

# 67<sup>th</sup> Meeting of the NCI Council of Research Advocates

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Max Wallace, Chair

Kelley Landy, Director  
Office of Advocacy Relations  
National Cancer Institute  
National Institutes of Health

Wednesday, March 4, 2015

# Agenda

1:00	
Roll Call	Ms. Landy
Welcoming Remarks and Overview of Agenda	Ms. Landy, Mr. Wallace, and Ms. Bulman
1:15	
NCI Update	Dr. Lowy
2:00	
Genomic Data Commons and Cloud Pilots Program	Dr. Kibbe
2:30	
NCRA Working Group Updates <ul style="list-style-type: none"><li>• Advocate Engagement</li><li>• Organization Engagement</li><li>• Informed Consent and Genomics Research</li></ul>	Ms. Delgado Harris, Ms. Landy, and Mr. Wallace
NCI Advisory Board Updates	Ms. Braun and Mr. Arons
2:50	
Closing Remarks and Future Meeting Dates	Ms. Landy and Mr. Wallace
Adjourn at 3:00	

# NCI Update

**Douglas R. Lowy, M.D.**

*Deputy Director, NCI*



# NCI Update

Douglas R. Lowy  
Deputy Director, NCI

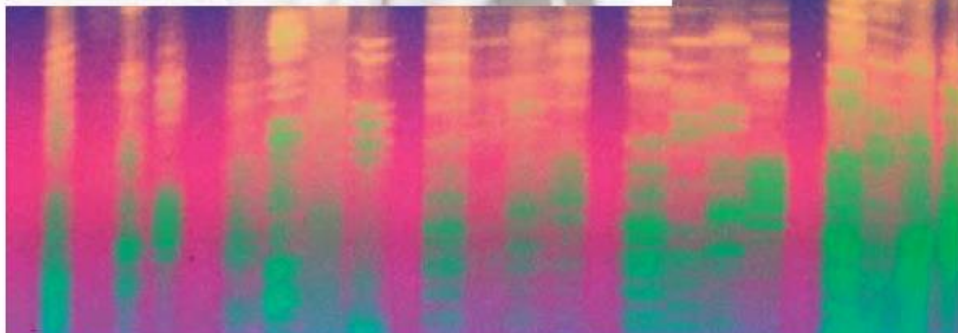
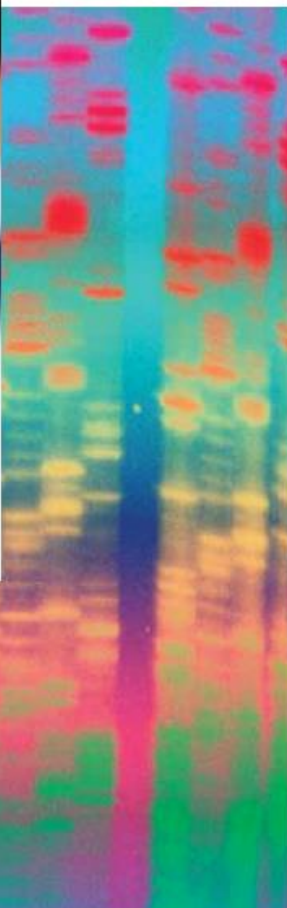
NCRA Webinar  
March 4, 2015

# ***Outline of Presentation***

- **NCI budget and research issues**
  - **The President's Precision Medicine Initiative**
  
- **HPV vaccine update**
  - **FDA approval of the 9-valent HPV vaccine**

# Building on Opportunities in Cancer Research

NATIONAL CANCER INSTITUTE  
AN ANNUAL PLAN AND  
BUDGET PROPOSAL FOR  
FISCAL YEAR  
2016

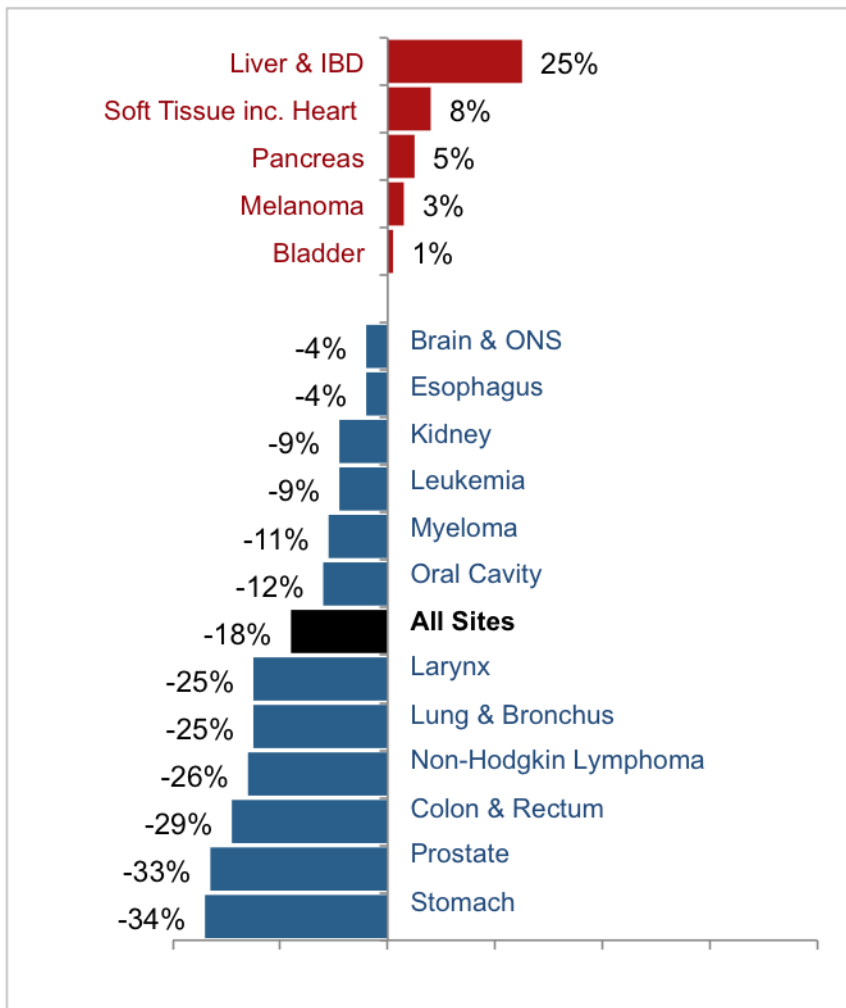


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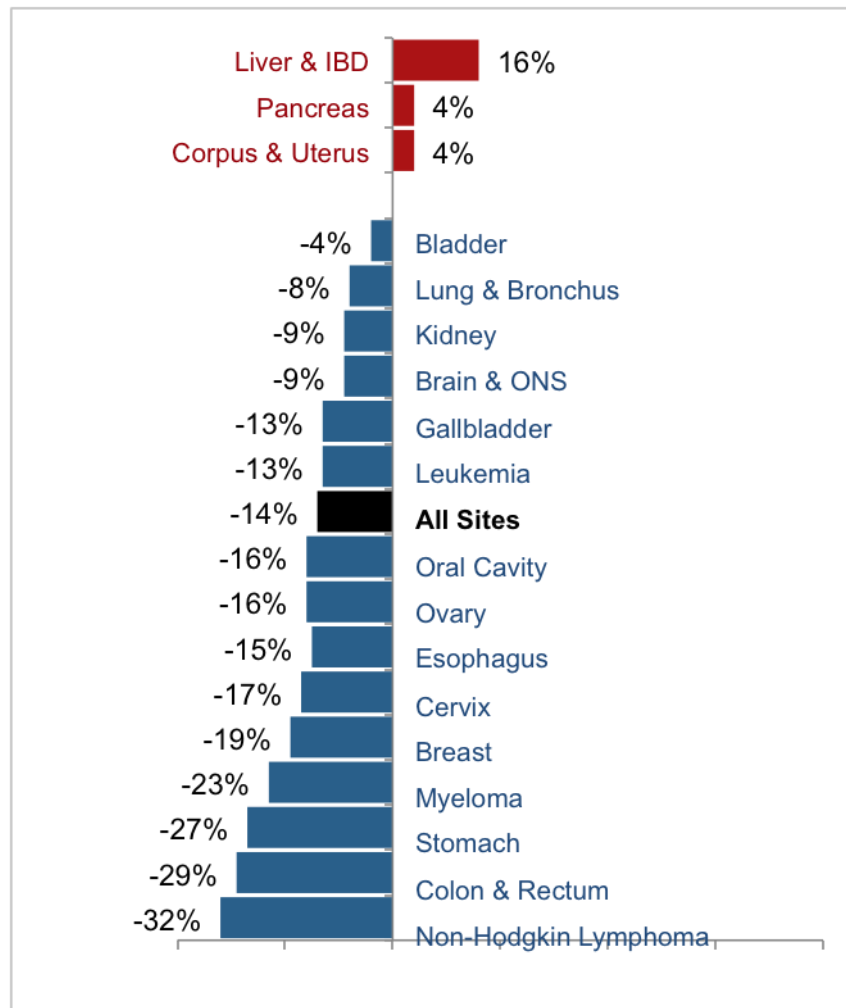
1	<b>Foreword</b>
4	<b>The Changing Cancer Landscape</b>
4	Lower Death Rates & More Survivors
6	Improved Prevention, Screening & Treatment
14	Rapid Progress Depends on Long-Term Support
16	<b>Building on the National Cancer Program</b>
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46	Developing Therapies for RAS-Driven Cancers
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61	NCI Professional Judgment Budget Recommendation

