REVIEW ARTICLE

Translational Research in Surgical Disease

Alexander Stojadinovic, MD; Nita Ahuja, MD; Susanna M. Nazarian, MD, PhD; Dorry L. Segev, MD; Lisa Jacobs, MD; Yongchun Wang, MD; John Eberhardt, MD; Martha A. Zeiger, MD

Objective: To review cutting-edge, novel, implemented and potential translational research and to provide a glimpse into rich, innovative, and brilliant approaches to everyday surgical problems.

Data Sources: Scientific literature and unpublished results.

Study Selection: Articles reviewed were chosen based on innovation and application to surgical diseases.

Data Extraction: Each section was written by a surgeon familiar with cutting-edge and novel research in their field of expertise and interest.

Data Synthesis: Articles that met criteria were summarized in the manuscript.

Conclusions: Multiple avenues have been used for the discovery of improved means of diagnosis, treatment, and overall management of patients with surgical diseases. These avenues have incorporated the use of genomics, electrical impedence, statistical and mathematical modeling, and immunology.

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Author Affiliations: Division of Surgical Oncology, Department of Surgery, Walter Reed Army Medical Center, Washington, DC (Dr Stojadinovic); Division of Endocrine and Surgical Oncology (Drs Ahuja, Jacobs, Wang, and Zeiger), Division of Vascular Surgery (Dr Nazarian), and Division of Transplantation (Dr Segev), Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland; and Healthcare DecisionQ Corporation, Washington, DC (Dr Eberhardt).

THE FOLLOWING REVIEW OF cutting-edge, novel, implemented and potential translational research is meant to provide a glimpse into rich, innovative, and brilliant approaches to everyday surgical problems. It is written primarily by young, innovative surgical scientists in their field of interest and often in their field of research. The contents include research on thyroid nodule diagnosis, treatment for gastrointestinal stromal tumors (GIST) and colon cancer, aortic aneurysm treatment, mathematic models for kidney donor–recipient matching, and breast cancer treatment. It encompasses mathematical, statistical, and molecular innovations.

THYROID NODULE DIAGNOSIS

Although it is the current standard of practice for the diagnosis of thyroid nodules, fine-needle aspiration biopsy's (FNAB) primary shortcoming rests with the differential diagnosis of indeterminate lesions. The National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference recently supported a 6-tier classification system for FNAB that includes (1) lesion (atypia) of undetermined significance, (2) follicular neoplasm, and (3) nodules suspicious for malignancy.[1] The risk of malignancy ranges from 5% to 10% for follicular lesions (atypia) of undetermined significance, 20% to 30% for follicular neoplasms, and 50% to 75% for nodules with cytological features suspicious of malignancy.[1] Because cytology results are indeterminate in up to one-third of FNABs, the frequency of diagnostic or nontherapeutic thyroid resection is significant. Hence, given a 30% rate of indeterminate cytology with an overall malignancy prevalence of 20% to 30% in these lesions, most patients with indeterminate cytology who have thyroid resection have benign histopathology.[2] Accurate diagnostic adjuncts to FNAB and clinically relevant treatment-directing decision-support tools that are capable of differentiating benign from malignant nodules therefore represent an unrealized need in thyroid surgery.

High-Throughput Analysis of Thyroid Tumors

We know from review of the Johns Hopkins experience that there are 8 histopathological subtypes of thyroid tumors that pose a diagnostic dilemma for the clinician: papillary thyroid cancer, follicular variant of papillary thyroid cancer, follicular cancer, Hürthle cell cancer, adenomatoid nodule, follicular adenoma, Hürthle cell adenoma,

