ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Safety Net Health Care Systems Can Deliver Equitable Care and Good Hypertension Outcomes

By Kurtis Pivert

Patients with CKD who rely on safety net health care systems may receive more equitable and effective care, concludes a study that compared one such system, the Community Health Network San Francisco (CHNSF), with a representative sample of the U.S. population.

Delphine Tuot, MDCM, of the University of California, San Francisco, and her colleagues observed that patients with mild CKD receiving care from CHNSF demonstrated better control of hypertension among racial and ethnic minorities than a similar cohort from the National Health Examination and Nutrition Survey (NHANES) (1). Yet despite these encouraging results, Tuot also reported that African Americans have an increased risk for uncontrolled hypertension when compared to whites, even in the public health care setting. Tuot spoke at Kidney Week 2012 in San Diego.

Although the study shows the potential of systems such as CHNSF to act as frontline agents to reduce disparities of care for a population that may have higher risks for developing CKD and progression to ESRD, it also raises the question of how their success could be translated to improve hypertension control among at-risk minorities with more severe CKD.

Research has shown that racial and ethnic minorities have a higher risk for developing CKD and progressing to ESRD than whites, yet the reasons behind this are unclear. Most likely, this may be due to a combination of factors, and uncontrolled hypertension could be a major contributor to the accelerated and early rate of disease progression that these at-risk populations exhibit.

Efrain Reisin, MD, FACP, FASN, professor of medicine and chief of the section of nephrology and hypertension at the Louisiana State University Health Science Center, New Orleans, who was not involved in the study, said there are congenital, behavioral, and health access factors that contribute to higher rates of uncontrolled hypertension among minorities.

"African Americans, with or without CKD, have a higher rate of associated conditions than Caucasians (e.g., diabetes in men and diabetes and obesity in women)," he said. They also have some congenital

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Health Reform Moves Forward

President Obama's re-election ensures that the Patient Protection and Affordable Care Act (ACA) will continue to move forward.

The election result, following the Supreme Court decision upholding its constitutionality earlier this year, apparently removes the final obstacle to a host of provisions taking effect in just over a year—including new patient protections, marketplaces for buying insurance, and taxes and fees to pay for the law (see sidebar).

Supporters predict that Obamacare—a term coined by opponents as a pejorative but now embraced by its namesake—will grow in popularity once these provisions come into force. But the law still faces opposition and considerable uncertainty about what the next few years will bring.

The ACA's main goal is to increase the number of Americans with health insurance coverage. According to the latest estimates from the nonpartisan Congressional Budget Office, the ACA will increase the number of people below Medicare age with health insurance coverage by 14 million in 2014 and by 29 to 30 million by 2022. That growth represents an increase from today's 82% to 92% of the nonelderly population, but is down from estimates made before the June Supreme Court decision that upheld most of the law's provisions, but gave states the power to opt out of the planned expansion of Medicaid.

The act's overarching goals, if not its specifics, have been supported by a wide range of medical organizations. A greater portion of the population having insurance, which implies a greater chance for early treatment of developing conditions, should benefit patients and reduce costs, said Thomas Hostetter, MD, chair of

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Safety Net

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characteristics that increase the incidence of hypertension, including lower plasma renin activity (PRA) levels with expansion of fluid volume, and higher prevalence of salt-dependent hypertension. Other barriers to controlling BP in African Americans include low access to medical care and poor adherence to treatment. Also, more populations of African Americans live in communities that lack safe environments for walking or exercising and less neighborhood grocery stores that may offer easy access to a fresh and healthy food supply."

Because public health care delivery systems act as safety nets and deliver care for vulnerable populations, including minorities, they have the potential to reduce disparities and improve the outcomes of those who are at highest risk for kidney disease. To assess their performance in BP control, Tuot compared the prevalence and odds of uncontrolled hypertension among patients with CKD in CHNSF—an integrated health care delivery system that cares for San Francisco's uninsured and publically insured residents—with national estimates using data from NHANES.

A total of 6681 patients with CKD who received care at CHNSF between 2010 and 2012 and 3108 NHANES participants with CKD who saw a physician between 2003 and 2010 were included in the study. Although the cohorts differed in age, racial composition, number of non-English speakers, and uninsured individuals, both had similar rates of diabetes. Diagnosis of CKD was confirmed by an eGFR 15–59 mL/min/1.73 m^2 or a dipstick albuminuria test result >30 mg/g, with uncontrolled hypertension defined as a mean systolic BP >140 mm Hg or a mean diastolic BP >90 mm Hg. Prevalence of uncontrolled BP in the both cohorts was calculated, as well as odds ratios for uncontrolled hypertension among racial minorities as compared to whites with CKD, controlling for age, gender, insurance status, and presence of diabetes.

In mild CKD (stages 1 and 2), African Americans in the CHNSF cohort had an 8 percent higher odds for uncontrolled hypertension compared with whites. This contrasted strongly with the results from NHANES, in which odds for uncontrolled BP were 153 percent higher among African Americans compared to whites. In CKD stages 3 and 4, the odds for uncontrolled BP in the CHNSF were 11 percent higher for African Americans and 6 percent higher for Hispanics versus whites, compared with a 27 percent higher odds but a 43 percent lower odds for those in NHANES, respectively. Overall adjusted rates of uncontrolled hypertension were higher in the CHNSF cohort compared to NHANES (25.42 percent versus 21.72 percent). When stratified by severity of CKD, rates remained higher for CHNSF in stage 3 and 4 CKD (28.06 percent versus 23.08 percent) but were lower for stage 1 and 2 CKD (18.00 percent versus 22.13 percent) compared to NHANES.

The results revealed that "differences in BP control among patients with CKD of different races/ethnicities were smaller in the CHNSF compared to the national average, and that CHNSF appears to provide more equitable care to patients with CKD," said Tuot.

Were the higher rates of uncontrolled hypertension among African Americans unexpected? Reisin didn't think so. "They have a higher rate of hypertension and resistant hypertension than Caucasians due to genetic and behavioral factors. In fact, previous reports from the VA Health Care sites have also shown a lower rate of hypertension control in African Americans when compared with Caucasian subjects, despite the fact that in the VA system both groups have the same access to medications and health care."

Reisin added that the better performance of CHNSF in managing hypertension in CKD 1 and 2 was also unsurprising given that "previous studies have proven that effectiveness of care may vary among providers. Some health providers may be slow to follow recommended treatment guidelines, or may not have all the resources needed to treat low-income populations or those with special needs, conditions that make it more difficult to control BP."

The higher rates of uncontrolled hypertension in patients with stage 3 and 4 CKD reported in this study are indicative of the difficulties in managing this population. "According to previous publications, the rate of resistant hypertension increases from 5 percent in general practice to 50 percent or higher in nephrology clinics that treat African Americans or Caucasian CKD patients. The decrease in GFR increases BP and impairs the maintenance of sodium balance and body fluid homeostasis," he said. "Also, the presence of associated diseases like diabetes, obesity, and sleep apnea are very important factors that increase the rate of resistant hypertension in more advanced CKD stages."

The work demonstrates that "public health delivery systems, similar to the CHNSF, may provide more equitable care for patients with CKD than national averages and do a good job of controlling BP in patients with early CKD, despite caring for a population with high rates of poverty, limited health literacy, and non-English speakers," Tuot said. Yet she noted more research is needed to better understand why results differed in patients with mild CKD compared to patients with moderate/severe CKD. "This may reflect challenges in timely and appropriate care for those with more severe disease, including access to nephrologists, but at this point, we do not know," she said. "But I would like to challenge our community to translate these results in mild stages of CKD to improve care for our patients with more moderate and severe stages of the disease."

Reisin agreed that more research is needed to "further investigate the pathogenesis of resistant hypertension in African Americans, Hispanics, and other minority communities. In addition, clinical studies should include higher minority participation in the enrolled population to facilitate the assessment of safety and efficacy of different therapeutic approaches in these subjects."

Reference

1. Tuot DS, et al. Blood pressure control among CKD patients in a public health system. (Abstract)

Health Reform

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ASN's public policy board.

"If we can have some 90 percent of the population covered, hopefully that would mean that people with chronic kidney disease could be treated earlier and more effectively, and their need for dialysis or transplantation prevented or forestalled," Hostetter said.

One of the major ways that the ACA will increase coverage is by expanding Medicaid eligibility to include those with incomes up to 133% of the federal poverty line, for a cutoff of about $29,000 for a family of four. The Supreme Court dealt this effort a blow with its unexpected ruling that states could decide whether or not they wanted to participate in the expanded program.

As of mid-November, governors of at least seven states had declared that they would not expand Medicaid (and these states generally have a higher proportion of poor and uninsured people).

States could change their positions as time goes on, as they did when Medicaid was introduced in 1965, according to John Poelman, senior director at Leavitt Partners, a nonpartisan health care consulting group established by Mike Leavitt, a former Utah governor, Bush administration official, and head of the transition team for the Romney campaign. Poelman said that most states had implemented Medicaid within five years, but the last state, Arizona, did not do so until 1982.

Tim Jost, JD, a law professor at Washington and Lee University with an extensive background in health care policy, said that over time states will find it hard to turn down the federal dollars. The federal government pays about 60% of the costs of the current Medicaid program. In the expanded version, the federal government will cover 100% of the cost for the newly eligible people in 2014 and 2015, then pay a share that declines to 90% from 2020 on. "I think when they look at it hard, they're going to see there are so many reasons to do it and no reason not to," Jost said.

For the moment though, many governors not only oppose Obamacare, but are suspicious about the federal government's ability to uphold its end of the bargain given its budget situation, and say they do not want to contribute to larger deficits.

State officials are likely to feel pressure from their local medical communities because, in the expectation of greater insurance coverage resulting in fewer uninsured patients showing up at their doors, hospitals acquiesced to cuts in Medicare and disproportionate share payments in the ACA.

"The hospital cuts in the ACA were hopefully to be balanced out by an expansion of insurance," said Atul Grover, MD, PhD, chief public policy officer of the Association of American Medical Colleges. "If states fail to follow through on the Medicaid expansion, that could lead to further, severe losses for many of our safety-net teaching hospitals that are already barely breaking even."

Softening opposition?

Although voters in several states took symbolic steps to express opposition to the law, there is evidence that opposition is softening. Alabama, Montana, and Wyoming passed referenda aimed at nullifying the individual mandate to buy insurance or pay a fee, but none of these measures can have any effect because federal law supercedes them. A similar amendment in Florida failed. Missouri passed a law that forbids the governor from setting up a health insurance exchange by executive order.

But a Kaiser Family Foundation poll taken after the election found that the proportion of Americans who want to see the law repealed has dropped to a new low of 33%, the lowest number since the legislation passed and a 7% drop since August.

State exchanges

Florida Gov. Rick Scott, one of the most vocal critics of the ACA, told the Associated Press that given the election results he is willing to consider setting up a state-run insurance exchange he had previously ruled out. These exchanges are designed to be online marketplaces where individuals and small businesses can shop for insurance by easily comparing policies. The exchanges will certify plans as meeting standardized essential benefit packages to make it easier for buyers to know what they are being offered, and provide information to help consumers understand the options. Because they will also streamline the process for enrolling in Medicaid and the Children's Health Insurance Program (CHIP), they could lead to an increase in Medicaid rolls if consumers shopping for a policy learn of their eligibility for Medicaid.

