

# Kidney News

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## Does Living Donor Age Matter in Kidney Transplantation?

*Recent study results should encourage more donor paired exchanges*

By Tracy Hampton



**A**cross the globe, numerous kidney transplant candidates and donors are linking up in often complicated ways to facilitate more transplants through exchange programs, or swaps. The largest swap so far, which was orchestrated by the National Kidney Registry (NKR) and involved 60 lives and 30 kidneys, was described recently in *The New York Times* ([http://www.nytimes.com/2012/02/19/health/lives-forever-linked-through-kidney-transplant-chain-124.html?\\_r=2](http://www.nytimes.com/2012/02/19/health/lives-forever-linked-through-kidney-transplant-chain-124.html?_r=2)). Also, in early February the NKR announced that it had facilitated its 400th exchange transplant. These efforts by the NKR and other programs could not come at a better time. Nearly 90,000 people in the United States are waiting for a kidney transplant, and

many will die before a suitable organ becomes available. The shortage is expected to worsen.

Such living donor chains and simpler closed-loop paired exchanges, which involve two pairs of donors and recipients, assume that kidneys from living donors are of comparable quality and anticipated longevity. But how true is this assumption? Potential recipients often wonder, will the kidney received from a stranger—particularly an older one—be as good as a kidney donated by a loved one?

“In a proposed kidney paired donation match, if an old donor–recipient pair is matched to a young donor–recipient pair, the young recipient may feel disadvantaged and may not be will-

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## Antiplatelet Therapy in Patients with Chronic Kidney Disease: Is It Safe?

By Tracy Hampton

**A**ntiplatelet therapy that inhibits blood clotting can be life-saving for individuals at high risk for cardiovascular disease or stroke. At first glance, this should apply to patients with chronic kidney disease (CKD), who are more likely to die of cardiovascular disease than of any other cause.

But nonatherosclerotic conditions such as cardiac failure, sudden cardiac death, and arrhythmia are more common causes of cardiovascular events in individuals with CKD than in the general population, and the bleeding risk of antiplatelet agents may be greater among people with CKD because of

impaired hemostasis.

Investigators recently published a review in the *Annals of Internal Medicine* on the benefits and harms of antiplatelet agents in these patients, focusing on cardiovascular events, mortality, and bleeding.

“Until now, data from studies done in the general population were extrapolated to people with chronic kidney disease,” said senior author Giovanni Strippoli, MD, PhD, who holds titles at the school of public health at the University of Sydney in Australia, the Mario Negri Sud Consortium in Italy,

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## Living Donor Age

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ing to trade with an older donor,” said Paolo Ferrari, MD, director of Australia’s national registry for paired kidney exchanges. “Refusal to participate in an exchange could break the chain of potential matches identified after a match run and could limit the success of a kidney paired donation program.”

A recent study by John Gill, MD, and his colleagues, of the University of British Columbia, in Vancouver, Canada, that appears in the *Clinical Journal*

*of the American Society of Nephrology* investigates this issue. The researchers analyzed the survival of kidneys from donors of different age groups that were transplanted into recipients of different age groups. Their study included data from all adult kidney transplants from living donors that were performed in the United States from January 1988 to December 2003, with follow-up through September 2007.

### Age not an issue

The investigators found that except for recipients aged 18 to 39, who benefited the most when they received kidneys

from donors aged 18 to 39, donor age between 18 and 64 had a minimal effect on the survival of transplanted kidneys. Specifically, the researchers noted a difference of only 1 to 2 years in allograft half-life, with no graded association, among different donor age groups.

“These findings show that in contrast to deceased donor transplantation, the age of a living donor has little impact on transplant survival,” Gill said. “This information should help increase participation and efficiency of living donor paired exchange programs because it alleviates patient concerns about receiving a kidney from an older aged living do-

nor that currently limits acceptance of a proposed transplant in paired exchange programs.”

More experience is needed to determine the outcome of transplants from living donors aged 65 and older relative to younger living donors, Gill said.

In addition to expanding participation in exchange programs by blood group and tissue-incompatible donor-recipient pairs, the results may also encourage participation of more compatible donor-recipient pairs. Finally, the information should prompt exchange programs to reexamine any matching algorithms that emphasize donor-recipient age matching.

“This study’s observation supports data from the Australian registry, where 13.8 percent of live donors were aged 60 years or older, showing that live donor-recipient age difference does not impact graft or patient survival,” said Ferrari, who was not involved with the study by Gill and his associates. Those findings were published by Ferrari and his colleagues in 2011 in *Nephrology Dialysis Transplantation*.

“Taken together, these findings of the two registry data are of major relevance for policy and decision making in kidney paired donation,” Ferrari said. They reinforce the view that it is acceptable to ignore donor-donor or donor-recipient age differences as a scoring parameter in ranking match combinations.”

### Weighing options

Gill and his team also juxtaposed their results against the probabilities that wait-listed patients would receive a kidney from a deceased donor and their risk of being excluded from transplantation during the study because of death or permanent removal from the wait-list.

The probability of deceased donor transplantation after 3 years of wait-listing ranged from 21 percent to 66 percent depending on patients’ blood type and antibody levels, whereas the probability of being excluded from transplantation ranged from 6 percent to 27 percent by age, race, and type of kidney disease. Gill noted that when patients consider these probabilities, many will likely find that participating in living donor paired exchanges—and possibly receiving a kidney from an older donor—is a better option than continuing to wait for a deceased donor transplant.

Yet the study included relatively few living donors aged 60 and older, the authors said, noting that there may be certain patient subgroups who tolerate dialysis relatively well, so that waiting while they continue to receive dialysis would be a reasonable consideration. Also, they were unable to evaluate the effect of other important donor factors that may affect transplant survival and confound the results, including predonation kidney function, donor blood pressure, and diabetes in the donor.

The authors stressed that their find-

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ings should not be interpreted as a dismissal of the importance of living donor age on transplant outcomes. Most recipient age groups with living donors between 40 and 64 had a small but statistically significant increased risk of allograft loss compared with those whose living donors were 18 to 39 years old, and in all recipient age groups, the greatest donor age-associated risk of allograft loss was among recipients from living donors aged 65 and older. This increased risk of allograft failure with older donor age is consistent with results from a recent single-center *American Journal of Transplantation* publication from the Mayo Clinic that showed an association between living donor age and the risk of death-censored graft loss. That study did not show an association between living donor age and patient death.

Although questions still remain about the comparable quality of different do-

nors' organs, the results shown by Gill and his team provide valuable information to transplant candidates and potential donors who are weighing their options. ●

Study co-authors include Peter Chang, MD, Jagbir Gill, MD, James Dong, Caren Rose, Howard Yan, MD, David Landsberg, MD (University of British Columbia, in Vancouver, Canada); and Edward Cole, MD (University of Toronto, in Canada).

**Disclosures:** The authors reported no financial disclosures.

The article "Living donor age and kidney allograft half-life: implications for living donor paired exchange programs," appeared online at <http://cjasn.asnjournals.org/> in March 2012, doi: 10.2215/CJN.09990911.

## Paired Donations Increase Scrutiny of Issues

**K**idneys are the most commonly transplanted organ, and now with the advent of transplant chains that use several sets of matched pairs, the numbers of these logistically challenging operations are poised to rise to levels unanticipated only a few years ago. At the same time, increased scrutiny of chain transplants, which rely on living donors, is emerging from all corners of the industry.

A recent conference of national and regional kidney transplant partners represented a first attempt to agree on the direction of their field. Insurers and representatives from several registries and the large federally run United Network for Organ Sharing (UNOS) also attended. UNOS manages the national transplant waiting list and maintains the database that has all organ transplant data, from every transplant that happens in the United States.

Held in late March in Herndon, VA, the Consensus Conference on Kidney Paired Donation had an ambitious goal—to seek consensus among the 70 participants on ways to increase the volume of transplants that involve kidney paired donation (KPD). The genesis of the conference was the idea that KPD is the most effective approach to recruit a substantial pool of high-quality kidneys from healthy living donors. These donors would not have volunteered otherwise because their kidneys weren't a compatible match for their family member or loved one. Despite the need and opportunities for this type of donation, KPD remains an often unused option.

An announcement from the University of California, San Francisco—where the conference's lead organizer Sandy Feng, MD, PhD, is a transplant surgeon—described the first consensus meeting and noted that "the emergence of multiple KPD programs with diverse approaches and processes attests to a lack of consensus as to how to maximize the benefit and minimize the risk of KPD."

While the participants expressed a desire for a unified registry that would provide a centralized system for storing and accessing data about donors and recipients, they ultimately could not agree over how this unifying effort would take place, according to Kevin Sack, who reported on the conference for *The New York Times*.

One mathematician from the U.S. Naval Academy, Sommer Gentry, who had been working on donation models, wanted to eliminate barriers to a national registry. "With two pools of 100, you get fewer opportunities than with one pool of 200," to match donors to recipients.

Sack noted that Feng was concerned that unifying all of the current registries into one system might stifle the innovations used by successful registries like the National Kidney Registry. "Maybe we can have different operations with common allocation methods and principles, [without complete unification of systems]," Feng said. ●

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## Antiplatelet Therapy

*Continued from page 3*

and Diaverum in Sweden. “Previous research from our group and others has shown that such extrapolations could be very dangerous, and interventions that may be very good in the general population may have no effect or even be harmful in people with chronic kidney disease

Paying particular attention to patients with CKD while conducting clinical trials will only become more important. Approximately 10 percent to 15 percent of the adult population worldwide have the disease, and its prevalence is on the rise because of increasing rates of diabetes and obesity.

## Analyzing available data

Mining Embase and Cochrane databases from 1980 through November 2011 without language restriction, Strippoli and his colleagues selected randomized trials that included adults with CKD and compared antiplatelet agents with standard care, placebo, or no treatment.

“Nephrology is lagging behind all other disciplines of internal medicine when it comes to randomized trials, and a strong effort is needed to do more trials and to summarize existing knowledge from the few small existing trials that have been published,” said Strippoli. Many of the trials in the analysis were not performed to study issues specifically in kidney disease but included a small portion of people with the condition.

Nine trials (9969 participants) provided information on antiplatelet treatment among persons with CKD who had acute coronary syndrome or were undergoing coronary artery intervention and were considered at high risk for subsequent vessel closure. All data for these trials were post hoc analyses for subgroups of participants with CKD from larger trials. The trials provided data for glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, or tirofiban) or clopidogrel (two trials, 4498 participants), and all involved coadministration of aspirin with or without heparin. The median follow-up time was 12 months.

Another 31 trials provided data on 11,701 persons with stable or no cardiovascular disease who received antiplatelet therapy. Twelve trials studied antiplatelet effects on mortality, progression of kidney disease, or safety in patients who had glomerulonephritis, diabetic nephropathy, or an impaired GFR regardless of cause. The agents administered included aspirin, dipyridamole, aspirin and dipyridamole, or a thienopyridine (clopidogrel or ticlopidine), and the median follow-up time was 12 months. Seventeen of the trials provided shorter-term data (median of 6 months of follow-up) for a variety of antiplatelet treatments in persons who were receiving or would soon require dialysis. Four trials administered antiplatelet therapy to kidney transplant recipients.

## Pros and cons of anticoagulating drugs

In general, the investigators found that the available information on antiplatelet therapy in patients with CKD is of low or very low quality, with considerable variation in trial duration, heterogeneity in the definitions and assessment of bleeding outcomes, reliance on subgroup data from major trials, and substantial methodologic limitations in data for patients with stable cardiovascular disease.

The researchers reported low-quality evidence that in people with acute coronary syndromes, glycoprotein IIb/IIIa inhibitors or clopidogrel plus standard care had little or no effect compared with standard care alone on all-cause or cardiovascular mortality or on myocardial infarction, but the treatments increased serious bleeding by up to 40 percent. Also according to generally low-quality evidence, antiplatelet therapy prevented myocardial infarction (lowering the risk by about 34 percent) but caused uncertain effects on mortality and increased minor bleeding by approximately 70 percent compared with placebo or no treatment in persons with stable or no cardiovascular disease.

These findings indicate that any benefits of antiplatelet therapy for people with CKD are uncertain and are potentially outweighed by bleeding hazards.

“All in all, these drugs should be used with care and attention, as all doctors do, and we should always think before we prescribe,” said Strippoli. Also, he and his coauthors noted that many patients would not be likely to accept the risk for major bleeding to reduce their risk for myocardial infarction without proven reductions in death or the need for coronary revascularization.

“This systematic review and meta-analyses primarily highlight the rather limited evidence from existing randomized trials about the efficacy and safety of antiplatelet agents for preventing cardiovascular events and death across the spectrum of chronic kidney disease and in those receiving dialysis or a renal transplant,” said Alan Go, MD, who is the director of the comprehensive clinical research unit and the regional medical director for clinical trials at Kaiser Permanente Northern California and who was not involved with the research.

Given the low quality of the available evidence, the investigators advocate for specific trials evaluating antiplatelet therapies, including newer agents, in individuals with CKD and coexisting acute or stable cardiovascular disease. They also note that no data are currently available on antiplatelet use in dialysis patients or kidney transplant recipients who have acute coronary syndromes or require coronary artery revascularization.

“Given the risks of bleeding associated with these agents, additional studies are needed to delineate the net clinical benefit or harm at different levels of renal function through randomized trials as well as studies done in large, diverse clinical practice populations that are more representative,” said Go. ●



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## IMPORTANT SAFETY INFORMATION

**WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE.**

### *Chronic Kidney Disease:*

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
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OMONTYS is contraindicated in patients with uncontrolled hypertension.

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- In controlled clinical trials of ESAs in patients with cancer, increased risk for death and serious adverse cardiovascular reactions was observed. These adverse reactions included myocardial infarction and stroke
- In controlled clinical trials of ESAs, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and deep venous thrombosis (DVT) in patients undergoing orthopedic procedures
- In 2 trials of OMONTYS, patients with CKD not on dialysis experienced increased specific cardiovascular events

**Increased mortality and/or increased risk of tumor progression or recurrence in patients with cancer:** The safety and efficacy of OMONTYS have not been established for use in patients with anemia due to cancer chemotherapy. OMONTYS is not indicated in patients with cancer receiving chemotherapy.

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**Laboratory monitoring:** Evaluate transferrin saturation and serum ferritin prior to and during OMONTYS treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%.

