TRANSPLANTATION !!!

Ethical Issues and Living Unrelated Donor Kidney Transplantation

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Keywords. kidney transplantation, ethics, tissue and organ procurement

During the past decades, the number of altruistic living unrelated kidney donations has substantially increased in developed countries. However, the altruistic supply of transplantable kidneys has remained much less than the demand. As a result, severe kidney shortage has been associated with increasing number of patient deaths and increasing number of commercial transplants and transplant tourism. Studies have shown that there is still a need for living kidney donation because even all potential braindead donors cannot supply the escalating need for kidneys. The use of living unrelated kidney donors should be morally and ethically justified and should be compatible with ethical principles. Many experts believe that increasing number of patient deaths and commercial transplants will continue to happen if kidney donation system remains merely altruistic. While some transplant professionals support a paid and regulated system to eliminate kidney shortage, others argue that it will be destructive. Iran has a 20-year experience with a compensated and regulated living unrelated kidney donation program. This transplantation model was adopted in 1988, and successfully eliminated kidney transplant waiting list by the end of 1999. Currently, more than 50% of patients with end-stage kidney disease in Iran are living with a functioning graft. This Iranian transplantation model has many ethical successes. However, because it has not been well regulated by transplant ethicists, some ethical shortcomings have remained. Unfortunately, due to lack of interest and expertise in health authorities, the number of serious ethical failures is also increasing in this transplantation model.

> IJKD 2009;3:183-91 www.ijkd.org



The ethical concerns about living kidney donation even from related donors were started from earliest days of kidney transplantation.¹ In 1964, Dr Francis D Moore, the surgeon-in-chief at the Peter Bent Brigham Hospital in Boston, mentioned in his article about new problems for surgery that "Thus, for the first time in the history of medicine,

a procedure is being adopted in which a perfectly healthy person is injured permanently in order to improve the well-being of another. Some laboratories have viewed this matter with such misgivings that under no circumstances have they used tissues from volunteer human donors.²" In addition to concerns about redefinition of an acceptable surgical procedure, there were also concerns about putting the donors at risk, their motivations for donation, and the validity of their consent when the life of

their loved one was in danger.^{3,4} However, during 1960s and 1970s, living related kidney donation for transplantation gradually became an accepted practice, mostly because maintenance dialysis was not available at that time and there were no effective alternative therapies for patients with end-stage kidney disease. It was also recognized that the motivation to save the life of a close relative is an admirable force, and the operative risk of unilateral nephrectomy for a healthy person is very low.^{5,6}

In 1980s and 1990s, the situation changed dramatically. Maintenance dialysis became increasingly available, and by introduction of new immunosuppressive drugs, the results of deceaseddonor kidney transplantation improved remarkably. As a result, even in the absence of a living related kidney donor, end-stage kidney disease was no longer considered to be equivalent to a "death sentence.7" In addition, a few postoperative donor deaths and some donor morbidities were reported.8 A few studies also raised concerns about longterm risk of unilateral nephrectomy.9 As a result of all these developments, the debate about using living kidney donors intensely reemerged such that some experts suggested this practice to be used only as a last option or not at all, 7,8,10 whereas some others continued to support living related kidney donation. 11-13 Currently, living related donor kidney transplantation is accepted ethically and it is carried out in a large scale all over the world.

LIVING UNRELATED DONATION History of Altruistic System

The use of living unrelated kidney donors for transplantation was also started from the earliest days of kidney transplantation (1960s and 1970s), but soon abandoned because of poor outcomes, as at that time, the results of such transplants were very similar to the results of deceased-donor kidney transplantation. 4,14,15 In addition, as many experts and ethicists raised strong ethical concerns about living unrelated donor's motivation and the risks involving the donor. Furthermore, as some commercial transplants and transplant tourism were reported from both developed and developing countries, living unrelated donor transplantation became almost ethically less and less acceptable worldwide.

