euroespes health

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EuroEspes Health Medical Bulletin

International Center of Neuroscience
and Genomic Medicine

Contents

July Editorial

Educate in Health

Gone are the days when the doctor, the priest, the teacher, and the mayor were the masters of the town; just as the time when the doctor's orders were divine mandate. Education also went from being vertical to being horizontal, with a regrettable decline in the moral authority of teachers and parents. Today the influence of Mr. Google or the opinion of the herd may be more than the experience lived within the family or school.

The concepts of health and disease have also changed. Disease is more than the absence of health, and health is more than the absence of disease. All these changes have been taking place gradually, with the inertia of the weight of progress; but we continue to get sick and we continue to need medical help. The school does not teach to preserve health or instruct in the art of avoiding illness. Society doesn't help either. They tell us that food is essential, and around us junk food proliferates; they tell us that caring for the environment is essential, and we live surrounded by toxicity, pollution, noise and dirt. There are contradictions in the messages, which is to say that education fails.

When it comes to health, something similar happens. A multitude of conflicting messages; a mixture of marketing, propaganda and floral aesthetics, yet little documentary background. The coronavirus pandemic is a paradigmatic example of confusion, press intoxication, sectarian messages, and lack of professional commitment. All public services, which should be available to serve the society that supports them, are self-excluded, including orthodox medicine, leaving all the burden to the quartermaster services. The rest, behind the window, on the phone or in front of the computer screen, with enough distance in between, to drive away the infested herd who provides the salary to civil servants but does not receive the consequent assistance.

What's wrong? What is making us enemies of ourselves? What keeps us from the efficiency thresholds in the social commitment to which we are all obliged?

Education. Also in health, because health is a consumer good for which we are individually responsible, but which, when it is altered, requires the financial assistance of all to cover the expense (lost work hours, diagnostic costs, pharmaceutical consumption, disability coverage, pension). That is Social Security. And when this bankrupt Bank does not give more of itself, each one has to face his own vulnerability with his patrimony. Therefore, the privilege of health, which we have turned into a right, has to be transformed into an obligation to preserve it; and the preservation of health requires education; an education that must begin at school and in the family, continue at university and in the workplace and culminate in the health services, where doctors have to move from giving orders to convincing and motivating the public; they must change from demanding homage to serving with humility the society whose health they must take care of, beginning with education before the pill; because medicine also has to shift from being restorative, when the damage has already been done, to predictive, when the damage can still be avoided through effective prevention.

Without Education there is no possible Prevention.

Diogenes Laërtius put in the mouth of **Aristotle** in *Lives and Opinions of Eminent Philosophers* a couple of sayings: "Education is an ornament in prosperity and a refuge in adversity"; "The roots of education are bitter, but its fruits are sweet." Health education requires a new pedagogical effort on the part of the doctor and a learning effort on the part of the patient. The doctor has to explain to the patient what happens to him, what he has to take, and the patient has to understand what happens to him (he/she or his family, when cognitive ability is limited) and why he has to take a specific drug; it is not enough to take it; more things must be understood (adverse effects, limitations, interactions), without forgetting that more than 60% of therapeutic failures are due to non-compliance with the treatment regimen ordered by the doctor; however, much of the failure is due to the lack of information from the patient about the importance of the medication they take to cure the disease they suffer or, at least, alleviate their symptoms.

A Chinese proverb says that by nature we are all the same, but by education we are all different. The new medicine today, thanks to genomics, also allows us to differentiate ourselves by our weaknesses and our strengths, to know how to protect ourselves against disease, to anticipate problems and to personalize treatments. This new medicine demands medical instruction; doctors should not be an obstacle to progress; doctors should not fall into disrepute when they incur the clumsiness of saying that what they do not know does not exist; and it requires lay instruction so that the user of medical services knows what to expect from genomic medicine, from genetic information, from pharmacogenetics, without falling into impossible fantasies. In one of his *Discourses*, **Epictetus** declared that "only educated people are free." **Euripides** said in *Phrixus* that "whoever neglects learning in his youth, loses the past and is dead for the future"; but learning about health and wellness is ageless; it is a permanent task while there is life. Education is an exercise in the cultivation of the will. In *The Crime of Sylvestre Bonnard*, **Anatole France** writes: "An education that does not cultivate the will is an education that depraves the mind." Education teaches to be and to be at all times, knowing how to keep the most appropriate composure in the face of pain, suffering, recovery or loss. **Robert Frost** wrote in the April 1960 issue of the *Reader's Digest*: "Education is the ability to listen to almost everything without losing control or self-confidence." Education has to be an active learning that allows us to understand what we do and why we do it, what we take and why we take it, the benefits it brings and the risks of any medication that we have to consume. In *Fragments*, **Heraclitus** said: "Much learning does not teach understanding." The dose is always very important; in life, in drugs, in vices, in love. The dose has to be adjusted to the effect; and education and treatment have to be directed

toward a goal. In a lecture at Harvard University on November 5, 1886, **Oliver Wendell Holmes** told his audience: "The main part of intellectual education is not the acquisition of facts, but learning to make facts come to life." In a speech at the same university in 1956, President **John F. Kennedy** stated that "the goal of education is the advancement of knowledge and the dissemination of truth"; and doctors have an obligation to educate in health so that new knowledge of medicine reaches their patients through knowledgeable people and not through the journalistic filter or the pool of interested opinions of the Internet. The American poet **Henry Wadsworth Longfellow** said in *Hyperion*: "A single conversation across the table with a wise man is better than ten years of mere study of books." Although the phrase is a bit exaggerated and the disregard of books is never good advice, Longfellow is loaded with reason about the importance of the teacher having knowledge of what he is talking about and bringing wisdom to the information.

