Cleveland Clinic performed 128 liver transplants in 2013. Its liver transplant program is the largest in the region and one of the largest in the nation.

The program’s patient survival rates compare favorably with national norms, as detailed in the graphs on the following pages. Notable data points include the following:

- A 6.1-month median time to transplant, less than half the national median of 14.4 months (January 2014 Scientific Registry of Transplant Recipients [SRTR])
- 100 percent one-year patient survival among adult and pediatric living-donor liver transplant recipients for the period 2011-2013 (N = 20)
- 100 percent three-year patient survival among pediatric patients (January 2014 SRTR)
- Comparable rates of five-year patient survival among primary liver transplant recipients with hepatocellular carcinoma (HCC) (N = 355) and without HCC (N = 768) over nearly three decades (75 vs. 76 percent survival, respectively)

Innovative techniques to broaden the donor pool

A hallmark of Cleveland Clinic’s liver transplant program is its effort to increase the donor pool while maintaining superior outcomes by using a range of alternatives to traditional donation-after-brain-death transplants, including:

- Living-donor transplant, in which part of the donor’s liver is resected
- Split-liver transplant, in which a deceased-donor liver is divided for two recipients
- Donation after cardiac death, in which a non-brain-dead donor is deemed to have no chance of recovery and donation occurs after withdrawal of life support and complete arrest of the cardiac and circulatory system

Cleveland Clinic’s is one of a handful of programs offering all these options, which play a critical role in addressing the shortage of liver grafts, collectively enabling the program to provide 36 more transplants to patients in need in 2013. These

128 liver transplants in 2013 (Cleveland location), including:
10 living-donor transplants
6 split-liver transplants
20 DCD (donation after cardiac death) transplants
7 liver-kidney transplants
2 as part of multivisceral transplants
9 additional liver transplants in 2013 at Cleveland Clinic Florida
Innovative approaches can substantially shorten wait times, and patients who are transplanted using these approaches tend to have lower MELD scores, which means lower priority on wait lists even if the need for transplant is urgent.

Leadership in living-donor transplantation

The number of living-donor liver transplants in the U.S. has recently plateaued, however, due to concerns over donor safety and other factors. Many centers are reluctant to perform living-donor transplants because they can pose ethical challenges and are technically demanding and labor-intensive.

Despite these trends, Cleveland Clinic performed 12 living-donor liver transplants in 2012 (its most in a single year), 10 in 2013, and a cumulative total of 67 through 2013. Outcomes have met the highest national standards, and the program is using advanced technology — including intraoperative ultrasound, real-time tracking of surgical instruments, 3-D imaging and now 3-D-printed models of donor livers (see sidebar) — to optimize donor safety.

Successful living-donor transplantation requires high levels of coordination, teamwork and clinical diligence to match the partial donor graft to the recipient anatomically and physiologically — and to ensure both donor and recipient are psychologically ready for the procedure.

Cleveland Clinic’s program is the only one in Ohio performing both adult and pediatric living-donor liver transplants, and it is dedicated to maintaining the collaborative culture, technology and technical skills needed to make this lifesaving option available to as many patients as possible.

Multidisciplinary by nature

The program’s multidisciplinary team brings physicians and surgeons specializing in liver disease, transplant, anesthesiology, infectious disease, bioethics and psychiatry together under one roof — the Liver Transplantation Clinic. This clinic helps improve patient experience by eliminating multiple appointments at various locations and by creating customized treatment plans for each transplant candidate.
CLEVELAND CLINIC CLINICAL AND TRANSLATIONAL RESEARCH

CLEVELAND CLINIC clinicians and researchers reported in the December *Liver Transplantation* (2013;19:1304-1310) on the development and clinical application of the world’s first complete 3-D-printed liver replicas.

The highly accurate replica models are being used by Cleveland Clinic liver transplant surgeons for presurgical planning and intraoperative guidance, particularly for resection and graft placement in living-donor liver transplants.

“Imagine you’re a surgeon who will be resecting half a liver for a transplant and you are provided with a 3-D model of the liver you’ll encounter the next day,” says Nizar Zein, MD, Medical Director of Liver Transplantation and principal investigator for Cleveland Clinic’s 3-D model work. “You can look at the 3-D ‘printout’ and better plan your surgery.”

The models were designed to build on 3-D imaging, which has been used for years in liver transplantation but has been limited by the need to still examine images through a 2-D computer screen. Replicas are constructed from 3-D digital files from the optimal visualization phases of contrast-enhanced CT and MRI scans of individual patients’ livers. They are then generated on one of two 3-D printers in the Medical Device Solutions unit of Cleveland Clinic’s Lerner Research Institute. A transparent flexible resin is used to represent the liver’s internal lumen geometry. Dyes are injected to color key structures, allowing easy visualization of the complex vascular and biliary networks.