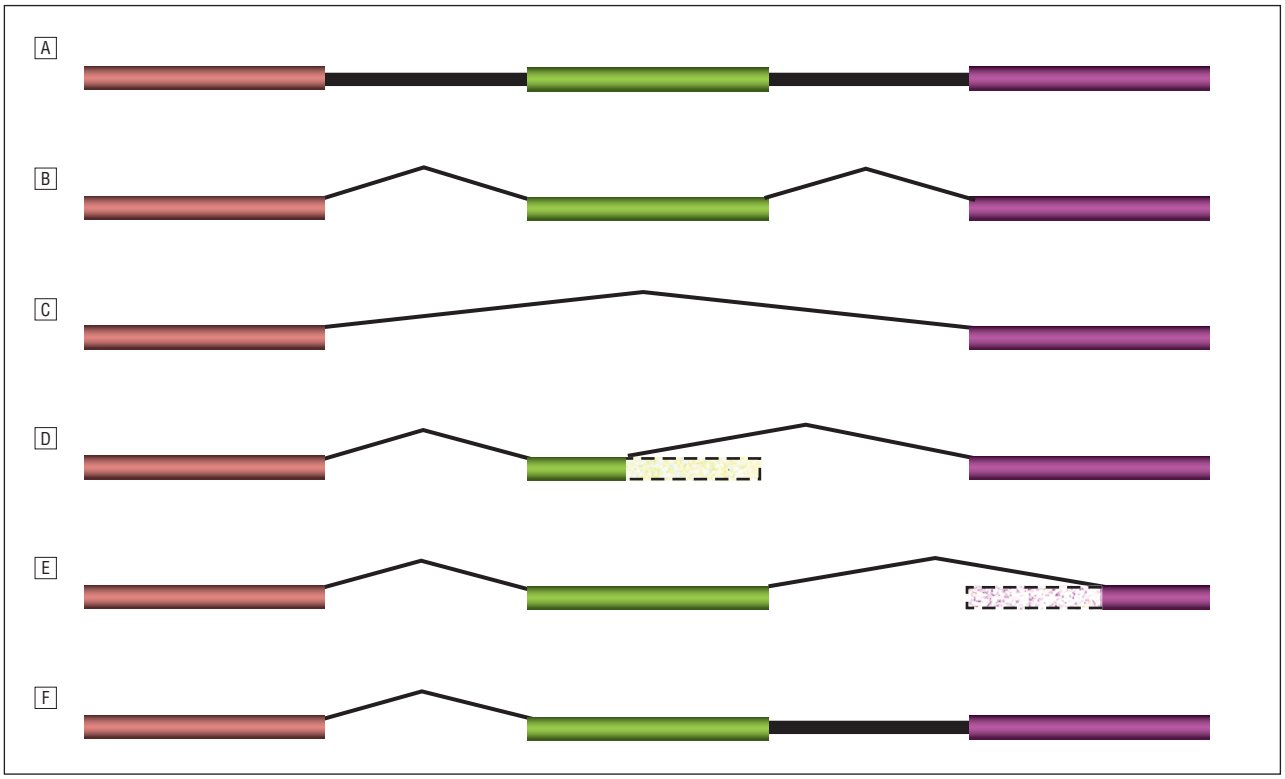

Figure 1. Patterns of RNA splice variants. Variants shown are pre–messenger RNA (exons are color coded) (A); wild-type mRNA with all exons used (B); exon skipping with second exon excluded (C); alternative 5′ splice site with only the first part of the second exon included (D); alternative 3′ splice site with only the last part of the second exon included (E); and intron retention with retention of the noncoding intron (F).

and lymphocytic thyroiditis nodule.[3] All 8 of these tumor types therefore require identification of distinguishing diagnostic markers. By microarray analysis, using data from the genome project, several authors have examined thyroid neoplasms for genetic markers that might be useful in the distinction of benign from malignant tumors.[4-9] However, no group has identified a panel of molecular markers that are useful in the distinction of the 8 thyroid tumor types that can be associated with indeterminate FNAB results, applied the markers to FNA diagnosis in the preoperative setting, and then proven their utility in distinguishing benign from malignant tumors.

Alternative Splicing of Genes

With completion of the genome sequence and the estimated 20 000 to 25 000 genes comprising its entirety, it has become clear to investigators that the complexity of humans cannot be fully explained by so few genes. Alternative splicing of messenger RNA (mRNA) provides an intricate means by which individual genes can be expressed in various isoforms and it is through this process that each mRNA can be translated into several different proteins. This mechanism thereby results in tremendous protein diversity and, in turn, the possibility of developing a robust diagnostic tool. Pre-mRNA splicing is a precisely regulated process in posttranscriptional modification and results in several types of events.[10] The 5 most common splice events are (1) exons are either skipped or (2) included in the final mRNA; (3) alternative 5′ (donor) and (4) 3′ (acceptor) splice sites cause shortening of the involved exons; and (5) an intervening intron can also be retained (**Figure 1**).[11,12]

Human Telomerase Reverse Transcriptase Alternative Splice Variant Patterns in Thyroid Tumors

Relevant to alternative splicing, Wang et al[13] have tested 133 thyroid tumors including 60 malignant and 73 benign tumors for human telomerase reverse transcriptase (hTERT) alternative splice variant patterns by reverse transcriptase polymerase chain reaction. The hTERT alternative splice transcripts tested for and identified included 4 isoforms: full length, which is the active form, and α-deletion, β-deletion, and α-β–deletion, which are the inactive or dominant-negative forms. Significant differences in the proportions of all splice variants between benign and malignant thyroid tumors were identified in this study ($P<.001$). The malignant tumors exhibited a significantly greater proportion of the functional full-length variant than the dominant-negative α-deletion or inactive β-deletion and α-β–deletion variants. The opposite was true for the benign tumors. These differences in splice patterns have also been seen in FNA samples (Yongchun Wang, MD, PhD, and Martha Zeiger, MD, unpublished data, 2008) and give credence to the concept that a more comprehensive splice array analysis will ultimately be successful in identifying a set of splice variant markers that are useful in the distinction between benign and malignant thyroid tumors.

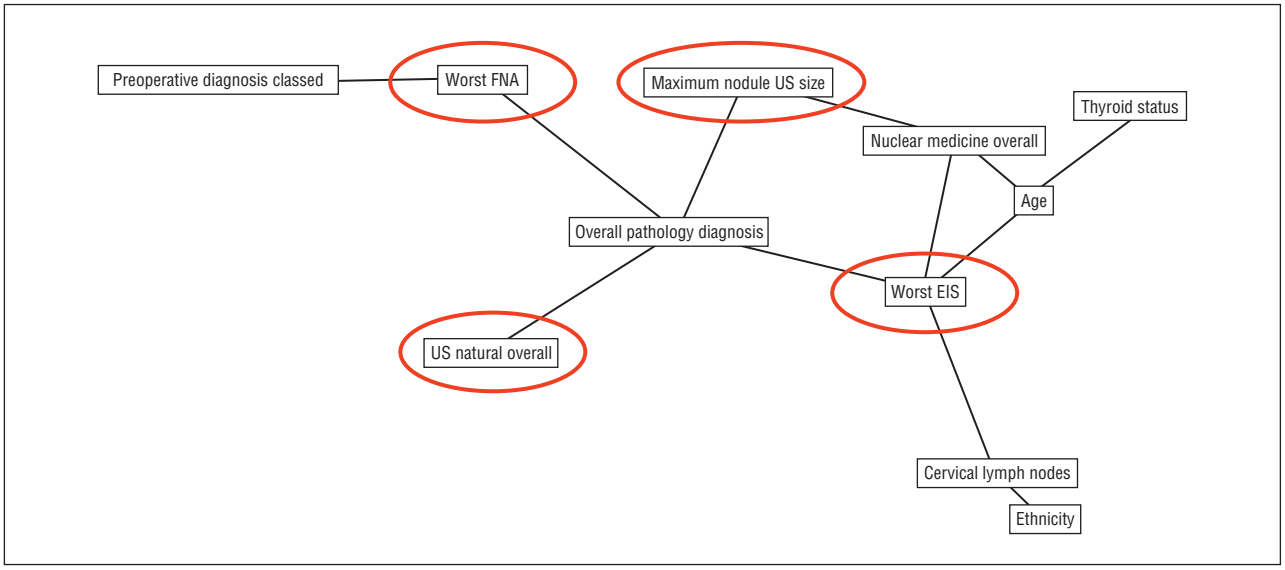

Figure 2. Bayesian Belief Network model. Four variables emerged as predominant predictors of the primary outcome variable, thyroid malignancy, on final histopathology: fine-needle aspiration cytology, maximum nodule size (determined by ultrasound), electrical impedance, and ultrasound characteristics of the nodule. EIS indicates electrical impedance scanning; FNA, fine-needle aspiration; and US, ultrasound.

