

Making Progress in Cancer Research

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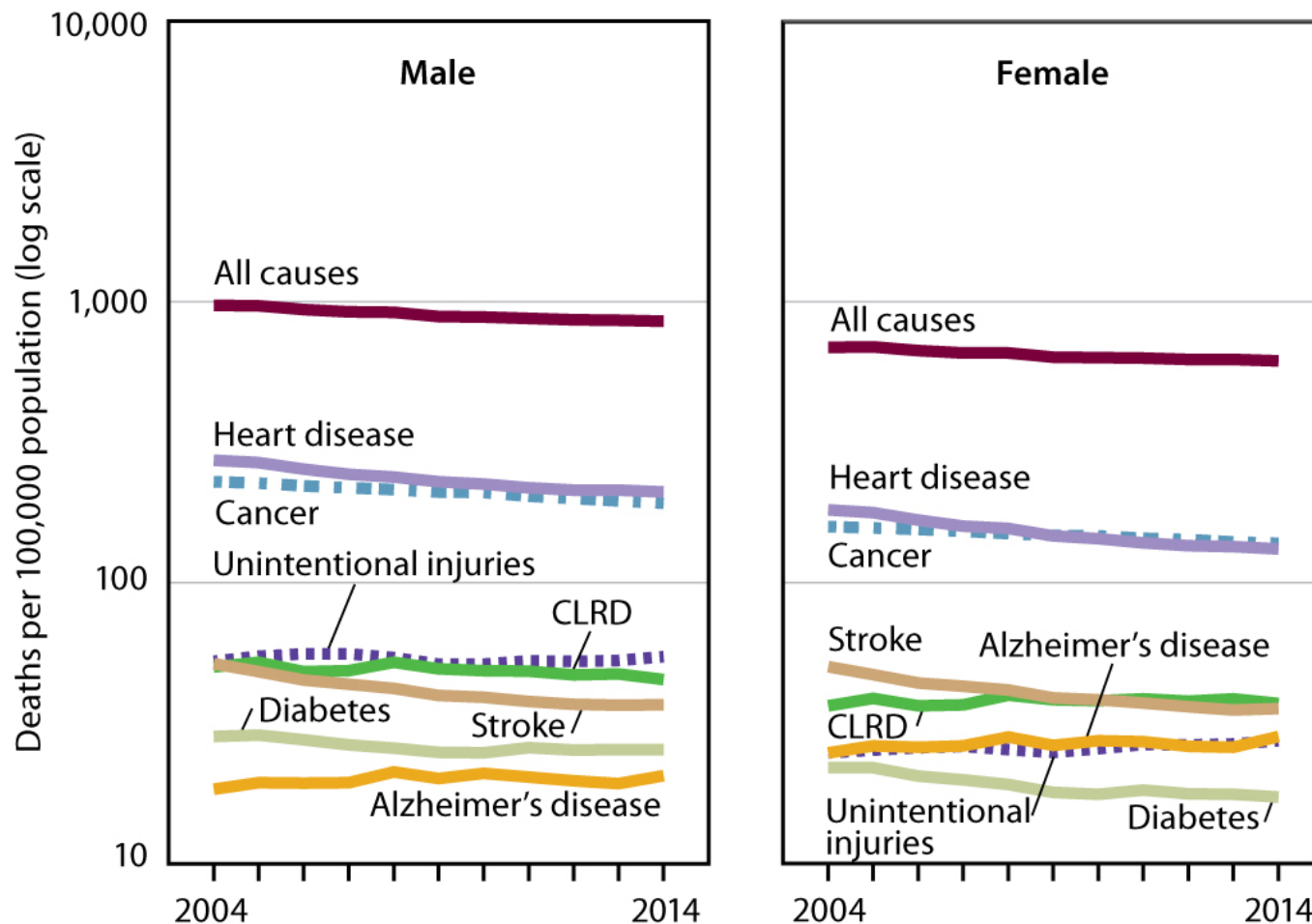
Outline of Presentation

- Cancer mortality trends
- Precision medicine: in prevention, screening, and treatment
- Cancer health disparities
- Investigator-initiated research
- The Cancer Moonshot

Assessing the achievements of the cancer research community

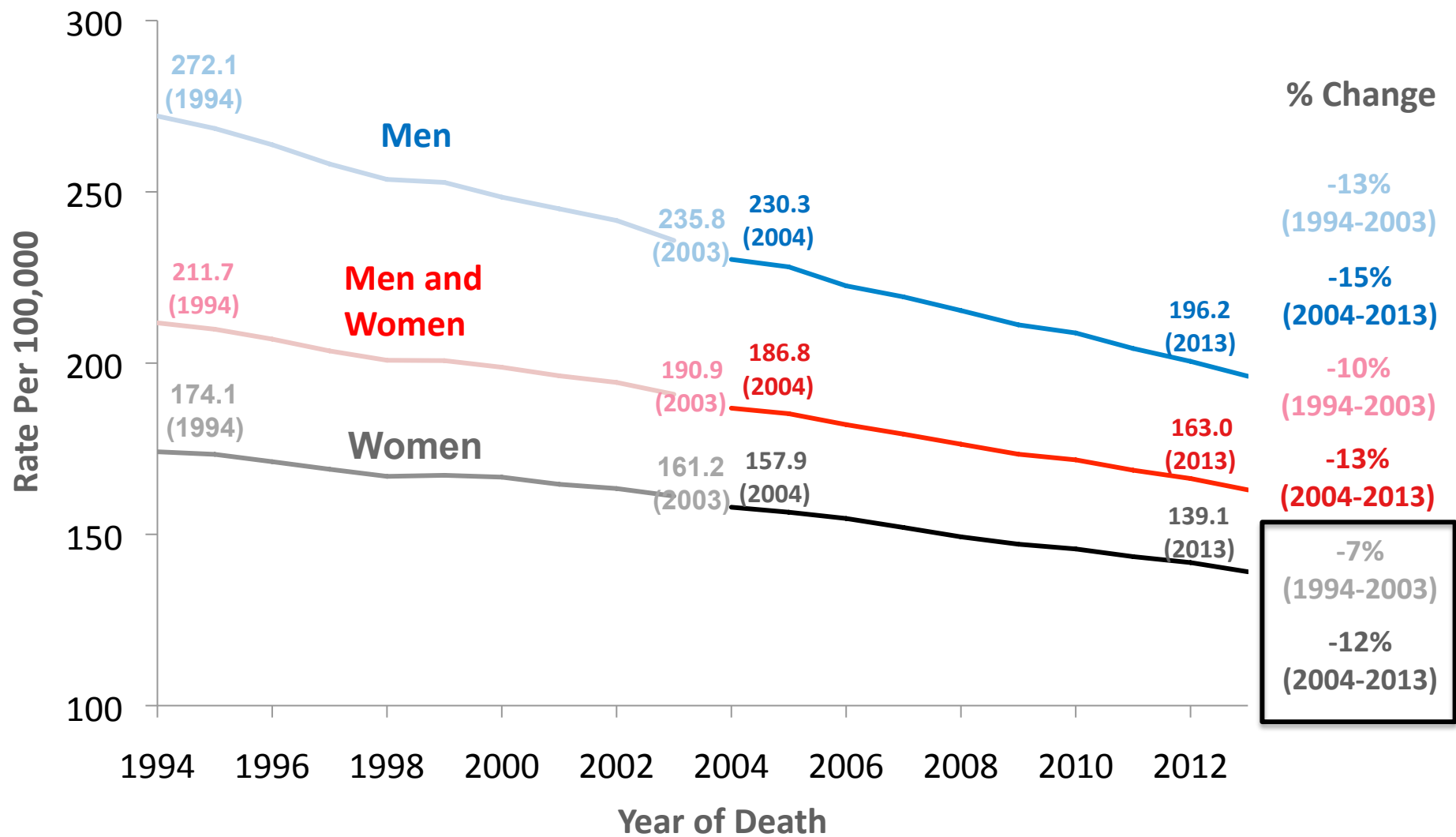
- Advancing the understanding of cancer, preventing it, screening for it, treating it, and improving quality of life after a cancer diagnosis
 - Importance of continuing to do what has never been done before
- Decreasing cancer mortality rates overall and for specific cancers
- Attract and retain high quality young investigators

