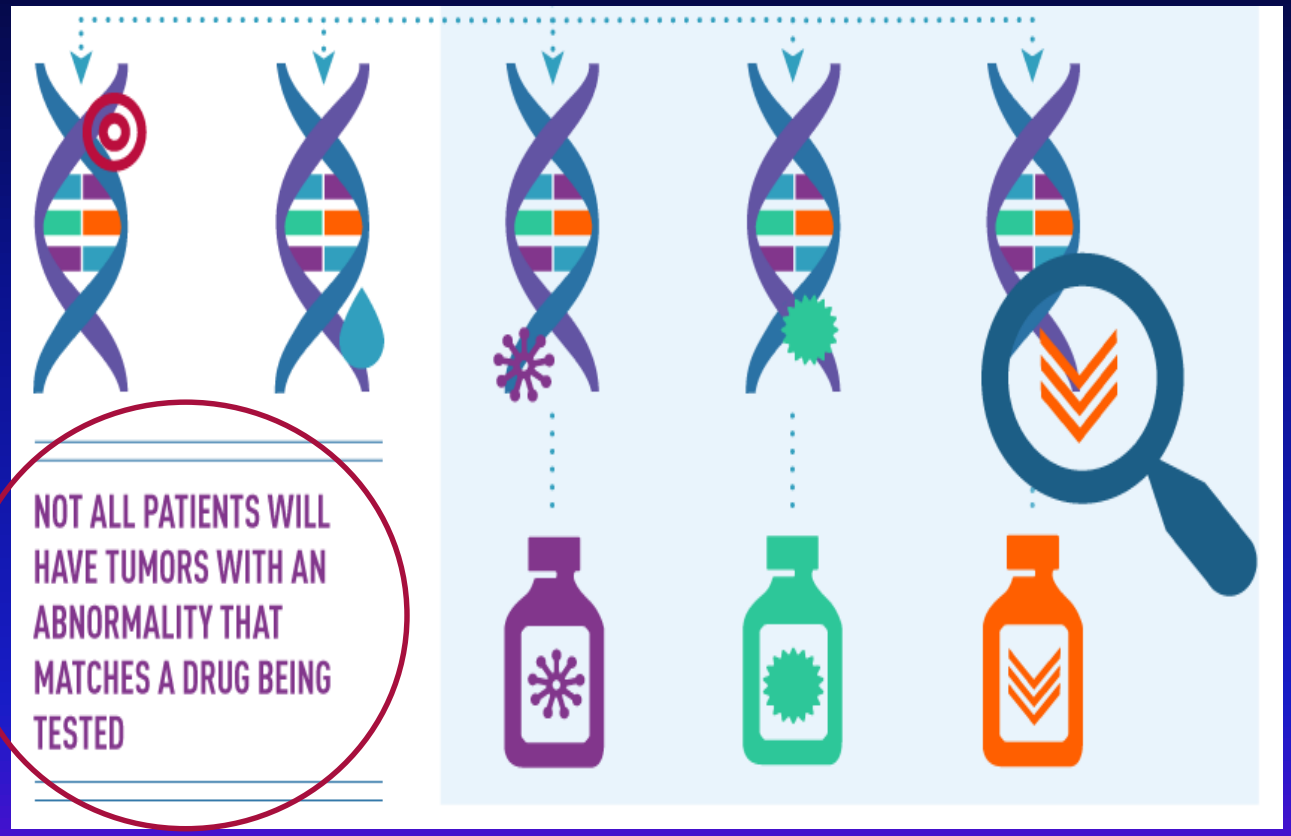
Nature **537**, S63 (08 September 2016)

- Foundation Medicine sequenced 18,000 patients
- 32 super responders

Nature **537**, S63 (08 September 2016)

NCI-MATCH Important Discovery

Targetable mutations in 0 to 3.4% of 6000 tested



C O N C L U S I O N

Precision oncology will benefit around 1.5% of patients

CAR-T

- In 2017, two CAR T-cell therapies were approved
- Children with ALL and the other for adults with advanced lymphomas

COST

- Priced at **$475,000** for a one-time treatment
- Total cost in excess of $1.5M
- The secret that is never talked about…

Kaiser Health News: https://endpts.com/cascade-of-costs-could-push-new-gene-therapy-above-1-million-per-patient/

