



# Precision Medicine

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# Precision/Personalized Medicine



“And that’s why we’re here today. Because **something called precision medicine -- in some cases, people call it personalized medicine** -- gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen.”

“And that’s the promise of precision medicine -- delivering the right treatments, at the right time, every time to the right person.” (President Obama)



PRESIDENT OBAMA'S PRECISION MEDICINE INITIATIVE WOULD  
**HELP DEVELOP BETTER TREATMENTS  
FOR DISEASES LIKE CANCER BY:**

- Accelerating the design and testing of effective **treatments tailored to individual patients**
- Expanding genetically based clinical cancer trials
- Establishing a national "**cancer knowledge network**" to guide treatment decisions

# US Moon shot program



- Clinical Trials
- Enhanced Data Sharing
- Cancer Immunology
- Implementation Science
- Pediatric Cancer
- Precision Prevention and Early Detection
- Tumor Evolution and Progression

# Recommendations

- **Establish a network for direct patient involvement**
- **Create a clinical trials network devoted exclusively to immunotherapy**
- **Develop ways to overcome resistance to therapy**
- **Build a national cancer data ecosystem**
- **Intensify research on the major drivers of childhood cancers**
- **Minimize cancer treatment's debilitating side effects**
- **Expand use of proven prevention and early detection strategies**
- **Mine past patient data to predict future patient outcomes**
- **Develop a 3D cancer atlas**
- **Develop new cancer technologies**

# How to keep people healthy

**Prevent disease**  
**Detect disease early**  
**Treat disease effectively**



# Assessing Risk



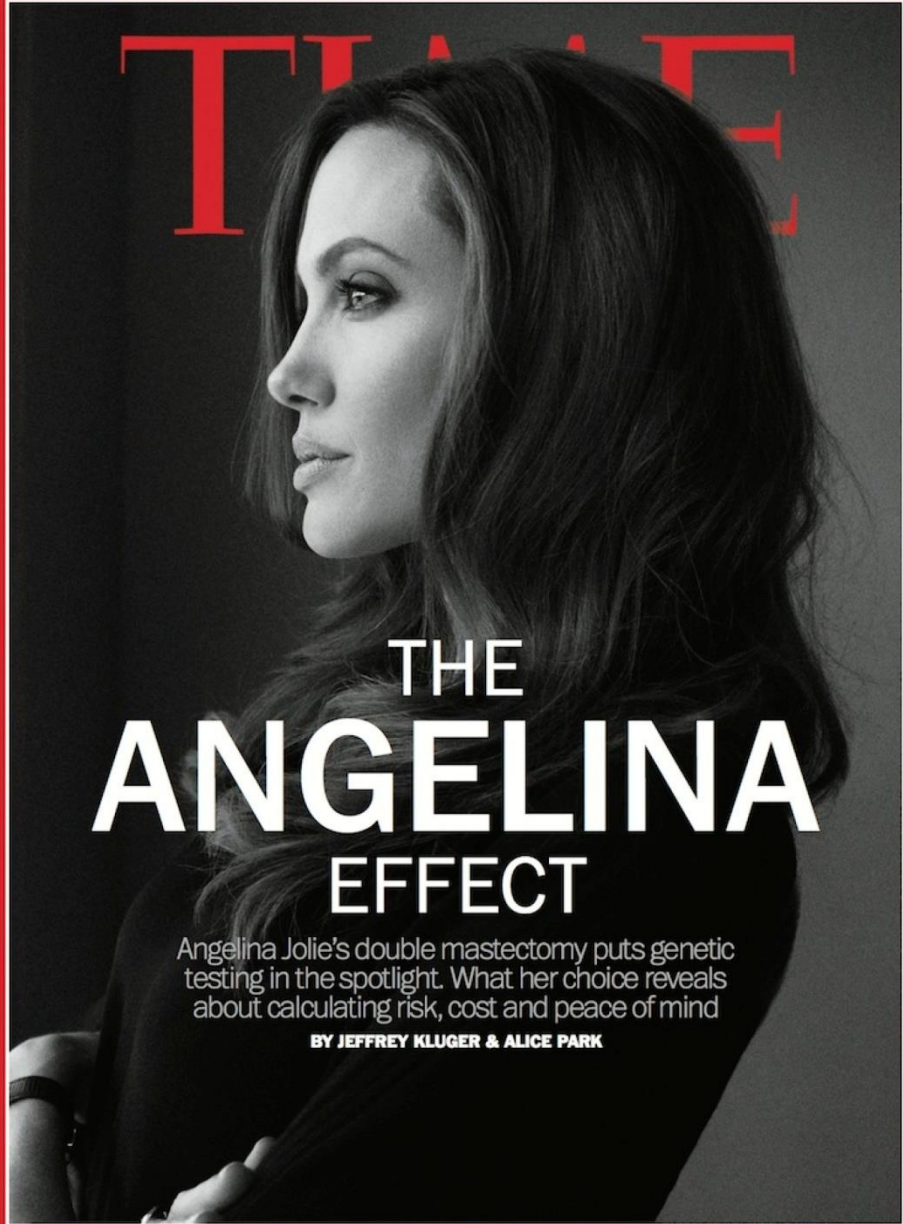
# Cancer Susceptibility



**OP-ED CONTRIBUTOR**  
**My Medical Choice**  
**By ANGELINA JOLIE**  
**Published: May 14, 2013**

**BRCA testing increased**  
**by 2 – 2.5X. ( Sept 2014.**  
**Several news reports)**

MAY 27, 2013



# THE ANGELINA EFFECT

Angelina Jolie's double mastectomy puts genetic testing in the spotlight. What her choice reveals about calculating risk, cost and peace of mind

BY JEFFREY KLUGER & ALICE PARK

time.com

# Cancer susceptibility genes

10% of all cancers are the result of gene predisposition

## Breast Cancer

BRCA1  
BRCA2  
ATM  
BLM  
CDH1  
CDKN2A  
MUTYH  
MLH1  
NBN  
PALB2  
PRSS1  
and SLX4

## Colon Cancer/Lynch syndrome

MLH1  
MLH3  
PMS2  
MSH2  
MSH3  
MSH6  
MUTY

NCCN: All CRC patients should be tested for Lynch syndrome

# Predisposition genes in pediatric cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Germline Mutations in Predisposition Genes in Pediatric Cancer

Jinghui Zhang, Ph.D., Michael F. Walsh, M.D., Gang Wu, Ph.D., Michael N. Edmonson, B.A., Tanja A. Gruber, M.D., Ph.D., John Easton, Ph.D., Dale Hedges, Ph.D., Xiaotu Ma, Ph.D., Xin Zhou, Ph.D., Donald A. Yergeau, Ph.D., Mark R. Wilkinson, B.S., Bhavin Vadodaria, B.A., Xiang Chen, Ph.D., Rose B. McGee, M.S., Stacy Hines-Dowell, D.N.P., Regina Nuccio, M.S., Emily Quinn, M.S., Sheila A. Shurtleff, Ph.D., Michael Rusch, B.A., Aman Patel, M.S., Jared B. Becksfort, M.S., Shuoguo Wang, Ph.D., Meaghann S. Weaver, M.D., Li Ding, Ph.D., Elaine R. Mardis, Ph.D., Richard K. Wilson, Ph.D., Amar Gajjar, M.D., David W. Ellison, M.D., Ph.D., Alberto S. Pappo, M.D., Ching-Hon Pui, M.D., Kim E. Nichols, M.D., and James R. Downing, M.D.