In 1980s, advances in immunosuppressive therapy improved patient and graft survival rates,

and kidney transplantation became the treatment of choice for many patients with end-stage kidney disease. Unfortunately, the supply of transplantable kidneys remained much less than the demand. In 1983, Dr H Barry Jacobs, a US physician whose medical license had been revoked after conviction of Medicare mail fraud, founded the International Kidney Exchange Ltd. He sent a brochure to 7500 American hospitals offering a broker contracts between patients with end-stage kidney disease and persons willing to sell one of their kidneys. His intention was to buy kidneys from the "Third World" countries for resale to kidney transplant candidates in the United States. He practically did not sell a single kidney. However, his testimony and his very offensive proposal, in the wake of press reports, helped legislators make the National Organ Transplant Act, a federal law. In 1984, this law was enacted in the United States without extensive legislative debate. The National Organ Transplant Act states "It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation if the transfer affects interstate commerce." In 1989, the Human Organ Transplant Act also was enacted by the British Parliament after it had been documented that a British physician had been involved in removing and selling a kidney from a poor Turkish citizen without his consent. During 1980s, many other countries passed similar legislation prohibiting monetary compensation for organ donation for transplantation. An ethical consensus developed around the world that all organ donations have to be altruistic, meaning that there should be no payment for people who are willing to have their organs or organs of their deceased family members used for transplantation. 16,17

In 1991, the World Health Organization in its guiding principles stated that "Adult living persons may donate organs but in general such donors should be genetically related to recipients. 18" However, over the past 2 decades, the number of kidney transplantations from living unrelated donors has substantially increased because of severe shortage of transplantable kidneys and because the outcome of such transplants have been superior to the outcome obtained with deceased-donor kidney transplants. 19,20 As a result, the World Health Organization has also revised its

guiding principles supporting living unrelated kidney donation by spouses and close friends. Since 1990s, kidney donations from all living donor groups have increased substantially in the US, but the greatest increase has been in altruistic nonspousal living unrelated donors which has grown from 47 in 1991 to 1341 in 2004 (> 25-fold) and still continues to increase.²¹ The altruistic living unrelated kidney donation has also increased in many other developed countries.²²

As mentioned, the outcome of living unrelated donor kidney transplantation has been superior compared with the outcome of deceased-donor kidney transplants. However, superior outcome alone does not justify recommendation of increasing number of transplants from living unrelated donors. Transplant medicine should be compatible with current medical ethics. Currently, kidney transplantation from living unrelated donors is either altruistic or compensated. The altruistic living unrelated kidney donation is ethically acceptable and is carried out in increasing number all over the world. The altruistic donation can be directed kidney donation by emotionally motivated donors such as spouses, close friends, and partners or it can be nondirected kidney donation by altruistic strangers. Compensated living unrelated donor kidney transplantation also can be regulated as the "Iranian model" which is ethically very controversial or unregulated like commercial transplants and transplant tourism that are ethically unacceptable and is illegal in almost all countries.

Altruistic System Fails to Alleviate Kidney Shortage

Unfortunately, during the past 3 decades, the altruistic supply of transplantable organs has remained much less than the demand, and the results of this altruistic system has been steadily worsening severe organ shortage. The severe shortage of transplantable kidneys has been associated first with increasing number of patients dying while in transplant waiting lists. This problem is more specific for developed countries with large-scale transplant programs and long transplant waiting lists. In order to alleviate kidney shortage, several strategies have been adopted by transplant experts and each of these approaches has modestly increased the number of altruistic kidney donations. However, the gap

between supply and demand has been worsened over time and the use of all these strategies have failed to eliminate or even alleviate severe shortage of transplantable kidneys. The second problem associated with severe shortage of kidneys is the increasing number of commercial transplants and transplant tourism. This problem is more common in developing countries; however, it is also seen in the "developed world." Many laws have been passed and many declarations and condemnations have been issued against buying and selling kidneys. Unfortunately, all have failed to stop the rapid growth of commercial kidney transplants and transplant tourism around the world. Because of these reasons, a number of transplant experts have been convinced that altruistic organ donation alone will not eliminate severe organ shortage, and some other approaches such as providing financial incentives or social benefits to organ sources is necessary to increase the number of transplantable organs.23 Some experts also believe that the use of self-interest (as financial incentives) to shape human behavior is much better understood than the use of altruism. They say only under certain and limited circumstances does the human being show willingness for uncompensated transfers and generosity toward others, whereas the forces of self-interest are basic for almost all of our daily activities. They believe this is the main reason why efforts to use altruism for organ donation have met with limited success and why by providing financial incentives it is excepted that the number of available organs for transplantation will increase. 17,24