Cancer & heart disease are the most Common causes of death



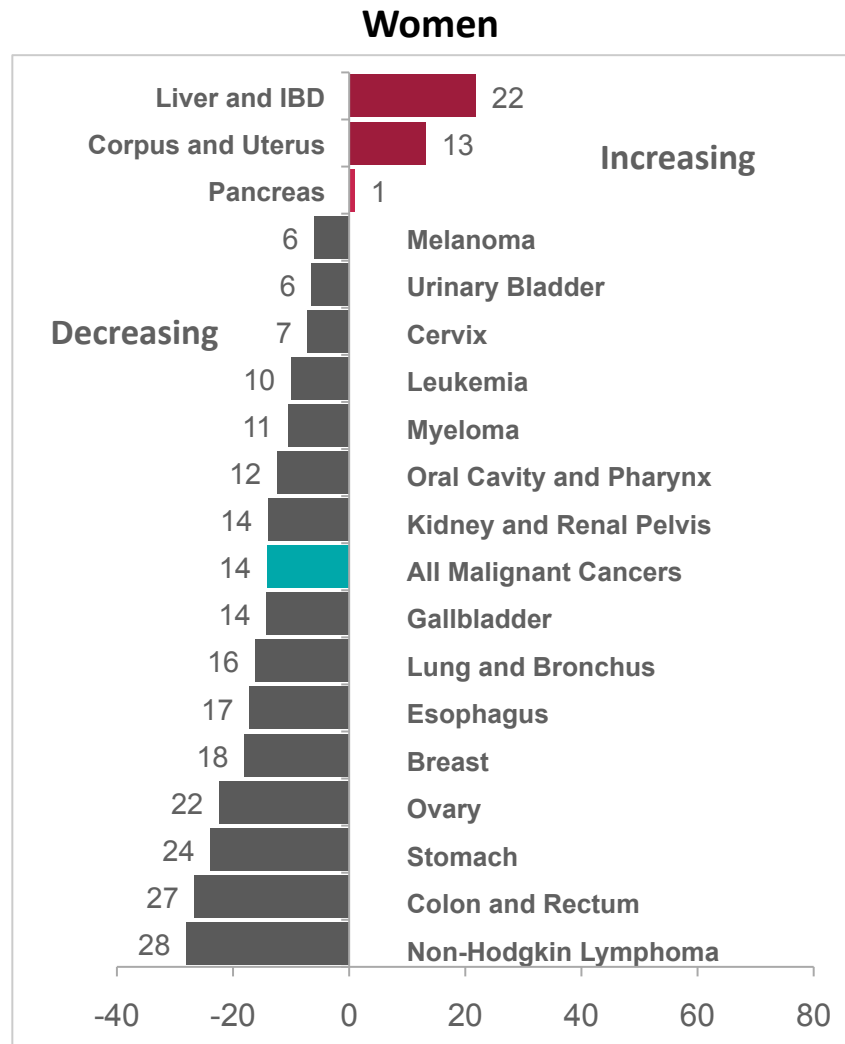
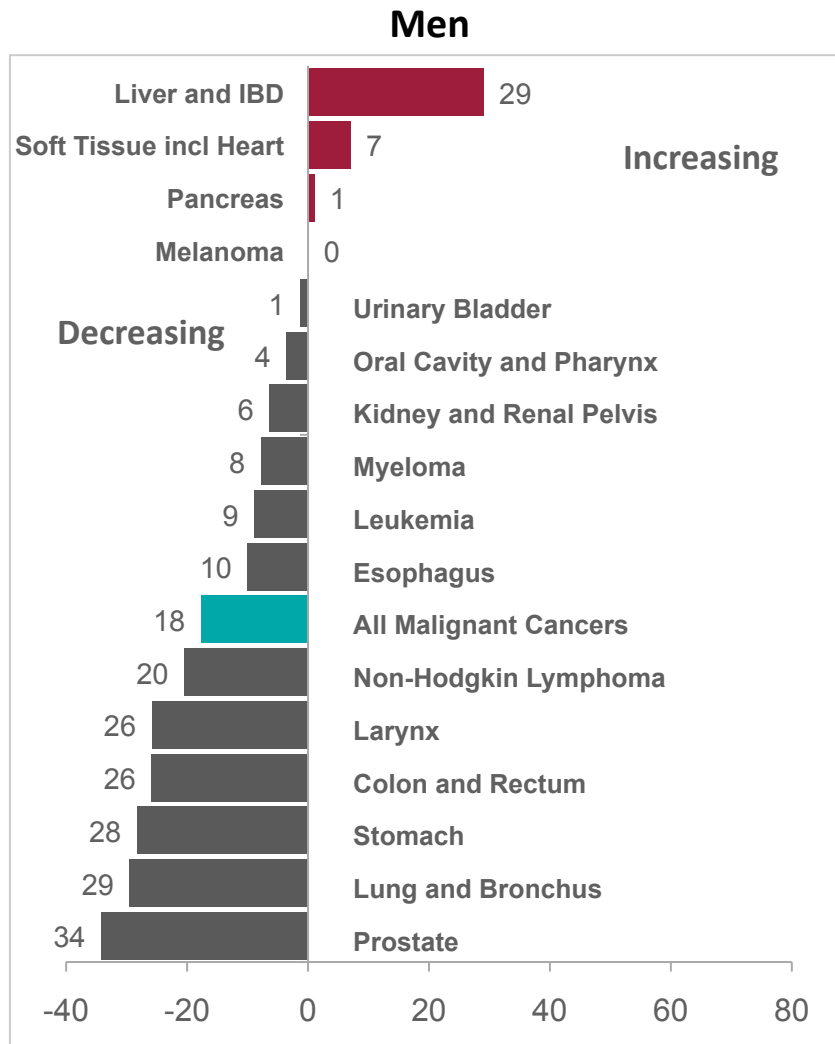
SOURCE: CDC/NCHS, *Health, United States, 2015*, Figure 2 and Table 17. Data from the National Vital Statistics System (NVSS).

US Cancer Mortality Rates for All Cancer Sites Declined By 10% During 1994-2003 and by 13% During 2004–2013



Mortality data source: National Center for Health Statistics (NCHS)

Mortality Rates Have Decreased at Most Cancer Sites: 2004-2013

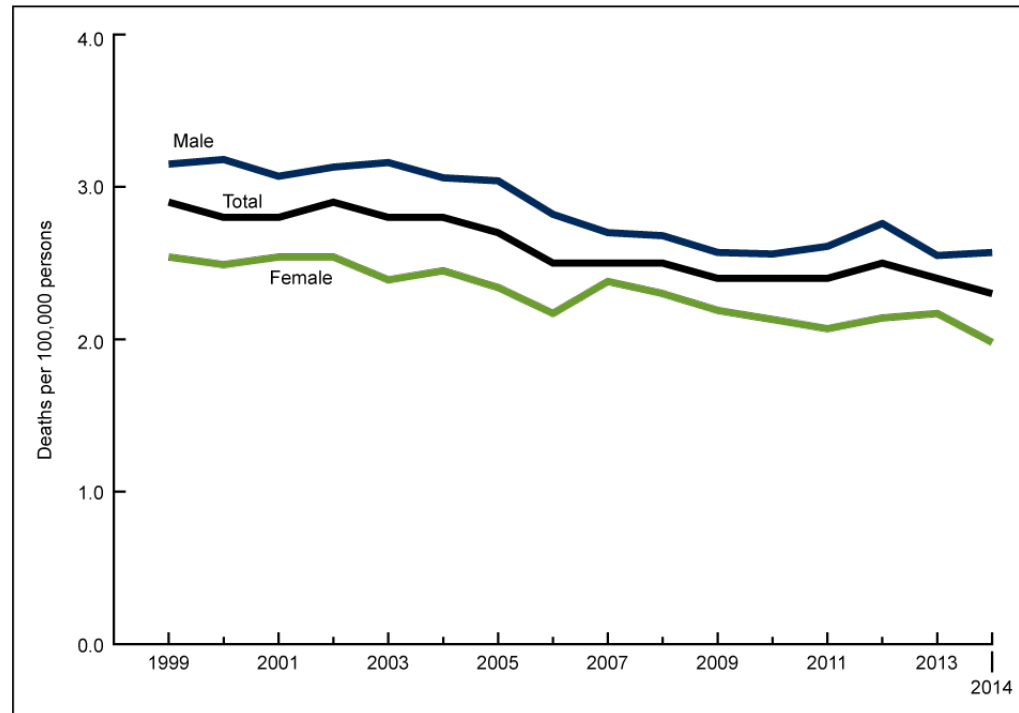


Percent Change 2004–2013

Mortality data source: National Center for Health Statistics (NCHS)

A 20% decline in childhood cancer mortality rates 1999-2014

Figure 1. Cancer death rates for children and adolescents aged 1–19 years, by sex: United States, 1999–2014



NOTES: Decline in rates from 1999 through 2014 was statistically significant for all groups ($p < 0.05$). Access data table for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db257_table.pdf#1.

