

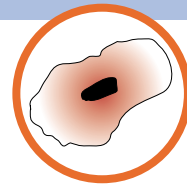
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GETTING NEW

ISLET CELLS

Facts About Clinical Islet Transplants



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PATIENT INFORMATION BROCHURE

CLINICAL ISLET TRANSPLANTS

HOW DO I GET INTO THE ISLET CELL TRANSPLANT PROGRAM?

Islet transplant is an experimental procedure. Doctors are still learning about it. There are not a lot of islet transplants available. For these reasons and for the safety of patients, centers are very careful about who gets an islet transplant. Most centers require patients to enter a clinical trial. That means that doctors will watch every step of the transplant program to see how you react. In the United States, the FDA inspects these trials. Being in a clinical trial is a lot of work, with extra visits to the clinic and extra blood work. Islet transplants are carried out on their own (**islet alone**) or together with a kidney transplant (**kidney and islet, or islet after kidney**). You can learn more about islet transplant by logging onto your center's Web site.



People who want to get an islet transplant must give a lot of information to the doctors working with the trial. There are a lot of forms in the application package that help you tell the doctors about your health. You might find the items listed in the box below in the package you will get from the center.

Items in the Application Package	Explanation
1. Inclusion/exclusion checklist	This is a checklist that allows you and your physicians to see if you might be able to get an islet transplant. You must complete the checklist before getting to the rest of the items. Each center uses a different checklist.
2. Laboratory requisition	This form is a list of the laboratory tests that you will need for your medical evaluation.
3. Medical history form	This form has questions about your medical history.
4. Diabetes questionnaire	This form has questions about diabetes history and treatments.
5. Physician referral form	The doctor who treats your diabetes will fill out this form.
6. Release of information	This form allows health-care workers to get your medical records. They read them to see if you qualify for the islet transplant.

When the center has all the information, the local research team will review it. They will see if your tests and information match what the doctors are looking for. If it does, and if there is room in the program for a new person, you will get an appointment at the assessment clinic. This appointment is to see if islet transplant is for you. If your tests and information do not match, the center will let you know. Your name can be added to a waiting list so that you can try again in the future.

There are many people who send tests and information to request a transplant. Only a **very small number** will get one. You may have to wait a while to hear from the center. Please be patient and know that many offices may not be able to respond to you as fast as you would like.



ASSESSMENT

What happens at the assessment clinic?

At the assessment clinic, you will get to meet the center's team, and they will get to know you. You will meet with the transplant doctors and nurses. They will ask about your health and do some more tests. They will discuss with you the benefits and risks (the pros and the cons) of islet cell transplantation. They will talk with you about the clinical trials at the center. You will then have a chance to think about what you heard. You can also think about what it might be like to join a clinical trial. The center will look at the information to see if you match what they need in the clinical study. If you want to join the study and you are a match, you will get another appointment at the center for a full assessment.

What is a full assessment?

If you decide that you would like to have a full assessment, you will spend from 2 to 4 days at the center. You will have more tests and answer more questions about diabetes and other health problems during that time. The tests and examinations will vary at each center.

Blood tests

The blood tests are done on the first day of your assessment. The staff will take many tubes of blood. The total amount of blood they take is less than what they take during a blood donation. It should not affect your health.

After the tests

The other tests take 2 to 3 days. After all the tests are done, you will need to wait for 3 or 4 days to hear from the center, at which time they will tell you if transplant is good for you or not. They might give you more tests if there is a concern about the result of the first tests. Once all tests are completed, the islet transplant team will look at the information and decide what to do next. The transplant coordinator will let you know about your results.

What happens if I meet the requirements for the program?

If you match what the program needs, you will meet the doctors involved with the transplant program. They will go over the program, the risks, and follow-up needed. If you still want to be part of the program, they will ask you to sign a consent form. Then you will meet with the coordinator to go over the plan for coming in for a transplant. They might give you a pager so they can get in touch with you.

ASSESSMENT (CONT.)

