Published in final edited form as:

Surgery. 2009 December ; 146(6): 971–978. doi:10.1016/j.surg.2009.10.023.

Personalized medicine: the future is not what it used to be:

Presidential address 2009 meeting of the American Association of Endocrine Surgeons

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“The future is not what is used to be.” - Malcolm Rifkind

“If I'd asked my customers what they wanted, they'd have said a faster horse.” - Henry Ford

People want personalized medical care. I would like to think that we doctors have always treated our patients based on their individual health status including factors such as their medical history, family history, laboratory data, results of imaging and patient wishes. Personalized medicine, as a term, has evolved to indicate that the results of various forms of genomic analysis are applied to tailor an individual patient's medical care. Patients don't know, and indeed, most doctors don't understand the future that the emerging molecular technologies can bring to the practice of medicine. Still, there are clear advantages that supplement but do not replace traditional clinical medicine. These advantages include the potential for predicting susceptibility to disease and as a result, more detailed screening or prophylactic preventative treatment. Personalized medicine also offers the potential for the diagnosis of disease at an early and more effectively treated time when the sequelae of the disease may be ameliorated. This is particularly true in the cancer field, where we work. Potential beneficiaries of the novel technologies will primarily be our patients but those who pay for medical care will also benefit. There are immense business opportunities for companies that develop diagnostics, drugs or methods for data analysis. My message today is to focus on how we as surgeons have an opportunity and a responsibility to become involved and influence the development of personalized medicine as a field of discipline. Already several medical schools have developed institutes, programs or curriculum focused on personalized medicine. Companies have been formed marketing individual analyses that purport to predict one's risk of the development of a myriad of diseases ranging from Alzheimer's disease or diabetes to male pattern baldness. In my address, I plan to review the current state of the field as it relates to our practice as endocrine surgeons.

Surgical Genomics

We are clearly in the early days of genomic surgery. Technology allowing for genomic analysis is evolving rapidly. What will the future bring? We commonly hear such terms as expression arrays, SNPs and microRNA. Technology is advancing rapidly but clinical correlation lags far

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behind. In some circumstances, we can suggest an increased risk for certain diseases based on genomic analysis but, with notable exceptions, we cannot precisely define the phenotypes associated with genomic aberrations in such a manner as to allow us to tailor treatment to a particular patient. There are well-described concerns associated with genomic testing including the risk of a loss of privacy or misuse of healthcare information resulting in discrimination. Patients have a right not to know if they so chose. Society should take steps to prevent profiteering from direct to consumer testing without proper genetic counseling. Perhaps someday, genetic surgeons will repair a mutated gene and restore normality in order to prevent the development of a cancer not only in patients but also in their potential offspring.

Surgical decisions are already made routinely based on genetic profiles of patients. Undoubtedly, as we learn more how specific mutations affect phenotype, we will increase our reliance on genetic analysis. Sam Wells, in his Grey-Turner address presented at the International Surgical Week in 2007, detailed the criteria for an optimal prophylactic surgical procedure based on genomics: (1) for given hereditary cancer, the causative genetic mutation must have a very high likelihood of causing the cancer regardless of environmental factors; (2) One must be able to reliably test for the genomic aberration and identify patients who have inherited the mutated gene; (3) the operation to remove the target organ must be associated with minimal morbidity and virtually no mortality; (4) there must be a feasible replacement for the function of the removed organ; and (5) there must be a reliable method of ascertaining over time that the patient has been cured by prophylactic operation.ⁱ There is perhaps no clinical scenario where these criteria are completely met but we can consider those where prophylactic operation based on genomic status is in common practice.