Electrical Impedance Scanning

Stojadinovic et al[14] are also studying a promising technological adjunct to FNAB, electrical impedance scanning. A pilot study supported the diagnostic utility of this minimal-risk, rapid, real-time technology in patients with thyroid nodules. A prospective clinical trial to define the diagnostic accuracy of electrical impedance scanning for thyroid nodules revealed that a noninvasive impedance scan correctly diagnosed 87% of patients with malignant and 71% of patients with benign dominant thyroid nodules.[15]

Statistical Modeling of Thyroid Nodules

Expanding on this technology, Stojadinovic has used Bayesian classification and a machine-learning platform, using clinical variables to develop an individualized malignancy risk–prediction model.[16] The purpose is to explore the incremental predictive value of electrical impedance characterization of thyroid nodules in codependent analyses in the context of ultrasound and FNAB testing. Elements critical to the development of decision-support tools include data collection, model training and optimization, clinical interpretation, and validation of the resulting model.

Computer models provide a useful mechanism to codify information in heterogeneous clinical situations. The machine-learned Bayesian Belief Network codifies the hierarchy of relationships between important variables and makes it available in a graphical user interface. The relationships between clinical variables are codified in a joint probability distribution, with the intention of supporting complex decision making.

A Bayesian Belief Network is a directed acyclic graph that represents conditional probabilities in a hierarchical, multivariate map. The network provides estimation of likelihood of an outcome of interest and identifies a hierarchy of conditional dependence, given prior evidence, that defines how independent covariates that influence the outcome of interest also influence one another. The network is transparent, providing a graphical explanation to the answers provided in the model structure. The networks developed by Stojadinovic are machine learned, meaning that a heuristic search algorithm is used to discover the hierarchy of information given available training data.

Data were analyzed from a prospective cohort trial involving 216 patients with thyroid nodules who had ultrasound, electrical impedance scanning, and FNAB cytology prior to surgery.[15] A probabilistic Bayesian Belief Network model was developed to estimate malignancy. The variables in the Bayesian Belief Network model included patient sex and age, thyroid nodule size, ultrasound and impedance characteristics, and FNAB cytology, which were associated with the primary outcome variable of thyroid malignancy (**Figure 2**). Based on a scoring criterion, strongly associated clinical variables become nodes in the resultant network. Each node has its own local probability, and conditional independence statements are embedded in the structure of the network through the arcs that connect the network's nodes. The network in Figure 2 shows that the nearest independent predictors of thyroid histopathology are FNAB cytology, maximum nodule size, electrical impedance, and ultrasound characteristics of the nodule. Patient age and cervical nodal status are conditionally independent of final nodule histopathology given knowledge of electrical impedance scanning results and nodule size.

Ten-fold cross-validation was used to validate the model by training models on each of 10 randomly created matched training and test sets, and then each pair was used to create a set of case-specific test predictions to calculate a receiver operating characteristics curve to establish Bayesian classification accuracy. This method provides estimates of robustness of the network model

and applicability of models in new patient populations. In this analysis, the sensitivity of detection of true positives (malignant thyroid nodule) and true negatives (benign thyroid nodule) was plotted against the false-positive fraction. The lift of the resulting area under the curve provided a metric of overall Bayesian model quality. Positive and negative predictive values on a patient-specific basis can then be calculated using assumed thresholds, and the model estimates refined iteratively, as its data set is expanded through additional patient study and data entry. Cross-validation of the first model created with Bayesian network analysis effectively predicted malignancy (area under the curve,0.88; 95% confidence interval [CI], 0.82-0.94) in thyroid nodules. Thyroid nodule size, FNAB cytology, ultrasound, and electrical impedance scanning characteristics were highly predictive of malignancy (Figure 2). The positive and negative predictive values of the model were 83% (95% CI, 76%-91%) and 79% (95% CI, 72%-86%), respectively.

The model can be used to derive patient-specific posterior estimates of malignancy using new data. This can be achieved by applying the model to new data sets in either batch inference mode or by tabulating all potential combinations of independent predictive variables with direct conditional dependence with outcome of interest in an inference table. These rules can then be used to assist clinical decision making by providing enhanced estimates of probability of malignancy.

GASTROINTESTINAL DISEASES

The GIST Story

One of the earliest success stories of targeted molecular therapies in cancers arose among a subset of soft-tissue sarcomas referred to as GIST. These are rare tumors but comprise one of the common mesenchymal tumors of the gastrointestinal tract. The GIST tumors were first recognized as a separate entity in the 1990s, based on the universal presence of activating mutations of the *KIT* (CD117) proto-oncogene.[17] Prior to this, these tumors were classified as a variety of smooth-muscle tumors such as leiomyomas, leiomyoblastomas, and leiomyosarcomas. In 1998, Hirota et al[17] reported that GIST tumors have activating mutations in the proto-oncogene *C-KIT* (CD117), a receptor tyrosine kinase. About 80% to 90% of GIST tumors have gain-of-function mutations in the *KIT* oncogene. The subset of GIST tumors that lack detectable *KIT* mutations have an activating mutation in the related tyrosine kinase platelet-derived growth factor receptor α (*PDGFRA*).[18] Activation of *KIT* by its ligand stem-cell factor results in activation of downstream signaling pathways that lead to uncontrolled cell proliferation and resistance to apoptosis. Gastrointestinal stromal tumors are diagnosed by their near-universal immunohistochemical staining of KIT as well as CD34.

