KIMMEL CANCER CENTER

Precision Medicine Impacting Cancer Care

Acquired Genetic/Epigenetic Defects
Diagnostics
Therapeutics
Immunotherapeutics

William G. Nelson, M.D., Ph.D.

JOHNS HOPKINS MEDICINE

William G. Nelson, M.D., Ph.D.
Disclosures

Member

Cancer Scientific Advisory Council, AbbVie Inc.
Scientific Advisory Board, ProQuest Investments, Inc.
Board of Directors, CHD Biosciences
Co-Founder, Digital Harmonics

Ad Hoc Consultant

GlaxoSmithKline Inc., Merck and Co., Jannsen Pharmaceuticals Inc., many others

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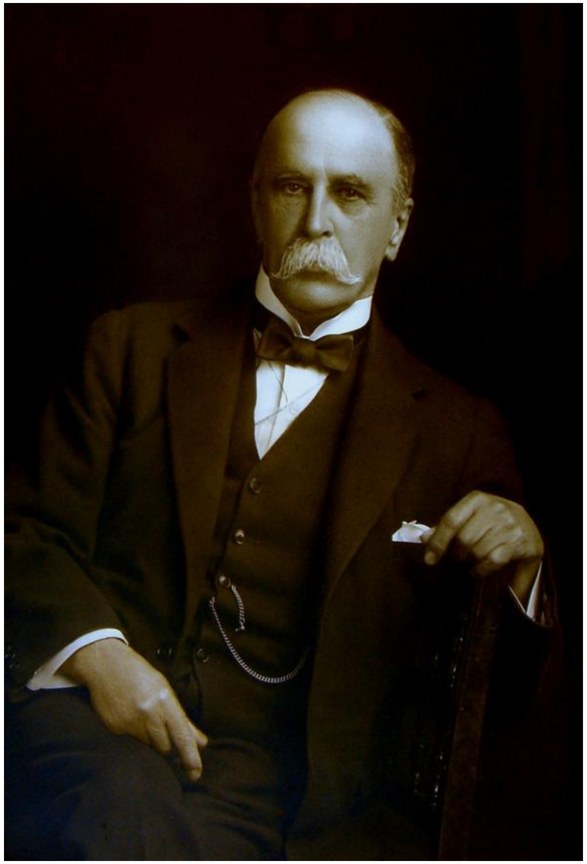
MDxHealth Inc., Veridex Inc., Aduro BioTech Inc., Clontech Laboratories Inc., Cepheid Inc., Digital Harmonics Inc.

Individualized Health, Precision Medicine, and Cancer

"*Variability* is the law of life, and as no two faces are the same, so no two bodies are alike, and *no two individuals react alike and behave alike under the abnormal conditions which we know as disease*."



Sir William Osler
1849 -1919

The Human Genome: Similarities and Differences among Individuals

Human genome size:

♀ 3,117,838,593 base pairs (6 feet)

23 Chromosomes

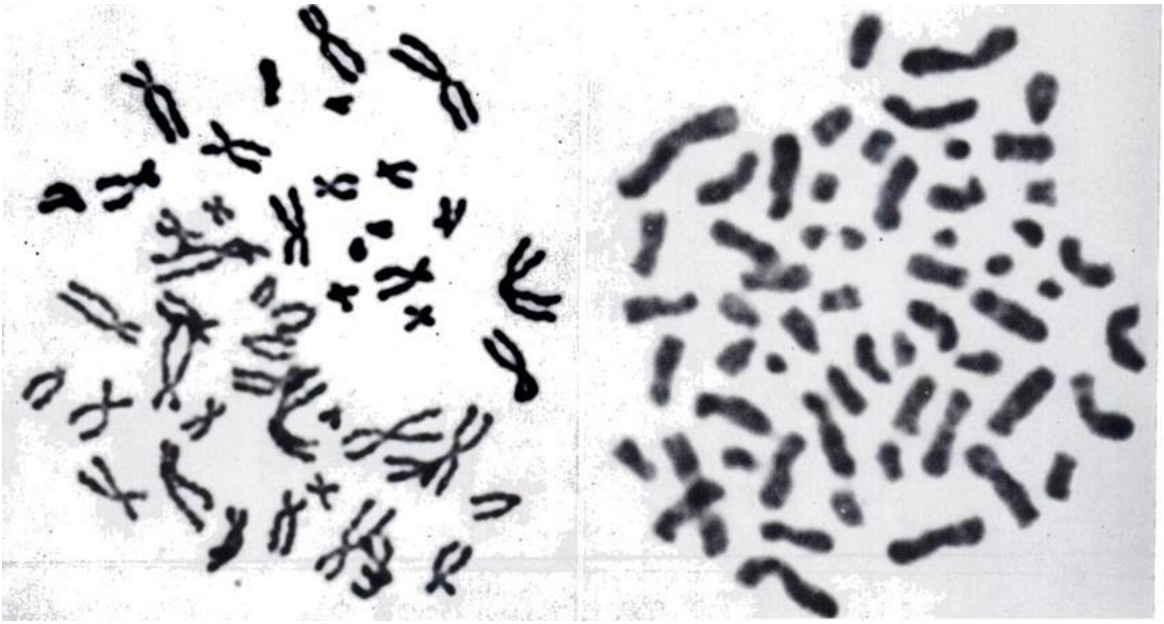
19-20,000 protein-coding genes

Different individuals:

99.9% identical

1 in every 1000 base-pairs are different (>3,000,000 differences between Individuals)

Corruption of the Cancer Genome/Epigenome:
Known for >5 Decades to be at the Root of Cancer



