Southeastern Actuaries Conference & Actuaries' Club of the Southwest Annual Meeting | November 17, 2022

Gen Re®

Genetic Testing: Hope vs. Reality

Loraine Oman-Ganes, MD, FRCPC, CCMG, FACMG
Medical VP

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Question

Should we all get our genomes sequenced to improve our health?

A. Yes

B. No

Whole Genome Sequencing

All of us: Release of Nearly 100,000 Whole Genome Sequences Sets stage for New Discoveries

Source: https://directorsblog.nih.gov/tag/whole-genome-sequencing

Outline – Genetic Testing: Hope vs Reality

- **Genetic Tests in all Areas of Medicine: Rapid Change, Complexity**
  - Rare, Single Gene Conditions
  - Common Diseases, including Cancer
- **What's a Genome?**
  - Types of Genetic Testing
- **Trends in Genetic Testing**
- **Hope vs. Reality**
  - Treatment Advances: Precision Medicine
  - Will Genomics Cure Cancer?
    - Liquid Biopsy and MCED Tests
- **Implications for Insurers: Risks and Benefits**

Source: A Global Look at Cancer Genomes – NIH Director's Blog

Analyses are product-specific

Single greatest shift in medicine and healthcare

"Modern" Medicine

- Chemotherapy standard of care
- Newborn diagnosis after birth
- Symptom-based, procedure driven, universally applied

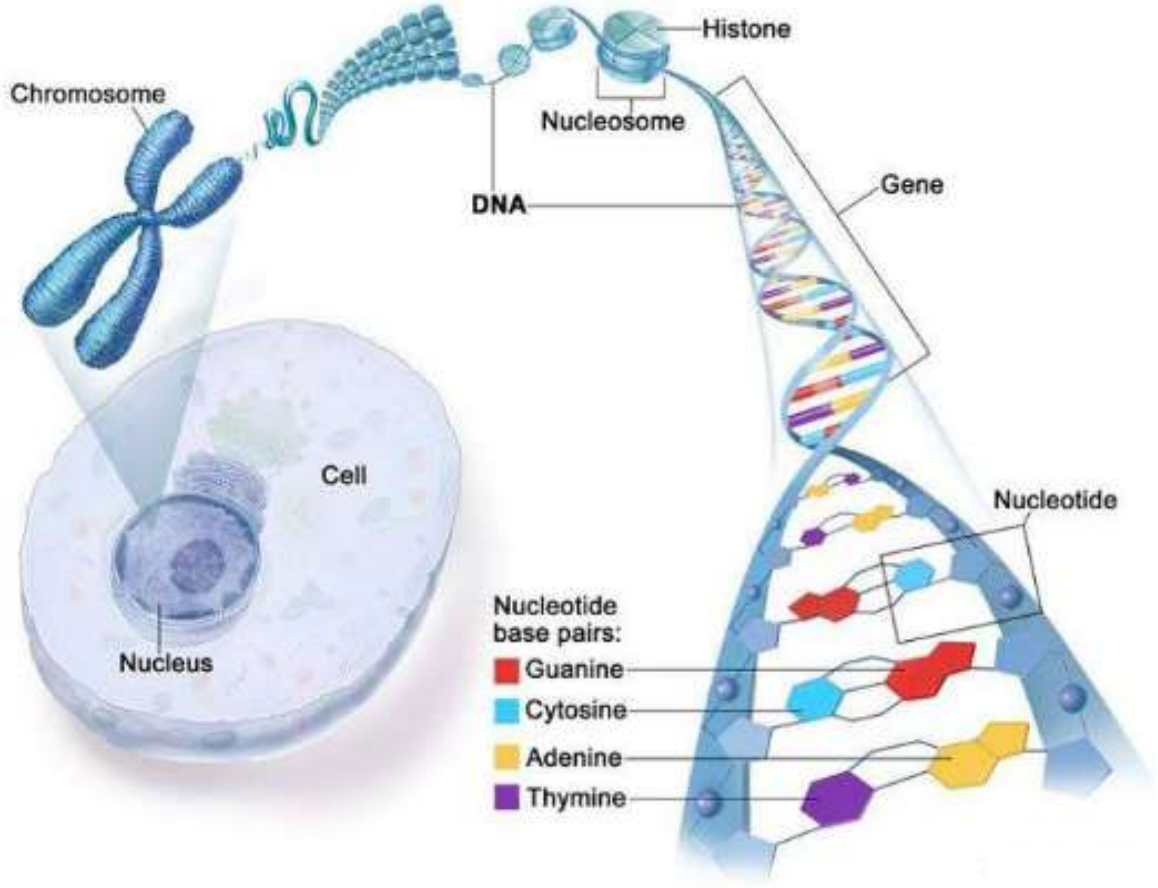
Genome Management

- Risk information = effective prevention
- Earliest detection – disease eradication
- Personalized therapy and biomarker driven monitoring
- Genomic informed healthcare throughout life
- 360° health wallet powers digitally enabled workflow and supports all decisions

INVITAE

What's a Genome?

DNA Structure



Source: https://www.cancer.gov/about-cancer/understanding/what-is-cancer; National Human Genome Research Institute's Talking Glossary of Genetic Terms

