

An Integrative Approach to the Treatment of Cancer

THE ROLE OF REPURPOSED DRUGS AND
METABOLIC INTERVENTIONS
IN TREATING CANCER



REPURPOSED
DRUGS



METABOLIC
TARGETING



MULTI-AXIS
STRATEGY



IMMUNE
SUPPORT



PERSONALIZED
CARE



Paul E. Marik, MD, FCCM, FCCP

DISCLOSURES



Conflicts of Interest

NONE



**Off-label use of
FDA approved drugs**

YES



The CANCER Library

A Different Way of Thinking About Cancer



A COMPREHENSIVE DIGITAL TEXTBOOK



EVIDENCE-INFORMED

Curated research and expert insights



INTEGRATIVE APPROACH

Bridging metabolic, biological and conventional therapies



PRACTICAL & ACTIONABLE

Strategies, dosing guidance and real-world application



100% DIGITAL

Accessible anywhere, anytime, on any device



YOUR COMPLETE GUIDE TO CANCER & METABOLIC HEALING



THE BIOLOGY OF CANCER

- Warburg Effect & Metabolic Reprogramming
- Fatty Acid Oxidation
- Cancer Stem Cells & Tumor Ecology
- Cancer Immunity



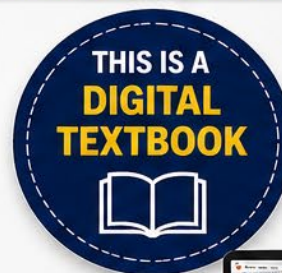
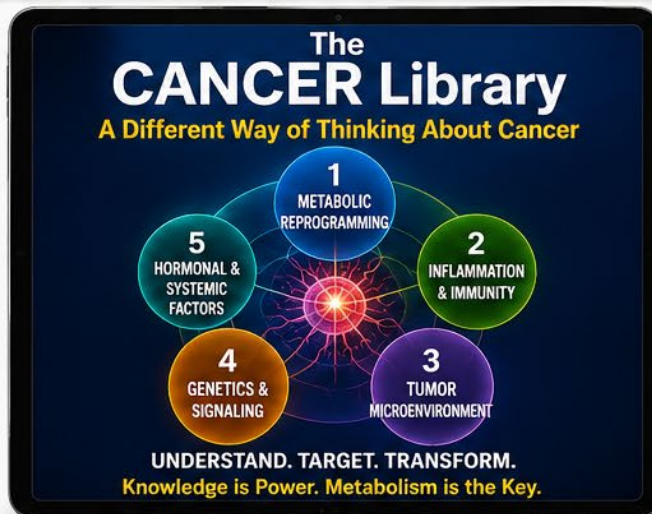
GENES, MUTATIONS & LIMITS OF PRECISION ONCOLOGY

- TP53, MYC, KRAS, BRAF, EGFR, BRCA1/2, APC & more
- Driver Mutations vs. Metabolism
- Why single-target approaches fail



DIET, METABOLISM & THE HOST

- Insulin Resistance
- Dietary Interventions & Fasting
- Gut Microbiome
- Vitamins, Minerals & Nutritional Support
- Cancer Cachexia



- ✓ Instant Access
- ✓ Searchable Content
- ✓ Clickable Navigation
- ✓ Regular Updates
- ✓ Works on All Devices
- ✓ Build Your Knowledge at Your Own Pace



Learn. Explore. Apply.
Anytime. Anywhere.



REPURPOSED DRUGS

Core Agents

- Ivermectin
- Mebendazole
- Doxycycline
- Metformin
- Propranolol
- Statins
- Aspirin/COX Inhibitors
- Melatonin & more

Emerging Agents

- Artemisinin
- Cimetidine
- Itraconazole
- Niclosamide
- IV Vitamin C
- Low Dose Naltrexone
- Thymosin alpha-1
- & many others



NUTRACEUTICALS & NATURAL COMPOUNDS

- Curcumin • EGCG • Berberine
- Sulforaphane • Resveratrol
- Quercetin • Luteolin/Genistein
- Aged Garlic Extract
- Modified Citrus Pectin
- IP6 (Inositol Hexaphosphate)
- Honokiol • Ashwagandha
- & many more



INTEGRATING CONVENTIONAL & METABOLIC THERAPY

- Chemotherapy & Metronomic Dosing
- Immunotherapy & Combinations
- Protecting Normal Tissue
- Perioperative Strategies
- Layering Metabolic Therapy with Oncology
- Bridging Gaps in Treatment
- PSK & Perioperative Support



RESISTANCE, DORMANCY & SURVIVORSHIP

- Why Cancer Recurs
- Cancer Resistance & How to Overcome It
- Cycling vs. Continuous Treatment
- Dormant Cancer Cells
- Long-Term Survivorship
- Quality of Life Strategies



SPECIAL TOPICS

- Children & Cancer
- Women's Cancers
- End-of-Life & Palliative Care
- Future Directions in Metabolic Oncology



"Cancer is complex.
Healing is possible.
Knowledge is your strongest weapon.."



UNDERSTAND
the science



TARGET
what matters



TAKE ACTION
with confidence



TRANSFORM
your outcomes

EMPOWER YOURSELF WITH KNOWLEDGE



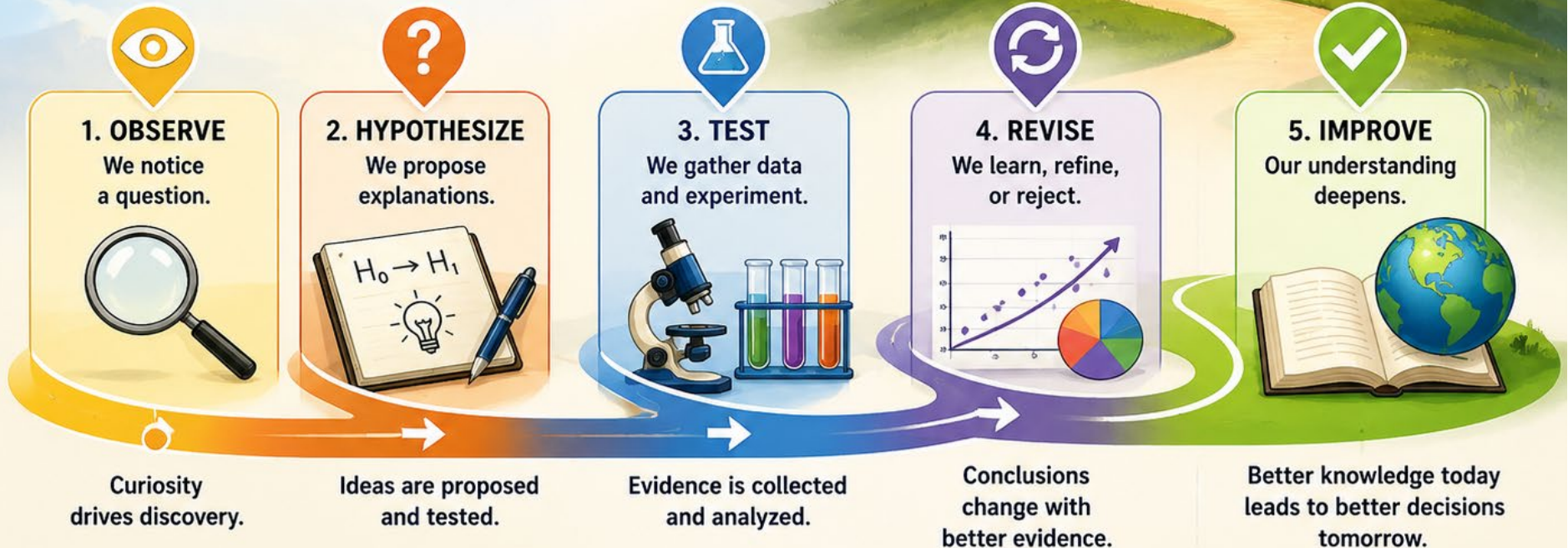
OPEN THE BOOK. CHANGE THE GAME.

The Cancer Library – Your Digital Textbook for Metabolic Healing and Integrative Cancer Care.

THE SCIENCE IS NOT SETTLED

It is a **DYNAMIC PROCESS**
that **EVOLVES** with **TIME**

New data, better tools, and critical thinking
continually refine our understanding.



SCIENCE IS SELF-CORRECTING.
It does not claim certainty—
it earns confidence.



Through open inquiry,
peer review, and replication,
knowledge advances.



Embrace change.
Demand evidence.
Trust the process.

The best science today may be improved tomorrow.
That is the strength, not the weakness, of science.

TREATMENT OF CANCER MUST BE INDIVIDUALIZED

No two cancers—and no two patients—are the same.

The best treatment plan is based on a comprehensive understanding of the tumor and the person.