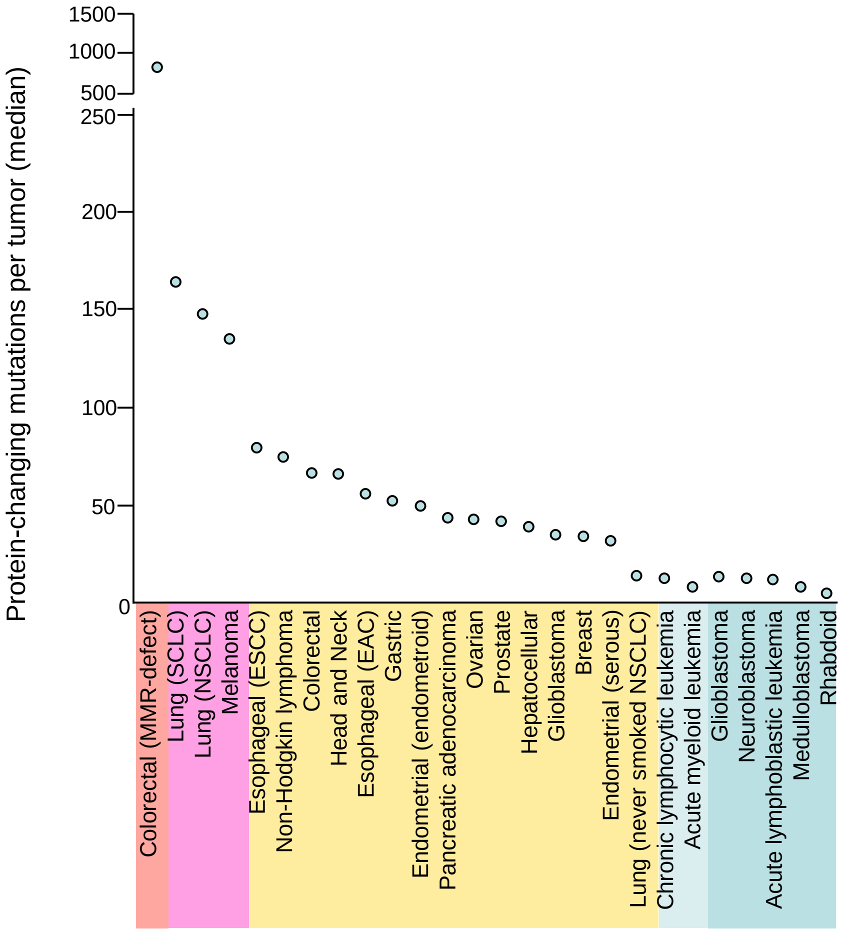
normal bone marrow   acute lymphocytic leukemia

Cancer karyotype

- too many chromosomes
- abnormal chromosomes
- “fuzzy” chromosomes (poor condensation)

*Sandberg AA Cancer Res 28: 2064-81 (1966)

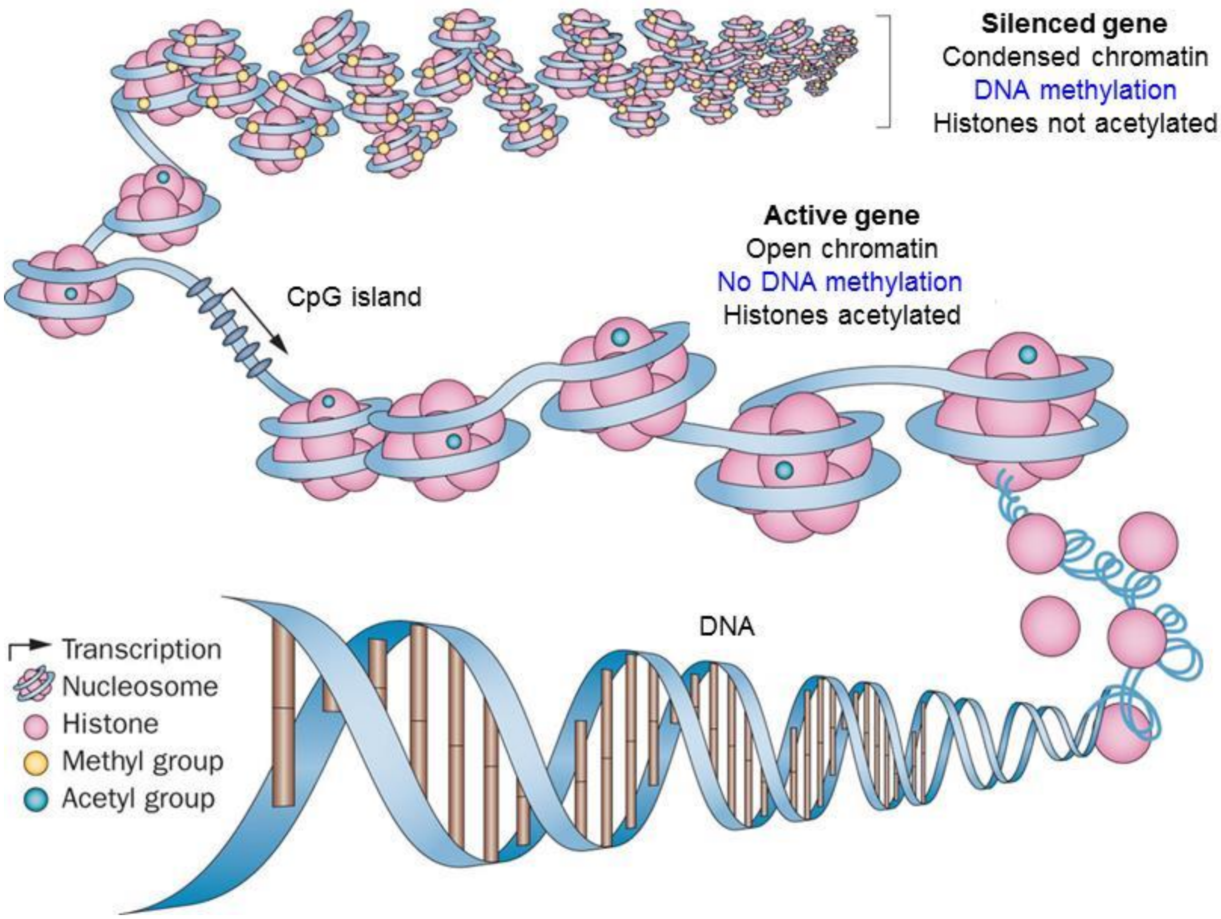
Human Cancers have Many Acquired Gene Defects:
eg. Mutations (Changes in DNA Sequence that Affect Proteins)