CAR-T

- Cannot distinguish between normal and cancer cells
- Kills the entire organ

Fiscal Toxicity

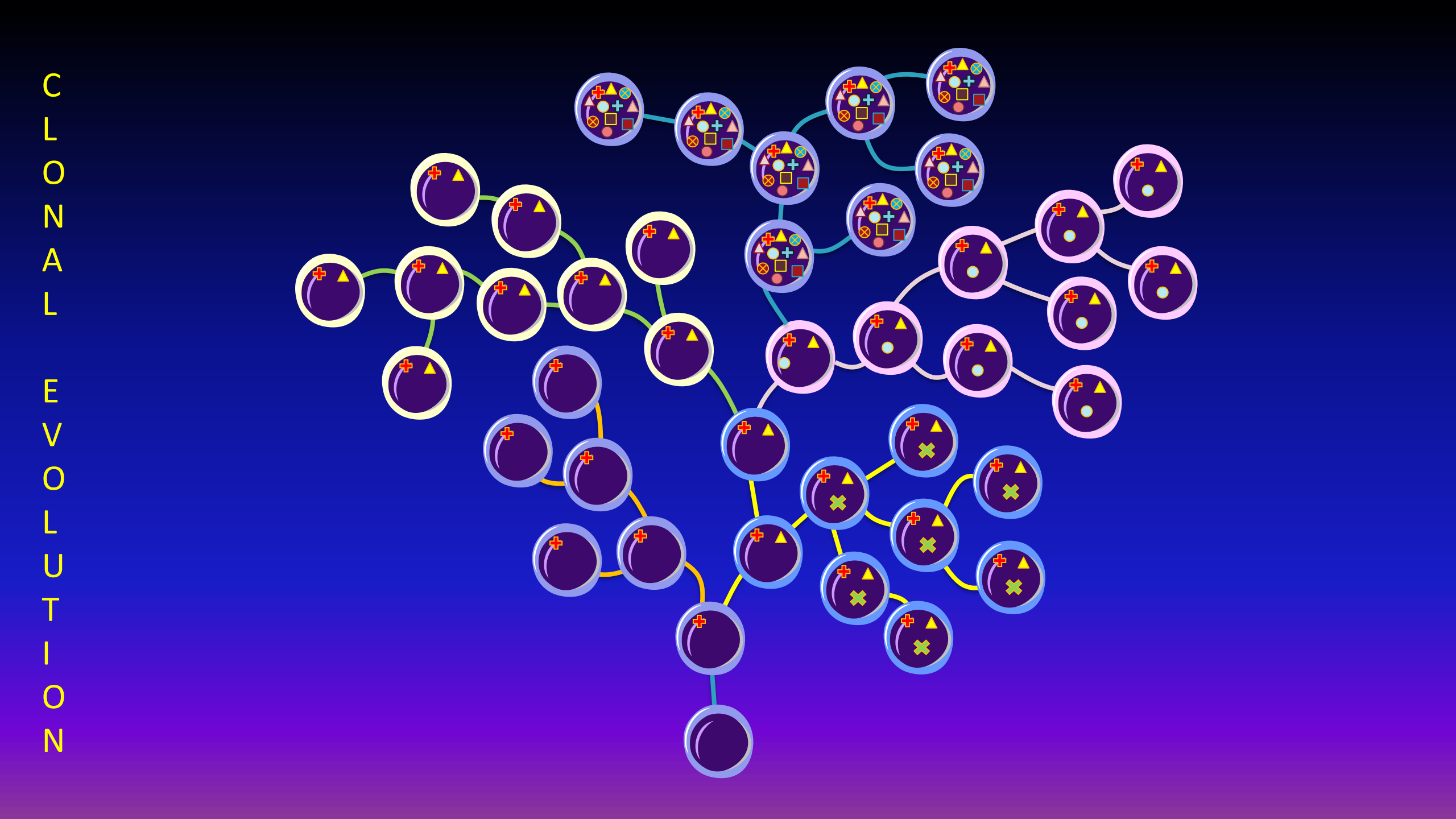
- 42% patients diagnosed with cancer today will lose every penny of their life saving by 2+ years
- 40% women with Stage 4 breast cancer are being hounded by Collection agencies while no one is cured
- Verge of a financial collapse: Healthcare cost $3.5 Trillion

Why the abysmal failure?

- Cancer is complicated
- It is a moving target

Cause of Cancer

- Hereditary predisposition
- Environmental exposure
- Pathogens
- Random DNA copying errors


CLONAL EVOLUTION

Reductionist Conceit

- One gene—one cancer—one magic bullet
- True for a couple of cancers (CML,APL)
- The rest of cancers contain many more mutations

Obsession with genetic mutations…

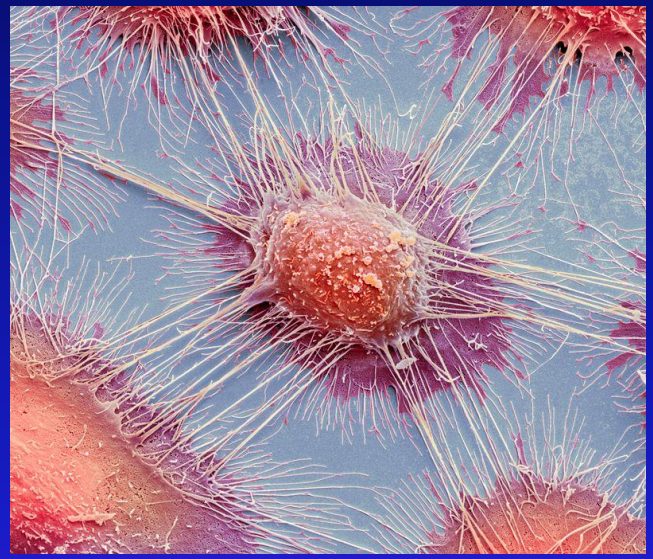
- Whole genome sequencing on 2600 samples from 38 cancers through collaboration among 750 institutions in 4 continents

