

# Kidney News

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## Kids and Transplants: Reduced Racial Disparities but Fewer Live Donor Transplants

By Tracy Hampton

Children in need of a kidney transplant have had priority over older candidates for organs from young deceased donors since a policy called Share 35 was implemented in 2005. A new study in the

*Journal of the American Society of Nephrology* looks at the effects of this policy on pediatric kidney transplantation, particularly as they relate to race.

“We sought to examine whether the Share 35 allocation policy improved deceased donor transplant access for children across races equally, because in the past, black and Hispanic children with end stage renal disease have had reduced access to transplantation,” said lead author Sandra Amaral, MD, of the Children’s Hospital of Philadelphia. “We also wanted to understand overall access to transplantation, meaning access to both living and deceased donors, because there have been previous concerns that children are not receiving as many kidneys from living donors since the implementation of the Share 35 policy.”

### Race and transplantation

Although everyone with ESRD deserves a well-functioning transplanted kidney, Share 35 prioritizes the allocation of organs from deceased donors younger than 35 years old, who are more likely to have been healthier at the time of their deaths than older donors, to pediatric candidates, who have the greatest long-term potential for a healthy future. Currently, more than 800 children and adolescents in the United States are waiting for a kidney transplant.

To see how Share 35 has affected kidney transplantation among children, Amaral and her colleagues analyzed data from the United States Renal Data System before and after Share 35 was implemented. These data applied to 2299 pediatric patients with kidney failure who received a transplant before Share 35 and 2467 patients who received one afterward.

The investigators found that, on average, pediatric patients were 46 percent

*Continued on page 2*



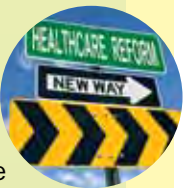
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## Comparative Effectiveness Research: Just How Effective Is It?

By Kurtis Pivert

With health care expenditures constituting more than 17 percent of the U.S. gross domestic product, lawmakers and physicians continue to search for ways to control costs while providing effective,

evidence-based care. Comparative effectiveness research (CER) is touted as a way to investigate and identify measures that can answer important clinical questions and improve the quality of care for patients.

The *Journal of the American Medical Association (JAMA)* recently devoted an entire special issue to the topic. Recent news coverage has been peppered with discussion of the value of randomized clinical trials, observational studies, and efforts such as the Choosing Wisely campaign, spearheaded by the American Board of Internal Medicine Foundation, to help physicians and patients make better choices about medical tests and procedures.

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## Kids and Transplants

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more likely to receive a deceased donor kidney transplant after being waitlisted in the post-Share 35 era than in the pre-Share 35 era.

“This study proves that the vision to change the allocation policy set up by the United Network for Organ Sharing is working, and more young patients are getting kidney transplants earlier,” said Mark Mitsnefes, MD, who was not involved with the study and is a pediatric nephrologist at

Cincinnati Children’s Hospital Medical Center. “This is an important achievement, since previous studies showed that shorter time on maintenance dialysis or preemptive kidney transplants results in a better long-term patient survival.”

The study also found that Share 35 has attenuated racial disparities in terms of how likely and how soon children will receive a deceased donor kidney transplant. Hispanics were 81 percent more likely to receive a deceased donor kidney transplant, blacks were 45 percent more likely, and whites were 37 percent more likely. Also, patients received a deceased donor kidney transplant earlier after Share 35: specifically, 201 days earlier for Hispanics, 90

days earlier for blacks, and 63 days earlier for whites. The authors noted that shorter time to kidney transplantation may be particularly beneficial to blacks and Hispanics because they are more likely to be older, be obese, have more anemia, and have less exposure to erythropoiesis-stimulating agents at incident ESRD (suggesting potential later referral) than are whites.

According to the researchers, there were fewer differences in the degree of HLA mismatch between races since Share 35 was implemented, but this seems to be primarily driven by whites receiving poorer HLA matches. It is unclear whether the benefits of shorter wait times and younger donors outweigh the risks of higher immunologic

discordance between pediatric recipients and their donors.

### Effects on living donation

Despite the benefits that have come from Share 35, the policy also seems to be having a negative effect on living donations for kidney transplants, as other studies have indicated. Investigators wonder whether the policy may be influencing parents and candidates to wait for a deceased donor organ rather than ask family members or friends to go through the living donation process. Also, perhaps parents and candidates may hope to save a living donor kidney for a future repeated kidney transplant that may be needed.

In this study, Amaral and her team found that all races experienced a shift from living donor to deceased donor sources after Share 35, with a 48 percent reduction in living donors for Hispanics, a 46 percent reduction for blacks, and a 25 percent reduction for whites. Because the researchers had no information on whether decision making by family members or providers about the use of living donors has changed with the enactment of the Share 35 policy, additional studies are needed to understand why this shift in donor source has occurred and why it varies by race.

“Reduced racial disparities in access to deceased donor kidney transplant for children with end stage kidney disease is a very positive step toward achieving equity in overall transplant access for all children, Amaral said. “However, greater declines in living donors for all pediatric patients, particularly for those of black or Hispanic ethnicity, may be a concern.

“Less access to living donors for children with end stage kidney disease may mean that these patients have less access to the best quality kidneys and less potential for the best graft survival,” Amaral explained. Data from the Scientific Registry of Transplant Recipients show that 59.3 percent of living-donor kidneys and 43.3 percent of deceased donor kidneys survive for at least 10 years. Greater efforts may be needed to encourage more living donations for recipients of every race, ethnicity, and socioeconomic status and to overcome some of the medical and logistic barriers that are associated with it.

Future studies should weigh the potential downsides of Share 35 against its positive attributes, Mitsnefes said. “Longer follow-up is needed to determine if the benefits of Share 35 are more significant than the loss of benefits from living donor transplantation,” he said. Additional studies are also needed to enable an understanding of how changes brought about by Share 35 ultimately affect racial differences in the long-term health of transplanted kidneys. ●

*Study coauthors include Rachel Patzer, PhD, Nancy Kutner, PhD, and William McClellan, MD (Emory University).*

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

The article, entitled “Racial Disparities in Access to Pediatric Kidney Transplantation Since Share 35,” is online at <http://jasn.asnjournals.org/>, doi: 10.1681/ASN.2011121145.

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# Comparative Effectiveness Research

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And as part of the next phase of federally backed CER efforts, last month the Patient-Centered Outcomes Research Institute (PCORI) announced they will spend \$120 million to fund comparative clinical effectiveness research.

Given the attention that CER has generated, what's behind the rapid growth in this field and how can clinicians evaluate and use the results from these studies to inform their current practice and provide the best care to their patients?

## Comparative effectiveness research

Only recently known as CER, this established methodology has long been used to evaluate the safety and effectiveness of prescription medications. Its goal is to provide evidence on the harms, benefits, and effectiveness of different treatments to help patients and physicians "...make informed decisions that will improve health care at both the individual and population levels," according to the Institute of Medicine.

Although CER can be performed prospectively, the majority of these studies are retrospective in nature. Unlike randomized controlled trials (RCTs), retrospective observational studies draw upon information in databases or registries and apply statistical tools to weigh the merits of different treatments. Observational investigations—and CER as a whole—also focus on pertinent clinical issues that lack evidence in the literature or cannot be answered with an RCT.

Because they utilize preexisting data, observational studies use standard and novel statistical methods, such as propensity scores, to reduce confounding variables and identify correlations between treatments and outcomes. The biggest threat to retrospective CER is confounding by indication "in which certain patients may preferentially receive one treatment or another based on their characteristics," said Wolfgang Winkelmayr, MD, a long-time proponent of CER. With advanced statistical analysis, employing diverse methodologies each with their own advantages and disadvantages, the confounding can be controlled and researchers can identify relevant results. "Ideally, you would like to apply a number of different analytical techniques, and if the analyses yield similar results, then we have greater faith in those findings," said Winkelmayr.

## Increasing interest in CER

Rising health care spending has prompted the federal government to examine options to rein in costs, such as value-based purchasing and quality improvement pro-

grams. Between 2009 and 2010 the U.S. government added more than \$1 billion of funding specifically for CER through the American Recovery and Reinvestment Act and the Affordable Care Act (ACA).

"The motivation for federal funding for CER is the cost and quality lapses brought on by immense variability in medical practice patterns across the country," said Carolyn Engelhard, director of health policy at the University of Virginia's department of public health sciences. She noted research from the Dartmouth Atlas Group has demonstrated "that Medicare spending varies by as much as 30 percent in different parts of the country even after the Medicare data has been controlled for severity of illness and other demographic factors." Another impetus was the frustration some felt with the well-funded "clinical research that didn't pertain to a lot of the clinical questions or the types of patients physicians encountered," Winkelmayr said.

