A Strategic Plan for Improving Biomarkers for Cancer

Report of Working Group on Biomedical Technology

February 2005

The Working Group on Biomedical Technology strongly recommends strategic improvements in the discovery and deployment of biomarkers in cancer research and treatment. For the purposes of this document, **"biomarkers" are defined as endogenous molecules (such as proteins or metabolites) or injected agents (such as imaging agents) whose presence or state correlates with important physiological processes, disease outcomes and treatment response (including toxicity and efficacy)**.

More effective biomarkers for disease have the potential to significantly improve cancer survival through early disease detection, improve treatment by more accurate diagnosis and prognosis, and greatly enhance clinical trials by rapidly revealing therapeutic response. The power of biomarkers has become evident in recent years through DNA and RNA profiling of tumors and imaging technologies. However, the field is still at an early stage: many of the most powerful technologies (notably proteomics) are still maturing and have not yet been broadly applied to cancer. Most biomarkers are yet to be discovered.

It is clear that dramatic advances can be made by undertaking certain strategic initiatives including: organizing team science, establishing data standards, providing informatics support, acquiring reagents, employing mouse models of disease, promoting academic–industry collaboration and translating advances to patient care more rapidly. **In this report, we recommend the creation of a standing NCI Biomarker Discovery Working Group to coordinate work across the institute on (i) discovery and validation of endogenous biomarkers of cancer in patient samples and (ii) creation and testing of imaging and other agents for in vivo monitoring of cancers and cancer therapeutics.**

1. Effective Biomarkers Will Improve Patient Outcomes

Individuals at risk for cancer or with cancer would benefit enormously by better methods for (i) determining cancer risk, (ii) detecting and localizing cancer at its earliest stage, (iii) profiling for therapeutic decision making, and (iv) monitoring response to therapy in real time. It is already evident that molecular diagnostics can improve diagnosis and treatment. Genetic translocations or transcript array profiles allow stratifying many organ-specific cancers (breast, leukemia, lymphoma, sarcoma) into different subtypes that have distinctive therapeutic outcomes. For example, *Myc* gene amplification status predicts the outcome for childhood neuroblastoma (Bhattacharyya et al. 1997). The quantity of Bcr-Abl transcript predicts disease recurrence in chronic myelogenous leukemia long before clinical symptoms recur (Radich et al. 1995).

1.1 DNA biomarkers are not sufficient. The HCGP will deliver the ability to type cancer by alterations in the cancer genome, which will facilitate risk assessment, diagnosis, prognosis, and treatment of cancer. However, DNA biomarkers alone are not enough. For example, proteins are more diverse and therefore

carry more information than nucleic acids, since alternative splicing and more than 100 different posttranslational modifications result in 10–100 species of protein from each gene. Moreover, proteins are much more dynamic and reflective of cellular physiology — protein phosphorylation can signal the presence of a single double-strand break in DNA within seconds to minutes of the activating event. In addition, proteins may be more accessible in body fluids and may be more useful for molecular targeted imaging. Metabolites are another source of dynamic biomarkers. It is important, therefore, that efforts be made to identify and implement effective types of biomarkers.

1.2 Biomarkers will empower imaging technology. Many important characteristics of cancer require positional information as well as *in situ* physiological information. Where is the cancer located? How large is it? Is it confined? Is it hypoxic? What is its metabolism? The establishment of a number of NCI-supported imaging centers throughout the United States has brought significant resources, expertise and focus to the problem of improving molecular contrast reagents. The development of micro-imaging technology for many modalities of small animal imaging in combination with recent improvements in mouse models of cancer provides new opportunities for molecular imaging that are inducible, targeted to specific tissues and genes, and that more accurately portray human cancer.

Molecular imaging (the *in vivo* measurement, characterization, and quantification of biological processes at the cellular and subcellular level) completes the overall picture for the future of molecular medicine. The ability to see the molecular signatures of cancer is critical to fulfilling biologically based technologies' promise of earlier detection and better disease management. Molecular imaging could one day be used throughout the cancer care pathway i) to detect early-stage alterations in gene expression, ii) to guide therapeutic choices, and iii) to evaluate and adjust treatment protocols. Ultimately, researchers envision molecular image-guided therapy systems to treat cancer as it is found.

