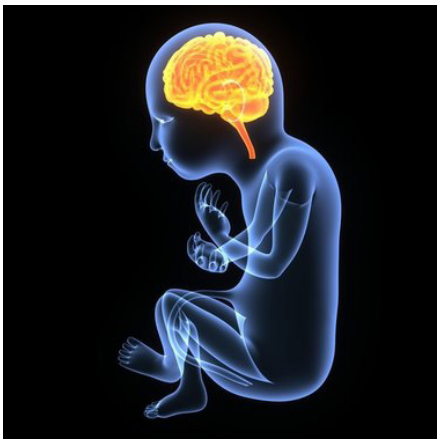
Association of Maternal Anxiety with Affects on the Fetal Brain

A new study by Children's National Hospital researchers sug- gests that anxiety in gestating mothers appears to affect the course of brain development in their fetuses. The findings, published in *JAMA Open Network*, help in explaining the longstanding links between maternal anxiety and neurodevelopmental disorders in their children and suggests an urgent need for interventions to diagnose and decrease maternal stress.



Dr. Limperopoulos, along with staff scientist Josepheen De Asis-Cruz, M.D., Ph.D., and their Children's National colleagues used a technique called resting-state functional magnetic resonance imaging (rs-fMRI) to probe developing neural circuitry in fetuses at different stages of development in the late second and third trimester. The researchers recruited 50 healthy pregnant volunteers from low-risk prenatal clinics in the Washington, D.C. These study participants, spanning between 24 and 39 weeks in their pregnancies, each filled out widely used and validated questionnaires to screen for stress, anxiety, and depression. Then, each underwent brain scans of their fetuses that showed connections between discrete areas that form circuits.

After analyzing rs-fMRI results for their fetuses, the researchers found that those with higher scores for either form of anxiety were more likely to carry fetuses with stronger connections between the brainstem and sensorimotor areas, areas important for arousal and sensorimotor skills, than with lower anxiety scores. At the same time, fetuses of pregnant women with higher anxiety were more likely to have weaker connections between the parieto-frontal and occipital association cortices, areas involved in executive and higher cognitive functions. "These findings are pretty much in keeping with previous studies that show disturbances in connections reported in the years and decades after the birth of children born to women with anxiety," says Dr. De Asis-Cruz. "That suggests a form of altered fetal programming, where brain networks are changed by this elevated anxiety even before babies are born."

These findings emphasize the importance of making sure pregnant women have support for mental health issues, which helps ensure current and future health for both mothers and babies.

New Treatment Options for Drug-Resistant Epilepsy

A recent study presented at the annual meeting of the American Epilepsy Society suggests that more than half of children treat- ed with magnetic resonance imaging (MRI)-guided laser interstitial thermal therapy (MRgLITT) achieve seizure freedom at one-year follow-up. Omar Yossofzai, from the University of Toronto, and colleagues used data from the MRgLITT registry to evaluate outcomes of MRgLITT in 129 children (mean age, 10.7 years) with drug-resistant epilepsy seen at six U.S. and two Canadian pediatric epilepsy surgery centers.

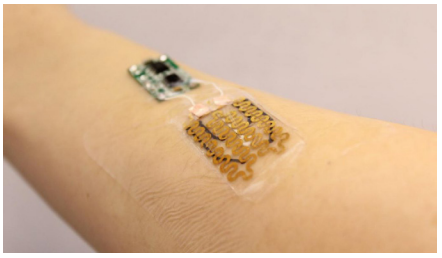
The researchers found that 86 percent of patients had abnormal MRI findings, with hypothalamic hamartoma is the most common lesion (33 cases), followed by focal cortical dysplasia (23 cases). In 22 percent of patients, there were complications relating to MRgLITT, including transient neurologic deficits (16 cases) and permanent neurologic deficits (two cases). One patient died within 30 days after MRgLITT. The mean length of hospital stay was 3.2 days. Seizure freedom was reported in just over half of 93 patients (56 percent) for whom one-year seizure outcome data were available. Twelve pa-

tients underwent more than one MRgLITT procedure, and seven of these patients achieved seizure freedom. "Compared to surgery, MRI-guided laser therapy can help reduce the risk of injury to critical brain structures and minimize serious neurological deficits," a co-author said in a statement.

