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OVERVIEW

ORGAN DONORS WITH POSITIVE VIRAL SEROLOGY OR MALIGNANCY: RISK OF DISEASE TRANSMISSION BY TRANSPLANTATION

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The widening disparity between the supply of and the demand for transplantable organs has led to efforts to better utilize organs from the current cadaveric donor pool. One of these efforts was a recent conference entitled "Maximizing The Use of Organs Recovered from the Cadaver Donor," jointly sponsored by the American Society of Transplant Surgeons, the American Society of Transplantation, and the Association of Organ Procurement Organizations (OPOs). Five working groups were established to delve into ways to increase and optimize cadaver organ utilization. Four considered each of the main organs (kidney, liver, heart, and lung) and a fifth was charged to consider the "marginal" donor, defined as one with a positive serology profile or history of malignancy. This article reports on the deliberations of the Marginal Donor Workgroup.

The fundamental premise is that organs from donors with positive viral serology or history of malignancy are underutilized. These donors are considered marginal because transplantation of their organs might transmit disease. It is likely that some of these organs are lost at early steps along the donation process and thus, never procured or offered to a potential recipient. Two strategies may enhance utilization of organs from these donors: increasing supply and increasing demand. Both of these strategies depend upon a clear understanding of the disease transmission risk inherent in each case of viral infection or cancer. A primary goal of our group was to critically assess the available data and define the risk associated with transplantation.

Although a definition of risk based upon the donor profile is critical to rational decision-making, each decision regarding organ utilization also depends upon recipient characteristics. Everyone is accustomed to the circumstance of medical urgency that dramatically enhances the potential benefit of transplantation. In the past, except for "life and death" situations, the additional risk of a marginal donor appeared prohibitive. As transplant physicians, we have been reluctant to make decisions that do not optimize the outcome for an individual patient. However, today's climate of critical organ shortage and protracted waiting times complicates the risk-benefit analysis. The risks of death and significant loss of quality of life while awaiting transplantation are increasingly recognized. Accepting an organ from a marginal donor in return for shortening of the waiting period may be a reasonable strategy for some transplant candidates.

Because the additional risk inherent in transplantation with an organ from a marginal donor may not be appropriate for every transplant candidate, the creation of alternative allocation algorithms may facilitate optimal organ utilization. Identifying individuals willing to receive organs from various flavors of marginal sources has multiple benefits. First, transplant centers can choose appropriate recipients deliberately and carefully. Then, they can present the individual risk-benefit analysis to each potential transplant candidate at a time significantly before transplantation. The candidate can then decide whether he wishes participate.

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This process is essentially that of informed consent, which is considered necessary for any circumstance in which risk is considered to exceed "standard" expectations. Finally, alternative allocation systems enable a "streamlining" of the organ placement process, which enhances both utilization and outcome.

VIRAL INFECTIONS

All potential cadaveric organ donors undergo serologic testing to determine previous exposure to infections and thus, the potential for disease transmission by organ transplantation. Although testing covers a broad range of infections, three are of primary interest: hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). The decision to proceed with transplantation, in the event of a positive test result, depends upon the specific test, the particular organ, and recipient characteristics including disease severity and serology profile. In the following sections, the implication of a positive result and the risk of disease transmission are presented to facilitate informed decision-making regarding the utilization of organs from donors with a positive serology profile.

Interpretation of Serology Results

Table 1 provides a summary of donor serologic testing and interpretation as determined by the Marginal Donor Workgroup. A positive hepatitis B surface antigen (HBsAg) or HIV antibody (HIVAb) result is considered reliable. In contrast, a positive result for hepatitis B core antibody (antibody against hepatitis B core antigen; HBcAb) needs to be interpreted with care and consideration of additional information may help discriminate between a false-positive versus true-positive result:

a. degree of HBcAb positivity (borderline result more likely to be false positive)

b. hepatitis B surface antibody (antibody again hepatitis B surface antigen; HBsAb) result (performed by some OPOs): HBsAb+ strongly suggests remote HBV infection

c. HBcAb IgM result (performed by some OPOs): IgM HBcAb indicates recent HBV infection

d. hepatitis C antibody (HCVAb) result: HCVAb+ strongly suggests that HBcAb+ is true positive

e. donor's social evaluation: ethnicity and behavioral risk factors for HBV infection

f. liver biopsy result: cirrhosis or hepatitis strongly suggests that HBcAb+ is true positive

The evolution of the HCVAb enzyme-linked immunoassay (EIA) during the last decade has resulted in significantly increased sensitivity at the cost of decreased specificity. The recombinant immunoblot assay, performed by some OPOs, can help discriminate between a true-positive and false-positive result.