- Results published in 6 papers in February 5, 2020 issue of Nature

Nature 578: 7-8, 2020

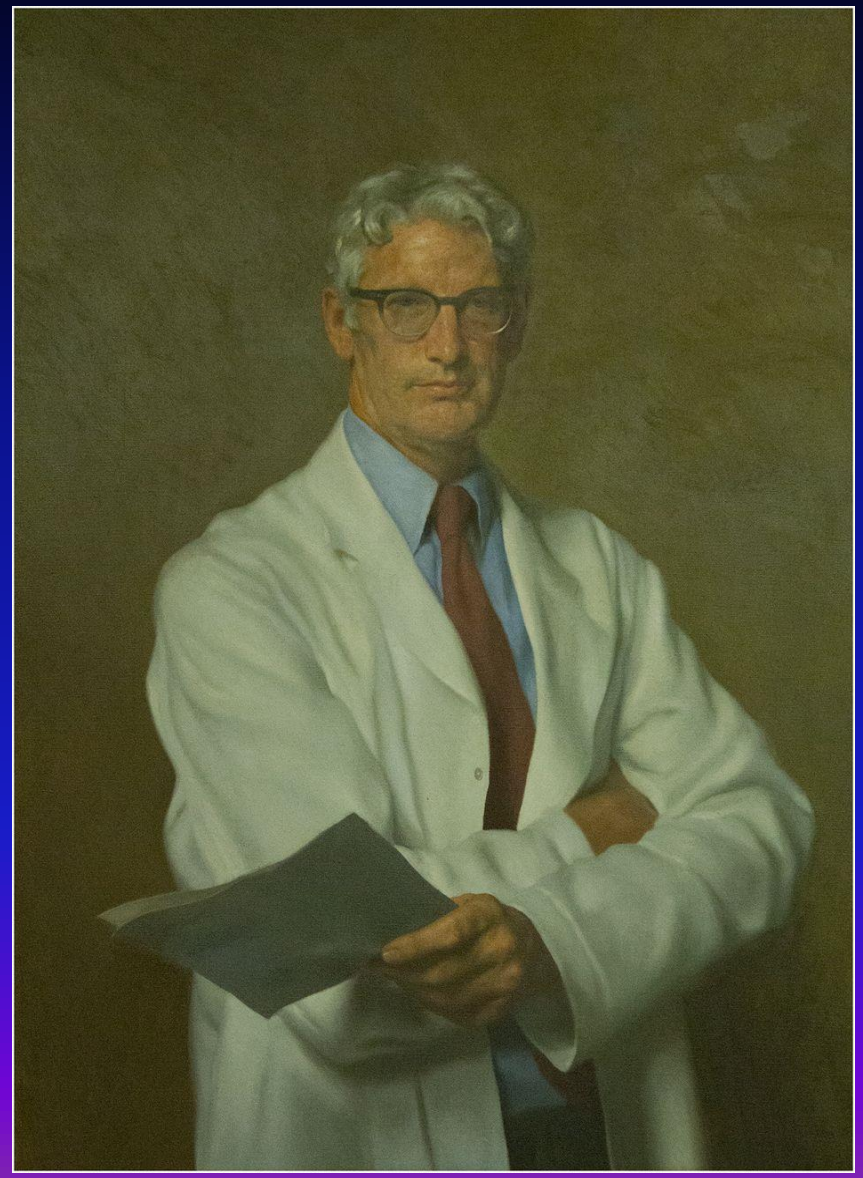
Whole Genome Sequencing

- Founder mutations in 95% cancers
- 4-5 are driver mutations
- Extremely heterogeneous
  - Patient to patient
  - Tumor to tumor
  - Clone to clone



Nature 578: 7-8, 2020

- In 1976, Peter Nowell showed that cancer evolves by stepwise, somatic cell mutations with sequential, sub-clonal selection
- I reviewed this paper for a lab meeting in 1977
- The WGS only confirmed what has been appreciated since 1976