In his 1859 work *On Liberty*, **John Stuart Mill** expressed the following: "Human nature is not a machine that must be built according to a model, and that is set up to do exactly the work prescribed for it, but a tree that needs to grow and develop everywhere, in accordance with the tendency of the inner forces that make it a living being". The nutrition of that tree will determine the nature of its fruits. This is how **Plato** saw it in his *Republic*: "The direction in which education begins to build a man will determine his future life." In health, too. The compulsive order is harmful; motivation, understanding why, perception of benefit is the way for the patient to assume the value of the therapeutic order. **Plato** said that "knowledge that is acquired under duress does not hold in the mind." **Plutarch**, in the section dedicated to The Education of Children in his work *Moralia*, showed it with great beauty and eloquence: "Nature without learning is blind, learning apart from nature is fractional, and practice in the absence of both is aimless".

Ramón Cacabelos
Professor of Genomic Medicine

Adverse drug reactions

Adverse drug reactions (ADRs) are becoming a serious global health problem. ADRs are among the top ten causes of illness and death in developed countries. In the United States alone, they represent a direct cost of more than 180 billion dollars a year. The side effects of drugs depend on the genotype of each person, age, sex, the pathology that is being treated with a certain category of drugs, the type of drug, the route of administration and interactions with other drugs. The problem is especially serious in children, women and the elderly. Women suffer more ADRs than men. Genomics plays a very important role in the appearance of ADRs. Today we know that pharmacogenetics determines more than 90% of the variability in the response that each person has to a drug. Defects in the pharmacogenomic apparatus, represented by pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes, are largely responsible for the toxicity of many drugs and for therapeutic failure. This is particularly important in the treatment of the most prevalent diseases (heart, cancer, brain), which account for 80% of world morbidity and mortality.

A study led by Dr. Ramón Cacabelos, prepared for the *Expert Review of Clinical Pharmacology,* catalogues the pharmacogenetics of drugs used in the treatment of cardiovascular diseases and associated disorders, including anti-hypertensive agents (ACE inhibitors, angiotensin II antagonists , β-blocking agents, calcium channel inhibitors), cardiotonic agents, diuretics, lipid-lowering agents (statins, fibrates), antithrombotic drugs (vitamin K antagonists, heparins, platelet aggregation inhibitors, thrombin inhibitors, factor Xa inhibitors) .

In a previous study (Cacabelos et al., Expert Rev Clin Pharmacol https://doi.org/10.1080/17512433.2019.1597706), the same was done with various antitumor agents and all categories of drugs used in the treatment of diseases of the nervous system.

In recent years, the *US Food and Drug Administration* (FDA) recommends that the pharmaceutical industry carry out pharmacogenetic studies with all new drugs, and advises doing the same with old drugs commonly in use in order to be able to indicate pharmacogenetic information in the package inserts of the product label. This would allow physicians to begin customizing drug treatments across the board.

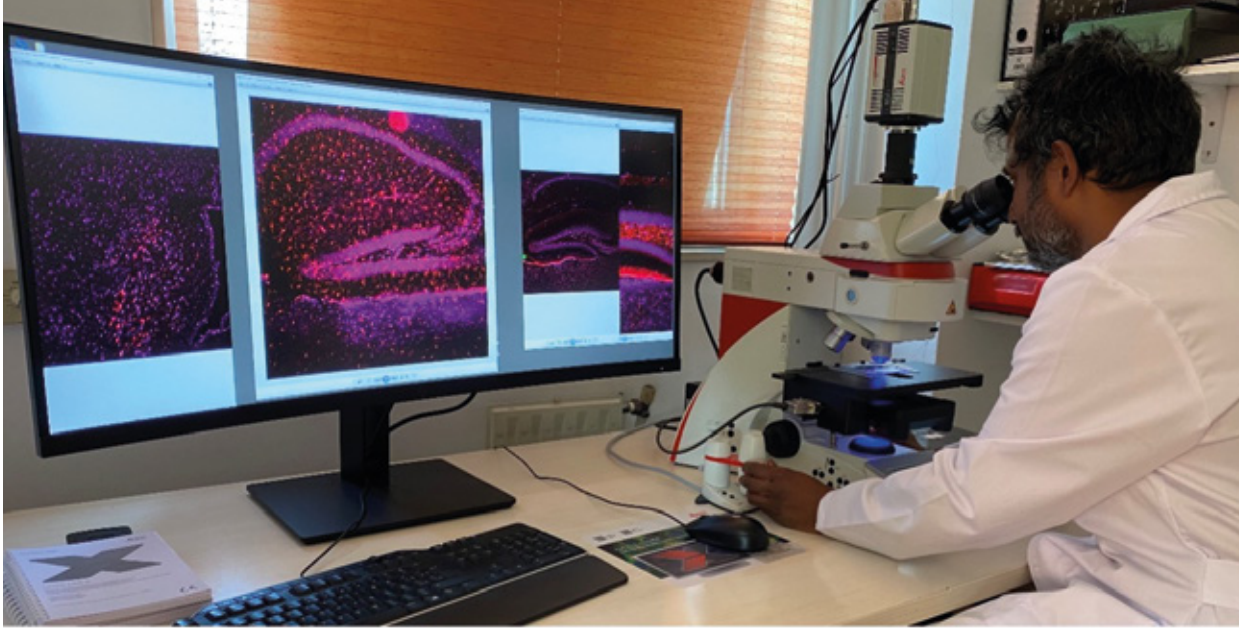
Several pharmacogenetic tests have already been formally approved by the United States health authorities for routine use, prior to the administration of drugs with a high possibility of producing ADRs. Typical examples are the marker HLA-B * 57: 01 for abacavir, HLA-B * 15: 02 and HLA-A * 31: 01 for carbamazepine, HLA-B * 58: 01 for allopurinol, CYP2C19 for clopidogrel, TPMT for 6 -mercaptopurine, azathioprine and cisplatin, CYP2C9 and VKORC1 for coumarin

derivatives, MTHFR for methotrexate, factor V Leiden for oral contraceptives, and CYP2D6 for psychotropic agents (neuroleptics, antidepressants).

