

The global role of kidney transplantation

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INTRODUCTION

Kidney transplantation is acknowledged as a major advance of modern medicine which provides high-quality life years to patients with irreversible kidney failure (end-stage renal disease, ESRD) worldwide. What was an experimental, risky and very limited treatment option fifty years ago, is now routine clinical practice in more than 80 countries. What was once limited to a few individuals in a small number of leading academic centers in high income economies, is now transforming lives as a routine procedure in most high- and middle-income countries – but can do much more. The largest numbers of transplants are performed in the USA, China, Brazil and India, while the greatest population access to transplantation is in Austria, USA, Croatia, Norway, Portugal and Spain. There are still many limitations in access to transplantation across the globe. World Kidney Day on March 8th 2012 will bring focus to the tremendous life-changing potential of kidney transplantation as a challenge to politicians, corporations, charitable organizations and healthcare professionals. This commentary raises awareness of the progressive success of organ transplantation, highlight concerns about restricted community access and human organ trafficking and commercialism, while also exploring the real potential for transforming kidney transplantation into the routine treatment option for ESRD across the world.

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OUTCOMES OF KIDNEY TRANSPLANTATION

The first successful organ transplantation is widely acknowledged to be a kidney transplant between identical twins performed in Boston on 23rd Dec 1954 which heralded the start of a new era for patients with ESRD¹.

In the development years between 1965 and 1980, patient survival progressively improved towards 90% and graft survival rose from less than 50% at one year to at least 60% after a first deceased donor kidney transplant, based on immunosuppression with azathioprine and prednisolone. The introduction of ciclosporin in the mid 1980s was a major advance, leading to one year survival rates of more than 90% and graft survival of 80%². In the last 20 years, better understanding of the benefits of combined immunosuppressant drugs coupled with improved organ matching and preservation, as well as chemoprophylaxis of opportunistic infections, have all contributed to a progressive improvement in clinical outcomes. Unsensitised recipients of first deceased donor kidney transplants and living donor recipients can now expect 1-year patient and transplant survival to be at least 95% and 90% respectively.¹ New developments have led several groups to report excellent results even from carefully selected ABO Blood group incompatible transplants in recipients with low titre ABO-antibodies³. Even for those with high titres of donor specific HLA-antibodies, who were previously ‘untransplantable, better de-sensitisation protocols⁴ and paired kidney exchange programs⁵ now afford real opportunities for successful transplantation.

Group members:

World Kidney Day (WKD) is a joint initiative of the International Society of Nephrology and the International Federations of Kidney Foundations.

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Ethnic minorities and disadvantaged populations continue to suffer worse outcomes; Aboriginal Canadians, for example, have lower 10-year patient (50% vs 75%) and graft (26% vs 47%) survival compared with white patients.⁶ African American kidney transplant recipients have shorter graft survival compared to Asian, Hispanic, and White populations in the United States of America.⁷ In New Zealand, Maori and Pacific Island recipients of deceased donor transplants have a 50% 8-year graft survival compared to 14 years for non-indigenous recipients, in part due to differences in mortality.⁸ By contrast, despite a resource poor environment, Rizvi et al report 1 and 5-year survival rates of 92% and 85%, respectively, among 2,249 living related kidney transplants in Pakistan,⁹ whilst in Mexico, 90% and 80% one-year survival for living and deceased donor kidney transplants, was reported among 1,356 transplants performed at a single centre.¹⁰ But, while it is possible to achieve such excellent long-term results, most patients and their families in resource poor environments are not able to afford the high cost immunosuppressants and antiviral medications needed to reduce the risk of graft loss and mortality.¹¹

THE PLACE OF KIDNEY TRANSPLANTATION IN TREATMENT FOR ESRD

Kidney transplantation improves long-term survival compared to maintenance dialysis. In 46,164 patients on the transplant waiting list in the USA between 1991-1997, mortality was 68% lower for transplant recipients than for those remaining on the transplant waiting list after >3 yrs follow-up.¹² The transplanted 20-39 year old patients of both sexes were predicted to live 17 years longer than those remaining on the transplant waiting list, an effect that was even more marked in diabetics.