Hereditary colorectal cancer syndromes include the familial adenomatous polyposis (FAP) and the hereditary nonpolyposis colorectal cancer (Lynch) syndromes. FAP is characterized by a germ line mutations in APC, a tumor suppressor gene, resulting in the formation of adenomatous polyps in the colon. These adenomatous polyps invariably develop into cancers as they acquire additional mutations and genetic aberrations. Patients with FAP should be considered candidates for prophylactic colectomy. The Lynch Syndrome is the most common hereditary form of colorectal cancer with a prevalence of one in 35 among patients with CRC. Lynch Syndrome is due to mutations in at least one of four DNA mismatch repair genes, MLH1, MSH2, MSH6 and PMS2. Patients who are affected have been shown to benefit from early and more frequent surveillance with colonoscopy,ⁱⁱ but the data supporting prophylactic colectomy is not as clear as it is for FAP and remains controversial.^{iii·iv}

The most well studied hereditary breast cancers are the result of germ-line BRCA1 and BRCA2 mutations. Between 5 and 10% of the 192,000 American women who develop breast cancer every year have one of the hereditary forms of this disease. The lifetime risk of a woman in the general population of developing breast cancer is 3.8% and ovarian cancer is 1.5%. In contrast for a woman harboring the BRCA1 mutation, the lifetime risks of breast cancer and ovarian cancer are 85% and 54–63%, respectively; for BRCA2 carriers the same risks are 86% and 23–27%.^{v,vi} With this knowledge, women and their treating physicians can choose to perform more intensive surveillance^{vii} to include measures such as regular physical exams, earlier and more frequent mammography, breast magnetic resonance imaging, transvaginal ultrasonography and serum CA-125 testing. Chemoprevention with tamoxifen^{viii} or other drugs has not been shown to be beneficial in significantly reducing the risk that a woman with BRCA1 or BRCA2 will develop breast cancer.^{ix}

Many patients who seek a real reduction in cancer risk, therefore, choose prophylactic surgery. While not completely eliminating its risk, these operations greatly reduce the chance of developing cancer.^{x,xi,xii} Risk reduction is not absolute because, with any of the several operations available including subcutaneous mastectomy, skin-sparing or nipple sparing

mastectomy, and total mastectomy, it is possible for residual breast tissue to remain. Prophylactic mastectomy is not without risk. While the operative mortality rate is very low, complications occur with the operation and the risks increase if one chooses reconstruction. There are long-term psychological effects as well, including emotional instability, stress, loss of self-esteem and problems with sexual relations in 9 to 25% of patients.^{xiii} In a large prospective study that controlled for many factors, the risk for gynecologic cancer was reduced by 80% following prophylactic oophorectomy. An important consideration relative to selecting this procedure is that screening options are less effective for ovarian cancer than they are for breast cancer. Many women wait to undergo oophorectomy until after finishing with their childbearing.

Members of the American Association of Endocrine Surgeons are well aware of the prototypical clinical scenario for prophylactic surgery in the prevention of medullary thyroid cancer. Approximately 5–10% of thyroid cancers arise from the parafollicular cells and of these medullary thyroid cancers, about 25% arise due to an inherited genetic mutation in the RET proto-oncogene as part of multiple endocrine neoplasia type 2A (MEN2A)(60%), MEN2B (5%), or familial medullary thyroid cancer (FMTC)(35%).^{xiv} The penetrance of MTC associated with the known mutations in RET is virtually 100%. Since the identification of RET as the susceptibility gene for MTC,^{xv}^{xvi} the phenotypic expression associated with mutations in the various “hot spots” has been better defined.^{xvii} Over 80% of patients with MEN2A have RET mutations in codon 634 of exon 11 but mutations have also been reported in exon 10 (codons 609, 611, 618, 620). Several studies have shown correlation of specific mutations with aggressive tumor behavior. In over 95% of the cases MEN2B, the RET mutation is present in exon 16 at position 918. The spectrum of mutations associated with familial MTC overlaps with that of MEN2A in about 50% of cases in that RET mutations occur in codon 634. Testing for these mutations is readily available and reliable. Therefore, genomic analysis translated to clinical practice allows for a total thyroidectomy prior to the development of cancer all but assuring a cure.^{xviii}

