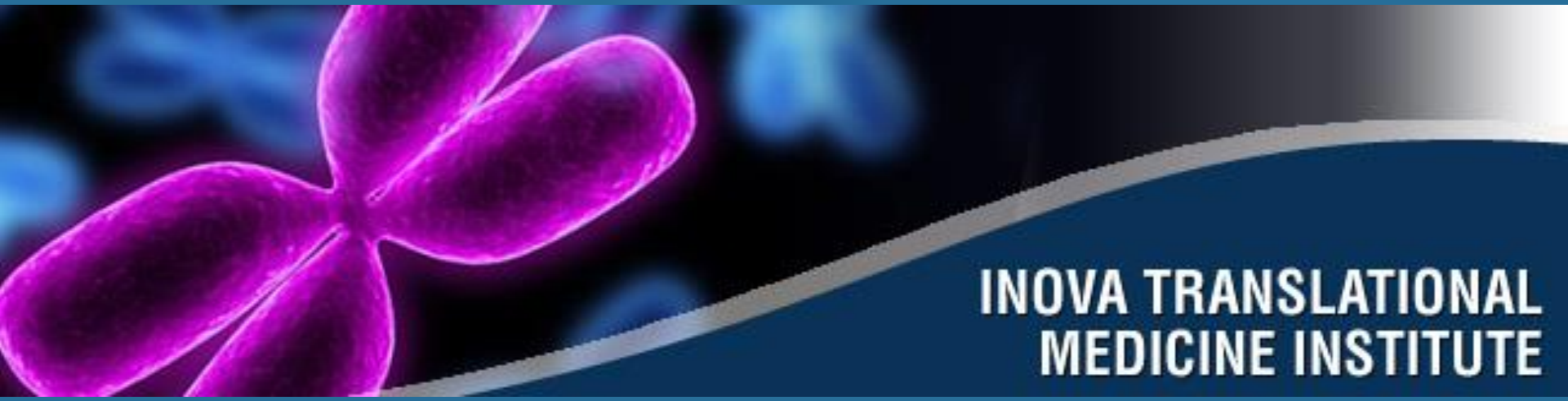
Role of Genetics in Cancer Control and Public Health



— individualized care through science and technology

20th Annual Maryland Council on Cancer Control Conference

November 19, 2013

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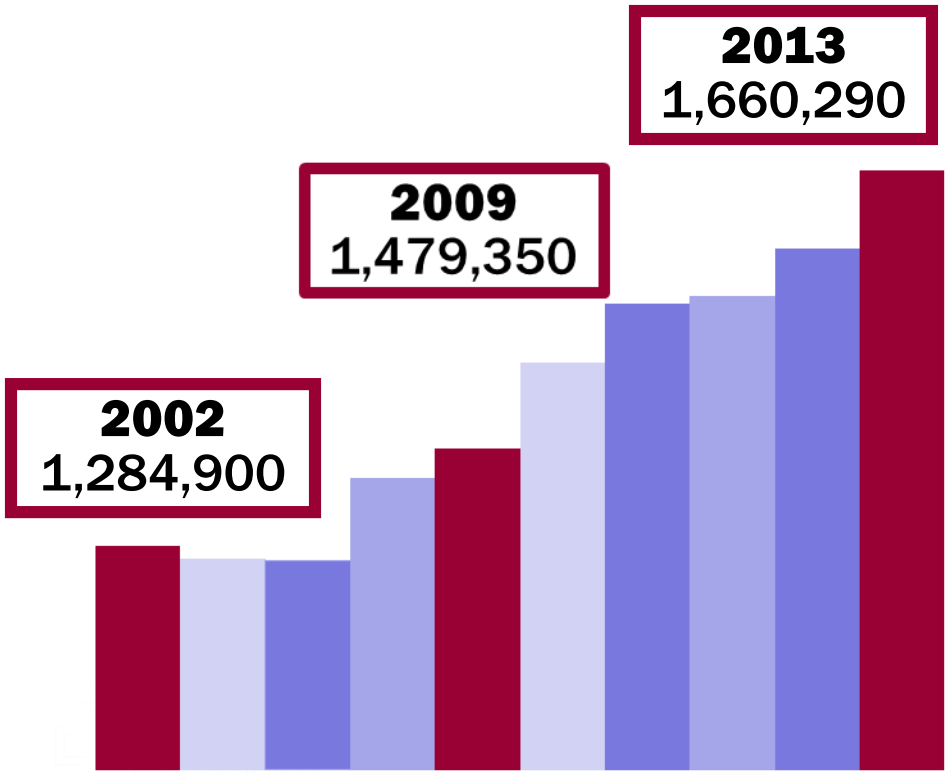
Why What We Are Doing is So Important

Human and Economic Burden of Cancer



Estimated # of New U.S. Cancer Cases

- **1,660,290** Americans will be diagnosed in 2013
- **580,350 are expected to die of cancer in 2013**
- More than 1,600 people a day die from cancer
- **Cost of cancer care was $157 billion in 2012**
- Second most common cause of death

Cancer Cases Are Rising Globally

- Today, more than half of new cancer cases and nearly two-thirds of cancer deaths occur in the low income, lower middle income, and upper middle income countries of the developing world
- **By 2030, the developing world is expected to bear 70% of the global cancer burden**

Data Source: "Breakaway: The Global Burden of Cancer — Challenges and Opportunities," Economist Intelligence Unit, 2009

A Transformation in Medicine

Chronic Diseases Account for >65% of Health Care Costs.

Aging Population

- The fastest growing component of the U.S. population is the age group > 75 years.
- Those > 65 years are more likely to have more than one chronic disease problem.

Life Style and Behavior

- Chronic diseases often share man-made causes – tobacco, obesity, substance abuse and inactivity.

Health Disparities

- Chronic diseases are often a greater burden in the poor and less educated population
- Access to care will be an increasing determinant of cost and of disease mortality

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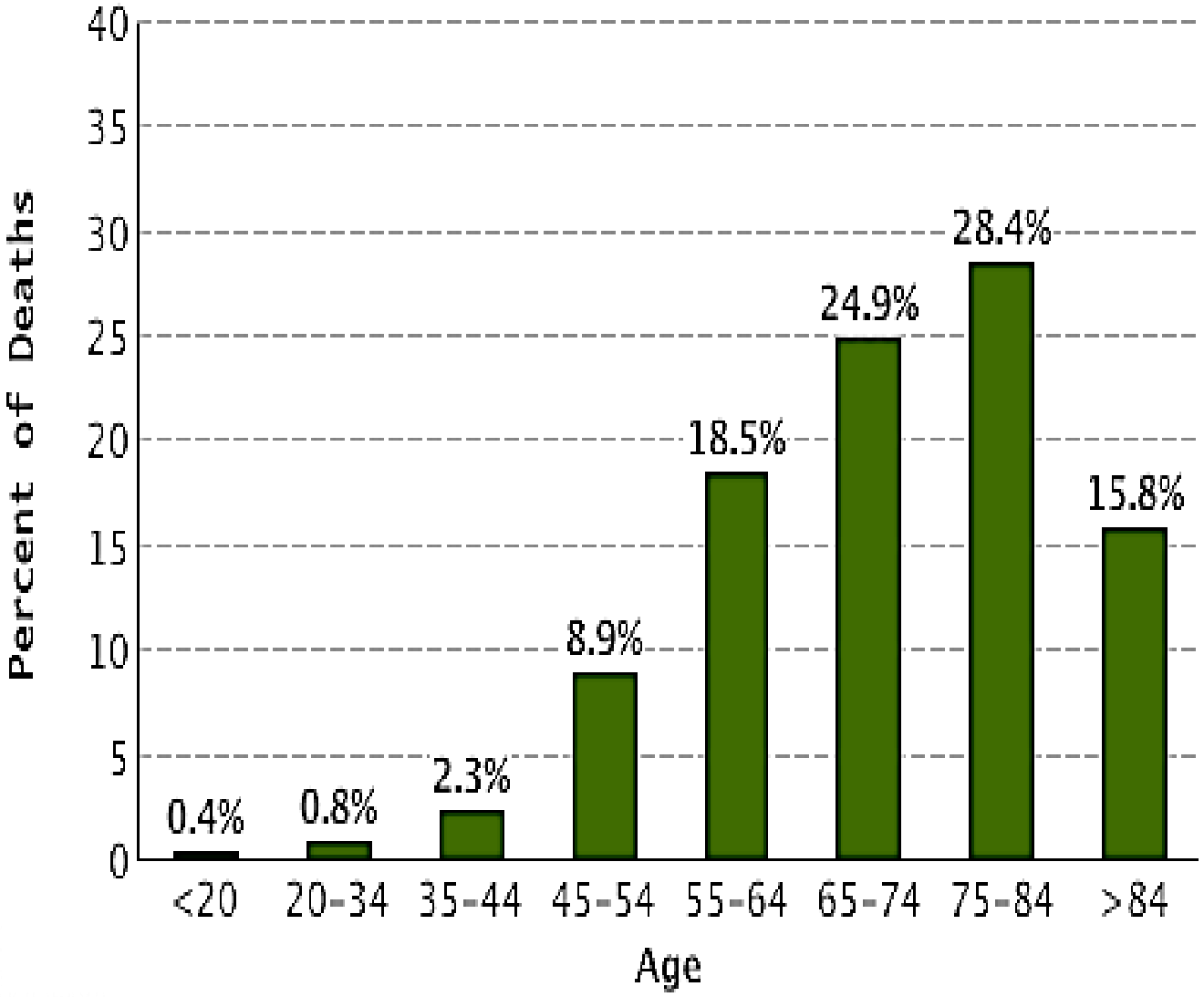
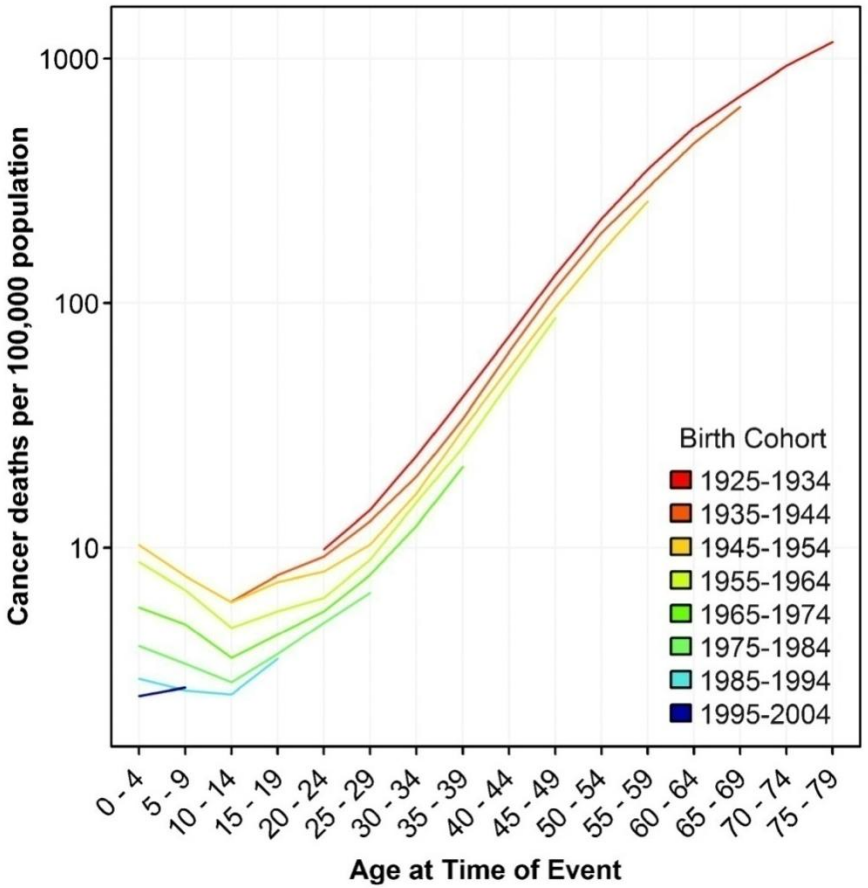
All-Site Cancer Death Rates by Age



