Integration of Molecular Profiling into the Lung Cancer Clinic

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Abstract

Individuals from five thoracic oncology centers in the United States recently met to discuss how to integrate molecular profiling into the care of all patients with carcinoma of the lung. Lung cancer is an area of medical oncology in which clinicians are beginning to use specific tumor-associated molecular aberrations to assign and/or prioritize targeted therapies for patients. At this early stage, multiple hurdles remain before molecular profiling becomes a routine part of thoracic oncology practice. Concrete collaborative next steps were discussed that could help lead to standardized methods across institutions. In particular, to develop specific targeted therapies for patients whose tumors harbor rare mutations, it will be important for multiple institutions to work together to identify appropriate candidates, design the appropriate trials, and execute the trials with adequate numbers to achieve the necessary end points. Implementation will facilitate realization of the promise of molecularly tailored therapy, which could lead to more effective treatments with fewer side effects. (Clin Cancer Res 2009;15(17):5317–22)

Lung cancer is the leading cause of cancer-related death in the United States and worldwide (1). Standard treatment for metastatic lung cancer involves empirical platinum-based combination chemotherapy. Despite recent advances in treatment of the disease, the overall 5-year survival in the United States remains only 15%, highlighting the need for novel therapeutic strategies.

Historically, the morphologic pathologic appearance of lung cancers has been used to guide treatment decisions, primarily distinguishing patients with small cell lung cancer from those with non–small cell lung cancer (NSCLC). Three major subtypes of NSCLC—adenocarcinoma, squamous cell carcinoma, and large cell carcinoma—were grouped together as a single entity for therapy for clinical trials. With the recent regulatory approvals of pemetrexed (Alimta) specifically for adenocarcinoma and large cell carcinoma (2), and bevacizumab (Avastin) for nonsquamous NSCLC (3), therapeutic differences among lung cancer subtypes has grown in significance.

Recent evidence indicates that adenocarcinomas have distinct genomic changes that allow their subclassification into clinically relevant molecular subsets. These subsets, which may seem morphologically similar, can be defined by a specific genomic change that is responsible for both the initiation and maintenance of the lung cancer. Such a genomic change is sometimes called a “driver” mutation. Importantly, specific mutations may cause a lung tumor to respond differently to targeted therapeutic agents. For example, tumors highly sensitive to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI; i.e., gefitinib or erlotinib) often contain dominant somatic mutations in exons that encode a portion of the tyrosine kinase domain of EGFR (4–6). Conversely, tumors with somatic mutations in KRAS, which encodes a GTPase downstream of EGFR, do not regress when treated with these drugs (7–9). Within a single gene, tumors can be further subclassified by their specific genetic modification. For example, EGFR exon 19 deletions and exon 21 point mutations (L858R) predict sensitivity to EGFR TKIs, whereas exon 20 insertions/duplications predict primary resistance (10).

When knowledge of specific genetic changes is linked to a targeted therapy, dramatic improvements in response and clinical benefit can be observed, and patients can be spared chemotherapy. Approximately 75% of patients whose tumors harbor drug-sensitizing EGFR mutations respond radiographically to EGFR TKIs (11), compared with <5% of NSCLC North American patients with a wild-type receptor (12), and <1% of patients with KRAS mutant tumors (13). By comparison, the response rate for standard platinum-based chemotherapy with bevacizumab is 35% (14).

Despite these data, however, mutational profiling has not yet been widely accepted or adopted into practice in thoracic...
oncology. In November 2008, a multi-institutional 1-day workshop was held to discuss how to move molecular profiling into the lung cancer clinic and what steps are needed to make it more broadly available to physicians treating lung cancer. The goal was to explore how academic medical institutions can generate relevant molecular data on every patient seen in the clinic, design appropriate clinical studies, and link the results of genomic tests to treatment decisions. Participants were from five cancer centers that have made an institutional commitment to developing personalized lung cancer therapy: the Massachusetts General Hospital (MGH) Cancer Center, Memorial Sloan-Kettering Cancer Center (MSKCC), the Dana-Farber/Brigham & Women's Cancer Center (DF/BWCC), the M. D. Anderson Cancer Center (MDACC), and the Vanderbilt-Ingram Cancer Center (VICC). The heads of thoracic oncology at each institution were asked to organize a multidisciplinary team of participants from each cancer center that included at least a molecular pathologist, a translational physician-scientist, and a clinical researcher with experience in genotype-driven trials.