In the absence of a family history of endocrinopathy, which patients with a medullary thyroid cancer or a pheochromocytoma should be tested for a genomic mutation? For patients with an apparent sporadic medullary thyroid cancer the risk of a germ-line RET mutation ranges between 1.5% and 22.7% depending on the series. The risk of a pheochromocytoma occurring the background of a RET mutation is about 2.5% but these tumors are the first manifestation of MEN2A in only 9 to 27% of cases. Recently, investigators including members of this organization have begun to link the penetrance of pheochromocytoma to specific mutations in RET.^{xix} Undoubtedly, these observations will continue be refined but at present no RET mutation fully distinguishes the risk of this tumor, as all have been reported in associated with syndromic pheochromocytomas.^{xx} Any patient with a malignant pheochromocytoma or a paraganglionoma, should be evaluated for a germ-line mutation in RET, the Von Hippel-Lindau gene, neurofibromatosis or the succinate dehydrogenase subunit B or D genes. A mutation in the VHL, SDHB or SDHD genes could have therapeutic importance in the treatment of a malignant pheochromocytoma because these patients' tumors have increased levels of hypoxia inducible factor 1 α and its downstream effector TrkA.^{xxi} Inhibitors of HIF1 α and TrkA are currently in phase I trials in our clinic.

In papillary thyroid cancer (PTC), emerging data regarding the role of BRAF mutation may alter the way we approach patients with this disease. Mutation in this gene occurs in about 44% of these tumors.^{xxii} We have long used clinical parameters such as age at presentation, gender, grade or extent of tumor, size, histological variant, presence of distant metastases and the like in order to classify tumors as being of low or high risk to a patient's health. Specialists continue to discuss whether one should perform a total thyroidectomy, add a central neck dissection to the thyroidectomy, administer radioactive iodine and if so, at what dose and a myriad of other

clinically relevant issues. The issues are unresolved, largely due to the relative rarity of aggressive papillary thyroid cancers and the long-term follow-up needed to answer such questions. Still the current annual mortality rate for thyroid cancer in the United States is 1530, most of these due to PTC.^{xxiii} The RET/PTC→Ras→Raf→MEK→MAPK/ERK pathway has been implicated as an important signaling pathway regulating cell functions as proliferation, differentiation, apoptosis and when perturbed, tumorigenesis.^{xxiv} While the role of activating mutations of *ras* in carcinogenesis is well established, only recently have investigators shown mutations in BRAF in many human cancers resulting in activation of the MAPK pathway.^{xxv} The most common such mutation in BRAF is the T1799A point mutation resulting in a substitution of glutamic acid for valine at position 600 and it is this mutation that is described in thyroid cancer.²² Many studies have now shown an association between BRAF mutation and extra-thyroidal extension, lymph node metastases and advanced stage.^{xxvi,xxvii} Furthermore, there is some evidence to suggest that for patients with low risk tumors by clinical criteria, a mutation in BRAF portends an increased risk of recurrence of PTC.^{xxviii} At this point, we are left to evaluate how one might alter treatment decisions based on whether an otherwise low-risk patient's tumor harbors a somatic BRAF mutation, in favor of more aggressive treatment. Should one perform a more extensive operation? Should one use more radioactive iodine? Should one suppress TSH? The perturbed MAPK pathway also poses an opportunity to develop novel drugs to treat radioiodine-resistant PTC. Several MEK inhibitors have been developed and are in various stages of clinical evaluation.

Novel therapeutic agents

Beyond prophylactic surgery to prevent disease, genomic data from tumors is being used to design novel therapeutic agents targeting identified aberrations. Progress has been remarkable resulting in more effective treatments for therapeutically challenging cancers. This discovery process is limited largely by a lack of access to well annotated clinical cancer samples and data regarding response to treatment. This is particularly true for rare tumors. Rare tumors are of particular interest to endocrine surgeons because we often deal with them. The hypothesis of our group at TGEN is that many rare tumors harbor a genomic Achilles heel. For example, such is the case of Gastrointestinal Stromal Tumors (GIST), c-kit mutations and the remarkable response to targeted therapy with imatinib mesylate (Gleevec®). Many refractory GIST tumors harbor mutations in the platelet derived growth factor receptor alpha gene and these patients often respond to the multiple tyrosine kinase inhibitor sunitinib malate (Sutent®). This agent is an oral kinase inhibitor of fms-like tyrosine kinase 3, and the Kit, vascular endothelial growth factor and platelet-derived growth factor receptors. In another success story for this drug, in March of this year, Pfizer announced that it was stopping its phase III trial of sunitinib in patients with advanced pancreatic islet cell cancers early because the drug was clearly effective in prolonging progression-free survival. This trial compared sunitinib to placebo plus best supportive care.