SOURCE: NCHS, National Vital Statistics System, Mortality, ICD-10 underlying cause-of-death codes malignant neoplasms (C00–C97).

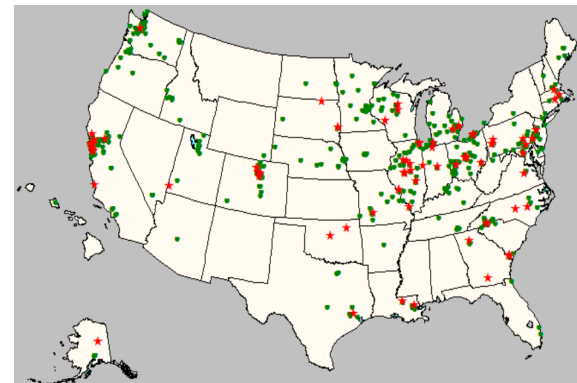
Cancer research leading to improved cancer treatment accounts for most of the improvement in childhood cancer

Decreasing Cancer Mortality Rates: Multiple Factors

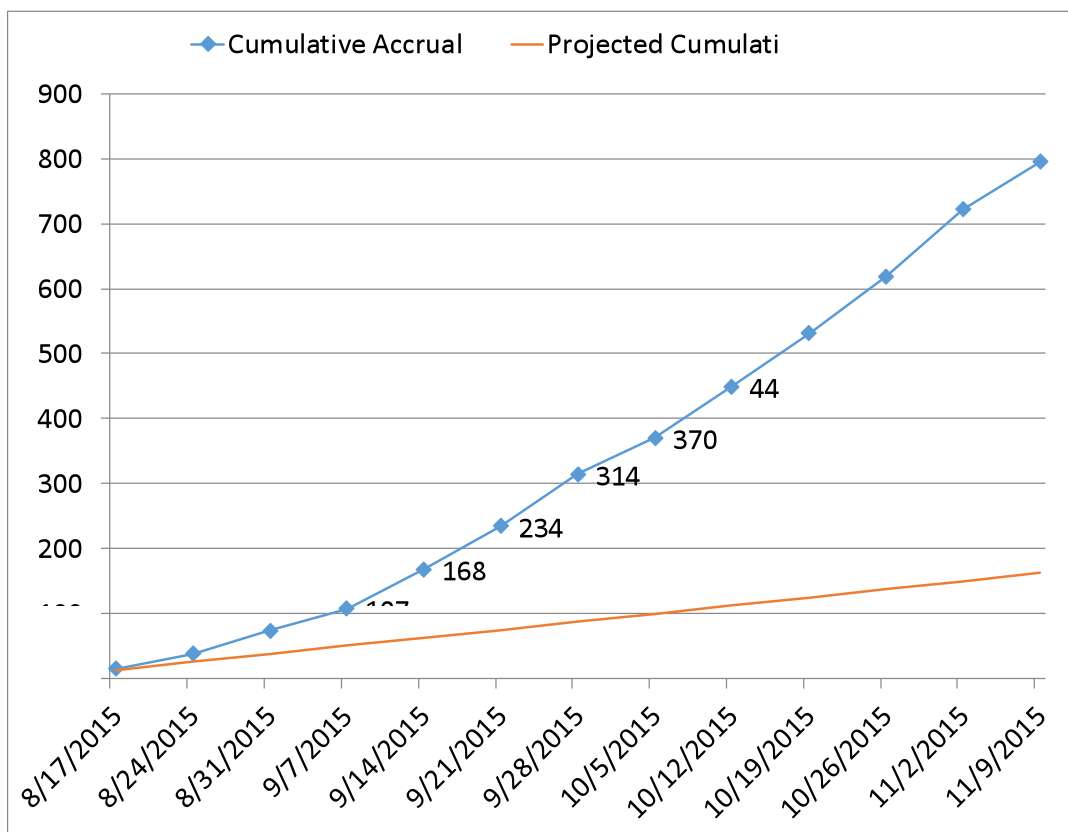
- Depending on the cancer type, decreased mortality may be attributable to **prevention** (or reduced incidence without specific interventions), **screening**, and/or **treatment**
- To induce further decreases, we must seek to improve all three areas, through research, implementation, and dissemination
- Precision oncology (broadly defined) is likely to play a progressively greater role in all three areas

The MATCH trial: a precision medicine cancer treatment trial

- MATCH = Molecular Analysis for Therapy Choice
- Initial opening August 2015; reopened May 2016
- Entry into trial is based on molecular abnormalities in the tumor, rather than on the site of origin of the tumor
- A national trial (>900 sites)
- 24 treatment arms
- >400 new patients/month



