



# Platinum Study Newsletter

SUMMER 2022

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Stay connected with The Platinum Study Team! If you have moved, changed your email address, or have a new phone number, please notify your clinic or study team or you may share your contact information with the current study headquarters at Indiana University by:

- Calling us toll-free at 833-770-8700
- Emailing us at [ptstudy@iu.edu](mailto:ptstudy@iu.edu)

## A Platinum Study Update

We would like to thank you, our research study participants, for your continued participation! Because of your contributions, we continue to move forward and learn more about the side effects of chemotherapy.

In TPS-I, we asked you to complete a questionnaire and a hearing test, and to provide us with a blood sample. The study has allowed us to answer many questions regarding the effects of your chemotherapy that are described on The Platinum Study website. If you opted in to receive study newsletters, we trust they have been informative. All newsletters are posted for your information on The Platinum Study website: <https://apps.cancer.iu.edu/platinum/>.

In 2019, The Platinum Study II received funding from the National Institutes of Health (NIH) so we can continue

to follow you for at least another five years. During this phase of the study, we are asking you to complete another questionnaire. You may also elect to be included in a group of approximately 200 people from Memorial Sloan Kettering Cancer Center and Indiana University Simon Comprehensive Cancer Center who will be invited to complete another hearing test and a short music questionnaire.

At the time of this writing, Memorial Sloan Kettering Cancer Center, New York was recently activated and opened. We are anticipating that the British Columbia Cancer Agency, Vancouver; Princess Margaret Hospital, Toronto; and the Royal Marsden Hospital, United Kingdom, will be activated in the upcoming months.

## Featured Clinician: Robert D. Frisina, PhD



Dr. Robert D. Frisina received his PhD in Bioengineering and Neuroscience from Syracuse University's College of Engineering. He pursued postdoctoral research as an NIH Fellow in Sensory Physiology and Biophysics at the University of Rochester (NY) Medical School.

Dr. Frisina is currently Distinguished University Professor, Department Chair, and Biomedical Engineering Director in the Medical Engineering Department at the University of South Florida at Tampa (USF). He also serves as Director of the Global Center for Hearing & Speech Research. Previously, he was Professor of

Otolaryngology, Neurobiology & Anatomy, and Biomedical Engineering (Founding Faculty), and Associate Chair of Otolaryngology at the University of Rochester Medical School for two decades.

Dr. Frisina's main research support is currently a Program Project Grant from NIH titled "The Aging Auditory System: Presbycusis and Its Neural Bases" as well as other NIH grants in areas related to auditory processing, drug delivery, and acquired hearing loss. These NIH grants include The Platinum Study (PI: Dr. Lois B. Travis), which focuses upon sensory side effects of cisplatin treatments in testicular cancer survivors. Dr. Frisina serves as the chief auditory researcher on this grant, based at Indiana University.

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Dr. Frisina's contributions on this long-standing NIH grant are to elucidate hearing deficits associated with cisplatin chemotherapy, paying particular attention to improving the lives of survivors, focusing upon better management strategies, understanding genetic factors, and advancing knowledge that can some day lead to medical preventive strategies.

Dr. Frisina currently serves as Chair of the Hearing/Deafness/Balance Study Section at NIH. Major themes of Dr. Frisina's lines of sensory neuroengineering research are aimed at developing novel therapies for diagnosing, preventing, delaying or treating cases of environmentally, chemical- or drug-induced hearing loss, and age-related hearing deficits.

## John Mark Cleland 1951-2022



In 1974, **John Cleland** was one of the first patients to receive experimental chemotherapy with cisplatin + vin-

blastine + bleomycin (PVB) to treat his advanced testis cancer. He became the first person in the world to be cured with this regimen. Prior to receiving PVB, Mr. Cleland received three different lines of chemotherapy with only brief benefit but severe toxicity. Because of his courage to continue fighting, PVB and later bleomycin + etoposide + cisplatin (BEP) became the worldwide standard therapy, increasing the cure rate for metastatic testis cancer from 5% to 80%.

Countless lives have been saved because Mr. Cleland was willing to be a test case for Dr. Einhorn's long-shot idea. Dr. Einhorn said "I will never forget the pure joy I had in telling John, back in 1974, that I thought he was going to make it."

And make it he did...Mr. Cleland lived 47 more years! You can read more about him in this 2014 Indianapolis Star story: <https://www.indystar.com/story/life/diet-fitness/2014/09/28/cancer-patients-wrenching-decision-leads-major-miracle-thousands/16382021>

## Summary of Publication

### Pharmacogenomics of Cisplatin-induced Neurotoxicities: Hearing Loss, Tinnitus, and Peripheral Sensory Neuropathy

Xindi Zhang<sup>1</sup>, et al. (Cancer Medicine 2022;00:1-16).