'Smart' Wearable Sensor Developed To Track Healing

Researchers from Skoltech and the University of Texas at Austin have presented a proof-of-concept for a wearable sensor that can track healing in sores, ulcers, and other kinds of chronic skin wounds, even without the need to remove the bandages. The paper was published in the journal *ACS Sensors*.

In the new study, the Russia-US team, led by Skoltech provost, Professor Keith Stevenson, explored electroanalytical methods that, due to their relative simplicity, sensitivity, durability, and other attractive characteristics, are particularly promising for clinical applications. For the new study, the researchers built an early prototype of an electroanalytical wound sensor based on carbon ultra- microelectrode arrays (CUAs) on flexible



substrates. To ensure flexibility, the authors developed a method of putting the arrays on a polyethylene terephthalate (PET) substrate.

The team used a simulated wound environment to test the sensitivity of their sensor to three critical biomarkers: pyocyanin, produced by *Pseudomonas aeruginosa*, nitric oxide (NO) secreted in response to bacterial infections by cells of the immune system; and uric acid, a metabolite which strongly correlates with the severity of a wound. All these compounds are electroactive and thus can be detected by an electroanalytical sensor.

Testing showed that both the sensor's limits of detection and linear dynamic ranges, which represent the ranges of concentrations where a sensor produces meaningful quantitative results, were within the biologically relevant concentration. The researchers also tested their sensor in cell cultures, where it successfully detected pyocyanin from P. aeruginosa and NO from macrophages. Finally, the sensor was also able to detect the influence of Ag+ silver ions that suppressed pyocyanin production by the bacteria. "The next step is to utilize this sensor technology for in vivo studies and real-time monitoring of wound treatment effectiveness on human subjects in clinical settings," Professor Keith Stevenson noted.

Anticholinergic Drug Exposure Is Associated with Dementia Risk

A new systematic review and meta-analysis confirm a link between the use of anticholinergic medications and dementia.

Taking anticholinergic agents for 3 months or longer increased the risk for incident dementia by an average of 46% compared with non-use based on a meta-analysis of 6 studies involving 645,865 patients across 5 countries, Roger R. Dmochowski, MD, MMHC, professor of urologic surgery at Vanderbilt University Medical Center in Nashville, Tennessee, reported in *Neurourology and Urodynamics*.

Most of the 21 studies included in the full systematic review reported an

increased neurological risk with anticholinergic use, either overall or for at least 1 anticholinergic exposure category, including 8 of 9 incident dementia studies, 4 of 4 incident Alzheimer disease studies, 2 of 2 incident mild cognitive impairment studies, and 7 of 11 cognitive impairment/decreased performance studies.

The drugs exert their effects by blocking the action of the neurotransmitter acetylcholine. Dementia risk (including Alzheimer's disease, Lewy body dementia, vascular dementia, and other subtypes) increased with longer drug exposure. Both male and female patients and those younger and older than 65 years were at risk.

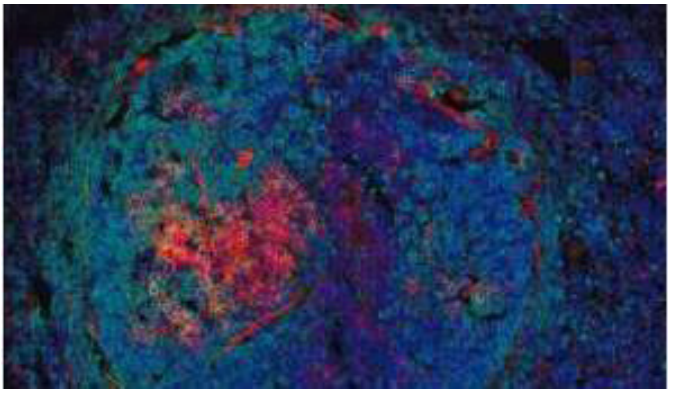
CNIC Scientists Identify a New Diagnostic and Therapeutic Target for CVD

