DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

53rd Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

March 4, 2013
Building 31C, Conference Room 10
Bethesda, Maryland

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
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MINUTES OF MEETING
March 4, 2013

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 53rd meeting on Monday, 4 March 2013, at 9:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Todd R. Golub, Director, Cancer Program, The Broad Institute of Massachusetts Institute of Technology and Harvard University, presided as Chair. The meeting was open to the public from 9:00 a.m. until 3:05 p.m. on 4 March for the NCI Director's report; a report on data replication; an update on the closing of The Cancer Genome Atlas (TCGA) project; a report on the NCI-Dream Challenge; consideration of a re-issue request for application (RFA) and Cooperative Agreement (Coop. Agr.) for the Pediatric Brain Tumor Consortium (PBTC); and program overviews of RFAs from NCI Divisions.

BSA Board Members Present:

Dr. Todd R. Golub (Chair)
Dr. Sangeeta N. Bhatia
Dr. Ethan Basch
Dr. Andrea Califano
Dr. Curt I. Civin
Dr. Graham Colditz
Dr. Robert B. Diasio
Dr. Daniel DiMaio
Dr. Jeffrey A. Drebin
Dr. Brian J. Druker
Dr. Karen M. Emmons
Dr. Betty R. Ferrell
Dr. Stanton L. Gerson
Dr. Joe W. Gray
Dr. Chanita Hughes-Halbert
Dr. Joshua LaBaer
Dr. Theodore S. Lawrence
Mr. Don Listwin
Dr. Maria E. Martinez
Dr. Luis F. Parada
Dr. Martine F. Roussel (Sherr)
Dr. Kevin M. Shannon
Dr. Mary L. Smith
Dr. Lincoln Stein
Dr. Bruce W. Stillman
Dr. Louise C. Strong
Dr. Frank M. Torti
Dr. Cheryl L. Walker
Dr. Irving L. Weissman

Board Members Absent:

Dr. Francis Ali-Osman
Dr. Arul M. Chinnaiyan
Dr. Chi V. Dang
Dr. Kathleen M. Foley
Dr. Gregory L. Verdine

Others present: Members of NCI's Scientific Program Leaders (SPL), NCI staff, members of the extramural community, and press representatives.

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I. CALL TO ORDER AND OPENING REMARKS--DR. TODD R. GOLUB

Dr. Todd R. Golub called to order the 53rd regular meeting of the BSA and welcomed current and new members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Golub reminded Board members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, comments regarding items discussed during the meeting.

II. CONSIDERATION OF THE 5 NOVEMBER 2012 MEETING MINUTES

Motion: The minutes of the 5 November 2012 meeting were approved unanimously.

III. REPORT OF THE DIRECTOR, NCI--DR. HAROLD VARMUS

Dr. Harold Varmus, Director, NCI, welcomed members and provided information about the Institute's budget and legislative news for the current and upcoming fiscal year (FY) as well as NCI news. Dr. Varmus informed members about the departure of several scientific leaders appointed by the Administration: Dr. Subra Suresh, Director, National Science Foundation (NSF); Dr. Stephen Chu, Secretary, Department of Energy (DOE); Dr. Jane Lubchenco, Administrator, National Oceanic and Atmospheric Administration (NOAA); Dr. Carolyn Clancy, Director, Agency for Healthcare Research and Quality (AHRQ); and Dr. Lisa Jackson, Director, Environmental Protection Agency (EPA). He noted that announcements had been made regarding replacements for several of the appointments. Recruitment efforts continue for NCI Directors of the Center for Cancer Genomics (CCG), Center for Biomedical Informatics and Information Technology (CBIIT), and Division of Cancer Epidemiology and Genetics (DCEG). He announced that Ms. Crystal Wolfrey had replaced Mr. Leo F. Buscher, Jr., Director, Office of Grants Administration, who had retired after more than 50 years of service at the NCI.

Budget. Dr. Varmus informed members that the budget sequestration went into effect on March 1 and would result in a loss of 5.1 %, i.e., ($1.45 billion [B]) to the NIH and specifically a 4.4 % ($219 million [M]) budget reduction for the NCI in fiscal years 2013 and 2014. He affirmed NCI's strong commitment to protecting critical investments and support for young investigators. Members were told that the NCI's operating rules during sequestration will be shared with grantees and contractors, and that the FY 2014 budget is being prepared.

Dr. Varmus informed members that the Continuing Resolution (CR) for FY 2013 likely would be extended through September at FY 2012 funding levels. A hearing on the NIH response to the sequestration is scheduled for the House of Representatives Appropriations Subcommittee. In addition, the House Science Committee is holding a meeting about data replication, specifically on how data are shared and used from NIH-funded studies.

Members were informed about the status of grant funding under the current CR and other budgetary restraints. The NCI continues to fund grants at the same level as FY 2012, with a similar funding success rate of approximately 14 %. A full accounting of the funding of research project grants (R01, R21) is available on the NCI's website.

NIH Activities. Dr. Varmus said that the NIH is reviewing the policy for public access of peer-reviewed publications that requires entry into PubMed Central within 1-year after publication. The Director of the White House Office of Science and Technology Policy, Mr. John P. Holdren, is proposing a similar policy for all government agencies that receive $100 M or more in funding per year. A congressional bill would require public access to publications produced with government research funds within 6 months after publication.

NCI Activities. Dr. Varmus described NCI activities in response to the Recalcitrant Cancer Research Act of 2012, which directs the NCI to develop plans and workshops on designated recalcitrant cancers. Reports from NCI Workshops on pancreatic ductal adenocarcinoma and small-cell lung cancers (SCLC), chaired by Dr. James L. Abbruzzese, Chairman, Gastrointestinal Medical Oncology and Digestive Diseases, University of Texas MD Anderson Cancer Center, and Dr. John Minna, Max L. Thomas Distinguished Chair in Molecular Pulmonary Oncology, University of Texas Southwestern Medical Center, respectively, will be distributed to the BSA when completed.

Dr. Varmus informed members that the NCI-Frederick Advisory Committee (NFAC), chaired by Dr. Zach Hall, President Emeritus, Institute for Regenerative Medicine, University of California, San Francisco, recently visited the Lawrence Berkeley National Laboratory to gain an understanding of how that organization has developed into a national laboratory with collaborations with nearby institutions. He noted that lessons learned will be used to inform the direction and activities of the Frederick National Laboratory for Cancer Research (FNLCR). Dr. Varmus stated that he had recently co-chaired a productive workshop in San Francisco, CA, with Dr. Frank McCormick regarding mutant *ras* genes, which is the focus of a planned megaproject being initiated at the FNLCR.

Dr. Varmus reminded members that the TCGA project will end in 2014. He shared NCI's concerns and proposed approaches to managing the large amounts of data being collected in clinical trials and genomic and other -omics studies. Two approaches being considered are: (1) a pilot study to evaluate how data currently are being collected and stored, with input from the National Cancer Advisory Board's (NCAB) Informatics Working Group, chaired by Dr. Dan Masys, Affiliate Professor, Biomedical and Health Informatics, University of Washington School of Medicine; and (2) an international alliance to manage data collection and storage that was discussed at a meeting with representatives from various countries in New York City, NY, on 29 January 2013.

Members were told that the Cancer Center Directors met in February 2013 and discussed the funding of NCI-designated Cancer Centers. The Cancer Centers Working Group was formed to review funding approaches and to determine if funding is equitable. Dr. Varmus also mentioned that the gene patent legal case against Myriad Genetics will be heard by the Supreme Court on 15 April 2013, which will determine whether genes and genetic mutations can be patented.

NCI Community Oncology Research Program (NCORP). Dr. Douglas R. Lowy, Deputy Director, updated members on NCORP, a new program to reorganize the NCI's community cancer research effort. Dr. Lowy stated that NCORP is proposed as a collaborative effort between the Division of Cancer Prevention (DCP) and the Division of Cancer Control and Population Sciences (DCCPS). Discussions

about NCORP were held at the Cancer Centers Directors meeting in February and a recent meeting with the research bases. It is expected that a new concept will be presented at the June Joint meeting.

In the discussion, the following points were made:

- The NCI is carefully planning for reallocation of funds in view of the CR and sequestration. Priority will be to maintain the number of new grants funded to ensure future progress. A letter will be sent to the cancer research community to communicate the effects of sequestration on the NCI research agenda.

- At the next joint BSA/NCAB meeting, a discussion of strategies to address the long term budget reductions anticipated with the sequestration, such as a decrease in the size of the national research system may occur.

- The relationship of the NCORP and the Cancer Centers will be encouraged to be stronger than past relationships between the Cancer Centers and the NCI Community Cancer Centers Program.

IV. DATA REPLICATION--DRS. HAROLD VARMUS AND LISA MCSHANE

Dr. Varmus provided an overview of NCI's activities on data replication. He informed members that, in response to a call for action from the scientific community and political leaders regarding the number of published trials that were not able to be replicated, the NCI held a workshop in September 2012 to determine if the data replication problems were real. This issue affects all research fields but is especially important in research for targets of therapeutic intervention. The consensus from the workshop was that the lack of data replication in research results is real. Causes include the use of unvalidated antibodies or cell lines, a number of substandard experiments, unblended data, and a variety of other reasons. Potential remedies developed at the workshop are changes in the manner researchers are evaluated by their colleagues and institutions, as well as methods and procedures for conducting laboratory research. There needs to be more training in scientific ethics, mentors to review articles pre-publication to provide input, and more publication of "negative" or failure to confirm results. Other remedies discussed at the workshop include checklists for journal articles and grant applications, greater access to underlying data, and changes in the NIH biosketch required for grant applications to focus on major contributions. NCI will conduct a pilot project on the new NIH biosketch format in the next year.

The data replication problem is an NIH-wide problem. The National Institute of Neurological Disorders and Stroke (NINDS) has taken steps to address the problem. Specifically, NINDS held a workshop, "Optimizing the Predictive Value of Preclinical Research," that made recommendations to: 1) require more transparent access to trial data; and, 2) change RFA instructions to encourage better descriptions of the design, execution, and interpretation of the proposed studies as well as in the supporting data. Another important step to address NIH-wide is the establishment of a trans-NIH committee to develop a checklist of standards for conducting research and publications.

Dr. Lisa McShane, Biometric Research Branch, Division of Cancer Treatment and Diagnosis (DCTD), informed members about a checklist-based guideline, Reporting Guidelines for Tumor Marker Prognostic Studies (REMARK). Irreproducible results can be generated from many junctures in trial design, conduct, and analyses. REMARK specifies recommended reporting elements that facilitate reproducibility in the tumor marker field where heterogeneity exists among studies investigating the same marker. Target studies for use of REMARK criteria are those relating marker values to clinical events (e.g., recurrence, death, response) and are encouraged for use in patients, specimens, and assays, but not for studies aimed at biological discovery.

REMARK elements are organized in the same manner as journal articles, and require both the identification of all marker(s) examined and clarity in the study objectives and pre-specified hypotheses. Dr. McShane reviewed the 20 items on the REMARK checklist including patient and specimen

characteristics, assay methods, study design, and statistical analysis methods. The 2012 re-analysis of a 2008 systematic review of the International Ki-67 Reproducibility Study for Ki-67 in early breast cancer using REMARK criteria indicated that, of the 43 studies used in the systematic review, 7 different antibodies for immunohistochemistry (IHC) were used, singly or in combination; 19 cutpoints were used, ranging from 0 to 30 %; and significant between-study heterogeneity and publication bias existed. The REMARK criteria checklist can eliminate such methodological errors. In addition, Dr. McShane shared examples of faults in the statistical analysis, results, and discussion sections of the Ki-67 study.

Poor study reporting has become a significant impediment to achieving reproducible research and must be corrected. Proper reporting can only occur if all stakeholders (e.g., researchers, journal editors, reviewers, and research institutions) accept standard reporting guidelines. Complete and transparent reporting is fairer because it holds everyone to the same standard. In addition, the effort spent on good reporting is a smaller burden than time, effort, and resources wasted on false results.

In the discussion, the following points were made:

- REMARK is most useful in making researchers think about the research they are conducting, and how to improve the process. Guidelines need to be included in the planning process for projects.

- Revealing the reviewers of submitted research articles may add transparency and accountability to the process. It may be possible to implement a venue for post-publication review, such as an anonymous commentary on journal websites, with commentators certified by some process.

- A member suggested that NIH training grants should include the ethics of publication in addition to the traditional focus on ethics in performing research.

- Finding appropriate reviewers for multidisciplinary research is becoming more challenging. A system of online peer review commentary to allow wider input into the review process may be an ideal solution.

- Validation efforts are complicated by the significant amount of clinical trial data that are never released, particularly for early phase studies.

V. POST TCGA (THE CANCER GENOME ATLAS)--DRS. LOUIS STAUDT AND STEPHEN CHANOCK

Dr. Louis Staudt, Senior Investigator, Metabolism Branch, NCI, provided an update on the closing of TCGA in 2014 and the shifting of its programs to the Center for Cancer Genomics (CCG). Dr. Staudt stated that TCGA has completed its work and achieved its goals. He informed members that the CCG is home to the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Program for pediatric cancer; a program for linking genomic analyses to therapeutic development; and the Cancer Target and Drug Discovery (CTD^2) Program, a component of the drug discovery and pathway function of the NCI's precision treatment program.

The focus of the CCG will be on exploring the role of driver mutations and mapping genetic pathways in cancer; determining the contribution of intratumor genetic heterogeneity to progression and treatment response; and investigating the genetic basis of metastasis. The CCG's 10K project is designed to address the goals of the CCG by identifying novel genomic targets in lung adenocarcinoma. Studies to identify a comprehensive list of mutations in lung adenocarcinoma resulted in the awareness that there is a high lung cancer mutation rate, making it difficult to identify significantly mutated genes. This was illustrated in a study comprised of approximately 230 lung adenocarcinomas where known mutated genes were identified but not at levels for statistical significance. From this analysis, the 10K project was developed to perform mutation analyses on 10,000 cases of lung adenocarcinoma. The goals of the 10K project are to identify common and less common genetic aberrations, define genetic pathways in cancer, investigate relationship of somatic alterations to germline variations and exposures, and correlate genetics with

clinical outcomes. Formalin-fixed, paraffin-embedded (FFPE) procedures can provide large enough samples to use for analysis.

An NCI-supported trial developed as part of the 10K project is ALchEMIST, which will look for biomarkers in lung adenocarcinoma. The trial will include molecular profiling on approximately 7,000 members of a cohort. Approximately 50% of cases will be re-profiled at relapse. The trial will collect epidemiologic information spanning tobacco, diet, alcohol, and work exposures.

In the discussion, the following points were made:

- The CCG should consider collecting viable, single-cell suspensions of the tumor, surrounding cells, and the stroma for epigenetic analyses.

- The issue of informed consent is a challenge for genomic studies and the NCI is reviewing its policies.

- Mutations of low penetrance (1 to 2%), presents a significant challenge, but low penetrance mutations may be critical for understanding genetic pathways.

- The NCI was encouraged to focus on understanding the biology of cells as well as the genomics. The Institute recognizes that phenotype is an important aspect of the 10K project.

VI. AN EXPERIMENT IN CROWD-SOURCING SCIENCE: THE NCI-DREAM CHALLENGE -- DRS. DINAH SINGER AND GUSTAVO STOLOVITZKY

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), informed members of the NCI Dialogue for Reverse Engineering Assessments and Methods (DREAM) Challenge program, an online project that challenges participants to propose solutions for fundamental questions about systems biology. Dr. Singer explained that the DCB has been conducting an experiment in the past year exploring the possibility of using online challenges or competitions as a research tool. One of the best known examples of this concept was known as "FoldIt,A an online game developed by the University of Washington that challenged players to solve protein structures. Within weeks of game initiation, a player had solved the structure of a retroviral protease. This success helped these types of endeavors gain acceptance.
Dr. Gustavo Stolovitzky Manager, Functional Genomics and Systems Biology at IBM Research, New York, launched a DREAM program as an annual competition, challenging players to infer cellular networks from available databases. The NCI supported a joint-challenge to use NCI datasets generated through DCB's Integrative Cancer Biology Program (ICBP).

Dr. Stolovitzky defined crowdsourcing as the practice of soliciting content, ideas, and solutions from a large group of people, especially the online community, to solve a problem. The benefits in performance evaluation are that one can discover the best methods to solve problems by blind, unbiased, and rigorous method assessment. Sampling the method space allows one to determine the diversity of methodologies presently being used to solve a problem. In addition, crowdsourcing tends to build a community of individuals willing to share data, foster collaborations, and develop community consensus for robust solutions. Dr. Stolovitzky described a challenge for breast cancer prognosis that resulted in 1,700 models being tested by 50 participating teams from 35 countries.

Dr. Stolovitzky informed members that the NCI-DREAM Challenge, which began in April 2012 with a meeting of 20 researchers active in the field of systems pharmacology who selected two subchallenges. Subchallenge 1 was to predict the sensitivity of 31 compounds in 18 cell lines given the compounds' sensitivity profiles in 35 cell lines and genomic information for all lines, and Subchallenge 2 was to predict responses to 91 pair-wise combinations of 14 compounds in Ly3 human B-cell lymphoma cells. The winner of Subchallenge 1 was TeamFIN from the Helsinki Institute for Information Technology, Aalto University, Helsinki, Finland using

multi-task learning; the winner of Subchallenge 2 was the University of Texas Southwestern Medical Center-Dallas (UTSW-MC), Texas. The next steps for the NCI-DREAM Challenge are for Subchallenge 1 to validate findings and conduct further testing on additional breast cancer cell lines, and for Subchallenge 2 to test the model on another lymphoma cell line. The winners are preparing an article about their winning model to be reviewed for publication in *Nature Biotechnology*. One of the most important lessons learned from this experience is that many approaches can be tested quickly and cheaply by using a well-framed problem and providing test and training data in a well-defined format.

In the discussion, the following points were made:

- The greatest benefits of the challenge approach are offering the ability to predict the outcome of clinical trials using *a priori* data, and investigating animal models.

- Crowdsourcing allows participation of a large number of talented people in the online community with different perspectives and experiences.

- This type of analysis makes a strong case for the public dissemination of clinical trial data to the scientific community. Members expressed the need to have some data kept private for predictive modeling before being released to the public.

VII. PEDIATRIC BRAIN TUMOR CONSORTIUM (PBTC) RFA/COOP.AGR.) -- SUBCOMMITTEE

Subcommittee Review. Dr. Curt I. Civin, Director, Center for Stem Cell Biology and Regenerative Medicine, University of Maryland School of Medicine, expressed the Subcommittee's support for the reissuance concept. Dr. Civin informed members that the PBTC is an important component of NCI's clinical research program for children, well integrated with the Children's Oncology Group, and has been productive since it was established in 1999. The Subcommittee also was impressed that the PBTC has an internal self-review process to assess the performance of the research centers. During the initial 5 years of the PBTC, the review resulted in multiple centers being removed from their consortium; they recycled 25% of the center awards, which showed their commitment for meeting accrual and performance standards from the beginning of the consortium. The productivity of the consortium also was lauded.

The first year costs are estimated at $2.594M for one UM1 award, with total costs of $13.096M for five years.

Motion. A motion to concur with the re-issue concept entitled "Pediatric Brain Tumor Consortium (PBTC) RFA/Coop. Agr." was approved unanimously.

VIII. PROGRAM OVERVIEW OF RFAS--DR. PAULETTE GRAY

Dr. Paulette S. Gray, Director, DEA, NCI, and BSA Executive Secretary, informed members about the types of NCI funding mechanisms, their requirements, and how they are used to support the NCI mission. Dr. Gray reviewed RFAs, Program Announcements (PAs), Program Announcements with Special Reviews/Receipt (PARs), and Request for Proposals (RFPs). A review of the number of NCI RFAs, PARs, and PAs published between FY 2008 and FY 2012 indicates an increase in the number of PARs and a decrease in the number of RFAs. An analysis of the number of RFAs published between FY 2008 and FY 2012 that have been reviewed by the BSA shows a slight decrease in the number of RFAs that have been presented to the BSA, but the average first year total costs of RFAs has remained essentially the same. Dr. Gray said that the presentations from the NCI Divisions would provide an overview of current and future RFAs.