Source: SEER, 2006-2010, All Races, Both Sexes

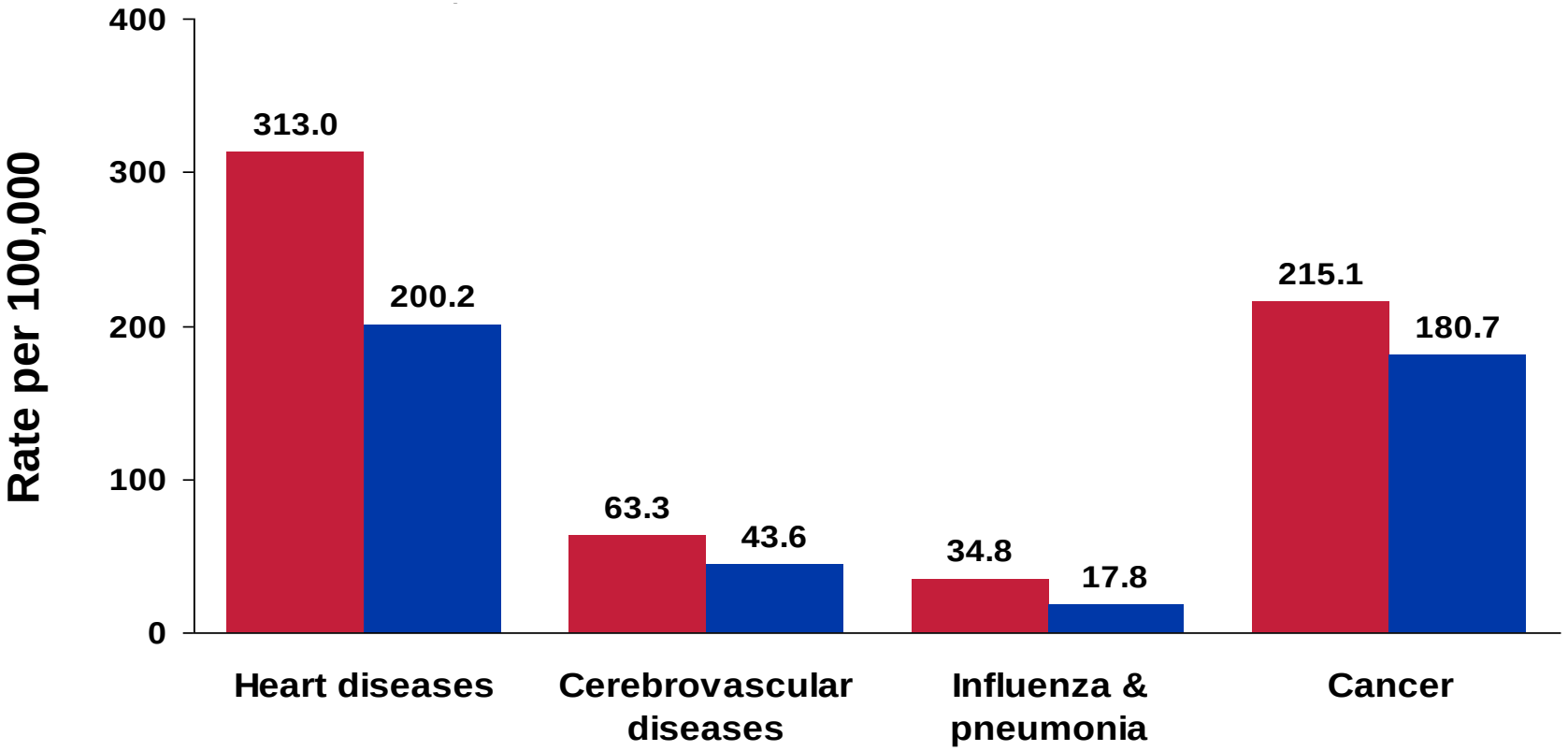
All-Site Cancer Rates in Successive Birth Cohorts by Age of Death



- Mortality rates for cancer in the U.S. have declined over past 50 years despite relatively stable incidence (except lung cancer)
- Declines suggest that better cancer detection, treatment and prevention have been effective
- **Effects may be even larger than currently observed**; cancer death rates at every age have been successively lower for each generation since 1925
- As younger groups age, their lower death rates will greatly impact (reduce) age-adjusted death rates utilized to mark our progress against cancer

Kort, E. J. et al. Cancer Res 2009;69:6500-6505

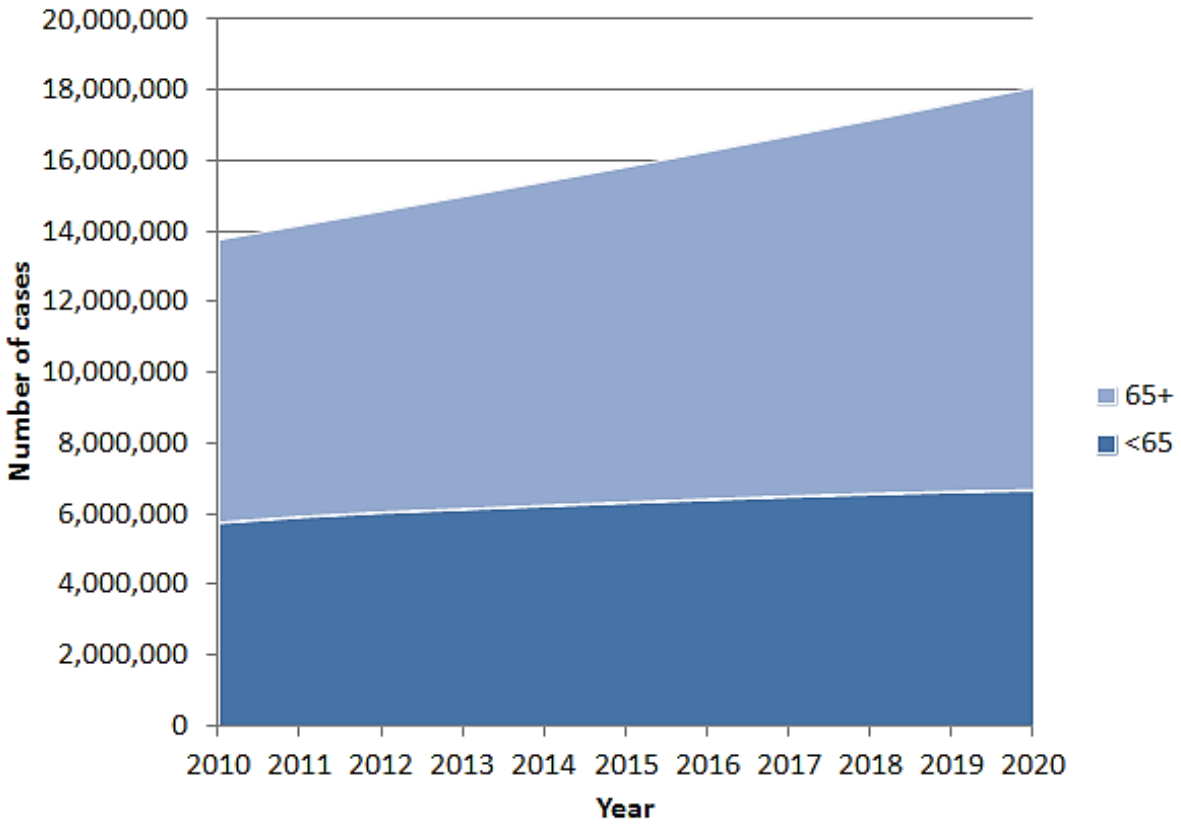
Declining U.S. Mortality Rates from 1991-2006



Rates are age-adjusted to 2000 U.S. standard population

U.S. mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention, 2009

Growth in the Population of Cancer Survivors by Age



Forsythe et al., Abeloff's Clinical Oncology 5th ed., 2013

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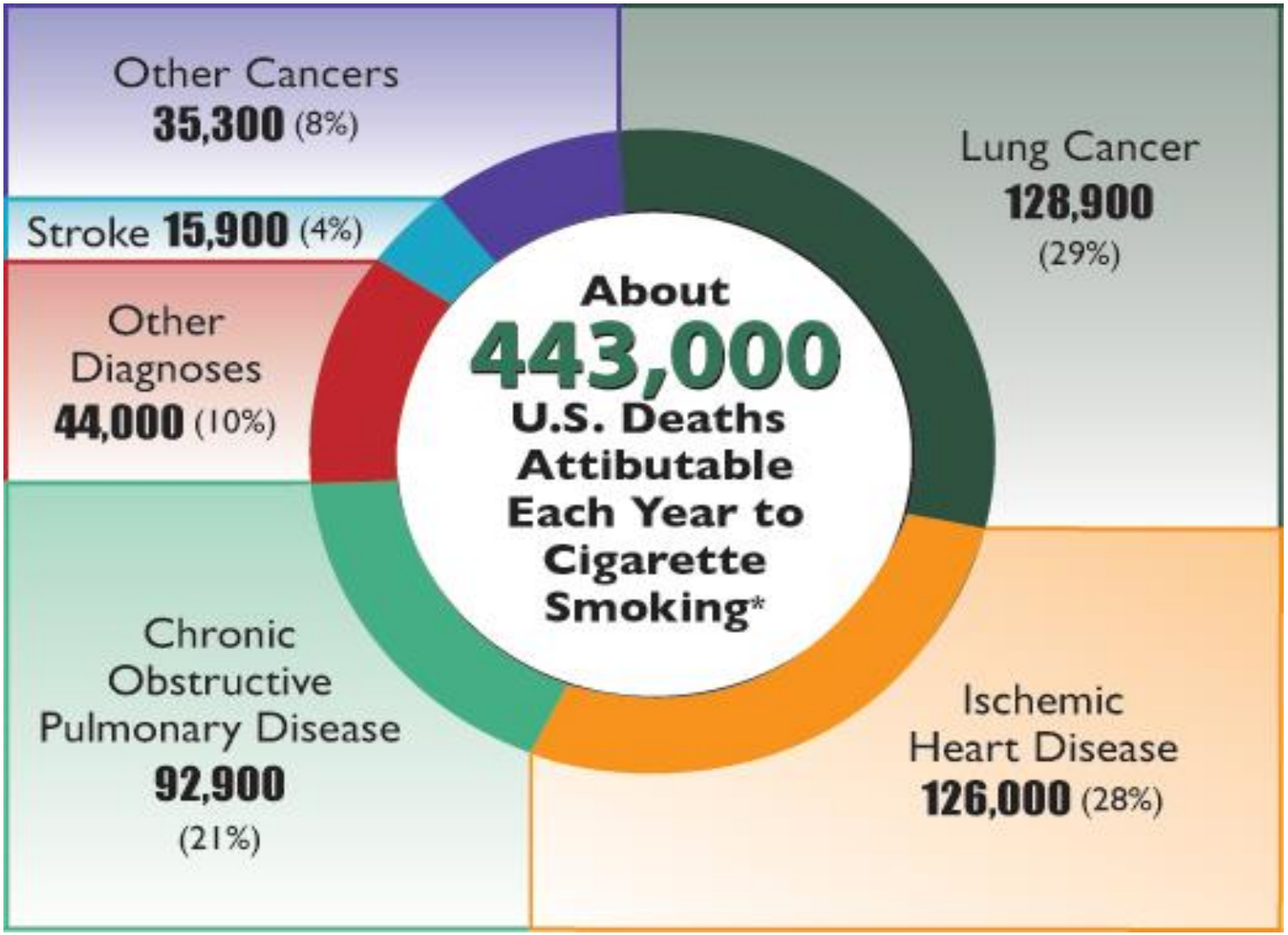
Annual Deaths Attributed to Tobacco