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# ASN Cosponsors Congressional Briefing on Racial Disparities in Kidney Disease

Kidney disease affects millions in the United States across all populations, but it is more common among minorities. African Americans, Hispanics, Pacific Islanders, and Native Americans face a disproportionately increased risk for developing kidney disease.

Broadening knowledge about the disparities in kidney care that minorities confront is essential to resolving those disparities. On April 19, 2012, the American Society of Nephrology (ASN), Dialysis Patient Citizens (DPC), and the National Urban League led a congressional briefing on kidney health disparities. Maria Cristina Arce, MD, and Neil R. Powe, MD, addressed members of Congress and Capitol Hill staffers about this critical issue on ASN’s behalf.

A nephrology fellow at Stanford University School of Medicine, Arce presented information on kidney disease in the Hispanic population. She noted that Hispanic ethnicity is associated with an increased risk for end stage renal disease (ESRD) compared with whites—an increase not explained by higher prevalence of diabetes or by diabetes severity. In addition, a higher number of younger Hispanics are starting dialysis, possibly due to worsening rates of obesity, earlier onset of diabetes and hypertension, and faster progression of kidney disease. Hispanics are 15 percent less likely to use arteriovenous access for their first hemodialysis session, Arce said.

Powe spoke to the audience at the congressional briefing about the many factors that contribute to a rate of kidney failure in minorities that is up to four times greater than in whites. Chief of Medicine at San Francisco General Hospital and Vice-Chair of Medicine at the University of California San Francisco, Powe noted that kidney disease occurs more often in minorities and starts earlier. Socioeconomic status, lifestyle and quality of care explain 44 percent of the threefold excess risk of chronic kidney disease (CKD) in African Americans compared to whites. African Americans are also much less likely to get transplants or to be placed on the transplant waiting list, said Powe. His presentation echoed Arce’s findings that minorities in the United States are referred to nephrologists much later than whites.

Powe emphasized to lawmakers the current and future opportunities for the federal government to ad-

dress racial and ethnic disparities in kidney care. These include comparative effectiveness studies of treatment in minorities, enhanced patient and provider education, and increasing support for demonstration projects to assess the effectiveness of changes in health care.

DPC board member Eric Edwards spoke to those assembled about liv-

ing with kidney disease. Also presenting at the briefing were Kafui Agbemenu, Health Advocate for the Urban League, who spoke about how the Urban League in Pittsburgh is improving minority access to health care. Dana Atwater of Baxter Healthcare presented general information on CKD in the United States.

The American Society of Neph-

rology supports a variety of efforts to address and resolve disparities in kidney care in the United States and worldwide, including support of Senate bill 2163 that promotes research regarding disparities and access to care. ASN encourages members to contact your members of Congress to support this bill at <http://capwiz.com/asn/home>.

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**Chronic Kidney Disease:**

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.**
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks [see Warnings and Precautions].**
- Use the lowest OMONTYS dose sufficient to reduce the need for red blood cell (RBC) transfusions [see Warnings and Precautions].**

**INDICATIONS AND USAGE**

**Anemia Due to Chronic Kidney Disease**  
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- In patients with CKD not on dialysis because of safety concerns in this population [see Warnings and Precautions].
  - In patients receiving treatment for cancer and whose anemia is not due to CKD, because ESAs have shown harm in some settings and the benefit-risk factors for OMONTYS in this setting have not been evaluated [see Warnings and Precautions].
  - As a substitute for RBC transfusions in patients who require immediate correction of anemia.
  - OMONTYS has not been shown to improve symptoms, physical functioning or health-related quality of life.

**CONTRAINDICATIONS**

OMONTYS is contraindicated in patients with:

- Uncontrolled hypertension [see Warnings and Precautions].

**WARNINGS AND PRECAUTIONS**

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism**
- In controlled clinical trials of other ESAs in patients with CKD comparing higher hemoglobin targets (13 – 14 g/dL) to lower targets (9 - 11.3 g/dL) (see Table 2), increased risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events was observed in the higher target groups.
  - Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.
  - In controlled clinical trials of ESAs in patients with cancer, increased risk for death and serious adverse cardiovascular reactions was observed. These adverse reactions included myocardial infarction and stroke.
  - In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and deep venous thrombosis (DVT) was observed in patients undergoing orthopedic procedures.
- The design and overall results of 3 large trials comparing higher and lower hemoglobin targets are shown in Table 2 (Normal Hematocrit Study (NHS), Correction of Hemoglobin Outcomes in Renal Insufficiency (CHOIR) and Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT)).

**Table 2 Adverse Cardiovascular Outcomes in Randomized Controlled Trials Comparing Higher and Lower Hemoglobin Targets in Patients with CKD**

|  | NHS<br>(N = 1265)  | CHOIR<br>(N = 1432)  | TREAT<br>(N = 4038)   |
|--|--|--|---|
| Time Period of Trial                             | 1993 to 1996   | 2003 to 2006   | 2004 to 2009  |
| Population                                       | Patients with CKD on hemodialysis with coexisting CHF or CAD, hematocrit 30 ± 3% on epoetin alfa | Patients with CKD not on dialysis with hemoglobin < 11 g/dL not previously administered epoetin alfa | Patients with CKD not on dialysis with type II diabetes, hemoglobin ≤ 11 g/dL |
| Hemoglobin Target; Higher vs. Lower (g/dL)       | 14.0 vs. 10.0  | 13.5 vs. 11.3  | 13.0 vs. ≥ 9.0  |
| Median (Q1, Q3) Achieved Hemoglobin level (g/dL) | 12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)  | 13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)  | 12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)  |
| Primary Endpoint                                 | All-cause mortality or non-fatal MI  | All-cause mortality, MI, hospitalization for CHF, or stroke  | All-cause mortality, MI, myocardial ischemia, heart failure, and stroke       |
| Hazard Ratio or Relative Risk (95% CI)           | 1.28 (1.06 – 1.56)   | 1.34 (1.03 – 1.74)   | 1.05 (0.94 – 1.17)  |
| Adverse Outcome for Higher Target Group          | All-cause mortality  | All-cause mortality  | Stroke  |
| Hazard Ratio or Relative Risk (95% CI)           | 1.27 (1.04 – 1.54)   | 1.48 (0.97 – 2.27)   | 1.92 (1.38 – 2.68)  |

**Patients with Chronic Kidney Disease Not on Dialysis**  
OMONTYS is not indicated and is not recommended for the treatment of anemia in patients with CKD who are not on dialysis.

A higher percentage of patients (22%) who received OMONTYS experienced a composite cardiovascular safety endpoint event compared to 17% who received darbepoetin alfa in two randomized, active-controlled, open-label, multi-center trials of 983 patients with anemia due to CKD who were not on dialysis. The trials had a pre-specified, prospective analysis of a composite safety endpoint consisting of death, myocardial infarction, stroke, or serious adverse events of congestive heart failure, unstable angina or arrhythmia (hazard ratio 1.32, 95% CI: 0.97, 1.81).

**Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients with Cancer receiving ESAs**  
OMONTYS is not indicated and is not recommended for reduction of RBC transfusions in patients receiving treatment for cancer and whose anemia is not due to CKD because ESAs have shown harm in some settings and the benefit-risk factors for OMONTYS in this setting have not been evaluated.

The safety and efficacy of OMONTYS have not been established for use in patients with anemia due to cancer chemotherapy. Results from clinical trials of ESAs in patients with anemia due to cancer therapy showed decreased locoregional control, progression-free survival and/or decreased overall survival. The findings were observed in clinical trials of other ESAs administered to patients with: breast cancer receiving chemotherapy, advanced head and neck cancer receiving radiation therapy, lymphoid malignancy, cervical cancer, non-small cell lung cancer, and with various malignancies who were not receiving chemotherapy or radiotherapy.

**Hypertension**  
OMONTYS is contraindicated in patients with uncontrolled hypertension. Appropriately control hypertension prior to initiation of and during treatment with OMONTYS. Reduce or withhold OMONTYS if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions.

**Lack or Loss of Response to OMONTYS**  
For lack or loss of hemoglobin response to OMONTYS, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding). If typical causes of lack or loss of hemoglobin response are excluded, evaluate the patient for the presence of antibodies to peginesatide. In the absence of antibodies to peginesatide, follow dosing recommendations for management of patients with an insufficient hemoglobin response to OMONTYS therapy. Contact Affymax, Inc. (1-855-466-6689) to perform assays for binding and neutralizing antibodies.

**Dialysis Management**  
Patients may require adjustments in their dialysis prescriptions after initiation of OMONTYS. Patients receiving OMONTYS may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

**Laboratory Monitoring**  
Evaluate transferrin saturation and serum ferritin prior to and during OMONTYS treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course



# Renal Quality Measures Endorsed



Twelve quality measures aimed at improving care for patients with kidney disease were recently endorsed by the National Quality Forum (NQF). The metrics cover several areas of renal care, including anemia, dialysis adequacy, and vascular access. “These measures will help ensure renal patients receive safe, high-quality, and compassionate care throughout the course of treatment,” said the president and CEO of NQF, Janet Corrigan, PhD, MBA.

Thirty-three possible measures for renal care were evaluated and then narrowed to the 12 endorsed by the NQF board of directors. Three new measures—for anemia and cardiovascular disease in patients with kidney disease—were added to the nine metrics previously endorsed by NQF.

The NQF renal quality measures pertain to aspects of care for patients with chronic kidney disease, end stage renal disease, and those undergoing dialysis. They include the serum phosphorus concentration in dialysis patients, metrics targeted at reducing the use of catheters and increasing the use of arteriovenous fistulas in vascular access for hemodialysis, and a risk-adjusted standardized mortality ratio for dialysis facilities.

Created to improve health care quality, the NQF works to find consensus on national goals for performance improvement, endorses standards for measuring performance, and promotes these goals through education and outreach. The NQF kidney disease criteria were determined in collaboration with several stakeholders including the Centers for Medicare & Medicaid Services, Kidney Care Quality Alliance, and the American Medical Association Physician Consortium for Performance Improvement

Members of the kidney community have until May 1, 2012, to appeal any of the 12 endorsed quality measures before final approval by NQF. ●

## Kidney Disease and Minorities in the United States

- Minorities are more likely to receive a late evaluation by a nephrologist
- Minorities in the United States with CKD are more likely to have uncontrolled blood pressure
- African Americans with kidney disease are 3.6 times more likely to progress to kidney failure than whites, and six times more likely to develop kidney failure related to hypertension
- Hispanics and Native Americans are approximately two times more likely to progress to kidney failure than whites
- African Americans are more likely to receive hemodialysis, and less likely to receive peritoneal dialysis and a transplant
- African Americans are less likely to be waitlisted for and receive a kidney transplant
- Research, education, and clinical care focused on prevention can help eliminate disparities in kidney disease

of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin every 2 weeks until the hemoglobin is stable and sufficient to minimize the need for RBC transfusion. Thereafter, hemoglobin should be monitored at least monthly provided hemoglobin levels remain stable.

### ADVERSE REACTIONS

The following serious adverse reactions observed during clinical trials with OMONTYS are discussed in greater detail in other sections of the labeling:

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism [see Warnings and Precautions]
- Hypertension [see Warnings and Precautions]

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of OMONTYS cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

#### Patients with Chronic Kidney Disease

Adverse reactions were determined based on pooled data from two active controlled studies of 1066 dialysis patients treated with OMONTYS and 542 treated with epoetin, including 938 exposed for at least 6 months and 825 exposed for greater than one year to OMONTYS. The population for OMONTYS was 20 to 93 years of age, 58.5% male, and the percentages of Caucasian, Black (including African Americans), and Asian patients were 57.9%, 37.4%, and 3.1%, respectively. The median weight adjusted dose of OMONTYS was 0.07mg/kg and 113 U/week/kg of epoetin.

Table 3 summarizes the most frequent adverse reactions (≥ 10%) in dialysis patients treated with OMONTYS.

**Table 3 Adverse Reactions Occurring in ≥10% of Dialysis Patients treated with OMONTYS**

| Adverse Reactions   | Dialysis Patients Treated with OMONTYS (N = 1066) | Dialysis Patients Treated with Epoetin (N = 542) |
|---|---|--|
| <b>Gastrointestinal Disorders</b>                           |   |  |
| Diarrhea  | 18.4%   | 15.9%  |
| Nausea  | 17.4%   | 19.6%  |
| Vomiting  | 15.3%   | 13.3%  |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>      |   |  |
| Dyspnea   | 18.4%   | 19.4%  |
| Cough   | 15.9%   | 16.6%  |
| <b>Injury, Poisoning and Procedural Complications</b>       |   |  |
| Arteriovenous Fistula Site Complication                     | 16.1%   | 16.6%  |
| Procedural Hypotension                                      | 10.9%   | 12.5%  |
| <b>Nervous System Disorders</b>                             |   |  |
| Headache  | 15.4%   | 15.9%  |
| <b>Musculoskeletal and Connective Tissue Disorders</b>      |   |  |
| Muscle Spasms   | 15.3%   | 17.2%  |
| Pain in Extremity   | 10.9%   | 12.7%  |
| Back Pain   | 10.9%   | 11.3%  |
| Arthralgia  | 10.7%   | 9.8%   |
| <b>Vascular Disorders</b>                                   |   |  |
| Hypotension   | 14.2%   | 14.6%  |
| Hypertension  | 13.2%   | 11.4%  |
| <b>General Disorders and Administration Site Conditions</b> |   |  |
| Pyrexia   | 12.2%   | 14.0%  |
| <b>Metabolism and Nutrition Disorders</b>                   |   |  |
| Hyperkalemia  | 11.4%   | 11.8%  |
| <b>Infections and Infestations</b>                          |   |  |
| Upper Respiratory Tract Infection                           | 11.0%   | 12.4%  |

Seizures have occurred in patients participating in OMONTYS clinical studies. During the first several months following initiation of OMONTYS, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely.

Advise patients to contact their healthcare practitioner for new-onset seizures, premonitory symptoms, or change in seizure frequency.

Allergic reactions have been reported in patients treated with OMONTYS. Discontinue OMONTYS and administer appropriate therapy if a serious allergic, anaphylactic or infusion-related reaction occurs.

### Immunogenicity

Of the 2357 patients tested, 29 (1.2%) had detectable levels of peginesatide-specific binding antibodies. There was a higher incidence of peginesatide-specific

binding antibodies in patients dosed subcutaneously (1.9%) as compared to those dosed intravenously (0.7%). Peginesatide neutralizing antibodies were detected *in vitro* using a cell-based functional assay in 21 of these patients (0.9%). In approximately half of all antibody-positive patients, the presence of antibodies was associated with declining hemoglobin levels, the requirement for increased doses of OMONTYS to maintain hemoglobin levels, and/or transfusion for anemia of CKD. No cases of pure red cell aplasia (PRCA) developed in patients receiving OMONTYS during clinical trials.

