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

MINUTES OF THE 55th DIRECTOR'S CONSUMER LIAISON GROUP MEETING
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Members Present

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Mr. Everett Dodson, Vice Chair
Dr. Jeff Allen
Ms. Susan Braun
Ms. Marie Dahlstrom
Ms. Joyce Wilcox Graff
Ms. Cheryl Jernigan
Dr. Michelle McMurry-Heath
Dr. Deborah Morosini
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Mr. Jon Retzlaff
Ms. Wendy Selig
Mr. Josh Sommer
Ms. Arlene Wahwasuck
Mr. Max Wallace

Speakers

Dr. Harold Varmus, Director, National Cancer Institute (NCI)
Dr. William Dahut, Clinical Director, Center for Cancer Research, NCI
Dr. Christina Annunziata, Assistant Clinical Investigator, Molecular Signaling Section, Medical Oncology Branch, Center for Cancer Research, NCI
Dr. Natasha Caplen, Head, Gene Silencing Section, Genetics Branch, Center for Cancer Research, NCI
Dr. Maria Merino, Head, Surgical Pathology Section, Laboratory of Pathology, Center for Cancer Research, NCI
Dr. J. Carl Oberholtzer, Chief, Laboratory of Pathology, Center for Cancer Research, NCI
Dr. Gregory Curt, U.S. Medical Science Lead for Emerging Products, AstraZeneca
Dr. John Marshall, Director, Ruesch Center for Gastrointestinal Cancers, Georgetown Lombardi Comprehensive Cancer Center
Mr. Robert Mittman, Facilitator

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Opening Remarks

Rules governing potential conflicts of interest were reviewed, and a quorum was determined to be present.

As a continuation of previous board discussions focused on "molecularly " or "genetically" informed research and medicine, this meeting focused on the implications for research and the advocacy community of research approaches that look across organ systems at molecular pathways implicated across cancer types.

Board Discussion with the NCI Director

Dr. Harold Varmus expressed his gratitude for the DCLG's efforts on behalf of the NCI. He cautioned that budget prospects are tight, and in the current political climate NIH cannot count on strong bipartisan support anymore, making the role of advocacy groups more even important.

Caution was urged about using the term "personalized medicine." Some have inferred that it means developing drugs for every individual set of mutations, but that is highly unlikely. Also, just knowing which genes are implicated in cancer development and progression is not enough; it is also necessary to learn about how the affected genes interact and are expressed. Success more likely will come from learning about commonalities among cancers, e.g., *KRAS* mutations, which are found in 90% of renal cancers, about half of colon cancers, and a third of lung cancers.

This discussion focused on three main topics: barriers to genetically targeted therapies, provocative questions in oncology, and global health.

Barriers to Genetically Targeted Cancer Therapies

- *More tools and genetically targeted therapies are needed for widespread use.* So far, only a few genetic and proteomic tests have shown that they are worthwhile, and few targeted therapies are ready for prime time. Most cancer patients are still treated with radiotherapy, surgery, and conventional cytotoxic chemotherapies. To develop new targeted agents and biomarkers, research is needed at all levels throughout the world, whether supported by NCI, industry, academia, or philanthropies.
- *Knowledge must be disseminated more effectively.* How can research findings be assembled in a way that makes them useful and broadly accessible by community physicians, patients, their caregivers, and others? Some entities, such as the Cancer Knowledge Alliance, are working to make knowledge more widely available. Some concerns about privacy and informed consent must be overcome to make this tool a reality, however. In general, patients are amenable to sharing their data and specimens as long as privacy concerns are respected and there is a prospect for direct or generalized benefit.
- *Regulatory and intellectual property hurdles must be mitigated.* Although targeted therapies are less toxic than cytotoxic chemotherapy, they do have side effects, and tumors develop resistance to them. Oversight of safety is necessary to ensure that the benefit-risk ratio is positive. The Clinical Laboratory Improvement Amendments have a role in regulating the gene tests and use of targeted therapies. Cancer biologists and

statisticians should be involved when sorting patients into study arms based on genes or gene expression profiles. Testing multiple drugs in trials will require engaging the Food and Drug Administration (FDA).