Outside the United States, regulatory agencies use CER to assess new therapeutics and best practices for physicians. In the United Kingdom, the National Institute for Health and Clinical Excellence uses CER along with economic models to evaluate new drugs and devices. Performance of the new treatment in comparison with established therapies determines coverage by the National Health Service. Other countries apply CER to make similar recommendations on diagnostic tests, and to control medication costs to ensure equal access.

The first wave of U.S. government-funded CER studies was overseen by the Agency for Healthcare Research and Quality (AHRQ) and covered such areas as hypertension, spinal disease, and stroke. The next phase of research will be administered through the newly formed PCORI.

## Putting the patient first

Patient-centered outcomes research reorients CER by focusing on patient priorities and integrating their perspective at each step in the process. The main distinction between the two approaches is "...the extent to which the preferences, decision-making needs, and characteristics of patients are addressed," notes PCORI (1).

"PCORI was established under the ACA to give CER a home and to invite various experts and stakeholders in the health industry to participate in the effort," said Engelhard. With the funding initiatives for PCORI and CER, the government expects "a movement toward consensus, based on scientific evidence, regarding the most effective treatments for various medical conditions." With that consensus, protocols can be established by professional medical societies to begin standardizing care nationwide, and "once medical care is more standardized it can be measured and managed, which will bring quality improvement," she said. "Whether it will save money remains to

be seen, but certainly it will bring greater value as appropriate care replaces less efficacious care patterns."

Using multiple criteria to ensure patient involvement in the process, PCORI recently issued its five national priorities for research: 1) assessing options for prevention, diagnosis, and treatment; 2) improving health care systems; 3) researching the best ways to disseminate and communicate findings and recommendations; 4) addressing disparities (which ASN recommended as "a core research priority"); and 5) accelerating patient-centered outcomes research and methodology.

## Kidney disease and CER

Because of the multiple facets of kidney disease, there are large gaps in evidence needed to guide many aspects of renal care. A study in the recent *JAMA* special issue examined one such area in kidney cancer that was missing data to inform treatment. Hung-Jui Tan, MD, and colleagues performed an observational study to compare outcomes after partial or radical nephrectomy for patients 65 years or older with early-stage kidney cancer (2). "In light of new trial data generating new uncertainty regarding the benefits of partial nephrectomy, we became interested in the comparative effectiveness of these treatment options. We elected to use SEER-Medicare data, and chose an instrumental variable approach because it offered the potential to balance both the measured and unmeasured confounders," said Tan. Their analysis demonstrated that for these patients with kidney cancer, partial nephrectomy was associated with improved survival.

New fields of investigation with CER in nephrology include the comparative effectiveness and safety of certain drug regimens to treat kidney disease, said Winkelmayr. With the inclusion of Medicare Part D data in the United States Renal Data System, researchers now have the opportunity to study medication-based therapeutic strategies for patients with end stage renal disease.

## Potential for improving care

Because of the primacy of RCTs, some clinicians may be dissuaded from considering and implementing findings from observational studies.

"Randomized trials often impact medical practice immediately and relatively strongly, and although CER studies may not carry the same weight, they can still be very influential," said Winkelmayr. Tan also noted that "a well-designed RCT is going to continue to be the gold standard, but they may not provide clear insight into the clinical scenario and they face their own limitations, especially for surgical interventions." Small patient populations, a long follow-up, or ethical considerations could also make them impractical and/or impossible to perform.

Yet, as a recent *JAMA* editorial (3) noted, there are important considerations

when conducting CER and interpreting the results. Physicians must weigh the statistical methods, effect sizes, and the origins of the data before applying the findings to their practice. A draft protocol for conducting observational CER was released last month by AHRQ and should be finalized this year.

Another concern with CER is using study results to individualize patient care. In their *JAMA* article (4), David M. Kent, MD, and Nilay D. Shah, PhD, stated that "inferring individual effects from average group effects is an example of the fallacy of division." However, Mullins et al. (5) noted that involving different groups of patients in the research process could yield "...CER results that go beyond 'average treatment effects' and produce results that are applicable to specific patient subgroups."

Perhaps the greatest challenge for CER is the effective communication and implementation of the recommendations, as several *JAMA* articles noted. No matter how studies are conducted, if physicians are unaware of new guidelines their clinical practice may remain unaltered. Research to find innovative approaches for disseminating findings and encouraging their incorporation will be funded by both AHRQ and PCORI.

Despite these concerns, CER and PCORI's approach of engaging populations to identify research goals that are meaningful to patients could help fill gaps in clinical knowledge and improve the health of individuals and communities. Regardless of the study design, Tan concludes "it's going to take a combination of methods to answer the questions needed to deliver the best care for patients." ●

*ASN will offer a two-day course entitled "Update on Patient-Centered Outcomes Research in Kidney Disease" October 30–31 as part of Kidney Week 2012.*

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# Kidney News

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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.
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest OMONTYS dose sufficient to reduce the need for red blood cell (RBC) transfusions.

### Contraindications

OMONTYS is contraindicated in patients with uncontrolled hypertension.

### Warnings and Precautions

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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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**Dialysis management:** 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%.

### Adverse reactions

The most common adverse reactions in clinical studies in patients with CKD on dialysis treated with OMONTYS were dyspnea, diarrhea, nausea, cough, and arteriovenous fistula site complication.

Please see accompanying Brief Summary.

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# Journal View

## Partial Nephrectomy Improves Survival in Early Kidney Cancer

For patients with small, early-stage kidney cancers, overall survival is better with partial nephrectomy than with radical nephrectomy, reports a study in the *Journal of the American Medical Association*.

The study included 7138 Medicare fee-for-service patients who had surgery for clinical stage T1a kidney cancer between 1992 and 2007: radical nephrectomy in 73 percent of patients and partial nephrectomy in 27 percent. Patients undergoing partial nephrectomy were younger: about one-third were less than 70 years old, compared with one-fourth in the radical nephrectomy group. They were also more likely to be men, about 58 percent versus 54 percent, and to have a higher income and more years of education. The median follow-up time was 62 months.

Overall mortality was significantly lower in the partial nephrectomy group: 25.3 percent versus 41.5 percent for those who underwent radical nephrectomy, adjusted hazard ratio 0.54. There was no significant difference in kidney cancer-specific mortality: 1.9 percent versus 4.3 percent, respectively.

The percentage-point difference in survival with partial nephrectomy increased over time: from 5.6 at 2 years to 15.5 at 8 years. The data suggested that for every seven patients undergoing partial rather than radical nephrectomy, one additional life would be saved.

Previous reports have suggested that partial nephrectomy achieves similar oncologic control of early-stage kidney cancer, with better preservation of renal function, compared with radical nephrectomy. This large retrospective study found substantially better overall survival after partial nephrectomy in older adults with early kidney cancers. “[O]ur findings support partial nephrectomy as the preferred treatment option for the ever-expanding pool of patients with kidney tumors measuring 4 cm or smaller,” the researchers write. [Tan H], et al. Long-term survival following partial vs radical nephrectomy among older patients with early-stage kidney cancer. *JAMA* 2012; 307:1629–1635.] ●

## No Increased Cancer Risk with ARBs vs ACEIs

Angiotensin-receptor blockers (ARBs) are not associated with an increased overall cancer risk, according to a study in the *British Medical Journal*.

The researchers analyzed British general practice data on nearly 378,000 patients with at least 1 year of initial treatment with ARBs or angiotensin-converting enzyme inhibitors (ACEIs). Overall and specific cancer risks were compared for the two types of antihypertensive drugs, considering the effects of cumulative treatment time. About 20,000 cancers were diagnosed during a median follow-up time of 4.6 years.

The overall cancer risk was not significantly different for patients taking ARBs versus ACEIs, after adjustment for a wide range of demographic and clinical factors. The rates of breast and prostate cancer were higher in ARB users: adjusted hazard ratios 1.11 and 1.10, respectively. However, the absolute excess risks were small: no more than 0.5 per 1000 person-years for breast cancer and 1.1 per 1000 person-years for prostate cancer.

Treatment with ARBs had a possible

protective effect against lung cancer: hazard ratio 0.84. The risk of colon cancer was not affected.

One recent trial reported increased cancer mortality among patients taking candesartan. Such an association is plausible because of the role of angiotensin II receptors in angiogenesis, cell proliferation, and tumor progression.