Each of the major imaging modalities would be enhanced with molecularly targeted imaging agents that offer the opportunity not only to see where but also to see what is going on — to visualize apoptosis, proteolysis, angiogenesis, metabolism, cell surface expression patterns and metastasis.

A variety of different imaging modalities in current use all lend themselves to different forms of molecularly specific contrast agents. PET imaging is noteworthy because its high sensitivity translates to low doses. Improvements in magnetic resonance contrast agents are also resulting in reduced doses, approaching those in PET. These tracer amounts should lower the barriers to FDA approval, which is a significant problem for new contrast agents. Near-infrared imaging permits deep penetration into tissues and the ability to image multiple targets (or biological processes) simultaneously at different wavelengths.

Functional information about tumors can be achieved by using enzymatic substrates (e.g., protease substrates) that produce signal when cleaved or by tagging antibodies with contrast cargo specific for the proteins that are localized and functioning at the site of disease. Labeled ligands for cell surface proteins, such as somatostatin receptor, melanocortin receptor and integrins, are already available and more are being developed. With informative imaging agents, we could, for example, tell which cells are currently repairing DNA damage, distinguish cell division from apoptosis, and image the characteristically leaky blood vessels in tumors.

1.3 Biomarkers can improve cancer diagnosis. Accurate diagnosis of the hundreds of different types of cancer will permit more effective choice of therapy and will make clinical trials more effective. Cancer diagnosis can be improved through more accurate molecular and functional phenotyping. As therapies become more targeted to specific signal transduction and metabolic pathways, it is becoming of paramount importance to document the existence of those pathways in the target cancers. For example, targeting of breast cancers with herceptin is not indicated if the patient's tumor cells do not over-express

Her-2/neu. Similarly, Gleevec is most effective against cancers that express the Bcr-Abl genotype. It is a reasonable goal that such molecular phenotyping can be expanded to include biomarkers for virtually all cancer subtypes, and that many of these can be accessible through non-invasive means, such as proteins in fluid samples or through imaging. Such information could improve the conduct of clinical trials, as segmentation of patients with biomarker-derived inclusion criteria will significantly reduce the numbers of patients required to achieve acceptable response rates.

1.4 Biomarkers can improve clinical trials. Better post-treatment diagnostics could greatly accelerate new drug development by shortening clinical trials, identifying responsive patients, and revealing toxic side effects. For example, one of the first trials approved with a molecular endpoint compares four treatments for chronic myelogenous leukemia and is currently underway. By using the endpoint of reduction in the DNA marker, Bcr-Abl, a trial that would have taken several years to complete will be reduced to 12 months.

The use of molecular markers can aid in the identification of a subset of patients that respond to therapy, thereby turning what would have been a failed clinical trial into a successful one. The remarkable response of some patients with gastrointestinal stromal tumors over-expressing the c-KIT kinase to the drug imatinib can be observed within days of treatment through PET imaging of glucose metabolism (Gayed et al. 2004). Similarly, response of breast cancer metastases to taxane therapies can also be observed with early changes in diffusion MRI signals (Theilmann et al. 2004, in press). Despite these notable successes, imaging is not used in most clinical trials to achieve rapid and specific assessment of response. This is due in part to the fact that few agents are being translated into the clinic to date and few agents are being accepted by the FDA.

1.5 Biomarkers can improve therapies. If we could routinely follow a patient's response to therapy in real time, both dosing and agent selection could be individualized**.** Currently some chemotherapeutic agents are individualized by adjusting dose to the patient's individual metabolic characteristics. Moreover, a series of agents could be tested on the same patient in a matter of weeks. A key factor in such a test is to optimize the negative predictive value and dynamic range of responses, so that non-responding patients can be accurately identified. Defining modalities appropriate for such tests will benefit from appropriate pre-clinical imaging of animal models.