HBsAg+ Donor

Organs from HBsAg+ donors carry a high risk of HBV transmission, which can result in significant morbidity and even mortality for immunocompromised recipients. Historically, organs from HBsAg+ donors have been sporadically transplanted into recipients of extreme medical necessity (*1*,*2*). This has been recently confirmed by the United Network for Organ Sharing (UNOS), who have found that organs from HBsAg+ donors represent approximately 0.04% of all organs recovered and transplanted (M. A. McBride, Ph.D., personal communication, 2001).

Recently, Ko et al. (*3*) have reported the virologic outcome of 19 heart transplants from HBsAg+ donors into recipients with various HBV serologic profiles. HBV disease developed in two recipients after transplantation. One of two HBV naïve recipients (HBsAg−, HBsAb−, and HBcAb−) developed hepatitis despite hepatitis B immune globulin (HBIg) administration. The second patient was one of seven positive for HBcAb and the only one of the seven positive for HBV DNA at the time of transplantation. Therefore, it is unclear whether the posttransplantation hepatitis was secondary to HBV transmission or reactivation. Interestingly, recipient immunity either by immunization (two recipients) or previous infection (eight recipients) was entirely protective. These data provocatively suggest that organs from HBsAg+ donors may be safely transplanted into appropriate recipients. A small prospective study may provide invaluable information to guide future practice regarding the appropriate use of these organs.

HBcAb+ Donor

All organs from HBcAb+ donors can transmit HBV, although the risk varies by organ. Figure 1 shows a gradual increase in utilization of organs from HBcAb+ donors. This trend likely reflects both the increasing severity of the organ shortage and the recent availability of efficacious anti-HBV agents such as HBIg and lamivudine.

The risk of transmission by liver transplantation from an HBcAb+ donor is high because HBV resides predominantly within hepatocytes (*4*–*7*). The donor's HBsAb status does not mitigate transmission risk. Although several reports suggest that recipient immunity may be protective (*5*,*7*,*8*), the presence of HBsAb is not completely protective against the development of posttransplantation HBV infection (*4*,*6*). Recognition of the significant risk of posttransplantation HBV

TABLE 1. Interpretation of donor serologic testing

Primary test	Sensitivity	Specificity	Confirmatory test	Comments
HBsAg (EIA)	High	High	Ab neutralization assay	False negatives: mutant HBV strains (uncommon) False positives: days after HBV vaccination (42–44)
HBcAb (EIA)	High	Moderate	None	Significant false positives: see text.
HCVAb (EIA)	High	Moderate-high	RIBA[a]	Some false positives: see text.
HIVAb (EIA)	High	High		

[a] Used by some but not all OPOs.

RIBA, recombinant immunoblot assay.

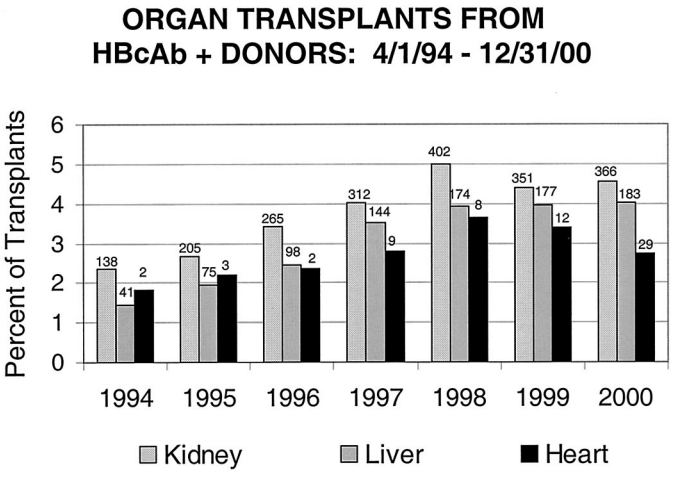

FIGURE 1. Kidney, liver, and heart transplants from HBcAb+ donors: UNOS, April 1, 1994 to December 31, 2000. Data are shown as percentage of total transplants by organ type. Absolute numbers of transplants are shown above each bar.