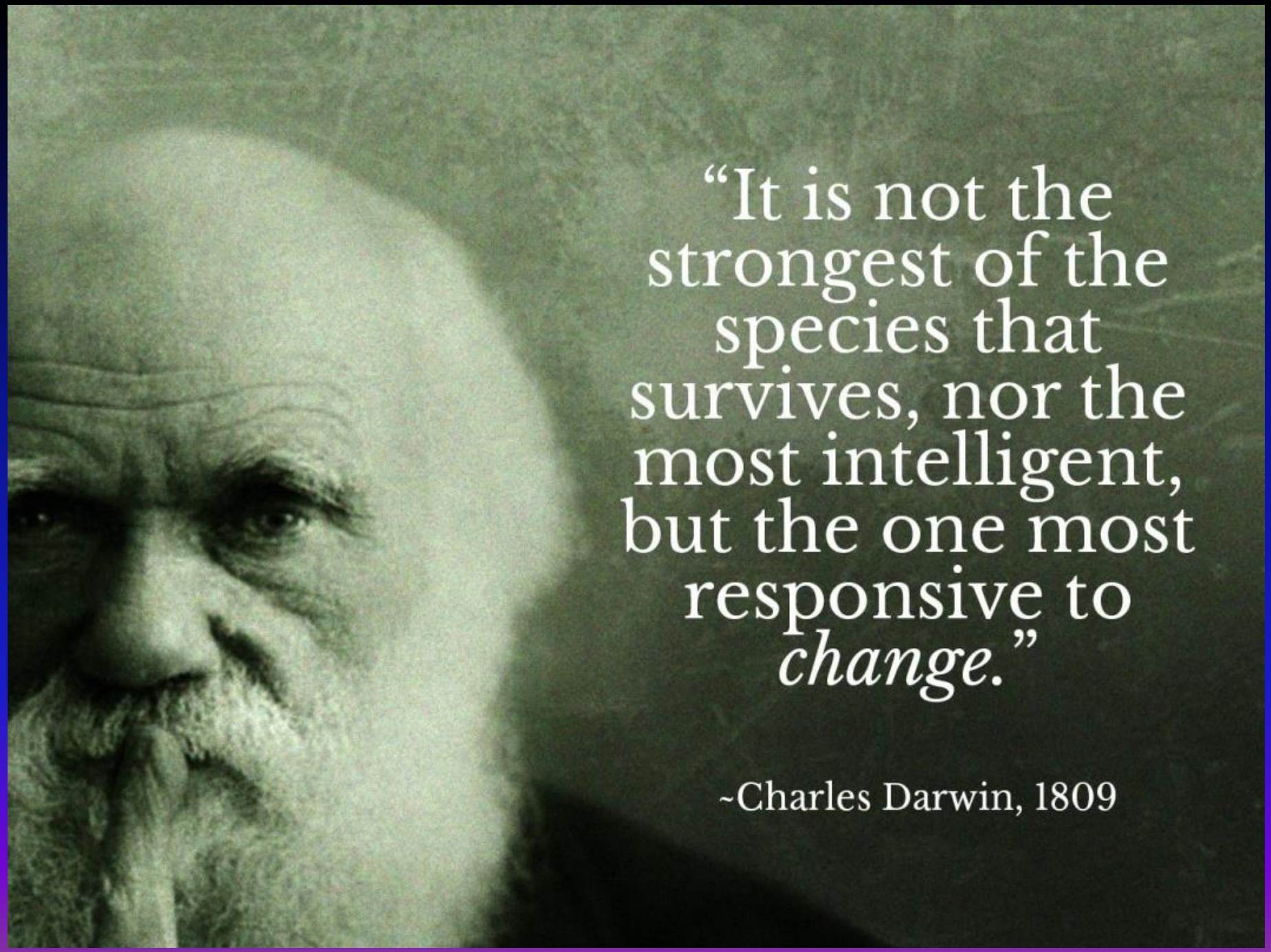


C O N C L U S I O N

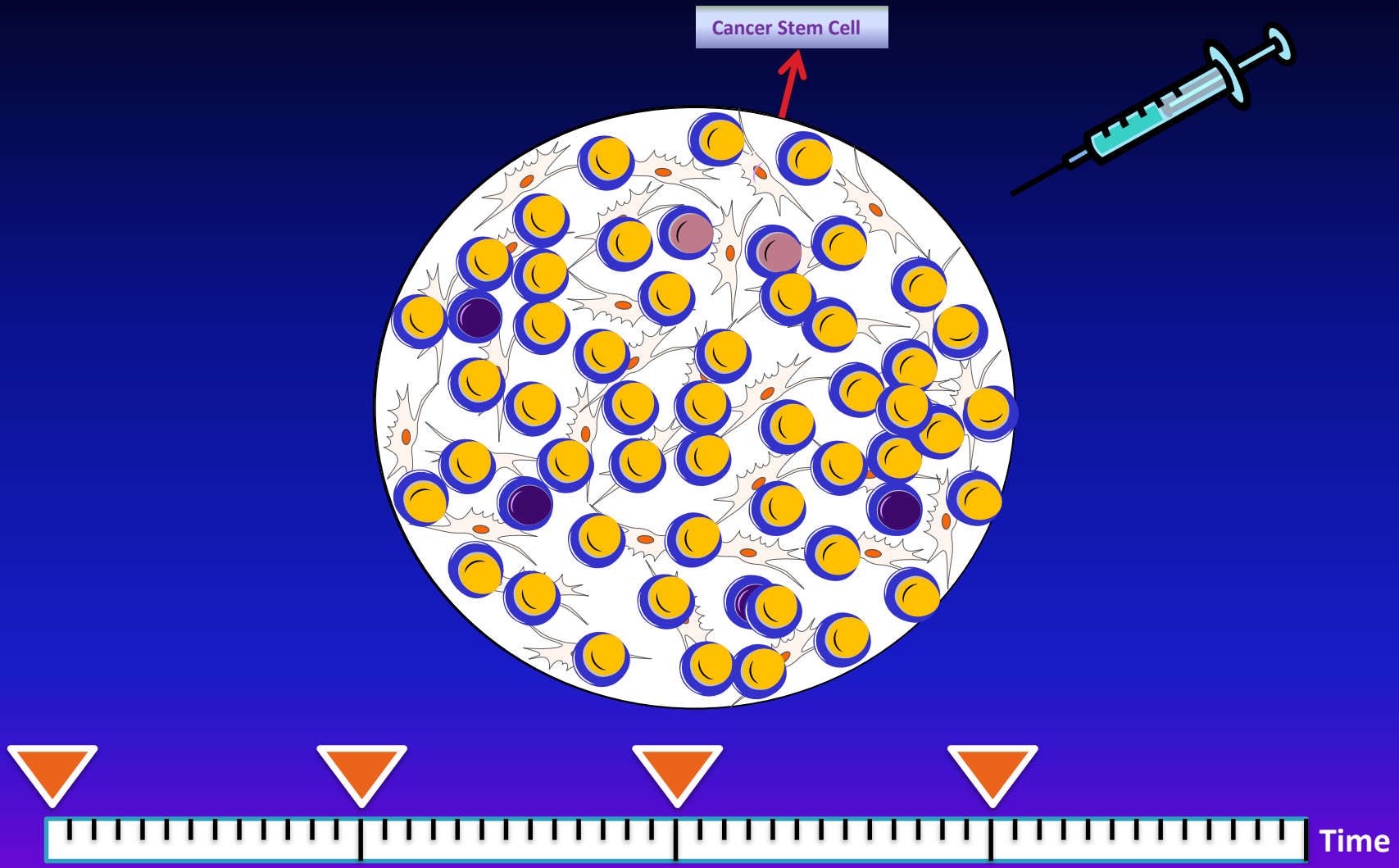
The future of cancer genomics lies in the clinic