Division of Cancer Treatment and Diagnosis (DCTD)--Dr. James Doroshow

Dr. James Doroshow, Director, DCTD, highlighted the current list of DCTD RFAs and provided background information and their future status. Dr. Doroshow indicated that within the next year, a new

RFA concept to support the Cooperative Group Banks, that will reflect the reconstituted NCI Clinical Trials Network (NCTN), will be brought to the Board. The NCTN has received applications, review will be completed in a few months, and it is hoped funding will begin in FY 2014. The Collaborative Human Tissue Network, which was reviewed by the Board in November 2012, is in the process of recompetition. Another RFA that is in recompetition is the early phase therapeutics network, which will involve more team science and increased interactions with Specialized Programs of Research Excellence (SPOREs) and the Cancer Centers. The Pediatric Phase 1 Pilot Consortium, similar in nature to the Adult Phase 1 Network, almost has completed its recompetition, and awards are expected soon.

Two RFAs will not be recompeted when they expire. The Network for Translational Research in Optical Imaging (NTROI) has been a productive enterprise but will be supported by investigator initiated R01s in the future. The Advanced *In Vivo* Imaging to Understand Cancer Systems RFA, which was a joint RFA with the DCB, has stimulated research on molecular imaging and now can be continued elsewhere.

Other RFAs that are expected to be offered for recompetition when their funding expires are the Data Resource for Analyzing Blood and Marrow Transplant, Blood and Marrow Transplant Clinical Trials Network, Cancer Immunotherapy Network, Childhood Cancer Survivor Network, and Pediatric and Adult Brain Tumor Consortia.

Dr. Doroshow informed the Board that the DCTD is making every effort to provide sufficient funding for the RFAs that are most promising, such as the cooperative groups and Early Phase Therapeutics Network, in this time of flat funding. RFAs that have either come to the end of their usefulness or that have not been as productive as envisioned have been discontinued. Overall, the Division makes difficult decisions about whether a project is ready for an RFA or can be funded under another mechanism to strengthen its scientific base before moving the concept into a clinical trial.

In the discussion, the following points were made:

- The immunotherapy RFA is highly focused to provide extensive correlative monitoring that is difficult to do in a large clinical trial.

Division of Cancer Biology (DCB)--Dr. Dinah Singer

Dr. Dinah Singer, Director, DCB, informed members that the DCB's philosophy regarding RFAs is to ensure continuing progress and stability in the current cancer biology portfolio and anticipate new areas and emerging concepts that will enhance specific research areas. Dr. Singer stated the DCB portfolio is comprised primarily of R01 and P01 investigator-initiated research. She noted that compared with other Divisions, the DCB sponsors relatively few RFAs; at present, there are only six. The oldest current RFA is the Mouse Models of Human Cancer Consortium, established to develop technologies for generating and validating genetically modified mouse models of human cancer. Although the consortium has been a great success over the years in providing models for preclinical, co-clinical, prevention, and systems genetics studies, the RFA will not be renewed.

Two RFAs, the Integrative Cancer Biology Program (ICBP) and the Tumor Microenvironment Network (TMEN), have met their goals and will not be renewed when their RFAs expire. The ICBP adopted a systems biology approach that brought together scientists, mathematicians, computational biologists, and experimentalists to address specific problems in cancer biology. The TMEN was established to identify the constituent parts of the tumor microenvironment and develop the reagents that are necessary to identify and isolate them. The Network identified cancer-associated fibroblasts and tumor-initiating cells, and made antibodies, reagents, and other vectors specific for stromal components. The Biology of Receptor-Negative Breast Cancer, Advanced *In Vivo* Imaging (a collaboration with the DCTD), and the Barrett's Esophagus Translational Research Network (BETRNet) are the remaining RFAs. Only the BETRNet is being considered for recompetition.

Dr. Singer informed members that a new RFA concept on early diagnosis is being developed in conjunction with DCP. The goal of the RFA will be developing molecular and cellular distinctive features that are predictive of whether an early detected lesion will progress to a cancer or not.

In the discussion, the following points were made:

- The decision on whether to ask for continuance of an RFA is based on the progress that was made during the first grant period, whether all goals have been met, and often, whether continued progress can be made through the R01 grant or some other mechanism.

Division of Cancer Prevention--Dr. Barry Kramer

Dr. Barry Kramer, Director, DCP, informed members that the philosophy of the DCP with regard to RFAs is to implement research priorities, offer flexibility in pursuing research opportunities, pursue innovation, and adjust the research directions of the core programs. The DCP also engages in numerous collaborative programs with other NCI divisions, other NIH Institutes and Centers (ICs), and in international collaborations. The RFA research priorities for the DCP include clinical studies and large trials, over diagnosis and precancerous lesions, and developing partnerships on clinical studies.

The Community Clinical Oncology Program (CCOP) began in the early 1980s and includes an RFA for the CCOPs; one for the Minority-based CCOPs (MB-CCOPs); and one for the Research Bases, which include cooperative groups and cancer centers. The CCOPS will be united under the NCORP, a new initiative that will be presented at the June meeting.

The Early Detection Research Network (EDRN) includes RFAs for 20 Biomarker Developmental Laboratories, 8 Clinical Validation Centers, 3 Biomarker Reference Laboratories, and a Data Coordinating and Management Center. The EDRN also has approximately 130 associate members, who receive no money from the RFAs but instead bring resources into the EDRN. The RFA for the Alliance of Glycobiologists for Cancer Detection was formed in collaboration with the NIH's National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of General Medical Sciences (NIGMS) for the study of molecular processes by which glycosylation contributes to cancer development. The single RFA supports eight Tumor Glycomics Laboratories, and additional funding comes from other NIH ICs. This network was established to identify promising glycans in cancer development that can be submitted to the EDRN for further investigation. The BETRNet has a single RFA with funding from the DCB and DCP to establish three research centers and one coordinating center for the investigation of the biology of preneoplastic lesions and invasive cancer.

Dr. Kramer said that the DCP maintains collaborations with numerous NIH ICs, including a jointly initiated project with the NHLBI on common pathological mechanisms of lung cancer and chronic obstructive pulmonary disease and a joint project with the NINDS on the biomechanisms of peripheral nerve damage by anticancer therapy. The DCP also has developed collaborations with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute on Aging (NIA) to investigate cancer endpoints in clinical trials for metformin therapy and aspirin, respectively. Upcoming projects include the NCORP and a collaborative effort with the DCB to improve the diagnosis of early lesions detected by cancer screening.

Center to Reduce Cancer Health Disparities (CRCHD)--Dr. Sanya Springfield

Dr. Sanya A. Springfield, Director, CRCHD, informed members that research and training are the Center's primary focus areas, especially diversity training. The philosophy of the CRCHD is to work within all NCI Divisions to support initiatives that will increase the number of applications from researchers who are interested in pursuing cancer health disparities research, as well as increase the representation of individuals from diverse populations in the NCI portfolio. Dr. Springfield described R21 program announcements, including those offered by the CRCHD in collaboration with the DCB. A series of PAs (e.g., F31, K01, K08, K22) are reissued every 3 years to support individuals from diverse populations who want to pursue careers in cancer research.

Dr. Springfield described a long-standing RFA, the Comprehensive Partnerships to Advance Cancer Health Equity (PACHE), which brings together minority-serving institutions with NCI's Cancer Centers to perform research, training, education, and outreach. The original RFA included a P20 planning grant, a U56 cooperative planning grant, and a U54 comprehensive partnership planning grant. It is anticipated that PACHE will be renewed as a PAR.

Dr. Springfield informed members that the Community Networks Program's (CNP) utilizes a community-based participatory research model. It is anticipated that the CRCHD will ask for renewal of this RFA in 2015 as a limited competition, allowing only those CNPs that are highly productive to apply.

Division of Cancer Control and Population Sciences (DCCPS)--Dr. Robert Croyle

Dr. Robert Croyle, Director, DCCPS, indicated that the division has developed collaborations across the NIH, Department of Health and Human Services (HHS), U. S. Food and Drug Administration (FDA), EPA, and numerous other federal departments and agencies and nongovernmental organizations. The DCCPS is transdisciplinary by virtue of its scope of initiatives and its responsiveness to scientific and health policy priorities. Evidence developed by the DCCPS is used by health care policy constituencies such as the Center for Medicaid and Medicare Services (CMS), the Health Resources and Services Administration (HRSA), the Centers for Disease Control and Prevention (CDC), and the AHRQ, as well as regulatory agencies like EPA and FDA. The range of its public health focus includes obesity, tobacco use, health disparities, and the social determinants and risk factors for many diseases.

Dr. Croyle stated that many of DCCPS' current RFAs will not be reissued after they expire. These include three RFAs for tobacco control research because of the new regulatory authority of the FDA, which will absorb some of these functions. The Centers for Population Health and Health Disparities (CPHHD) will not be reissued by the DCCPS but is being considered for continuation by the NHLBI, one of the current partners. The Centers for Transdisciplinary Research on Energetics and Cancer (TREC) is now part of the trans-NIH Obesity Task Force and will not be reissued, although the division will continue to work with the Task Force on obesity-related initiatives.

Dr. Croyle explained that the Population-Based Research Optimizing Screening through Personalized Regimens (PROSPR) RFA focuses on monitoring, evaluation, and comparative effectiveness studies in cancer screening for breast, colon, and cervical cancer. PROSPR is being considered for expansion to incorporate lung cancer screening. Also due to be reissued is the RFA to support the infrastructure for the Cancer Research Network (CRN), a broad consortium that includes large, integrated health plans. Success of the CRN has spawned a trans-NIH collaboration known as the Health Care Systems Collaboratory.

The final RFAs reviewed by Dr. Croyle were the Cancer Intervention and Surveillance Modeling Network (CISNET), which will be reissued; the Genetic Associations and Mechanisms in Oncology (GAME-ON) RFA, which will not be reissued; and the Breast Cancer and the Environment Research

Program (BCERP), which is led by the National Institute of Environmental Health Sciences (NIEHS).

Dr. Croyle informed members about a partnership with FDA's new Center for Tobacco Products that will provide funding (from tobacco users fees rather than appropriations) to the NIH for P50 grants (Tobacco Centers of Regulatory Science for Research Relevant to the Family Smoking Prevention and Tobacco Control Act) and competitive supplements for P30 cancer centers. This will provide significant funds for continuing research in tobacco prevention and control at the DCCPS and across the NIH.

In the discussion, the following points were made:

- Many of the tobacco-related programs funded by the NCI are eligible for FDA funding, but certain portions will continue to be funded by the NCI.

- When projects (e.g., the Cancer Families Registry) end, collected samples can be used for cohort studies under separate contracts. In general, the determination of the distribution of resources at the end of an RFA takes place either at the preplanning stage or during the term of the RFA.

- Results from the CRN are expected to spur consortia members to apply for R01 grants to continue the research.

Office of the Director (OD)--Dr. Edward Harlow

Dr. Edward Harlow, Special Advisor to the NCI Director, informed members of RFAs issued by the OD. Dr. Harlow stated that unique characteristics of RFAs issued by the OD are that they are trans-NCI and originate at the Director or senior staff level. RFAs that are scheduled to be reissued include the NCI Alliance for Nanotechnology in Cancer, Physical Sciences in Oncology, Clinical Proteomic Technologies for Cancer, Provocative Questions Initiative, and Innovative Molecular Analysis Technologies Program. Each of these involves emerging technologies and processes that are expected to advance cancer research in the years to come. For example, the nanotechnology RFA focuses on new ways to target tumors for therapeutics (small molecules) and imaging. Dr. Harlow said that two RFAs, TCGA Network: Genome Characterization and Genome Data Analysis Centers and Cancer Target Discovery and Development Network Centers, will not be recommended for reissuance.

In the discussion, the following points were made:

- Members requested a final scientific assessment of all of NCI's RFAs after 10 years of support and an assessment of remaining Aprovocative@ questions. A further suggestion was that scientific assessment reports should be provided to the Board for all RFAs that were discontinued after 5 years.

- For RFAs that will not be reissued, members suggested that the NCI provide the Board with a summary report indicating the successes of the project and reasons for nonrenewal. This provides the Board with an opportunity to provide input on the decision.

- The NCI was encouraged to consider a way to communicate the recommendations of the Board to study sections reviewing PAs. Staff noted that the Center for Scientific Review (CSR) is under new leadership, which is taking seriously IC concerns in terms of how PAs are reviewed and how the initiatives are communicated to the peer reviewers.

- RFAs with collaborations among nontraditional cancer researchers (e.g., engineers, physicists) should be allocated more than one funding cycle to become established.

- The NCI should consider funding more clinical trials for drugs developed at academic, rather than commercial, research institutions. It was noted that the Early Phase Therapeutics Network uses

agents from small biotech and academic investigators.

IX. ADJOURNMENT--DR. TODD R. GOLUB

There being no further business, the 53rd regular meeting of the Board of Scientific Advisors was adjourned at 3:20 p.m. on Monday, 4 March 2013.

_____ _____

Date Todd R. Golub, M.D.
Chair, Board of Scientific Advisors

_____ _____

Date Paulette S. Gray, Ph.D.
Executive Secretary, Board of Scientific Advisors

HOW RELIABLE ARE THE PUBLISHED RESULTS OF NIH-FUNDED RESEARCH?

- **Multiple reports of failures to replicate data**

Raise standards for preclinical cancer research

C. **Glenn Begley** and **Lee M. Ellis** propose how methods, publications and incentives must change if patients are to benefit.

Beware the creeping cracks of bias

Evidence is mounting that research is riddled with systematic errors. Left unchecked, this could erode public trust, warns **Daniel Sarewitz**.

NCI CONVENED A WORKSHOP ON SEPTEMBER 14, WITH ALL CONSTITUENCIES REPRESENTED, TO ASK

- are the alleged phenomena real?

  --a new problem?
  --rising incidence? (cf increased "retractions")

- if real, what is the explanation?

  --different criteria in academia and industry?
  --different and difficult methodologies?
  --actual errors?
  —intentional or sloppiness?

- what encourages errors?

  who is responsible?
  --investigators, trainees, grantee
  institutions, journals, funders?

- what are the remedies? how would they be implemented?

CONSENSUS

UNANIMOUS AGREEMENT THAT THERE IS A PROBLEM:

MANY PUBLISHED RESULTS ARE MISLEADING OR WRONG

COMMON CHARACTERISTICS OF NON-REPLICABLE DAT

- Inadequate numbers of samples or subjects
- Failure to validate reagents
- Substandard number of experiments
- Data "selection," manipulation, subjective bi
  failure to "blind" observers

ETC

POSSIBLE EXPLANATIONS FOR SLOPPY WORK

THE EVALUATION PROCESS

LABORATORY PRACTICE

REVIEWERS/EDITORS AT JOURNALS

PUBLICATION METRICS (IMPACT FACTORS, "CNS DISEASE", ETC)

APPOINTMENT AND PROMOTION COMMITTEES

STUDY SECTIONS

NATURE OF BIOSKETCH

GROUP DYNAMICS IN LABORATORIES

NEED TO PUBLISH

ASPIRATIONS TO NOVELTY

INADEQUATE ETHICS TRAINING OR TEACHING OF SCIENTIFIC METHOD

REMEDIES DISCUSSED AT NCI WORKSHOP

--First, do no harm!

--Mentorship and training to improve practice and ethical standard

--More publication of "negative results" or failure to confirm, with means to award credit

--Post-publication commentary (cf PMC initiative)

--Change biosketch to focus on major accomplishments and to reward contributions to team efforts

--Greater access to underlying data

--Checklists for journal articles and grant applications

--Subsidized validations? (Who would pay? Who would choose?)

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EXAMPLES OF ACTIONS

AT NINDS

Actions taken by NINDS:
Workshop
"Optimizing the Predictive Value of Preclinical Research"

- ✓ *Guidance crafters*
- ✓ *Journal editors*
- ✓ *Reviewers*
- ✓ *End users*

A call for transparent reporting to optimize the predictive value of preclinical research

Story C. Landis[1], Susan G. Amara[2], Khusru Asadullah[3], Chris P. Austin[4], Robi Blumenstein[5], Eileen W. Bradley[6], Ronald G. Crystal[7], Robert B. Darnell[8], Robert J. Ferrante[9], Howard Fillit[10], Robert Finkelstein[1], Marc Fisher[11], Howard E. Gendelman[12], Robert Golub[13], John L. Goudreau[14], Robert A. Gross[15], Amelie K. Gubitz[1], Sharon E. Hesterlee[16], David W. Howells[17], John Huguenard[18], Katrina Kelner[19], Walter Koroshetz[1], Dimitri Krainc[20], Stanley E. Lazic[21], Michael S. Levine[22], Malcolm Macleod[23], John M. McCall[24], Richard T. Moxley III[25], Kalyani Narasimhan[26], Linda J. Noble[27], Steve Perrin[28], John D. Porter[1], Oswald Steward[29], Ellis Unger[30], Ursula Utz[1] & Shai D. Silberberg[1]

Actions taken by NINDS:
Notice in the Guide

Improving the Quality of NINDS-Supported Preclinical and Clinical Research through Rigorous Study Design and Transparent Reporting

NOT-NS-11-023

Release Date: August 10, 2011

Issued by: National Institute of Neurological Disorders and Stroke (NINDS)

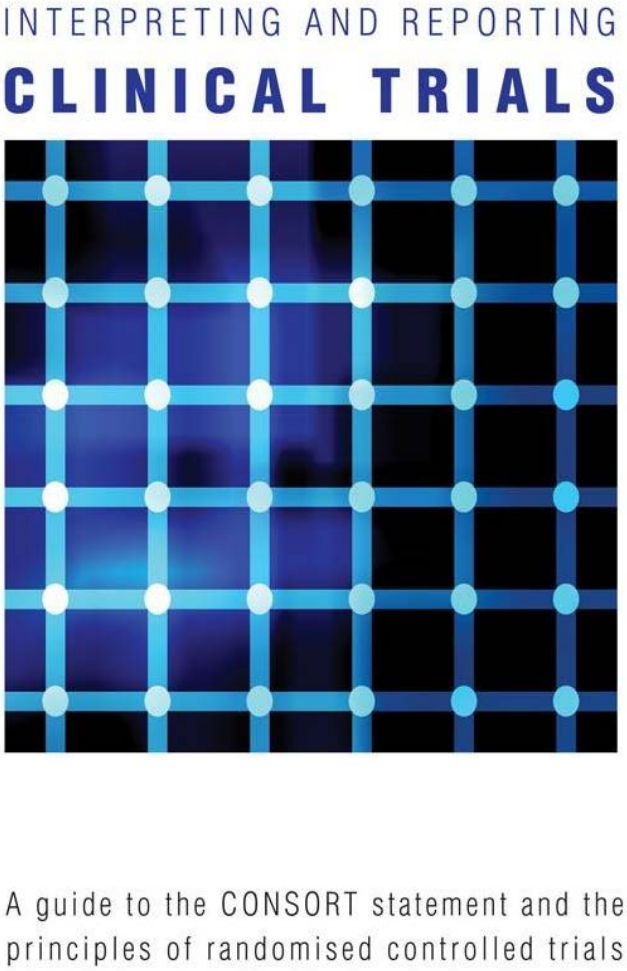
Purpose:

> …..NINDS believes that applications that propose preclinical research, or that are based on previous preclinical data, will be greatly strengthened if the design, execution, and interpretation of the proposed studies and supporting data are adequately described. NINDS encourages investigators, whenever possible, to address these elements directly in their applications.

The CONSORT statement provides guidelines for reporting clinical trials

"Randomized trials can yield biased results if they lack methodological rigour.

