

THE TIME IS NOW

What is the Ovarian Cancer Institute and where is it located?

The Ovarian Cancer Institute, Inc. (the "OCI") is a Georgia nonprofit corporation. It is exempt from federal income taxation under section 501(c)(3) of the Internal Revenue Code, which means a donor may deduct gifts to it as charitable contributions.

The Ovarian Cancer Institute was founded in 1999 as a unique collaboration between Benedict B. Benigno, M.D. (a world-renowned gynecologic surgeon and oncologist who has spent his career treating women with ovarian cancer), and an internationally renowned scientist, John F. McDonald, PhD, who is the Director of the Integrated Cancer Research Center at the Georgia Institute of Technology. *The curriculum vitae of Drs. Benigno and McDonald are attached as Appendix A.*

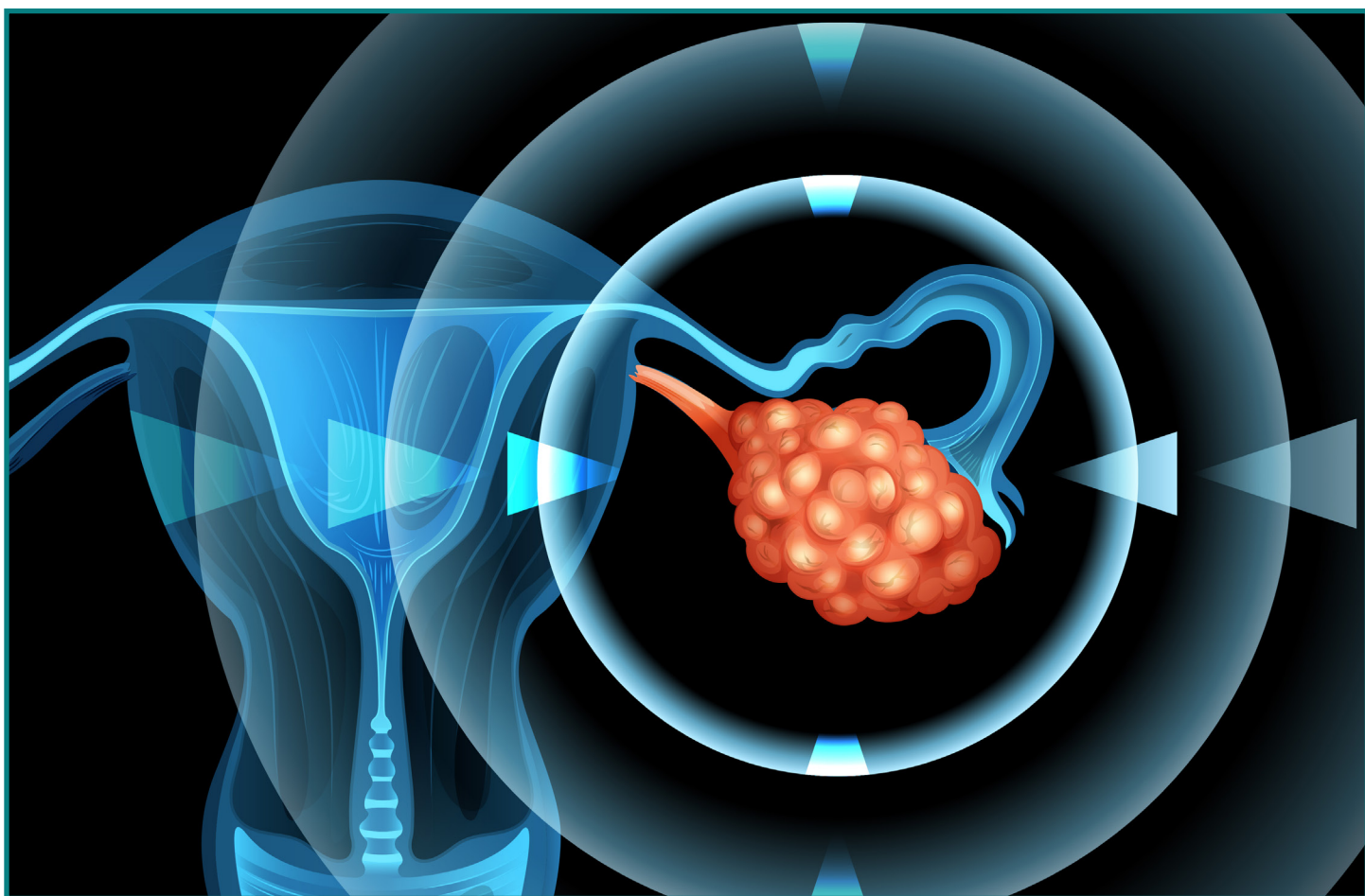
The OCI is located in Atlanta, Georgia in the office of our founder and Chief Executive Officer, Ben Benigno, at Northside Hospital, which is a major cancer hospital.