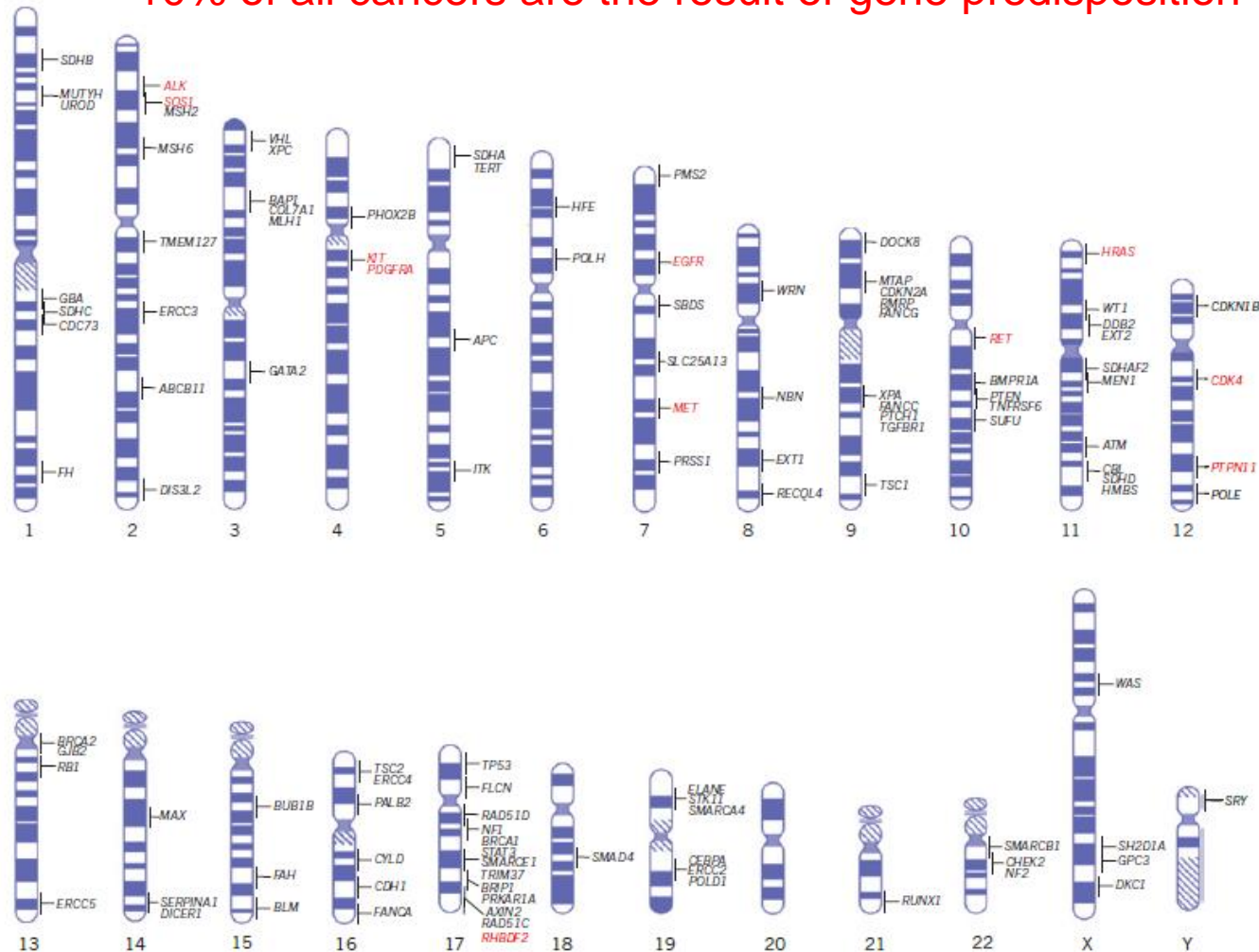
NEJM 373:2336-2346.  
2015

“Germline mutations in cancer-predisposing genes were identified in 8.5% of the children and adolescents with cancer. Family history did not predict the presence of an underlying predisposition syndrome in most patients.”