Center for Disease Control and Prevention, U.S. 2000-2004

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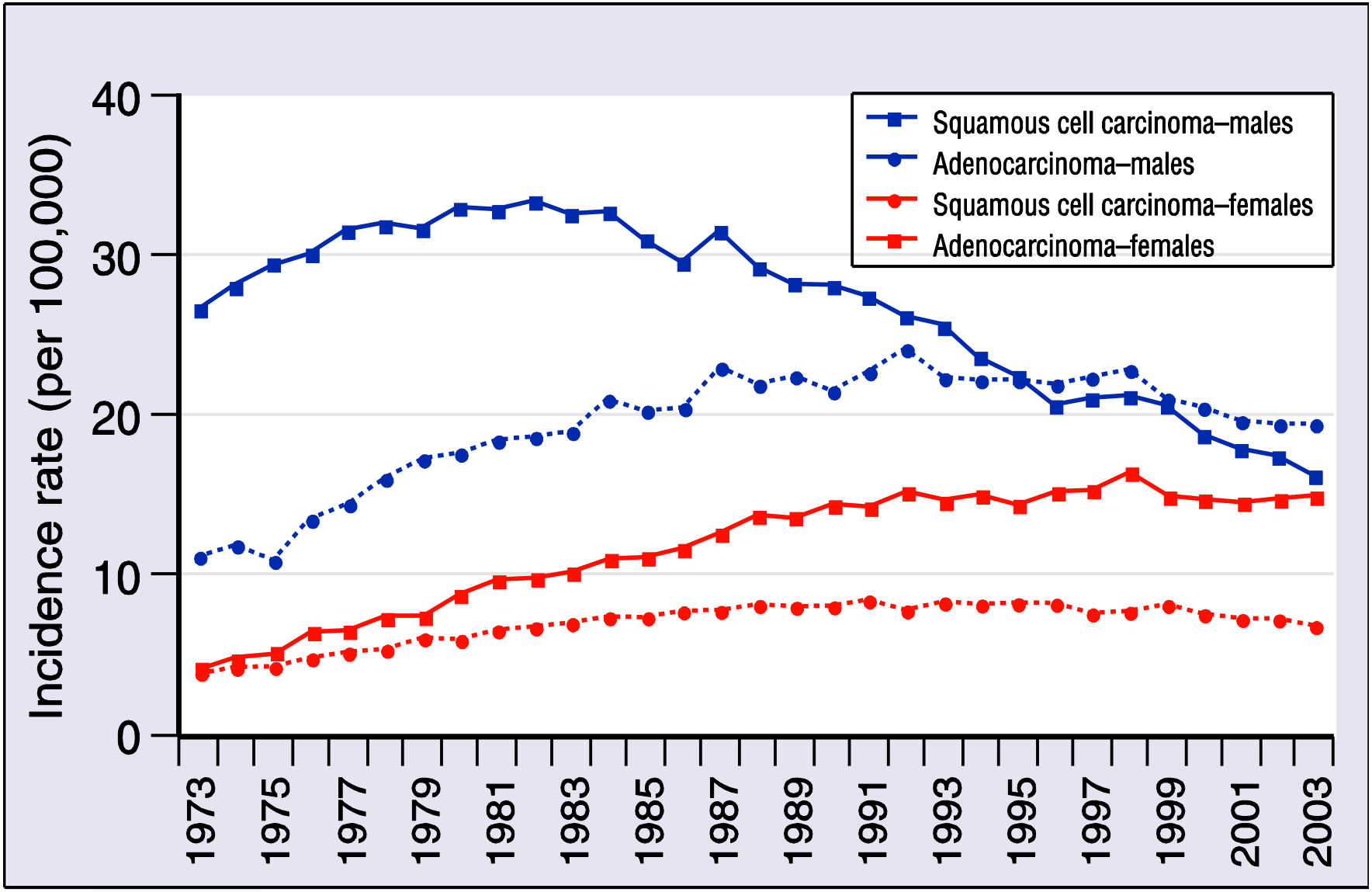
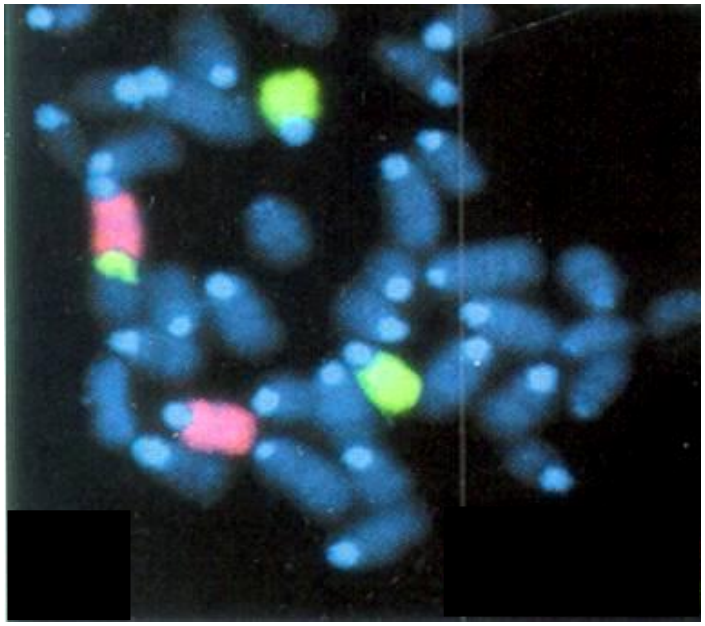
Age-Adjusted NCI SEER Lung Cancer Incidence