Zero clinical data

- Why was a project of this magnitude started with NO CLINICAL INFORMATION?


“It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to *change*.”
~Charles Darwin, 1809

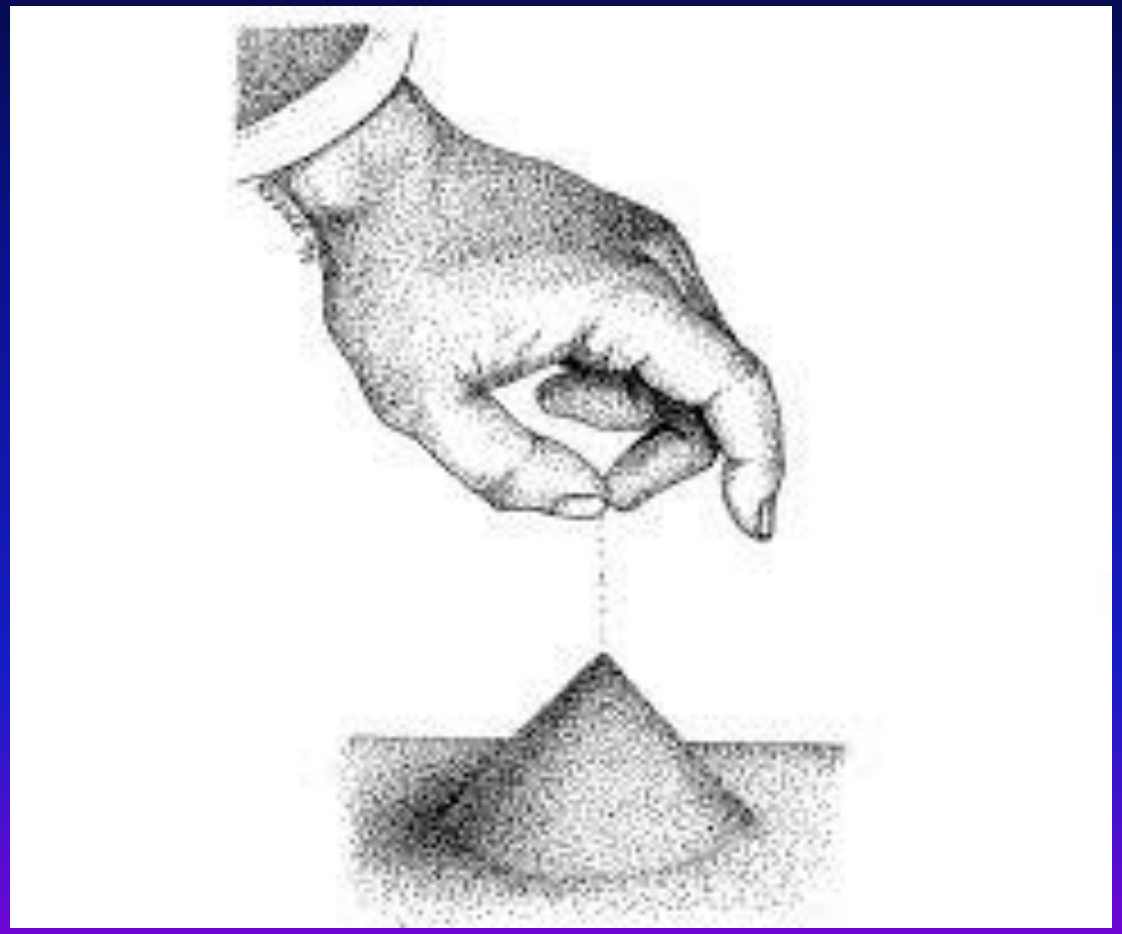
Thousands of Cancers within one



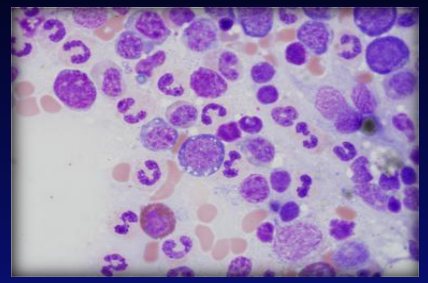
Biggest carcinogen?