Scientists at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) have identified a mitochondrial protein as a potential marker for the diagnosis of cardiovascular disease (CVD) and as a possible target for future treatments. The study is published in *Nature.*

The new study showed that the mitochondrial protein ALDH4A1 is an autoantigen involved in atherosclerosis. "ALDH4A1 is recognized by the protective antibodies produced during atherosclerosis, making it a possible therapeutic target or diagnostic marker for this disease," said Study leader Dr. Almudena Ramiro, of the CNIC. The study characterized the antibody response associated with atherosclerosis in mice lacking the low-density lipoprotein receptor (LDLR-/-) and fed a high-fat diet. During the study, the CNIC team collaborated with researchers at the German Cancer Research Center (DKFZ), the Spanish Cardiovascular Biomedical Research Network (CIBERCV), the Fundación Jiménez Díaz Institute for Medical Research, and the Universidad Autónoma de Madrid.

First author Cristina Lorenzo said, "We found that atherosclerosis is associated with the generation of specific antibodies in the germinal centers, where B cells diversify their antibodies and differentiate into high-affinity memory B cells and plasma cells."

To study the repertoire of antibodies produced during atherosclerosis, the research team performed a high-throughput analysis based on isolating individual B cells and sequencing their antibody genes. Among the atherosclerosis-associated antibodies, the research



team found that the antibody A12 was able to recognize plaques not only in the atherosclerosis-prone mice but also in samples from patients with atherosclerosis in the carotid arteries. "Proteomics analysis showed that A12 specifically recognized a mitochondrial protein called aldehyde dehydrogenase 4 families, member A1 (ALDH4A1), identifying this protein as an autoantigen in the context of atherosclerosis," said Lorenzo. Ramiro adds, "The study shows that ALDH4A1 accumulates in plaques and that its plasma concentration is elevated in the atherosclerosis-prone mice and human patients with carotid atherosclerosis, establishing ALDH4A1 as a possible biomarker of the disease." The team also found that infusion of A12 antibodies into the atherosclerosis-prone mice delayed plaque formation and reduced the circulating levels of free cholesterol and LDL, suggesting that anti-ALDH4A1 antibodies have therapeutic potential in the protection against atherosclerosis.

Preventing Liver Failure: Sensor Can Detect Scarred or Fatty Liver Tissue

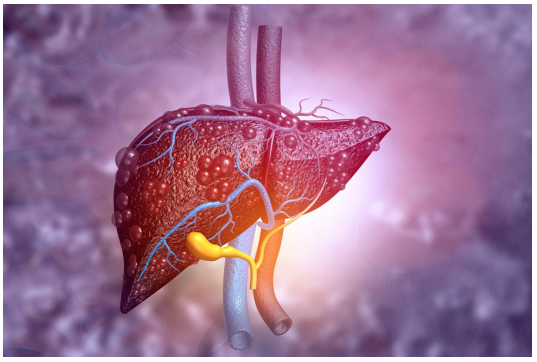
MIT engineers have developed a diagnostic tool, based on nuclear magnetic resonance (NMR), which could be used to detect both of those conditions. "Since it's a non-invasive test, it can be possible to screen people even before they have obvious symptoms of the compromised liver, and be able to say which of these patients had fibrosis," says Michael Cima, the David H. Koch Professor of Engineering in MIT's Department of Materials Science and Engineering, a member of MIT's Koch Institute for Integrative Cancer Research, and the senior author of the study.