However, this large database study found no increase in the overall risk of cancer among patients starting treatment with

ARBs compared with ACEIs. The risk of lung cancer may even be reduced in ARB users. Small increases in the risk of breast and prostate cancer were unrelated to the duration of ARB treatment, raising the possibility of a noncausal explanation. [Bhaskaran K, et al. Angiotensin receptor blockers and risk of cancer: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database. *BMJ* 2012; 344:e2697.] ●

### Brief Summary of Prescribing Information for: OMONTYS (peginesatide) Injection for intravenous or subcutaneous use

**WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE. See full prescribing information for complete boxed warning.**

#### 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

OMONTYS is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

##### Limitations of Use

OMONTYS is not indicated and is not recommended for use:

- 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 (N = 1265)	CHOIR (N = 1432)	TREAT (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

## Fish Oil Reduces Thrombosis Risk in Synthetic Dialysis Grafts

For patients with new synthetic dialysis grafts, daily fish oil supplements may lower the risk of thrombosis, and possibly cardiovascular events, reports a trial in the *Journal of the American Medical Association*.

The randomized controlled trial included 201 adults with stage 5 chronic kidney disease at 15 dialysis centers in Canada and the United States. Seven days

after the creation of a new synthetic hemodialysis graft, patients were randomly assigned to supplementation with fish oil, four 1-g capsules per day, or placebo. Each fish oil capsule contained 400 mg of eicosapentaenoic acid and 200 mg of docosahexaenoic acid.

At 1 year, there was no significant difference in the primary outcome of native graft patency (i.e., freedom from graft

thrombosis or radiologic or surgical intervention): 48 percent with fish oil and 62 percent with placebo. However, the overall graft failure rate was significantly lower with fish oil supplementation: 3.43 versus 5.95 per 1000 access days, incidence rate ratio 0.58.

The fish oil group also had a lower overall number of thromboses: 1.71 versus 3.41 per 1000 access-days, incidence

rate ratio 0.50. The rates of radiologic or surgical interventions were 2.89 versus 4.92 per 1000 access-days, relative risk 0.59. Fish oil was also associated with increased cardiovascular event-free survival, hazard ratio 0.43, and a reduction in mean systolic blood pressure of 8.10 mm Hg.

Synthetic vascular access grafts for hemodialysis are prone to recurrent stenosis and thrombosis. With its anti-proliferative, antioxidant, and vasodilatory effects, fish oil may help avoid these problems.

Despite the lack of significance for native patency, the new trial suggests beneficial effects of fish oil on key secondary outcomes, including thrombosis risk and graft patency. “[T]he potential benefits of fish oil on cardiovascular events deserve confirmation in future studies,” the researchers write. [Lok CE, et al. Effect of fish oil supplementation on graft patency and cardiovascular events among patients with new synthetic arteriovenous hemodialysis grafts: a randomized controlled trial. *JAMA* 2012; 307:1809–1816.] ●

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*).

Marketed by:

**Affymax, Inc.**  
Palo Alto, CA 94304

Distributed and Marketed by:

**Takeda Pharmaceuticals America, Inc.**  
Deerfield, IL 60015

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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## Renal Cysts in Potential Kidney Donors—Are They a Problem?

Renal cysts are a common finding in potential kidney donors and are associated with markers of early kidney injury, according to a study in the *American Journal of Kidney Diseases*.

The researchers gathered data on renal cystic and solid lesions detected on contrast-enhanced computed tomography scans performed during evaluation of potential kidney donors. The analysis included 1948 potential donors evaluated from 2000 to 2008 (excluding those with cystic disease—mainly autosomal dominant polycystic kidney disease).

Analysis of cysts measuring 5 mm or larger showed cortical cysts in 12 percent of patients, medullary cysts in 14 percent, and parapelvic cysts in 2.8 percent. Older patients were more likely to have cysts, to have a greater number of cysts, and to have larger cysts. Cortical or medullary cysts 2 mm or larger were present in 39 percent of patients under 50 years versus 63 percent of those aged 50 to 75 years of age. The rates were 22 percent versus 43 percent for cysts 5 mm or larger, 7.9 percent versus 43 percent for cysts 10 mm or larger, and 1.6 percent versus 7.8 percent for cysts 20 mm or larger.

Men also had an increased presence and number of cysts. After adjustment for age and sex, the presence of cortical or medullary cysts 5 mm or larger was associated with increased urinary

*Continued on page 8*

## Journal View

### Renal Cysts

*Continued from page 7*

albumin excretion. In some analyses, cysts were also associated with increased body surface area, high blood pressure, and higher GFR.

Angiomyolipomas were found in 2.2 percent of potential donors, hyperdense cysts in 1.2 percent, and enhancing masses or cysts of concern for malignancy in 0.6 percent. All of these findings were more common in older patients.

A few renal cysts in a healthy adult are generally not regarded as problematic. This study of potential kidney donors undergoing contrast-enhanced computed tomography showed substantial rates of renal cysts, particularly in older men.

Associations with albuminuria, hypertension, and hyperfiltration suggest that these cysts might be a marker of early kidney injury. Inasmuch as potential kidney donors are selected for apparent health, “the associations revealed by this study may be even stronger in the general population,” the researchers write. [Rule AD, et al. Characteristics of renal cystic and solid lesions based on contrast-enhanced computed tomography of potential kidney donors. *Am J Kidney Dis* 2012; 59:611–618.] ●



## Something to Say?

**ASN Kidney News accepts correspondence in response to published articles. Please submit all correspondence to [kidneynews@asn-online.org](mailto:kidneynews@asn-online.org)**

# Study Questions Rituximab's Benefit For Children with Hard-To-Treat Idiopathic Nephrotic Syndrome

By Tracy Hampton

The drug rituximab recently emerged as a potential treatment for the childhood kidney disorder known as idiopathic nephrotic syndrome (INS). This anti-CD20 monoclonal antibody has been used successfully to treat immune disorders such as lymphoma and arthritis, but it does not appear to benefit children who have INS that is resistant to standard treatments. That was the conclusion of a recent study by Magnasco et al. in the *Journal of the American Society of Nephrology*.

### Rituximab for INS

Although the cause of INS in children is not fully known, it is believed to be an immune disorder. The disease mechanisms are poorly understood, with the exception of the most severe cases that are caused by molecular defects in genes that encode functionally important glomerular epithelial-cell (podocyte) proteins. Cases not associated with these gene mutations are thought to be due to an immunological dysfunction leading to a circulating factor that modifies the permeability of the glomerular filtration barrier.

Idiopathic nephrotic syndrome is a continuum of clinical disorders characterized by severe proteinuria, hypoalbuminemia, dyslipidemia, and hypercoagulability. There are three histological variants of primary INS: minimal-change nephrotic syndrome, focal segmental glomerulosclerosis, and membranous nephropathy.

With an estimated incidence of two to seven cases per 100,000 children and a prevalence of nearly 16 cases per 100,000, the syndrome causes considerable hardships including fatigue, decreased appetite, weight gain, facial swelling, abdominal swelling or pain, foamy urine, edema, and food intolerances or allergies. Relapses may occur throughout childhood, but once a child reaches puberty the disease typically stays in remission. Although the long-term outcome of the disease is favorable, the treatments' adverse effects can negatively impact the quality of life of children and their families.

Gian Marco Ghiggeri, MD, of the IRCCS Giannina Gaslini Children Hospital in Genoa, Italy, and his colleagues recently reported that rituximab can successfully reduce proteinuria in children with idiopathic nephrotic syndrome that responds to standard treatments consisting of ster-

oids and calcineurin inhibitors (such as cyclosporin). Therefore, rituximab may allow these patients to discontinue these potentially toxic medications.

Rituximab could help these children by interacting with regulatory elements of the cytoskeleton, and therefore directly modifying the podocyte structure. The drug also affects regulatory elements of B cells positive for CD20 that are implicated in innate immunity and affect Th17 cells. Rituximab also appears to reduce monocyte expression of soluble urokinase-type plasminogen activator receptor, which plays a direct pathogenetic role in focal segmental glomerulosclerosis.

### Hard-to-Treat Cases

Up to 80 percent of children with INS respond to steroids, with complete remission usually occurring within 30 days. The remaining cases can be particularly difficult to treat and can lead to end stage renal disease. To test the potential of this agent in children with INS that is unresponsive to standard treatments, Ghiggeri and his team conducted the first open-label randomized controlled trial of rituximab in 31 children with INS that was refractory to steroids and calcineurin inhibitors. All the children, who ranged in age from 2 to 16 years, continued taking steroids and calcineurin inhibitors at the same doses as before they enrolled. Half of the patients also received two doses of rituximab (375 mg/m<sup>2</sup> intravenously) as add-on therapy.