Vogelstein B *et al.* Science *339:*1546-58 (2013)

Human Cancers also have Many Acquired Defects in Gene Function (Epigenetic):

eg. DNA Methylation Changes Affecting Protein Expression



Azad N *et al.* Nat Rev Clin Oncol *10:* 256-66 (2013)

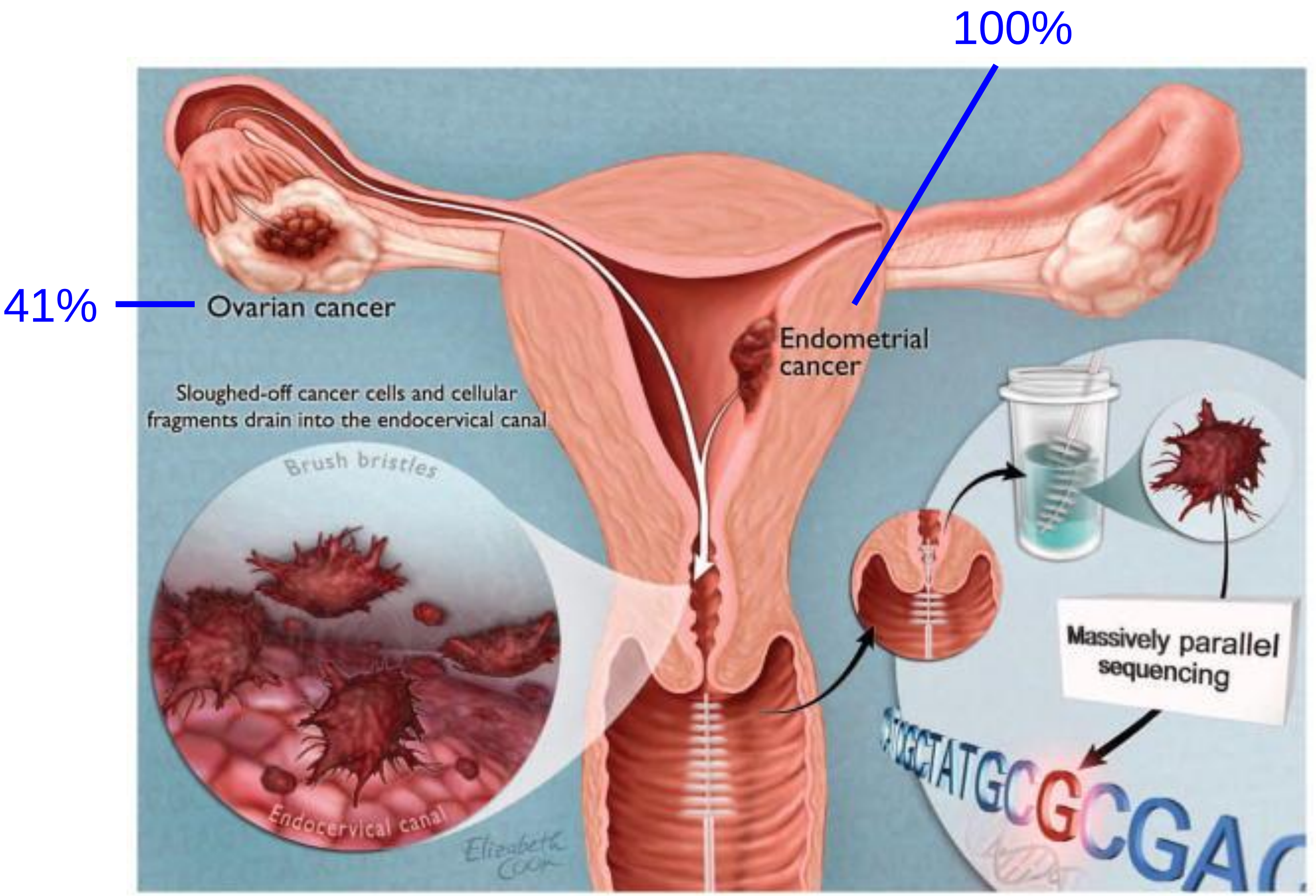
Somatic Gene Defects in Human Cancers

	Genetic	Epigenetic
Number of somatic alterations in each cancer case	10-10^4	10^3-10^4 (Hypermethylation)
Number of alterations that are “drivers” versus “passengers”	1-10^2	Majority or all (Hypermethylation)
Heterogeneity in somatic changes	Mutations: Cell-to-cell: High Lesion-to-lesion: High Case-to-case: High Other Defects: Cell-to-cell: High Lesion-to-lesion: High Case-to-case: High	Hypermethylation: Cell-to-cell: Low Lesion-to-lesion: Low Case-to-case: Medium Hypomethylation: Cell-to-cell: High Lesion-to-lesion: High Case-to-case: High
Rate of accumulation in cancer cells	10^{-9}/cell each division or higher	Unknown
Number of alterations that can be therapeutically targeted	1-3	All?