The device is small enough to fit

on a table, uses NMR to measure how water diffuses through tissue, which can reveal how much fat is present in the tissue. This kind of diagnostic, which has thus far been tested on mice, could help doctors catch the fatty liver disease before it progresses to fibrosis, the researchers say. MIT Ph.D. recipient Ashvin Bashyam and graduate student Chris Frangieh are the lead authors of the paper published in *Nature Biomedical Engineering*.

To create an easier way to check for fibrosis, Cima and his thought that a detector could be used for identifying liver disease because water diffuses more slowly when it encounters fatty tissue or fibrosis. Tracking how water moves through tissue over time can reveal how much fatty or scarred tissue is present.

"If you watch how the magnetization changes, you can model how fast the protons are moving," Cima says. "Those cases where the magnetization doesn't go away very fast would be ones where the diffusivity was low, and they would be the most fibrotic." In a study of mice, the researchers showed that their detector could identify fibrosis with 86 percent accuracy and fatty liver disease with 92 percent accuracy. It takes about 10 minutes to obtain the results.



The current version of the sensor can scan to a depth of about 6 millimeters below the skin, which is enough to monitor the mouse liver or human skeletal muscle. In this study, the researchers tested the monitor on human liver tissue and found that it could detect fibrosis with 93 percent accuracy.

Retinal Transplant Opens Door to Treat Eyesight Loss

Dying retinal cells send out a rescue signal to recruit stem cells and repair eye damage, according to the findings of a new study published in the journal *Molecular Therapy*. The findings open the door to restoring eyesight by modifying stem cells to follow the signal and transplanting them into the eye. Martina Pesaresi, Ph.D., together with a group led by Pia Cosma at the Centre for Genomic Regulation (CRG), identified two cell signals—known as Ccr5 and Cxcr6—using different models of retinal degeneration in humans and mice.

They then genetically engineered the stem cells with an overabundance of Ccr5 and Cxcr6 cell receptors. When these modified stem cells were transplanted back into the models, they displayed a significantly higher rate of migration to degenerating retinal tissue, rescuing them from death and preserving their function.

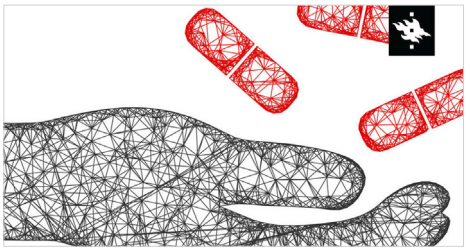
"One of the main hurdles in using stem cells to treat damaged eyesight is low cell migration and integration in the retina," says Pia Cosma, ICREA Research Professor and Group Leader at the CRG and senior author of the study. "After the cells are transplanted they need to reach the retina and integrate through its layers. We have found a way to enhance this process using stem cells commonly found in the bone marrow, but in principle can be used with any transplanted cells."

In this study, the mesenchymal stem cells were modified using lentiviruses, but the authors believe that using other methods such as the adeno-associated virus vector (AAV) can express the chemokine receptors in the transplanted cells. "AAV is gaining popularity as the ideal therapeutic vector, and Europe and the U.S. have already given regulatory approval for the commercial use of AAV-based therapies in patients. There is still considerable work to be done, but our findings could make stem cell transplants a feasible and realistic option for treating visual impairment and restoring eyesight," concludes Pia Cosma.

New AI Model May Help Treat Cancer More Effectively, Study Says

Researchers at Aalto University, University of Helsinki, and the University of Turku in Finland developed a machine learning model that accurately predicts how combinations of cancer drugs kill various types of cancer cells. The new AI model was trained with a large set of data obtained from previous studies that investigated the association between drugs and cancer cells. "The model learned by the machine is a polynomial function familiar from school mathematics, but a very complex one," says Professor Juho Rousu from Aalto University. The research results were published in *Nature Communications,* and demonstrate that the model found associations between drugs and cancer cells that were not observed previously.