- *Overcome reimbursement challenges for targeted drugs and testing.* The setting of reimbursement rates is becoming a critical issue. Even reimbursement for testing for harmful mutations in the *BRCA1/2* genes is far from being a settled matter. Other tests are being developed to evaluate risk. Some packaged tests can be very expensive, and some are flawed because they do not provide reliable substantiation of risk.
- *There is a need to ensure equity in access to care, preventive health practices, and participation in clinical trials.* NCI can have a role, especially in efforts to get more community programs involved in clinical trials. Equitable access to trials can improve accrual and ensure broad participation by all population groups. Also, by engaging community oncologists in trials, the NCI can learn about what is happening in the field. NCI can help build adequate infrastructure (e.g., telemedicine) to improve access to trials.

Provocative Questions in Oncology

Dr. Varmus is engaging the science community in thinking about some provocative but answerable questions, such as: Why can some solid tumors, such as testicular cancer, be cured with conventional chemotherapy? Does reversing obesity—a known risk factor for certain cancers—through bariatric surgery or other means reduce the risk? Is it possible to determine whether an early nonmalignant lesion (e.g., ductal carcinoma in situ) poses a high or low risk of going on to become malignant?

New technology may provide answers to some of these questions. The provocative questions will be posted on a Website and funds will be set aside for research grants to try to answer them.

Global Health

Most people who die of cancer live in poor countries. Many countries have rising life expectancies, and so cancer will become increasingly important. Great strides have been made in the areas of infectious disease and maternal and child health, but an overarching plan is needed to reduce the burden of cancer in the world through prevention activities (e.g., vaccination programs, cancer screening, smoking cessation, obesity prevention). Some important anticancer drugs (e.g., tamoxifen, imatinib) will be going off patent in a few years; with price reductions, these drugs will be increasingly available throughout the globe.

NCI is making large investments in international activities, including research projects and training initiatives. In addition, NCI is establishing a Center for Global Cancer Research. The search for a director is under way.

Also, more research is needed in the area of cancer care delivery. PEPFAR (the United States President's Emergency Plan for AIDS Relief) has done a good job setting up HIV treatment clinics around the world. Perhaps PEPFAR's facilities and personnel could be engaged in cancer treatment and prevention as well.

Board Dialogue

The DCLG members raised a number of points with Dr. Varmus:

Biospecimens

- The DCLG is exploring ways to engage the advocacy community to promote the donation of biospecimens. Patients are generally willing to provide tissues and data, but they must be asked in the right way; therefore, the informed consent process is of paramount importance. Advocacy groups have been integral in establishing a cancer research program and a biospecimen resource at the Swedish Medical Center in Seattle, Washington.
- Patients need to have the option of donating tissue at the time of surgery in community institutions, where 85% of cancer care is provided. Dr. Varmus said that NCI has been promoting more community research, (e.g., the NCI Community Cancer Centers Program). He went on to say that people are being told about putting unused tissue away for research, but it might be important for the patient's own benefit if and when that person's primary tumor metastasizes 5 or 10 years hence. Also, specimens need to be frozen for genomic and proteomic studies, not merely embedded in paraffin.

Education and Communication

- With regard to cancer knowledge management and ways to educate different areas of the public, advocates can effectively communicate knowledge to their communities. Educational efforts for the general public do not always succeed, but it is critical to make the knowledge available when and where it is needed.
- Messages have to be consistent, but they can be delivered with different levels of complexity, different voices, and different delivery methods to meet the needs of a variety of populations, especially the underserved.

Provocative Questions

- On the topic of cancer and obesity, some obesity factors might play a role in or occur concomitantly with cancers (e.g., growth factors, "obesogens"). Such factors might be modifiable and help prevent cancer. Dr. Varmus commented on the difficulties associated with developing therapeutics of prevention because the target population is people who are basically well. Therefore, the drugs need to have excellent safety profiles.

Global Health

- Many DCLG members have worked on global initiatives in the past or are currently working on such initiatives. The Director is seeking a reasonable country-by-country plan for global cancer research. The first question is what *should* be done in resource-limited settings to reduce cancer? Second, what *can* be done?
- Dr. Varmus was encouraged to engage advocacy organizations as he puts together the Center for Global Cancer Research.