The number of people known to have ESRD worldwide is growing rapidly, as a result of improved diagnostic capabilities and also the global epidemic of type 2 diabetes and other causes of chronic kidney disease (CKD). Dialysis costs are expensive even for developed countries, but prohibitive for many emerging economies. The majority of patients commencing dialysis for ESRD in low-income countries die or stop treatment within the first 3 months of initiating dialysis due to cost restraints.¹³ The cost of maintenance hemodialysis varies considerably by country and healthcare system. In Pakistan maintenance hemodialysis reported to be US\$1680 per year, which is beyond the reach of most of the population without humanitarian financial aid.¹⁴ Despite exemplars, both provision of hemodialysis facilities and uptake of peritoneal dialysis remain very limited in middle and low-income countries. Whilst the costs of transplantation exceed those of maintenance dialysis in the first year post-transplantation (eg. in Pakistan US\$5245 vs US\$1680 in the first year), the costs are much reduced compared to dialysis in subsequent

years, especially with the advent of inexpensive generic immunosuppression.¹⁵ Transplantation thus expands access and reduces overall costs for successful treatment of ESRD.

Pre-emptive transplantation is an attractive option for both patients and payers with both reduced costs and improved graft survival.¹⁶ Pre-emptive transplantation is associated with a 25% reduction in transplant failure and 16% reduction in mortality compared to recipients receiving a transplant after starting dialysis.¹⁷

Transplantation of the kidney, when properly applied, is thus the treatment of choice for patients with ESRD because of lower costs and better outcomes.

GLOBAL DISPARITIES IN ACCESS TO KIDNEY TRANSPLANTATION

Substantial disparities in access to transplantation across the world are demonstrated in Figure 1 (derived from the World Health Organisation/Organisation Mondiale de la Sante (WHO/OMS) Global Observatory on Donation and Transplantation.¹⁸) which demonstrates the relationship between transplant rate and Human Development Index (HDI). There is a reduced transplant rate in low and middle HDI countries, and a large spread of transplant rates even amongst the richer nations. Transplant rates of more than 30 per million population (pmp) in 2010 were restricted to Western Europe, USA, and Australia, with a slightly broader spread of countries achieving between 20 and 30 pmp.

There are also within-country disparities in transplant rates among minorities and other disadvantaged populations. In Canada, all minority groups have significantly lower transplant rates; compared to whites, rates in Aboriginal and African Canadians, Indo Asians, and East Asians were 46%, 34%, and 31% lower respectively.¹⁹ In the US, transplantation rates are significantly lower among African-Americans, women, and the poor, compared to Caucasians, men and the more affluent populations.²⁰ The situation is similar in Australia where Aboriginal Australians fare worse than non-indigenous Australians (12% vs 45%) and in New Zealand where Maori/Pacific Islanders are disadvantaged (14% vs 53%).²¹ In Mexico, the transplant rate among uninsured patients is 7 pmp compared with 72 pmp among those with health insurance.²²

Multiple immunologic and non-immunologic factors contribute to social, cultural, and economic disparities in transplant outcomes, including biological, immune, genetic, metabolic, and pharmacological factors as well as associated co-morbidities, time on dialysis, donor and organ characteristics, patient socio-economic status, medication adherence, access to care, and public health policies.²³ Developing countries often have especially poor transplant