To assess a trial accurately, readers of a published report need complete, clear, and **transparent** information on its methodology and findings."



POSSIBLE NEXT STEPS FOR THE NIH?

- Trans-NIH committee on the topic (Story Landis, NINDS, chair)
- More workshops to gather information and propose solutions
- Experiments to evaluate existing checklists (e.g. REMARK criteria for biomarker studies published in *Clinical Cancer Research)* or new ones
- A "failure analysis initiative" for individual cases
- Educational campaigns to change the culture via mentoring, ethics training, better evaluation processes (e.g. altered biosketch) statement of norms for "team science", etc.
- Trials of new publication practices: post-publication commentaries; links to unpublished data sets; means to encourage (or mandate) publication and dissemination of, and credit for, "negative" results
- Statements of concern about non-reproducibility with various constituencies (investigators, institutions, journals, industry)

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AN EXAMPLE: HOW CHECKLISTS MIGHT WORK…

- List standards, such as:
  Validate all reagents
  Meet statistical criteria
  Conform to other "best practices"

- Acknowledge differences appropriate for basic, pre-clinical, and clinical work

- Learn from "Omics" report from the IOM

- Develop NIH panels, employed at various stages of scientific process, to create or vet lists

- Encourage use by research groups, institutions, journ (reviewers and editors), and/or NIH study sectio

AN NCI EXAMPLE:

"REMARK" GUIDELINES

Lisa McShane, DCTD

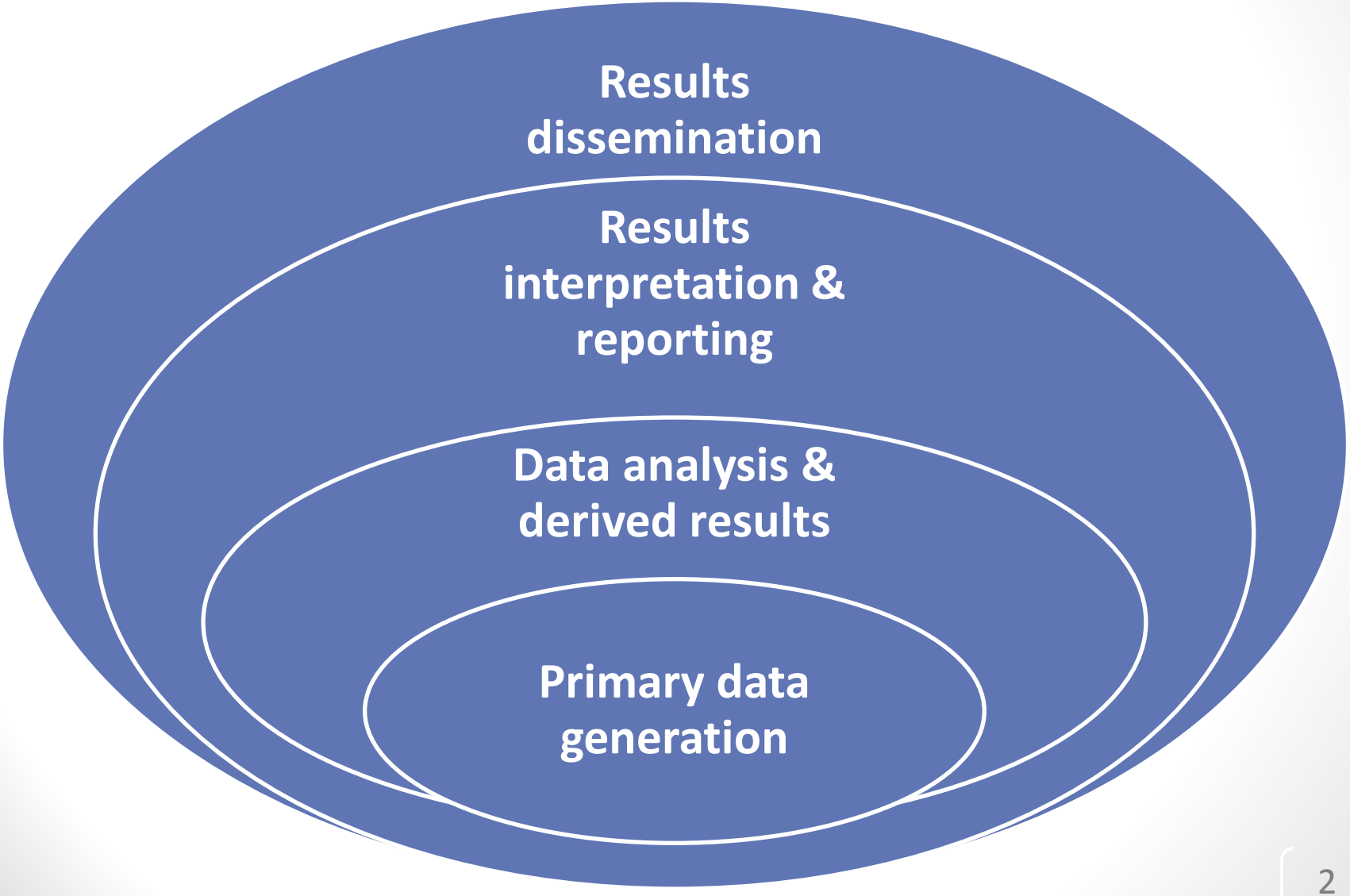
The Role of Reporting Guidelines in Promoting Reproducible Research

Presentation to the
NCI Board of Scientific Advisors

Lisa McShane, PhD
Biometric Research Branch, DCTD
National Cancer Institute

March 4, 2013

Propagation of Irreproducible Research



REMARK: **RE**porting guidelines for tumor **MARK**er prognostic studies

Lisa M. McShane, Douglas G. Altman, Willi Sauerbrei, Sheila E. Taube, Massimo Gion, and Gary M. Clark for the Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics (*J Natl Cancer Inst* 2005; 97:1180-1184, and simultaneously in *BJC, EJC, JCO, NCPO)*

Recommended reporting elements to facilitate

- Evaluation of **appropriateness & quality** of study design, methods, and analysis
- Understanding of **context** in which conclusions apply
- **Reproducibility**
- **Comparisons** across studies, including formal meta-analyses

REMARK: Target Studies

- Studies relating marker values to clinical events (e.g., recurrence, death, response)
- NOT primarily aimed at biological discovery studies, but use encouraged to extent possible
  - Patients
  - Specimens
  - Assays
- NOT sufficient for studies developing multiplex classifiers/risk scores (e.g., derived from omics data), but applicable to studies assessing them

State of the Tumor Marker Literature

VOLUME 25 · NUMBER 33 · NOVEMBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

Lyndsay Harris, Herbert Fritsche, Robert Mennel, Larry Norton, Peter Ravdin, Sheila Taube, Mark R. Somerfield, Daniel F. Hayes, and Robert C. Bast Jr

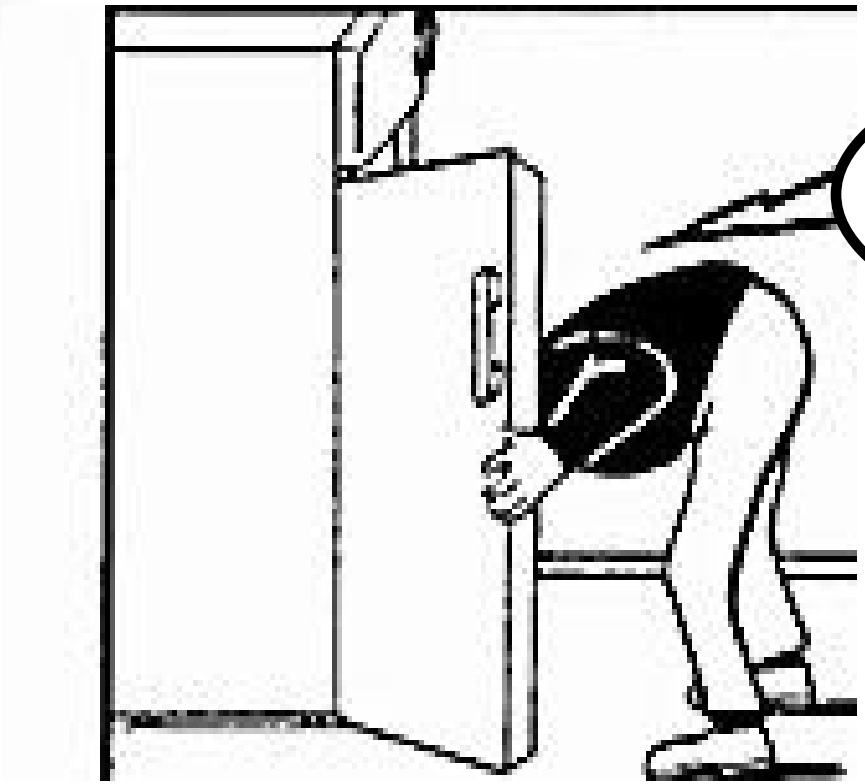
Purpose: To update the recommendations for the use of tumor marker tests in the prevention, screening, treatment, and surveillance of breast cancer.

". . . primary literature is characterized by studies that included small patient numbers, that are retrospective, and that commonly perform multiple analyses until one reveals a statistically significant result. . .many tumor marker studies fail to include descriptions of how patients were treated or analyses of the marker in different treatment subgroups. The Update Committee hopes that adherence to . . . REMARK criteria will provide more informative data sets in the future.

REMARK Elements: Introduction

- State all marker(s) examined
- Study objectives
- Pre-specified hypotheses

Common Tumor Marker Study Design



What can we do with our marker on these 89 specimens?

- "Convenience" specimens
- Heterogeneous patient characteristics
- Treatments: Unknown, non-randomized, not standardized
- Insufficient sample size (underpowered)
- Uncertain specimen and data quality

REMARK Elements: Materials & Methods

- Patients
  - Inclusion/exclusion (e.g., stage, subtype), source, treatments
- Specimen characteristics
  - Format, collection, preservation, storage
  - See BRISQ criteria (Moore et al, *Cancer Cytopathology* 2011; 119:92-101)

REMARK Elements: Materials & Methods (cont.)

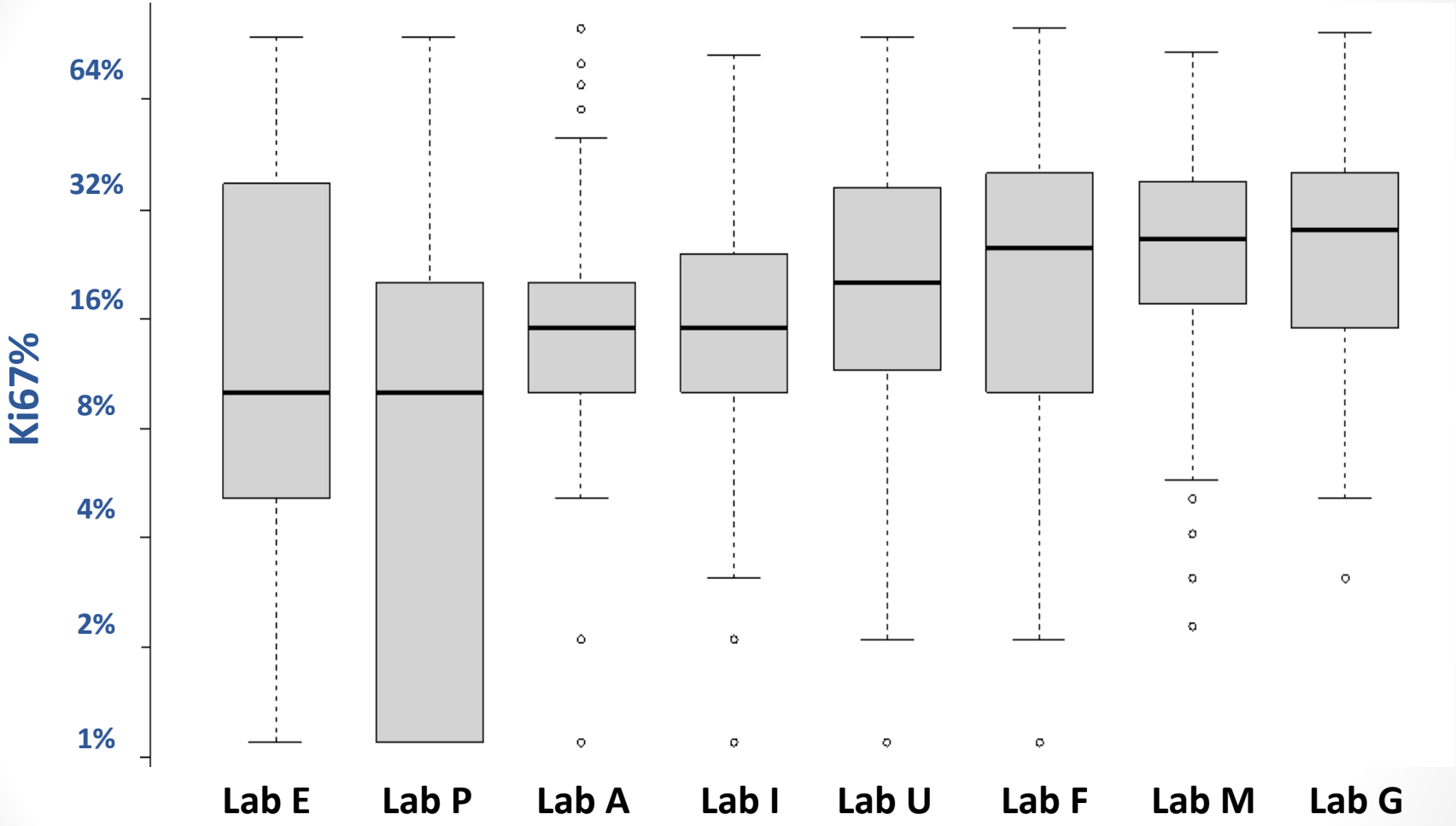
- Assay methods
  - Detailed protocol (reagents/kits), quantitation, scoring & reporting, reproducibility, blinding

Example: Systematic review (43 studies) of Ki67 in early breast cancer (Stuart-Harris et al, *The Breast* 2008; 17:323-334)

- English publication, Jan. 1995 – Sept. 2004
- ≥ 100 patients, OS or DFS endpoint

- Results
  - 7 different antibodies for IHC, single or combination
  - 19 different cutpoints, ranging from 0-30%
  - Significant between-study heterogeneity and publication bias

International Ki-67 Reproducibility Study
(Nielsen et al, *SABCS* 2012 abstract)



median: 10%

median: 28%

Consecutive TMA sections, single assay batch

REMARK Elements: Materials & Methods (cont.)

- Study design
  - Case selection (e.g., random, case-control), clinical endpoints, variables considered, sample size
- Statistical analysis methods
  - Models, variable selection, handling of missing data, multiple testing adjustments, validations

Statistical Analysis Methods

EUROPEAN JOURNAL OF CANCER 43 (2007) 2559–2579

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Almost all articles on cancer prognostic markers report statistically significant results

Panayiotis A. Kyzas[a], Despina Denaxa-Kyza[a], John P.A. Ioannidis[a,b,c,]*

[a]*Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece*

[b]*Biomedical Research Institute, Foundation for Research and Technology-Hellas, Ioannina, Greece*

[c]*Institute for Clinical Research and Health Policy Studies, Department of Medicine, Tufts-New England Medical Center, Boston, USA*

"If you torture the data long enough they will confess to anything."

Source unknown

Statistical Analysis: Multiple Testing

- Multiple markers
- Multiple endpoints
- Multiple subgroups
- Multiple marker cutpoints
- Multiple models with multiple variables

Example: 8 subgroups defined by 3 binary factors

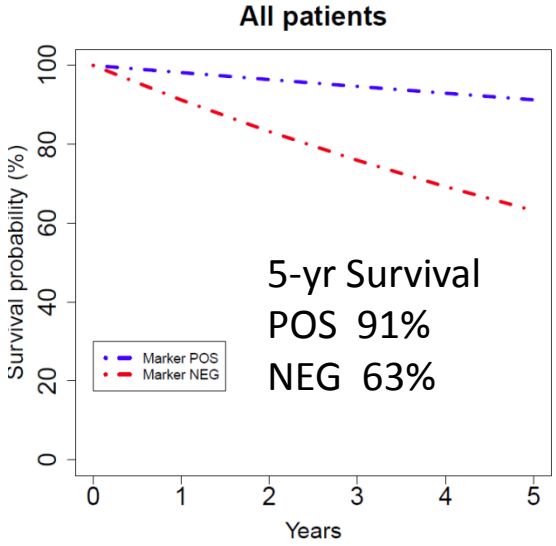
Number of independent tests ($\alpha = 0.05$ per test)	Probability observe ≥ 1 statistically significant ($p<0.05$) result
1	0.05
2	0.10
3	0.14
4	0.19
5	0.23
6	0.26
7	0.30
8	0.34
9	0.37
10	0.40

REMARK Elements: Results

- Data
  - Numbers of patients and events
  - Demographic characteristics
  - Standard prognostic variable distribution
  - Tumor marker distribution
- Analysis & presentation
  - Univariate analyses (marker vs. standard prognostic variables, marker vs. outcome)
  - Multivariable analyses (association of marker with outcome after adjustment for standard prognostic variables)
  - Measures of uncertainty for reported effect estimates

REMARK Elements: Results (cont.)

- Viewing in context of standard factors and treatments received



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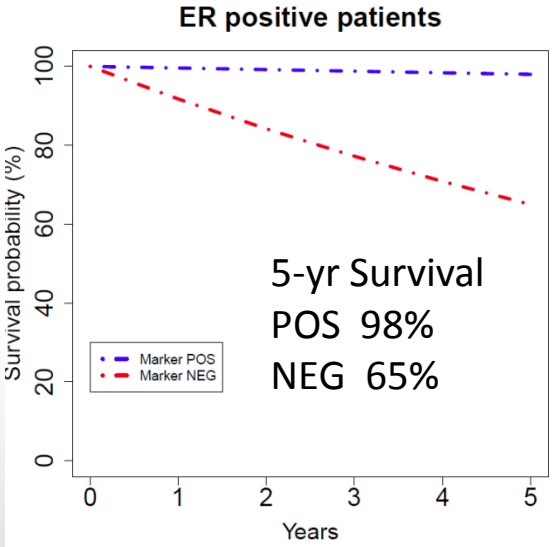

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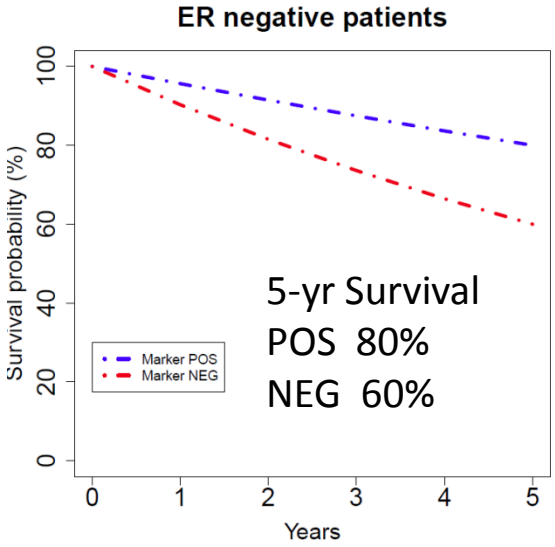


REMARK Elements: Discussion

- Interpretation in context of pre-specified hypotheses
- Relevance to other studies
- Limitations
- Future research
- Clinical value

REMARK Status & Future

- Explanation & Elaboration: Altman et al, *PLoS Medicine* 2012; 9(5):e1001216 (also *BMC Medicine* 2012; 10:51)
- Plans for "before vs. after" comparisons of reporting
- Journals stating REMARK adherence requirements: *Ann Oncol, Breast Cancer Res Treat, Clin Cancer Res, J Clin Oncol, J Natl Cancer Inst, J Pathol*

Statement of editorial intent

Annals of Oncology 2012; 23:1931-1932

"Studies of 'prognostic' markers of no real future clinical utility and single biomarker studies will not be considered. Reports of studies into prognostic markers should be prospective and have a clear view of the practical clinical applications of the results. Retrospective analysis of biomarkers can be considered, if done within the framework of data collected from a prospective trial, with appropriate statistics and with multivariate analysis that includes established predictive/prognostic markers. Reports of prognostic tumor marker studies should follow the REMARK guidelines (available from www.equator-network.org)."

