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At Dana-Farber/Brigham and Women’s Cancer Center, thousands of oncologists and cancer researchers are united in one common goal – to discover new ways to more effectively diagnose, treat, and prevent cancer.

We offer more than 500 clinical trials and receive hundreds of NIH-sponsored grants each year. From extensive genetics research to advanced image-guided therapies, our teams of physicians and scientists are leading discoveries that are changing how we approach cancer now and in the years ahead. We are employing novel techniques in genomics and functional assays to personalize care, uncover new targets of cancer growth, predict how patients will respond to treatment, and determine aggressiveness of disease, as well as assess a patient’s overall risk of cancer. We are pioneering image-guided therapies that are vastly improving surgical and radiation outcomes and reducing treatment morbidities. Together, our efforts will better inform clinical decisions and guide the best options for each patient.

This issue of Oncology Advances features just a few of our current endeavors. We invite you to visit our website at dfbwcc.org or contact us at (877) 332-4294 to learn more about Dana-Farber/Brigham and Women’s Cancer Center and how we are advancing care for all patients with cancer.

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**Pioneering New Discoveries in Genetic Risk Profiling in Prostate Cancer**

At Dana-Farber/Brigham and Women’s Cancer Center, groundbreaking research studies in genetic risk profiling in prostate cancer span somatic and germline mutations and are designed to identify new targeted therapies for prostate cancer, distinguish aggressive prostate cancer from indolent forms of the disease, and predict who is at higher risk for the disease.

“To maximize the benefits from genomic cancer research requires collaboration among investigators in a number of areas,” said William C. Hahn, MD, PhD, Director of the Center for Genome Discovery at Dana-Farber/Brigham and Women’s Cancer Center and Deputy Chief Scientific Officer at Dana-Farber Cancer Institute. “Our goal in bringing together the many essential pieces of this research puzzle is to improve how we diagnose, treat, and prevent prostate cancer, not just here but everywhere.”
 Insights gleaned from Profile® are expected to increase as additional mutations, variations, and arrangements are added, and some patients have already been identified with actionable mutations. The database of tumor genomic profiling data derived from a large number of patients linked to clinical information makes Profile® a powerful tool for discovery and personalized cancer medicine, supporting proposals for new research studies and clinical trials.

**Whole Genome Sequencing**

Dr. Garraway has performed whole exome or whole genome sequencing of more than 100 aggressive prostate cancers and has characterized the genomic architecture of aggressive localized prostate cancer. His efforts include the use of genomic and functional approaches to uncover possible new treatment avenues for prostate cancer patients who have progressed on hormone therapy.

“Genome sequencing gives us new understanding as to why prostate cancers arise and evolve and teaches us how best to use this full spectrum of information to determine the genes that serve as drivers in individual prostate tumors,” said Dr. Garraway. “It is this knowledge that will enable us to design the precise clinical trials for that disease.”

Significant findings based on whole genome and whole exome sequencing research in prostate cancer performed by Dr. Garraway and his colleagues include:

- Genomic rearrangements may arise from transcriptional or chromatin aberrancies and engage prostate tumorigenic mechanisms (Nature 2011 Feb 10;470(7333):214-20);

- Prostate cancers with mutant SPOP lacked ETS family gene rearrangements and show a distinct pattern of genomic alterations, therefore, SPOP mutations may define a new molecular subtype of prostate cancer (Nat Genet. 2012 May 20;44(6):685-9. doi: 10.1038/ng.2279.).

**A Closer Look at Risk Variants**

Researcher Matthew L. Freedman, MD, is studying how inherited variants, such as single nucleotide polymorphisms (SNPs), influence disease risk and prognosis.

“Genome wide association studies have uncovered almost 80 variants that are associated with prostate cancer risk. An unanticipated complexity is that most of these variants are outside of known protein coding regions,” said Dr. Freedman. “Our understanding of the non-protein coding portion of the genome is more rudimentary than our understanding of the protein coding region.”