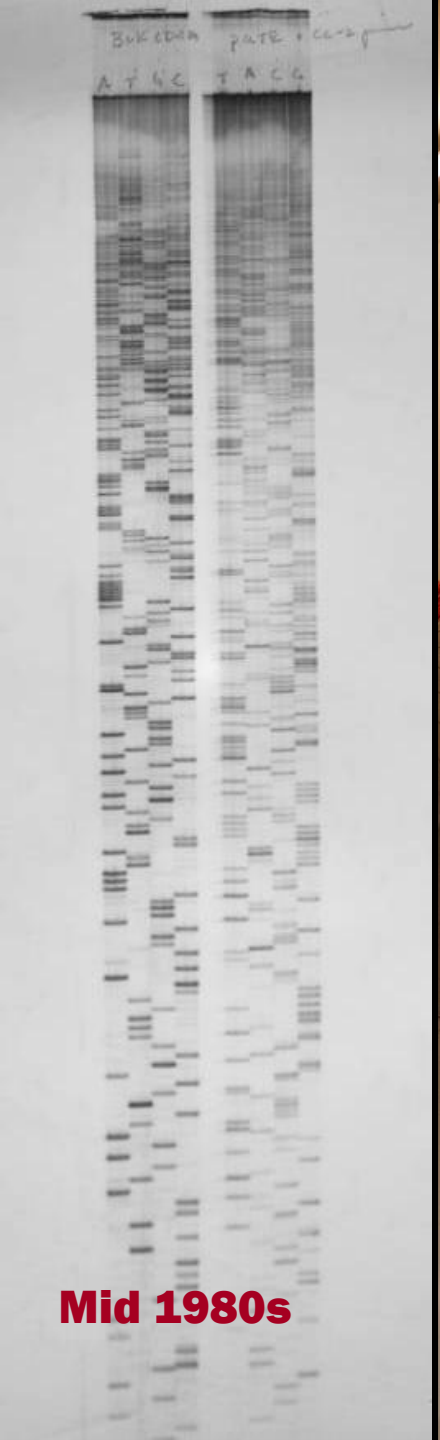
Cancer is a Disease of the Genome

It arises from changes within the DNA of our cells during their lifespan

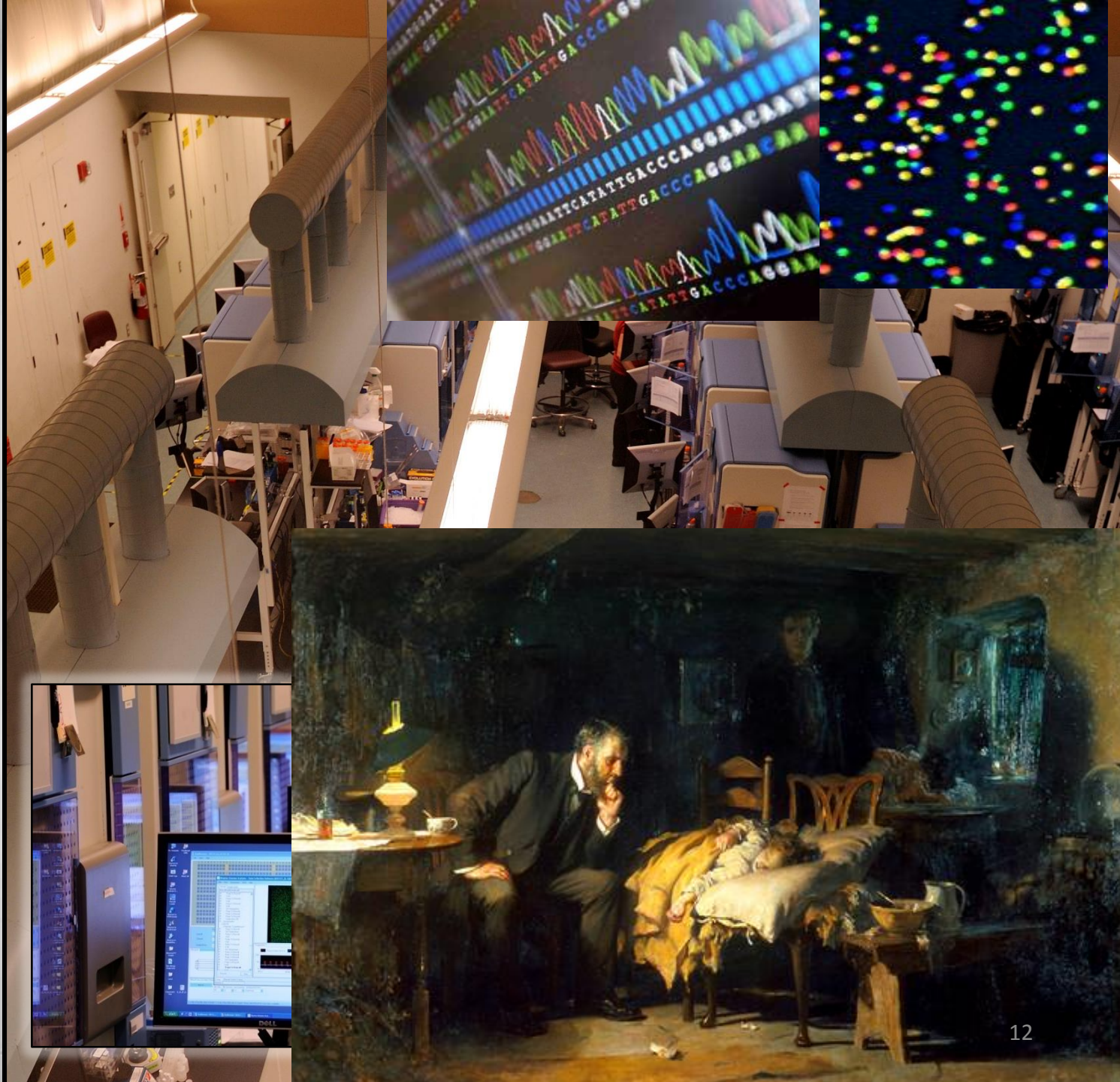


- Deletions
- Amplifications
- Mutations
- Translocations
- Epigenetic changes

- **Transcriptional/translational regulation**

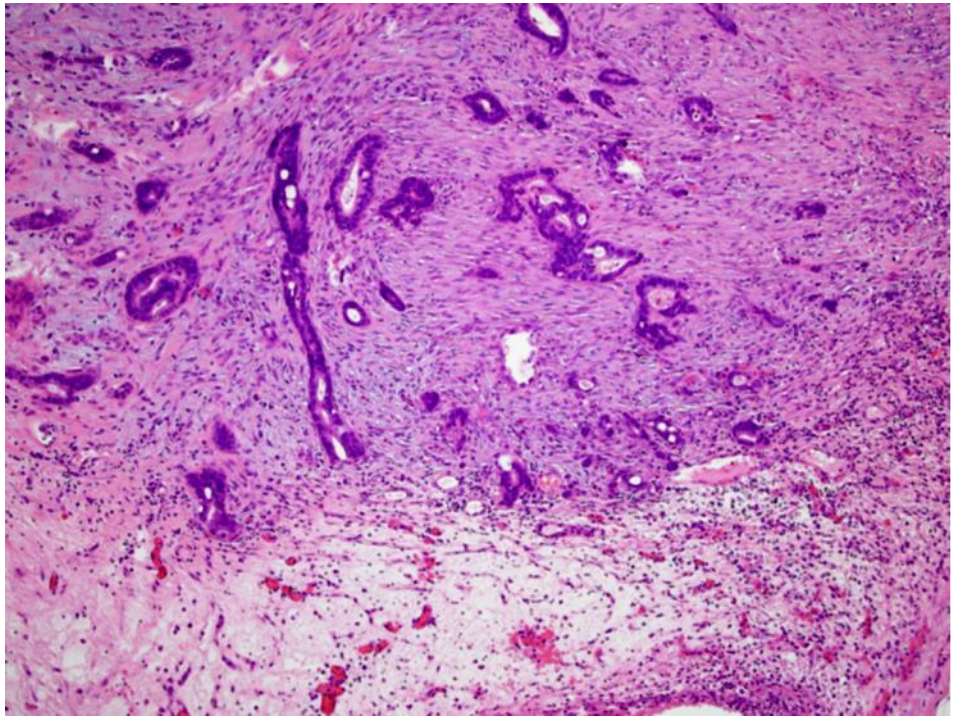


Mid 1980s



Tumors as "Organ" Systems

Tumors are more than just a mass of cancer cells.



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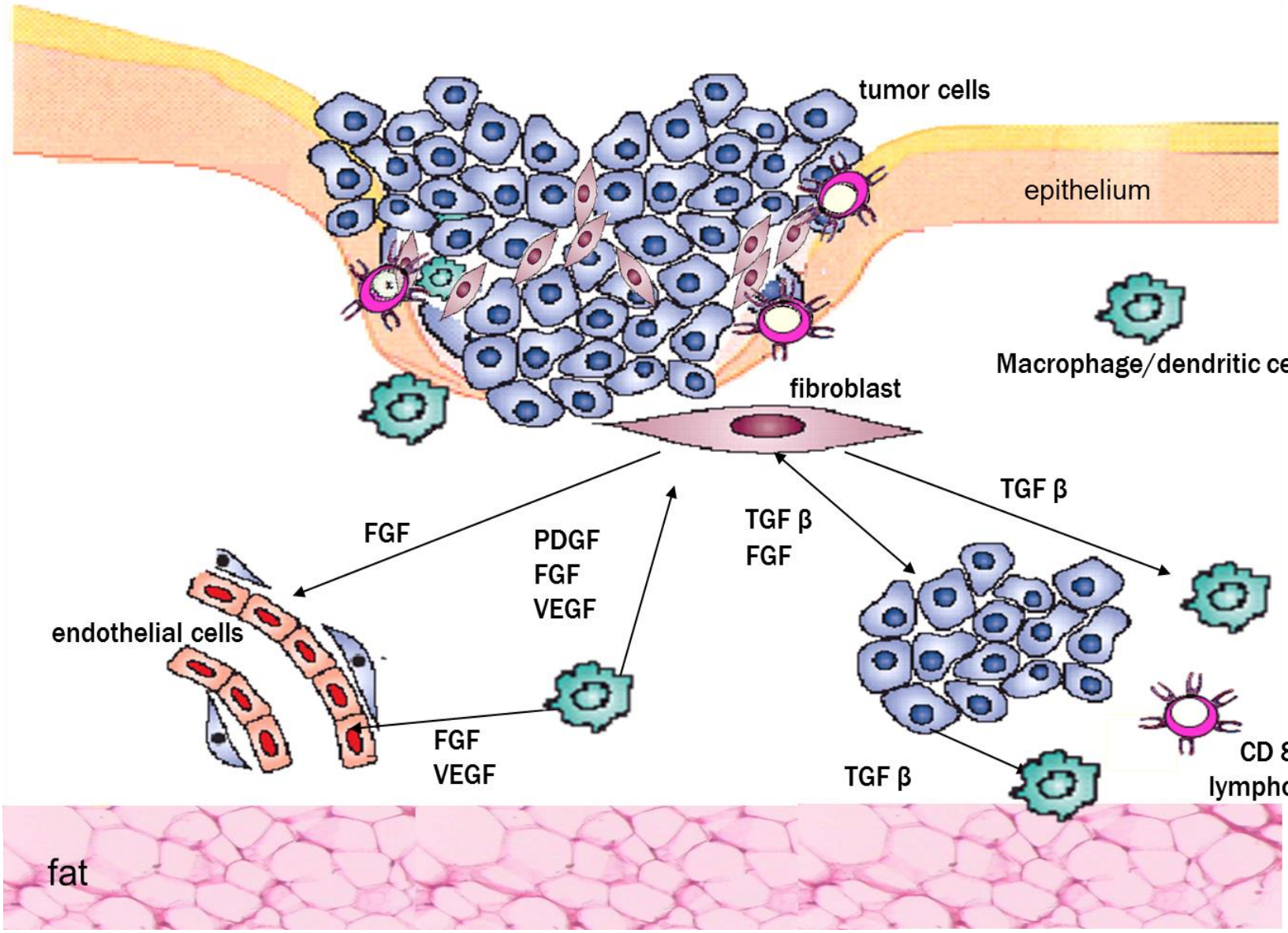
Tumors as "Organ" Systems



Individualized Cancer Care

Today - some thoughts regarding Genomics and Cancer.

- Determining risk
- Managing risk
- Noval molecular targets
- Pharmacogenomics
- Each cancer an N of 1

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Translational Science: The Paradigm Shift

The 20th Century Paradigm:

Organ site-based, single agent based trials

- Reactive
- Based on gross differences
- Toxic (MTD/DLT)
- Emerging resistance
- Poor life quality

Research

- Human genome
- Genomics
- Proteomics
- Immunology
- Mechanisms
- Rational design

The New Paradigm:

Multiple, highly targeted agents matched to molecularly selected patients

- Proactive
- Rational/targeted
- Less toxicity
- Biomarker endpoints (subcellular target imaging)
- Significant savings of cost and time

21st Century Cancer Science

Creating the repair manual.

- Derive a functional understanding of the causal defect/dependance; e.g. Wnt, P13K, NF-kB…
  - ✓ Distinguish passenger defects from true drivers.
- Determine dependence of cancer cells and micro-environment cells on genes that are amplified, translocated, mutated or epigenetically altered.
  - ✓ "Oncogene addiction"
- Find genes to which cancer cells are addicted but that are not mutated, translocated or amplified.
  - ✓ "Non-oncogene addiction"

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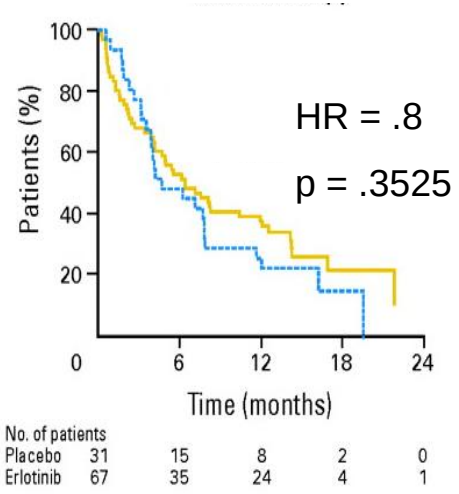
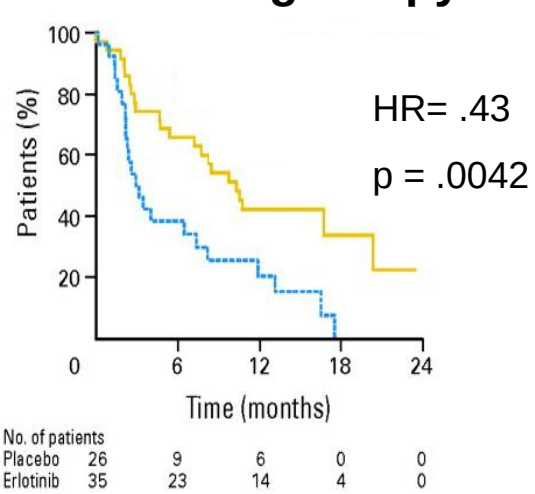
Kaplan-Meier Survival Curves According to EGFR Copy Number and Impact of Erlotinib

EGFR Low Copy Number



EGFR High Copy Number

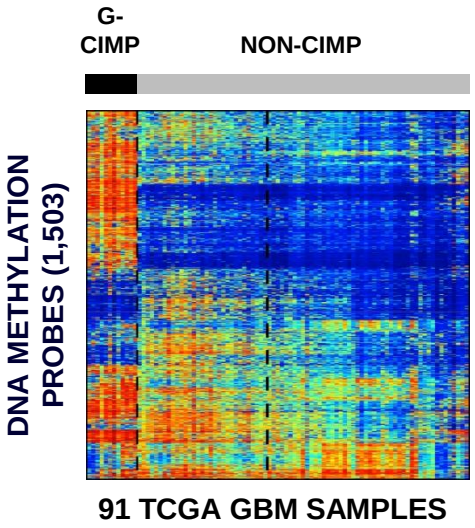


Erlotinib

Placebo

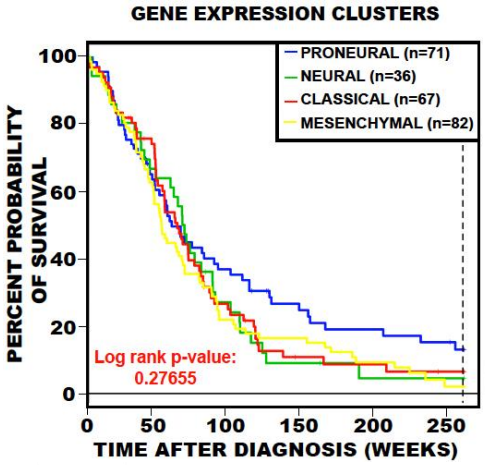
Zhu, C.-Q. et al. J Clin Oncol; 26:4268-4275 2008

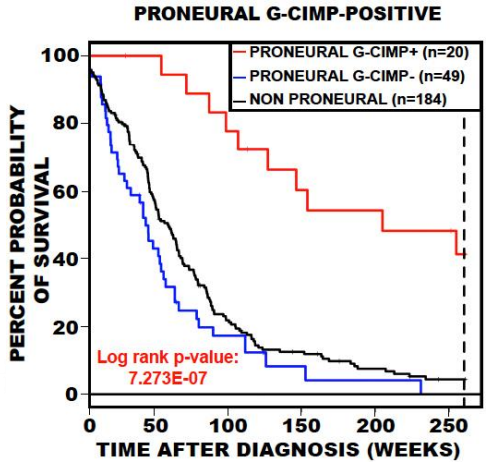
GBM: CpG Island Methylator Phenotype Linked to *IDH1* Mutation and Better Survival



G-CIMP.....

