Clinical Significance

Liver or intestine transplantation is the treatment of choice for liver or intestinal failure in children. The Pleximmune blood test uses the functional response of the recipient to donor antigens to predict the risk of rejection for that recipient.

The Test

The Pleximmune test measures the risk of transplant rejection at any given time. This risk is measured by recipient T-cytotoxic memory cells (TcM), which express an inflammatory marker, CD154 (CD154+TcM). TcM are a type of lymphocyte among white blood cells. Results are reported as the immunoreactivity index (IR).

Reference Range

An immunoreactivity index (IR) ≥ 1.13 indicates increased risk of rejection.

An immunoreactivity index (IR) < 1.13 indicates decreased risk of rejection.

For samples obtained before transplantation, the respective IR values indicative of increased or decreased risk of rejection are ≥ 1.18 and <1.18.

The immunoreactivity index is the ratio of CD154+TcM induced upon stimulation with donor and non-identical or third-party antigens. Table 1 shows the mean (SD) frequency (%) of donor- and third-party-induced CD154+TcM in 54 blood samples from children with liver or intestine transplantation who are receiving anti-rejection drugs.

Table 1.	Donor-specific	Third-party-specific	Immunoreactivity Index
Patient samples	7.2 ± 0.9	7.0 ± 0.8	1.11 ± 0.08

Individuals suitable for testing

Children who have received or are about to receive liver or intestine transplantation.

Type of sample: Whole blood, 5 milliliters.

Additional information needed: Serologic or molecular typing information at the HLA-A, HLA-B and HLA-DR antigenic loci for donor(s) and recipient.

Collection: After 5AM and before 10 AM. Use sodium heparin (green top) tubes. Invert 8-10 times.

Shipping: Overnight delivery before 10 AM at ambient temperature. Use courier services such as FEDEX or UPS. To arrange local pickup call +1(855)753-9474. Transit time not to exceed 30 hours between collection and delivery.

Shipping address: Plexision Inc., 4424 Penn Avenue, Suite 202, Medical Building, Pittsburgh, PA, 15224, Phone +1(855)753-9474 or +1(855)-PLEXISI, Fax: +1(412)224-2706.

Examples of unacceptable samples: Samples that are delivered >30 hours after collection, arrive with broken container seals, are clotted, sent in tubes other than green top sodium heparin tubes, are <3 ml in volume, and have no information about donor and recipient HLA.

Reporting of results: within 24 hours of receiving blood sample.

Clinical Background: Rejection affects 30-60% of children after liver or intestine transplantation, and can lead to poor graft function or graft loss, or high-dose anti-rejection drug therapy and its life-threatening side effects (1-3). Rejection happens when recipient immune cells called cytotoxic T-cells attack donor cells: hence the term acute cellular rejection or ACR. The likelihood of rejection is an essential consideration in most clinical decisions involving transplant recipients. Currently, rejection-risk assessment is based on history, exam and laboratory findings, and can be inexact. The cross-match, which predicts antibody-mediated rejection, and is the only prognostic test available for clinical use, does not show a significant association with rejection, and is not used for clinical decision during liver transplantation. Biopsies detect ongoing rejection, but can cause life-threatening bleeding and perforation, and are not predictive. The Pleximmune blood test addresses the need for a non-invasive test to predict rejection reliably, and improve clinical decision-making to manage transplant patients.

In the Pleximmune test, rejection-risk is measured with T-cytotoxic memory cells (TcM), which express the inflammatory marker, CD154 (CD154+TcM) (4-7). The expression of CD154 is stimulated by culturing lymphocytes from the recipient's blood with donor or donor-like cells, and with immunologically dissimilar third-party cells. Immunologic similarity or dissimilarity is determined by the HLA-A, HLA-B, and HLA-DR antigenic loci. HLA or human leukocyte antigens have been used to test the degree of similarity between donor and recipients in transplantation since their discovery in the 1960s and are routinely evaluated during transplantation. Post-transplant testing of 124 pediatric liver or intestine recipients shows that the Pleximmune test predicts rejection within 60 days after the test with sensitivity and specificity of 94% and 86%, respectively. Pre-transplant testing of 73 children with liver or intestine transplants shows that the Pleximmune test predicts rejection within 60 days after transplantation with sensitivity and specificity of 83% and 72%, respectively.

References

1. Martin SR, Atkison P, Anand R, Lindblad AS; SPLIT Research Group. Studies of PediatricLiver Transplantation 2002: patient and graft survival and rejection in pediatric recipients of a first liver transplant in the United States and Canada. Pediatr Transplant. 2004 Jun;8(3):273-83. PMID: 15176966.
2. Grant D. Current results of intestinal transplantation. The International Intestinal TransplantRegistry. Lancet. 1996 Jun 29;347(9018):1801-3.PMID:8667925.
3. Grant D, Abu-Elmagd K, Reyes J, Tzakis A, Langnas A, Fishbein T, Goulet O, Farmer D; Intestine Transplant Registry. 2003 report of the intestine transplant registry: a new era has dawned. Ann Surg. 2005 Apr;241(4):607-13.PMID:15798462.
4. Ashokkumar C, Talukdar A, Sun Q, Higgs BW, Janosky J, Wilson P, Mazariegos G, Jaffe R, Demetris A, Dobberstein J, Soltys K, Bond G, Thomson AW, Zeevi A, Sindhi R. Allospecific CD154+

T cells associate with rejection risk after pediatric liver transplantation. Am J Transplant. 2009 Jan;9(1):179-91. Epub 2008 Oct 31. PMID:18976293.

5. Ashokkumar C, Gupta A, Sun Q, Ningappa MB, Higgs BW, Mazariegos G, Fazzolare T, Remaley L, Soltys K, Bond G, Abu-Elmagd K, Sindhi R.Allospecific CD154+ T cells identify rejection-prone recipients after pediatric small-bowel transplantation. Surgery. 2009 Aug;146(2):166-73. Epub 2009 Jun 26.PMID:19628070.
6. Sindhi R, Ashokkumar C, Higgs BW, Gilbert PB, Sun Q, Ranganathan S, Jaffe R, Snyder S, Ningappa M, Soltys KA, Bond GJ, Mazariegos GV, Abu-Elmagd K, Zeevi A. Allospecific CD154 + T-cytotoxic memory cells as potential surrogate for rejection risk in pediatric intestine transplantation. Pediatr Transplant. 2012 Feb;16(1):83-91. doi: 10.1111/j.1399-3046.2011.01617.x. Epub 2011 Nov 29. PMID: 22122074
7. Sindhi R, Ashokkumar C, Higgs BW. Cellular alloresponses for rejection-risk assessment after pediatric transplantation. Curr Opin Organ Transplant. 2011 Oct;16(5):515-21. Review. PMID: 21844808.