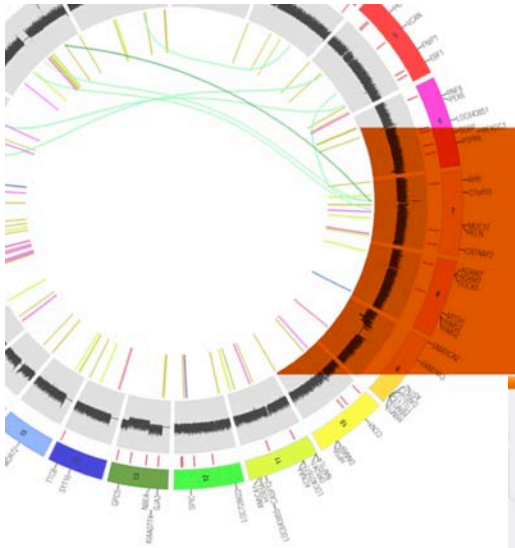
J. B. Vermorken
Editor-in-Chief

Concluding Remarks

- Poor study reporting is a significant impediment to achieving reproducible research
- Reporting will improve only with effort from all stakeholders
- Complete & transparent reporting is more fair
- Effort spent on good reporting is a smaller burden than time, effort and resources wasted on false leads

What is the NCI Center for Cancer Genomics (CCG)?

NCI Center for Cancer Genomics Programs



The Cancer Genome Atlas

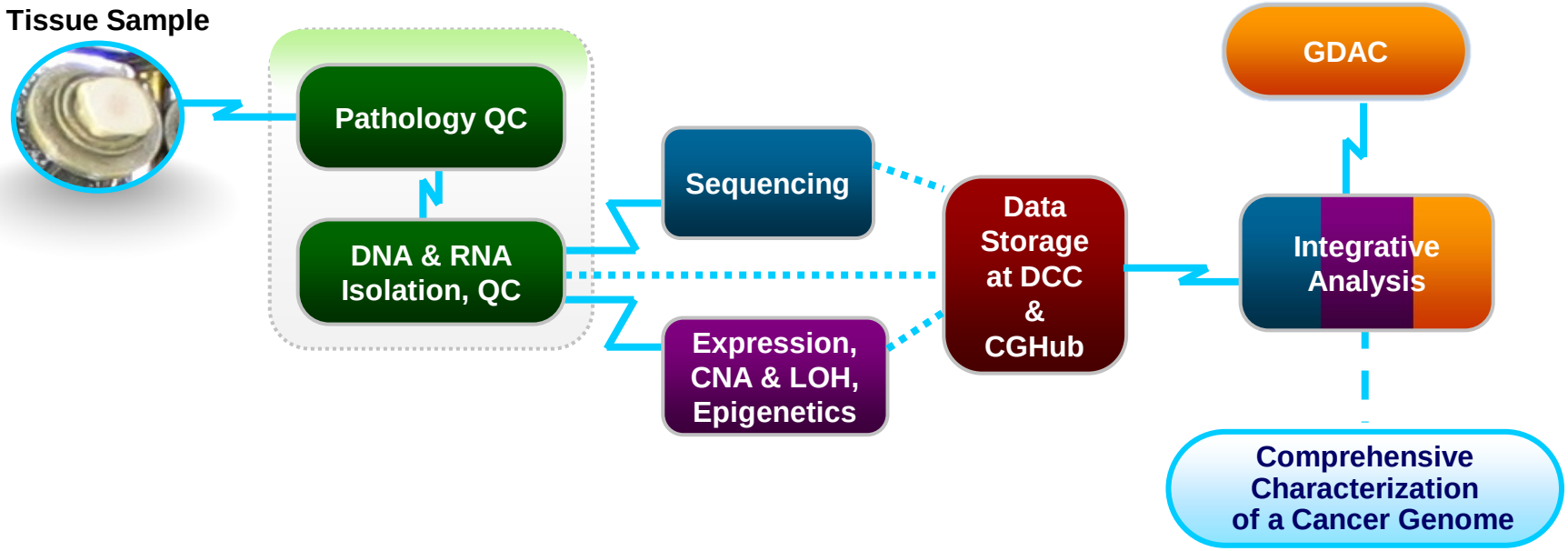
TCGA

TARGET

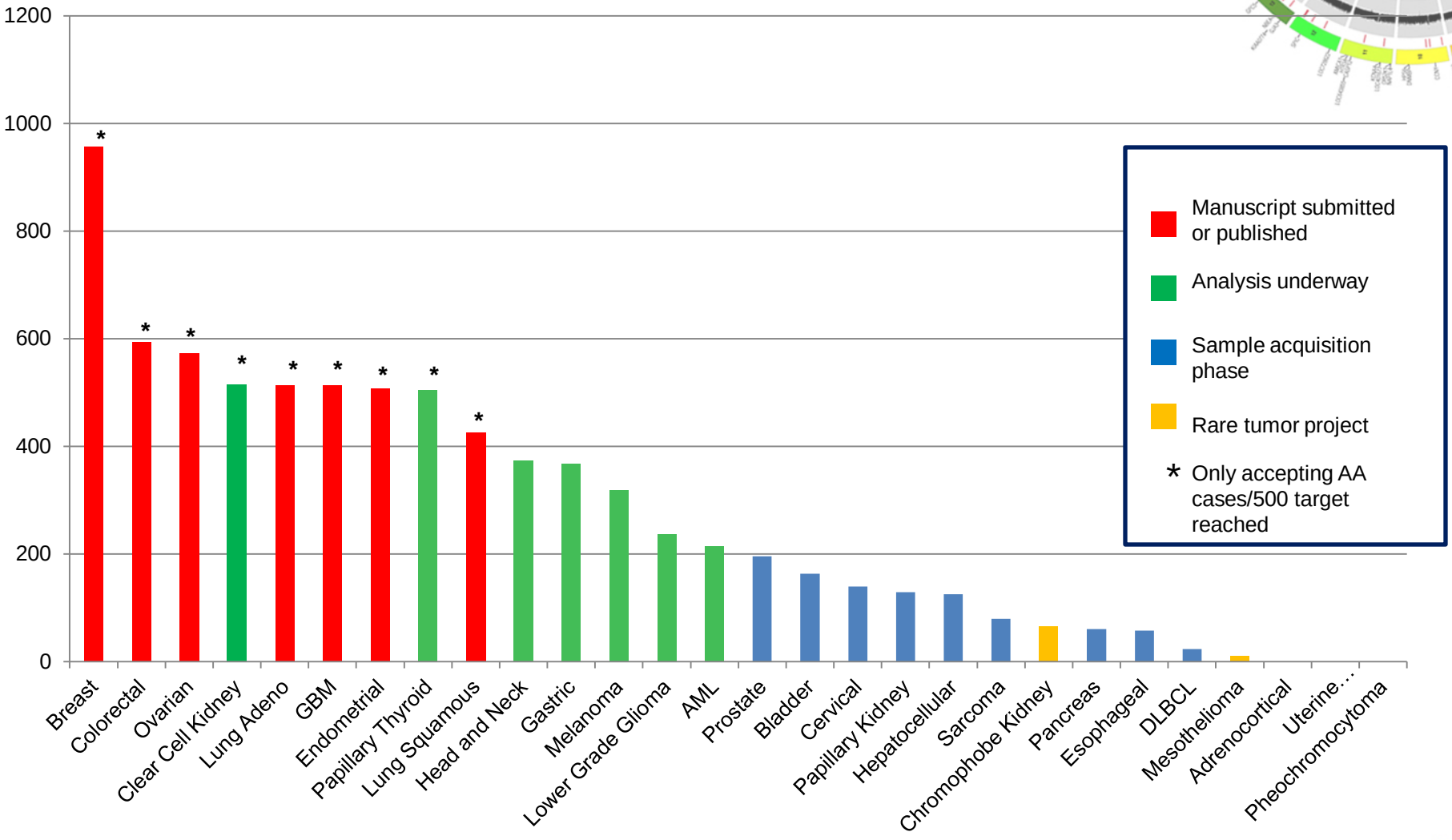
Therapeutically Applicable Research to Generate Effective Treatments

CTD²: A Bridge from Genomics to Cancer Therapeutics

TCGA: The Pipeline for Comprehensive Characterization of the Tumor Genome



TCGA Tumor Project Progress



The Cancer Genome Atlas

Whither the NCI Center for Cancer Genomics (CCG)?

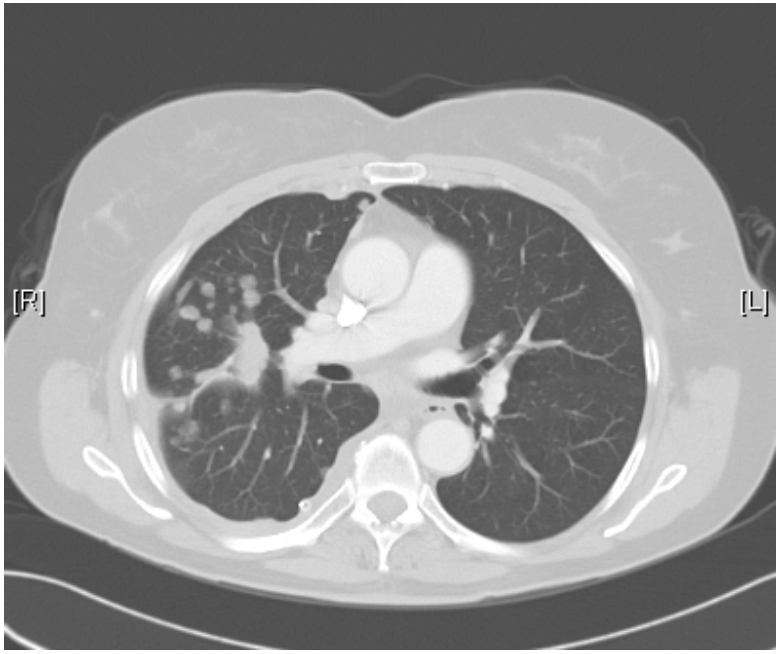
Open Questions in Cancer Genomics

- What is the full extent of driver mutations and genetic pathways in cancer?
- What is the contribution of intratumor genetic heterogeneity to progression and treatment response?
- What is the genetic basis of metastasis?

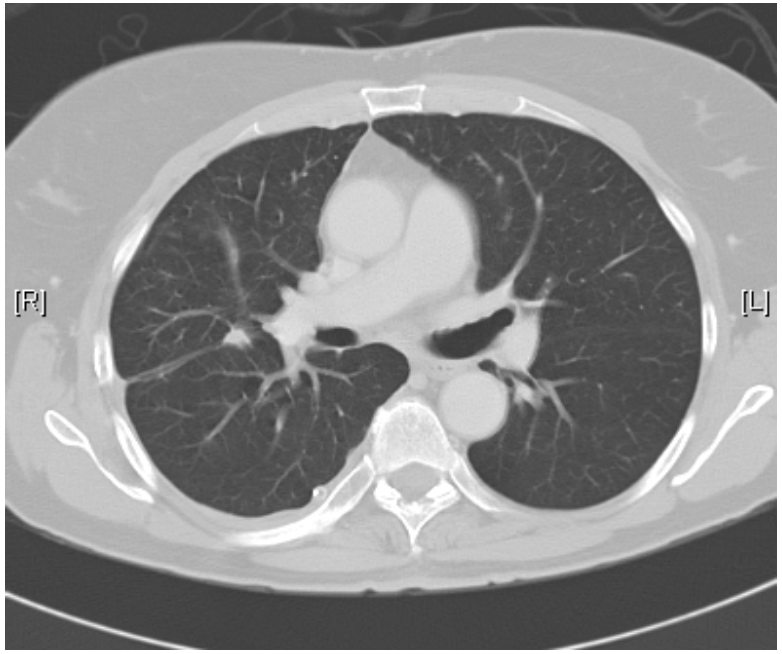
The 10K Concept

Targeted Therapy of Lung Adenocarcinoma From Cancer Genomics

Lung adenocarcinoma with *EGFR* deletion mutant in exon 19

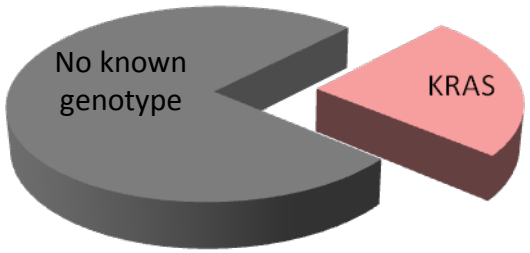


Before treatment

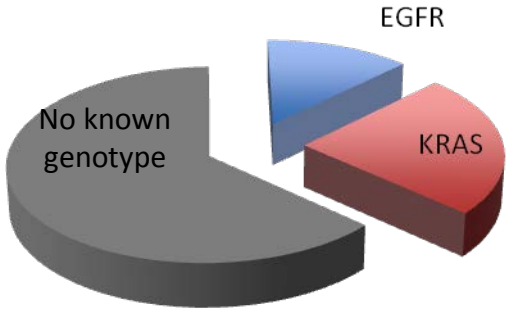


Erlotinib treatment (2 months)

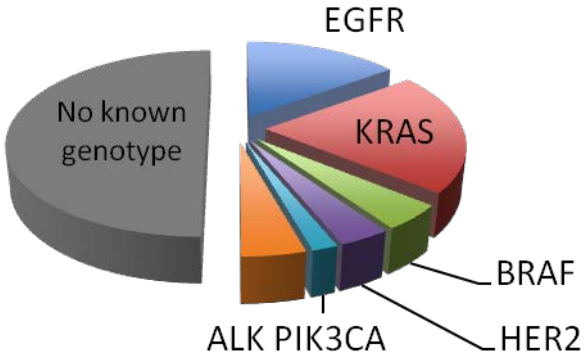
Identifying Novel Genomic Targets in Lung adenocarcinoma



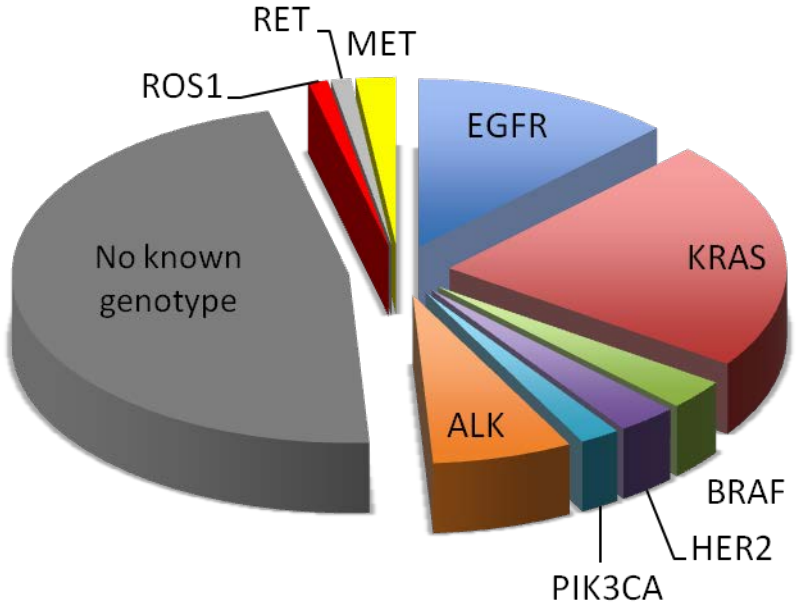
1984 - 2003



2004



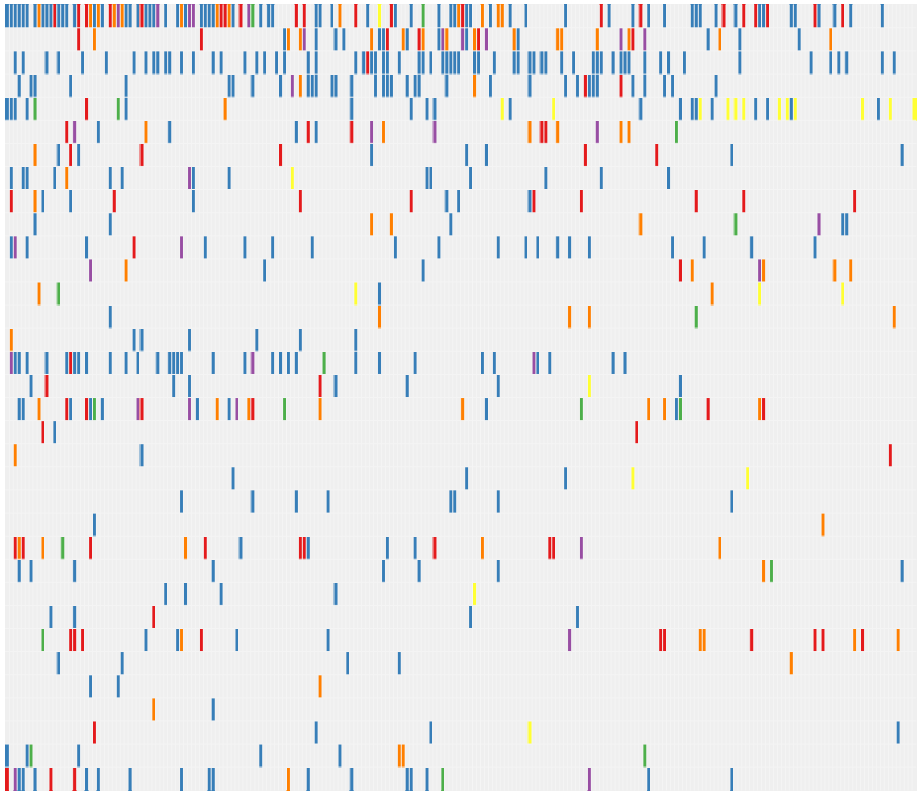
2009



2012

Matt Meyerson

Significantly mutated genes in 230 lung adenocarcinomas



Mostly known genes

Mixture of novel significant genes and false positives

Juliann Chmielecki, Mara Rosenberg, Matt Meyerson

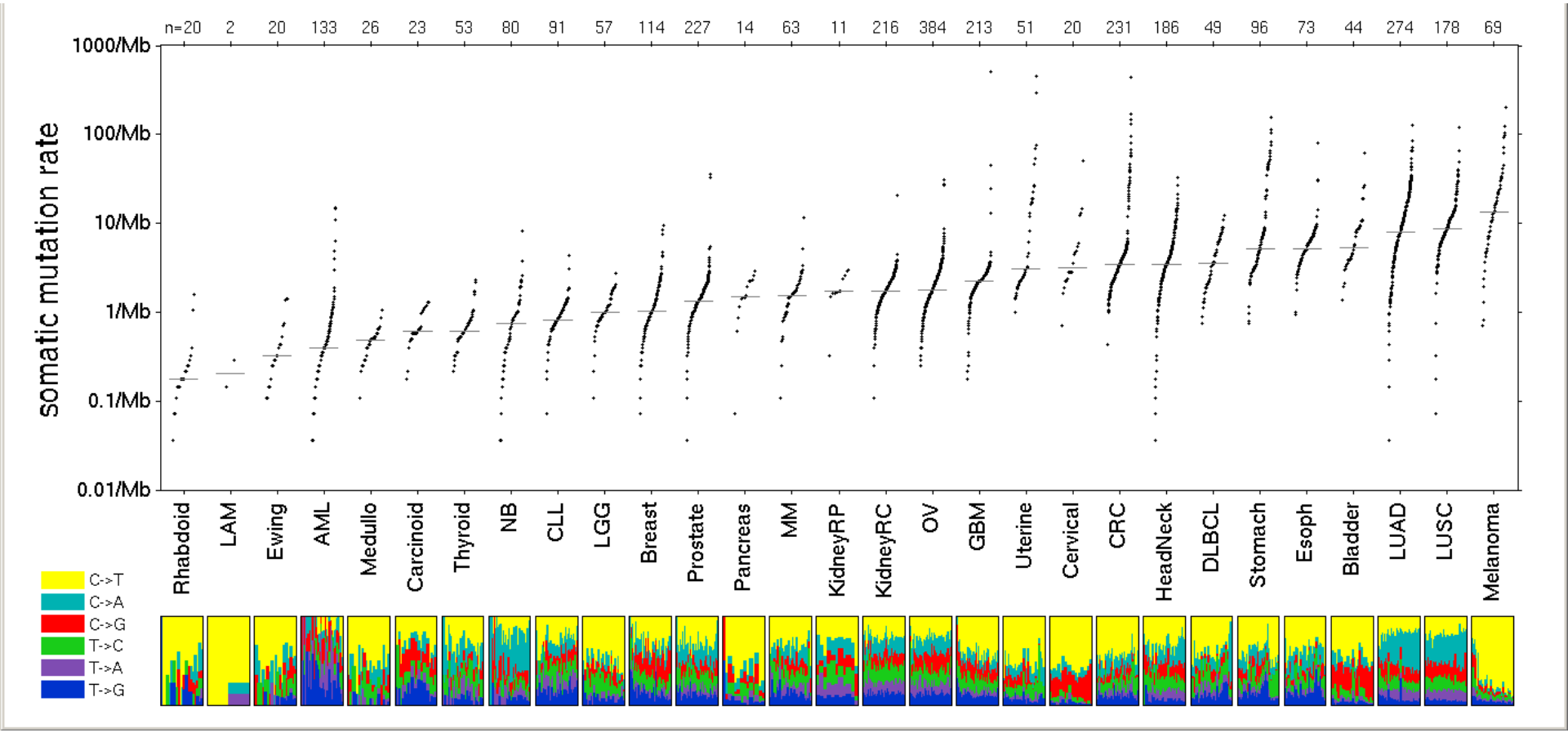
High lung cancer mutation rates pose a major problem in identifying significantly mutated genes