For another less well-known story of successful targeted therapy, I cite recent work by my colleagues at TGEN and Scottsdale Healthcare as reported by Dr. Von Hoff at the 2008 meeting of the American Association of Cancer Research. This study reports remarkable results of a hedgehog pathway inhibitor, GDC-0449, in the treatment of patients with invasive aggressive basal cell carcinomas. The remarkable story starts in the 1950's with the observation by shepherds in Iowa that cyclopic lambs were born to ewes that ate certain corn lily plants. It turns out that a chemical in the corn lily, when eaten by pregnant sheep stopped development of the lambs' second eye by turning certain genes off and on. It was subsequently established that a chemical, called cyclopamine, from this plant inhibits the hedgehog pathway. The Sonic Hedgehog protein (SHH) is secreted from producing cells to reach the surface of target cells where it interacts with its receptor, the multipass transmembrane protein Patched (PTCH1).^{xxix} In the absence of its ligand, PTCH1 inhibits Smoothened (SMO). SHH binding

relieves Patched-mediated SMO inhibition resulting in cell proliferation and transcriptional activation of SHH target genes. Virtually all basal cell cancers arise from mutations in PTCH (90%) and SMO (10%). When treated with GDC-0449, an investigational compound that inhibits signaling in the Hedgehog pathway, eight of nine patients with metastatic basal cell carcinoma had durable clinical benefit with minimal toxicity. Improvement lasted for a median duration of 176 days and for as long as 438 days. Curis Inc., a Massachusetts drug company, is partnering with Genentech to develop synthetic forms of cyclopamine.

Last month at the 2009 annual meeting of the American Association for Cancer Research, Dr. Von Hoff presented our group's experience with molecular profiling used to select chemotherapy for patients with refractory cancers. This study cohort included patients with cancers to at least 2 prior chemotherapy regimens. The new chemotherapy regimens were selected on the basis of immunohistochemistry and expression array analysis of tumor biopsies. With each patient's time to progression while on his or her previous course of therapy used as a basis for comparison, we found molecularly targeted treatment was associated with a longer progression-free survival. Survival of responders nearly doubled to 9.7 months compared to only 5.0 months for the entire cohort. Amongst the 66 evaluable patients, there was 1 complete remission and 5 partial remissions. Many others responded to a lesser degree or had stable disease. Keep in mind that these are the sickest of the sick cancer patients. This pilot trial has encouraged us to continue this work with additional clinical trials using molecular profiling specifically aimed at patients with breast cancer, colon cancer and rare tumors including endocrine cancers. These proof of principle trials have the potential to take the field of personalized cancer treatment forward and have attracted funding from several agencies including the Side-out Foundation, the Bisgrove Foundation and the National Foundation for Cancer Research.

A prototypical rare tumor: Adrenocortical Cancer

Rare tumors pose particular challenges for patients who are afflicted by them and to those investigators who chose study their disease. Patients may have problems finding a doctor with any experience in their type of tumor so they are turning to the Internet for information. They are increasingly proactive in seeking information and expertise. As a result, many find us because as most of you are aware, my own lab's interest is finding new treatments for adrenocortical cancer. It is a rare tumor with an incidence of approximately 1 in 1.7 million people. There has been no new drug approved since mitotane over 50 years ago. Mitotane has a narrow therapeutic window and significant toxicity. Standard therapy is generally considered to be the so-called Italian Regimen, a combination of etoposide, doxorubicin, cisplatin, and mitotane. The response rate to this regimen is less than 50% and there is no recognized second-line treatment regimen. I hope to share with you some of what we have learned. Our efforts would not have been possible without the collaboration of other surgeons who have banked fresh tumor samples and have been kind enough to share these samples with our lab for research purposes.

We are pursuing a strategy of finding potentially drugable targets in adrenocortical cancer by analysis of gene expression using array-based technologies. Following the clue that ACC occurs in patients who have Beckwith-Wiedeman Syndrome which is characterized by increase expression of IGF2, others have shown, and we have confirmed that ACC typically over-expresses insulin-like growth factor 2. Several companies have developed monoclonal antibodies or small molecule inhibitors of its receptor IGF1R that block downstream signaling via the PI-3 kinase pathway. It is hoped that use of one of these agents either alone or in combination with mitotane or other drugs could be effective in the treatment of metastatic ACC. We also have seen marked over-expression of the motor proteins including the kinesin Eg5, another potentially attractive target. Drugs that act on the microtubules have had some

efficacy in ACC and these agents targeting kinesins have promise in that their effect is more specific to the mitotic spindle. Our group at the TGEN Clinical Research Service at Scottsdale Healthcare currently has an Eg5 inhibitor in a phase I clinical trial which is open to patients with ACC.