The major question addressed was what are the shared challenges our cancer centers face in obtaining and incorporating molecular information about a patient's tumor into all clinical treatment decisions? Participants were first asked to present their current institutional approaches to molecular profiling. Specific topics were then addressed, including (a) organization/workflow, (b) mutation detection technologies, (c) clinical protocols and reporting, and (d) patient consent. Finally, participants discussed strategies and made recommendations for accelerating the widespread use of molecular profiling.

**Current Institutional Approaches to Clinical Molecular Profiling**

Each center is approaching the overall goal—to use molecular analyses of tumor specimens to guide care and focus research—with complementary approaches. Most are focused on assessing tumor specimens for known genetic alterations before assignment of therapy, with a near-term objective of linking these findings to therapeutic choices with available drugs (Fig. 1). These efforts are distinct from programs to discover new mutations and other molecular abnormalities, which are also ongoing.

At the MGH, the Cancer Center and the Department of Pathology jointly established the Translational Research Laboratory (TRL) to take an institution-wide approach across all disease types. Drs. Leif Ellisen and A. John Iafrate described the TRL and its mission to conduct real-time, high-throughput genetic analysis of tumor specimens for clinical decision-making and to advance clinical research studies. Its priorities, rank-ordered, are (a) pretreatment screening as enrollment criteria in genotype-directed trials, (b) prospective correlative analysis of relationships between tumor genotype and drug response, and (c) correlative studies, which may be retrospective, exploratory, or hypothesis-generating.

MSKCC has recently established the Lung Cancer Mutation Analysis Project. Dr. Marc Ladanyi described how all lung tumor specimens will be profiled prospectively for use in clinical management and research. The results of mutational profiling will be available for patient care, for institutional research, as well as for future use (e.g., at the time of disease recurrence). The project has been designed to serve as a scalable prototype that can be applied to assessment of all solid tumors at MSKCC.

At DF/BWCC, lung cancer patients can readily have their tumors tested for **EGFR** and **KRAS** mutations through a commercially available resource. Dr. Pasi Jänne reported that in the near-term, they plan to (a) increase the number of genes interrogated in tumor specimens, (b) expand the scope of work by adding studies on copy number alterations and translocations (which are assayed by **in situ** hybridization), and (c) shorten the turnaround time and cost of analyses.

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**Fig. 1.** Integration of molecular profiling into the lung cancer clinic. *A,* traditional tumor analysis. *B,* integrated molecular analysis.
MDACC reported on the organization of their Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) clinical program. Drs. Edward Kim and Ignacio Wistuba reported that eligible patients undergo core biopsies involving at least three separate passes to collect adequate tumor tissue, which is then profiled for 11 biomarkers (including mutations in EGFR, KRAS, BRAF, and other immunohistochemical markers). Biomarker results are reported within 14 days and then used to assign trial participants to one of five arms involving targeted therapies. Discovery projects include expression profiling of collected tissue and proteomic analysis of patient serum. Experience gained in the BATTLE program has prompted the MDACC thoracic group to pursue biomarker-driven clinical trials in lung cancer and to develop a system to transition novel biomarkers from research to diagnostic molecular pathology laboratories.

At VICC, Dr. David Carbone reported that they plan to establish a comprehensive molecular pathology laboratory to analyze tumor specimens. However, he emphasized the need to consider trials involving biomarkers obtained from sources other than tumor-derived nucleic acids. For example, VICC has established a tissue proteomic profile that predicts for benefit from EGFR TKIs, and they have conducted another trial measuring urinary 11α-hydroxy-9,15-dioxo-2,3,4,5-tetranor-prostone-1,20-dioic acid (PGE-M; the major metabolite of prostaglandin E2) to assign specific therapy. Vanderbilt has also established a DNA Biobank in which DNA from leftover blood specimens is extracted and stored for future use on nearly all patients at the medical center.