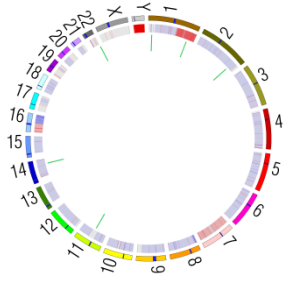
- Genes near statistical threshold may be true positives (oncogenes or tumor suppressors), or false positives
- Known recurrently mutated genes (e.g. *ERBB2*, *CTNNB1*) aren't detected as significant regardless of method used
- In the end, a much larger sample size will be required to elucidate "all" causative mutations in lung adenocarcinoma

10K Goals

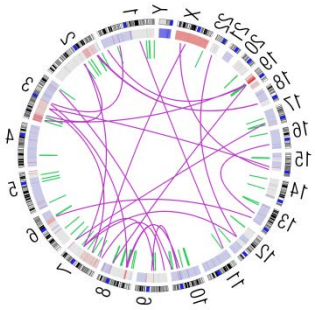
- Oncogenes and Tumor Suppressors
  Define comprehensive set of driver genes with ≥ 1% frequency in a particular cancer subtype
- Genetic Pathways
  Identify epistatic or cooperative relationships between cancer genes that are altered in ≥ 1% cases
- Interactions
  Investigate relationship of somatic alterations to germline variations & exposures (e.g. tobacco)
- Clinical Implications
  Correlate genetics to clinical outcomes (e.g. local growth vs. 1° / 2° metastasis) and treatment response

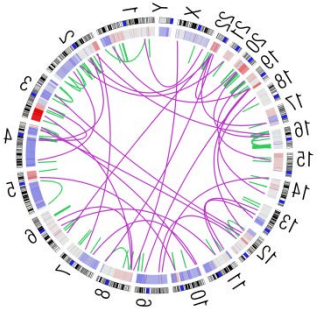
The Problem: High Background Mutation Rate in Cancer

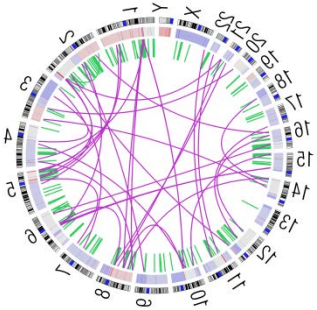




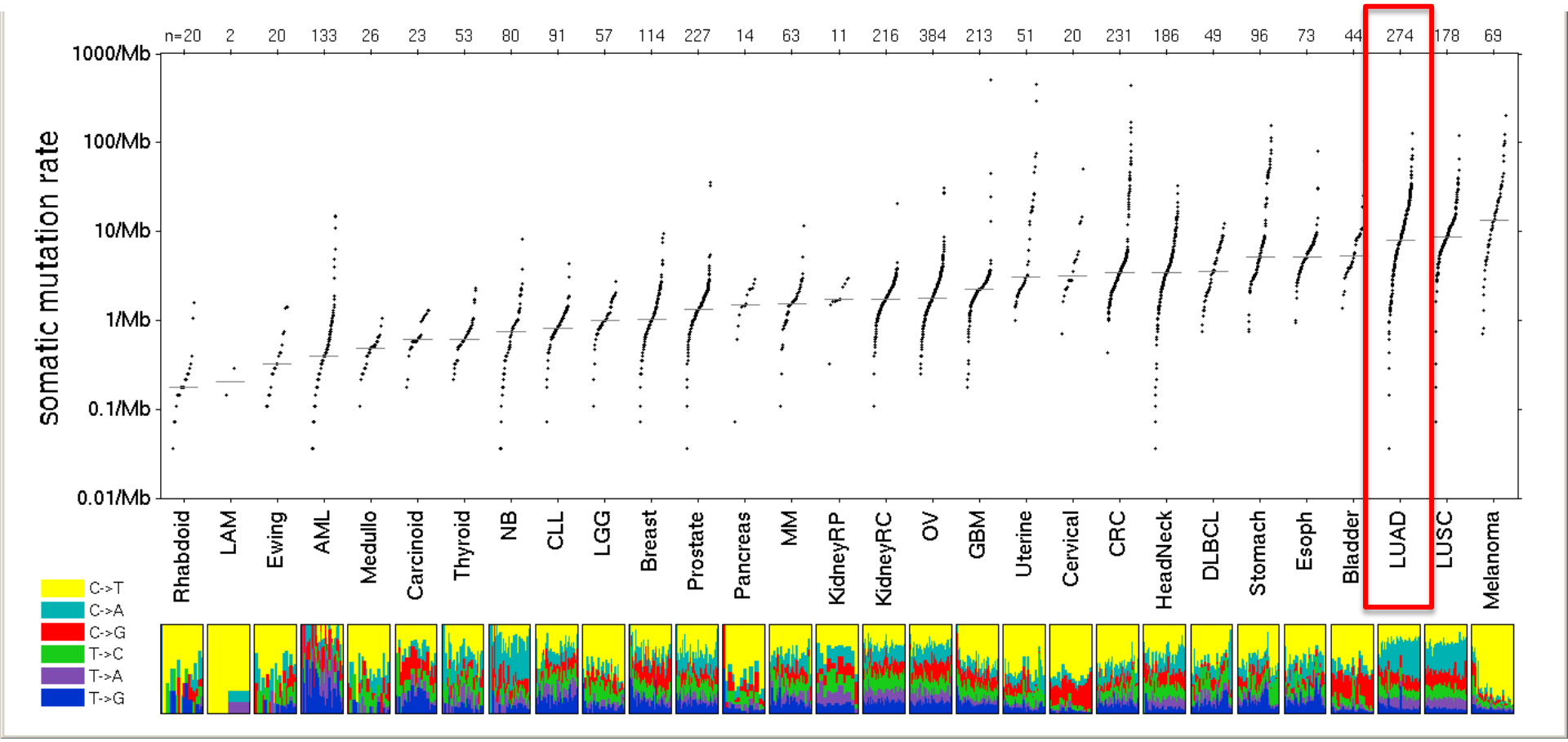
Mike Lawrence and Gaddy Getz

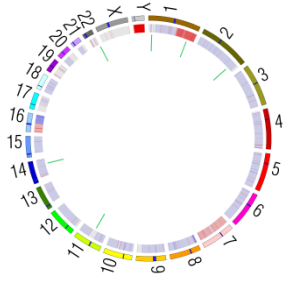




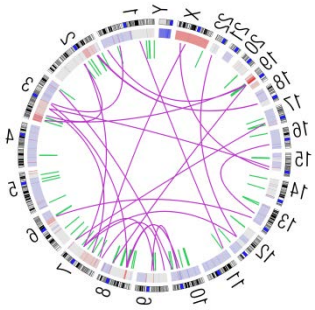


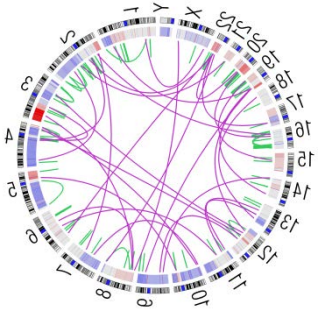
Lung Adenocarcinoma has Extensive Genetic Damage

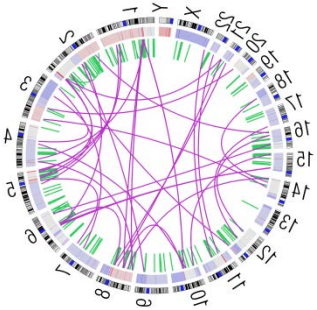




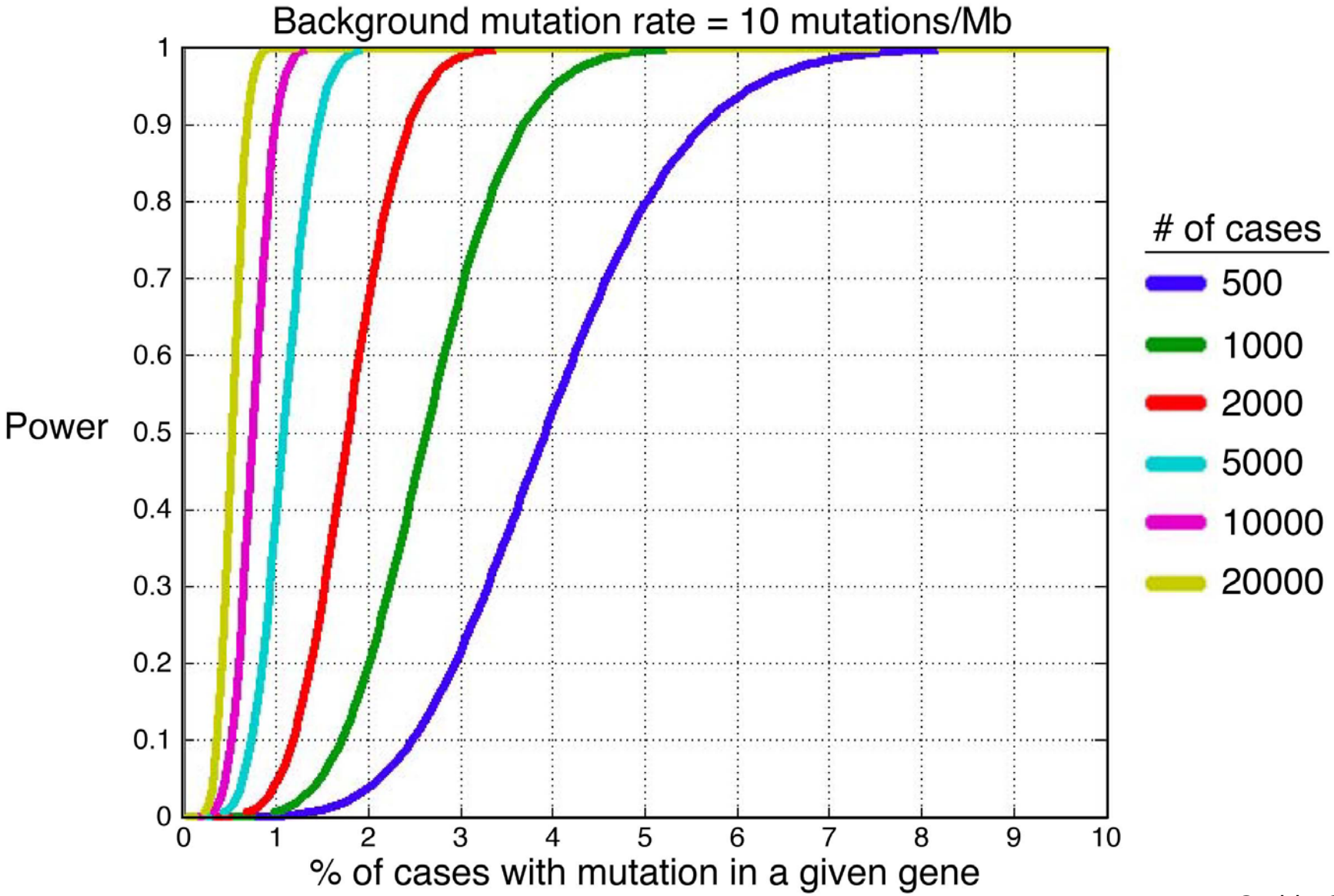
Mike Lawrence and Gaddy Getz





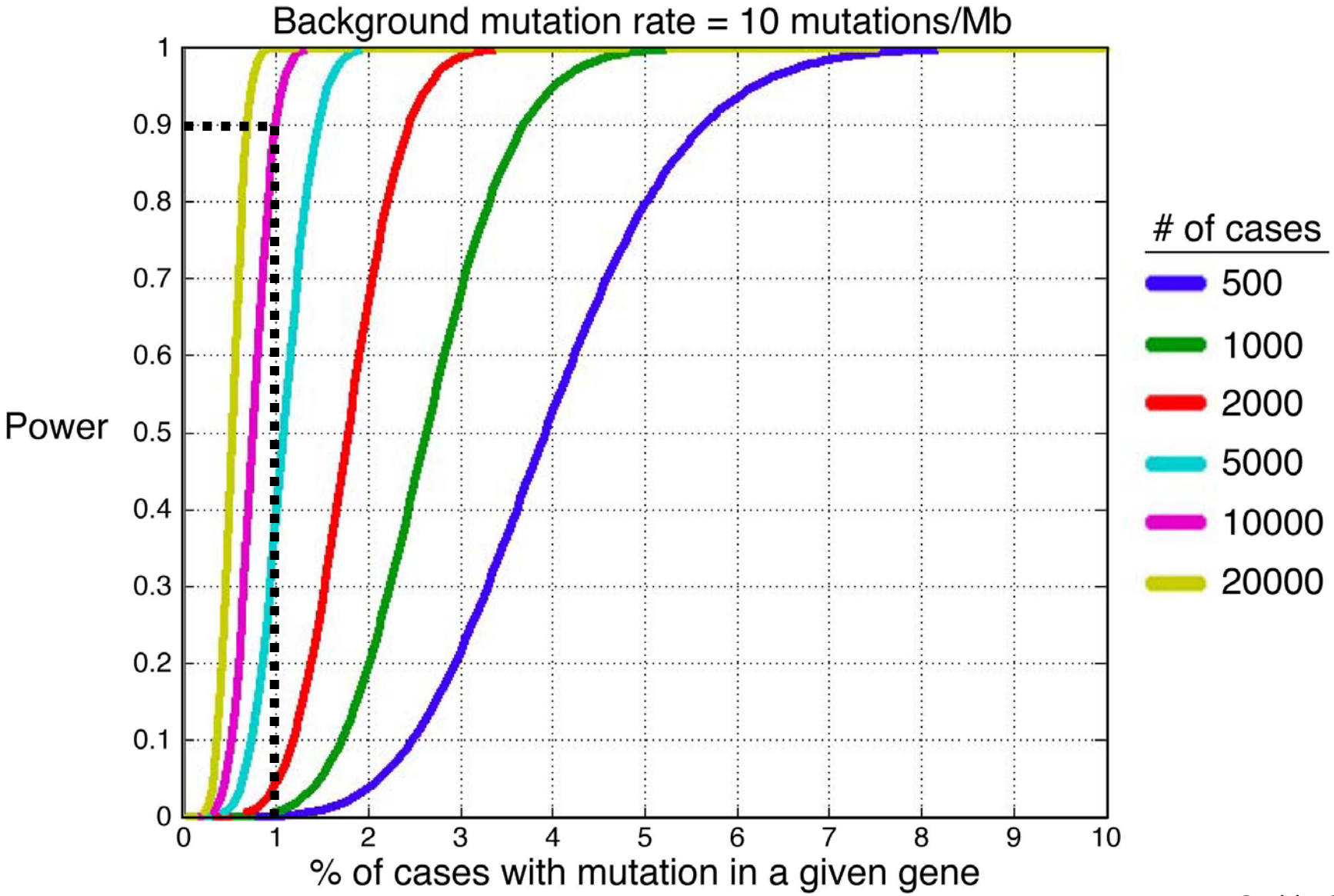


Large Numbers of Tumors Needed to Discover Less Common Oncogenes and Tumor Suppressors



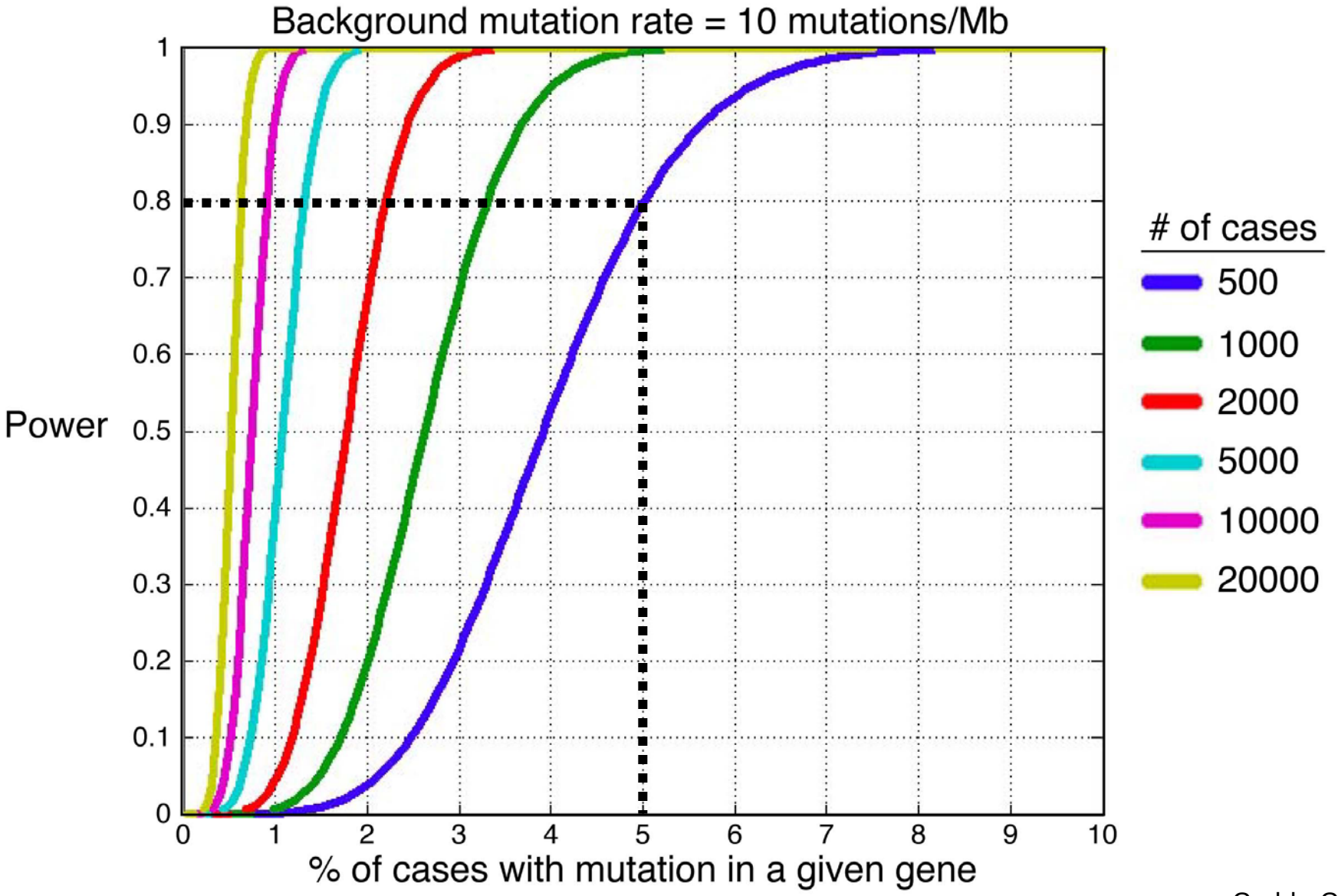
Gaddy Getz

Large Numbers of Tumors Needed to Discover Less Common Oncogenes and Tumor Suppressors