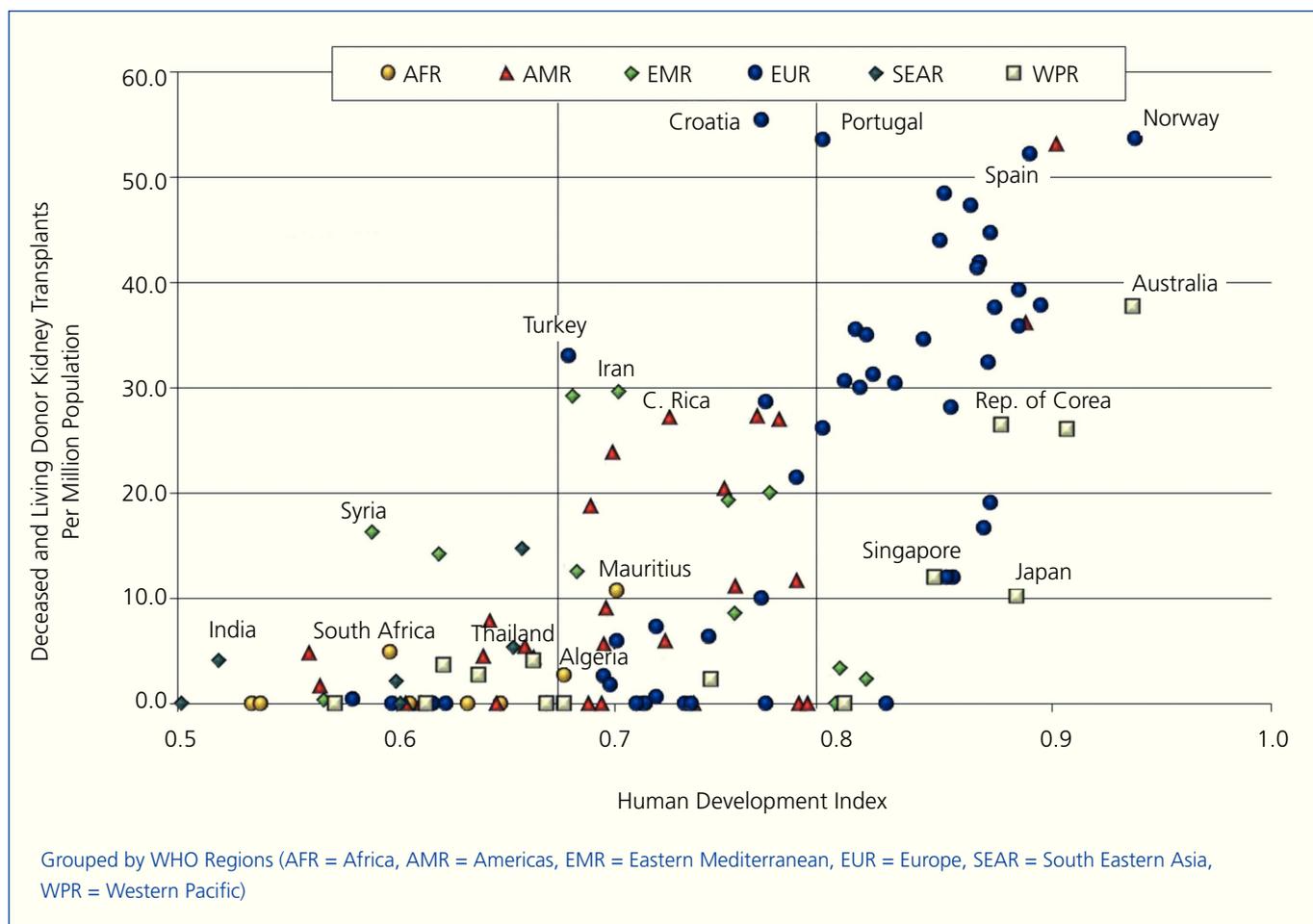
rates not only because of these multiple interacting factors, but also because of inferior infrastructure and an insufficient trained workforce. Deceased donation rates may also be impacted by lack of a legal framework governing brain death and by religious, cultural and social constraints. When these factors are all compounded by patient anxieties about the success of transplantation, physician bias, commercial incentives favoring dialysis and geographical remoteness, poor access to transplantation is almost inevitable for most of the world's population.

IMPROVING ACCESS TO TRANSPLANTATION

Both living donation and deceased donor donation are now recognized by the WHO as critical to the capacity of nations to develop self-sufficiency for organ transplantation.²⁴ No country in the world, however, generates sufficient organs from these sources to meet the needs of their citizens. Austria, USA, Croatia, Norway, Portugal and Spain stand out as countries with high rates of

deceased organ donors, and most developed countries are trying to emulate their success. A return to 'donation after cardiac death' instead of the now standard 'donation after brain death', has enhanced the deceased organ donation numbers in several countries, with 2.8 DCD donors pmp in the US and 1.1 pmp in Australia now emanating from this source. Protocols for rapid cooling and urgent retrieval of kidneys after cardiac death, and in some circumstances other organs, have developed over the past five years to reduce the duration and consequences of warm ischaemia.²⁵ Another strategy for increasing the rate of transplantation has been to extend the acceptance criteria for deceased organ donors. Such 'extended criteria' donors require additional consideration and specific consent by the recipient. There is risk in accepting an 'extended criteria' kidney since the transplants are less successful in the long term, but also a risk to waiting longer on dialysis for a standard criteria donor.