*Vogelstein B *et al.* Science *339:*1546-58 (2013); Bozic I *et al.* eLife *2:* e00747 (2013)

Diagnostics

Can a DNA Sequencing-Based Test Provide an Opportunity to Screen for Ovarian and Endometrial Cancers Using PaP Smears?

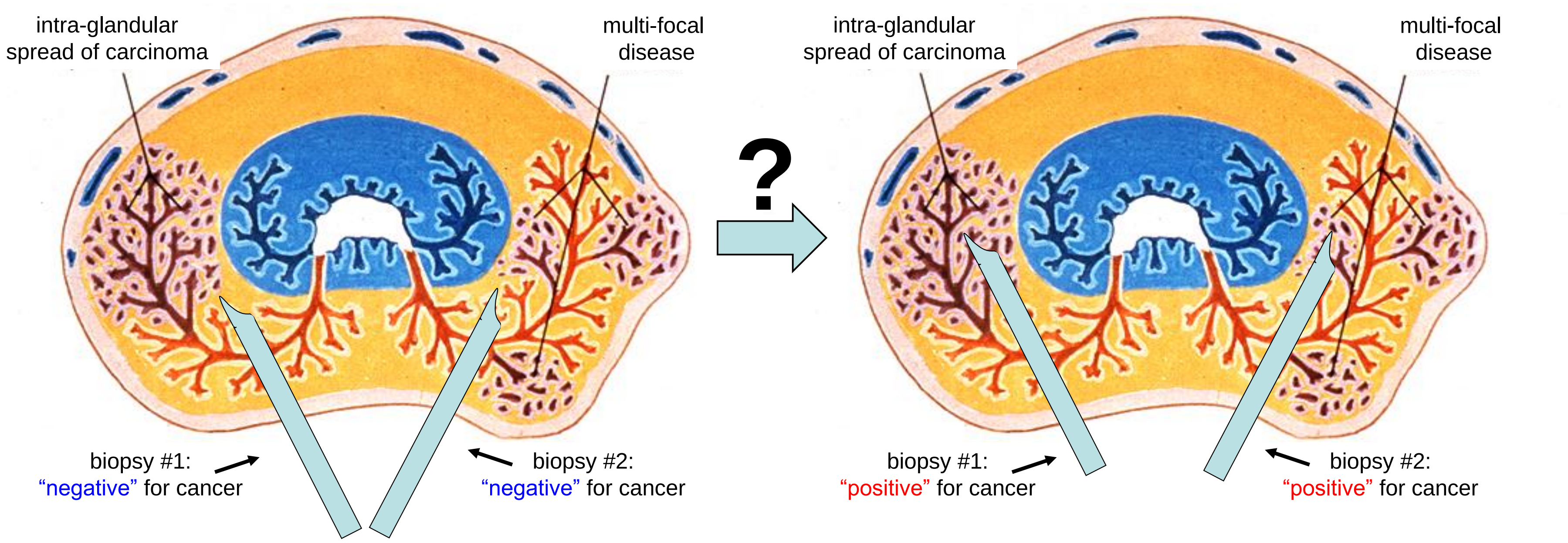


Kinde I *et al.* Sci Transl Med. *5:* 167ra4 (2013).

Can a DNA Methylation Test Improve Upon Patterned Core Biopsy Sampling of the Prostate?

Unmet medical need: as many as 25% of men or more with an initial "negative" prostate biopsy have cancer on a subsequent biopsy.*

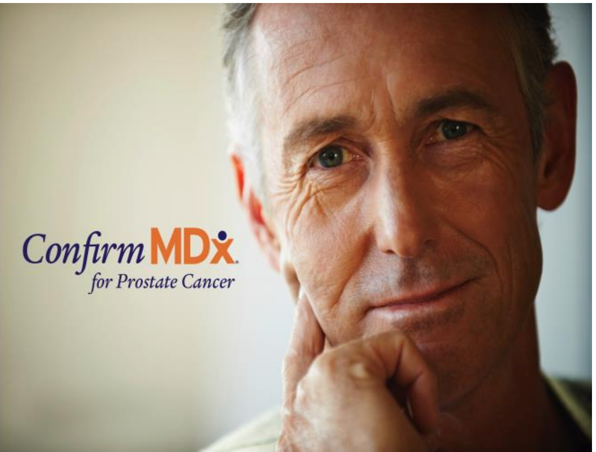
Can a DNA methylation test predict which men need a second prostate biopsy procedure and which men do not?



*Andriole GL *et al.* New Engl J Med *362:* 1192-202 (2010)

United States Food and Drug Administration Approval of a DNA Methylation Test for Prostate Cancer: Pivotal Registration Trial Data*

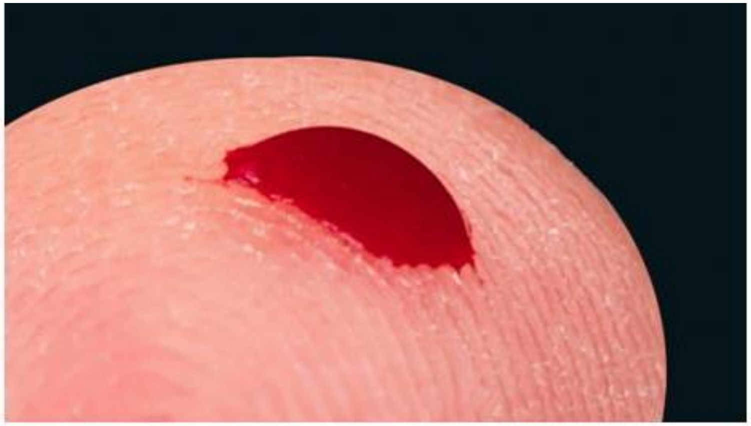
Investigators	Study	Number of Men	Odd Ratio for Cancer on Second Biopsy	Negative Predictive Value
Steward GD *et al.* (2013)	MATLOC	498	3.17 (95% CI of 1.81-5.53)	90% (95% CI of 87-93)
Partin AW *et al.* (2014)	DOCUMENT	350	2.69 (95% CI of 1.60-4.51)	88% (95% CI of 85-91)