Therapeutic strategies can also directly benefit from an understanding of the proteins that are prominent in each type of cancer. A search for these sentinels of disease would enable a whole industry of new molecularly targeted therapeutic approaches. Many of the broadly toxic agents could become cancer-specific reagents if coupled to targeting moieties (e.g., antibodies, engineered ligands) or other vehicles that deliver them specifically to the cancer cells. There is at least one FDA-approved targeted therapy of this type and many more are in development. The FDA-approved therapy, Myelotarg, couples an antibody specific for tumor cells with a toxic reagent, calicheamicin. Such targeting will be required for effective internal radiotherapies.

Short of prevention, improved diagnostics to detect cancer at an early, curable stage would provide the greatest benefit for cancer patients. For most cancers, 5-year and even 10-year survival is often near 90% for cancer detected at stage one, while it may be only 10% or less for cancer detected at stage four (Etzioni et al. 2003). We have, of course, known for a long time that if we could detect cancer earlier, we could save more lives. The Pap smear strongly reduces mortality through early detection of cervical cancer as does colonoscopy for colon cancer. Furthermore, both tests have been embraced by the community despite their significant inconvenience, cost and requirement in clinical expertise. These successful screening examples have created a social environment that should lead to the rapid application

of new tests. What we need are affordable and effective diagnostic tests for more types of cancer. A recent success is the finding that DNA markers are more effective than histologic analysis at detecting those patients with Barrett's esophagus who are likely to progress to cancer. Placing these high-risk patients under intensive surveillance for early detection has been shown to increase 5-year survival from less than 10% to more than 80% (B.J. Reid, personal communication).

The risk of cancer recurrence is high in patients who have previously had cancer, even for those who have been in remission for 5 or more years. Cancer survivors constitute a high-risk group that is most likely to be the first beneficiaries of improved tests for early detection of disease. Monitoring CML patients during Gleevec therapy and in the post-transplant setting for the persistence of the Bcr-Abl translocation is already an effective technique.

1.6 Biomarkers may contribute to risk assessment. Screening individuals for early cancer detection will be more cost-effective and efficacious if we can segment the population into smaller groups at increased risk for specific cancers. Success in identifying individuals at increased risk has, of course, been achieved for many cancers through epidemiological studies that identify strong environmental or behavioral risk factors and by genetic studies that identify mutations underlying rare inherited cancer syndromes. With a few exceptions, such as serum PSA, the use of molecular markers in the assessment of risk for sporadic malignant disease remains largely unexplored.

Epidemiologic studies indicate that lifestyle, diet and environmental exposures significantly affect the risk for sporadic disease, but little advance has been made in identifying markers reflective of the stable, cumulative molecular changes associated with, or mediating, this risk. Stochastic genetic alterations occur infrequently and are difficult to detect, but there is increasing interest in more common, stable genetic and epigenetic changes in histologically normal or pre-malignant tissue, reflective of deleterious exposure, and associated with increased risk for malignant progression. In Barrett's esophagus, DNA mutation, methylation, and ploidy changes are highly correlated with increased risk for cancer (also see Zöchbauer-Müller et al. 2003). Another epigenetic risk marker is the loss of imprinting of IGF2 in peripheral blood lymphocytes in subjects at risk for colorectal cancer.

It should be possible to identify individuals at risk by functional tests for cellular processes that protect against cancer; for example, the effectiveness of DNA repair. Most familial cancer-prone syndromes are due to defects in DNA repair. A study by Scott and Roberts revealed that about 40% of breast cancer patients, prior to treatment, exhibit a defect in DNA double-strand break repair in their white blood cells (Scott et al. 1999). Cell-based and biochemical tests have been developed for about ten different pathways that participate in DNA repair, many of which would likely contribute to cancer risk if defective. There are also a number of case-control molecular epidemiology studies that apply functional assays of DNA repair capacity as potential risk factors for sporadic cancers, although these data have not been validated in prospective studies. In general, more effort is required to understand risk stratification based on various cancer-related phenotypes.