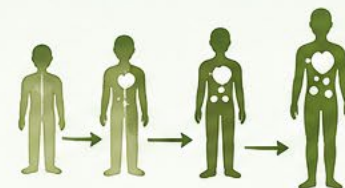
1 TYPE OF TUMOR

- Organ of origin and histologic subtype
- Molecular and pathologic features
- Rarity and clinical behavior



2 STAGE OF DISEASE

- Localized, locally advanced, or metastatic
- Extent of spread
- Resectable vs. unresectable



6 TUMOR MICROENVIRONMENT (TME)

- Stromal cells and fibroblasts
- Blood vessels and hypoxia
- Inflammation
- Extracellular matrix
- Factors that promote tumor survival and resistance



7 IMMUNE STATUS AND IMMUNE CONTEXT

- Immune cell infiltration
- PD-L1 and other biomarkers
- Immune competence
- Likelihood of response to immunotherapy



8 FUNCTIONAL STATUS OF PATIENT

- Performance status (e.g., ECOG)
- Comorbidities and organ function
- Frailty and physiologic reserve
- Ability to tolerate treatment



9 PATIENT PREFERENCES AND GOALS

- Values, goals and treatment priorities
- Willingness to accept potential benefits, risks and side effects
- Quality of life considerations



3 AGGRESSIVENESS OF TUMOR

- Growth rate and doubling time
- Grade and proliferation rate
- Risk of recurrence



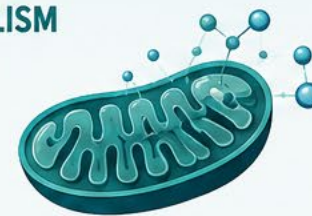
4 DRIVER MUTATIONS AND GENOMIC PROFILE

- Actionable mutations and fusions
- Genomic alterations
- Predictive biomarkers



5 TUMOR METABOLISM

- Metabolic dependencies
- Energy pathways
- Vulnerabilities that can be targeted



THE RIGHT TREATMENT
FOR THE RIGHT PATIENT
AT THE RIGHT TIME

Personalized. Precise. Purposeful.



PERSONALIZED CARE. BETTER OUTCOMES. STRONGER TOMORROWS.

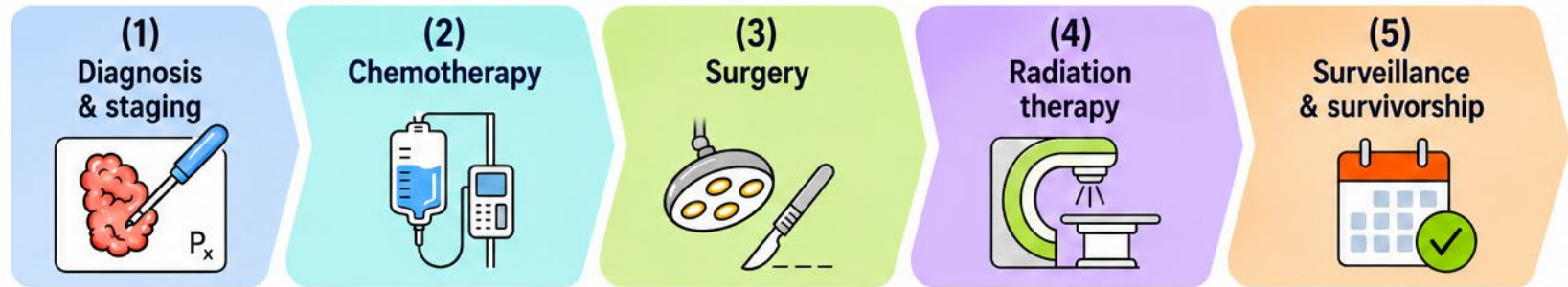
Ongoing reassessment and adaptation ensure that treatment evolves with you.



COMBINING STANDARD CANCER CARE WITH INTEGRATIVE CARE

Two Approaches. One Patient. Better Outcomes Together.

STANDARD CANCER CARE



INTEGRATIVE CARE



COMBINED, PATIENT-CENTERED CARE

Working together for better results

SYNERGISTIC BENEFITS: GREATER THAN THE SUM OF OUR PARTS



**BETTER
OUTCOMES
TOGETHER**



TOGETHER, THEY ACT SYNERGISTICALLY—TREATING THE CANCER AND STRENGTHENING THE PATIENT.

TOGETHER, THEY HEAL.



Two approaches.



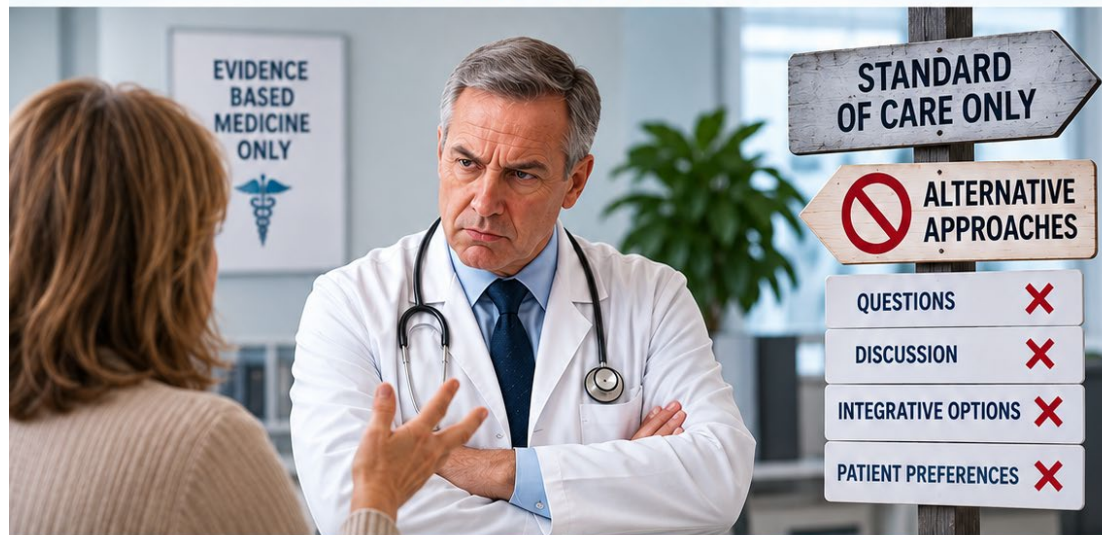
One patient.



Better outcomes—together.

“ My experience was that all the oncologists I have known (including recently as of May of this year) are sadly & tragically resistant to **ANY alternative usage of anything outside their standard of care.** The **arrogance** we encountered when civilly asking pertinent questions of the oncologist was stunning & the **narrow-mindedness numbing.** ”