# Mortality Rates for Most Cancers are Decreasing: Percent change 2001-2010

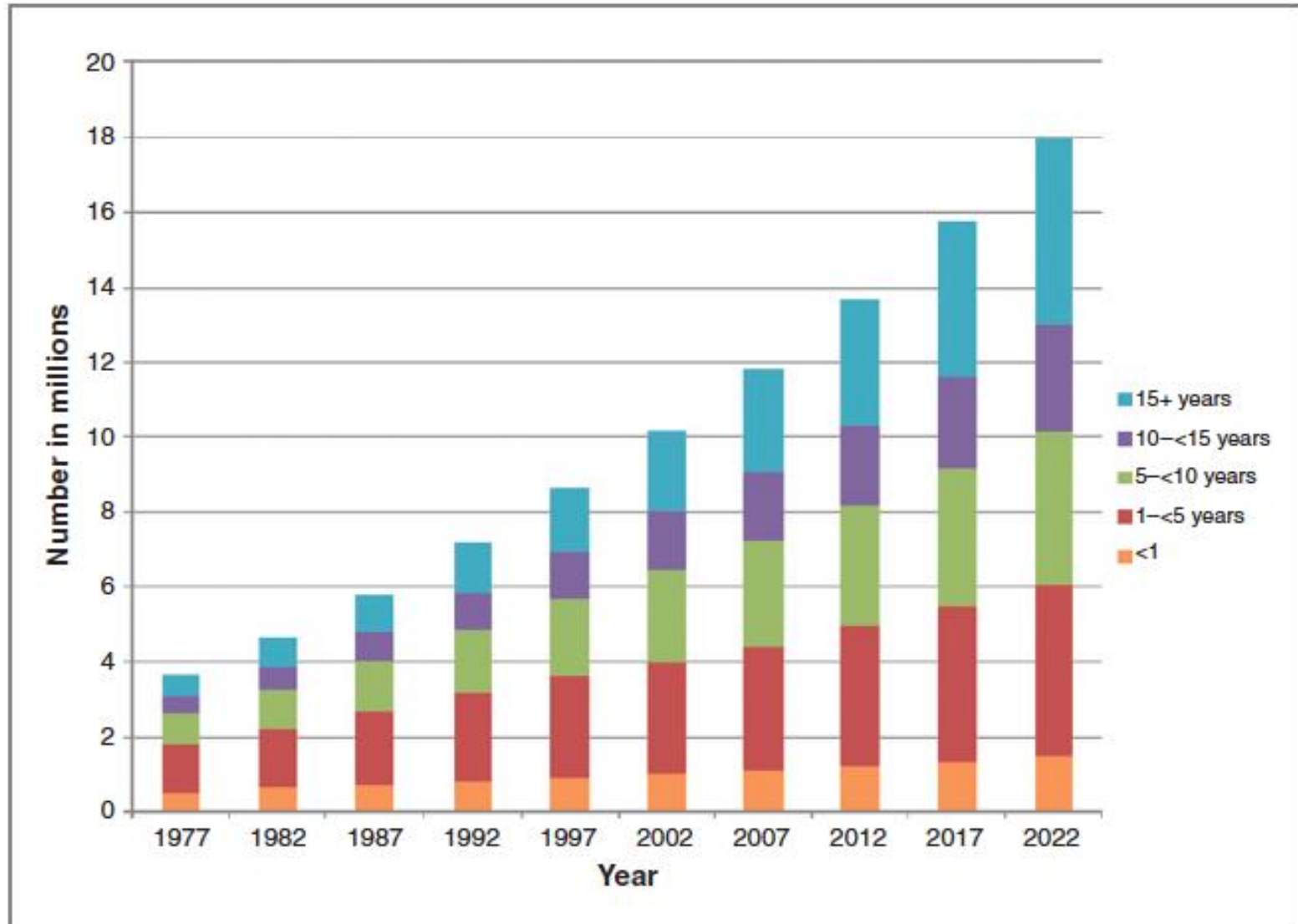
## Men



## Women

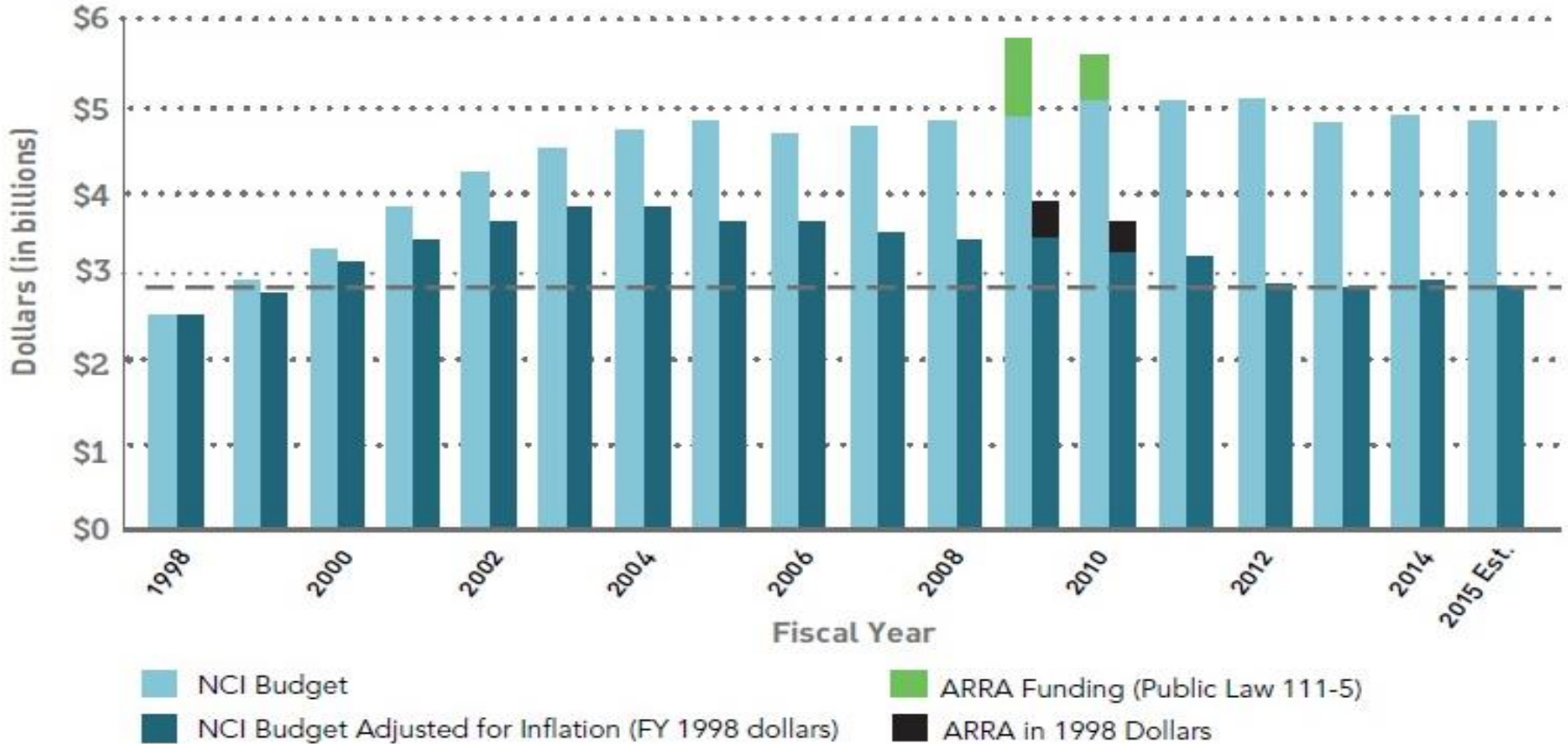


# A Progressive increase in Cancer Survivors: USA



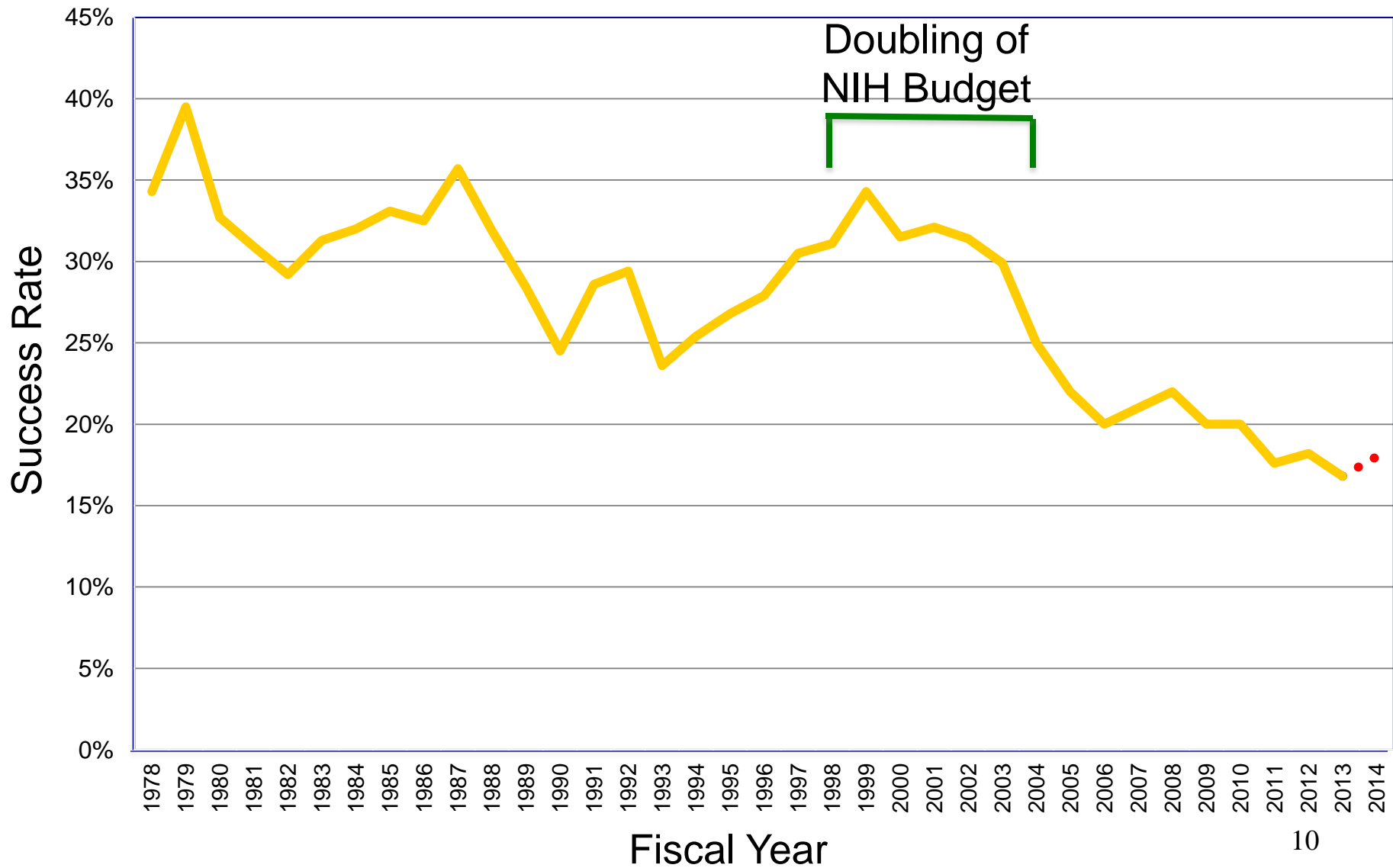


# NCI Budget 2004-2014: A Decade of Level Budgets and Progressively Decreasing Purchasing Power

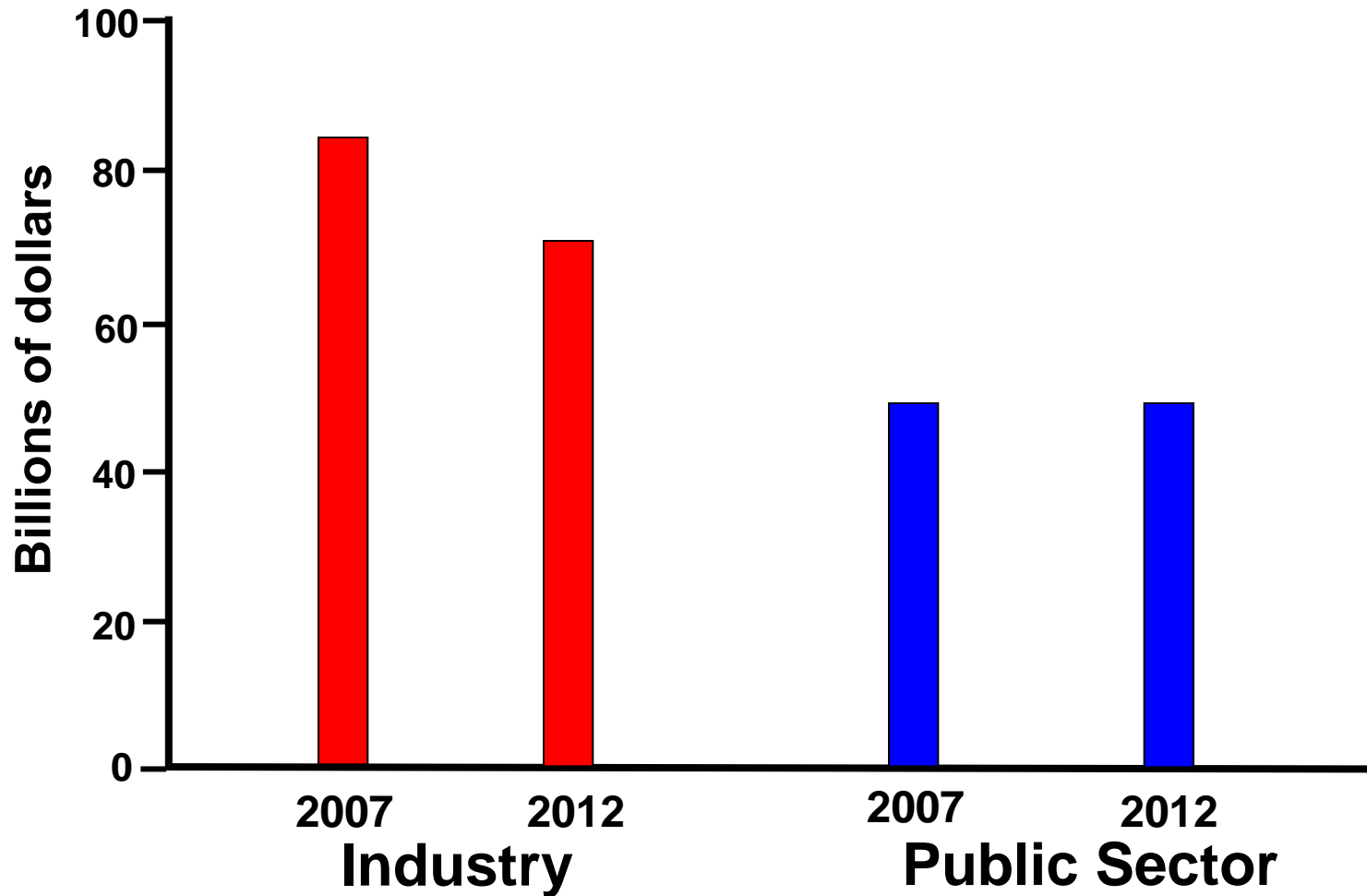


The horizontal dotted line at \$2.9 billion indicates the inflation-adjusted 2014 budget was similar to the 1999 budget, the first year of the “NIH doubling”<sup>9</sup>

# Current Grant Success Rates: The Lowest



# ***Decreased Research & Development in Industry, No Change in Public Sector, 2007-2012***



*Data from Chakma et al, New Eng J Med 370:3-6, 2014*

# ***Some Implications of Current Budget Levels***

- **Historically low success rates for research grant applications:** currently 14%; previously, 25% was considered a “bad period”
  - Difficult to know what findings might have been made if success rates were higher; **harder to recruit and retain “the best minds”**
- More **difficult to embark on new large-scale projects**
- **Genomically oriented clinical trials are more expensive per patient:** need to limit the number of patients
- **Insufficient support for infrastructure:** core grants for the 68 NCI-designated cancer centers (where most NCI-supported research is conducted)
- NCI has recently demonstrated it can make ***judicious use of additional funds***: TCGA/TARGET & ARRA (America Reinvestment & Recovery Act)

# ***The Precision Medicine/Oncology Initiative***

- President Obama has proposed \$70 million in his FY16 budget for this initiative
- To expand NCI-supported cancer genomics-based clinical and preclinical studies

# ***Precision (personalized) Medicine***

- ***Interventions to prevent, diagnose, or treat a disease (e.g., cancer)***, based on a molecular and mechanistic understanding of the causes and pathogenesis of the disease
- Approaches to prevention and treatment are becoming progressively more **oriented towards molecular abnormalities** than towards the organ site of the cancer

# ***A key TCGA take-home message: Cancer is very heterogeneous***

- Even within the **same tumor type**, there may be **many variations** (e.g., which genes are mutated)
- However, some **variations may be amenable to therapeutic intervention**
- Two key issues:
  - Must demonstrate patients with the identified abnormality will benefit from the treatment
  - When possible, use a molecular test to identify those patients

# ***NCI-sponsored clinical trials are mainly testing targeted agents***

- Trials that **match the drugs to the molecular profile** of the individual tumors
- Some trials are **focusing on the molecular abnormalities** in a tumor, rather than on the tumor site
  - However, most treatment trials continue to emphasize the treatment a specific tumor type at a particular tumor site



# ***The MATCH Clinical Trial***

- A trial that **emphasizes the molecular abnormality in the tumor** instead of the site of the tumor
- It will examine ~20 FDA-approved and experimental drugs that have shown activity against a known molecular target
- It will **test each drug in a range of tumors** containing the relevant molecular abnormality
- A public-private partnership (including several pharmaceutical companies)

# ***Precision Medicine Initiative***

- Expand NCI-supported genomics-based clinical & pre-clinical studies
  - To bring the most promising therapeutic approaches with immediate impact to the larger oncologic community
- Genomic master protocols in common malignancies, including a Pediatric Cancer Match trial
- Mutationally-driven targeted agent **drug combination** trials, to overcome/pre-empt molecular resistance mechanisms
- **Develop repository of patient-derived models for development of targeted therapeutics** to overcome clinical drug resistance
- National, public, **cancer database**: composed of data from clinically-annotated, molecularly characterized tumors/normal tissues and patient-derived models, using genomically-informed consent procedures

# Overview of Cooperative Group/NCTN Program



≈ 2,400  
Institutions

14,000  
Investigators

21,000+ pts  
enrolled/yr

≈ 120 phase 3  
& 215 early  
phase trials  
open for  
enrollment at  
any one time

Accrual  
Distribution

FY2007 - FY2013:

Phase 3: 81%

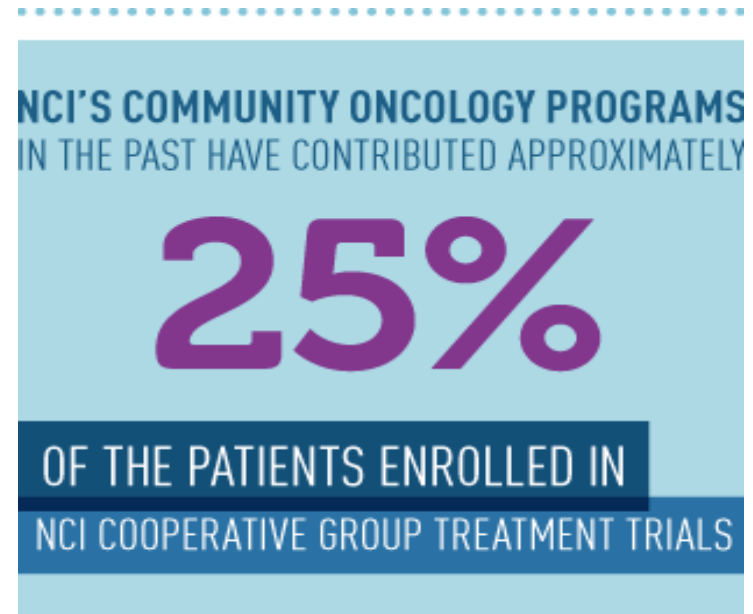
Phase 2: 16%

Phase 1/Phase 0: 3%

Adult & Pediatric Trials	FY2007	FY2008	FY2009	FY2010	FY2011	FY2012	FY2013
All Phases: Treatment & Primary Imaging Trials	24,619	25,682	29,221	23,446	19,775	21,164	21,810

# ***NCI Community Oncology Research Program (NCORP)***

NCORP provides an important connection to community-based cancer care, **ensuring that people have access to the benefits of the latest research** regardless of where they live.