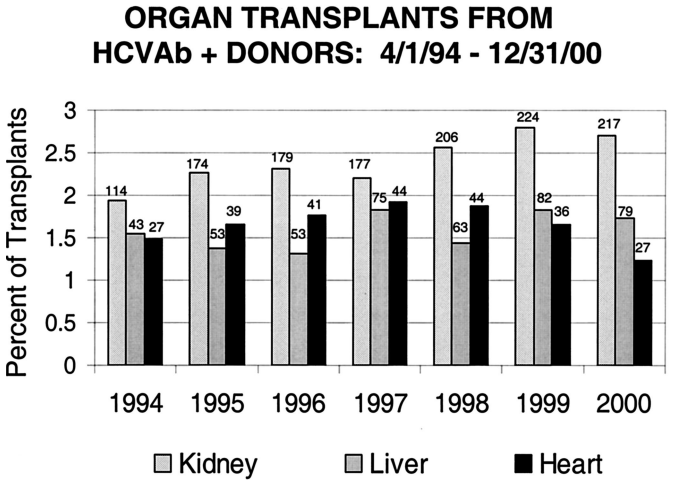

FIGURE 2. Kidney, liver, and heart transplants from HCV Ab+ donors: UNOS, April 1, 1994 to December 31, 2000. Data are shown as a percentage of total transplants by organ type. Absolute numbers of transplants are shown above each bar.

infection resulting in potentially severe graft damage has led to prophylactic treatment of liver recipients with HBIg, lamivudine, or both (*6*,*9*,*10*) with excellent efficacy. Nevertheless, ideal recipients of livers from HBcAb+ donors may be those undergoing transplantation for HBV cirrhosis who are already committed to posttransplantation anti-HBV therapy. Alternatively, those with extenuating medical circumstances may also be appropriate recipients, with informed consent regarding the risk of viral transmission and the efficacy of antiviral strategies.

In contrast to liver transplantation, transplantation of kidneys from HBcAb+ donors seems to carry minimal risk of clinically significant viral transmission. A meta-analysis of the literature shows that only 1 of 133 recipients converted to HBsAg positivity after transplantation of a kidney from an HBcAb+ donor (*11–14*). It should be noted, however, that the actual rate of viral exposure as measured by development of anti-HBV antibodies (either HBsAb or HBcAb) is considerably higher. Twenty-seven percent of kidney recipients from HBcAb+ donors demonstrated seroconversion compared with 4% of kidney recipients from HBcAb− donors, for an odds ratio of 4.94 (*11*). A similar analysis was performed using the UNOS database with similar results (W. S. Cherikh, Ph.D., personal communication, 2001).

Although the collective data indicate that clinically significant HBV transmission is uncommon, ideal recipients for kidneys from HBcAb+ donors may be those with immunity or chronic HBV. Arguably, considering both the low risk of disease transmission and the availability of effective prophylactic and therapeutic reagents, the recipient pool may be justifiably expanded to all candidates with appropriate informed consent. The postoperative management strategy may be tailored to the recipient's HBsAb status. Overall, the low risk of posttransplantation disease suggests that a prophylactic treatment strategy may not be warranted.

HCVAb+ Donor

Transplantation of an organ from an HCV+ donor is known to be an efficient mode of viral transmission (*15–18*). Figure 2 shows stable utilization of organs from HCVAb+ donors.

Several centers have reported their experience in the transplantation of livers from HCVAb+ donors into HCV+ recipients, demonstrating no increase in short or medium term (1–5 year) morbidity or mortality associated with the use of a liver from an HCVAb+ donor compared with an HCVAb− donor (*19–22*). Specifically, there has been no difference in either patient survival, graft survival, or the incidence, timing, or severity of recurrent HCV disease. Several studies examining the dynamic interaction of donor and recipient HCV strains after transplantation have found no consistent pattern of viral repopulation (*21*,*23*). Because genotype is only predictive of response to interferon-based therapy and not of disease severity, genotype is not an important consideration in the decision to use a liver from an HCVAb+ donor into an HCV+ recipient.

Multiple reports speak to the transplantation of kidneys from HCVAb+ donors. Because viral transmission rate is extremely high (*16*,*24*), most centers transplant kidneys from HCVAb+ donors exclusively into HCV+ recipients. However, some centers will transplant these kidneys into a carefully selected subset of HCV− recipients with extenuating circumstances.