One of the challenges with adrenocortical cancer is that mitotane has a response rate of only about 22% and is also associated with substantial toxicity, such that many patients are reluctant to take the drug. It would be a significant advance in the treatment of ACC if one could find a biomarker that would predict response to the drug. Here is where knowledge mining of information from disparate databases has been valuable. Kim Bussey, in our lab, used information from a mitotane synthetic lethal RNAi screen in drosophila, expression profiling of human ACC tumors and information contained in the NCI60 cell-line data base to identify that decreased SIRT1 is a putative marker of mitotane resistance in ACC. She has gone on to test this hypothesis by using ACC cell lines. SW13 cells under-express SIRT1 and are insensitive to mitotane *in vitro*. When she transfected SW-13 cells to make them over-express SIRT1, she found that they became more sensitive to mitotane. Conversely, when H295R cells, which are sensitive to mitotane, had their SIRT1 levels decreased by siRNA their response to mitotane decreased. The next step is to test this hypothesis further by examining patient samples where the response to mitotane is known. This can be accomplished in a multicenter collaboration better than it can be done at any single site.

The benefits and limitations of developing targeted therapies

The marked successes of trastuzumab (Herceptin®) in the treatment of breast cancers expressing Her-2/Neu and imatinib in chronic myelogenous leukemia and GIST may be rather exceptional cases.^{xxx} The pace of new drug approval has slowed and the hurdles, particularly financial, are considerable. The premise behind targeted therapy is attractive. One determines pathways that are aberrant in cancer cells and on which cancer cells are dependent for growth, invasion, metastases, angiogenesis or other essential tumor functions. By selectively targeting these pathways, one hopes to treat the cancer with less toxicity than with less targeted anti-cancer agents. Some investigators have argued that the complexity of cancer is an impediment to pursuing curative strategies and because we don't fully understand the biochemical pathways involved in disease, unintended consequences may occur.^{xxxi} For example, inhibition of angiogenesis may reduce the delivery of chemotherapeutic agents into tumors. Conversely, numerous genomic aberrations may cause cancer cells to stand on a proverbial precipice such the cancer cell is vulnerable to the targeting of one or two key pathways.

So how do we prove that rare tumors have an Achilles heel? Progress will be greatly aided by novel methods for applied informatics, artificial intelligence and powerful computers. Researchers need to work in teams because the scope of talents required is great. An individual who is an expert clinician, molecular geneticist, computational biologist, biostatistician, medicinal chemist and drug developer does not exist. Access to tumor material annotated with clinical information and response to treatment is the starting point. For relatively rare cancers, large prevalence studies for genomic aberrations are not possible, but deep dive analysis of relatively small numbers of tumors can be very informative. Novel techniques for knowledge mining allow one to leverage the findings from a relatively small numbers of tumors against the much more extensive body of knowledge in the medical literature related to more common cancers. In this way, an abnormality in a pathway or pattern of mutations seen in a small number of tumors when examined in the context of similar abnormalities in other tumors can yield insights regarding the pathogenesis, biologic behavior or vulnerabilities of the rare tumors.

One of the concerns commonly expressed by pharmaceutical firms investigating potential uses for their agents in rare tumors is whether one has the ability to accrue sufficient numbers of

patients into their trials. No one site may see sufficient numbers of patients with rare endocrine tumors such as parathyroid cancer, malignant pheochromocytoma or ACC but if several sites cooperate to enroll patients, sufficient numbers of patients could be accrued. This is certainly a role the American Association of Endocrine Surgeons should fulfill. Our participation could also encourage a pharmaceutical company to pursue approval of a drug targeted to a rare tumor. Although the potential market for such a drug is small and the potential for a return of their investment is limited, the federal government has implemented incentives in the Orphan Drug Act designed to increase development of new drugs for rare diseases. The measures provided for in the Orphan Drug Act include tax credits for clinical research used to generate the data required for approval, and seven years of marketing exclusivity for the designated drug or biological product once approved by the FDA. These incentives have stimulated considerable interest in the development of orphan drug and biological products.