Through the end of 2013, 24 liver models had been printed for use in transplant planning and guidance as well as for clinical training. Some have helped avert unnecessary surgery in patients with potentially unsuitable anatomy.

The group’s *Liver Transplantation* paper concluded that the 3-D-printed models demonstrate identical anatomic and geometric landmarks relative to the native livers they aim to replicate, making them highly accurate hands-on tools to aid surgical planning and help reduce surgical complications. The group continues to refine the replicas to improve the efficiency and cost of producing them.

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**First published report on highly accurate 3-D-printed liver models for living-donor transplant planning and operative guidance**

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*Cleveland Clinic observed vs. 91.6% expected vs. 90.2% national average (Cleveland location only)*

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**Better transplant planning through 3-D printing**

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**2013 Quick Take**

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The clinic benefits from frequent communication and shared meetings with the liver transplant team at Cleveland Clinic Florida, directed by renowned liver transplant surgeon Andreas Tzakis, MD, PhD (see p. 7).

Comprehensive in approach and mission

The Liver Transplantation Clinic and liver transplant team are part of a broad hepatology program of unsurpassed size and depth of expertise committed to highly comprehensive liver care. The staff of expert hepatologists in Cleveland Clinic’s Digestive Disease Institute is integral to the liver transplant program, offering superb clinical management to optimize patients for transplant when it is necessary — and to avoid transplant entirely when possible.

One example of how the program’s expertise extends beyond transplant is Cleveland Clinic’s multidisciplinary Liver Tumor Clinic. This clinic, which saw 555 patients in 2013, enables patients with liver tumors to be seen, in a single visit, by a hepatologist, an oncologist, a surgeon and an interventional radiologist. Since the clinic opened in 2009, the time from initial consultation to treatment has been reduced threefold. The Liver Tumor Clinic refers patients to the Liver Transplantation Clinic when transplant may be an option, and the two clinics’ teams collaborate closely.

Innovative use of anti-HCV regimens before and after transplant

Another example is the liver transplant team’s pioneering role in using novel pharmacologic therapies to achieve virologic cure of hepatitis C virus (HCV) infection prior to transplant whenever possible. Doing so greatly reduces the risk of post-transplant HCV recurrence, and avoiding recurrence promotes improved transplant outcomes and survival.

Cleveland Clinic hepatologists have been designing protocols to drive down HCV viral load before transplant for many years, but the advent of new “direct-acting agents” over the past two years has made this possible in many more patients than before. Direct-acting agents produce sustained virologic response at rates far higher than the rates with earlier HCV treatment regimens, and they do so with less toxicity and
FUTURE OF TRANSPLANTATION: LIVER STUDIES LAUNCH EFFORTS TO BRING NORMOTHERMIC EX VIVO PERFUSION TO ABDOMINAL ORGANS

Cleveland Clinic is among a small number of medical centers worldwide testing a new method of preserving abdominal organs. The technology, called normothermic ex vivo perfusion, involves providing oxygen and nutrition to organs for a smooth “live” transition from donor to recipient. (See p. 6 for a profile of Cleveland Clinic’s normothermic ex vivo perfusion efforts across multiple organs.) By using a miniaturized heart-lung machine and whole blood to perfuse organs awaiting transplantation, the aim is to enable use of more marginal organs that wouldn’t thrive during the traditional cold storage process. A primary goal is to increase the number of organs available for transplant. Organ reconditioning and even organ repair are also possible, which would improve the quality of organs as well. Cleveland Clinic’s efforts to expand normothermic ex vivo perfusion beyond the lungs and heart have started with the liver. Cristiano Quintini, MD, a surgeon with the liver transplant program, has performed pioneering studies of normothermic ex vivo perfusion in large animal models, with positive outcomes. Every parameter evaluated has shown perfusion to be superior to traditional cold storage (the standard of care). The next step is testing in human liver transplantation, which Cleveland Clinic researchers hope to begin within the next year. “Normothermic ex vivo perfusion offers the potential to increase the number of donor organs that are usable for transplant by 15 to 20 percent,” says Dr. Quintini. He adds that another groundbreaking feature of the process is the ability to assess the organ during preservation and to predict its function. “The implications are tremendous, considering that transplant of a failing liver almost invariably means the patient’s death unless a retransplant is performed.” For now, normothermic ex vivo liver perfusion is highly labor-intensive and demands the resources and deep staffing of a center of excellence like Cleveland Clinic. But after development and refinement by a handful of leading programs, normothermic ex vivo liver perfusion may one day become routine, just as machine perfusion is now widely used for kidney transplants.

Continuing research on innovative normothermic ex vivo perfusion to improve the supply and quality of donor livers
Members of Cleveland Clinic’s liver transplant program published in January 2014 the first report, to their knowledge, of successful use of the protease inhibitor telaprevir to treat HCV recurrence after liver transplant in a patient coinfected with HIV (Transplantation. 2014;97[2]:e14-e15).