Rare diseases, Single Gene Disorders, Pathogenic Variants

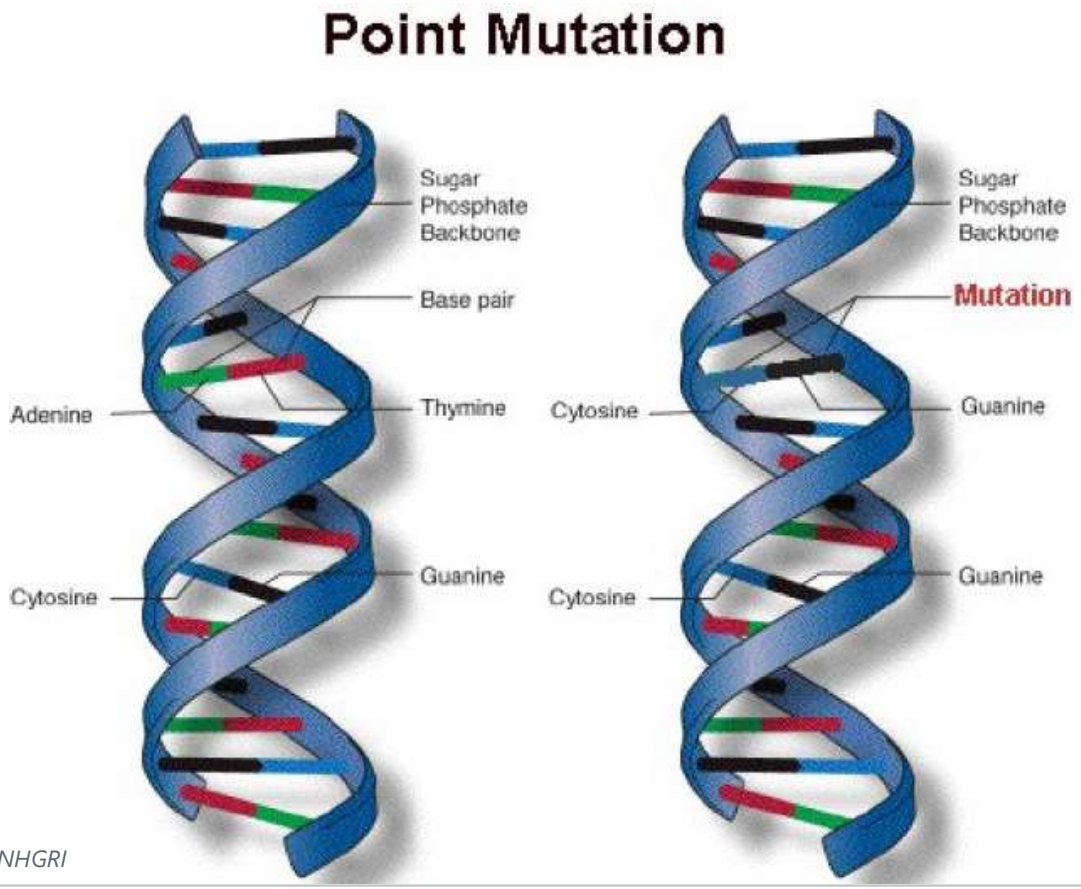


Photo Credit: Image Credit: Darryl Leja, NHGRI

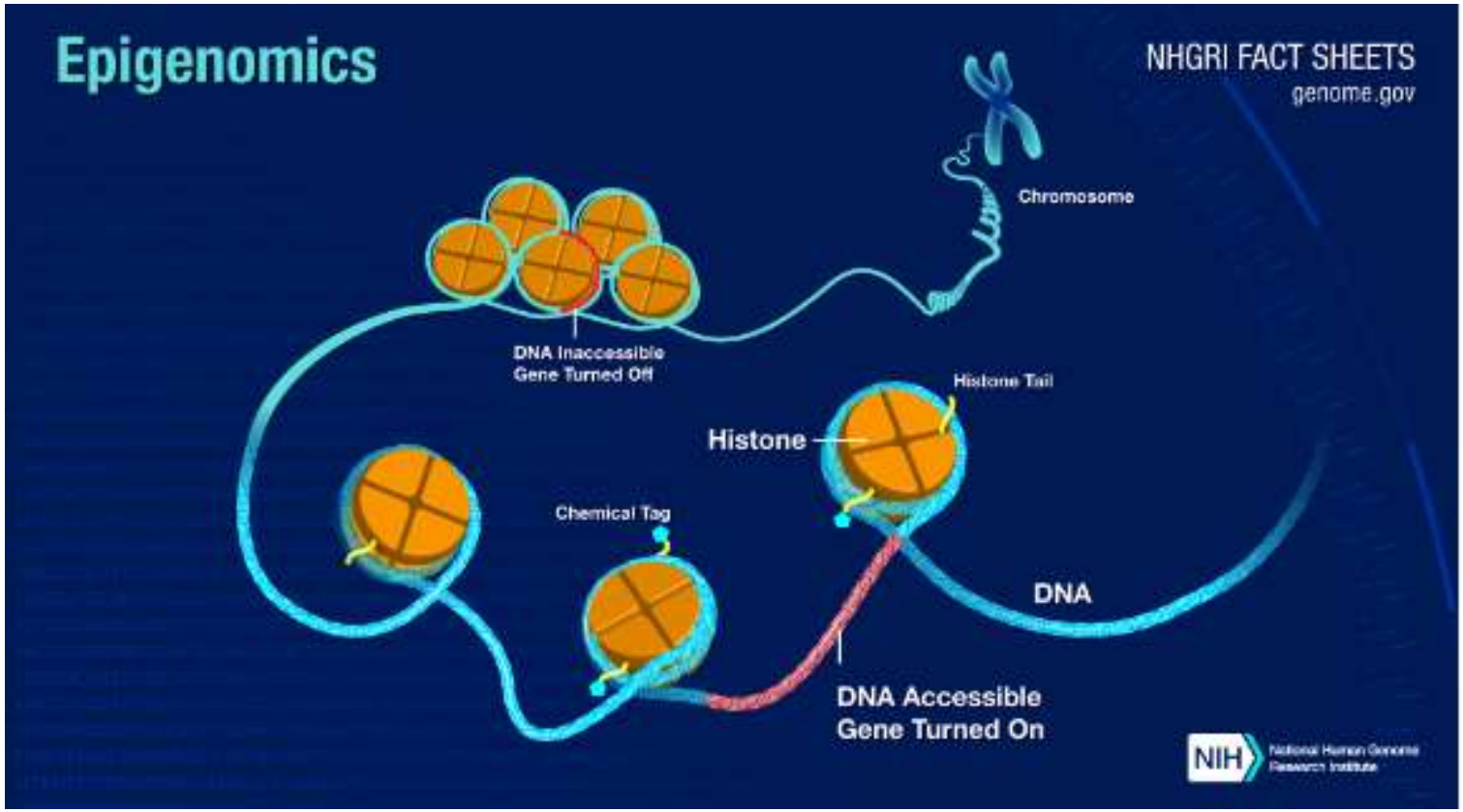
The most common type of mutation is a Point Mutation

A point mutation changes a single nucleotide base pair

Gene Expression – The Science of Epigenetics

Source: www.cambridgenetwork.co.uk

Gene Regulation and Expression – Epigenomics

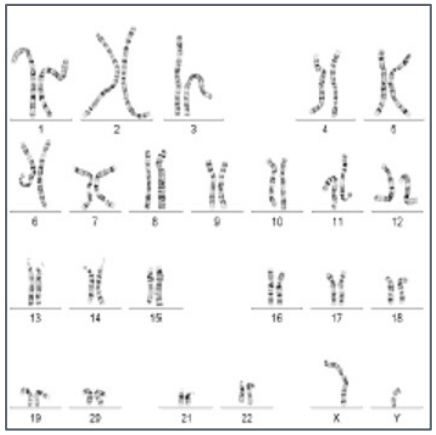


Source: https://www.genome.gov/about-genomics/fact-sheets/Epigenomics-Fact-Sheet

A Technology Timeline

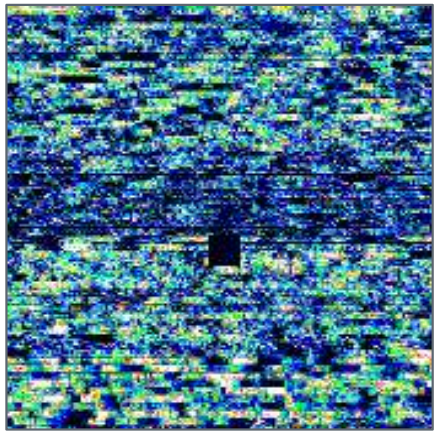
Technologies to scan the genome!

