Foreword on Personalized Medicine by David C. Whitcomb, MD, PhD

Personalized medicine is a promising futuristic concept for which few successful examples exist. Personalized medicine is needed for disorders in which multiple pathologic gene-environment interactions result in the same phenotype, where the disease severity and complications are unpredictable, and when possible responses to therapy may be ineffective or even toxic. Our aim is to understand complex inflammatory disorders and their complications of organ dysfunction, scarring, failed regeneration, pain and oncogenesis and to use this knowledge for modeling disease processes and outcomes.

This Digest describes high tech approaches to enhance patient care. Dr. Dunn highlights the use of electronic health records (EHRs) in the following article, and on page 3, Dr. Watson discusses accessibility among physicians and patients through telemedicine.

EHRs and Personalized Digestive Medicine

by Michael A. Dunn, MD

Accurate information is critical to medicine. Electronic information must guarantee privacy and “meaningful use.” “Meaningful use” requires EHRs to improve quality of care in a quantifiable manner. The term now appears in law and policy concerning the distribution of more than $20 billion in federal funding.

The primary purpose of electronic records has been to capture and code billing workload. Existing systems are optimized to deliver revenue in the fee for service marketplace. New capabilities are required to support such meaningful uses as preventive care, improved outcomes and translational research.

Most current records display information in a similar format to what was once written on paper. Value and meaning may be added by changing the presentation to show relationships among key variables on one screen. For example, transfused blood and hemoglobin/hematocrit may be shown on one timeline. Administration of antibiotics, pressors, or immunosuppressants can be displayed on the same screen as the evidence of their clinical effects. Drug ordering can be set up to trigger interaction alerts.

With such basic upgrades, electronic records support better organization of thought and decision-making.

To make electronic health record delivery useful for personalized medicine, it is critical for accurate phenotypic and biomarker data to be defined, classified, recorded and transferred to predictive models. These predictive models must integrate genetic information with other risk data to produce results to optimize clinical decision making.

Priority implementation of the next generation of medical records must be a focal point for translational research design, where the term “translation” defines effective communication between multiple clinical and scientific disciplines. Standardized terms must be defined precisely, whether the term represents a drug, vital sign, diagnosis or lab value, and definitions continued on page 7
Regardless of politics, medicine must become more effective and less costly. The Division of Gastroenterology, Hepatology and Nutrition is taking a broad, holistic view of the healthcare landscape. We intend to provide leadership with the bold use of the smart technologies described in this issue by Michael Dunn, MD and Andrew Watson, MD. Practice technology may influence practice management strongly in the future.

Additional patient care enhancements are explored by GI cancer team member and genetic counselor, Sheila Solomon, MS. Case study reviews for this issue are provided by Priya Roy, MD, Matthew Rockacy, MD and David Brokl, MD, all Gastroenterology Fellows in our program.

Please join us in Pittsburgh this year for three physician education courses: Hepatitis C Virus Infection on June 3 & 4, 2011, PancreasFest 2011 on July 28, 29 & 30, 2011 and our annual general gastroenterology and hepatology conference slated for September 22 & 23, 2011 at the Rivers Club in downtown Pittsburgh. See the back cover of this issue for registration information.

We also invite you to Chicago for the DDW 2011 AGA-Postgraduate Course, Emerging Concepts and Their Practical Applications. I am honored to co-direct this course with Dr. Maria Abreu from the University of Miami. The following University of Pittsburgh faculty will join us as speakers: Jaideep Behari, MD, PhD, Klaus Bielefeldt, MD, PhD, Miguel Regueiro, MD, Eva Szigethy, MD, PhD, and Dhiraj Yadav, MD, MPH.

Sincerely,

David C. Whitcomb, MD, PhD
Giant Eagle Foundation Professor of Cancer Genetics
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Genetic Counseling: Patient-Centered Approach

by Sheila Solomon, MS

Ms. Solomon is a certified genetic counselor with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition. Her clinical and research activities focus on genetic counseling and testing for familial pancreatic cancer, hereditary pancreatitis and other inherited GI cancer syndromes.

Genomic technologies are moving forward with great speed allowing scientists to answer questions and develop novel approaches to address human disease. This concept of translational medicine incorporates the entire genome into clinical practice, including DNA, RNA, proteins and patterns of cellular communication.

Personalized medicine marries genomic medicine to the unique clinical history of an individual. It predicts an individual’s disease risk, identifies treatment viability and can even prevent symptoms of an underlying genetic disorder altogether. This evidence-based approach depends on a multidisciplinary team effort of lab researchers, biostatisticians, physicians and research coordinators, as well as genetic counselors.