States have the option of setting up their own exchange, participating in a state-federal partnership, or leaving it to the federal government to run an exchange in their state. At least in part in response to a letter from the Republican Governors Association asking the Obama administration to push back the date until it had answered more questions from governors and promulgated final regulations, the administration extended the deadline for states to decide until Dec. 14. As of mid-November, 16 states and the District of Columbia had opted to set up their own exchanges, six had opted for a partnership, and 19 had opted for a federal exchange.

But Laura Summers of Leavitt Partners said that states are running into difficulties because they are encountering a daunting number of rules and regulations, yet many requirements have still not been released or finalized. "States are having to make these decisions with a lot of uncertainty, and so they don't really know yet whether it would be beneficial," she said.

Republican Virginia Gov. Bob McDonnell made this point the day after the election when he announced that his state would not expand its Medicaid program or establish a state-sponsored insurance exchange. "I don't want to buy a pig in a poke for the taxpayers of Virginia," he said at a news conference, contending that the administration has not provided enough

information. But McDonnell left the door open to setting up an exchange at a later date.

The choice for states' rights advocates—to accede to the directives of a federal law they object to by setting up an exchange or cede this activity to the federal government—can be a sticky one. For example, Colorado established a bipartisan board to set up its exchange. One of the sponsors of the enabling legislation was Republican state representative Amy Stephens. She told National Public Radio that she opposes Obamacare, but: "I believe Colorado knows how to do health better than the federal government."

The exchanges are due to be operating by Oct. 1, 2013, for coverage starting Jan. 1, 2014, and many observers doubt that the administration will be able to keep to the schedule, given the complaints about the lack of guidance thus far. But Michael Hash, director of the office overseeing the efforts, said that his office has the contractors in place and is on track to meet the deadlines.

Kidney care and the ACA

Kidney care is one area that illustrates the uncertainty in the essential benefit packages to be offered in policies on the exchanges. The packages will be defined mostly by each state based on their customary policies already available, but will have to meet standards for deductibles and out-of-pocket costs. Important unresolved issues include the availability of immunosuppressive drug coverage for kidney transplant recipients, the interface between exchange-based insurance coverage and Medicare's end stage renal disease program, and the treatment of living organ donors, according to Dolph Chianchiano, JD, MBA, health policy adviser to the National Kidney Foundation. Chianchiano said that federal regulators may be allowing states the latitude to design their own approaches to these issues. The National Kidney Foundation and groups like the American Medical Association have urged that the essential benefits package be modeled on Medicare Part D, which includes anti-rejection medications on its list of protected drug classes, but federal regulators have yet to give a specific response on the issue.

One way that Republican House of Representatives opponents of the law have threatened to block implementation is through the power of the purse, by withholding appropriations. How effective this tactic could be is a subject of debate, but the need to set up more federal exchanges because so many states are refusing to set up their own could require increased federal expenditures.

Michael Cannon of the libertarian Cato Institute has encouraged this approach, blogging that "Congress authorized no funds for federal 'fallback' exchanges. So Washington may not be able to impose exchanges on states at all." Another potential area they might look to cut could be the subsidies for buying insurance.

"Restricting funding for implementation is a lever that still exists," Leavitt Partners' Poelman said. "But all funding of the government . . . requires both chambers to agree. The House will certainly move to restrict funding for implementing the Affordable Care Act but that will be negotiated as part of a larger funding package. When it comes down to making a final deal there will have to be compromises on both sides. It is quite likely that the administration won't get all the money it wants to implement the law but the overall enactment won't be halted."

With the fiscal cliff approaching, negotiations could address almost any aspect of the budget. "The House and the Senate and the president are going to have to get together on a whole bunch of financial issues," said Washington and Lee's Jost. "And the Republicans have already said they will be gunning for the Affordable Care Act through the appropriations process. Having fought this hard for the Affordable Care Act, the president is going to fight pretty hard to keep the funding there, and frankly, there aren't a lot of places to cut [in the ACA]."

Although the election settled some questions, the coming years will still be full of uncertainty and some dislocations. Some employees may find it easier to change jobs because of the prohibition of exclusions based on pre-existing conditions. Those who already have coverage should be largely unaffected except for greater protections, although the possibility exists that some employers may drop coverage.

A U.S. Government Accountability Office analysis of several studies found that microsimulation studies predicted little change in employer-sponsored coverage, but surveys of employers varied widely in results. Of course, these projections come in a context in which for the past decade the share of employers offering coverage has declined and employees have been asked to pay a larger share of costs. Massachusetts has seen a small increase in employer coverage since its plan was enacted, Jost said.

Another concern is whether the health care system will be able to cope with an influx of new patients, especially with shortfalls of providers already on the horizon. A recent study in the *Annals of Family Practice* estimated a need for 52,000 more primary care doctors by 2025. But it said that most of these are necessitated by population growth and the aging of the population, with only 15% chalked up to the expansion of coverage from the ACA.

Massachusetts has shown creative ways of coping with the greater demand, with increased reliance on use of physician's assistants and nurse practitioners, according to Grover of the Association of American Medical Colleges.

Research benefits

From the point of view of the kidney community, the ACA moving forward means continuity for a pair of research centers the act has already established. The Patient-Centered Outcomes Research Institute is a nonprofit with the mission of funding comparative effectiveness research—research that can be particularly difficult to find sponsors for. ASN's Hostetter said that nephrology is a discipline that could particularly benefit from this research. Another new agency, the Center for Medicare and Medicaid Innovation, is charged with finding new payment and delivery methods that improve care while lowering costs. As part of this effort, Medicare has begun contracting with accountable care organizations (ACOs)—team-based efforts in which doctors and other providers coordinate care for Medicare patients. Medicare has contracted with 153 ACOs so far, but expects that number to double to 300 in January. ASN has weighed in with recommendations on how ACOs could provide better integrated care in kidney disease, since it is particularly suited to a team approach.

The ACA promises big changes, so the debate over it is sure to continue, but many in the kidney community say they are seeing benefits and anticipating more.

Key Milestones in Implementation of the Affordable Care Act

The Affordable Care Act is designed to increase protections for patients, increase the number of people covered by health insurance, and require more people to contribute dollars to the health-care coverage pool. Its approach is based on some trade-offs: Because more people are required to buy insurance, insurance companies can drop pre-existing conditions requirements. Because hospitals will treat fewer uninsured patients, it reduces some government payments to hospitals.

One of the most important dates in the implementation is Jan. 1, 2014, still a little more than a year away, when many provisions take effect. Although the act was passed in 2010, implementation was staged to give consumers, insurance companies, state governments, and the federal government time to adjust to the changes. Here is a summary of some of the main provisions.

Requirements already in place

The law includes a "patient's bill of rights" that ends lifetime limits on coverage, restricts the conditions under which insurers can cancel coverage, requires plans to allow parents to include any children under 26, and ends pre-existing condition exclusions for children under 19, among other things. It created a special insurance pool for patients with pre-existing conditions.

Starting in 2010, health plans are required to cover preventive services such as mammograms and colonoscopies without charging a deductible, co-pay, or co-insurance.

Protections scheduled to start Jan. 1, 2014

- Eliminates pre-existing conditions exclusions: Insurance companies cannot refuse to sell coverage because of an individual's pre-existing conditions or to exclude pre-existing conditions from coverage.
- Prohibits insurance companies from charging higher rates due to gender or health status.
- Eliminates annual limits on insurance coverage.
- Requires insurance to cover patients who participate in clinical trials.
- Requires efficient administration by insurers: At least 85% of premium dollars collected for large employer plans and 80% for individuals and small employers must be spent on health care services and quality improvement. Any amount that doesn't meet these goals must be rebated to consumers.

Paying for expanded coverage

Starting Jan. 1, 2014, most individuals who can afford it must either buy health insurance or pay a fee designed to help offset the costs of caring for the uninsured. The fee is $95 or 1% of income in 2014, $325 or 2% of income in 2015, and $695 or 2.5% of income in 2016 (but no more than the cost of an average basic plan). These fees are generally much less than the cost of insurance, but the ACA is modeled on the Massachusetts model, where similar fees have been effective in getting people to enroll in insurance plans.

To make insurance affordable, federal tax credits will be available to people with incomes up to four times the federal poverty line (400 percent of the poverty level is about $43,000 for an individual and $88,000 for a family of four).

Individuals will be able to shop for policies at insurance exchanges.

Incentives and requirements for businesses

Small businesses with fewer than 25 workers will receive tax credits for up to 50% of the premium cost, and may find coverage more easily through the exchanges.

Employers with 50 or more full-time employees that do not offer coverage or offer coverage deemed unaffordable will incur penalties. Employers with more than 200 employees must automatically enroll new full-time employees in coverage.

New taxes and fees

The Congressional Budget Office projects that the ACA's net effect will be to lower the federal deficit because it includes revenues from new taxes, fees, and limits on deductions. For example, it lifts the cap on Medicare taxes paid by those with high incomes and taxes so-called "Cadillac" health insurance policies. It also institutes new fees on insurers, drug makers, and medical device companies.

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Congress: The Road Ahead

By Grant Olan

Voters resoundingly re-elected U.S. President Barack Obama on Election Day in November, but the balance of power in Congress remains essentially the same. Democrats gained two seats in the House of Representatives; however, Republicans will retain control by nearly 40 seats.* In the Senate, Democrats expanded their majority by two seats, but did not earn enough representation to overcome a Republican filibuster.

Because Democrats remain in control of the Senate and Republicans remain in control of the House, both parties will need to compromise to avert a "fiscal cliff" before January 2013, when automatic across-the-board cuts to federal discretionary spending would take effect (including cuts to medical research) and tax cuts would expire. Medicare physician payments would also be reduced 26.5 percent—as mandated by the Sustainable Growth Rate formula—unless the President and Congress reach a deal.

In the days following the election, both parties have begun to indicate a greater willingness to work together to avoid the fiscal cliff. "For the purposes of forging a bipartisan agreement that begins to solve the problem," House Speaker John Boehner (R-OH) said, "[Republicans are] willing to accept new revenue, under the right conditions." Senate Majority Leader Harry Reid (D-NV) said, "Compromise is not a dirty word. I'm willing to negotiate any time on any issue. I'm going to do everything in my power to be conciliatory."

Despite more conciliatory tones from both parties, the scuttlebutt is that Congress will likely push back the planned cuts to discretionary spending and extend the expiring tax cuts six months to give Democrats and Republicans more time to work out some kind of agreement.

If Congress fails to act, NIH funding will be cut by 8.2 percent, eliminating up to 2300 NIH research grants. In response to this threat, ASN has joined more than 3000 national, state, and local organizations, including other medical specialty societies and research organizations, to raise awareness of and build support for vital federal programs like medical research. For more information about how you can help, go to http://www.asn-online.org/policy/.

Other challenges for the President and Congress remain. The federal government will soon hit the "debt ceiling" again, a legal limit to how much debt the government can assume. A deal to avoid the fiscal cliff may include raising the debt ceiling. And challenges also remain for implementation of the Affordable Care Act—principally, Republican opposition to funding and meeting new deadlines for enactment of the law's provisions.

While the President and Congress work through these many issues in the coming months, ASN will be at the forefront advocating for support of promising kidney disease research that generates jobs, stimulates the economy, improves patient health, and drives down health care costs. Visit http://www.asn-online.org/policy/ to learn how you can make a difference.

*Election outcomes of six U.S. House seats were still pending at time of publication.

113th Congress Balance of Power

Senate			House of Representatives*	
53	2	45	233	196
Democrats	Independents	Republicans	Republicans	Democrats

*Election outcomes of six U.S. House seats still pending at time of publication.

Help Avert Cuts to Medical Research: Join ASN in Calling for a Balanced Approach to Deficit Reduction

By Thomas H. Hostetter

ASN needs your support to protect medical research funding. It's one of the smartest investments our country can make.