2. Biomarker Discovery Can Be Improved

2.1 Many advances in fundamental knowledge are not being translated into molecular diagnostics. During the last 40 years, we have achieved an impressive understanding of the molecular fundamentals of cancer. We now understand that cancer arises in a single cell as a result of genetic changes that alter a number of cellular processes — growth control, immortality, apoptosis, somatic evolution, angiogenesis, metastasis — and many cancers appear to have activated a wound healing genetic expression program (Chang et al. 2004). These changes are driven by abnormal methylation or a high rate of mutation. The

proteins that function in each of these cellular circuits provide not only potential drug targets, but also signals that may allow us to non-invasively visualize and monitor physiology.

Moreover, new advances continue at an astonishing rate. In just the last few years we have seen: the sequencing of the human genome, providing a catalogue of all human genes; the development of RNAi technology, permitting the sophisticated loss of function analysis of human cells, and the identification of cancer stem cells, defining a potential new paradigm for cancer etiology.

Such recent advances, however, have been translated into effective diagnostics in only a few cases to date – for example, imaging agents that detect DNA replication, apoptosis, or proteolysis. In some respects, the discovery of new biomarkers appears to have been undervalued and under-funded relative to drug discovery. For example, the the NCI Early Detection Research Network (EDRN), charged with discovering and validating new biomarkers, has not yet brought new agents to patient care.

It is time to unleash the diagnostic and informational content of our knowledge of altered molecular circuits into improved diagnostic agents for cancer patients.

2.2 Technologies for identifying protein biomarkers are being ineffectively utilized. There are many different approaches to discovering biomarkers for cancer. The variables include the type of technology approach, the cancer site, the source of tissue for candidate discovery, the choice of biological pathway or class of molecule to examine. The discovery can be made more rational. Rather than sift randomly through thousands of proteins in disease vs. non-disease looking for rare differences, one could interrogate proteins enriched in tumor tissue, in fluids near cancer cells, or secreted by human cancer cells in culture or in xenograft capsules. In addition, one could develop strategies to look in blood specifically for the ~1,000 proteins known to play roles in cancer (e.g., angiogenesis, apoptosis, cell cycle, etc.) by a variety of approaches, including antibody enrichment. Special attention might be given to the identification of cell surface proteins and the preparation of reagents for detecting them, which would allow for sorting cells belonging to developmental lineages within tissues and tumor.

2.3 DNA methylation markers are promising but under-explored. Altered DNA methylation patterns provide one promising platform for cancer biomarker development, because these changes are pervasive in cancer, appear to be detectable in free, tumor-derived DNA in bodily fluids of cancer patients, and are based on a chemically and biologically stable analyte. The successful development and implementation of DNA methylation-based biomarkers has thus far suffered from the following four impediments:

- Lack of a comprehensive, genome-wide description of baseline methylation patterns in normal tissues. A Human Epigenome Project is underway in Europe, although it is still at an early stage and there is no comparable effort in the US.
- Lack of a coordinated and comprehensive approach to methylation marker identification. Only about 1% of known CpG islands and fewer than 10% of anonymous CpG islands have been evaluated to any extent for their tumor-specific methylation behavior.
- Lack of standardized technology for DNA methylation analysis. This inhibits cross-platform comparisons and cross-validation studies. Genome-wide marker identification approaches rely mostly on methylation-sensitive restriction enzyme digestion, while sensitive detection technologies useful in clinical tests rely largely on bisulfite-based methylation-specific PCR.
- Lack of a systematic optimization of sample processing to maximize detection sensitivity. Such mundane, non-innovative but necessary technology optimization is difficult to fund through investigator-initiated funding mechanisms.

These impediments result from insufficient coordination, communication and standardization.

2.4 Few new imaging agents are being applied to patients. Cancer diagnostics and therapeutics requires the ability to locate incipient disease, determine its extent, and monitor response to therapy. At present, we can image larger cancers by cross-sectioning imaging techniques such as CT, MRI, and PET/SPECT and by optical techniques such as endoscopy or intravital microscopy. In order to use imaging to pinpoint early cancers and pre-neoplasia (often only a few millimeters in size), we will need higher resolution technologies. This size range is below the detection threshold for most state-of-the-art CT, MRI, and PET. One example of *in vivo* high-resolution imaging is fiberoptic confocal microscopy performed during endoscopy. This technology could be particularly well suited for surveying epithelial surfaces at cellular resolution.