"The model gives very accurate results. For example, the values of the so-called correlation coefficient were more than 0.9 in our experiments, which points to excellent reliability," says Professor Rousu. The model accurately predicts how a drug combination selectively inhibits particular cancer cells when the effect of the drug combination on that type of cancer has not been previously tested.



"This will help cancer researchers to prioritize which drug combinations to choose from thousands of options for further research," says researcher Tero Aittokallio from the Institute for Molecular Medicine Finland (FIMM) at the University of Helsinki.

Active Vitamin D Levels Linked to Gut Microbiome

Our gut microbiomes play important roles in our health and risk for disease in ways that are only beginning to be recognized. University of California San Diego researchers and collaborators recently demonstrated in older men that the makeup of a person's gut microbiome is linked to their levels of active vitamin D. The study, published in *Nature Communications*, also revealed a new understanding of vitamin D and how it's typically measured.

Vitamin D can take several different forms, but standard blood tests detect only one, an inactive precursor that can be stored by the body. To use vitamin D, the body must metabolize the precursor into an active form.

Kado led the study for the National Institute on Aging-funded Osteoporotic Fractures in Men (MrOS) Study Research Group, a large, multi-site effort that started in 2000. She teamed up with Rob Knight, Ph.D., professor and director of the Center for Microbiome Innovation at UC San Diego, and co-first authors Robert L. Thomas, MD, Ph.D., a fellow in the Division of Endocrinology at UC San Diego School of Medicine, and Serene Lingjing Jiang, a graduate student in the Biostatistics Program at Herbert Wertheim School of Public Health and Human Longevity Sciences.

"Our study suggests that might be because these studies measured only the precursor form of vitamin D, rather than an active hormone," said Kado, who is also a professor at UC San Diego School of Medicine and Herbert Wertheim School of Public Health. "Measures of vitamin D formation and breakdown may be better indicators of underlying health issues, and who might best respond to vitamin D supplementation." The team analyzed stool and blood samples contributed by 567 men participating in MrOS. The participants live in six cities around the United States, their mean age was 84, and most reported being in good or excellent health. The researchers used a technique

called 16s rRNA sequencing to identify and quantify the types of bacteria in each stool sample based on unique genetic identifiers. They used LC-MSMS to quantify vitamin D metabolites (the precursor, active hormone, and the breakdown product) in each participant's blood serum.

In addition to discovering a link between active vitamin D and overall microbiome diversity, the researchers also noted that 12 particular types of bacteria appeared more often in the gut microbiomes of men with lots of active vitamin D. Most of those 12 bacteria produce butyrate, a beneficial fatty acid that helps maintain gut lining health. "Gut microbiomes are complex and vary a lot from person to person," Jiang said. "When we do find associations, they aren't usually as distinct as we found here."

UofL Researcher Uses Fruit for Less Toxic Drug Delivery

University of Louisville researchers have found a less toxic way to deliver medicines by using the natural lipids in plants, particularly grapefruit and ginger. The resulting intellectual property portfolio consisting of 12 patient families, invented by Huang-Ge Zhang, Ph.D., of UofL's James Graham Brown Cancer Center and Department of Microbiology and Immunology, has been licensed to Boston-based Senda BioSciences. UofL's technology is part of Senda's efforts to develop novel drug delivery platforms to solve the challenges of transferring therapeutics across biological barriers and throughout the body.

The UofL technologies use exosomes to transport various therapeutic agents, including anti-cancer

drugs, DNA/RNA, and proteins such as antibodies. These exosomes help ensure the drug is properly absorbed by the body. The UofL edible-plant-derived exosomes don't have these problems, Zhang said since they come from natural, readily available sources. More importantly, these exosomes have anti-inflammatory effects.