# 114 Cancer Predisposition Genes

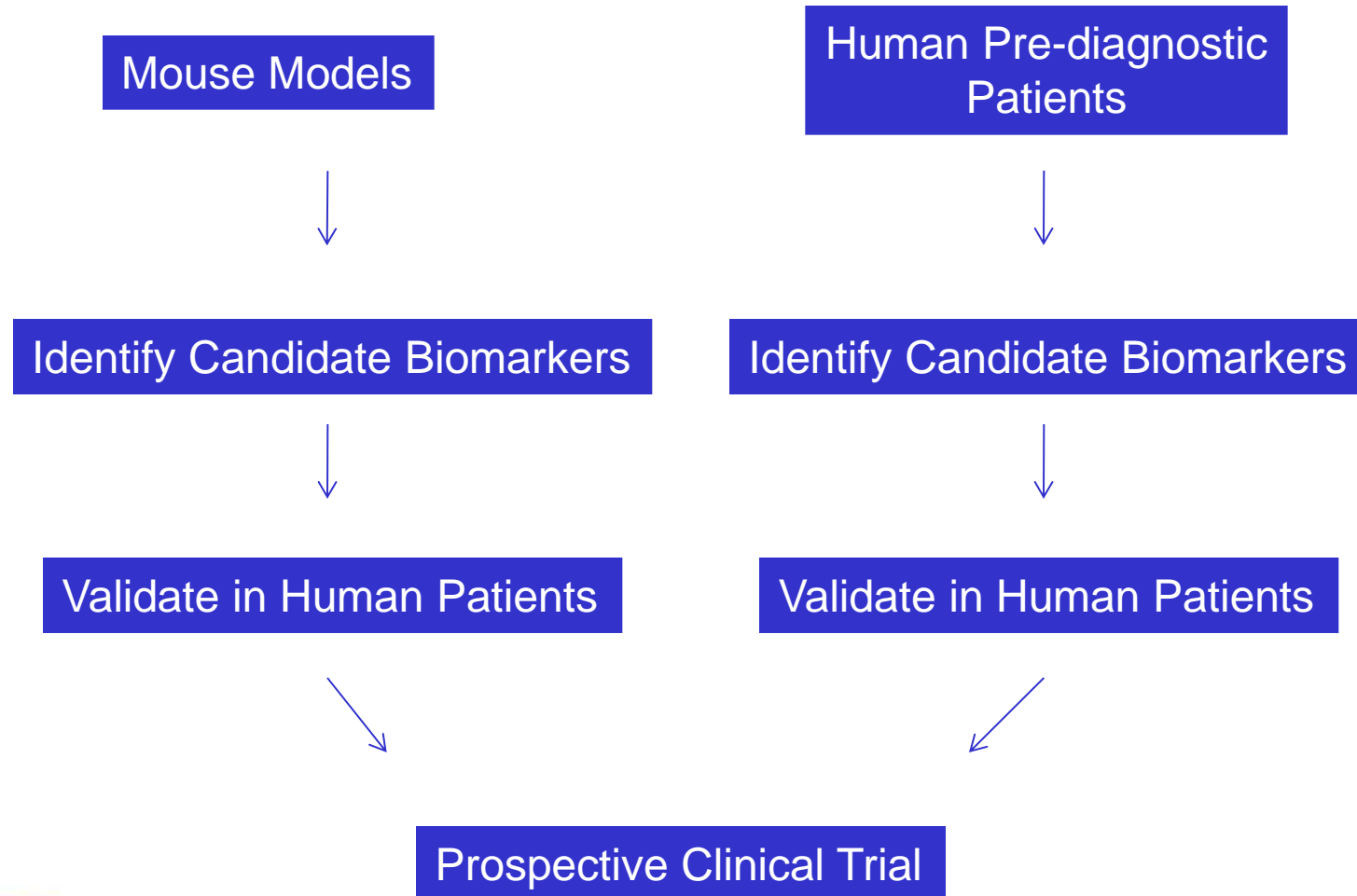
10% of all cancers are the result of gene predisposition



Rahman Nature 505: 302. 2014

# Early Detection

# Biomarker Discovery Approaches



# Lung Cancer Signatures in Plasma Based on Proteome Profiling of Mouse Tumor Models

Ayumu Taguchi,<sup>1</sup> Katerina Politi,<sup>2,8</sup> Sharon J. Pitteri,<sup>1</sup> William W. Lockwood,<sup>2,9</sup> Vitor M. Faça,<sup>1</sup> Karen Kelly-Spratt,<sup>1</sup> Chee-Hong Wong,<sup>1</sup> Qing Zhang,<sup>1</sup> Alice Chin,<sup>1</sup> Kwon-Sik Park,<sup>3</sup> Gary Goodman,<sup>1</sup> Adi F. Gazdar,<sup>4</sup> Julien Sage,<sup>3</sup> Daniela M. Dinulescu,<sup>5</sup> Raju Kucherlapati,<sup>6</sup> Ronald A. DePinho,<sup>7</sup> Christopher J. Kemp,<sup>1</sup> Harold E. Varmus,<sup>2,9</sup> and Samir M. Hanash<sup>1,\*</sup>

Gene	Lung Mouse Models			
	EGFR	Kras	Urethane	SCLC
Sftpb	4.83	3.41	1.99	—
Morc3	*	10	10	—
Fgfr2	9.8	*	—	—
Adam10	7.85	1.5	—	—
Man2b2	4.22	1.46	—	—
Tfpi2	10	*	—	—
Son	*	10	—	—
Eif2ak3	*	9.03	—	—
Hamp2	*	3.07	—	—
Ncan	*	1.45	—	—
Sftpd	10	—	10	—
Mocs1	1.71	—	1.3	—
Nup188	—	*	10	—
Igsf4a	3.55	1.48	1.55	3.32
Pbbp	1.63	1.7	5.12	1.39
Prtg	10	10	—	10



# Woman's Health Initiative

**Established by NIH in 1991 to address cardiovascular disease, cancer, and osteoporosis**

**Observational study to identify predictors of disease**

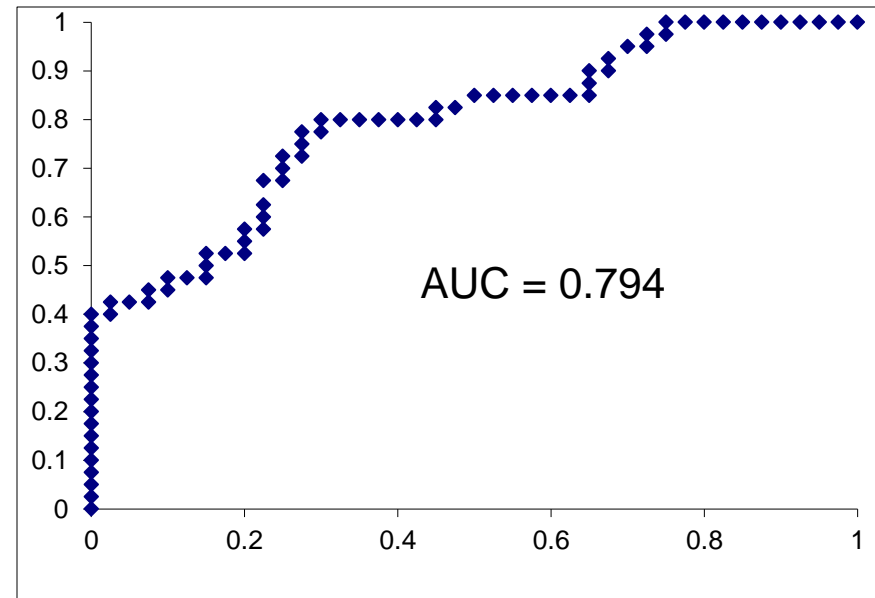
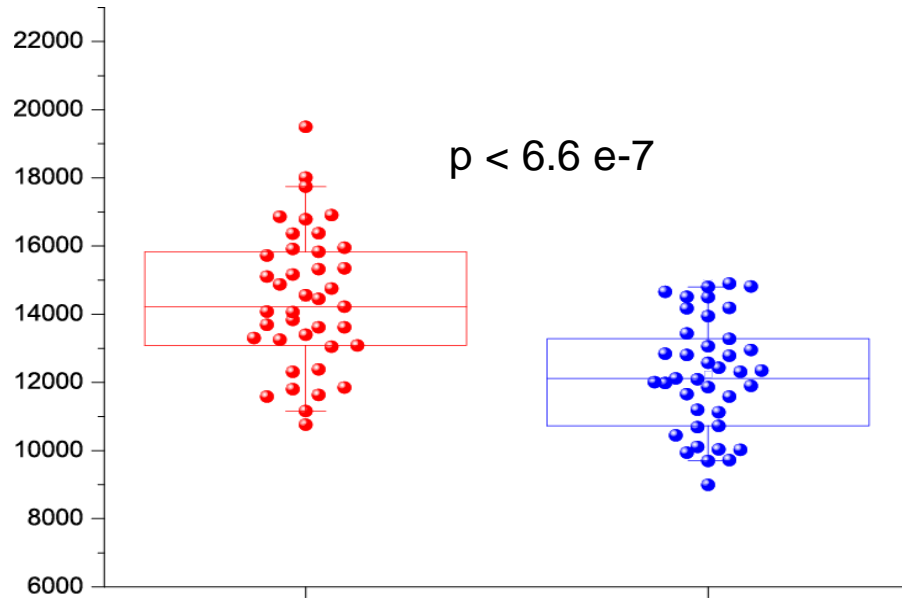
Clinical data