- Occurs in Younger Patients
- Is a Subset of Proneural Expression Subtype
- Is Associated with Better Survival
- Is More Frequent in Low-Grade Gliomas
- Is Not Associated with *MGMT* Methylation
- Is Tightly Linked to *IDH1* Mutation

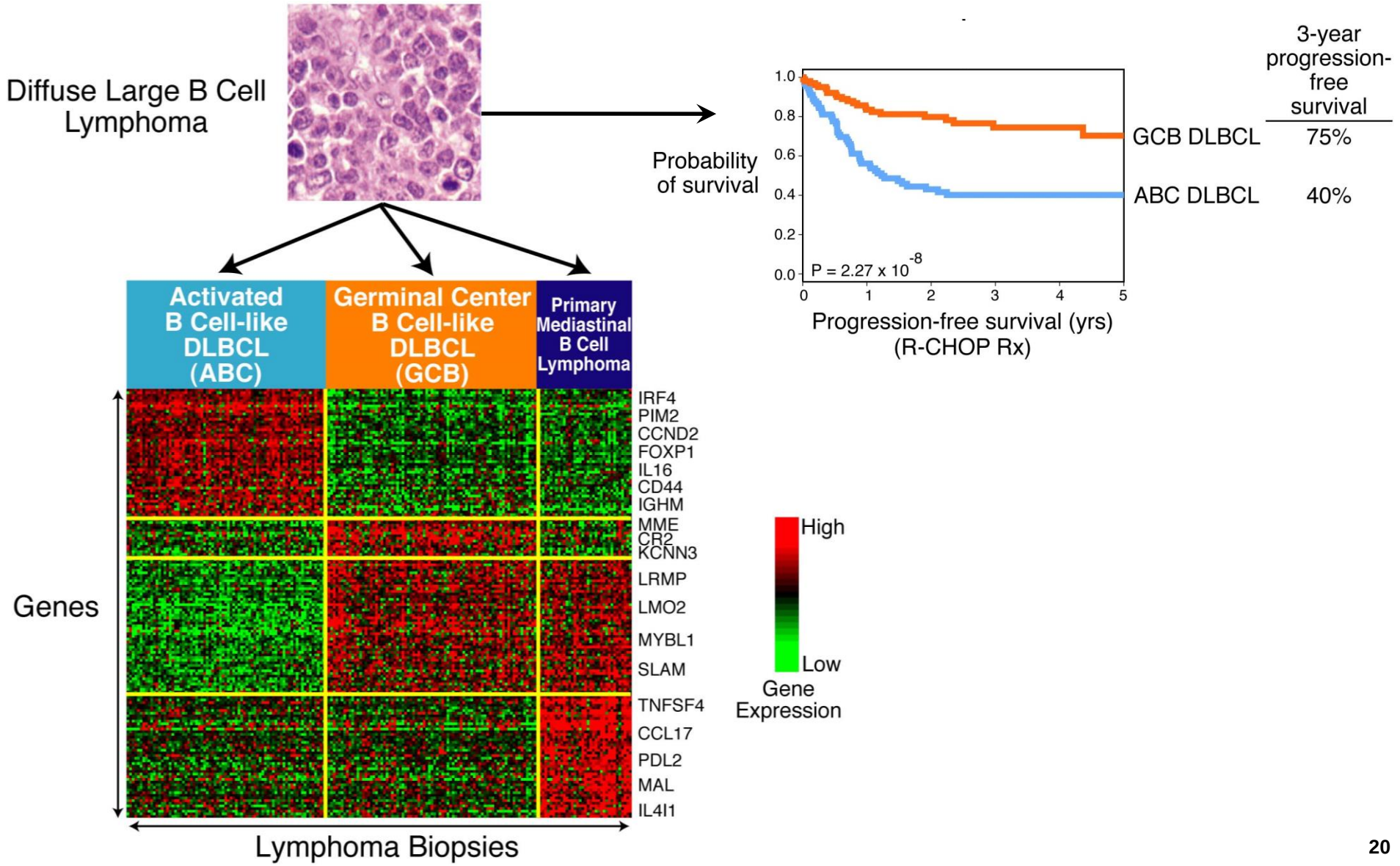




ALL TUMORS		G-CIMP		TOTAL
		–	+	
IDH1	Wild-type	184	5	189
	Mutant	0	18	18
TOTAL		184	23	207

Noushmehr et al. (2010) Cancer Cell, Online

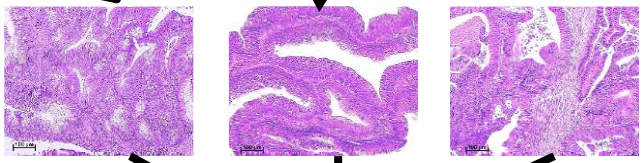
Dissecting Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling



Individualized Cancer Therapy

Same Organ Site

Today



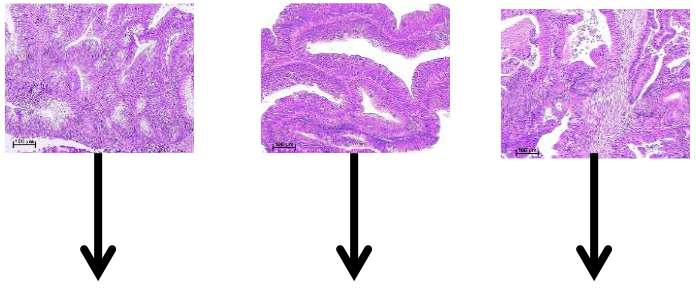
Pt. #1 #2 #3

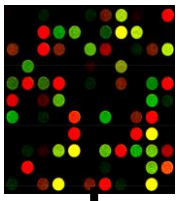
Standard Therapy

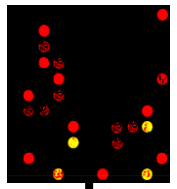
1 in 3 Patients Benefit

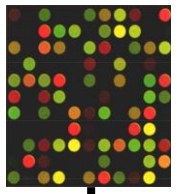
Research
- Genomics
- Proteomics
- Immunology
- Mechanisms
- Rational drug design

Future

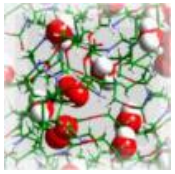








Therapy 1 Therapy 2 Therapy 3



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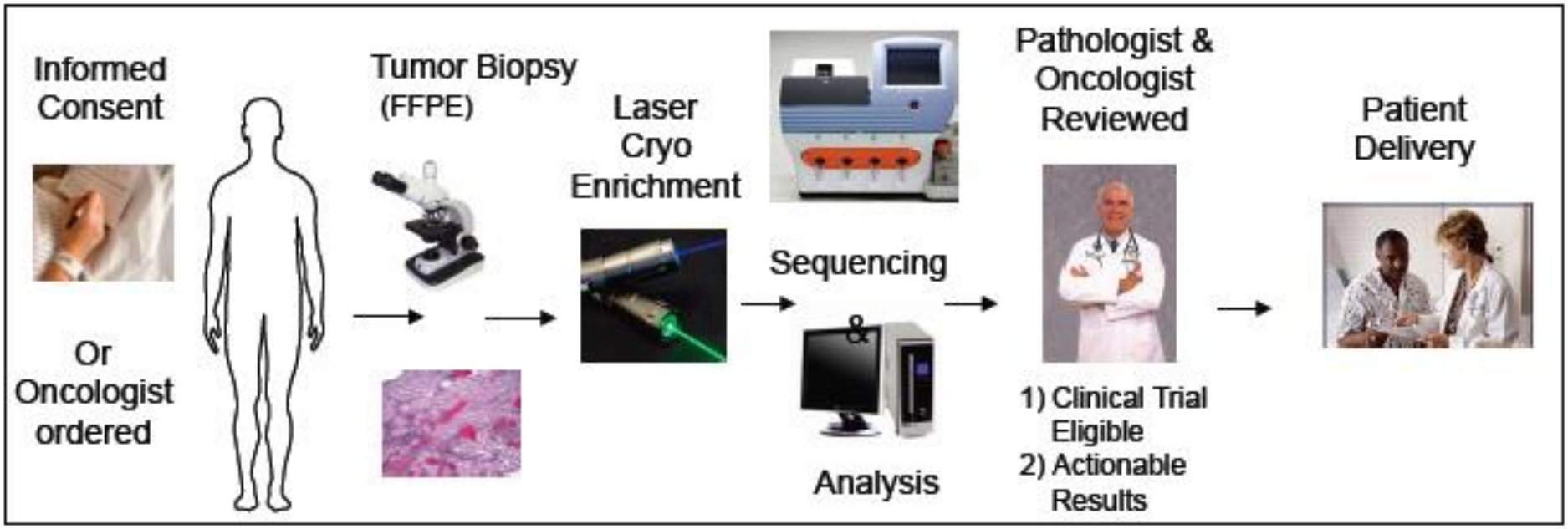
Cancer Diagnosis and Treatment



- **Service offered through three commercial vendors and several academic centers.**
- **Used to diagnose and direct therapy based on genomic identification of biomarkers & targets.**

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ITMI Genomics Data Base

- **Maternal-child genomic studies >2000 families.**
- **WGS @ >40X of mother, father and newborn.**
- **SNP, CNV, SV.**
- **RNAseq expression, CpG methlylation.**
- **Clinical study specific data and eHR information.**

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Cancer Susceptability Genes

Germline Variations Impacting Cancer Predisposition.

- **WGS from ancestrally-diverse cohort of 681 healthy adults – negative pers./fam. Hx.**
- **Profiled nonsynonymous variation in 158 genes causally implicated in cancer.**
- **Selected five genes for in depth analysis *BRCA1, BRCA2, KRAS, TP53, and PTEN.***

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Cancer Susceptability Genes

Germline Variations Impacting Cancer Predisposition.

- 2,688 distinct genetic variants identified within the cohort.
- All individuals carry variants that may impact cancer susceptibility.
- Average of 68 variants per individual.
- Most variants are very rare with 75% found in only one or two individuals.
- Allele frequencies vary between ancestral groups.