Research generates jobs, stimulates the economy, and enables life-saving medical advances. If Congress doesn't act by January 2013, federal funding for the National Institutes of Health will be cut by 8.2 percent, eliminating up to 2300 NIH research grants.

We can't let these cuts happen. ASN has joined more than 3000 other organizations urging Congress to adopt a balanced approach to deficit reduction that would protect medical research and other essential federal programs like education, public safety, and infrastructure.

The society needs your help, too.

Tell your Congressional representatives that cuts alone will not solve our federal budget problems.

Go to http://www.asn-online.org/policy/ for all the tools to connect you with your members of Congress, including talking points and fact sheets.

Congress won't act unless they hear from constituents like you.

I'm going to meet with my representatives. I urge you to join me.

Thomas H. Hostetter, MD, is Chair of the ASN Public Policy Board.

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Something to Say?

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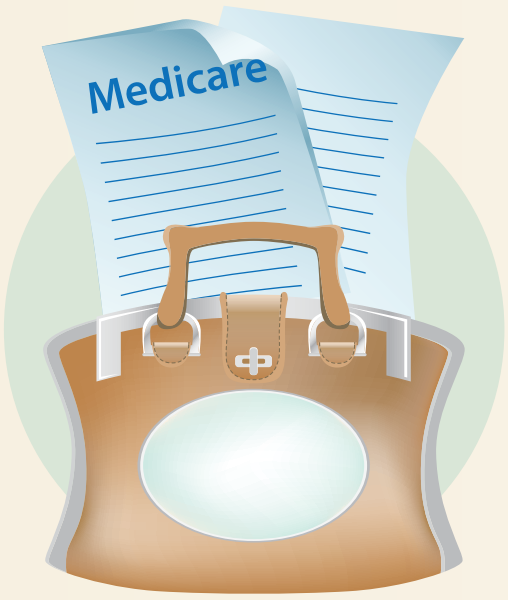
ALEXION

Kidney Week Session Highlights Health Care Allocation



The 40th Anniversary of Medicare's ESRD program served as the backdrop at Kidney Week's public policy session on health care allocation, featuring the Christopher R. Blagg Endowed Lecture in Renal Disease and Public Policy. Although the passage of the Medicare ESRD program in 1972 resolved the basic need for life-saving dialysis therapies, issues about appropriate allocation remain.

This year's endowed lecturer was Bruce Vladeck, PhD, a former administrator at the Health Care Financing Administration, currently serving as an adviser at Nexera, Inc. The major allocation issues in the care of dialysis patients today are poor management of those with the highest needs, conflicts between clinical care and financial incentives, and increasing expenditures for terminally ill patients, Vladek said. Although the work done at the institutional level by Blagg and his colleagues was invaluable in shaping the policies of the 1960s and 1970s, Vladeck called on clinicians to come back into the fold and to be the drivers of making policy and guidelines.

Although we live in a country that refuses to ration care on principle, it is often rationed implicitly, Vladek said, usually by socioeconomic status. Using data from the United States Renal Data System to back up his argument, Vladek said less than 50 percent of total Medicare expenditures for ESRD are actually spent on dialysis services, and the dialysis population is rife with comorbidities requiring other services and hospitalizations. He stressed that comprehensive primary and coordinated care could help reduce costs, but such care is not available to the sickest and poorest patients, who need it most.

The comprehensive care model envisioned by Vladeck would also include frank and open discussion about end-of-life care, another issue that has been part of heated debates on rationing care. Public and political discourse on providing palliative or hospice care in the place of life-sustaining procedures has often turned into talk of "death panels." But with an increasing numbers of frail and elderly individuals starting dialysis, Vladeck said the real issue is lack of appropriate training for health care providers to discuss issues related to prognosis, death, and expectations for treatment for patients nearing the end of life.

Creating policies that better address palliative care was discussed by Manjula Kurella Tamura, MD, associate professor of nephrology at Stanford University School of Medicine. Palliative care, defined as care that relieves symptoms without a curative effect on an underlying disease or cause, is unlike hospice care in that it can be used during the entire course of the disease, not just in the last 6 months. Tamura described

research showing that although palliative and hospice care is not cheap, it is not necessarily more expensive than regular care. Research has also shown that palliative care has been associated with increased patient and family satisfaction and improved bereavement outcomes; it has also been shown to lower costs, primarily by reducing the number of visits to the intensive care unit.

Unfortunately, ESRD patients typically receive only 3–4 days of palliative care on average, and confusion about how Medicare and hospice care work together for dialysis patients remains an issue (hospice care is not covered for dialysis patients unless their primary need for hospice is due to a different disease). There is also a scarcity of providers trained in palliative care and a need for rigorous trials to measure the effects of palliative care, especially for the dialysis population.

Tamura laid out five ways practitioners and other stakeholders can use policies to promote palliative care for this population: 1) universal screening for palliative care during transitions to care; 2) incorporating palliative care as a process measure in Medicare's quality improvement program; 3) payment reforms, including concurrent care models and adding palliative care as an accountable care organization designation; 4) palliative care training for ESRD providers; and 5) increased funding for research into palliative care.

Like dialysis, allocation issues also abound for transplant patients. Milagros Samaniego-Picota, MD, associate professor at the University of Michigan, tried to present balanced arguments both for and against the use of financial incentives to increase donation. In the United States, the demand for organs continues to far outweigh the supply, with only a nominal increase in the number of donors in the past few years. Many states have implemented programs to help living donors through tax credits or deductions, and a national donor assistance program now exists, but direct reimbursement for the donation of organs remains illegal under the National Organ Transplant Act.

In her "for" argument, Samaniego-Picota cited an economic model used to estimate the benefits of providing reimbursement to living donors. The authors of the paper argued that the effects of reimbursement (increase in the donor pool) would outweigh the costs (possible abuse and corruption), but they included the caveat that donors should be paid upwards of $100,000 and that compensation should be included as part of the medical procedure. They suggested that signing up for living organ donation is much like joining the military and that compensation for donation is similar to a family member receiving life insurance.

To argue against compensation, Samaniego-Picota described regulated incentive programs already in place in several countries, including Iran, Israel, Pakistan, and the Philippines. Although many of these programs have shown a demonstrable increase in kidney donations, ethical and legal concerns remain. For example, although Iran's kidney transplant wait list has been virtually eliminated, most organs come from an impoverished population more vulnerable to exploitation. In the Philippines, rules regulating the percentage of foreign recipients have been ignored, causing rampant transplant tourism. Clinical guidelines for donors in other countries are not as stringent as those in the United States, possibly leading to an increase in adverse outcomes for this already vulnerable population.

How best to use and protect living kidney donors remains a complex problem, and Samaniego-Picota's arguments highlighted many ongoing issues in incentivizing donation.

Hot Science Presentations Push Boundaries of Kidney Knowledge

The Hot Science session at Kidney Week 2012 covered a wide variety of both basic and clinical science, from podocyte functioning to genome-wide association studies. Here's a selection of some of the groundbreaking work that was presented in San Diego.

T Cell Autophagy a Key Mechanism in Preventing Transplant Rejection

T cell autophagy is crucial for induction of transplant tolerance, according to a study by Divya Anna Verghese, PhD, and colleagues from Mount Sinai School of Medicine. "Our study sets the stage for future work aimed at manipulating autophagy machinery in a clinical setting providing new opportunities to intervene in the alloimmune response," Verghese said, adding "targeting autophagy could be exploited as a means to manipulate pathogenic and/or protective immunity."

"The induction and maintenance of stable transplant tolerance involves both regulatory and deletional mechanisms, the latter of which have been attributed to T cell apoptosis," Verghese noted. "Autophagy is responsible for the degradation of protein aggregates and damaged organelles, and while usually a pro-survival mechanism, it can contribute to cell death."

Her group observed the costimulatory blockade with anti-CD154 mAb was associated with increased autophagy in allografts and immune cells, and chemical or genetic inhibition of autophagy led to allograft rejection despite donor specific transfusion/MR1. Reconstitution experiments in Rag2-/- mice confirmed that the defect mapped with lymphocytes. "Using mice conditionally deficient for Atg7 we showed that transplant tolerance required intact autophagy in T cells but not in B cells or dendritic cells," Verghese said. "T cells from autophagy-deficient animals proliferated more, expanded better, and died less in vivo during tolerance induction compared to those from wild type animals, while regulatory T cells from autophagy deficient animals functioned normally."

Verghese concluded, "our findings indicate autophagy-mediated T cell death is a requisite mechanism underlying transplant tolerance." Interestingly, she adds "the mTOR inhibitors rapamycin and everolimus are used as part of immunosuppressive regimens and their main effector mechanism is to inhibit T-cell proliferation. Inhibition of mTOR is a potent inducer of autophagy and the use of rapamycin, in combination with costimulatory blockade, provides strong synergy and favors peripheral tolerance."

Genetic Breakthrough into ANCA-Associated Vasculitis

The first genome-wide association study of antineutrophil cytoplasm antibody (ANCA)–associated vasculitis (AAV) has identified key genetic distinctions between the two major clinical syndromes of the disease. Although the syndromes—granulomatosis with polyangiitis and microscopic

polyangiitis—can be differentiated in extreme versions, many patients "fall into the middle in sort of a gray zone where physicians classify them inconsistently," said Kenneth Smith, MD, PhD, of the University of Cambridge. The confirmation that the syndromes have different genetic underpinnings could lead to improved diagnoses and better clinical trial designs for possible treatments.

Previous genome-wide association studies have successfully identified single nucleotide polymorphisms associated with several disease states, including diabetes, Parkinson disease, and Crohn disease. Presenting on behalf of the European Vasculitis Genetics Consortium, Smith showed the results of the first genome-wide association study in AAV that validated the genetic differences between granulomatosis with polyangiitis and microscopic polyangiitis, both of which cause kidney failure. The analysis included a discovery cohort of 1233 patients with AAV and 5884 controls from the United Kingdom and a replication cohort of 1454 patients with AAV and 1666 controls from Europe.

Researchers found that the disease exhibited familial clustering (similar to rheumatoid arthritis), and also observed genetic distinctions with anti-genetic specificity—anti–proteinase 3 AAV and anti–myeloperoxidase AAV. The identification of the two distinct autoimmune syndromes and associated risk alleles has implications for the etiology of AAV and for future research that could lead to disease-specific pathways and therapeutic targets.

Information for Patients
See Medication Guide in the full prescribing information

- Inform females of reproductive potential that use of Myfortic during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, and advise them as to the appropriate steps to manage these risks including that they must use acceptable contraception (**see WARNINGS: Embryofetal Toxicity, PRECAUTIONS: Pregnancy Exposure Prevention and Planning**).
- Discuss pregnancy testing, pregnancy prevention and planning with females of reproductive potential. In the event of a positive pregnancy test, the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.
- Females of reproductive potential must use acceptable birth control during entire Myfortic therapy and for 6 weeks after stopping Myfortic, unless the patient chooses to avoid heterosexual sexual intercourse completely (abstinence) (**see PRECAUTIONS: Pregnancy Exposure Prevention and Planning, Table 4**).
- For patients who are considering pregnancy, discuss appropriate alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of Myfortic should be discussed with the patient.
- It is recommended that Myfortic be administered on an empty stomach, one hour before or two hours after food intake (**see DOSAGE AND ADMINISTRATION in the full prescribing information**).
- In order to maintain the integrity of the enteric coating of the tablet, patients should be instructed not to crush, chew, or cut Myfortic tablets and to swallow the tablets whole.
- Give patients complete dosage instructions and inform them about the increased risk of lymphoproliferative disease and certain other malignancies.
- Inform patients that they need repeated appropriate laboratory tests while they are taking Myfortic.
- Advise patients that they should not breastfeed during Myfortic therapy.