Serum bank

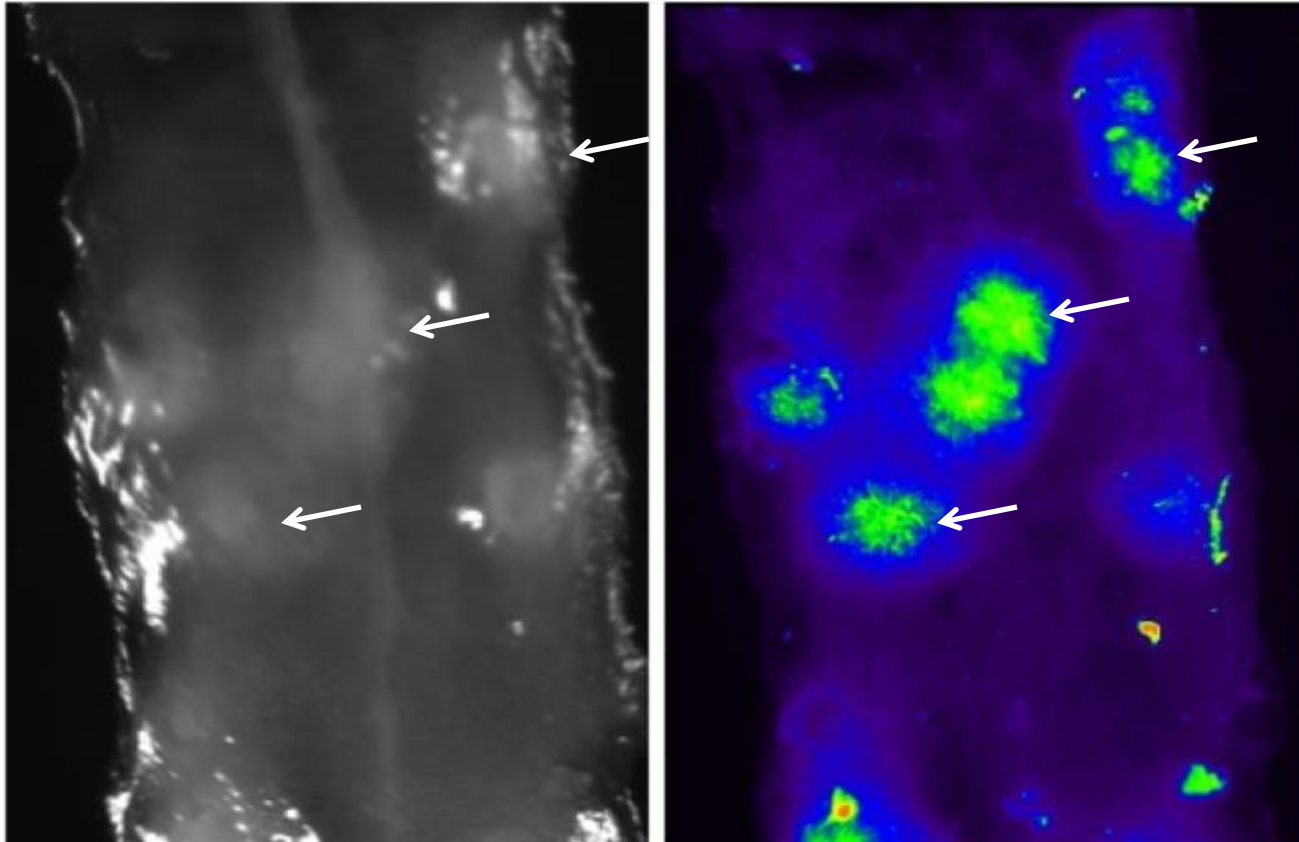
**Pre-diagnostic serum from 100 cases and 120 controls**