- Aging
- Mutations with each cell division
- Immune Dysfunction
- Senescence
- Tissue Loss

SAND PILES AND CANCER

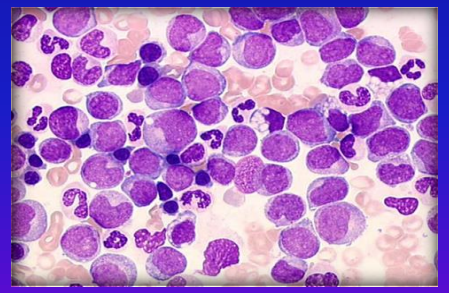


Early Detection



Pre-leukemia
MDS

INTERCEPT



Acute Myeloid
Leukemia

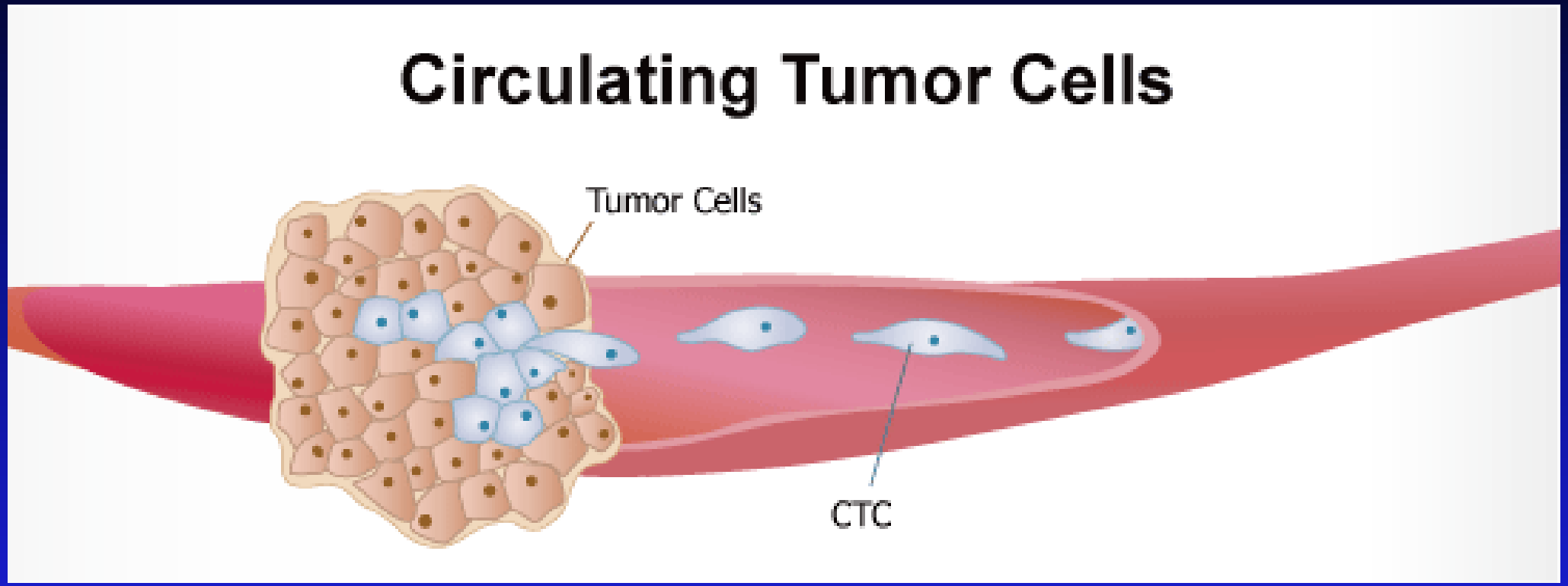
TISSUE REPOSITORY

- 3 decades (1984)
- >60,000 samples
- Pathology and clinical information

Early Detection

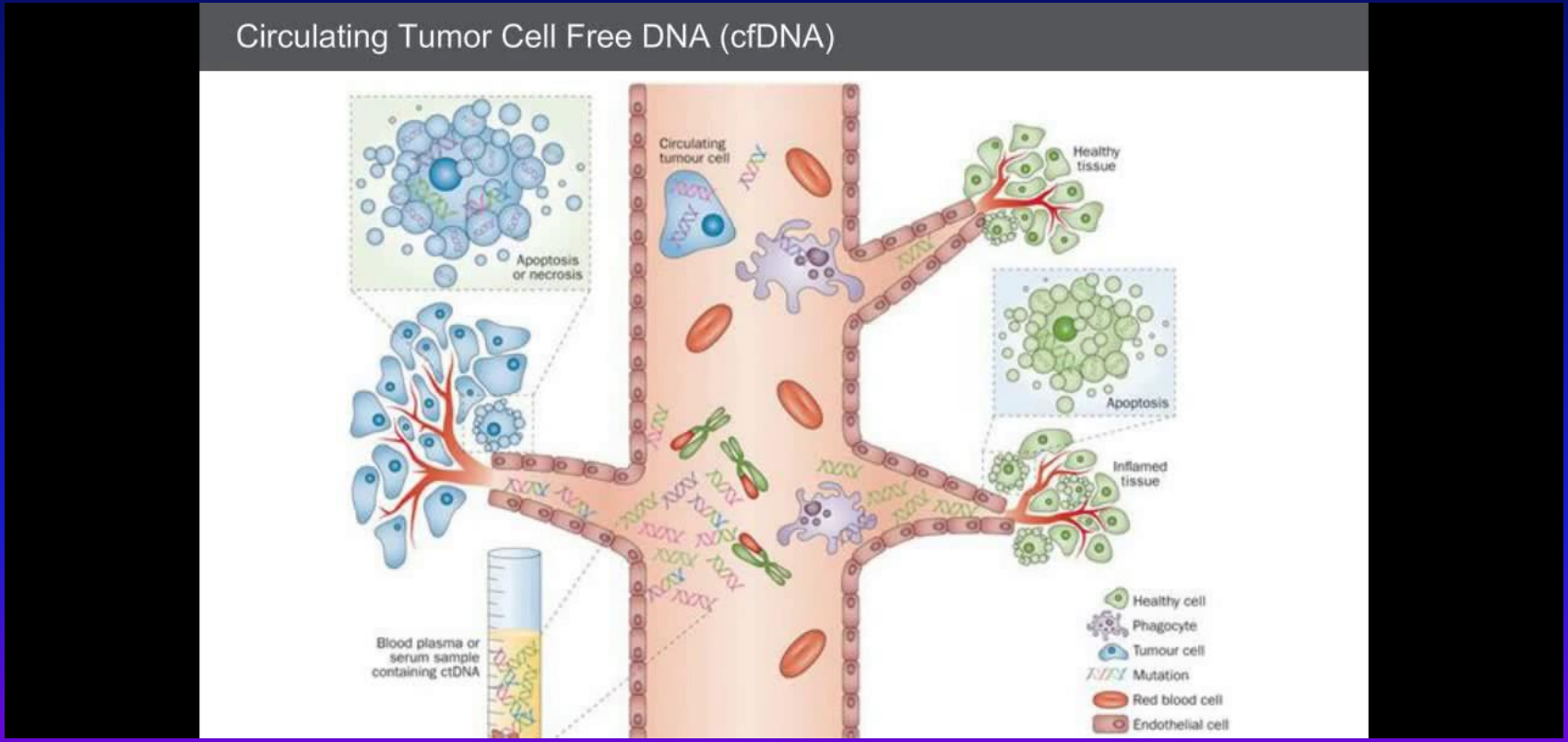
- Not just stage 1 and 2 cancers but pre-cancerous footprints
- The old methods are not of universal benefit
  - Mammogram
  - PSA
  - PAP Smear
  - Colonoscopy
- Use the latest technologies

L



CytoQuest™ CR - Circulating Rare Cell Positive Enrichment & Retrieval System

Cf-DNA fragments



cfDNA and Methylation

- Different cell types in the body have unique DNA methylation patterns
- GRAIL reported detecting 12 different common cancer types through liquid biopsies
- A tissue of origin result was accurately traced in 97% (265/272) cases

https://www.nature.com/articles/d42473-020-00079-y

CancerSeek

- Mutations in 16 cancer driver genes