Transplantation of kidneys from HCVAb+ donors, when compared with kidneys from HCV Ab− donors, had no adverse impact with follow-up periods of up to 5 years (*25–28*) for recipients with preexisting HCV infection. There was no difference in patient or graft survival, renal function, incidence or severity of rejection, infectious complications, or liver dysfunction. Interestingly, one center reported that HCV+ recipients who received a kidney from an HCVAb+ donor had significantly shorter waiting times of 9±3 months compared with 29±3 months for HCV+ recipients who received a kidney from an HCVAb− donor (*27*). Because the incidence of hepatitis C in the waitlist population may even exceed that of the donor population, widespread practice of transplanting kidneys from HCVAb+ donors into HCV+ recipients will erode this benefit.

HBsAg+, HBcAb+, or HCVAb+ Donors for Cardiothoracic Transplantation

Figures 1 and 2 show that trends observed for the utilization of hearts from donors with positive serology parallel those observed for livers and kidneys. Overall, limited available data validate the assumption that heart or lung transplantation presents a similar risk of HBV or HCV transmission as kidney transplantation. Finally with regard to outcome, no conclusions can be drawn because the specific impact of the donor's positive serology cannot be discerned from the available data.

HIVAb+ Donor

Organs from HIVAb+ donors carry a high risk of viral transmission (*29–31*) because the infectivity of a small inoculum has been demonstrated by blood transfusion studies (*32*). All potential organ donors have been screened for HIV since 1985. The rare instances of HIV transmission despite negative HIVAb test results illustrate some limitations of serologic testing. In one instance, massive transfusion of blood and blood components decreased the antibody titer below the sensitivity limits of EIA (*29,33*). In a second case, transmission occurred from a donor during the "window period" (see below) (*31*).

High-Risk Donors

Donors are considered "high risk" because their social behavior(s) poses ongoing risks for exposure to HBV, HCV, and HIV. Considerable concern that organs from these donors may transmit disease even in the face of a negative serology profile arises because of the window period—the time delay between viral exposure and detectible antiviral antibodies. Historically, organs from these donors were utilized only in situations of medical urgency.

Nucleic acid amplification technology (NAT) may be useful to evaluate high-risk donors. NAT detects the genetic material of a virus after its amplification by polymerase chain reaction with a sensitivity of as few as 10 genome equivalents per milliliter. Caution must, however, be exercised with such exquisitely sensitive methodology. If broadly applied to low disease prevalence populations that include blood and organ donors, the incidence of false-positive results increases, thereby decreasing the positive predictive value of the test. Currently, transfusion medicine is trying to determine the appropriate use of NAT for blood product screening (*34–37*). A similar analysis will need to be performed for evaluation of organ and tissue donors.

Table 2 shows the window period associated with serologic versus NAT testing as determined by blood transfusion studies. The degree of window period closure achieved by NAT depends upon the sensitivity of the specific assay and several virologic parameters, such as the length of the preinfectious or "eclipse" phase (the time between exposure and viremia), the viral load doubling time, and the time to seroconversion. Currently, some OPOs have already incorporated HIV NAT testing into their algorithm of donor evaluation, using assays that yield results in less than 8 hours. Although the broad application of NAT testing to all potential organ donors in the United States may be financially costly and may ironically result in a loss of organs secondary to false-positive tests, the selective application of HCV and HIV NAT testing for high-risk donors may be a wise strategy. Substantial closure of the window period should significantly enhance general willingness to transplant organs from high-risk donors.

TABLE 2. The window period associated with serologic and NAT testing

Virus	Window period	
	Serologic testing	NAT testing
HBV	60 days	25 days
HCV	70 days	8–10 days
HIV	23 days	13 days

NEOPLASMS

Three major sources of information help us evaluate the relative risks of utilizing donors with malignancies. The Israel Penn International Transplant Tumor Registry (IPITTR) provides worldwide data, whereas UNOS provides United States data on outcomes associated with transplantation from donors with malignancies. It should be noted that although registry data is important, its "voluntary" nature results in a distinct possibility of underrepresenting the actual incidence of cancer transmission. The general medical literature on the natural history and outcome of central nervous system (CNS) tumors (*38*) and solid malignancies also provides useful information.

CNS Tumors

In the United States, although there are approximately 13,000 deaths yearly as a result of CNS tumors, only about 1.0% of those patients are organ donors. Contrast this to 6,353 deaths recorded in 1999 while on the waiting list for a transplant.