After 3 months of treatment, rituximab did not reduce proteinuria (change, -12 percent [95 percent confidence interval, -73 percent to 110 percent] p = 0.77). Additional adjustment for previous remission and interaction terms (treatment by baseline proteinuria and treatment by previous remission) did not change the results. According to the authors, these data do not support the addition of rituximab to prednisone and calcineurin inhibitors in children with resistant idiopathic nephrotic syndrome.

By identifying which patients benefit from rituximab and which do not, “our work represents a step forward on the road to treating nephrotic syndrome in children and it helps define the potentiality and limits of new therapies based on humanized antibodies for the disease,” said Ghiggeri.

Previous studies investigating the use of rituximab in patients with persistent resistance to the classic combination of steroids and calcineurin inhibitors include a short series from 2009 that showed no effect in six of eight patients and a partial response in the remaining two patients after four or six treatments (Fernandez-Fresnedo G, et al. *Clin J Am Soc Nephrol* 2009; 4:1317–1323). Another study based on questionnaires sent to members of the International Pediatric Nephrology Association found that 44 percent of patients with steroid-resistant nephrotic syndrome had a good initial response to rituximab (Prytula A, et al. *Pediatr Nephrol* 2010; 25:461–468). Also, a 2010 study reported complete or partial remission in 16 of 33 patients with steroid-resistant nephrotic syndrome who were otherwise refractory to all proven therapies (Gulati A, et al. *Clin J Am Soc Nephrol* 2010; 5:2207–2212).

“Within the last decade several case reports with positive effects of rituximab in different forms of pediatric nephrotic syndrome were published, but randomized trials were lacking. Despite the negative outcome of the study by Magnasco et al., it is very important as it is the first prospective randomized trial on the effect of rituximab in pediatric steroid-resistant nephrotic syndrome,” said Kerstin Benz, who was not involved with the study and is a nephrologist at the University of Erlangen-Nürnberg, in Germany. The results suggest that researchers and clinicians need a much better understanding of INS to develop effective therapies against hard-to-treat cases. A total of 12 renal genes involved in resistant forms of the disease have been characterized to date, and the list will likely grow. Future molecular analyses will enable researchers to conduct a more comprehensive analysis of all genes potentially involved in the syndrome and to characterize patient populations in whom new therapies may be successful. ●

**Disclosures:** The study was supported by the Renal Child Foundation (Genoa, Italy) and La Fondazione La Nuova Speranza (Milan, Italy).

The article “Rituximab in Children with Resistant Idiopathic Nephrotic Syndrome,” appeared online at <http://jasn.asnjournals.org/> in May 2012, doi: 10.1681/ASN.2011080775.



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### IMPORTANT DATES (2012)

#### Abstracts

Wednesday, April 4	Abstract Submission Site Opens
Wednesday, June 6	Abstract Submission Site Closes (11:59 p.m. EDT)
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



# Health Reform in the States: Implementation Continues While Law Remains In Flux

By Caroline Jennette

While the nation awaits a ruling this month from the Supreme Court on the constitutionality of the Affordable Care Act (ACA), activities working toward implementation—or lack thereof—continue to be a complicated issue for states, especially those wrestling with differing views on health reform among state policymakers, governors, insurance commissioners, and attorneys general. Many states continue to move forward with implementation even as their governors decline or return federal funding to assist in development (Table 1).

## Health exchanges

With a deadline to have a basic proposal in place by January 2013, creation of health care exchanges has been at the top of the priority list. Scheduled to begin in 2014, these exchanges will act as health care marketplaces for consumers looking to purchase individual health plans, and will also act to streamline eligibility and enrollment processes for Medicaid and the Children's Health Insurance Programs (CHIP).

So far, 17 states and the District of Columbia have established exchanges. Most have hit the ground running to gather stakeholder reports, convene task forces, and network with other states working on implementation through websites like [www.statereform.org](http://www.statereform.org). States are also studying the failures and successes of the Massachusetts Health Connector, the only operating health exchange and the model for the exchange language in the ACA. Early reports on the Massachusetts model look promising. Access to care has increased without any discernible “crowd-out” (consumers dropping care and crowding into public plans), but high health care costs remain an issue.

Most states created exchanges through legislation, but governors from New York and Rhode Island used executive orders to bypass bills that failed in the legislature. Nineteen states are in the process of reviewing their options for developing an exchange and 12 have not made any moves. Legislative bodies in two states, New Jersey and New Mexico, were able to get bills passed only to see them vetoed.

At press time, 16 of 34 states that do not yet have an exchange established are now out of session until the new year. If the Supreme Court upholds the law, these states may be scrambling in special sessions this fall to put something together or else be subjected to a federal exchange program, the details of which have not been clarified by the Obama administration. Two states, Arkansas and Louisiana, have chosen the default option of letting the federal government operate exchanges in their states.

If the Supreme Court repeals the ACA in full, federal funding will not be available and states with legislatively mandated exchanges not yet up and running could be in dire straits, although some states have decided to go forward regardless of the Supreme Court's decision. Exchanges could be further damaged if most of the law stands but the “individual mandate” is deemed unconstitutional. The individual mandate requires that everyone who is not covered under an employer group health plan be insured. In that case, state health exchanges may see an influx of only the poorest and sickest patients who cannot receive public assistance in another way.

## Medicaid expansion

Another element of the ACA awaiting a Supreme Court decision is the provision to expand Medicaid to all individuals with incomes of up to 133 percent of the federal poverty level (\$25,390 for a family of three in 2012). This expansion, scheduled to start in 2014, would primarily affect childless adults not typically covered unless they are eligible through age (<65 years) or on disability, but would also increase eligibility for parents, as most states do not cover them over 100 percent of the federal poverty level, with many covering only up to 50 or 60 percent.



Six states have taken advantage of federal funds available to expand Medicaid eligibility before 2014. Income limits for childless adults in these states range from 23 percent of the federal poverty level in New Jersey to 200 percent in California and New York. If Medicaid expansion is not struck down, the federal government will assume 100 percent of the costs to cover newly eligible enrollees between 2014 and 2016 and will continue to pay approximately 90 percent of the costs until 2022.

## Funding opportunities through the ACA

States, as well as health care and research institutions, are taking advantage of funding opportunities coming out of the Center for Medicare & Medicaid Innovation, created and funded through the ACA as a means to help design and evaluate new models of care for Medicare, Medicaid, and CHIP beneficiaries.

Grants have been awarded through the innovation center for 26 projects in 41 states, including several interstate projects. George Washington University, for example, has received funding to provide telemedicine services for peritoneal dialysis patients in the District of Columbia, Pennsylvania, and Maryland. Goals include training health care professionals and decreasing comorbidities through coordinated care. A project targeting poor and underserved areas in North Carolina and Virginia will focus on reducing complications from diabetes through coordinating care through local teams of health care professionals. The second round of innovation grants will be announced this summer, although the repeal of the ACA could deauthorize funding for these projects.

Funding has also been extended to 15 states to design better models of care for individuals who receive both Medicare and Medicaid. These individuals are known as “dual eligibles.” These patients make up a small portion of the Medicare population but account for a large portion of expenses, as they are often older, poorer, and suffer from multiple, chronic medical conditions. States that have been awarded contracts now have the chance to create demonstration projects outlining the logistics and implementation strategy of the coordinated care model they initially submitted. Approximately 32 percent of prevalent end stage renal disease patients are classified as dual eligible, but it is unclear how these demonstration projects will address this complicated population.

For more information on Center for Medicare & Medicaid Innovation funding opportunities and program descriptions, visit [www.innovations.cms.gov](http://www.innovations.cms.gov).