What happens while I am waiting for the call?

You need to make sure that someone can take you to the hospital when the center calls. The center might call on the weekend, late at night, or early in the morning. When they call, you need to go. Make a list of 5 or 6 people you can call for a ride to the hospital. If one cannot take you when the hospital calls, call the next person on your list.



You might have to pay for tests, medicine, or a ride to the center. If you have any questions, please ask your transplant nurse coordinator or the social worker at the program. Make sure you know what you need to pay for and that you have the money ready.

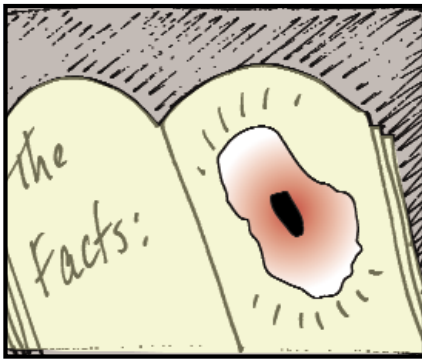
There is no guarantee that being on the islet transplant list means that you will get an islet transplant. If it does happen, there is no telling when it will happen. It is best to be ready. Have arrangements made for your responsibilities at home to be taken over by others. Often patients will make a list of chores and who will do them while they are away. These friends and family can be called to help at any time. Transplants often are performed on weekends or at night.

It is important to have a bag packed and ready. Check the bag often. Make sure you take everything you need. You should bring any medications you are currently taking when you are called in for the transplant. It is important that you bring your glucose monitor. It is also important to monitor your glucose regularly even while in the hospital.

Some work while you wait

If your condition changes, it is important that you see your regular doctor. Also, tell the transplant team of any change and treatment that you need.

While waiting you will need to: continue to test your blood sugars daily (at least four tests a day). A glucose meter with memory may be used by your center. This will allow them to download your readings and compare your glucose control before and after the islet transplant. The type of meter depends on your center's regulations.



THE TRANSPLANT PROCEDURE

It is your responsibility to be available when the center calls. If the center cannot reach you, you could lose your chance for a transplant.

When the center calls, here is what they might tell you (depending on the center's regulations):

- Do not eat or drink anything after the call.
- Monitor your glucose.
- Call friends and family and tell them that you might be having your transplant.
- Go to the Transplant Center.
- Take your pager or cell phone with you. This way, if the transplant is cancelled, they can reach you while you are on your way to the hospital.

When a pancreas is available, the doctors take out the islet cells. They might not get enough islet cells to make a transplant work; if not, they will cancel the transplant. Some patients are already in the hospital when their transplant is cancelled. Do not think that just because you get the call you will get an islet transplant. There are many steps in getting the islet cells ready. The transplant might be cancelled at any step, and you will be sent home.

Where does the pancreas come from?

The pancreas comes from the same donors that give hearts, lungs, livers, and kidneys. These people tell their family and friends that they want to give their heart, kidneys, eyes, pancreas, or other organs to someone else after they die. These donors give the gift of life to others.

Centers need 1, 2, or maybe 3 pancreas organs for each transplant patient. The goal is to have the patient off insulin. Because the transplant requires a full pancreas, a relative cannot donate a part of his or her pancreas. It is not the same situation as with kidneys, where you could donate one and remain healthy with the one you have left.

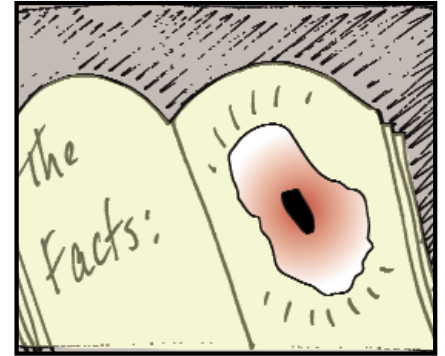
In the United States, we have an organ procurement system called UNOS. This system makes sure that donated organs are transported to the patients who need them. These teams make arrangements for the removal, storage, and transportation of all acceptable donated pancreases to the center's islet preparation laboratory.

