67th Meeting of the NCI Council of Research Advocates

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 • Advocate Engagement • Organization Engagement • Informed Consent and Genomics Research	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

National Cancer Institute

NCI Update

Douglas R. Lowy
Deputy Director, NCI

NCRA Webinar
March 4, 2015

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

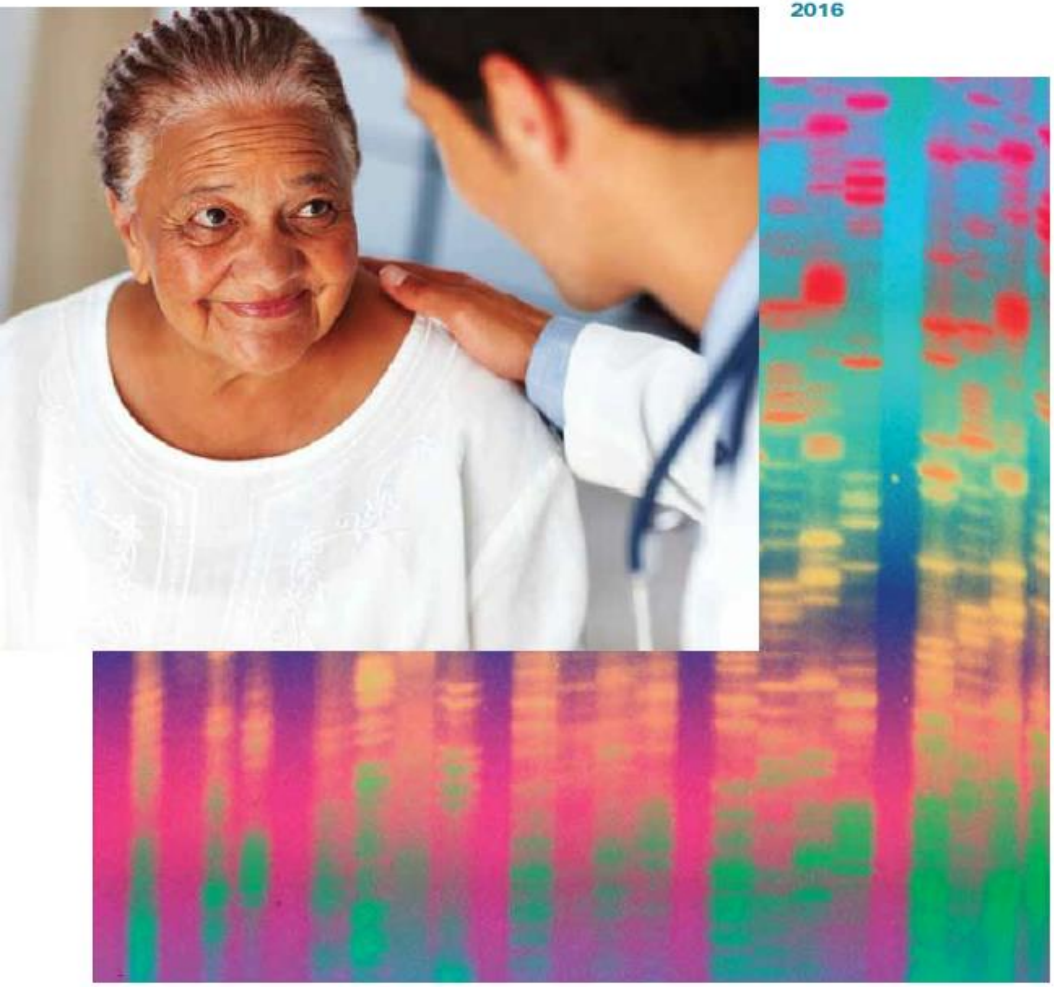
Outline of Presentation

- **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



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

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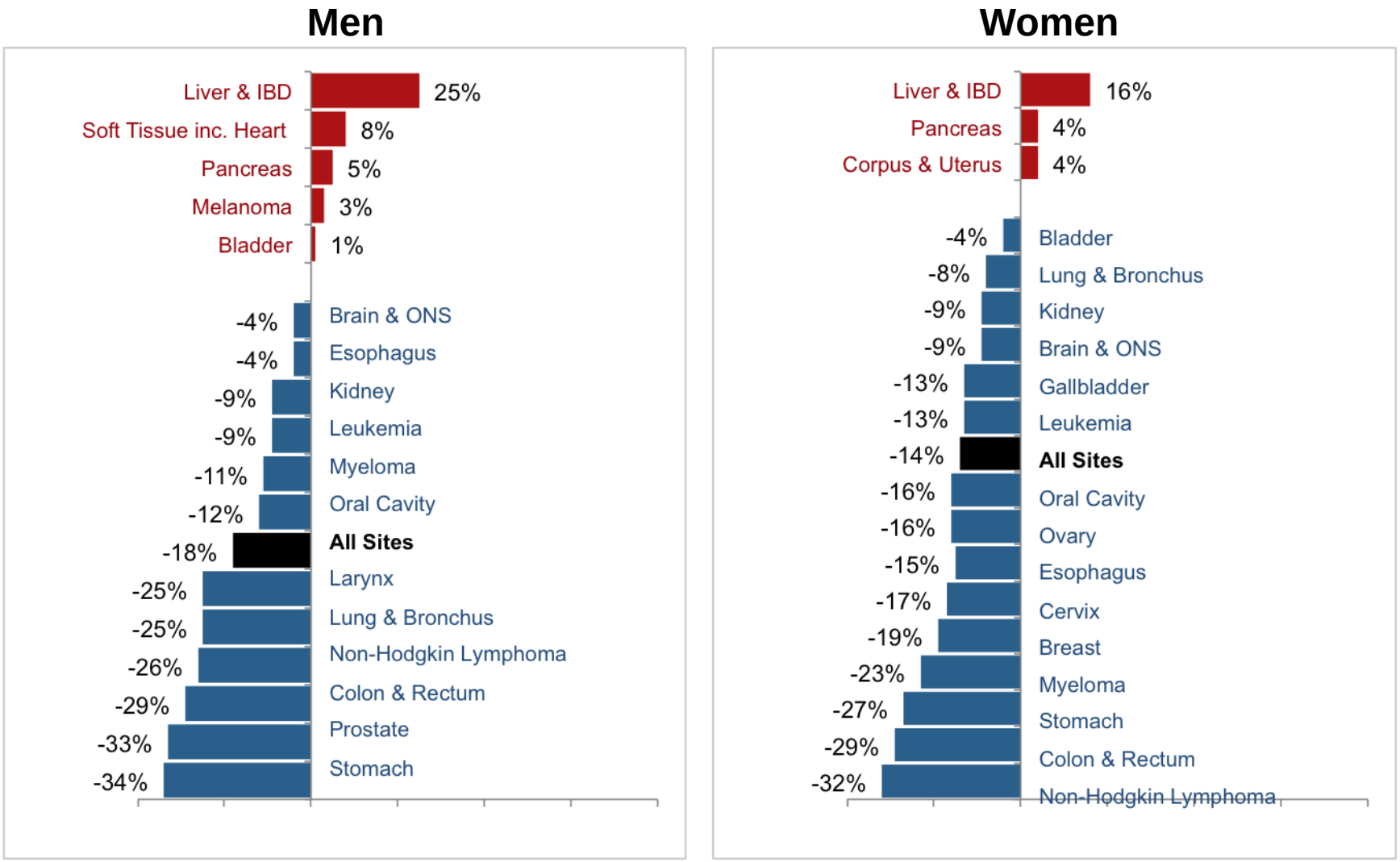
61 NCI Professional Judgment Budget Recommendation

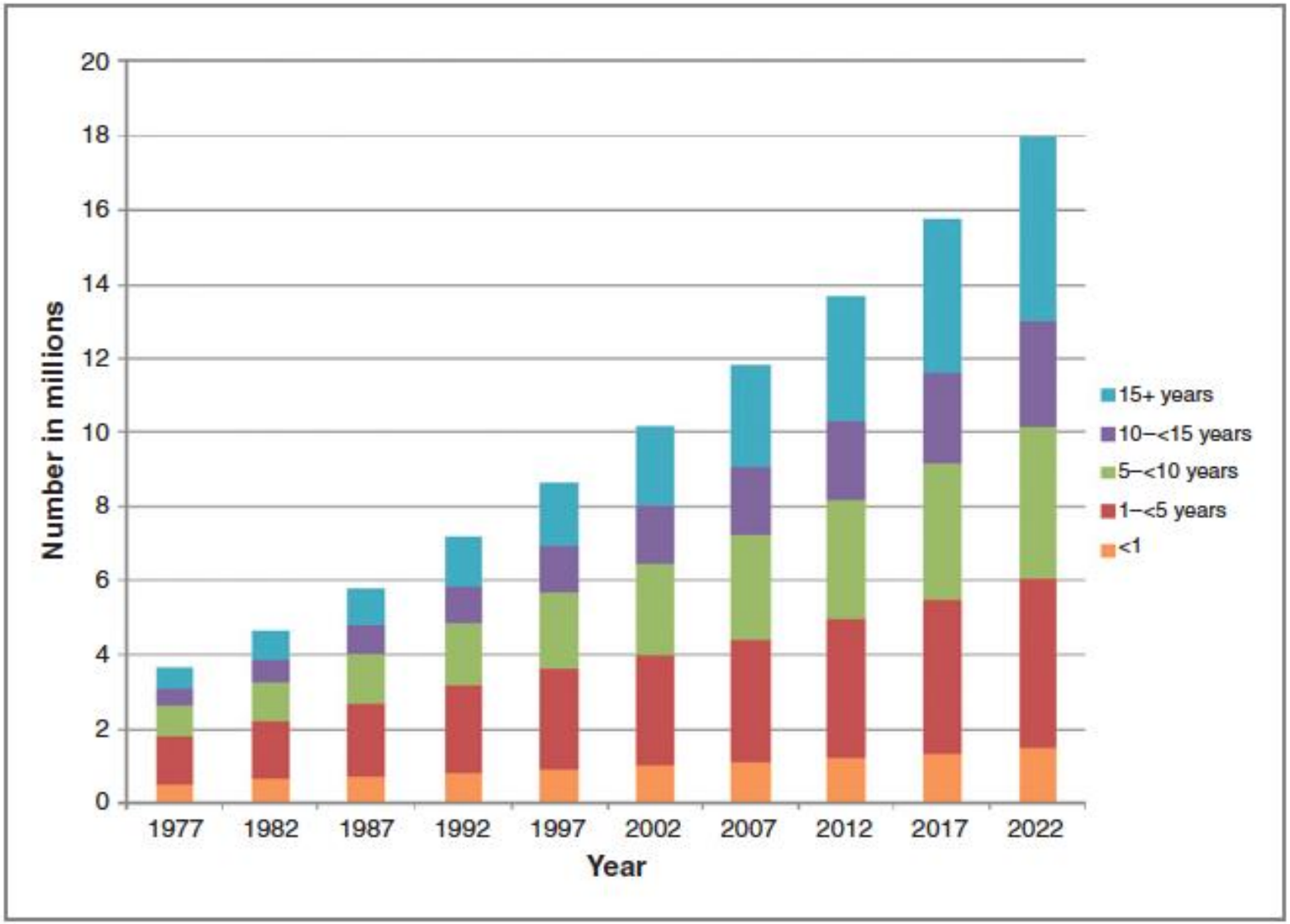
http://www.cancer.gov/aboutnci/budget_planning_leg/plan-2016