Developing Molecularly Targeted Oncology Drugs

- Does NCI hope to increase the number of targeted therapies in the pipeline, and what are the plans for doing so? Is there a performance dashboard, for example? Is there a role for advocacy groups in making more targeted therapies available? In response to a suggestion that more animal models are needed, Dr. Varmus clarified that safety (but not efficacy) is always tested in animals, as it is not possible to develop an animal model for every disease. First, NCI's goal is to pave the discovery process and hand off further development to industry. There is a big push through TCGA (The Cancer Genome Atlas) and other initiatives to identify new targets (mutated genes) and understand signal pathways. Second, there is an increasing recognition of the importance of screening candidate drugs and investing only in the more promising ones. NCI performs cell-based screening and makes good manufacturing practice (GMP)-grade materials available for drug developers. There is a great deal of work to be done in terms of discovery, validation, and functional testing before genetically based cancer medicines can be put to work.
- A recent Institute of Medicine report, *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program,* was discussed. Dr. Varmus outlined some actions being taken to design trials in a way that allows more questions to be answered and to use retrospective samples to identify biomarkers that can distinguish responders from nonresponders.

DCLG Debriefing Session

The DCLG conducted a debriefing, which focused on identifying action points for the DCLG based on the messages conveyed by Dr. Varmus:

- With NCI's increased emphasis on global health, the DCLG might benefit by adding members from other parts of the globe, holding a meeting outside of the United States, and providing the members with training in global health.
- The Translational Medicine Alliance Forum recently released a Personalized Health Manifesto. Although not endorsed by NCI, this document reflects what is happening in the community and might offer opportunities for the DCLG and NCI.
- Patient navigators have a clinical role, but they also can help enrollment in trials by ensuring that participants remain engaged in the research. There might be a need to study how navigators reduce disparities and improve outcomes.
- An obligation exists to communicate to the taxpayers about what NCI does.
- The DCLG could recommend that NCI be more active with NIH's Office of Science Education.
- Translational research is needed to discover what educational modalities are best to get NCI's message outside of its walls.
- The Board suggested a holistic discussion about what NCI does with the bypass budget.

Gene and Target-based Research in the NCI Intramural Program

Dr. William Dahut

Dr. William Dahut, the clinical director of the Center for Cancer Research (CCR), gave an overview of how genomics has influenced thinking about cancer diagnosis and treatment. Genomics-based research has revealed the heterogeneity within and across tumor types and the high rates of gene mutations and expression abnormalities (making it necessary to distinguish "driver" from "passenger" mutations). Among his main points were the following:

- NCI would like to deliver more accurate, pathway-based diagnoses, offer new hope for patients with rare cancers, improve the reporting of adverse events across linked databases, and refine the design of trials to test targeted therapies. Cancer funding should evolve so that it is not based on cancer site only; instead the focus should be on cancer pathways.
- CCR is the world's largest cancer-focused clinical research center. NCI's intramural research program, because it closely ties clinical and basic research, has led directly to advances in translational research. Laboratory, imaging, and molecular studies can be done quickly because CCR does not rely upon third-party payers.
- Treatment science tailors the treatment of cancer to individuals and populations using molecular and clinical characterizations of disease. The hope is that treatment science will bring an end to phase 2 studies performed in unselected populations and negative phase 3 studies after "promising" phase 2 studies.
- Because of its infrastructure and setup, CCR can take a long view on its research. Most research projects are investigator initiated, but there is a process for external peer review to ensure that studies are scientifically sound.

Debrief of Project Cancer Education

Mr. Mittman facilitated a debriefing of the tour of the NIH Clinical Center. The tour is part of Project Cancer Education, an NCI initiative to inform state-based representatives about how genomics strengthens genomically informed cancer care.

What Was Learned during the Tour?

- Intramural clinical trials are accessible to the general public and without cost so that patients could come here for care if they are eligible to enroll on a trial.
- It appears that there is a missed opportunity insofar as storing and studying tissues collected after treatment. Many large cancer centers are collecting and curating tissues collected during clinical trials; NIH should do this as well.
- It was very good to see NIH taking a leadership role in training the next generation of scientists, starting with high school students.
- There is a disturbing lack of progress with standardization and quality assurance for the laboratory testing of tissues. All patients should have access to good-quality test results.
- The tour did not reveal NCI's strategic orientation. Project Cancer Education should articulate why some research is best done at NCI and not elsewhere.
- The differences between intramural and extramural research should be highlighted.
- The intramural program's decisions about which trials to undertake appear to depend on where the investigators' particular interests lie. Each project should connect clearly to

NCI's strategic goals. Having layers of review, both within and outside of NCI, helps ensure a good balance in the research portfolio. The balance is driven by the opportunities of science, and so the number of studies might not be balanced between breast and prostate cancer, for example.