NCI-MATCH Weekly Accruals Far Exceeded Projections

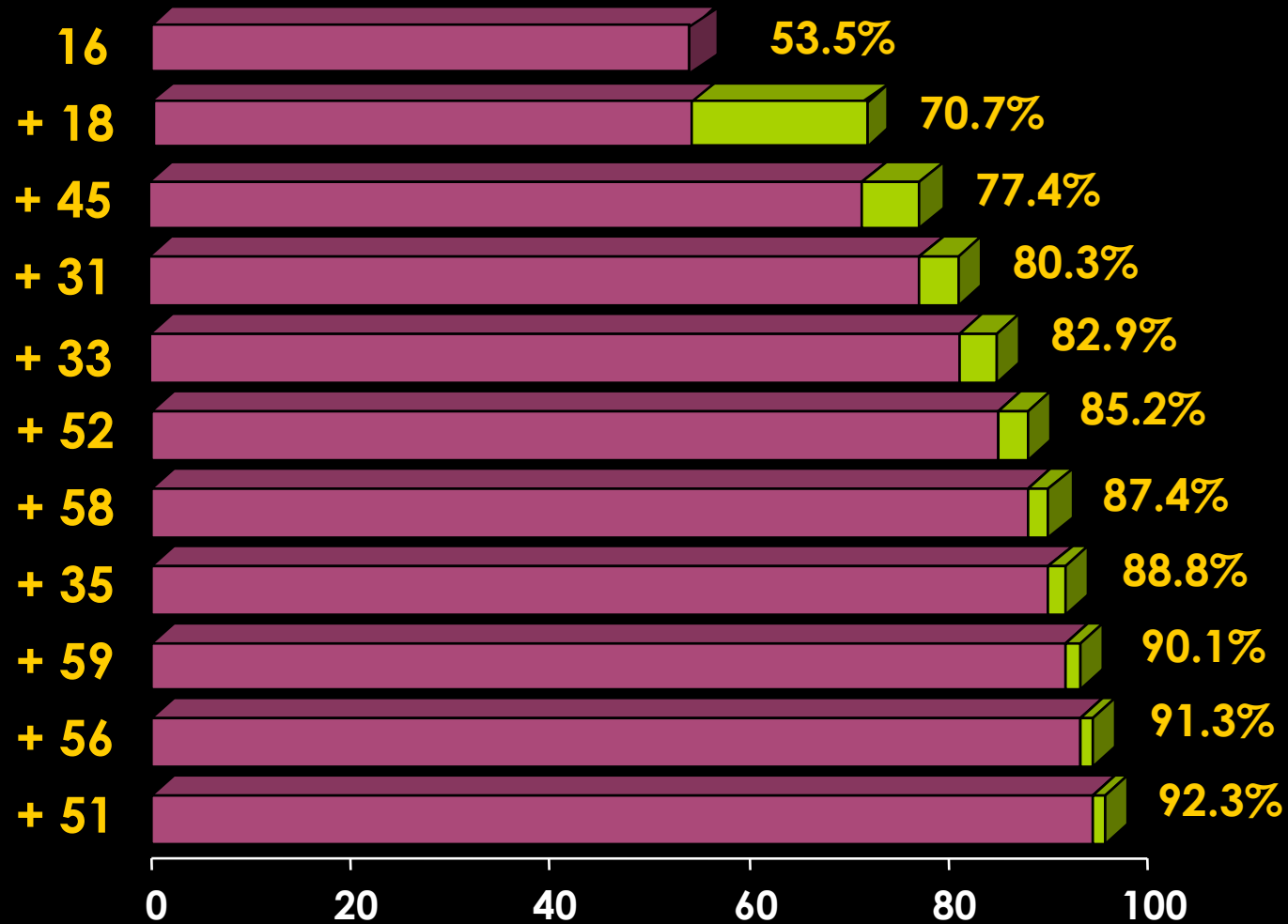


Projected 50 Cases/Month at Start and Gradual Ramp-up in Year 1

Precision Medicine in Prevention and Screening

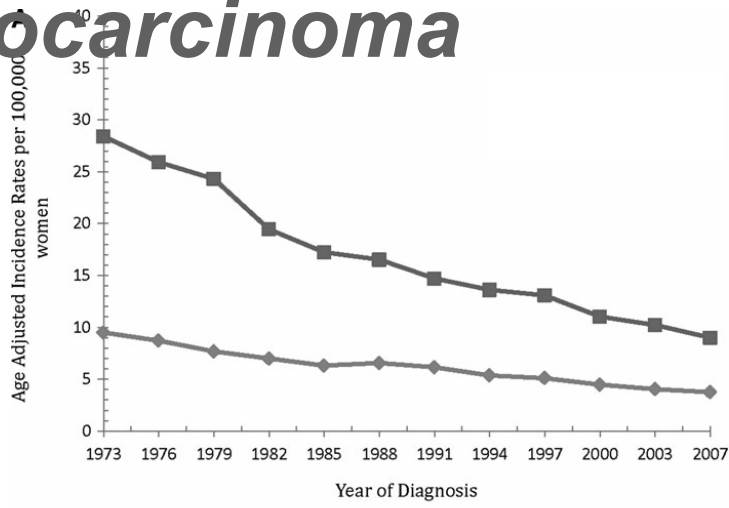
- The genetic and epigenetic changes in normal and premalignant tissues are less complex than in cancer; these changes may also be relevant to a higher proportion of premalignant lesions
 - Etiology-based screening is likely to be relevant to a high proportion of the screened individuals
- Resistance is less likely to develop against interventions that target early changes
- Therefore, if you ***like*** targeted interventions for the ***treatment*** of cancer, you ***will love*** targeted interventions for ***prevention and screening*** of cancer

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

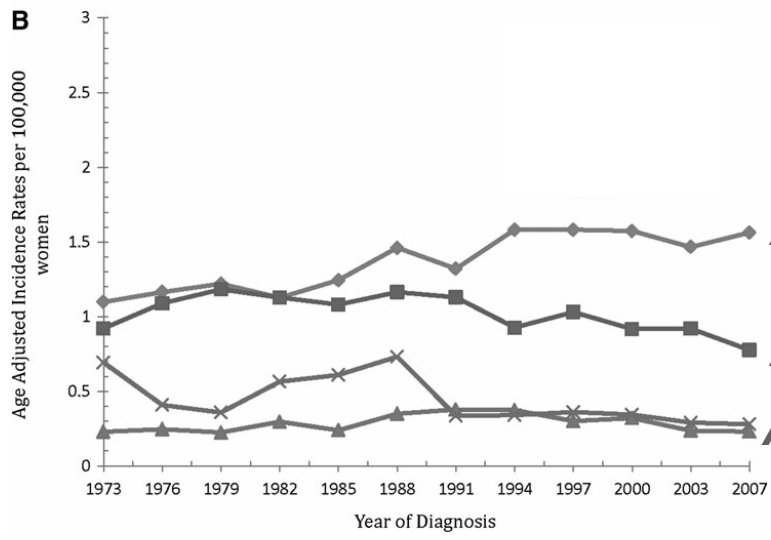


Adapted from Munoz et al, *Int J Cancer* 111: 278-85, 2004

Cervical cancer rates (USA): Decreasing squamous cell cancer, stable adenocarcinoma

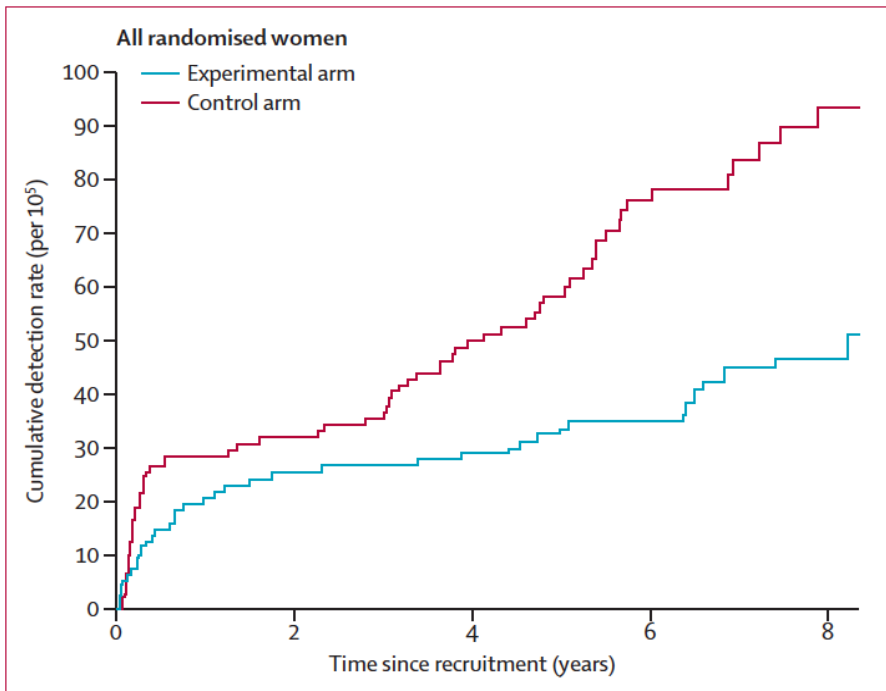


Squamous cell: blacks
Squamous cell: whites



Adenocarcinoma: whites
Adenocarcinoma: blacks
Adenosquamous: blacks & whites

HPV testing can prevent more cervical cancers, especially adenocarcinomas, than cytology



Pooled rate ratio*
(95% CI)

Morphology

Squamous-cell carcinoma	0.78 (0.49–1.25)
Adenocarcinoma	0.31 (0.14–0.69)
Adenocarcinoma vs squamous-cell carcinoma	0.34 (0.12–0.90)