A clear strength of imaging approaches is the high connectivity between pre-clinical and human use. For example, most equipment manufacturers (e.g., GE, Siemens, Phillips) are developing human and animal imaging platforms with common interfaces to facilitate the translation from animal to human. Nonetheless, testing new agents in patients is challenging due to regulatory (FDA) and reimbursement (CMS) issues, the lack of incorporating imaging endpoints into therapeutic trials, and high costs for perceived small markets. Also, pharmaceutical companies are not making significant investments to develop imaging in concert with drug development and, as a result, imaging agent development often lags 2–3 years behind drug development for a given target. Finally, another limitation is the need for more creative chemistry to design and synthesize informative probes.

3. How to Improve Biomarker Discovery

3.1 The need for team science. A consistent theme that emerged from focus group sessions was the need for more team science. While much fundamental discovery in cancer research is best pursued through individual investigator awards, many of the important goals discussed here require collaboration. The NCI should bring together the strengths within and across academic institutions into a highly interactive network of contributing laboratories. A systematic and integrative approach will be required with teams of investigators sharing and aggregating data.

Achieving the goals will require bringing together expertise in genomics and proteomics, small and large animal studies, and clinical and epidemiological studies. Informatics support will be needed for data extraction, data transfer and data storage, and standard algorithms for data analysis that work across platforms and enable common resources for universal access to the successes and failed efforts of other investigators. Chemistry, radiopharmacy, engineering and bioengineering expertise can improve imaging and biomarker discovery. Basic and clinical scientists need to be included to aid in identifying questions of biologic significance and facilitate the translation of discovery to therapy. Expertise in outcomes research is needed to demonstrate the clinical and economic value of evolving approaches to screening cancer patients, at risk individuals, and healthy populations.

Because of the complexity of approaches that can and should be pursued both in biomarker discovery and the development of imaging agents, an effective search for these sentinels of cancer will require a team effort – including many labs working on the same samples, sharing data, developing standards, and comparing information. Sharing data across labs will require an informatics platform that can support these coordinated activities — something that does not currently exist in the academic sector.

Moreover, because of the variety of disciplinary expertise required, there will be an ever-increasing need for cross-trained scientists. Indeed the shortage of cross-trained scientists is a major impediment to more rapid development of validated imaging approaches.

3.2 The need for data standards. Currently, it is impossible to compare performance across different laboratories for most fields of biomarker discovery and molecularly targeted imaging due to the lack of uniform standards for reporting data and the use of different samples and technologies for analysis. There is an urgent need for communities of scientists working with each analytic approach to meet and establish data standards that will facilitate comparing data across laboratories and instruments. In some cases this can best be accomplished by incorporating known molecular standards in each sample analyzed or including a sample containing standards in each experiment. Current funding mechanisms tend not to support work to ensure reproducibility because it is often not considered "innovative".

3.3 The need for an informatics platform. Each laboratory and imaging center typically maintains its own database and generally finds it impractical to aggregate its data with that from other sites. Moreover, analysis software is typically written by individual centers or is proprietary. It will be impossible to exchange data across laboratories and compare results quantitatively until standard analysis tools are readily available and widely shared. The field of biomarker discovery needs highly functional databases, data transfer standards, a variety of analysis and comparison tools, and the ability to aggregate data from many sources. If highly functional systems were readily available, it would be the first choice for most investigators in the field and would assure a uniformity of data acquisition across many discovery laboratories.

3.4 The need for reagents. A common complaint among investigators is the lack of reagents necessary for biomarker discovery. It is difficult for any single laboratory to obtain the diverse array of reagents needed, and the development of reagents independently by different laboratories increases the lack of reproducibility in data. Reagents are needed in the form of tissue and blood samples, chemical libraries, peptide standards and antibodies.

Initial evaluation of biomarkers will require large numbers (hundreds) of clinically annotated plasma (and solid tissue) samples that could be collected and stored for many cancer sites. To evaluate early detection capability, collection of plasma from early stage patients is needed (together with stored tissue) as well as pre-symptomatic blood samples from individuals later diagnosed with cancer. To evaluate clinical response, plasma obtained from well-controlled clinical trials with clinical outcomes is essential.