The patient was a 62-year-old man with a history of HIV infection, chronic HCV genotype 1b infection complicated by cirrhosis, and hepatocellular carcinoma. Nine months after he underwent liver transplant in August 2011, liver biopsy revealed recurrent hepatitis C with grade 2/4 inflammation and stage 2/4 fibrosis.

The patient’s immunosuppression regimen consisted of tacrolimus and mycophenolate mofetil. To address his HCV recurrence while accounting for these immunosuppressants, the team tried triple therapy with the direct-acting protease inhibitor telaprevir plus ribavirin and pegylated interferon. To avoid having the patient on both HCV and HIV protease inhibitors, the darunavir-ritonavir component of his highly active antiretroviral therapy (HAART) regimen for HIV was stopped before telaprevir was started, at which time the integrase inhibitor raltegravir was also initiated.

From day 1 of the telaprevir-based therapy, the team monitored the patient’s serum tacrolimus level very closely. Despite the need for frequent adjustments to his tacrolimus dosage, management was successful: His HCV RNA became undetectable at eight weeks of therapy and remained undetectable 12 weeks after the end of his HCV treatment regimen, indicating sustained virologic response. There were no harmful effects to the liver graft or to renal function. Two months after the end of telaprevir therapy, the patient was switched back to his original HAART regimen.

This case shows that telaprevir-based triple therapy can be used to treat HCV recurrence in patients coinfected with HIV so long as they are monitored closely at a center with experience in transplanting HIV patients. Notably, this patient was treated when telaprevir was the highest level of therapy for patients with HCV; regimens based on newer direct-acting agents would be used now, though the need for vigilant monitoring would still apply.
simpler, shorter dosing schedules. These agents include three new protease inhibitors and the nucleotide analog inhibitor sofosbuvir, which is a component of the first all-oral, interferon-free regimen to be approved by the FDA for HCV infection.

The direct-acting agents are not yet FDA-approved for treating HCV after liver transplant, but Cleveland Clinic is among a few centers studying this off-label use, which requires complex monitoring for toxicity and interactions with immunosuppressants (see case study on opposite page). Outcomes to date have been good, with high virologic response rates and favorable tolerability, and the program is developing protocols for using direct-acting agents in the pre- and post-transplant settings.

**Diverse research to improve outcomes — and sometimes avoid transplant**

In addition to these studies to clear HCV in the transplant setting, Cleveland Clinic is involved in cutting-edge research in multiple areas related to liver transplantation, including:

- Development of 3-D-printed liver replicas for surgical planning and education (see sidebar, p. 25)
- Studies of normothermic ex vivo perfusion for liver preservation in animals (see sidebar, p. 27) with the near-term goal of its use in transplantation of a human liver
- A multicenter clinical trial testing the safety and efficacy of the ELAD® System (Vital Therapies Inc.) in patients with alcohol-induced liver decompensation. ELAD is a blood pumping system that uses a proprietary line of allogeneic human liver cells to provide continuous liver support to patients with liver failure. It can serve as a bridge to transplant or as destination therapy in patients whose livers may regenerate enough to avoid the need for transplant.

**Prolific pediatric program**

Cleveland Clinic’s pediatric liver transplant program is one of the most experienced in the nation, dating back to 1986. Medical care of the youngest transplant recipients is managed by a dedicated medical director of pediatric hepatology and liver transplantation and a team of additional pediatric hepatologists.

The program offers a full range of liver transplant options for children, including:

- Partial grafts from living donors
- Whole-organ and split-liver transplants from deceased donors (including donation after cardiac death)
- Liver transplant in the context of multivisceral transplantation

These living-donor and split-liver capabilities enable surgeons to place smaller grafts in children’s small bodies, increasing transplant opportunities — and often slashing wait times — for pediatric patients in need (see patient sidebar).

Between 2005 and 2013, the pediatric program performed 45 liver transplants in patients 6 months to 19 years old. More than half of those transplants involved split livers from deceased donors or partial livers (left lateral segments) from living donors.

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**LETA SAUNDERS: RECIPIENT OF A PARTIAL LIVER GRAFT FROM A LIVING DONOR**

After being born with biliary atresia, Leta developed refractory ascites and related infections at age 8. The ascites compromised Leta’s ability to play and go to school, requiring her abdomen to be drained of fluid every two weeks.

When it was clear in late 2012 that Leta needed a liver transplant imminently, she was quickly matched to a partial liver graft from an anonymous living adult donor. This allowed Leta to receive a graft well suited to her small body size and avoid being added to an organ waitlist. Her transplant was performed within a month after it was recommended. Less than four months later, she was back at school part-time in Fairport Harbor, Ohio, and more energetic than ever.