Unfortunately, in the current altruistic system of organ donation, transplantation has become the victim of its own success.²⁵ Because advances in organ transplant technology has substantially increased the demand for transplantable organs, while the altruistic system of organ donation has limited the supply of transplantable organs to a level much less than the demand. The result has been severe shortage of organs that has steadily worsened during past 2 to 3 decades. As mentioned, one of undesirable consequences of sever organ shortage is the increasing number of patients dying while waiting for organ transplantation. In the United States, of more than 75 000 patients who were on deceased-donor kidney waiting lists in 2007, 4642 (6.2%) died while waiting for a kidney. As the median waiting time to receive a deceased-donor kidney is around 7 years, more than 40% of all wait-listed candidates die before transplantation. In a recent analysis of the waiting list and death among candidates waiting for a kidney transplant, Delmonico and McBride argued that many deaths belong to those who were wait-listed as inactive. They say in 2007, 24 624 candidates on the kidney waiting list in the United States (32.8%) were categorized as inactive and 2431 of them died while waiting for a kidney. Inactive patients were not eligible to receive an offer for a deceased-donor kidney even though they were on the list. However, the remained 2211 patients who died in 2007 were active on the waiting list.²⁶

In developed countries, many patients with end-stage kidney disease seriously decide to be transplanted from a living kidney donor when they understand that there is a high risk of death before receiving a deceased-donor kidney transplantation and that the quality of life with transplantation is much better than dialysis, especially regarding the fact that the sooner the transplant the better posttransplant outcomes and that the results of living donor transplantation is much better than deceaseddonor transplantation. If they fail to receive a kidney from relatives and friends, they will consult web sites or will advertise themselves disparately needing a kidney. If all of these approaches also fail, some patients will consider traveling to the developing countries where they can buy a kidney. Kidney markets have been documented in India, China, Pakistan, Philippines, South Africa, South America, and Eastern Europe. 25,27 It is estimated that organ trafficking accounts for 5% to 10% of the kidney transplants performed annually throughout the world.²⁸ All these happen for patients from the developed countries. In some developing countries where dialysis therapy is not funded by the government and where deceased-donor kidney transplantation is essentially nonexistent because of infrastructural deficiencies, the diagnosis of endstage kidney disease is still equivalent to a "death sentence" and the only option for some patients to survive is buying a kidney. The situation is very clear and easily understandable. As far as we have only altruistic system of organ donation, we are going to have severe organ shortage. Severe organ shortage will continue to be associated with many patient deaths and with many commercial transplants. If we decide to change this sad and

grimy situation, we need to change our approaches. Any unnecessary restrictions on living kidney donation would needlessly worsen the severe kidney shortage. One alternative strategy to altruistic system of organ donation is providing financial incentives or social benefits for organ sources or developing a regulated system of organ sale. This approach is very controversial and will raise many ethical arguments.

In 2008, the International Summit on Transplant Tourism and Organ Trafficking was organized by the Transplantation Society in Istanbul, Turkey, and more than 150 representatives of scientific and medical bodies from both developed and developing countries attended this meeting. The most important message of the Istanbul Declaration was to prevent organ trafficking, transplant commercialism, and transplant tourism and to encourage legitimate transplantation programs. The other message was to increase deceased organ donation. It is obvious that if the number of transplantable organs does not increase around the world, commercial transplantation will continue to happen and the Istanbul Declaration will gradually become ineffective.29

Need for Living Unrelated Kidney Donation

Living kidney donation is not risk free and the perioperative donor mortality rate is around 0.02% to 0.03%. The major and minor perioperative complications reported from our center were 1.5% and 8.5%, respectively.30 One of the important questions to be answered is that in spite of all these risks, is there still a need for living kidney donation, especially from living unrelated donors? Unfortunately, the answer is yes. According to the Organ Procurement and Transplant Network data, on February 29, 2008, a total of 74 634 patients were on the waiting list for deceased donor kidneys in the United States, and in 2007, 4642 patients died while awaiting a kidney. The median waiting time to receive a deceased-donor kidney has been longer than the median waiting time to receive other organs such as the liver, heart, lung and small intestine. In a study by Sheehy and coworkers, the annual number of brain-dead potential donors in the United States was predicted to be between 10 500 and 13 800 with an overall conversion rate of 42%. These authors have shown that even if the organs of all potential brain-dead donors are utilized, the supply

of kidneys would still be inadequate to meet the escalating demand.³¹ In other words, there is still a need for living kidney donation. And as living related kidney donation has its own limitations, the need for increasing number of living unrelated kidney donations will still be continued.