### DRUG INTERACTIONS

No formal drug/drug interaction studies have been performed. Peginesatide does not bind to serum albumin or lipoproteins as demonstrated in *in vitro* protein binding studies in rat, monkey and human sera. *In vitro* studies conducted with human hepatocytes or microsomes have shown no potential for peginesatide to induce or inhibit CYP450 enzymes.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Peginesatide was teratogenic and caused embryofetal lethality when administered to pregnant animals at doses and/or exposures that resulted in polycythemia. OMONTYS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of peginesatide by intravenous injection to rats and rabbits during organogenesis was associated with embryofetal toxicity and malformations. Dosing was every third day in rats for a total of 5 doses and every fifth day in rabbits for a total of 3 doses (0.01 to 50 mg/kg/dose). In rats and rabbits, adverse embryofetal effects included reduced fetal weight, increased resorption, embryofetal lethality, cleft palate (rats only), sternum anomalies, unossification of sternebrae and metatarsals, and reduced ossification of some bones. Embryofetal toxicity was evident in rats at peginesatide doses of ≥ 1 mg/kg and the malformations (cleft palate and sternoschisis, and variations in blood vessels) were mostly evident at doses of ≥ 10 mg/kg. The dose of 1 mg/kg results in exposures (AUC) comparable to those in humans after intravenous administration at a dose of 0.35 mg/kg in patients on dialysis. In a separate embryofetal developmental study in rats, reduced fetal weight and reduced ossification were seen at a lower dose of 0.25 mg/kg. Reduced fetal weight and delayed ossification in rabbits were observed at ≥ 0.5 mg/kg/dose of peginesatide. In a separate embryofetal developmental study in rabbits, adverse findings were observed at lower doses and included increased incidence of fused sternebrae at 0.25 mg/kg. The effects in rabbits were observed at doses lower (5% - 50%) than the dose of 0.35 mg/kg in patients.

#### Nursing Mothers

It is not known whether peginesatide is excreted in human milk. Because many drugs are excreted into human milk, caution should be exercised when OMONTYS is administered to a nursing woman.

#### Pediatric Use

The safety and efficacy of OMONTYS in pediatric patients have not been established.

#### Geriatric Use

Of the total number of dialysis patients in Phase 3 clinical studies of OMONTYS, 32.5% were age 65 and over, while 13% were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

### OVERDOSAGE

OMONTYS overdosage can elevate hemoglobin levels above the desired level, which should be managed with discontinuation or reduction of OMONTYS dosage and/or with phlebotomy, as clinically indicated. Cases of severe hypertension have been observed following overdose with ESAs [see Warnings and Precautions].

### PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

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For more detailed information, see the full prescribing information for OMONTYS at [www.omontys.com](http://www.omontys.com) or contact Takeda Pharmaceuticals America, Inc.

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More and more, the world depends on electronic information. The Internet has changed how we communicate, learn, and discover. In this issue of *Kidney News*, a series of articles explores the impact of the Internet on nephrology. Dealing with a deluge of information? Looking for new ways to connect? We have some answers.



## The New World of Medical Tweeting

By Afreen I. Shariff, MD, and Tejas Desai, MD

Twitter has taken the world by storm. No one could have predicted that just 6 years after its inception Twitter would have 300 million users generating 300 million messages every day (1). If you are among the uninitiated, you should become familiar with how Twitter works and why it's one of the most popular micro-blogging websites in the world.

Twitter is an open forum for sharing real-time information through "tweets." A tweet is a short message of 140 characters or less that can convey absolutely anything to your "followers" (people who subscribe to your "feed" of tweets). And with Twitter you aren't just limited to text. Using third-party providers, you can insert Web addresses and link to photos, videos, and more. If you like a message you can copy and paste it to your followers, or in Twitter parlance "retweet it," which is how a message is amplified. A recent study found that although 40 percent of messages on Twitter were pointless babble, 38 percent were conversational—transferring information and spreading content (2).

The popularity of Twitter with the media, celebrities, and public figures is well documented, but members of the medical community seem hesitant to associate themselves with it. There could be many reasons for this: physicians may be unaware or unfamiliar with Twitter, they may be too busy, or they may fear potential privacy issues (3). Anticipating this, the American Medical Association has released a public statement about professionalism in social media:

"Participating in social networking and other similar internet opportunities can support physicians' personal expression, enable individual physicians to have a professional presence online, foster collegiality and camaraderie within the profession, provide opportunity to widely disseminate public health messages and other health communication. Social networks, blogs, and other forms of communication online also create new challenges to the patient-physician relationship. Physicians should weigh a number of considerations when maintaining a presence online." (4)

Because Twitter is a large pool of raw information and opinions, there are networking opportunities for those who can tap its potential. The news media analyze Twitter posts to gain insights into elections, and politicians focus campaigns based on public sentiment sifted from the site (5). This concept can be used in medical conferences for networking within the medical community and with patients. Journals and conferences, including the American Society of Nephrology (ASN) Kidney Week, want to reach the widest possible audience, and using the large platform and audience Twitter provides ensures their important information is carried far and wide. By analyzing Twitter messages sent with conference or journal "hashtags" (short unique identifiers starting with "#"), it is possible to identify and understand patterns and how these impact a message's reach. During ASN Kidney Week 2011, we identified 172 unique tweeters who produced 993 tweets. Analysis of the content, citation, and sentiment have led to some interesting findings about conference-based tweeting and ways to improve conferences' impact and popularity.

This opens a door to advanced medical informatics where physicians can interact with patients and network with consultants, students, and prospective residents. Twitter has many potential health care applications, such as recruiting potential organ donors, creating online communities for families with special needs, reporting new advances in therapy, initiating clinical case discussions among attending physicians and residents, and health marketing.

In a recent *JAMA* study (6), investigators analyzed 5156 tweets from physician accounts and found a majority (78 percent) identified themselves with their full name, with surgeons occupying the top spot for the highest number of tweets (39 percent) closely followed by internal medicine (29 percent). Physicians holding MDs (70.2 percent) were also more likely to tweet than their DO friends (2 percent) (6). Another group of researchers followed 125 students over a semester and found that those students in the Twitter-based education group were more engaged in the subject and scored better than their other classmates (7). These data suggest that Twitter can be a strong educational tool. Research-

ers at East Carolina University are studying the use of Twitter to communicate during conferences and are developing strategies to better engage the student and physician populations.

In summary, Twitter has the power to spread knowledge and engage many people in conversations. It is the best one-to-many communication system to build your brand, network, give advice, or just have fun. Especially in an age of shrinking health care budgets, Twitter is an effective solution to the need for cheap mass communication (8). With Twitter, the future of communications is here, and it's both free and easy. ●

*Afreen I. Shariff, MD, is with the department of internal medicine and Tejas Desai, MD, is with the division of nephrology and hypertension, at East Carolina University in Greenville, NC.*

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# How to Deal with Information Overload

By Walter Jessen, PhD, and Simon Frantz

Suffering from information overload is a frustrating and all-too-common condition today. If it isn't hard enough to clear your overflowing email inbox, there's the stress of staying on top of the blossoming number of journals and medical blogs in your field, papers uncovered through regular PubMed or Medline searches, not to mention the pressure of keeping up-to-date with the latest must-use social media tools. And yet, a small number of people seem to stay afloat while the vast majority of us are drowning in information. What's their secret?

Every year, the Science Online conference in North Carolina brings together some of the most savvy digital natives in science and journalism. This provided a perfect opportunity for us to pose the question in the session *Drowning in Information! How Can We Create Organization & Balance—Tools and Strategies for Managing Information Overload (Science and Otherwise)* (<http://scio12.wikispaces.com/D3S2d.+Drowning+in+Information>). Below are some of the main themes and tips that emerged for managing the data deluge that hits you on a daily basis.

## Find signals among the noise

You don't need to subscribe to everything! Find the information gathering tools that suit your content needs. If you regularly read journals and magazines, subscribe to their RSS feeds so that you can read them all in one place. Google Reader ([www.google.com/reader](http://www.google.com/reader)) is a free, Web-based aggregator that allows you to organize, read, and search all of your favorite news sites and blogs in one place. If you like staying on top of the latest trends in a particular discipline, join Twitter (<https://twitter.com>) and follow people in your field and/or people that share your interests and have your news curated. If you have an iPhone or iPad, the Flipboard app (<http://flipboard.com>) collates content from several social media sources.

## Filter, filter, filter

For many people, reading and responding to email consumes the most time during a normal business day. Take back some of the time used to manage email by using folders to stay organized. In your email client, create specific folders based on topic, task, or person. Whether it's for must-read content or

for messages you can turn to at a later date, automate the task of sorting email based on keyword(s) and/or sender. This allows you to immediately focus on the message rather than on the action of sorting. Color-code emails to distinguish family and friends from meeting requests or table of content alerts, and do the same for RSS feeds, Twitter, and other online sources. Divide information flows into folders or lists, such as "Daily reads" or "Weekend reads" or other categories that reflect your desired reading habits and content organization. For more advanced management between different services and devices, use ifttt (If This Then That; <http://ifttt.com>), which enables the creation of customized, automated tasks.

## Organize and archive

There are numerous free online tools that can help you store your information, but three repeatedly came up in the discussion: Dropbox (<https://www.dropbox.com>), which allows you to share files between your work and home computer; Mendeley (<http://www.mendeley.com>), a reference manager that allows you to organize, read, and annotate PDF documents; and Evernote (<http://www.evernote.com>), a note-taking app

which saves your most valuable notes, clippings, and photos on your computer and across all your mobile devices. Pinboard (<http://pinboard.in>) was also mentioned; although it is a paid service it allows you to bookmark and organize links, effortlessly saving those shared via Twitter.

## Get into the habit

It's easy to give up on a tool within days, especially if it becomes stressful to deal with its backlog after a deadline, conference or, heaven forbid, a vacation. People recommended throwing yourself into a method for 30 days and see if it works before ditching it. And try regular cleansing sessions—for instance, try clearing your information streams every Sunday evening. That way, you'll start each week without the pressure or guilt of looking at old content that you are unlikely to read anyway. ●

Walter Jessen is a computational biologist, knowledge curator, and Web developer at Walter Jessen Discovery New Media (<http://www.walterjessen.com>). Simon Frantz is the Science/Technology Features editor at BBC Future (<http://www.bbc.com/future>).

# Doximity

By Sara Reistad-Long

The *Journal of the American Medical Association* has reported that one in nine Americans now have chronic kidney disease, and that figure is believed to be growing. At the same time many publications (among them, *Kidney News*) are tracking a drop in the number of nephrologists entering the field, and others have documented the strain on those already practicing as dialysis resources are stretched thin.



As awareness of kidney disease within the general population increases, so will nephrologists' need for a safe, efficient, and Health Insurance Portability and Accountability Act (HIPAA)—compliant system for securely managing incoming referrals and discussing patient information with a treatment team. Although doctors themselves are often early adopters of information technology—81 percent now own a smartphone, for example—medicine as a whole has been slow to catch up. Email and Short Message Service (SMS), for instance, are not considered HIPAA secure, a point that the Joint Commission on Accreditation of Healthcare Organizations emphasized in November 2011 when it issued a ban on texting. This, of course, leaves physicians reliant on telephones, pagers, and faxes to communicate patient information.

Doximity was founded to address what we see as one of the next big challenges in health care—facilitating communication among physicians. Our company has been described as a kind of LinkedIn for doctors, and with nearly 30,000 physicians signed up, we're already the largest medical professional network in the country. Enabling doctors to find and make connections in their practices and with alumni is valuable in itself, but what may be even more essential to our

specific community is a private and HIPAA-secure method of exchanging information. We assign dual passwords to each user so each message is encrypted end to end. And because Doximity has been optimized for both smartphones and tablets, messages can be sent, and referrals made, from the operating room—or far from the nearest hospital—as easily as from a computer.

Equally integral to safe communication is real-name interaction. At Doximity, we verify each of our users. We believe that ensuring every member's identity creates a framework of trust, expertise, and professionalism that reflects the effective physician interaction in the real world. The difference, of course, is that these communications are increasingly happening as ongoing written discussions across thousands of miles.

In many ways, our newest feature, iRounds, grew out of these changes. Not unlike social networking sites such as Twitter, Facebook, and Google, iRounds allows users to tap into larger communities to discuss patient cases, new research, emerging medical technologies, and more.

"Doximity offers an easy way to keep up to date on the latest news, best blog posts, and journal articles from our specialty," said Joshua Schwimmer, MD, a nephrologist at Lenox Hill Hospital and The Mount Sinai Hospital in New York. "For example, a review article on focal segmental glomerulosclerosis (FSGS) in the *New England Journal of Medicine* was the basis for a discussion among multiple specialties about the presentation of FSGS, the differences between FSGS and diabetic nephropathy, and the indications for renal biopsy. The easy-access via smartphone and the Web, the user-friendly design, and the ready availability of physicians' credentials makes it simple to collaborate and learn from your colleagues." ●

Sara Reistad-Long is affiliated with Doximity.





# Understanding Research Impact

By Kristi L. Holmes and Cathy C. Sarli

Understanding the true value of a scholar's research and output is no small feat. Although it's fairly straightforward to track the number of publications or total dollar amount of awarded funding, it can be a greater challenge to assess the reach of scholarly efforts and determine how others are utilizing the research results. Metrics for assessing research performance, quality, and impact cover a wide range of the scholarly ecosystem and are used for a variety of purposes: individual career planning, promotion, and tenure; benchmarking to track group or institutional performance; marketing and strategic planning purposes; and reporting research outcomes to the public.

## Author-level metrics

Author-level metrics allow individuals to track their scholarly output and serve as a reflection of a researcher's productivity. Enumerating such things as the number of publications in the scholarly literature, number of books published, and number and amount of funding awards can all serve to understand the efforts of individual researchers. One commonly used metric is the Hirsch index ( $h$  index). The  $h$  index, developed by Jorge E. Hirsch, PhD, in 2005 (1), offers a numeric index to measure the productivity and impact of a given researcher. The  $h$  index is a quantitative metric based on analysis of publication data, using publications and citations to provide "an estimate of the importance, significance, and broad impact of a scientist's cumulative research contributions" (1). According to Hirsch, the  $h$  index is defined as follows: "A scientist has index  $h$  if  $h$  of his or her  $N_p$  papers have at least  $h$  citations each and the other ( $N_p - h$ ) papers have  $\leq h$  citations each" (1), where  $N_p$  is total number of papers published.