OCI-funded research staff

Why was the OCI formed and what is its mission?

Ovarian cancer is the most lethal of all gynecological malignancies and the fifth leading cause of death among women living in the United States. Ovarian cancer is called "the cancer that whispers" for a reason. These women are usually symptom-free until the cancer has spread throughout the abdomen, requiring extensive surgery and multiple rounds of toxic chemotherapy. As if this were not bad enough, the recurrence rate is as high as 80%.



OCI was established with the mission of supporting promising new approaches to the early diagnosis and more effective treatment of ovarian cancer. The Institute seeks to fund the development of research strategies that have the potential to revolutionize the care of ovarian cancer patients. Such novel

Fewer than **15%** of ovarian cancer cases are diagnosed early

The **5-year rate of survival** for women diagnosed in Stage 1 ovarian cancer is

90%

approaches are often considered of “high risk” and thus not considered fundable by federal agencies. The OCI is designed to fill this gap.

- Recent breakthroughs resulting from OCI funding include the development of a novel machine learning approach to ovarian cancer diagnostics that identifies metabolic patterns in the blood of women that is diagnostic of early stage ovarian cancer with extremely high (100% in initial tests) accuracy
- A similar OCI-funded machine learning approach has resulted in the development of algorithms that input the genomic profiles of individual patient tumors to predict optimal personalized drug therapies with high accuracy (84%)
- A third highly successful research project funded by OCI is the development of nanoparticles for the targeted delivery of chemotherapies directly to patient tumors thereby bypassing the negative side effects associated with current treatments. This technology was recently selected by the National Cancer Institute (NCI) for accelerated development in the NCI supported Nanotechnology Characterization Laboratories in Fredrick, MD. We are currently applying for FDA approval to evaluate the technology in early stage human trials

Are some women genetically at increased risk of ovarian cancer?

Unfortunately, yes. Women with Ashkenazi Jewish or Polish ancestry may carry a mutation of the BRCA1 or BRCA2 genes. The BRCA gene is a gene that suppresses the development of breast and ovarian cancers, and so a mutation on this gene increases the risk of developing these cancers. Jewish women have the highest incidence of these mutations.

Has the OCI actually developed an early diagnostic test?

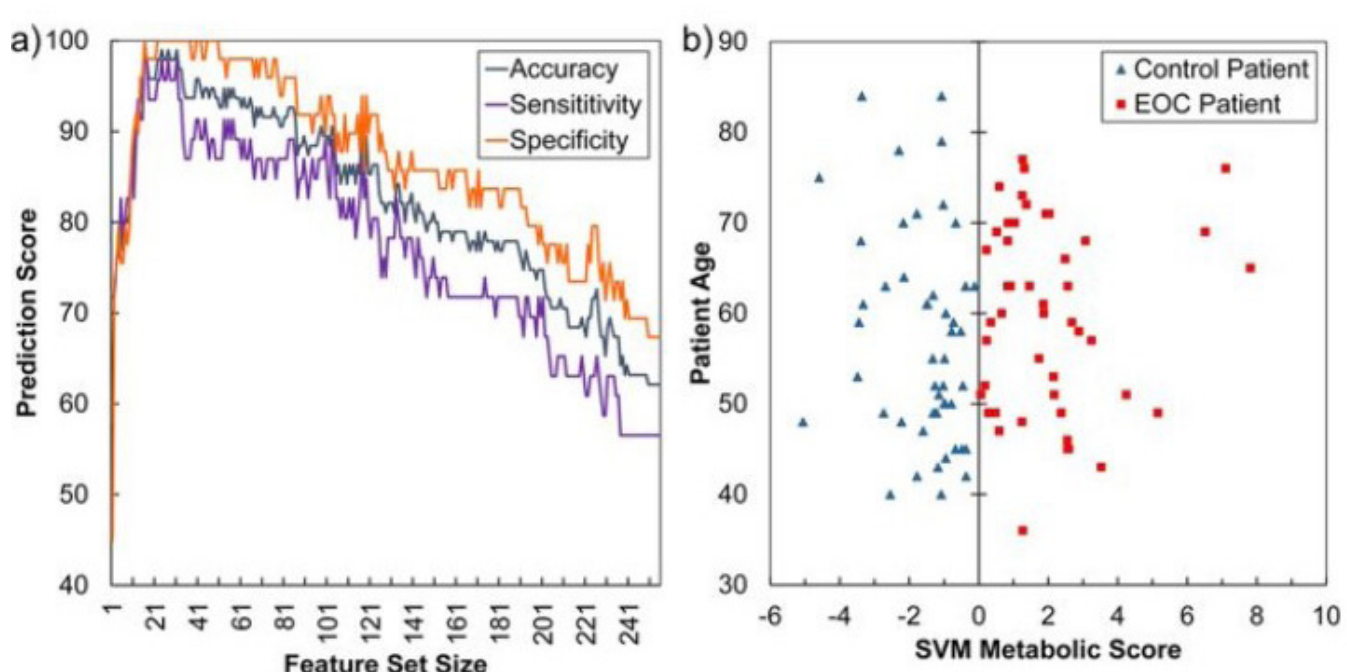
YES! AS DESCRIBED ABOVE SCIENTISTS SUPPORTED BY OCI HAVE DEVELOPED A 100% SENSITIVE AND SPECIFIC STAGE I DIAGNOSTIC BLOOD TEST FOR OVARIAN CANCER!

