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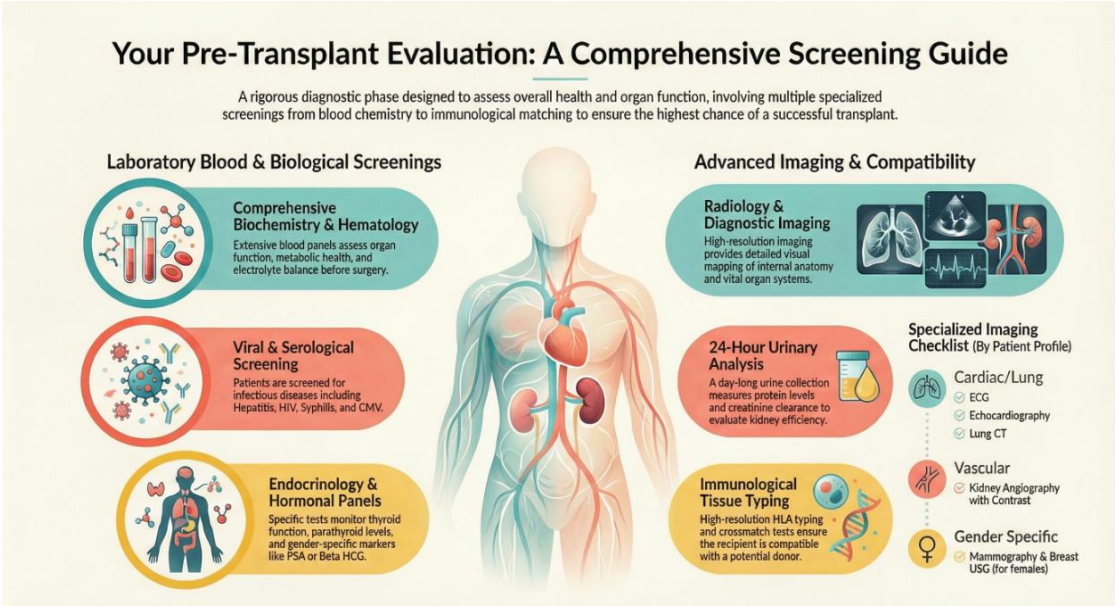
PRETRANSPLANT EVALUATION OF COUPLES

The pre-transplant evaluation for couples is based on two main ideas. First, living donors should not have a higher risk of kidney disease after donating. Second, the transplanted kidney should last as long as possible, considering immune risks and other health issues. A thorough evaluation looks at all important factors to keep the donor safe and predict how well the new kidney will work for the recipient. Both donor and recipient have similar tests to gather the needed information. The process begins with meeting the couple and reviewing their medical histories. Standard tests include blood and urine work, as well as scans of the abdomen and chest. The transplant team, which includes a surgeon and a kidney specialist, reviews these results. A heart check is almost always required. If needed, other specialists, such as those for the lungs, stomach, blood, or joints, may also help.

An efficient and cost benefit way to begin the pre-transplant evaluation is by checking immunologic risk first. If the recipient has not had a blood transfusion, pregnancy, or a previous transplant, basic immunologic tests are enough. If the immunologic risk is high, it means the recipient's immune system is already sensitive to the donor's HLA antigens, so more immunosuppression will be needed. This approach works up to a certain risk level, but if the risk is too high, the chances of rejection, infections, and cancer go up. The cost of pre-transplant evaluation depends on which immunologic tests are needed to check the recipient's risk. Other health problems, such as diabetes, past cancer, or genetic diseases, may also mean extra tests and specialist opinions are needed.