We need more donors. Please sign your organ donation cards and make sure your family understands that you want to give someone else the gift of life.

THE TRANSPLANT PROCEDURE (CONT.)

Preparation for the transplant

Once you arrive at the hospital, the Admitting Department staff will register you and assign a room to you. Once you arrive on the unit, your nurse will usually take down your medical history and start an intravenous line for medications. You will have blood drawn and have a chest x-ray film taken. You will usually be asked to sign consent forms for the transplant and the medications. Then you will wait for the call to go down to the Radiology Unit or Operating Room, where the transplant will take place. You will need to take medicine while you are waiting. You need to monitor your glucose and tell the nurse what your level is each time.



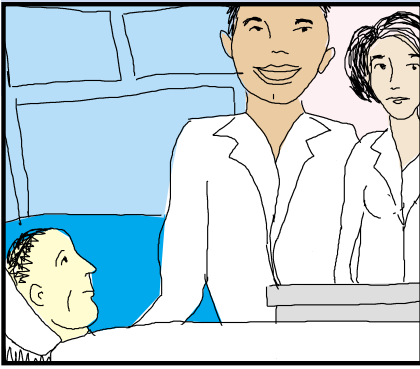
Islet cell transplant is done in the Radiology Department or in the Operating Room.

In the Radiology Unit, local anesthetic is injected on the right side of the abdomen where the liver is located. The radiologist then places a needle and a tube into the main vein in the liver called the portal vein. They use a special x-ray machine (fluoroscopy) and dye. Once the tube is in place, a solution containing the islet tissue is injected. The catheter is then removed, and you are taken back to the Nursing Unit. There you will stay in bed for several hours. During this time, they will tell you to lie on your right side to lower the chance of bleeding from the operation.

Some centers prefer to do the islet transplant procedure in the Operating Room. They will make a small incision. Your center may prefer this option if you will already be in the Operating Room under general anesthesia for a kidney transplant. This will avoid the small risk of bleeding whenever a needle and catheter are used to directly enter the liver. In the operating room, the surgeon will inject the islets while looking into a vein that flows into the liver rather than injecting the islets directly into the liver.

Back on the Nursing Unit

The personnel will monitor your vital signs and serum glucose levels. After about 6 hours, you will have some blood drawn for testing. You will also go for an ultrasound to make sure that there is no bleeding around the liver and that the blood is flowing well in your liver. If the test results from the blood and ultrasound are good, you may be able to go home. Time in the hospital varies from 12 hours to 4 days, depending on the treatment regulations used at your center.



AFTER YOUR ISLET TRANSPLANT

Now what?

After leaving the hospital, the care of the islet cells becomes your job. You will need to take strong antirejection drugs for as long as the islet cells are working. Your body will always know that the new islet cells came from someone else. If you do not take the antirejection drugs, your body will get rid of the islet cells by a process of rejection. The islet cells will not work after that.

You need to monitor your blood glucose very carefully. At first you will need to take insulin. Your insulin needs will change with each islet cell transplant. The transplant team will help you adjust the amount of insulin. It is important to remember that the islet cells will take some time to settle into their new home in your liver. We do not want to stress the islet cells, so during this time, we will ask you to keep your glucose at a good level. You do not want to make the new islets work too hard at first. This is similar to when you plant a crop: Not every seed that you put in the ground will grow into a plant. If you prepare the soil and feed and water the seeds, you increase your chance for a good harvest. So it is with the islet cell transplant: If you take good care of the islet cells right after the transplant, you have a better chance of good islet cell function. **This means sticking to your diet and a healthy, balanced way of living.**

What is rejection?

Rejection is the body's natural defense against outside cells or particles like bacteria and viruses. Your immune system knows that your new islet cells are not part of your own body and will begin to destroy them.

How do we keep your body from destroying the islet cells?