**Organization/workflow.** Workflow varies depending on each institution’s organizational structure and how resources are allocated. MGH and MSKCC are attempting to build integrated programs within their respective pathology departments that perform morphologic pathologic review in addition to molecular pathology, whereas other institutions, such as MDACC (for the BATTLE program), DF/BWCC, and VICC, have thus far established facilities separate from their Pathology Departments. The latter type of structure may make it more difficult in the future to create units that are fully integrated with practicing oncologists caring for the vast majority of patients that are not participating in clinical trials.

One concern is how to handle patient specimens from outside institutions. Many pathology labs are unwilling to release entire pathology blocks, but rather will provide unstained slides that need to be requested by patients themselves. At MSKCC, new patients coming to the institution for the first time are asked to bring with them for the initial visit 15 unstained slides. About one-third of patients comply. This avoids the need for tissue requests after the visit and enables prospective testing, whereas other institutions, such as MDACC and other immunohistochemical laboratories.

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Notably, MSKCC has since 2005 successfully implemented “reflex testing” for surgically resected adenocarcinomas. Without having to make a specific request, all adenocarcinoma patients who undergo surgery at MSKCC receive the results of prospective EGFR and KRAS mutational analysis. In a 1-year period, for example, there were 297 adenocarcinomas of 500 lung resections; 58 of 295 (20%) had EGFR mutations, and 85 of 295 (28%) had KRAS mutations.

**Technologies for clinical molecular profiling.** Real-time prospective genotyping of tumors is hindered by the fact that multiple different types of molecular alterations need to be assessed. For example, fusions/chromosomal rearrangements are detected by reverse transcription-PCR or fluorescent/chromogenic in situ hybridization (FISH/CISH) with fusion-specific probes. The former requires high quality mRNA, whereas the latter requires intact cells fixed in a specific manner. DNA amplification for MET or HER2 is also assessed by FISH. Immunohistochemistry (IHC) requires paraffin-embedded tissues sectioned properly, and tumor mutation testing requires quality DNA that represents the tumor. Moreover, not all types of mutations are readily detected by the same assay. For example, although point mutations are readily amenable to allele-specific PCR-based assays, insertions and deletions are not. Additionally, all of these different types of assays are often done by different units within a Department of Pathology. Therefore, truly integrated molecular profiling requires multiple assays, and tumor tissue needs to be processed properly in multiple ways.

MGH’s TRL carries out traditional pathology functions—pathologic review/diagnosis, preparation, and selection of formalin-fixed paraffin-embedded tissue samples—as well as a full range of molecular analyses. For mutational analysis, after testing a variety of platforms, they have adapted Applied Biosystems’ SNaPshot system of multiplex PCR, single base extension, and capillary electrophoresis. They have developed a fully operational assay with an automated panel that detects mutations in 58 different loci from 13 cancer genes in 8 multiplexed reactions (Table 1). In addition, a separate PCR reaction using primers flanking EGFR exon 19 is used to detect in-frame-activating deletions in EGFR that may not be detected using SNaPshot. The panel has a modular design, so that new sets of mutations can be tested by simply by designing new PCR primers. The SNaPshot assay can detect a mutation in a sample in which only 5% to 10% of the DNA has the mutant allele. The specific assays done were selected to be compatible with formalin-fixed paraffin-embedded tumor specimens. FISH/CISH are carried out to detect chromosomal rearrangements and amplification, and IHC is used for protein biomarker analysis.

MSKCC is using, and DF/BWCC is planning to use, Sequenom’s MassARRAY system for mutational profiling (Table 1). This system involves a multiplex, high-sensitivity (5-10% mutant allele) assay. MSKCC’s assay can detect 37 mutations in 7 genes using 7 multiplexed PCR reactions. Once the machine has been purchased, per assay cost of this test is reasonable, because it essentially costs the same to run one mutation as all 37 mutations. The assay can also be used on DNA extracted from formalin-fixed paraffin-embedded samples.

MDACC’s BATTLE program currently performs IHC, FISH, and direct sequencing on fresh frozen samples. Messenger RNA profiling and proteomic analysis using a quantitative multiplex bead assay are used for discovery. VICC performs proteomic and urinary PGE-M assays.