Laboratory Tests
Complete blood count should be performed weekly during the first month, twice monthly for the second and the third month of treatment, then monthly through the first year. If neutropenia develops (ANC <1.3×10^3/μL), dosing with Myfortic should be interrupted or the dose reduced, appropriate tests performed, and the patient managed accordingly (**see WARNINGS**).

Drug Interactions
The following drug interaction studies have been conducted with Myfortic:

Gastroprotective agents
Antacids with magnesium and aluminum hydroxides:
Absorption of a single dose of Myfortic was decreased when administered to 12 stable renal transplant patients also taking magnesium-aluminum-containing antacids (30 mL): the mean C_{max} and $AUC_{(0-t)}$ values for MPA were 25% and 37% lower, respectively, than when Myfortic was administered alone under fasting conditions. It is recommended that Myfortic and antacids not be administered simultaneously.

Proton Pump inhibitors:
In a study conducted in 12 healthy volunteers, the pharmacokinetics of MPA were observed to be similar when a single dose of 720 mg Myfortic was administered alone and following concomitant administration of Myfortic and pantoprazole, which was administered at a dose of 40 mg BID for 4 days.

Cyclosporine: When studied in stable renal transplant patients, cyclosporine, USP (MODIFIED) pharmacokinetics were unaffected by steady-state dosing of Myfortic.

The following recommendations are derived from drug interaction studies conducted following the administration of mycophenolate mofetil:

Acyclovir/Ganciclovir: May be taken with Myfortic; however, during the period of treatment, physicians should monitor blood cell counts. Both acyclovir/ganciclovir and MPAG concentrations are increased in the presence of renal impairment, their coexistence may compete for tubular secretion and further increase in the concentrations of the two.

***Azathioprine/Mycophenolate Mofetil*:** Given that azathioprine and mycophenolate mofetil inhibit purine metabolism, it is recommended that Myfortic not be administered concomitantly with azathioprine or mycophenolate mofetil.

***Cholestyramine and Drugs that Bind Bile Acids*:** These drugs interrupt enterohepatic recirculation and reduce MPA exposure when coadministered with mycophenolate mofetil. Therefore, do not administer Myfortic with cholestyramine or other agents that may interfere with enterohepatic recirculation or drugs that may bind bile acids, for example bile acid sequestrates or oral activated charcoal, because of the potential to reduce the efficacy of Myfortic.

Oral Contraceptives: In a drug-drug interaction study, mean levonorgesterol AUC was decreased by 15% when coadministered with mycophenolate mofetil. Although Myfortic may not have any influence on the ovulation-suppressing action of oral contraceptives it is recommended to co-administer Myfortic with hormonal contraceptives, (e.g. birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods must be used. (**see PRECAUTIONS: Pregnancy Exposure Prevention and Planning**).

Live Vaccines: During treatment with Myfortic, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective. Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination (**see PRECAUTIONS, Immunizations**).

Drugs that alter the gastrointestinal flora may interact with Myfortic by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 104-week oral carcinogenicity study in rats, mycophenolate sodium was not tumorigenic at daily doses up to 9 mg/kg, the highest dose tested. This dose resulted in approximately 0.6-1.2 times the systemic exposure (based upon plasma AUC) observed in renal transplant patients at the recommended dose of 1.44 g/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil was not tumorigenic at a daily dose level as high as 180 mg/kg (which corresponds to 0.6 times the proposed mycophenolate sodium therapeutic dose based upon body surface area).

The genotoxic potential of mycophenolate sodium was determined in five assays. Mycophenolate sodium was genotoxic in the mouse lymphoma/thymidine kinase assay, the micronucleus test in V79 Chinese hamster cells, and the *in-vivo* mouse micronucleus assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay (*Salmonella typhimurium* TA 1535, 97a, 98, 100, & 102) or the chromosomal aberration assay in human lymphocytes. Mycophenolate mofetil generated similar genotoxic activity. The genotoxic activity of MPA is probably due to the depletion of the nucleotide pool required for DNA synthesis as a result of the pharmacodynamic mode of action of MPA (inhibition of nucleotide synthesis).

Mycophenolate sodium had no effect on male rat fertility at daily oral doses as high as 18 mg/kg and exhibited no testicular or spermatogenic effects at daily oral doses of 20 mg/kg for 13 weeks (approximately two-fold the therapeutic systemic exposure of MPA). No effects on female fertility were seen up to a daily dose of 20 mg/kg, which was approximately three-fold higher than the recommended therapeutic dose based upon systemic exposure.

Pregnancy
Pregnancy Category D (See WARNINGS)
Following oral or IV administration, MMF is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. 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.

Risks and benefits of Myfortic should be discussed with the patient. When appropriate, consider alternative immunosuppressants with less potential for embryofetal toxicity. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. For those females using Myfortic at any time during pregnancy and those becoming pregnant within 6 weeks of discontinuing therapy, the healthcare practitioner should report the pregnancy to the Mycophenolate Pregnancy Registry (1-800-617-8191). The healthcare practitioner should strongly encourage the patient to enroll in the pregnancy registry. The information provided to the registry will help the Health Care Community to better understand the effects of mycophenolate in pregnancy.

In the National Transplantation Pregnancy Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of these 18 infants had structural malformations (22%). In postmarketing data (collected from 1995 to 2007) on 77 women exposed to systemic MMF during pregnancy, 25 had spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed offspring had ear abnormalities. Because these postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. These malformations are similar to findings in animal reproductive toxicology studies. For comparison, the background rate for congenital anomalies in the United States is about 3%, and NTPR data show a rate of 4-5% among babies born to organ transplant patients using other immunosuppressive drugs. There are no relevant qualitative or quantitative differences in the teratogenic potential of mycophenolate sodium and mycophenolate mofetil.

In a teratology study performed with mycophenolate sodium in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia. The systemic exposure at this dose represents 0.05 times the clinical exposure at the dose of 1.44 g/day Myfortic. In teratology studies in rabbits, fetal resorptions and malformations occurred from 80 mg/kg/day, in the absence of maternal toxicity (dose levels are equivalent to about 0.8 times the recommended clinical dose, corrected for BSA).

Nursing Mothers
It is not known whether MPA is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from MPA, a decision should be made whether to discontinue the drug or to discontinue nursing while on treatment or within 6 weeks after stopping therapy, taking into account the importance of the drug to the mother.

Pediatric Use
De novo Renal Transplant
The safety and effectiveness of Myfortic in *de novo* pediatric renal transplant patients have not been established.

Stable Renal Transplant
There are no pharmacokinetic data available for pediatric patients <5 years. The safety and effectiveness of Myfortic have been established in the age group 5-16 years in stable pediatric renal transplant patients. Use of Myfortic in this age group is supported by evidence from adequate and well-controlled studies of Myfortic in stable adult renal transplant patients. Limited pharmacokinetic data are available for stable pediatric renal transplant patients in the age group 5-16 years. Pediatric doses for patients with BSA <1.19 m² cannot be accurately administered using currently available formulations of Myfortic tablets (**see CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION in the full prescribing information**).

Geriatric Use
Patients ≥65 years may generally be at increased risk of adverse drug reactions due to immunosuppression. Clinical studies of Myfortic did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
The incidence of adverse events for Myfortic® (mycophenolic acid) was determined in randomized, comparative, active-controlled, double-blind, double-dummy trials in prevention of acute rejection in *de novo* and maintenance kidney transplant patients.

The principal adverse reactions associated with the administration of Myfortic include constipation, nausea, and urinary tract infection in *de novo* patients and nausea, diarrhea and nasopharyngitis in maintenance patients.

Adverse events reported in ≥20% of patients receiving Myfortic or mycophenolate mofetil in the 12-month *de novo* renal study and maintenance renal study, when used in combination with cyclosporine, USP (MODIFIED) and corticosteroids, are listed in Table 5. Adverse event rates were similar between Myfortic and mycophenolate mofetil in both *de novo* and maintenance patients.

Table 5 Adverse Events (%) in Controlled de novo and Maintenance Renal Studies Reported in ≥20% of Patients

	de novo Renal Study		Maintenance Renal Study	
	Myfortic® 1.44 g/day (n=213)	mycophenolate mofetil 2 g/day (n=210)	Myfortic® 1.44 g/day (n=159)	mycophenolate mofetil 2 g/day (n=163)
Blood and Lymphatic System Disorders				
Anemia	21.6	21.9	–	–
Leukopenia	19.2	20.5	–	–
Gastrointestinal System Disorders				
Constipation	38.0	39.5	–	–
Nausea	29.1	27.1	24.5	19.0
Diarrhea	23.5	24.8	21.4	24.5
Vomiting	23.0	20.0	–	–
Dyspepsia	22.5	19.0	–	–

(continued)

Kidney Regeneration in Zebrafish Requires Wnt Signaling

The Wnt signaling pathway is critical to nephron regeneration in zebrafish, according to research presented by Caramei Kamei, PhD, at Kidney Week 2012. The zebrafish's ability to restore skin, organs, and muscle without the use of stem cells has made it a model of interest for a wide range of potential therapeutic areas, including cardiovascular disease, retinopathy, and cancer. Identification of Wnt signaling involvement in kidney repair in zebrafish opens a pathway for new research into the understanding of kidney regeneration."In contrast to mammalian kidneys, the zebrafish continuously adds new nephrons throughout its adult life," said Kamei. Because zebrafish can repair and generate new nephrons from adult progenitor cells, she and her co-investigator Iain Drummond, PhD, of Massachusetts General Hospital wanted to determine what signaled the repair function to begin in the kidney.

An in situ hybridization study revealed that adult kidney progenitor cells and differentiating cell condensates that are used to regenerate nephrons were observed to express the Wnt receptor Frizzled-9b (FZD9B) and the Wnt target Lymphoid enhancer-binding factor 1 (LEF1). Colocalization of FZD9B and LHX1A-positive kidney progenitor cells also suggested Wnt signaling involvement in zebrafish nephrogenesis.

Induction of acute kidney injury using gentamicin increased the number of FZD9B-positive nephron progenitors; however, when Wnt signaling was blocked after injury, the number of progenitor cells declined. An increase in FZD9B expression with activation of Wnt signaling in the absence of injury further confirmed Wnt signaling's role in kidney regeneration. "FZD9B is a new marker for newly forming nephrons as well as single cortical cells that are candidate kidney progenitor cells," Kamei said. Because FZD9B is expressed in the human kidney, Wnt signaling may be a target of interest in further research.

Podocyte Development and Function Are Dependent on Endophilin

Endophilin is critical to the development and maintenance of podocyte function in the kidney. This is the conclusion of Keita Soda, PhD, and co-workers from Yale University, who presented work at the Hot Science session at Kidney Week 2012 that described the connection between the protein endophilin and the synaptic proteins dynamin and synpato-

Continued on page 10

Podocyte Developement

Continued from page 9

janin 1, as well as the vital role endophilin plays in the formation and maintenance of the glomerular filtration barrier.

Expanding on their previous investigation of synaptic proteins, Soda and coworkers tried to determine the function of clathrin-coated pits that are seen in the podocyte foot processes.

They hypothesized that endophilin may play a role in podocyte function.