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



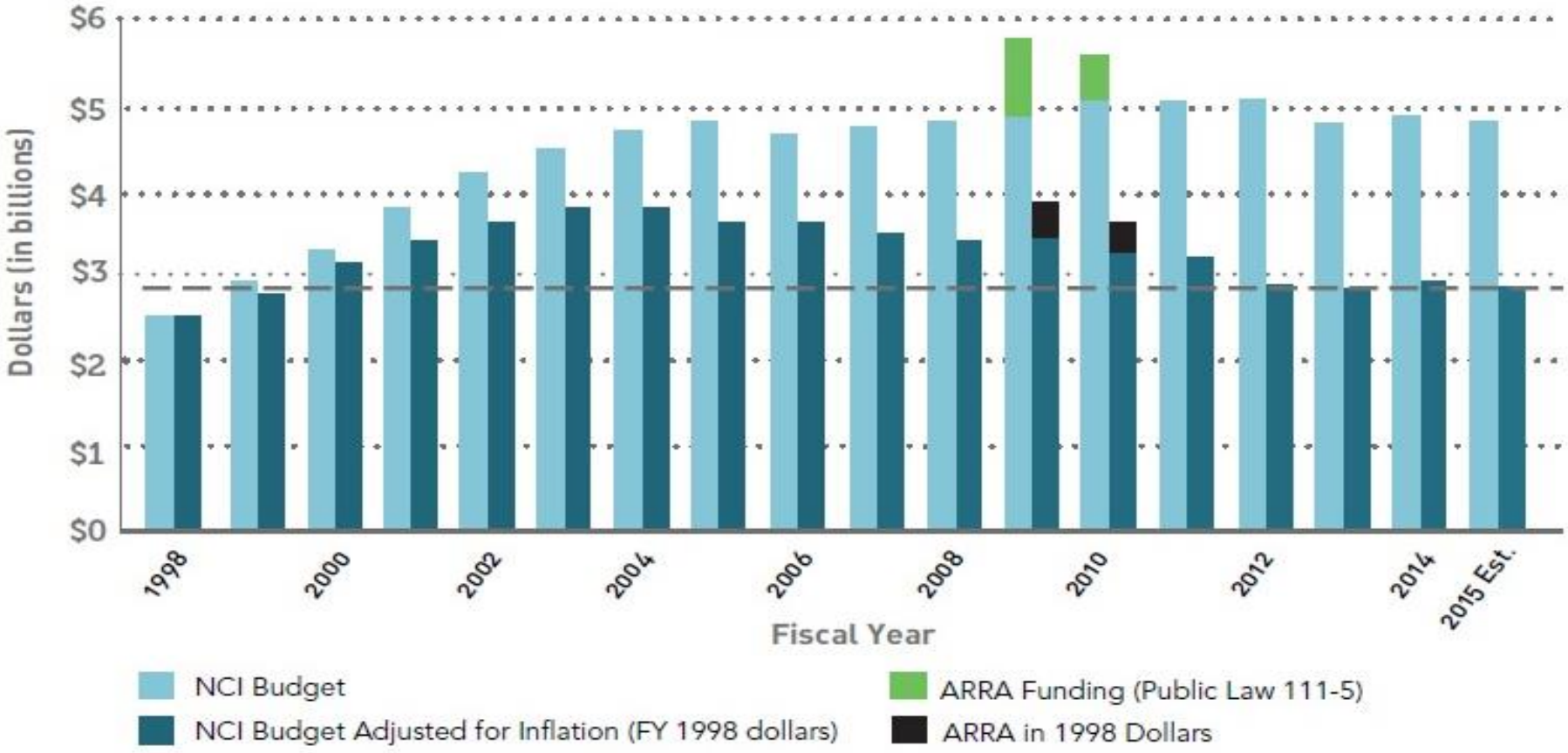
Edwards et al, Annual report to the nation on the status of cancer. Cancer, 2014

A Progressive increase in Cancer Survivors: USA



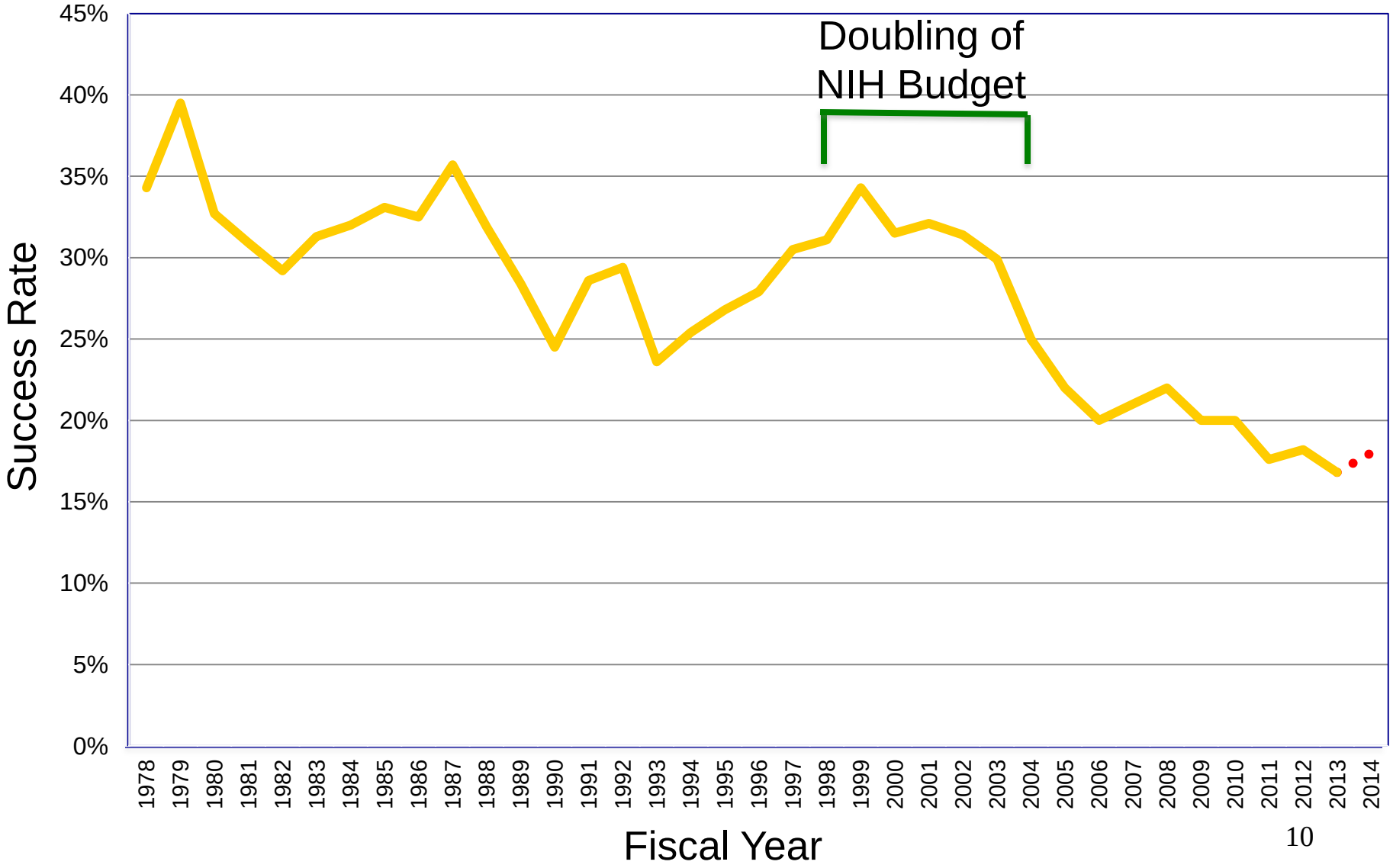
De Moor et al, Cancer Epidemiol Biomarker Prev 2013

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

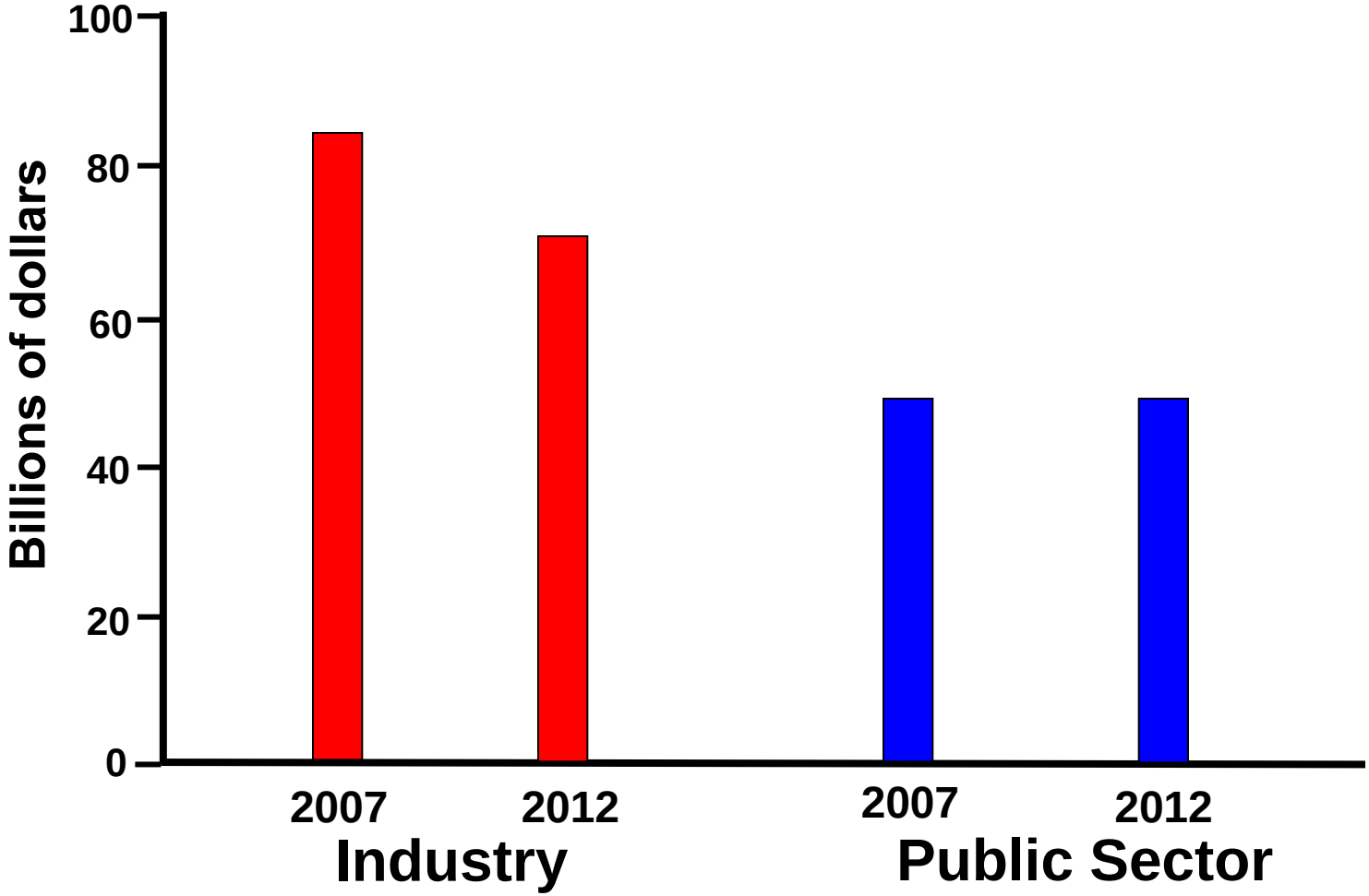


The horizontal dotted line at $2.9 billion indicates the inflation-adjusted 2014 budget was similar to the 1999 budget, the first year of the "NIH doubling"

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

National Cancer Institute

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

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

Accrual Distribution FY2007 - FY2013:

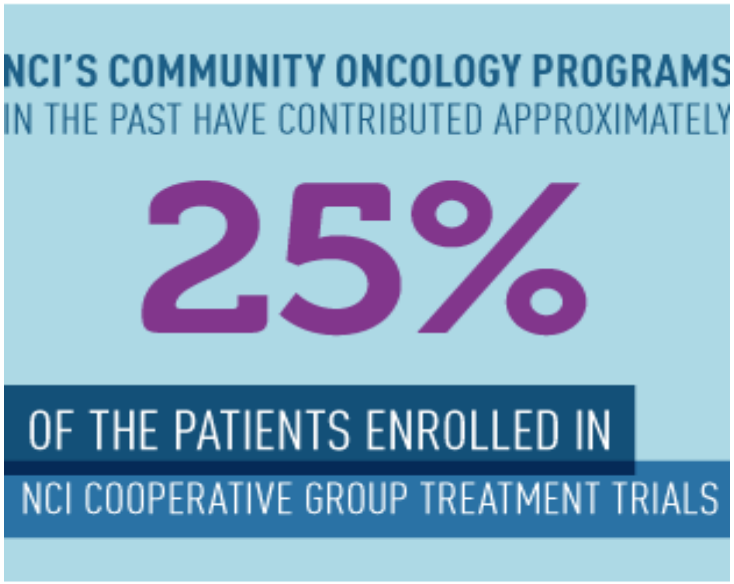
Phase 3: 81%

Phase 2: 16%

Phase 1/Pilot: 3%

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.