The main limitations for the routine use of pharmacogenetics in the daily clinic are the lack of education and training of physicians and pharmacists, the limited documentation available on the pharmacogenetics of the most common drugs, the lack of specific biomarkers to quantify the efficacy and the drug safety, the cost of pharmacogenetics tests, administrative bureaucracy in hospitals and health centers, and the scarcity of regulatory principles for the efficient use of pharmacogenetics in medical institutions.

The implementation of pharmacogenetics in the daily clinic requires: (i) education of physicians and health personnel; (ii) prospective studies to demonstrate the benefit of knowledge of the pharmacogenetic profile for the physician and patient, which enables treatment to be personalized; (iii) standardization of pharmacogenetic procedures; (iv) the mandatory inclusion of pharmacogenetics information on drug labelling; and (v) improvements in genotyping technology to streamline and lower the cost of processes.

The incorporation of pharmacogenetics into the daily clinic is the most efficient option to reduce ADRs and improve the efficacy and safety of drugs.



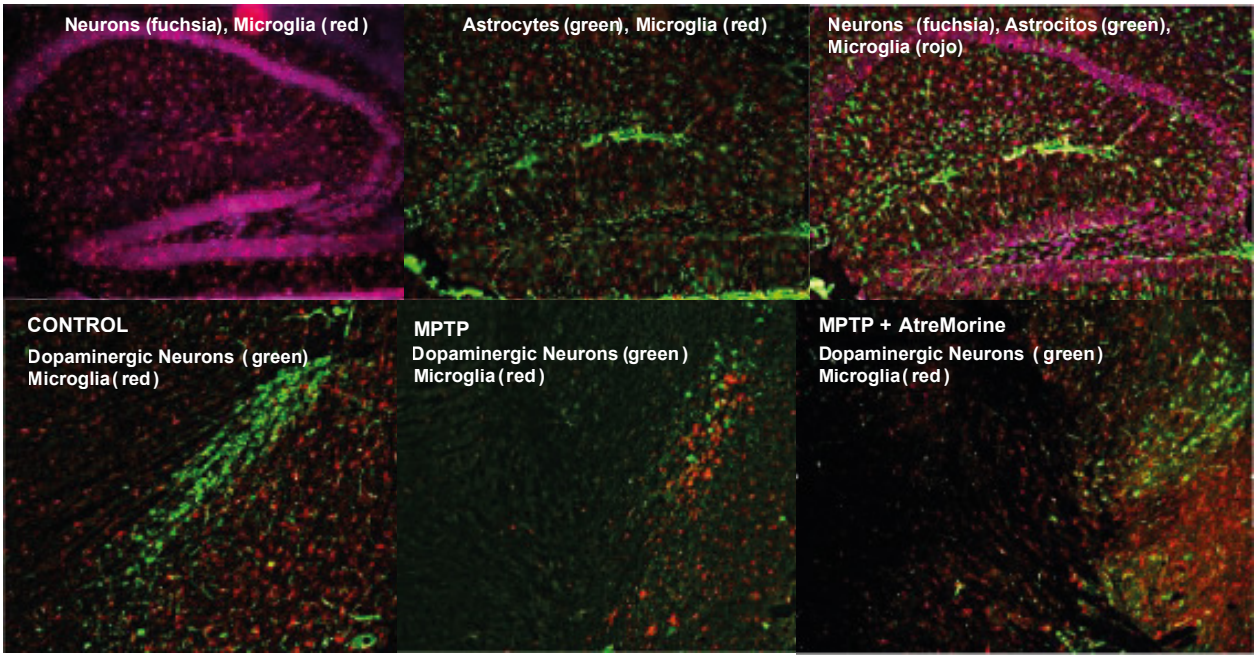
Great Advances in Molecular Imaging of the Brain

The Department of Basic Neurosciences of the Research and Development Division, led by Dr. Vinogran Naidoo, is achieving important advances in Confocal Microscopy and Molecular Neurobiology to show images of the brain at the molecular level, check the expression of genes with specific functions in higher activities of the nervous system, such as memory and learning, and in the development of new biomolecules for brain diseases and other priority health problems, such as cardiovascular disease and cancer.

Dr. Vinogran Naidoo is a prestigious neuroscientist, educated in the United States and at the Karolinska Institute in Sweden. Since joining Dr. Cacabelos' team at the International Center of Neurosciences and Genomic Medicine, Dr. Naidoo has participated in important research projects and has contributed to the development of new biomolecules and epinutraceutical agents, such as Atremorine for Parkinson's disease and BrainRex for Alzheimer's disease.