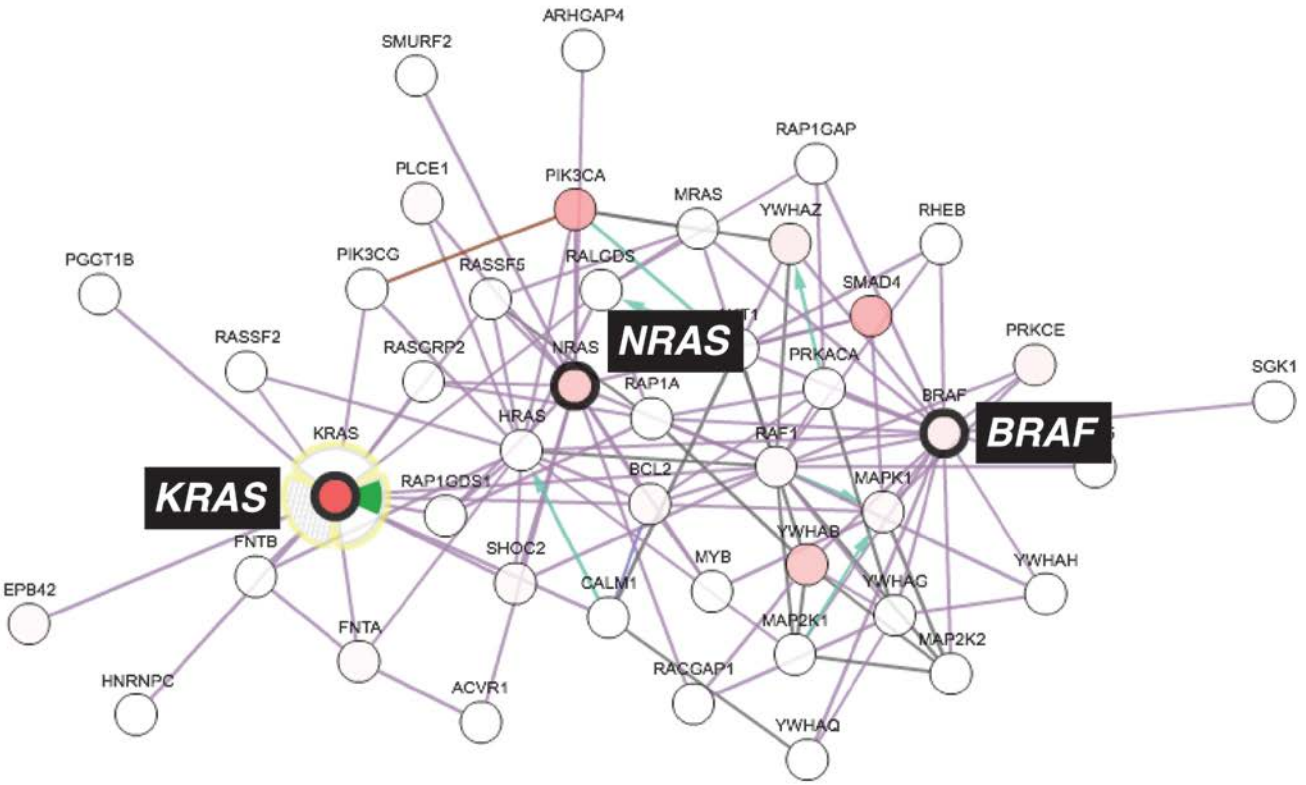
Gaddy Getz

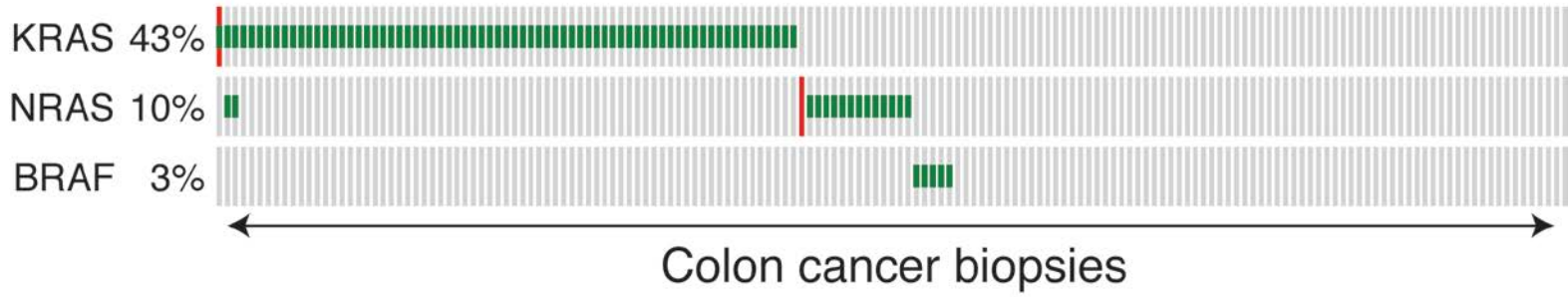
Large Numbers of Tumors Needed to Discover Less Common Oncogenes and Tumor Suppressors



Gaddy Getz

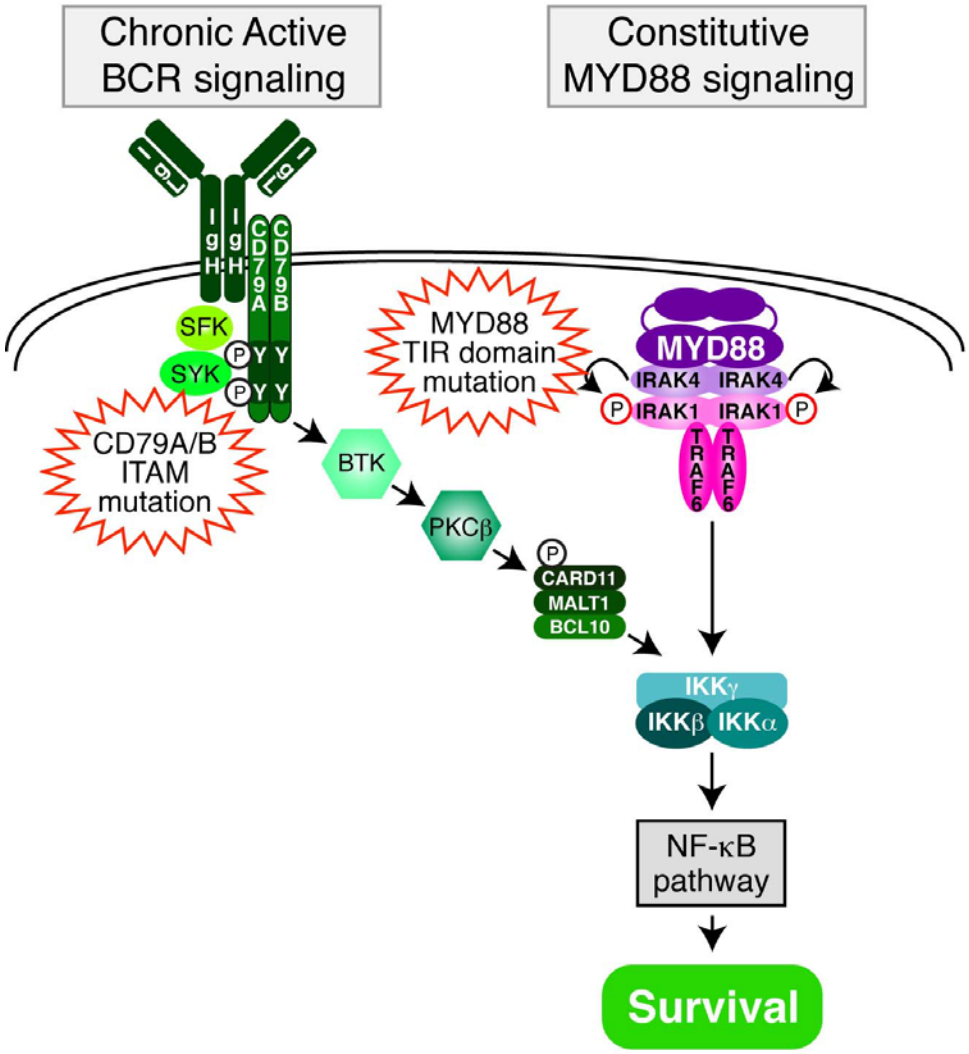
Mutual Exclusion of Genetic Aberrations Defines Genetic Pathways in Cancer

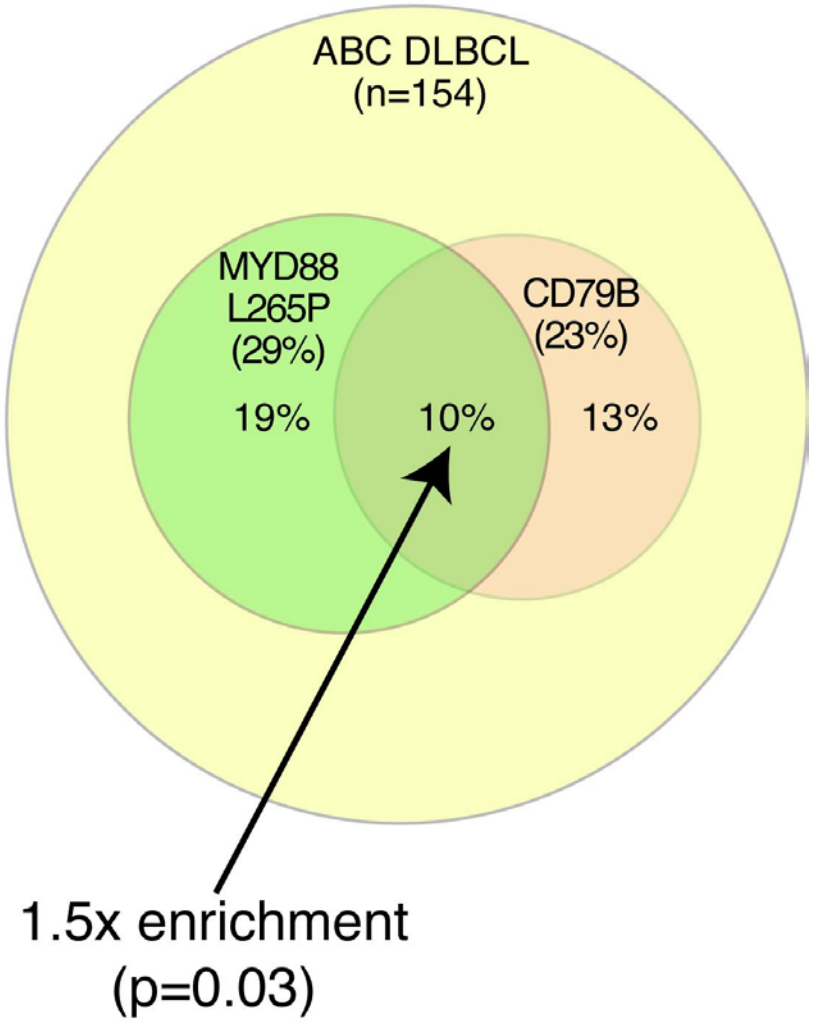




TCGA, *Nature* 2012 *487:330*

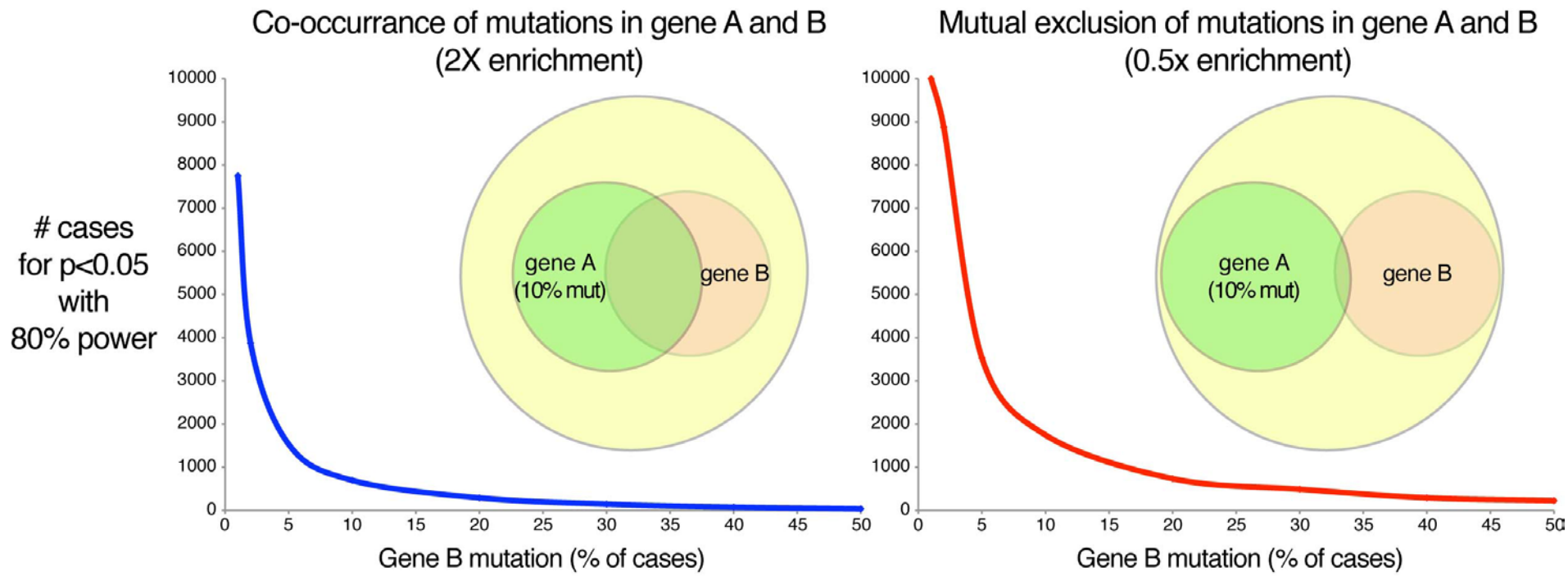
Co-occurrence of Genetic Aberrations Defines Genetic Pathways in Cancer





Ngo et al. Nature 2006 441:106

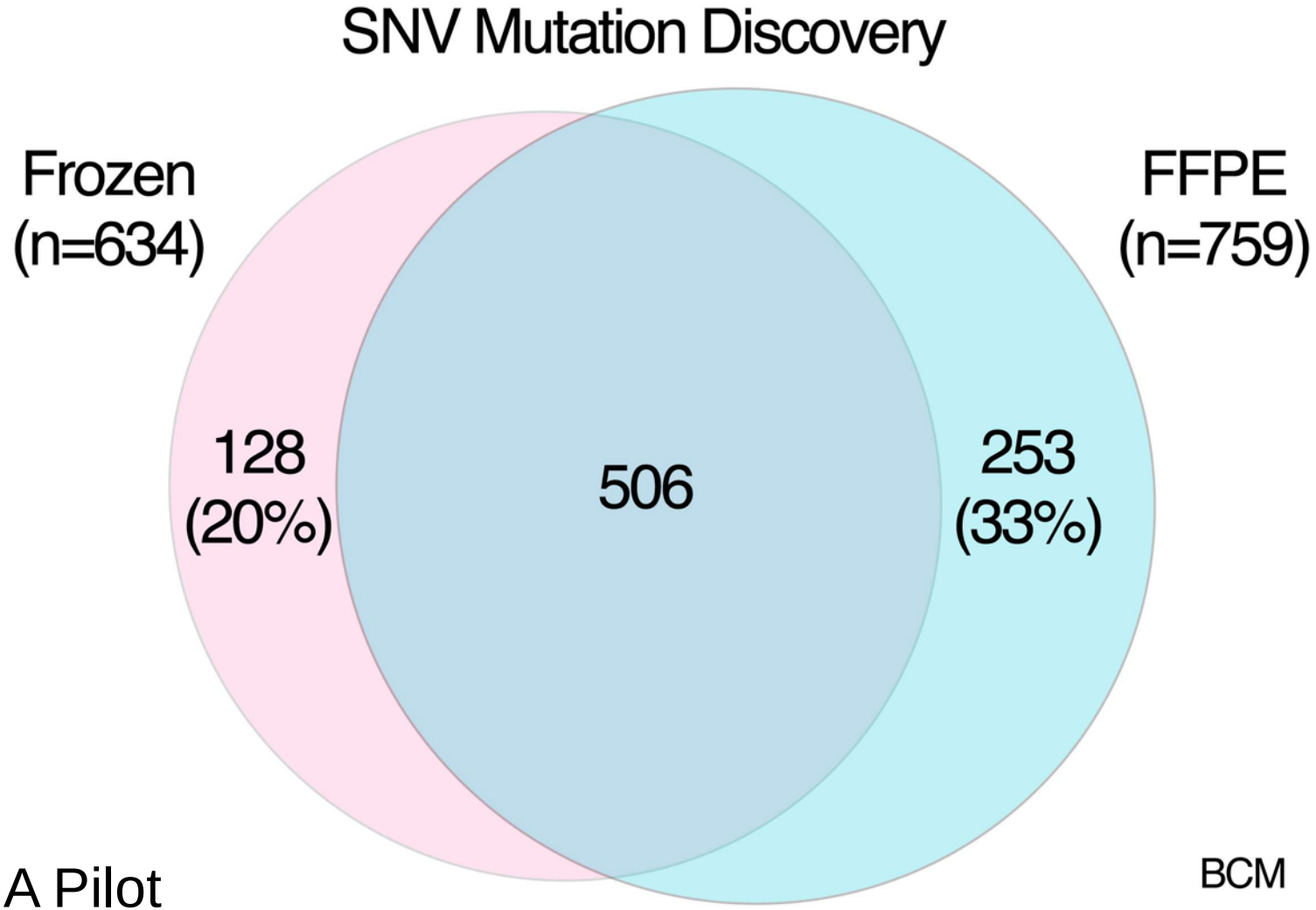
Large Case Numbers Needed to Assign Less Common Cancer Genes to Genetic Pathways



George Wright

How to find 10K tumor biopsies?