1960: 46 units



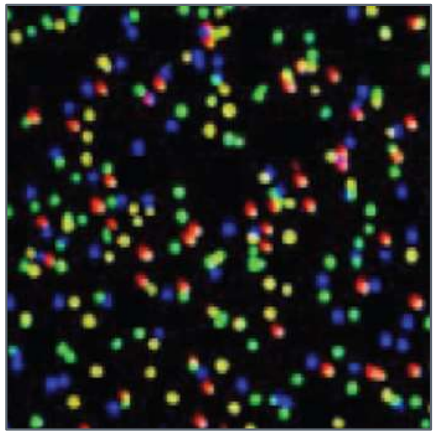
Karyotype
~$300/scan

2007: 1x10^6 units



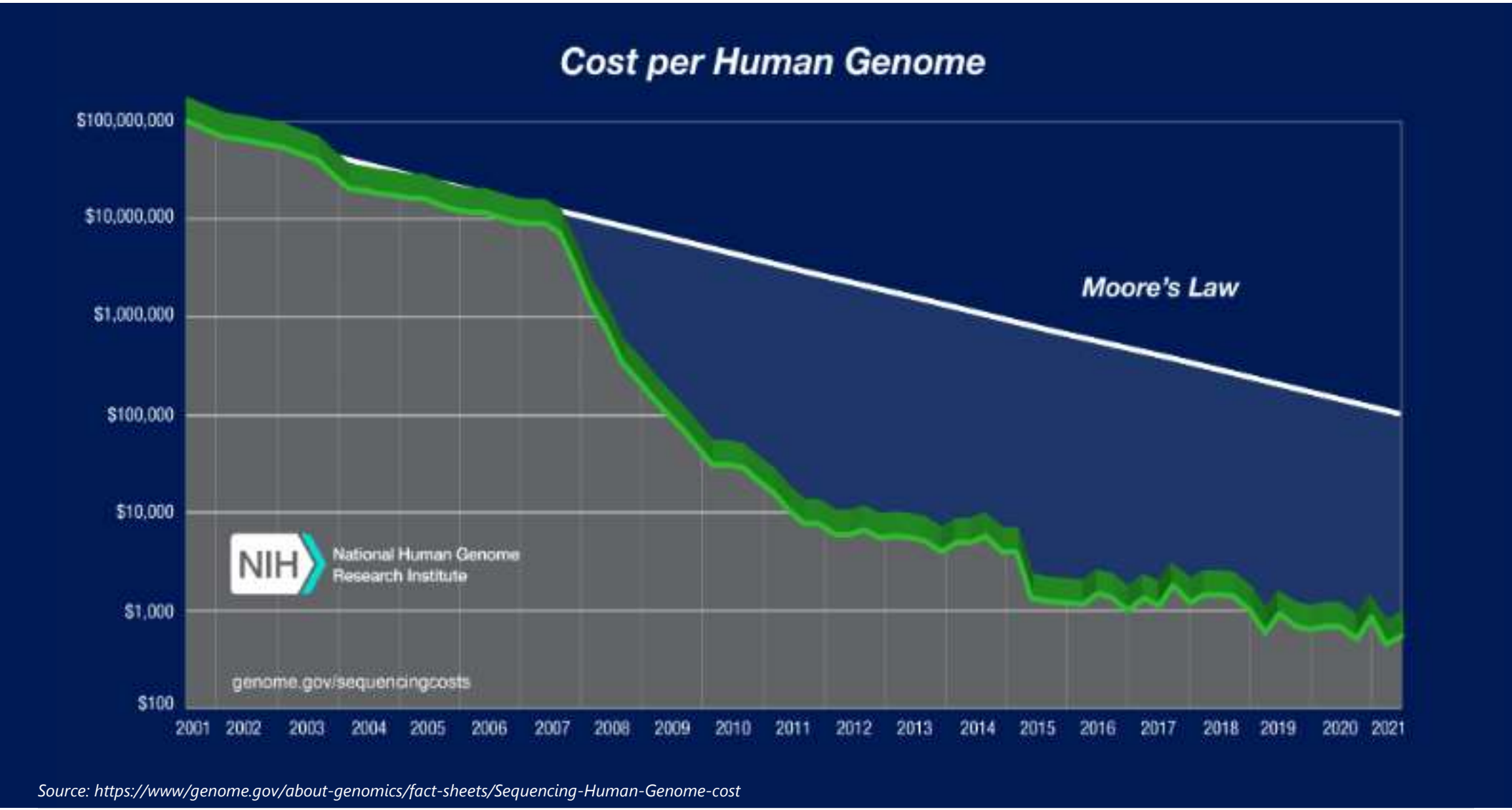
Microarray
$350/scan

2010: 6x10^9 units



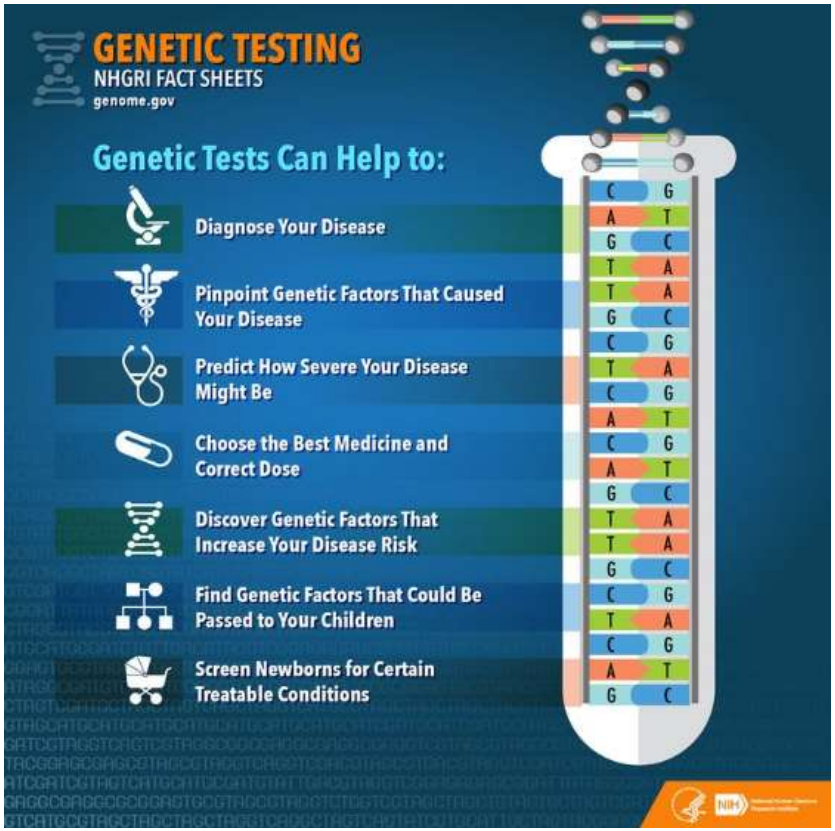
NGS sequence
$3,500/exome (genes)
$5,000/genome

Courtesy: Dr. S. Scherer



Source: https://www/genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost

Genetic Test



- A **laboratory test** to examine an **individual's** DNA (RNA or proteins) for variations
- Typically performed in the context of **medical care**, ancestry studies or forensics
- **Diagnosis/Risk**
- Prenatally or after birth
- Study the **genomes of tumors** in cancer cases

Source: https://www.genome.gov/genetics-glossary/Genetic-Testing; National Human Genome Research Institute (NHGRI)

Focus on Specific Genetic Tests

- Validated for Clinical Use
- **Actionable**
- Predictive, Diagnostic, Prognostic
- **Not:**
  - Carrier Testing
  - Prenatal Testing
  - Newborn Screening
  - Ancestry
  - Nutrigenomics, etc.

"Actionable" Genetic Test Results:

- Medical value in disease prevention and treatment

Most Genetic Testing Is Done for Medical Indication

- **Family history**
- **Disease present or diagnosis uncertain**
- **Predictive**
- **Confirm diagnosis**
  - Prognosis
  - Management
  - Risk to family members including future children

Variable Routes to Access Genetic Testing

TRADITIONAL – via Genetics Professionals*

***May be remote via 3rd party**

- Targeted analysis
  - Example: Known family-specific pathogenic variant, or ancestry-specific panel
  - Sequencing entire gene (BRCA1/2)
- Panels of gene sequencing (GS) tests
- Whole Genome/Whole Exome sequencing- (WGS/WES)
  - Secondary Findings

NONTRADITIONAL – Direct to Consumer

Direct to Consumer Genetic Testing

New resource for healthcare professionals focused on direct-to-consumer genetic testing

FDA NEWS RELEASE

FDA issues warning letter to genomics lab for illegally marketing genetic test that claims to predict patients' responses to specific medications

Share Tweet LinkedIn Email Print

For Immediate Release: April 04, 2019

Source: NHGRI publishes new fact sheets on genomics (genome.gov)
https://www.fda.gov/news-events/press-announcements/fda-issues-warning-letter-genomics-lab-illegally-marketing-genetic-test-claims-predict-patients

Uncertainty – What Does the Genetic Test Mean?

BENIGN ← **PATHOGENIC** →

Strong | Supporting | Supporting | Moderate | Strong | Very Strong

Searching for pathogenic variants

Variants of unknown significance (VUS)

Pathogenicity classification of germline gene variants related to disorders with Mendelian inheritance

Classification	Interpretation*
Pathogenic	Associated with disease risk
Likely pathogenic	>90% likelihood of disease risk association
Variant of uncertain significance (VUS)	Available data do not allow classification into one of the other categories
Likely benign	>90% likelihood that variant is not associated with disease risk
Benign	Not associated with disease risk

Adapted from: ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015; 17:405.

Supported by an unrestricted educational grant from AncestryHealth®.

UpToDate®

Source: UpToDate

Informed Consent – "Opting out" of obtaining Actionable Secondary Results from Genome Sequencing

Published: 13 November 2014

ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing

ACMG Board of Directors

Genetics in Medicine **17**, 68–69 (2015) | Cite this article

Predictive Genetic Testing for Medical Indication – Hereditary Breast and Ovarian Cancer (BRCA1/2)

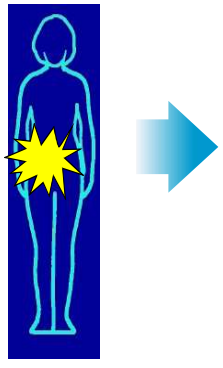
Source: https://en.wikipedia.org/wiki/Angelina_Jolie#/media/File:Angelina_Jolie_Cannes_2011.jpg

All Cancer Is Genetic – Only 10% Is Hereditary
Which Genome to test?

Germline Genetic Test
(hereditary: 10%)

Parent → Child

Mutation in egg or sperm



All cells in offspring have the mutation

- Present in egg or sperm
- Pass from one generation to next
- Cause hereditary cancer syndromes

Somatic Genetic Test
(100% of cancer)

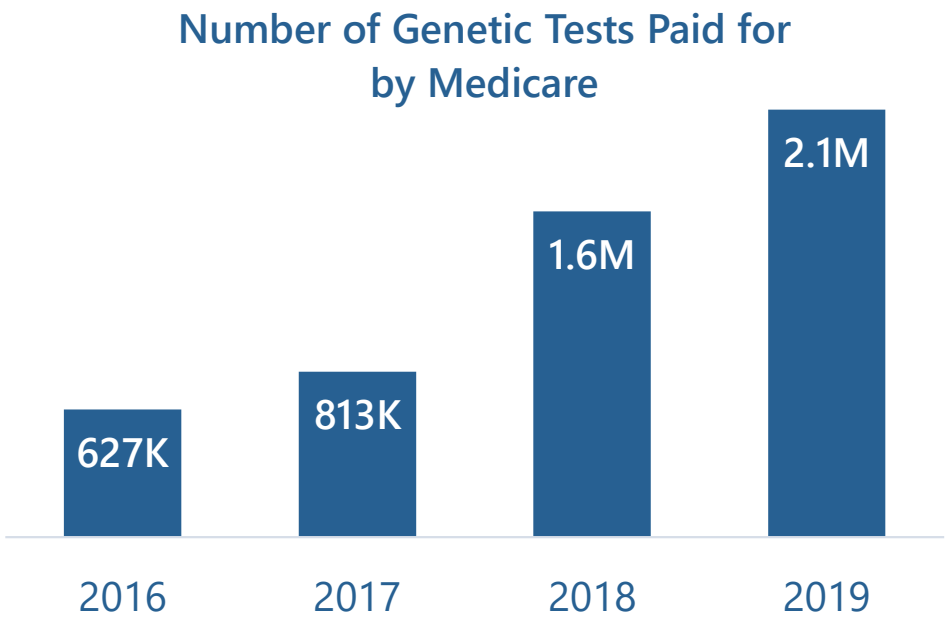
Somatic mutation (in tissue where cancer forms: e.g., breast) **Accumulate with AGE**

- Occur in nongermline tissues
- Are not passed from one generation to next

Source: ASCO

Genetic Testing Prevalence and Trends – Data Limitations, Underestimates

- Diverse data sources/data collation issues
  - Payors
    - Commercial
    - Public
    - Self-pay
  - Research-based
  - NIH Genetic Testing Registry: voluntary
- Fragmented laboratory industry
- Sequential testing/claims
- Clinical vs. Direct to Consumer



*"As a result of efforts to target genetic testing fraud schemes nationwide, OIG and its law enforcement partners charged 35 individuals for their alleged participation in genetic-testing fraud schemes, involving **$2.1 billion** in losses to the Medicare program."*