There are about 5000 new GIST cases in the United States annually. These tumors most commonly occur in the stomach (50%), followed by the small bowel (25%) and rectum (10%).[19] They also can develop in the mesentery, omentum, retroperitoneum, and pelvis.[20] About 50% of GIST tumors are metastatic at presentation.[20] Prior to 2001, there was no effective therapy for advanced metastatic disease. In 2001, Joensuu et al[21] published a case report of a patient with metastatic GIST tumor treated with a selective small-molecule inhibitor of *KIT*, imatinib (previously known as ST1571; now Gleevec in the United States and Glivec in Europe; Novartis Pharmaceuticals, Basel, Switzerland) that resulted in marked clinical, radiologic, and pathologic improvement. It was this discovery that revolutionized the treatment of the once fatal disease. Imatinib was initially tested in chronic myeloid leukemias, which involve the Philadelphia chromosome (a translocation of the long arms of chromosome 9 and 22), resulting in the *BCR-ABL* fusion protein, and constitutive activation of tyrosine kinase. Imatinib was shown to function via competitive inhibition of adenosine triphosphate binding and inhibits only the Abl, platelet-derived growth factor rector, and *C-KIT* tyrosine kinase. Based on the clinical efficacy of this drug in chronic myeloid leukemias, the drug was then tested in the GIST tumors.[22]

Imatinib has become the treatment of choice for advanced inoperable or metastatic GISTs based on data from multiple trials. In 2002, Demetri et al[22] described a multicenter trial of imatinib that compared treatment with doses of 400 or 600 mg/d in patients with advanced GIST. Patients were randomized to either of the 2 doses, and at a 9-month follow-up visit, 53.7% of patients had developed a partial response and 27.9% of patients had stable disease. Therapy was well tolerated, with mild to moderate edema, diarrhea, and fatigue only. Long-term results from this trial showed that nearly 50% of patients with advanced GIST who were treated with imatinib mesylate survived more than 5 years.[23] Additional studies include that of the American College of Surgeons Oncology Group, which conducted a randomized trial comparing the efficacy of imatinib vs placebo in patients with completely resected GIST (>3 cm) in 708 patients. Accrual in this trial was halted owing to results from an interim analysis that showed that the 1-year relapse-free survival rate was 97% in the imatinib arm and 83% in the placebo arm, with a hazard ratio of 0.325 (95% CI, 0.198-0.534; $P<.001$). Recently, it has also been shown that the specific type of mutation in *C-KIT* determines the response to therapy to imatinib. Mutations in exon 11 of *C-KIT* are seen in approximately 70% of GIST cases and are associated with a response rate of 85%. However, patients with mutations in exon 9 of *C-KIT* seen in about 17% of GIST have much lower response rates of only 45%. Patients with no mutations have no response. Most patients will eventually develop resistance to imatinib with long-term therapy but, based on the success of this targeted therapy, other targeted therapies have now been developed. Sunitinib, a multitarget tyrosine kinase inhibitor, has now been developed and approved by the Food and Drug Administration for use in patients who have an imatinib-resistant GIST or are intolerant to GIST.[19]

KRAS Mutations in Metastatic Colorectal Cancer

There also has been recent evidence of the use of personalized targeted therapy in metastatic colorectal cancer. Evolving data suggest that response to biologic thera-

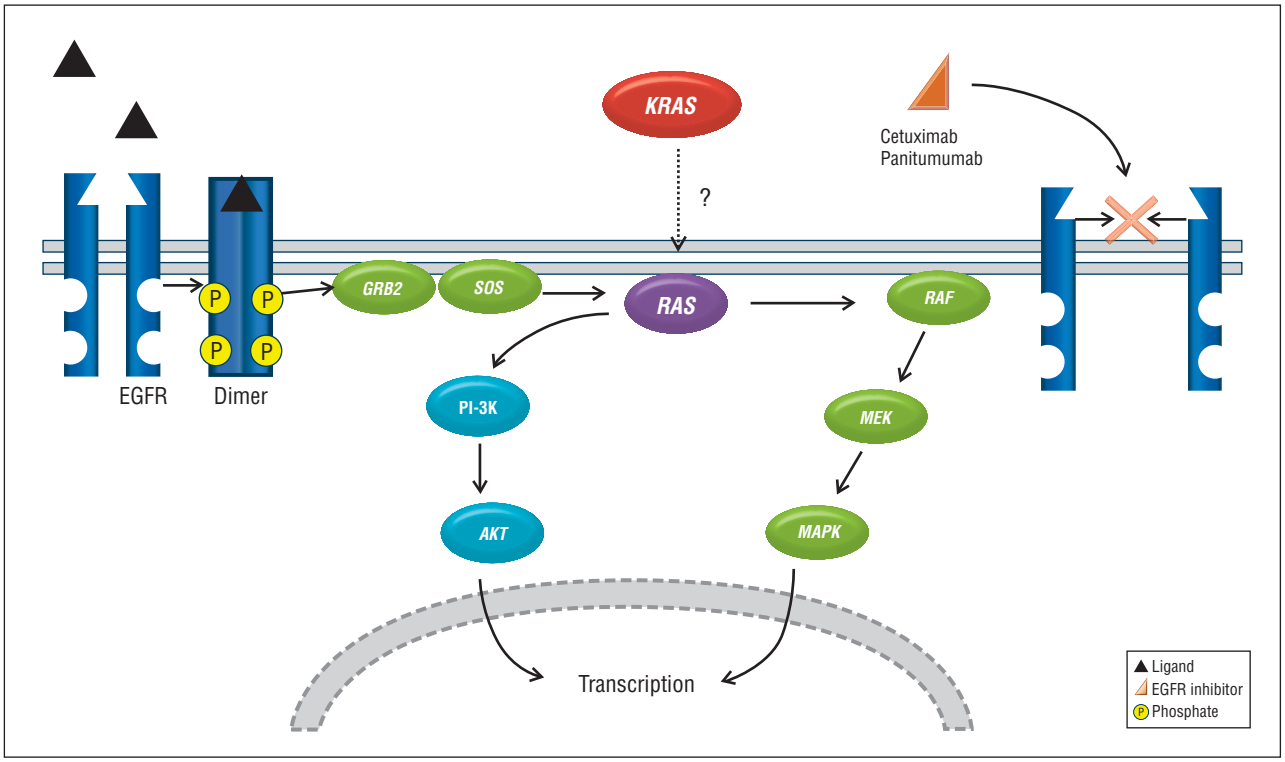

Figure 3. Epidermal growth factor receptor (EGFR) transduction pathway. Normally, stimulation of the EGF receptor by ligands results in dimerization and phosphorylation of the receptor. This leads to activation of *RAS* that then activates signaling of the phospho-inositol-kinase (*PI3K*) and *RAF* pathways. Activation of *PI3K via AKT* leads to inhibition of apoptosis while *RAF* activation stimulates cellular proliferation via the MAP kinase (*MAPK*) pathway. Both cetuximab and panitumumab are monoclonal antibodies that target EGFR drugs that bind to the extracellular domain of EGFR and lead to the inhibition of its downstream signaling. In patients with *KRAS* mutations or *BRAF* mutations, which are downstream, these would lead to constitution activation of the pathway and the drugs would be ineffective.