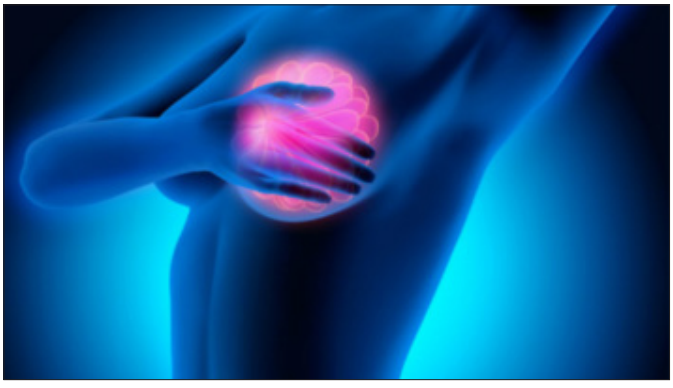
"Our exosomes come from fruit or other edible plants that you buy in the grocery store and that humans have eaten forever," said Zhang, an endowed professor of microbiology and immunology who holds the Founders Chair in Cancer Research. "And, they don't require synthetic formulation." The exosomes made from fruit lipids also can be modified to target and deliver medications to specific cell types within the body—like homing missiles, Zhang said. For example, the exosomes could be engineered to deliver cancer therapeutic directly to cancer cells.

The results of the work were published in *Nature Communications, and Cell Host & Microbe.* "These technologies could make a real difference in drug delivery, improving access and costs while reducing side effects," said Guillame Pfefer, CEO of Senda Biosciences.

Deep Learning Can Predict Breast Cancer Risk

Researchers at Massachusetts General Hospital (MGH) have developed a deep learning model that identifies imaging biomarkers on screening mammograms to predict a patient's risk for developing breast cancer with greater accuracy than traditional risk assessment tools.

Dr. Leslie Lamb, M.D., M.Sc., breast radiologist at MGH, and a team of researchers developed the new deep learning algorithm to predict breast cancer risk using data from five MGH breast cancer screening sites. The model was developed on a population that included women with a personal history of breast cancer, implants, or prior biopsies. The study included 245,753 consecutive 2-D digital bilateral screen-



ing mammograms performed in 80,818 patients between 2009 and 2016. From the total mammograms, 210,819 exams in 56,831 patients were used for train-

ing, 25,644 exams from 7,021 patients for testing, and 9,290 exams from 3,961 patients for validation. Using statistical analysis, the researchers compared the accuracy of the deep learning image-only model to a commercially available risk assessment model in predicting future breast cancer within five years of the index mammogram. The deep learning model achieved a predictive rate of 0.71, significantly outperforming the traditional risk model, which achieved a rate of 0.61.

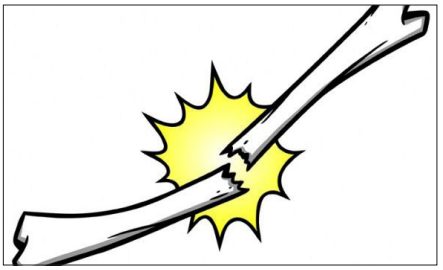
"Our deep learning model can translate the full diversity of subtle imaging biomarkers in the mammogram that can predict a woman's future risk for breast cancer," Dr. Lamb said.

"A deep learning image-only risk model can provide increased access to more accurate, less costly risk assessment and help deliver on the promise of precision medicine," Dr. Lamb said.

Researchers develop new biomaterial that helps bones heal faster

Scientists have developed a new biomaterial that helps bones heal faster by enhancing adults' stem cell regenerative ability. The study, led by researchers from RCSI University of Medicine and Health Sciences and CHI at Temple Street, is published in *Biomaterials.*

The researchers had previously discovered a molecule called JNK3, which is a key driver of children's stem cells being more sensitive to their environment and regenerating better than adults'. This explains, at least partially, why children's bones can heal more quickly.



Building on this knowledge, they created a biomaterial that mimics the structure of bone tissue and incorporates nanoparticles that activate JNK3.