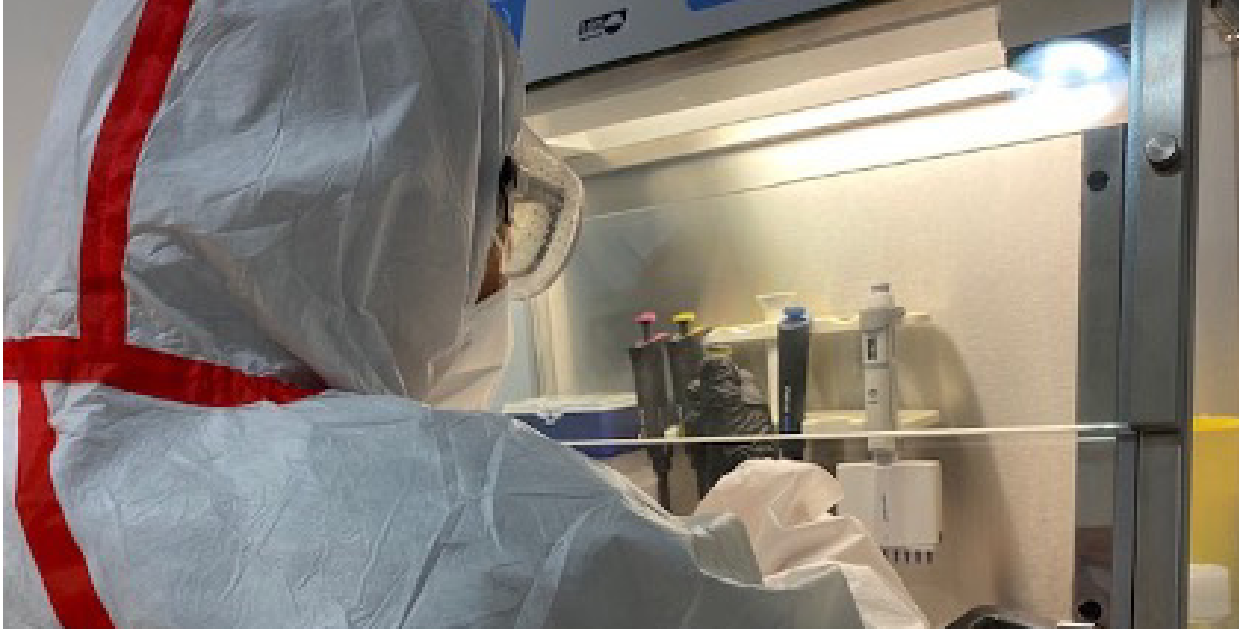
Dr. Vinogran Naidoo

Head of the Department of Basic Neurosciences at the International Center of Neurosciences and Genomic Medicine EuroEspes



Microscopic images of neurons (fuchsia), microglia (red) and astrocytes (green) in the hippocampus (upper row); and dopaminergic neurons (green) and microglia (red) in the substantia nigra pars compacta of control mice (left image, bottom row), MPTP-treated animals (Parkinson's disease model) (center bottom image), and reparative effect of Atremorine on MPTP-damaged dopaminergic neurons (lower right image).

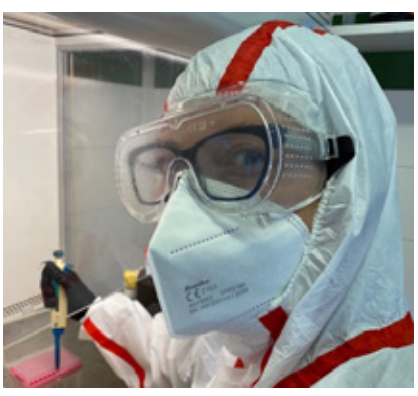
Courtesy of Dr. Vinogran Naidoo, Department of Basic Neurosciences, International Center of Neurosciences and Genomic Medicine EuroEspes.



Epigenetic biomarkers for early diagnosis and therapeutic monitoring

Epigenetics is a newly created discipline, with enormous momentum in the last two decades. The idea arises from the studies of Hans Selye in 1936, who postulated the "general adaptation syndrome" when describing how environmental stress could affect the physiological functions of a living organism and cause disease, and from the pioneering concepts of Conrad Waddington who, about 20 years later, introduced the concept of epigenetics associated with transgenerational inheritance. Since Waddington's pioneering ideas in 1956 on the heritability of characteristics acquired in response to environmental stimulus, the field of epigenetics has seen explosive growth, especially over the last decade.

Epigenetics is conceived as a natural extension of genetics to explain the expression of genes and the dialogue of the genome with the external environment. However, the conceptual breadth of epigenetics has grown in parallel with the current understanding of the mechanisms that shape the epigenetic phenomenon. Some of the most genuine characteristics of epigenetics are the transgenerational inheritance of certain phenotypic characters without apparent changes in the structure of DNA; the regulation of gene expression at the transcriptional and post-transcriptional level under the control of the epigenetic machinery regulated by mechanisms such as DNA methylation, the modification of chromatin and histones or the regulation of gene expression by micro-RNAs that block gene expression (gene silencing); and another fundamental characteristic of epigenetics is its potential reversibility through exogenous intervention with drugs, nutrition or environmental changes. These are the most relevant characteristics of epigenetics; but perhaps the most relevant, in terms of health, is the possibility of reversing epigenetic changes, something that cannot be done with genetics, except in those cases where gene therapy is feasible.