ETHICAL TRANSPLANTATION What is Major Ethical Dilemma?

Another important question is that what is the major ethical dilemma in living kidney donation, especially from living unrelated donors? Over 40 years ago, Woodruff mentioned that living kidney donation is similar to a heroic rescue; "the opportunity of saving a life by pulling someone out of a fire, or rescuing them from drowning, is comparable to the situation of the kidney donor, with just the difference that the kidney donor has a little longer to make his mind up.32" However, there is a fundamental difference between a such heroic action carried out by a volunteering person and kidney donation, which requires the help of transplant team. Harris, in his book on the ethics of biotechnology, has written that "If I decide that I would like to donate one of my kidneys and run the risk of the procedure and the risk that I might subsequently have kidney failure, then it seems that it is a matter of me. Like all other risks that I choose to run [...] these are matters of personal choice.33" Again, what is missing from this type of statements is that kidney donation cannot be carried out by donor himself. Donors need the help of a transplant team to accomplish their goal. Members of the transplant team are not mere instruments of the kidney donor's wishes. They are moral agents, and they should be hold accountable for their action. In other words, the transplant team will help for kidney donation if they feel it is morally and ethically justified. If buying and selling kidneys were possible only by wishes of donors and recipients and without the help of transplant teams, the commercial transplantation would be carried out in a large-scale worldwide and the exploitation of poor people would be culturally accepted as many other existing unfair transactions between the poor and the rich.

Ethical Principles and Living Unrelated Kidney Donation

During evaluation of a potential living unrelated

kidney donor transplant, the physician should consider several ethical principles. These principles are respect for autonomy, nonmaleficence (do no harm), beneficence (do good for others), and justice. Respect for autonomy means that an unrelated kidney donor is acting freely and rationally. But, how can a transplant physician be sure that a potential kidney donor is acting voluntarily and autonomously? This can be achieved by obtaining an informed consent.34 Such informed consent should have the following components: (1) the living unrelated kidney donor should be competent to understand and decide. This can easily be detected by the transplant physician during medical and psychological evaluation of potential donors. (2) All relevant information should be disclosed to the kidney donor. Most transplant centers prepare all information about risks and benefits of kidney donation in simple writing, and they hand it to volunteering kidney donor. In order to prevent inadequate disclosure of information resulting from a conflict of interest, it is suggested that the transplant team appoint a donor physician (donor advocate) who is not involved in the care of potential recipient.³⁵ (3) The living kidney donor should understand the information disclosed to him or her. Because the majority of donors volunteer immediately in the face of limited understanding of the risks and benefits of kidney donation, the transplant physician should postpone evaluation of the donor by more appointments. In addition to providing information, the physician should ask some questions until becomes sure that the potential living unrelated kidney donor has understood all relevant information. (4) The living unrelated kidney donor should be able to choose donation freely. Many volunteering donors who are emotionally motivated, such as spouses, may feel obligated to donate or they may feel that they have no other real choices, or they may feel guilty if not to donate. Pressure to kidney donations can be external, ie, the pressure is brought by another person such as a family member, or it can be internal, arising out of sense of duty. In case of paid or commercial transplantation, potential donors are almost under pressure to receive a payment that they seriously are in need. All potential donors should receive information that the transplant physician is prepared to offer a medical excuse for not donating even when no excuse exists.1

The second ethical principle, nonmaleficence (do no harm), emphasizes that no body should be injured intentionally. In living kidney donation, physical harm is unavoidable and this ethical principle has to be violated, because living kidney donation is associated with a mortality rate of 0.03% in donors and some surgical complications. However, it provides enormous benefit to the recipient. For justification, the transplant physician must carefully consider its risks, its benefits for the donor as well as the recipient, and the balance of the two. The third ethical principle, beneficence, instructs to do good for others. In the presence of severe shortage of transplantable kidneys, it is clear that living unrelated kidney donation provides enormous benefit to patients. However, the enormous benefit to the recipient does not provide enough justification for accepting all kidney donors. The donor's benefit and welfare should be considered first. The donor may receive benefits from restored health of the recipient, as in spousal transplantation. Many donors benefit psychologically by making a major sacrifice and saving a life. Some living donors benefit physically when their treatable health problems are detected during the donor evaluation. In fact, as a result of this medical screening process, more lives can be saved than lost by kidney donation. The final ethical principle is justice. It refers to fair and equitable treatment and is more relevant to deceased-donor transplantation. Also, the paid living unrelated kidney donation program in Iran has been so regulated that all patients from either a rich or poor socioeconomic class have nearly equal access to kidney transplantation.36