The transplant doctors will use medications to interfere with parts of the immune system. They will reduce your immune system enough so that you do not reject your islet cells. These medications are called immunosuppressants. These medicines include tacrolimus (Prograf[®]), sirolimus (Rapamune[®]), and daclizumab (Zenapax[®]). These drugs work together to stop the immune system so it does not destroy your new islets cells. They may use other medicines or antibodies to prevent rejection as a result of other studies.

The center must monitor blood levels of your drugs closely to make sure that you do not reject your islet cells or have too much of these drugs in your system. Once you are at a stable level, your monitoring will be less and less.

How to prevent and treat infection

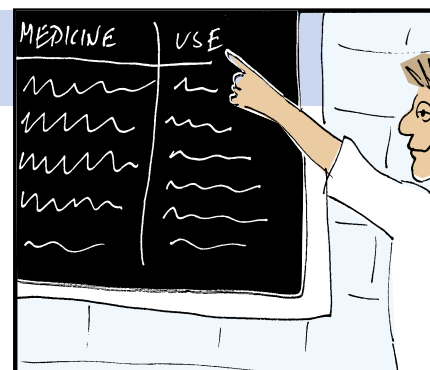
You will need to be more careful about preventing infections.

- Wash your hands well.
- Do not visit friends who are sick.
- Get an annual flu shot.
- Practice safe sex (use condoms). Have yourself and your partner tested for any sexually transmitted diseases.
- Report symptoms of infection right away. These include fever, chills, aches, pains, vomiting, or diarrhea.

AFTER YOUR ISLET TRANSPLANT (CONT.)

Do what you can to lower your chances of developing cancer.

- Use SPF 15 sunblock. Every time you are in the sun, wear a hat. Do not lay or sit out in the sun. Also, avoid the hottest time of the day (between 10:00 AM and 2:00 PM).
- Get mammograms or prostate examinations every year if you are older than 40 years of age.
- Do breast or testicular self-examinations for early detection.
- Have any unusual skin growths checked right away.



Note: The information below about drugs is provided as an example of the drugs you might take. Your center might give you different drugs. Ask the center to tell you about the drugs they give you. Make sure you know when to take them and how much to take.

Some common medications given to prevent infection after transplant:

Septra[®], Bactrim[®]—Part of the family of medications called “sulfa drugs.” They are used to prevent pneumonia.

Pentamidine—This medication is used to treat infections. It is used as an alternative when cotrimoxazole is not a good choice.

Ganciclovir (Cytovene[®])—These pills are used to prevent infections from your donor organ. In the event that you develop infection, you will take larger doses intravenously to control the infection.

Nystatin (Nilstat[®])—Nystatin helps prevent yeast infection in your mouth. If you develop a yeast infection, you will take this medication.

What about vitamins?

Do not take vitamins until you have not used insulin for 3 months. After 3 months, you might need high doses of vitamins. When the islet cells are transplanted, they are injured and produce oxygen/free radicals that hurt the cells. There is some proof that vitamins may help reduce the levels of these toxic radicals. The vitamins have almost no side effects when you take them in the doses that we prescribe.

WHAT IS THE SCHEDULE AFTER THE TRANSPLANT?



Blood testing

You might need to go to the center often for blood tests. For these tests, you must be fasting. Ask what time you should stop eating before the test. Do not take your morning insulin until after the tests have been completed. You might have to wait until after the blood tests to take your other drugs.

The number of blood tests will be lower over time as your islet cells begin to work and your drug levels are even. Eventually, you can have your blood work done in a laboratory closer to your home.

You will also have your fat levels (lipids) tested. You will not be able to eat or drink anything other than water for 12 hours before the test.

Keep track of your daily blood glucose and bring your records to the appointments.

Clinic appointments

You will meet the transplant doctors at the Transplant Clinic often. They will tell you what changes to make to your medication. They will also tell you how often you have to come for blood work and appointments.

Medication

Always keep a 2-week supply of your medication on hand.

Glucose monitoring

Initially, you must monitor your blood glucose levels 7 times a day. The frequency will be lower over time as your glucose levels are more even. On the first 2 days of each month, you must monitor before and after meals and before bed.