Source: https://oig.hhs.gov/oas/reports/region9/92003027.pdf

Genetic Testing – Highly Variable Pricing

Concert Genetics:

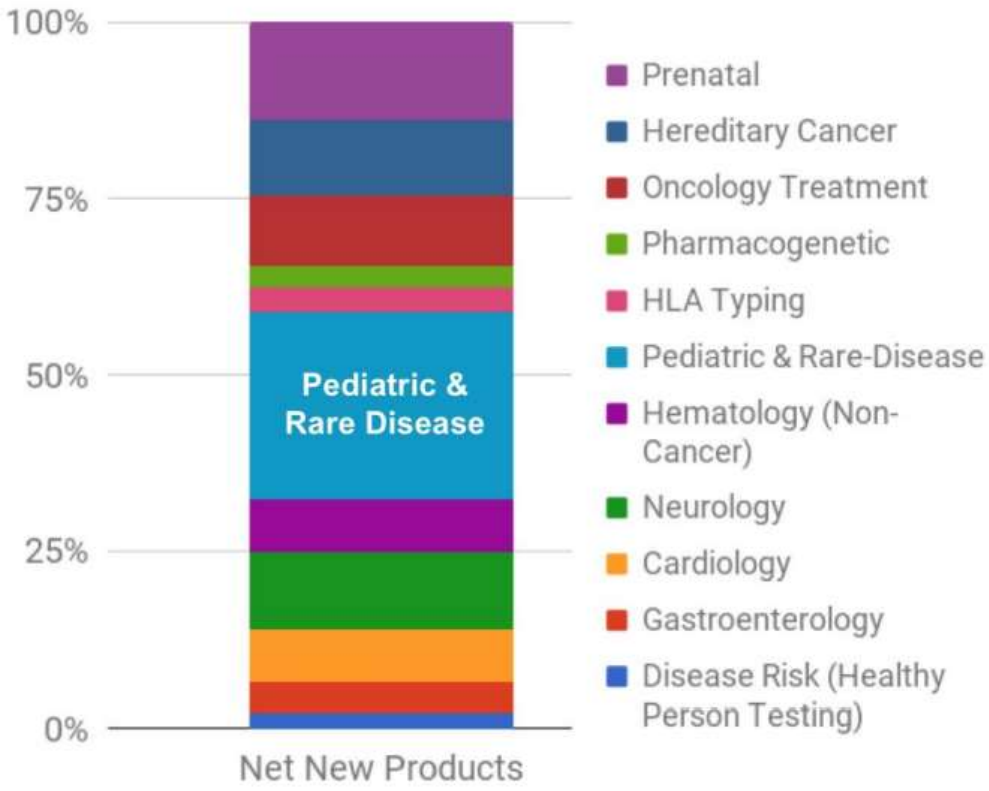
- Organizing more than 175,000 testing products by practice area, domain and clinical category
- Largest and most comprehensive registry of genetic tests in the world.
- Using patented machine learning, Concert applies this taxonomy to enrich a claims dataset of more than 45 million commercial lives.

Source: Genetics Concert 2022-Genetic-Test-Price-Transparency-Report.pdf

“Genetic testing is the lynchpin of precision medicine, but the rapid pace of change in the market makes it enormously complex. Today, there are more than 140,000 unique genetic testing products on the market, and an average of 10-15 new products are added each day. This growth confounds the processes through which tests are ordered, resulted, billed and reimbursed.”

Source: https://www.concertgenetics.com/about-us

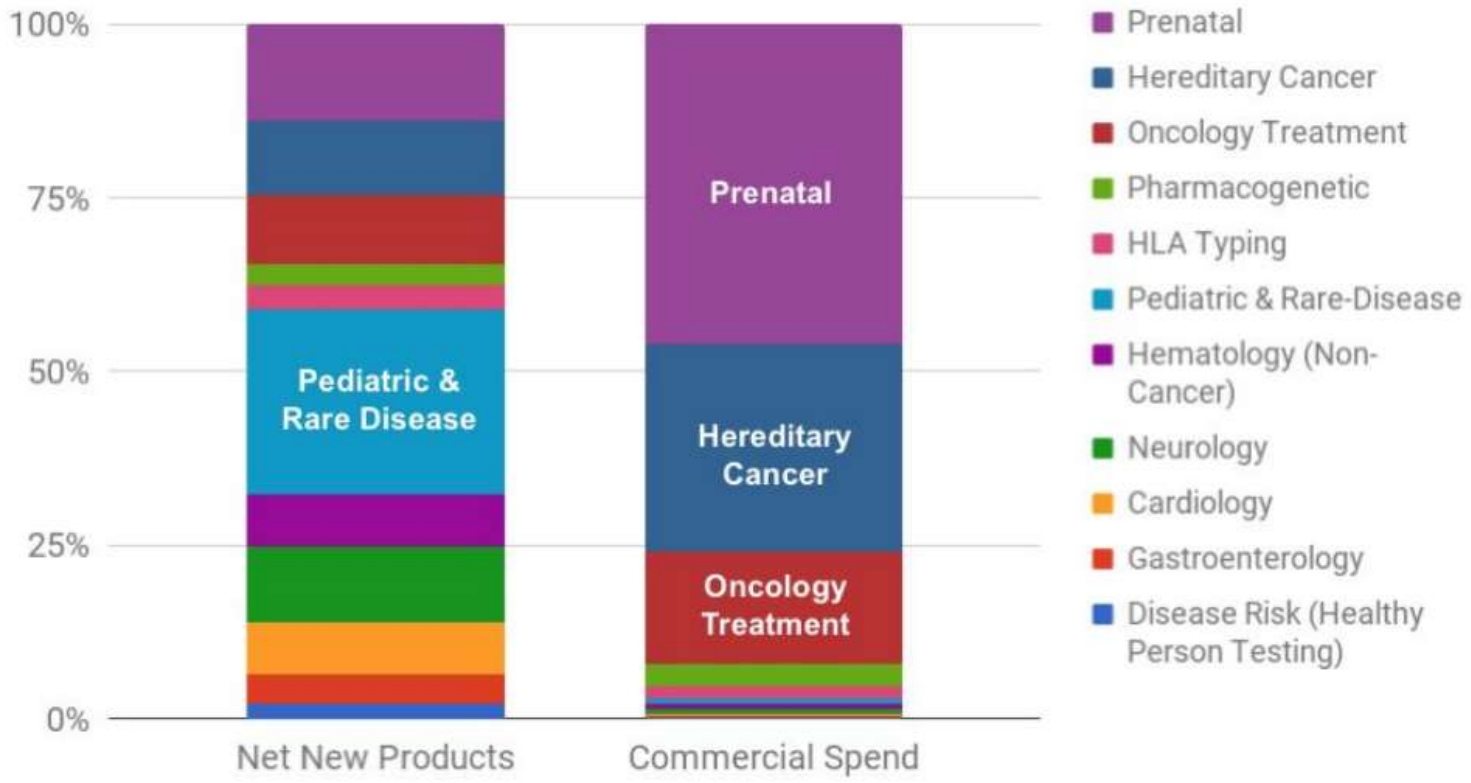
New Genetic Test Products 2017 – Diverse Clinical Domains



Rapid Growth

Source: Concert Genetics: "The Current Landscape of Genetic Testing" Whitepaper 2018 Edition

New Test Types Do Not Correlate with Commercial Reimbursement



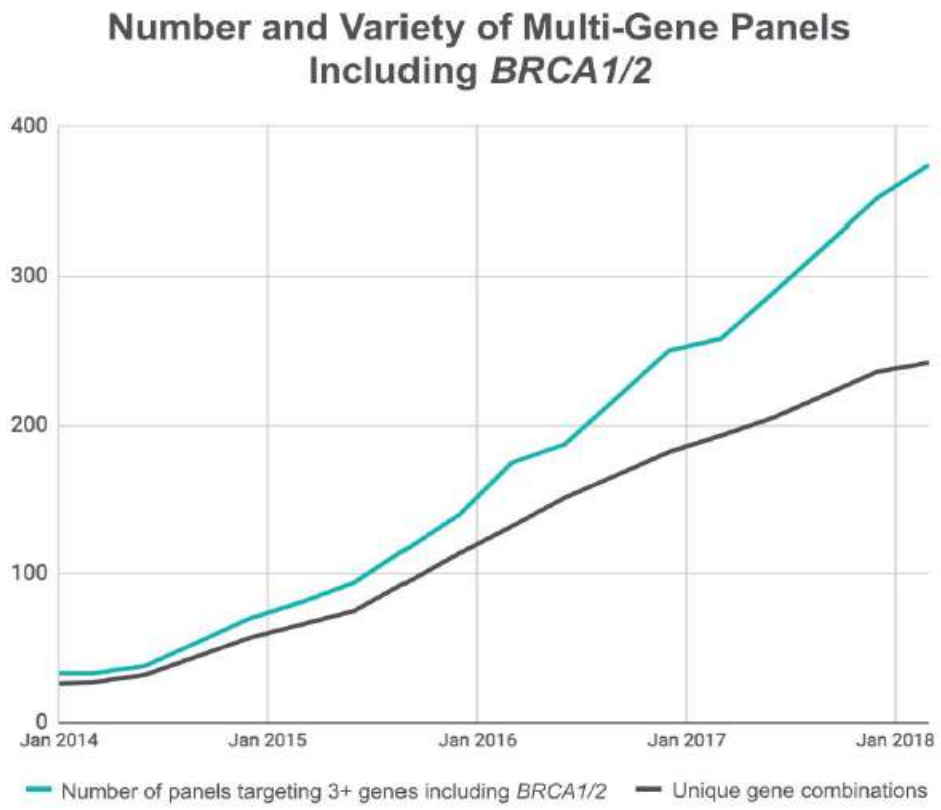
Source: Concert Genetics: "The Current Landscape of Genetic Testing" Whitepaper 2018 Edition