— A PATIENT'S EXPERIENCE —



**Patients deserve respect, open dialogue
and a willingness to consider all reasonable options.**



LISTEN
to patients



DISCUSS
the evidence



CONSIDER
safe, integrative
approaches



RESPECT
patient values
and preferences



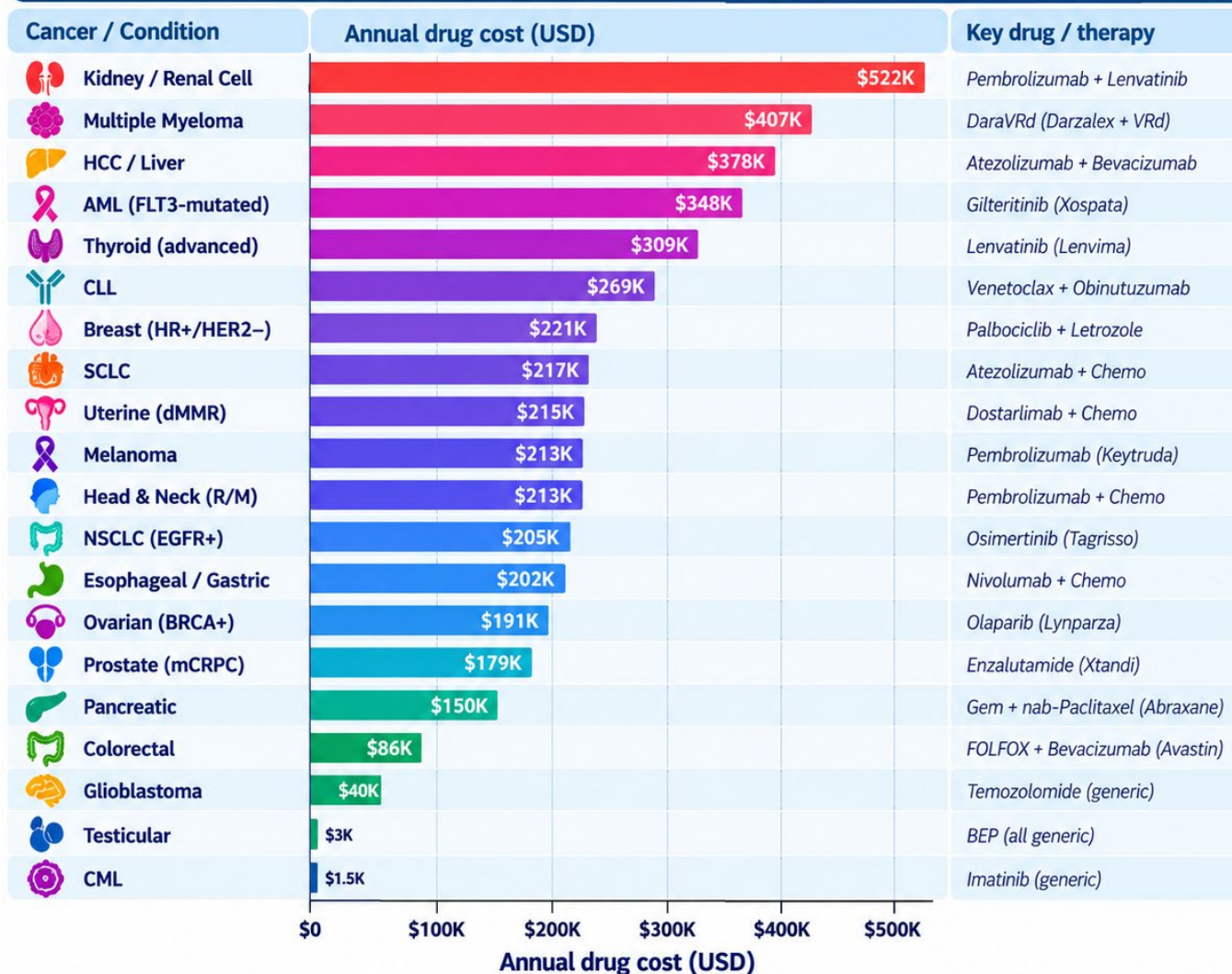
TREAT
the patient,
not just the tumor

— BETTER CONVERSATIONS. BRIGHTER OUTCOMES. —



THE STICKER PRICE OF MODERN CANCER CARE

Annualized list prices of selected cancer drug regimens at a median \$220k/year



Source: Jori

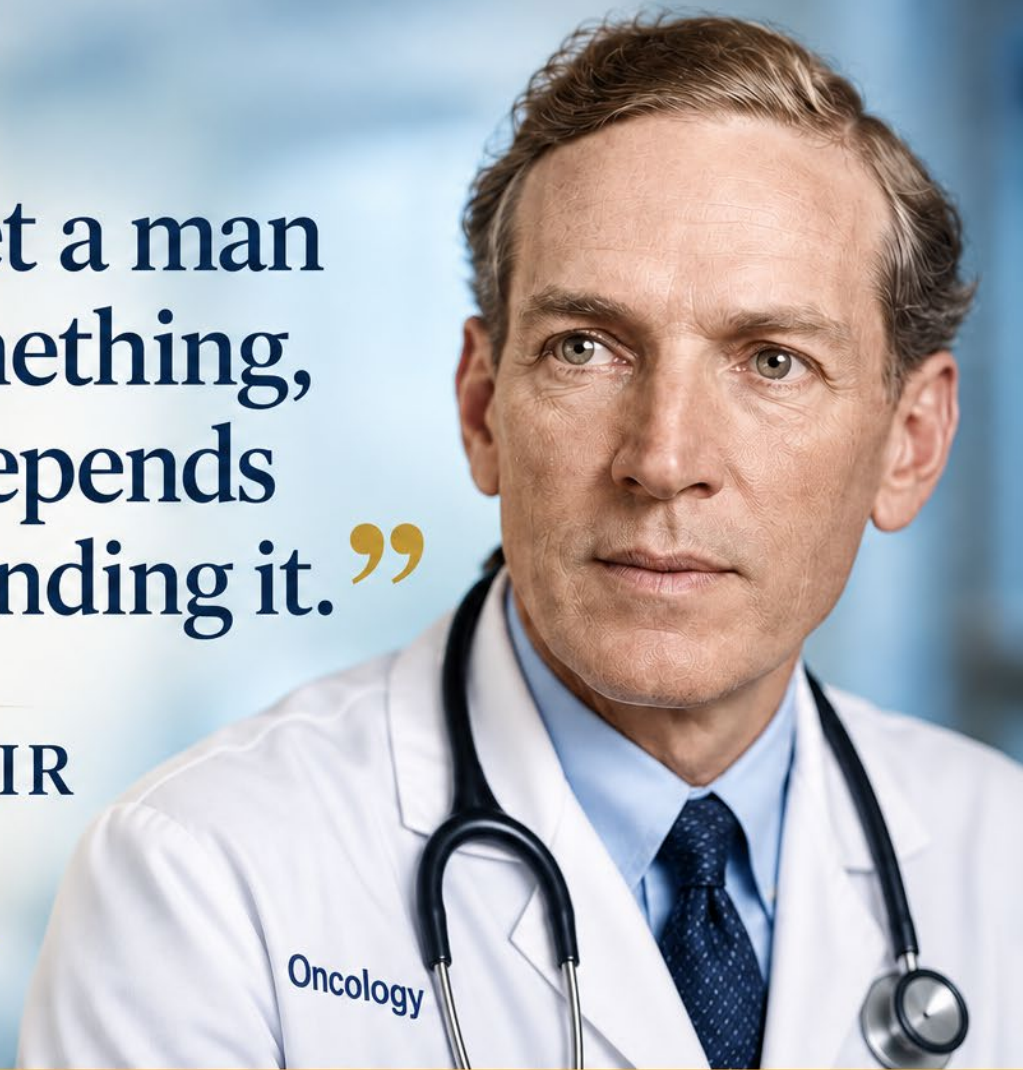
US manufacturer WAC disclosures (Genentech Co, Merck, Pfizer, Astellas, AstraZeneca, Eisai), CMS ASP Q3 2026, Drugs.com, GoodRx, JHEOR – 2025–2026 branded WAC USD & published cost-effectiveness analyses. Note: Finite-duration regimens (e.g., fixed-cycle induction or adjunct therapies) are annualized to 12-month equivalent dosing schedules for comparative analysis. Bevacizumab priced at branded Avastin WAC.

“

“It is difficult to get a man to understand something, when **his salary** depends on his not understanding it.”

UPTON SINCLAIR

American author



TRUTH MATTERS



KNOWLEDGE EMPOWERS

U.S. Cancer Statistics: 2013–2024

Year 	New Cases 	DEATHS/year 	DEATHS/day 
2013	1,660,290	580,350	1,590
2014	1,665,540	585,720	1,605
2015	1,658,370	589,430	1,615
2016	1,665,210	595,690	1,632
2017	1,688,780	600,920	1,646
2018	1,743,350	609,640	1,670
2019	1,762,450	606,880	1,663
2020	1,806,590	606,520	1,662
2021	1,898,160	608,570	1,667
2022	1,918,030	609,360	1,670
2023	1,958,310	609,820	1,671
2024	2,001,140	611,720	1,676
Increase (2013–2024)	 17.0%	 5.1%	 5.1%

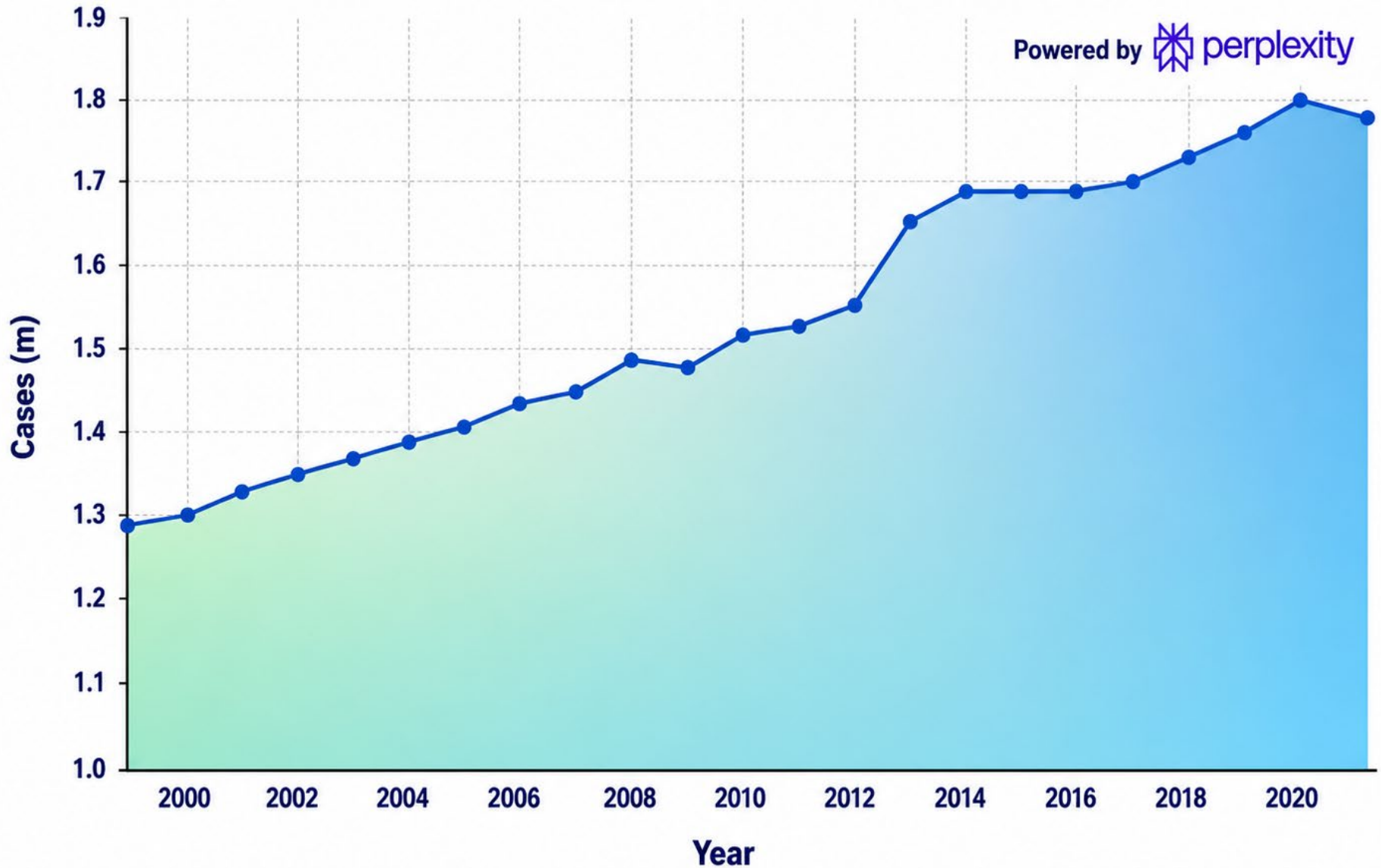


KEY TAKEAWAY: From 2013 to 2024, new cancer cases increased by **17.0%**, while annual deaths increased by **5.1%** (5.1% more deaths per day).