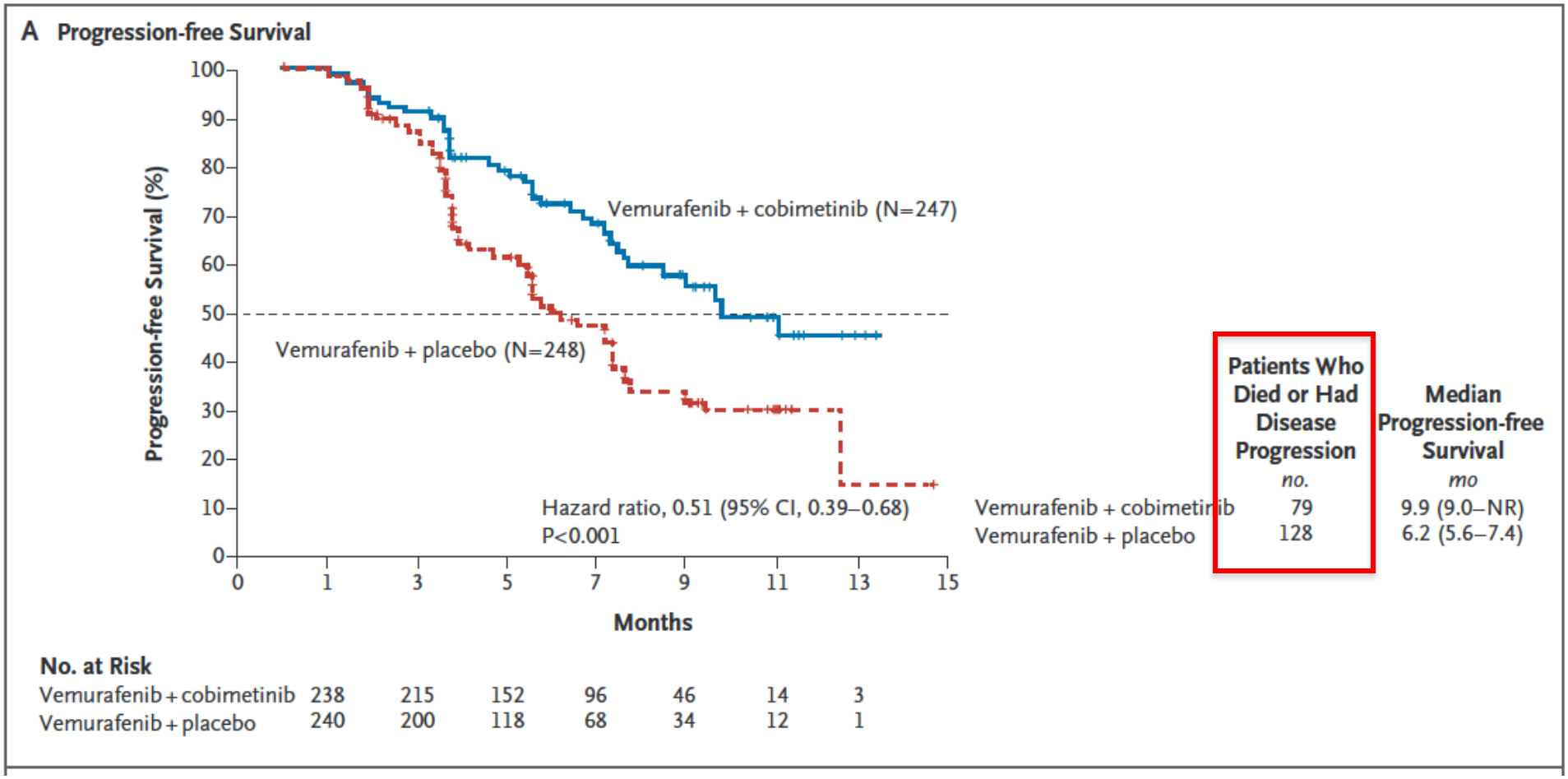


Source: NCI Division of Cancer Prevention

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



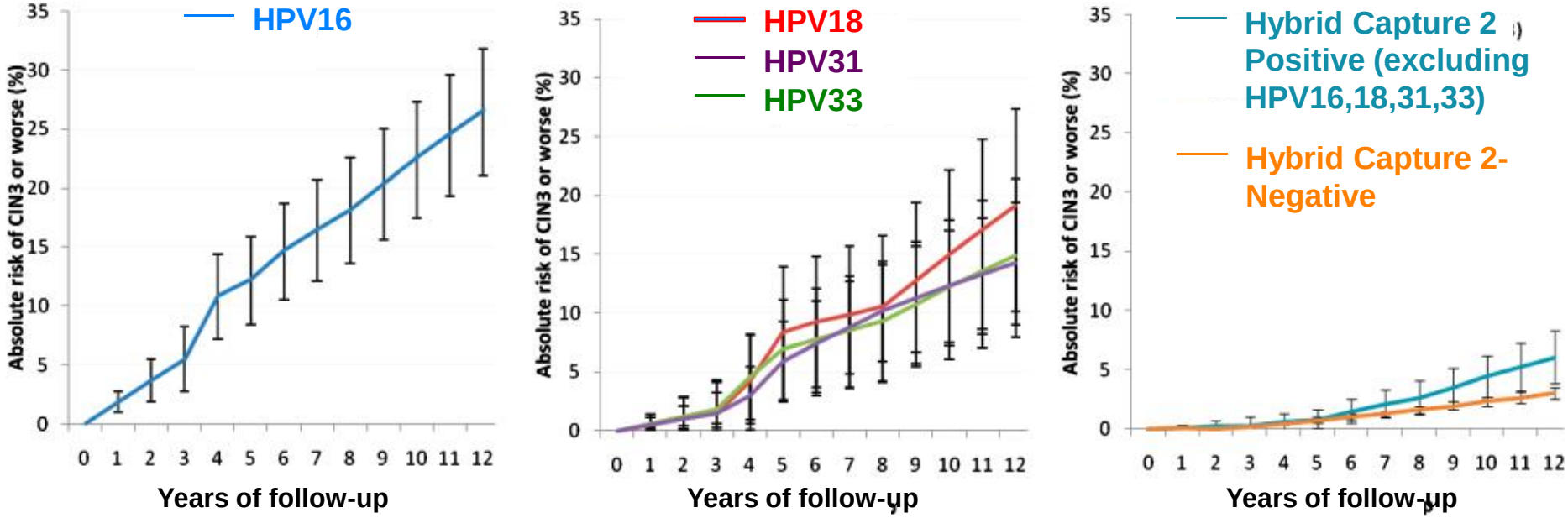
Larkin et al, New Eng J Med, November 13, 2014

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**

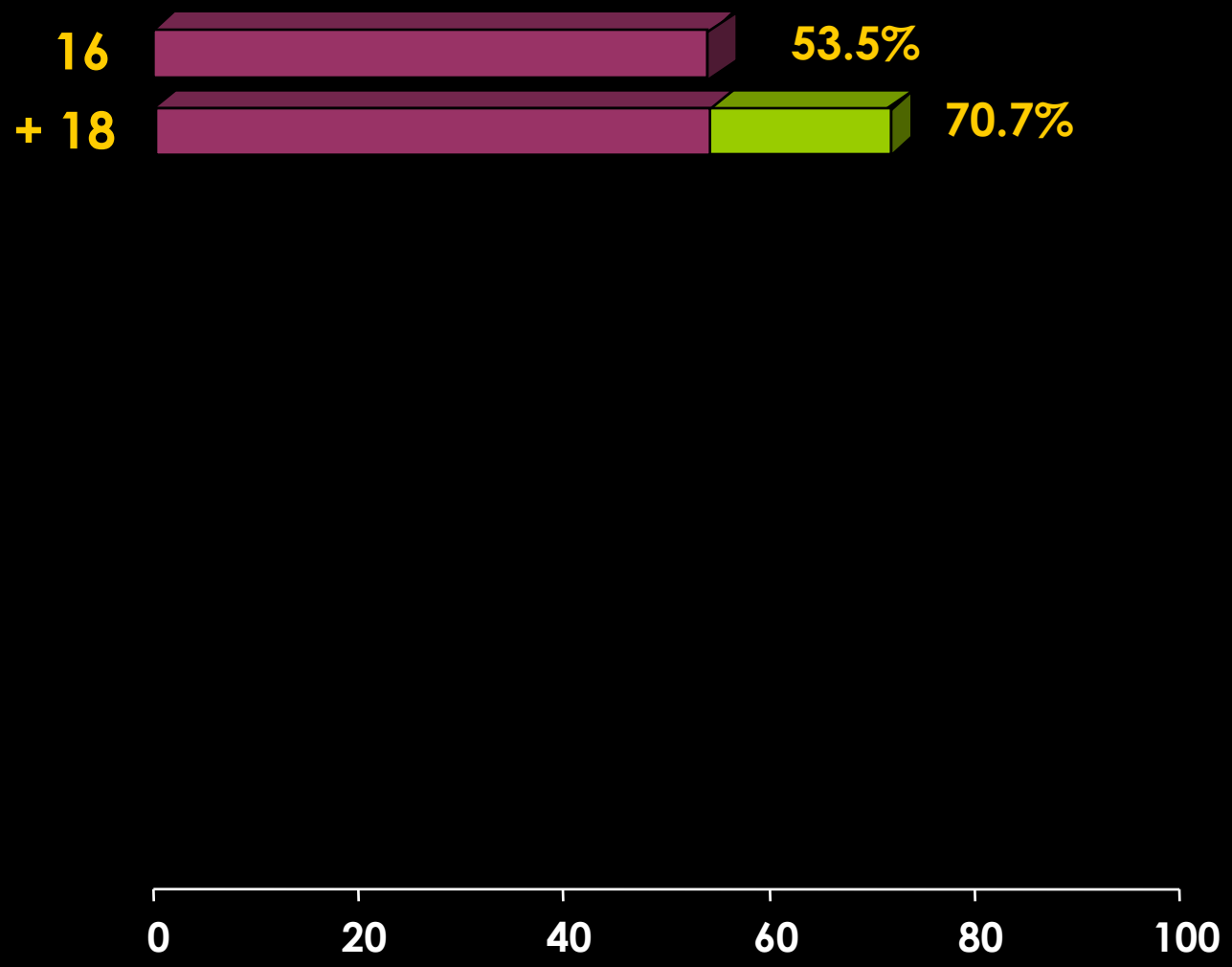
HPV Type Affects the Rate of Development of CIN3 or worse in women with normal cytological findings at baseline: The Danish Cohort Study



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

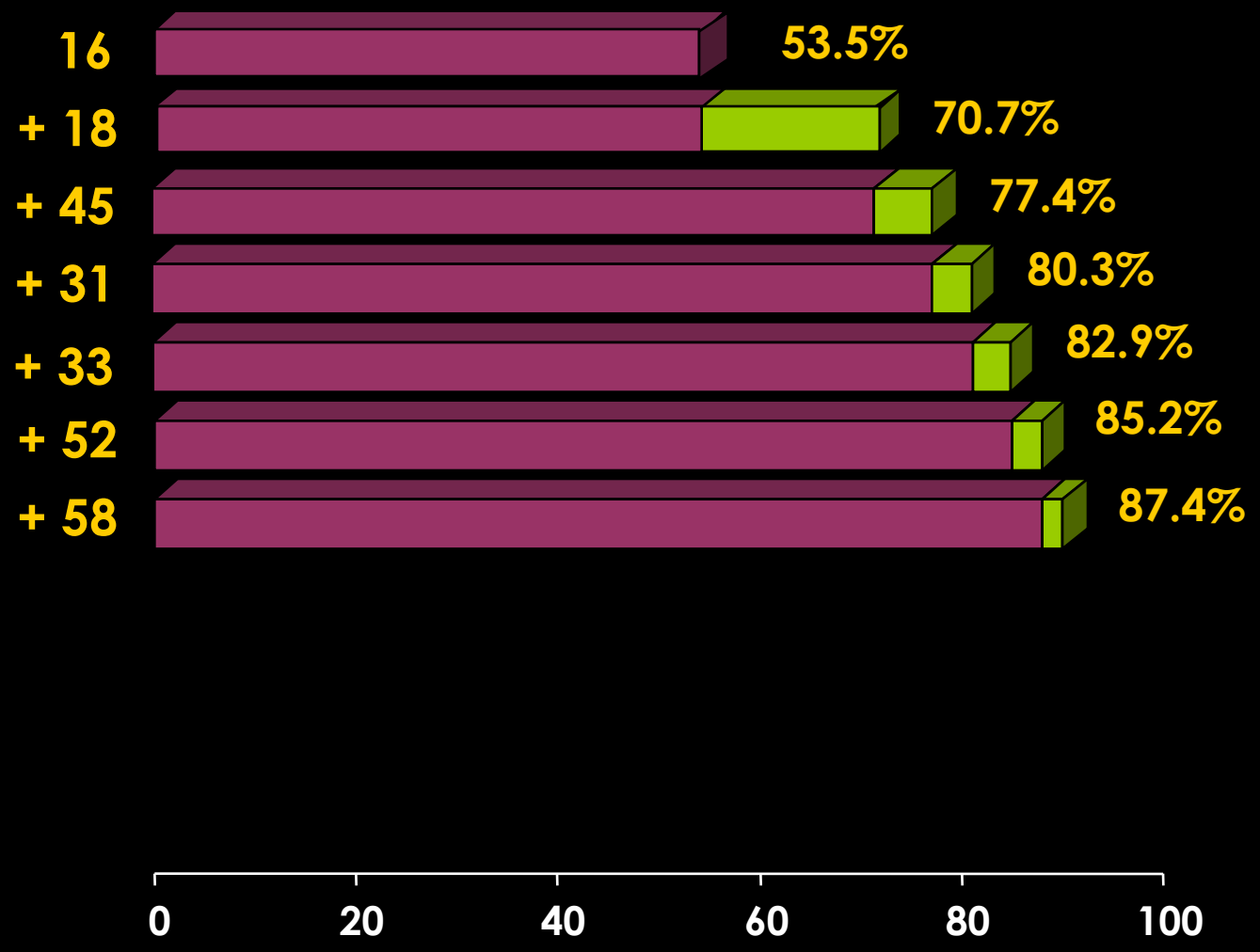
From Kjaer et al, J Natl Cancer Inst 102: 1478-88, 2010