**Clinical protocols, test reporting, patient consent.** Molecular profiling conducted for clinical purposes must comply with standards, regulations, and approvals required of all clinical tests for patient care. For example, for molecular profiling data to be entered into a patient’s medical records, testing needs to be carried out using the standards of the Clinical Laboratory Improvement Amendments (CLIA) mandated by the U.S. Congress in 1988. Currently, MGH performs multiplex genotyping
for multiple mutations, including EGFR and KRAS, in a CLIA-certified manner (Table 1). Patients sign consent for mutation testing. At MSKCC, DF/BWH, and MDACC, EGFR and KRAS tumor genotyping are considered routine clinical tests without the need for patient consent.

For testing of other rarer mutations, most institutions felt that these would be tested for on a research basis until enough clinical data were obtained to confirm their usefulness. For example, at MSKCC, patients can sign consent to use “leftover” material after routine pathology studies are completed (see Appendix 1). The purpose of the meeting was not to decide which exact mutations should be assayed in CLIA labs.

Another major question concerns patent rights on tumor mutation testing. Will academic health care institutions be able to obtain licenses to test for tumor mutations for their own patients and bill for this clinical service, will they be able to perform such testing in the absence of licensing if done for their own patients, or will the testing be restricted to central facilities that have already licensed some tests? For example, if a commercial entity owns the rights to testing of specific mutations, and the company offers the test centrally, some academic centers are reluctant to perform such testing on their own. Ironically, patenting of mutation testing in this manner may actually hinder mutational profiling rather than facilitate it.

### Strategies for Accelerating the Integration of Molecular Profiling into Routine Care of Persons with Lung Cancer

During the second half of the workshop, participants discussed broadly applicable strategies to accelerate the process of moving molecular profiling into the lung cancer clinic. Clinical molecular profiling by academic health care centers to assign therapy of its patients will involve complex, far-reaching operational changes and will demand rapid, responsive implementation driven by a large body of new knowledge. A collaborative approach of “learning by doing” will allow more effective adoption and integration of the best practices identified at each institution. In addition, identifying common priorities on which to focus, resolving roadblocks and developing effective starting points for changing a complex system are needed. Processes will be tailored to the specific situations encountered at each institution, but an accepted standard for accuracy and validation of molecular profiling tests is needed for the adoption of widespread testing. Thus, a collegial formulation of guiding principles and standards rather than rigid rules or unique solutions should be adopted. Specifically, there were four major areas addressed as follows:

- **Mutational analysis.** To assign therapy based on the genetic makeup of individual tumors rather on clinical characteristics, institutions should ideally perform prospective genotyping of all lung cancers. This will require platforms to assay multiple genetic lesions at the same time. Analyses must be precise and conducted in a timely manner to permit optimal care. Institutions should share protocols, experiences, and reagents (e.g., positive control samples) to facilitate the development of platforms at each center and validate their techniques.

- **Molecular enrollment criteria for clinical trials.** The results of molecular analyses should be coupled to genotype-driven clinical trials. Proof-of-concept trials are needed to link each mutation to its cognate targeted drug therapies.

- For rare mutations, found in <5% of tumors [such as those involving ALK (ref. 15) or BRAFT (ref. 16)], multiple centers should collaborate to identify appropriate patients for specific targeted agents in development. One representative example of a collaborative trial is AZD6244 in Cancers With BRAF Mutations (NCT00888134) involving MGH, Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, MSKCC, and the National Cancer Institute. Only patients whose tumors harbor BRAFT mutation will be eligible for study. No single institution could efficiently enroll enough patients. If single-arm trials such as these show dramatic activity, then the data are sufficient to warrant further testing of the agent in question in more advanced trials using the molecular criteria. Which type of follow-up trial would be the best or would be approved by the Food and Drug Administration was not a topic of discussion.

- **Education of health care professionals.** All individuals involved in patient care require education about the process and procedures involved, as the very basis of “routine care” is redefined. Educational forums will also be needed to disseminate

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**Table 1. Current practice for detection of mutations in lung tumors at five cancer centers**