Genetic counselors are defined by the National Society of Genetic Counselors as “healthcare professionals with specialized graduate training in the areas of medical genetics and counseling … [who] work as members of a healthcare team, providing information and support to families who … may be at risk for a variety of inherited conditions.” This definition implies the preventive approach of the genetic counselor, who educates patients about disease risk based on genetic, genomic, metabolic and family history data.

While the concept of personalized medicine appears straightforward, its integration is quite complex. Physicians have limited clinic time to counsel patients about genetics, risk assessment and prevention data, so genetic counselors have unique opportunities to interpret a patient’s family history and offer risk assessment, education and testing options. A “patient-centered approach” is the cornerstone to the genetic counseling profession.

continued on page 6
Telemedicine: Times Have Changed

by Andrew R. Watson, MD

Telemedicine is a way to examine, work-up and diagnose patients remotely. Telemedicine originated in the early 1990’s but was limited by expensive technology, lack of consumer awareness, and lack of adoption. Times have changed.

In the mid-1990’s a novel and disruptive surgical technique divided surgeons and led to years of controversy. Driven by enhanced patient care, this new technology was called the laparoscopic cholecystectomy. It is now the standard of care, and seldom do surgeons offer an open cholecystectomy. Telemedicine is today’s laparoscopic cholecystectomy.

Times have changed for a number of reasons. Healthcare resources and provider shortages are driving new pathways for care. The smartphone revolution has transformed desktop computing into cloud-based pervasive communications and computing. Consumers (patients) are familiar with communication that is not face-to-face (e.g., SMS, email, Skype, Facebook and other social media) and often prefer these types of communication. Broadband is now available through cellular networks with speeds that rival expensive home based networks of three years ago. Technology to practice telemedicine is now available at a fraction of the cost. In short, the patients are ready, and the consumer electronics market has empowered them.

Telemedicine may be divided into three types:

The “live” option uses cameras and video screens (i.e., videoconferencing), allowing patients and doctors to communicate in real time. Dedicated rooms and specialized equipment may be used, while a doctor supervises a nurse performing a remote examination.

“Store and forward” involves capturing a test such as an EKG or radiology film and moving it across a network for a doctor to examine. Then, an actionable opinion is sent back to the original site to support the medical decision.

The third type of telemedicine, “remote monitoring,” is the use of asynchronous data collection from a home or portable system. Data can include WBC, Hct, weight, O2 saturation and so on. This data is aggregated and recorded in a centralized fashion for medical decision-making.

Telemedicine examples include specialty clinics in remote areas, emergency assistance such as tele-stroke or tele-trauma, and in-patient hospital rounding from remote locations. Telementoring using live telemedicine will be here soon; procedure and patient care mentoring will be done in real time but remotely. Furthermore, virtual collaborations will ensure fast and accurate second opinions to provide safer and more cost effective care.

While current healthcare reform is pushing the medical community to provide enhanced care, the Centers for Medicare and Medicaid Services (CMS) reimburse for telemedicine on a limited basis in Health-Professional Shortage Areas (HPSAs). This may change in the near future, since more widespread coverage was supported at the 2010 American Telemedicine Association meeting.

Patients are also beginning to realize the power of smartphones and “app stores.” Health-based applications are on the rise, and live teleconferencing is available on smart phones. Some phones enjoy speed that outperforms DSLs and matches advanced landline networks. The current model of forcing patients to travel to providers regardless of geography, weather or cost, results in delayed or fragmented care.

Leaders in telemedicine hope that the provider community learned a key lesson from the gallbladder surgery revolution in the 1990’s: technology can equally transform care and also empower patients for choice of hospital or provider.

At UPMC, gastroenterologists have begun initial work with surgical colleagues in this domain, and several complex patients have been seen virtually in a rural clinic at UPMC Bedford (two hours east of Pittsburgh). Neither patients nor providers had to drive, so travel costs were erased. Interestingly, Pennsylvania is the third most rural state in the U.S. With our highly specialized clinics concentrated in Pittsburgh, telemedicine can surface quickly in this region.

Telemedicine will not replace healthcare. But, it will augment collaboration among colleagues and empower patients. We will be able to see patients in referring provider offices, on the road or at home. Mobility will remove the growing barrier of access, a critical topic in healthcare reform.

Healthcare reform will make us rethink how we practice medicine, and telemedicine is a powerful tool to enable efficient care when and where patients need it. Minimally invasive surgery showed surgeons how technology can herald change. If telemedicine seems to be perplexing now, providers can learn from history.