"Endophilin interacts with CD2AP, a critical protein which when lost in mice or mutated in humans results in nephrotic syndrome," Soda said. "Morever, it interacts with dynamin and synaptojanin, which when also deleted in mice results in severe proteinuria. This made endophilin an attractive candidate."

Soda and colleagues used fluorescent images to demonstrate that endogenous endophilin colocalized with podocyte marker-nephrin in glomeruli. The protein was also found in late-stage clathrin-coated pits with F-actin, dynamin, and synaptojanin 1, verifying endophilin's role in maintaining the glomerular filtration barrier. A second experiment comparing triple knockout mice (bred lacking all three isoforms of endophilin) with wild type mice found the knockout mice had a significantly high level of proteinuria, as well as dilated tubules and accumulation of mesangial matrix in glomeruli.

When asked if the confirmation of endophilin's role in podocyte functioning could lead to potential targets for treating nephrotic syndrome, Soda said that "stabilizing endocytic pathways regulated by endophilin/synaptojanin or dynamin may result in possible therapeutic interventions, but one must be cognizant as not all mechanisms of nephrotic syndrome are identical," Soda said, concluding "further investigation and research will be required."

Tolvaptan Trial Shows Benefit in Slowing Progression of Autosomal Dominant Polycystic Kidney Disease

A phase III clinical trial of tolvaptan for autosomal dominant polycystic kidney disease (ADPKD) demonstrated the drug slowed the rate of disease progression by almost half over the study period compared with placebo. While encouraging, the trial results presented at Kidney Week 2012 are investigative and have yet to be evaluated by the FDA. The 3-year multicenter, double-blind, placebo-controlled study (the TEMPO 3/4 Trial) found that patients with ADPKD who took tolvaptan experienced an average increase in total kidney volume of 2.8 percent per year compared with 5.51 percent for those in the placebo group (1). Given these results, how could this trial expand our understanding of ADPKD and change the investigative approach to the fourth leading cause of ESRD?

Prior to this study, physicians caring for patients with ADPKD were limited "to treating its complications (strict blood pressure control, dietary protein restriction, a low salt diet, and statin use for cardiovascular effects), since no treatment capable of inhibiting the development and progression of the cysts has been available," said Vicente Torres, MD, PhD, of the Mayo Clinic and first author of the TEMPO trial. "In many patients, the growth of numerous cysts within the kidneys is accompanied by painful complications (such as bleeding into cysts or into the urinary tract, cyst infections, and passage of kidney stones), hypertension, and kidney failure."

Vasopressin has been a pathway of interest to investigators in the ADPKD community, and has included research into the therapeutic use of water intake as a method to reduce vasopressin levels (2). A vasopressin V2 receptor antagonist, tolvaptan is currently indicated for hypervolemic and euvolemic hyponatremia. "Vasopressin causes production of the molecule cyclic adenosine monophosphate (cAMP), which is thought to accelerate the progression of ADPKD by stimulating proliferation of the cells lining the cysts and fluid secretion into the cysts," said Torres. "By blocking the production of cAMP, it was expected that tolvaptan would slow the progression of ADPKD."

Initiated in 2007, TEMPO 3/4 trial (Tolvaptan Efficacy and Safety in Management of Polycystic Kidney Disease and Its Outcomes) involved 1445 adult patients with ADPKD from 15 countries who were randomized to receive either tolvaptan (one of three dosages as tolerated) or placebo. The study's primary end point was reduction of total kidney volume over the course of the study. Secondary end points included the rate of decline in kidney function and time to clinical progression events, including hypertension and pain.

At the end of the 3-year study, the annual increase in total kidney volume (2.8 percent per year for tolvaptan versus 5.51 percent for placebo) and the slope of renal function decline (–2.61 $[mg/mL]^{-1}$/year for tolvaptan versus –3.81 $[mg/mL]^{-1}$/year for placebo) were significantly reduced in the tolvaptan group (both $p < 0.001$). Patients taking tolvaptan also demonstrated significant reductions in risk for secondary end points including worsening kidney function (61 percent) and pain requiring intervention (36 percent).

"The trial results show that Tolvaptan, given over 3 years, slowed the increase in kidney volume and the decline in kidney function," said Torres. "If these results are sustained beyond 3 years, tolvaptan would substantially extend the time before patients with ADPKD would need renal replacement therapy. Kidney pain, hematuria, and urinary tract infections, complications associated with ADPKD, occurred less frequently in the patients treated with tolvaptan compared to those treated with placebo. By reducing the rate of these complications, tolvaptan may lead to an improvement in quality of life."

Yet Torres cautions that tolvaptan is not without risks. "The most common adverse effects were anticipated and related to high urine output with more frequent voiding. Unexpected liver test abnormalities were observed in approximately 5 percent of patients and led to the discontinuation of tolvaptan in 1.8 percent of the patients." Adverse events led to a higher discontinuation rate in the tolvaptan group (23 percent) than in the placebo arm (14 percent).

"Although tolvaptan is already approved for treatment of other medical conditions, it is not approved for the treatment of ADPKD. The doses of tolvaptan used in the TEMPO trial were higher than used in previous studies of other diseases," Torres said. "In addition, ADPKD patients are a unique patient population. Further analysis of the benefits and risks of this potential therapy will need to be performed by the sponsor (Otsuka Pharmaceuticals) and regulatory agencies. Therefore, although the results are encouraging, at the present time, patients with ADPKD should not be treated with tolvaptan outside of approved research studies."

Terry Watnick, MD, of the University of Maryland School of Medicine and an investigator in the TEMPO trial, found the results of the trial's primary end point very encouraging. But Watnick added that "it is still important that we control blood pressure and other cardiovascular risk factors in ADPKD patients since this population may still require renal replacement therapy. While tolvaptan may delay disease progression, it will not completely prevent or reverse established disease based on the data presented."

There are other important questions with respect to tolvaptan that remain to be answered, Watnick said. For example she wondered if tolvaptan would be more beneficial if the drug was initiated earlier in the course of disease when patients had fewer cysts or smaller kidneys. In addition, the applicability of treatment in patients with milder disease severity, or the consequences of longer-term drug administration remain to be defined. She also pointed to a need for more basic research into the mechanisms underlying ADPKD pathogenesis. "Blocking the V2 receptor improves the disease course, but it doesn't completely stop progression. ADPKD is a complicated disorder, and the PKD community has invested a lot in research over the past 15 years. The signaling pathways involved in cyst formation are complex, and we still don't know everything we need to know about this disease. Blocking the V2 receptor provides one therapeutic approach, but I believe that there are likely to be others."

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Renal Replacement Therapy:

Cautiously Expanding the Donor Pool and Disparities in Transplant Access for Children

Two studies presented at Kidney Week 2012 offer a cross-section of the state of renal replacement therapy in the United States. The first study demonstrated that living kidney donors with prediabetes did not experience an increased risk for developing diabetes over a mean follow-up of 10 years. It indicates that the living kidney donor pool may be cautiously expanded to include prediabetic individuals, which could contribute to a reduction in the duration patients spend waiting for kidney transplants. The second study confirmed that minority children with kidney disease face disparities in access to renal replacement therapy, especially preemptive transplantation, compared to whites. Although transplantation is the preferred treatment option for children with ESRD, white children were four times more likely to receive a transplant as their initial renal replacement treatment compared with black children. Both studies reflect the complex situation that patients with kidney disease encounter when selecting renal replacement options, and identify knowledge gaps for future research that could contribute to improved decision making and outcomes.

Cautiously expanding the living kidney donor pool

Potential living donors receive extensive screening before being approved for kidney donation, and a diagnosis of prediabetes (defined as impaired fasting glucose level of 100–125 mg/dL) may prevent some from donating a kidney. Current clinical guidelines lack consensus on the suitability for donation of individuals with prediabetes, which by current estimates may include as much as 35 percent of the U.S. population. To determine if the condition is truly a contraindication for donation, Sindhu Chandran, MD, of the University of California, San Francisco, and colleagues studied a single-center cohort of living kidney donors who were prediabetic at the time of donation and who agreed to a clinical follow-up after their operation (1).

Thirty-five donors who had a fasting glucose level ≥100 mg/dL at time of donation underwent a telephone interview and laboratory testing. At the time the study was conducted, the mean duration between donation and follow-up was 10.2 years (range 5.1–15.9 years). Results revealed four donors (11.4 percent) had progressed to diabetes, two

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donors (5.7 percent) had microalbuminuria, and kidney function was well preserved in all donors (mean eGFR 68.9 mL/min/1.73 m^2). In addition, 60 percent of prediabetic donors reverted to normal glycemic levels, which Chandran noted was higher than the commonly cited rate of approximately 25 percent.

"However, the reversion rate varies depending on factors such as race, family history, and obesity, and because donors are screened for these they are healthier than the average population," Chandran said. "Also, the majority of our donors were white (75 percent) so it is perhaps not surprising."

"Studies such as these can be controversial," said William Harmon, MD, of Boston Children's Hospital and Harvard Medical School, who was not involved in either study. "The major issue for living donation is that you never want to put the donor at risk for the recipient. As we've expanded the donor pool to include people with mild hypertension or those with a history of kidney stones, you always worry that as you expand the pool farther that we're going to see more morbidity and mortality, which then gets to be counterproductive." But he added the study "is good news and it will allow some other programs to say that being prediabetic is probably not a contraindication to donation."

Although the results appear to be encouraging, what further data are needed to convince physicians to change their practice patterns and consider expanding the donor pool to include donors with prediabetes?

"This data would preferably have larger numbers of patients (to ensure major events aren't missed); more minorities, including blacks and Hispanics because they are at higher risk; more transplant centers, to ensure that center-specific practice patterns (such as being too selective) aren't influencing outcomes; and finally a control group," Chandran said. "The ideal controls would be prediabetics who ended up not donating for nonmedical reasons, but because this is impracticable the next best thing would be to compare them to similar patients with normal blood glucose who donated at the same time. We have already enrolled such controls and are working on data analysis."

Harmon added that generating consensus for clinical guidelines to assess the risk of donor pool expansion requires studies like Chandran's. But he pointed to a bigger problem. "The bottom line is we need more information on more donors," he said. "Living kidney donation programs are supposed to send data at certain intervals post-transplant, yet it's difficult to get those data because donors tend not to return because they're not sick and don't want to take the time. Switzerland has long-term data on their living kidney donors because laboratory tests are covered by national health system and information gathered via their primary care physicians, yet similar testing in the United States could be denied by insurance or physicians may be penalized financially for ordering the test. Our system is not very friendly for getting data for otherwise healthy people."

Chandran echoed Harmon's concerns, noting currently there are no good established data sources for living donors to verify her research. "There are two current NIH-sponsored cohorts—ALTOLD, with follow-up of 36 months, and RELIVE, which was just completed in June 2012," she said. A registry of living donors could address this gap, but she said that cost and willingness of donors to participate remain barriers to establishing such a registry. New policies enacted by the United Network for Organ Sharing in November 2012 that require a mandatory 2-year follow-up of all donors may help address the gap in donor data.

Disparities in renal replacement options for minority children

Health care disparities have been less well documented in the U.S. pediatric population than in adults. Previous studies have shown that black children are more likely to receive hemodialysis instead of peritoneal dialysis as their initial renal replacement therapy compared with white children, yet there

have been few investigations regarding the preferred treatment for ESRD—preemptive transplantation. To determine if children experienced racial and ethnic disparities in renal replacement options and to determine the factors behind such disparities, Roshan George of Emory University School of Medicine and Children's Healthcare of Atlanta and her co-workers examined a pediatric and adolescent cohort (<20 years of age) from the United States Renal Data System (USRDS) who initiated renal replacement therapy between January 2005 and September 2009 (2).