*Ratio of incidence with HPV testing vs. incidence with cytology

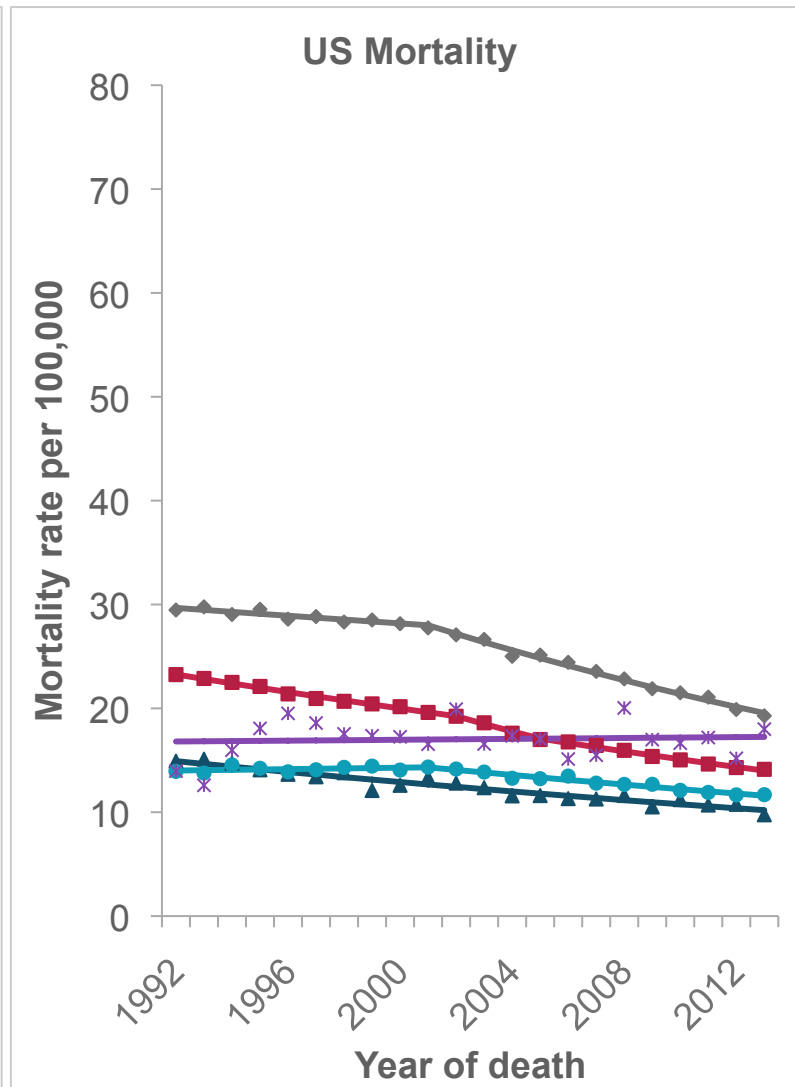
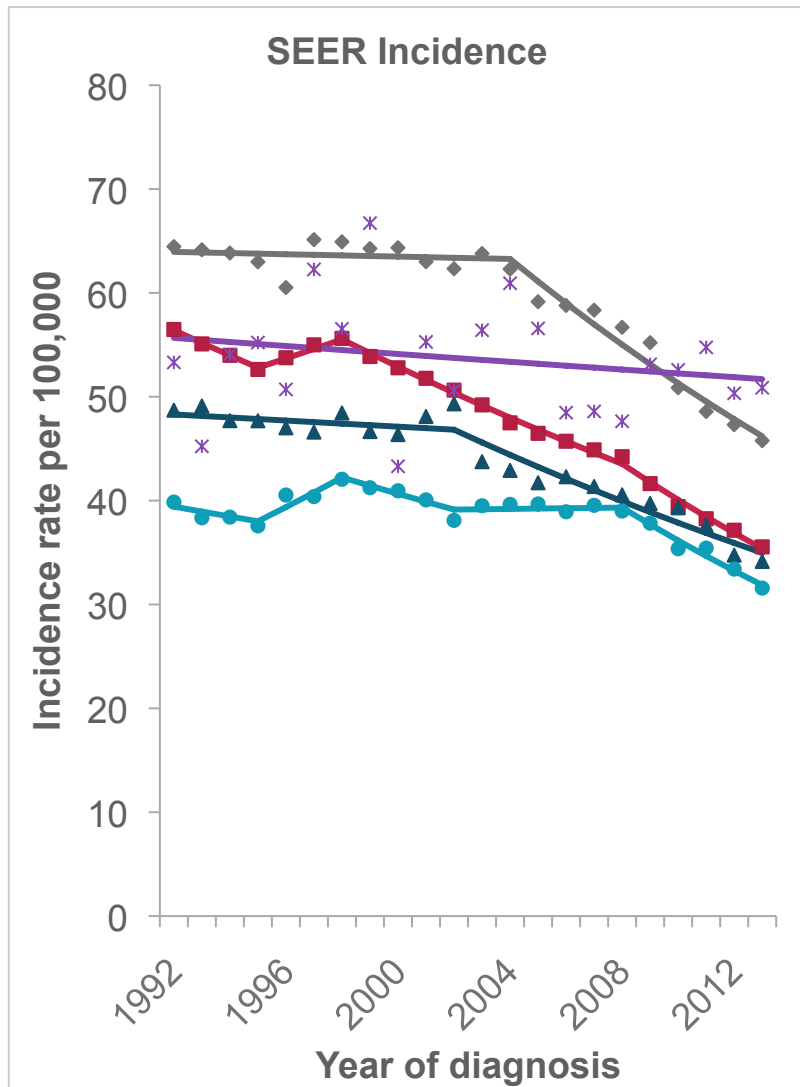
Pooled cervical cancer incidence from 4 randomized controlled trials of **cytology (control arm)** vs. **HPV testing (experimental arm)**

Ronco et al, *Lancet* 383: 524-33, 2014

Focus on specific cancers with health disparities

- Some examples: lung cancer, colorectal cancer, liver cancer, breast cancer, prostate cancer, multiple myeloma
- Identify the risk factors and their relative contribution to the disparities: **biologic factors, life-style factors, health care access/utilization**
- Explore efforts to mitigate the risk factors

Colon & Rectum



- White
- ◆ Black
- ▲ API
- * AI/AN
- Hispanic*

*Hispanic is not mutually exclusive from other groups
 Incidence data from SEER 13 1992–2013, Mortality data from NCHS