Dr. Watson is an assistant professor of surgery with the University of Pittsburgh Division of Surgical Oncology. He serves as the vice president for UPMC’s International & Commercial Services Division and is medical director for the UPMC Center for Connected Medicine.
Pathology was notable for a polymorphous B-cell infiltrate with strong CD3, 20 and 30 expression along with EBV positivity consistent with an Epstein Barr virus positive lymphoproliferative disorder (EBV-LPD). A PET-CT failed to demonstrate nodal disease or extranodal involvement beyond the distal esophagus. A bone marrow biopsy was negative.

EBV is the cause of infectious mononucleosis, which is often characterized by fever, sore throat, lymphadenopathy and atypical lymphocytosis. By adulthood, more than 90 percent of individuals have been infected but have antibodies to the virus. After recovery from an acute infection, up to 50 per one million B-cells remain infected, and B-cells are the reservoir for EBV in the body. Proliferation is kept in check by CD8+ T-cells. If T-cell immunity is compromised, EBV-infected B-cells may begin to proliferate.

EBV-LPDs represent a spectrum of disorders ranging from atypical hyperplasia to overt lymphoma, which may be found in patients with congenital, acquired, or iatrogenic immunodeficiencies. Most common is post-transplant lymphoproliferative disorder (PTLD) affecting one to 20 percent of transplant patients with higher incidences in heart and small bowel transplant recipients. Cases have also been reported in apparently immunocompetent patients, particularly the elderly due to immunosenescence of aging. Treatment varies based on the type and severity of the LPD present and includes reduction or cessation of immunosuppression if possible, chemotherapy (CHOP regimen), rituximab and/or antiviral therapy.

Location can be nodal or extranodal. The GI tract is one of the most common sites of extranodal disease occurring.
An Elusive Source of GI Bleeding

by Priya M. Roy, MD
Gastroenterology Fellow

Case Presentation

A 67-year-old male was admitted to an outside hospital with melena followed by two days of hematochezia. His medical history was significant for clear cell cancer which required a right nephrectomy thirty years ago, a left renal mass treated with cryotherapy two years prior and coronary artery bypass grafting. Pertinent medications included Celebrex®, Nexium® and aspirin. Family history was significant for renal cancer. Social history was significant for remote tobacco use and consumption of four glasses of wine daily. His physical exam was normal. Labs at admission were as follows: white blood count 9.7, hemoglobin 10.6, INR 1, platelets 225, sodium 134, creatinine 2.5, BUN 66.

After admission to an outside hospital, he became hypotensive and required eight units of packed red blood cells (PRBCs) within 24 hours. Endoscopy demonstrated bleeding in the third and fourth parts of the duodenum with no clear source. A subsequent angiogram showed bleeding in a branch of the inferior pancreaticoduodenal artery. A percutaneous transcatheater embolization was performed, yet the patient continued to bleed. Over the next few days, his tagged red blood cell (RBC) scan was normal, and an enteroscopy demonstrated no bleeding.

Following transfer to UPMC Presbyterian Hospital, work up included normal enteroscopy and tagged RBC scan. Capsule endoscopy demonstrated blood in the distal small bowel and possible bleeding in the proximal small bowel. A non-contrast CT scan of the abdomen was unrevealing. During an acute bleeding episode, another tagged RBC scan showed bleeding in the right lower quadrant, possibly in the distal ileum or proximal colon. However, follow-up angiography was negative. Colonoscopy demonstrated a normal distal ileum and a large cecal AVM that was treated with injection and cautery. The patient bled again, and, by this point, had received 26 units of PRBCs over ten days. He was taken to the operating room where an intra-operative endoscopy revealed an adherent clot at the junction of the second and third portion of the duodenum. Exploratory laparotomy demonstrated that the duodenum was retracted to the right nephrectomy bed and was densely adherent to the retroperitoneum and vena cava. A near full thickness defect was found in the duodenal wall near a previous surgical clip, and a duodenocaval fistula was discovered. The fistula was repaired during surgery.

Enterovascular communications are responsible for less than one percent of upper gastrointestinal bleeds. Duodenocaval fistulas are rare, and only 43 cases were reported in literature through 2008. The majority of cases occur in men, with a mortality rate of approximately 40 percent. Most cases occur in patients with migrating caval filters or a history of right nephrectomy with radiation. Other predisposing causes include duodenal ulceration, abdominal injury, an ingested foreign body or cancer. Many patients present with signs of sepsis and gastrointestinal bleeding, and bleeding may range from occult bleeding to frank gastrointestinal hemorrhage. Other symptoms include isolated fevers, abdominal pain and weight loss. Rarely, patients can have pulmonary embolism from food particles entering the vasculature.

Diagnosis is difficult and may be made by a CT scan or contrast swallow study. Laparotomy may be required to determine diagnosis. Endoscopy can be used but may, theoretically, cause air embolism. If a duodenal ulcer is revealed, its depth may not be appreciated on endoscopy.