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



Adapted from Munoz et al, Int J Cancer 111: 278-85, 2004

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



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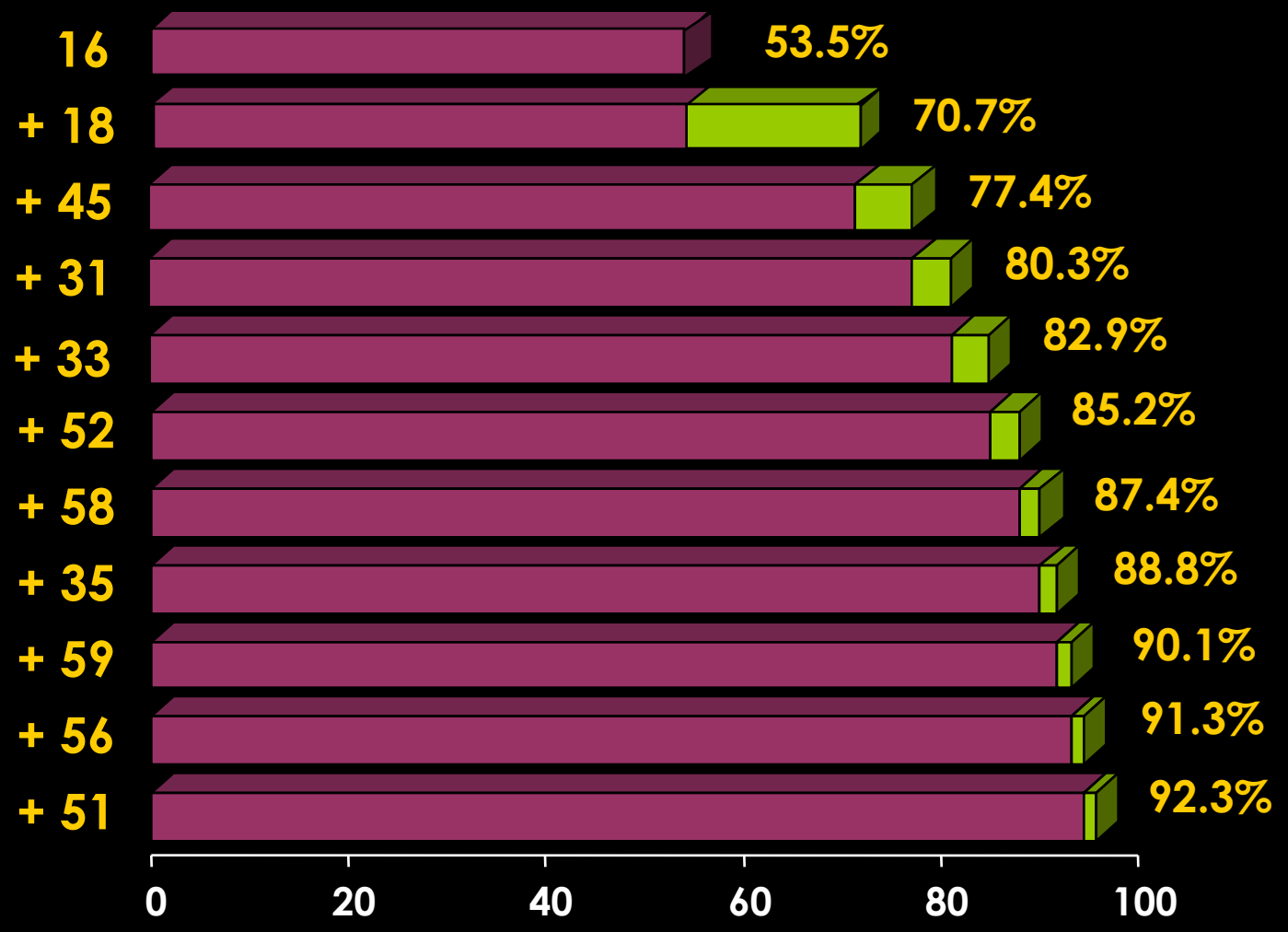


Adapted from Munoz et al, Int J Cancer 111: 278-85, 2004

The NEW ENGLAND JOURNAL of MEDICINE

FEBRUARY 19, 2015

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*

The NEW ENGLAND JOURNAL of MEDICINE
FEBRUARY 19, 2015

EDITORIALS

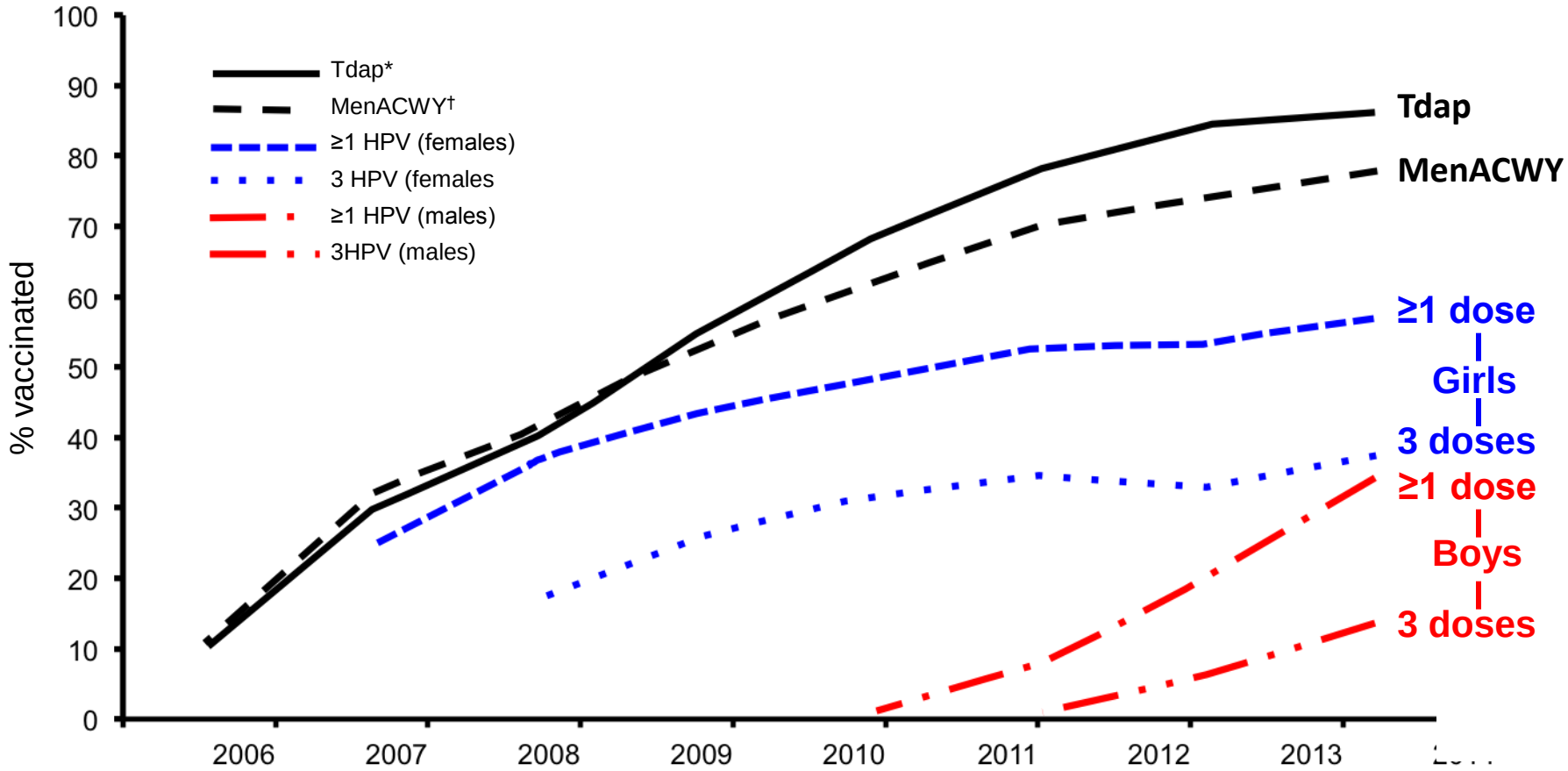
HPV "Coverage"

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

National Cancer Institute

Genomic Data Commons and Cloud Pilots

Warren Kibbe, Ph.D.
warren.kibbe@nih.gov
March 2015

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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

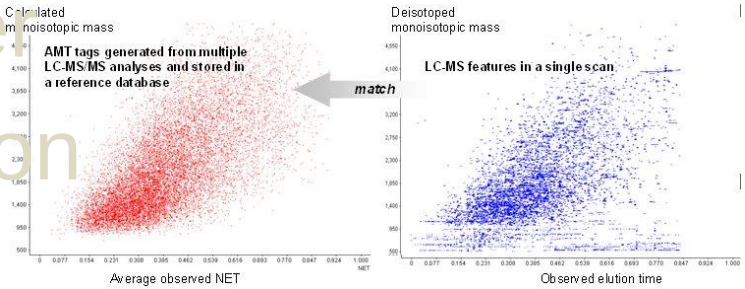
- The era of precision medicine and precision oncology is *predicated* on the integration of research, care, and molecular medicine and the *availability of data* for modeling, risk analysis, and optimal care

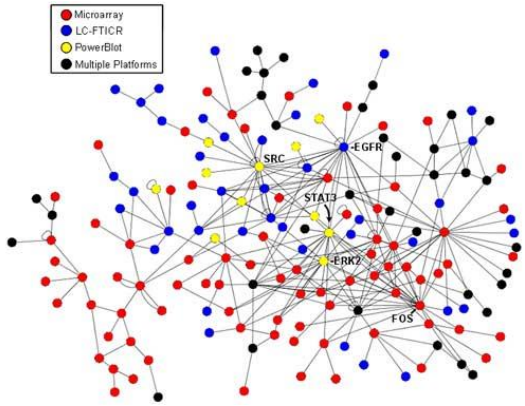
How do we re-engineer translational research policies that will enable a true ***learning healthcare system*** *and put the* ***patient at the center*** *of healthcare?*

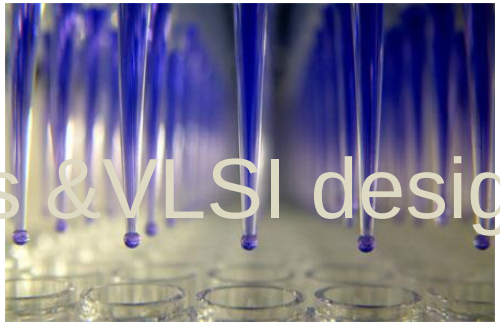
Disruptive Technologies

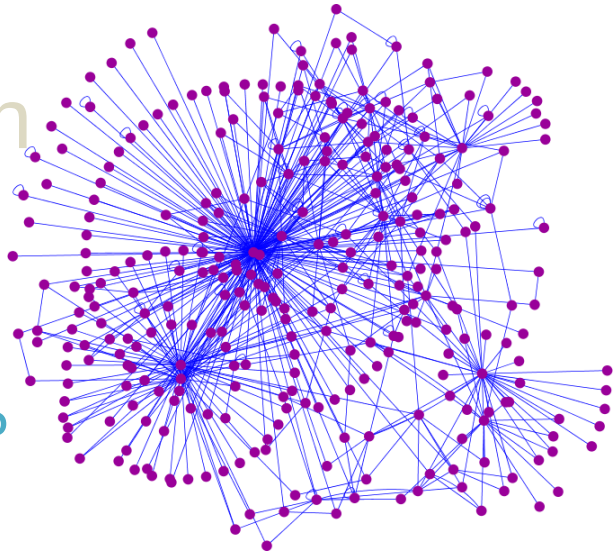
- Printing
- Steam power
- Transportation
- Electricity
- Antibiotics
- Semiconductors &VLSI design
- http
- High throughput biology

Systems view - end of reductionism?