- Policymakers who take this tour might think that CCR and the Clinical Center facilities do not measure up to the large cancer centers in their own districts. The tour should highlight the factors that differentiate NCI's intramural program from research conducted elsewhere.
- One area in which NCI is uniquely suited is trials of combination therapies, which are challenging because of hurdles involving legal issues and intellectual property. NCI could set up agreements and develop template agreements to allow such studies to be done.
- There needs to be an effort to declare some regional consolidation points for rare tumor pathology specimens. The Armed Forces Institute of Pathology (AFIP) is a major point for collecting tumor specimens and pathological diagnoses. AFIP has annotated sets of slides and large curated collections going back to the Civil War; it does not preserve specimens using methods that would be acceptable for TCGA.
- It appears that NCI has few telemedicine resources available.
- Taking part in a study is free of cost at NCI, but the system to support families coming along with the patient is an important differentiating factor in terms of access. Members of Congress would be interested in supporting research that involves genuine access and equity.
- NCI is the main user (70%) of the Clinical Center.
- With regard to cancer research supported by NCI, 85% of funds go to extramural recipients (cancer centers and programs). It would be important to highlight accomplishments of the intramural program.
- NCI needs outside groups, such as advocacy groups, to broadcast what the Institute is doing.

Dr. Dahut responded to questions raised by the DCLG:

- *How is a balanced portfolio maintained when intramural studies are all investigator initiated?* Dr. Dahut explained that the vast majority of research at NCI is based on ideas generated here or in collaboration with outside groups. Some intramural trials are done to mentor a young investigator or to fill a need to study a rare disease. NCI is now in the process of analyzing the protocols in the portfolio. The main criteria used to evaluate a potential research study are (a) whether the expertise is available at CCR, and (b) whether the research is designed to quickly answer an important clinical question. This is a new way of thinking that was instituted about 18 months ago.

- *What makes the intramural program unique—or is it just another cancer center?* One often hears that NCI supports "high-risk, high-impact trials," but we need to parse the meaning of those words. Does the research present a high risk to the patient? Is it high risk in terms of investment? Is it high impact because it involves research on a common tumor? A trial of a drug could be deemed high risk because no one ever gave that drug to humans before.

  With regard to differentiators, Dr. Dahut explained that NCI intramural program will never treat the same volume of patients as the big cancer centers do. Good clinical care is still important. Intramural researchers can study patients in greater detail than can be

done on the outside. The NCI intramural program can also move things more quickly between the laboratory and the patient, especially in the area of imaging.

Another differentiator is immunotherapy studies, in which NCI excels. For example, for some prostate cancer studies, NCI researchers are doing immunomonitoring (studies of regulatory T cells and other cell types, cytokine responses, and so forth). This information can be used by outside collaborators who are doing trials.

- *What is the intramural program's sustainable competitive advantage?* It is difficult to ignore a resource like the Clinical Center. Patients can come here and stay for weeks, even months. There is a culture here that attracts patients, nurses, and researchers. NCI perhaps has less to offer its researchers and staff on the personal financial side and less ability to conduct large phase 3 studies, but it has the ability to move things back and forth quickly. The focus is on driving collaborative work forward and capitalizing on the Clinical Center, where it is possible to conduct imaging studies, immunomonitoring, and pharmacokinetic/ pharmacodynamic profiles. NCI has the ability to do difficult science. The DCLG recommended developing an "elevator pitch," a 3- or 4-minute talk.
- *Is there a central strategic approach underpinning all of this brilliant work?* In general, the research model has been investigator driven, but NCI leaders have decided that some areas are real strengths (e.g., Centers of Excellence) and thus deserving of prioritization. If a proposal comes from one of these Centers, it is regarded differently because it has already been recognized that it has attracted a critical mass of interest and, therefore, is likely to garner more support from the top.
- *Is there a layer of decisionmaking that gives priority to ideas of limited commercial interest?* At NCI, the potential exists to focus on discoveries that could lead to financial benefit in the future but not necessarily in the short term. There is interest in opening the Clinical Center to the extramural community for studies of rare tumors or complicated treatments that are challenging or expensive to do on the outside. Children with a rare tumor, for example, could be brought to the Clinical Center, as could investigators interested in the particular tumor.
- *We think of NCI as one of the best research institutions, but is patient care based on research evidence, too? That would be an important differentiator.* Care at the Clinical Center is excellent and driven by science. Patients like to come here. The nursing staff is well educated, and the ratio of patients to nurses is low.
- *Does the Clinical Center still rely on paper patient records instead of EMR?* The Clinical Center has EMR and uses electronically entered orders. There are still some vestiges of paper records in the outpatient clinic. Older records are being transferred to EMR.
- *Is the intramural program doing whole genome sequencing and expression profiling on Clinical Center patients?* The first step is to identify the patients who would be more likely to benefit from such genetic testing in order to set some priorities. The intramural program is not doing these tests on all patients. They will become more commonplace as the cost comes down.
- *Researchers are very interested in patient samples that have been exposed to drugs. Is there an initiative at the Clinical Center to store these?* Decisions about specimen storage