Treatment is surgical. Typically, suturing of the duodenal perforation and IVC is performed, although other approaches include more extensive surgeries with duodenal excision and placement of epiploic or jejunal patches to prevent fistula recurrence.
The CT scan of the abdomen revealed innumerable small- to medium-sized cysts replacing much of the pancreatic parenchyma. Few known diseases present with such dramatic pancreatic cyst accumulation. Genetic testing was positive for von Hippel-Lindau disease (VHL).

VHL is an inherited, autosomal dominant syndrome which results from a mutation in the VHL gene, present in about 1 in 36,000 newborns. The gene product is a tumor suppressor protein, VHL, which normally prevents cell division of abnormal cells. Without functional VHL, abnormal growths develop throughout the body. Common manifestations include renal cell carcinoma, pancreatic cystic lesions, acute pancreatitis, and chronic pancreatitis, as well as other GI disease control subjects.

Patients have an increased risk for development of pancreatic abnormalities, including malignant disease, as well as other GI malignancies. The goal is to improve early detection of GI malignancies including pancreatic cancer, colonic neoplasia, and bile duct cancers through this revolutionary approach. For more information, contact Dr. Randall Brand at solomonsr@upmc.edu or 1-888-PITT-DNA.
Electronic Health Records continued from page 1

must be consistent across all data input and usage sites. Our Division of Gastroenterology, Hepatology and Nutrition has received funding to develop a new system to assemble and ensure consistent meaning among diverse clinical data sets, including UPMC’s famous Medical Archive Retrieval System (MARS). System implementation will involve input from multidisciplinary physicians and scientists who will use these data to develop the modeling tools to make personalized medicine a reality.

The structured assessment of thousands of patients in prospective registries and cohort studies runs parallel to electronic medical record development. Registries in our group include inflammatory bowel disease, pancreatic diseases, liver disease and other complex disorders, through which detailed case report forms link DNA and biological samples to new disease biomarkers. This provides an iterative process through which the electronic health record enhances research, and the research strengthens and validates the health record.

Our goal is to develop the procedures necessary for personalized medicine. The goal of the new electronic health record is to connect these pieces in the clinic, so that “meaningful use” means better care at lower cost.

Dr. Dunn is a clinical professor of medicine and biomedical informatics with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition, where he serves as the associate chief for Translational Research. Dr. Dunn is a retired Army Brigadier General whose leadership led to successful interoperability between military and veterans’ medical records as well as command of the Walter Reed Health Care System and the Army’s hospitals in the western U.S.

... PhenX Toolkit ...

Analyses and comparisons of large genetic studies have revealed inconsistent terms and measures, resulting in confusion and variability for large genome wide association studies (GWAS). Also, most GWAS have had relatively few phenotypic and exposure measures in common. To combat these issues, the NIH National Human Genome Research Institute (NHGRI) initiated the PhenX Toolkit in 2006 to identify “high-priority phenotype and exposure measures for cross-study analysis in GWAS.” From UPMC, David Whitcomb, MD, PhD chaired the PhenX Gastrointestinal Working Group. Division faculty member David Binion, MD also served on this committee. Tools for gastrointestinal disorders are now available at www.phenxtoolkit.org.

Esophageal Ulcer continued from page 4

in approximately ten to twenty percent of patients. Isolated G1 tract extranodal lesions are rare, and only a limited number of cases with extranodal esophageal lesions have been cited in the literature.

In 2010, Dojcinov, et. al. published a series of 26 patients with localized mucosal and/or cutaneous EBV-LPDs. These subjects demonstrated a common distinctive pathological appearance identical to that of our patient. There was no progression to disseminated disease in any of these cases, and nearly all experienced rapid resolution following treatment. These cases represent a distinct clinicopathologic entity with an indolent course which responds well to treatment.

Our patient’s mycophenolate mofetil was discontinued, and methotrexate was substituted for multiple sclerosis treatment. She was referred to Hematology and was placed on single agent rituximab. Following treatment, repeat EGD demonstrated complete resolution of her esophageal ulcer, and her oral ulcers healed as well. She continues to have mild dysphagia, presumably as a sequela of her previous ulcer, and is undergoing repeat dilations as needed.

Cratered ulcer in distal esophagus.
A 60-year-old Caucasian male with a history of HTN, CAD and chronic back pain developed sudden onset of episgastic pain. He reported similar less intense episodes over the past several years. He denied any alcohol use or cigarette smoking. Family history is unknown. A CT scan of the abdomen revealed an abnormal pancreas.

*Compare your answer to Dr. Broki’s on page 6.*

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