Normally, a person's immune system does not make antibodies against Human Leukocyte Antigens (HLA), which are unique to each person. Immunologic risk means a patient has lab or clinical signs of past exposure to the donor's HLA antigens, such as blood transfusions, pregnancy, or a previous transplant. This risk is measured in the lab using the Panel Reactive Antibody Screen (PRA) and HLA crossmatch tests. PRA checks for HLA antibodies in the recipient. If there is significant immune sensitization, we need two advanced tests: the Single Antigen Bead Assay to detect HLA antibodies in the recipient, and High-Resolution HLA Typing to identify the donor's HLA subtypes. There are two types of HLA antibodies: Class I (HLA-A, HLA-B) and Class II (HLA-DR, HLA-DQ). The first test is usually an ELISA to detect whether the recipient has HLA antibodies. If antibodies are detected, a more advanced Luminex test, the Single Antigen Bead Assay, is used. This test uses beads coated with specific HLA antigens to detect and quantify antibodies in the recipient's blood, providing highly detailed results. For example, an ELISA might show antibodies against HLA A34, but the Single Antigen Bead Assay can specify the exact type, such as Anti-HLA B:34:01. Once we know the recipient's exact HLA antibodies, we then do detailed HLA typing of the donor. High-Resolution HLA Typing provides a precise, four-digit match for the donor's tissue. For example, if the donor's tissue is HLA B;34;13 and the recipient has antibodies against HLA B 34, but not against these exact subtypes, the transplant can go ahead with reasonable risk.



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Clinical Protocol: Comprehensive Pre-Transplant Physiological and Immunological Evaluation

1. Framework for Pre-Transplant Medical Necessity

Standardizing the pre-transplant evaluation is key for a successful transplant. The tests are similar both for the donor and the recipient. The only difference is that Computed Tomography is not performed by contrast agents for preemptive patients, and some patients with long duration at hemodialysis can stop making urine which makes cancelling urinary tests. By creating a detailed baseline of the patient's health, these tests help the team lower surgery risks and improve the kidney's long-term survival. This protocol is more than just screening; it is a structured way to assess risk, confirm medical need, and protect the new kidney. The goals of this protocol are:

• Checking overall stability: Making sure the patient is healthy enough to handle the stress of major surgery.

• Screening for hidden cancers and infections: Finding any conditions that could become serious or cause graft loss after starting immunosuppression.

• Ensuring immune compatibility: Measuring the risk of immediate or long-term rejection using detailed lab tests.

This detailed evaluation starts with metabolic and biochemical tests, which form the basis for all later surgical and medication decisions.

2. Systemic Metabolic and Organ Function Profiling

Checking metabolic balance and basic organ function, especially the kidney, liver, and pancreas, is essential. The patient must be able to process anesthesia and handle possible kidney and liver side effects from ongoing immunosuppression. Missing hidden organ problems at this stage can make surgery unsafe.

Metabolic and Biochemical Assessment Matrix

Organ System / Metabolic Indicator	Specific Tests	Clinical Implication for Surgery
Renal/Metabolic Baseline	Hemogram, Glucose, HbA1C, BUN, Creatinine, Sodium, Potassium	Dictates fluid management, baseline GFR, and glycemic control; high HbA1C mandates surgical delay for metabolic optimization to prevent impaired wound healing.
Mineral/Bone Health	Calcium, Phosphor, Magnesium	Identifies risk for renal osteodystrophy and vascular calcification, which directly impact intraoperative hemodynamic stability and post-operative mobility.
Lipid Profile	Total Cholesterol, HDL, LDL, Triglyceride	Quantifies long-term cardiovascular risk; essential for baseline before initiating steroids or calcineurin inhibitors known to exacerbate dyslipidemia.
Hepatic/Pancreatic Function	Total Bilirubin, Amylase, Lipase, AST, ALT, GGT, ALKP	Evaluates synthetic capacity and biliary health; abnormal GGT/ALKP mandates pre-transplant liver imaging or biopsy to rule out cirrhosis, which would trigger a dual-organ transplant strategy.

Clinical Commentary on Systemic Markers: These markers are central to deciding whether surgery can proceed. For example, severe imbalances in potassium or sodium, or high liver enzyme levels, are clear reasons to delay surgery and require urgent

treatment to stabilize the patient. Also, baseline kidney markers must be compared with imaging results to ensure the patient's blood vessels and kidney function can support the new graft.

These basic lab results prepare for more detailed blood and hormone tests that help keep the patient's body in balance.