depend on the tumor type. For some types, NCI has collections of tumors that have been exposed to drugs. For other tumor types, sera and cells have been stored. In general, NCI has less storage of tumor tissue than many large cancer centers because fewer surgeries are performed here. As NCI collaborates more with Suburban Hospital in Bethesda, more tumor specimens will be obtained, stored, annotated, and shared.

The Process, Tone, and Approach of Project Cancer Education

The DCLG discussed the following points about the tour:

- Major messages and an orientation to the intramural program should be delivered in an amphitheater, not in the labs.
- The tour and presentations should justify why the intramural program is worthy of taxpayers' money. That aspect would come through better if the human story is told. The most instructive presenter tried to tie the research to a patient.
- Those who come to NCI and participate in Project Cancer Education are an interested audience. Therefore, the tour should offer compelling information—something that justifies visiting the lab instead of just viewing the information online or in a book or journal.
- The tour was too long and entailed too much walking, and it was not clear how the various sites and labs were connected physically or how they dovetailed with the strategic plan of NCI. It would be useful to have a map to show the tour route and how the venues and activities are valuable.
- Some of the presenters did a good job reinforcing their roles in training future professionals. It was excellent to see high school students in the lab.
- Use of outdated technology (carousel projector) did not make a favorable impression.
- The tour and presentations would benefit from editing and better sequencing. A narrative arc could lead the participants through a certain thought process. The goal should be to convince policy makers that this should be a national priority by weaving a story about how these activities fit together. Perhaps one person could introduce each section to highlight what the participants are going to see and then pull everything together at the end.
- Choose the right people to deliver the messages and tell the stories.
- All of the presenters should have a time limit. Including only one lab on the tour would probably suffice. The entire program should take no more than one and one-half hours.
- Ultimately, the goal is to equip participants to spread NCI's message. Edit the stories and infuse them with messaging about the intramural program.
- Researchers should be prepared to answer questions about the number of minorities, including Native Americans, involved in clinical trials.
- Posters are designed to present to two or three people at a time, not 15 or 20.
- To demonstrate the goals of the intramural program, Project Cancer Education could describe the process that has led to success and NCI's part in that success. Examples could be the development of trastuzmab or imatinib.
- Collaboration and training are unique facets of NCI's work. These need to be emphasized in Project Cancer Education.
- Policy makers on Indian reservations could be audiences for messages about NCI, but the tour did not equip the DCLG members to discuss the NCI intramural program with them.
- The area on the 12th floor of the Clinical Center looked empty and unused. An explanation that the clinics are time-shared among the different disciplines would have helped.

- Take-away materials would have been helpful.
- Presenters for Project Cancer Education could benefit from training and counseling from communications professionals.
- Consider using video segments for story telling by scientists and patients.
- Ensure that a diverse group of staff conducts the presentations.
- Create video and audio clips and PowerPoint slides that advocates can bring home to share NCI's message.
- The DCLG could play a role in encouraging policy makers to engage with Project Cancer Education, but the program needs to be improved first.

The most important messages that NCI could deliver to policy makers through Project Cancer Education include the following:

- We are making a difference.
- Cancer research costs a lot and takes time.
- We are leading the war on cancer.
- We are bringing drugs to market.
- This is not commercial research. NCI has no shareholders to answer to and is not subject to the restraints of the market.