- Combined with protein biomarkers for some cancers
- PET Scans
- Nearly 10,000 women screened
- Detected 26 previously unknown tumors
- 17/26 had early stage cancer
- Most had surgery or undergoing treatment and 12 are in remission

Science, April 28 2020 doi:10.1126/science.abc4550

Early Cancer Detection Using Micro RNA

- Toshiba detects 13 cancer types in 4 hours from a single drop of blood for $180
- 99% accuracy
- Reduced to less than two hours by combining a microRNA and testing devices

https://www.japantimes.co.jp/news/2019/11/25/business/corporate-business/toshiba-test-cancer-blood/#.Xt66a0VKhPY

PANSEER - DNA methylation-based Liquid Biopsy

- 414 cancer-free at least five years after and 191 diagnosed with stomach, colorectal, liver, lung or esophageal cancer within 4 years

- Identified 88% with cancer and 95% who later developed it

Nature Communications volume 11: 3475 (July 21, 2020)

From “One gene-One protein” to Systems Biology
Use blood as a window into health and disease

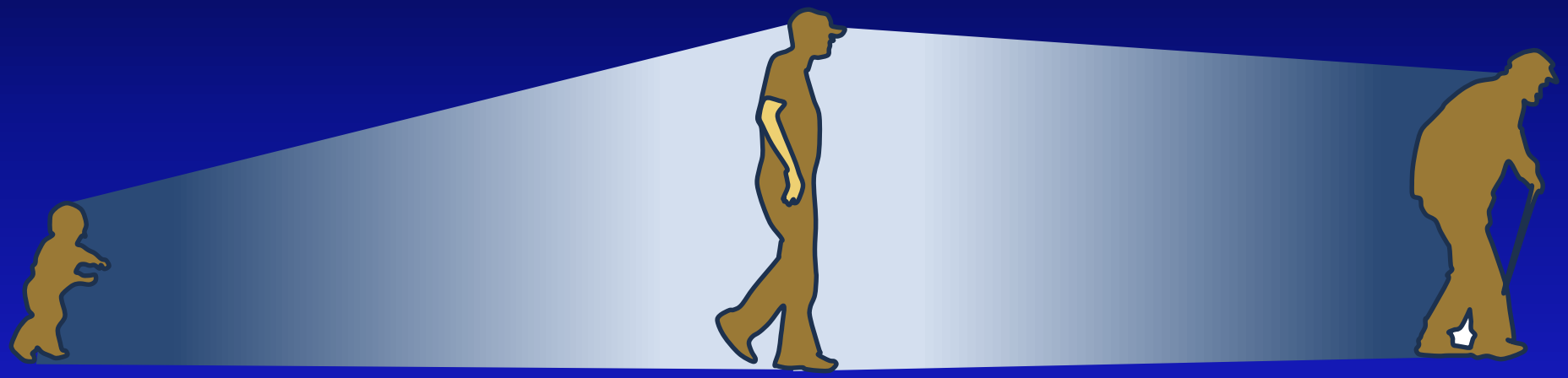
Not just detect early stage cancer, but…