3. Hematologic Stability and Endocrine Homeostasis

Careful checks of blood type, clotting, and hormone balance are crucial to prevent bleeding during surgery and problems afterward. In patients with long-term organ failure, hormone changes are common and must be managed for a safe recovery.

• Primary Compatibility: The ABO Blood group test remains the absolute foundational requirement for donor-recipient matching.

• Coagulation Profile: Assessment of Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) is mandatory to quantify bleeding risk and guide the intraoperative use of blood products.

• Inflammatory and iron markers: CRP checks for hidden inflammation. Ferritin, iron, and iron-binding tests show if the patient has enough iron. Any iron deficiency should be treated before surgery to lower the risk of anemia and reduce the need for transfusions, which can affect the immune system.

• Endocrine and Cancer Screening:

◦ Thyroid Axis: Free T3, Free T4, and TSH monitoring is essential, as thyroid dysfunction can lead to intraoperative cardiovascular instability.

◦ Mineral metabolism: Parathormone (PTH) levels are checked to find any parathyroid problems. If not managed, these can cause high calcium after the transplant, which can harm the new kidney.

◦ Gender-specific tests: PSA for men and Beta HCG for women are required to rule out prostate cancer or pregnancy, as either would change or stop the transplant process.

Once blood and hormone levels are stable, the next step is to assess infection risks.

4. Infectious Disease and Serological Screening

Immunosuppression can make hidden infections a serious problem. Blood tests for infections are an important safety step and help plan care after the transplant.

Mandatory Serological Checklist and Clinical Impact

• [ ] **HBsAg / Anti-HBs / Anti-HBc (total):** Determines Hepatitis B status. A positive HBsAg mandates the initiation of lifelong antiviral therapy prior to transplant.

• [ ] **Anti-HCV:** A positive status informs the potential use of HCV-positive donors, significantly expanding the donor pool in the current clinical landscape.

• [ ] **Anti-HIV:** A critical screen for immunodeficiency that dictates specialized management protocols.

• [ ] **Syphilis:** Identification of Treponema infection; requires a complete course of penicillin prior to the initiation of induction immunosuppression to prevent neurosyphilis or systemic relapse.

• [ ] **CMV IgG:** The "D+/R-" or "D-/R-" status dictates the intensity and duration of post-transplant Valganciclovir prophylaxis.

• [ ] **Ebv Vca Ig G:** Essential for identifying candidates at high risk for Post-Transplant Lymphoproliferative Disorder (PTLD).

After infection tests are done, the team can focus on detailed checks of kidney and urinary health.

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5. Quantitative Renal Function and Urinary Analysis

Serum creatinine provides a general indication of kidney function, but it is not sufficient for surgical planning. 24-hour urine tests and local cultures provide more detailed information about kidney health and recovery potential.

Dual-Track Urinary Assessment

Routine Urinary Assessment	24-Hour Urine Panel
Complete Urinalysis: Establishes the baseline for urinary sediment and pH.	**Microalbuminuria (24h):** Detects early-stage glomerular stress and vascular disease.
Urine Culture: Identifies occult infections; a positive culture mandates antibiotic clearance before surgical incision.	**Total Protein (24h):** Quantifies proteinuria; high levels may signal a primary glomerulonephritis that necessitates bilateral native nephrectomy.
	Creatinine Clearance (24h): The gold-standard measurement of GFR. For recipients, this determines residual function; for living donors, this is the definitive "go/no-go" metric for donation.

After these lab tests, structural and imaging studies are needed to help the surgical team plan the operation clearly.

6. Radiographic Imaging and Cardiovascular Clearance

Advanced imaging finds structural problems, heart issues, and hidden cancers that lab tests cannot show. These results help decide how surgery will be done and whether the patient's body can handle the transplant.

• **Pulmonary Clearance: Lung Computed Tomography** is utilized to rule out active infections, pulmonary nodules, or structural lung disease.

• Heart health: Electrocardiograms and heart ultrasounds are required to check heart function. Patients with serious heart problems cannot have surgery until a heart specialist approves.