For protein biomarker discovery it is essential to have access to many antibodies for detection of candidates in low concentration. It would be straightforward to draw up a list of at least 1,000 proteins known to be involved in cancer-related processes, such as apoptosis, angiogenesis, and metastasis, that are all potential candidate biomarkers. While the cost of individual laboratories producing antibodies against these proteins is prohibitive, it would be an modest investment by the NCI to do so. Such an investment would be justified by its potential to empower the entire research community with accessible and standard reagents. A similar situation exists for chemical libraries for developing contrast agents for imaging. Efforts are needed to create libraries with chemistries that are favorable for imaging agent development.

Finally, validation of early detection markers will require large cohort studies in which samples are obtained and stored from healthy people prior to disease onset. This resource will be needed within a couple of years, making the initiation of such a collection imperative.

3.5 The need to implement new technology improvements. Technology improvement is also crucial to advance the field. Examples of recent technologies that could dramatically improve biomarker discovery are proximity-based oligonucleotide coupling that links antibodies to DNA tags for PCR-based signal amplification, and recombinant antibodies produced using yeast surface display. Technology

improvement should be considered in imaging modalities, combinatorial synthesis of contrast agents, mass spectrometry, protein arrays, protein fractionation, protein detection, protein quantitation, DNA methylation analysis, new detector technologies and other appropriate methodologies.

Molecular probes will require a variety of pharmacological profiles and half-lives, as well as continued development of "smart" imaging reagents whose signal depends on biochemical activities. Desirable performance enhancements include decreasing the time and barrier required to conduct imaging tests to make them more feasible for large-scale trials and clinical implementation, multiplexing contrast agents to compare several biochemical and physiological process at the same time, and developing better transducers to support three-dimensional imaging.

A number of existing and developing imaging approaches do not rely on exogenous molecularly specific contrast reagents yet retain high specificity for aspects of tumor behavior, such as vessel permeability, cellularity, metabolism and organization. These should be developed in parallel with molecularly specific reagents and biomarkers to generate complete pictures of tumor behavior.

4. General Recommendations

Based on the analysis above, the working group makes a number of general recommendations concerning the directions needed to advance work on biomarker discovery. The next section discusses how to ensure their implementation.

4.1 Foster team science. The NCI should create new models for funding team science that will assure that promote collaboration in biomarker discovery, by encouraging groups of investigators with critical mass and diverse expertise to work together on key problems.

4.2 Establish data standards. The NCI should bring scientists together to develop data standards for each technology platform (imaging modalities, proteomics, DNA markers, metabolomics, etc) and to improve reproducibility across laboratories on a specific imaging modality. Such an effort will likely require the development and dissemination of uniform reference standards that can be used by laboratories to confirm results for existing, newly developed or proposed biomarkers.

One or more technology assessment centers should be funded to compare different technologies head-to-head on the same samples to establish methods for best performance.

4.3 Build informatics platforms. The NCI should create a centralized and publicly available database for technology platforms in which investigators can aggregate data across studies on a common tumor type. For contrast reagents, tracked information should include formulation, source, biodistribution, chemical structure, pharmacokinetics, and *in vivo* stability. For endogenous approaches, tracked information should include profiles and variance of normal tissues, acquisition and analysis conditions

4.4 Provide reagents to the community. The NCI should support production of common reagents needed for each technology platform –such as molecular imaging probes, small-molecule libraries as sources of new imaging probes, antibodies against cancer-related proteins, isotopically labeled peptides for mass spectrometry and other reagents as needed.

4.5 Development new technologies. The NCI should support the development of new technologies, methodologies and approaches within discovery programs. Mechanisms could include pilot grant programs to encourage the development of improved technologies, reagents and procedures. Where

appropriate, efforts to automate of technologies for higher throughput and greater reproducibility should be supported.