Data from American Cancer Society

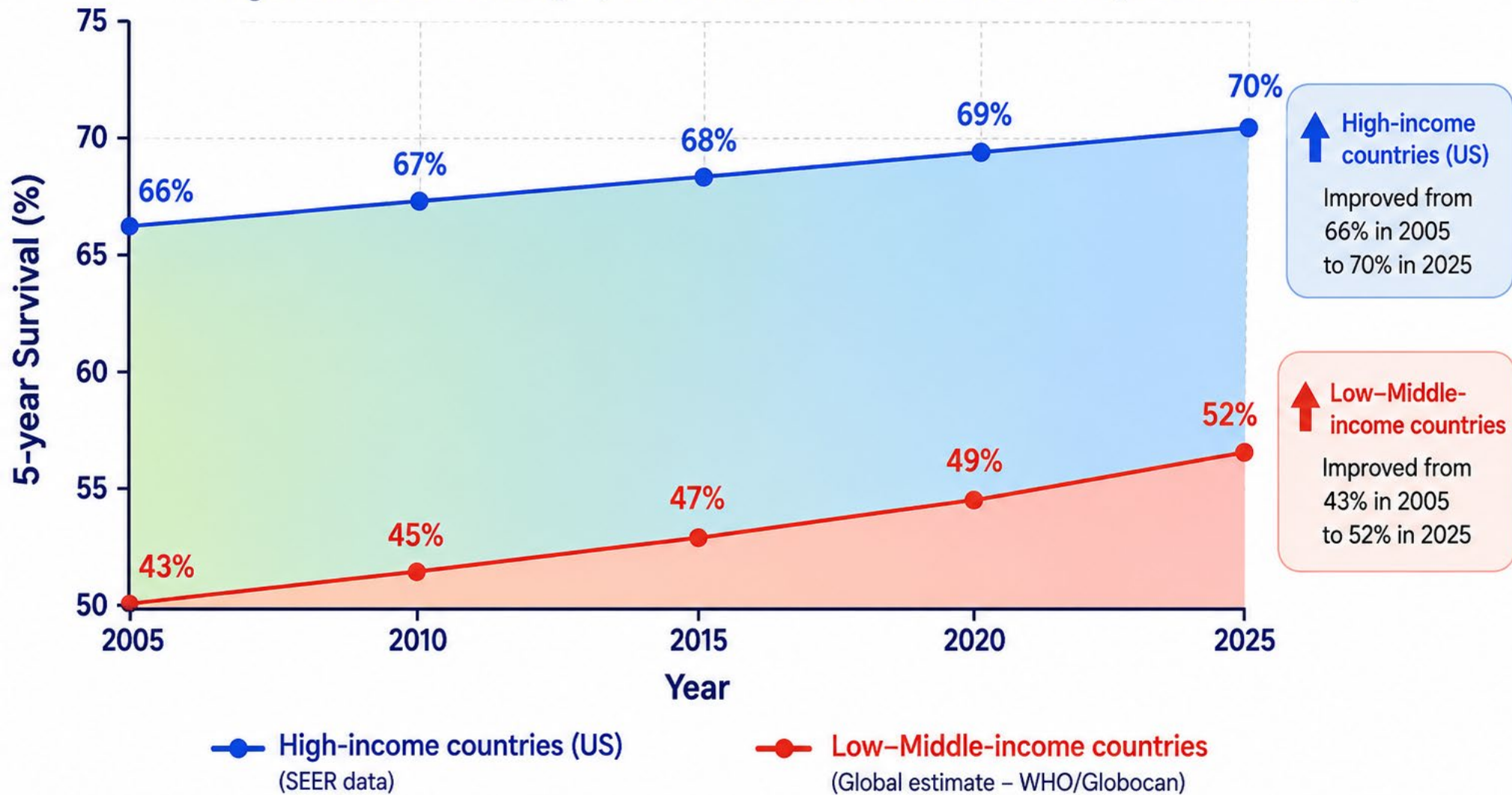
Number of new cancer cases in the United States, 1999–2021 (Statista)

38% increase over two decades reflects aging population



5-year survival after cancer diagnosis (2005–2025)

High-income countries (US) vs. Low–Middle-income countries (Global Estimate)



Sources: SEER Cancer Statistics Review (2005–2025)

WHO / Globocan 2020 & 2025 projections for Low–Middle-income countries

PROGRESS

JAMA Oncology | Original Investigation

Evolution of the Randomized Clinical Trial in the Era of Precision Oncology



DESIGN, SETTING, AND PARTICIPANTS:

Trends with RCTs published between 1995 to 2004 and 2005 to 2009.



RESULTS:

Of 298 RCTs, 265 (89%) were funded by industry. Among positive trials, median improvement in overall survival and progression free survival was **3.4 and 2.9 months**, respectively.



CONCLUSION:

To demonstrate that new cancer treatments are high value, the oncology community needs to consider the extent to which study end points and target effect size provide meaningful benefit to patients.



LIMITATIONS:

Limitations of the RCT.

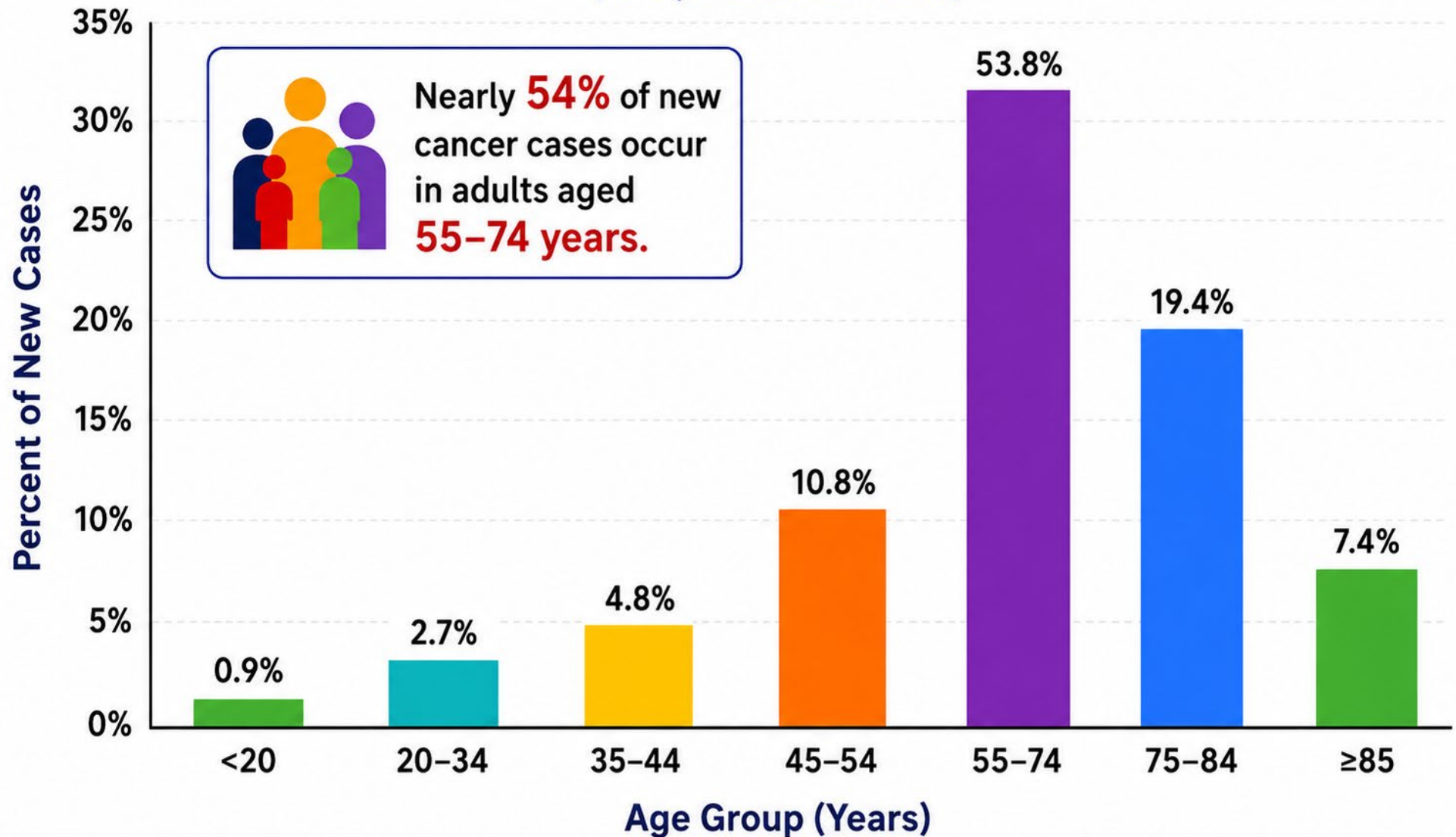


JAMA Oncol. 2021;7(5):728-734.
doi:[10.1001/jamaoncol.2021.0379](https://doi.org/10.1001/jamaoncol.2021.0379)
Published online March 25, 2021.