The Department of Medical Epigenetics, led by Dr. Olaia Martínez-Iglesias, at the International Center of Neurosciences and Genomic Medicine, develops epigenetic biomarkers to predict the risk of prevalent diseases, such as diseases of the central nervous system, cancer, and cardiovascular diseases, and to monitor the effect of drugs and specific treatments for various diseases. Pioneering studies by Dr. Martínez-Iglesias show that neurodegenerative diseases, especially Alzheimer's and Parkinson's, are characterized by a state of global DNA hypomethylation that can be reversed with appropriate treatment. She was the first to show that treatment with Atremorine, a bioproduct developed by EuroEspes scientists for the treatment and prevention of Parkinson's disease, was able to reverse the hypomethylation present in Parkinson's patients, in parallel with their clinical improvement. Similarly, she demonstrated that various genes related to neurotrophic factors and enzymes that regulate epigenetic phenomena showed profound alterations in their expression, which allowed her to develop effective epigenetic biomarkers for Alzheimer's and Parkinson's diseases that are now being used in routine clinical practice with a high level of sensitivity and specificity.

Dr. Olaia Martínez-Iglesias

Head of the Department of Medical Epigenetics at the International Center of Neurosciences and Genomic Medicine EuroEspes

Microbiome and Gut-Brain Axis

In recent years there has been an informational explosion about the brain's connection to the gastrointestinal tract and the microbiome, represented by the microbes that colonize the intestinal tract. Studies in experimental animals show that the gut microbiome can affect emotions, behavior, pain and various forms of appetitive behavior.

The communication between the gut and the brain responds to chemical, immunological and neurochemical signals. Various intermediate metabolites generated by gut microbes, such as short-chain fatty acids, secondary bile acids, and tryptophan metabolites, can reach the central nervous system. These metabolites can interact with enteroendocrine and enterochromaffin cells and with the immune system of the intestinal mucosa to propagate their signals, although it is unknown whether they have sufficient capacity to penetrate the brain and exert a direct action on brain functions. Other metabolites can enter the bloodstream and reach the brain by crossing the blood-brain barrier. An alternative route is communication through neural pathways involving the vagus nerve and spinal afferents. Gut microbes can use the neurotransmitters that are made in the human brain and influence brain neurochemistry and brain activities. The brain, in turn, can communicate directly with the intestine through endocrine signals and messengers capable of interacting with microbial receptors. Catecholamines exert a direct action on the intestine, while the autonomic nervous system exerts an indirect action.

The existence of five communication routes between the intestine and the brain can be considered: a neural brain-gut route, a neuroedocrine (hypothalamic-pituitary-adrenal) route, an entero-immune route, a neurochemical route, and an entero-vegetative route.

Various types of bacteria (commensal, probiotic, pathogenic) can directly affect the nervous system causing emotional and behavioral disorders. Irritable bowel syndrome is a prototype of a microbiological disease with involvement of the gut-brain axis. It has also been argued that the microbiome could be responsible for neurodegenerative disorders.

The microbiome is in permanent contact with the environment and environmental signals can be channeled to the brain through entero-cerebral routes, with the participation of epigenetic mechanisms. Another important aspect of the microbiome is related to the genomic structure of intestinal microbes and the DNA endowment that they contribute to the human body. This microbial DNA may represent genomic noise in some studies and may affect the pharmacogenetic apparatus, influencing the efficacy and safety of drugs,

contributing to their toxicity or ineffectiveness. Pharmacomicrobiomics and toxicomicrobiomics have experienced increasing interest to explain how variations in the microbiome (genome of microbes in the gut, vagina, skin, respiratory tract) affect the bioavailability, metabolization and elimination of drugs, with the consequent impact on the efficacy and pharmacological safety. In the human body there are about 3.0×10^{13} cells and more than 3.8×10^{13} microorganisms, with a ratio close to 1: 1 between resident microbes and human cells. The genomic load of the microbes that colonize the living spaces of the human body influences health and the pharmacokinetics and pharmacodynamics of drugs. Also, many drugs, especially antibiotics, antifungals, and non-steroidal anti-inflammatory drugs, cause severe dysbiosis that disrupts the balance of the microbiome. The intestinal microbiome is the second genome that contributes the most to the biotransformation of xenobiotic agents that penetrate the human body. Imbalance and instability in the microbiome can disrupt natural detoxification mechanisms and cause disease, poisoning, and systemic and brain damage.