4.6 Employ mouse models of cancer. The NCI should take maximal advantage of the power of mouse models for both technology improvement and biomarker discovery. Animal models provide controlled experimental conditions and an opportunity for reproducibility that cannot be achieved with human subjects. Variables that can be controlled include genotype, environment, precise cancer type and disease stage. Initial development and evaluation of technologies for biomarker discovery may be best performed on highly uniform animal samples rather than on human samples. The NCI mouse models of human cancer consortium (MMHCC) has created mouse models of many different human cancers, and these provide an important resource for this work.

4.7 Promote academia-industry collaboration. The NCI should promote appropriate collaborations between academia and industry. Since an effective discovery of biomarkers is of great benefit to both academia and industry, it should be possible to collaborate across industry–academic partnerships to facilitate the process. Such collaborations should bring together pharmaceutical, image acquisition and biotech companies with molecular probe development and biomarker discovery efforts. Biomarker endpoints should be developed at the earliest stage of drug discovery, to connect drug actions to a specific biomarker endpoint at all stages of development through the clinic.

4.8 Translate advances to patient care . The NCI should encourage rapid translation of biomarkers to the clinic. Endpoint based on biomarker (including endogenous proteins and imaging readouts) should be incorporated into therapeutic trials. One way to encourage this would be to create imaging cores and/or centers focused on tumor response assessment in cancer centers. Another step would be to ensure the participation of biomarker scientists in the protocol review and startup phase at individual cancer centers. Positive single-trial results should be confirmed with multi-center tests. ACRIN is available for radiology-based trials, and oncology groups are available for therapeutic trials; however, there is no current mechanism in place to disseminate therapy trials that include an imaging endpoint.

Clear guidelines for IRB and FDA approval for human use should be established to provide a framework within which imaging approaches and agents can be more readily approved for human trials. This should also include clear guidelines for acceptance of INDs.

4.9 Promote work on standards for approval and reimbursement of biomarkers . The NCI should promote broad discussions concerning guidelines for approvability of new biomarkers by the FDA and utility of the biomarkers in a clinical setting. In addition, the NCI should support scholarship in areas related to reimbursement for the clinical use of biomarkers. Because the effective use of biomarkers may well decrease procedures, it is important to explore the benefits of 'outcome-based' rather than 'activity-based' models of reimbursement to ensure that reimbursement policies do not create disincentives for the use of biomarkers.

4.10 Promote work on public understanding of biomarkers . The NCI should promote patient and physician education related to biomarkers, because probabilistic risk assessments will create challenges for both groups. In addition, the NCI should promote work to understand the potential for discrimination based on information about biomarkers.

5. Specific Recommendation

Biomarkers hold tremendous promise for improving the detection, diagnosis and treatment of cancer. In the previous section, we have outlined a number of general recommendations concerning how to advance progress on the development and validation of biomarkers. The remaining issue is how best to ensure the implementation of these steps.

We are not recommending the creation of organized large-scale projects – for example, an effort to discover serum biomarkers for all common cancer. The technologies for biomarkers discovery (beyond the DNA level) are not yet well enough developed to make such focused goals feasible. At present, the key issues are to advance the state of the art of the technology (including through the development of standards, tools and approaches) and to achieve some dramatic successful to serve as models (including the identification of endogenous biomarkers for a few cancers and the development of some new types of imaging agents). Such progress may set the stage for large-scale efforts at a later date.

We are also not recommending the creation of a specific new NCI program for biomarker discovery. There are currently nearly 20 programs or initiatives within NCI relevant to this area (listed in Section 6). The creation of yet another program would not suffice to accomplish the important goals outlines above.

Instead, the NCI needs to take a more comprehensive approach to this crucial area by evaluating the success of existing efforts relative to overall goals, identifying key areas that are not being addressed and modifying or creating programs to address them.