*Steward GD et al. J Urol 189: 1110-6 (2013)
Partin AW et al. J Urol 192: 1081-7 (2014)

DNA-Based Tests for Cancer:

(1) Improved Screening, Early Detection, and Diagnosis
(2) ‘Liquid Biopsies” for Treatment Monitoring



Therapeutics

Genome Sequencing, Molecular Diagnostics and "Targeted" Anti-Cancer Drugs

Trastuzumab
(Herceptin®)

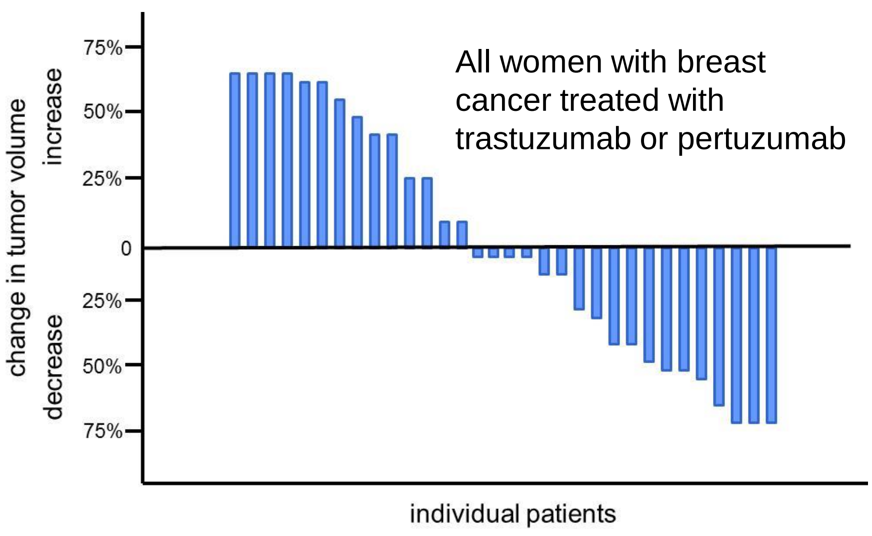
FDA-approved 1998

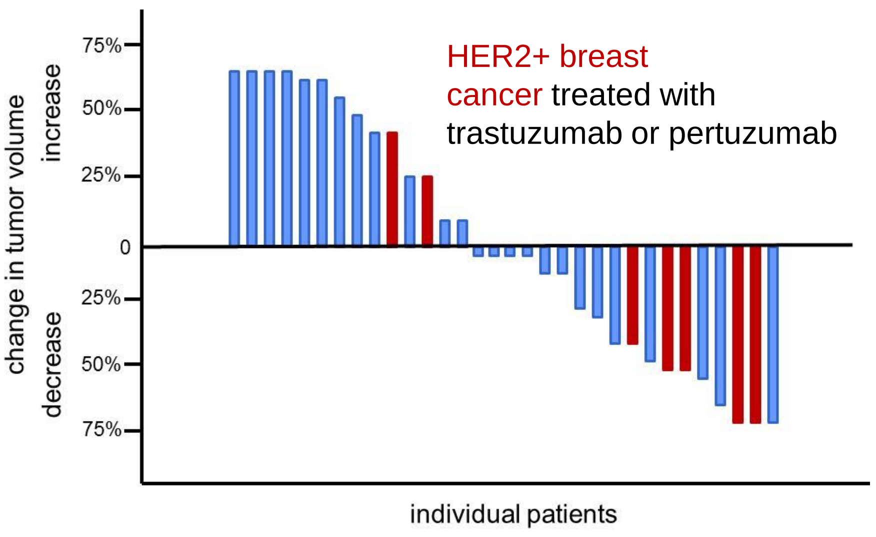
Imatinib
(Gleevec®)

FDA-approved 2001

"Waterfall Plots" Show Individual Differences in Responses to Cancer Treatments Attributable to Differential Sensitivities of Cancers with/without Specific Acquired Gene Defects

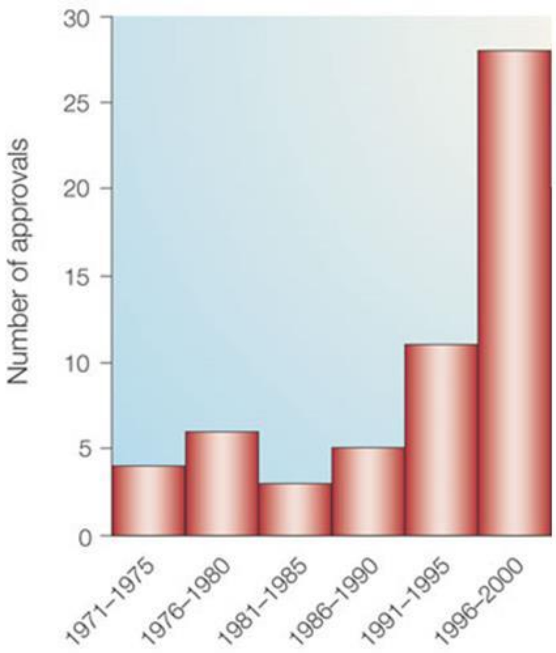
Breast Cancers with/without HER2 Amplification
Treated with Trastuzumab or Pertuzumab