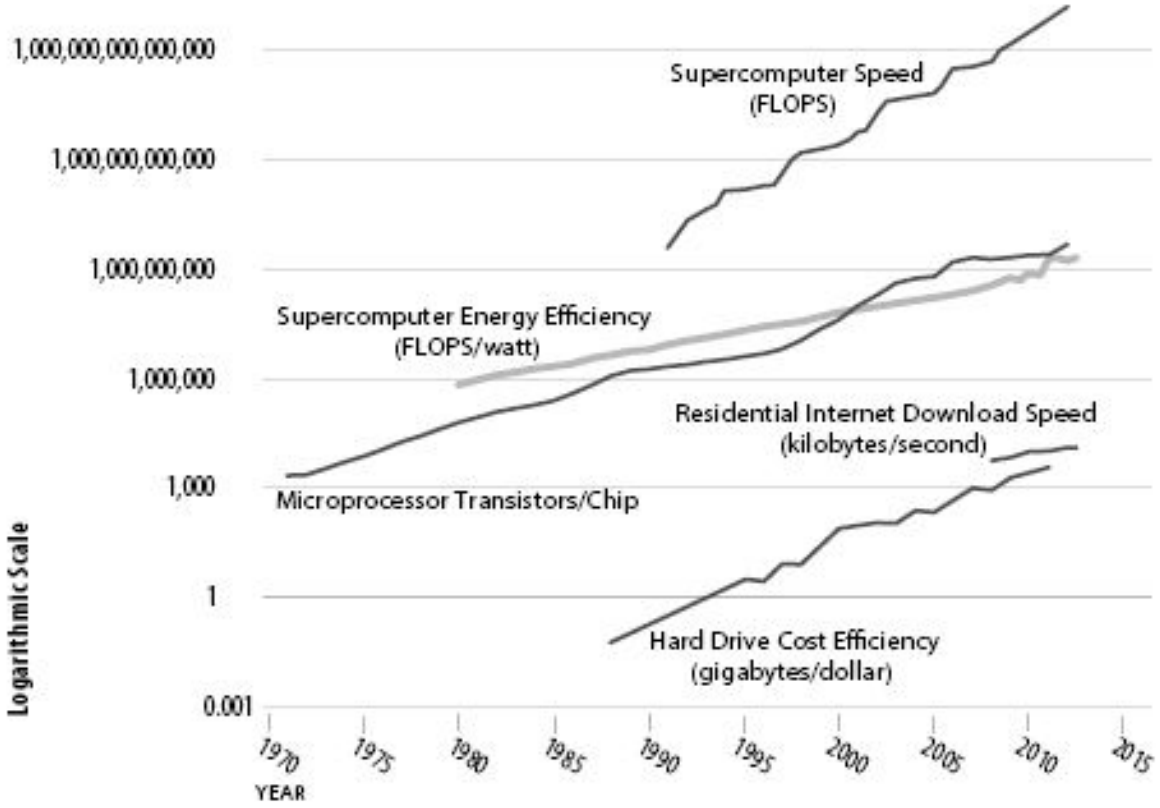






From the Second Machine Age

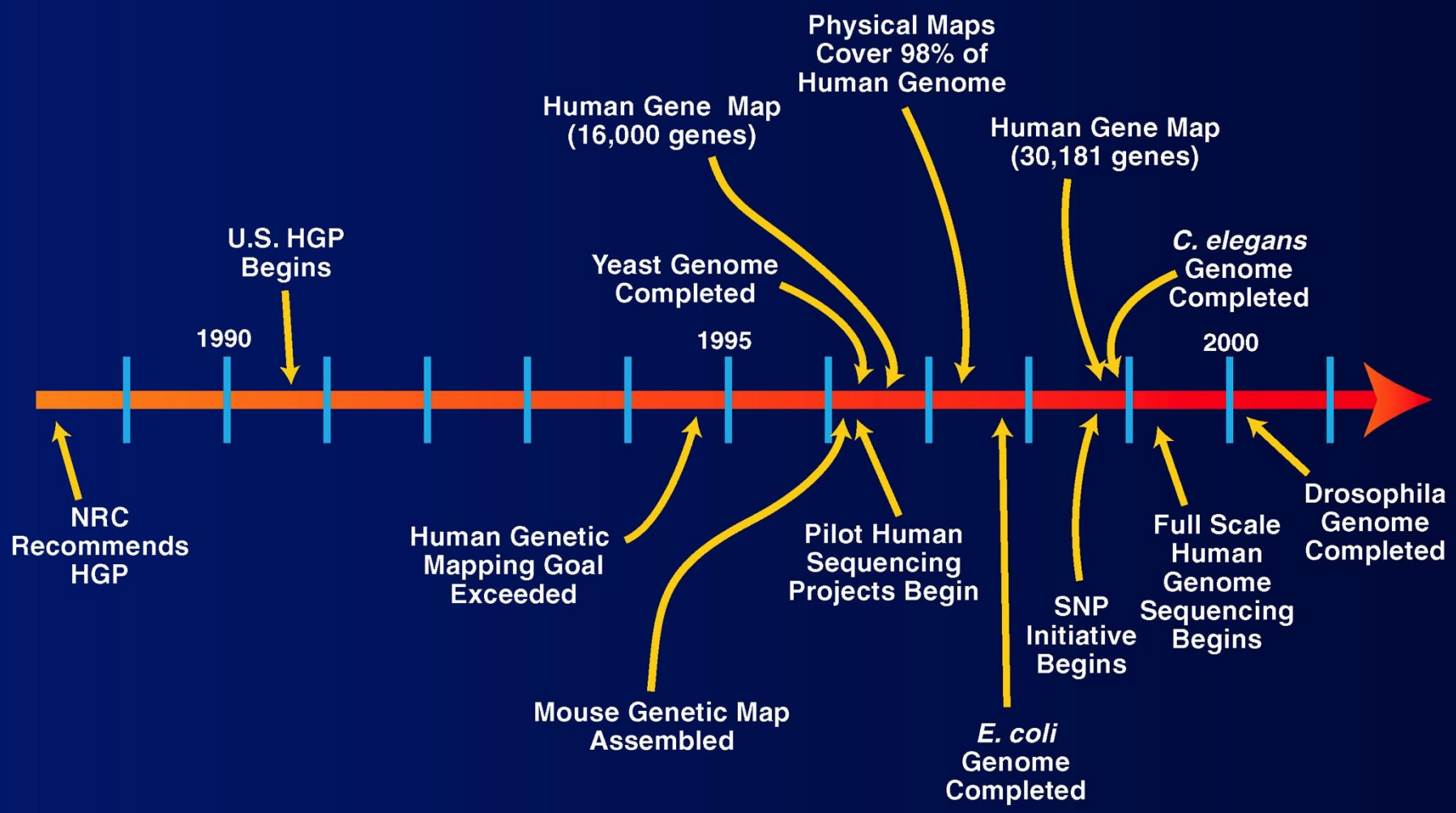
FIGURE 3.3 The Many Dimensions of Moore's Law

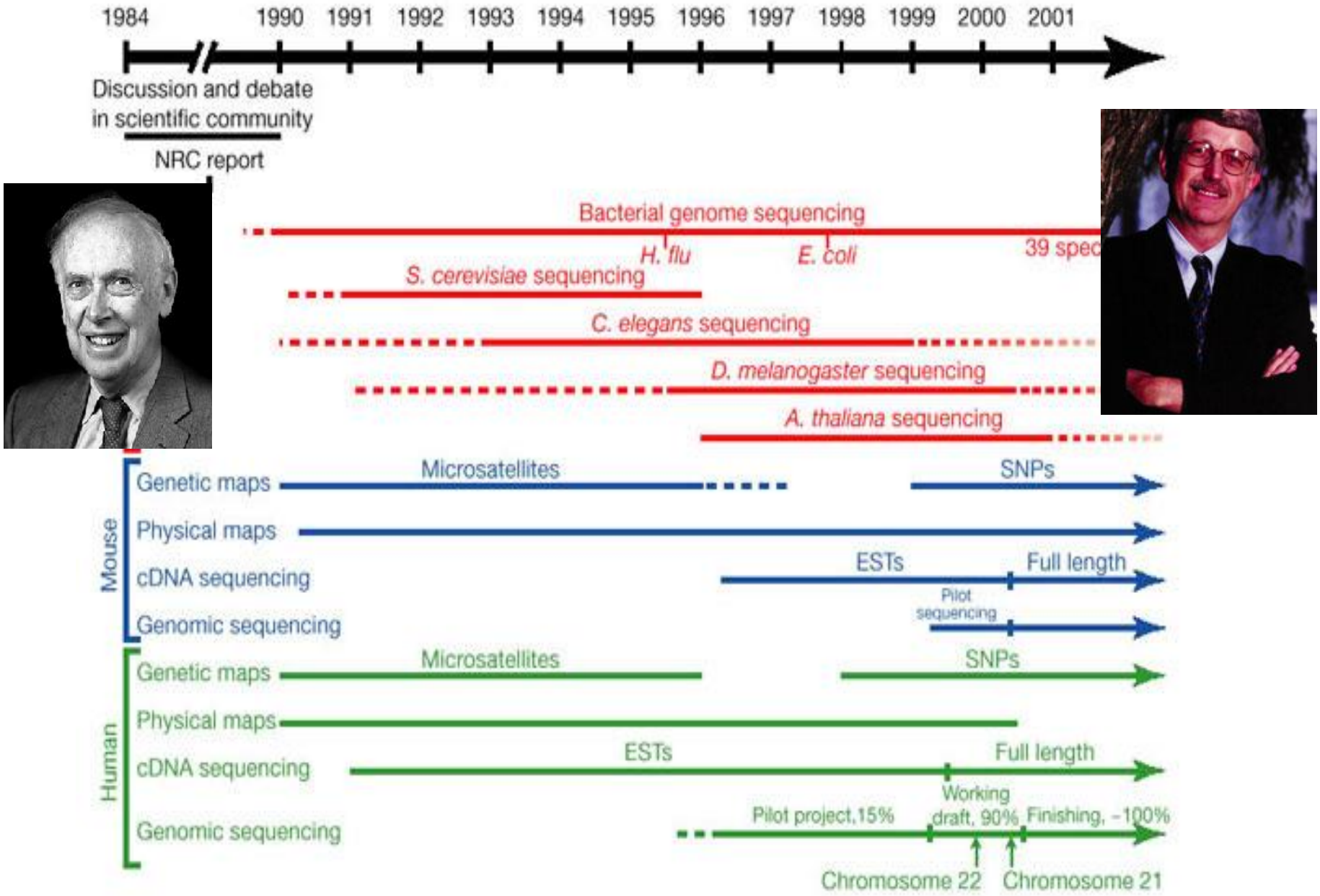


From: The Second Machine Age: Work, Progress, and Prosperity in a Time of Brilliant Technologies by Erik Brynjolfsson & Andrew McAfee