Tumor Stratification According to Response to Chemotherapy

Cancer Curable	Improves Survival	Palliation Only (metastatic)
 Choriocarcinoma	 Breast cancer	 Colorectal, gallbladder
 Acute lymphatic leukemia	 Ovarian Cancer	 Pancreatic, stomach
 Chronic lymphatic leukemia	 ALL in adults	 Esophageal, liver
 Acute promyelocytic leukemia	 AML	 Prostate, bladder, kidney
 Testicular cancer	 Thyroid Cancer	 Endometrial and cervical
 Ovarian germ cell tumor	 Small cell lung cancer	 NSCLC (lung cancer)
 Hodgkin's lymphoma	 Multiple myeloma	 Brain, adrenal, melanoma
 High Grade non-Hodgkin's lymphoma	 Osteosarcoma	 Adenocarcinoma primary unknown
 Rare childhood malignancies	 Wilms tumor	 H&N cancer

AGE DISTRIBUTION OF NEW CANCER CASES (US, ALL SITES)

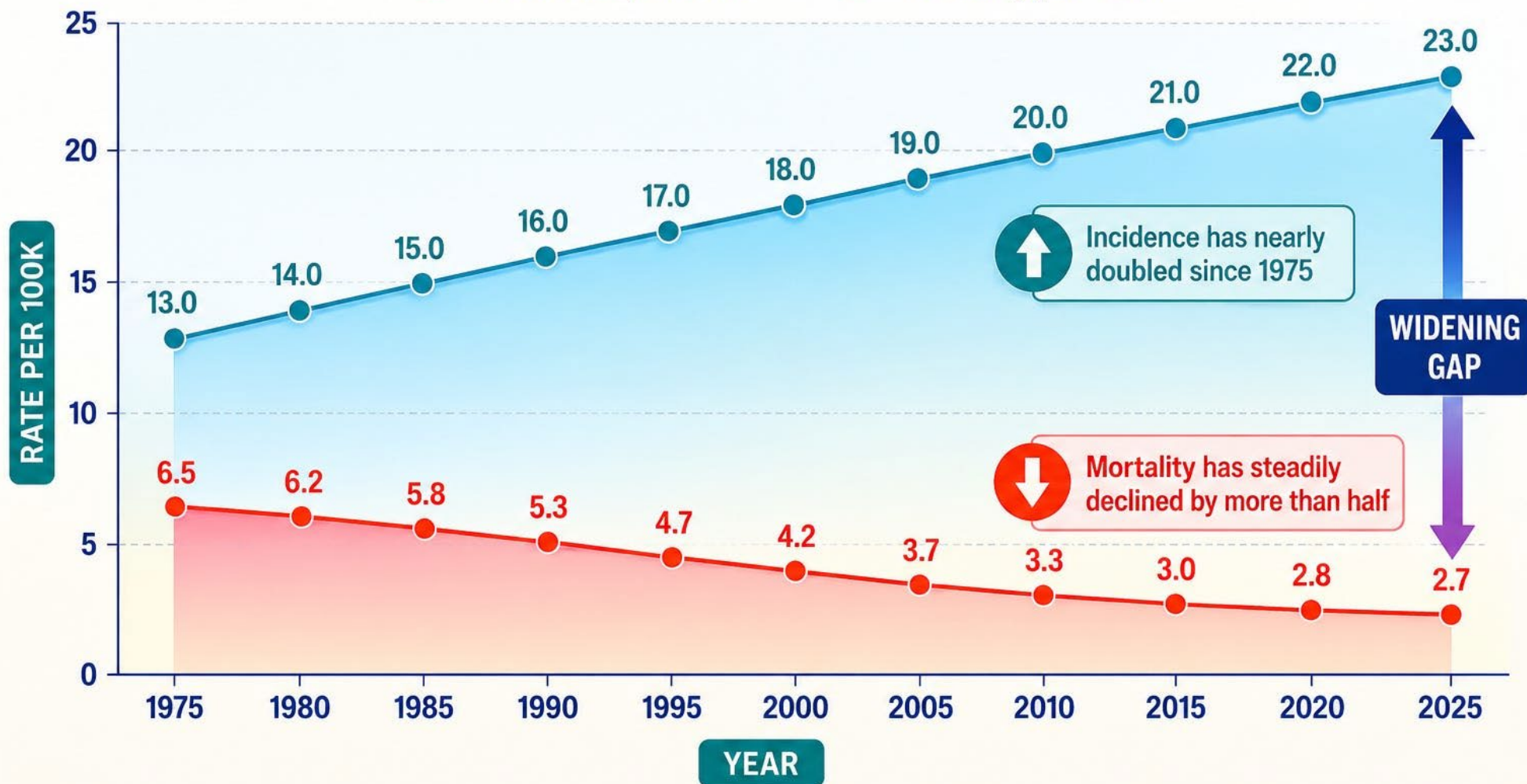


CHILDHOOD CANCER INCIDENCE VS MORTALITY DIVERGENCE (1975-2025)



Source: Illustrative synthetic data based on SEER trends

Incidence per 100k Mortality per 100k





CHILDHOOD vs ADULT CANCERS – KEY DIFFERENCES



Cancers in children and adults differ in their causes, biology, risk factors, treatment, and outcomes.

FEATURE	CHILDHOOD CANCER	ADULT CANCER
 Incidence	Rare (~1–2% of all cancers)	Very common
 Dominant Types	Leukemia, brain tumors, embryonal tumors (neuroblastoma, Wilms tumor, retinoblastoma)	Carcinomas (lung, breast, colon, prostate, pancreas), lymphomas, myeloma
 Cell of Origin	Often embryonal / developmental cells	Epithelial cells (carcinomas) or mature blood/immune cells
 Genetic Basis	Fewer mutations; often driver mutations or chromosomal translocations	Multiple accumulated mutations over time in oncogenes and tumor suppressor genes
 Mutation Burden	Low	High
 Etiology	Largely unknown, developmental biology and random events	Strongly linked to environment and lifestyle factors over many years
 Risk Factors	Rarely lifestyle-related	Smoking, diet, obesity, alcohol, physical inactivity, UV exposure, infections, environmental carcinogens
 Latency Period	Short (months–years)	Long (decades)
 Age Association	Peak incidence in early childhood and adolescence	Incidence increases steadily with aging
 Growth Rate	Often rapidly proliferative	Variable; often slower growing
 Response to Therapy	Generally highly chemosensitive and radiosensitive	Often less sensitive; more treatment-resistant
 Curability	High cure rates (>80% in high-income countries) for many cancers	Variable; many cancers incurable, especially when advanced
 Treatment Approach	Intensive chemotherapy, risk-adapted protocols, multidisciplinary long-term follow-up	Surgery, radiation, chemotherapy, targeted therapy, immunotherapy, hormonal therapy
 Role of Surgery	Limited; used in some solid tumors (e.g., brain tumors, Wilms tumor)	Often central for cure or control (e.g., breast, colon, lung, prostate cancers)
 Role of Prevention	Limited (few modifiable risks)	Major role (lifestyle modification, vaccination, screening)
 Screening	Rare (only for specific syndromes or high-risk groups)	Common (mammography, colonoscopy, Pap test, PSA test, low-dose CT for lung cancer, etc.)
 Long-term Effects	Major issue: growth, fertility, neurocognitive effects, secondary cancers, organ toxicity	Also present but different profile; more related to aging and comorbidities
 Second Malignancies	Increased due to therapy/genetic predisposition	Often due to environmental exposures, lifestyle or aging
 Tumor Biology	Often driven by developmental pathways, epigenetic dysregulation	Driven by accumulated DNA damage, genomic instability, chronic inflammation
 Microenvironment	Less complex tumor microenvironment	More complex (chronic inflammation, stromal cells, immune evasion, angiogenesis)

KEY TAKEAWAY

Childhood cancers are biologically distinct from adult cancers, with different causes, biology, and clinical behavior. Advances in pediatric oncology have led to high cure rates, while prevention and early detection are critical in adult cancers.

CHILDHOOD CANCER HIGHLIGHTS



Often caused by random genetic events during development.



Highly responsive to therapy with excellent cure potential.



Long-term follow-up essential to manage late effects and secondary cancers.



Research focuses on precision medicine and reducing toxicity.

ADULT CANCER HIGHLIGHTS



Heavily influenced by lifestyle and environmental exposures.



Develops over many years; early detection saves lives.



Treatment is more complex and tailored to molecular characteristics.



Prevention, screening, healthy lifestyle and vaccination are key tools.



WHAT THE PUBLIC IS **NOT TOLD** **ABOUT CANCER PREVENTION**

THE POWER TO PREVENT IS IN YOUR HANDS—EVERY CHOICE MATTERS.