Of 5623 patients included in the study, 43.3 percent were white, 30.3 percent were black, and 26.4 percent were Hispanic. The results, though as expected, were stark: the percentage of black children receiving preemptive transplants was one-fourth and the percentage of Hispanic children was one-half that of white children who underwent preemptive transplantation. Hemodialysis was the renal replacement for a majority of blacks (70.8 percent) and Hispanics (60 percent) as well as whites (49.1 percent). Yet the rates of white children initiating peritoneal dialysis (32.4 percent) or receiving preemptive transplantation (18.6 percent) were higher than in the other groups. Adjusting for demographic, clinical, and socioeconomic differences attenuated the differences in renal replacement therapy for Hispanics, yet when compared with hemodialysis, black children still had a 75 percent lower chance for preemptive transplantation than white children. Examining rates of pre-ESRD access to a nephrologist also revealed significant differences between

black and Hispanic children when compared with whites.

"The study is important because typically children have safety nets in terms of prejudice and poverty," said Harmon. "You would hope that what's true for adults, where socioeconomic disparities may account for differences in care, wouldn't apply to children. Showing that these things are true in children is an important finding, and shows that we still have a ways to go in terms of the transplant process."

The results mirrored those in the incident adult population, said George, who noted that black adults are more likely to initiate therapy with hemodialysis and face delays in getting on a transplant wait list.

"It is true that there is a very big disparity between whites and blacks in terms of how soon they get on the waiting list," Harmon said. "Until recently, physicians would place their patients on the waiting list way before they needed a transplant and keep them inactive where they could still accumulate waiting time points, whereas blacks often wouldn't get on until after they had started dialysis, and even then there'd be a long delay in terms of giving them the opportunity to get on the transplant list.

"Some of this has been ameliorated by recent movements to not count waiting time until the patient is either on dialysis or has a GFR <20 mL/min/1.73 m^2," Harmon said. "But once on the list, the time to transplant for blacks doesn't seem to be as affected because the listing criteria are clear."

George concluded that further research examining patient and physician perspectives when choosing renal replacement options could be helpful in resolving disparities and determining unmeasured factors that typically are not captured in most data sources.

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Diet and Nutrition Can Play a Pivotal Role in Improving Outcomes among Minorities and Reducing Health Disparities

Improving dietary habits and ensuring access to healthy foods are important to reducing health disparities and improving outcomes among lower-income individuals and minorities, at-risk populations for developing kidney disease in the United States. This was the conclusion of two new studies presented at Kidney Week 2012 that demonstrated 1) increased intake of fruit and vegetables can ameliorate metabolic acidosis, and 2) an unhealthy diet lacking nutrients that indicate adherence to a DASH (Dietary Approaches to Stop Hypertension) diet—which is high in whole grains and fruits and vegetables—among individuals living in poverty can adversely impact their chances for developing CKD, some of whom already have an increased odds for disease progression. Both studies offer evidence that diet and nutrition present targets for reducing health disparities in individuals facing an increased risk for kidney disease.

Previous research into the effects of diet on CKD focused on limiting protein intake, most notably in the Modification of Diet in Renal Disease (MDRD) study, said Frank C. Brosius III, MD, of the University of Michigan Health System, who was not involved in either of the studies. The MDRD study, however, found no significant difference in outcomes based on diet, and despite interest in how nutrients and antioxidants impact kidney disease, "there have been no conclusive studies stating that dietary intervention leads to a statistically significant improvement in outcomes," he said.

"This is why studies like these are exciting, because improving diet can be a low-cost high-safety intervention," Brosius said. "The focus of this research is great, because if dietary changes can be shown to have an impact on progression of disease, particularly in those groups who are at highest risk for kidney disease, you can get the biggest bang for your buck."

Dietary habits of individuals living in poverty

Research has demonstrated that lower socioeconomic status is connected with reduced kidney function and an increased risk for progression to ESRD. To determine if dietary habits were contributing to this increased risk for CKD, Deidra Crews, MD, FASN, of the Johns Hopkins University School of Medicine, and her colleagues studied a large urban population to determine if adherence to a DASH-style diet was linked with reduced prevalence of kidney disease among those living in poverty.

Crews used the Healthy Aging in Neighborhoods of Diversity Across the Lifespan (HANDLS) cohort, an intramural study of the National Institute on Aging that focuses on the influence of socioeconomic status and race on health outcomes. A total of 2058 participants from diverse backgrounds in Baltimore were included, 42 percent of whom were classified as living in poverty. The poverty group had a significantly higher number of black and uninsured individuals and tobacco users compared with the non-poverty group. Although participants were not instructed in the DASH diet, their report, via 24-hour dietary recall of intake of foods containing the macro- and micronutrients considered in DASH adherence scoring were used to assess their dietary habits. Kidney disease was defined by reduced eGFR and/or elevated urinary albumin–creatinine ratio.

The majority in both poverty and non-poverty groups in the HANDLS cohort were found to be non-adherent to a DASH-style diet (only 4.5 percent and 6.1 percent, respectively, were adherent). Despite this, those in the poverty group fared significantly worse in levels of nutrients (cholesterol, fiber, magnesium, calcium, and potassium) and had a significantly higher rate of CKD compared with the non-poverty group (5.6 percent versus 3.8 percent).

When the entire cohort was stratified across tertiles of DASH adherence (lowest, middle, and highest) prevalence of CKD remained higher in the low and middle adherence tiers of the poverty group, while there was no statistically significant difference across the tiers in the non-poverty group. Logistic regression revealed similar findings, even after inclusion of sociodemographic, hypertension, diabetes, and tobacco use variables.

Given these results, could specific factors lead to increased risk for individuals in the poverty group? Crews said the reasons behind this relationship were unclear.

"The specific nutrient profiles could be the main drivers, as could additives in the foods of the poverty group (which we did not directly assess)," Crews said. "It is also possible that dietary habits do not play as much of a role in CKD risk for higher income individuals because their risk is largely mitigated by access to health care, access to recreation, and less psychological stress. On the converse, dietary habits may play a big role in risk of CKD for poor individuals because they have so many risk 'amplifiers' (poor access to health care, limited access to recreation, significant stress, or discrimination), and thus when dietary habits are favorable, CKD risk might be lessened even in the setting of poverty."

Brosius noted that although "it is a complex study, the results are consistent with the fact that the DASH diet tends to be more expensive, and the poverty group is more likely to be living in 'food deserts' where there is less access to DASH-style diets. However, those people in poverty groups who do adhere to DASH-style diets have a significantly reduced risk of CKD." He added that a follow-up study would need to control for more than presence or absence of diabetes and hypertension, "but also how well these are being controlled. But in these groups, a DASH diet might be an effective preventative intervention."

Crews is planning a tailored interventional study in a similar population, aimed at educating the participants on how to follow a DASH-style diet even with limited finances and limited access to healthy foods.

"As more evidence is revealed regarding the detrimental and costly effects of limited access to healthy foods we will see changes in policies on zoning and more incentives for full-service grocery stores opening in what are now food deserts," Crews said. "I consider ours, and other studies of its kind, a call to action for members of the kidney community to get involved in public policy."

Fruits and vegetables can mitigate metabolic acidosis

Metabolic acidosis can commonly affect individuals with CKD and is associated with higher levels of angiotensin II, a pathway that powerfully promotes hypertension, a decline in renal function, and irreversible fibrosis of kidney tissue. This condition is exacerbated by a diet rich in fat and animal proteins, which generate a higher acid load than impaired kidneys can handle. Current clinical guidelines indicate alkali therapy for severe (<22 mM $PTCO_2$) but not for milder (22–24 mM $PTCO_2$) cases. To determine if patients with stage 3 CKD and less severe metabolic acidosis could also benefit from therapy, Nimrit Goraya, MD, of the Texas A&M College of Medicine and her co-workers investigated if adding fruits and vegetables (which generate a net alkaline load) or oral doses of sodium bicarbonate could reduce the decline in kidney function.

Building on their previous research, they performed a prospective trial with

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108 patients receiving antihypertensive medications and who were randomized to receive fruits and vegetables, oral sodium bicarbonate, or neither (control) for a period of 3 years. At the conclusion of the study, both the fruits and vegetables group and the oral bicarbonate group demonstrated significantly better outcomes in mean systolic blood pressure, urine angiotensinogen (a biomarker for angiotensin II activity), and eGFR when compared to controls. The fruits and vegetables group had a larger, but statistically significant, reduction in eGFR decline and lower increase in systolic blood pressure than those receiving oral bicarbonates. Goraya added that her group's other studies have demonstrated the benefits of fruits and vegetables for patients with stage 4 CKD as well. "Although you can't make conclusions from a single randomized trial with a small population such as this one, the initial results look encouraging for those with mild metabolic acidosis," said Brosius.

Goraya noted further benefits to those who received fruits and vegetables: a beneficial lifestyle change and weight loss. "They mainly received potatoes and raisins, which are relatively inexpensive, and it was easy for the participants to follow the diet and incorporate these changes." The potato is the most alkali vegetable, and raisins, apples, and berries also have high alkali levels, she added. The study's benefits weren't limited to study participants because of a novel intervention mechanism: individuals received their fruits and vegetables at a local food bank and were provided enough for their entire family. In addition, "patients were followed for risk of potassium increases at serial 4 weekly intervals and no additional hyperkalemia risk was noted," she said. Of note, the study population excluded diabetics and patients with potassium >4.6 mEq/L at baseline.

Can improved nutrition help reduce the effects of health disparities in these at-risk populations for developing CKD? Brosius says that these studies suggest that it might. "The implication of these studies, which have yet to be validated by other studies, is that the kind of diet that these studies recommend—high in fruits and vegetables and lower in animal protein and fat and lower in sodium—will in the long run have a significant impact on the outcome of patients who are at highest risk and live in poverty situations, and will mitigate some of that risk."

Brosius cautions that physicians need to be aware of potassium levels, to ensure they don't become elevated in patients with CKD, especially. "These are high-potassium diets and that's the only risk associated with them, although it is a relatively modest one. These studies suggest that nutrition could possibly help in ameliorating the disparities in health care that individuals in poverty face," which he concludes is "potentially a very positive low-cost intervention that may help long-term outcomes."

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Celebrating 10 Years of the Physician Charter on Medical Professionalism

The American Board of Internal Medicine (ABIM) Foundation joined the American College of Physicians (ACP) Foundation and the European Federation of Internal Medicine in 2002 to produce "Medical Professionalism in the New Millennium: A Physician Charter." Translated into 12 languages, the "Physician Charter" has been endorsed by more than 130 organizations worldwide, including ASN, during the past decade.

The medical profession faces a proliferation of technology, fluctuating market forces, health care delivery challenges, and globalization, the Physician Charter observed 10 years ago. "As a result, physicians find it increasingly difficult to meet their responsibilities to patients and society," stated the charter. "In these circumstances, reaffirming the fundamental and universal principles and values of medical professionalism, which remain ideals to be pursued by all physicians, becomes all the more important."

As a guide to help physicians understand their professional responsibilities to individual patients and society as a whole, the charter focuses on three fundamental principles:

- Primacy of Patient Welfare. "The principle is based on a dedication to serving the interest of the patient. Altruism contributes to the trust that is central to the physician-patient relationship. Market forces, societal pressures, and administrative exigencies must not compromise this principle."
- Patient Autonomy. "Physicians must have respect for patient autonomy. Physicians must be honest with their patients and empower them to make informed decisions about their treatment. Patients' decisions about their care must be paramount, as long as those decisions are in keeping with ethical practice and do not lead to demands for inappropriate care."
- Social Justice. "The medical profession must promote justice in the health care system, including the fair distribution of health care resources. Physicians should work actively to eliminate discrimination in health care, whether based on race, gender, socioeconomic status, ethnicity, religion, or any other social category."