Some Ethical Concerns in Current Altruistic Living Unrelated Kidney Donation

Over the past 2 to 3 decades, the number of altruistic living unrelated, emotionally motivated kidney donation has substantially increased in developed countries. This is because of severe shortage of deceased-donor kidneys and because the result of these transplants have been superior to those obtained with deceased donors. During this period, attitudes of western transplant centers towards living unrelated donor have also become very positive, and the vast majority of the United States transplant centers are now willing to accept emotionally related volunteers such as spouses, close

friends, and altruistic strangers as kidney donors.³⁷ However, in developing countries, altruistic living unrelated kidney donations are less common and the majority of living unrelated donors are paid for commercial transplants.

The most ethically acceptable kidney transplants from living unrelated donors are spousal transplants.1 Several studies suggest that the vast majority of people would donate a kidney to their spouse and a smaller majority would likely donate to a close friend.6 Many also would rather donate a kidney to their spouse than to one of their brothers or sisters. Spousal donors will benefit greatly from restored health of their recipients. It has been estimated that spouses could provide functioning kidneys for as many as 25% of all adult potential kidney transplant recipients. In the United States, the number of spousal transplants has increased until 2001. Since then, it has plateaued to 700 transplants per year. Unfortunately, there is a gender disparity in spousal transplantation around the world. In the United States, wives are donors of 70% of spousal transplants and husbands are recipients.21 The reason of this disparity has not been well documented. Whether it is due to human leukocyte antigen sensitizations, social reasons, or some degrees of unnoticed family pressure on wives is not known. It is expected that emotional pressure on the wife to donate a kidney to her husband to be more common in developing countries, but it has been reported from the developed world, too.³⁸

Kidney transplantation from altruistic nonspousal living unrelated donors has also increased in the United States and in the other western countries. Transplant professionals believe that in emotionally motivated kidney donors, commercialism is not an issue. However, this is not always true even in developed countries.³⁸

Financial Incentives as an Alternative to Altruistic Kidney Donation: Is Iranian Model Ethically Acceptable?

Unfortunately, the current altruistic system of organ donation is associated with many patient deaths and increasing number of commercial transplants around the world. Many transplant experts believe that these problems, including the buying and selling kidneys will continue to happen if the kidney donation system remains only altruistic. One of the alternative approaches

is adopting a regulated system of kidney donation by providing financial incentives and social benefits to kidney donor sources. Some experts believe that the regulated system can eliminate commercial transplants and transplant tourism, which are unacceptable to all transplant professionals and ethicists. While some experts support a regulated system of kidney sales, 39,40 others believe that this practice will be similar to the Trojan horse of old; once permitted it will bring destruction and not relief.⁴¹ Obviously, establishing a regulated system of kidney sales will be ethically very controversial and will raise many questions. The important question is: would it be a successful strategy to eliminate shortage of transplantable kidneys? There are not enough data available to provide a definitive answer to this question, because providing financial incentives to kidney donors have been illegal in almost all countries.

There is a 20-year experience with the Iranian model, a compensated and regulated living unrelated kidney donation program which was adopted in 1988 and successfully eliminated kidney transplant waiting list by the end of 1999. Currently, Iran is the only country with no kidney transplant waiting list, and more than 50% of patients with end-stage kidney disease in the country are living with a functioning graft. Background for development, characteristics, results, elimination of kidney transplant waiting lists, and ethical issues surrounding the Iranian model have previously been reviewed extensively. 42 Another question is that what would be the ethical shortcomings of paid and regulated kidney transplantation program? Again, there are not enough data available to provide a definitive answer. In the Iranian model, many ethical problems that arise from paid kidney donation have been prevented. However, because this program has not been well regulated by transplant ethicists, several ethical shortcomings either has remained or has appeared in it.