WHAT YOU'RE TOLD



EARLY
DETECTION



NEW DRUGS &
TREATMENTS



IT'S
GENETICS



ADVANCED
TECHNOLOGY

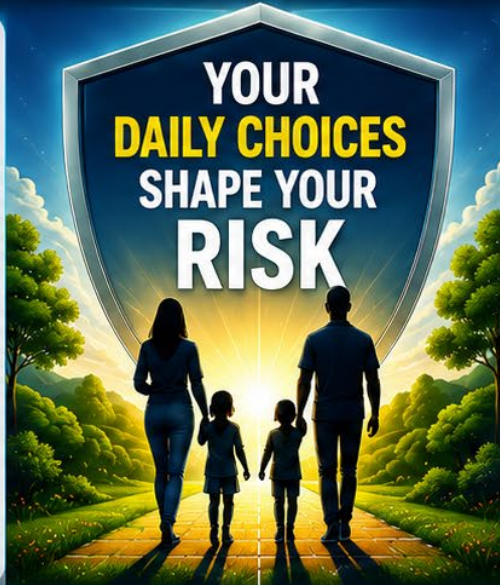


IMPORTANT?

Yes. These matter.

**But this is only part
of the story.**

YOUR DAILY CHOICES SHAPE YOUR RISK



WHAT YOU'RE **NOT** TOLD



DIET &
NUTRITION



EXERCISE &
MOVEMENT



INSULIN
RESISTANCE



WEIGHT &
BODY FAT



CHRONIC
INFLAMMATION



SLEEP &
CIRCADIAN
HEALTH



TOXIC CHEMICAL
EXPOSURE



STRESS &
MENTAL HEALTH



ALCOHOL &
TOBACCO



GUT HEALTH &
MICROBIOME



CANCER IS COMPLEX.
BUT PREVENTION IS POSSIBLE.

TAKE CONTROL. BUILD RESILIENCE.
REDUCE RISK. LIVE LONGER, BETTER.



**YOUR HEALTH.
YOUR FUTURE.
YOUR CHOICE.**



INFORM YOURSELF. EMPOWER YOURSELF. PROTECT YOURSELF.

PREVENTION IS POWER. USE IT EVERY DAY.

RISK FACTORS

Some factors **INCREASE** cancer risk.
Some help **PROTECT** against it.

MAJOR RISK FACTOR PROCESSED FOODS



High in refined sugar, unhealthy fats, salt and additives.
Linked to inflammation, obesity and cancer risk.



CHILDHOOD FEBRILE ILLNESS
(Some infections may increase risk)



BREASTFEEDING
(Helps protect)

MAJOR RISK FACTOR SMOKING



Tobacco smoke contains carcinogens that damage DNA and increase cancer risk.

MAJOR RISK FACTOR PESTICIDE EXPOSURE



Exposure may disrupt hormones, damage DNA and increase cancer risk.



HIGHER AGE AT FIRST MOTHERHOOD
(Increases risk)



GREAT FAMILY SIZE
(May protect)



CAESAREAN BIRTH
(Increases risk)



STRESS
(Increases risk)



SLEEP DEPRIVATION
(Increases risk)



ANTIBIOTICS
(Long-term/overuse may increase risk)



SEDENTARY LIFESTYLE
(Increases risk)



AIR POLLUTION
(Increases risk)



INDOOR LIVING
(Increases risk)



RADON EXPOSURE
(Increases risk)

 **PRO-CANCER EFFECT**
(Increases risk)

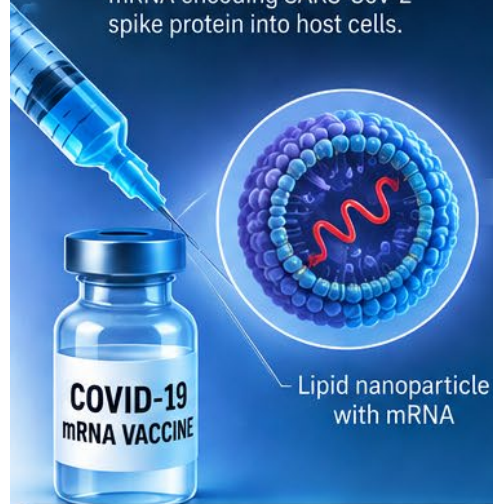
 **ANTI-CANCER EFFECT**
(Reduces risk)

FROM COVID-19 VACCINE TO **AGGRESSIVE CANCER**

A PLAUSIBLE BIOLOGICAL PATHWAY SUPPORTED BY EMERGING EVIDENCE

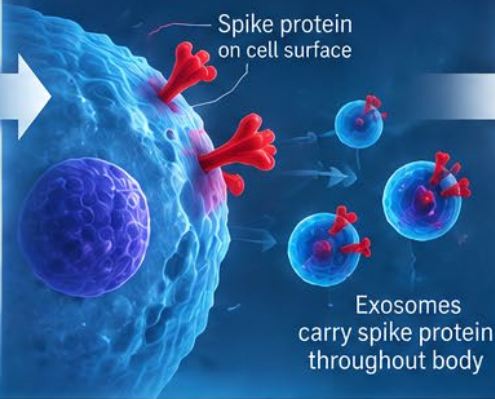
1 COVID-19 mRNA VACCINATION

Lipid nanoparticle (LNP) delivers mRNA encoding SARS-CoV-2 spike protein into host cells.



2 SPIKE PROTEIN EXPRESSION AND PERSISTENCE

Cells produce spike protein, which can persist for weeks to months and circulate systemically in exosomes.

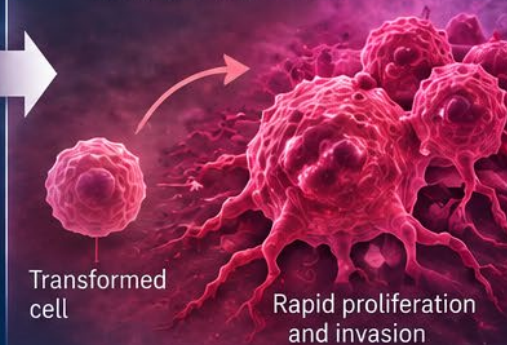


3 BIOLOGICAL EFFECTS THAT PROMOTE CANCER

- ↑ Chronic inflammation (↑ NF- κ B, cytokines)
- ↑ DNA damage and impaired DNA repair
- ↑ Immune dysregulation (↓ NK cell activity, T cell exhaustion)
- ↑ Microenvironment changes (↑ VEGF, angiogenesis)
- ↑ Reactivation of latent viruses (e.g., EBV, HPV)
- ↑ Altered tumor suppressor pathways (p53, BRCA)

4 INITIATION AND ACCELERATION OF TUMOR GROWTH

These changes can transform pre-cancerous cells or accelerate growth of existing cancer cells, leading to more aggressive, faster-growing tumors.



RESULT: **MORE AGGRESSIVE CANCERS**

Observed features in post-vaccine cancers include:

- Rapid onset after vaccination
- Higher grade, more aggressive histology
- Unusual types and locations (e.g., turbo cancers)
- Advanced stage at diagnosis
- Poor response to standard therapy
- Shorter survival

EXAMPLES REPORTED

- Breast cancer
- Colon cancer
- Lung cancer (including non-smokers)
- Lymphomas (including aggressive T-cell lymphomas)
- Leukemias
- Head and neck cancers
- Rapidly progressive metastatic cancers

**A FASTER, DEADLIER
CANCER TRAJECTORY**

THE COVID VACCINE MAY CAUSE CANCER — IT MAY CREATE THE BIOLOGICAL CONDITIONS FOR MORE AGGRESSIVE CANCERS.

The Somatic Mutation Theory of Cancer

Cancer is a genetic disease caused by the accumulation of somatic mutations in key genes that drive uncontrolled cell growth.

1 Normal Cell

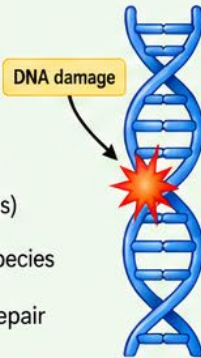
- Regulated cell growth, division and death (apoptosis)
- Intact DNA repair mechanisms
- Maintains normal tissue architecture



Normal cell

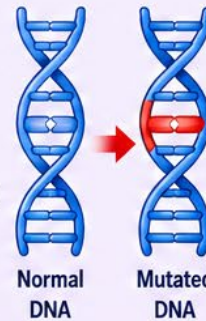
2 DNA Damage Occurs

- Errors during DNA replication
- Environmental carcinogens (e.g., tobacco, UV, radiation, chemicals)
- Reactive oxygen species
- Inadequate DNA repair



3 Somatic Mutation

- DNA damage can lead to permanent changes (mutations) in the genetic code
- These are somatic mutations (not inherited)
- Mutations can activate oncogenes or inactivate tumor suppressor genes



Normal DNA

Mutated DNA

4 Key Driver Mutations

- Mutations in critical genes can confer a growth advantage
- Commonly affected genes include:
 - **Oncogenes** (e.g., KRAS, BRAF, EGFR, MYC)
 - **Tumor suppressor genes** (e.g., TP53, RB1, APC, PTEN)
 - **DNA repair genes** (e.g., BRCA1/2, MMR)

Oncogenes
(gain-of-function)
Drive cell proliferation

Tumor suppressor genes
(loss-of-function)
Remove brakes on cell growth

5 Clonal Expansion and Tumor Progression

Single mutated cell



Initial mutation confers a growth advantage

Clonal expansion



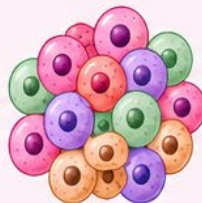
Daughter cells inherit the mutation

Additional mutations



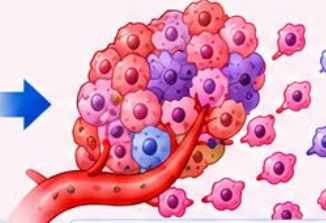
Accumulation of additional mutations increases fitness

Heterogeneous tumor



Genetic heterogeneity within the tumor

Invasive and metastatic cancer



Further mutations enable invasion, metastasis and treatment resistance

6 Hallmarks of Mutation-Driven Cancer (Hanahan & Weinberg, 2011)



Sustained proliferative signaling



Evasion of tumor suppressors



Resistance to cell death (apoptosis)



Induction of angiogenesis



Tissue invasion and metastasis



Resistance to therapy



Genetic heterogeneity and evolution



Mutations can start the fire, but other factors help it spread.