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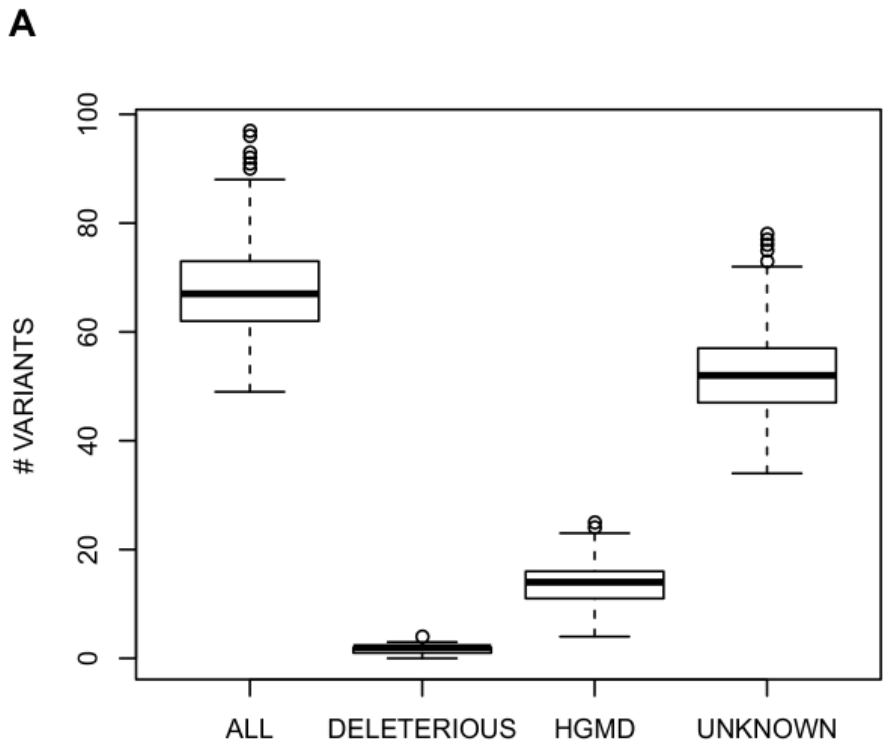
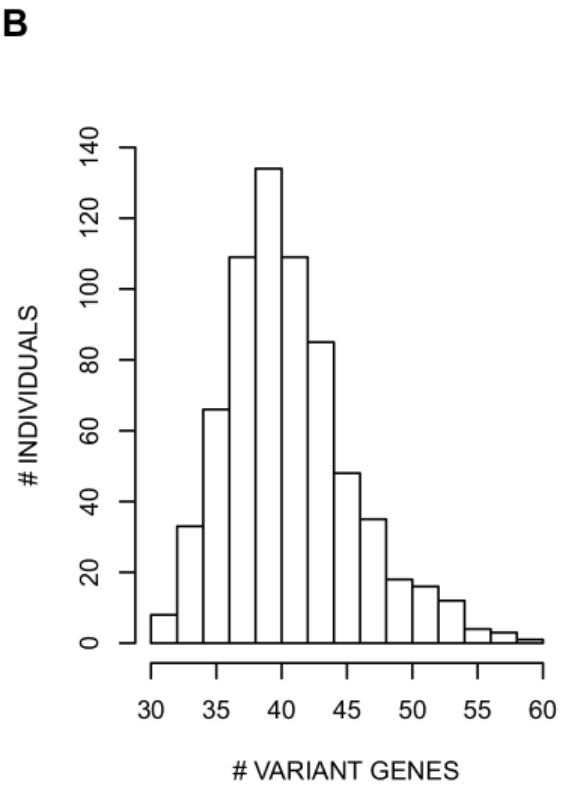
Cancer Susceptability Genes

Germline Variations Impacting Cancer Predisposition.





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Cancer Susceptibility Genes

Ancestry-based subpopulations in study.

Subpopulation	# Individuals
African	43
African-European	46
Central Asian	50
East Asian	62
European	331
Hispanic	118
Other	31
	681

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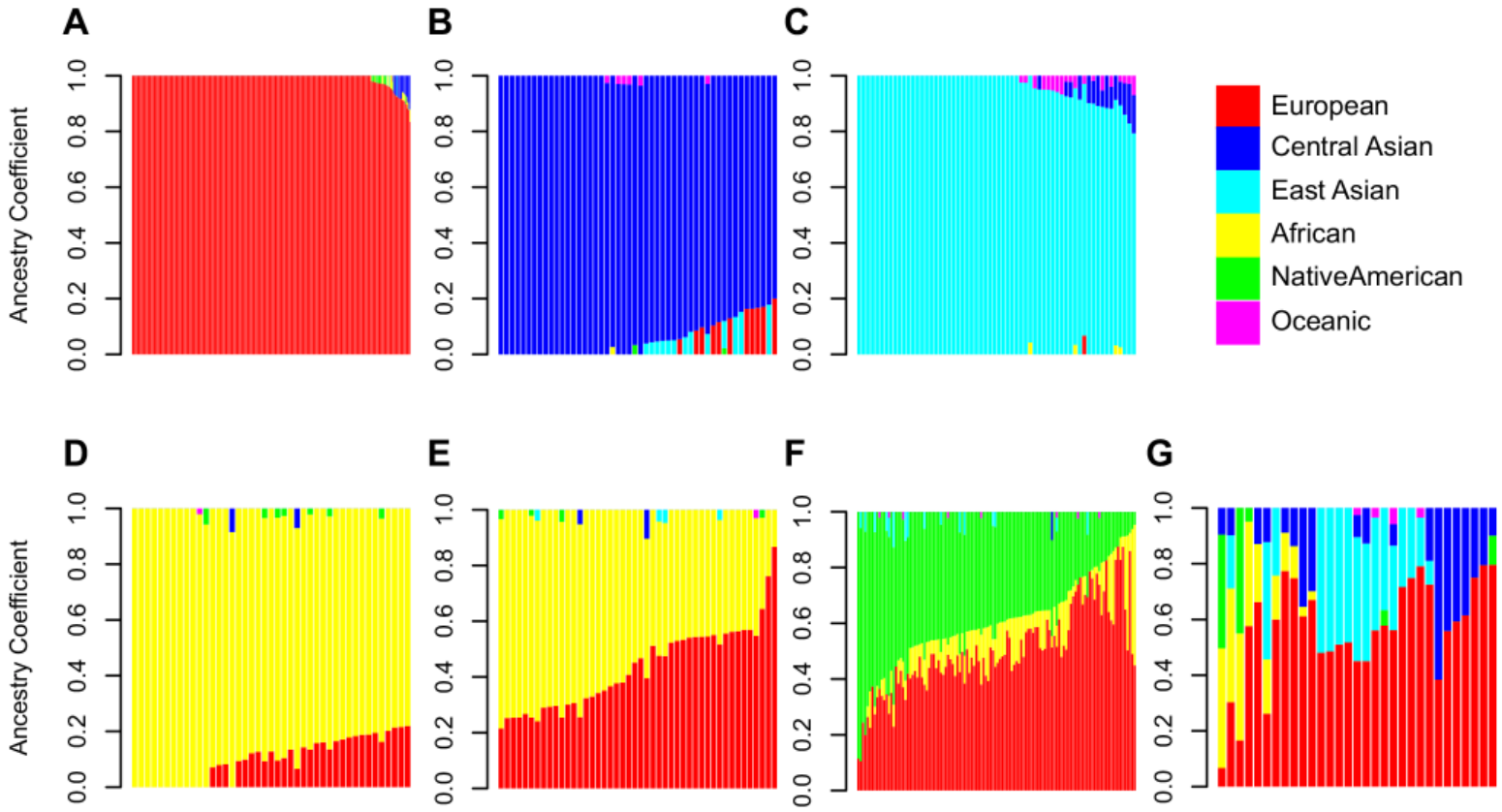
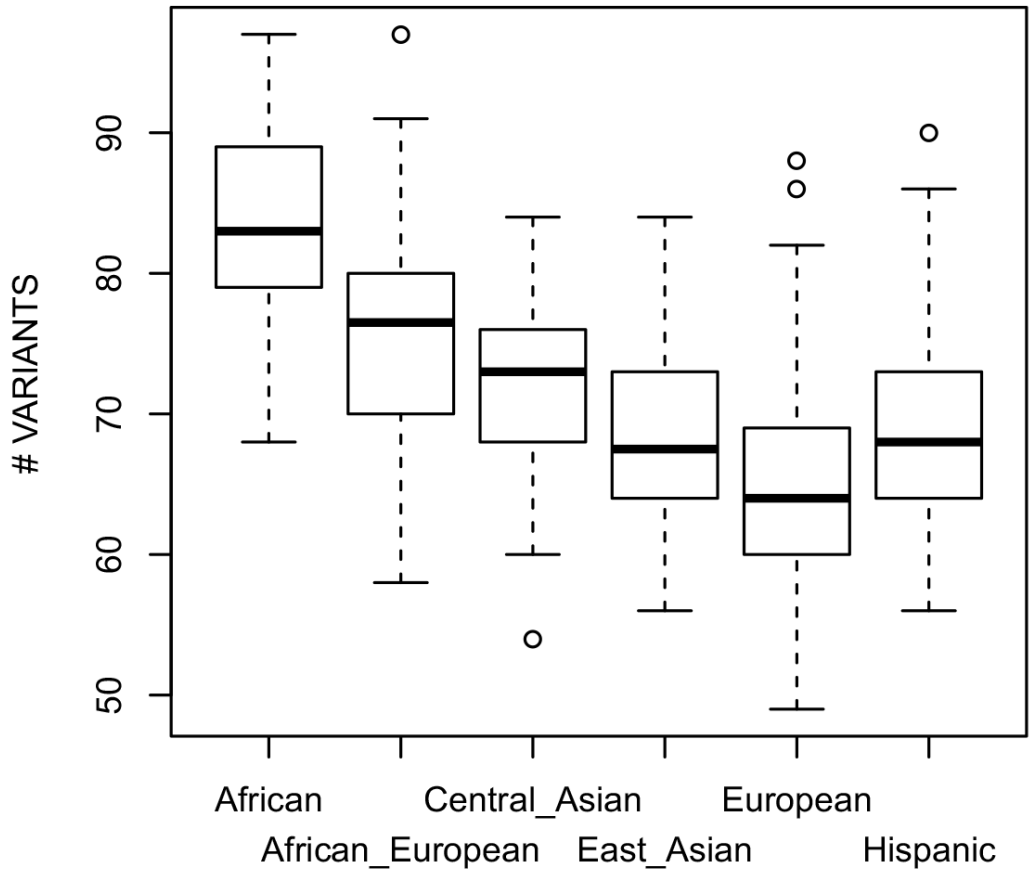
Cancer Susceptability Genes

Germline Variations Impacting Cancer Predisposition.



Cancer Susceptability Genes

Germline Variations Impacting Cancer Predisposition.



ITMI Genomics Projects

Importance of Ancestral Specific Reference Genomes in Genomic Medicine.

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The Reference Genome

- The information used in whole genome sequencing to assemble a person's sequence information into a complete genome. (ncbi37)
- The reference genome is the basis for identifying relevant variants in a person's genome.
- It directly impacts the ability to determine the disease-causing mutations.
- The NIH reference genome is not suited to medically relevant sequencing.