Covid-19 News

Genetic map of susceptibility to COVID-19 and severity of symptoms

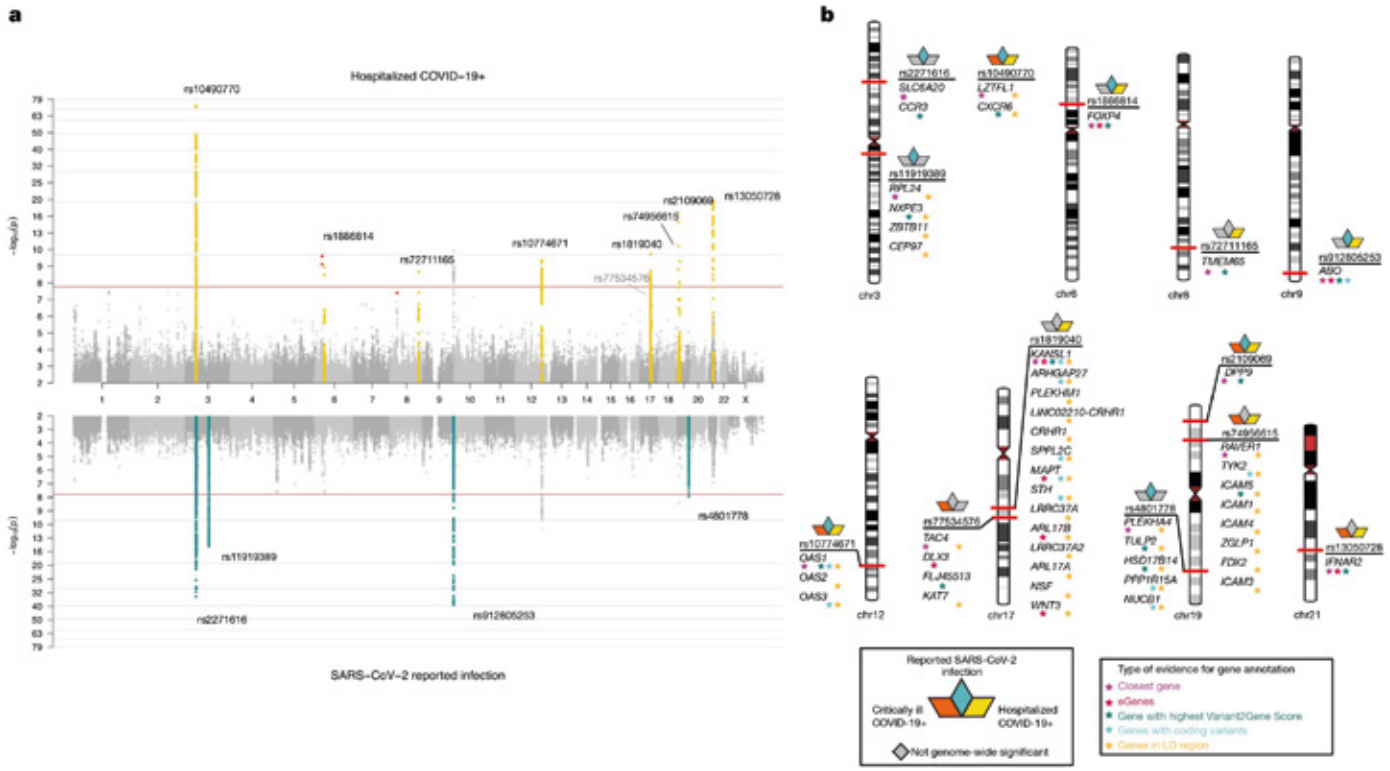
A study of 49,562 COVID-19 patients in 19 countries has identified 13 genomic regions associated with vulnerability and severity of coronavirus infection. A study by the *COVID-19 Host Genetics Initiative* identified 9 closely related regions on chromosomes 3 (rs2271616, rs10490770, rs11919389), 6 (rs1886814), 8 (rs72711165), 9 (rs912805253) (ABO, 12 (rs10774671), 17 (rs77534576, rs1819040), 19 (rs4801778, rs74956615) and 21 (rs13050728), in hospitalized patients with moderate to severe infection. Pharmacogenetic studies link 14 genes of interest in anti-COVID-19 treatmen *(CYP2C19, CYP2C9, CYP2D6, CYP3A5, DPYD, G6PD, HLA-A, HLA-B, IFNL3, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1)* with potential utility to personalize drug treatment in patients with coronavirus infection. With the use of pharmacogenetics, 20% to 40% of the side effects (sometimes fatal) of commonly used drugs that turn out to be inappropriate in certain patients could be avoided.

The SARS-CoV-2 virus uses ACE2 (angiotensin converting enzyme 2) as the host receptor and uses host proteases to enter cells. Various ACE2 variants [p. (Asn720Asp), p. (Lys26Arg), and p. (Gly211Arg)] interfere with protein structure and other variants [p. (Leu351Val); p. (Pro389His)] interfere with the spike protein of SARS-CoV-2. These and other ACE2 variants contribute to interindividual variability (predisposition, clinical characteristics, severity) in infected patients. ACE2 variants c.2158A> G p. (Asn720Asp), c.77A> G p. (Lys26Arg), and c.631G> A p. (Gly211Arg) are the three most common, with important gender differences (the ACE2 gene is located on the X chromosome) and racial differences. Sex differences justify the greater severity of COVID in men, with the participation of the TMPRSS2 gene. ACE2 and TMPRSS2 levels correlate with the age of the patient and the degree of respiratory distress. High levels of ACE2 in the nasopharynx are protective and the TMPRSS2 / ACE2 ratio is associated with COVID risk and prevalent symptoms (cough, 70.42%; fever, 63.85%; headache, 61.50%; anosmia, 57.28%; myalgia, 55.87%).

Dr. Juan Carlos Carril, Head of the Department of Genomics and Pharmacogenomics, developed the COVID-19 GenoPredictor, which integrates different categories of genes: (i) genes for predicting COVID risk and lung involvement (*ACE2 rs2285666; TPMRSS2 rs2070788*), (ii) genes associated with vascular risk (*ACE1 rs4332; ACE2 rs2285666; AGT rs4762, rs699*), thromboembolic risk (*F2* rs1799963; *F5* rs6025), immune response (*IL1B* rs1143634; *IL6* rs1800795; *IL6R* rs693; *TNF* rs708272), and metabolism (*MTHFR* rs1801133); and (iv) metabolic genes (Phase-I Reactions (*CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5*) and Phase-II Reactions (*NAT2*)) and transporter genes (*ABCB1, ABCC2, SLCO1B1*) for drugs commonly used in patients with COVID-19.

In the Spanish population, people at risk (ACE2-G) represent 90%, with a higher risk in men than in women. The frequency of *ACE2* genotypes in women is the following: *ACE2*-A / A 8.33%; *ACE2*-A / G 22.22%; and *ACE2*-G / G 69.45%; and in men, *ACE2*-A 12.20% and *ACE2*-G 87.80%.