pies such as cetuximab and pemtumomab (anti–epidermal growth factor receptor [EGFR]) may be related to the presence or absence of *KRAS* mutations. Cetuximab and pemtumomab are monoclonal antibodies that target EGFR and are approved for patients with metastatic colorectal cancer whose tumors express the EGFR protein, documented by immunohistochemistry. The EGFR is a transmembrane tyrosine kinase receptor that, upon ligand binding, leads to autophosphorylation of its intracellular domain and triggers signaling in the *RAS-RAF-MAPK* pathway involved in cell proliferation and the *P13K-PTEN-AKT* pathway involved in cell survival and motility (**Figure 3**).

The EGFR pathway is commonly activated in colorectal cancer by extracellular binding of a ligand to its receptor and activation of downstream signaling pathways. Both cetuximab and pemtumomab bind to the extracellular domain of EGFR and lead to inhibition of its downstream signaling. Because only 8% to 23% of patients with metastatic colorectal cancer have an objective response to therapy, it is important to identify subgroups that will benefit. However, the presence of EGFR by immunohistochemistry has not correlated with response in patients with colorectal cancer. Furthermore, it has been shown that response to these drugs can occur even in patients who do not express EGFR. Multiple studies in the last year have shown that the presence of *KRAS* mutations is an independent predictive marker for resistance to anti-EGFR monoclonal antibody therapy.[24-27] Mutations in *KRAS* result in acquired activation of the *RAS-RAF-MAPK* pathway independent of ligand activation of EGFR and therefore induce resistance to therapy with EGFR inhibitors. In the largest of these studies, Karapetis et al[25] used stored tumor blocks from 394 patients who were randomly assigned to receive cetuximab plus best supportive care or best supportive care alone to determine the relevance of *KRAS* mutation status. They showed that patients who had mutated *KRAS* derived no benefit from cetuximab compared with supportive care only (hazard ratio, 0.98; $P = .89$) whereas those with wild-type *KRAS* benefited from the drug compared with best supportive care (median survival, 9.5 vs 4.8 months; hazard ratio for death, 0.55; 95% CI, 0.41-0.74; $P < .001$).[25] Based on the data from such studies, it is now recommended that all patients with advanced colorectal cancer who are being considered for anti-EGFR therapy should first have *KRAS* testing. Furthermore, Di Nicolantonio et al[26] recently showed that alterations in other members of the *RAS-RAF-MAPK* pathway can result in resistance to therapy with EGFR inhibitors. They found that, of 113 patients, 10% had mutations in *BRAF* (B-type Raf kinase), a kinase gene downstream from *KRAS* in the *MAPK* pathway, which also resulted in resistance to EGFR inhibitors.

VASCULAR DISEASES

Transforming Growth Factor β and Marfan Syndrome

Exciting study has emerged from investigations of medical therapies for the aortic manifestations of Marfan syn-

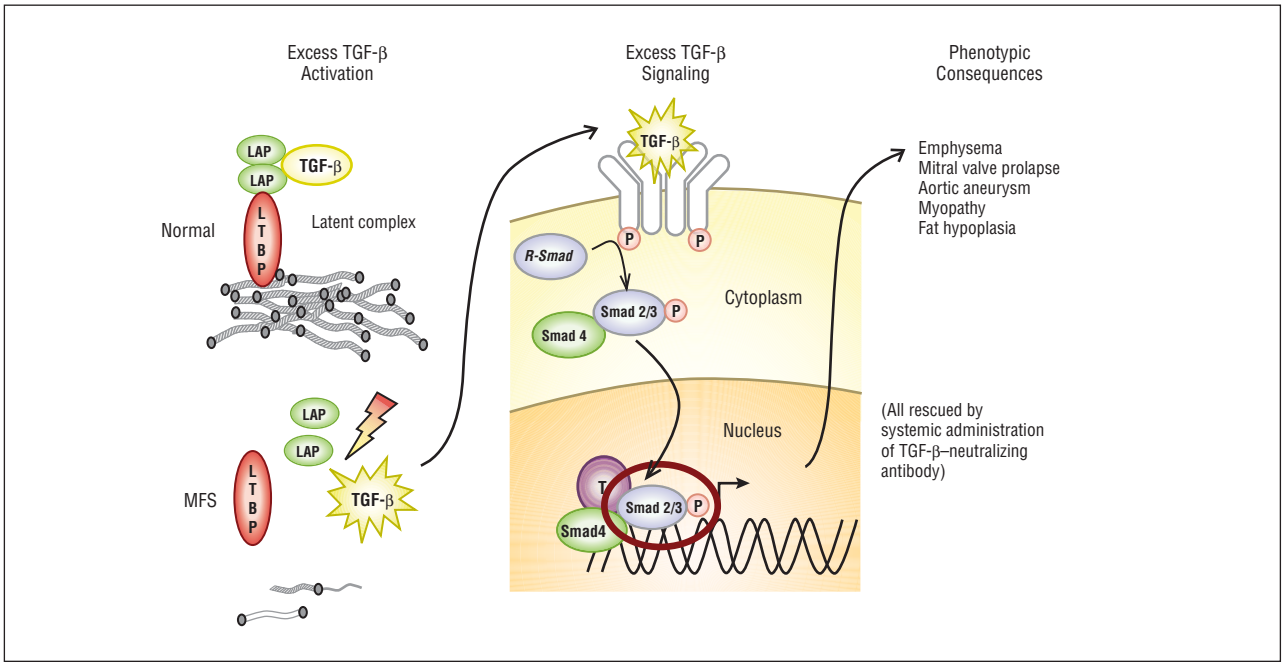

Figure 4. Normally, a lattice of microfibrils binds the large latent complex of the growth factor, transforming growth factor β (TGF-β), which includes latency-associated peptide (LAP) and latent TGF-β–binding proteins (LTBP). A deficiency of microfibrils seen in Marfan syndrome (MFS) leads to the activation (release) of TGF-β that interacts with its receptor and stimulates the Smad-mediated intracellular signaling cascade. This contributes to many of the manifestations of MFS that can be attenuated or prevented in animal models by treatment with TGF-β–neutralizing antibodies. P indicates phosphate. Figure provided by Harry C. Dietz III, MD.