Dr. Freedman and his team have been at the forefront of connecting the risk alleles with their target genes. They were among the first to connect the chromosome 8q24 prostate risk loci with the proto-oncogene MYC (ProcNatlAcadSci USA. 2010 May 25;107(21):9742-6) and performed one of the largest studies to reveal the genes for an additional four prostate cancer risk loci (ProcNatlAcadSci USA. 2012 Jul 10;109(28):11252-7.). They also articulated a clear strategy to pursue this type of work (Nat Genet. 2011 Jun;43(6):513-8.) In addition, Dr. Freedman and his team have studied associations between previously identified prostate risk variants and prostate cancer-specific mortality and discovered that two common polymorphisms, rs2735839 at chromosome 19q13 and rs7679673 at 4q24, are associated with prostate cancer-specific mortality (Cancer Prev Res (Phila). 2011 May;4(5):719-28. Epub 2011 Mar 2.).

“In order to fully utilize inherited variants associated with prostate cancer risk in the clinical setting, it is critical to understand the implications of carrying these risk alleles,” said Dr. Freedman. “We developed this study to determine whether these variants can differentiate men who develop low-risk, indolent forms of the disease from men who develop lethal prostate cancer.”

Researchers at the Center for Genitourinary Oncology also are using risk variants to identify patients at increased risk of developing prostate cancer in order to consider new interventions, screening approaches, counseling, and other prevention measures.

“Ultimately, these studies will have great implications on clinical decision making and on outcomes for patients,” said Adam S. Kibel, MD, Surgical Director of the Center for Genitourinary Oncology at Dana-Farber/Brigham and Women’s Cancer Center and Chief of Urology at Brigham and Women’s Hospital.
Advanced Multimodality Imaging Enables New Interventions and Builds on Groundbreaking Approaches to Cancer Treatment

Specialists at Dana-Farber/Brigham and Women’s Cancer Center are collaborating to employ new image-guided techniques in the Advanced Multimodality Image Guided Operating (AMIGO) suite at Brigham and Women’s Hospital (BWH) in order to advance treatment for many forms of cancer.

AMIGO’s innovative design enables multidisciplinary teams of surgeons, interventional radiologists, radiation oncologists, imaging physicists, computer scientists, biomedical engineers, nurses, and technologists to use multi-modality imaging to efficiently and precisely guide treatment - before, during, and after the procedure - without the patient or medical team leaving the operating room.

“AMIGO has been highly instrumental in refining and expanding image-guided techniques pioneered at BWH, as well as in introducing entirely new approaches to image-guided therapy for many forms of cancer,” said Clare M. Tempany, MD, Co-Principal Investigator of the National Center for Image-Guided Therapy (NCIGT) at BWH and radiologist at Dana-Farber/Brigham and Women’s Cancer Center.

Cancer therapies under investigation in AMIGO span treatment for malignant and benign tumors of the brain, prostate, breast, kidney, liver, lung, adrenal gland, bone, cervix, uterus, and vagina.

Prostate Cancer Evaluation and Treatment
Several significant areas of investigation in AMIGO are designed to improve evaluation and treatment of prostate cancer. Examples include:

• MRI-guided prostate biopsy and mapping – This approach enables image-guided targeted biopsy of prostate tissue based on abnormalities seen on 3T multi-parametric MRI. The technique used in AMIGO is an extension of an established MRI-guided prostate biopsy approach pioneered more than a decade ago at BWH. Additional efforts include fusing MR imaging with real-time ultrasound-guided biopsy, a technique that can be more widely adapted in other hospitals;