Novel recurrently mutated genes in African American colon cancers

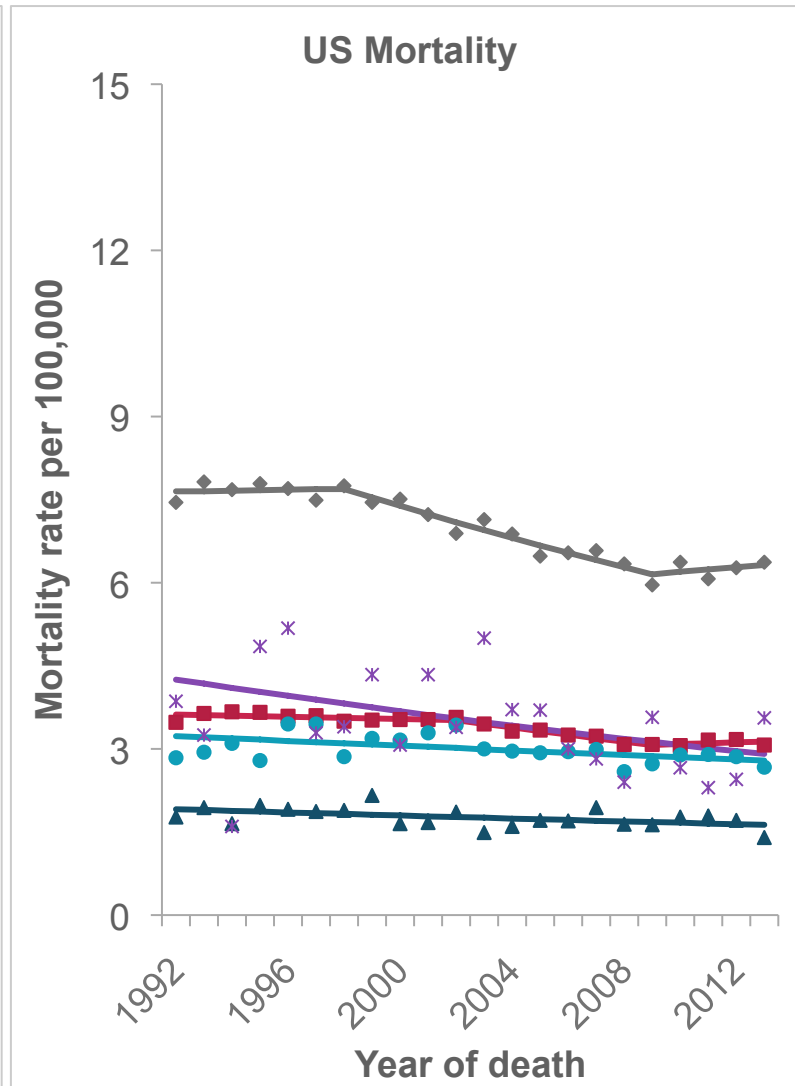
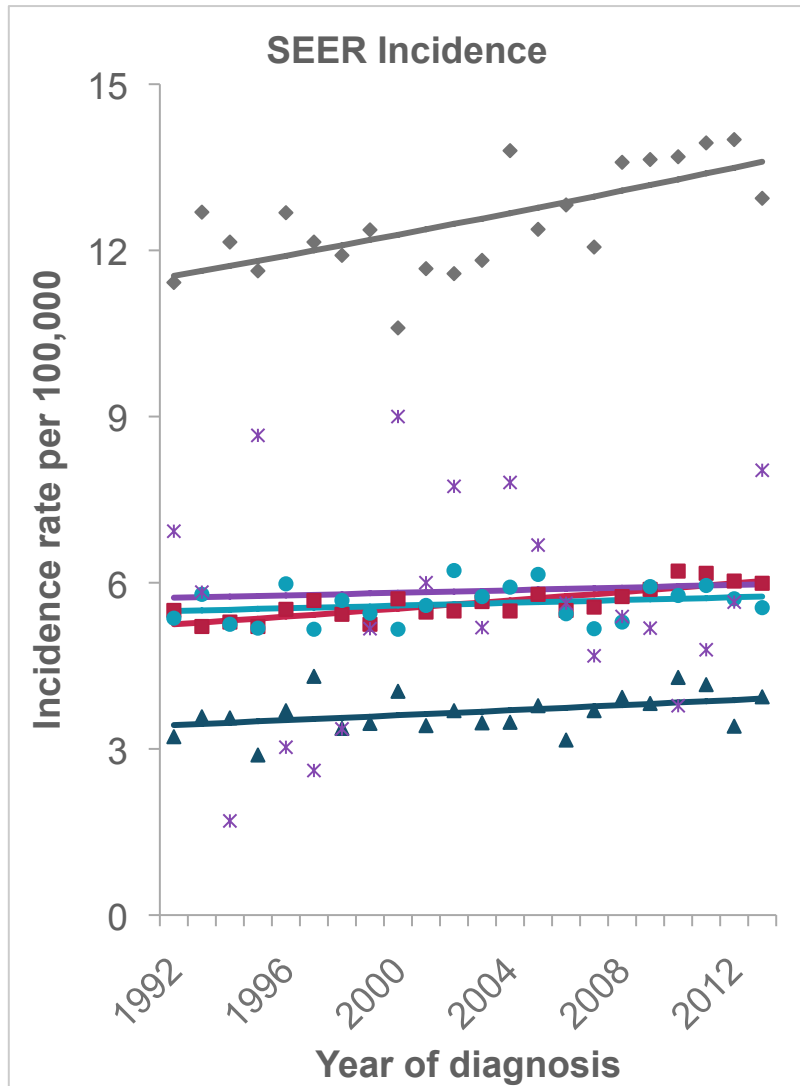
Kishore Guda^{a,b,c}, Martina L. Veigl^{b,c,1}, Vinay Varadan^{a,b,1}, Arman Nosrati^d, Lakshmeswari Ravi^d, James Lutterbaugh^d, Lydia Beard^d, James K. V. Willson^e, W. David Sedwick^{b,c,d}, Zhenghe John Wang^{b,f}, Neil Molyneaux^f, Alexander Miron^f, Mark D. Adams^g, Robert C. Elston^{b,h}, Sanford D. Markowitz^{b,c,d,i,2,3}, and Joseph E. Willis^{b,c,i,j,2}

^cDepartment of Medicine, ^fDepartment of Genetics and Genome Sciences, ^hDepartment of Epidemiology and Biostatistics, ⁱDepartment of Pathology, ^aDivision of General Medical Sciences-Oncology, ^dDivision of Hematology and Oncology, ^bCase Comprehensive Cancer Center, and ¹Case Medical Center, Case Western Reserve University, Cleveland, OH 44106; ^eHarold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX 75390; and ^gJ. Craig Venter Institute, La Jolla, CA 92037

“...Mutations in a set of 15...genes appear to be strongly preferentially associated with CRCs arising in AA versus Caucasian individuals, suggesting an important difference in the mutational landscapes of CRCs arising in different ethnic groups. “

Guda et al., 2015. Proc. Natl. Acad. Sci. 112:1149

Myeloma



- White
- ◆ Black
- ▲ API
- * AI/AN
- Hispanic*

*Hispanic is not mutually exclusive from other groups
 Incidence data from SEER 13 1992–2013, Mortality data from NCHS

Some Principles to Follow

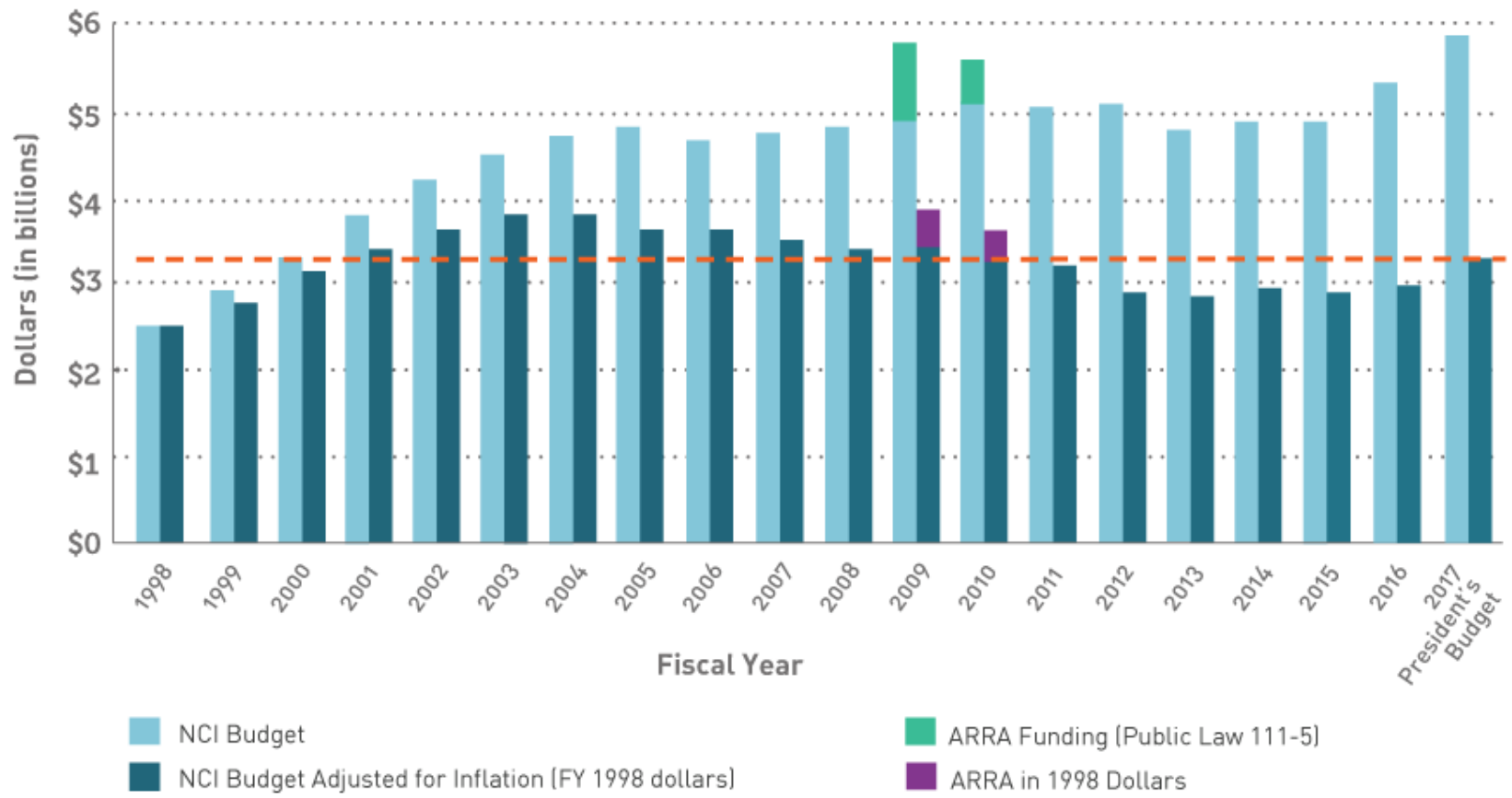
- Develop better genomic, biologic, environmental, and treatment response information about cancer in minority populations
- Minority populations represented in clinical trials & preclinical cancer models
- Ensure from the beginning that appropriate minority representation will be included