Cases were diagnosed with CRC within 18 months

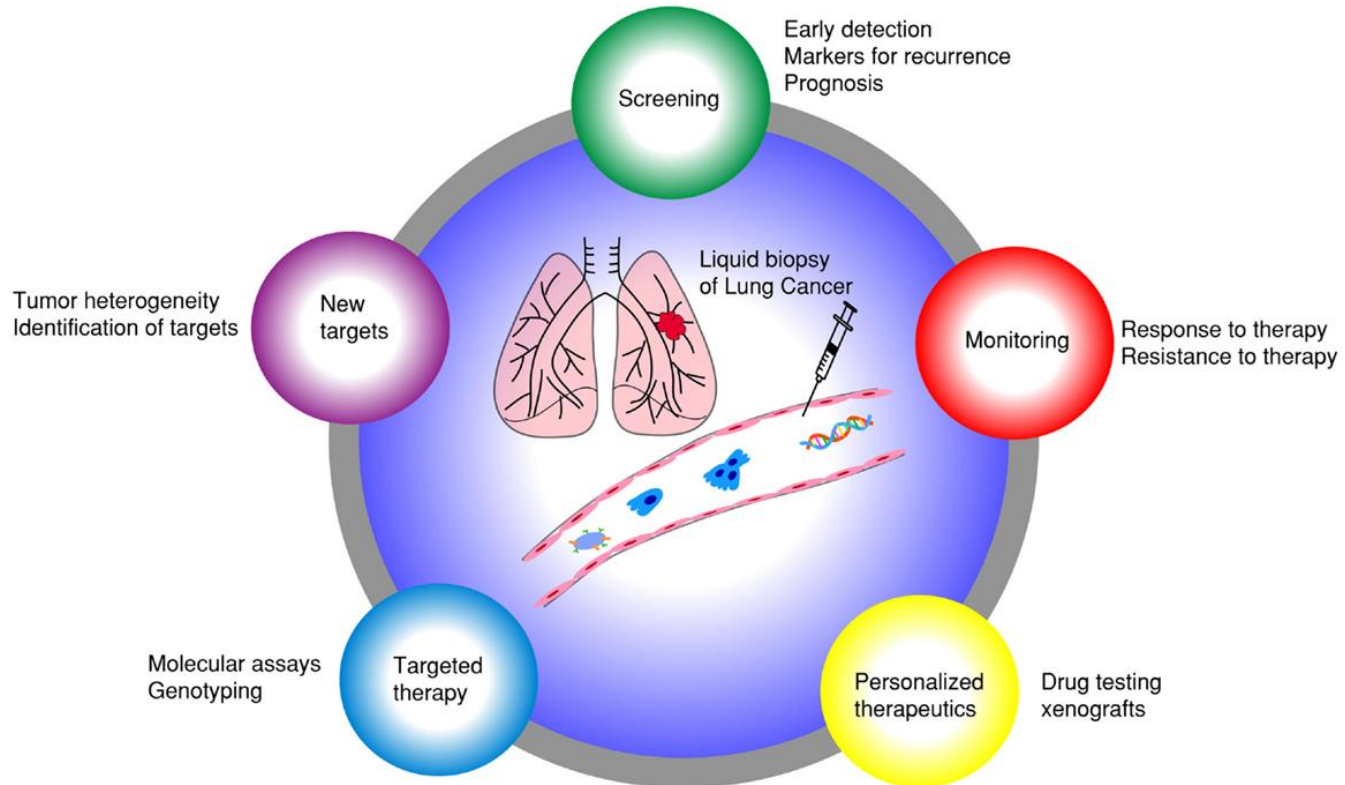
# Cathepsin D



# Prosense Imaging

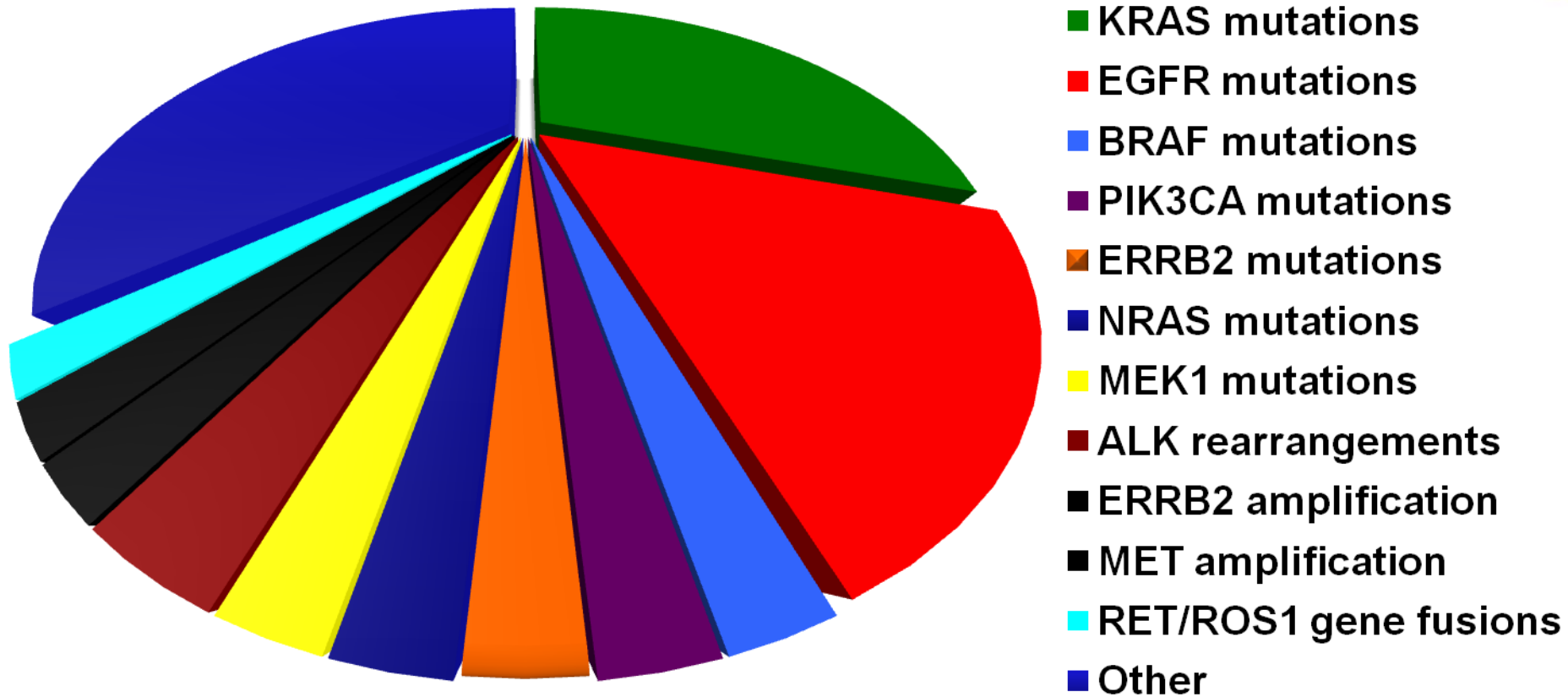


# Liquid biopsy



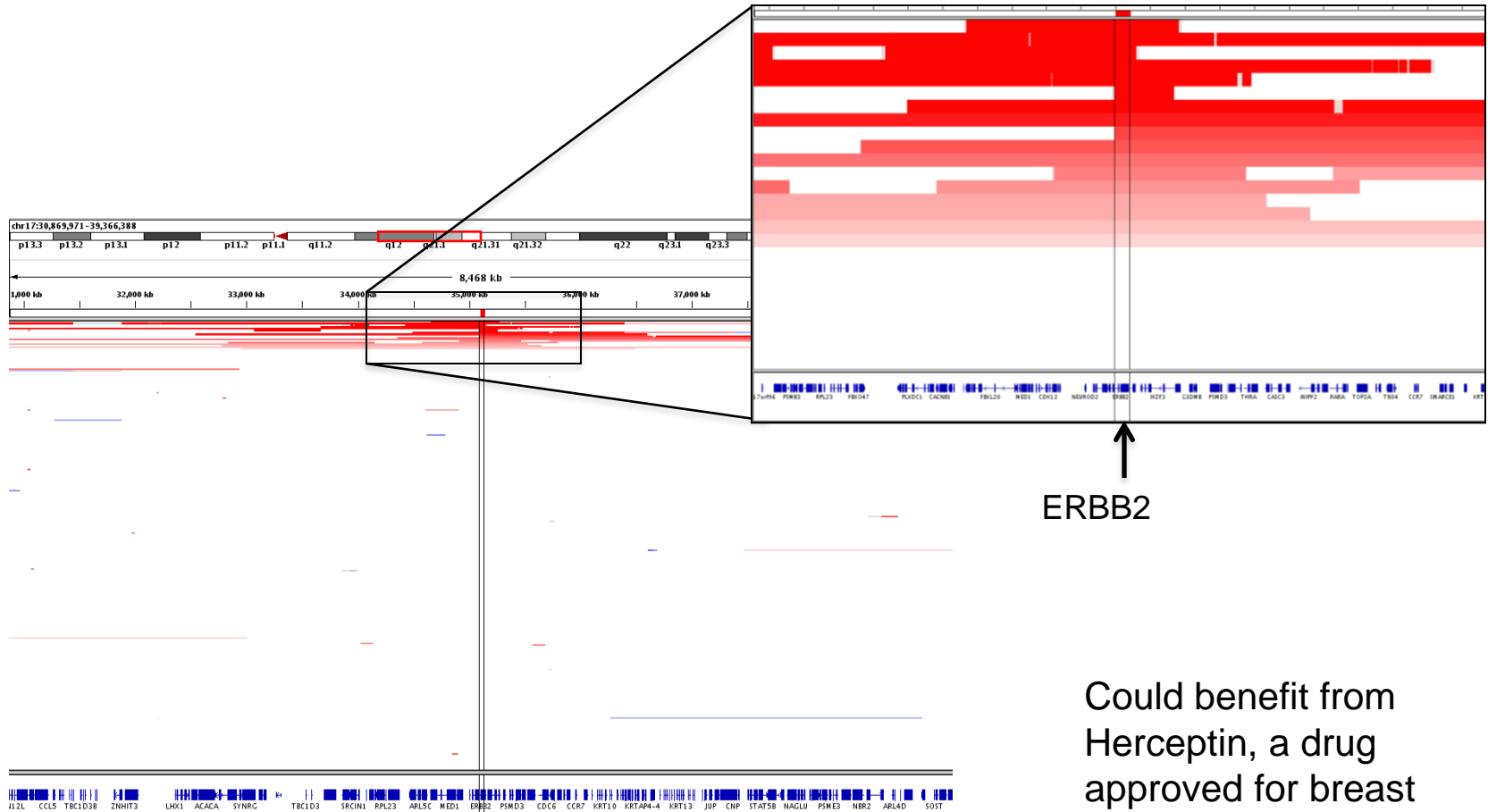