• MRI-guided focused ultrasound surgery – Brigham and Women’s Hospital will be among few sites in the nation to participate in an upcoming study of this technique (Focal MR-guided Focused Ultrasound Treatment of Localized Low Risk Prostate Cancer: A Feasibility Study), led by Principal Investigator Clare M. Tempany, MD, in collaboration with Adam S. Kibel, MD, Chief of Urology at BWH and Surgical Director of the Center for Genitourinary Oncology at Dana-Farber/Brigham and Women’s Cancer Center and Jerome P. Richie, MD, Emeritus Chief of Urology at BWH and urologic surgeon in the Center for Genitourinary Oncology. This study is evaluating high-intensity focused ultrasound (HIFU) therapy for patients with localized prostate cancer as an alternative to active surveillance, prostatectomy, or radiation. During this non-invasive approach, focused ultrasound will be used to ablate the tumor, guided by real-time MR imaging to map temperature changes. Expected to open in 2013, the trial is the first in the United States to study MRI-guided focused ultrasound (MRgFUS) therapy for prostate cancer. Enrolled patients will be followed long-term via PSA screening, imaging, and targeted biopsy.

Percutaneous Tumor Ablation
Kemal Tuncali, MD, Associate Director of the AMIGO suite and interventional radiologist at Dana-Farber/Brigham and Women’s Cancer Center, is performing image-guided ablation of kidney, liver, bone, lung, soft tissue, and adrenal tumors in the AMIGO suite. The approach employed in
AMIGO is an enhancement to a long-standing CT-guided percutaneous ablation technique at BWH, including more than 1,000 tumor ablation procedures. Ablative approaches include cryoablation, radiofrequency ablation, and microwave ablation.

AMIGO offers high-performance, high-field strength MR imaging and PET/CT imaging during percutaneous ablation of tumors, providing better visualization of tumor margins and surrounding critical structures. This technique enables real-time monitoring during the ablation to achieve complete treatment of the tumor and to reduce risk of injury to nearby critical structures.

Percutaneous cryoablation of renal tumor using 3 Tesla MRI guidance (left) compared with CT guidance (right). Arrows show the “iceball” during the procedures.

MR Imaging in Breast-conserving Surgery
A Phase I breast imaging pilot study in AMIGO, led by Mehra Golshan, MD, Director of Breast Surgical Services at Dana-Farber/Brigham and Women’s Cancer Center in collaboration with radiologist Eva Gombos, MD, is using advanced imaging to help improve surgical outcomes with breast-conserving therapy.

While long-term results of lumpectomy followed by radiation and medical therapies are comparable to mastectomy, for patients undergoing lumpectomy as many as 40 percent of surgical procedures must be repeated to achieve clear margins. In AMIGO, the surgeon receives real-time intraoperative images as the procedure progresses, seeing results of the surgical resection while the patient is in the operating room. Additional tissue can then be resected as needed, without requiring a second surgery. Diagnostic images prior to surgery are taken with patients in the prone position, and visualization of the tumor is optimal (Figure 1). In AMIGO, an MR image is taken just prior to the start of the procedure with the patient in the supine position (Figure 2). This provides the surgeon with a clear view of the tumor location during surgery. After the tumor is removed the breast is temporarily closed and another MRI scan is performed of the cavity boundaries (Figure 3) to check for presence of residual tumor. Further surgery is done for any margins felt to have residual cancer. Initial results from this study are promising.

Interstitial Laser Ablation of Brain Lesions
MRI-guided laser ablation neurosurgery was pioneered by Dr. Jolesz and neurosurgeons at BWH. A new study of this technique in AMIGO, led by Dr. Jolesz in collaboration with Alexandra J. Golby, MD, Director of Image-guided Neurosurgery, Clinical Co-director of the AMIGO suite, and neurosurgeon in the Center for Neuro-Oncology at Dana-Farber/Brigham and Women’s Cancer Center is currently evaluating efficacy of this procedure in patients with recurrent brain metastases. The procedure also is being offered for patients with radiation necrosis.

Interstitial laser ablation is particularly advantageous for reaching lesions deep in the brain that are otherwise difficult to access by other treatment methods. During the procedure, a cooling catheter is inserted into the brain via a stereotactic approach. Placement is confirmed with MR imaging and a laser fiber is passed through the catheter. MR imaging is continuously repeated, and test heating is performed at a low level. Temperature mapping is provided with MR imaging, and ablation is monitored with MR imaging and software outlining damage to the treatment area.
Defining Predictors of Success to Tailor Therapy for Patients with Leukemia

Researchers at Dana-Farber/Brigham and Women’s Cancer Center have developed a novel predictive biomarker for success in treatment for leukemia. This assay is able to determine which patients who initially respond to chemotherapy for acute myelogenous leukemia (AML) will continue in remission with standard chemotherapy alone and which patients are likely to relapse and may benefit from an allogeneic bone marrow transplantation.