Genomic Analysis of FFPE Biopsies: A Game Changer



TCGA Pilot

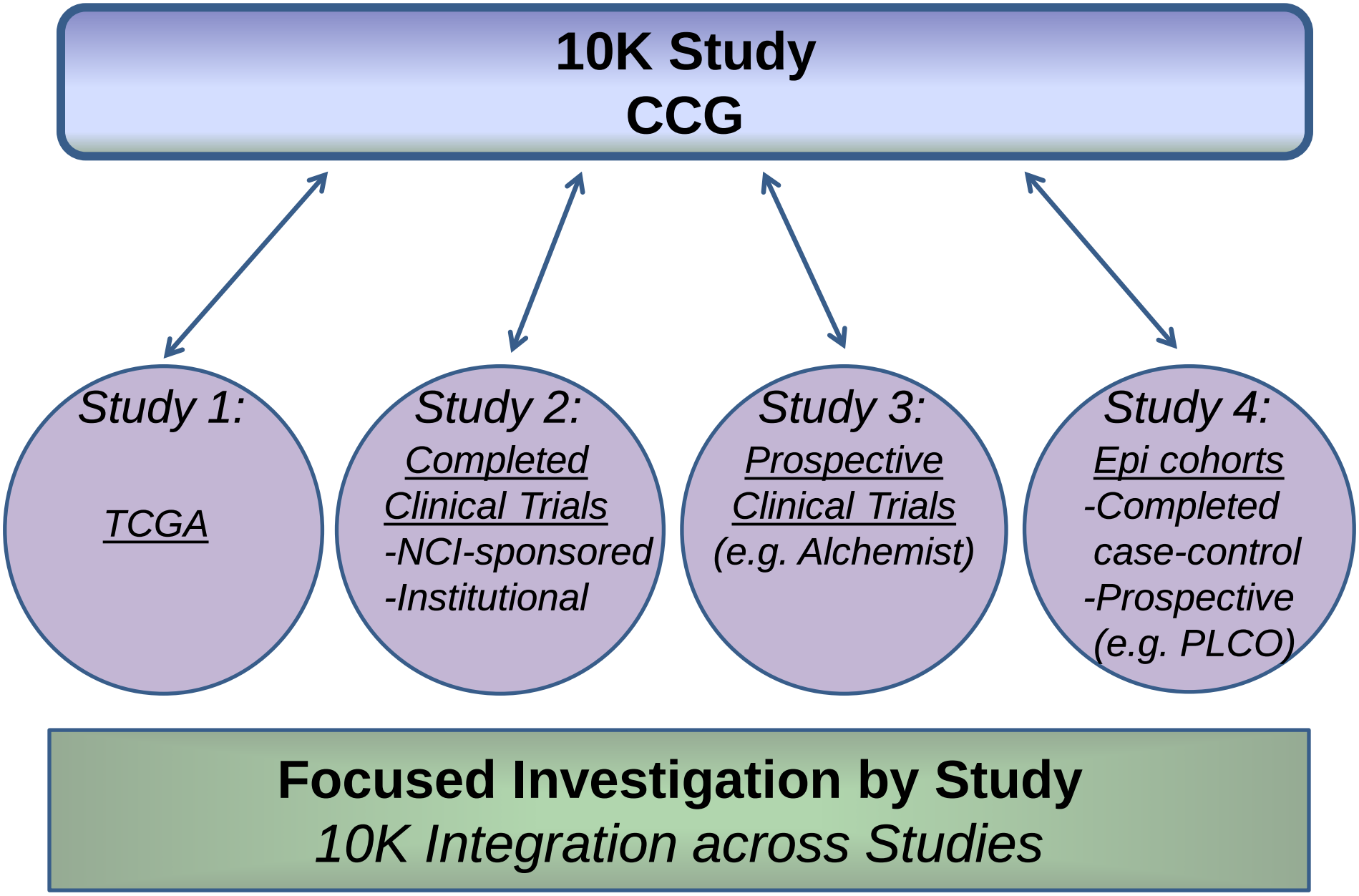
BCM

10K Tumor Biopsies

Sample criteria

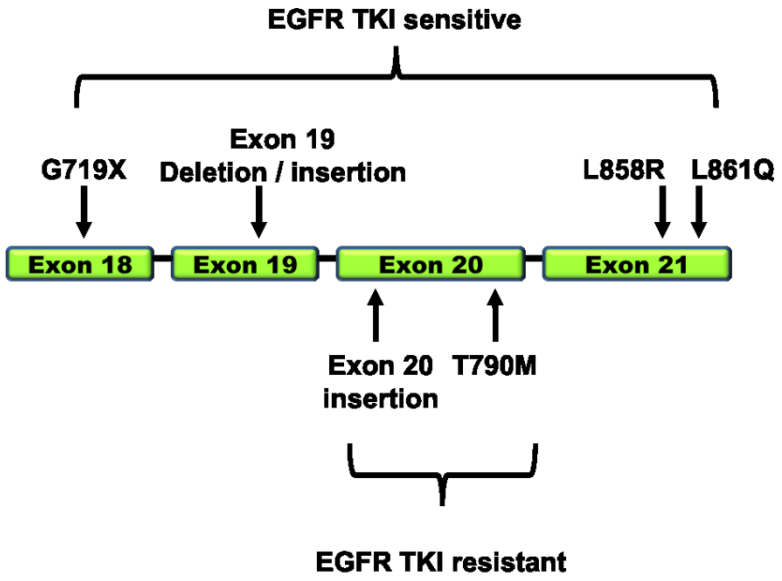
- FFPE or frozen biopsy samples large enough for whole exome and RNA-seq analysis (i.e not FNAs)
- Clinical annotation and treatment response necessary
- Matched normal tissue in most (maybe not all) cases
- Consent for genomic analysis
- Likely focus on common cancers (lung, colon, breast, prostate etc.)

Building a 10K Study

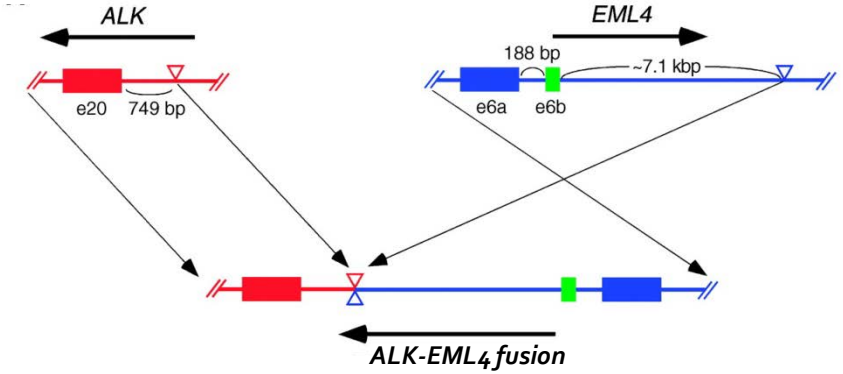


ALChEMIST
Drug Biomarkers in Lung Adenocarcinoma

TKI-sensitizing EGFR mutations:
10% in Western population
Up to 50% in Asian population
Enriched in:
•females
•non-smokers
•younger patients
Multiple tests in clinical use
No FDA-approved clinical assay

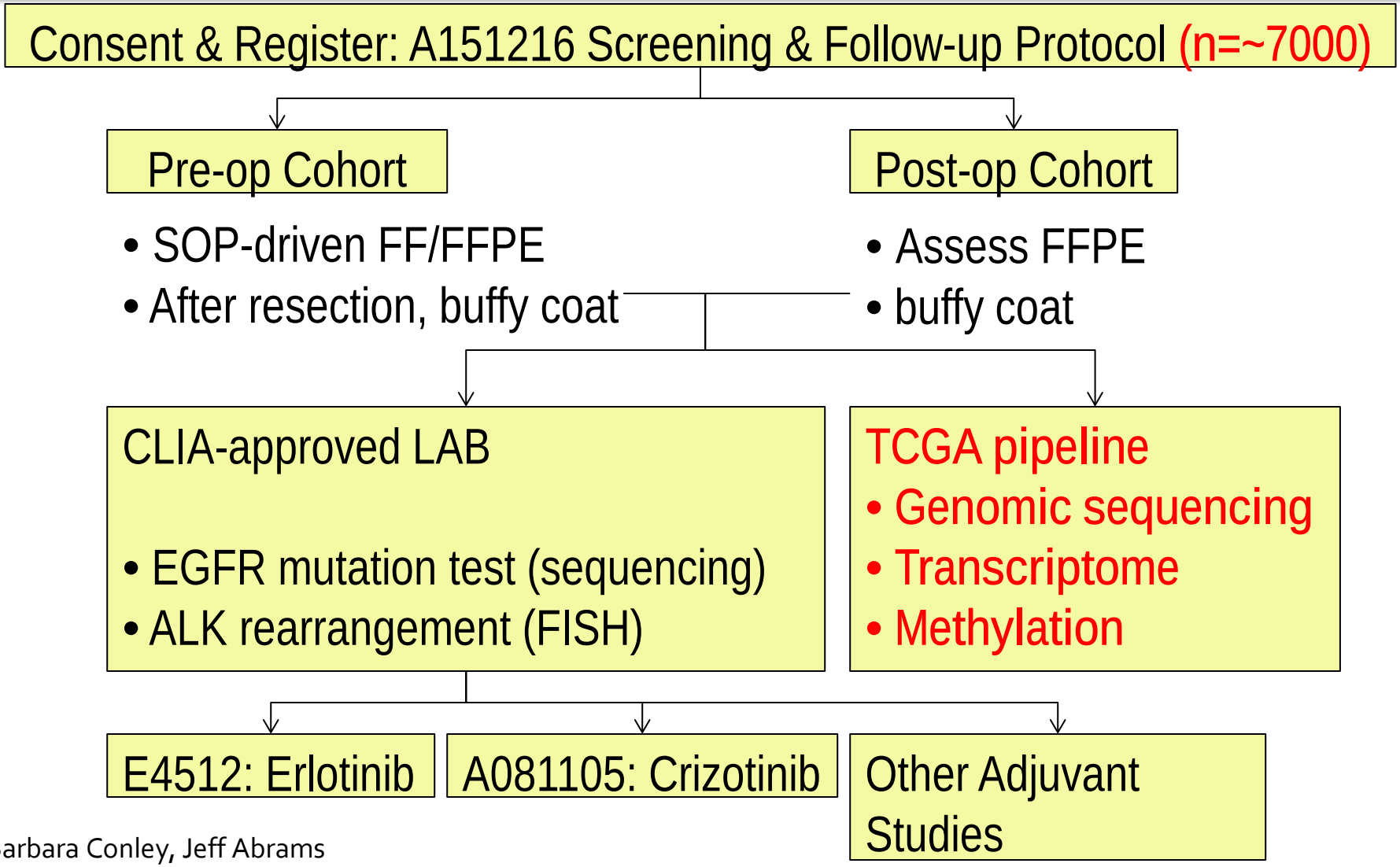


ALK Rearrangement
5-7% in Western population
FDA approved companion diagnostic:
Vysis Break Apart FISH probe



Barbara Conley, Jeff Abrams

ALChEMIST Tissue Flow



Barbara Conley, Jeff Abrams

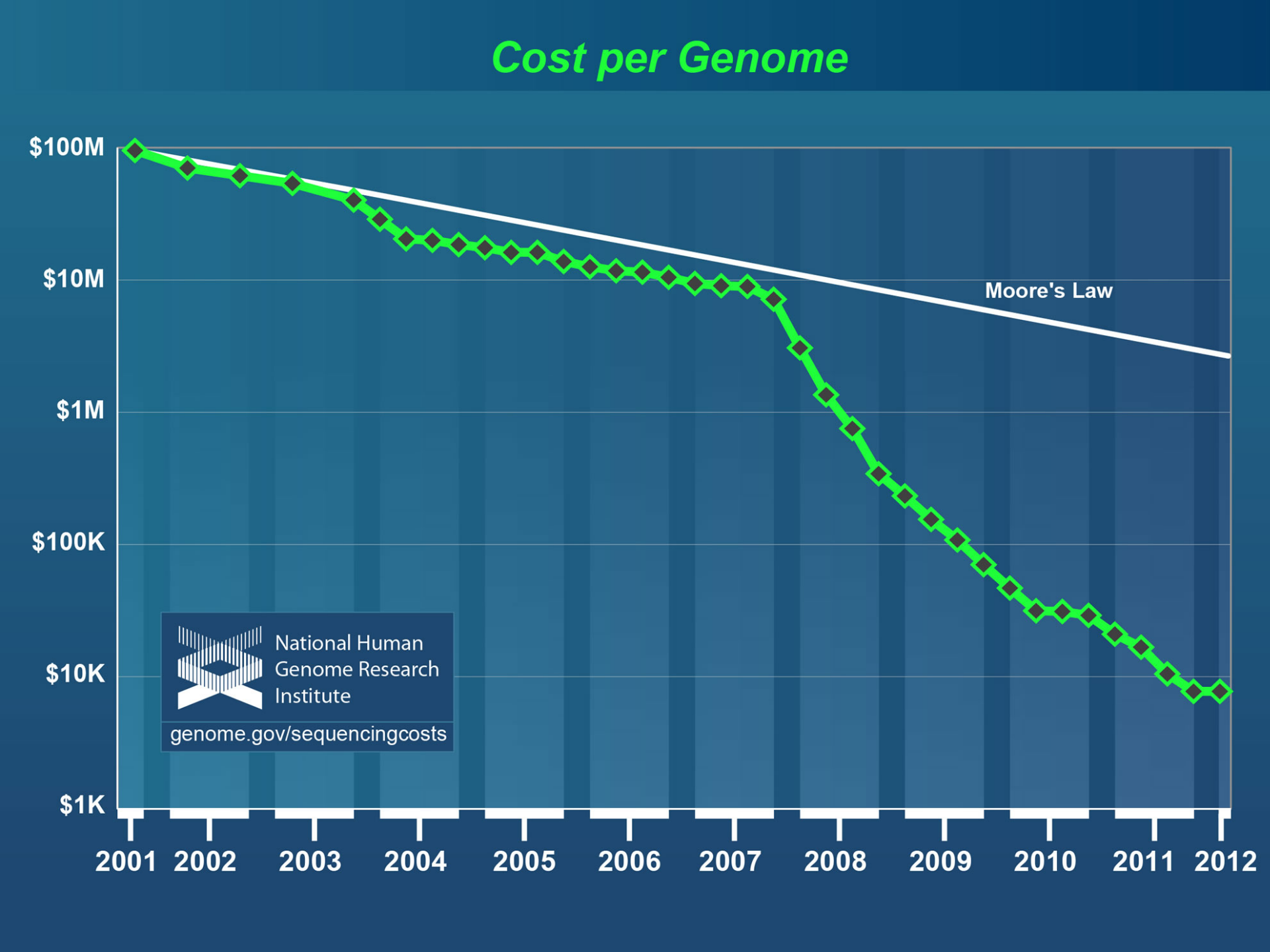
ALChEMIST
Beyond Treatment Endpoints

- Molecular profiling studies on large cohort (~ 7000 pts)
- Ability to re-profile at relapse in about 50% of cases ("natural genomic history")
- Opportunity to collect epidemiologic info spanning tobacco, diet, alcohol and work exposures

Barbara Conley, Jeff Abrams

Questions?

Cost per Genome



IBM Computational Biology Center, IBM Research
gustavo@us.ibm.com

SEEKING THE WISDOM OF THE CROWDS THROUGH CHALLENGE-BASED COMPETITIONS IN BIOMEDICAL RESEARCH

Outline

- Crowdsourcing and challenges
- Benefits of crowd-sourcing through collaborative-competitions
- The Sage-DREAM Breast Cancer Prognosis Challenge
- The NCI-DREAM Drug Sensitivity Prediction Challenge

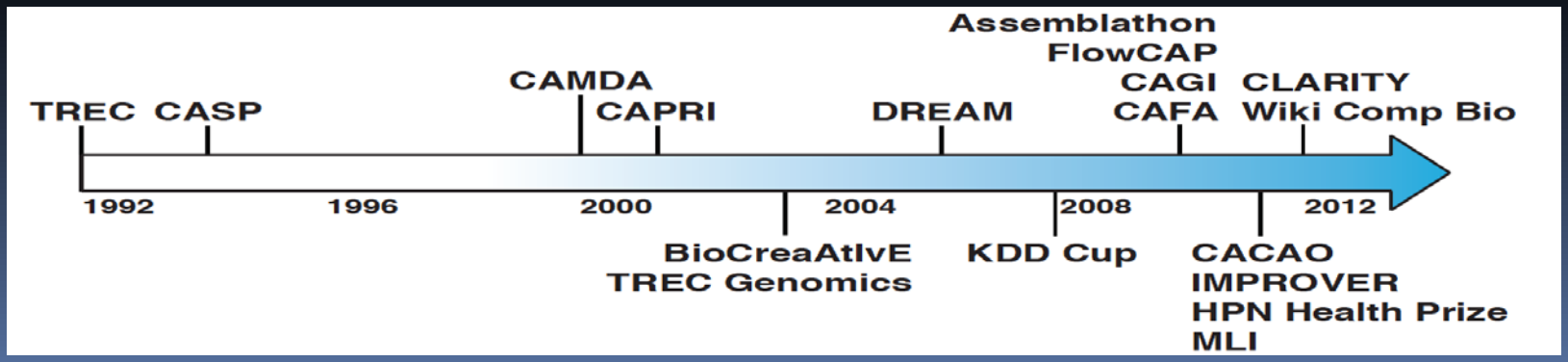
Crowdsourcing and Challenges

Crowdsourcing: The practice of soliciting content, ideas, solutions from a large group of people, especially the online community.

E.g., Protein folding solutions have been generated through a crowdsourcing game: FoldIt.

Challenge: A crowdsourcing based approach to solve a problem

E.g., Dialogue for Reverse Engineering Assessment and Methods (DREAM) challenges in cellular network inference



Benefits of crowdsourcing

- Performance Evaluation
  - Assess whether relevant problems can be addressed computationally: E.g., can drug sensitivity be predicted?
  - Discover the best methods via blind, unbiased, and rigorous method assessment

- Sampling the method space
  - Understand the diversity of methodologies presently being used to solve a problem

Benefits of crowdsourcing

- Community Building
  - Make high quality, well-annotated data accessible.
  - Foster community collaborations on fundamental research questions.
  - Determine robust solutions through community consensus: “The Wisdom of the Crowds.”

The Sage Bionetworks/DREAM Breast Cancer Prognosis Challenge

Goals: Use crowdsourcing to assess whether breast cancer survival can be accurately predicted

Training data set: Genomic and clinical data from 2000 women diagnosed with breast cancer (Metabric data set).