As an example, an  $h$  index of 10 means that among all publications by one author, 10 of these publications have received at least 10 citations each. The  $h$  index is but one metric for author-level assessment.

No single metric is sufficient for measuring performance, quality, or impact by an author; indeed, the discovery of a scholar's most impactful work may be gleaned only through qualitative forms of assessment that do not rely solely on publication data.

## Article-level metrics

Citation counts are perhaps the most frequently used metric at the article level. A citation is a reference to a specific publication. The inherent assumption is that significant articles will have high numbers of citations. Further analysis is required to discover why select publications garner a higher citation rate than others. Many databases provide tools for authors to track citations to their work, with some offering citation maps that can be downloaded for reporting purposes.

A growing article-level metric is based on the usage of a publication; several journals and third-party service providers are making it possible to assess the Web-based use and subsequent dissemination of individual articles. The Public Library of Science (PLOS) journals offer perhaps the most highly developed publisher-based platform for this type of tracking. Articles published in PLOS journals include an article-level metrics tab that shows such details as article usage statistics (e.g., HTML page views, PDF and XML downloads, and accesses from PubMed Central; number of users via Mendeley; and number of Facebook mentions); citations from the scholarly literature (currently from CrossRef, PubMed Central, SciVerse Scopus, and Web of Science); social bookmarks from CiteULike and Connotea; PLOS reader evaluation (i.e., readers' feedback on the article in the form of comments, notes, and star ratings); and discussion of the article in blogs (2). These alternative metrics (or "altmetrics" as they are commonly known) for articles and even datasets and presentations are becoming easier to track via Web services such as Total-Impact (<http://total-impact.org>) and Altmeter (<http://www.postgenomic.com>), who offers explorer and browser-based bookmarklet applications.

## Journal-level metrics

Journals are also assessed by different criteria. The impact factor, listed in Thomson Reuters' Journal Citation Reports, assigns journals a numeric score based on the frequency with which the average article in the journal is cited over a set period of time (3). Whereas the impact factor tracks straight citations, the Eigenfactor score (<http://www.eigenfactor.org>) is derived from a formula based on citations from a journal over a 5-year period, with citations from highly ranked journals given more weight. Journal self-citations are not included in the Eigenfactor score, unlike the impact factor score.

A caveat of note for journal-level metrics: specialized journals or those published by societies may disseminate your work more efficiently to colleagues in your field than a "high-impact" general-interest science journal. Reaching your intended audience is the surest way to enhance the visibility and impact of your research.

## Going beyond the metrics: the Becker model

It is tempting to use these metrics as an objective way to assign value or worth to a researcher's output or to an individual journal. Although these metrics can be helpful in understanding research efforts, they cannot be evaluated in a vacuum. To understand the true impact of research, metrics derived from publication data must be supplemented with indicators that demonstrate tangible outcomes such as clinical implementation, benefit to the community, influence on legislation or policy, and economic benefit. Publication data alone do not provide a full narrative of research impact, nor are they predictive of meaningful health outcomes.

The Becker Medical Library Model for Assessment of Research Impact (4,5) serves as a framework to quantify and document research impact based on research outputs and activities. It includes resources for locating evidence of research impact and

strategies for enhancing research impact. The site offers reporting templates, a glossary, and examples of relevant indicators of impact across the research process as well as a sample of a completed report. The use of publication data in tandem with the Becker Model provides a more robust overview of the impact of research to accomplish a host of higher-order activities that are critical in today's biomedical research world, including the following:

- Justification of future requests for funding
- Quantification of return on research investment
- Discovery of how research findings are being used
- Promotion and tenure activities
- Identification of possible collaborators
- Demonstration that research findings are resulting in meaningful health outcomes
- Discovery of community benefit as a result of research findings

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## 20

## Strategies to Enhance the Impact of Your Research

Improving access to, and retrieval of, your research articles is the surest way to enhance their impact. Repetition, consistency, and an awareness of the intended audience form the basis of most of the following strategies in areas related to preparation for publication, dissemination of content, and keeping track of your research.

1. Authors should use the same variation of their name consistently throughout their academic careers. If your name is a common one, consider adding your full middle name to distinguish it from other authors. *Consistency enhances retrieval.*
2. Consider adding the name of the research study or your center, institute, division, or program as a corporate author, and use the same name consistently. This will allow for enhanced retrieval of publications generated by a particular research study or center, institute, division, or program in a database or resource search. See the National Library of Medicine's *Fact Sheet: Authorship in MEDLINE* (1).
3. Assign Medical Subject Headings (MeSH) terms to the manuscript. Contact your health sciences library for assistance with MeSH terms.
4. Formulate a concise, well-constructed title and abstract. Include crucial key words in the abstract. See Wiley-Blackwell's *Optimizing Your Article for Search Engines* (2).
5. Retain the rights to your manuscripts to allow for maximum flexibility in reusing your work.
6. If your work involves potential translational medicine applications, include a discussion of how the research could translate to clinical outcomes. "Impact of journal articles will be improved if they provide a direct line of reasoning for how findings might translate into useful information for real-world behaviors or technologies. This will enhance the probability that the article will affect public policy and thus increase its impact." (3)
7. Submit the manuscript to a digital subject repository or your institution's facility, if they have one. Contact your health sciences library for assistance with identifying appropriate locations.
8. Publish your work in an open access journal. Open access journals allow authors to retain rights to their work, which allows for other options for dissemination of the research. Open access articles may garner greater impact than traditional publication models (4).
9. Set up a website devoted to the research project, and post manuscripts of publications, conference abstracts, and supplemental materials—such as images, illustrations, slides, specimens, and progress reports—on the site.
10. Share the research data and deposit it in appropriate repositories, such as GenBank (<http://www.ncbi.nlm.nih.gov/genbank>) and other databases at the National Center for Biotechnology Information, or with journal publishers willing to post the data. Sharing of this information may lead to more rapid analysis and identification of genetic contributions to diseases and medical conditions. One study (5) has demonstrated a correlation between shared research data and an increased number of citations.
11. Present preliminary research findings at a meeting or conference, and after the event consider making your figures available through Figshare (<http://figshare.com>) and your presentation materials available in your institutional repository or on a slide-sharing site such as SlideShare ([www.slideshare.net](http://www.slideshare.net)) so that others may discover and share your knowledge.
12. Consider communicating information about your research via Twitter (<https://twitter.com>). Twitter provides an efficient platform for communicating and consuming science. For some practical guidance on getting started and some background, see *Twitter 101: How should I get started using Twitter?* (6). To get a better idea of how and why scientists and physicians are using Twitter, you might find *What is Twitter and Why Scientists Need to Use It* (7), *How Could Twitter Influence Science (and Why Scientists Are on Board)* (8), and *Physicians on Twitter* (9) of interest, as well.
13. Research is not just text and figures. Create a podcast describing the research project, and submit it to YouTube (<http://www.youtube.com>) or Vimeo (<http://vimeo.com>). The Washington University YouTube channel offers good examples (<http://www.youtube.com/user/wustlpa#p/c/F4A14AEE489425B0>). Another option for distributing podcasts is BioMed Central (<http://www.biomedcentral.com>), an organization that recognizes video as an increasingly important way for researchers to communicate their results and that welcomes podcast submissions. Links to these podcasts are located on the BioMed Central YouTube channel.
14. Issue press releases for significant findings, and partner with your organization's media office to deliver findings to local media outlets.
15. If there is a website for the study, provide information tailored for consumers. According to the 2009 Pew Internet & American Life Project report (10), 61 percent of Americans use the Internet for health information.
16. Conduct outreach visits and/or provide seminars to other institutions, scientists, practicing physicians, and health care providers to discuss your research project.
17. Consider discussing the results of your research with policy makers and other governing bodies that issue policies, guidelines, and standards. See *Feeding your Research into the Policy Debate* (11) for a review of the pros and cons of doing this.
18. Keep your profile data up to date on social networking sites aimed at scientists, researchers, and/or physicians. Inquire about these tools within your organization. Some highly adopted institution-wide platforms include VIVO (<http://vivoweb.org>) and Profiles (<http://profiles.catalyst.harvard.edu>). These institutional efforts leverage structured data about researchers to provide current and validated information that can be used to visualize research efforts and identify new collaborators.
19. Sign up for other social networking sites to increase your visibility and connect with colleagues. Some useful sites are ResearcherID (<http://www.researcherid.com>) and LinkedIn (<http://www.linkedin.com>). Sites such as Nature Network

(<http://network.nature.com>) allow and encourage interaction between users. Social network tools provide a forum for disseminating your research, promoting discussion of your work, sharing scientific information, and forming new partnerships.

20. Alternative metrics allow users to understand how their work is being used in the online world via bookmarks and links to the article or data, conversations on Twitter, in blogs about the work, and in the various methods of sharing and storing content. Some great sites for viewing these "altmetrics" include Total-Impact, ReaderMeter (<http://readermeter.org>), and resources at Altmetric, including an explorer and a bookmarklet that is easily incorporated into your Web browser bookmark bar. ●

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Adapted from the *Becker Medical Library Model for Assessment of Research Impact*, available at <https://becker.wustl.edu/impact-assessment/strategies>.





## INDICATION

VOTRIENT is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

## IMPORTANT SAFETY INFORMATION

**WARNING: HEPATOTOXICITY**  
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. See "Warnings and Precautions," Section 5.1, in complete Prescribing Information.

- **Hepatic Effects:** Patients with pre-existing hepatic impairment should use VOTRIENT with caution. In patients with pre-existing moderate hepatic impairment, the starting dose of VOTRIENT should be reduced to 200 mg per day or alternatives to VOTRIENT should be considered. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. Increases in serum transaminase levels (ALT, AST) and bilirubin were observed. Severe and fatal hepatotoxicity has occurred. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Concomitant use of

VOTRIENT and simvastatin increases the risk of ALT elevations and should be undertaken with caution [see *Drug Interactions*]. Before the initiation of treatment and regularly during treatment, **monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.**

- **QT Prolongation and Torsades de Pointes:** Prolonged QT intervals and arrhythmias, including torsades de pointes, have been observed with VOTRIENT. Use with caution in patients at higher risk of developing QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes within the normal range should be performed.
- **Hemorrhagic Events:** Fatal hemorrhagic events have been reported (all Grades [16%] and Grades 3 to 5 [2%]). VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients.
- **Arterial Thrombotic Events:** Arterial thrombotic events have been observed and can be fatal. In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke, and transient ischemic attack (all Grades [3%] and Grades 3 to 5 [2%]) were

observed. Use with caution in patients who are at increased risk for these events.

- **Gastrointestinal Perforation and Fistula:** Gastrointestinal perforation or fistula has occurred. Fatal perforation events have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula.
- **Hypertension:** Hypertension, including hypertensive crisis, has been observed. Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor for hypertension and treat as needed. Hypertension was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks). In the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT may be reduced. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of VOTRIENT.
- **Wound Healing:** VOTRIENT may impair wound healing. Temporary interruption of therapy with VOTRIENT is recommended in patients undergoing surgical procedures. VOTRIENT should be discontinued in patients with wound dehiscence.



# Move Forward With VOTRIENT

In a phase 3, randomized, double-blind, placebo-controlled trial, VOTRIENT provided significant improvement in progression-free survival (PFS) in both treatment-naïve and cytokine-pretreated patients with advanced RCC<sup>1,2</sup>

**All patients**  
**9.2 months**  
**(95% CI, 7.4-12.9)**

overall median PFS with VOTRIENT (n=290)  
vs **4.2 months** (95% CI, 2.8-4.2)  
with placebo (n=145) ( $P<0.001$ )<sup>1,3</sup>

**Treatment-naïve patients**  
**11.1 months**  
**(95% CI, 7.4-14.8)**

median PFS with VOTRIENT (n=155)  
vs **2.8 months** (95% CI, 1.9-5.6)  
with placebo (n=78) ( $P<0.001$ )<sup>1,3</sup>

**Cytokine-pretreated patients**  
**7.4 months**  
**(95% CI, 5.6-12.9)**

median PFS with VOTRIENT (n=135)  
vs **4.2 months** (95% CI, 2.8-5.6)  
with placebo (n=67) ( $P<0.001$ )<sup>1,3</sup>

## NCCN Guidelines® Category 1 recommendation<sup>4</sup>

- As a first-line therapy for relapsed or Stage IV unresectable RCC of predominant clear cell histology. These Guidelines also include therapies other than VOTRIENT as first-line treatment options

### WARNING: HEPATOTOXICITY

Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. See "Warnings and Precautions," Section 5.1, in complete Prescribing Information.

## VOTRIENT: Safety Profile Summary<sup>1</sup>

- Most common adverse events observed with VOTRIENT were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting
  - Grade 3/4 fatigue occurred in 2% of patients; all grades, 19% of patients
  - Grade 3/4 asthenia occurred in 3% of patients; all grades, 14% of patients
- For any individual adverse reaction in the VOTRIENT arm, the rate of Grade 3/4 adverse events is  $\leq 4\%$

## Most common laboratory abnormalities were ALT and AST increases<sup>1</sup>

- Grade 3 ALT increases occurred in 10% of patients; grade 4, 2% of patients; all grades, 53% of patients
- In clinical trials, 92.5% of all transaminase elevations of any grade occurred in the first 18 weeks of treatment with VOTRIENT
- Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic monitoring should then continue after this time period

- Hypothyroidism:** Hypothyroidism was reported as an adverse reaction in 26/586 (4%). Monitoring of thyroid function tests is recommended.
- Proteinuria:** Monitor urine protein. Proteinuria was reported in 44/586 (8%) (Grade 3, 5/586 [ $<1\%$ ] and Grade 4, 1/586 [ $<1\%$ ]). Baseline and periodic urinalysis during treatment is recommended. Discontinue for Grade 4 proteinuria.
- Pregnancy Category D:** VOTRIENT can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while taking VOTRIENT.
- Drug Interactions:** CYP3A4 Inhibitors (eg, ketoconazole, ritonavir, clarithromycin): Avoid use of strong inhibitors. Consider dose reduction of VOTRIENT when administered with strong CYP3A4 inhibitors.