The frequency of *TMPRSS2* genotypes in the Spanish population is distributed as follows: *TMPRSS2*-C / C 27.27%, *TMPRSS2*-C / T 51.95% and *TMPRSS2-T* / T 20.78%, with a higher risk in men than in women.

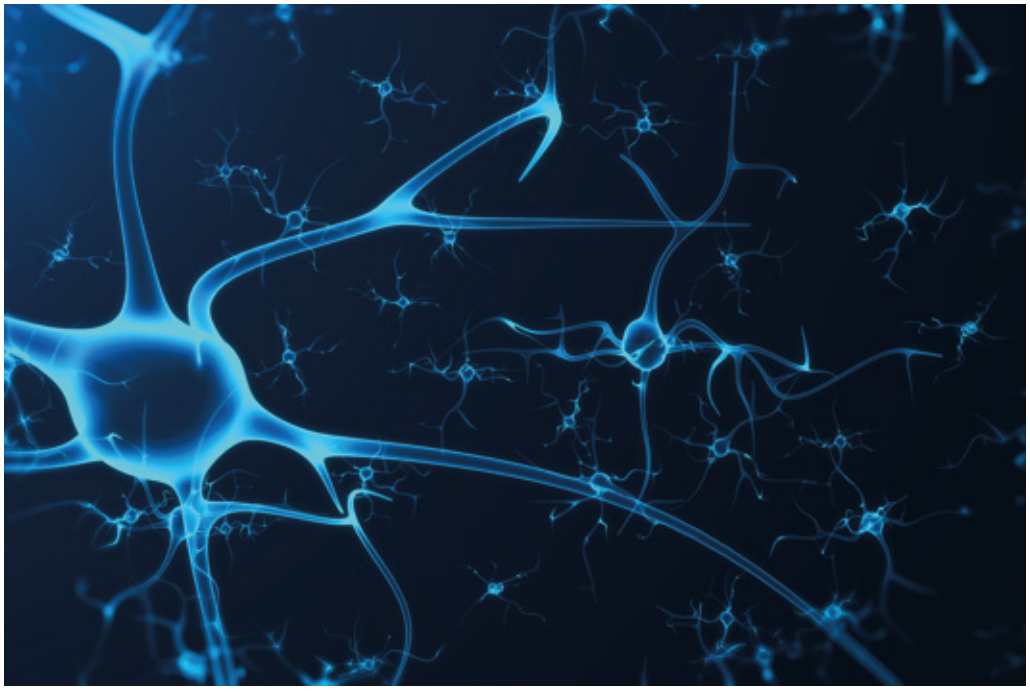


Source:

COVID-19 Host Genetics Initiative. Mapping the human genetic architecture of COVID-19. Nature https://doi.org/10.1038/s41586-021-03767-x (2021).

COVID-19 Brain Damage

Certain symptoms and research into the brains of COVID-19 patients indicate that SARS-CoV-2 can colonize brain tissue. Although the coronavirus shows a predilection for the respiratory tract, causing pneumonia in two thirds of infected patients (15-20% of severe cases, 5% with acute respiratory distress syndrome, 2% of mortality), cases of encephalitis, vascular encephalopathy, stroke, cranial neuropathy, epilepsy, dysexecutive syndrome, Miller-Fisher syndrome, Guillain-Barrè syndrome, myositis and rhabdomyolysis have been described in patients with COVID-19 and in patients vaccinated against COVID-19. Taste and olfactory alterations are primary symptoms of COVID due to possible viral tropism towards sensory structures that affect taste and smell. The autopsy of patients with COVID demonstrates the presence of inflammation, edema and axonal damage in the olfactory bulb. The olfactory mucosa is believed to be the gateway for SARS-CoV-2 to the brain. Other cranial nerves may be affected, such as the facial, oculomotor, and trochlear nerves. Demyelination processes often accompany Guillain-Barrè syndrome in adults with COVID. Myalgia is a common symptom, along with headache, cough, fever, and sore throat. Patients with myositis and rhabdomyolysis often have severe lung involvement. In 15-30% of patients, the kidneys, liver and heart can also be affected. In hospitalized patients, neurological symptoms appear in 30-40% of cases, although the frequency varies according to studies and countries. The manifestation of cerebral ischemia and stroke can reach 30% of the cases; sensory alterations appear in more than 20%; and various neuropsychiatric symptoms, from delirium and cognitive impairment to depressive disorder, insomnia, autolytic ideation and psychosis can be seen in more than 35% of cases. Some of these symptoms may remit spontaneously, but it is advisable to treat them in a personalized fashion based on the pharmacogenetic profile of each patient so that the side effects of psychotropic treatments, anticoagulants, corticosteroids and non-steroidal anti-inflammatory drugs do not affect the respiratory capacity and/or the fragile immunity of COVID-19 patients.



Infection of vaccinated patients

The study of millions of patients in the world is raising a series of unknowns that require scientific explanation, such as why are there new waves with 50% of the population vaccinated, why 20% of the population does not respond to vaccines, why 40% of those vaccinated have an insufficient level of antibodies to guarantee an effective vaccination, why more than 10% of those vaccinated are becoming infected, or why infected people can be reinfected.