Accelerating Pace of Anti-Cancer Drug Discovery, Development, and Approval*

Oncology Drug Approvals by the Food and Drug Administration

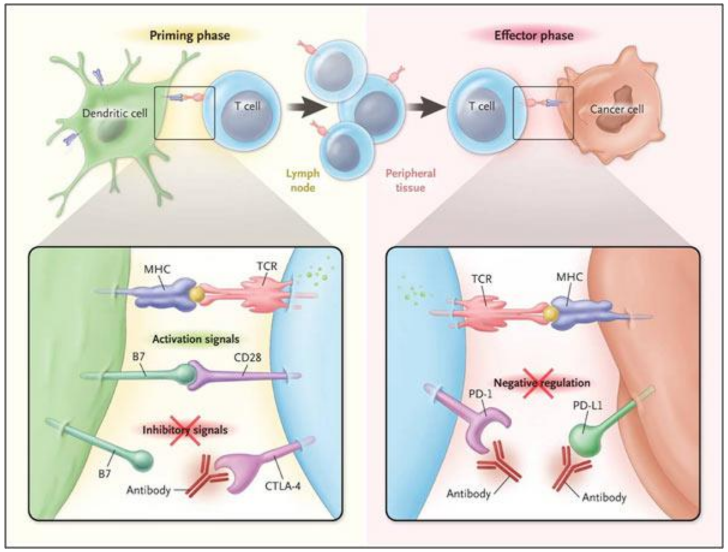


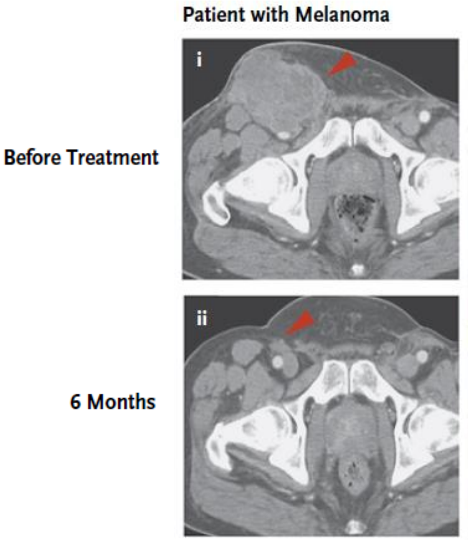
- 12 oncology approvals in 2013
- 10 oncology approvals in 2014
- 8 oncology approvals so far in 2015

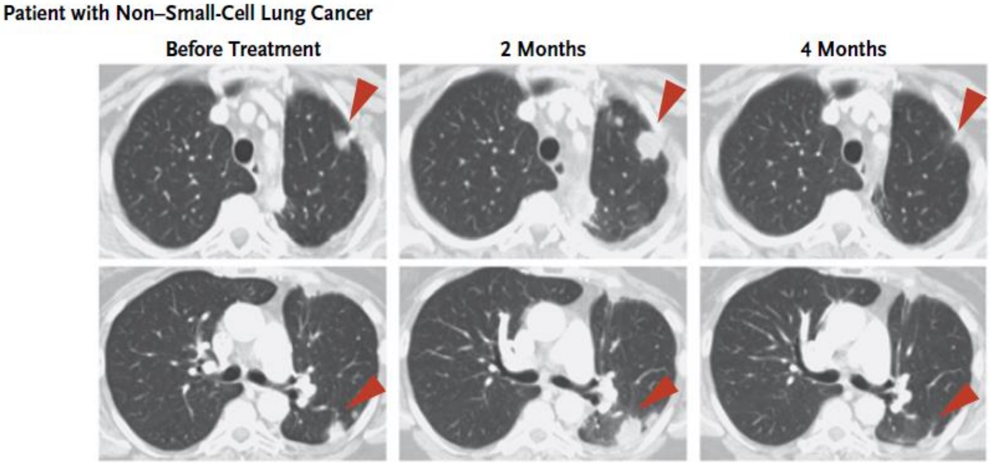
*Chabner BA and Roberts TG Nat Rev Cancer *5:* 65-72 (2005); fda.gov

Immunotherapeutics

Immune Checkpoint Inhibitors Transforming Cancer Care: Development of Ipilumumab, Nivolumab, and Pembrolizumab*