Rejection

We will know your body is rejecting your new islet cells when they no longer produce insulin. By the time this happens, it will probably be too late to treat the rejection preventively. You can avoid rejection by taking your antirejection medications the right way and by doing what you can to prevent infections.

Infection

The drugs you are taking to prevent rejection suppress your immune system. This means that you must do what you can to prevent infections. You need to immediately treat any infections you might get. See your doctor immediately and tell your transplant team if you have any symptoms of infection. These symptoms are fever, vomiting, diarrhea, or pain.

WHAT IS THE SCHEDULE AFTER THE TRANSPLANT? (CONT.)

Additional tests

There are a variety of other tests to take for the next 5 years after your transplant. These tests will be scheduled at intervals that are consistent with your first transplant and the date you become insulin free.

Possible risks

Some risks associated with islet transplantation are listed below.



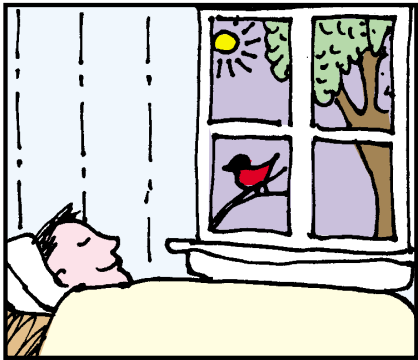
1. Excessive bleeding requiring blood transfusion or surgery.
2. Decrease in blood flow through the liver because of a large blood clot in the portal vein that may require blood thinners or other liver failures.
3. Puncture (or hole) in the bowel or gallbladder that may require surgical repair.
4. Low blood glucose levels after islet cell injection. The nurses monitor this right after the transplant, and you monitor it at home.
5. An allergic reaction to the dye used to locate the portal vein.
6. Infection carried with the islet cells.
7. Slowing down of bowel movements due to manipulation of a tube in your body.
8. Shoulder and abdominal pain.

Immunosuppressive drugs

You will be on these drugs for as long as your islet cells are functioning. They prevent your body from rejecting your islet cells. Risks include the following:

1. Increased risk of infection and cancer due to suppression of your immune system. It is very important to check for these, have regular exams to detect cancer, and maintain a healthy lifestyle to prevent infection.
2. Mouth sores are common and usually resolve with treatment. Some patients may need minor surgery for cleaning mouth sores.
3. Upset stomach and diarrhea are common.
4. Thin nails.
5. Elevated cholesterol levels.
6. Less functioning of the kidneys.
7. There is no information on the effects of the medicines daclizumab and rapamycin in pregnancy. It is therefore recommended that women have children before considering islet cell transplantation. Also, women must not get pregnant while on these medications.

WHAT IS THE SCHEDULE AFTER THE TRANSPLANT? (CONT.)



Complications of diabetes

A period of intensive insulin therapy during the first year can be associated with progression of eye disease that can lead to injury or loss of vision. *Preliminary data from those who have received islet cell transplants indicate an 8% risk.* This deterioration appeared to occur during the first year after the transplant. Because of this risk, the backs of your eyes will be checked frequently during the first year and annually thereafter to identify these possible changes early on. If any changes are observed, you will be referred to an eye specialist who will give you therapy to stabilize the changes.

Immune problems from the islet graft

Transplant of human islets from another person could lead to the development of antibodies against the proteins. These proteins are antigens on the islet tissue. The antibodies will create memory against these antigens and mark them for destruction. This memory could increase the difficulty of obtaining another transplant at a later date because the immune response will be much quicker the next time these antigens are seen by the immune system, which lowers the chances of success for your kidney and/or other organ transplants.

Cost

Can I buy an islet transplant procedure?

No. Organ donation depends on the donors' choice to give their organs. Patients cannot buy their way onto any transplant list. This applies to islet transplant lists as well.

What is the cost involved?