Accordingly, we recommend the creation of a standing NCI Biomarker Discovery Working Group to coordinate work across the institute on (i) discovery and validation of endogenous biomarkers of cancer in patient samples and (ii) creation and testing of imaging and other agents for in vivo monitoring of cancers and cancer therapeutics. The working group should report, on an annual basis, to both the NCI Director and the Board of Scientific Advisors. Its charge would be to:

- **i) evaluate the extent to which the recommendations are already being addressed through one or more of the existing programs;**
- **ii) determine the extent to which different programs are successful in their goals and the extent to which they may have redundant elements;**
- **iii) propose steps to improve coordination of activities across programs;**
- **iv) ensure that each of the recommendations above has an appropriate programmatic home, either through an existing program or through the creation of a new effort;**
- **v) determine whether current funding is adequate to ensure rapid implementation of the recommendations;**
- **vi) propose new funding, where existing funding is inadequate to achieve the goals; and**
- **vii) prepare an annual assessment of progress on these recommendations.**

It is clear that achieving the goals set forth here will require additional funding for biomarker discovery. This is particularly the case with respect to mechanisms to encourage team science, provision of community reagents (such as antibodies and chemical libraries of imaging agents), technology assessment mechanisms, and development of informatics platforms.

6. Appendix

Some of the NCI programs related to biomarker discovery are:

- Early Detection Research Network (EDRN)
- In Vivo Cellular and Molecular Imaging Centers (ICMICs)
- Small Animal Imaging Resource Program (SAIRPs)
- Mouse Models of Human Cancers Consortium (MMHCC)
- Imaging Working Group, which aims to enhance collaborations between SAIRPs and MMHCC
- Development of Clinical Imaging Drugs and Enhancers (DCIDE) program, which aims to provide funds for pre-clinical testing for submission to the FDA
- Contract program to validate imaging methodologies for pre-clinical testing of new drugs
- Unconventional Innovations Program (UIP), which sims to stimulate development of radically new technologies in cancer care
- caBIG initiative, which works with cancer centers in developing access to key bioinformatics platforms
- Specialized Programs of Research Excellence (SPOREs), which aims to speed bi-directional exchange between basic and clinical science focused on specific cancer sites
- Innovative Molecular Analysis Technologies (IMAT) program, which supports research projects to develop and carry out pilot applications of novel technologies for the molecular analysis of cancer
- Clinical Trials Cooperative Group program, which is designed to promote and support clinical trials of new cancer treatments, explore methods of cancer prevention and early detection
- Small Business Innovation Research (SBIR) grants, which aims to support to small business for innovations in cancer
- NCI Alliance for Nanotechnology in Cancer, which will establish Centers for Cancer Nanotechnoloy Excellence to design and test nanomaterials and nanodevices, with the aim of introducing novel diagnostic tools and techniques to combat cancer processes
- NIH Roadmap initiatives, including the Molecular Imaging and Contrast Agent Database (MICAD);
- Interagency Oncology Task Force (NCI-FDA IOTF)
- Clinical Proteomics and Biomarker Discovery, a new program currently under consideration at NCI

7. References

Bhattacharyya N, Thornton AF, Joseph MP, et al. Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation. Results in 9 cases. *Arch Otolaryngol Head Neck Surg* 1997;123(1):34–40.

Chang HY, Sneddon JB, Alizadeh AA, et al. Gene expression signature of fibroblast serum response predicts human cancer progression: Similarities between tumors and wounds. *PLoS Biol* 2004;2(2):206–214.

Etzioni R, Urban N, Ramsey S, et al. The case for early detection. *Nat Rev Cancer* 2003;3(4):243–252.

Gayed I, Vu T, Iyer R, et al. The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. *J Nucl Med* 2004;45(1):17–21.

Radich JP, Gehly G, Gooley T, et al. Polymerase chain reaction detection of the BCR-ABL fusion transcript after allogeneic marrow transplantation for chronic myeloid leukemia: Results and implications in 346 patients. *Blood* 1995;85(9):2632–2638.

Scott D, Barber JB, Spreadborough AR, et al. Increased chromosomal radiosensitivity in breast cancer patients: A comparison of two assays. *Int J Radiat Biol* 1999;75(1):1–10.

Theilmann et al. Neoplasia and response to antiogenic drugs can be monitored directly with changes in dynamic contrast enhanced MRI or SPECT. JOURNAL 2004;Vol.:Page #s.

Zöchbauer-Müller S, Lam S, Toyooka S, et al. Aberrant methylation of multiple genes in the upper aerodigestive tract epithelium of heavy smokers. *Int J Cancer* 2003;107(4):612–616.