Two new NCI research initiatives

- Early onset malignancy initiative: the first minority-based cancer tissue bank; early onset tumors; collect information on treatment, response, and outcome
 - Detailed molecular characterization of fully annotated tumors
 - Organized through NCORP (NCI Community Oncology Research Program)
- Develop new cancer models from tumors of minority patients

NCI BUDGET 2005 – 2015: A PERIOD OF LEVEL BUDGETS & PROGRESSIVELY DECREASING PURCHASING POWER

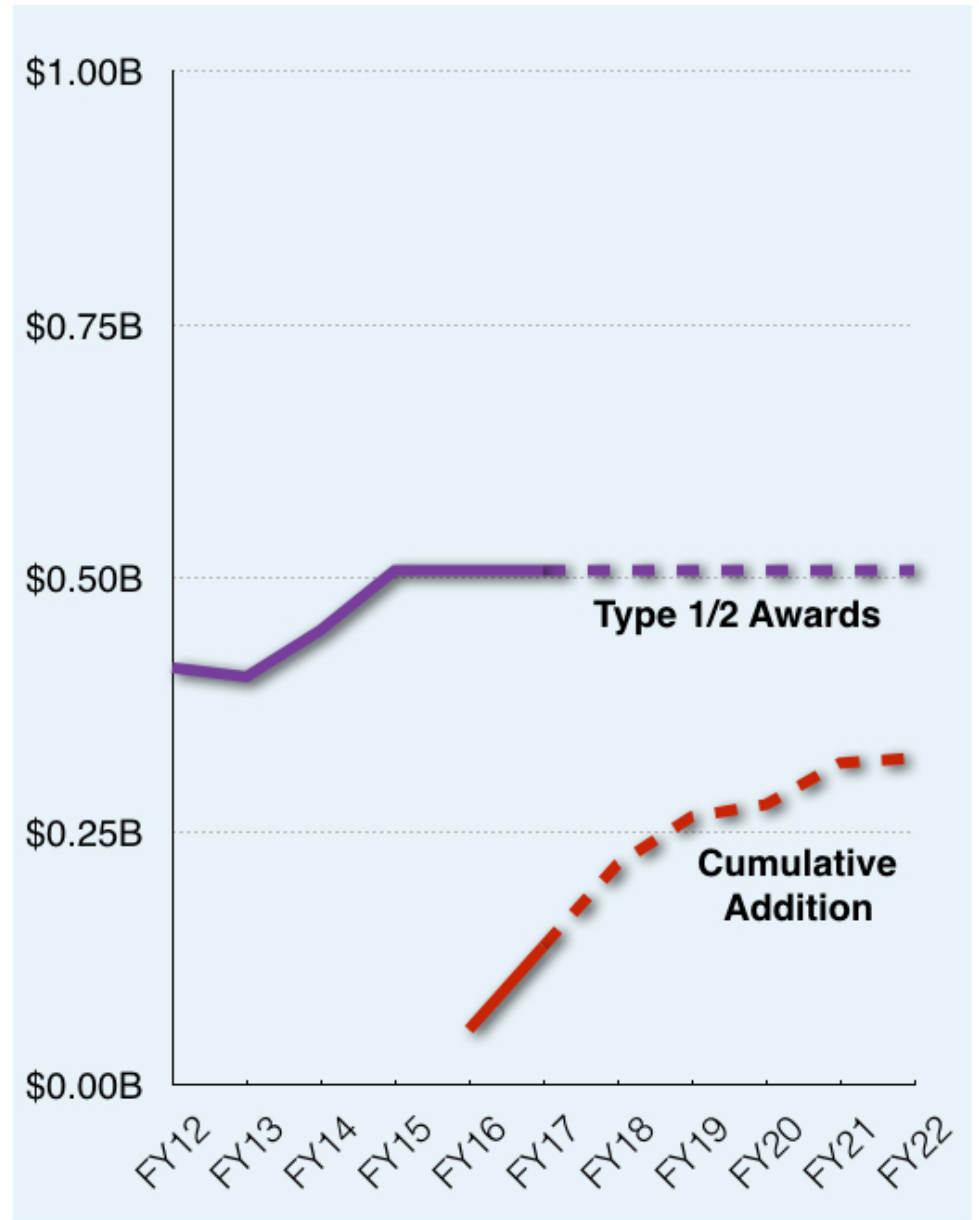
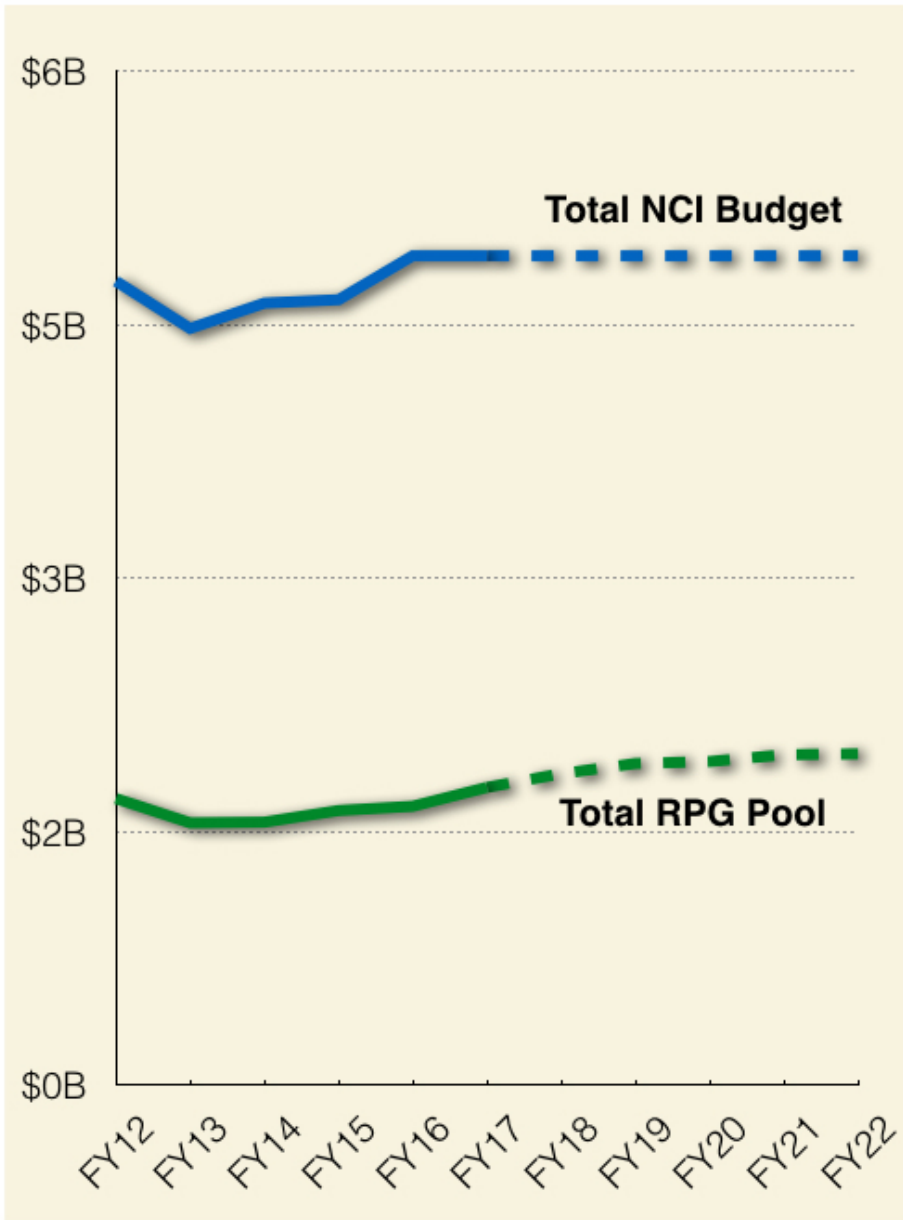
FY 2016 & 2017: AN ENCOURAGING TREND