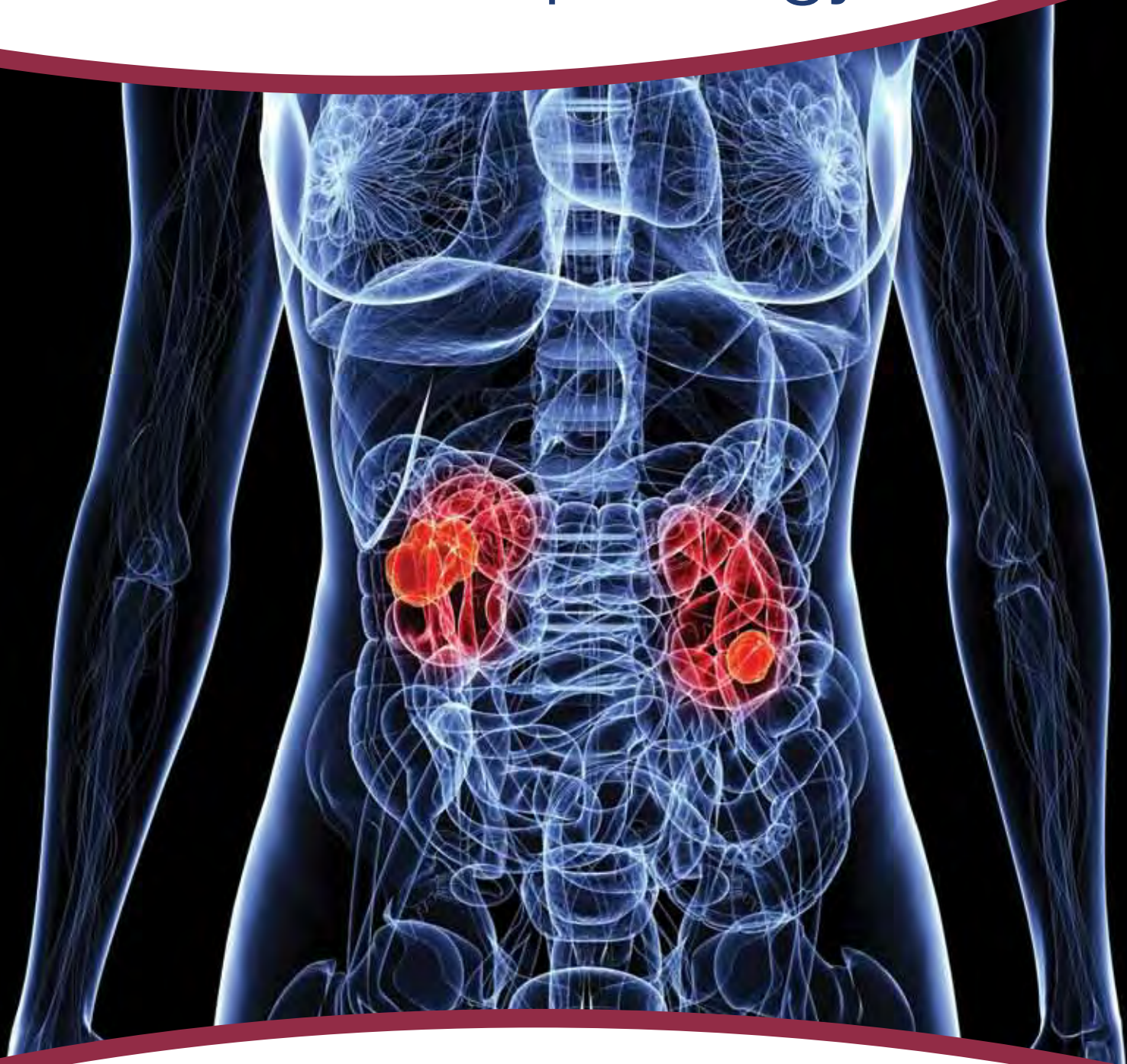
**Table 1. Health reform characteristics by state\***

	Included in federal lawsuit	Exchange established	Returned/declined federal \$ for exchange development	Early Medicaid expansion	CMS innovation project	Dual-eligible program design contracts
Alabama	●					
Alaska	●		●			
Arizona	●					
Arkansas						
California		●		●	●	●
Colorado	●	●			●	●
Connecticut		●		●	●	●
Delaware						
District of Columbia		●		●	●	
Florida	●		●		●	
Georgia	●				●	
Hawaii		●				
Idaho	●					
Illinois		●			●	
Indiana	●					
Iowa	●					
Kansas	●		●			
Kentucky						
Louisiana	●		●		●	
Maine	●					
Maryland		●			●	
Massachusetts		●			●	●
Michigan	●					●
Minnesota				●	●	●
Mississippi	●	●				
Missouri						
Montana						
Nebraska	●				●	
Nevada	●	●				
New Hampshire			●		●	
New Jersey				●	●	
New Mexico					●	
New York		●			●	●
North Carolina					●	●
North Dakota	●					
Ohio	●				●	
Oklahoma			●			●
Oregon		●			●	●
Pennsylvania	●				●	
Rhode Island		●			●	
South Carolina	●					●
South Dakota	●				●	
Tennessee					●	●
Texas	●				●	
Utah	●	●				
Vermont		●			●	●
Virginia	●	●				
Washington	●	●		●	●	●
West Virginia		●			●	
Wisconsin	●		●			●
Wyoming	●					
<b>TOTAL</b>	<b>27</b>	<b>18</b>	<b>7</b>	<b>6</b>	<b>27</b>	<b>15</b>

\*Data current as of May 11, 2012

Sources: Kaiser Family Foundation ([www.kff.org](http://www.kff.org)), Kaiser State Health Facts ([www.statehealthfacts.org](http://www.statehealthfacts.org)), Center for Medicare & Medicaid Innovation ([www.innovations.cms.gov](http://www.innovations.cms.gov))

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# Are Chronic Kidney Disease Patients Misclassified?

## Newer Equation May Be More Accurate For Disease Detection and Risk Stratification

By Tracy Hampton

**G**lomerular filtration rate (GFR) has been the mainstay for diagnosing chronic kidney disease (CKD), and it provides a powerful tool for helping clinicians predict all-cause and cardiovascular mortality and kidney failure in patients. But what is the best equation for estimating an individual's GFR? A new meta-analysis published in the *Journal of the American Medical Association* set out to answer this question.

### Comparing two equations

Although the Modification of Diet in Renal Disease (MDRD) Study equation is recommended for estimating GFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recently proposed an alternative equation that applies different coefficients to the same four variables used in the MDRD Study equation: age, sex, race, and serum creatinine level.

In June 2011, only 4 percent of U.S. laboratories that reported estimated GFR used the CKD-EPI equation to do so; 92 percent still used the MDRD Study equation, while 4 percent used other equations. To comprehensively evaluate whether estimated GFR computed by the CKD-EPI equation predicts risk for adverse outcomes more accurately than the MDRD Study equation in different populations of individuals, Kunihiro Matsushita, MD, PhD, of Johns Hopkins University, in Baltimore, and his colleagues conducted a meta-analysis of data from 1.1 million adults from 25 general population cohorts, seven high-risk cohorts of vascular disease, and 13 CKD cohorts. The participants were from 40 countries or regions of Asia, Europe, North America and South America, the Middle East, and Oceania. Data transfer and analyses were conducted between March 2011 and March 2012.

Adverse outcomes included all-cause mortality (84,482 deaths from 40 cohorts), cardiovascular mortality (22,176 events from 28 cohorts), and end stage renal disease (7644 events from 21 cohorts). The goal of the analysis was to provide information to help clinicians, laboratories, and policy makers decide whether estimated GFR reporting should be based on the MDRD Study equation or the CKD-EPI equation.

### Should patients be reclassified?

Estimated GFR was classified into six categories (90 or greater, 60–89, 45–59, 30–44, 15–29, and <15 mL/min/1.73 m<sup>2</sup>) by both equations. The researchers found that approximately one-fourth of participants were reclassified to a higher estimated GFR category by the CKD-EPI equation compared with the MDRD Study equation (24.4

percent in the general population cohorts, 15.4 percent in the high-risk cohorts, and 6.6 percent in the CKD cohorts). This lowered the prevalence of CKD in all cohorts except for the elderly. Approximately 0.6 percent of participants were reclassified to a lower estimated GFR category.

Study participants who were reclassified upward had lower risks of mortality and end stage renal disease compared with those not reclassified even after adjusting for various factors. Individuals who were reclassified downward had higher risks than those who were not reclassified.

The prevalence of CKD stages 3 to 5 (<60 mL/min/1.73 m<sup>2</sup>) was lower by the CKD-EPI equation than by the MDRD Study equation in the general population cohorts (6.3 percent vs. 8.7 percent) as well as in the high-risk cohorts (14.6 percent vs. 17.7 percent).

“Overall, the CKD-EPI creatinine-based equation more accurately classified individuals with respect to risk of mortality and end stage renal disease compared with the MDRD Study equation,” the authors wrote. “Given more accurate GFR estimation, lower CKD prevalence estimates, and better risk categorization by the CKD-EPI equation without additional laboratory costs, its implementation for estimated GFR reporting could contribute to more efficient and targeted prevention and management of CKD-related outcomes.”

Kamyar Kalantar-Zadeh, MD, MPH, PhD, who was not involved with the research, agreed that fewer individuals should be diagnosed with CKD.