A number of strategies have been designed and implemented to reduce disparities among disadvantaged populations. The



Transplantation Society has established the Global Alliance for Transplantation in an effort to reduce worldwide disparities in transplantation. The program includes collecting global information, expanding education about transplantation, and developing guidelines for organ donation and transplantation. The International Society of Nephrology (ISN) Global Outreach program has catalysed the development of kidney transplant programs across a large number of countries with targeted fellowship training and creation of long term institutional links between developed and developing transplant centers through its Sister Center Program. This has led to the establishment of successful kidney transplantation in countries such as Armenia, Ghana and Nigeria where none existed before and expansion of existing programs in Belarus, Lithuania and Tunisia.

A model of collaboration for dialysis and transplantation between government and the community in the resource poor world has been successfully established in Pakistan with government assistance for infrastructure, utilities, equipment, and up to 50% of the operating budget, while the community, including affluent individuals, corporations and the public, donate the remainder.¹⁴ In 2001, in Central America, a specialized unit of pediatric nephrology and urology was opened in Nicaragua with funds provided initially by the Associazione per il Bambino Nefropatico, a kidney foundation based in Milan, Italy supplemented by a consortium of private and public organizations, including the International Pediatric Nephrology Association and the Nicaraguan Ministry of Health. Subsequently the Nicaraguan government and a local kidney foundation recognized the success of the program and accepted gradual transfer of the costs of treatment, including the provision of immunosuppressive medications for renal transplantation. A similar successful partnership between government and private sector has recently been reported in India.²⁶

There are tremendous opportunities to correct disparities in kidney disease and transplantation worldwide, but it is important to recognize that funding of ESRD treatment should be associated with funding for early detection and prevention of the progressive kidney diseases that lead to ESRD. Comprehensive programs should include community screening and prevention of CKD, especially in high-risk populations, as well as dialysis and transplantation for ESRD.

An integrated approach to the expansion of transplantation requires training programs for nephrologists, transplant surgeons, nursing staff, and donor coordinators; nationally funded organ procurement organizations providing transparent and equitable retrieval and allocation; and the establishment of national ESRD registries.

ETHICAL CHALLENGES AND THE LEGAL ENVIRONMENT

The impact of the global organ donor shortage and the dramatic disparities demonstrated by the WHO data, are experienced in many different ways requiring varied responses. But one common factor is the relative wealth of the nation and the individual. The poor receive the fewest transplants and the rich are most often transplanted either in their own country or through finding an organ through illegal purchase from the poor or an executed prisoner. Trafficking in human organs and commercialisation of the beneficial act of organ donation were unusual and extremely hazardous in the 1980's, became frequent but still very hazardous in the 1990's, then becoming a gruesomely burgeoning trade from the turn of the century. The WHO has estimated that up to 10% of all organ transplants were of commercial origin by 2005.²⁷

The first WHO Guiding Principles in this field were agreed in 1991 and made clear by the decision of national governments to ban commercialization of organ donation and transplantation.²⁸ This principle was reaffirmed unanimously by the World Health Assembly in 2010 when the updated WHO Guiding Principles for human organ and tissue donation and transplantation, were endorsed.²⁹ Almost all countries with transplantation programs and even some without active programs have carried that ban on commercialism through to their own legislation, making it illegal to buy or sell organs. Sadly this has not prevented continuation of the trade illegally in countries such as China and Pakistan, nor has it prevented new entrants to this lucrative trade from taking advantage of their own or other nations' impoverished and vulnerable populations to provide kidneys and even livers for the desperate wealthy in need of transplantation.

Iran, alone, claims to have resolved national self sufficiency for kidney transplantation through a scheme of part government, part patient-funded sale of kidneys by vendors. The resultant slow development of deceased organ donation in Iran restricting liver, heart and lung transplant programs, as well as the disparity of socioeconomic status between donors and recipients, both testify to the universality of the problems that arise from organ transplant commercialisation. The restriction of transplantation to Iranian nationals only under this program has however largely ensured that this national experiment has not flowed on to create commercial organ trafficking across Iranian national borders.