• **Vascular and Structural Roadmap: Kidney angiography with contrast CT is the main** mapping tool. It finds arterial and venous problems, such as multiple renal arteries, that may require complex surgery on the graft before implantation.

◦ *Note:* If Section 2 reveals impaired Creatinine Clearance, the Angiography must be performed using a non-contrast or pre-hydration protocol to prevent further renal insult.

• Cancer screening for women: Mammograms are required for all women over 40, and breast ultrasounds are needed for all female patients to lower the risk of cancer after immunosuppression.

After these physical and imaging tests, the final and most detailed step is checking immune compatibility.

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7. Immunological Compatibility and Tissue Typing

The main factor in whether a transplant will work is how well the donor's and recipient's tissues match at the molecular level. These tests help prevent immediate rejection and are the best predictors of long-term kidney survival.

Immunological Assessment Requirements

• HLA typing (A, B, DR, DQ): This test finds the main tissue match points. High-resolution typing is needed for patients with high PRA or those in paired exchange programs. This helps the team find "unacceptable antigens" and avoid poor matches when organs are offered.

• Crossmatch Protocols:

◦ CDC-XM (Complement-dependent cytotoxicity): The standard requirement to identify pre-formed, complement-fixing antibodies.

◦ FC-XM (Flow cytometric lymphocyte crossmatch): This sensitive test finds low levels of donor-specific antibodies that CDC-XM might miss and helps decide how strong the initial treatment should be.

Bringing together the immunological profile with the patient's systemic, metabolic, and imaging data helps the clinical team determine the surgical risk. The final decision for transplant readiness is made only when all factors are optimized and the immune barrier is considered manageable.

How do pregnancies or blood transfusions create HLA antibodies?

HLA antibodies develop, a process known as **HLA alloimmunization**, because the immune system tells the difference between what belongs in the body and what does not. Human Leukocyte Antigens (HLA) work like ID cards on cell surfaces. If the immune system encounters an unfamiliar ID card, it treats it as foreign and produces antibodies to fight it.

Pregnancies and blood transfusions are two of the most common ways this "non-self" biological material enters the body:

Pregnancy

• **Inherited Markers:** A baby inherits half of its HLA markers from its father.

• **Biological Exchange:** During pregnancy, and especially at delivery, the mother's and baby's blood can mix. Even pregnancies that end early can cause blood mixing, leading to sensitization.

• **Immune Recognition:** The mother's immune system recognizes the baby's **paternal HLA markers** as foreign.

• **Antibody Production:** As a result, the mother may make antibodies against the baby's paternal HLA markers. This is why women who have had several pregnancies often have more HLA antibodies.

Blood Transfusions

• **Leukocyte Exposure:** Blood transfusions mainly provide red blood cells and platelets, but they often also contain small amounts of **white blood cells (leukocytes)**.

• **HLA on White Cells:** These white blood cells are covered in the donor's unique HLA markers.

• **Alloimmunization:** When someone receives these donor cells, their immune system recognizes the foreign HLA markers and makes antibodies to attack them. This is called **alloimmunization**.

• **Risk Mitigation:** Today, blood banks lower this risk by filtering out white blood cells or treating the blood, but some risk remains, especially with platelet transfusions.

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After these exposures, a patient can become **"sensitized,"** meaning they have antibodies ready to attack any tissue with those specific HLA markers in the future. This makes it harder to find a matching organ donor, since the recipient's body may reject any organ that matches their existing antibodies.

What are the next steps for a highly sensitized patient?

A **highly sensitized patient i**s someone with a high **Calculated Panel Reactive Antibody (cPRA)** score, such as 99%, who is likely to reject most potential donors. For these patients, the medical team must use advanced molecular and digital strategies instead of just basic testing.

The next steps involve a highly specialized immunological workflow:

1. Advanced Antibody Profiling (Single Antigen Bead Assay)

The first important step is a **Single Antigen Bead (SAB) Assay using Luminex technology**. Unlike basic tests that only show if antibodies are present, this test identifies **exactly which HLA antibodies** are present and measures their **Mean Fluorescence Intensity (MFI)**. The brightness of the result shows how many and how strong these antibodies are in the recipient's blood.