The Iranian model has many ethical successes. In this paid kidney donation program, there is no role for a broker or an agency. The Dialysis and Transplant Patients Association (DATPA) is a charitable organization that performs preliminary matching potential donors with recipients and receives no incentives from them. All hospital expenses of kidney transplantation are paid by the government. All transplant candidates, either

rich or poor, educated or uneducated, receive kidney transplantation.43 This paid living kidney donation model has not inhibited the establishment of deceased-donor organ transplantation program and the annual number of deceased-donor kidney, liver, heart, and lung transplantations have increased steadily in the country.44 In addition, it has eliminated the many illegal and commercial kidney transplantations and has prevented transplant tourism and the development of kidney market for foreigners. 45 Of many refugees residing in Iran, no one has been used as a kidney donor. However, if a refugee has been in need of kidney transplantation, he has been transplanted by this model, meaning that the donor and recipient have been either related family members or from the same nationality.46 Finally, the Iranian model have prevented many patient deaths and suffering in the country.

Unfortunately, in recent years because of lack of interest and expertise in health authorities, the number of serious ethical failures has increased in the Iranian model kidney transplantation. Over the past 2 decades, in spite of severe inflation in the country, the government has not increased the amount of donor award. The government award has become a small amount of money that does not satisfy volunteering donors any more. As a result, the program has remained completely directed paid kidney donation system where the major part of payment for kidney comes from the recipient and not from the government. This means that the transplant candidate and the volunteering kidney donor meet each other in a DATPA meeting for arrangement of rewarded gifting to be paid by the recipient to the donor after transplantation. 42 In front of our kidney hospital entrance in Tehran, there are always dozens of advertisements on the walls for selling the kidney. In each advertisement, the vendors have included their age, blood group, and a phone number to be reached by any person who is looking for a kidney. However, our transplant teams only accept volunteering donors who are referred by the DATPA. Donors also know that the major part of payment comes from the recipient and its amount is negotiable, so why they should not sell their kidneys for a higher price? Providing a fixed and sufficient amount of financial incentive and some social benefits to each volunteering donor by the government will eliminate the rewarding gift that comes from the recipient and will make the Iranian model a nondirected paid kidney donation program whereby the donors and the recipient will not see and know each other before transplantation. All transactions for financial incentives can be carried out by the DATPA. Unfortunately, this approach has not been adopted by health authorities. In addition, it has recently been discovered that some Omani and a few Saudi nationals have been transplanted in Iran from Iranian paid donors (based on personal communications with Nabil Mohsin, Muscat, Oman and the cited reference). 47 In April 2008, the Ministry of Health had to close the transplantation unit of a university hospital in Tehran after it was documented that this transplantation team has been involved in a commercial transplantation scandal.⁴⁸

The Iranian model has been so regulated that foreign nationals can be transplanted in Iran, but they are not permitted to receive a kidney from an Iranian donor. The donor should either be related to the recipient or should be from the same nationality as the recipient. During the past 20 years, many Afghan refugees with end-stage kidney disease residing in Iran have been transplanted. In Afghanistan, there are no dialysis or kidney transplant facilities, and the diagnosis of end-stage kidney disease is equal to a death sentence. Unfortunately, Iran has also become a kidney transplant destination for patients from Azerbaijan. In this country, no kidney transplantation program has been established and the quality of dialysis is very poor resulting in a high rate of mortality and morbidity. Eighteen of 139 patients who underwent kidney transplantation in 2008 at Hashemi Nejad Hospital in Tehran came from Azerbaijan. The majority of these patients received kidneys from paid Azeri donors. The DATPA has no role on these transplants. Many of these paid donors have been arranged by brokers inside Azerbaijan. Pressure should be exerted to health authorities of Azerbaijan to establish their own transplantation program. Iranian health authorities should also understand that these kidney transplants should not be considered as medical tourism to be proud of. These kidney transplants are in the category of unethical commercial transplant tourism and should be avoided.

CONFLICT OF INTREST

None declared.

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Received May 2009 Revised August 2009

Part of this paper was presented in the Key Opinion Leader (KOL) Meeting of the Transplantation Society in July 2007, Ankara, Turkey