The costs for the assessment and the procedure are different at each center. Most costs are paid by research programs. Be sure you ask what costs you will need to pay before you join the program. The patient usually pays for transportation, housing, and medications after leaving the hospital. Ask if there are other programs to help pay the costs. The drug companies or clinical trial sponsors might pay for some medicine for awhile. Ask how long they pay for the drugs so you know when you need to pay for them. Ask what will happen at the end of 1 or 2 years, when the initial study ends. Possible costs include the following:

Medisense® strips

Glucose meters and strips might be provided to you by your program. Again, you must check up front so you know what to expect.

Medication

The cost of medication will depend on your treatment. At first, the cost will be higher because you will have more drugs to take. Costs will decrease after the first 6 months. Make sure that you have medical coverage to help pay these costs. If you have any concerns, please discuss them with your transplant coordinator so that he or she can help you find programs to help you pay.

WHAT IS THE SCHEDULE AFTER THE TRANSPLANT? (CONT.)

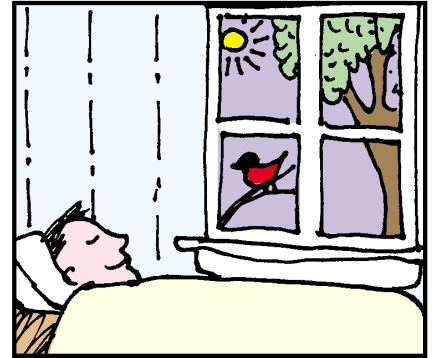
The future

If I am not a match now, how can I become a match later?

Keep checking your center's Web page for new studies and what the center needs for a match.

When will this be widely available to all people with diabetes?

Islet transplant procedures are now being studied. The studies are happening presently at a number of different centers in the United States, Canada, and Europe. Further safety data must be collected before the treatment will become fully insured as the standard of care in the United States.



The next challenge is to improve our supply of islet cells. With the organ donation rate at the current level this treatment is available to only a very few patients. We need more organ donors and must look for other sources of islet tissue.

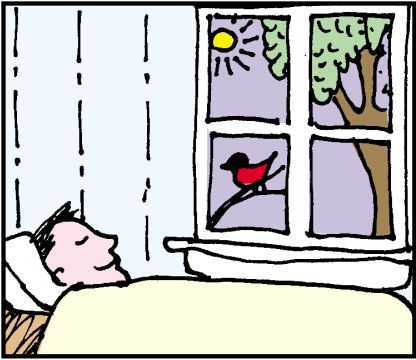
We need to improve the function and capability of the islet cells we transplant. We also need to do for more research.

Lifelong immunosuppressive drugs have side effects. More research is needed to be able to perform these transplants without medications. We also need to do more research to develop medications with fewer side effects.

We hope to learn how to prevent diabetes.

To start or continue research related to diabetes and transplants, funding is critical.

FREQUENTLY ASKED QUESTIONS ABOUT ISLET CELL TRANSPLANTATION



1. Is this a cure? Yes.

However, after islet cell transplantation, patients exchange insulin shots for immunosuppressive drugs and glucose levels. They also exchange irregular glucose levels for immunosuppressive drugs and stable glucose levels. This is a possible long-term treatment option for people who suffer from type 1 diabetes. Islet cells make insulin. Islet cells will carry out the same function as long as they are healthy at the time of transplant and as long as there are enough cells transplanted. The islet cells are at risk for rejection by your body's immune system. Islet cell transplantation is considered

developmental, and long-term outcomes are still not known.

2. Who can donate?

The pancreas comes from the same donors that give hearts, lungs, livers, and kidneys after they die. The donor or the donor's family had decided previously that in the event of brain death, they wish to donate their organs and give the gift of life. This area highlights the critical need for more donors. Please sign your organ donation cards and discuss your wishes with your family. Currently, more than one donor pancreas is needed for every patient who receives an islet transplant. Because we need a full pancreas, a relative cannot donate a part of his or her pancreas.