Highest Spend Concert Genetics Test Categories

2021 Spend Rank	2020 Spend Rank	Concert Genetics Test Category	2021 Average Codes	2021 Price Variability	2021 Median Price	2017-2021 Price Change
1	1	FIT-DNA Colorectal Cancer Screening Tests*	1.00	3%	-	0.31%
2	2	**Non-invasive Prenatal Testing (NIPT) for Chromosome 13, 18, 21, X, and Y Aneuploidies**	1.01	39%	$645	-14.0%
3	4	**Expanded Carrier Panel Tests**	9.42	250%	$1,518	-22.7%
4	3	**BRCA1/2 Sequencing Tests**	1.00	126%	$1,825	-27.7%
5	5	Breast Cancer Treatment and Prognostic Algorithmic Tests	1.00	10%	$4,067	5.3%
6	6	**Thyroid Cancer Diagnostic Algorithmic Tests**	1.19	37%	$3,600	11.7%
7	7	**Tumor-Type Agnostic Molecular Solid Tumor Profiling Panel Tests (51 or more genes)**	2.45	65%	$2,950	-9.5%
8	11	**Pharmacogenetic Neuropsychiatric Panel Tests**	8.15	99%	$1,200	176.6%
9	9	Non-invasive Prenatal Testing (NIPT) Expanded Panel Tests	2.02	93%	$1,123	16.3%
10	8	Basic Carrier (CFTR, FMR1, SMN1/2, HBB) Panel Tests	2.47	94%	$660	-7.2%
11	12	Exome Sequencing Tests	2.65	257%	$8,810	19.7%
12	10	**Pan-Cancer Hereditary Cancer Panel Tests**	3.46	125%	$1,483	-56.7%

Source: Genetics Concert 2022-Genetic-Test-Price-Transparency-Report.pdf

Multi-Gene Panel Testing – Market Growth



- 12 months ending March 1, 2018: **801 new panels entered the market**
- Growth Rate: 15+ per week

Source: Concert Genetics "The Current Landscape of Genetic Testing" Whitepaper April 2018

Evolution of Testing – Multi-Cancer Panels

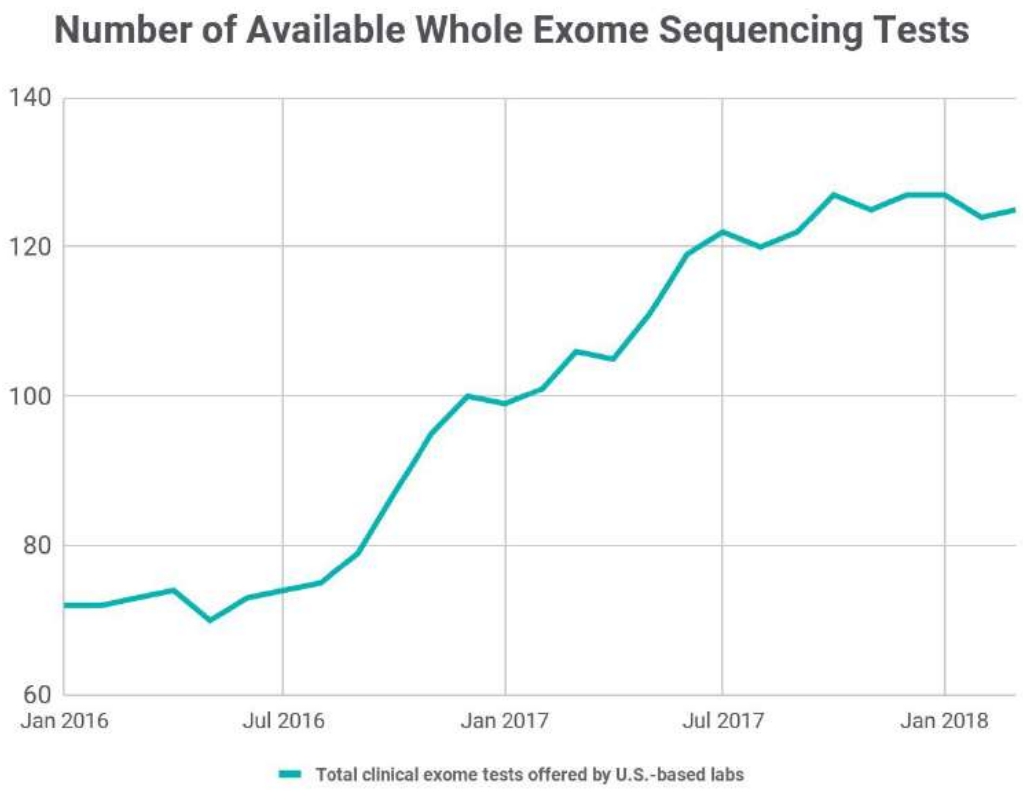
Test Description

The Invitae Multi-Cancer Panel analyzes 84 genes associated with hereditary cancers across major organ systems including:

- Breast and gynecologic (breast, ovarian, uterine)
- Gastrointestinal (colorectal, gastric, pancreatic)
- Endocrine (thyroid, paraganglioma/pheochromocytoma, parathyroid, pituitary)
- Genitourinary (renal/urinary tract, prostate)
- Skin (melanoma, basal cell carcinoma)
- Brain/nervous system
- Sarcoma
- Hematologic (myelodysplastic syndrome/leukemia)

Source: https://www.invitae.com/en/providers/test-catalog/test-01101; Courtesy: Invitae

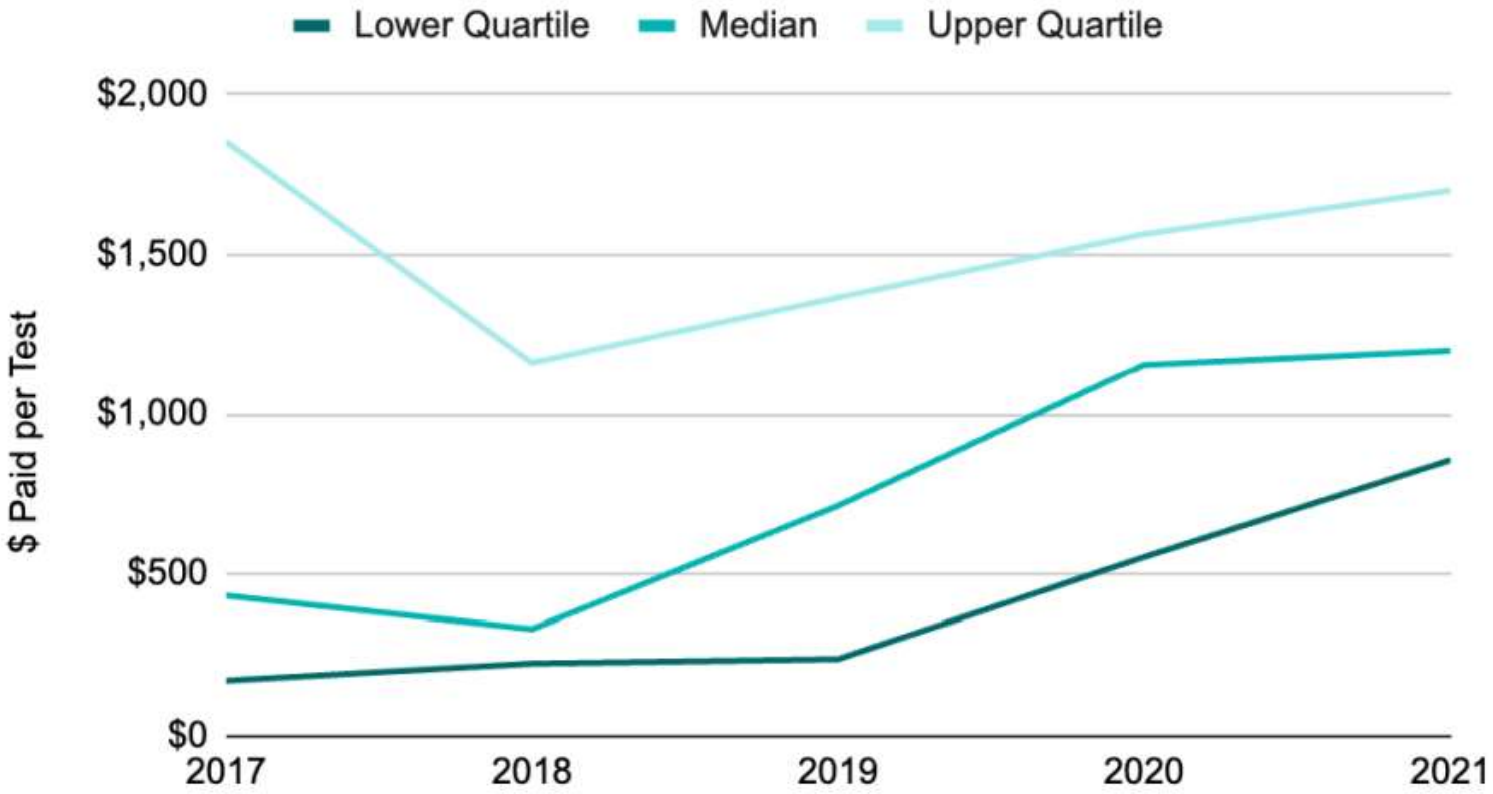
Whole Exome Sequencing – Rapid Growth



Exome sequencing tests on the market saw particularly rapid growth between July 2016 and July 2017. During this time, more than 40 new exome sequencing GTUs were released.