A more complete understanding of cancer requires integrating genetics with metabolism, the microenvironment and the immune system.



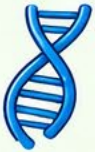
THE MUTATION TRAP

THE BILLION-DOLLAR ILLUSION OF PRECISION ONCOLOGY

Cancer is a genetic disease caused by the accumulation of somatic mutations in key genes that drive uncontrolled cell growth.

THE PROMISE

Target the right mutation. Right drug. Right patient.



INDIVIDUALIZED THERAPY

Match treatment to each patient's mutations.



TARGET THE MUTATION

Block the key driver of the cancer.



DESIGNER ONCOLOGY DRUGS

More effective, fewer side effects.



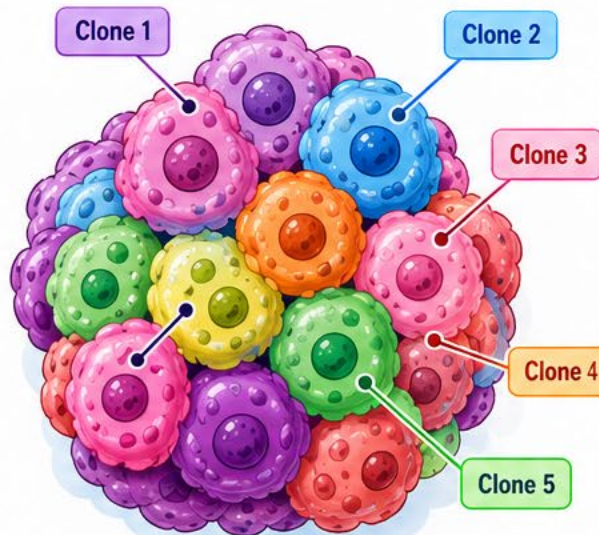
BETTER OUTCOMES

Longer survival and improved quality of life.

Precision oncology cures!

CANCER IS COMPLEX

Millions of mutations. Many different clones.



Each tumor contains many different clones with different mutations. As the cancer evolves, new mutations emerge.

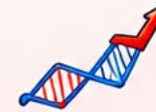
THE REALITY

Cancer is not simple. It adapts. It evolves. It wins.



TUMOR HETEROGENEITY

Many different clones with different mutations.



EVOLUTIONARY ADAPTATION

Rapidly evolves under treatment pressure.



COMPENSATORY SIGNALING

Alternative pathways take over when one is blocked.



DRUG RESISTANCE

New mutations emerge, leading to treatment resistance.



CANCER STEM CELLS

A small population can survive and seed relapse.

Precision oncology is powerful, but it is not a magic bullet.



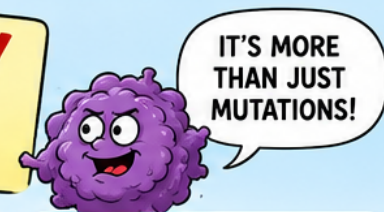
**CANCER IS BEST VIEWED AS A COMPLEX ADAPTIVE SYSTEMS DISEASE—
NOT PURELY A GENETIC DISEASE.**

Better science.
Smarter strategies.
Better outcomes.





5 REASONS WHY THE **SOMATIC MUTATION THEORY** IS **INCORRECT** (AS THE SOLE CAUSE OF CANCER)

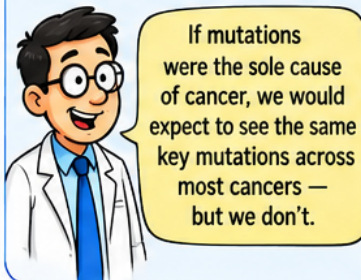


1 NO UNIVERSAL CANCER MUTATION EXISTS

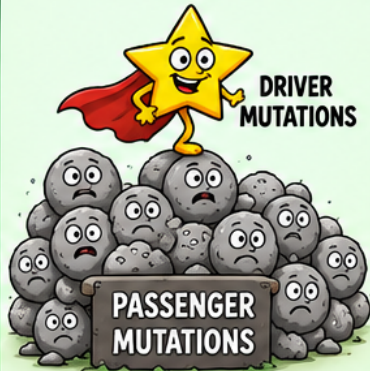


The Cancer Genome Atlas (TCGA) and other studies show extraordinary mutational heterogeneity.

Even tumors of the same type share surprisingly few mutations.



2 MOST MUTATIONS ARE "PASSENGERS"

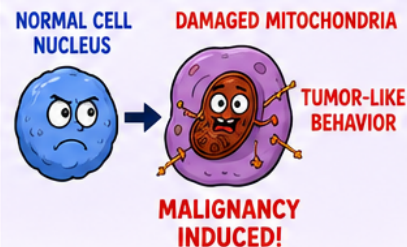
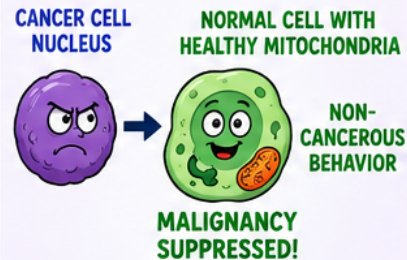


Cancer genomes contain hundreds to thousands of mutations, but the vast majority do not drive cancer growth.

Many mutations may be consequences of metabolic dysfunction, oxidative stress and genomic instability — not the initial cause.



3 NUCLEAR TRANSFER EXPERIMENTS SUPPORT A MITOCHONDRIAL ROLE

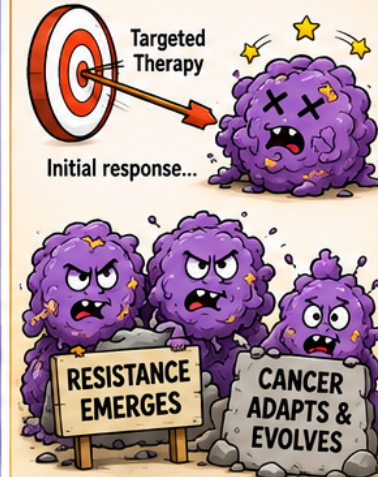


Healthy mitochondria can suppress cancer traits, while damaged mitochondria can promote them.

This suggests mitochondrial dysfunction and altered energetics may be upstream of many genetic abnormalities.



4 TARGETING MUTATIONS OFTEN PRODUCES ONLY TEMPORARY RESPONSES



Many targeted therapies yield modest survival benefits, and resistance commonly develops.

Cancer behaves like a dynamic, adaptive metabolic ecosystem — not a static genetic disease.



5 THE WARBURG EFFECT IS NEARLY UNIVERSAL ACROSS CANCERS



Most cancers show high glucose uptake and aerobic glycolysis (producing lactate even with oxygen present).

This metabolic phenotype is remarkably consistent across diverse cancers despite enormous genetic variability.

Metabolism may be a more fundamental, unifying hallmark of cancer than specific mutations.



THE BOTTOM LINE:

Cancer is not caused by mutations alone. It arises from a complex interplay of metabolism, genetics, epigenetics, immune signaling, the microenvironment and cellular adaptation.

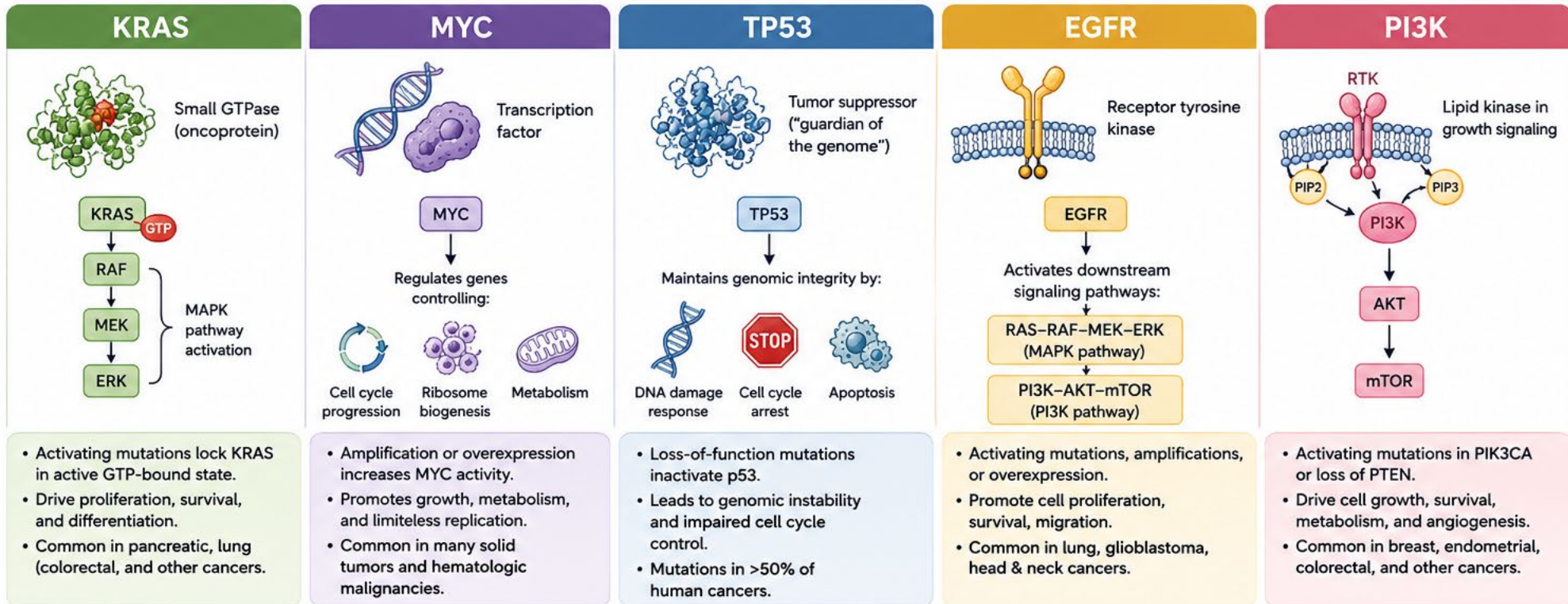
WE NEED A SYSTEMS BIOLOGY APPROACH TO TRULY DEFEAT CANCER!