3. How do I get on the list for an islet transplant?

Review the criteria with your physician to see if you are a candidate. If you decide that you would like to participate in your center's study, you will need to have some preliminary blood work. You also need to fill out a questionnaire and sign a release form. This way, the program can contact your physician. These forms are usually available on the Web site or at your center. Once all this information is received at the center, they will review it. If you meet the criteria, they will ask you to come to the center for a clinic appointment. If you do not meet the current criteria, they will let you know. They'll also keep your name on file so that at some time in the future, they may offer you the opportunity of participating in a study. Following the clinic appointment, you will have a more in-depth assessment. If you meet the study criteria, you will be placed on a waiting list.

4. Can I buy my way on to your list? No.

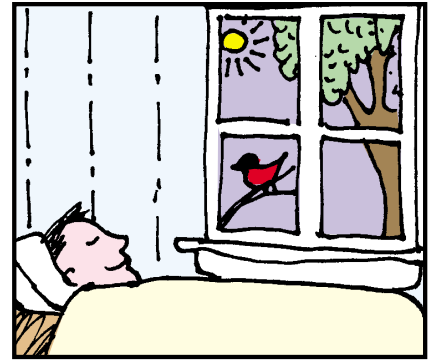
The process of organ donation is built upon public good will. Ethically, patients cannot buy their way onto any transplant list. This applies to islet transplant lists as well.

5. Are there risks involved? Yes.

Islet transplantation remains investigational, and with treatment of larger numbers of patients, the possibility exists that we will see more complications. (See section on risks.) Some common problems patients have experienced include painful mouth sores that have resolved with conservative treatment and time. They also have thinner nails and diarrhea sometimes. More severe problems that could be seen include bleeding associated with the procedure, clot formation in the blood vessels that supply the liver, liver failure, and development or progression of kidney

FREQUENTLY ASKED QUESTIONS ABOUT ISLET CELL TRANSPLANTATION (CONT.)

disease. The medications that we use to suppress the immune system lead to decreased effectiveness of your ability to fight infections and cancer. These medications also have side effects that can lead to kidney dysfunction, ulceration of the mouth, high blood pressure, and diarrhea. These drugs are new. There is very little known about long-term use or how they will affect a pregnancy. We ask all female patients to agree not to become pregnant in the future.



6. What would be my commitment to the program?

The initial assessment requires about 10 days, depending on the center and the protocol. After the transplant, the patient will usually have to attend clinics for checks at different times. Once everything is stable and the risks are reduced, the frequency of visits will be less. Blood work is required initially three or more times a week. Eventually, you will need blood work only once a month. The center will usually expect to follow your progress closely for many years after the transplant. The center will also monitor you for as long as the islets are working.

7. What is the cost of the assessment?

The costs for the assessment and the procedure may be paid by the study protocol. The costs for transportation, accommodation, and medications when you leave the hospital are generally your responsibility. The drug companies sometimes cover the cost of immunosuppressive medications within the project. However, if your transplant is not part of a study, these costly expenses will be your responsibility. For specific details, you must ask your local center for more information.

8. If I have previously had a transplanted kidney or other organ can I be a candidate? Yes.

Some centers are actively transplanting patients with combined kidney and islet transplants, either at the same time or one after the other. The islets may occasionally be prepared at the same time as the kidney. They can also be prepared at a later time, from a different donor, once the kidney function is stable. For these protocols, it may be necessary to adjust your antirejection medications. There is also the possibility of adding more antirejection medications that are “friendly” to the islet.

9. When will this be widely available to all people with diabetes?

The first step is to prove that islet transplant can be performed successfully in many different centers across the world. The next step is to establish islet cell transplantation as the clinical standard of care. The ultimate step will be to improve the supply of islet cells. At the current organ donation rate, this treatment would only be available to a few patients. We need to improve organ donation. We also need to improve the function and viability of the islet cells we transplant and do more studies. Lifelong use of immunosuppressive drugs has side effects, so we need to be able to do these transplants without medications. Ultimately, it is hoped that we may learn how to prevent future generations from getting this harmful disease.