The role of the AAES

So then how do we, the members of the American Association of Endocrine Surgeons, get involved? We can begin by agreeing to work together in order to develop an infrastructure to facilitate collaborative research. There are hurdles including individual interests for primacy in projects and the desire to get academic credit for the purpose of obtaining promotion and tenure at one's institution. Institutions want protection of intellectual property and are reluctant to surrender oversight of research projects to external agencies or Institutional Review Boards (IRB). The result of these types of arguments is that the work doesn't proceed and no one gets much done. Many institutions, however, have agreed to accept external IRB approval, in lieu of that from their own IRB, such as that provided by commercial national boards such as the Western IRB. This type of IRB approval provides for uniformity of protocols and speeds the process of implementation of protocols at a site. The concerns detailed are real but our patients need us to find ways to accommodate our individual needs and get the job done.

We should also work to develop joint tumor registries and annotated tumor banks. Most of our institutions already participate in regional or national tumor registries so in all likelihood, much of the infrastructure needed already exists to allow a focus on the tumors of interest to our specialty. The clinical information in most registries, however, is not linked to tumor samples, even paraffin-embedded sample collections maintained in pathology departments. Annotated frozen tumor banks which are best suited for analysis of genomic material particularly RNA is an even more rare resource. We can begin by gathering a collection of paraffin-embedded tumor samples and providing the clinical annotation of these samples. Samples are much more valuable if linked to clinical information and response to treatment. In many cases, these samples will not ever be used if they remain in the archives of the host institution but if joined with samples from other sites, they can be fashioned into tissue microarrays and shared with other investigators. In return, an investigator from each donor institution would have access to the entire set of samples. The cost is relatively low for this type of initiative. Moving forward, frozen tumors should be banked. We should develop repositories of cancers, benign tumors and adjacent normal tissue as well as serum samples from patients. Longitudinal tumor samples from patients who later undergo surgery for recurrent or metastatic disease and clinical annotation detailing response to therapy are particularly valuable. Once developed, the tumor sample banks would be managed as a resource. A committee of the AAES would review applications for samples much as one would review a grant in that the requestor would have to show background and pilot data, a valid and important hypothesis along with methodology to assure that the work could be completed to test the given hypothesis.

In closing, it is very exciting to be working in this nascent era of truly personalized medicine. Our participation requires that we continue to educate ourselves as the field progresses. We are looking at Henry Ford's faster horse. We are looking at changing the way we think about

diseases and how we treat them. We have the opportunity and I feel, the responsibility, to participate in clinical research to improve the options for treatment for our patients with endocrine cancers. We can do this best by collaborating with each other.

Acknowledgments

Lastly, I would like to acknowledge several mentors. I have learned so much from many of the members of this organization who have shared their knowledge and experiences with me. I would like to in particular, however, recognize Tony Edis and Orlo Clark who were my mentors as a fellow in endocrine surgery. I learned from them how to operate on the endocrine glands and to conduct scientific investigation in the pursuit of new knowledge. My time in Orlo's lab gave me essential tools need to pursue my academic career. I can't stress enough the value of time in the lab for an academic surgeon. I learned from Stu Wilson how to take care of patients as people first. He is an excellent surgeon and a caring person who is the best role model a young surgeon could have had. I learned from Bob Condon about integrity and fairness in a leadership role. He provided opportunities for me and guided me in my young academic career. Lastly, I have the pleasure of working now with Dan Von Hoff. He is the quintessential translational investigator. His knowledge, dedication, drive and devotion continue to amaze me. All of these mentors have set standards to which I can only aspire, but I will continue to try. I wish to express my gratitude to all these terrific physicians and others who have taught me so much. On a personal note, I have been very fortunate to be a member of the American Association of Endocrine Surgeons and this past year, it has been my great honor to be your president. This is particularly humbling when I review the impressive roster that comprises the list of former presidents. I hope I have contributed in some small ways to make the AAES better serve its members and our patients.

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