The defined biologic behavior of CNS neoplasms including their propensity for extracranial spread facilitate decisions about using organs from donors with these diagnoses. The relative risks of CNS tumor transmission determined by the Transplant Commission of the Council of Europe (*39*) are summarized in Table 3. Others have recently delineated the outcomes of recipients who have received organs from donors with CNS tumors (*40,41*). Because extensive craniotomy and ventriculoperitoneal or ventriculojugular shunts have emerged as additional risk factors for extracranial CNS tumor metastasis, patients who have undergone such procedures should probably be avoided as organ donors.

Routine steps should occur when a donor with CNS malignancy is undergoing evaluation. A thorough history should be obtained with particular attention to information regarding tumor diagnosis, previous interventions, and histology. In the case of an intracranial mass or hemorrhage of unclear etiology, we recommend that a postdonation autopsy be performed before transplantation of organs. There are no laboratory values or radiologic findings that are useful in the absence of histology for CNS tumors. A meticulous exploration for solitary masses or lymphadenopathy at the time of procurement is extremely important.

The IPITTR has recorded 276 transplant recipients at risk for tumor transmission from 155 donors between 1994 and 2000 (J. F. Buell, M.D., personal communication, 2001). Ninety-four percent (146) of these donors had a single malignancy; 21% (33) had CNS tumors. Fifty-three transplanted

TABLE 3. Relative risk of donor CNS tumor transmission to organ transplant recipients: Select Committee of Experts on the Organizational Aspects of Cooperation in Organ Transplantation, Council of Europe, 1997

Lowest risk
Benign meningiomas
Pituitary adenomas
Acoustic schwannomas
Craniopharyngiomas
Astrocytoma grade I
Epidermoid cysts, colloid cysts
Low-grade oligodendromas
Gangliogliomas, gangliocytomas
Pineocytomas, ependymomas
Well-differentiated teratomas
Papillomas
Hemangioblastomas
Moderate risk
Astrocytoma grade II
Gliomatosis cerebri
Highest risk
Anaplastic astrocytoma (grade III)
Glioblastoma multiforme
Medulloblastoma
Anaplastic oligodendroglioma
Pineoblastomas
Chordomas
Malignant ependymomas
Intracranial Sarcoma
Germ cell tumors (x well-differentiated teratoma)
Primary cerebral lymphomas

organs originated from donors with CNS malignancies, including astrocytoma, glioblastoma, and medulloblastoma. There were a total of nine instances (17%) of tumor transmission. Of organs from donors with astrocytoma (n=25), one organ from a donor with grade III astrocytoma transmitted malignancy leading to the recipient's death. Organs from donors with glioblastoma (n=21) transmitted malignancy in five instances, resulting in the death of four recipients. Medulloblastoma was the donor histology for seven transplanted organs; transmission occurred in three recipients with two resultant deaths (Table 4).

UNOS has information on 1,129 organ recipients from 418 donors with a history of CNS malignancy from 1992 to 2000 (H. M. Kauffman, M.D., personal communication, 2001). Fifty four percent (610) were kidney recipients, 28% (314) were liver recipients, and 18% (205) were heart recipients. Unfortunately, little is known about specific CNS tumor diagnoses. However, no definitive transmission was identified.

TABLE 4. Neoplastic transmission to organ transplant recipient from donors with CNS tumors: IPITTR, 1994–2000

CNS tumor	Transmission Number (%)	Deaths Number (%)
Astrocytoma (n=25)	1[a] (4%)	1 (4%)
Glioblastoma (n=21)	5 (23.8%)	4 (19%)
Medulloblastoma (n=7)	3 (42.9%)	2 (28.6%)

[a] Grade III astrocytoma.

Non-CNS Tumors

The IPITTR has found that transmission of donor malignancy (69 donors) in the allograft itself occurred most commonly with renal cell tumors (57%) followed by melanoma (10%) and choriocarcinoma (9%). Overall, of 68 recipients at risk from donors with renal cell carcinoma, transmission occurred in 43 recipients (63%). Melanoma was also identified as high risk for donor transmission: 23 (77%) of 30 recipients at risk had documented transmission, and notably, 22 of the 23 developed metastatic disease. Choriocarcinoma from young female donors was transmitted to 13 (93%) of 14 recipients at risk. This is one donor population for which serum testing can be helpful in diagnosis (β-HCG). Other solid tumors demonstrating a high risk of transmission are lung (41%), colon (19%), breast (29%), prostate (29%), and Kaposi's sarcoma (67%). No transmission was identified in organ recipients from donors with thyroid, head and neck, lymphoma-leukemia, hepatobiliary, or testicular malignancies.