CYP3A4 Inducers (such as rifampin): Consider an alternate concomitant medication with no or minimal enzyme induction potential or avoid VOTRIENT.

CYP Substrates: Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.

Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT elevations. If a patient

develops ALT elevations, follow dosing guidelines for VOTRIENT, consider alternatives to VOTRIENT or discontinuing simvastatin. There are insufficient data to assess the risk of concomitant administration of alternative statins and VOTRIENT.

- Adverse Reactions:** The most common adverse reactions ( $>20\%$ ) for VOTRIENT versus placebo were diarrhea (52% vs 9%), hypertension (40% vs 10%), hair color changes (depigmentation) (38% vs 3%), nausea (26% vs 9%), anorexia (22% vs 10%), and vomiting (21% vs 8%).

Laboratory abnormalities occurring in  $>10\%$  of patients and more commonly ( $\geq 5\%$ ) in the VOTRIENT arm versus placebo included increases in ALT (53% vs 22%), AST (53% vs 19%), glucose (41% vs 33%), and total bilirubin (36% vs 10%); decreases in phosphorus (34% vs 11%), sodium (31% vs 24%), magnesium (26% vs 14%), and glucose (17% vs 3%); and leukopenia (37% vs 6%), neutropenia (34% vs 6%), thrombocytopenia (32% vs 5%), and lymphocytopenia (31% vs 24%).

VOTRIENT has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 4/586 patients ( $<1\%$ ).



Please see Brief Summary of Prescribing Information on adjacent pages.

**References:** 1. VOTRIENT® (pazopanib) Tablets [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2012. 2. Sternberg CN, et al. *J Clin Oncol*. 2010;28(6):1061-1068. 3. Data on file, GlaxoSmithKline. 4. Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology® for Kidney Cancer V.2.2012. ©National Comprehensive Cancer Network, Inc 2012. All rights reserved. Accessed March 22, 2012. To view the most recent and complete version of the guideline, go online to [www.nccn.org](http://www.nccn.org). NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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# Journal View

## Would you trade life expectancy to avoid dialysis?

Many patients approaching end stage renal disease (ESRD) are willing to accept significant reductions in survival to avoid some of the burdens and limitations associated with dialysis, suggests a study in the *Canadian Medical Association Journal*.

The researchers performed a “discrete choice” experiment including 105 adult patients with stage 3 to 5 kidney disease at Australian renal clinics. The study looked at how various treatment characteristics affected patients’ preferences for dialysis versus conservative care for progressive kidney disease. Variables included life expectancy, number of visits to the hospital per week, ability to travel, time spent undergoing dialysis, and other factors.

Patients were more likely to opt for dialysis if it increased their average life expectancy: odds ratio (OR) 1.84. Other factors affecting the preference for dialysis were the availability of dialysis during the evening as well as during daytime hours, OR 8.95; and the availability of subsidized transportation, OR 1.55. By contrast, patients were less likely to choose dialysis if it involved more hospital visits, OR 0.70; or if it placed more limits on their ability to travel, OR 0.47.

Patients would accept a 7-month reduction in life expectancy to avoid one extra hospital visit per week, and a 15-month reduction to decrease their travel restrictions. Patient age was not a significant influencing factor.

The results suggest that, even if dialysis means longer survival, many patients with ESRD would prefer conservative care under certain circumstances. Patients are “willing to trade considerable life expectancy to reduce the burdens and restrictions of dialysis,” the researchers write. They call for further study of decision making in older patients with ESRD, and of patient preferences regarding the type and location of dialysis [Morton RL, et al. Factors influencing patient choice of dialysis versus conservative care to treated end-stage kidney disease. *CMAJ* 2012; 184:E277–E283]. ●

## Mesenchymal stem cells as induction therapy for kidney transplant

For living-related donor kidney recipients, induction therapy with autologous mesenchymal stem cells (MSCs) can improve transplant outcomes, reports a study in the *Journal of the American Medical Association*.

The trial included 159 patients who were scheduled for living-related donor kidney transplantation from an ABO-compatible, cross match–negative donor. In a 2:1 ratio, patients were randomly assigned to induction therapy with marrow-derived autologous MSCs or anti-interleukin-2 antibody (basiliximab). Autologous MSCs were given at a con-

centration of 1 to 2 x 10<sup>6</sup>/kg at the time of kidney reperfusion, repeated at 2 weeks. All patients also received calcineurin inhibitors (CNIs); one-half of the MSC group received CNIs at 80 percent of the standard dose.

At 13 and 30 months, there were no significant differences in patient or graft survival. The 6-month rates of biopsy-confirmed graft rejection were lower in patients receiving autologous MSCs: 7.5 percent with standard-dose CNI and 7.7

percent with low-dose CNI, compared with 21.6 percent in the basiliximab group. Induction therapy with MSCs also led to faster recovery of renal function during the first month after transplant in comparison with control individuals: mean difference 6.2–10.0 mL/min per 1.73 m<sup>2</sup>. At 1 year, patients in the MSC groups had a significantly lower rate of opportunistic infections: hazard ratio 0.42.

Autologous MSCs are a possible alternative to induction therapy with anti-in-

terleukin-2 antibody, with the potential to lower rejection risk. This open-label trial finds several advantages of MSC induction therapy, including a lower acute rejection rate, more rapid return of kidney function, and a lower rate of opportunistic infections. Long-term follow-up studies are planned [Tan J, et al. Induction therapy with autologous mesenchymal stem cells in living-related kidney transplants: a randomized controlled trial. *JAMA* 2012; 307:1169–1177]. ●

### BRIEF SUMMARY

#### VOTRIENT (pazopanib) tablets

The following is a brief summary only; see full prescribing information for complete product information.

#### WARNING: HEPATOTOXICITY

**Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. [See Warnings and Precautions (5.1).]**

#### 1 INDICATIONS AND USAGE

VOTRIENT® is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

#### 2 DOSAGE AND ADMINISTRATION

**2.1 Recommended Dosing:** The recommended dose of VOTRIENT is 800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal) [see *Clinical Pharmacology* (12.3) of full prescribing information]. The dose of VOTRIENT should not exceed 800 mg. Do not crush tablets due to the potential for increased rate of absorption which may affect systemic exposure. [See *Clinical Pharmacology* (12.3) of full prescribing information.] If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

**2.2 Dose Modification Guidelines:** Initial dose reduction should be 400 mg, and additional dose decrease or increase should be in 200 mg steps based on individual tolerability. The dose of VOTRIENT should not exceed 800 mg. **Hepatic Impairment:** No dose adjustment is required in patients with mild hepatic impairment. In patients with moderate hepatic impairment, alternatives to VOTRIENT should be considered. If VOTRIENT is used in patients with moderate hepatic impairment, the dose should be reduced to 200 mg per day. VOTRIENT is not recommended in patients with severe hepatic impairment. [See *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3) of full prescribing information.]

**Concomitant Strong CYP3A4 Inhibitors:** The concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations and should be avoided. If coadministration of a strong CYP3A4 inhibitor is warranted, reduce the dose of VOTRIENT to 400 mg. Further dose reductions may be needed if adverse effects occur during therapy. This dose is predicted to adjust the pazopanib AUC to the range observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. [See *Drug Interactions* (7.1).]

**Concomitant Strong CYP3A4 Inducers:** The concomitant use of strong CYP3A4 inducers (e.g., rifampin) may decrease pazopanib concentrations and should be avoided. VOTRIENT should not be used in patients who can not avoid chronic use of strong CYP3A4 inducers. [See *Drug Interactions* (7.1).]

**4 CONTRAINDICATIONS**  
None.

**5 WARNINGS AND PRECAUTIONS**  
**5.1 Hepatic Effects:** In clinical trials with VOTRIENT, hepatotoxicity, manifested as increases in serum transaminases (ALT, AST) and bilirubin, was observed [see *Adverse Reactions* (6.1)]. This hepatotoxicity can be severe and fatal. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Across all monotherapy studies with VOTRIENT, ALT >3 X ULN upper limit of normal (ULN) was reported in 138/977 (14%) and ALT >8 X ULN was reported in 40/977 (4%) of patients who received VOTRIENT. Concurrent elevations in ALT >3 X ULN and bilirubin >2 X ULN regardless of alkaline phosphatase levels were detected in 13/977 (1%) of patients. Four of the 13 patients had no other explanation for these elevations. Two of 977 (0.2%) patients died with disease progression and hepatic failure. Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic monitoring should then continue after this time period. Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on VOTRIENT with weekly monitoring of liver function until ALT return to Grade 1 or baseline. Patients with isolated ALT elevations of >8 X ULN should have VOTRIENT interrupted until they return to Grade 1 or baseline. If the potential benefit for reinitiating treatment with VOTRIENT is considered to outweigh the risk for hepatotoxicity, then reintroduce VOTRIENT at a reduced dose of no more than 400 mg once daily and measure serum liver tests weekly for 8 weeks [see *Dosage and Administration* (2.2)]. Following reintroduction of VOTRIENT, if ALT elevations >3 X ULN recur, then VOTRIENT should be permanently discontinued. If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN, VOTRIENT should be permanently discontinued. Patients should be monitored until resolution. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome [see *Clinical Pharmacology* (12.5) of full prescribing information]. Patients with only a mild indirect hyperbilirubinemia, known Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations. Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring [see *Drug Interactions* (7.3)]. Insufficient data are available to assess the risk of concomitant administration of alternative statins and VOTRIENT. In patients with pre-existing moderate

hepatic impairment, the starting dose of VOTRIENT should be reduced or alternatives to VOTRIENT should be considered. Treatment with VOTRIENT is not recommended in patients with pre-existing severe hepatic impairment, defined as total bilirubin >3 X ULN with any level of ALT. [See *Dosage and Administration* (2.2), *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3) of full prescribing information.]

**5.2 QT Prolongation and Torsades de Pointes:** In clinical RCC studies of VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 11/558 (<2%) of patients. Torsades de pointes occurred in 2/977 (<1%) of patients who received VOTRIENT in the monotherapy studies. In the randomized clinical trial, 3 of the 290 patients receiving VOTRIENT had post-baseline values between 500 to 549 msec. None of the 145 patients receiving placebo had post-baseline QTc values ≥500 msec. VOTRIENT should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. When using VOTRIENT, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g., calcium, magnesium, potassium) within the normal range should be performed.

**5.3 Hemorrhagic Events:** In clinical RCC studies of VOTRIENT, hemorrhagic events have been reported [all Grades (16%) and Grades 3 to 5 (2%)]. Fatal hemorrhage has occurred in 5/586 (0.9%) [see *Adverse Reactions* (6.1)]. VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients.

**5.4 Arterial Thrombotic Events:** In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke, and transient ischemic attack [all Grades (3%) and Grades 3 to 5 (2%)] were observed. Fatal events have been observed in 2/586 (0.3%). In the randomized study, these events were observed more frequently with VOTRIENT compared to placebo [see *Adverse Reactions* (6.1)]. VOTRIENT should be used with caution in patients who are at increased risk for these events or who have had a history of these events. VOTRIENT has not been studied in patients who have had an event within the previous 6 months and should not be used in those patients.

**5.5 Gastrointestinal Perforation and Fistula:** In clinical RCC studies of VOTRIENT, gastrointestinal perforation or fistula has been reported in 5 patients (0.9%). Fatal perforation events have occurred in 2/586 (0.3%). Monitor for symptoms of gastrointestinal perforation or fistula. **5.6 Hypertension :** In clinical studies, events of hypertension including hypertensive crisis have occurred. Blood pressure should be well-controlled prior to initiating VOTRIENT. Patients should be monitored for hypertension and treated as needed with anti-hypertensive therapy. Hypertension (systolic blood pressure ≥150 or diastolic blood pressure ≥100 mm Hg) was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks). [See *Adverse Reactions* (6.1).]

In the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT may be reduced [see *Dosage and Administration* (2.2)]. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of VOTRIENT.

**5.7 Wound Healing:** No formal studies on the effect of VOTRIENT on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as pazopanib may impair wound healing, treatment with VOTRIENT should be stopped at least 7 days prior to scheduled surgery. The decision to resume VOTRIENT after surgery should be based on clinical judgment of adequate wound healing. VOTRIENT should be discontinued in patients with wound dehiscence.

**5.8 Hypothyroidism:** In clinical RCC studies of VOTRIENT, hypothyroidism reported as an adverse reaction in 26/586 (4%) [see *Adverse Reactions* (6.1)]. Proactive monitoring of thyroid function tests is recommended. **5.9 Proteinuria:** In clinical RCC studies with VOTRIENT, proteinuria has been reported in 44/586 (8%) [Grade 3, 5/586 (<1%) and Grade 4, 1/586 (<1%)] [see *Adverse Reactions* (6.1)]. Baseline and periodic urinalysis during treatment is recommended. VOTRIENT should be discontinued if the patient develops Grade 4 proteinuria. **5.10 Pregnancy:** VOTRIENT can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, VOTRIENT is expected to result in adverse reproductive effects. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. There are no adequate and well-controlled studies of VOTRIENT in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking VOTRIENT. [See *Use in Specific Populations* (8.1).]

**6 ADVERSE REACTIONS**  
**6.1 Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Potentially serious adverse reactions with VOTRIENT included hepatotoxicity, QT prolongation and torsades de pointes, hemorrhagic events, arterial thrombotic events, gastrointestinal perforation and fistula, and hypertensive crisis [see *Warnings and Precautions* (5.1-5.5)]. The safety of VOTRIENT has been evaluated in 977 patients in the monotherapy studies which included 586 patients with RCC at the time of NDA submission. With a median duration of treatment of 7.4 months (range 0.1 to 27.6), the most commonly observed adverse reactions (≥20%) in the 586 patients were diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, and vomiting. The data described below reflect the safety profile of VOTRIENT in 290 RCC patients who participated in a



Ten percent rate of chronic kidney disease in children with acute kidney injury

At least 10 percent of children with acute kidney injury (AKI) in a children’s hospital intensive care unit (ICU) will experience chronic kidney disease (CKD) within the next few years, according to a report in the *American Journal of Kidney Disease*. The researchers analyzed prospective follow-up data on 126 children with AKI admitted to the pediatric ICU in a Canadian children’s hospital from 2006 to 2008.