2. High-Resolution HLA Typing

Standard 2-digit antigen-level typing is not enough for sensitized patients. The team needs to do **High-Resolution (4-digit) Molecular Typing** for both the patient and possible donors. This finds the exact genetic versions, or alleles, of HLA markers. It is important because a patient may have antibodies against one HLA marker, such as HLA-A02:01, but not another, such as HLA-A02:05.

3. The Virtual Crossmatch (VXM)

Based on the SAB assay results, the team prepares a list of **"unacceptable antigens**." A computer then does a **Virtual Crossmatch**, comparing the patient's antibodies to a donor's HLA markers. This digital check helps the team quickly rule out donors who are not a match, saving time and avoiding situations where a patient is prepared for surgery but sent home after a failed test.

4. Enrollment in Kidney Paired Donation (KPD)

For highly sensitized patients, it is often impossible to find a match in their family or local area. **Paired Exchange** programs use national registries and computer algorithms to find matches among many donor-recipient pairs. These programs require **High-Resolution HLA typing and Single Antigen Bead screening to ensure computer matches are almost always correct, helping prevent problems** that could affect several patients.

5. Specialized Laboratory Testing (C1q Assay)

If antibodies are detected but a match is still possible, the lab may use a **C1q Assay**. This test shows which antibodies can trigger the chemical process that destroys the organ. If an antibody is present but the C1q test is negative, the transplant may still be safe in some cases.

6. Physical Confirmation and Desensitization

Before surgery, doctors usually do a physical crossmatch to check for compatibility.

• **Flow Cytometric Crossmatch (FCXM):** This is a very sensitive test that uses lasers to find even small amounts of antibody binding, which could cause long-term problems.

• **CDC Crossmatch:** This is the final check. If donor cells die when mixed with the recipient's blood, the transplant is usually cancelled to prevent immediate rejection.

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If a match is found but there is still some immune risk, the patient may have desensitization treatment. This means taking extra medication to weaken the immune system and reduce the risk of rejection. If the immunologic risk is too high, it's better to participate in the Paired Exchange Program to match with a kidney that is suitable based on HLA typing.

What are the factors influencing the cost of the transplantation Process?

The main factors affecting the cost of transplantation are the complexity of medical evaluation, the patient's medical history, and the level of immunologic risk.

1. Immunologic Risk and Sensitization The biggest factor affecting cost is the recipient's immunologic risk. If a recipient is sensitized, meaning they have developed antibodies against foreign tissue, more advanced and costly tests are needed to make sure the match is safe.

• **Sensitizing Events:** A history of **pregnancies** (even early terminations), **blood transfusions** (especially complete blood), or **previous organ transplants** increases the likelihood of sensitization and the need for more complex testing.

• **Cost of Advanced Testing:** For a "high-risk" (sensitized) couple, this cost increases to **3-fold, including** a **Single Antigen Class I and II assay** and **High-Definition HLA Typing**.

2. Comorbid Diseases and Specialist Consultations The presence of underlying health issues necessitates additional testing and expert views, which add to the total cost:

• **Cardiac Status:** Patients with low exercise tolerance, a history of **myocardial infarction**, or previous interventions (stents, bypass, pacemakers) require more intensive cardiac evaluations. Angiography and stenting can cost more and also postpone the surgery for another month for cardiac performance.

• **Chronic Conditions:** Diseases like **Diabetes Mellitus** (monitored via HbA1C and screening for complications like retinopathy) or **Hypertension** increase the evaluation complexity.

• **Cancer Screening:** Previous malignancies or the need for age-specific screenings (e.g., **Mammography** for women over 40 or **PSA** for males) are also factors.

4. Routine Diagnostic and Follow-up Requirements

• **Standard Lab Panels:** Comprehensive blood biochemistry, serology (Hepatitis, HIV, CMV), and 24-hour urinary panels are standard for both donors and recipients.

• **Radiology:** Costs include imaging such as **Lung CT**, **Kidney Angiography with Contrast CT**, and **Echocardiography**. Further testing to screen for other diseases like cancer can have additional cost.