"For the past 10 years, the Physician Charter has provided a framework for ensuring the personal commitment of physicians to their patients as well as our collective effort to improve health care and benefit society," said Donald E. Wesson, MD, FASN, who chairs the ABIM Foundation Board of Trustees. "Together, medical professionals, including nephrologists, and society must clearly understand the principles and responsibilities of medical professionalism," added Dr. Wesson, who also serves as ASN Secretary-Treasurer. More than any external incentives or disincentives, according to Dr. Wesson, "actions driven by values internal to physicians, outlined in the Physician Charter, will help us successfully navigate through the crises facing modern medicine to improved and maintained health of the public that we have the privilege to serve."

Commitment to medical professionalism

The Physician Charter articulates 10 professional commitments of physicians and health care professionals, including improving access to high quality health care, advocating for a just and cost-effective distribution of finite resources, and maintaining trust by managing conflicts of interest. The charter also includes a "commitment to professional competence" that states: "Physicians must be committed to lifelong learning and be responsible for maintaining the medical knowledge and clinical and team skills necessary for the provision of quality care."

"ASN contributes to this commitment to professional competence by helping ABIM develop practice improvement modules, offering the Board Review Course and Update, producing the Nephrology Self-Assessment Program (NephSAP), and providing opportunities for continuing education credits to physicians and other health professionals," said ASN President Bruce A. Molitoris, MD, FASN. "Helping nephrologists maintain professional competence is core to ASN's mission."

Dr. Wesson noted that several of the challenges to medical professionalism the Physician Charter identified still remain present 10 years later: "We need to address growing disparities among the legitimate needs of patients, bolster available resources to meet those needs, harness the power of market forces to transform health care systems, and help physicians maintain their traditional commitment to the primacy of patients' interests."

Since 1999, the ABIM Foundation has been "working towards improving health care through the advancement of medical professionalism." To accomplish this goal, the foundation promotes "organizational and policy forces to advance professional values and behaviors," learns from international comparisons, engages physicians in advancing care, and supports new competencies to improve quality.

What is your reaction to "Medical Professionalism in the New Millennium: A Physician Charter"? How is the Physician Charter still relevant today? How do you teach medical students, residents, fellows, and other trainees about professionalism? If you could provide one suggestion for strengthening the charter on its 10th anniversary, what would you recommend? Please email your feedback about the charter to communications@asn-online.org. Thank you.

For example, the ABIM Foundation partnered with *Consumer Reports* and nine specialty societies, including ASN, on April 4, 2012, to launch the "Choosing Wisely Campaign." Each society identified "Five Things Physicians and Patients Should Question" to help initiate conversations between physicians and patients about the actual need for many frequently ordered tests or treatments. ASN's contribution to the "Choosing Wisely Campaign" is available at http://www.asn-online.org/policy/choosing-wisely/. More than 20 societies are scheduled to join the campaign in 2013.

To learn more about "Medical Professionalism in the New Millennium: A Physician Charter" or the ABIM Foundation, please visit http://www.abim-foundation.org/.

Policy Update

Medicare Announces Changes to ESRD Program for 2013 and Beyond

By Rachel Shaffer

The Centers for Medicare and Medicaid Services (CMS) announced final plans for modifications to the End-Stage Renal Disease (ESRD) Program. The payment-related revisions set forth in its rulemaking will affect the ESRD Prospective Payment System (PPS) beginning in 2013, and quality-related changes will affect the ESRD Quality Incentive Program (QIP) in 2014, 2015, and beyond.

ASN was among the 55 commenters that submitted input to CMS regarding its preliminary proposals for changes to the ESRD PPS and QIP during the summer of 2012. The majority of ASN's feedback focused on how CMS's proposed alterations related to the QIP might affect patient access to the highest quality dialysis care—and many, though not all, of the society's recommendations were reflected in CMS's November final rule. "We appreciate that CMS responded to several of our key concerns in this rulemaking cycle," stated ASN Public Policy Board Chair Thomas H. Hostetter, MD, "and we look forward to continuing to work with the agency in the coming months and years to shape a QIP program constituting not only measures that ensure a minimum standard of care, but measures that catalyze improvement in meaningful patient outcomes."

Mineral Metabolism Reporting Requirements for Payment Year 2014

One of the key ASN recommendations that CMS adopted in the final rule was that facilities should exclude patients who received fewer than seven dialysis sessions in a month from QIP data reporting for the mineral metabolism measure that month. CMS originally proposed that data from patients receiving just two sessions should be included in QIP data reporting, but ultimately concurred with ASN—and other commenters—that treating a patient twice may not provide enough time to ensure (or assess) high-quality patient outcomes. Similarly, CMS responded to concerns that requiring facilities to obtain and report data for patients who received dialysis treatments in other environments may be overly burdensome and not accurately reflect patient care provided in the facility. In the final rule, CMS stated that it recognizes "it may be difficult for facilities to coordinate with hospitals and other care providers in order to obtain lab values" and would not require reporting for those patients.

Home Dialysis

ASN urged CMS to ensure, to the extent possible, that all QIP measures include patients who dialyze via peritoneal dialysis or home hemodialysis (HHD). The society specifically recommended expanding the existing National Health Safety Network infection reporting measure to PD and HHD patients. While CMS did not implement the recommendation, it stated that it "will take these suggestions into consideration during future measure development and rulemaking." Notably, CMS did integrate a peritoneal dialysis measure into the composite dialysis adequacy measure for the QIP in 2015. ASN will continue to advocate for equitable, evidence-based QIP measures that apply to patients who dialyze at home.

Additions and Changes to QIP Measures for 2015

CMS finalized that, parallel to previous years, it will use all of calendar year (CY) 2013 as the performance period for payment year (PY) 2015. In 2015, CMS will continue to use five of the six QIP measures from PY 2014, but made changes to two measures and added four new ones:

- Clinical Measure for Dialysis Adequacy, a composite of three measures:
  - o Hemodialysis Adequacy Minimum Delivered Dose (NQF # 0249)
  - o Peritoneal Dialysis Adequacy Delivered Dose Above Minimum (NQF #0318)
  - o Minimim spKt/V for Pediatric Hemodialysis Patients (NQF #1423)
- Anemia Management Reporting Measure

In 2011, the U.S. Food and Drug Administration changed the erythropoiesis stimulating agent (ESA) label, removing the recommended hemoglobin level of 10–12 g/dL, stating it could not identify a minimum safe target. CMS followed suit by eliminating a QIP measure ensuring a minimum hemoglobin level of 10 g/dL. Since then, many in the nephrology community have been concerned about potential for compromised patient access to ESA therapy or increased transfusions to treat anemia.

CMS acknowledged these concerns in its November ruling. While it recognized that there has been a slight but noticeable increase in transfusion rates since FDA and PPS modifications, the agency noted that any possible associations between the changes "are not yet known." CMS explained that it is "working through our ESRD QIP monitoring and evaluation program to further assess the effects of the ESRD PPS." Moreover, CMS finalized its proposal to implement an Anemia Management Reporting Measure, requiring facilities to report ESA dosage (if applicable) and hemoglobin/hematocrit values on at least one monthly claim. Similar to the mineral metabolism reporting measure for 2014, and in alignment with recommendations from ASN and others, CMS determined that it would exclude any patient who is treated by a facility fewer than seven times in the reporting month.

Addressing ASN's most significant concern, CMS did not finalize a proposed clinical hypercalcemia measure. Citing, and agreeing, with commenters that the performance standards, benchmarks, and achievement thresholds were not calculated using data from all facilities—and could therefore contain a systemic bias—CMS determined not to require reporting for the measure. ASN's concerns stemmed from the fact that insufficient evidence exists to support the proposed serum calcium and serum phosphorus targets. CMS stated that it "intend[s] to use this measure in subsequent payment years." However, ASN will continue to strongly urge CMS not to implement this or other measures incentivizing providers to achieve performance targets that have not been scientifically validated.

In addition to the four new measures, CMS finalized its proposals to modify the National Health Safety Network Dialysis Event Reporting Measure (implementing more frequent reporting) and finalized the PY 2014 exclusions for the Mineral Metabolism measure for 2015 and beyond.

Future QIP Years

Looking ahead to future years of an expanded QIP, CMS requested comment on potential Standardized Hospitalization Ration (SHR) for Admissions, a Risk-Adjusted Standardized Mortality Ratio (SMR), and a 30-day Hospital Readmission measure. In the final rule, CMS stated that most commenters—including ASN—"strongly opposed" the SHR and SMR measures, given that it is "a measure over which facilities have little control" and due to concerns that SMR could promote cherry-picking patients. While CMS did not finalize any of these measures as part of the QIP at this time, it will be reporting SHR and SMR via the Dialysis Facility Compare Website.

In the coming months, ASN will be working with CMS and the greater kidney community to ensure that subsequent additions to the QIP are appropriate and evidence-based, and critically important, to ensure that the impending addition of oral-only drugs to the PPS bundle is fair and maintains patient access. Read more about ASN's comments to CMS about the ESRD program online at www.asn-online.org/policy, and stay tuned to *Kidney News* in 2013.

Innovators Place Unveiled at Kidney Week 2012

Among the new features introduced at Kidney Week 2012 in San Diego was Innovators Place: a dedicated space to exhibit medical technologies not yet approved by the U.S. Food and Drug Administration (FDA). Inaugural exhibitors were selected by an ASN committee based on a set of criteria including the technology's relevance to curing kidney disease and the exhibit's educational value for Kidney Week attendees.

The exhibitors—mostly U.S. and European start-up companies, as well as nonprofit academic labs—presented innovations ranging from a benchtop instrument for early detection of severe acute kidney injury (AKI) to a compression device to reduce postdialysis clotting time. For most participants, Innovators Place provided an opportunity to secure potential partners and investors.

One exception was Semprus Biosciences, which was acquired 5 months before Kidney Week 2012 by Teleflex, Inc., and whose vascular access catheter received 501(k) clearance from the FDA 2 weeks after the meeting. Designed to reduce thrombus accumulation inside and outside the device, the catheter was exhibited at Innovators Place to generate awareness of the new technology, according to a Semprus Biosciences representative. Based on biomaterial discoveries by Robert Langer, ScD, of the Massachusetts Institute of Technology, the catheter received European market clearance in July 2012.

Other exhibitors presented innovations that are in the early stages of development. Joris Rotmans, MD, PhD, from the Leiden University Medical Center (LUMC) in the Netherlands

said that he and his colleagues are searching for a commercial partner for the joint preclinical and clinical development of the Dutch group's new technique for generating in vivo tissue–engineered blood vessels for hemodialysis vascular access. He noted the technique was developed at LUMC labs as part of the DialysisXS consortium, a research collaboration with the University of Twente in the Netherlands, the Dutch Kidney Foundation, and the Swiss biotech firm Xeltis.

Also searching for partners is the French nephrologist Mokhtar Chawki, MD, founder of the Nephrokit compressive device named IRIS, which is designed to reduce the postdialysis time to clot by securing dialysis needle vascular access puncture sites. The device speeds up coagulation time from 10.5 minutes, the average duration for conventional techniques, to 2 to 3 minutes, said Chawki. Nephrokit already has a nonexclusive agreement for IRIS distribution with Bellco in France and Belgium and Gambro in France, and the device is also sold in dialysis kits by Mölnylcke Health Care in Europe, he said.

