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
<table>
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<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter(s)</th>
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<tbody>
<tr>
<td>1:00</td>
<td>Roll Call</td>
<td>Ms. Landy</td>
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<tr>
<td></td>
<td>Welcoming Remarks and Overview of Agenda</td>
<td>Ms. Landy, Mr. Wallace, and Ms. Bulman</td>
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<tr>
<td>1:15</td>
<td>NCI Update</td>
<td>Dr. Lowy</td>
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<td>2:00</td>
<td>Genomic Data Commons and Cloud Pilots Program</td>
<td>Dr. Kibbe</td>
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<td>2:30</td>
<td>NCRA Working Group Updates</td>
<td>Ms. Delgado Harris, Ms. Landy, and Mr. Wallace</td>
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<td>• Advocate Engagement</td>
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<td>• Organization Engagement</td>
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<td>• Informed Consent and Genomics Research</td>
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<td>NCI Advisory Board Updates</td>
<td>Ms. Braun and Mr. Arons</td>
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<td>2:50</td>
<td>Closing Remarks and Future Meeting Dates</td>
<td>Ms. Landy and Mr. Wallace</td>
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<td>Adjourn at 3:00</td>
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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
Mortality Rates for Most Cancers are Decreasing: Percent change 2001-2010

Men

Liver & IBD: 25%
Soft Tissue inc. Heart: 8%
Pancreas: 5%
Melanoma: 3%
Bladder: 1%
-4%: Brain & ONS
-4%: Esophagus
-9%: Kidney
-9%: Leukemia
-11%: Myeloma
-12%: Oral Cavity
-18%: All Sites
-25%: Larynx
-25%: Lung & Bronchus
-26%: Non-Hodgkin Lymphoma
-29%: Colon & Rectum
-33%: Prostate
-34%: Stomach

Women

Liver & IBD: 16%
Pancreas: 4%
Corpus & Uterus: 4%
-4%: Bladder
-8%: Lung & Bronchus
-9%: Kidney
-9%: Brain & ONS
-13%: Gallbladder
-13%: Leukemia
-14%: All Sites
-16%: Oral Cavity
-16%: Ovary
-15%: Esophagus
-17%: Cervix
-19%: Breast
-23%: Myeloma
-27%: Stomach
-29%: Colon & Rectum
-32%: Non-Hodgkin Lymphoma

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

Success Rate vs Fiscal Year

Doubling of NIH Budget
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)
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: 15%
- Phase 1/Pilot: 3%

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<td>All Phases: Treatment &amp; Primary Imaging Trials</td>
<td>24,619</td>
<td>25,682</td>
<td>29,221</td>
<td>23,446</td>
<td>19,775</td>
<td>21,164</td>
<td>21,810</td>
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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.
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

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

“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

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: 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
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?
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
- U.S. HGP Begins
  - 1990
- NRC Recommends HGP
- Human Genetic Mapping Goal Exceeded
- Physical Maps Cover 98% of Human Genome
- Human Gene Map (16,000 genes)
- Yeast Genome Completed
- Pilot Human Sequencing Projects Begin
- Mouse Genetic Map Assembled
- Human Gene Map (30,181 genes)
- C. elegans Genome Completed
- E. coli Genome Completed
- Full Scale Human Genome Sequencing Begins
- SNP Initiative Begins
- Drosophila Genome Completed
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
TCGA Publications since 2010
Assays and Data Types

Long-range regulatory elements (enhancers, repressors/silencers, insulators)

Promoters

Transcripts

5C ChIA-PET, DNase-seq, FAIRE-seq, ChIP-seq, DNA methylation, Computational predictions and RT-PCR, RNA-seq, CLIP-seq, RIP-seq

Hypersensitive Sites

RNA polymerase

CH\textsubscript{3}

CH\textsubscript{3}CO

Gene

CH\textsubscript{3}
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

Childhood cancers

Carcinogens
Molecular Subgroups Refine Histological Diagnosis Of Endometrial Carcinoma

POLE (ultra-mutated)  MSI (hypermutated)  Copy-number low (endometrioid)  Copy-number high (serous-like)

Mutations Per Mb
PoLE
MSI / MSH2
Copy #
PTEN
p53

Histology

Serous misdiagnosed as endometrioid?

Histology
Endometrioid
Serous

Molecular Diagnosis of Endometrial Cancer May Influence Choice of Therapy

- **POLE** (ultramutated)
- **MSI** (hypermutated)
- Copy-number low (endometrioid)
- Copy-number high (serous-like)

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<th>p53</th>
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Histology

- Surgery only?
- Adjuvant radiotherapy?
- Adjuvant chemotherapy?
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

GDC

NCI Genomics Data Commons
NCI Cancer Genomics Data Commons

Genomic + clinical data

Citizen Scientist Patient

NCI Genomics Data Commons

GDC

TCGA

TARGET

ALChEMIST

International Cancer Genome Consortium
Relationship of the Cancer Genomics Data Commons and NCI Cloud Pilots

NCI Genomics Data Commons

GDC

NCI Cloud Computational Centers

Search / retrieve

Analysis

Periodic Data Freezes
The future

- Elastic computing ‘clouds’
- Social networks
- Big Data analytics

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

*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
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
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.

- 14 million survivors in 2014
- 18 million survivors in 2022

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.

68 Cancer Centers
in 38 states, 56 cities, and Washington, DC

Clinical trials
at 3,100 hospitals and medical centers across the country

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% to 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.

![Image of Basic Science](basic-science Icon)

- Prevention
- Detection & Diagnosis
- Treatment

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

![Chart showing increase in survivors]

- **1992**: 7 million survivors
- **2012**: 14 million survivors
- **2022**: 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.

![Graph showing spending power loss](spending-power-graph)

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
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.

![Stomach cancer genetic type](image)

**Targeted and specialized therapies**

- **Prevention**
- **Diagnosis**
- **Treatment**
- **Prognosis**

![Diagram showing stomach cancer genetic type and targeted therapies](image)
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