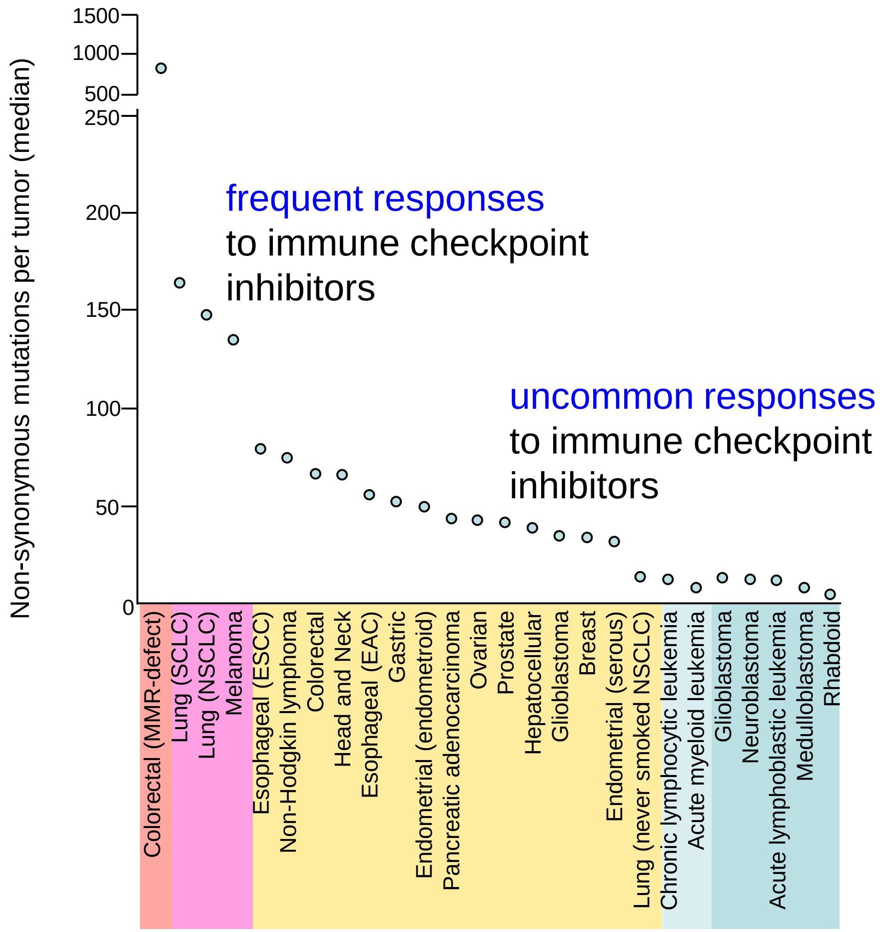






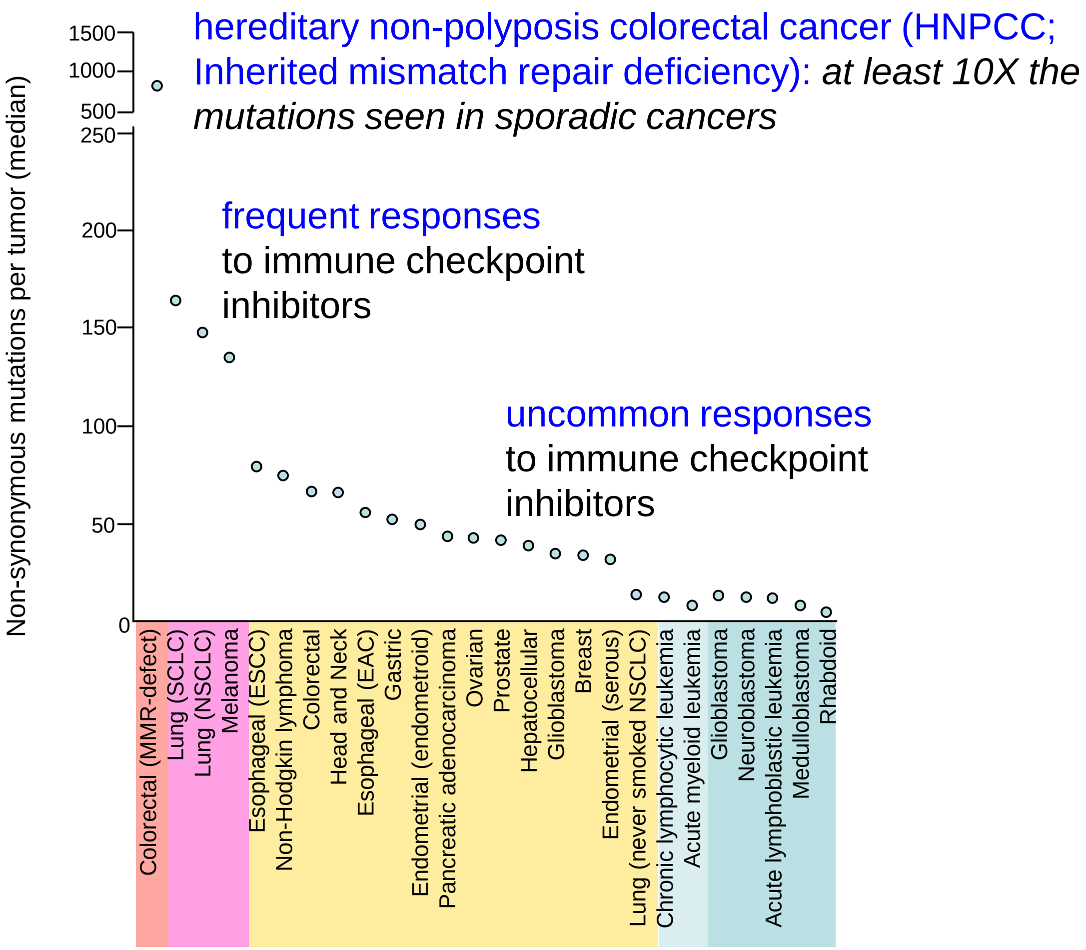
*Topalian SL *et al.* New Engl J Med *366:* 2443-54 (2012)

Acquired Protein-Changing Gene Mutations and Responses to Immune Checkpoint Inhibitors



Vogelstein B *et al.* Science *339:*1546-58 (2013)