drome. Aortic root enlargement in these patients has been linked to excessive signaling by transforming growth factor β (TGF-β) (**Figure 4**). Consequently, the TGF-β antagonists, angiotensin II-receptor blockers, have been tested as potential treatments for aortic enlargement in both mouse models and in a small cohort of pediatric patients with Marfan syndrome.[28] Use of an angiotensin II-receptor blocker for 12 to 47 months resulted in a statistically significant decrease in the rate of increase of aortic-root diameter enlargement in the patients (3.54 mm/y prior to therapy vs 0.46 mm/y after therapy; $P<.001$). Losartan, an angiotensin II-receptor blocker, can reverse many of the manifestations of Marfan syndrome in mouse models including abnormal aortic wall architecture, ascending aortic aneurysms, developmental emphysema, and skeletal muscle myopathy (**Figure 5**). Separate investigators studied patients using the angiotensin-converting enzyme inhibitor perindopril compared with a placebo group.[29] The patients who received perindopril demonstrated increased systemic arterial compliance (mean, 0.33 vs 0.54 mL/mm Hg; $P=.004$), reduced central and peripheral pulse wave velocities ($P<.001$), and diminished aortic root diameters ($P<.01$ for systole, $P<.001$ for diastole). Although the mechanism of perindopril has yet to be elucidated, reduced levels of active TGF-β were noted in patients treated with the study drug ($P=.02$). Others have focused on blocking enzymes important to the pathogenesis of abdominal aortic aneurysms, matrix metalloproteinases, using a mouse model of Marfan syndrome.[30] Doxycycline is a nonspecific matrix metalloproteinase inhibitor, and mice treated with this antibiotic lived significantly longer than mice with Marfan syndrome treated with placebo (132 vs 79 days; $P<.01$). Moreover, mice with Marfan syndrome treated with doxycycline demonstrated lower matrix metalloproteinase 2 and matrix metalloproteinase 9 levels and decreased elastic fiber degradation than those that received placebo.

Gene Therapy

Another line of inquiry has focused on gene therapy in hopes that recombinant genes could ultimately be produced to combat an array of vascular diseases. Mononuclear cells isolated from peripheral blood have been differentiated into blood-derived smooth muscle cells.[31] Blood-derived smooth muscle cells have similar characteristics to vascular-derived smooth muscle cells and have been successfully transfected with a retroviral vector, raising the potential for ex vivo genetic engineering. Other investigators have transferred recombinant tropoelastin to aortic vascular smooth muscle cells of rats with abdominal aortic aneurysms.[30] Rats who received tropoelastin experienced shrinking of their abdominal aortic aneurysm's diameters by 23% compared with 40% to 48% increases in size seen in the placebo groups ($P<.01$). The presence of reconstructed elastic fibers and elastase messenger RNA in the aneurysmal wall were confirmed.

Neointimal Hyperplasia After Endovascular Grafting

Finally, some investigators have focused on combating neointimal hyperplasia following endovascular grafting. Thrombomodulin is an important endothelial cell surface glycoprotein that normally serves an anticoagulant role by binding thrombin. Recombinant thrombomodulin has been previously identified as an inhibitor of arterial neointimal hyperplasia after experimental bal-