Panel Discussion: Gene- and Target-Based Research across the Research Continuum

Dr. Gregory Curt, U.S. Medical Science Lead for Emerging Products, AstraZeneca
Dr. John Marshall, Director, Ruesch Center for Gastrointestinal Cancers, Georgetown Lombardi Comprehensive Cancer Center

Dr. Curt, a medical oncologist, worked at NCI in several capacities starting in the 1980s and is now with the AstraZeneca (AZ) oncology group. Among the key points that he made are:

- AZ has seen signals of activity (e.g., immunomodulation) that could not have been detected without collaboration with NCI. Some important efficacy signals have been found in rare diseases, thanks to collaboration with NCI's intramural program that brought patients to the Clinical Center for participation in trials.
- Companies can work together or individually with NCI's intramural and extramural programs. Industry uses NCI as a safe harbor to help put together contracts for head-to-head comparisons and for trials of combination therapies.
- With regard to developing standard biomarkers for clinical trials, all companies could present their programs in confidentiality to NCI, which could help develop and validate assays so that all companies can access a standard toolkit of biomarkers.

Dr. John Marshall, also a medical oncologist, is with Georgetown University's Lombardi Cancer Center. Discussion covered several areas:

- In terms of cancer drugs, there have been many great successes, but what is their value to patients? For example, from 1957 to 2000 the only treatment available for colorectal cancer was 5-fluorouracil. Then, in 2000, a host of new chemotherapies and biologics came to market. Now, patients with advanced colorectal cancer die in 2 years instead of 1 year and at a cost of $30,000 to $50,000 per month. Where is the value?

- Only 3% of U.S. patients are on clinical trials. Many trials are conducted in Eastern Europe and elsewhere in the world. The FDA then approves the drugs based on the results of those trials, giving access to patients in the United States. Because of the drugs' cost, people in Eastern Europe have limited, if any, access to them.
- The National Comprehensive Cancer Network (NCCN) guidelines are often the basis for reimbursement decisions. If physicians deviate from the NCCN guidelines they run the risk of not being paid and could even be sued. Consequently, oncologists have to practice "cookie-cutter medicine."
- It is important to stratify patients based on molecular profiling. Stratified trial designs can help companies conduct trials more quickly and with fewer participants. The I-SPY2 study is using prospective molecular profiling in a breast cancer trial (adaptive trial design).
- Companies should be encouraged to collaborate on trials so that different drugs can be tested for different molecular categories.
- Use the term "graduate" to change patients to different treatment arms, instead of "failure."
- Design more small phase 2 trials with a larger delta. Patients accrue quickly to niche protocols that use molecular profiling, e.g., imatinib for gastrointestinal stromal tumors.
- Enrich clinical trials (in terms of patient selection) from the very start. One problem has been that traditional funding mechanisms will not support such trials. At the Lombardi Cancer Center, there is an effort to run such studies using philanthropic donations. The trials entail a great deal of tissue acquisition and analysis, and companies have been cooperative about providing study drugs.
- Pharmaceutical companies have concerns about intellectual property. Many of the new agents, however, should be used in combination with or in a series with other drugs (usually from other companies), thus raising the concerns. NCI can provide a safe harbor for studies that use different companies' products.
- Companies have to answer to their shareholders. Pharma has been successful in part because it sells drugs to people who will not benefit; how does that factor into companies' decision making? The business model is changing away from blockbuster drugs toward the idea of "mini-buster drugs."
- Targeting allows companies to get a drug in a directed way to the people who need it. The idea is to have payers pay only when the results show the drugs work in the selected patient population. Also, targeted drugs can be used more easily and with fewer side effects. People will take the drugs for years, as is the case with imatinib for treatment of chronic myeloid leukemia.
- The current incentive for oncologists is to use more drugs because that is the basis for their payment. When the patient has to bear more of the cost, there will be radical changes in participation in clinical research and the use of medicines, and there will be a change in how doctors perform.
- The public should be angry about the lack of new and better cancer treatments. There is no other area in medicine in which 20% is considered good! HIV research was largely propelled by people banding together and demanding new therapies.
- The regulatory system poses a significant challenge. The FDA was quick to point out that I-SPY2 is an exploratory phase 2 study and that approval will still require a phase 3 trial. But, what would an adaptive phase 3 trial add? Even with studies that the FDA codesigned, the FDA has changed its mind about using the findings for licensure once the data come out. We need an act of Congress to change how cancer drugs are approved.

Other end points (e.g., ease of administration, patient-reported outcomes) should be taken into consideration. An investigational drug could be scored along a host of such parameters, and if it achieves a designated score, it would be approved automatically. This may be an area where advocates could apply pressure.

