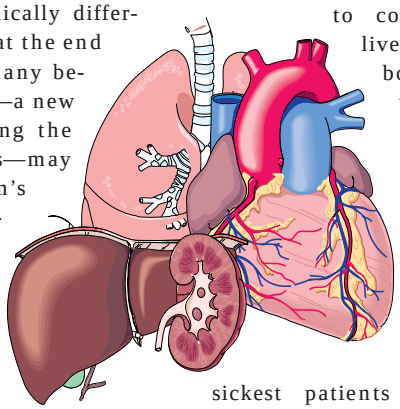
Controversial allocation rules for liver transplants

More than most developed countries, the US system for organ transplants is plagued by shortages of donor organs, long waiting lists and geographic inequities. For livers at least, authorities will implement a radically different allocation policy at the end of this month. But many believe that the change—a new formula for identifying the most needy recipients—may not solve the system's problems, and will increase post-transplant mortality.



Under the old system, most patients received livers based on time spent on the waiting list. This had the potential for abuse, as the best-informed, least scrupulous patients engineered their way onto lists before they needed a transplant.

Waiting-list time becomes largely moot with the new formula, known as 'model for end-stage liver disease' (MELD), and the sickest patients, in theory, will always be first in line. "MELD is clearly more objective [and] reduces the role of waiting time to a minimum," says United Network for Organ Sharing president and prominent transplant surgeon Jeremiah Turcotte.

Turcotte helped devise the old scoring formula, the Child-Turcotte-Pugh (CTP) system, in the 1960s. CTP included several objective and some subjective measures, particularly the presence of ascites and encephalopathy. This laid CTP scores open to manipulation since people could be rated to appear sicker than they actually were, although to what extent such exploitation of the system occurred remains controversial.

CTP was a 15-point scale, and most transplant candidates fell into a narrow upper range. MELD is a continuous scale with many more possible values, meaning that far fewer people will end up with tied scores.

But MELD does have shortcomings. Some suggest that its relative disregard for waiting list time may lead those who are tired of waiting to seek living donor liver transplants. Such partial transplants—usually the left lobe is donated—has accompanying health risks for both donors and recipients. Also, MELD is based on only three blood tests—creatinine and bilirubin levels, and prothrombin time—and thus fails to consider people with liver cancer and metabolic disease in whom these blood values may be normal, but who are very much in need of transplantation. Under MELD, they could score as if they were healthy.

Another problem is that more of the sickest patients will now undergo transplant surgery, and inevitably, more post-transplant deaths will occur, generating fears that donor livers will be 'wasted'. Under the current system, survival rates have been good, since many relatively healthy patients receive organs after joining the waiting list early even if their liver disease is not advanced. Also, failure to solve the sometimes absurd geographic disparities could have dire political consequences. For example, according to a 1998 report by the US Department of health and Human Services, a patient in New York City with Type O blood in need of a liver transplant may wait 511 days for a new organ, while the same category patient might wait only 56 days in Newark, New Jersey, just a short distance away. Adopting MELD will not necessarily fix such inequities.

In short, the MELD approach to rationing, if it fails, could reignite the political furor surrounding the allocation system (*Nature Med.* **6**, 611, 2000 and **4**, 376; 1998). Pressure for a national (cadaveric) organ sharing system could erupt again since MELD does not address the underlying problem: too many patients, not enough livers.

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Pharmacogenomics research to improve transplants

In an effort to improve the outcome for organ transplant patients, New York University's School of Medicine has embarked on a pharmacogenomics study with a small, Florida-based company to exploit pharmacogenomic data. NYU's Mary Lea Johnson Richards Organ Transplantation Center will provide samples from several hundred patients—responders and nonresponders to immunosuppressive drugs—to DNAPrint genomics, to identify the polymorphisms associated with better drug responses.

NYU transplant surgeon, Thomas Diflo, explains, "people respond to immunosuppressives in different ways. African Americans on cyclosporines tend to have a lot of [organ] rejections. What difference is there between whites and African Americans? One absorbs cyclosporines well, the other doesn't." Currently, says Diflo, transplant patients are treated with combinations of as many as five immunosuppressive drugs, and doctors have no way of determining which patients will respond to which drugs. A genomic tool that would profile a patient's likely response to immunosuppressives before transplant surgery would allow physicians to base a drug regimen on that profile.

The project will take at least a year, and so will not benefit the patients donating the samples. Assuming DNAPrint can identify the genetic backgrounds that lead to positive responses to immunosuppressives, it will seek regulatory approval for the test.

DNAPrint is also determining single nucleotide polymorphism (SNP) maps for patient responses to drugs such as angiotensin-converting enzyme (ACE) inhibitors, statins and anti-cancer drugs. But their first product, the Retinome classifier, is not a means to determine drug response, but a set of genetic markers that can predict human eye color based on a DNA sample for forensic use.

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