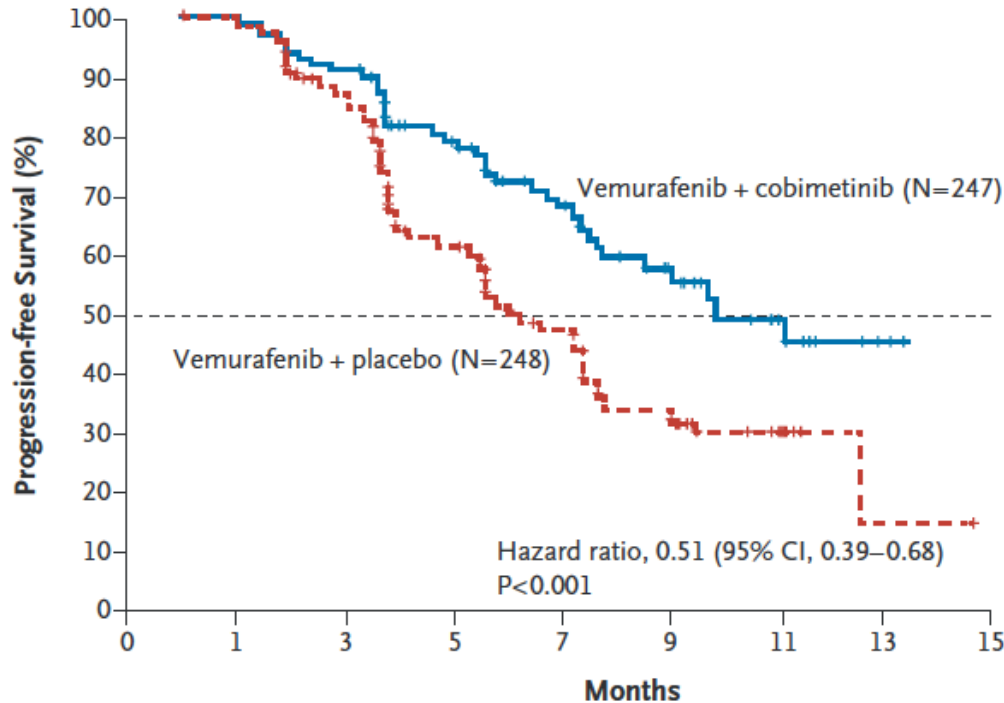
Source: NCI Division of Cancer Prevention [www.cancer.gov](http://www.cancer.gov)  
Source: NCI Division of Cancer Prevention

# ***Molecular Findings in One Cancer Can Have Implications for Other Cancers***

- ***Initial basic observation:*** Finding a “new” protein, Mesothelin, in mesothelioma (a rare cancer)
- ***Follow-up basic observation:*** Mesothelin is also present in common cancers (e.g., ovarian, pancreatic, lung)
- ***Initial treatment trial:*** Targeting a toxin directed at Mesothelin in mesothelioma can induce long-term remissions
- ***Follow-up treatment trial:*** Target Mesothelin in the common cancers where it is found

# Combination of a MEK inhibitor (Cobimetinib) and B-Raf Inhibitor (Vemurafenib) Improves Progression-free Survival in Melanoma with Mutant B-Raf

**A Progression-free Survival**



	Patients Who Died or Had Disease Progression	Median Progression-free Survival
	<i>no.</i>	<i>mo</i>
Vemurafenib + cobimetinib	79	9.9 (9.0–NR)
Vemurafenib + placebo	128	6.2 (5.6–7.4)

**No. at Risk**

Vemurafenib + cobimetinib	238	215	152	96	46	14	3
Vemurafenib + placebo	240	200	118	68	34	12	1

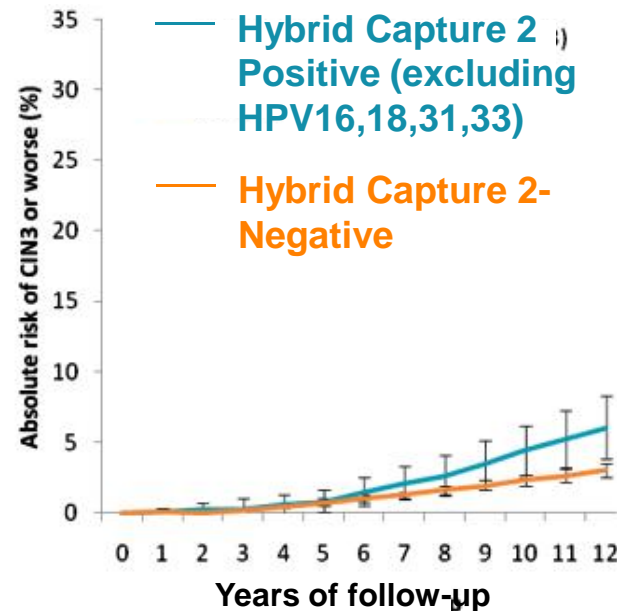
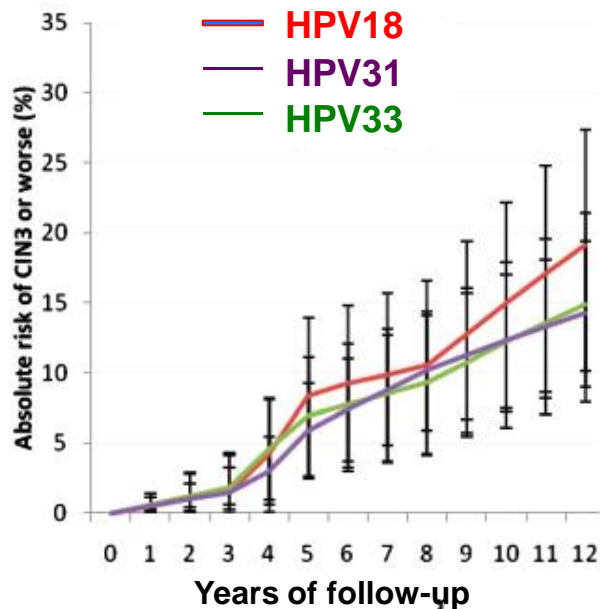
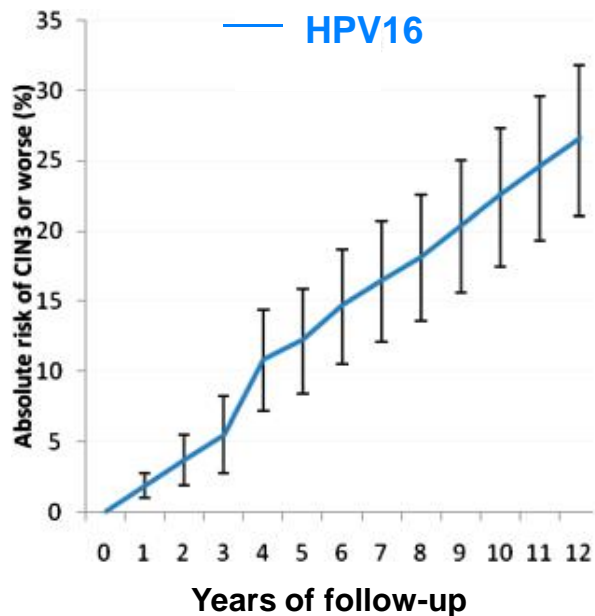
# ***HPV vaccine update***

# ***FDA Approval & ACIP Recommendations for 9-valent HPV Vaccine (Gardasil 9)***

- **FDA approval (December, 2014)**
  - Females 9-26; males 9-15
- **ACIP recommendations (February, 2015)**
  - Females and males 9-21; target age: 11-12



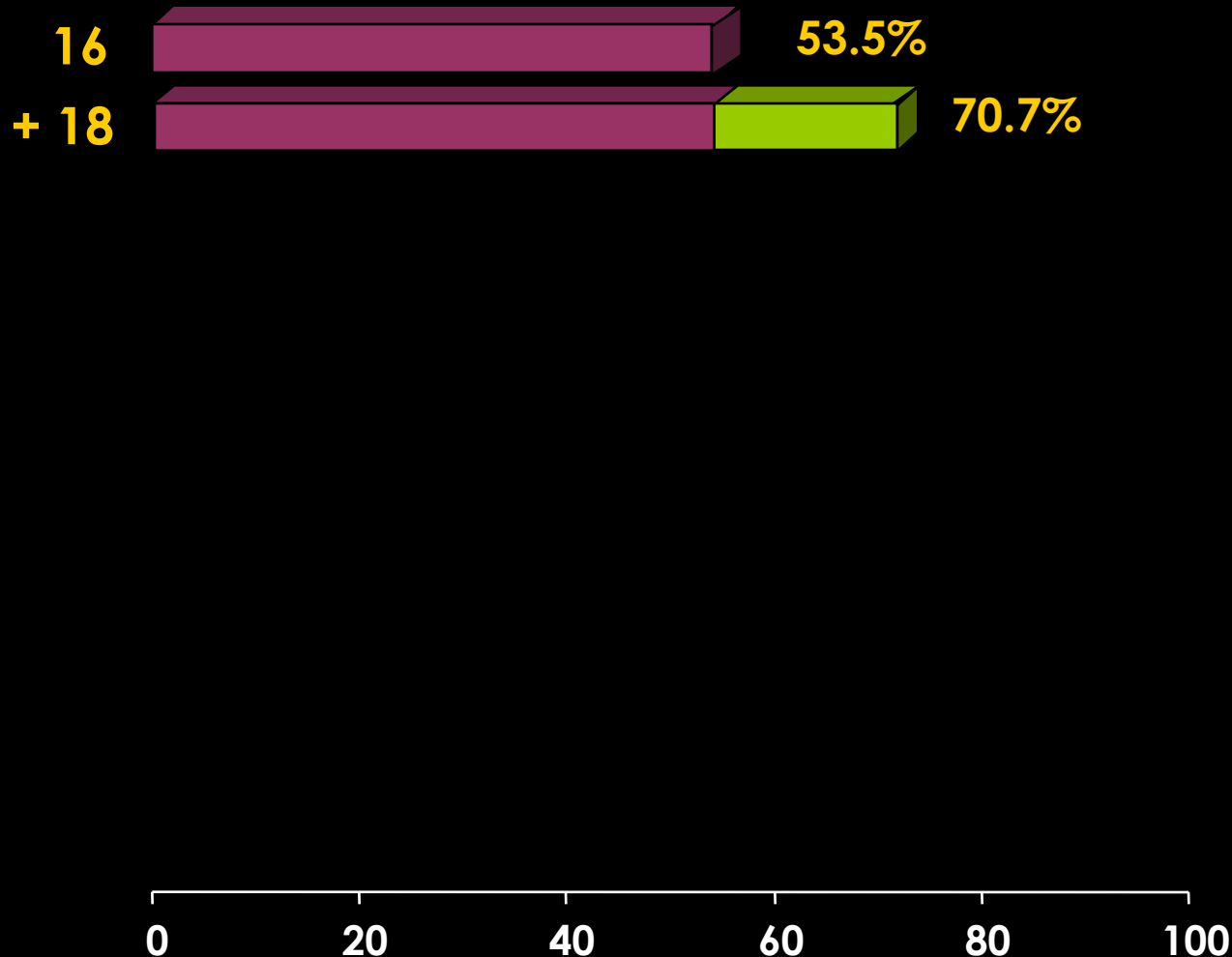
# HPV Type Affects the Rate of Development of CIN3 or worse in women with normal cytological findings at baseline: The Danish Cohort Study



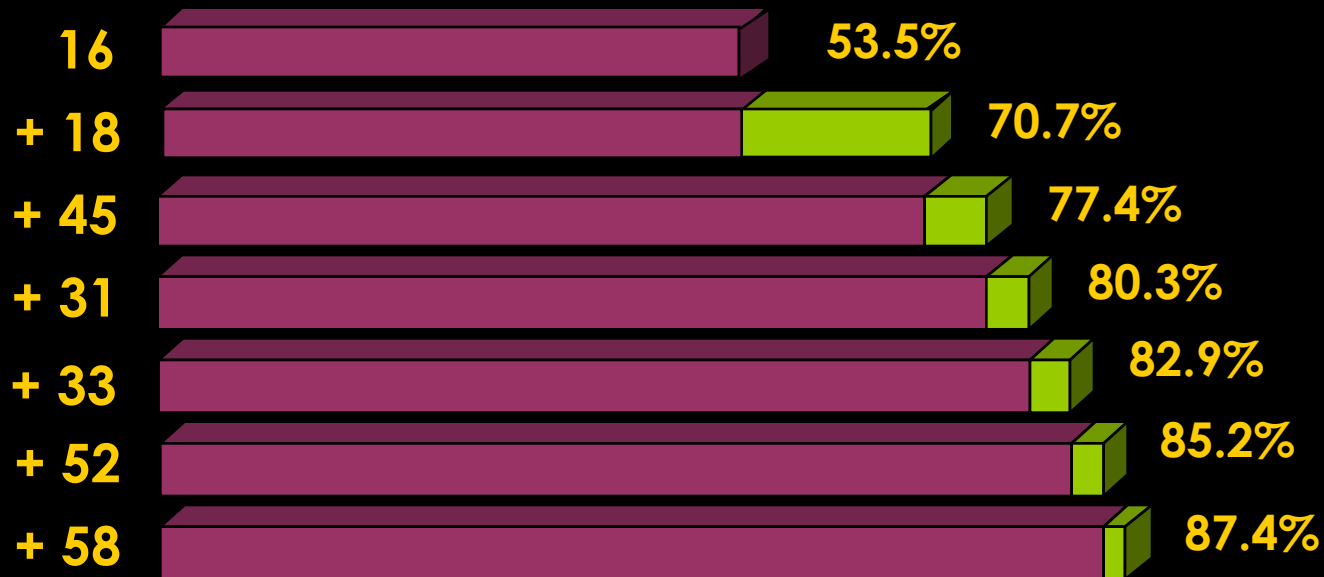
**A single HPV test predicts 10-fold increased risk of CIN3 for >10 years**