Molecular data is Big Data

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


Physical Maps Cover 98% of Human Genome
Human Gene Map (16,000 genes)
Human Gene Map (30,181 genes)
U.S. HGP Begins
Yeast Genome Completed
C. elegans Genome Completed
1990
1995
2000
NRC Recommends HGP
Human Genetic Mapping Goal Exceeded
Pilot Human Sequencing Projects Begin
Full Scale Human Genome Sequencing Begins
Drosophila Genome Completed
SNP Initiative Begins
Mouse Genetic Map Assembled
E. coli Genome Completed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Discussion and debate in scientific community
NRC report
Bacterial genome sequencing
H. flu
E. coli
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S. cerevisiae sequencing
C. elegans sequencing
D. melanogaster sequencing
A. thaliana sequencing
Mouse
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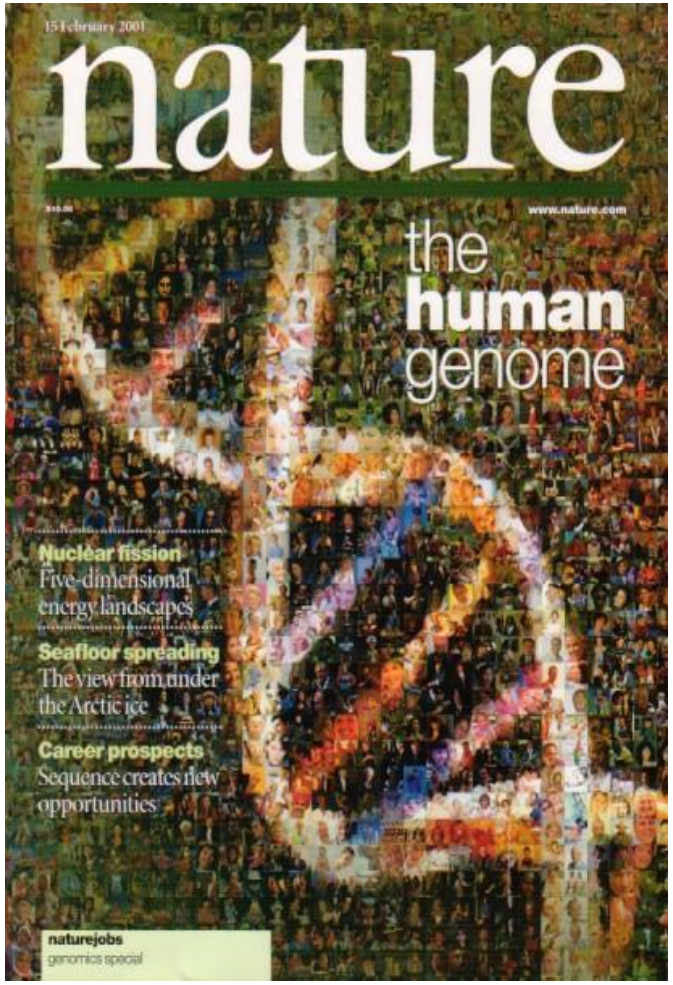
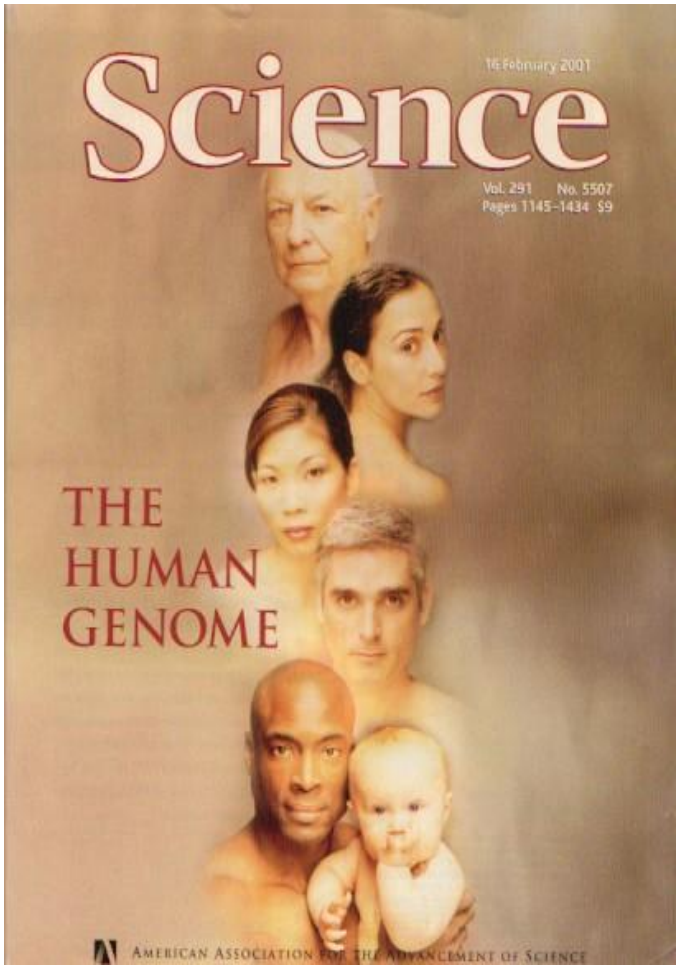
Microsatellites
SNPs
Physical maps
cDNA sequencing
ESTs
Full length
Pilot sequencing
Genomic sequencing
Human
Genetic maps
Microsatellites
SNPs
Physical maps
cDNA sequencing
ESTs
Full length
Genomic sequencing
Pilot project,15%
Working draft, 90%
Finishing, ~100%
Chromosome 22
Chromosome 21

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

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TERT Promoter Mutations in Familial and Sporadic Melanoma

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Antje
Kari H

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TERT promot

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

Pat
Alla
Yipi
B. A
Mic
Rog
and

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

Julius Gudmun
Kristrun R Bene
Droplaug N Mag
Stefania B Olafs
Fernando Fuerte
Inge M van Oor
Kin-Mang Lau[17]
Gudmundur V
Lambertus A Ki

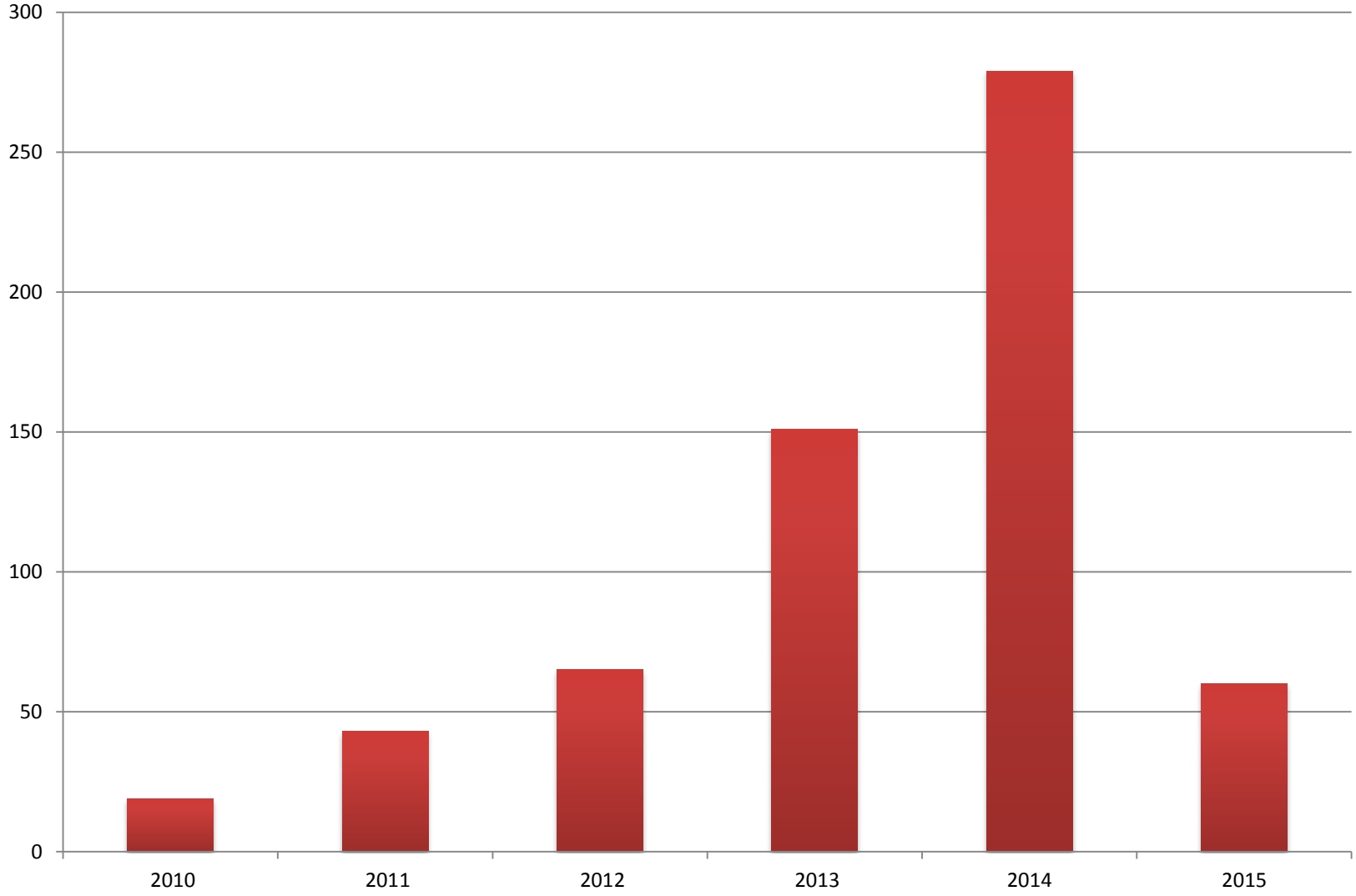
Epigenomic Enhancer Profiling Defines a Signature of Colon Cancer

Batool Akhtar-Zaid
Cynthia F. Bartels,
Awad Jarrar,[5] Matt
Thomas Laframbois

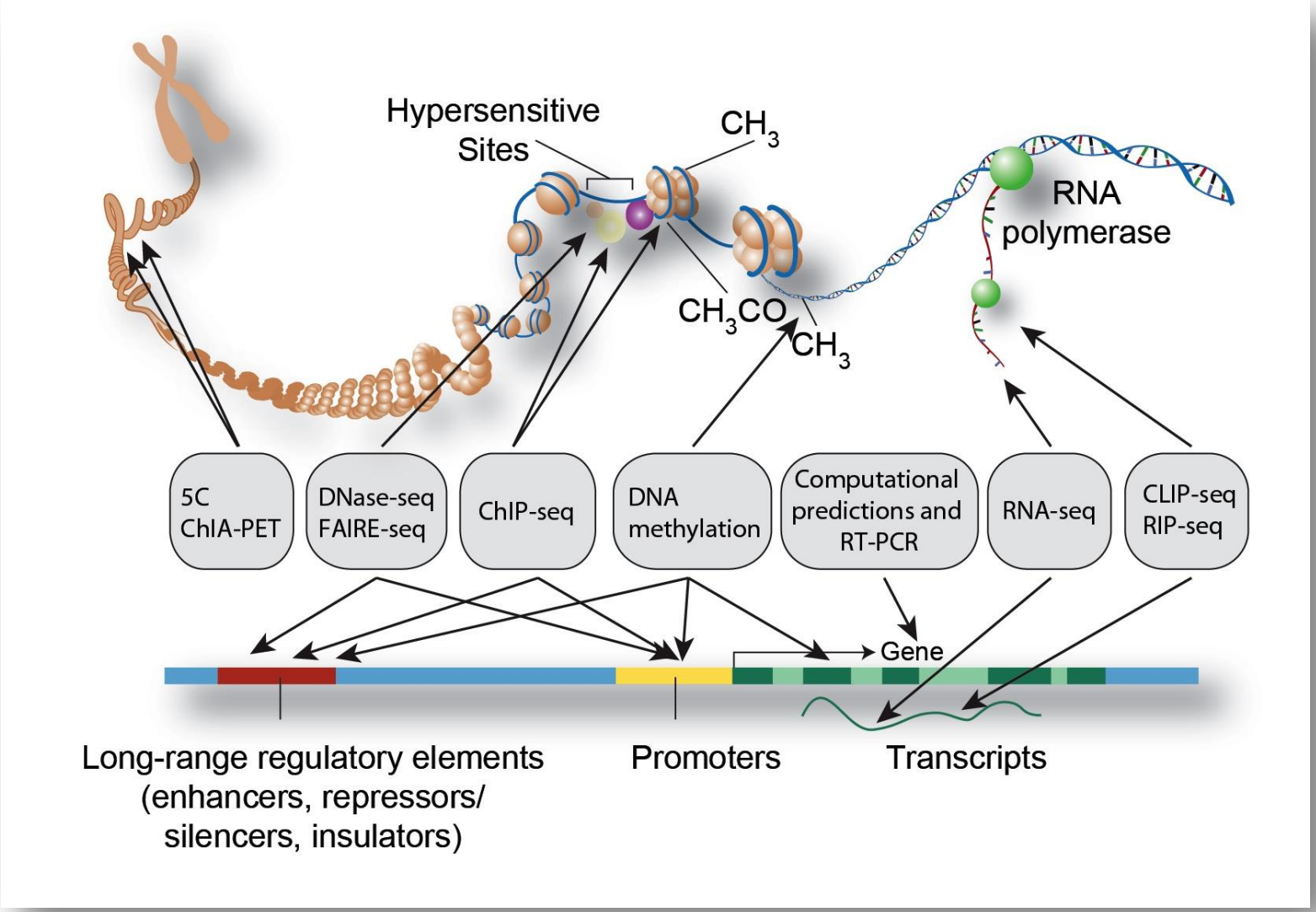
Cancer is characteri
coding sequences and promoters, even though distal regulatory elements play a central role