(Another 173 children were lost to follow-up.) One-fourth of the patients were newborns; in more than half, AKI was associated with open-heart surgery. As defined by AKI Network criteria, severity was stage 1 in 35 percent of children, stage 2 in 37 percent, and stage 3 in 28 percent. At 1–3 years of follow-up, the rates of CKD—defined as the presence of albuminuria and/or glomerular filtration

rate (GFR) less than 60 mL/min/1.73 m<sup>2</sup>—was assessed. At follow-up, the criteria for CKD were met in 10.3 percent of children who had stage 1 AKI, 10.6 percent with stage 2 AKI, and 17.1 percent with stage 3 AKI. Another 46.8 percent of children were considered at risk of CKD on the basis of mildly to moderately reduced kidney function (GFR 60–90 mL/min/1.73 m<sup>2</sup>), high

blood pressure, or hyperfiltration (GFR 60–90 mL/min/1.73 m<sup>2</sup>). Of these tertiary care pediatric ICU patients with AKI, more than 10 percent go on to experience CKD. Overall, most of these children either have CKD or are considered at risk for the development of CKD at follow-up. The authors believe that all children with AKI should receive regular monitoring for possible kidney damage [Mammen C, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. *Am J Kidney Dis* 2012; 59:523–530]. ●

Clinical role of DPP-4 inhibitors in type 2 diabetes

Dipeptidyl peptidase-4 (DPP-4) inhibitors are an effective alternative for second-line therapy in patients with type 2 diabetes, reports a meta-analysis in the *British Medical Journal*. The analysis pooled data from 19 randomized trials, including 7136 patients assigned to a DPP-4 inhibitor and 6745 to other hypoglycemic treatments. The results showed a smaller decrease in glycated hemoglobin (HbA1c) with DPP-4 inhibitors compared with metformin alone, weighted mean difference 0.20; and a lesser decrease in body weight, weighted mean difference 1.50.

As second-line treatment to reduce HbA1c, DPP-4 inhibitors were less effective than glucagon-like peptide-1 (GLP-1) agonists and sulfonylureas but were similar to pioglitazone. The DPP-4 inhibitors led to more favorable changes in body weight compared with sulfonylureas or pioglitazone but not compared with GLP-1 agonists.

Studies comparing DPP-4 inhibitors against metformin alone or with pioglitazone or against a GLP-1 agonist included few episodes of hypoglycemia. Most studies comparing a DPP-4 inhibitor plus a sulfonylurea against metformin showed a higher risk of hypoglycemia in patients taking sulfonylureas. The DPP-4 inhibitors had a lower rate of serious adverse events than did pioglitazone. They did not increase the risks of nasopharyngitis, upper respiratory tract infection, or urinary tract infection.

The updated review and meta-analysis may help to clarify the clinical role of the DPP-4 inhibitors, a newer class of oral hypoglycemic drugs. These medications appear to be effective in lowering HbA1c in patients with type 2 diabetes who do not respond to metformin alone. Further study is needed to assess their cost effectiveness and long-term safety outcomes [Karagiannis T, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. *BMJ* 2012; 344:e1369]. ●

randomized, double-blind, placebo-controlled study [see *Clinical Studies* (14) of full prescribing information]. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent (42%) of patients on VOTRIENT required a dose interruption. Thirty-six percent (36%) of patients on VOTRIENT were dose reduced. Table 1 presents the most common adverse reactions occurring in ≥10% of patients who received VOTRIENT.

Table 1. Adverse Reactions Occurring in ≥10% of Patients who Received VOTRIENT

| Adverse Reactions  | VOTRIENT<br>(N = 290)   |         |         | Placebo<br>(N = 145)    |         |         |
|--------------------|-------------------------|---------|---------|-------------------------|---------|---------|
|                    | All Grades <sup>a</sup> | Grade 3 | Grade 4 | All Grades <sup>a</sup> | Grade 3 | Grade 4 |
|                    | %                       | %       | %       | %                       | %       | %       |
| Diarrhea           | 52                      | 3       | <1      | 9                       | <1      | 0       |
| Hypertension       | 40                      | 4       | 0       | 10                      | <1      | 0       |
| Hair color changes | 38                      | <1      | 0       | 3                       | 0       | 0       |
| Nausea             | 26                      | <1      | 0       | 9                       | 0       | 0       |
| Anorexia           | 22                      | 2       | 0       | 10                      | <1      | 0       |
| Vomiting           | 21                      | 2       | <1      | 8                       | 2       | 0       |
| Fatigue            | 19                      | 2       | 0       | 8                       | 1       | 1       |
| Asthenia           | 14                      | 3       | 0       | 8                       | 0       | 0       |
| Abdominal pain     | 11                      | 2       | 0       | 1                       | 0       | 0       |
| Headache           | 10                      | 0       | 0       | 5                       | 0       | 0       |

<sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other adverse reactions observed more commonly in patients treated with VOTRIENT than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus <1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%), and weight decreased (9% versus 3%).

Table 2 presents the most common laboratory abnormalities occurring in >10% of patients who received VOTRIENT and more commonly (≥5%) in patients who received VOTRIENT versus placebo.

Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients who Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus Placebo

| Parameters                | VOTRIENT<br>(N = 290)   |         |         | Placebo<br>(N = 145)    |         |         |
|---------------------------|-------------------------|---------|---------|-------------------------|---------|---------|
|                           | All Grades <sup>a</sup> | Grade 3 | Grade 4 | All Grades <sup>a</sup> | Grade 3 | Grade 4 |
|                           | %                       | %       | %       | %                       | %       | %       |
| <b>Hematologic</b>        |                         |         |         |                         |         |         |
| Leukopenia                | 37                      | 0       | 0       | 6                       | 0       | 0       |
| Neutropenia               | 34                      | 1       | <1      | 6                       | 0       | 0       |
| Thrombocytopenia          | 32                      | <1      | <1      | 5                       | 0       | <1      |
| Lymphocytopenia           | 31                      | 4       | <1      | 24                      | 1       | 0       |
| <b>Chemistry</b>          |                         |         |         |                         |         |         |
| ALT increased             | 53                      | 10      | 2       | 22                      | 1       | 0       |
| AST increased             | 53                      | 7       | <1      | 19                      | <1      | 0       |
| Glucose increased         | 41                      | <1      | 0       | 33                      | 1       | 0       |
| Total bilirubin increased | 36                      | 3       | <1      | 10                      | 1       | <1      |
| Phosphorus decreased      | 34                      | 4       | 0       | 11                      | 0       | 0       |
| Sodium decreased          | 31                      | 4       | 1       | 24                      | 4       | 0       |
| Magnesium decreased       | 26                      | <1      | 1       | 14                      | 0       | 0       |
| Glucose decreased         | 17                      | 0       | <1      | 3                       | 0       | 0       |

<sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

**Hepatic Toxicity:** In a controlled clinical study with VOTRIENT for the treatment of RCC, ALT >3 X ULN was reported in 18% and 3% of the VOTRIENT and

placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received VOTRIENT and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on VOTRIENT and 2/145 (1%) on placebo. [See *Dosage and Administration* (2.2) of full prescribing information and *Warnings and Precautions* (5.1).] **Hypertension:** In a controlled clinical study with VOTRIENT for the treatment of RCC, 115/290 patients (40%) receiving VOTRIENT compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving VOTRIENT compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with antihypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension. VOTRIENT has been associated with hypertensive crisis in patients with various cancer types including RCC. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT. [See *Warnings and Precautions* (5.6).] **QT Prolongation and Torsades de Pointes:** In a controlled clinical study with VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with VOTRIENT compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with VOTRIENT in the RCC studies. [See *Warnings and Precautions* (5.2).] **Arterial Thrombotic Events:** In a controlled clinical study with VOTRIENT, the incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)], cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher in patients treated with VOTRIENT compared to the placebo arm (0/145 for each event). [See *Warnings and Precautions* (5.4).] **Hemorrhagic Events:** In a controlled clinical study with VOTRIENT, 37/290 patients (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with VOTRIENT died from hemorrhage compared with no (0/145) (0%) patients on placebo. [See *Warnings and Precautions* (5.3).] In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with VOTRIENT. **Hypothyroidism:** In a controlled clinical study with VOTRIENT, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in VOTRIENT compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm. [See *Warnings and Precautions* (5.8).] **Diarrhea:** Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact. **Proteinuria:** In the controlled clinical study with VOTRIENT, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. [See *Warnings and Precautions* (5.9).] **Lipase Elevations:** In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%). **Cardiac Dysfunction:** Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

7 DRUG INTERACTIONS

**7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes:** In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib. **CYP3A4 Inhibitors:** Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations. A dose reduction for VOTRIENT should be considered when it must be coadministered with strong CYP3A4 inhibitors [see *Dosage and Administration* (2.2)]. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. **CYP3A4 Inducers:** CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers can not be avoided [see *Dosage and Administration* (2.2)]. **7.2 Effects of Pazopanib on CYP Substrates:** Results from drug-drug interaction studies conducted in cancer patients suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19 [see *Clinical Pharmacology* (12.3) of full prescribing information]. Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events. [See *Clinical Pharmacology* (12.3) of full prescribing information.] **7.3 Effect of Concomitant use of VOTRIENT and Simvastatin:** Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with VOTRIENT, ALT >3 X ULN was

# Industry Spotlight

## New Medicare Code For Anemia Medication

In March 2012, Affymax and Takeda Pharmaceuticals obtained U.S. Food and Drug Administration approval for Omontys (peginesatide) injection, a once-a-month treatment for anemia in patients with chronic kidney disease

(CKD) who are on dialysis.

By mid-April, the Centers for Medicare & Medicaid Services (CMS) singled out the medication for a temporary Q-code for federal reimbursement, according to Affymax. CMS deemed the product important for all

dialysis centers that are treating patients who receive Medicare-covered services. This new Q-code will go into effect on July 1, 2012.

The new Q-code provides dialysis centers with an immediate reimbursement code so they can submit



claims in a standardized manner and reduce the turnaround time for payment. “The designation of this Q-code by CMS will help simplify their billing process for reimbursement when using this new once-monthly anemia treatment for CKD patients on dialysis,” said John Orwin, chief executive officer of Affymax. “The ability of dialysis centers to receive timely reimbursement for Omontys is important.”

According to CMS, the Q-code is used by CMS contractors when the existing, permanent national codes do not have an exact code for a product or service covered by Medicare. By the end of the first quarter of 2012 there were more than 200 Q-codes in effect for all types of medical services.

The unique aspects of dialysis make its related treatments a fertile ground for Q-codes. Beginning January 1, 2010, Feraheme (ferumoxytol), a different anemia medication, received two Q-codes for its use in patients—one code for patients with CKD, and the other code for patients with end stage renal disease.

The entire Medicare coding system, including the Q-codes and other specialized codes, is called the Healthcare Common Procedure Coding System (HCPCS) code set. If you have questions about HCPCS coding or would like further information, visit [http://www.cms.gov/Medicare/Coding/MedHCPCSGen-Info/HCPCS\\_Coding\\_Questions.html](http://www.cms.gov/Medicare/Coding/MedHCPCSGen-Info/HCPCS_Coding_Questions.html).

reported in 126/895 (14%) of patients who did not use statins, compared with 11/41 (27%) of patients who had concomitant use of simvastatin. If a patient receiving concomitant simvastatin develops ALT elevations, follow dosing guidelines for VOTRIENT or consider alternatives to VOTRIENT [see *Warnings and Precautions* (5.1)]. Alternatively, consider discontinuing simvastatin [see *Warnings and Precautions* (5.1)]. Insufficient data are available to assess the risk of concomitant administration of alternative statins and VOTRIENT.

### 8 USE IN SPECIFIC POPULATIONS

**8.1 Pregnancy:** Pregnancy Category D [see *Warnings and Precautions* (5.10)]. VOTRIENT can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of VOTRIENT in pregnant women. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis at a dose level of  $\geq 3$  mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification. In addition, there was reduced fetal body weight, and pre- and post-implantation embryolethality in rats administered pazopanib at doses  $\geq 3$  mg/kg/day. In rabbits, maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion) was observed at doses  $\geq 30$  mg/kg/day (approximately 0.007 times the human clinical exposure). In addition, severe maternal body weight loss and 100% litter loss were observed at doses  $\geq 100$  mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at doses  $\geq 3$  mg/kg/day (AUC not calculated). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking VOTRIENT. **8.3 Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VOTRIENT, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **8.4 Pediatric Use:** The safety and effectiveness of VOTRIENT in pediatric patients have not been established. In repeat-dose toxicology studies in rats including 4-week, 13-week, and 26-week administration, toxicities in bone, teeth, and nail beds were observed at doses  $\geq 3$  mg/kg/day (approximately 0.07 times the human clinical exposure based on AUC). Doses of 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC) were not tolerated in 13- and 26-week studies with rats. Body weight loss and morbidity were observed at these doses. Hypertrophy of epiphyseal growth plates, nail abnormalities (including broken, overgrown, or absent nails) and tooth abnormalities in growing incisor teeth (including excessively long, brittle, broken and missing teeth, and dentine and enamel degeneration and thinning) were observed in rats at  $\geq 30$  mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC) at 26 weeks, with the onset of tooth and nail bed alterations noted clinically after 4 to 6 weeks. **8.5 Geriatric Use:** In clinical trials with VOTRIENT for the treatment of RCC, 196 subjects (33%) were aged  $\geq 65$  years, and 34 subjects (6%) were aged  $> 75$  years. No overall differences in safety or effectiveness of VOTRIENT were observed between these subjects and younger subjects. However, patients  $> 60$  years of age may be at greater risk for an ALT  $> 3$  X ULN. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **8.6 Hepatic Impairment:** In clinical studies for VOTRIENT, patients with total bilirubin  $\leq 1.5$  X ULN and AST and ALT  $\leq 2$  X ULN were included [see *Warnings and Precautions* (5.1)]. An analysis of data from a pharmacokinetic study of pazopanib in patients with varying degrees of hepatic dysfunction suggested that no dose adjustment is required in patients with mild hepatic impairment [either total bilirubin within normal limit (WNL) with ALT  $>$  ULN or bilirubin  $> 1$  X to  $1.5$  X ULN regardless of the ALT value]. The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin  $> 1.5$  X to  $3$  X ULN regardless of the ALT value) was 200 mg per day (N = 11). The median steady-state  $C_{max}$  and  $AUC_{(0-24)}$  achieved at this dose was approximately 40% and 29%, respectively of that seen in patients with normal hepatic function at the recommended daily dose of 800 mg. The maximum dose explored in patients with severe hepatic impairment (total bilirubin  $> 3$  X ULN regardless of the ALT value) was 200 mg per day (N = 14). This dose was not well tolerated. Median exposures achieved at this dose were approximately 18% and 15% of those seen in patients with normal liver function at the recommended daily dose of 800 mg. Therefore, VOTRIENT is not recommended in these patients [see *Clinical Pharmacology* (12.3) of full prescribing information]. **8.7 Renal Impairment:** Patients with renal cell cancer and mild/moderate renal impairment (creatinine clearance  $\geq 30$  mL/min) were included in clinical studies for VOTRIENT. There are no clinical or pharmacokinetic data in patients with severe renal impairment or in patients undergoing peritoneal dialysis or hemodialysis. However, renal impairment is unlikely to significantly affect the pharmacokinetics of pazopanib since  $< 4\%$  of a radiolabeled oral dose was recovered in the urine. In a population pharmacokinetic analysis using 408 subjects with various cancers, creatinine clearance (30-150 mL/min) did not influence clearance of pazopanib. Therefore, renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary.