*From Kjaer et al, J Natl Cancer Inst 102: 1478-88, 2010*

# Potential Reduction in Cervical Cancer from the Addition of Multiple HPV Types to L1 VLP Vaccine

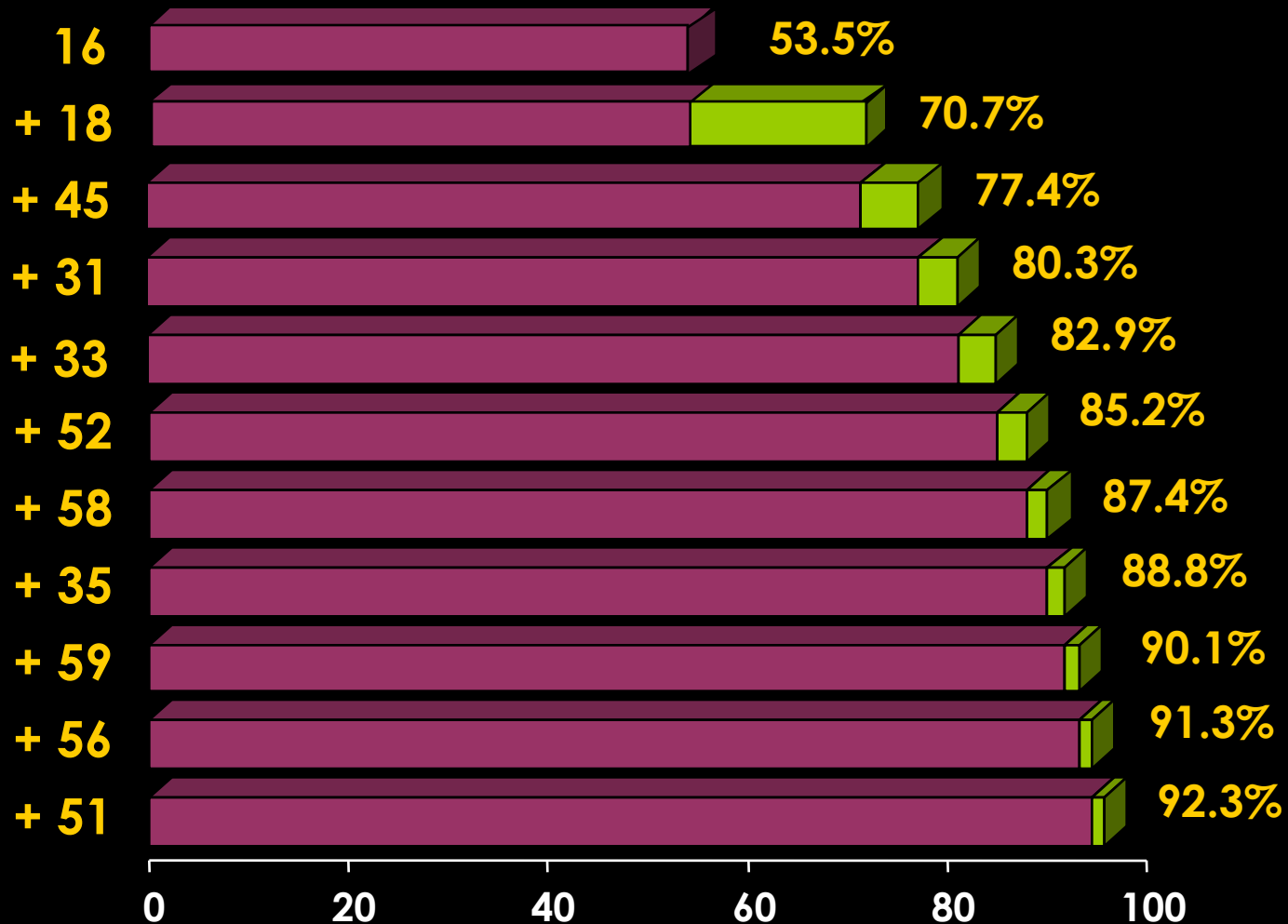


# Potential Reduction in Cervical Cancer from the Addition of Multiple HPV Types to L1 VLP Vaccine



0 20 40 60 80 100

# Potential Reduction in Cervical Cancer from the Addition of Multiple HPV Types to L1 VLP Vaccine



ORIGINAL ARTICLE

# A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women

E.A. Joura, A.R. Giuliano, O.-E. Iversen, C. Bouchard, C. Mao, J. Mehlsen, E.D. Moreira, Jr., Y. Ngan, L.K. Petersen, E. Lazcano-Ponce, P. Pitisuttithum, J.A. Restrepo, G. Stuart, L. Woelber, Y.C. Yang, J. Cuzick, S.M. Garland, W. Huh, S.K. Kjaer, O.M. Bautista, I.S.F. Chan, J. Chen, R. Gesser, E. Moeller, M. Ritter, S. Vuocolo, and A. Luxembourg, for the Broad Spectrum HPV Vaccine Study\*

## EDITORIALS



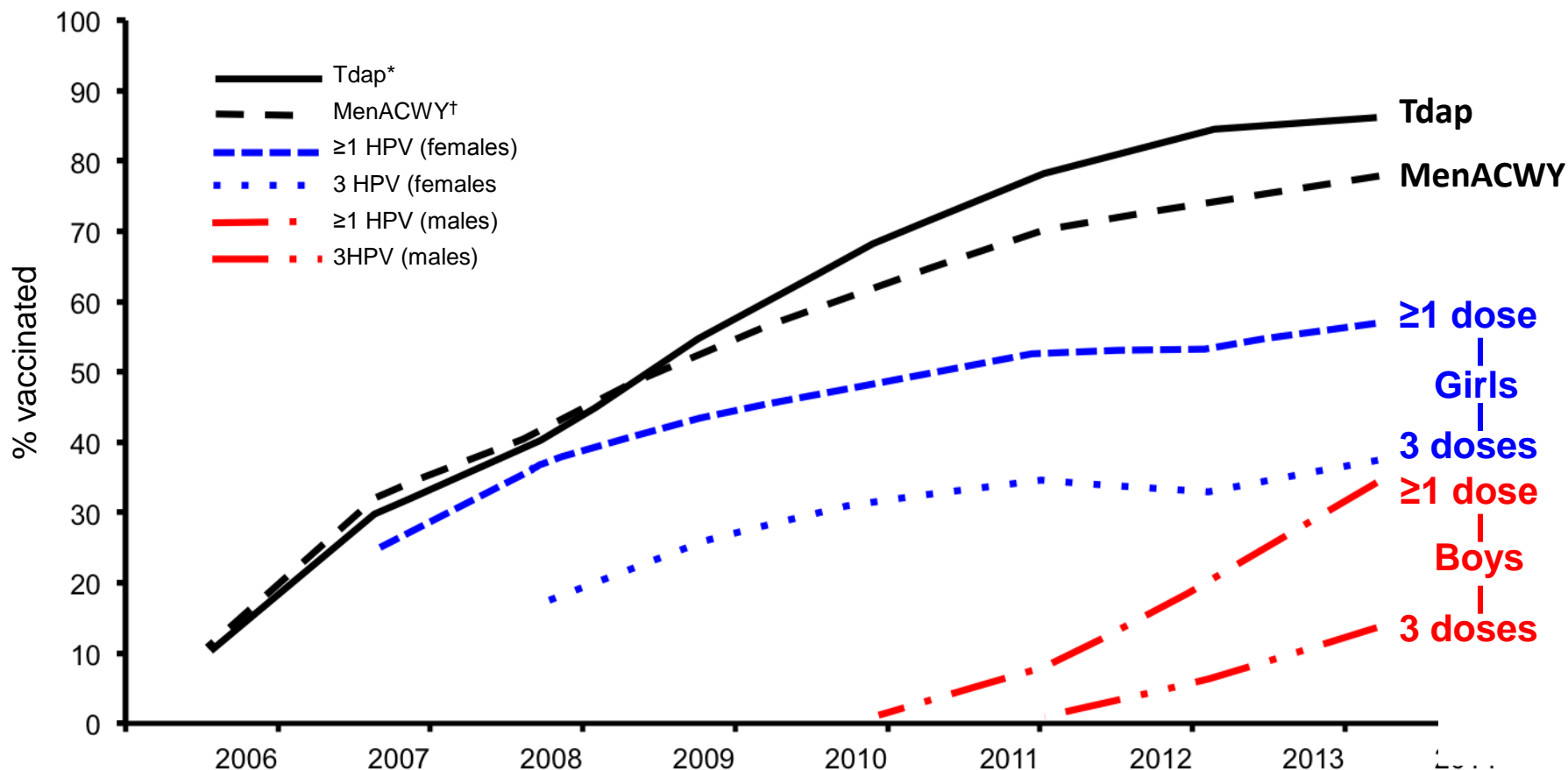
### HPV “Coverage”

Anne Schuchat, M.D.

- “The new vaccine had an efficacy of nearly 97% against high-grade cervical, vulvar, and vaginal disease related to HPV types 31, 33, 45, 52, and 58.”
- “I hope that in a few decades we will be able to tell a generation of adults who never had HPV-associated cancers or precancers that when they were teenagers, we had them covered.”

# Trends in U.S. Vaccination Rates: Ages 13-17 Yrs

MMWR Vol 63, #29, July 25, 2014



**Abbreviations:** Tdap = tetanus, diphtheria, acellular pertussis vaccine; MenACWY = meningococcal conjugate vaccine; HPV-1 = human papillomavirus vaccine, ≥1 dose; HPV-3 = human papillomavirus, ≥3 doses.

\* Tdap and MenACWY vaccination recommendations were published in March and October 2006, respectively.

† HPV vaccination recommendations were published in March 2007.

# ***Ambivalent Reception in Some Medical Circles***

- Editorial: Human papillomavirus vaccination — reasons for caution. C. Haug, N Eng J Med 2008
- Editorial: The risks and benefits of HPV vaccination. C. Haug, JAMA 2009
  - “***The relationship between infection at a young age and development of cancer 20 to 40 years later is not known...***It is impossible to predict exactly what effect vaccination of young girls and women will have on the incidence of cervical cancer 20 to 40 years from now.”



# *Moving to two doses in the US?*

- ACIP recommendations usually follow FDA approval. There has been no FDA approval for 2 doses
- Merck is conducting a non-inferiority immunogenicity trial of the 9-valent vaccine; compares two doses (0,6 months & 0,12 months) in 9-15 years old girls & boys to three doses in 16-26 year old women (clinicaltrials.gov)
- Positive results from immunogenicity trial should lead to two dose approval in 9-15 year olds by FDA and recommendation by ACIP
- Catch-up vaccination for 15-26 year old females will presumably still be for 3 doses

# *Summary*

- **Mortality rates for most cancers are continuing to go down**, but there are some notable exceptions
- The NCI continues to support a lot of outstanding research, from basic to applied. However, the **budgetary situation means** that many meritorious **proposals cannot be funded** or are **funded at levels that slow their rate of progress**
- The President's precision medicine initiative in oncology may provide additional support for this important area of research

***Thank you!***

# Genomic Data Commons

**Warren A. Kibbe, Ph.D.**

*Director, NCI Center for Biomedical Informatics and Information Technology*



# Genomic Data Commons and Cloud Pilots

Warren Kibbe, Ph.D.  
[warren.kibbe@nih.gov](mailto:warren.kibbe@nih.gov)

March 2015

# Overview

- Setting the stage
- Cancer Genomics - TCGA and TARGET
- Cancer Genomics Data Commons
- NCI Cloud Pilots
- Building a national learning health system for cancer clinical genomics

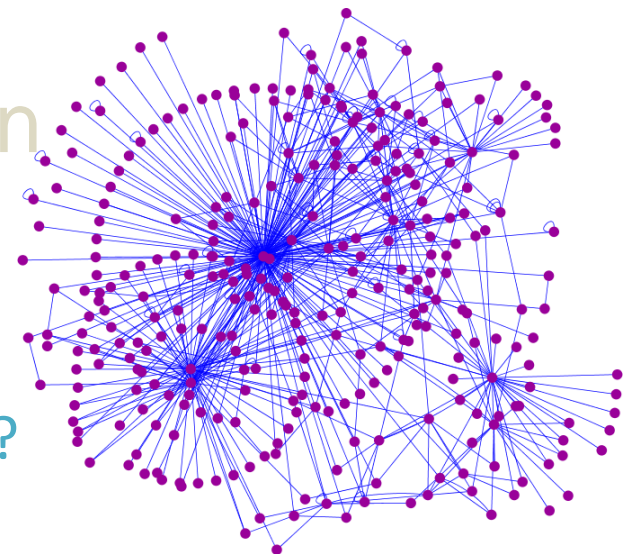
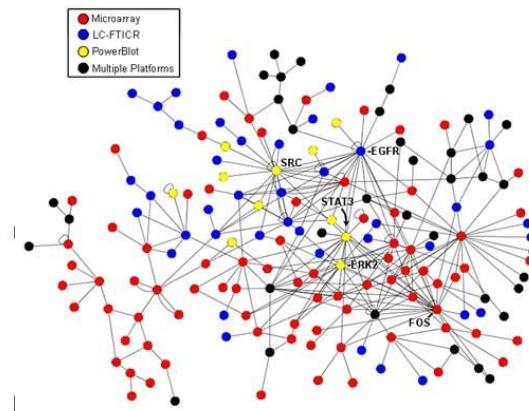
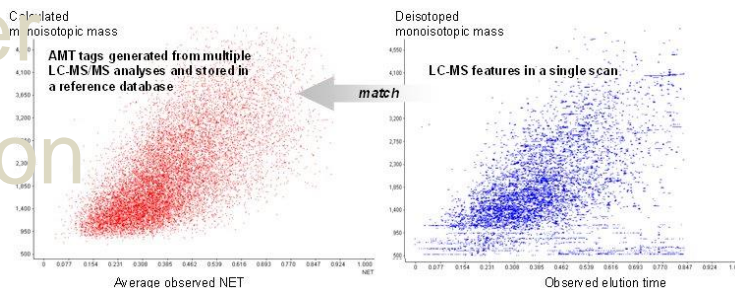
# Precision Oncology

