

ISI Questions about Z-tubes

Question 1 -Tell us more about ISI laboratories?

Answer provided by ISI- Inter Science Institute, Inc. (ISI) was established in 1969 to provide patients, researchers and physicians access to research procedures and tests that were formerly only available in academic institutions.

ISI is licensed by CLIA, CAP, California, and other states that require certification.

ISI participates in clinical research and clinical trials for global studies with pharmaceutical companies, academic institutions and hospitals.

Question 2 – How many patients have you served?

Answer provided by ISI- It is estimated that ISI has served over 150,000 patients in the field of NETs beginning in the 1970's continuing to the present with numbers growing annually by 8-10% per year as more patients are accurately diagnosed and learn how ISI's biomarkers can guide their treatment.

The first neuroendocrine tumor patient sample (then called Carcinoid) was received in the early 1970's when ISI performed Gastrin tests for many academic institutions and identified Zollinger-Ellison patients' tumor sites for Dr. Ellison at the University of Wisconsin.

Continuing in the 1980-1990's, ISI tested Bradykinin and VIP samples for Dr. Richard Warner and others and continued to help identify patients whose tumors changed from Gastrinoma's to VIPomas through the use of ISI's tests.

With the establishment of the second G.I. Council in 2004, ISI was directly connected with physicians and patients needing these biomarkers to help diagnose patients and guide their treatments therein.

Question 3 -How many research publications have you published?

Answer provided by ISI -ISI has over a dozen peer-reviewed research publications with many more independently published papers by other physicians whom have used ISI's biomarkers to guide treatment and diagnosis of neuroendocrine tumors and carcinoid syndrome. ISI has also been at the forefront of providing educational materials to patients, caregivers, researchers, academicians and physicians through the Neuroendocrine Tumor handbooks that is now in its fifth publication and expecting the sixth publication in 2017.

Follow up question – How can a patient get a book? Can a support group leader request some as well for the group?

Follow up answer - Just email us (requests@InterScienceInstitute.com) and we will mail you a copy. Also, if you want to look online, the book is there, too. The research papers are on the website:

InterScienceInstitute.com under the tab "recently published papers."

Question 4 -What are your listings of testing panels that your lab does, for different groupings of patients. For example, what is the grouping of blood tests typical for gut and what is the grouping typical for a non-confirmed case?

Answer provided by ISI -The NETs handbook devotes several chapters to providing guidelines for the various types and locations of tumors. Each chapter in the book provides specific information about this, including ICD-10 codes for insurance. The appendix has worksheets if your doctor is not a specialist and needs guidance as to what to order.

(See question 10 for more information about guidelines)

Question 5 - Is there an actual test to see the levels of the long-term shots, Sandostatin or Somatuline (Lanreotide) in the blood?

Answer provided by ISI -Yes, ISI developed these blood tests so you can see what the quantitative level of the drug is in your body via trough levels. Blood must be collected immediately prior to your next injection, usually the day before.

Question 6- Why is the 5hiala serum more accurate than the urine 5hiala. In fact NIH has told several NET patients the urine test is better.

Answer provided by ISI -There are inherent problems with collecting 5-HIAA in urine, such as:

1. Foods – with the urine test you must fast from all the serotonin producing foods (bananas, strawberries, chocolate, wine, hot dogs, kiwi, to name just a few) for 72 hours. Many people have told me they forgot and ate a banana a day or two before the test, but had it done anyway because it was “scheduled” and their doctor needed the result. False-positive results are frequent because of diet.

2. Temperature: 5-HIAA has to be refrigerated during the collection and shipping process. This includes not only while you're collecting the urine for the entire 24 hours, but also when you transport it to the lab. Does the lab let the jug sit out at room temperature before processing? What temperature does your lab thaw frozen jugs? These are a few pre-analytical factors to be aware of.

3. "Clean collection:" if you're having diarrhea, can you be sure that what you're collecting is just urine or are there other "things" going into that collection?