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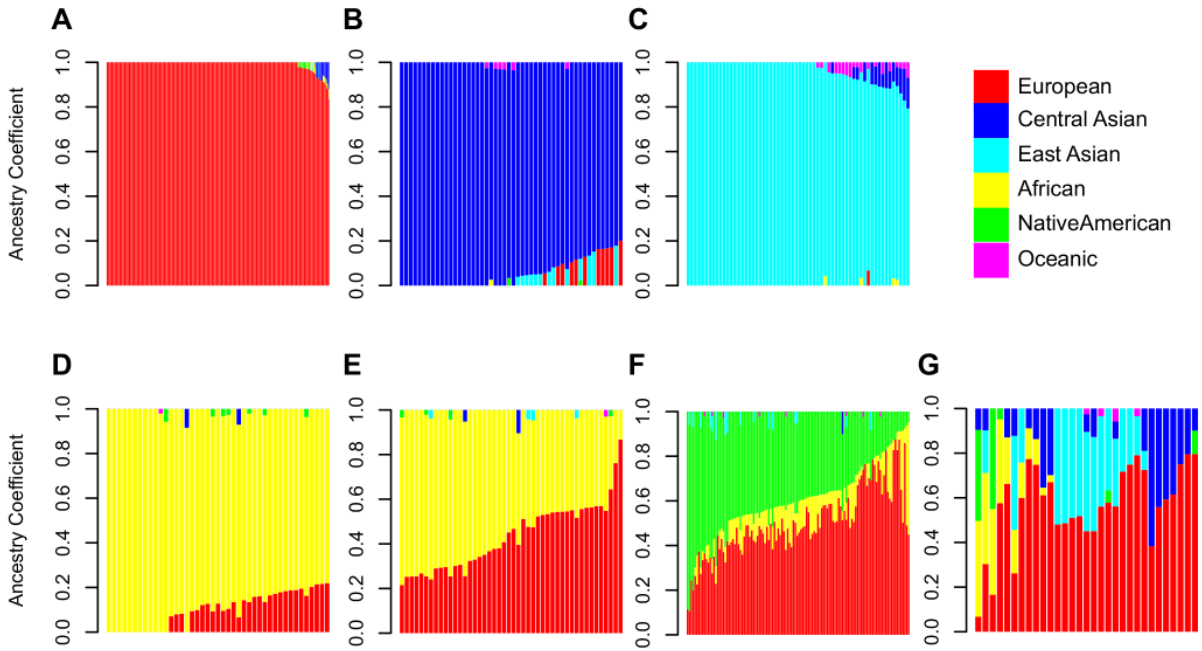
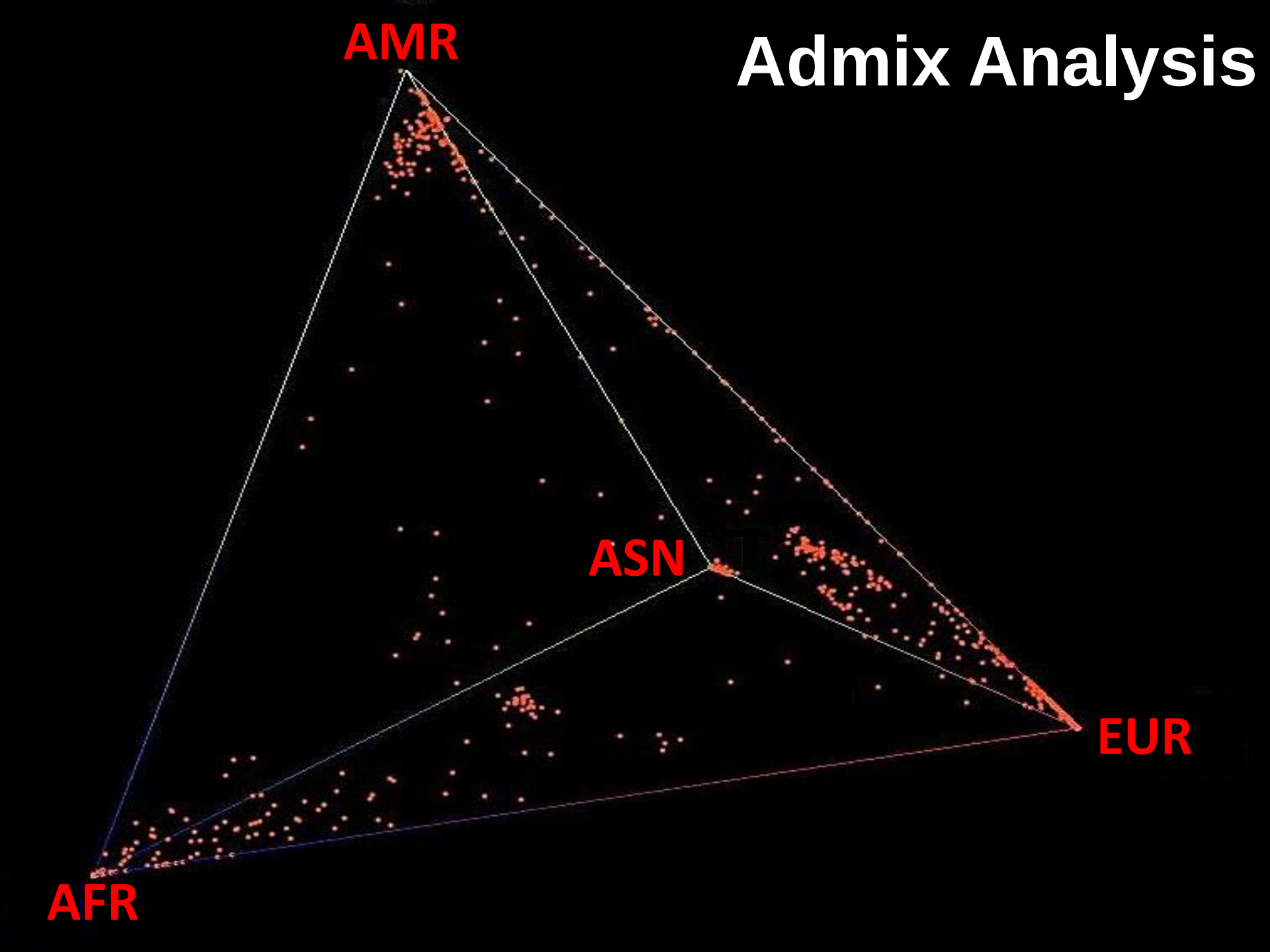
Admix Analysis



Build 37 Reference Genome

Donors were recruited by advertisement in *The Buffalo News*, on Sunday, March 23, 1997. DNA was extracted from the blood of 10 male and 10 female volunteers. About 80 percent of the reference genome came from eight people and one male individual accounts for 66 percent of the total reference genome.


AMR
Admix Analysis
ASN
EUR
AFR

Pre-Term Birth: Country of Birth

- Country of Birth = 79
- Ancestry currently not used in WGS assembly

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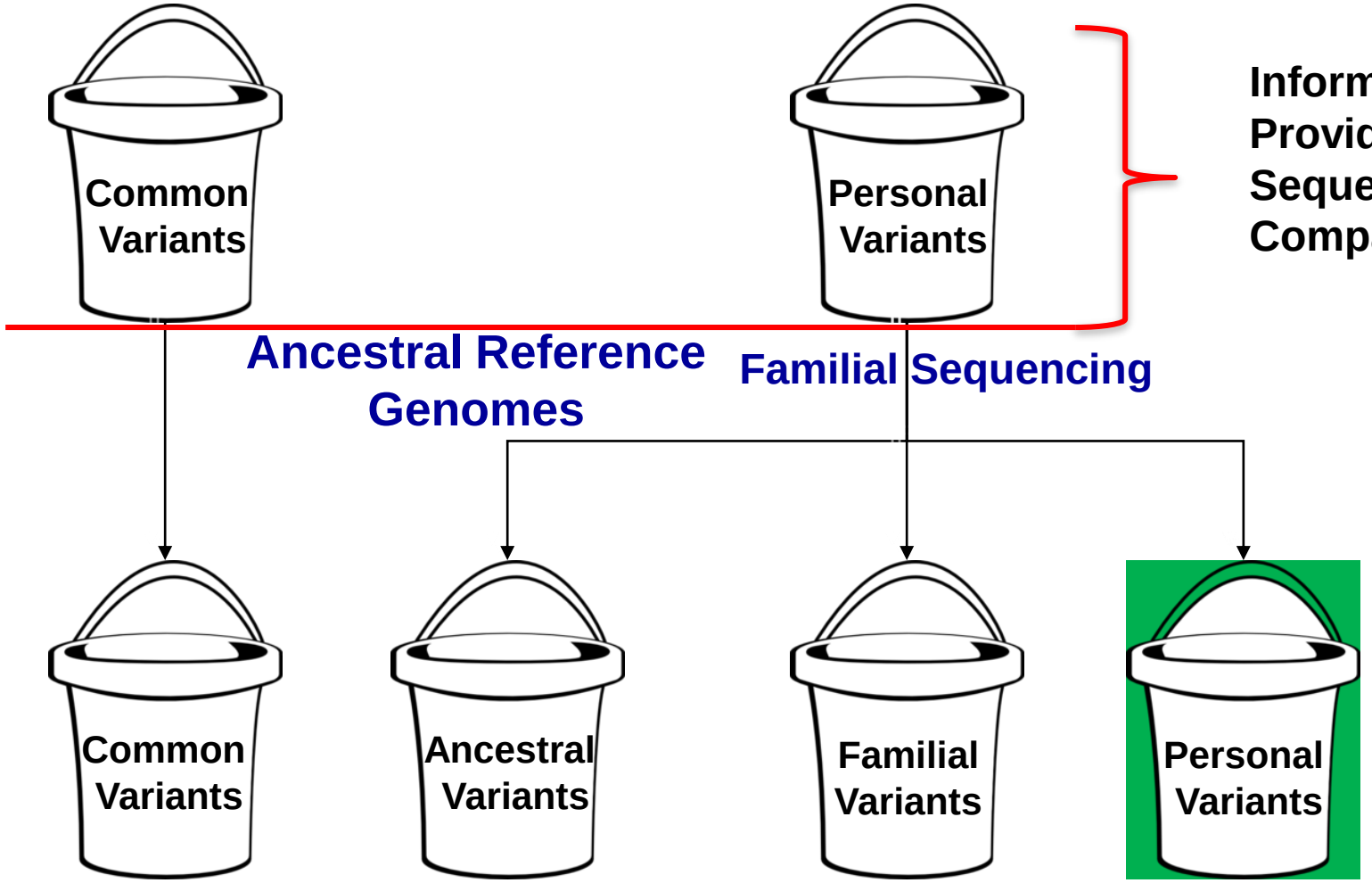
Re-distribution of Personal Variants



Genomic Medicine Today

- **Medicine in a reactive discipline, while genomic medicine focuses on prediction (risk) and prevention.**
- **Pharmacogenomics and cancer genomics lead the field in utility.**
- **Through analysis of WGS data we can screen for many actionable genomically based alterations:**
  - **germline cancer predisposition genes, metabolic defects, autism, childhood obesity, cardiovascular disease risk.**
- **Sequence banking will be common practice.**

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Genomic Medicine: Pharmacogenomics

Gene	Total Drugs	Drugs in Key Service Lines	Oncology Drugs	Cardiovascular Drugs	Neurocsicence Drugs
CYP2D6	35	11		Coreg, Toprol, Rhythmol, Innopran Quinidine	Nuedexta, Razadyne Xanazine, Codine Ultracet
CYP2C19	15	4		Plavix, Effient, Brilinta	Onfi
TPMT	4	4	Platinum Purinethol Thioguanine		Imuran
CYP2C9	3	3	Coumadin	Coumadin	Celebrex
DPD	3	2	Xeloda, Fluorouracil		
G6PD	3	1	Elitek		
UGT1A1	3	2	Camptosar Tasigna		
HLA-B*1502	2	1			Tegretol, Dilantin
NAT1;NAT2	2	1		Bidil	
HLA-B*5701	1	0			