The Transplantation Society and the ISN have taken a joint stand against the despoiling of transplantation therapy and victimization of the poor and vulnerable by doctors and other providers operating in these illegal programs. In 2008, more than 150 representatives from across the world from different disciplines of health care, national policy

development, law and ethics came together in Istanbul to discuss and define professional principles and standards for organ transplantation. The resultant Declaration of Istanbul³⁰ has now been endorsed by more than 110 professional and governmental organizations and implemented by many of these organizations with a goal to eliminate transplant tourism and enhance the ethical practice of transplantation globally.³¹

SUMMARY

There remain major challenges to providing optimal treatment for ESRD worldwide and a need, particularly in low income economies, to mandate more focus on community screening and implementation of simple measures to minimize progression of CKD. The recent designation of renal disease as an important non-communicable disease at the UN High Level Meeting on NCDs is one step in this direction.³² But early detection and prevention programs will never prevent ESRD in everyone with CKD, and kidney transplantation is an essential, viable, cost-effective and life-saving therapy which should be equally available to all people in need. It may be the only tenable long-term treatment option for ESRD in low-income countries since it is both cheaper and provides a better outcome for patients than other treatment for ESRD. However, the success of transplantation has not been delivered evenly across the world, and substantial disparities still exist in access to transplantation, we remain troubled by commercialization of living donor transplantation and exploitation of vulnerable populations for profit.

There are solutions available. These include demonstrably successful models of kidney transplant programs in many developing countries; growing availability of less expensive generic immunosuppressive agents; improved clinical training opportunities; governmental and professional guidelines legislating prohibition of commercialization and defining professional standards of ethical practice; and a framework for each nation to develop self sufficiency in organ transplantation through focus on both living donation and especially nationally managed deceased organ donation programs. The ISN and TTS have pledged to work together in coordinated joint global outreach programs to help establish and grow appropriate kidney transplant programs in low and middle income countries utilizing their considerable joint expertise. World Kidney Day 2012 provides a focus to help spread this message to governments, all health authorities and communities across the world.

Conflicts of interest

Authors declare no potential Conflicts of interest.

REFERENCES

- Murray JE. Ronald Lee Herrick Memorial: June 15, 1931-December 27, 2010. *Am J Transplant* 2011;11(3):419.
- Clayton P, Excell L, Campbell S, McDonald S, Chadban S. Transplantation. In: McDonald S, Excell L, Livingston B (eds.). ANZDATA Registry Report 2010. Australia and New Zealand Dialysis and Transplant Registry. Adelaide, South Australia; p. 8.1-8.31. Available at <http://www.anzdata.org.au/anzdata/AnzdataReport/33rdReport/Ch08.pdf>. [Accessed nov 29, 2011].
- Shimmura H, Tanabe K, Ishida H, Tokumoto T, Ishikawa N, Miyamoto N, et al. Lack of correlation between results of ABO-incompatible living kidney transplantation and anti-ABO blood type antibody titers under our current immunosuppression. *Transplantation* 2005;80(7):985-8.
- Peng A, Vo A, Jordan SC. Transplantation of the highly human leukocyte antigen-sensitized patient: long-term outcomes and future directions. *Transplantation Reviews* 2006;20:46-156
- Warren DS, Montgomery RA. Incompatible kidney transplantation: lessons from a decade of desensitization and paired kidney exchange. *Immunol Res* 2010;47(1-3):257-64.
- Weber CLC, Rush DN, Jeffery JR, Cheang M, Karpinski ME. Kidney transplantation outcomes in Canadian aboriginals. *Am J Transplant* 2006;6:1882-9.
- Gordon EJ, Ladner DP, Caicedo JC, Franklin J. Disparities in kidney transplant outcomes: A review. *Semin Nephrol* 2010;30(1):81-9.
- Collins JF. Kidney disease in Maori and Pacific people in New Zealand. *Clin Nephrol* 2010;74:S61-S65.
- Rizvi SA, Naqvi SAA, Zafar MN, Hussain Z, Hashmi A, Hussain M, et al. Living related renal transplants with lifelong follow-up. A model for the developing world. *Clin Nephrol* 2010;74 Suppl 1:S142-9.
- Monteón FJ, Gómez B, Valdespino C, Chavez S, Sandoval M, Flores A, et al. The kidney transplant experience at Hospital de Especialidades, Centro Médico Nacional de Occidente, IMSS, Guadalajara México. In: Cecka JM, Terasaki P (eds.). *Clinical Transplants 2003*. Los Angeles: UCLA Immunogenetics Center; 2003. p. 165-74.
- Jha V. Current status of end-stage disease care in South Asia. *Ethn Dis* 2009 Spring;19(1 Suppl 1):S1-27-32.
- Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation and recipients of a first cadaveric transplant. *N Engl J Med* 1999;341:1725-30.
- Sakhuja V, Sud K. End-stage renal disease in India and Pakistan: Burden of disease and management issues. *Kidney Int Suppl* 2003;(83):S115-8.
- Rizvi SAH, Naqvi SAA, Zafar MN et al. A Renal Transplantation Model for developing countries. *Am J Transplant* 2011;11:2302-7.
- Sud K, et al. *Indian J of Nephrology* 1999;9:83-91.
- Meier-Kriesche HU, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes. *Transplantation* 2002;74(10):1377-81.
- Kasike BL, Snyder JJ, Matas MD, Ellison MD, Gill JS, Kausz AT. Pre-emptive kidney transplantation: The advantage and the advantaged. *J Am Soc Nephrol* 2002;13:1358-6.
- World Health Organization. Global Knowledge Base on Transplantation. Available at <http://www.who.int/transplantation/knowledge-base/en/>. [Accessed nov 29, 2011].