- The era of precision medicine and precision oncology is *predicated* on the integration of research, care, and molecular medicine and the *availability of data* for modeling, risk analysis, and optimal care

*How do we re-engineer translational research policies that will enable a true learning healthcare system and put the patient at the center of healthcare?*

# Disruptive Technologies

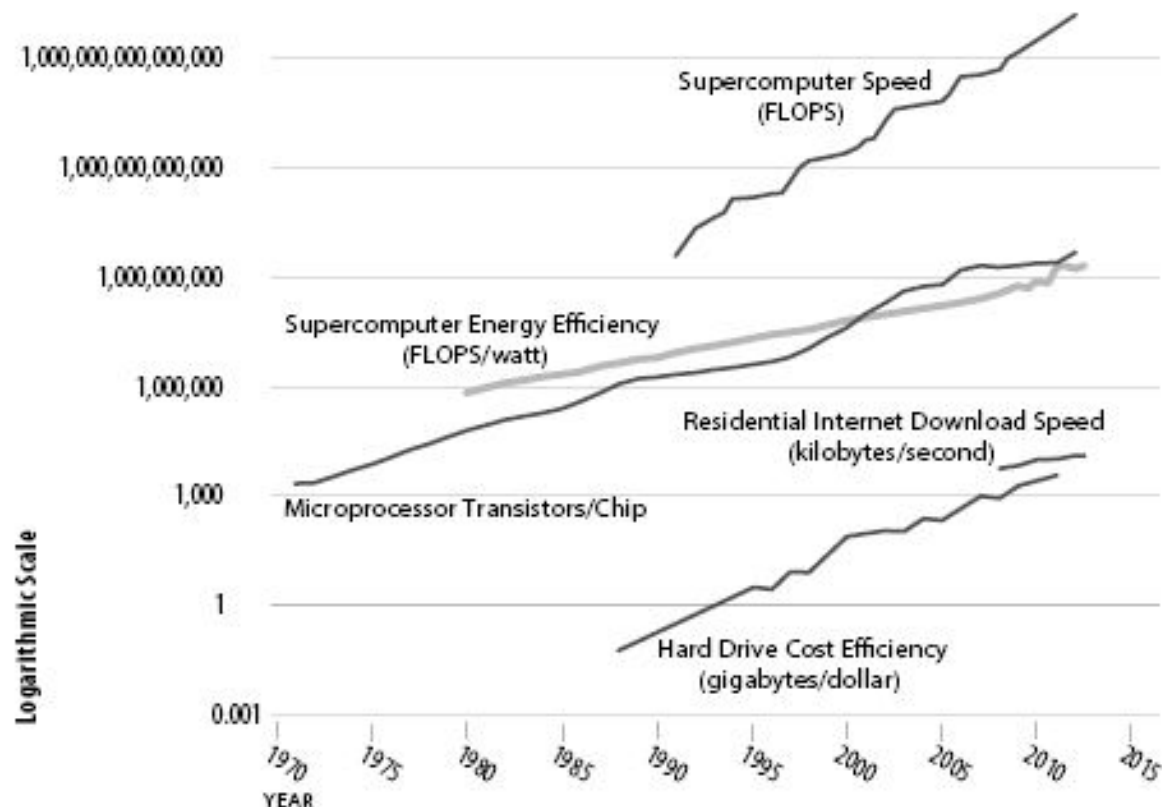
- Printing
- Steam power
- Transportation
- Electricity
- Antibiotics
- Semiconductors & VLSI design
- http
- High throughput biology  
Systems view - end of reductionism?





# From the Second Machine Age

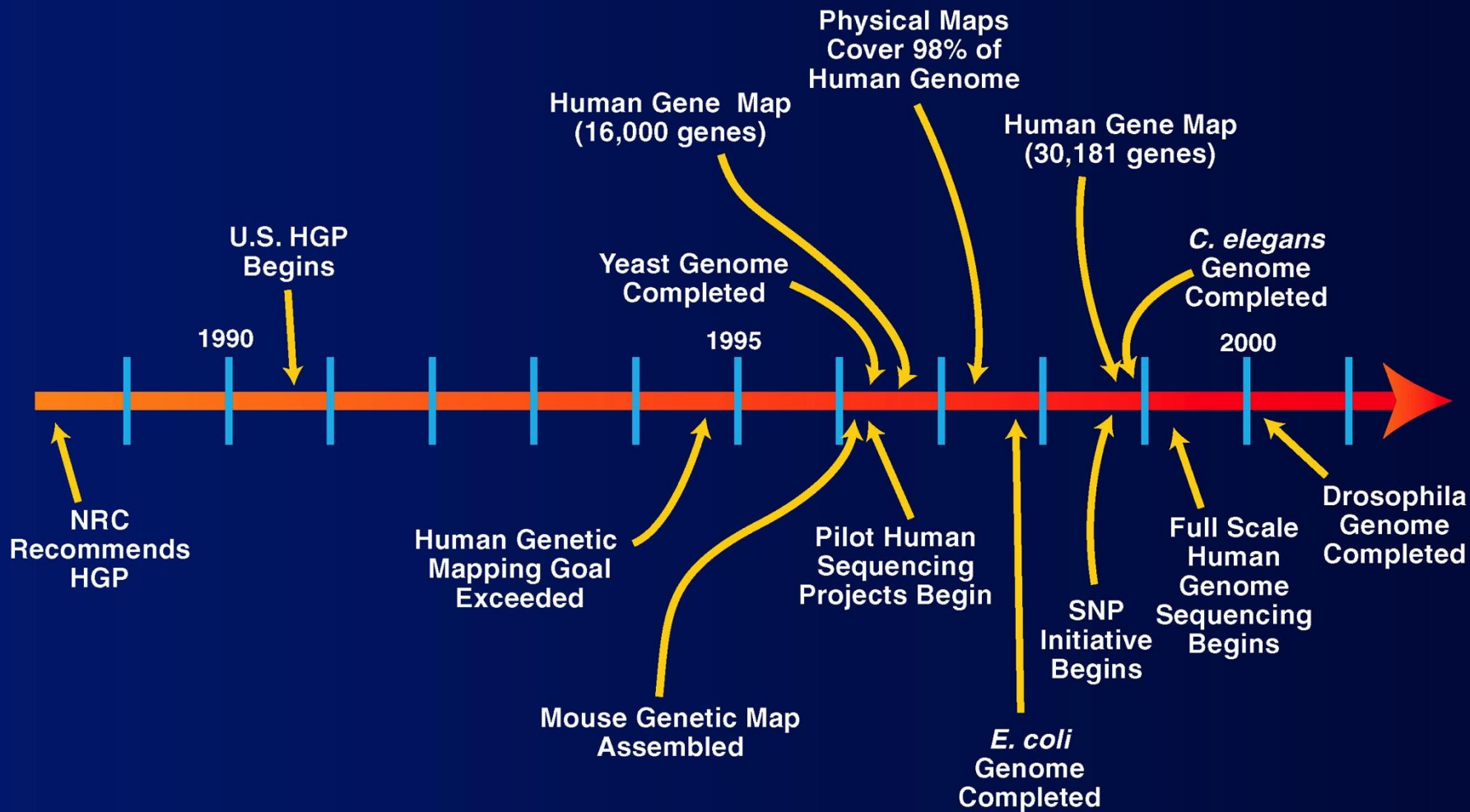
**FIGURE 3.3** The Many Dimensions of Moore's Law

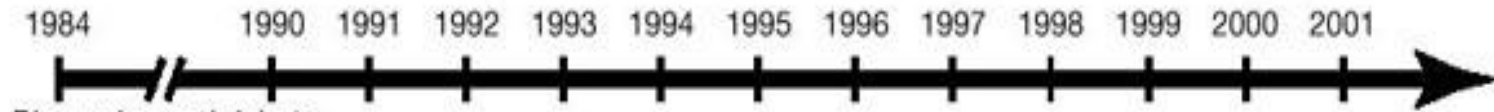


From: *The Second Machine Age: Work, Progress, and Prosperity in a Time of Brilliant Technologies* by Erik Brynjolfsson & Andrew McAfee

# Molecular data is Big Data

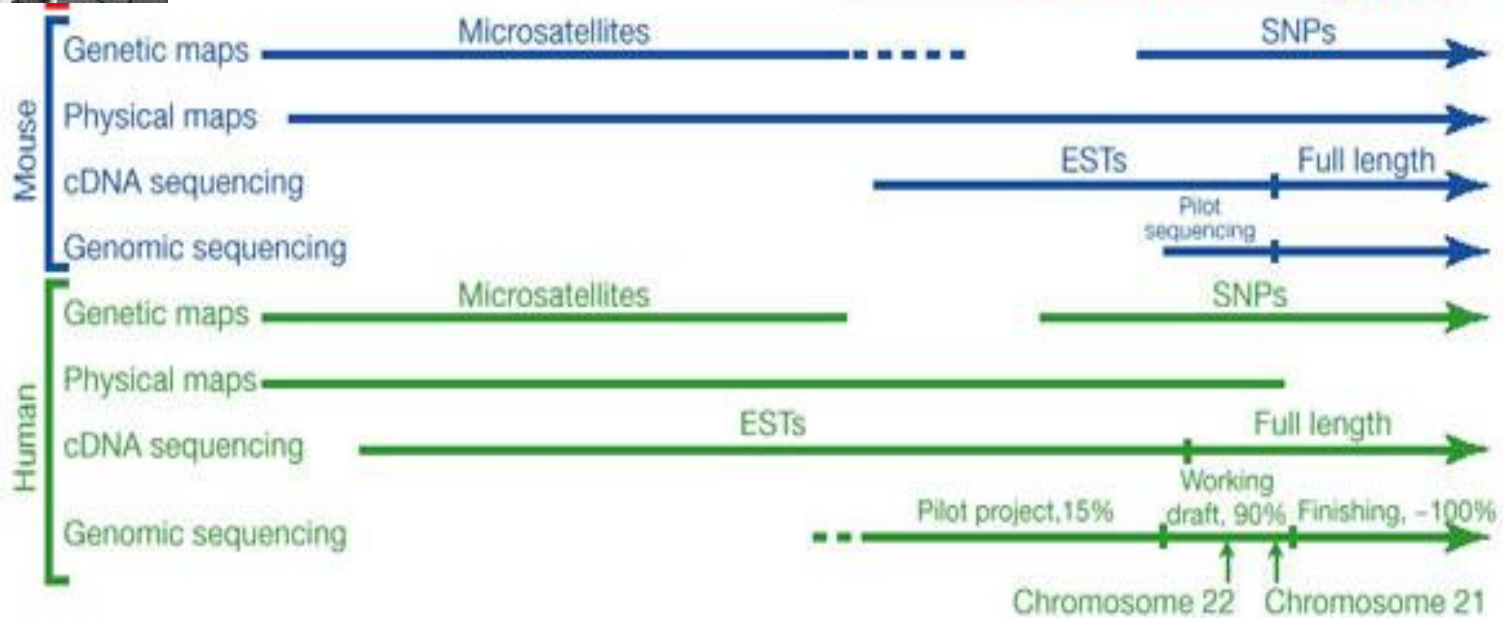
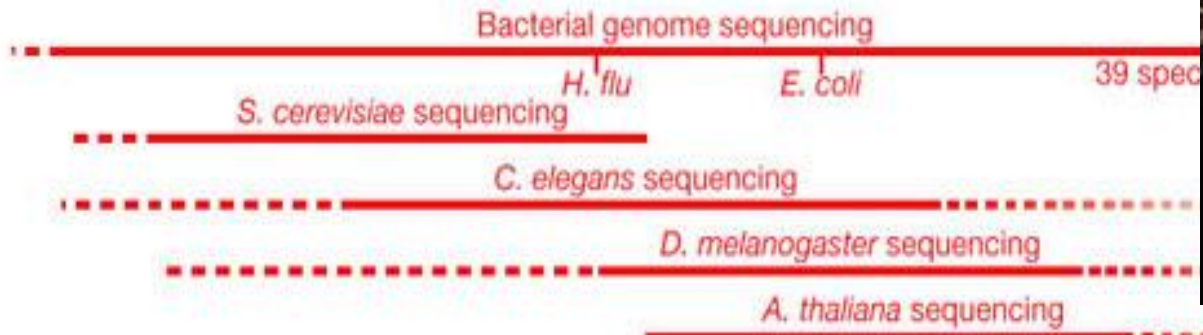
- Brief trip down memory lane
- Sequencing and the Human Genome Project