“Many feel that an estimated GFR <60 mL/min/1.73 m<sup>2</sup> is too high and too imprecise of a threshold level to diagnose CKD be it with MDRD or CKD-EPI,” said Kalantar-Zadeh, director of the Harold Simmons Center for Kidney Disease Research & Epidemiology within the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, in Torrance, CA. “A lower and more conservative estimated GFR such as <45 mL/min/1.73 m<sup>2</sup> should replace <60. It is wrong to diagnose so many elderly individuals and women with CKD and cause stigma when they really do not have the disease.”

Kalantar-Zadeh and his colleague Alpeh Amin, MD, MBA, of the University of California-Irvine Medical Center, published an accompanying editorial in the same issue of *JAMA*, writing that “even though CKD staging using the more conservative CKD-EPI equation seems valid because it produces more meaningful risk profiles, it is premature to conclude that the ultimate tool for estimated GFR accuracy has been found.”



They noted that inherent limitations of the MDRD equation remain essentially unchanged in the CKD-EPI equation. For example, both equations rely on creatinine as a renal filtration marker. Creatinine is a close correlate of skeletal muscle mass but also likely varies with individuals' nutritional status and how much meat they eat. “Neither MDRD nor CKD-EPI offers any adjustment for body size or muscle mass. A less muscular person or a vegetarian may have lower serum creatinine level and hence artificially better estimated GFR,” said Kalantar-Zadeh.

The editorial noted that a panel of several filtration markers combined with some surrogate markers of nutritional status and body composition may provide a more accurate and clinically meaningful estimate of GFR. ●

Matsushita K, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 2012; 307:1941–1951.

Kalantar-Zadeh K, Amin AN. “Toward more accurate detection and risk stratification of chronic kidney disease. *JAMA* 2012; 307:1976–1977. (editorial)

# ASN in Action: Leaders Take 2012 Policy Priorities to Congress

By Rachel Shaffer and Grant Olan

On April 26, 2012, the ASN Public Policy Board, Council, and Board of Advisors ascended Capitol Hill to participate in the second annual ASN Hill Day. ASN leaders and staff met with nearly 60 congressional offices in both the House and Senate to address four key issues of importance to ASN's members and the patients they treat:

- The evolving practice environment in nephrology and the Medicare End Stage Renal Disease (ESRD) Program:** ASN leaders discussed with policymakers the reality that regardless of what the Supreme Court rules regarding the Affordable Care Act (ACA), the changes in the Medicare ESRD Program—including bundled payments and pay-for-performance—will move ahead, as they were mandated by a 2008 law. ASN leaders noted that it's important that Congress not make any further changes to the program until we have the data to understand the implications for patients, and evaluate how the Medicare ESRD Program may serve as a model for other areas of medicine considering similar payment reforms in the future.
- Increasing interaction between the nephrology community and the Food and Drug Administration (FDA):** ASN is committed to promoting dialog and collaboration with the FDA to promote kidney health and protect patient safety. ASN leaders, including President Ronald Falk, MD, FASN, and President-Elect Bruce Molitoris, MD, FASN, discussed these goals with key members of Congress.
- Providing lifetime immunosuppressive drug coverage for kidney transplant recipients:** ASN remains dedicated to advocating support for S.1454/H.R.2969, which would extend lifetime coverage of immunosuppressive drugs for patients with kidney transplants. ASN leaders met with approximately a dozen offices, specifically targeting members of Congress who supported this bill when it was introduced in the 111th Congress, but who had not signed onto the bill in the 112th Congress (the current session). ASN received three commitments from lawmakers to support the bill, bringing the legislation closer to its goal of passage this year.
- The importance of the National Institutes of Health (NIH) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) medical research funding, requesting a 4.5 percent increase over the Fiscal Year 2013 budget:** Protecting medical research funding is a sound investment that helps bring new cures to patients, drives economic growth, and defends the United States' position as the world leader in medical research.

Besides meeting with their own congressional delegations, ASN members also conducted key strategic meetings with members of Congress who sit on committees with jurisdiction over ASN's key issues, including leaders on the Senate and House Appropriations Subcommittees on Health, House Energy and Commerce Subcommittee on Health, Senate Finance Subcommittee on Health, and the Senate Health, Energy, Labor, and Pensions Committee. And for the first time, ASN "live-tweeted" Hill Day, complete with live pictures and captions describing the issues that were covered in each meeting.

"ASN is committed to advancing care of kidney patients," ASN Public Policy Board Chair Thomas H. Hostetter MD, said. "On ASN Hill Day, we asked lawmakers to keep patients in mind. We recognize that at this time Congress has to make tough choices about how it spends taxpayer dollars. But ASN's policy priorities—such as extending Medicare coverage for immunosuppressive drugs and investing in medical research—are clear wins. Besides saving lives, they generate jobs, drive economic growth, and keep America competitive in research and development. I hope we can count on Congress' continued bipartisan support of these important issues." ●



Nearly 30 ASN leaders visited congressional offices for ASN Hill Day 2012.



Sen. John Cornyn's (R-TX) health fellow Scott Kercheville, MD, discussed the evolving practice environment in nephrology with (back row) Councilor Jonathan Himmelfarb, MD, FASN; Public Policy Board member Suzanne Watnick, MD; ASN Manager of Policy and Government Affairs Rachel Shaffer; (front row) Public Policy Board member Barry Straube, MD; and Secretary-Treasurer Donald Wesson, MD, FASN.



Rep. Pete Stark (D-CA), ranking member of the House Ways and Means Health Subcommittee, and Public Policy Board member Barry Straube, MD, discussed ASN's principles related to integrated nephrology care delivery models.



Councilor Eleanor Lederer, MD, FASN (center), explained the value of NIH and NIDDK funding to the Louisville, KY, economy with Rep. John Yarmouth's (R-KY) health care staff.



Councilor Sharon Moe, MD, FASN, and Rep. Rodney Alexander (R-LA) concluded their meeting about health disparities in kidney disease and the importance of research.



Rep. Ron Kind (D-WI) (center, yellow tie) listened to ASN Public Policy Board members and staff explain the Medicare ESRD Program's early experiences with health reforms, such as pay-for-performance, that precede similar components of the Affordable Care Act.



House Ways and Means Health Subcommittee Chair Rep. Wally Herger (R-CA) and his staff listen to Public Policy Board member Barry Straube, MD, discuss implementation of bundled payments and the Medicare ESRD Program.



ASN leaders met with four staff members for the Congressional Kidney Caucus leadership. President Ronald Falk, MD, FASN, (center) spoke about kidney health and the FDA drug approval process with caucus Co-Chair Rep. Jim McDermott, MD (D-WA) health counsel Andrew Adair (Dr. Falk's immediate left); caucus Co-Chair Rep. Tom Marino (R-PA) legislative director Drew Kent (Dr. Falk's immediate right), along with (clockwise) ASN President-Elect Bruce A. Molitoris, MD, FASN; ASN Manager of Policy and Government Affairs Rachel Shaffer; and ASN Executive Director Tod Ibrahim. Not shown: Kathleen Hall, legislative assistant to caucus Vice-Chair Rep. Jesse Jackson Jr. (D-IL) and Katie Doherty, senior legislative assistant to caucus Vice-Chair Rep. John Fleming, MD (R-LA).



ASN President Ronald Falk, MD, FASN, and Monica Volante, legislative director for Rep. Joseph Pitts (R-PA), chairman of the House Energy and Commerce Health Subcommittee, discussed how to achieve ASN's goals for increasing interaction between the FDA and the nephrology community to promote kidney health.

## Policy Update

### ASN to CDC: Data Collection of Creatinine Levels Will Advance Research

By Grant Olan

Having access to nationally representative data for one routine lab test—creatinine levels—could help researchers better understand and slow the progression of kidney disease that affects up to 26 million Americans. Recently, ASN urged the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics to add patients' serum creatinine levels to the list of laboratory data the center collects in the National Ambulatory Medical Care Survey (NAMCS).

NAMCS gathers information on patients, providers, and visit characteristics from community health centers and non-federally employed office-based physicians who are primarily engaged in direct patient care. Physicians representing approximately 15 major medical specialty groups are sampled, and health care researchers, medical schools, congressional staff, and many others use the data to improve their knowledge of medical practice patterns.

In 2010, NAMCS began collecting laboratory test results, including total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, glycohemoglobin A1c, and fasting blood glucose, to improve the understanding of how physicians manage hyperlipidemia and diabetes.