During the period from April 1, 1994 to December 31, 2000, UNOS recorded 35,503 cadaveric donors resulting in 109,749 transplanted organs. Nine donors transmitted malignancy (0.025% donor transmission rate) to 12 recipients (0.01% organ transmission rate). Organ-specific transmission was 0.025% (n=7) for liver recipients, 0.006% (n=3) for kidney recipients, and 0.013% (n=2) for heart recipients (Table 5). Tumor types included melanoma (four recipients), pancreatic, leukemia, lung, prostate, neuroendocrine, oncocytoma, and posttransplantation lymphoproliferative disease of donor origin. During the 57-month period between April 1, 1994 and December 31, 1998, there were 488 donors with a history of skin or solid tumor malignancy responsible for 1,276 transplanted organs. Recipients of these organs did not demonstrate a higher incidence of posttransplantation malignancy compared with recipients who received organs from donors without a history of malignancy. Finally, no instances of cancer transmission was identified (Table 6).

When considering donors who have only a history (no active disease) of solid organ neoplasm, the general biologic behavior of the tumor type, the histology and stage at the time of diagnosis, and the length of the disease-free interval should be considered. Additional caution must be exercised when considering tumor types such as breast and lung, which are known to have potential for unpredictable behavior, such as late recurrence (*42–44*).

CONCLUSIONS

The critical organ shortage and the morbidity and mortality to patients who await transplantation have mandated careful reconsideration of potential donors who are not considered ideal, including those with positive serology or history of malignancy.

Utilization of organs from donors with positive viral serology poses a threat of viral transmission and subsequent

TABLE 5. Organ-specific incidence of donor tumor transmission to transplant recipients: UNOS, 4/1/94-12/31/00

Organ	Transmission Number (%)
Liver (n=27,910)	7 (0.025%)
Kidney (n=52,539)	3 (0.006%)
Heart (n=15,379)	2 (0.013%)

TABLE 6. Cancers arising in recipients of organs from donors with a history of malignancy: UNOS, 4/1/94-12/31/98

Organ	Recipients with cancer after transplantation[a]	Cancer histology		
		Skin	PTLD	Solid
Kidney (n=679)	28 (4.1%)	14 (2.1%)	1 (0.15%)	9 (1.3%)
Liver (n=359)	9 (2.5%)	5 (1.4%)	1 (0.28%)	3 (0.83%)
Heart (n=144)	13 (9.0%)	10 (6.9%)	0	3 (2.1%)
Lung (n=46)	4 (8.7%)	0	3 (6.5%)	1 (2.2%)

[a] No donor-derived tumors.

PTLD, posttransplant lymphoproliferative disease.

disease. The literature indicates that transplantation of livers and kidneys from HBcAb+ and HCVAb+ donors into recipients with appropriate serologic and viral disease profile poses minimal risk of posttransplantation morbidity or mortality from viral transmission or disease. This conclusion seems to extend to transplantation of cardiothoracic organs from these donors. In contrast, the literature fails to define the risk associated with utilization of organs from HBsAg+ donors, particularly in the context of newly available therapeutics. Pilot studies to provide virologic outcome data should be performed to guide future practice. Finally, testing methods that have tremendous sensitivity for detecting the genetic material of HIV, HCV, and HBV are now available. Although their appropriate role in the assessment of all potential organ donors is unclear, at present, their selected application for high-risk donors may optimize utilization of these organs.

Rational use of organs from donors with tumors can increase opportunities for transplantation. Donors with medulloblastoma, glioblastoma, and anaplastic astrocytoma represent a significant risk for cancer transmission. Non-CNS tumors in potential organ donors with high likelihood to transmit disease include melanoma and choriocarcinoma. The decision to use organs from a donor with a history of a solid tumor should be based upon the known biologic behavior of that tumor, including its propensity to recur at a time point distant from its original diagnosis and treatment.

The Marginal Donor Workgroup has attempted to define the risk of viral and malignant disease transmission with the goal of enlarging the pool of transplantable cadaveric organs. Understanding the incremental risk enables the clinician to accurately perform the risk-benefit analysis of using a particular marginal organ for a particular candidate recipient. Development of alternative allocation plans may promote earlier identification of appropriate potential recipients and facilitate the informed consent process. Overall, these measures should increase organ transplantation with a benefit not only to individuals but to the entire waiting transplant community.

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