DNA Methylation of Transcriptional Enhancers and Cancer Predisposition

TCGA Publications since 2010



Assays and Data Types



National Cancer Institute

TCGA – Lessons from structural genomics

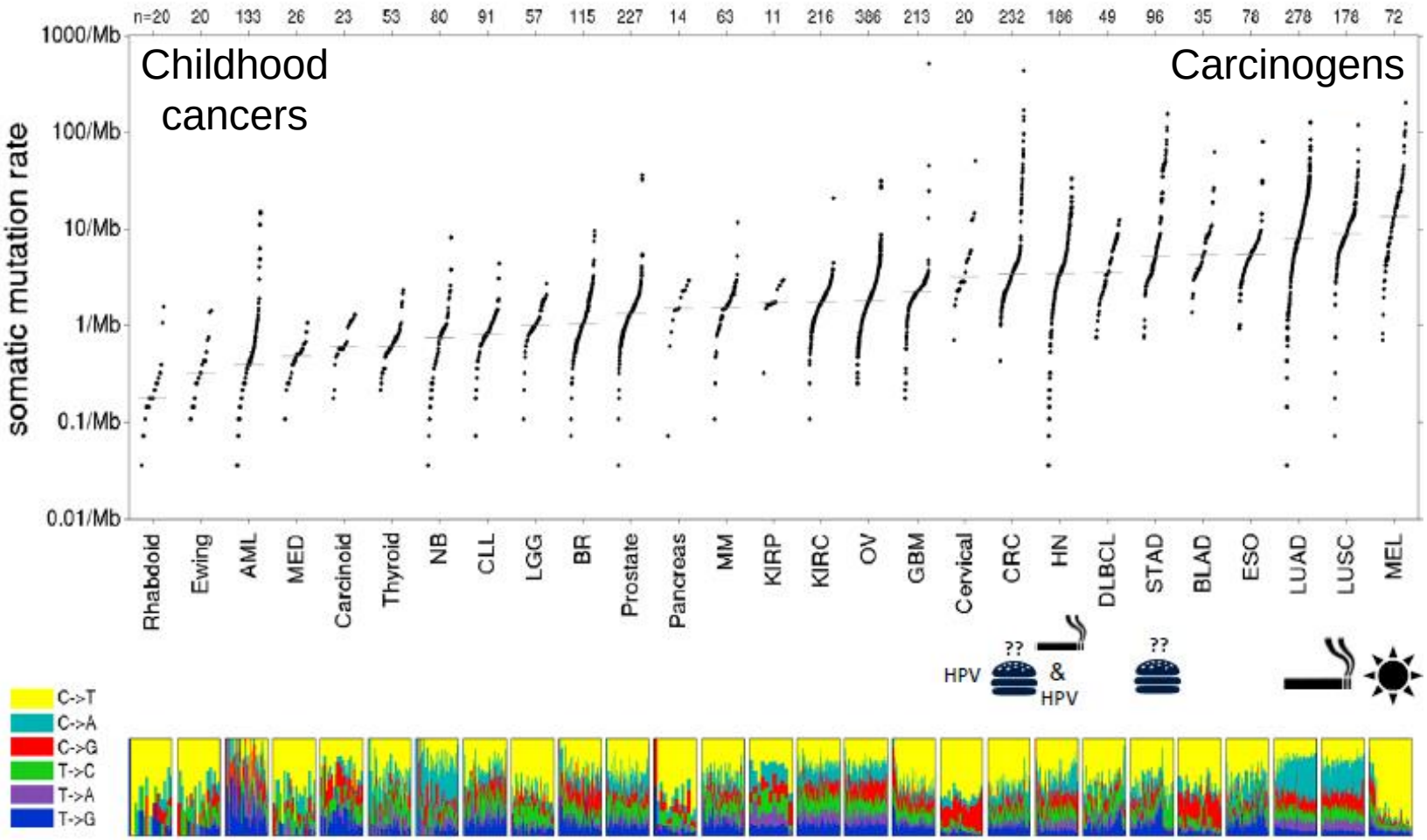
Jean Claude Zenklusen, Ph.D.

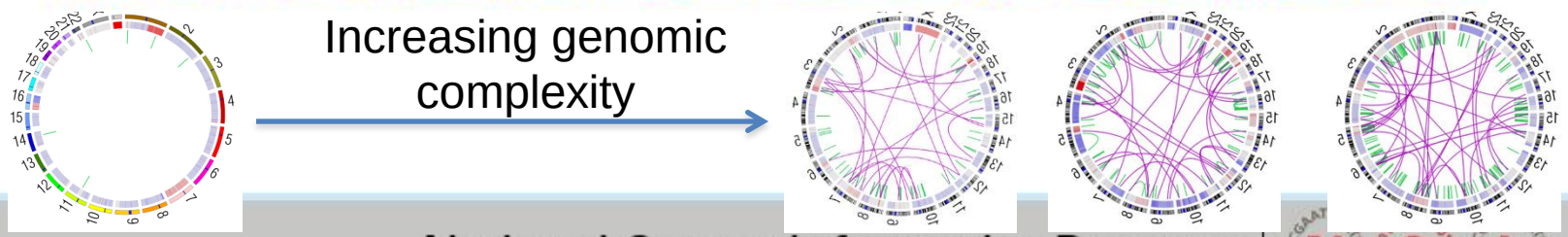
Director

TCGA Program Office

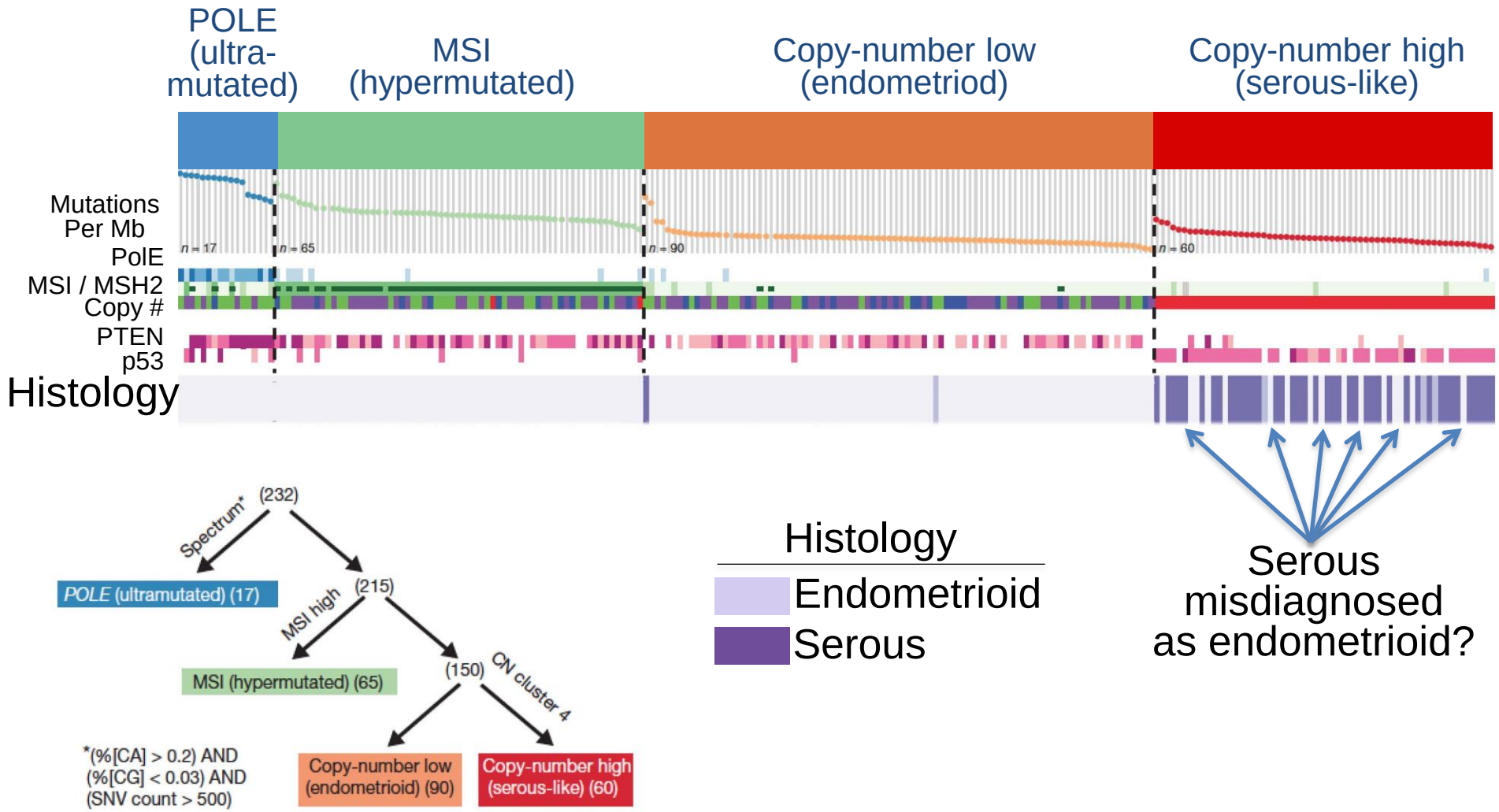
National Cancer Institute

The Mutational Burden of Human Cancer



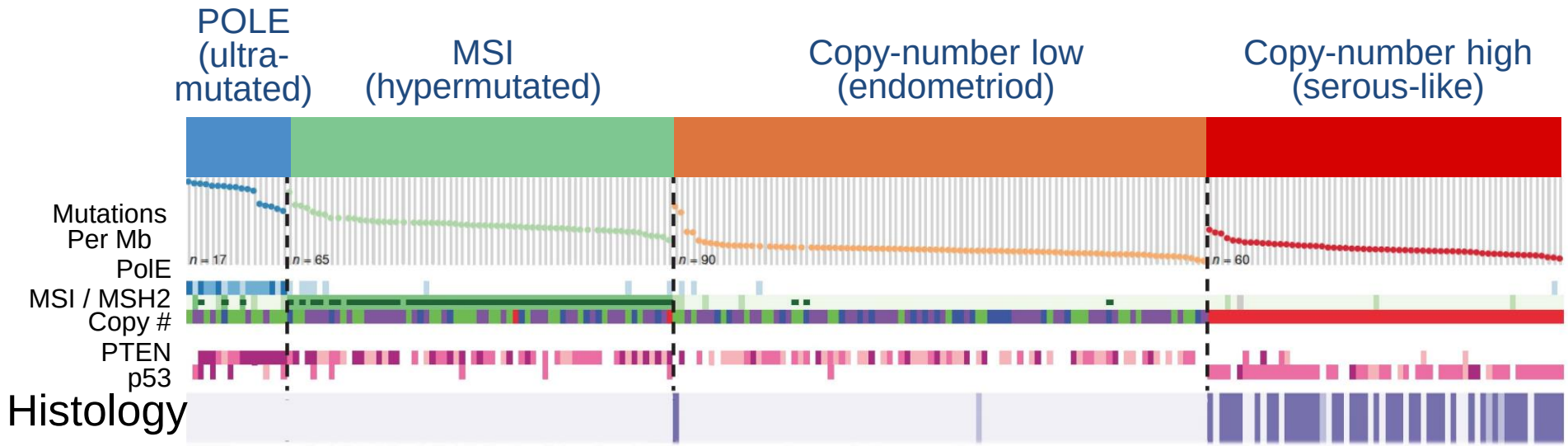


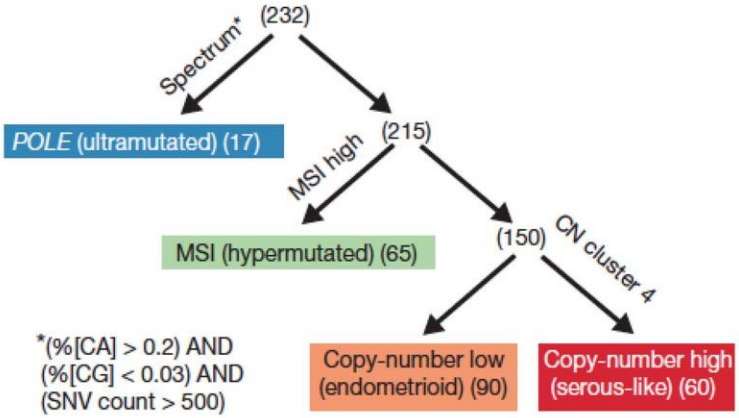
Molecular Subgroups Refine Histological Diagnosis Of Endometrial Carcinoma

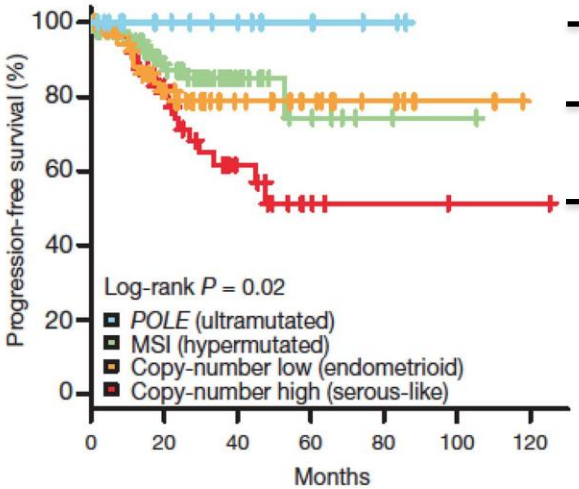


TCGA Nature 497:67 (2013)

Molecular Diagnosis of Endometrial Cancer May Influence Choice of Therapy







→ Surgery only?

→ Adjuvant radiotherapy?

→ Adjuvant chemotherapy?