The addition of creatinine levels, the most common measure of kidney function and collected with a simple blood test, will generate a critical resource for investigators studying prevalence, management, and treatment of patients with kidney disease in community settings. This information

can be used to better understand practice patterns in order to enhance knowledge of kidney disease in a number of ways. For instance, researchers could better understand how certain types of physician practices are able to slow progression of chronic kidney disease (CKD) and prevent the development of kidney failure, or end stage renal disease (ESRD).

The availability of this vital public health information could not be more timely. The combination of an aging population and epidemic increases in obesity and diabetes means the number of Americans with ESRD could continue to rise. Current projections estimate 774,000 Americans will have ESRD by 2020, and the same forces are increasing the population burden of CKD.

"Having measures of kidney function from a nationally representative group of clinical facilities would provide powerful information on how physicians and other health care providers in outpatient medical facilities are addressing early stages of kidney disease," said ASN Public Policy Board Member Neil R. Powe, MD, FASN.

Besides being the right thing to do, the addition of creatinine levels to NAMCS makes smart economic sense: information that helps slow the progression of CKD will help stem the rising tide of costs associated with this disease and maintain patients' overall health. ASN is committed to working with the CDC, National Institutes of Health, other federal agencies, and Congress to advance research and the highest quality care for patients. ●

## Industry Spotlight

### Abbott Buys Potential Kidney Injury Drug

Abbott Laboratories is expanding its pipeline into renal care drugs with a new addition, a potential kidney treatment from the privately held Danish company Action Pharma, Abbott announced May 3.

The company will pay \$110 million to buy the compound, which is in midstage clinical testing, according to an Associated Press report. The drug is designed to prevent acute kidney injury in patients undergoing major cardiac surgery.

Action Pharma recently completed a phase IIb clinical trial evaluating the efficacy, safety, and tolerability of AP214 in preventing kidney injury and systemic inflammatory response in patients undergoing cardiac surgery.

According to Action Pharma, more than 500,000 patients each year in the United States and in the European Union undergo major thoracic surgery. About 10–20 percent of these patients experience various degrees of kidney injury, which is associated with a marked increase in death, comorbidity, and prolonged hospitalization.

Currently, there is no treatment to prevent or treat kidney injury associated with major thoracic surgery, Action noted. "There is a major unmet medical need," the company stated on its website.

The AP214 molecule targets systemic inflammation and cellular death caused by lack of blood flow, which may happen when a patient is in surgery.

Abbott noted that this purchase would enhance renal care drugs under development, which include two potential treatments for chronic kidney disease.

Abbott will own the global rights to develop and sell AP214 to prevent acute kidney injury. It will not make milestone or royalty payments to Action Pharma,



Abbott said. The deal would have Abbott incur a second-quarter charge tied to its payment, the company said.

Action Pharma develops novel drug candidates targeting melanocortin receptors. Action brings these candidate compounds to the point of clinical proof of concept and then seeks partners, like Abbott, capable of bringing drugs to market. The drug candidates at Action Pharma are the first in several new drug classes, according to company literature.

Last August, the *Journal of the American Society of Nephrology* published two studies on acute kidney injury showing that this common but preventable complication after surgery could benefit when doctors used biomarkers to assess the condition. Three protein measurements indicated which patients might have a high risk for the development of kidney injury. ●

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## Nephros Eyes Larger Markets

Nephros Inc. (OTC Bulletin Board: NEPH) has been busy lately. First, it arranged for global marketing of ultrafiltration (UF) technology products under an agreement made April 23 with an Italian firm, Medical S.p.A.

On April 30, Nephros announced that it had received 510(k) clearance from the U.S. Food and Drug Administration (FDA) to market its hemodiafiltration (HDF) system for the treatment of chronic renal failure when used with UF-controlled dialysis machines that provide ultrapure dialysate. The company noted that the system is in accordance with current standards of the Association for the Advancement of Medical Instrumentation (AAMI), the American National Standards Institute, and the International Organization for Standardization in the United States.

The company's latest 510(k) clearance is for a system comprising a hemodiafilter and a hemodiafiltration module, Nephros's OLPur MD220 Hemodiafilter and Nephros's OLPur H2H Hemodiafiltration module, which are designed to work together.

"Nephros can now offer the only on-line HDF therapy available in the U.S.," said John C. Houghton, who was appointed president and chief executive officer of Nephros, Inc., on April 20, 2012. "Nephros will first pursue a limited launch of its HDF system before expanding into the broader market. In parallel, Nephros will evaluate opportunities to leverage the resources of a strategic partner to most effectively address the market."

Houghton most recently served as president and chief executive officer of CorMedix Inc., a pharmaceutical company focused on therapeutic products for the treatment of cardiorenal disease.

In 2011, Nephros positioned itself for its new efforts by completing \$3.2 million in financing and raising ultrafiltration product revenues to approximately \$618,000, an increase of 24 percent from the year before.

Two years earlier, Nephros marketed its first FDA-cleared product, Dual Stage Ultrafilters (DSU) for in-line purification of dialysate water and bicarbonate solution for hemodialysis.

The AAMI had adopted more stringent water purity standards for dialysis applications. Nephros noted that the new AAMI standards combined with "significant observational studies showing a substantial reduction in required erythropoietin" dosing when the Nephros DSU is used in dialysis accounted for increased interest in Nephros ultrafiltration products recently, according to Medical-News.net. ●

# 2011



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### Diamond Level



### Platinum Level



# Detective Nephron

**Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. L.O. Henle, a budding nephrologist, presents a new case to the master consultant.**



**Nephron** Nephrology seems to be attracting fewer medical students and residents. I wonder why? It's such a fascinating field. We need to do something as a community.

**L.O. Henle enters the room.**

**Nephron** Henle, why did you choose nephrology as your career path?

**Henle** I enjoy the variety it has to offer. My mentors in the past left an impression on me, and you are cultivating it more. I love it. Now I have a case for us.

**Nephron** Great—what do you have for us?

**Henle** Hyponatremia.

**Nephron** Oh, nice!

**Henle** A 45-year-old with a sodium level of 180 mmol/L, and he was completely asymptomatic. I shall stop there, as you usually suggest.

**Nephron** In hyponatremia, I think of osmostat/thirst, antidiuretic hormone (ADH) and/or the kidney as potential culprits. Of course, the problems with ADH can be in the production or responsiveness. But first, let me ask a simple question. Do you think the hyponatremia is due to a positive balance of sodium?

**Henle** No, he was not given hypertonic saline, nor did he ingest excessive sodium bicarbonate.

**Nephron** Ah-ha! Now, has there been any nonrenal water loss?

**Henle** Not at all. He had no signs of gastrointestinal loss from vomiting or diarrhea, no sweating or hyperventilation. And no renal losses either. He is not taking any loop diuretic, nor is there any evidence of osmotic diuresis.

**Nephron (chuckling)** No, my dear apprentice. You might want to stop a bit and think back to the renal causes.

**Henle** Did you mean water shift into the intracellular fluid compartment, perhaps due to rhabdomyolysis and/or convulsions? If so, the creatine phosphokinase and lactate levels were normal, with no signs of that at all.

**Nephron** Wow, you really are taking the fun out of this. When you said renal losses, did you mean inappropriate renal water losses as in nephrogenic and central diabetes insipidus (DI)?

**Henle** Oh, I see. So now you are done with ruling out primary sodium gain and nonrenal losses, and we are now thinking of possible renal losses via lack of ADH or inaction of ADH.

**Nephron** I believe you!

**Henle** Let me start with the kidney first, as that's easier. To my knowledge, he is not significantly polyuric; he makes only approximately 1 L of urine daily. His urine osmolarity is 1100 mOsm/kg.

**Nephron** So do you think the kidney is the culprit?

**Henle** Just to add, he doesn't take lithium or a loop diuretic. He doesn't have any hypercalcemia or hypokalemia and shows no signs of abnormal renal function. He is not taking any medications such as phenytoin that interfere with ADH production, and he's had no recent brain trauma. Like I said—completely asymptomatic. Given his hyponatremia, a high urine osmolarity, and a relatively low urine flow, I think I can safely discard DI. If he indeed was polyuric, with a urine osmolarity lower than serum osmolarity, I would consider it an ADH problem. In that case, a desmopressin test would help differentiate a loss of ADH production or ineffective ADH response in the kidney. But the urine osmolarity is high in this case and close to maximum response. So, there is ADH on board, and it is effectively working on the kidneys. Hmmmm.

**Nephron** Good work, my friend. So you are telling me that he doesn't have any signs of DI. You have shown that he has an intact ADH axis and that his tubules are responsive to ADH, and now you are going to test...? Well... what is his serum osmolarity?