Could you give us more detail about the early diagnostic test?

Years ago, researchers at the OCI-supporter lab stopped working with proteins, as they are large, cumbersome molecules, and switched to the study of metabolites. Using machine learning in conjunction with the massive main frame computers at Georgia Tech, the research team studied metabolites that were present in the serum of patients with ovarian cancer but were not present in the serum of healthy controls. Each one of these metabolites is called a feature. The recursive feature elimination method was used to delete 100 features at a time until we reached a hundred, at which time they removed one feature at a time until they got down to the magic number – 16. THIS IS THE BASIS OF THE TEST – A SERUM SAMPLE THAT DEMONSTRATES SIGNIFICANT CHANGES IN LEVELS OF THESE 16 METABOLITES IS INDICATIVE OF AN EARLY CANCER.

These pioneering early studies were conducted using 100 patient samples. Over the past year, the lab has initiated a considerably expanded metabolic study that, when completed in 2019, will include 1,000 patient samples, which have been purchased. A large team of GA Tech biochemists and computer scientists are involved in this monumental study with the goal of leading to FDA approval of the test for clinical application.

Figure 1 : Recursive feature elimination (RFE) selects 16 metabolic features that distinguish early stage serous epithelial ovarian cancer (EOC) serum samples with high accuracy.



Here is what Dr. Benigno wrote about the OCI's test in his letter dated October 11, 2018

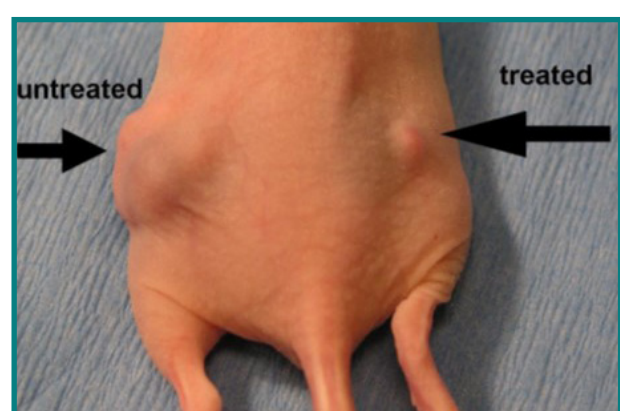
(a copy of which is attached as Appendix B):

"Our very first foray into the world of basic science occurred almost 20 years ago and concerned itself with the discovery of an accurate diagnostic test for early-stage ovarian cancer. As you may know, this dreadful disease is diagnosed almost always in an advanced stage, requiring barbaric surgery and multiple regimens of toxic chemotherapy. I began collecting tissue and serum samples, which were immediately flash-frozen in my operating room, and then transferred to John McDonald's laboratory at Georgia Tech. At first, we studied proteins, but these are large cumbersome molecules which were soon abandoned for metabolites. While prior efforts to develop diagnostic tests for ovarian cancer had been focused on proteins (like the CA 125 protein), we chose to explore the use of metabolites as potential diagnostic markers because emerging evidence indicated that these molecules might be more immediately reflective of the disease.