<table>
<thead>
<tr>
<th>Cancer Center</th>
<th>Routine Tests</th>
<th>In CLIA-certified lab</th>
<th>Multiplex Genotyping?*</th>
<th>In CLIA-certified lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH</td>
<td>See Multiplex Genotyping</td>
<td>Y</td>
<td>Y - SNaPshot†</td>
<td>Y</td>
</tr>
<tr>
<td>MSK</td>
<td>EGFR, KRAS, BRAFT</td>
<td>Y</td>
<td>Y - Sequenom†</td>
<td>N</td>
</tr>
<tr>
<td>DF/BWH</td>
<td>EGFR, KRAS, BRAFT, ERBB2, PIK3CA</td>
<td>Y</td>
<td>Sequenom planned</td>
<td>N/A</td>
</tr>
<tr>
<td>MDA</td>
<td>EGFR, KRAS, BRAFT</td>
<td>Y</td>
<td>Planned</td>
<td>N/A</td>
</tr>
<tr>
<td>VICC</td>
<td>BRAFT, Serum proteomics, urine PGE-M</td>
<td>Y</td>
<td>Planned</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviation: N/A, not applicable.

*SNaPshot and Sequenom are done on tumor DNA extracted from formalin-fixed paraffin-embedded samples.

†The entire TRL SNaPshot version 1 assay has been validated and approved for clinical use based on CLIA regulations. It currently detects mutations in 58 different loci from 13 cancer genes: APC, BRAF, CTNNB1, EGFR, FLT3, JAK2, KIT, KRAS, NOTCH1, NRAS, PIK3CA, PTEN, and TP53.

†The MSK Sequenom MASSArray assay currently detects mutations in 37 different mutations from 7 cancer genes: AKT1, BRAF, EGFR, HER2, KRAS, MEK1, and PIK3CA.
rapidly how to implement such programs nationwide and to teach others how this approach can be beneficial to patients. Professional societies such as the American Society for Clinical Oncology and the International Association for the Study of Lung Cancer have been invaluable in keeping the field abreast of emerging practices. In fact, the theme of the American Society for Clinical Oncology 2009 annual meeting—“Personalizing Cancer Care”—is germane to the integration of molecular profiling into the lung cancer clinic. Education will also involve emphasizing the importance of ongoing and anticipated clinical trials of novel drugs, or combinations of drugs, which demand histologic or molecular classification for enrollment.

Some studies, such as those testing new drugs for patients with acquired resistance to erlotinib or gefitinib, have been informed by molecular changes acquired during TKI therapy observed in patients who have been subjected to serial biopsies during their clinical course. Thus, even in routine care of patients, educational efforts should be made to encourage the acquisition of more tissue than what is contained in a cytology specimen (i.e., performing at least a core biopsy rather than a fine-needle aspirate biopsy). Outreach should include interventional radiologists, pulmonologists, and surgeons, who actually perform the procedures to obtain tissues.

**Expectations for targeted therapies.** Independent outcomes and quality research are needed to develop science-driven criteria to assess the cost-effectiveness and full potential of targeted therapeutics, so that expectations of targeted therapeutics—and the best ways to combine them with surgery, radiation, and other therapeutics—have a rational basis.

**Next steps.** In addition to these four topics, several concrete issues were discussed that could be taken as next steps:

1. Because Pathology departments are the repository for clinical specimens and today house the core capabilities needed, a second workshop was proposed to be held including pathology chiefs, molecular pathologists, and clinical operations leaders to streamline procedures from the identification of the tumor specimen, retrieving tumor tissue, studying the tumor, and reporting the molecular characteristics in the medical record. With a continued emphasis on process and workflow, an objective would be to propose a framework process and identify the top roadblocks to be resolved and/or missing steps to be designed, vetted and approved.

2. Pathology and research data need to be integrated into each institution’s existing information systems and medical records. Thus, it was proposed that the chief information officers or equivalents at the five cancer centers designate relevant informatics and medical records representatives to work with molecular pathologists to define project scope, user needs, and outputs.

3. To avoid the need to “reinvent the wheel” at each institution and to facilitate the development of tests for rarer mutations, it was suggested that the five institutions should create a set of “dosed” sample standards to validate technologies for mutational analysis, for FISH/CISH, and for IHC, such that any technology capable of detecting these reproducibly is acceptable. This standard sharing would be coordinated by the molecular pathologists performing the relevant assays.

**Appendix 1. Patient Consent Form and Clinical Protocol for “Reflex” Testing**

**Complete list of participants**

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**Disclosure of Potential Conflicts of Interest**

W. Pao is a consultant for Molecular MD. The other authors disclosed no potential conflicts of interest.

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