----- The dashed line at approximately \$3.3 billion indicates that the inflation-adjusted FY 2017 proposed budget is similar to the FY 2000 budget

***Continuing to
strongly support
investigator-initiated
research***

Changes in RPG pool: FY12-FY16 and beyond



The President's Precision Medicine Initiative in Oncology

- A presidential initiative to improve cancer treatment through cancer genomics
- A foundational clinical trial
- Preclinical models to advance predictive oncology: the right drugs for the right patient at the right time
- A large annotated database of cancer patients: for researchers, health care providers, and patients (Genomic Data Commons)

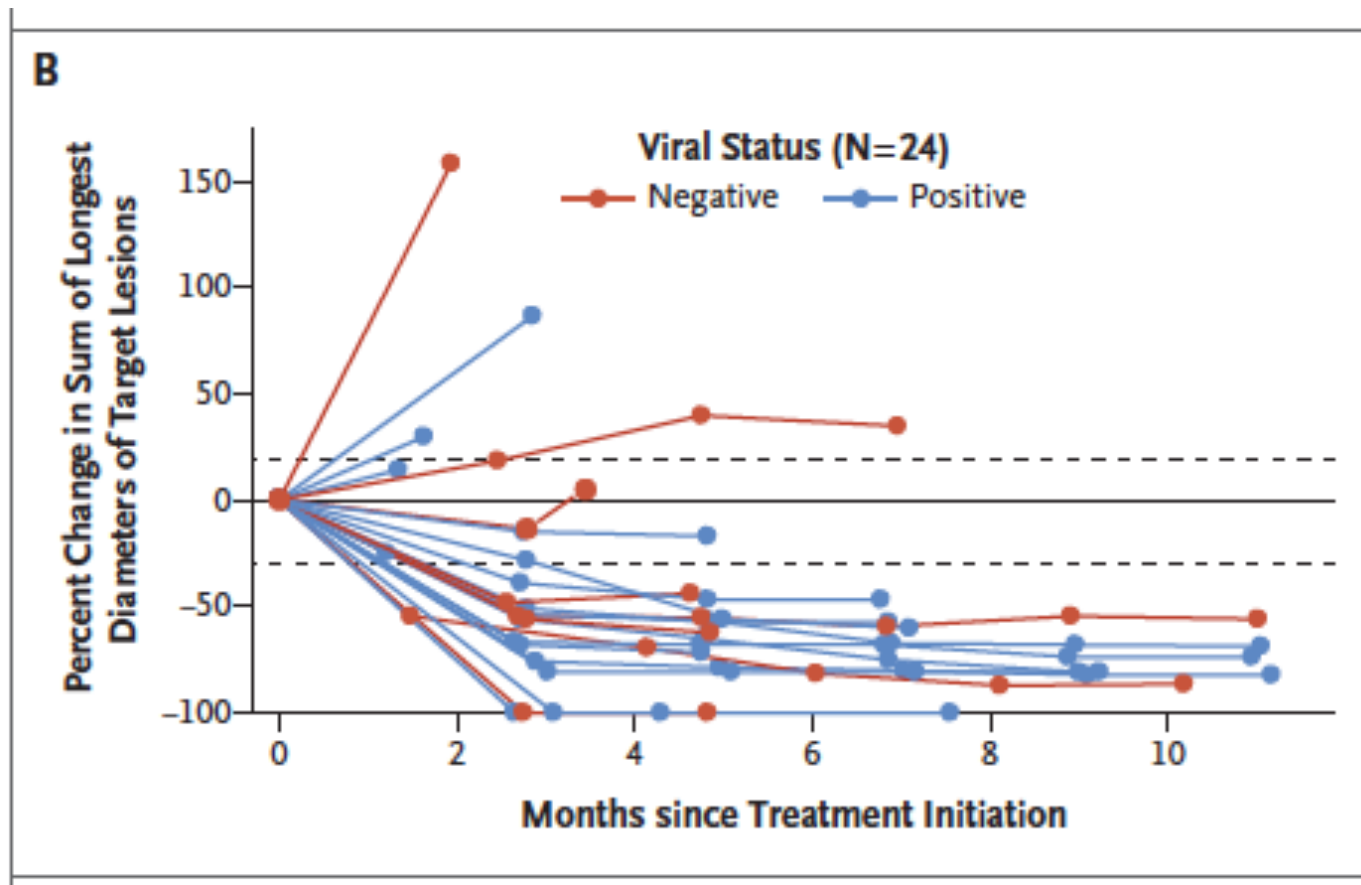
The Vice President's Cancer Moonshot

- Accelerate progress in cancer, including prevention & screening
 - From cutting edge basic research to wider uptake of standard of care
- Encourage greater cooperation and breaking down silos
 - Within and between academia, government, and private sector
- Importance of data sharing: Genomic Data Commons, annotated patient level clinical data & -omics

Cancer Moonshot: Why now?

- The science is ready, and would benefit from a major infusion of additional resources
- Lots of opportunities for bold, but feasible, initiatives that could have important implications for our understanding of cancer and for patients through improved prevention, screening, and treatment
- Immunotherapy has come of age

A PD1 immune checkpoint inhibitor Pembrolizumab is useful in advanced Merkel-cell carcinoma



Unintentional communication that cancer is now a technological/engineering problem?

- Terms such as “precision medicine”: do they inadvertently imply understanding that is greater than it is, and that advances in cancer no longer depend on scientific discovery of the unknown?
- Immune checkpoint inhibitors: based on understanding immune regulation, but still much that we don't understand
- Emphasize: progress in cancer remains heavily dependent on developing new knowledge

An Opportunity for Focused Research to Accelerate Progress

- Take advantage of current advances in the understanding of cancer and recent technological innovation
- Apply the knowledge and innovation to focus on specific projects that can have a substantial impact on understanding and/or improvement for patients
- NB: NCI will continue to support a great deal of other meritorious research

BRP Working Groups

Working Group	Co-Chair	NCI Staff
Cancer Immunology	Liz Jaffee, Jim Allison	Toby Hecht, Kevin Howcroft
Precision Prevention and Early Detection	Mary Bekerle, Jennifer Pietenpol	Elisa Woodhouse Tracy Lively
Tumor Evolution	Chi Dang, Levi Garraway	Joanna Watson, Suresh Mohla, Tony Dickherber
Clinical Trials	Charles Sawyers, Mitch Berger	Jeff Hildesheim Meg Mooney
Implementation Sciences	Elena Martinez, Augusto Ochoa	Bob Croyle, Wortá McCaskill- Stevens, Jennifer Couch
Pediatric Cancer	Peter Adamson Jim Downing	Judy Mietz Malcolm Smith
Enhanced Data Sharing	Angel Pizarro Gaddy Getz	Juli Klemm Betsy Hsu

BRP Recommendations (1)

- Creation of a human tumor atlas
 - Catalog genetic lesions and cellular interactions in tumor/immune/other cells in tumor microenvironment in cancer and precancer
- Cancer immunotherapy translation network
 - To discover and evaluate novel immune-based approaches for adult and pediatric cancers, and develop immunoprevention of cancer not attributable to infection
- Therapeutic target identification to overcome drug resistance
 - Launch interdisciplinary studies to delineate mechanisms that lead cancer cells to become resistant to previously effective treatments

BRP Recommendations (2)

- Fusion oncoproteins in pediatric cancer resources
 - Improve understanding of the abnormal fusion proteins that result from chromosomal translocations and drive many pediatric cancers and develop inhibitors
- Precision prevention and early detection:
 - Implementation of evidence-based approaches. Conduct implementation science research to encourage broader adoption of HPV vaccination, colorectal cancer screening, and tobacco cessation
- Symptom management research

(Presidential Memo 2016)

Next Steps for Blue Ribbon Panel Recommendations

- NCI now needs to consider how to implement the Blue Ribbon Panel recommendations
- Extent and rate of implementation will depend on Congressional appropriations
- NCI will look to the Blue Ribbon Panel and its advisory boards for implementation advice
- Continued investments in investigator-initiated research and in research initiatives beyond the scope of the Blue Ribbon Panel remain a high priority for NCI



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