*The computer science division at Tech created a custom, support vector learning algorithm which we used to discard millions of unimportant features, allowing us to arrive at the magic number 16. We found 16 metabolites which were present in all the cancer samples and none of the controls. Because we studied only 100 samples, we could not go to the FDA for approval. **We have just purchased another 1000 samples and we hope to complete the metabolic analysis of these samples by the end of 2019.** If our test proves to be 100% sensitive AND specific, we hope to obtain FDA approval. I cannot tell you how excited I am to imagine this test becoming a part of every woman's annual visit to her physician, along with the time-honored pap smear! We published this groundbreaking work in the prestigious [journal Nature Scientific Reports](#)."*

What about OCI's research on more targeted, less toxic therapy?

SCIENTISTS SUPPORTED BY THE OCI HAVE DEVELOPED AND ARE CURRENTLY TESTING A UNIQUE NANOPARTICLE SYSTEM THAT DELIVERS THERAPEUTIC RNA DIRECTLY TO THE CANCER CELLS IN A WOMAN'S OVARIAN TUMOR, SPARING HER THE TOXICITY OF TRADITIONAL CHEMOTHERAPY. In early tests, this innovative treatment has successfully eradicated ovarian cancer tumors.



Initial results of the RNA therapeutic project

SCIENTISTS FUNDED BY THE OVARIAN CANCER INSTITUTE HAVE ALSO DEVELOPED AND TESTED A NEW TREATMENT ALGORITHM FOR OVARIAN CANCER. It will help doctors accurately predict which chemotherapy a patient's cancer will respond to – based on her own DNA. The research team used the massive computers at Georgia Tech to examine millions of correlates in order to predict

the exact chemotherapeutic agent to give to an individual patient's cancer, and we are showing an 84% accuracy, which is far greater than the results of the commercially available companies such as FOUNDATION MEDICINE and CARIS LIFE SCIENCES. With this information, a woman's doctor could prescribe the correct medicine, instead of using "trial and error," the only methods currently available.

Here is what Dr. Benigno wrote about the OCI's diagnostic test and targeted therapies:

"We have just been awarded \$60,000 from the Georgia Research Alliance to allow our work with the nanoparticle targeted gene delivery project to go forward. The McDonald laboratory in collaboration with Dr. Andrew Lyon, a material scientist at GA Tech, developed a new methodology whereby [therapeutic molecules are injected into the bloodstream and circulate until they find cancer cells and destroy them](#). This will allow the drug to be attached to a small molecule RNA, which will be used to deliver treatment directly to the nucleus of the cancer cell and nowhere else. At the present time, chemotherapy is infused into a vein and it travels to all tissues in the body with the same dose absorption and does not discriminate between cancer cells and normal cells. This technique will be a major advance over current modalities of treatment, allowing massive doses of the drug to target the cancer cell while sparing all normal cells (NO HAIR LOSS). The recent award from GRA is to conduct expanded tests to prepare for an application to FDA in early 2019 for approval for phase I human trials.

Our latest paper on the use of machine learning in precision medicine (prediction of optimal drug therapies based on genomic profiles of patient tumor samples) was just published in [Nature Scientific Reports](#). Machine learning will help us to determine the precise treatment to be used for an individual cancer, allowing us to discard time-honored treatments which we know will not work in a predictable percentage of patients. Our preliminary results show an incredible 84% accuracy, far better than the results currently obtained from commercially available companies."

How can the Ovarian Cancer Institute compete with huge hospital-based cancer research organizations such as MD Anderson, Johns Hopkins and Memorial Sloan Kettering?

Because the OCI-funded laboratory is relatively small, we needed to take different approaches from those used at traditional cancer research institutes at large universities. The lab's out-of-the-box research is rooted in concepts from the fields of engineering, nanotechnology, computer science, machine learning and chemistry – in other words research based more on technology than on medical lab work. To do this, Dr. McDonald, a professor at Georgia Tech, utilizes the expertise of computer scientists at Tech (of whom there are more than 200). That enables the lab to study ovarian cancer in a completely new, more efficient way, including using technology to analyze tissue samples with high speed and accuracy. Because the OCI teams up with Tech, it isn't so small after all!