TCGA Nature 497:67 (2013)

Extending TCGA and TARGET

- **Cancer Genomics Data Commons**
- **NCI Cloud Pilots**

- Molecular Clinical Trials:
  - MPACT, MATCH, Exceptional Responders

NCI Cancer Genomics Data Commons

The Cancer Genome Atlas
TCGA

TARGET
Therapeutically Applicable Research to Generate Effective Treatments

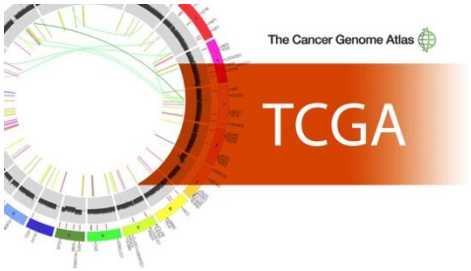
ALChEMIST
Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial

International Cancer Genome Consortium

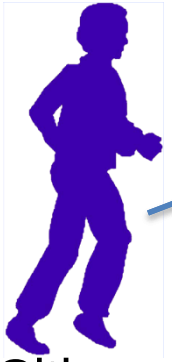
Genomic + clinical data

NCI Genomics Data Commons

NCI Cancer Genomics Data Commons



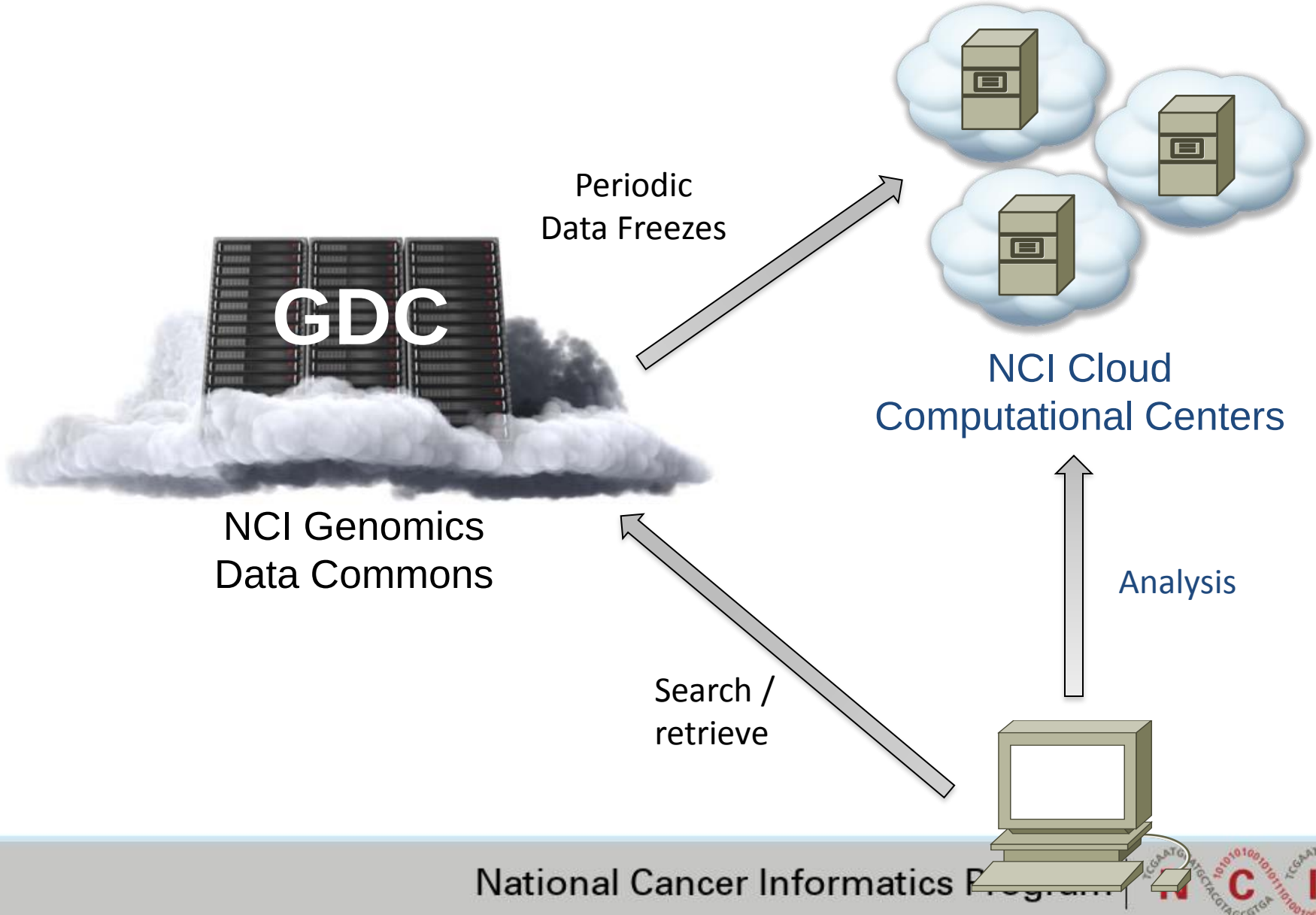
Genomic + clinical data



Citizen Scientist Patient

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

Semantic and synoptic data

- Precision Medicine
- Connected Health
- Measuring health
- Practicing protective medicine

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

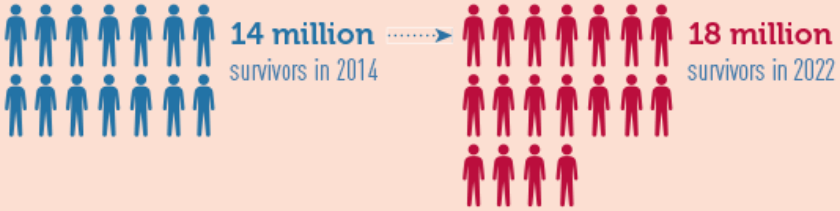
ORGANIZATIONAL ENGAGEMENT WORKING GROUP

Progress update from:

Kelley Landy

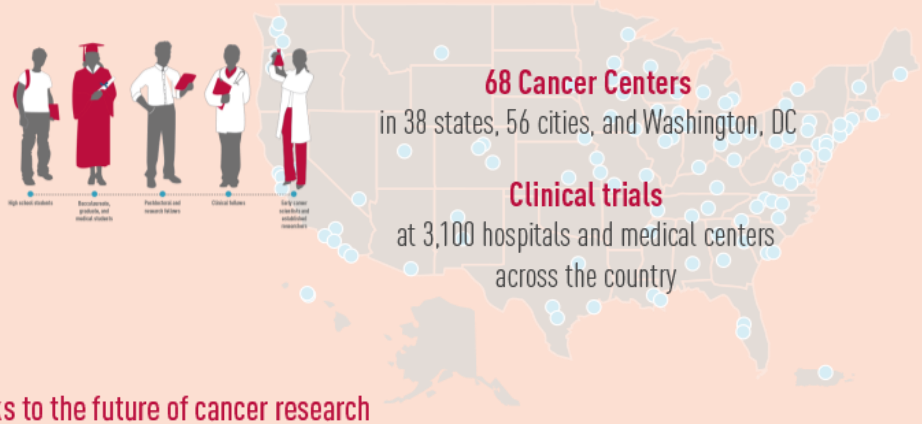
Investing in the Future of Cancer Research

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

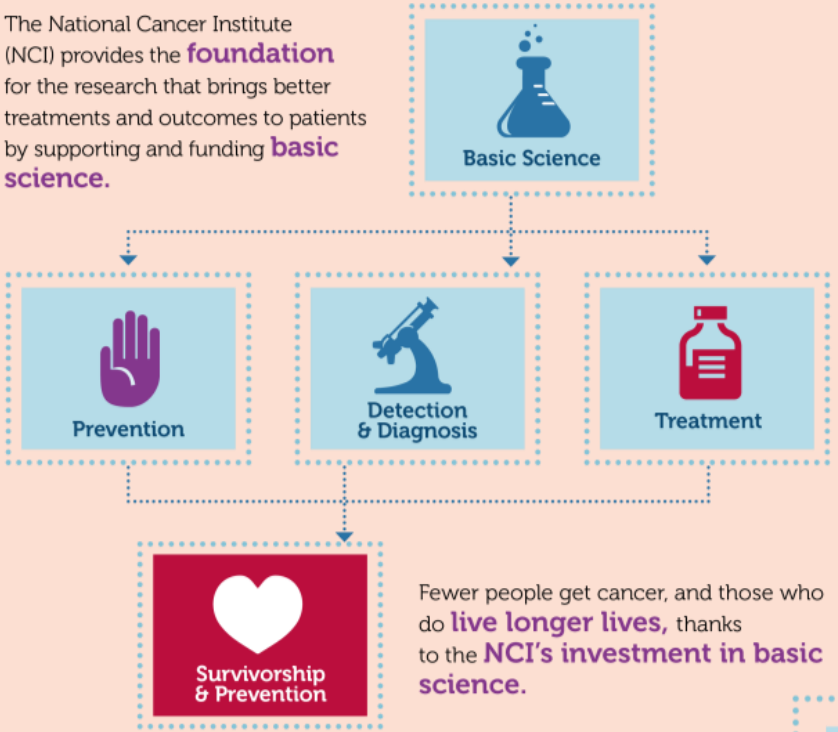
- **Fewer students** choosing to enter the field of cancer research
- **Fewer cancer research and clinical jobs** in communities across the country
- **Diminished infrastructure** to support the cancer research of tomorrow

NIH National Cancer Institute

Investing in Science for Progress Against Cancer

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.**

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

1992	2012	2022
7 million survivors	14 million survivors	18 million survivors, or 5% of the U.S. population

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

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

NIH National Cancer Institute

Investing in the Genetics of Cancer

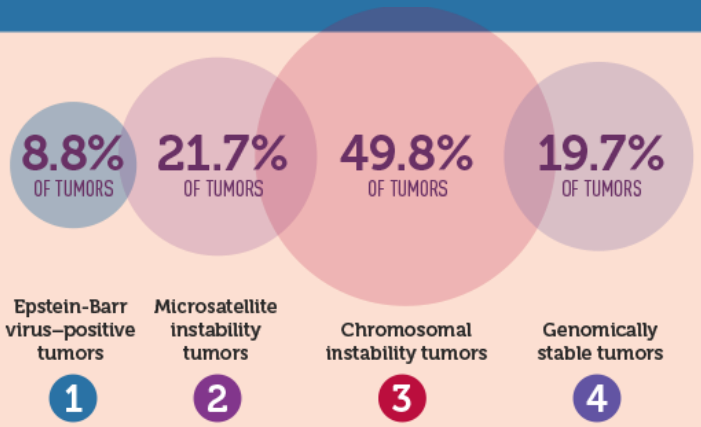
The National Cancer Institute's (NCI's) investment in basic science initiatives like The Cancer Genome Atlas (TCGA) has helped researchers understand cancer genetics, leading to better patient outcomes.

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

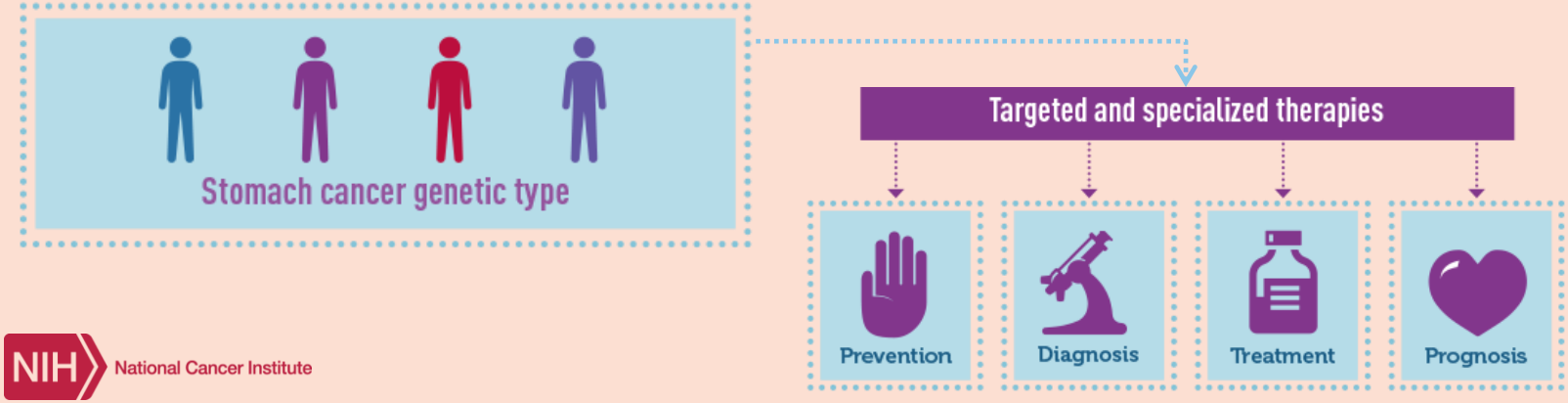
Worldwide 3rd leading cause of cancer-related deaths worldwide.

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.



NIH National Cancer Institute

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