DRIVER MUTATION vs PASSENGER MUTATION

FEATURE	DRIVER MUTATION "The engine of cancer"	PASSENGER MUTATION "A hitchhiker in the cancer genome"
 DEFINITION	A mutation that gives the cancer cell a selective growth or survival advantage and contributes to cancer development or progression.	A mutation that is present in the cancer genome but does not contribute to the growth or survival advantage of the cancer cell.
 ROLE IN CANCER	Drives key cancer hallmarks such as uncontrolled growth, resistance to cell death, invasion, metastasis, or immune escape.	Does not affect cancer behavior; has little or no impact on how aggressively the cancer grows or responds to treatment.
 SELECTIVE ADVANTAGE	Provides a selective advantage ; cells with this mutation are more likely to expand and dominate the tumor.	Provides no selective advantage ; cells with this mutation neither grow faster nor survive better because of it.
 FREQUENCY IN TUMORS	Usually found in a substantial fraction of cells in the tumor (clonal) and often in early stages of tumor development.	Often present in a small fraction of cells (subclonal) and typically appears later as the tumor accumulates random mutations.
 DETECTABLE BY SEQUENCING?	Yes. Detected by genomic sequencing and often recurrent across many patients with the same cancer type.	Yes. Detected by sequencing but usually not recurrent ; occurs randomly.
 CLINICAL IMPORTANCE	May be targetable with specific drugs or inform prognosis and treatment decisions.	Usually not targetable ; rarely guides treatment or prognosis.
 ANALOGY	 Driver of the car – controls the direction and speed.	 Passenger in the car – just along for the ride, no control over destination.
 EXAMPLE	KRAS mutation in pancreatic cancer, EGFR mutation in lung cancer, BRAF V600E in melanoma, TP53 loss in many cancers.	Random synonymous mutation in a gene that does not affect protein function, or a mutation in a gene not involved in cancer-related pathways.

KEY DRIVER MUTATIONS IN CANCER

Driver mutations are genetic changes that provide a growth advantage to cells and promote tumor initiation, progression, and resistance.



COMMON EFFECTS OF DRIVER MUTATIONS

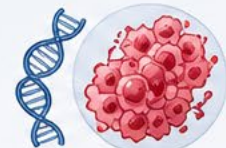


TAKE-HOME MESSAGE

KRAS, MYC, TP53, EGFR, and PI3K are key driver genes that promote cancer through dysregulated signaling, impaired genomic control, and enhanced survival.



Understanding these mutations enables precision oncology and the development of targeted therapies.





EXAMPLES OF TARGETED THERAPIES IN CANCER



Targeted therapies are designed to attack specific genetic alterations or proteins that drive cancer growth.

WHAT THEY TARGET & WHAT THEY DO				APPROXIMATE U.S. COST*
CANCER	MUTATION / TARGET	DRUG CLASS (EXAMPLE)	OUTCOME	MONTHLY COST (APPROXIMATE)
 CML (Chronic Myeloid Leukemia)	 BCR-ABL	 Tyrosine Kinase Inhibitor (e.g., Imatinib)	 Transformational	\$200 – \$1,500/month (generic; brand) Historically > \$10,000/month ↓ LOWER COST
 EGFR-mutant NSCLC (Lung Cancer)	 EGFR mutation	 Tyrosine Kinase Inhibitors (EGFR inhibitors)	 Significant responses	\$18,000 – \$22,000/month ↑ HIGH COST
 ALK-positive NSCLC (Lung Cancer)	 ALK fusion	 Tyrosine Kinase Inhibitors (ALK inhibitors)	 Major benefit	\$20,000 – \$22,000/month ↑ HIGH COST
 HER2-positive breast cancer	 HER2 amplification	 Monoclonal Antibody (e.g., Trastuzumab) ± other agents	 Improved survival	\$4,000 – \$8,000/month (biosimilars generally less) ↓ MODERATE COST
 BRAF-mutant melanoma	 BRAF mutation	 Targeted Therapy (BRAF inhibitors)	 Rapid responses	\$28,000 – \$35,000/month combined ↑ VERY HIGH COST
 BRCA-associated cancers (Ovarian, Breast, Pancreatic, Prostate)	 DNA repair defects (BRCA1 / BRCA2)	 Targeted Therapy (PARP inhibitors)	 Meaningful benefit	\$16,000 – \$19,000/month ↑ HIGH COST



Costs are approximate wholesale acquisition costs in the U.S.



Actual patient costs vary based on insurance coverage, discounts, assistance programs, and country.



Targeted therapies can dramatically improve outcomes for the right patients with the right mutation.



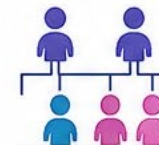
Ongoing research continues to expand the number of actionable targets and available therapies.

*Costs are approximate wholesale acquisition costs in the U.S. Actual patient costs vary based on insurance coverage, discounts, assistance programs, and country.



HEREDITARY CANCER SYNDROMES

Inherited gene mutations that increase the risk of developing certain cancers.



WHAT ARE THEY?

Caused by pathogenic variants in specific genes passed down from a parent.



WHO IS AT RISK?

Individuals with a family history of certain cancers, especially at young ages or in multiple relatives.



WHY IT MATTERS

Early identification allows for targeted screening, prevention, and personalized management.



WHAT CAN BE DONE?

Genetic counseling, testing, enhanced surveillance, risk-reducing strategies, and lifestyle modifications.

COMMON HEREDITARY CANCER SYNDROMES

BRCA1/BRCA2 Hereditary Breast and Ovarian Cancer Syndrome



GENES: BRCA1, BRCA2

INCREASED RISK:

- Breast cancer
- Ovarian cancer
- Prostate cancer
- Pancreatic cancer
- Melanoma (BRCA2)



Lynch Syndrome (HNPCC)



GENES: MLH1, MSH2, MSH6, PMS2, EPCAM

INCREASED RISK:

- Colorectal cancer
- Endometrial cancer
- Ovarian cancer
- Stomach cancer
- Small intestine cancer
- Urinary tract cancers
- Others



Familial Adenomatous Polyposis (FAP)



GENE: APC

INCREASED RISK:

- Colorectal cancer (nearly 100% if untreated)
- Duodenal cancer
- Thyroid cancer
- Desmoid tumors



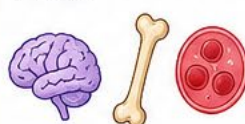
Li-Fraumeni Syndrome (LFS)



GENE: TP53

INCREASED RISK:

- Soft tissue sarcoma
- Breast cancer
- Brain tumors
- Adrenocortical carcinoma
- Leukemia
- Others



Cowden Syndrome (PTEN Hamartoma Tumor Syndrome)



GENE: PTEN

INCREASED RISK:

- Breast cancer
- Thyroid cancer
- Endometrial cancer
- Colorectal cancer
- Renal cell carcinoma
- Melanoma



Multiple Endocrine Neoplasia Type 1 (MEN1)



GENE: MEN1

INCREASED RISK:

- Parathyroid tumors
- Pancreatic neuroendocrine tumors
- Pituitary tumors
- Adrenal tumors



Peutz-Jeghers Syndrome (PJS)



GENE: STK11

INCREASED RISK:

- Gastrointestinal polyps and cancer
- Pancreatic cancer
- Breast cancer
- Gynecologic cancers



WARNING SIGNS SUGGESTING A HEREDITARY SYNDROME

- ✓ Multiple relatives with the same or related cancers
- ✓ Cancers diagnosed at a young age (before 50)
- ✓ Multiple primary cancers in the same individual
- ✓ Rare cancers (e.g., ovarian, pancreatic, sarcoma, male breast)
- ✓ Three or more relatives with cancer on the same side of the family



Personalized cancer screening and early detection



Risk-reducing options and prevention



Informed family planning and testing for relatives



Improved outcomes and peace of mind



KNOW YOUR FAMILY HISTORY. TALK TO YOUR DOCTOR. CONSIDER GENETIC COUNSELING.



Knowledge today, healthier tomorrow.