**Background:** The first choice chemotherapy drug, cisplatin, has been used for almost 50 years to successfully treat testicular cancer. Unfortunately, cisplatin can also cause harm to the body. Medical researchers are trying to determine the best way to use cisplatin so that it has maximum anti-cancer effect, but causes the least amount of unwanted harm.

**What we did:** We asked testicular cancer survivors if they would like to participate in a research study. 1,680 survivors dedicated their time and effort to answer survey questions, participate in a medical exam (and hearing test), and provide a blood sample. We then looked to see if cisplatin treatment is associated with health problems in survivors (e.g. hearing loss), and whether or not these health problems got worse if a survivor also participated in unhealthy behaviors (e.g. smoking). Finally, we looked at the blood sample to see if differences in groups of genes might make some people more likely to have more harm from cisplatin.

**What we found:** Most survivors were treated with bleomycin, etoposide, and cisplatin (BEP; 54.4%) or etoposide and cisplatin (EP; 37.5%). 46.5% of survivors received <400 mg/m<sup>2</sup> cumulative cisplatin dose, and 53.5% of survivors were treated with ≥400 mg/m<sup>2</sup>. We found that a substantial number of survivors treated with cisplatin-based chemotherapy experience hearing loss, tinnitus and peripheral neuropathy, and those that do experience these problems were more likely to have hypertension and describe their health as poor. We also observed greater risk of both tinnitus and peripheral neuropathy for chronic smokers and current smokers. Further, problems like peripheral neuropathy seem to worsen in those survivors who received greater amounts of chemotherapy. Additionally, we identified a few genes that might make someone more likely to develop hearing loss or tinnitus, but more research is needed in this area.

**What does the study mean:** Doctors and patient care teams should make sure that patients are aware of potential harms of chemotherapy, including high blood pressure and high blood cholesterol. Patients should also be closely monitored for changes in blood pressure and cholesterol level, and be encouraged to stop smoking and avoid non-work-related loud noises. One way to better balance risks and benefits of chemotherapy might be to develop individualized risk assessments to identify patients who are more susceptible to developing these harms. Another way is to develop personalized education, counseling, treatment and monitoring plans.

The full published version of this article can be accessed on our website at:

<https://apps.cancer.iu.edu/platinum/published-research.php>

## Dr. Travis Earns Highest Honor Presented by Harvard-Chan Alumni Association

**Lois B. Travis, MD, ScD** was a recipient of the 2021 Alumni Award of Merit from the Harvard T.H. Chan School of Public Health in recognition of “her research that has led to significant changes in cancer treatment, her contributions to the field of cancer survivorship, her insights that have improved the quality of life for cancer survivors, and her dedication to her students and mentees.” It is the highest honor presented by the school’s alumni association.

Dr. Travis developed and leads the research team for The Platinum Study (TPS), which is looking at ways to predict who is susceptible to the toxicities of cisplatin-based chemotherapy to eventually provide the foundation to develop preventive measures to protect patients from long-term adverse side effects. This groundbreaking study has the potential to impact the nearly six million people worldwide who are eligible for treatment with a platinum-based agent.

Long before TPS, Dr. Travis dedicated her career to understanding and preventing health risks for cancer survivors, producing research and clinical applications, creating international research teams that address these issues, and mentoring the next generation of professionals in the field of cancer survivorship. She has a broad academic background and a varied career as a physician, researcher, and teacher.

Dr. Travis served in a number of roles at federal agencies, including the National Cancer Institute, before taking academic appointments at the University of Rochester and her present position as the Lawrence H. Einhorn Professor of Cancer Research at Indiana University School of Medicine. While at the National Cancer Institute, Dr. Travis’ research on cancer survivors advanced the medical community’s understanding of dose-response relationships between radiotherapy and chemotherapy and the risk of second malignant neoplasms. For her work, Dr. Travis was awarded the National Cancer Institute’s Public Health Service Outstanding Service Medal. A committee she chaired for the National Council on Radiation Protection and Measurements (NCRP) released a highly cited report of over 400 pages entitled “Second Malignant Neoplasms and Cardiovascular Disease Following Radiotherapy.” She also received an Outstanding Service Award from the NCRP for this accomplishment. She also served on the inaugural Steering Committee for the National Cancer Institute’s Office of Cancer Survivorship and the first cancer survivorship task force



*Dr. Travis as a child, with her grandfather Karl Gottlieb Baurichter, and her brother Theodore August.*

convened by the American Society of Clinical Oncology (ASCO).