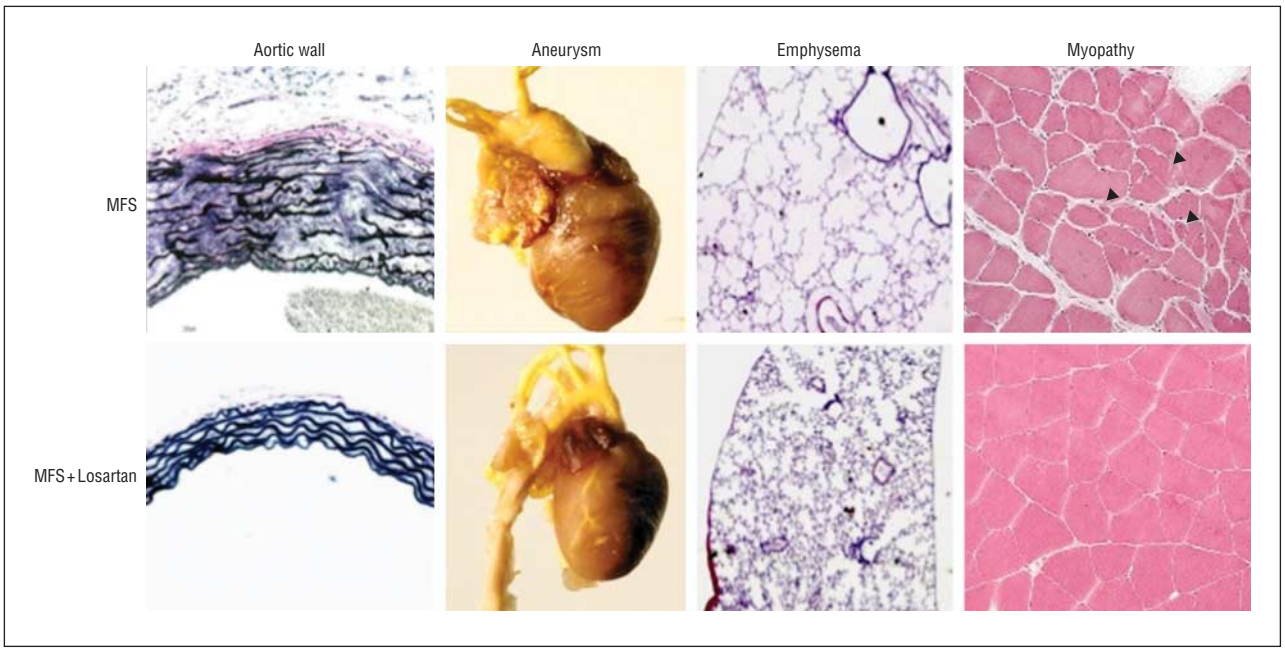

Figure 5. Manifestations seen in Marfan syndrome (MFS). Manifestations in mouse models include abnormal aortic wall architecture (fragmentation and disarray of elastic fibers, wall thickening, ascending aortic aneurysm, widening of the distal airspace due to developmental emphysema, and skeletal muscle myopathy that reflects impaired muscle regeneration). Treatment of mice with losartan (an angiotensin receptor blocker) attenuates or prevents these findings. Verhoeff–Van Gieson stain was used for aortic wall panels; for lung and muscle tissue, hematoxylin-eosin stain, magnification ×40 for all images. Arrowheads show split fibers. Figure provided by Harry C. Dietz III, MD.

loon injury.[32] Recently, the same group studied the outcomes of recombinant thrombomodulin–coated expanded polytetrafluroethylene stent grafts vs standard expanded polytetrafluroethylene in balloon-injured porcine carotid arteries.[33] The carotid arteries of the pigs that received recombinant thrombomodulin–coated stents maintained their original diameter compared with the control group (93% vs 67% of original diameter; $P=.006$). Another approach to combating neointimal hyperplasia includes giving the antioxidant α-tocopherol to rabbits that were fed a high-cholesterol diet.[34] Animals that received the antioxidant demonstrated superior endothelialization of their aortic grafts compared with those that received solely the high-cholesterol diet (70% vs 46%), as well as lower intima/graft-thickness ratios (0.17 vs 0.76) (both $P<.05$). Others have demonstrated that a single dose of interleukin 18 binding protein significantly decreased intima/media ratios and reduced the quantity of lipid-laden macrophages.[35] Interleukin 18 is a proinflammatory and proatherogenic cytokine that induces interferon γ, an important cytokine in atherogenesis.

KIDNEY TRANSPLANTATION AND MATHEMATICS

Recent study has linked fundamental mathematical and computational science with clinical practice in the field of kidney paired donation (KPD). With a kidney waiting list that far exceeds the deceased donor supply, facilitating live donation has become paramount. There is an estimated 30% to 40% chance that a transplant candidate will be unable to accept a kidney from a healthy, willing live donor because of preformed human leukocyte antigen or blood type antibodies. For a recipient/donor pair in this circumstance, 3 options exist: foregoing live donor transplantation, eliminating antibodies in the recipient, or finding a different live donor. The first option is clearly undesirable, as one donor is lost from the potential supply and one more transplant candidate adds to the demand. Eliminating antibodies through desensitization has been associated with encouraging results, although these are work-intensive, expensive, and potentially risky.[36-39] It is the third option, the search for a different live donor, that inspired KPD.

In KPD, an incompatible donor/recipient pair is matched to another pair with a reciprocal incompatibility.[40-43] Ten years ago these matches were made between 2 incompatible pairs, but have since expanded to involve many more pairs per KPD, altruistic nondirected donors, and compatible pairs seeking younger donors.[44-46] The link to mathematical and computational science arose from the realization that there are millions of ways to match even a few dozen incompatible pairs and from the desire to match these pairs so that the most, best, and highest priority transplants would occur. **Figure 6**, A and B illustrate the potential effect of 1 match selection on the opportunities for other pairs in the pool. For the last 3 years, clinically relevant discoveries in graph theory, optimization, and integer programming methods have shaped the field of KPD and laid the groundwork for a national KPD program.[47]

In 2005, Segev et al[47] showed how medical data from pools of incompatible pairs could be expressed using tools from graph theory and how the challenges of matching these pairs could be addressed using a novel application of an algorithm known as maximum edge-weight matching. Weights would be set by combining information about predicted outcomes such as allograft longevity, logistic