The DCLG offered several comments and questions:

- Large co-payments for expensive targeted drugs deprive the large, medically underserved population of the United States of access. Only in the United States is reducing co-payments for those who participate in trials considered to be coercive or undue influence.
- Biospecimens are needed for trials of targeted therapies. Getting insurance approval for biopsies is a major challenge.
- For advanced melanoma, there is no standard therapy that is worthwhile for many patients. Therefore, the idea of conducting big trials and splitting the population so that half the group is randomized to standard of care (which is not much better than placebo) does not seem realistic or desirable.
- There is a role for retrospective analyses of tumors to detect genotypes associated with treatment response (or resistance). Among the barriers to such studies are tissue ownership and privacy considerations.
- The country is unprepared to deliver cancer care to match the shifting balance of majority and minority populations.
- Emerging markets are very important to pharmaceutical companies. In places where medical care is not available, industry is reaching out to help by providing free or low-cost drugs (e.g., helminth treatments, antiretroviral drugs). Globalization will improve lifestyles and the incomes of more people.
- How can we achieve genomically informed medicine unless we do genomic profiling? Even the Clinical Center is not doing much whole genome sequencing. TCGA is doing genomic profiling of tumors to see if there are commonalities. Massachusetts General Hospital and M.D. Anderson Cancer Center are sequencing every patient's tumor.
- How do conflict-of-interest regulations restrict progress at NIH? The agency's employees cannot receive honoraria and, many times, cannot even accept reimbursement for travel costs. Such policies will eventually isolate intramural researchers, and, to the extent that they are excluded from planning meetings, they will miss opportunities.
- Comorbidities bar many people from participating in trials.
- Limitations in information technology may be a barrier to sharing across platforms. If we overcome them, then the primary barrier will be the Health Insurance Portability and Accountability Act (HIPAA).

Dr. Curt identified the lack of biomarkers and surrogate markers as the most important barrier which, if dismantled, would have the biggest effect on advancing research. We have cholesterol as a marker for cholesterol drugs, and we have viral load as a marker for HIV drugs. We need circulating DNA and circulating tumor cells as biomarkers so it is not necessary for people's cancers to progress to get the answers we need. There will be different biomarkers for different tumors and different drugs.

Dr. Marshall said that the United States is losing ground compared with the rest of the world. Our system is the "$300 NASA hammer." We need to spend our resources more wisely. Public-

private partnership is part of answer. Intellectual property concerns are another important barrier to the development of molecularly targeted drugs.

NCI and DCLG Project Updates

- The DCLG asked for information about NIH's policies and grant-making activities that could offer opportunities to leverage community resources to promote the collection of biospecimens.
- Best practices in the collection and storage of biospecimens are published by NCI's Office of Biorepositories and Biospecimen Research (OBBR). The guideline is periodically updated based on new research. Implementing the guidelines is not easy, particularly because biospecimen collection is not reimbursed. Are there opportunities to engage in dialogue with the Centers for Medicare & Medicaid Services about coverage for biospecimen collection?
- Mr. Carollo reported on possible efforts to conduct an environmental scan of treatment guidelines, which guide therapy selection and may influence reimbursement decisions. NCCN is the gold standard for oncology.
- Dr. Gregory Foltz's presentation at the Swedish Medical Center during the last DCLG meeting is being transformed into a Web-based format.

Board Discussion around Opportunities and Clinical Barriers in Gene- and Target-based Research

- Adaptive clinical trials, similar to I-SPY2, should be undertaken in different tumors.
- To ensure equity and access, medically underserved populations must have a seat at the table during discussions about genomically informed research and cancer care.
- Find out who is working on issues of equity and access and make alliances to widen the circle. An environmental scan should include groups outside of the cancer field.
- Research must have a racially diverse base.
- Remember that "global health" includes the United States, where many people face barriers in terms of access and cost. Many lack adequate health insurance.
- Convene a conference on equity and the underserved in terms of biospecimens and genetic profiling.
- The DCLG would like to hear more about gene expression profiling. There are sometimes many different phenotypes associated with a particular mutation. Perhaps this topic could be covered at a future meeting.
- The DCLG would like to learn more about issues of privacy, informed consent issue, and institutional review boards.
- The DCLG would like to have a general update on OBBR at an appropriate time.
- The DCLG asked for periodic updates on NCI's progress with biospecimen collection.
- Convene groups around common pathways rather than on the basis of tumor site.
- The DCLG suggested a presentation on overlapping pathways, especially as TCGA broadens to study other tumors. What do the outcomes of TCGA show and how do the results differ from those of previous trials?