Data access and analyses: Sage Bionetworks' Synapse

Compute resources: Standardized virtual machines for each participant donated by Google

Model scoring: models submitted to Synapse for scoring on a real-time leaderboard

Participation: 1,700 models tested by 48 participating teams, 35 countries

Unique Attributes

- Open source and code-sharing:
  - Standardized computational infrastructure helps participants use code submitted by others in their own models
  - All models' behavior and performance must be reproducible
- New dataset for final validation to determine winning model:
  - Derived from approx. 200 breast cancer samples
  - Data generation funded by Avon
  - Winning model: the most accurate in predicting survival for independent datasets, following training on the Metabric dataset
- Challenge assisted peer-review
  - Overall winner team can submit a pre-accepted article about their winning model to Science Translational Medicine

7

NCI-DREAM Summit

- DRUG Challenges and timelines
  - On April 23, 2012 about 20 researchers active on systems pharmacology of cancer gathered at the NCI
  - After a day of discussion and breakout sessions, several possible challenges were suggested
  - In subsequent discussions, based on available blind data, two candidate challenges were selected for refinement.
    - Predicting drug sensitivity in a large collection of BC cell lines
    - Predicting drug synergy in human B cells
  - Challenge data was released in early June 2012, submissions were received in early October, and results were announce in late October

The NCI-DREAM Drug Sensitivity Prediction Challenge

- Goals: Use crowdsourcing to identify computational approaches that best predict therapeutic responses
- Challenges:
  - Sub-challenge 1. Predict sensitivity of 31 compounds in 18 cell lines, given their sensitivity profiles in 35 cell lines and genomic information for all lines
  - Sub-challenge 2. Predict responses to 91 pairwise combinations of 14 compounds in Ly3 human B-cell lymphoma cells
- Data provenance and accessibility:
  - Generated in ongoing ICBP studies but yet unpublished. Data was curated for the challenge and made accessible via the DREAM website upon registration
- Participants:
  - 47 teams and 31 teams participated in sub-challenge 1 and 2, respectively, from more than 30 countries

Best Performers

Sub-Challenge 1:

TeamFIN: Helsinki Institute for Information Technology, Aalto University, Helsinki Finland

- Approach
  - Combining all data with additional prior knowledge
  - Gene set views
  - Discretized views, i.e., Binary conversion
  - Non-linear regression, multitask learning, Bayesian inference

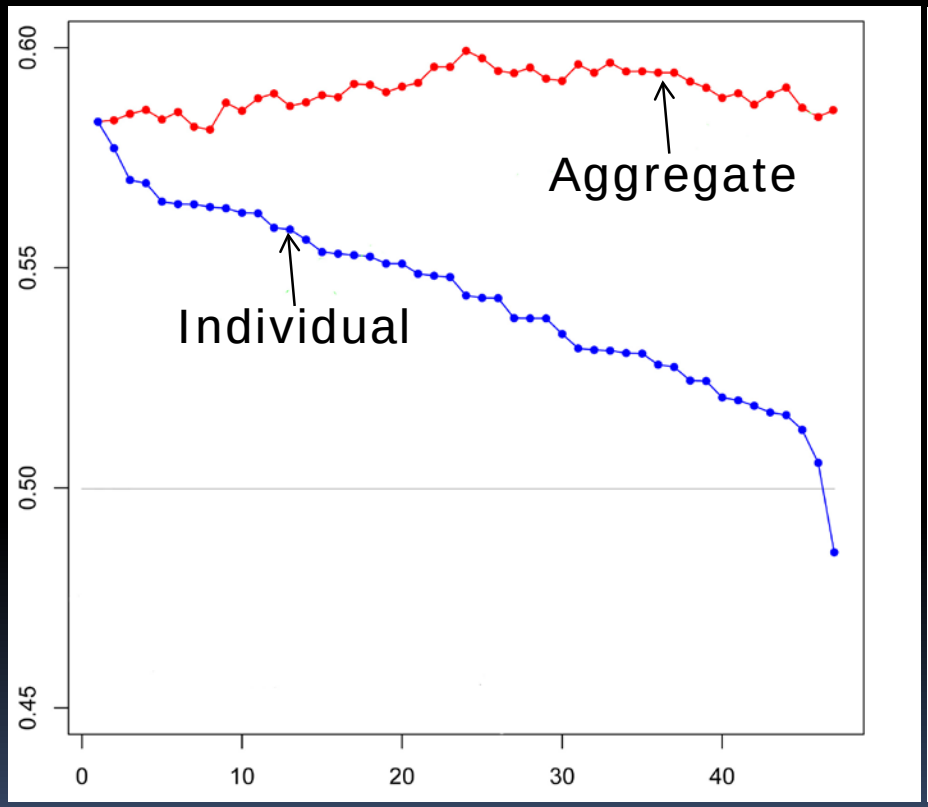
Sub-Challenge 2:

UTSW-MC: University of Texas Southwestern Medical Center- Dallas, TX, Jichen Yang and colleagues

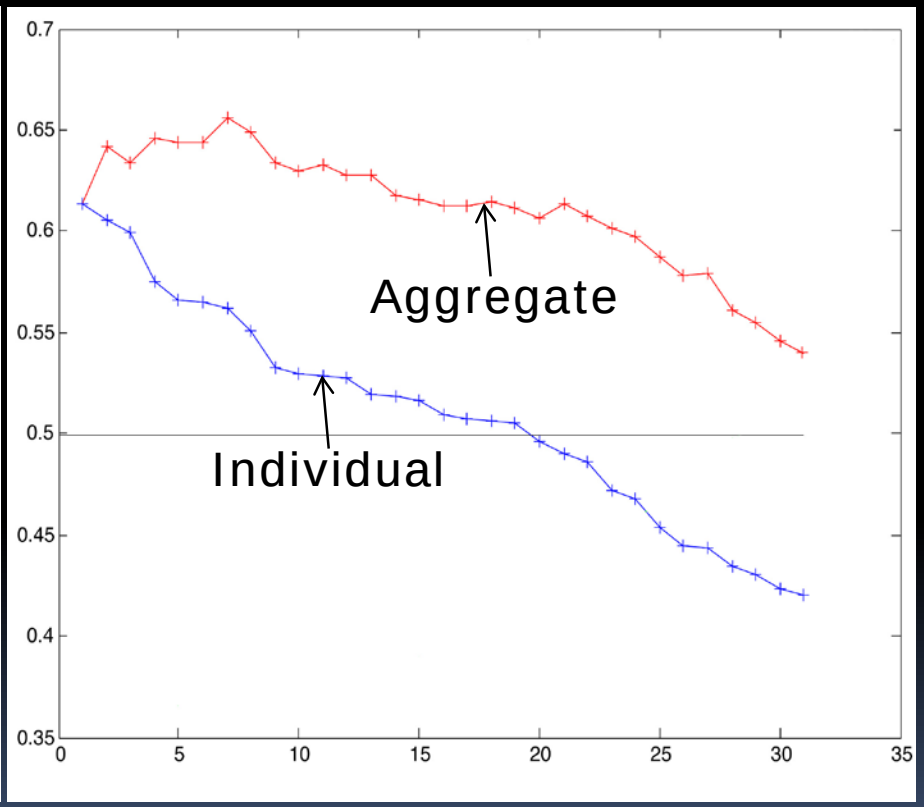
- Approach
  - Combining all data with additional data sets
  - Matrix analysis of similarity between treatment “a” and “b”
  - Used only “growth” genes
  - Non-supervised approach
  - 8 pathways, 835 genes

Aggregation of results: The wisdom of the crowds

Sub-challenge 1



Sub-challenge 2



Next step for NCI-DREAM Challenge

- Further validation (Internal NCI- DREAM Team)
  - Sub-challenge 1: Additional breast cancer cell Lines from Joe Gray's lab
  - Sub-challenge 2: Test model on another lymphoma cell line
- Support winners to continue
  - Refining and enhancing their models, "hardening" and documenting software, making tools available to community
- Challenge assisted peer-review
  - Winners are writing an article about their winning model to Nat. Biotech, which was pre-approved to go to review

Lessons Learned

- Challenges:
  - Many approaches can be tested quickly and cheaply by clearly framing the problem and providing test and training data in well-defined format
- Community:
  - Hundreds to thousands of computationally sophisticated groups around the world will try to solve well-posed questions – even though some of them may miss the background to pose the questions themselves
  - Comparison of multiple approaches by crowdsourcing will accelerate learning in systems biomedicine and outcome optimization
- Models:
  - The wisdom of the crowd almost invariably outperformed that of individual teams
  - Not all computational approaches work equally well and we are still in early stages of identifying best approaches
  - Better performing approaches are those trained on other publically available data

Acknowledgements

- Sage Bionetworks
  - Stephen Friend
  - Adam Margolin
  - Erich Huang
  - Mike Kellen
  - Thea Norman
- Columbia University
  - Andrea Califano
  - Mukesh Bansal
  - Chuck Karan
- OHSU
  - Joe Gray
  - Laura Heiser
- NCI
  - Dinah Singer
  - Dan Gallahan
- DREAM
  - Gustavo Stolovitzky (IBM)
  - Erhan Bilal (IBM)
  - Jim Costello, BU
  - Julio Saez Rodriguez, EBI
  - Michael Menden, EBI
  - Thomas Cokelaer, EBI
- All DREAMers
  - From more than 40 different countries and 100 Institutions

Conclusions and Discussion

- What have we learned about data and models?
  - Challenges provide strong rationale for making well-curated data sets, computational platforms, and evaluation frameworks publically available
  - Wisdom of the crowd is a powerful mechanism to select tools of general value to the research community
  - Challenges help focus the attention of hundreds of researchers on relevant problems in need of analytical/computational solution

- Future challenges
  - To predict whether an *in vitro* study will or will not be validated in a pre-clinical context?
  - To predict *in vivo* compound toxicity? Efficacy? Outcome of clinical trials?
  - To predict genetic, transcriptional or metabolic interactions

National Cancer Institute

DCTD
Overview of
Current and Future RFAs

James H. Doroshow, M.D.

BSA Meeting

March 4th , 2013

National Cancer Institute

DCTD RFAs

TITLE	RFA	MECH ANISM	FUNDING	APPROVAL DATE	EXPIRES
Support for Human Specimen Banking in NCI-supported clinical trials-Cooperative Group Banks	CA-09-504	U24	$43.75 M	03/02/2009	2014
Cooperative Human Tissue Network Collaborative Human Tissue Network	CA-08-503 CA-13-007	U01 / UM1	$29 M $29 M	006/28/2007? 11/05/2012	2013 2019
Network for Translational Research: Optical Imaging in Multimodal Platforms	CA-08-002	U54	$20.5 M	06/28/2007	2013
Advanced In Vivo Imaging to Understand Cancer Systems	CA-11-005	R01	$24.3 M	11/01/2010	2015
Early Trials of New Anti-Cancer Agents with Phase 1 Emphasis/ NCI Experimental Therapeutics- Clinical Trials Network with Phase 1 Emphasis (ET-CTN)	CA-07-031 CA-13-006	U01 /UM1	$50.9 M /($50 M)	9/11/2012	2014/2019
Pediatric Phase 1 / Pilot Consortium	CA-12-502	U01	$15 M	11/07/2011	2017
A Data Resource for Analyzing Blood and Marrow Transplant (CIBMTR)	CA-12-503	U24	$12.9 M	11/07/2011	2018
Blood & Marrow Transplant Clinical Trials Network (BMT CTN)	HL-11-013	U10	$18.5 M	11/03/2009	2017
Cancer Immunotherapy Network (CITN)	CA-10-007	U01		03/09/2009	2015
NCI Clinical Trials Network (NCTN)	CA-12-010 -> CA-12-014, CA-12-504	U10 / U24	$160.5 M	11/07/2011	2019
Childhood Cancer Survivor Study	CA-11-501	U24	$21.1 M		2016
Pediatric Brain Tumor Consortium	CA-08-206	U01	$12 M	03/03/2008	2014
Adult Brain Tumor Consortium	CA-08-504	U01	$10 M	06/28/2007	2013

Division of Cancer Biology Current RFA Portfolio

RFA Title	BSA Approval Date	Approved Total Costs	Expiration	Plan to Renew
Mouse Models of Human Cancer Consortium (MMHCC)	November 2007	$104M over 5 years	2014	No
Integrative Cancer Biology Program (ICBP)	November 2008	$112M over 5 years	2015	No
The Biology of Estrogen Receptor-Negative Breast Cancer in Various Racial and Ethnic Groups	March 2009	$6M over 5 years	2015	No
Barrett's Esophagus Translational Research Network (BETRNet) (collaborative with DCP)	March 2010	$35M over 5 years	2016	TBD
Tumor Microenvironment Network (TMEN)	June 2010	$45M over 5 years	2016	No
Advanced in Vivo Imaging to Understand Cancer Systems (collaborative with DCTD)	June 2010	$25M over 5 years	2016	TBD
Early Diagnosis (collaborative concept with DCP)	TBD			

National Cancer Institute

Division of Cancer Prevention RFAs and Research Priorities

Barry Kramer, M.D., M.P.H.
Director

Lori Minasian, M.D.
Deputy Director

Division of Cancer Prevention
National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Realizing Our Research Priorities Using RFAs in a Time of Limited Resources

- Pursue flexibility in opportunities
- Use innovative and efficient approaches to stimulate research
  - Adjust research of core programs
  - Collaborate to build upon common interests

RFA Research Priorities

- Clinical Studies and Large Trials
- Overdiagnosis and Precancerous Lesions
- Partnering on Clinical Studies

Core Programs Using RFAs (FY 2012)

Community Clinical Oncology Program Network

- 3 RFAs ($87 M / U10s)

Early Detection Research Network

- 4 RFAs ($24 M / U01s & U24s)

Alliance of Glycobiologists for Cancer Detection

- 1 RFA ($3.5 M / U01s)

Barrett's Esophagus Translational Research Network (BETRNet)

- 1 RFA ($2.5 M / U54s)

Community Clinical Oncology Program Network (CCOP)

Funds community physicians' prevention, control, and treatment clinical trials

- **Initiated in 1983**
- **3 RFAs:**
  - **CCOPs (49)**
  - **Minority-based CCOPs (17)**
  - **Research Bases (13)**
    - **Cooperative Groups & Cancer Centers**

Early Detection Research Network (EDRN)

Key network for research to identify, test and validate cancer biomarkers for early detection

- **Initiated in 2000**
- **4 RFAs:**
  - **Biomarker Developmental Laboratories (20)**
  - **Clinical Validation Centers (8)**
  - **Biomarker Reference Laboratories (3)**
  - **Data Coordinating and Management Center (1)**
- **Associate Members (130) No RFA Funds**

Alliance of Glycobiologists for Cancer Detection (with NIGMS, NHLBI)

Network to study molecular processes by which changes in glycosylation contribute to cancer development

- **Initiated in 2007**
- **1 RFA for Tumor Glycomics Laboratories (8)**
- **Other ICs fund additional investigators and laboratories in the Alliance**
- **Promising glycans can be validated by EDRN**

Barrett's Esophagus Translational Research Network (BETRNet)

Goal is to understand the biology of the preneoplastic lesions and invasive cancer

- **Initiated in 2011**
- **1 RFA:**
  - **DCP funds 2 research centers**
  - **DCB funds 1 research center**
    1 coordinating center

Collaborations to Build Upon Common Interests (FY 2012)

Jointly Initiated Projects

- Common Pathogenic Mechanisms of Lung Cancer and COPD (RFA-HL-11-002) with NHLBI ($2.0 M / R01s)
- Biomechanisms of Peripheral Nerve Damage by Anti-Cancer Therapy (PA-12-082 and PA-12-083) with NINDS

Building on Existing Trials for Cancer Endpoints

- Diabetes Prevention Program Outcomes Study
  NIDDK ($0.7 M / U01s)
- Aspirin in Reducing Events in the Elderly/ ASPREE
  NIA ($0.9 M / U01)

Upcoming Projects

NCI Community Oncology Research Program (NCORP)

- Two existing programs to be aligned to expand the scope of research to include clinical trials, cancer care delivery, and cancer disparities research
- BSA presentation in June 2013 (tentative)

Improving the Diagnosis of Early Lesions Detected by Cancer Screening (with DCB)

- Characterize cellular and molecular patterns to distinguish indolent vs progressive lesions
- Determine the cellular and molecular phenotypes of early lesion cells and associated microenvironment

Center to Reduce Cancer Health Disparities Current RFA/PAR Portfolio

RFA Title	BSA Approval Date	Approved Total Costs	Expiration	Plan to Renew
Comprehensive Partnerships to Advance Cancer Health Equity* (PACHE) (U54)	June 2010	$6 M over 1 year	2011	Converted to PAR (Limited Competition) in 2011 (PAR-12-055)
Community Networks Program to Reduce Cancer Disparities Through Education, Research and Training (U54)	June 2009	$104 M over 5 years	2015	Yes

* Formerly the Comprehensive Minority Institution/Cancer Center Partnership (MI/CCP) Program

Cancer Control and Population Sciences – RFA Initiatives

Presentation to the Board of Scientific Advisors

Robert T. Croyle
Director, Division of Cancer Control
and Population Sciences
March 4, 2013

DCCPS RFA Themes

- Collaborative (multiple partners across NIH, HHS agencies, and NGOs)
- Interdisciplinary
- Responsive to scientific and health policy priorities
- Focused on compelling public health problems (obesity, tobacco use, health disparities)

Division of Cancer Control and Population Sciences – Current RFA Portfolio

RFA Title	Partners	BSA Approval Date	Approved Total Costs	Final Year of Funding	Plan to Renew
Centers for Population Health and Health Disparities (CPHHD)	NHLBI OBSSR	June 2008	$45M over 5 years	FY 2014	NHLBI considering
Centers for Transdisciplinary Research on Energetics and Cancer (TREC)	Trans-NCI	June 2009	$40M over 5 years	FY 2015	No
State and Community Tobacco Control Policy and Media Research		March 2009	$46M over 5 years	FY 2015	No
Smoking Cessation in Low-Income Populations		March 2008	$32M over 5 years	FY 2013	No
Smokeless Tobacco Use Prevention and Cessation		March 2008	$13M over 5 years	FY 2013	No

Division of Cancer Control and Population Sciences – Current RFA Portfolio

RFA Title	Partners	BSA Approval Date	Approved Total Costs	Final Year of Funding	Plan to Renew
Population-Based Research Optimizing Screening through Personalized Regimens (PROSPR)	Trans-NCI AHRQ CDC	June 2010	$45M over 5 years	FY 2015	Expand Cervix and Lung
Cancer Research Network Research Resource (CRN)		June 2011	$16M over 5 years	FY 2016	Yes, infrastructure only
Cancer Intervention and Surveillance Modeling Network (CISNET)	CDC	March 2009	$30M over 5 years	FY 2014	Yes
Genetic Associations and Mechanisms in Oncology (GAME-ON)	DCB	June 2008	$65M over 5 years	FY 2014	No
Breast Cancer and the Environment Research Program (BCERP)	NIEHS DCB	June 2009	$13M over 5 years	FY 2014	NIEHS is the lead

Other Recently Ended RFAs

- Transdisciplinary Tobacco Use Research Centers
- Centers of Excellence in Cancer Communication Research
- Breast and Colon Cancer Family Registries
- Cancer Care Outcomes Research and Surveillance Consortium

NIH-FDA Partnership
Tobacco Regulatory Science Program

- Program Announcements – R01, R03, R21
- Tobacco Centers of Regulatory Science for Research Relevant to the Family Smoking Prevention and Tobacco Control Act (TCORS) (P50) – $40M set-aside for FY13
- NIH Competitive Revision Applications for Research Relevant to the Family Smoking Prevention and Tobacco Control Act (P30 Center Core Grants) – $20M set-aside for FY14

FDA Funding to NIH

- FY12 – $31.5M in grants across NIH (NCI, NIDA, NHLBI, NIMH, NIEHS)
- $18.6 (59%) for NCI awards – all for new awards except $1.9M for year 2 of awards beginning in FY11.
- Intramural – 2 projects at NCI (DCEG and CCR)
  - Epigenomic effects of hookah tobacco smoke in respiratory epithelia, PI David Schrump, $250K direct costs per year FY13 – FY15
  - Impact of tobacco use on oral health and the oral microbiome, PI Christian Abnet, $385K direct costs per year FY13 – FY 14

Office of the Director Current RFA Portfolio

RFA Title	BSA Approval Date	Approved Total Costs	Expiration	Plan to Renew
NCI Alliance for Nanotechnology in Cancer (K99, R25, U01, U54)	November 2008	$170M over 5 years	2015	Yes
Physical Sciences in Oncology (U54)	March 2009	$105M over 5 years	2014	Yes
The Cancer Genome Atlas Network: Genome Characterization and Genome Data Analysis Centers (U24)	March 2009	$100M over 5 years	2014	No
Clinical Proteomic Technologies for Cancer (U24)	March 2010	$104M over 5 years	2016	Yes
Cancer Target Discovery and Development Network Centers (U24)	March 2011	$50M over 5 years	2017	No
Provocative Questions Initiative (R01, R21)	June 2011	$75M over 5 years	2016	Yes
Innovative Molecular Analysis Technologies Program (R21, R33)	November 2011	$27M over 3 years	2013	Yes