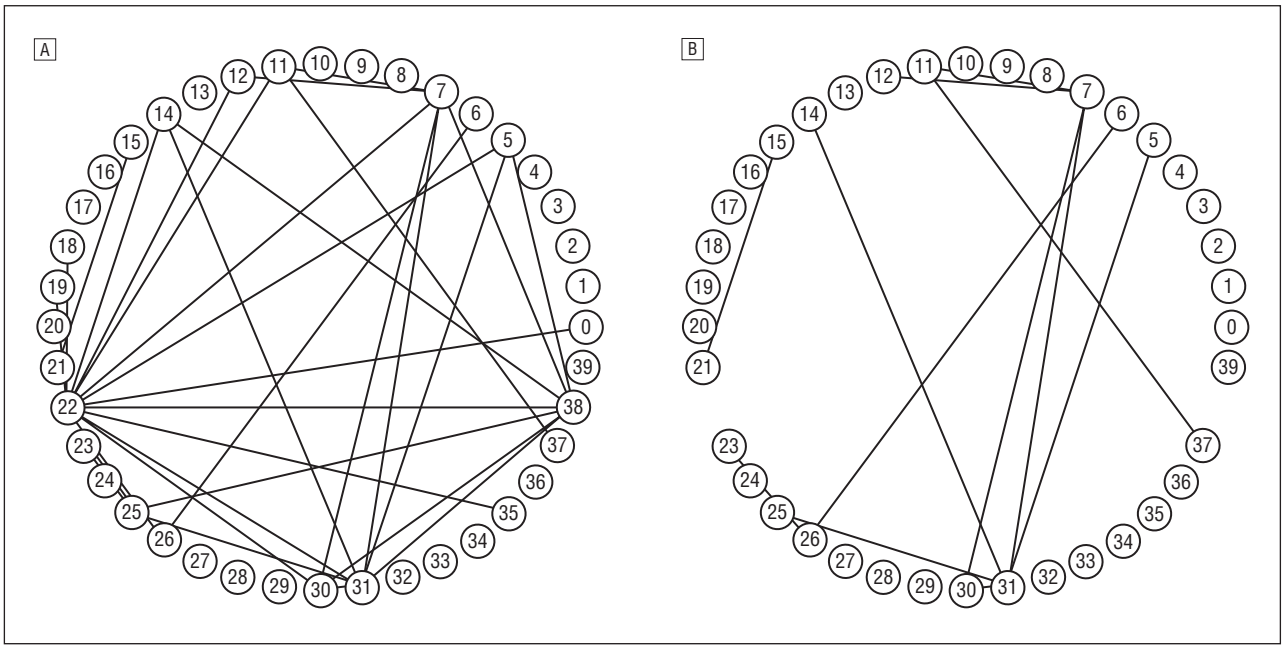

Figure 6. Nodes representing incompatible donor/recipient pairs. A, The most links (13) are seen by pair 22, a blood type A recipient and a blood type O donor who are both willing to travel. Pairs 31 and 38 have the same donor and recipient types as pair 22 but see only 7 links each because these pairs are unwilling to travel outside of their region. Pair 5 sees 3 links with a type O recipient (who is restricted to only type O donors) and a type A donor. Pairs 6 and 35 also have the same blood type configuration as pair 5, but see only 1 link each because pair 6 is unwilling to trade with older donors and pair 35 is unwilling to travel. B, By matching the strategically wrong pairs without first considering all possible combinations of matches, many future possibilities are lost. The same nodes and links from panel A are shown here after matching pair 22 with pair 38. Reproduced with permission from *JAMA*. 2005;293:1883-1890. Copyright © (2005) American Medical Association. All rights reserved.

complexities such as geography, and priorities from the community such as the transplantation of children. The limitation of this application was that there was no system (other than trial and error) for selecting weights that assured the highest number of transplants. In other words, care was needed when assigning weights to avoid the pitfall that, for example, geographic logistics would be improved minimally but at a substantial cost of losing transplants. Sommer Gentry, PhD (unpublished data, January 2009), et al, proved mathematically that weights could be assigned to graph edges such that maximal edge-weight algorithms (which considered priorities listed) would also yield maximum cardinality (a guarantee of the most pairs matched). The possibility that KPD at a national level might eventually exceed computing power has recently inspired Abraham et al[48] to design an integer program solver specific to the types of integer programs seen in KPD.

Thus, the translational collaboration between clinicians, mathematicians, and computational scientists has allowed KPD to grow from a single-center solution for transplanting incompatible pairs to something that, at a national level, is predicted to facilitate live donor transplantation for thousands of patients.

BREAST CANCER PROGNOSIS AND TREATMENT

Breast cancer management currently involves the use of surgery, chemotherapy, radiation therapy, and hormonal therapy. The improvements in surgery and radiation therapy for breast cancer have resulted in refinements in technique. In contrast, translational research has had the greatest effect on chemotherapy and hormonal therapy regimens.

Development of sensitive and quantitative reverse transcriptase polymerase chain reaction has allowed molecular characterization of tumors to predict tumor behavior. A major improvement in this technology was the development of these assays using formalin-fixed paraffin-embedded tissue, allowing extraction of RNA from archived tissues.[49,50] The technique was tested against archived samples from women who participated in prior national randomized clinical trials. One study identified 16 genes that predicted breast cancer recurrence and death.[51] The original arrays were developed for women with estrogen receptor–positive tumors that were node negative. These arrays have allowed molecular characterization of a patient's tumor to select women who are more likely to benefit from chemotherapy. The molecular assessment of the tumor currently puts patients into 1 of 3 categories to assess the risk of recurrence (http://www.genomichealth.com/oncotype). For patients with a low risk of recurrence, chemotherapy is avoided, and only hormonal therapy is recommended. In the group with high risk of recurrence, chemotherapy is recommended. In the intermediate-risk group, the decision to treat with chemotherapy is less clear. To further define the recommendations in this group, there is currently a national cooperative group study that is randomly assigning those patients to chemotherapy or no chemotherapy.[51]

In addition to more selective application of chemotherapy, more selective agents have been developed through translational research. Approximately 25% of patients overexpress the *HER-2-NEU* gene. This overex-

pression is associated with both a reduced overall and relapse-free survival.[52] A humanized monoclonal antibody (trastuzumab) was developed against the human epidermal growth factor receptor 2 (HER2/neu).[53] Trastuzumab was initially investigated and implemented in patients with metastases, demonstrating improved survival in the treated groups. Two phase III studies demonstrated that patients treated with trastuzumab had a 33% lower risk of death.[54,55] In addition to the adjuvant setting, trastuzumab has been investigated in the neoadjuvant setting. This method of investigation allows a very early and accurate assessment of the ability of the agent to treat the tumor. In a study completed at the MD Anderson Cancer Center, trastuzumab was associated with an impressive 65% pathologic complete response rate compared with 26% in the standard chemotherapy arm.[56] A multicenter phase III cooperative group trial evaluating trastuzumab in the neoadjuvant setting is ongoing.

Limited use of chemotherapy in the management of breast cancer has been made possible by optimizing the use of adjuvant hormonal therapy. The aromatase inhibitors are a new class of agents that block the production of estrogen in postmenopausal women. These agents are grouped into steroidal and nonsteroidal aromatase inhibitors. They have been studied in large randomized trials that compared them with tamoxifen. Each of these studies has shown an improved survival rate for women treated with the aromatase inhibitors compared with tamoxifen in postmenopausal women.[57-59] Selection of the best aromatase inhibitor and potential combination or sequencing with tamoxifen has yet to be determined.

The overall result of translational research in breast cancer care is a reduction in the extent of treatment that covers all components of care. Women are receiving less extensive local regional treatments, and many women are now able to avoid chemotherapy owing to improvements in the ability to predict tumor behavior and the development of more selective agents.

SUMMARY

Multiple avenues have been used for the discovery of improved means of diagnosis, treatment, and overall management of surgical diseases. These avenues have incorporated the use of genomics, electrical impedance, statistical and mathematical modeling, and immunology. By no means is this review comprehensive, but it should serve as an example of the potentially vast possibilities for improvements in medicine.

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Correspondence: Martha A. Zeiger, MD, 600 N Wolfe St, Blalock 606, Baltimore, MD 21287 (mzeiger@jhmi.edu).
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