Source: Concert Genetics "The Current Landscape of Genetic Testing" Whitepaper April 2018

Pharmacogenetic Neuropsychiatric Panel Tests

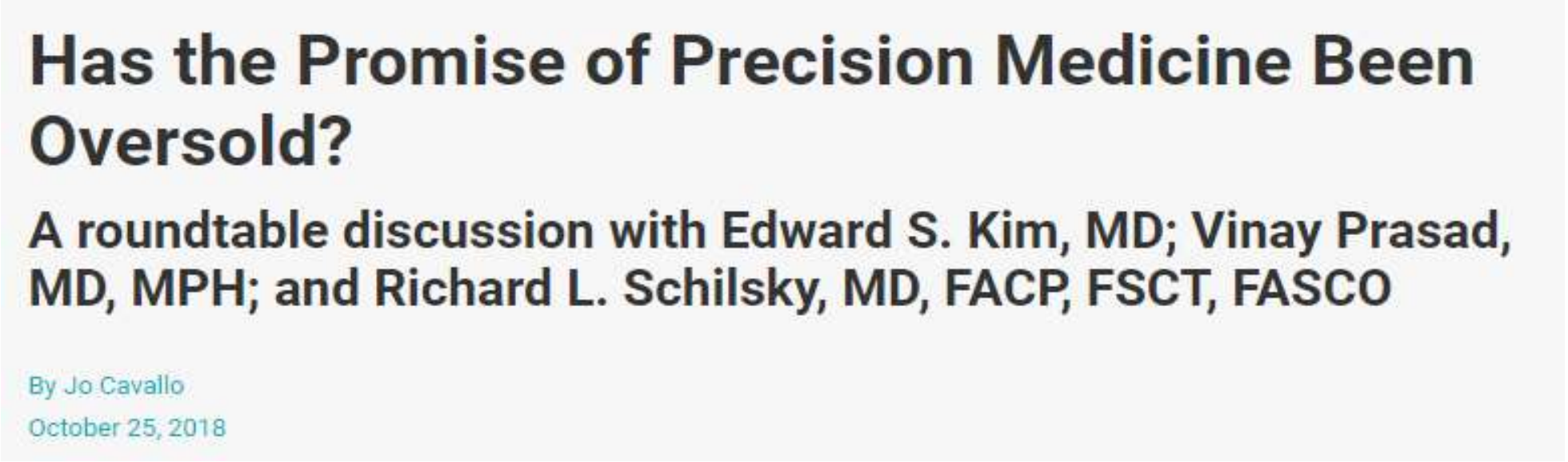


Source: Genetics Concert 2022-Genetic-Test-Price-Transparency-Report.pdf

The Hope

Therapeutics – Will Genomics Cure Cancer ?

Or…



Has the Promise of Precision Medicine Been Oversold?

A roundtable discussion with Edward S. Kim, MD; Vinay Prasad, MD, MPH; and Richard L. Schilsky, MD, FACP, FSCT, FASCO