Dr. Travis notes that her grandfather (see photo) has been the most important influence in her life, crediting him for instilling a work ethic that served her well through medical school, residencies, and fellowships at the Mayo Clinic and the National Cancer Institute, and master’s and doctoral degrees at the Harvard T.H. Chan School of Public Health. Celebrated as a teacher and advisor, Dr. Travis was honored with the Rubin-Mitchell Award for excellence in mentoring young physicians and scientists while at the University of Rochester Medical Center. More recently, she completed the prestigious University of Michigan Rudi Ansbacher Leadership Scholars Program, which seeks to accelerate the development of women for senior positions in academic medicine and health care.

The Harvard Chan Award video can be found on YouTube: <https://youtu.be/3Sjt8gl-ioQ>. Please join us in congratulating Dr. Travis. In her remarks on the award video, she thanks her Creator, her family, and the many mentors, teachers, and colleagues at various institutions with which she has been affiliated. Dr. Travis also notes that the Harvard award “...brings cancer survivors to the forefront, where they belong.” As many of you know, Dr. Travis’s husband is also a cancer survivor. She is indebted to every survivor in TPS for their effort and sacrifices in participating in research in order to advance knowledge, improve treatment, and optimize care for cancer survivors.

## Clinician's Corner



*Helen Bernie, DO.  
Assistant Professor  
of Urology, IU  
School of Medicine*

**Infertility** is the inability to conceive a child or achieve a pregnancy after 1 year of unprotected sex. In the general population, infertility affects roughly 15-20% of all individuals. Studies suggest that after 1 year of unprotected sex, 15% of couples are unable to conceive, and after 2 years, 10% of couples still have not had a successful pregnancy. Overall, 1/3 of infertility cases are caused by male reproductive issues, 1/3 by female reproductive issues, and 1/3 by both male and female reproductive issues or by unknown factors. Male infertility may be the result of having no sperm in the ejaculate, low counts of sperm, low or no motility, or abnormal shape of the sperm.

**Causes of Infertility:** The testicles make testosterone and sperm. Many things can impact a man's fertility which impairs the production or quality of sperm: alcoholism, smoking, whether the testicles were descended at birth in the scrotum, illnesses, medications, hormone imbalances, tumors and exposure to radiation or chemotherapy agents like cisplatin.

**Cisplatin and Infertility:** Cisplatin is considered "spermatotoxic" or toxic to the production of sperm. Cisplatin's impact on male fertility is dose-dependent. This means the longer the duration one is on cisplatin and the higher the cumulative dose, the more likely the patients might have impairment in sperm production which can be permanent in some cases. Many men with testicular cancer can have impaired spermatogenesis (or the production of sperm) even before undergoing chemotherapy due to the nature of how the tumor itself impacts the testicles and sperm production. Whenever possible, we usually recommend that men bank sperm prior to or immediately after an orchiectomy and before starting chemotherapy. After undergoing cisplatin chemotherapy, it may take 2-3 years before the testicles are able to produce sperm again and a patient sees return of sperm to the ejaculate. In some cases, sperm may never return. In other cases, sperm may return to the ejaculate sooner than 2 years. However, due to possible DNA damage in the sperm from the chemotherapy, it is usually recommended that couples wait 2 years after chemotherapy ends before trying to conceive.

**Evaluation of infertility:** Evaluation of infertility is done by performing a physical exam, specifically to evaluate the size and consistency of the testicles, obtaining blood work to check testosterone levels and follicle-stimulating hormone (FSH, the hormone that tells the

testicles to make sperm), and performing a semen analysis (SA). Labs are best obtained in the early morning as testosterone and the results of fertility labs are highest in the morning and drop significantly within the first hour after waking. To obtain an SA, a patient manually collects a sample of ejaculate. This specimen is examined within 1 hour of collection. Collection is best done with 2-3 days of abstaining from sexual activity prior to collection. When an SA is performed, the number of sperm (concentration), motility (movement), and morphology (shape) are assessed by a specialist. A slightly abnormal SA does not mean that a man is necessarily infertile. Instead, an SA helps determine if and how male factors are contributing to infertility.

**Treatments for Infertility:** When a man has infertility or an abnormal SA, there are several things we can do to help improve the sperm quality and/or a couples' chance of achieving a pregnancy: lifestyle/behavioral modifications, supplements/medications and surgery. It might start with modification of lifestyle factors such as smoking cessation or minimizing frequent hot tub/hot bath use, which are known to negatively impact sperm quality. We also often recommend men take daily supplements that consist of vitamins and antioxidants that are known to impact and improve sperm quality. If a man's testosterone level is low, we can prescribe a medication called clomiphene that can improve testosterone levels and help support sperm production. There are also surgical treatment options such as a testis biopsy or microdissection, and testicular sperm extraction that can be performed to evaluate the testicle and look for sperm that could be used for assisted reproductive techniques such as in vitro fertilization (IVF). Seeing a urologist who specializes in male reproduction can help you explore your options and treatments for infertility.

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