4. Ease of collection for the Plasma test: one simple blood test collected with a z-tube, spun down and frozen and only requires a simple overnight fast from all the special foods.

(Read and/or download ISI's published paper comparing 5-HIAA plasma to 5-HIAA urine on ISI's website.)

Question 7- For NET patients, it seems that the top specialists have stopped using Cga in favor of pancreastatin can you explain why that is?

Answer provided by ISI - CgA is a general marker for NETs and is not specific for midgut tumors. False positives are also found with atrophic gastritis and can also be from use of proton-pump inhibitors (PPIs).

The pancreastatin is also a more sensitive marker for midgut patients because it is the "tail" of the Chromogranin A molecule. We can measure Pancreastatin down to the picogram level; whereas, CgA only measures down to the nanogram level. There is a hundred-fold (mole-for-mole) difference in these measurements. Therefore, it is possible that the measurement of pancreastatin may be better reflect the maturity of a NET

and, perhaps, be a sensitive and specific marker of early increases in tumor activity/burden.

(Read and/or download ISI's three published papers about Pancreastatin on ISI's website. There are also several papers about Pancreastatin that can be found via a PubMed search.)

Question 8- Certain top NET full time doctors do everything possible to only use ISI labs. Please explain how and why your pancreastatin test is considered more accurate than the pancreastatin tests run by other labs.

Answer provided by ISI - ISI has used the same test with the same reagents for over 15-20 years. We have the ability to continue on this path into the future. What you're looking for in these biomarkers is change. When the reagents change, you do not know if changes in your results are occurring because there is change internally or because the test has changed. ISI's test alleviates this concern.

(Read and/or download ISI's three published papers about Pancreastatin on ISI's website. There are also several papers about Pancreastatin that can be found via a PubMed search.)

Question 9- Can you explain what the Neurokinin A is?

Answer provided by ISI - This is a biomarker that has the potential to portend a poor prognosis in patients. Serial determinations of neurokinin A (NKA) in midgut patients may offer a significant advantage over other markers in predicting a 3-year or 5-year survival rate. In a retrospective study, patients with midgut tumors whose NKA was over 50pg/ml had a 3-

year survival rate of 10% in contrast to a 65% survival rate from those who had an NKA with a result of less than 50pg/ml.

(Read and/or download ISI's NKA published paper on ISI's website.)

Question 10- What new protocols utilize ISI testing?

Answer provided by ISI - The American Joint Committee on Cancer (AJCC) 2017 has just recently added several of ISI's tests, such as Pancreastatin, Neurokinin A and Plasma 5-HIAA to the list of "Emerging Prognostic Factors for Clinical Care."

(See the M.B. Amin et al. AJCC Cancer Staging Manual, Eighth Edition, DOI 10.1007/978-3-319-40618-3_29, chapters 29-34.)

Question 11- Do Trazadone side effects increase serotonin level? How far in advance should a patient stop taking it if they are doing labs?

Answer-We apologize that we are unable to comment here. We do not have data regarding Trazadone and Serotonin and are not qualified to comment on the side effects. Consult your specialist or pharmacy for more information.

Question 12- Is there a time during the shot cycle that tests should or should not be done?

Answer provided by ISI -ISI's biomarkers should be collected immediately preceding your next LAR shot to see the trough level of the drug. When

doing this, you have consistency of collecting blood and measuring hormones levels.

(Read and/or download the published papers about Octreotide on ISI's website.)

Question 13- Should patients fast or avoid foods for Z-tubes?

Answer provided by ISI -It is recommended to fast when collecting blood tests, especially for 5-HIAA and Substance P, Secretin, VIP, and some of the other gut hormones.

(See Chapter 4 in the Neuroendocrine Tumor Handbook for specific requirements for each test before having blood drawn.)

Follow up question - Is it the same protocol for Somatuline depot also correct?