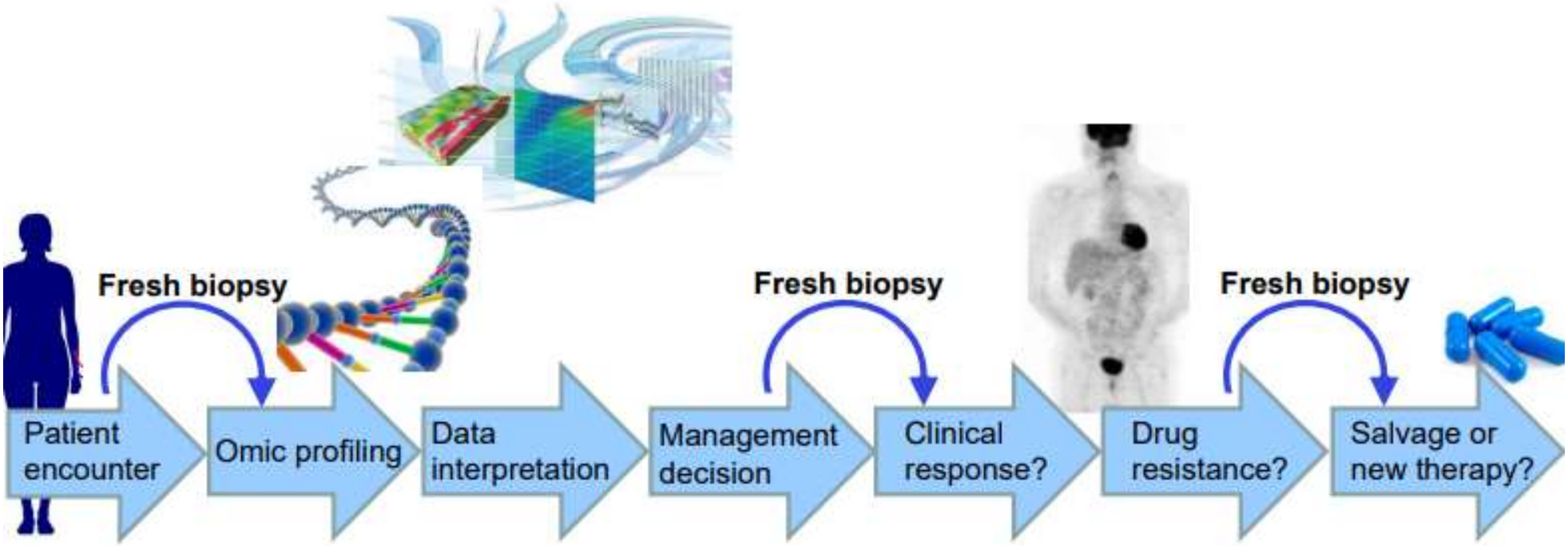
By Jo Cavallo

October 25, 2018

Source: Has the Promise of Precision Medicine Been Oversold? - The ASCO Post

Cancer Continues to Evolve and Evade Treatment

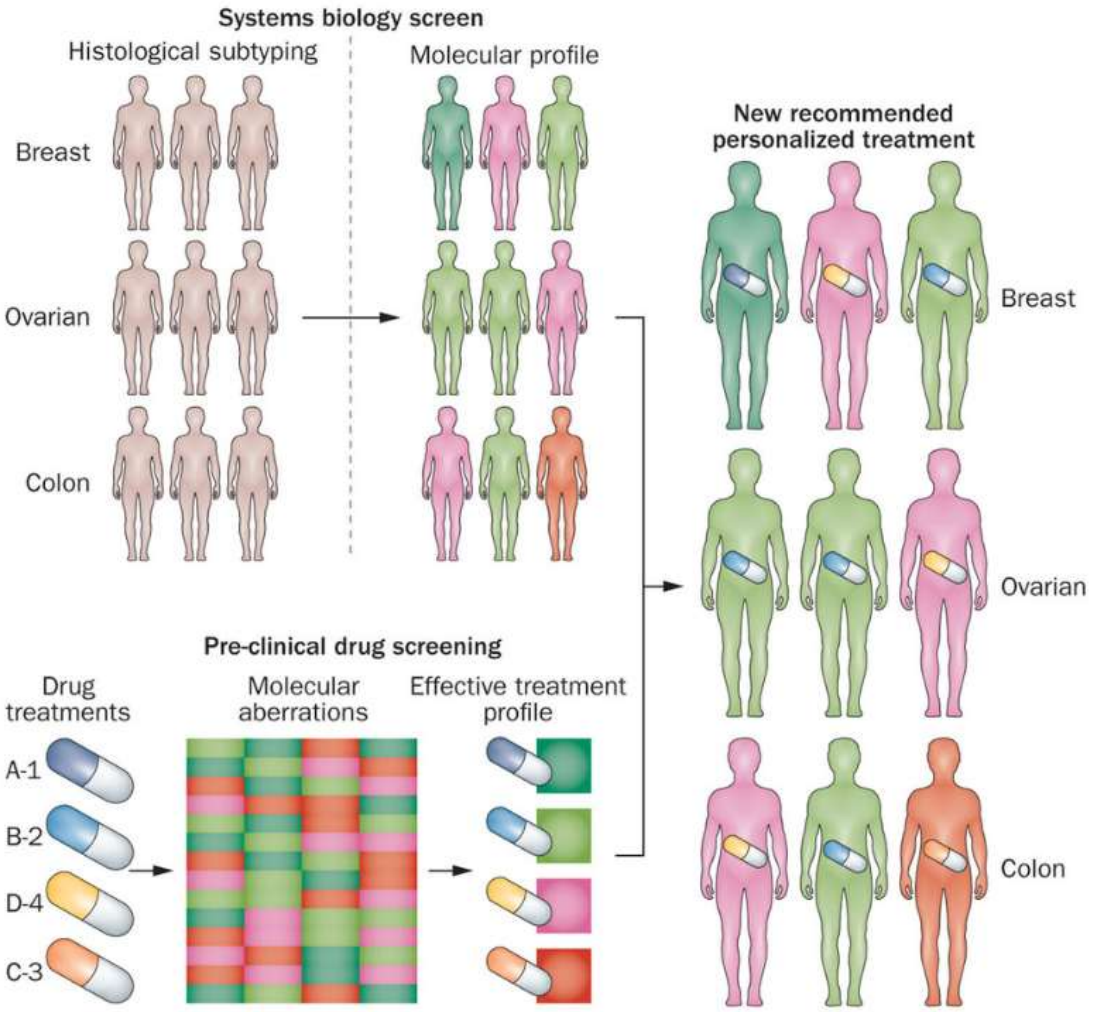
The Engine of Precision Cancer Medicine



Source: https://www.genome.gov/Multimedia/Slides/GenomicsInMedicine2013-2014/Staudt_11-1-13.pdf

The Molecular "Footprint" of Cancer Guides Treatment

Classification and therapy 'agnostic' to tissue of origin

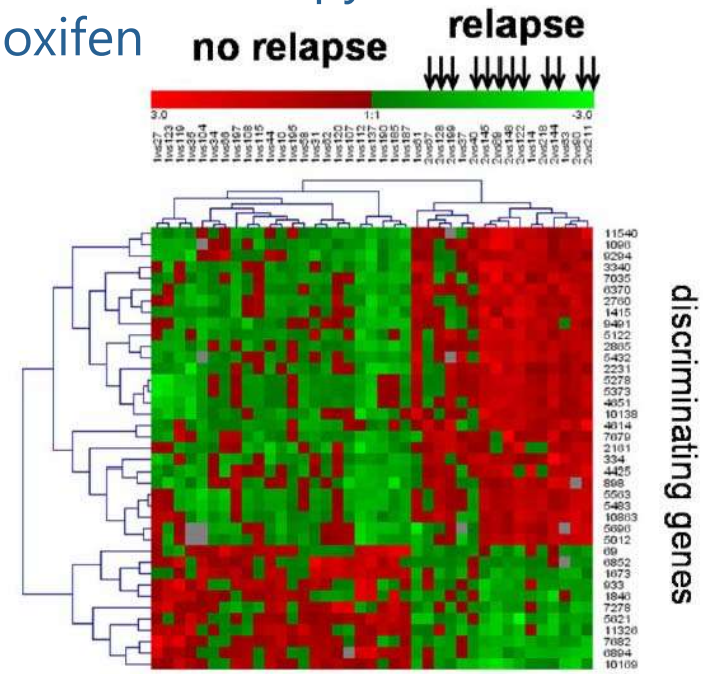


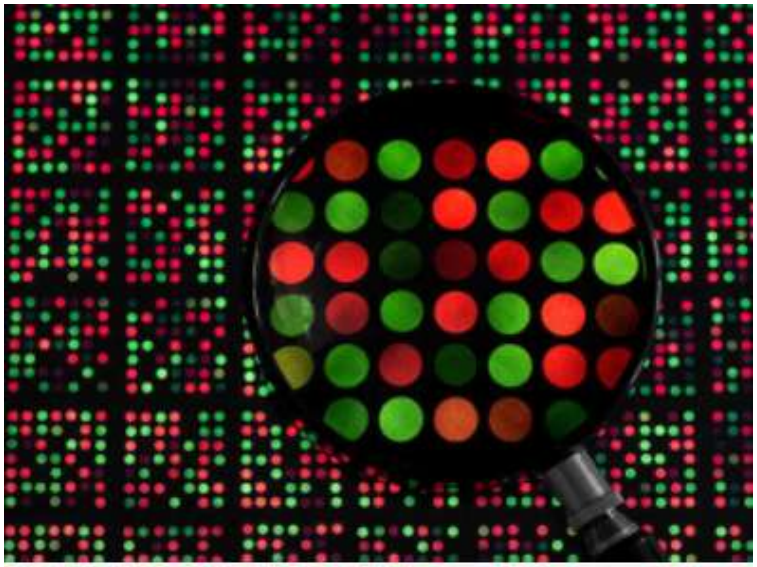
Source: Werner, H. et al. Nature Reviews Clinical Oncology 11, 167-176 (2014)

Gene Expression Biomarkers Inform Prognosis and Treatment

21 Genes, **Recurrence Score (RS; 0-100)**

Predicts risk relapse, chemotherapy benefit despite tamoxifen



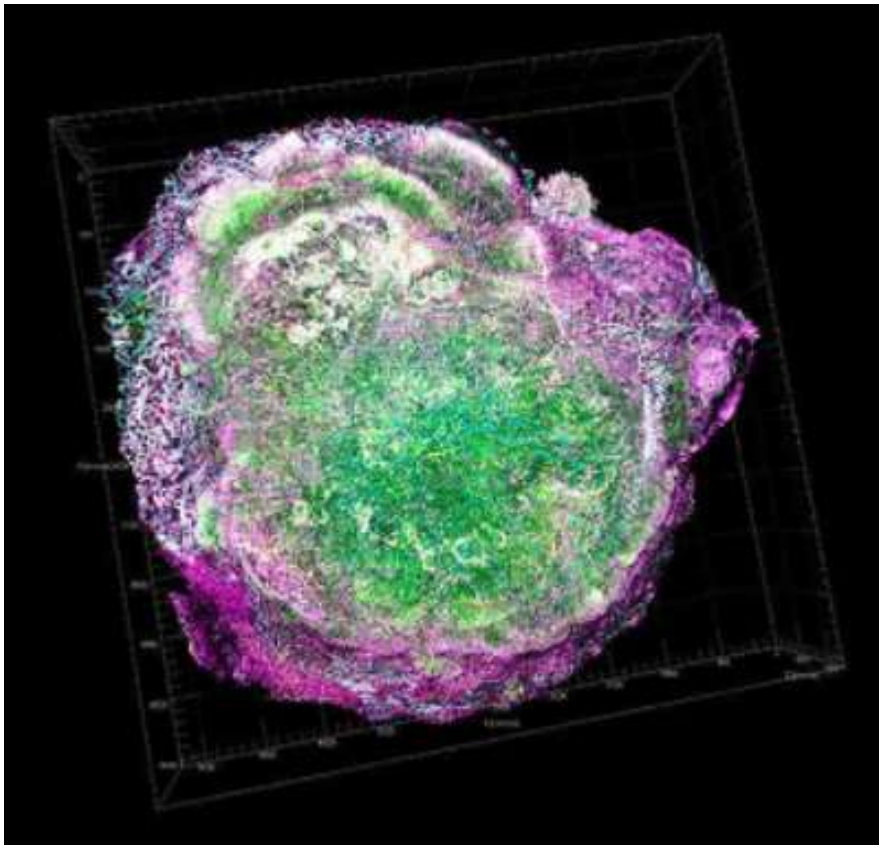


DNA microarrays are used in the TAILORx trial to determine the likelihood of breast cancer recurrence by assessing the level of expression of a particular group of genes.
Credit: iStock

Source: https://www.cancer.gov/types/breast/research/tailorx-low-risk

Precision Therapy 20 Years Later – HER2 Positive Breast Cancer

Single breast cancer cell and microenvironment visualized by transparent tumor tomography