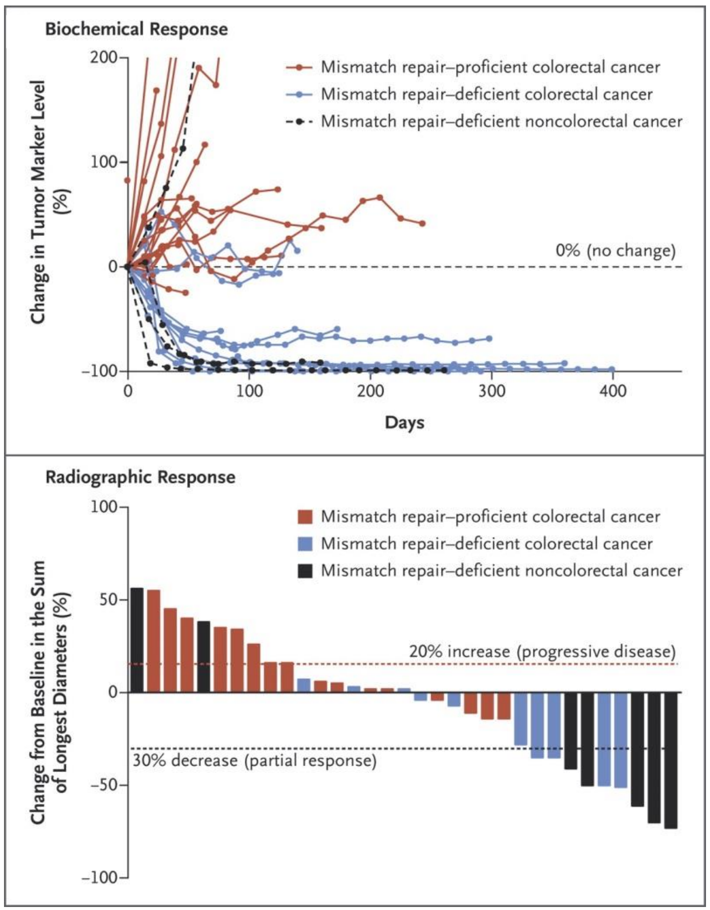
Acquired **Protein-Changing Gene Mutations** and Responses to **Immune Checkpoint Inhibitors**

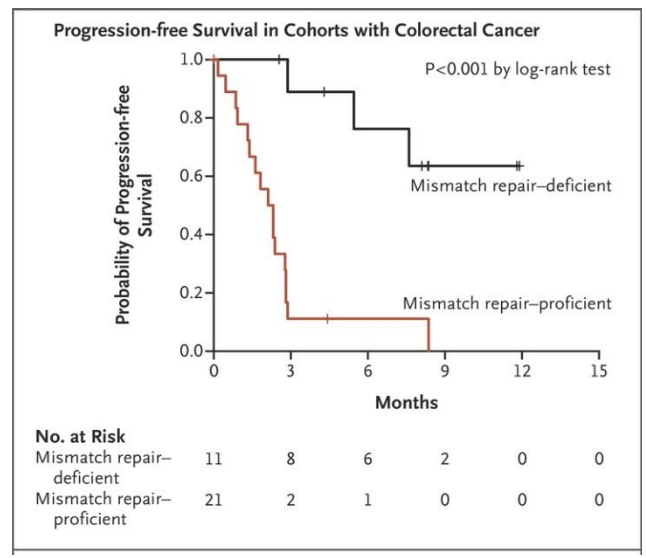


Vogelstein B *et al.* Science *339:*1546-58 (2013)

Cancers from Families with HNPCC (Mismatch Repair Deficiency): an Indication for Immune Checkpoint Inhibitors?

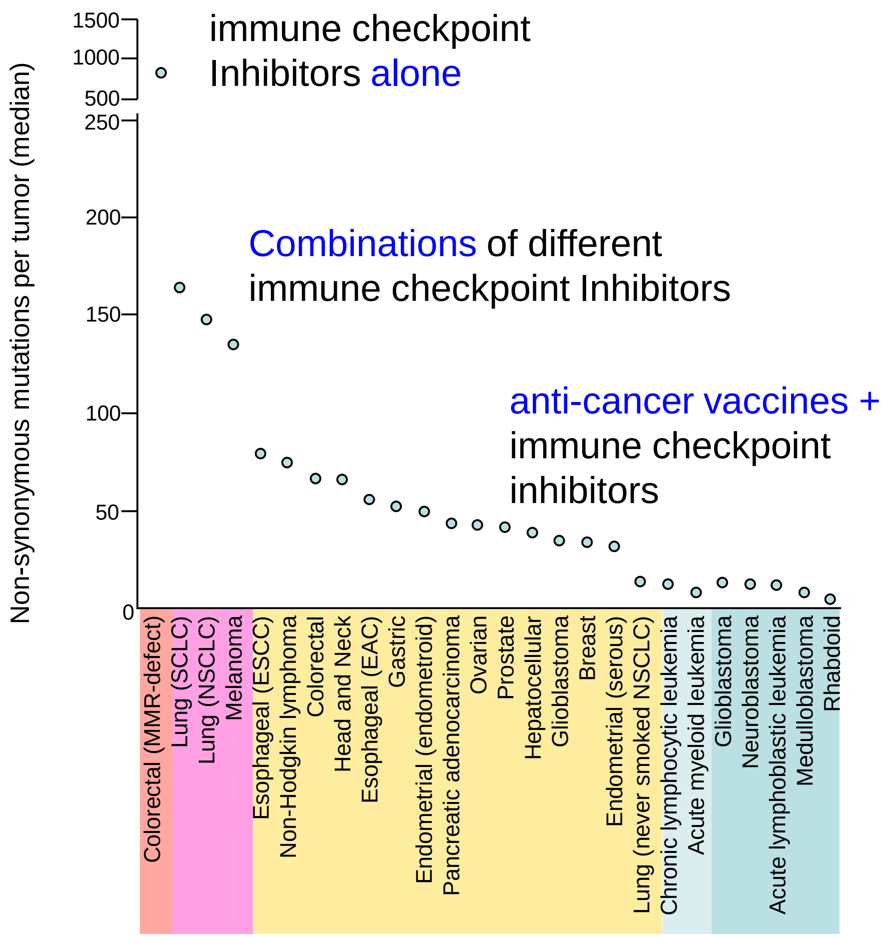
Clinical Trial of Pembrolizumab for Cancers with and without Mismatch Repair Defects*





*Le DT *et al.* N Engl J Med *372:* 2509-20 (2015)

Future Best Uses of Immune Checkpoint Inhibitors in Cancer Treatment



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