When tested in a pre-clinical model, the biomaterial quickly repaired large bone defects and reduced inflammation after a month of use. The biomaterial also proved to be safer than and as effective as other drug-loaded biomaterials for bone repair whose use has been controversially associated with dangerous side-effects, including cancer, infection, or off-site bone formation. "While more testing is needed before we can begin clinical trials, these results are very promising," said Professor Fergal O'Brien, the study's principal investigator and RCSI's Director of Research and Innovation.

New Research Suggests Plant-Based Diet Improves Metabolism

A plant-based diet boosts after-meal burn, leads to weight loss, and improves cardiometabolic risk factors in overweight individuals, according to a new randomized control trial published in *JAMA Network Open* by researchers with the Physicians Committee for Responsible Medicine. The study randomly assigned participants—who were overweight and had no history of diabetes—to a control group in a 1:1 ratio. For 16 weeks, participants in the intervention group followed a low-fat, plant-based diet based on fruits, vegetables, whole grains, and legumes with no calorie limit. The control group made no diet changes. Neither group changed exercise or medication routines unless directed by their doctors.

Researchers used indirect calorimetry to measure how many calories participants burned after a standardized meal at both the beginning and end of the study. The plant-based group increased after-meal calorie burn by 18.7%, on average, after 16 weeks. The control group's after-meal burn did not change significantly. Within just 16 weeks, participants in the plant-based group lowered their body weight by 6.4 kg, on average, compared to an insignificant change in the control group. The plant-based group also saw significant drops in fat mass and visceral fat volume.

The researchers also teamed up with Yale University researchers Kitt Petersen, MD, and Gerald Shulman, MD, to track intramyocellular lipid and hepatocellular

lipid in a subset of participants using magnetic resonance spectroscopy. Those in the plant-based group reduced the fat inside the liver and muscle cells by 34% and 10%, respectively, while the control group did not experience significant changes. "When fat builds up in liver and muscle cells, it interferes with insulin's ability to move glucose out from the bloodstream and into the cells," adds Dr. Kahleova. "After just 16 weeks on a low-fat, plant-based diet, study participants reduced the fat in their cells and lowered their chances for developing type 2 diabetes."

The plant-based group decreased their fasting plasma insulin concentration by 21.6 pmol/L, decreased insulin resistance, and increased insulin sensitivity—all positive results—while the control group saw no significant changes. The plant-based group also reduced total and LDL cholesterol by 19.3 mg/dL and 15.5 mg/dL, respectively, with no significant changes in the control group.

Study Finds a Blood Test Could Accurately Predict Alzheimer's

Scientists had developed a way of predicting if patients will develop Alzheimer's disease by analyzing their blood.

Scientists in Sweden and Britain believe blood tests can be used to predict Alzheimer's years before the onset of symptoms. . Their work has been published in *Nature Aging*. They described how they developed and validated models of individual risk based on the levels of two key proteins in blood samples taken from more than 550 patients with minor cognitive impairments.

The model-based off of these two proteins had an 88 percent success rate in predicting the onset of Alzheimer's in the same patients over four years. They said that their prediction method could have a significant impact on Alzheimer's cases, given that "plasma biomarkers" from blood tests are "promising due to their high accessibility and low cost".

Richard Oakley, head of research at the Alzheimer's Society, said the main struggle in battling the disease was diagnosing cases early enough to intervene with experimental treatments. "If these blood biomarkers can predict Alzheimer's in larger, more diverse groups, we could see a revolution in how we test new dementia drugs," he said.

Musaid Husain, professor of neurology at the University of Oxford said, "For the first time, we have a blood test that can predict well the risk of subsequent development of Alzheimer's disease in people who have mild cognitive symptoms. We need further validation (of the results) but in the context of other recent findings this could be a transformative step to earlier diagnosis, as well as testing new treatments at earlier stages of the disease."