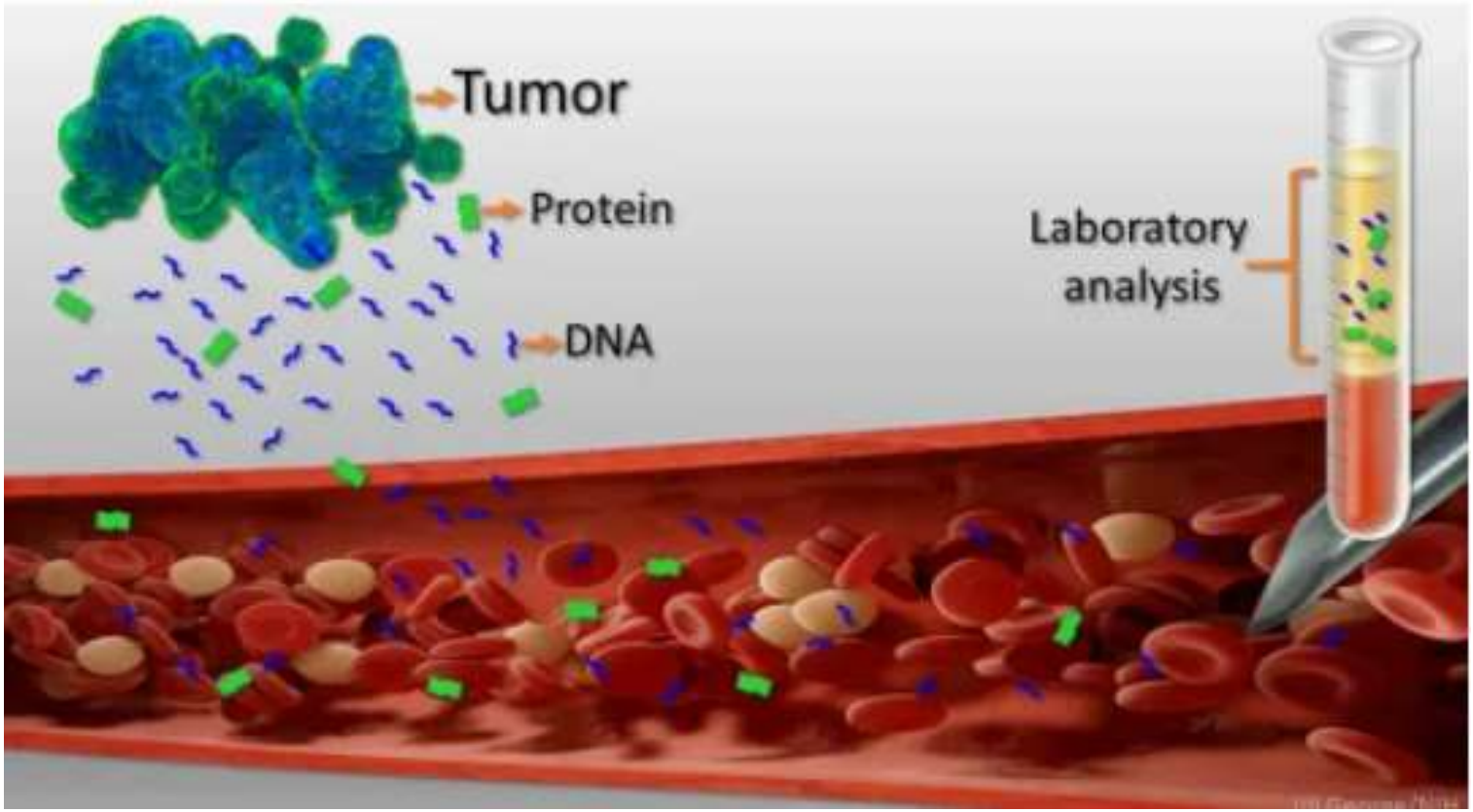


Improved chemotherapy approaches

Better tolerated and more effective

Sources: https://www.cancer.gov/research/progress/discovery/her2

Liquid Biopsy and Multi Cancer Early Detection (MCED) Tests



Sources: https://directorsblog.nih.gov/2018/01/30/new-liquid-biopsy-shows-early-promise-in-detecting-cancer; https://www.mirror.co.uk/news/uk-news/nhs-trialling-new-holy-grail-24968387

MCED Tests
Tumor Markers for Screening, Not Diagnosis

Uncertain Clinical Utility

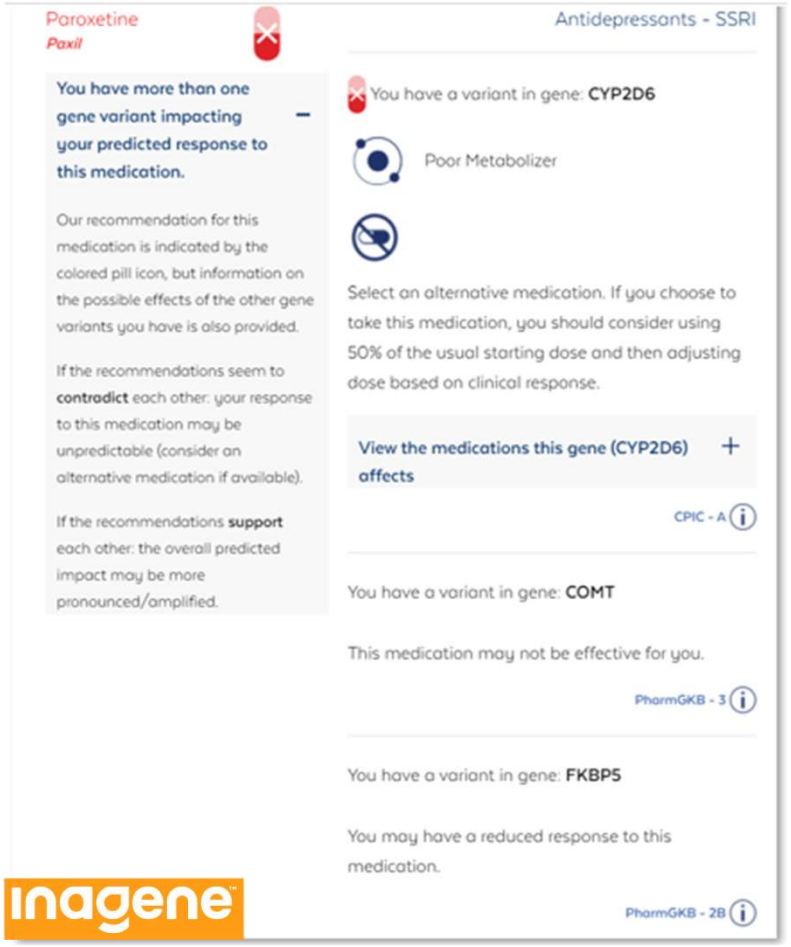
MCEDs Are Promising and Unproven

- As a screening tool for early cancer, multi-cancer detection assays, while promising, investigators say, raise concerns about overdiagnosis of indolent disease and potential harm from unnecessary and invasive procedures in individuals with no known malignancies.
- "Many of these assays are being heavily marketed to both providers and to patients (for early detection), but their true value is not yet clear," said Marie Wood, M.D., the principal investigator of the new biobank study. She is also the medical director of the Cancer Clinical Trials Office at the University of Colorado Cancer Center.

Sources: Samples from People With and Without Cancer Could Help Verify Future Blood Tests to Detect Cancer Early | Division of Cancer Prevention

Pharmacogenomics

- **Evidence-basis for use in Psychiatry**
- **Depression:**
  - History of 2 drug trial failures:
    - Fluoxetine (lack of response)
    - Paroxetine (discontinued due to side effects)



Source: Dr. K. Siminovitch

Disparities and Diversity – Access, Diagnosis, and Treatment

Transdisciplinary Collaborative Centers for Health Disparities Research Focused on Precision Medicine

Program Contact
Dr. Nishadi Rajapakse
Division of Scientific Programs

Diagnosis

Genetic misdiagnoses of heart condition in black Americans

At a Glance

- A new analysis found that several genetic variations previously linked with a heart condition were harmless.
- The misclassification resulted in a higher misdiagnosis of black Americans, highlighting the importance of using genome data from diverse populations.

Treatment

NEWS September 2022: Low neutrophil count in African Americans may result in under-treatment with chemotherapy

Cause: A genetic variant misinterpreted as chemotherapy effect

Solution: Genotype for variants

Sources: https://www.nimhd.nih.gov/programs/extramural/research-centers/tcc/precision-medicine.html; https://www.nih.gov/news-events/nih-research-matters/genetic-misdiagnoses-heart-condition-black-americans

Should Healthy People Have Whole Genome Sequencing to Limit Health Risk?

- **Germline Whole Genome Sequencing (WGS): for Medical Indication**
- **Focus: Hereditary Conditions**
- **Results: Uncertainty**
  - Accuracy, Interpretation
  - Interpretation may change with time
  - **Secondary Findings: Actionable?**
    - Non-actionable (e.g., Alzheimer's disease)
- **Informed consent:**
  - Do you understand implications of "Opting Out"?
- **If risk increased:**
  - Fear, Anxiety
    - about management, surveillance including cost
    - about Risk to family members
    - of Discrimination- employer, insurance
- **Access to Care/Cost**
- **Nonpaternity**

Implications for Insurers

Genetic Testing: Rapid Change, Increased Use in All Areas of Medicine

Opportunities

- Enhancing Health
- Mortality Improvements? will take years to determine
- Develop Best Practices
- Product Innovation:
  - Cancer
  - Wellness
- Risk Mitigants including Product, Pricing
- Enhanced Partnerships

Risks

- Evolving Legal Landscape
- Response to Rapid Change, Complexity
- Anti-selection
- Health: Cost of Testing, Investigations, Management, Therapeutics
- Stop Loss: Specialty Drugs
- Morbidity? Prolonged: DI, LTCI
- CI: definitions, hereditary cancer syndromes
- Reputational

Thank you! Questions?

Loraine Oman-Ganes, MD, FRCPC, CCMG, FACMG
loraine.omanganes@genre.com

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