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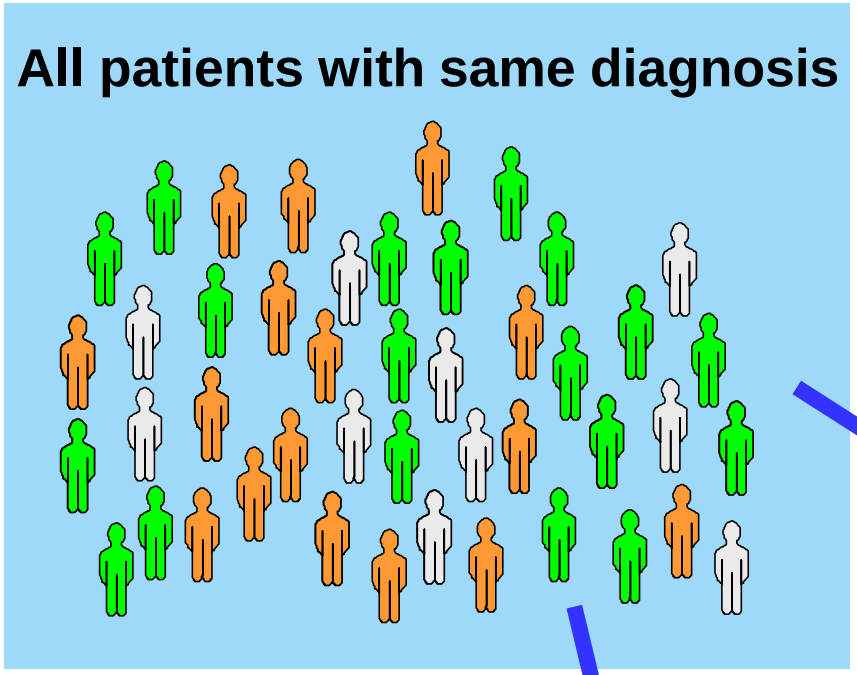
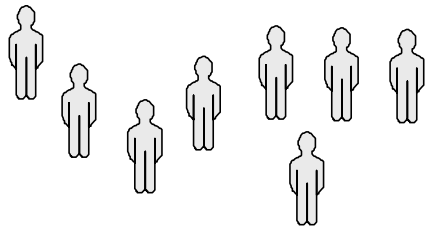
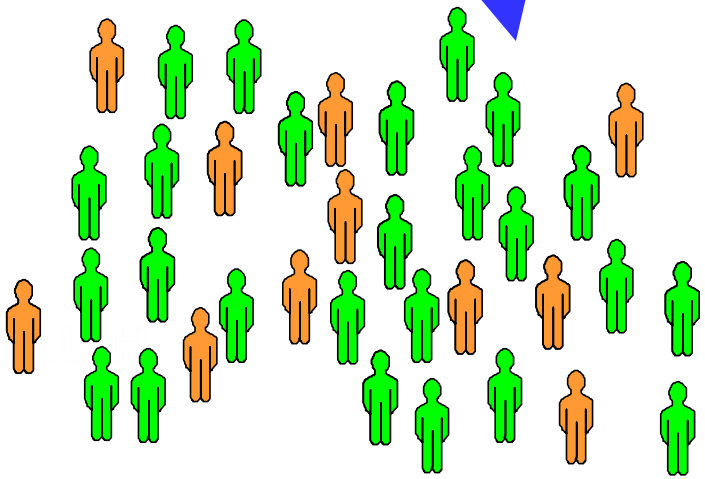
Pharmacogenomics



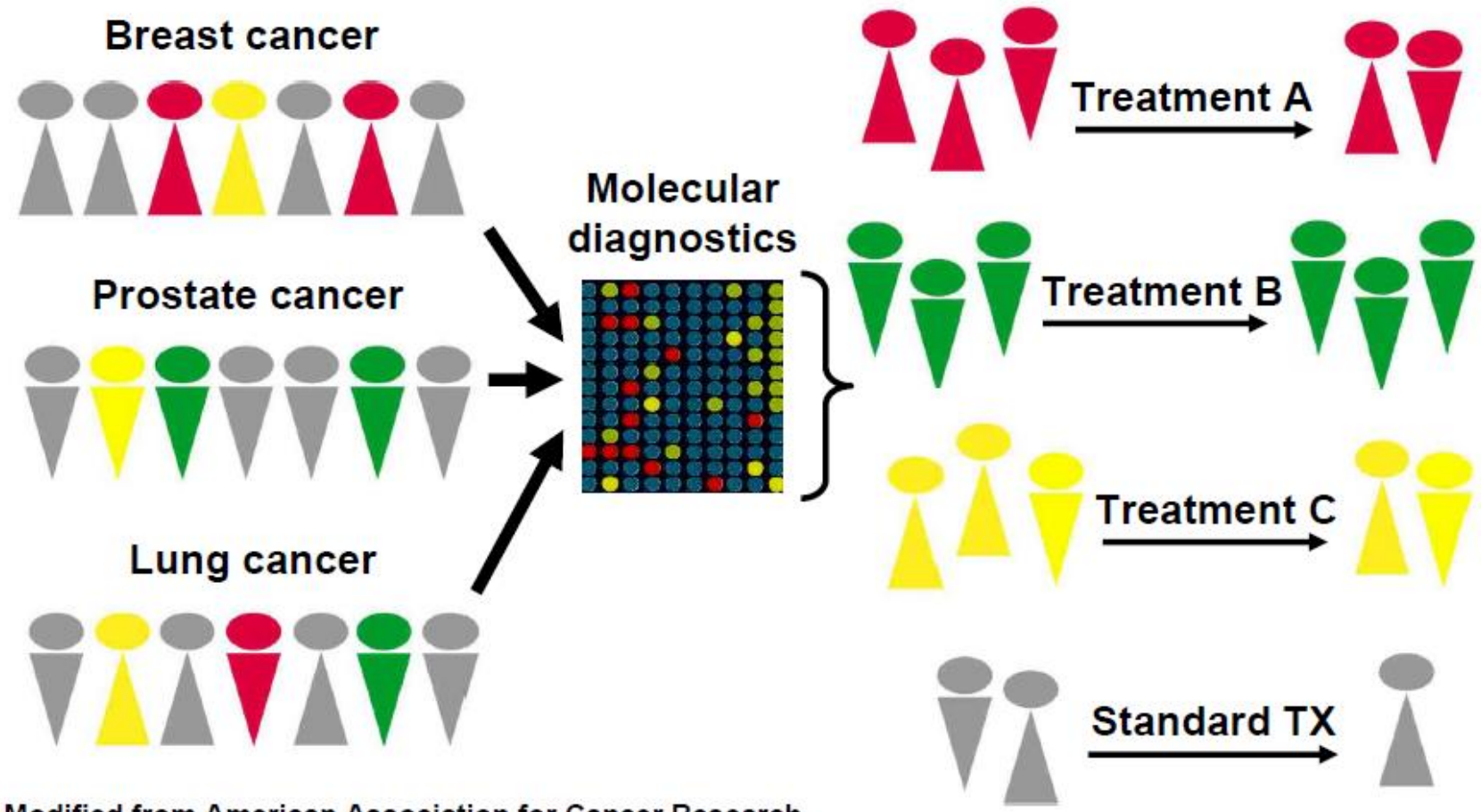
Responders and patients not experiencing severe toxicity





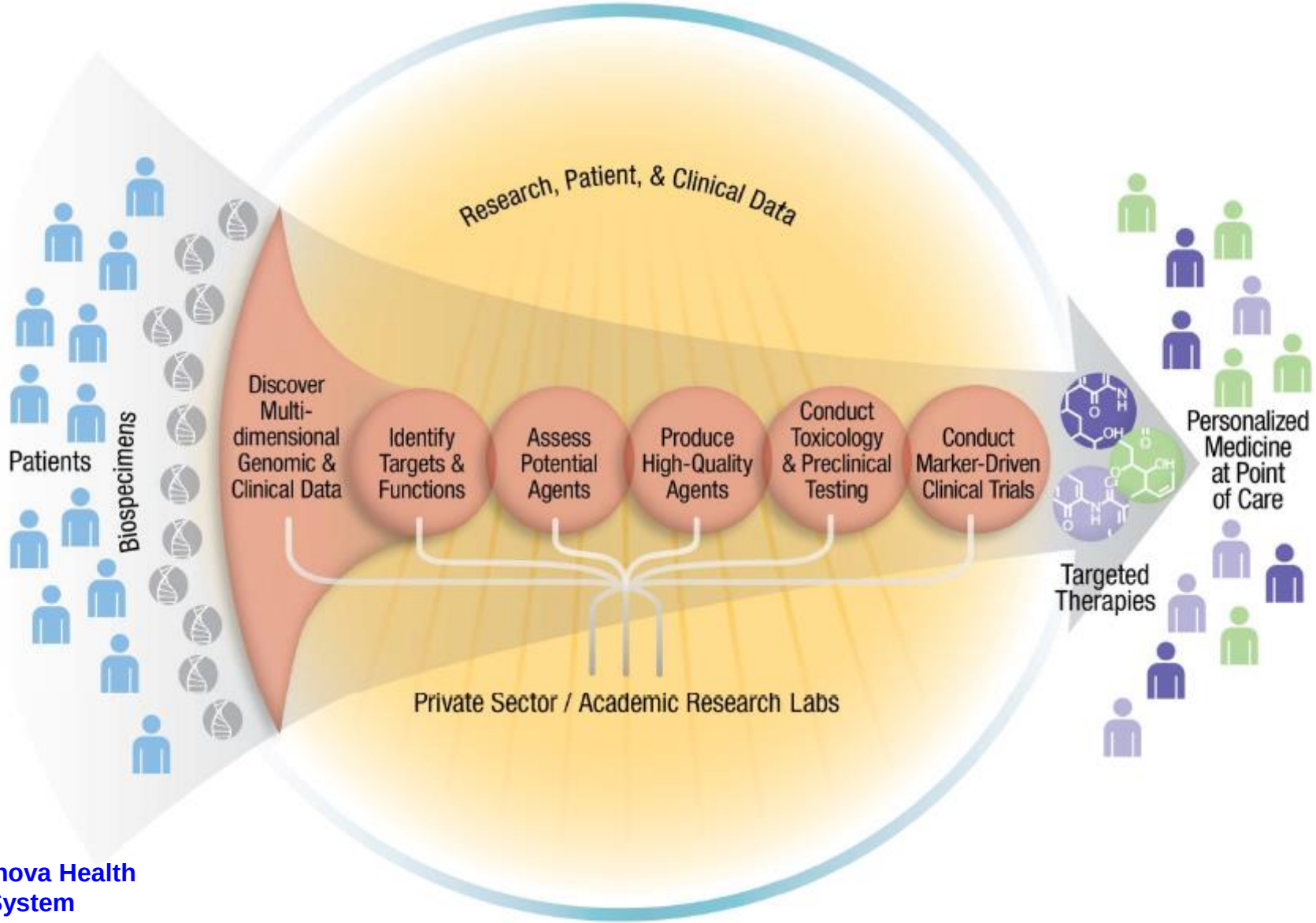
Non-responders and toxic responders

Example: Cancer Therapies



Modified from American Association for Cancer Research

Genomic Driven Drug Discovery



Inova Health System

The goal of individualized cancer medicine is to use genomic characterization to manage disease risk and to optimize patient therapy.

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Patients & Families