# Treatment

# Genetic changes in non-small cell lung cancer



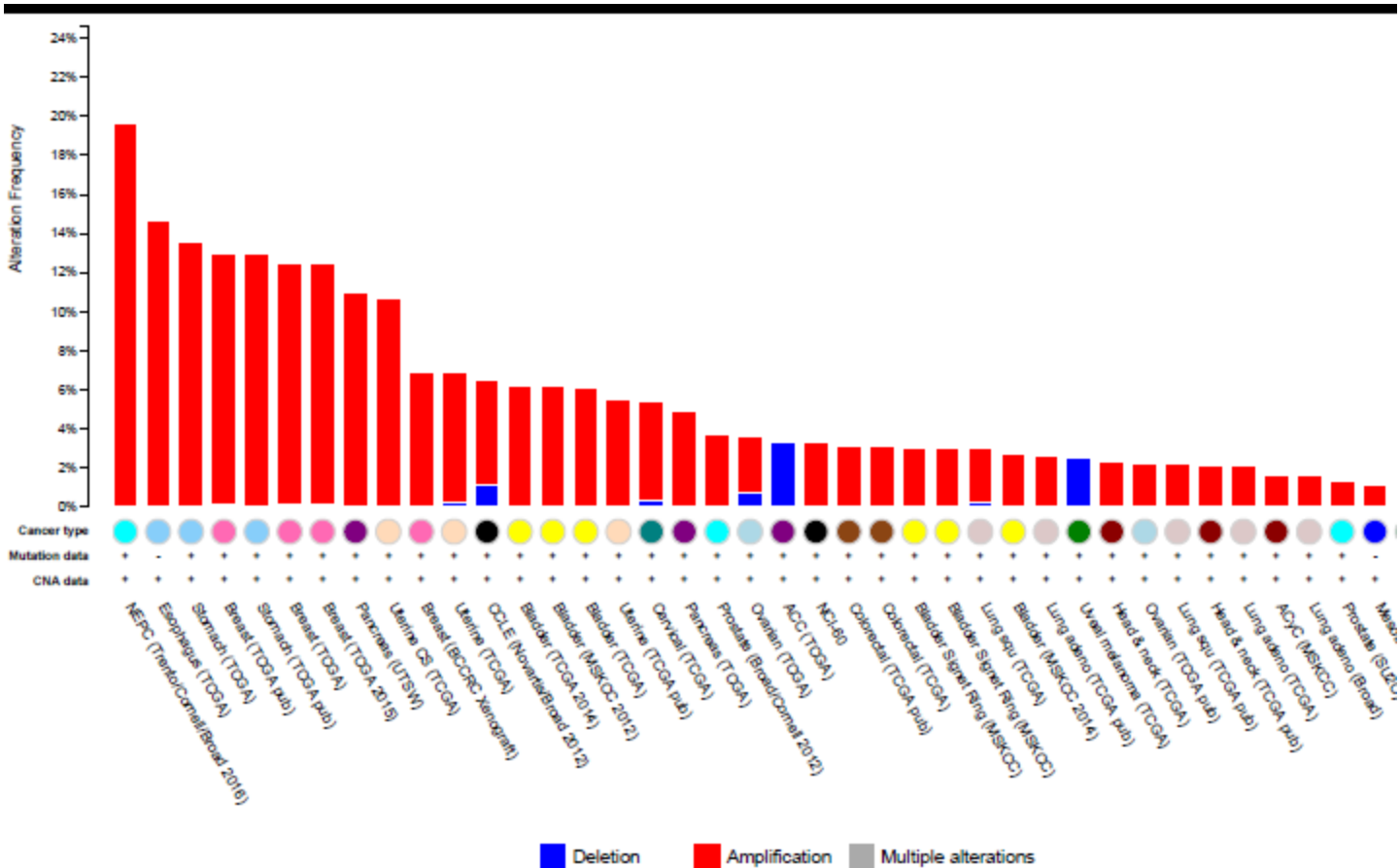
Targeted therapies for all of these genetic alterations are approved or in development