### 10 OVERDOSAGE

Pazopanib doses up to 2,000 mg have been evaluated in clinical trials. Dose-limiting toxicity (Grade 3 fatigue) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2,000 mg daily and 1,000 mg daily, respectively. Treatment of overdose with VOTRIENT should consist of general supportive measures. There is no specific antidote for overdose of VOTRIENT. Hemodialysis is not expected to enhance the elimination of VOTRIENT because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

### 13 NONCLINICAL TOXICOLOGY

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies with pazopanib have not been conducted. However, in a 13-week study in mice, proliferative lesions in the liver including eosinophilic foci in 2 females and a single case of adenoma in another female was observed at doses of 1,000 mg/kg/day (approximately 2.5 times the human clinical exposure based on AUC). Pazopanib did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the in vitro cytogenetic assay using primary human lymphocytes and in the in vivo rat micronucleus assay. Pazopanib may impair fertility in humans. In female rats, reduced fertility including increased pre-implantation loss and early resorptions were noted at dosages  $\geq 30$  mg/kg/day (approximately 0.4 times the human clinical exposure based on AUC). Total litter resorption was seen at 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC). Post-implantation loss, embryolethality, and decreased fetal body weight were noted in females administered doses  $\geq 10$  mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC). Decreased corpora lutea and increased cysts were noted in mice given  $\geq 100$  mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given  $\geq 300$  mg/kg/day for 26 weeks (approximately 1.3 and 0.85 times the human clinical exposure based on AUC, respectively). Decreased corpora lutea was also noted in monkeys given 500 mg/kg/day for up to 34 weeks (approximately 0.4 times the human clinical exposure based on AUC). Pazopanib did not affect mating or fertility in male rats. However, there were reductions in sperm production rates and testicular sperm concentrations at doses  $\geq 3$  mg/kg/day, epididymal sperm concentrations at doses  $\geq 30$  mg/kg/day, and sperm motility at  $\geq 100$  mg/kg/day following 15 weeks of dosing. Following 15 and 26 weeks of dosing, there were decreased testicular and epididymal weights at doses of  $\geq 30$  mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC); atrophy and degeneration of the testes with aspermia, hypospermia and cribriform change in the epididymis was also observed at this dose in the 6-month toxicity studies in male rats.

### 17 PATIENT COUNSELING INFORMATION

See Medication Guide. The Medication Guide is contained in a separate leaflet that accompanies the product. However, inform patients of the following:

- Therapy with VOTRIENT may result in hepatobiliary laboratory abnormalities. Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of VOTRIENT and at least once every 4 weeks for the first 4 months of treatment or as clinically indicated. Inform patients that they should report any of the following signs and symptoms of liver problems to their healthcare provider right away.
  - yellowing of the skin or the whites of the eyes (jaundice),
  - unusual darkening of the urine,
  - unusual tiredness,
  - right upper stomach area pain.
- Gastrointestinal adverse reactions such as diarrhea, nausea, and vomiting have been reported with VOTRIENT. Patients should be advised how to manage diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs.
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- Patients should be advised to inform their healthcare providers of all concomitant medications, vitamins, or dietary and herbal supplements.
- Patients should be advised that depigmentation of the hair or skin may occur during treatment with VOTRIENT.
- Patients should be advised to take VOTRIENT without food (at least 1 hour before or 2 hours after a meal).

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Research Triangle Park, NC 27709

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## IMPORTANT DATES (2012)

### Abstracts

|                           |   |
|---------------------------|---|
| <b>Wednesday, April 4</b> | <b>Abstract Submission Site Opens</b>                           |
| <b>Wednesday, June 6</b>  | <b>Abstract Submission Site Closes (11:59 p.m. EDT)</b>         |
| Wednesday, July 18        | Late-Breaking Abstracts Submission Site Opens                   |
| Wednesday, September 12   | Late-Breaking Abstracts Submission Site Closes (11:59 p.m. EDT) |

### Registration & Housing

|                         |                                |
|-------------------------|--------------------------------|
| Wednesday, June 6       | Registration and Housing Opens |
| Wednesday, September 12 | Early Registration Closes      |
| Friday, September 28    | Housing Closes                 |
| Wednesday, October 24   | Advance Registration Closes    |
| Tuesday, October 30     | Onsite Registration Opens      |

### Kidney Week

Tuesday, October 30 – Wednesday, October 31 Early Programs  
Thursday, November 1 – Sunday, November 4 Annual Meeting



# Medical Education Research Can Improve the Future of Nephrology and Applies to All Types of Practice

By Laura Maursetter and Mary Thompson

*Have you considered sharing your experience in medical education research and helping others learn about effective changes you have implemented in your program? Consider submitting your abstract to the Medical Education Abstract category at the ASN Kidney Week 2012.*

An important task for all physicians is to educate. This may apply to those teaching the next generation of nephrologists, but it also goes far beyond that task. Medical education includes information provided to patients, colleagues, nursing staff, dieticians, and trainees about concepts concerning physiology or pathophysiology. For example, teaching a patient the reason to keep phosphorus levels controlled and noting the improvement in subsequent laboratory results is an effective educational intervention. In medical education research, the project must have a specific question with a measurable outcome to determine the success of the change.

Although it might seem that medical education research is meant for academic institutions, this type of research may be performed in all practice settings. The number of investigations linking medical education and quality of care or patient outcomes is minimal (1). Research is needed to determine whether the changes in medical education implemented are useful or wasted effort. An example is this could easily apply to fellowship training, where outcomes-based education has been implemented without strong evidence to back this change (2). Specifically, further investigation is necessary to determine whether the type of education given to the next generation will create nephrologists who provide higher-quality care with improved patient outcomes. The following examples will highlight some potential areas of practice where medical education research can be applied (Table 1).

### Quality improvement projects

Quality improvement is a recertification requirement for all nephrologists. This project could bring many members of a team together for collaboration on enhancing an educational aspect of practice (2). The Plan-Do-Study-Act method is a model for testing a change that is implemented (3). The four steps guide the thinking process and lead to an outcome that is measured for success.

### Teaching at work

Sharing knowledge is a significant part of patient care delivery as well as trainee education. However, teaching without measuring effectiveness does not answer whether the methods used to relay information are as good as they can be. Taking the time to frame a deficiency, pose an intervention, and test the results over time can optimize best teaching practices.

### Simulation

Medical simulation is a rapidly growing field, and credentialing organizations are requiring it as part of the training curriculum. Simulation can be used to perfect technical skills in performing procedures but also to assist in improving interactions with patients. Whichever skill is being practiced, simulation provides an opportunity for feedback to be given to participants. Repeating these sessions can provide a way to evaluate learning over time (4).

### Novel ideas for delivering care

Innovation can come in many forms. Examine teaching techniques or delivery of care methods that are new to the field. For example, increase the time you spend with patients by grouping those with similar medical problems together, such as monthly peritoneal dialysis visits. This gives patients a way to connect with others in a similar situation, and it also allows teaching concepts of care only once to the group instead of repeatedly in separate patient visits. Assess whether this improves patients' satisfaction with their care, their medical knowledge, or ultimately their outcomes.

### Steps to educational research

No matter the practice model, there are ways to implement educational research. Innovation and energy for a project are important, but without the tools to accomplish the task, no project will be successful. The process of educational research should parallel the familiar scientific methods (5).

#### Step 1: Formulate the question

The research question should be specific, with a measurable outcome. For example, you might notice that dialysis patients go through multiple cannulations before starting their treatment. A research question could be this: Does staff education about cannulation improve successful needle placement rates?

#### Step 2: Measure the baseline

The measure used to determine success should be assessed before the intervention. This will validate that the perceived deficiency is truly present, and it will set the baseline for comparison after intervention. Determining the measure can be difficult. Traditional teaching has suggested quantitative findings to be the optimal assessment: "The proof is in the numbers." Educational research may focus on qualitative findings as a better measure. Examples of measures can be found in Table 2.

#### Step 3: Plan the intervention

The intervention must be planned to address the specific topic. Keep the difficulty of material at the level of the audience. Use teaching methods that provide information in a variety of ways to target the largest audience. Some people learn by hearing (lectures), seeing (written word), or doing (simulation or workshops); therefore, it is wise to focus on interventions that address multiple means of knowledge delivery (6–8).

**Table 1. Educational research areas and implementation and analysis methods**

| Research Area                           | Implementation (Analysis Method)  |
|---|---|
| Quality Improvement Project             | <ul style="list-style-type: none"><li>• Requirement for recertification</li><li>• Audience: trainees, nurses, dieticians, dialysis technologists, colleagues</li><li>• Teach concepts to help with patient compliance (laboratory review)</li><li>• Create a class to assist with the transition to dialysis (patient satisfaction survey)</li></ul>  |
| Teaching at Work                        | <ul style="list-style-type: none"><li>• Study how you deliver your message for efficacy</li><li>• Audience: trainees, nurses, dieticians, dialysis technologists, colleagues</li><li>• Learning at lunch: short nursing lectures (medical knowledge test)</li><li>• Create a video for dialysis patients (pretest and posttest)</li><li>• Supply handouts to improve medical knowledge (multiple methods)</li></ul> |
| Simulation                              | <ul style="list-style-type: none"><li>• Requirement for credentialing organizations</li><li>• Audience: trainees, nurses, dieticians, dialysis technologists, colleagues</li><li>• Can be high-level or low-level technology</li><li>• Master procedure skills (direct observation)</li><li>• Practice patient interaction skills: delivering bad news, difficult patient (video observation)</li></ul>             |
| Novel Ideas for Delivering Patient Care | <ul style="list-style-type: none"><li>• Test creative concepts</li><li>• Audience: trainees, nurses, dieticians, dialysis technologists, colleagues</li><li>• Measure patient satisfaction after changing clinic structure (patient satisfaction survey)</li><li>• Assess exercise tolerance after starting a dialysis work out routine (interval analysis)</li></ul>   |

**Table 2. Educational research outcome measures**

| Qualitative Measures              | Quantitative Measures               |
|-----------------------------------|-------------------------------------|
| Presurvey and postsurvey: opinion | Presurvey and postsurvey: numerical |
| Patient satisfaction survey       | Medical knowledge test              |
| Video observation                 | Laboratory review                   |
| Interval analysis                 | Patient outcomes                    |
| Direct observation                | Provider performance                |
| Interview                         | Chart review                        |



#### Step 4: Implement the change

More is not always better. Focus on finding the most effective tool to deliver the information. It may take more than one session to have the learner retain the information. For example, it is advisable to give a lecture and then provide written language for review. Similarly, teaching patients and having them teach it back is another effective method to get repetition and check understanding.

#### Step 5: Measure the intervention

Not all changes improve the outcome; in fact, change might make it worse. Prove that the intervention is worth the extra effort, and make sure that the old way is not better. If the desired outcome is not met, reevaluate the intervention and try again.

#### Step 6: Share your findings

Most importantly, unless all concerned work together to share their successes and failures, progress in the field of nephrology education will be slow. Similar problems are seen in many practices, and if ideas for change can be shared with the community, improvement in the field will be enhanced (5). There has been a decline in the number of learners choosing nephrology as a career, which may be attributed to the style of presenting subject matter or to a lack of dedicated mentorship (9). Optimizing the delivery of curriculum material to enhance understanding might be one way we can lead more trainees to a career in the field.

An excellent avenue to share projects is through the ASN Kidney Week Educational Abstracts Category. This category was developed in 2008 and is a place for sharing changes in educational programs that can make a difference in patients' lives. These projects can be initiated and submitted by any part of the care team. Take time to consider adding a submission to the category this year. More information can be found at the ASN website. ●

*Laura Maursetter, DO, is a member of the ASN Workforce Committee and assistant professor in the Division of Nephrology at the University of Wisconsin-Madison, where she serves as the associate program director. She is a member of the ASN Workforce Committee that is focused on increasing interest in nephrology as a career for trainees.*

*Mary K. Thompson is a PhD educator in the department of medicine at the University of Wisconsin-Madison. She works with fellowships across the department supporting education and curricular needs.*


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## Policy Update

# Hill Day 2012: ASN Leaders Put Kidney Disease in Legislative Spotlight

By Grant Olan and Rachel Shaffer

The ASN Council, Public Policy Board, and Board of Advisors met with legislators on Capitol Hill as part of the biannual Board of Advisors meeting on April 26, 2012. The second annual ASN Hill Day provided ASN leaders an opportunity to talk directly with lawmakers and House and Senate staff about issues of importance to ASN and the kidney care community. ASN leaders met with more than 50 congressional offices, including more than a half-dozen meetings with senators and representatives themselves, and were divided into four teams to discuss one of the following issues:

- National Institutes of Health (NIH) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funding and investigation of kidney health disparities, including a bill (S.2163) recently introduced by Sen. Kent Conrad (D-ND) that promotes research regarding disparities and access to care.
- Support for legislation to extend lifetime coverage of immunosuppressive drugs for kidney transplant recipients (S.1454/H.R.2969).
- ASN's efforts to increase interaction between the nephrology community and the U.S. Food and Drug Administration (FDA).
- A complex set of issues and upcoming changes related to the Medicare end stage renal disease (ESRD) program and the practice of nephrology.

ASN leaders met not only with senators and representatives from their home states and districts, but also with key members of congressional committees with jurisdiction over the issues ASN discussed, either from an "authorizing" perspective (meaning that the committee can tell a certain program or agency what it is allowed to, or must, do) or from an "appropriations" perspective (meaning that the committee is in charge of determining how much funding an agency or a program receives).