Anthony Letai, MD, PhD, a medical oncologist in the Center for Hematologic Oncology at Dana-Farber/Brigham and Women’s Cancer Center, is senior author of the study, which was supported by the National Institutes of Health (NIH), Gabrielle’s Angel Foundation, and the Leukemia and Lymphoma Society and published in Cell (Cell. 2012 Oct 12;151(2):344-55.). The study uses a functional approach to determine how differential mitochondrial readiness for apoptosis, known as mitochondrial priming, may explain individual variation in clinical response to treatment.

“Oncologists currently predict outcome by assessing pathological features and the presence of certain mutations,” said Dr. Letai. “These indicators, however, do not explain patients’ differing responses to treatment.”

The researchers found that mitochondrial priming is a determinant of initial response to induction chemotherapy, relapse after remission, and need for allogeneic bone marrow transplantation. Using BH3 profiling on stored AML cell samples, they were able to determine the degree to which mitochondria were primed for apoptosis. BH3 profiling exposes mitochondria in cancer cells to BH3 molecules, which mimic protein death signals. If the mitochondrial membrane is rapidly and easily disrupted during this process, the cells are considered to be highly primed for apoptosis and likely to respond well to chemotherapy. If the mitochondria strongly resist the disruption, the leukemia cells are less likely to respond to chemotherapy. Normal hematopoietic stem cells were found to be less primed to apoptosis than leukemia cells that were readily destroyed by chemotherapy. Cells from AML patients who had responded poorly to chemotherapy were even less primed than normal hematopoietic stem cells to apoptosis.

“Our data suggest that applying our assay, in addition to conventional indicators, yields a much better predictive tool,” said Dr. Letai. “The information gleaned from this biomarker will help us tailor treatments for patients based on their likelihood to respond, as well as avoid toxic effects of aggressive therapies where they may not be warranted.”

Through BH3 profiling, researchers in the study also found that AML cells, compared with normal hematopoietic stem cells, are more dependent on molecular signals generated by the BCL-2 protein for survival. Experimental drugs that inhibit BCL-2 are being tested in clinical trials and may provide a potential way to better prime leukemia cells for apoptosis.

Dr. Letai and his team are planning to initiate validation studies of the biomarker approach in 2013 and expect prospective clinical trials to open in 2014. Using an independent set of patients, validation studies will assess the test’s accuracy in determining which young patients with AML who achieve complete remission in induction chemotherapy should receive bone marrow transplantation or consolidation chemotherapy, as well as the best initial therapy for AML patients over the age of 60.
Novel Tests Determine Prognosis and Confirm Diagnosis in Mesothelioma

Gene expression ratio tests, developed and validated by Raphael Bueno, MD, Associate Chief of Thoracic Surgery at Brigham and Women’s Hospital and thoracic surgeon in the Center for Thoracic Oncology at Dana-Farber/Brigham and Women’s Cancer Center, confirm differential diagnosis and predict survival in patients undergoing surgical treatment for mesothelioma. These tests are expected to be available for clinicians in 2013.

“This work of Dr. Bueno’s laboratory is a game-changer in the surgical management of this disease,” said Dr. David Sugarbaker, Chief of Thoracic Surgery at Brigham and Women’s Hospital and thoracic surgeon in the Center for Thoracic Oncology at Dana-Farber/Brigham and Women’s Cancer Center and the Director of the International Mesothelioma Program (IMP).