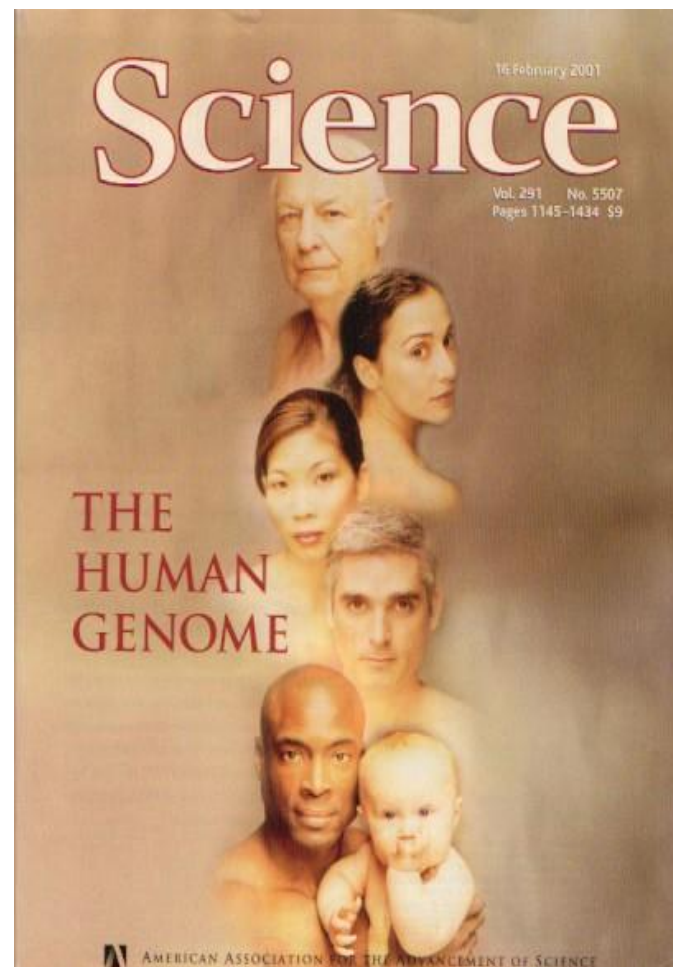
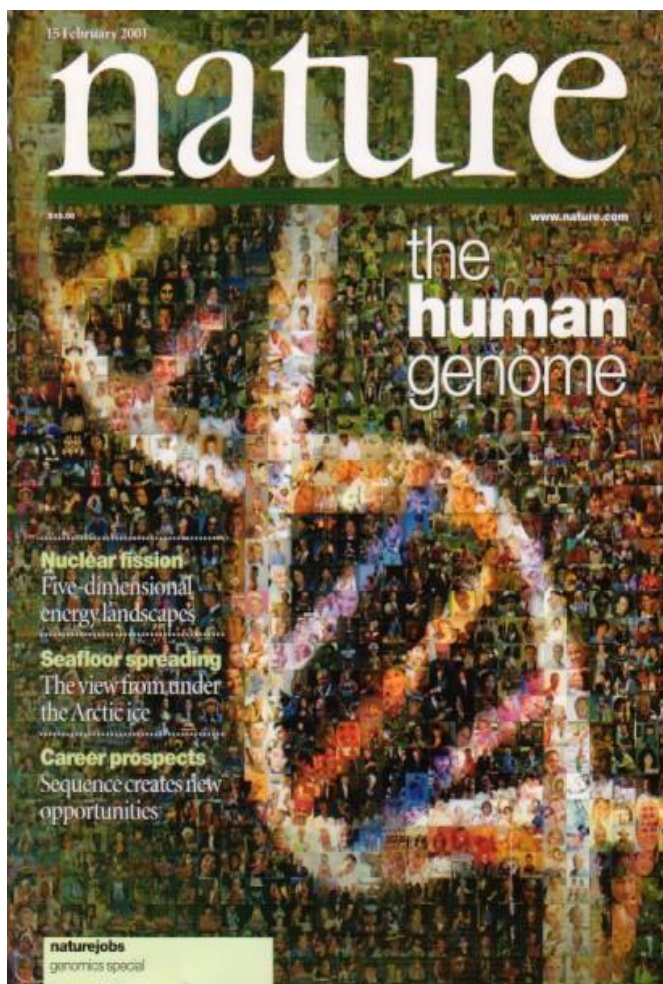


Discussion and debate  
in scientific community

NRC report



# February 12, 2001



# HGP outcomes

- \$5.6B investment in 2010 dollars
- \$800B economic development
- Enabled many basic discoveries, clinical therapies and diagnostics, and applied technologies

# TCGA history

- About three years post-Human Genome Project
- Initiated in 2005
- Collaboration of NHGRI and NCI to examine GBM, Lung and Ovarian cancer using genomic techniques in 2006.
- Expanded to 20+ tumor types.

# TCGA drivers

- Provide high quality **reference sets** for 20+ tissue types
- Provide a platform for **systems biology** and **hypothesis generation**
- Provide a test bed for understanding the real world implications of **consent and data access policies** on **genomic and clinical data.**



# Highly Recurrent *TERT* Promoter Mutations in Human Melanoma

## *TERT* Promoter Mutations in Familial and Sporadic Melanoma

*TERT* promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal

A study based on whole-genome sequencing yields a rare variant at 8q24 associated with prostate cancer

## Epigenomic Enhancer Profiling Defines a Signature of Colon Cancer

## DNA Methylation of Transcriptional Enhancers and Cancer Predisposition

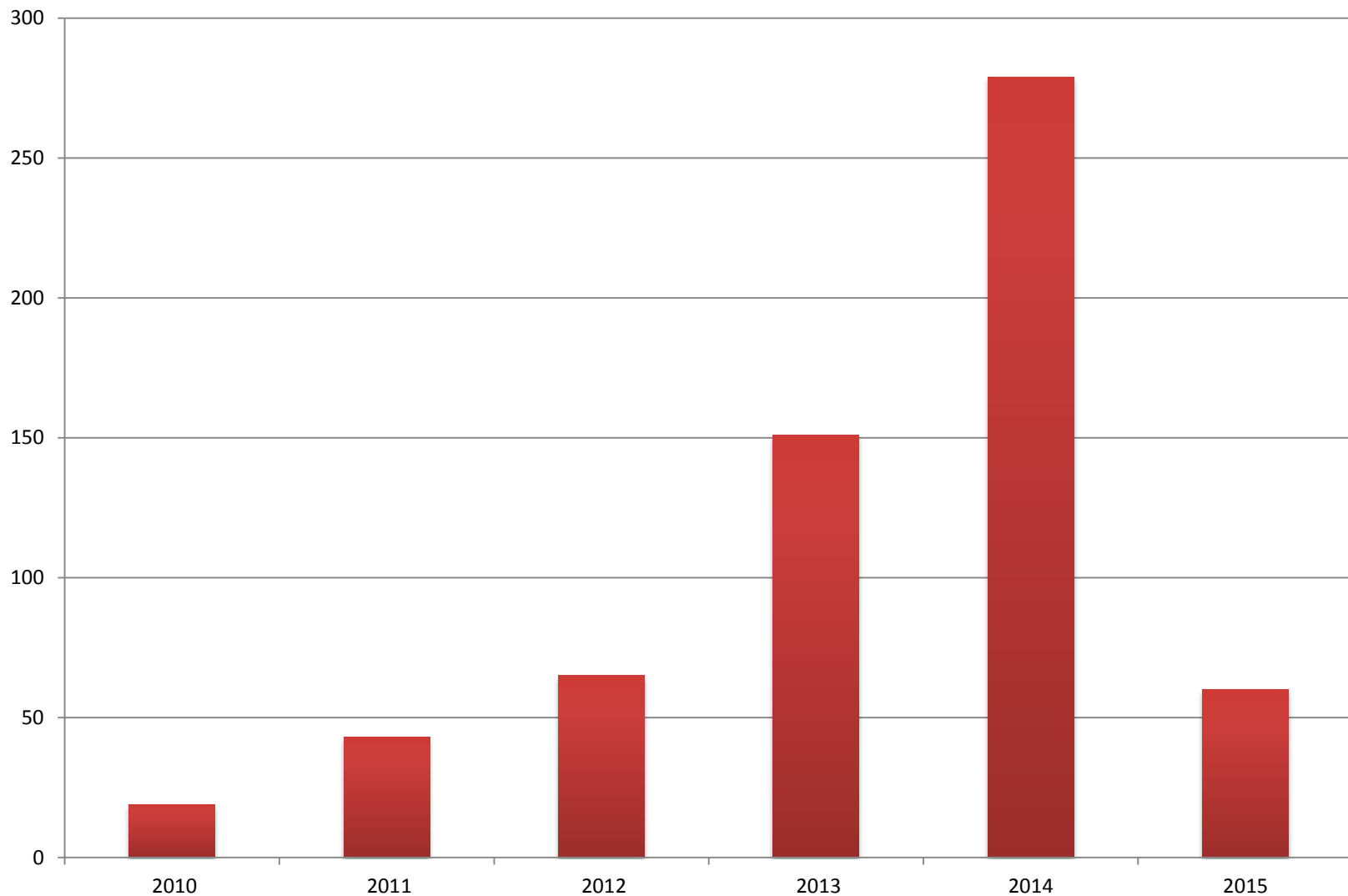
Julius Gudmundsson, Kristrun R Benediktsson, Droplaug N Magnúsdóttir, Stefania B Olafsson, Fernando Fernandez, Inge M van Oort RP, Kin-Mang Lau, Gudmundur Vignir, Lambertus A Kiemeny

Batool Akhtar-Zaidi, Cynthia F. Bartels, Awad Jarrar,<sup>5</sup> Matt Thomas Laframboise

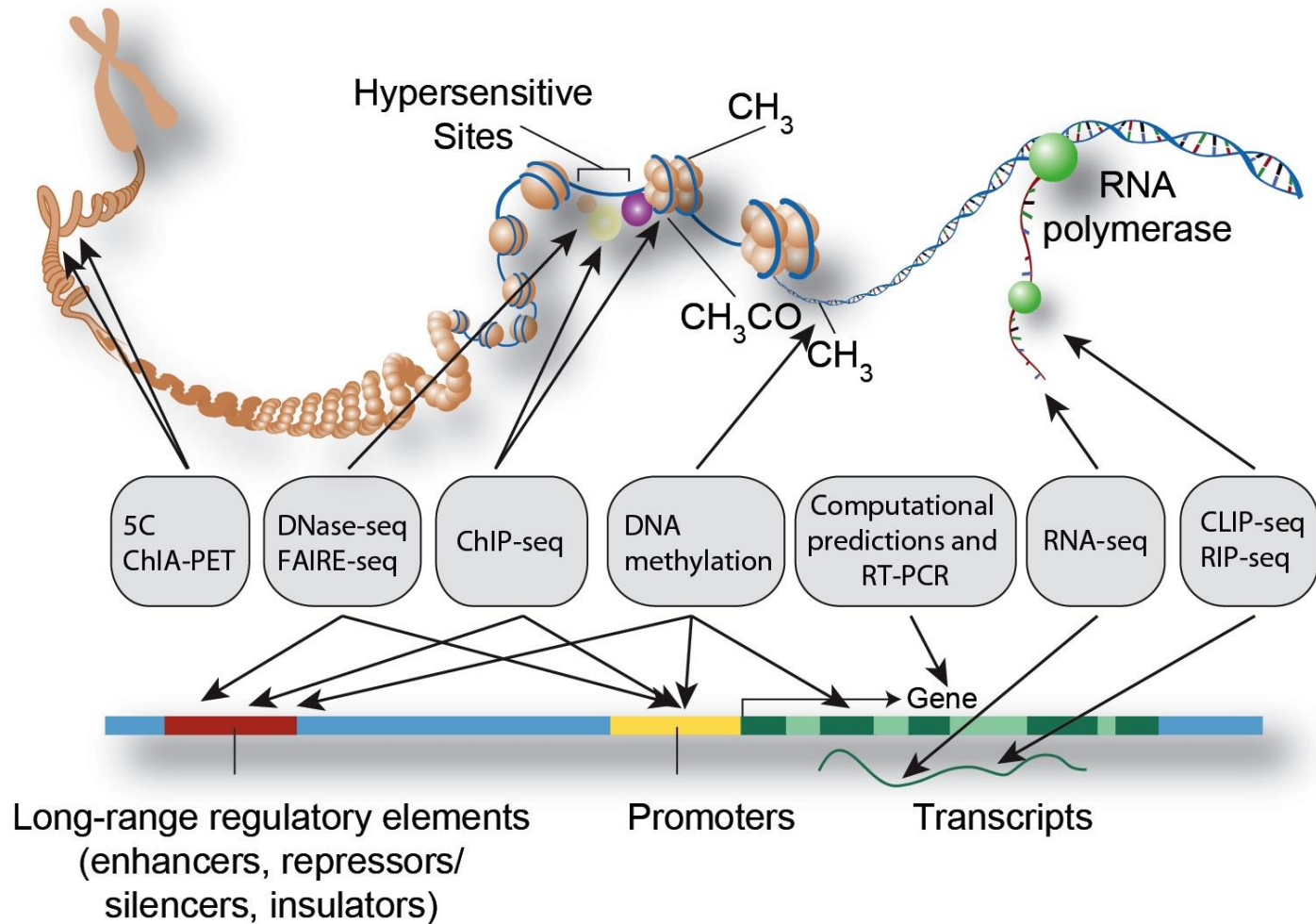
Cancer is characteri

coding sequences and promoters, even though distal regulatory elements play a central role