This *Policy Update* gives an in-depth description of the issues for ASN Hill Day 2012, and includes an article from members of the ASN Transplant Advisory Group that illustrates why advocating for legislation to extend lifetime coverage of immunosuppressive drugs was—and continues to be—a top ASN policy priority.

As noted above, ASN's collaboration with the FDA is one of the society's top policy priorities in 2012. Several ASN leaders discussed this priority with members of Congress who oversee the FDA. Although ASN is still in the early stages of outlining this collaborative initiative with the FDA to protect kidney health, the society received positive feedback about its goals from members in both the House and Senate. Stay tuned to *Kidney News* for

more details about this vitally important initiative in the coming months.

### ASN Addresses NIH Research, Health Disparities, and S.2163

During office meetings with House and Senate appropriators and other lawmakers, ASN leaders discussed the importance of supporting the NIH, which in turn supports innovative kidney disease research that will improve patient care, cut costs, and preserve the investigator pipeline. The bottom line—funding NIH is a smart investment because NIH research generates jobs, stimulates the economy, and enables life-saving medical advancements.

ASN leaders spoke about the public health importance and economic benefits of kidney disease research. ASN supports the work of Congress to reduce the federal debt in a socially and fiscally responsible manner, which is why we urge continued investments in medical research. Publicly funded research supports one of every 500 full-time jobs in the United States, and every dollar invested in medical research generates \$2.60 of economic activity. Furthermore, according to a 2010 study, research funding also generated 487,900 new jobs nationally and produced more than \$68 billion in new economic activity in the United States.

Most developed countries are dramatically increasing their budgets for medical research. China in particular is ramping up investments in this arena. Currently, the United States is the world leader and can attract the best and brightest investigators from across the globe, but in order to maintain this position it is critical to protect medical research funding. Without this investment, the ability to sustain a pipeline of researchers from this country and abroad—and their future contributions to improving patient care and treatment and possible cures—will be lost.

Consequently, ASN leaders asked the House and Senate offices they met with for their support of \$32 billion for the NIH and specifically \$2.03 billion for the NIDDK in the fiscal year 2013 budget—the minimum investment necessary to avoid further loss of promising research and allow NIH's and NIDDK's budgets to keep pace with the rising cost of conducting biomedical research.

ASN leaders also explained the importance of health disparities research and requested support for the *Kidney Disease Equitable Access, Prevention, and Research Act of 2012* (S.2163). Research has helped physicians understand some of the reasons why many minority populations are at higher risk for kidney disease, but without support for additional research we cannot move forward to address and resolve disparities in kidney care.

Sen. Kent Conrad (D-ND) introduced S.2163 to help resolve inequities in kidney disease health

policy by addressing barriers to transportation, patient education, and access to insurance. For example, S.2163 would provide key education for Medicare beneficiaries with stage V chronic kidney disease (CKD) through medical and clinical staff at dialysis facilities. Senate bill 2163 would also allow individuals with kidney failure to maintain their private insurance by extending the Medicare Secondary Payer period from 30 to 42 months after they qualify for Medicare, which would achieve important savings for the Medicare program.

Leading up to Hill Day, ASN laid the groundwork on the medical research advocacy front, including collaborating with the American Society of Pediatric Nephrology (ASPN) to send a letter supporting kidney disease research to both the House and Senate appropriations committees that was signed by numerous other members of the kidney community, representing patients, providers, and industry. ASN has received positive feedback regarding the letter, including a request from the office of Rep. Jeff Flake (R-AZ), who sits on the House Ways and Means Appropriations health subcommittee (which has significant influence over the NIH budget) to discuss kidney disease research and the NIDDK budget in particular. While this is a difficult time for Congress to make spending-related decisions, the importance of kidney disease research is squarely on the radar screens of those members with influence.

ASN and ASPN are deeply grateful for the support of the Congressional Kidney Caucus, which submitted language for inclusion in the report the House Appropriations Committee submits to the full House of Representatives highlighting the importance of kidney disease research across the NIH and directed at patients of all ages. This report is vitally important, as it explains to Congress the reasons for including the spending proposals in appropriations bills. In addition, ASN and ASPN worked with the caucus to include a specific funding recommendation of \$2.03 billion for the NIDDK budget—the first time a specific budget level has been supported by the kidney community.

ASN has taken a number of other steps such as:

- Joining more than 165 organizations in sending a letter urging Congress to support \$32 billion in funding for NIH.
- Involving the ASN membership in a petition-signing campaign urging the White House to support more funding for NIH.
- Joining more than 900 organizations in sending a letter urging Congress to avert cuts to the overall Health and Human Services budget.
- Launching an ASN membership email campaign to urge their members of Congress to



support more research funding for NIH. Contact your member at <http://capwiz.com/asn/home/>.

ASN is grateful to the society's leaders for helping make Hill Day 2012 a success, and the society will continue to engage lawmakers and their offices in the months to come as the budget process plays out and other pieces of legislation important to the kidney community move forward.

### Helping Congress Understand the Evolving Practice Environment in Nephrology

Congress made a commitment to save the lives of people with kidney failure by establishing the Medicare ESRD program in 1972, a program that covers all citizens experiencing kidney failure, regardless of age. This essential government program and the kidney professionals who implement it are at the forefront of the innovations, system transformations, and pioneering changes that will affect other areas of health care.

A key goal of ASN Hill Day was informing those lawmakers with oversight of the Medicare ESRD program, or those with a history of commitment to kidney disease and the Medicare ESRD program, of the implications these profound reforms could have for patients and physicians. In order for ASN to achieve success in this area, it is crucial to gain the support of lawmakers who understand the complexity of these changes, who will support kidney professionals' effort to enact change that focuses on improving care for a vulnerable population, and who will allow time to assess efforts to reduce costs and measure the quality of care.

ASN representatives discussed four key components of the "evolving practice environment in nephrology."

First is the ongoing process of implementing the Medicare Improvements for Patients and Providers Act (MIPPA), including bundled payments for dialysis care. At the heart of ASN's message was the principle that Congress should avoid future Medicare payment changes until recently enacted MIPPA changes are fully implemented. Meaningful cost reductions will succeed only if patient care remains uncompromised. Evaluating the success of the program's experience with bundled payment systems and pay-for-performance quality programs will serve as a model for needed changes to other areas of health care.

Second, it is important for Congress to understand the complexity of addressing the measures and programs related to improving the quality of health care. Because nephrology professionals provide care to a highly vulnerable patient population, achieving this goal requires consistent, evidence-based evaluations of the quality of care provided. Promoting the use of the same measures across programs is crucial to facilitate consistent care, reduce unnecessary reporting burdens, and prevent costly data duplication. ASN is dedicated to helping develop and ensure the consistency of quality metrics that fulfill these essential standards.

Third, ASN discussed the society's principles

related to the potential development of integrated care delivery models. Foremost among these principles (available in full at <http://asn-online.org>) is preservation of the patient-physician relationship. ASN's advocates addressed the very real potential that such pilot or demonstration programs could pave the way to dramatic improvements in kidney care, but cautioned that establishing successful ones requires careful consideration of the potential effects on a vulnerable patient population.

The fourth component of ASN's message was the vital need to repeal the flawed sustainable growth rate and replace it with a sensible alternative. Addressing this fundamentally defective formula is key to ensuring that patients maintain access to care, and that physicians can count on the Medicare program to provide payments that accurately reflect the cost of care.

### Making the Case for Lifetime Immunosuppressive Drug Coverage

*Advocating for legislation to extend lifetime coverage of immunosuppressive drugs (S.1454/H.R.2969) is a cornerstone of ASN's public policy and Hill Day 2012 messages. ASN leaders met with more than a dozen offices, specifically focusing on members of Congress who supported this bill when it was introduced in the 111th Congress, but who have not signed onto the bill in the 112th Congress (the current session). Here, members of the ASN Transplant Advisory Group Alan Leichtman, MD, David Cohen, MD, and Chair Michelle Josephson, MD, outline the history of this legislation and why it's the right thing for Congress to do from every perspective, illustrating the many reasons that this issue is at the top of ASN's public policy priorities.*

Transplantation, for nearly all suitable transplant candidates, is the preferable and most cost-effective treatment for ESRD, and typically provides superior longevity, health, and quality of life when compared with dialysis. Median 5-year survival is nearly double for patients following renal transplantation compared with patients who remain on dialysis. For those patients with Medicare coverage from ESRD, Medicare will cover the costs of dialysis indefinitely but only the initial costs of a kidney transplant (1). For most transplant patients Medicare coverage ends after 36 months, leaving many patients unable to pay for the immunosuppressive medications required indefinitely to prevent rejection. Consequently, financial hardship forces many to become non-adherent with their medical regimens—reducing their doses or discontinuing their immunosuppressive medications entirely. Financial hardship-related non-adherence in turn leads to rejection, transplant dysfunction with the associated costs of CKD, and the premature return to dialysis. Once patients return to dialysis they are again covered by Medicare, at minimal estimated costs exceeding \$82,000 annually compared with approximately \$11,000 to maintain a kidney transplant. It clearly makes neither clinical nor financial sense to pay indefinitely for the less efficacious and more expensive treatment, while denying long-term coverage for the more effective

and less costly alternative.

In addition there is a shortage of kidneys, and the deficit in the number of kidneys available for transplantation is exacerbated by the 15 percent of waitlisted patients seeking repeat transplantation. With lifetime immunosuppressive drug coverage, there is little doubt that many transplants would last longer, resulting in fewer patients returning to the waiting list for repeat transplantation, and thus more kidneys would be available for other transplant candidates.

How widespread is this problem? While precise numbers are hard to come by, a survey conducted by the United Network for Organ Sharing and the American Society of Transplantation indicated that 70 percent of kidney transplant programs reported that many of their patients had an extremely serious or very serious problem paying for their medications, and 68 percent reported deaths or graft losses attributable to cost-related immunosuppressive medication non-adherence (2). While extending Medicare coverage for immunosuppressive medications will not entirely solve this problem, it would help a substantial number of these patients.

Federal expenditures for kidney disease currently cost taxpayers more than \$30 billion a year, about 6 percent of the Medicare budget. Expanded immunosuppressive medication coverage offers a more cost-effective way for the federal government to manage these expenses. For nearly 10 years the transplant community has lobbied Congress to extend coverage of immunosuppressive medications for kidney transplant recipients for the lifetime of the organ. A bill has been introduced in both the House and Senate to provide for this, and it has broad bipartisan support. The current lead sponsors are the physician Rep. Michael Burgess (R-TX), Rep. Ron Kind (D-WI), Sen. Dick Durbin (D-IL), and Sen. Thad Cochran (R-MS). The current House Ways and Means Committee Chairman Dave Camp (R-MI) was the lead sponsor for many years. ASN will continue to work with a coalition of transplant organizations to keep the patient immunosuppressive medication coverage extension bill at the top of many legislative priority lists. This current policy of paying for a kidney patient's transplant but not providing the drugs necessary to keep the transplant and the patient alive defies common sense, is life threatening for patients, and costs the federal government untold millions in avoidable expenditures. When will common sense prevail?

Please visit the ASN's Legislative Action Center (<http://capwiz.com/asn/home>) and send your members of Congress a message telling them how important this bill is for all patients with kidney disease. ●

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# Leader of ASN Grants Review Committee Named Editor-in Chief of *Kidney International*; New Chair Named

After leading the American Society of Nephrology (ASN) Grants Program for 3 years, Detlef Schlondorff, MD, has been named editor-in-chief of *Kidney International*. Under his guidance, the ASN Grants Review Committee added two new opportunities for career development grants: the ASN–Association of Specialty Professors (ASP)–National Institute of Aging (NIA) Junior Development Grant in Geriatric Nephrology, and the NephCure Foundation–ASN Research Grant. Schlondorff was also instrumental in expanding the ASN Student Scholar Grant Program and launching the new ASN Research Fellowship Program, which will fund its first 10 fellows later this year.

The ASN Grants Program distributes more than \$3 million each year in research funding to medical students, fellows, new investigators, and established investigators. Last year ASN awarded a total of 31 research grants.

“Dr. Schlondorff has been instrumental in maintaining the high caliber of quality of the ASN Grants Program, and expanding the program to reach more researchers,” said ASN Past-President Joseph

Bonventre, MD, PhD, FASN. “I am particularly impressed by his ability to manage an increasingly complex grants portfolio with increasing numbers of applications, and his leadership in strengthening ASN’s partnerships with the Halpin Foundation, the NephCure Foundation, ASP, and NIA.”

In addition to his success overseeing the ASN Grants Program, Schlondorff has a long list of academic and professional achievements. He currently serves as visiting professor of medicine at Mount Sinai School of Medicine, where he leads an active research laboratory. Schlondorff has authored more than 300 peer-reviewed original and review articles and book chapters, and has edited two textbooks. He is a member of numerous professional societies and has received the Franz Volhard Medal from the German Nephrology Society and the International Prize Luis Hernando from the Spanish Renal Foundation.

Schlondorff received his medical degree at Ludwig Maximilians University in Munich, and continued his training in Germany and at the Albert Einstein

College of Medicine and Montefiore Hospital in New York. He was professor of medicine and chief of the nephrology division at the Albert Einstein College of Medicine from 1988 to 1993, when he became chair and professor of medicine and director of the University Medical Policlinic Hospital Innenstadt of the Ludwig Maximilians University and eventually professor emeritus in 2007.

ASN is pleased to announce that Roy Zent, MD, PhD, will succeed Schlondorff as chair of the ASN Grants Review Committee. Zent is professor of medicine at Vanderbilt University School of Medicine and has served on the Grants Review Committee since 2008. “I am confident that Dr. Zent will provide excellent leadership as ASN continues to expand and innovate its grants program,” said ASN President Ronald Falk, MD, FASN. “In particular, I’m excited that Dr. Zent agreed to help launch the ASN Research Fellowship Program this year.” ●

### ASN Research Grants

- **Career Development Grants for New Investigators**
  - Carl W. Gottschalk Research Scholar Grant (established in 1996)
  - John Merrill Grant in Transplantation (established in 2001)
  - The Halpin Foundation–ASN Research Grant (established in 2006)
  - Normal Siegel Research Scholar Grant (established in 2007)
  - The NephCure Foundation–ASN Research Grant (established in 2012)
  - ASN-ASP-NIA Junior Development Grant in Geriatric Nephrology (established in 2011)
- **M. James Scherbenske Grants for Established Investigators** (established in 1996)
- **Student Scholar Grants** (established in 2000)
- **Research Fellowships** (established in 2012)

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