- Continuously screen healthy bodies to find footprints of impending disease
- Monitor wellness to prevent illness

DEVICES: mChip

Sia Lab, Columbia University

Implantable devices monitoring the human body like a machine

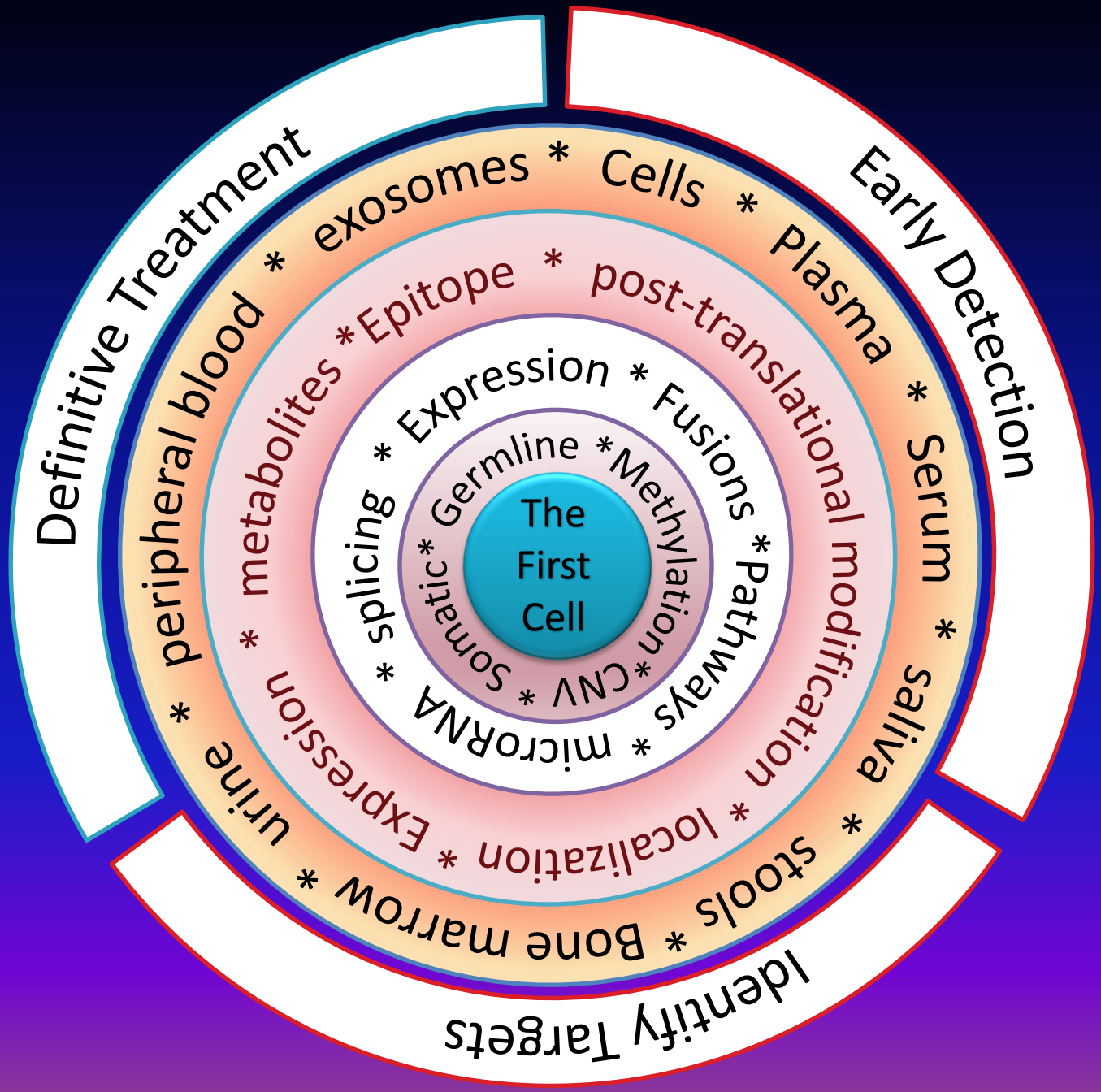


DNA

RNA

Protein and Metabolites

Compartments



Finding the first cell…now what?

Single Cell Analysis

The First Cell Center for Cancer Survivors

- One in five new cancers occur in a cancer survivor
- If 1.7M new cases each year, ~340,000 in survivors
- Screen survivors aggressively
- TIME Center at Rush University in 1996

- If I asked my customers what they want, they would have said “A faster horse!”

- ……Henry Ford

- Cannot fit a faster horseshoe on a car

SUMMARY 1

- Cancers diagnosed early are curable
- Cancers detected late are incurable
- Spectacular advances in cancer research
- Fore the patients, diagnosed early or late, not much has changed in 100 years

SUMMARY 2

- Early detection of pre-cancerous changes
- Proactive rather than reactive strategies
- Prevention rather than cure chronic diseases

Let us imagine a new world

Let us make that new world in our lifetimes

“For the one with eyes, the Dawn has already arrived…”

…Ali ibn Abi Talib

THE END