# CRC: ERBB2 Amplifications (4%)



Could benefit from Herceptin, a drug approved for breast cancer

# ERBB2 amplification in many tumor types

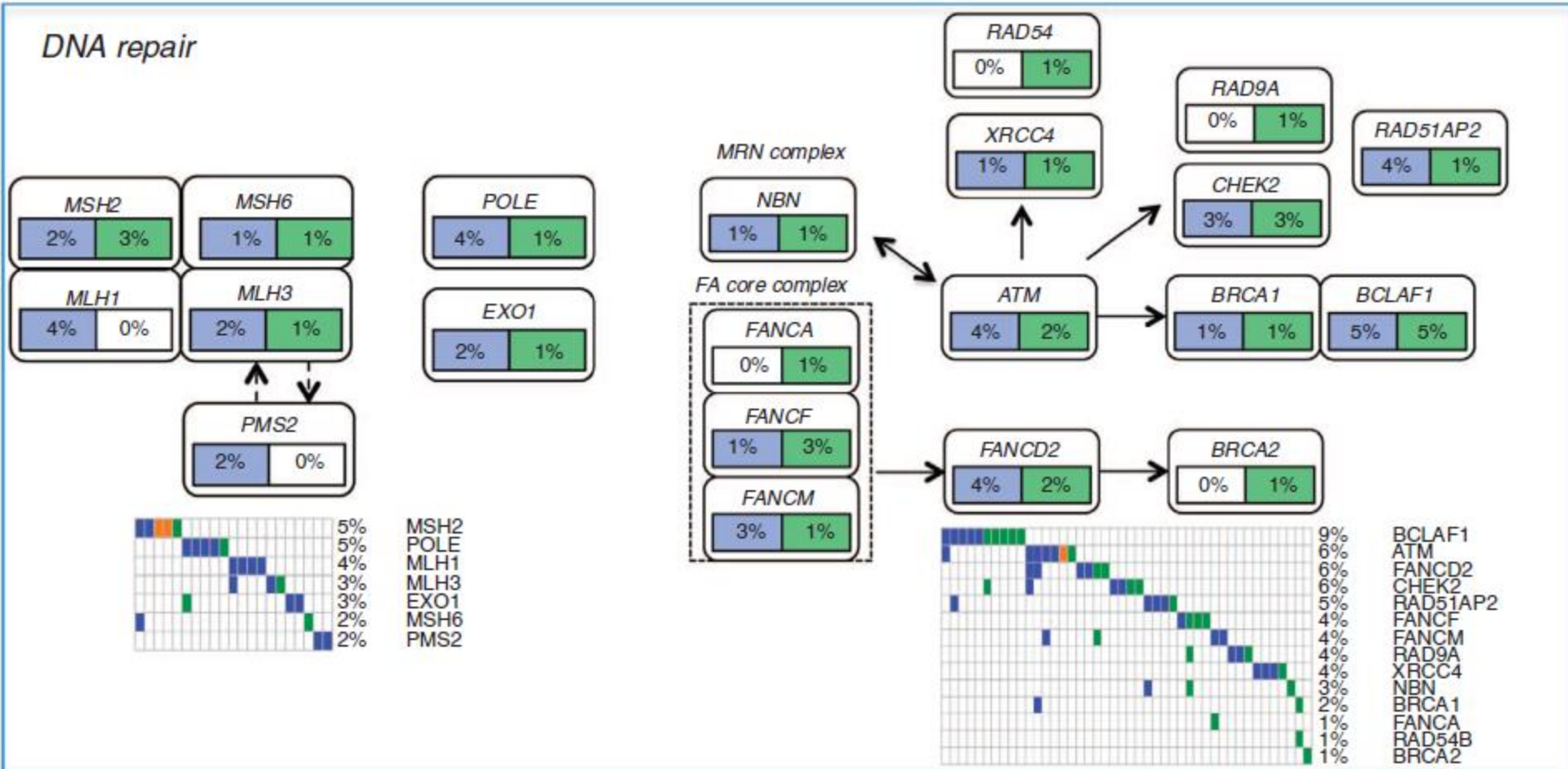


from cBIO Portal



# Pancreatic cancer

## DNA repair



Witkiewicz et al. Nature Comm. 6: 1-10, 2015

# Mutation burden

Colorectal adenocarcinoma mutation rates (224 patients)