# TCGA Publications since 2010



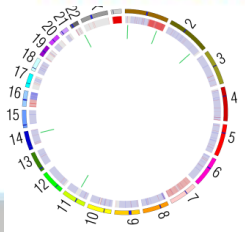
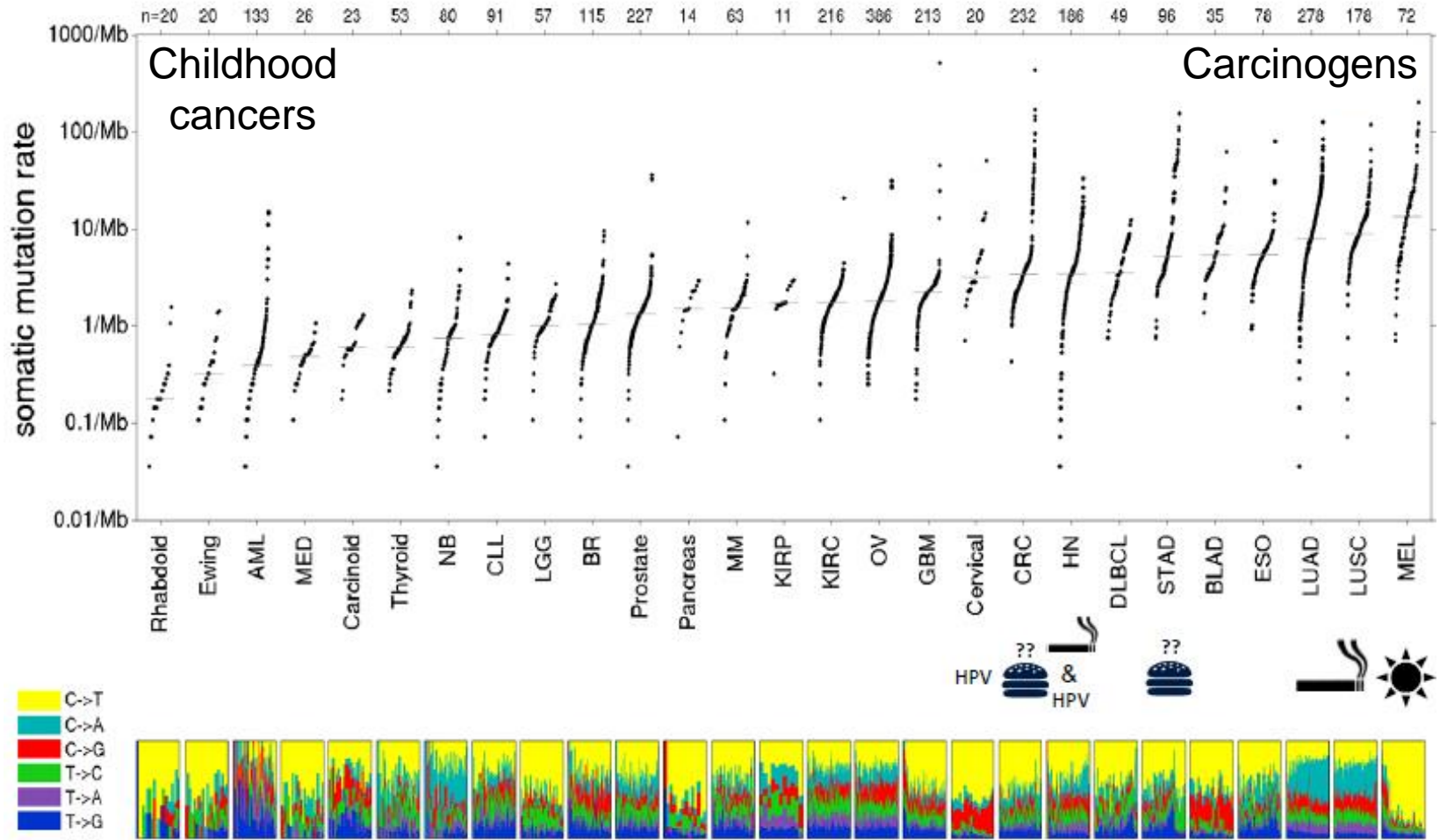
# Assays and Data Types



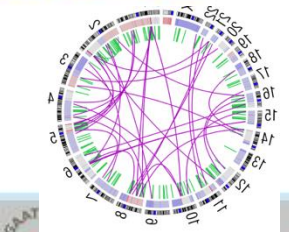
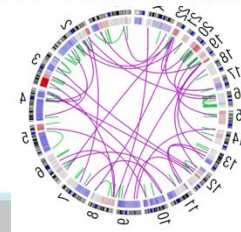
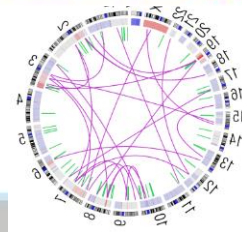
# TCGA – Lessons from structural genomics

Jean Claude Zenklusen,  
Ph.D.  
Director  
TCGA Program Office  
National Cancer Institute

# The Mutational Burden of Human Cancer



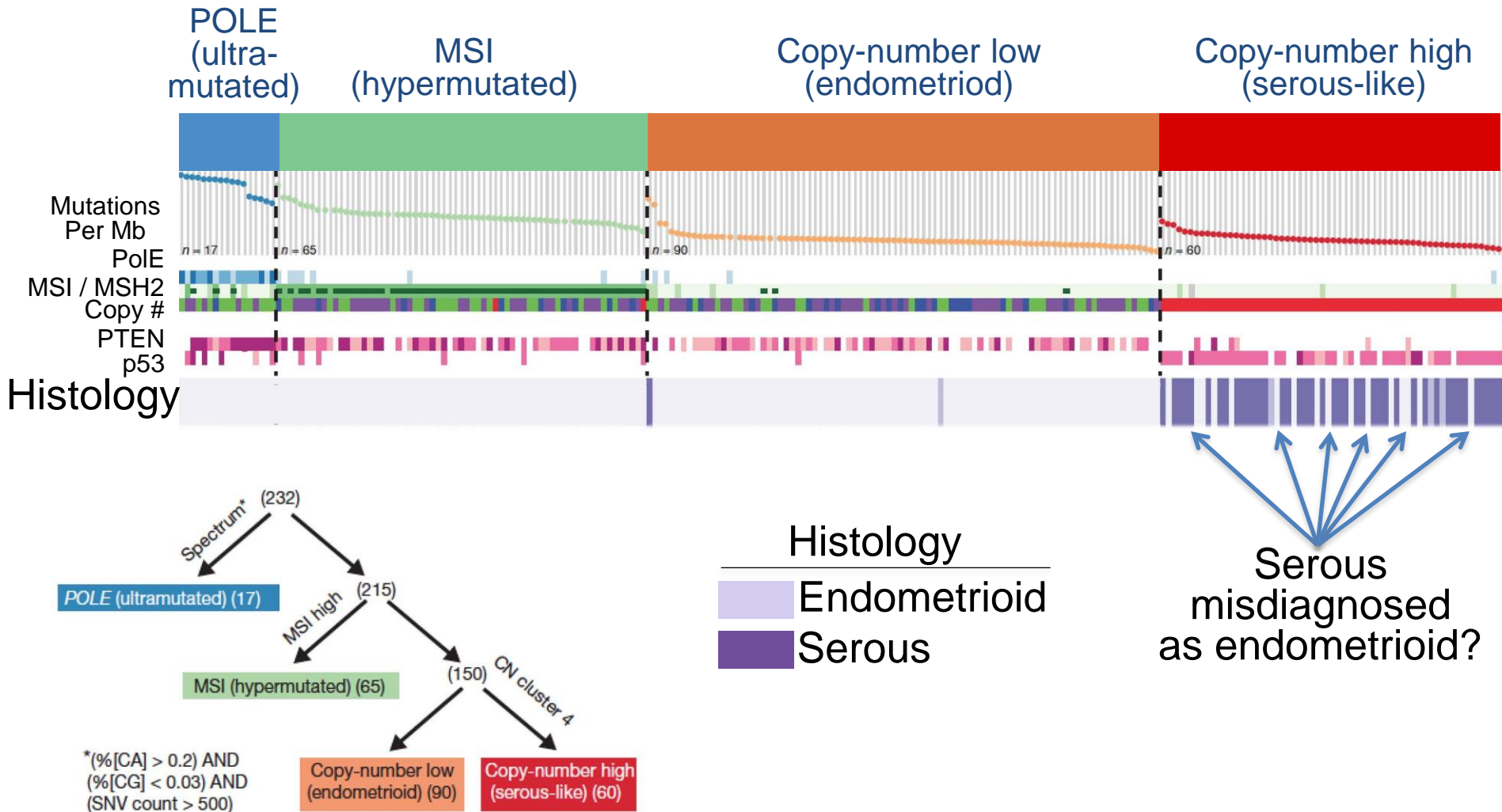
Increasing genomic complexity



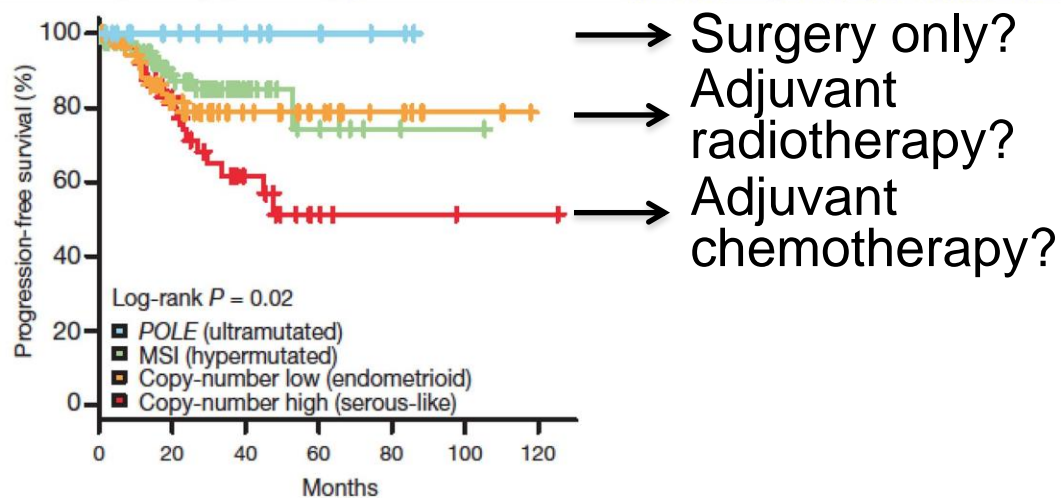
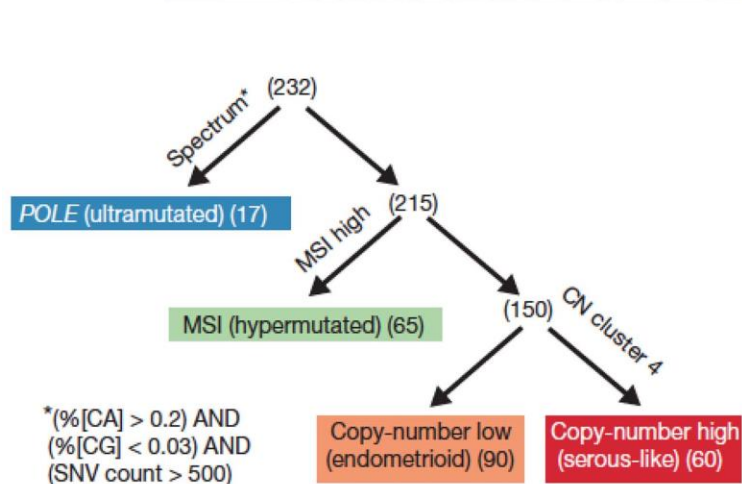
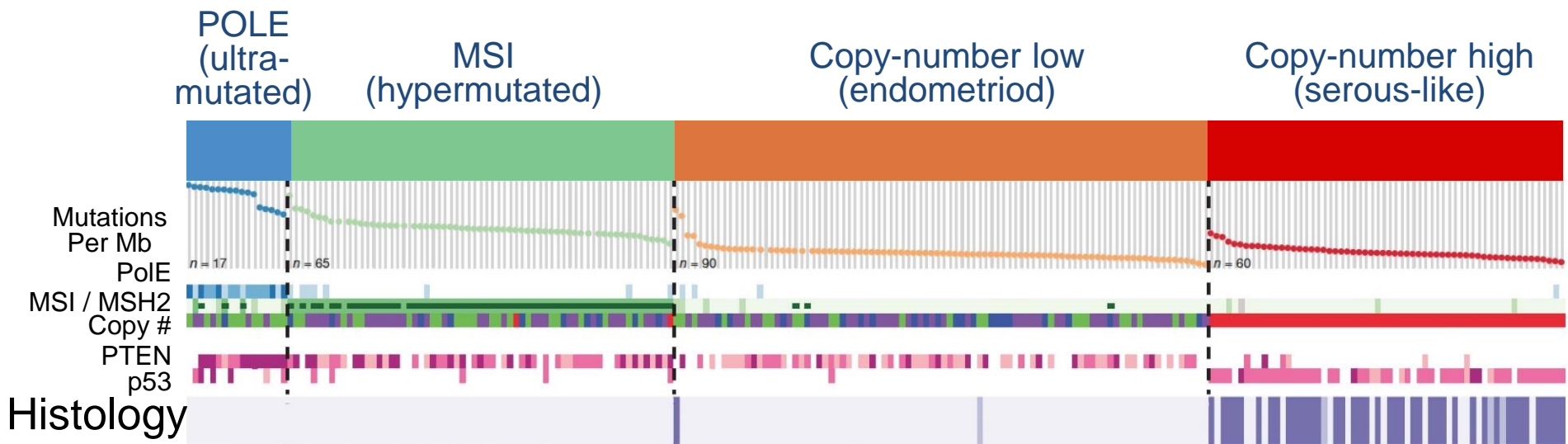
National Cancer Informatics Program



# Molecular Subgroups Refine Histological Diagnosis Of Endometrial Carcinoma



# Molecular Diagnosis of Endometrial Cancer May Influence Choice of Therapy

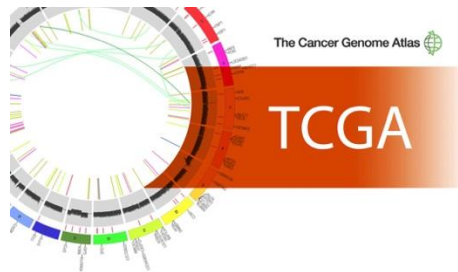


# Extending TCGA and TARGET

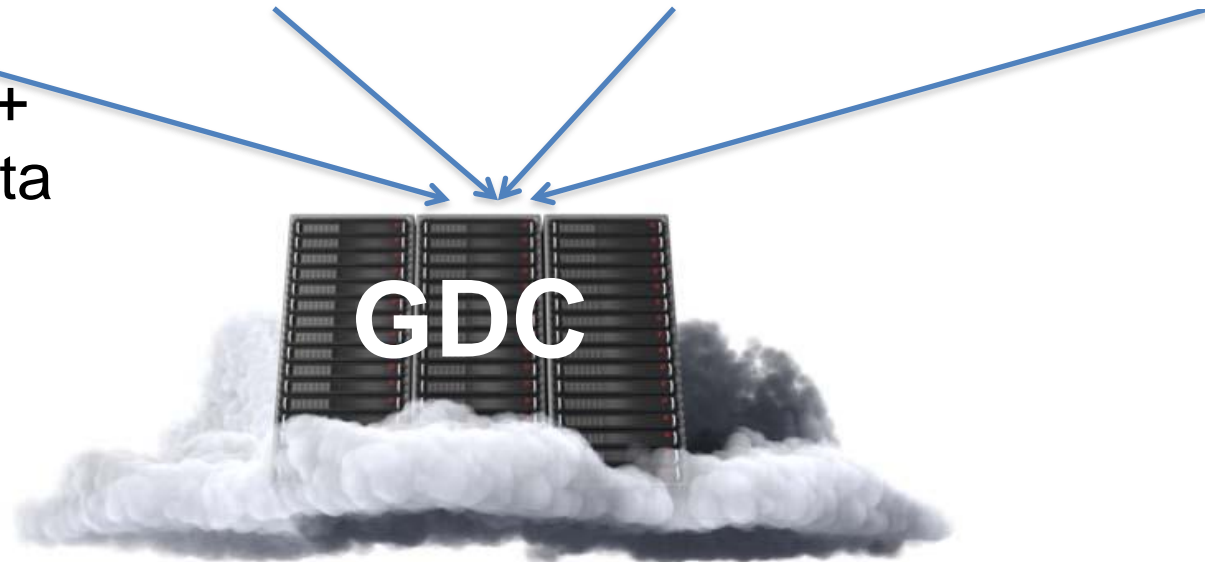
- **Cancer Genomics Data Commons**
- **NCI Cloud Pilots**
  