“Current treatment for mesothelioma usually requires aggressive surgery to remove all the tumor and perform complete macroscopic cytoreduction. This concept and surgical approach were developed and refined by David Sugarbaker, MD, and surgery is on occasion associated with a long recovery period,” said Dr. Bueno. “Being able to identify which patients will most likely benefit from this therapy is extremely valuable in the clinical management of patients with mesothelioma, helping clinicians and patients to make more informed decisions regarding care.”

Demonstrated Robust Predictive Value

In a validation study published in the Journal of the National Cancer Institute (J Natl Cancer Inst. 2009 May 6; 101(9): 678–86.), clinical data were obtained prospectively from 120 consecutive patients with malignant pleural mesothelioma who underwent debulking surgery at Brigham and Women’s Hospital. Specimens were obtained at the time of surgery and by pleural biopsy examination. Expression data for four genes were collected from tumor specimens, and three ratios of gene expression (TM4SF1/PKM2, TM4SF1/Novel Tests Determine Prognosis and Confirm Diagnosis in Mesothelioma ARHGDIA, and COBLL1/ARHGDIA) were determined by quantitative reverse transcriptase–polymerase chain reaction. Patients were assigned to good or poor outcome groups by the gene ratio test.

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The prognostic test accurately predicted overall survival and cancer-specific survival in a highly significant manner. The test was reproducible within patients and repeatable between two determinations for specimens with widely varying tumor cell contents. Combining the gene ratio prognostic test and other prognostic factors allowed prospective discrimination between patients at high risk (median survival = 6.9 months and 3-year survival = 0 percent) and low risk (median survival = 31.9 months and 3-year survival = 42 percent).

A second gene ratio test serves as a diagnostic assay, which confirms mesothelioma and distinguishes it from other potential confounding diagnoses that may present clinically in a similar manner. These two tests are licensed by Castle Biosciences, and availability is anticipated in 2013.

Based on the results of these tests and other genomic sequencing studies, specialists at Dana-Farber/Brigham and Women’s Cancer Center, led by David Sugarbaker, MD and Raphael Bueno, MD, are designing novel neoadjuvant and adjuvant therapies for subsets of mesothelioma patients with specific genetic mutations. Clinical trials are expected to open in the first half of 2013.

<table>
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<th>Model and risk group</th>
<th>Risk factor</th>
<th>Patients, No. (%)</th>
<th>Median OS, mo (95% CI)</th>
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<td>31.9 (21.9 to 41.7)</td>
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<td>6.9 (2.6 to 8.9)</td>
<td>18 (6 to 57)</td>
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<td>Three subgroups†</td>
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<td>High</td>
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<td>15 (12)</td>
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</tr>
</tbody>
</table>

* OS = overall survival; CI = confidence interval.
† Total number of adverse risk factors among mixed or sarcomatoid histology, presence of cancer in a lymph node, and a poor predictive gene ratio test result.
‡ In this model, the intermediate-risk groups from the four-subgroup model were combined.
Advanced Multimodality Imaging Enables New Interventions and Builds on Groundbreaking Approaches to Cancer Treatment... continued from page 5

Flexibility in positioning of the laser fiber enables surgeons to begin the approach at the middle or the edge of the target area and to reposition the catheter as necessary throughout the procedure.

**Brachytherapy for Gynecologic Cancers**

MRI-guided brachytherapy for gynecologic tumors is performed in AMIGO by Akila N. Viswanathan, MD, MPH, Director of Gynecologic Radiation Oncology at Dana-Farber/Brigham and Women’s Cancer Center. Dr. Viswanathan was the first in the nation to offer this technique and led the first prospective clinical trial using real-time MRI image-guided brachytherapy ([Int J Radiation Oncology Biol Phys, Vol 66, No 1, pp. 91-99, 2006](https://doi.org/10.1016/j.ijrobp.2006.01.050)). Suitable for select patients with cervical, vulvar, vaginal, and uterine cancers, including patients with recurrent gynecologic cancer, this approach is performed using real-time MRI guidance.

MRI-guided brachytherapy for gynecologic cancer offers an alternative to surgery and is designed to protect surrounding tissues in the bladder and the rectum, reducing the risks of rectal bleeding and bladder ulceration.