Follow up answer – Yes

Follow up question in general - Do you need z tubes or special tubes for this test?

Follow up Answer - Nothing special is required. You can use serum 9red topped tube) Plasma (lavender topped tube. Or it can be shared from the Z-tube.

Question 14- How do we know that our Z-tubes are being sent directly to ISI?

Answer provided by ISI -The labs are generally pretty good about noting this on the paperwork. It is a pre-analytical requirement to state sample

type and most labs will note Z-tube plasma on the vials and/or paperwork that is sent with each sample. If it is unclear, we contact the client and they have to verify this prior to the test being run. Pre-analytical factors are significant.

(See list of lab codes for each major referral laboratory on ACOR or contact us directly via email: requests@InterScienceInstitute.com.)

Question 15 - Does ISI ever send a representative to talk at support group meetings?

Answer provided by ISI -Yes, we appreciate meeting patients face to face! We try to attend meetings and support meetings as requested and are dedicated to sharing our educational materials with you. ***Email preferred dates and requests to: mtepper@InterScienceInstitute.com***

Question 16 – How do patients get their oncologist on board for Z-tubes? If the oncologist is game to try them, can ISI be contacted to work with a willing office?

Answer provided by ISI -Yes, we can work with physician and medical practices. If your physician is able to bill your insurance, we can set up their account directly with us or you can pay out of pocket.

However, what often happens is that the patient's insurance dictates how the samples are routed to ISI. The national referral labs have contracts with the patients' insurance companies.

Question 17 - A patient comes in to be diagnosed because they have trending elevated biomarkers and symptoms. But alas, no visible tumor imaged, Would a NET surgeon schedule surgery on just the elevated markers alone? Or are all these blood tests for clinical research only?

Answer provided by ISI -We cannot speak to the best practices of surgeons. It depends upon the surgeon's background and experience. It is best to consult them for their opinion! Several specialties are involved with respect to NETs and the blood tests provide a quantitative response for tumors that are excreting hormones.

Question 18 – Can we get a list of clinics or labs that have these Z-tubes/tests readily available?

Answer provided by ISI -Every major laboratory chain in America has access to ISI's Z-tubes. They call ISI and request them and then Z-tubes are shipped on demand.

Continued: How do I get Z-tubes?

Answer provided by ISI -The national laboratories have smaller collection sites called Patient Service Centers (PSCs) in most cities around the country that collect blood for their main labs, so they may not have tubes readily on hand and may have never heard of them before. We recommend contacting your PSC before you need your blood drawn to make sure they have time to contact their main hub. If all else fails, contact our terrific Client Service staff and we can assist you with calling the PSC. Some PSC's do not allow patients to walk in with preservative tubes; please check with them prior to your scheduled blood draw.

Question 19 – Is there any special training that needs to be done for a proper draw?

Answer provided by ISI -ISI's preservative tubes have instructions on them:

1. Blood should be drawn into a chilled tube.
 2. The 10mL preservative tube should be filled completely.
 3. The tube will then be centrifuged.
 4. The plasma will be poured off.
 5. The plasma will be kept frozen until it is shipped frozen to ISI in dry ice.
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Question 20 – Explain Substance P and why is it is important?

Answer provided by ISI -According to one NETs expert, Dr. Thomas O'Dorisio explains that the Substance P rises under extreme stress and threat of life. Elevated levels can cause flushing, diarrhea, sweating like Serotonin. Substance P can be co-released with serotonin in carcinoid patients. Substance P levels can be affected by diet and should be collected only when fasting.

(Read papers by Dr. O'Dorisio and Dr. Oberg to understand more about Substance P and carcinoids.)

Further Follow up question - Z tubes not necessary for which specific test? Substance P?

Follow up answer - The z-tubes are not necessary for the

octreotide/Sandostatin or Lanreotide tests; however, the substance p,

pancreastatin, 5-hiaa plasma and other tests do need the z-tube for proper

collection.