At an adjacent Innovators Place booth, several nephrologists from the Henry Ford Health System in Detroit presented their universal regional citrate anticoagulation (RCA). Balazs Szamosfalvi, MD, said that he and his fellow nephrologists designed the sustained low-efficiency dialysis (SLED)-RCA technology to provide 100 percent–effective RCA with automated delivery using integrated intravenous pumps and optical blood and dialyzer effluent sensing. It can be adapted to most commercial renal replacement therapy devices with a customized RCA protocol and dialysis machine data interface program, Szamosfalvi said. In over 50,000 hours of clinical use, the technology prevented systematic citrate accumulation in patients with severe liver failure, and predictive-calcium infusion dosing maintains normal systematic ionized calcium levels, according to the display material.

Another Innovators Place participant was FAST BioMedical, whose cofounders include ASN President Bruce A. Molitoris, MD, FASN, of Indiana University. The Indianapolis medical device company has developed a small, durable bedside device to accurately measure GFR in approximately 40 minutes, based on technology licensed from Indiana University, said co-founder and president James Strickland. Over 30 clinical trials of FAST (Filtration Assessment and Surveillance Technology) have been conducted in Europe, Strickland said.

Argutus Medical of Dublin, Ireland, likely demonstrated the most professional marketing display at Innovators Place, where visitors learned about RenaStat, a new point of care test benchtop device for early detection of AKI in critical care requiring 100 µL of patient urine. Argutus Medical also provided scientific information about the development and use of biomarkers for AKI detection.

Journal View

Age Interacts with Kidney Measures on Mortality Risk

Although effects on relative versus absolute risk differ, low estimated glomerular filtration rate (eGFR) and high albuminuria are linked to increased mortality in all age groups, reports a study in *The Journal of the American Medical Association*.

The meta-analysis examined whether age modified the associations of eGFR and albuminuria with clinical outcomes. The investigators pooled individual-level data on more than 2 million members of Chronic Kidney Disease Prognosis Consortium (CKD-PC) cohorts. The data included 33 non-kidney disease cohorts (general population or people at high vascular disease risk) and 13 CKD cohorts. Clinical associations with eGFR and albuminuria were examined across age groups, with adjustment for other risks.

In non-CKD cohorts, individuals with lower eGFR and higher albuminuria were at higher risk of death and end stage renal disease (ESRD). At an eGFR of 45 mL/min/1.73 m^2 (versus 80 mL/min/1.73 m^2), the adjusted hazard ratio for death decreased with age: from 3.50 for people aged 18 to 54 years, to 2.21 at 55 to 64 years, 1.59 for 65 to 74 years, and 1.35 at 75 years or older. In contrast, absolute risk increased with age: excess deaths per 1000 person-years were 9.0, 12.2, 13.3, and 27.2, respectively.

The absolute risk of death associated with higher levels of albuminuria also increased with age. At an albumin-creatinine ratio of 300 mg/g (versus 10 mg/g), excess mortality per 1000 person years was 7.5 at 18 to 54 years, 12.2 per 1000 at 55 to 64 years, 22.7 per 1000 at 65 to 74 years, and 34.3 per 1000 at age 75 or older.

The CKD cohorts showed no age-related decrease in the adjusted relative hazards of mortality. For all cohorts, the relative risks of ESRD and the absolute risk differences associated with both kidney markers were similar across age groups.

It has been suggested that the CKD classification system should be revised to include a combination of eGFR and albuminuria levels. Before this is done, it is important to understand how age affects the clinical risks associated with these measures.

This meta-analysis finds that low eGFR and high albuminuria affect mortality risk in all age groups, across a wide range of populations. At older ages, the relative risk is lower but the absolute risk differences are higher. The researchers call for "a common definition and staging of CKD based on eGFR and albuminuria for all age groups" [Hallan SI, et al: Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*. 2012; doi:10.1001/jama.2012.16817].

Industry Spotlight

Trials for Best Ways to Treat Non-Dialysis–Dependent CKD

The search for effective treatments for non-dialysis–dependent chronic kidney disease (NDD-CKD) is gaining renewed interest. In the United States, more than one and a half million people suffering from stages 3 to 5 non-dialysis dependent NDD-CKD have iron deficiency anemia, but no oral iron supplements have yet been approved by the FDA for use for the condition. Likewise, no FDA-approved phosphate binders exist for use in NDD-CKD.

The federal government issued a request for application (RFA) for CKD clinical trials that closed on Nov. 21. That RFA sought pilot studies that optimize critical elements of a full-scale, randomized controlled trial design in return for U01 grant funding. The National Institute of Diabetes and Digestive and Kidney Diseases noted in its RFA that studies to date have looked at treatments and effects in small groups of patients, and that many questions remain regarding optimal dosing and drugs' ability to reach appropriate patient outcomes.

One new NDD-CKD study that builds on earlier work was announced in early November. Keryx Biopharmaceuticals said that it had started a phase 2 study of its drug Zerenex (ferric citrate) for the treatment of patients with stage 3 to stage 5 non-dialysis dependent chronic kidney disease.

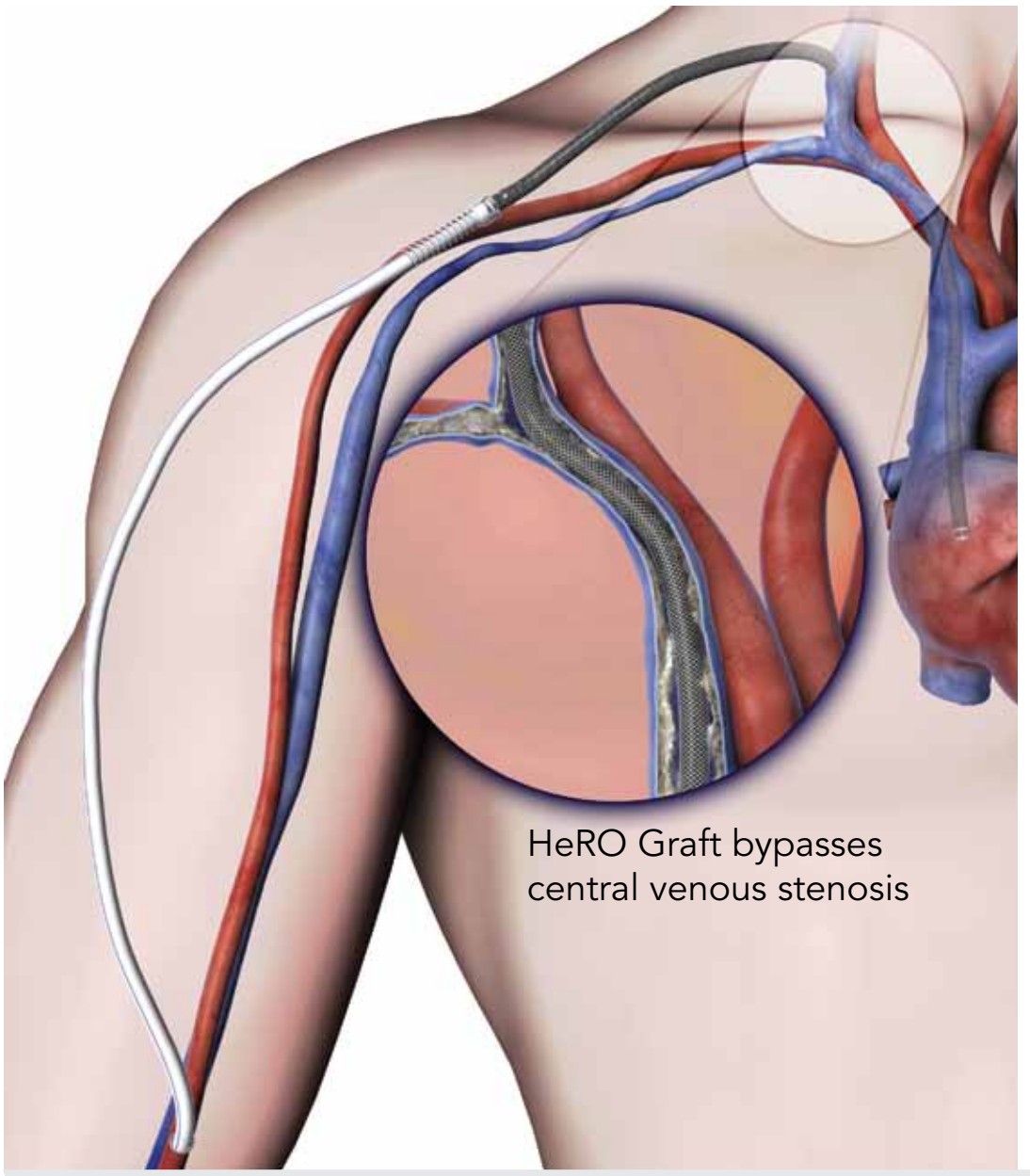
Zerenex is a ferric iron–based phosphate binder drug candidate for managing serum phosphorus and iron deficiency in anemic patients with NDD-CKD.

Several studies have shown that higher serum phosphorus concentrations may be associated with increased mortality and morbidity in CKD.

The phase 2 study will be a multicenter, randomized, safety and efficacy clinical trial designed to compare the ability of Zerenex to manage serum phosphorus and iron deficiency versus placebo in anemic patients. Eligible patients will be randomized in similar groups to receive either Zerenex or placebo for a 12-week treatment period.

The primary endpoints of the study are designed to demonstrate changes in ferritin, transferrin saturation (the ratio of serum iron and total iron-binding capacity), and serum phosphorus levels over the 12-week treatment period.

The study plans to randomize about 150 patients from about 15 sites in the United States. Patient enrollment should take about six months, and Keryx expects the study to wrap up in mid-2013.



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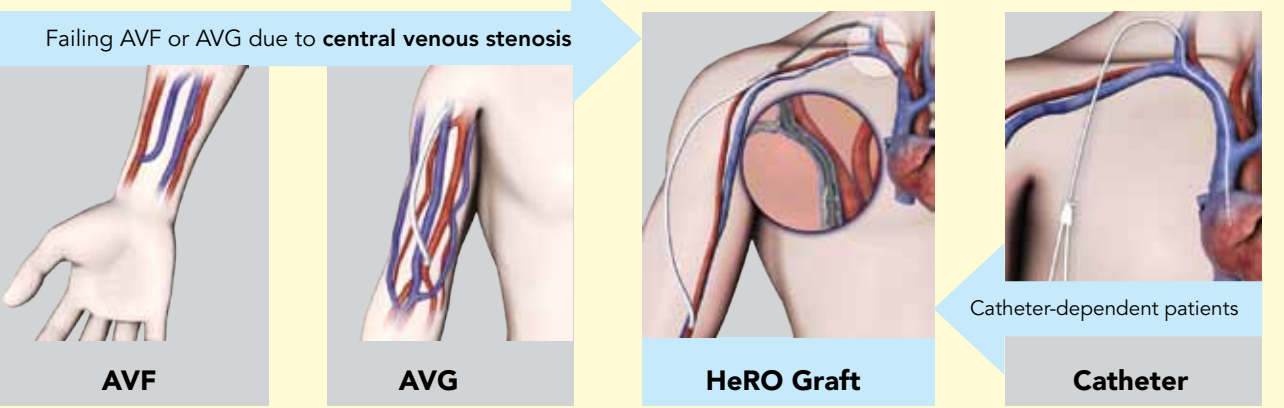

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References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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