19. Yeates K. Health Disparities in renal disease in Canada. *Semin Nephrol* 2010;30:12-8.
20. Alexander GC, Sehgal AR. Barriers to cadaveric renal transplantation among blacks, women, and the poor. *JAMA* 1998;280:1148-52.
21. McDonald S. Incidence and treatment of ESRD among indigenous peoples of Australasia. *Clin Nephrol* 2010;74:suppl 1:S28-31.
22. Garcia-Garcia G, Renoirte-Lopez K, Marquez-Magaña I. Disparities in renal care in Jalisco, Mexico. *Semin Nephrol* 2010;30:3-7.
23. Gordon EJ, Ladner DP, Caicedo JC, Franklin J. Disparities in kidney transplant outcomes: A review. *Semin Nephrol* 2010;30:81-9.
24. 3rd Global WHO Consultation March 2010. Organ Donation and Transplantation: Striving to Achieve Self-Sufficiency. *Transplantation* 2011;91 11S:S27-S114.
25. Bernat JJ, D'Alesandro AM, Port FK, Bleck TP, Heard SO, Medina J, et al. Report of a National conference on donation after cardiac death. *Am J Transplant* 2006;6:281-91.
26. Abraham G, John GT, Sunil S, Fernando EM, Reddy YNV. Evolution of renal transplantation in India over the last four decades. *NDT Plus* 2010;3:203-7.
27. Shimazono Y. The state of the international organ trade: a provisional picture based on integration of available information. *Bull World Health Organ* 2007;85(12):955-62.
28. World Health Organization. Forty-fourth World Health Assembly, resolution and decisions. Geneva, Switzerland: World Health Organization; 1991 (WHA 44/1991/REC/1). Annex 6.
29. World Health Organization. Sixty-third World Health Assembly. Geneva, Switzerland: World Health Organization; 2010. Available at: http://www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf. [Accessed nov 29, 2011].
30. Participants in the International Summit on Transplant Tourism and Organ Trafficking Convened by the Transplantation Society and International Society of Nephrology in Istanbul, Turkey, April 30-May 2, 2008. The Declaration of Istanbul on organ trafficking and transplant tourism. *Transplantation* 2008;86(8):1013-8.
31. Delmonico FL, Domínguez-Gil B, Matesanz R, Noel L. A call for government accountability to achieve national self-sufficiency in organ donation and transplantation. *Lancet* 2011;378(9800):1414-8.
32. United Nations General Assembly. Political declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases A/66/L. 1, September 16, 2011.