- **Molecular Clinical Trials:**
  - MPACT, MATCH, Exceptional Responders



# NCI Cancer Genomics Data Commons

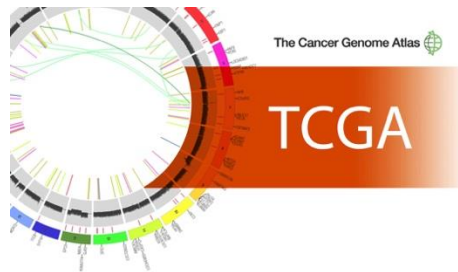


Genomic +  
clinical data



NCI Genomics  
Data Commons

# NCI Cancer Genomics Data Commons

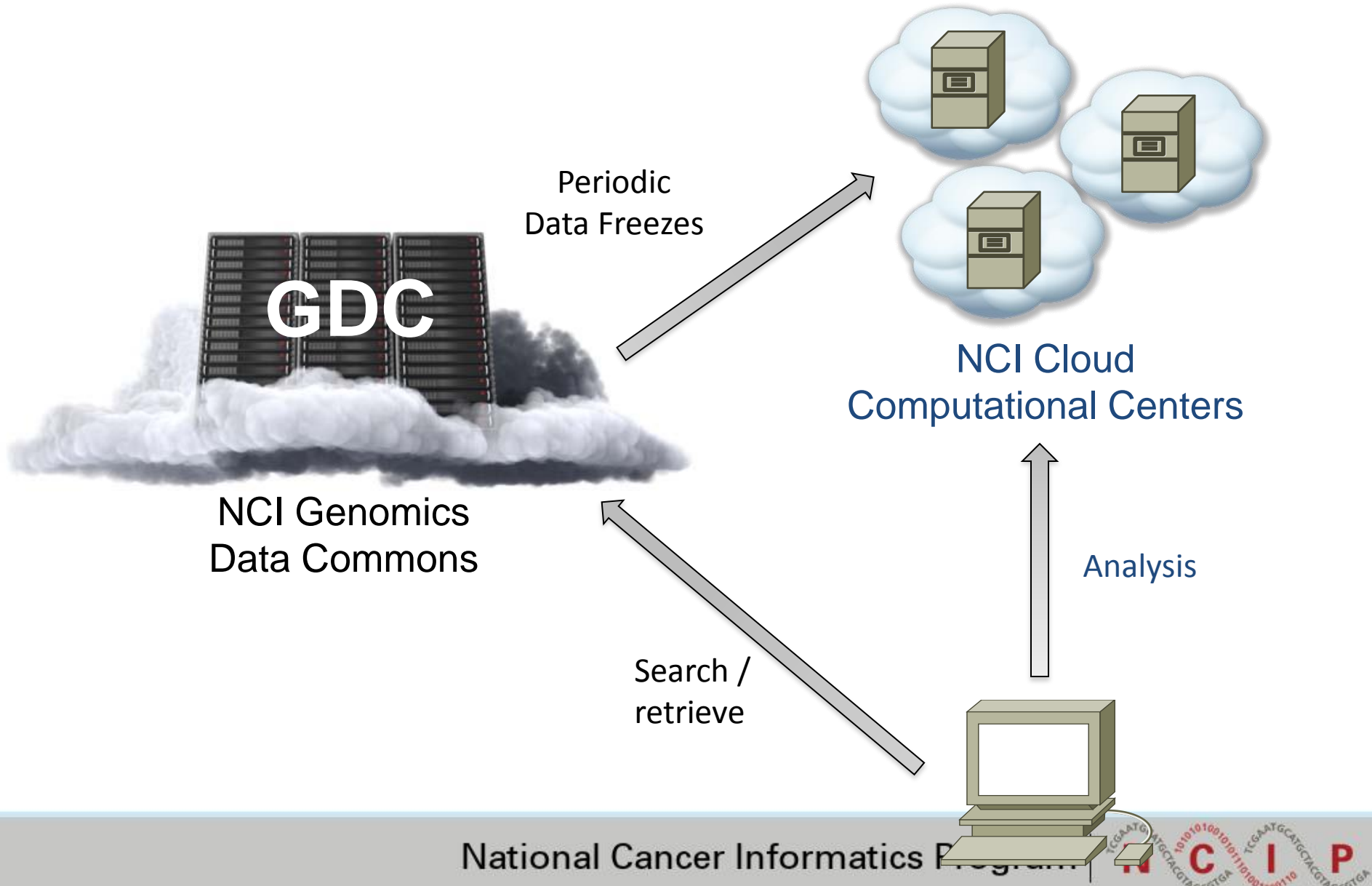


Genomic +  
clinical data



NCI Genomics  
Data Commons

# Relationship of the Cancer Genomics Data Commons and NCI Cloud Pilots



# The future

- Elastic computing 'clouds'
- Social networks
- Big Data analytics
- Precision Medicine
- Connected Health
- Measuring health
- Practicing protective medicine

Semantic and synoptic data

Intervening **before** health is compromised

*Learning systems that connect **everyone** and enable learning from **every cancer patient***

# Thank you

Warren A. Kibbe  
Warren.kibbe@nih.gov



# ADVOCATE ENGAGEMENT WORKING GROUP

Progress update from:  
Joya Delgado Harris

# Advocate Engagement Working Group (AEWG)

## Progress to Date:

- Inaugural meeting in October 2014; identified 3 priority areas:
  - Identify appropriate advocates
  - Engage advocates and identify opportunities
  - Advocate training
- Hosted webinar in December 2014 to examine “Identify Advocates” priority
  - AEWG provided feedback on OAR research advocate system
  - Planning a broader pilot test of the OAR research advocate system

# Advocate Engagement Working Group (AEWG)

## Next Steps:

- Planning a webinar in April 2015 to finish strategies for “Identify Advocates” focus area:
  - Present findings from pilot test of OAR’s research advocate system
  - Begin the “Engage Advocates” focus area
- Tentative in-person meeting in June 2015
- Continue discussions on priority areas and strategies through 2015

***Anticipate presenting AEWG summary of activities and suggestions to NCRA in early 2016***

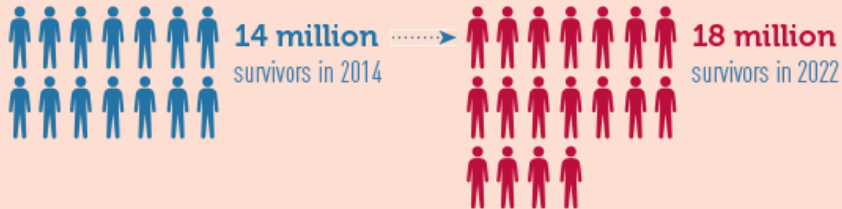


# ORGANIZATIONAL ENGAGEMENT WORKING GROUP

Progress update from:  
Kelley Landy

# Investing in the Future of Cancer Research

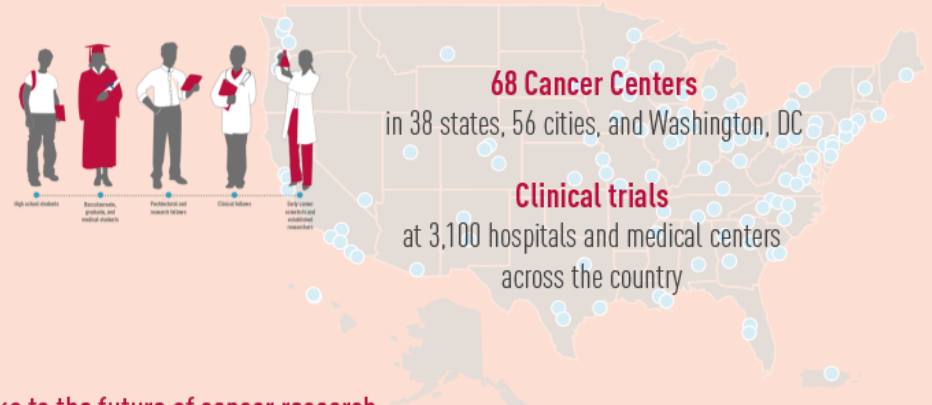
Thanks in part to the talent, facilities, and ideas supported by the National Cancer Institute (NCI), cancer patients are now living longer.



The NCI supports the development of a strong workforce of scientists and health professionals who make up the cancer research community nationwide.

The NCI funds the infrastructure for **cutting-edge research** and **state-of-the-art cancer care** to patients.

The NCI's ability to advance cancer research has declined due to financial constraints, which poses a risk to cancer research.



FUNDED GRANTS  
HAVE PLUMMETED BY

50%

FROM

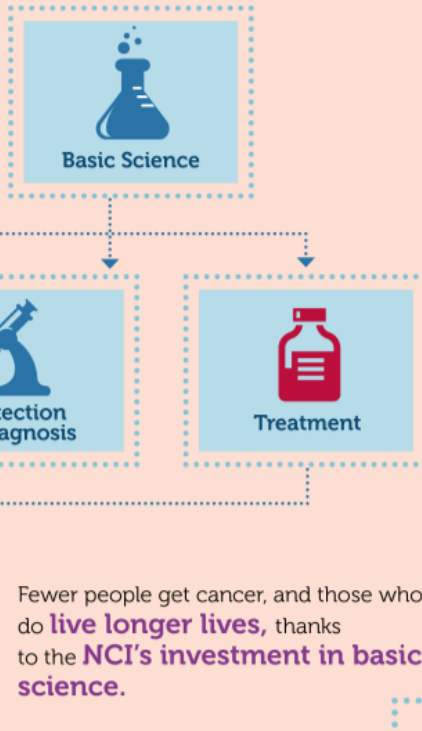
30% → 14%

## Risks to the future of cancer research

- ! Fewer students choosing to enter the field of cancer research
- ! Fewer cancer research and clinical jobs in communities across the country
- ! Diminished infrastructure to support the cancer research of tomorrow

Funding basic science leads to discoveries that are needed to advance cancer research.

The National Cancer Institute (NCI) provides the **foundation** for the research that brings better treatments and outcomes to patients by supporting and funding **basic science**.

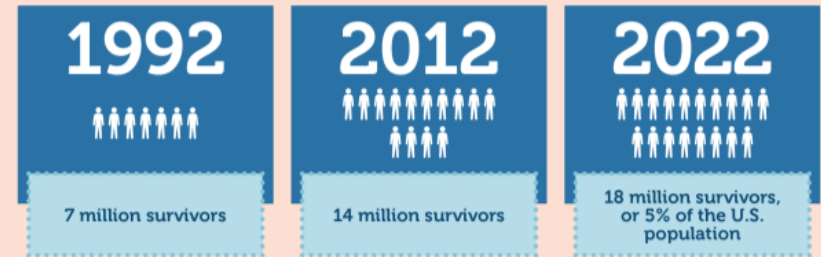


Fewer people get cancer, and those who do **live longer lives**, thanks to the **NCI's investment in basic science**.

Over the past decade, the NCI has suffered an overall 25% loss in spending power, which threatens progress against cancer.

# Investing in Science for Progress Against Cancer

The number of people living beyond a cancer diagnosis has doubled. Improved cancer survivorship starts with the NCI's investment in basic science.



This loss in budget is due to:

- ⚠️ A stop in financial growth in the nation's investment in cancer research
- ⚠️ Inflation
- ⚠️ Increased expense of research

# Investing in the Genetics of Cancer

The National Cancer Institute's (NCI's) investment in basic science initiatives like The Cancer Genome Atlas (TCGA) has helped researchers understand cancer genetics, leading to better patient outcomes.

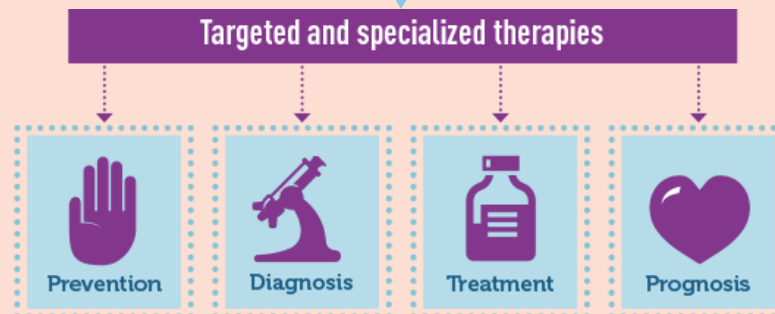
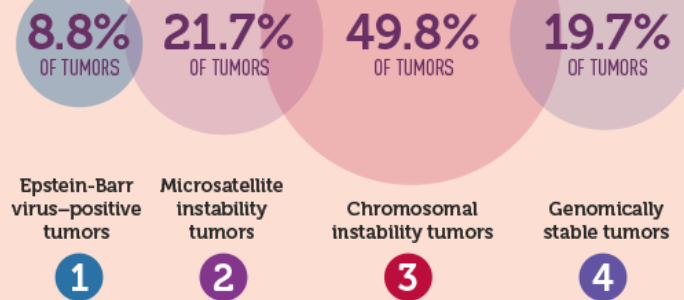
TCGA researchers examined the genetics of over 20 types of cancer, including stomach cancer.

**Worldwide** 3<sup>rd</sup> leading cause of cancer-related deaths worldwide.

**United States** 10,990 deaths and 22,220 new cases in the U.S. in 2014.

Stomach cancer has always been thought of as one disease. Through the NCI's commitment to TCGA, we now know that stomach cancer is actually four different diseases.

Now, researchers can develop targeted and personalized therapies for stomach cancer.



# INFORMED CONSENT WORKING GROUP

Progress update from:  
Max Wallace

# NCI ADVISORY BOARD UPDATES

CTAC update from:  
David Arons

# THANK YOU

## Upcoming Meetings:

June 10, 2015, Bethesda, Maryland

October 19, 2015, Bethesda, Maryland