It is BECAUSE the laboratory is located within a technology university that the research team can selectively collaborate with other scientists, engineers, and technologists at Georgia Tech to accomplish its goals. No other research institution has this advantage and the results have overshadowed all the competition. Scientists can now study ovarian cancer in a completely new, more efficient way, including analyzing tissue samples with high speed and 100% accuracy through this improved technology. Applying the unequalled power of machine learning to the OCI's huge bank of ovarian and control samples has led to discoveries that traditional research – no matter how well intentioned or well-funded – has not been able to accomplish.

Largely through the efforts of Dr. Benigno, going back to 1999, the OCI-supported lab at Tech now houses one of the world's largest ovarian cancer sample banks, and the samples are in pristine condition. OCI-funded scientists use the power of machine learning to test huge sample databases, which vastly improves scientists' predictive abilities. (A massive machine learning instrument belonging to Tech, some 15 feet tall, called a "spectrometer," is close by the lab and its' samples.) The research team uses the results of these tests to create more accurate diagnostic tests and targeted, personalized therapies.



The OCI believes its accurate early detection test and innovative treatments are UNIQUE BREAKTHROUGHS in the war against ovarian cancer. IT IS NOT AWARE OF ANY OTHER OVARIAN CANCER RESEARCH ORGANIZATION IN THE WORLD THAT HAS MADE THESE BREAKTHROUGHS. Its work has been published in highly regarded scientific and medical journals.

All the graduates of the gynecologic-oncology program at MD Anderson meet once a year, and in 2018 the meeting was held in Barcelona in conjunction with the annual meeting of the European Society of Gynecologic Oncology. Dr. Benigno was asked to present a talk, and he chose to present the latest work supported by the Ovarian Cancer Institute which involves machine learning in the management of patients with ovarian cancer. We recently published a paper on this topic in the prestigious journal, [Nature Scientific Reports](#).

Please define some of the technical terms used above.

A **"100% sensitive and specific test"** is one that is always positive when disease is present – that is, it has no false negatives. A 100% specific test is one that never has any false positives.

An **"algorithm"** is a set of mathematical instructions or rules that, especially if given to a computer, will help to calculate an answer to a problem.

Machine learning is the use of computers to identify correlations in large data sets (e.g., the correlation of changes in levels of 16 metabolites that correlates with the presence of early stage ovarian cancer) that can be used to build predictive models. The great potential of machine learning in ovarian cancer diagnostics and therapeutics is more fully explained in a brief synopsis by Dr. McDonald, recently published in the journal [Gynecologic Oncology](#). "Machine learning" is a field of artificial intelligence that uses statistical techniques to give computers the ability to 'learn' – that is, to improve their ability to make predictions based on large sets of data, without being explicitly programmed. In ML, models, called 'algorithms,' emerge from inputs into computers of large

data sets. These algorithms lend themselves to predictions. We might say that, because machine learning is blind, not programmed, it searches all the data fed to it, and misses nothing.

“Metabolites” are small molecules that are the product of the various chemical reactions in cells needed for cellular growth and other functions.

A **“nanoparticle”** is a microscopically small particle that can be loaded with chemotherapeutic agents for targeted delivery to cancer cells.

With your support now, the Ovarian Cancer Institute will fund the research that will change ovarian cancer diagnosis and therapy forever. Because they will have the benefit of early diagnosis and cancer treatment, OUR GOAL is to fund necessary additional testing of these three technologies and prove their validity according to the most stringent, FDA-required standards. If we succeed, then women with ovarian cancer will be able to plan for bright futures, because they will have cancer treatment with a high rate of success. Financial support will enable us to take these next crucial steps, so we can bring a highly accurate early diagnostic test, highly targeted therapeutic delivery mechanism, and highly personalized cancer treatment selection test to the women who need it now – and in the future.

You are Invited to Tour the Lab

Meet the research team and OCI’s executive team. If you are interested in walking through the laboratory where all this amazing work happens, we would be honored to host you. To schedule your visit, or speak with Dr. Benigno or Dr. McDonald please contact OCI’s Executive Director, Kathryn Harper, at kh Harper@ovariancancerinstitute.org or (404) 300-2997.

We look forward to meeting you!



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Hard copies of our linked articles are available upon request.

In 2013, Dr. Benigno published an inspiring book for the general reader titled “The Ultimate Guide to Ovarian Cancer.” The book is available on Amazon, and the OCI has several extra copies.

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