**Henle** 375 mOsm/kg.

**Nephron** So, you have someone here who walked into your office with a sodium level of >170 mmol/L and a significantly elevated serum osmolarity and normal ADH response. Is this person thirsty?

**Henle** No; as I said before, he is completely asymptomatic. You are right. His thirst mechanism should have been activated with those numbers.

**Nephron** Tight regulation of water balance is accomplished via the thirst mechanism and ADH. Both are crucial to maintaining a remarkably narrow range of plasma osmolarity of 282–298 mOsm/kg. Osmoregulation of ADH is mediated by osmoreceptors located in the anteromedial hypothalamus near the neurohypophysial cell bodies in the supraoptic nucleus. These osmoreceptors are extremely sensitive to changes in osmotic pressure. For example, an increase in osmolarity of 1 to 2 percent increases ADH secretion. However, ADH secretion alone is not adequate to prevent dehydration, and an intact thirst mechanism is vital for water homeostasis.

**Henle** Thirst is a major player as well. Right?

**Nephron**

Thirst is regulated by hypothalamic osmoreceptors that are sensitive to changes in effective osmotic pressure of body fluids. The osmotic threshold at which the thirst mechanism is activated begins approximately 5–10 mOsm higher than the threshold for ADH release. These two systems work together to maintain plasma osmolality. With both systems intact, hypernatremia is a rare development, but can occur in patients who have lost their ability to maintain or increase free water intake, for example hospitalized patients and particularly the geriatric population. Much rarer causes of hypernatremia from decreased intake are the adipsic disorders. These disorders result from alterations in the thirst mechanism that prevent patients from taking in adequate free water despite elevations in plasma osmolality. Should I continue?

**Henle**

Hmm; so you are telling me that he has net primary water loss caused by a thirst disorder. Should I arrange for imaging of the brain? Could he have a lesion that is destroying the thirst center?

**Nephron**

Defects in ADH synthesis or secretion cause central DI (CDI) or in some instances partial CDI. These patients are polyuric and cannot concentrate their urine but maintain normal serum osmolality by drinking large amounts of water. Their thirst mechanism is intact. These patients do relatively well until they physically cannot drink water or their access to free water is lost. Conversely, a lesion in the thirst center in the hypothalamus can lead to an abnormal or no thirst response to hyperosmolality but a normal ADH response. A defect in osmoregulated thirst mechanism is termed hypodipsic or adipsic hypernatremia. It is frequently associated with defective ADH production as well, either CDI or partial DI. Because of their lack of thirst sense, patients with this condition may fail to drink spontaneously and are at risk of hypernatremia.

**Henle**

So, it is very likely this person has an adipsic hypernatremia.

**Nephron**

There are four variants of adipsic hypernatremia. Type A adipsia is characterized by an upward setting of the osmotic threshold for both thirst and vasopressin release, sometimes called essential hypernatremia. Type B adipsia is characterized by subnormal thirst and vasopressin responses to osmotic stimuli. This is due to partial destruction of the osmoreceptors. Complete destruction of these receptors is classified as type C adipsia, and these patients have complete absence of ADH release and a lack of thirst mechanism. Type D is an extremely rare form that manifests as only a thirst mechanism failure with an intact ADH production.

It seems that our friend here has a good intact ADH release—right?

**Henle**

I agree. What lesions in the brain cause adipsia?

**Nephron**

Classically the ones reported are sarcoidosis, craniopharyngioma, anterior communicating artery aneurysm (ACOM), traumatic injury, and prolactinomas.

**Henle**

Given his age, the most likely cause is an ACOM.

**Nephron**

Let me know when you find out.

*Henle exits without questioning.*

**Nephron (to himself)**

What a mix of endocrinology and nephrology! This is why renal medicine is fun.

*A day later:*

**Nephron**

You're back.

**Henle (very excited)**

Magnetic resonance imaging of the brain confirmed ACOM.

**Nephron**

Good work!

**Henle**

Now what?

**Nephron**

Forced drinking to make him eunatremic—that is, scheduled water drinking because there is no thirst mechanism, with some desmopressin if need be—is usually what helps. But he might need some surgical intervention here.

**Henle**

Nothing is better than a cup of warm coffee. And a great case! And that's usually your line.

**Nephron**

Great work, Henle. Again, my dear apprentice, never underestimate the power of the nephrologist. Again, you made a marvelous discovery of a central nervous system finding from a single electrolyte disorder. The power of nephrology continues! ●

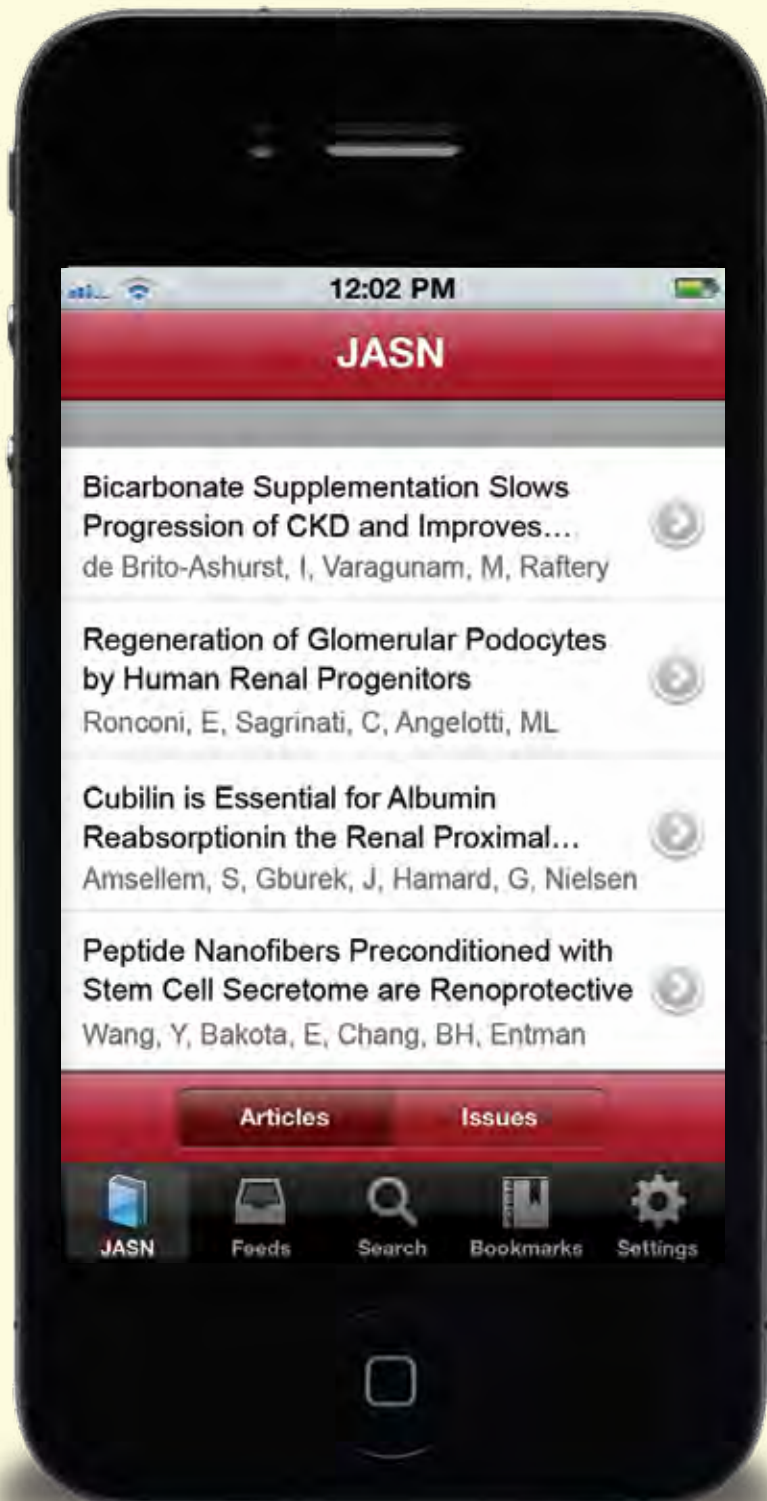
*Detective Nephron was developed by Kenar Jhaveri, MD, assistant professor of medicine at Hofstra North Shore LIJ School of Medicine. Thanks to Dr. Michael Gitman, assistant professor of medicine at Hofstra North Shore LIJ School of Medicine, and Dr. Rimda Wanchoo, instructor of medicine at Weill Cornell Medical Center for their editorial assistance. Send correspondence regarding this section to kjhaveri@nshs.edu or kdj200@gmail.com.*



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