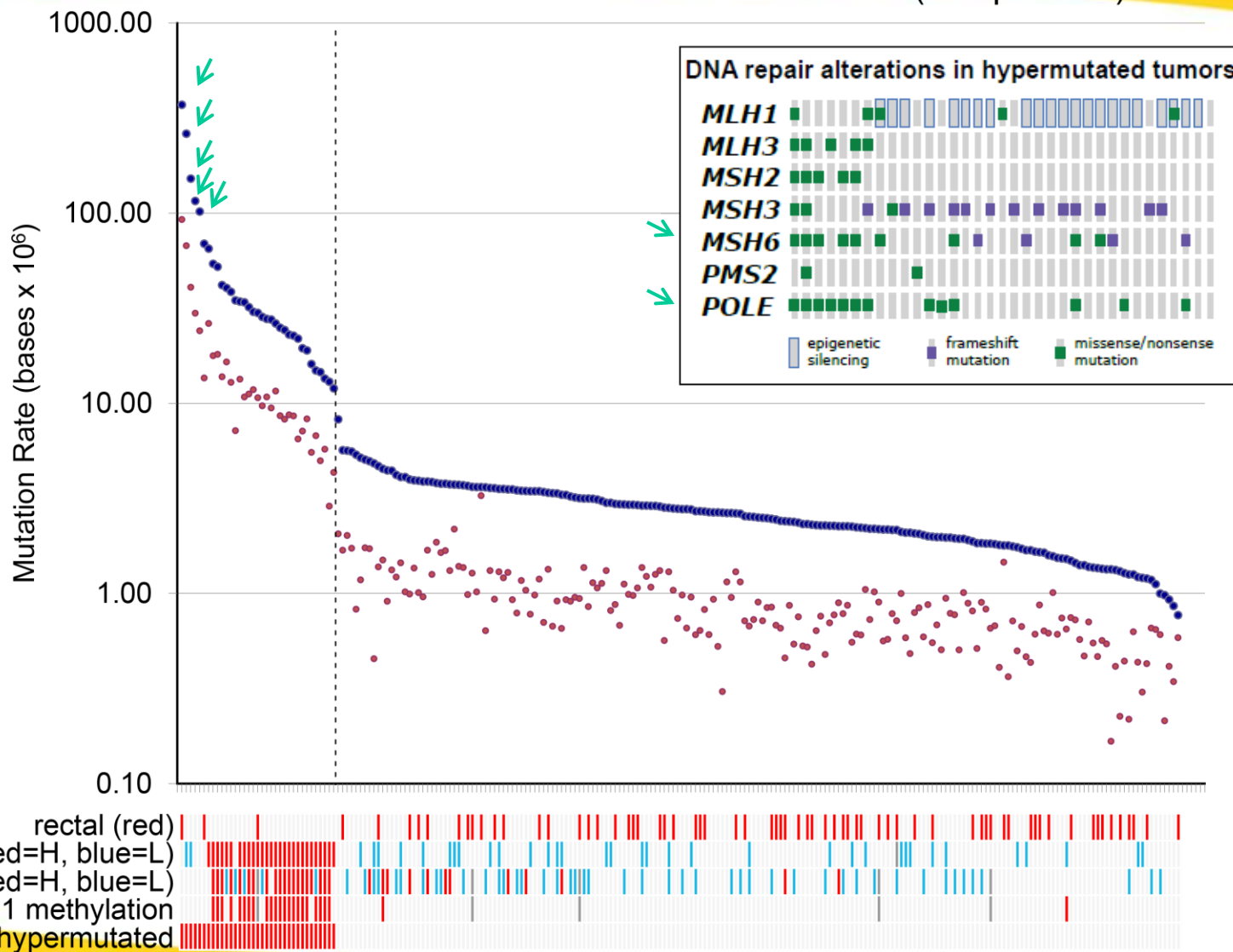
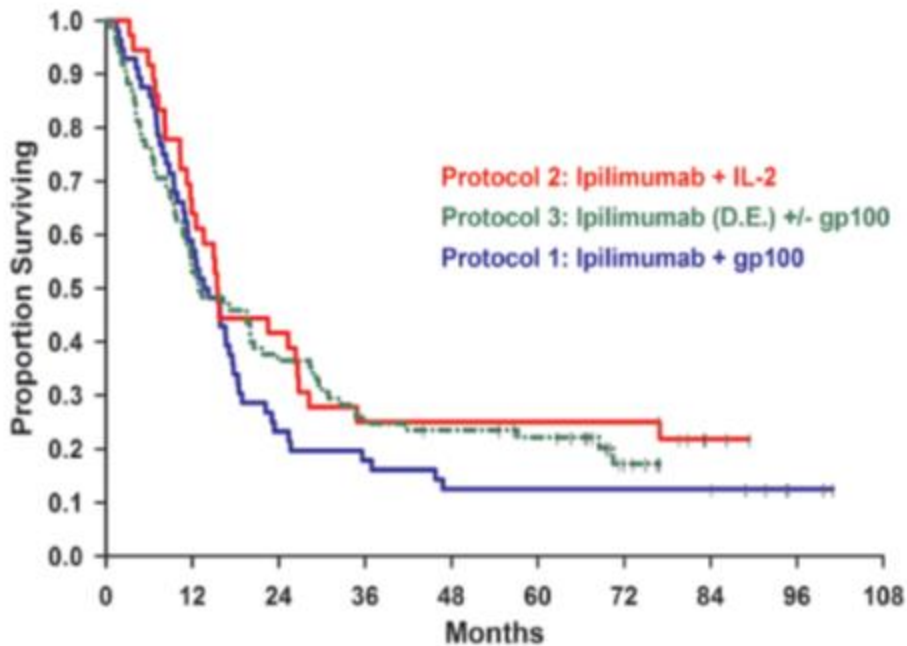




Image courtesy of Bristol-Myers Squibb

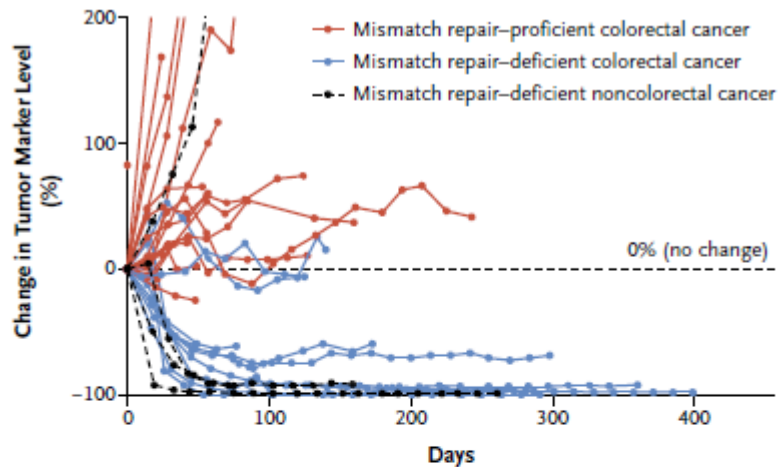


## PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

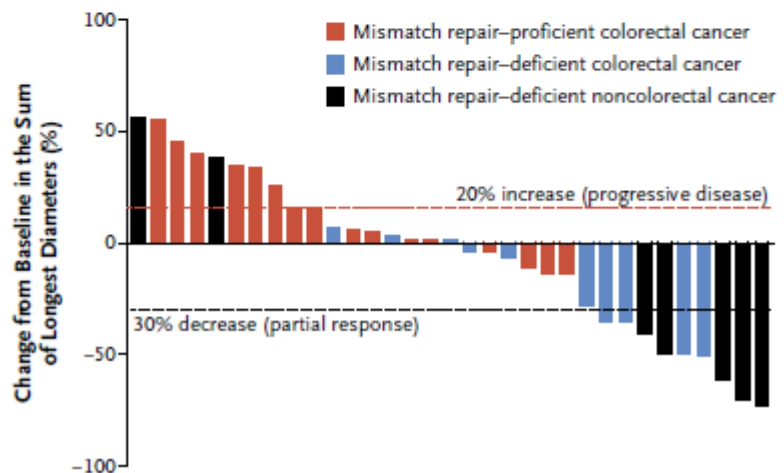
D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhajee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

*N Engl J Med* 2015;372:2509-20.

### A Biochemical Response



### B Radiographic Response



# Outlook

# Future for Precision Medicine

- **Scientific knowledge about the role of genetics in many disease is increasing rapidly**
- **This knowledge is leading to development of novel drugs and therapies**
- **Continued reductions in cost of DNA sequencing is making genetic testing more affordable**
- **It is likely that genetic/genomic testing will play a more important role in cancer drug development and patient care**
- **New approaches for clinical trials are needed**