- The DCLG should frame up the barriers identified by Dr. Varmus and identify where the boundaries lie (or consider them holistically). The barriers could help the DCLG decide on areas for action.
- Is there a movement in Congress to modify HIPAA?
- Could social networking tools be used to keep participants engaged in research?

Wrap-up Activities

The DCLG's Big Questions

- How do we ensure there is transparency in knowledge dissemination to communities (especially those that are behind barriers) about new discoveries and new science and clinical trial participation?
- How can we expand the population base to accrue studies and expand the array of study designs for approval of targeted therapies?
- How do we take what we have learned in molecular biology and pathways and apply it to precancerous states so we can better understand treatment possibilities, as well as assess and mitigate risk?
- Can we rigorously and scientifically study some of these areas—early detection, extension of life with palliative care, early disease management, lifestyle modification—to learn about their effects on outcomes? Look at the full spectrum of the disease (early and late) instead of in the middle, where the main focus currently lies (point of metastasis).
- How can we ensure that new technologies and treatments are available to all Americans, regardless of socioeconomic status, geography, race/ethnicity, and insurance status?
- What needs to be done to maintain continuity and keep building on what we have learned?
- How do we make sure we are prepared to deal with the changing demographics (e.g., aging, race/ethnicity, rural/urban balance) of the United States?
- How can we modify eligibility criteria to encourage broader representation by difference race/ethnicities in clinical trials?
- How can we encourage more Native Americans to participate on trials?
- What is the return on investment in cancer research? How can we ensure that we are maximizing the return on our investment of resources, including dollars, tissues, and data?
- What must we do to prepare for the time when more cancers could be treated with these smart therapies? Will the regulatory world be ready when science gets to this point?
- Every organization should be able to answer three questions when asked to prove its value. Can NCI answer these questions?
    - What are we trying to accomplish? What are our goals?
    - What are our metrics of success? (e.g., improve participation from 3% to 10%, get 500 drugs in the pipeline instead of 50, set up X number of cancer centers)? These examples are all process measures. We need outcome measures.
    - What are our tactics to achieve those goals?
- How can NCI ensure its relevance?
- How do we effectively define and communicate about "personalized medicine" to help people buy into programs that will need their data and specimens?
- How do we better reconcile the American notion of privacy with the needs of genomic research that relies on sharing of information?

- How do we move society to focus on prevention rather than diagnosis and treatment?
- Why aren't we mad as hell?
- How can we create a collaborative culture to overcome barriers that impede industry, academia, patients, advocates, and government from working together? What are the policy and legal barriers to protection of patients and achievement of better outcomes?
- How do we establish new champions of NCI in Congress?
- How do we develop a space for sharing otherwise unpublished data and findings?
- What is the patient's role in this new paradigm of target-based research?
- What is the strategic plan of NCI to overcome the five barriers identified by Dr. Varmus?
- Whom does NCI really serve? To what degree is the consumer or patient represented? What is the appropriate level of that voice within NCI?
- Where is NCI insofar as looking at how cancer starts in terms of our environment? Are we blaming the genes instead of our political and personal choices?

Five Overarching Categories for the DCLG's Big Questions

1. How do we engage the public, Congress, patients, researchers, payers, and clinicians?
2. What is the high-level vision, purpose, and strategy of NCI? And what are the outcomes?
3. How do we ensure equitable access to trials, information, treatment, facilities, and care?
4. What is the appropriate distribution of resources upstream and downstream from the current focus on treatment (e.g., prevention, palliative care)?
5. How do we engage clinicians, patients, researchers, payers, communities, and policy makers in the dissemination of information and knowledge?

Privacy and transparency issues cut across several of the categories. It was suggested to add language about incentives, global economics, and reimbursement to one of the categories or to add another category to capture these concepts.

Next Steps

OAR staff will meld these questions and categories (including entities to engage around each question or category) into a document and distribute it to the DCLG for feedback. Additionally, the DCLG will send a letter to the Director regarding their plans for future issues.

The meeting adjourned at 11:58 a.m.

Certification

I hereby certify that the foregoing minutes are accurate and complete.

_____	_____
Date	Chair Director's Consumer Liaison Group
_____	_____
Date	Executive Secretary Director's Consumer Liaison Group