All these questions have a common answer. The efficacy of a vaccine depends on (i) the nature of each vaccine (antigenicity, manufacture, interactions, side effects); (ii) the individual genomics of each person, as well as their sex and their immunological status: the genome determines the risk of infectivity and vulnerability to the pathogenic invasiveness of the virus, and also conditions the antibody response to anti-COVID vaccines; men are more vulnerable to infection and there are sex differences in antibody response; and immunosuppressed patients (e.g., transplanted under immunosuppressant treatment) respond poorly or do not respond to conventional vaccines; (iii) those who have low levels of antibodies, insufficient to be protected against the virus, can be perfectly infected even if they are vaccinated; and (iv) people who have suffered COVID-19, after 6-12 months run out of antibodies and can become reinfected. Vaccine ineffectiveness is also increased by the multiple mutations that the virus can undergo when it feels threatened. A vaccine can be very effective against one viral strain and ineffective against a different strain.

Bearing these observations in mind, it is prudent to call for caution in the face of certain (non-scientific) political decisions. For example, issuing the vaccination certificate is useless if a sufficient post-vaccination antibody titer is not guaranteed. It does not make much sense to close restaurants at certain times or force PCRs in order to enter places of apparent risk while the virus circulates freely in buses, trains and planes where users travel crowded. Blaming the youth of the fifth wave is unfounded, since for a year it was already known that the rate of infected increased among young people, but the health authorities opted for a vaccination policy that did not give priority to the group of 20 to 40 years. There are still 10-20% of asymptomatic people who can be carriers and spread the virus within their social, family and work environment. The EU community guidelines that each state interprets in its own way and applies in a tribal way do not seem very intelligent.

Dr. Ramón Cacabelos
Fleming Award for Health Excellence 2021

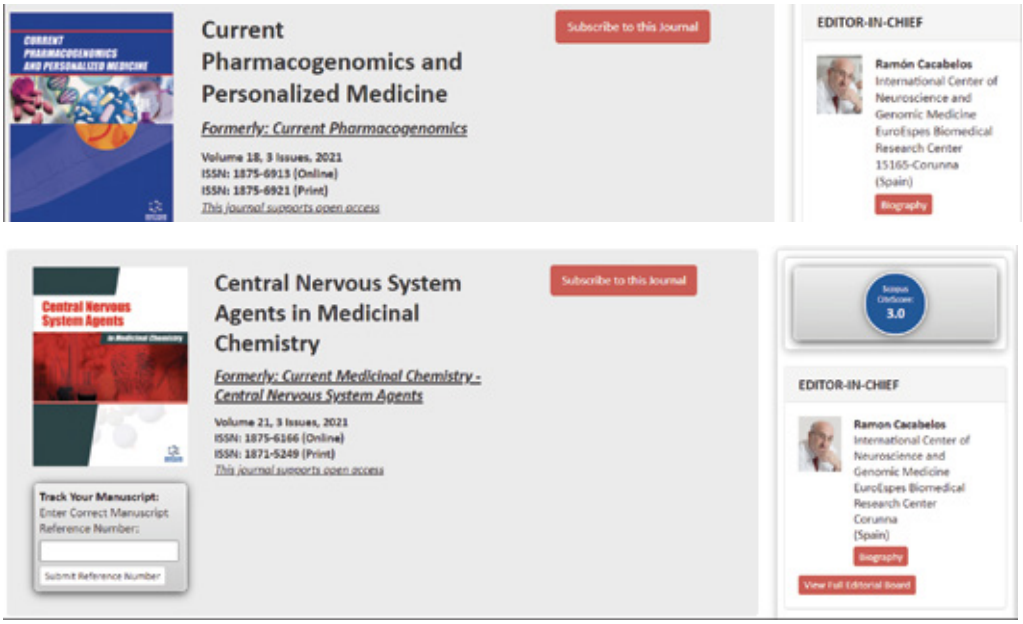
On July 23, the **European Society for Social and Cultural Promotion**, chaired by the academic **Mr. Luís María Ansón**, awarded Dr. Ramón Cacabelos, President of the EuroEspes Group, the **Dr. Fleming Award for Health Excellence 2021**. In a brief speech of thanks, in the presence of the General Director of EuroEspes, Jaime Pombo, the Chief Financial Officer, Francisco Álvarez, and a distinguished group of professionals from the International Center of Neurosciences and Genomic Medicine, Dr. Cacabelos emphasized the importance of multidisciplinary work in Genomic Medicine and the importance of Predictive Medicine based on genomic analysis to identify early the risk of suffering from prevalent diseases and to be able to intercept their evolution through preventive programs with personalized treatments based on the principles of pharmacogenomics.

Editorial News

We are pleased to report that the Impact Factor *(IF)* of the **International Journal of Molecular Science** of the MDPI publishing house, based in Geneva and Wuhan, China, of which Dr. Ramón Cacabelos is *Guest Editor* for the special issues *Pharmacogenomics and Genomics of Brain Disorders*, has risen from 4,556 to 5,923

(https://www.mdpi.com/journal/ijms).

Likewise, the journal Life, for which Dr. Ramón Cacabelos is *Section Editor-in-Chief of Pharmaceutical Science*, has raised its IF from 2,991 to 3,817.



The journal ***Frontiers in Pharmacology***, of the *Frontiers group*, based in Lausanne, Switzerland (https://www.frontiersin.org/journals/pharmacology), prepares a special edition on Personalized Medicine in Neuropsychiatric Disorders. The Editors of this special issue are Dr. Alessio Squassina, University of Cagliari, Italy, currently at Dalhousie University in Halifax, Canada; Dr. Claudia Pisanu, from Cagliari; and Dr. Ramón Cacabelos, Professor of Genomic Medicine, at the International Center of Neurosciences and Genomic Medicine EuroEspes in A Coruña and at the Faculty of Medicine of the Continental University based in Peru.

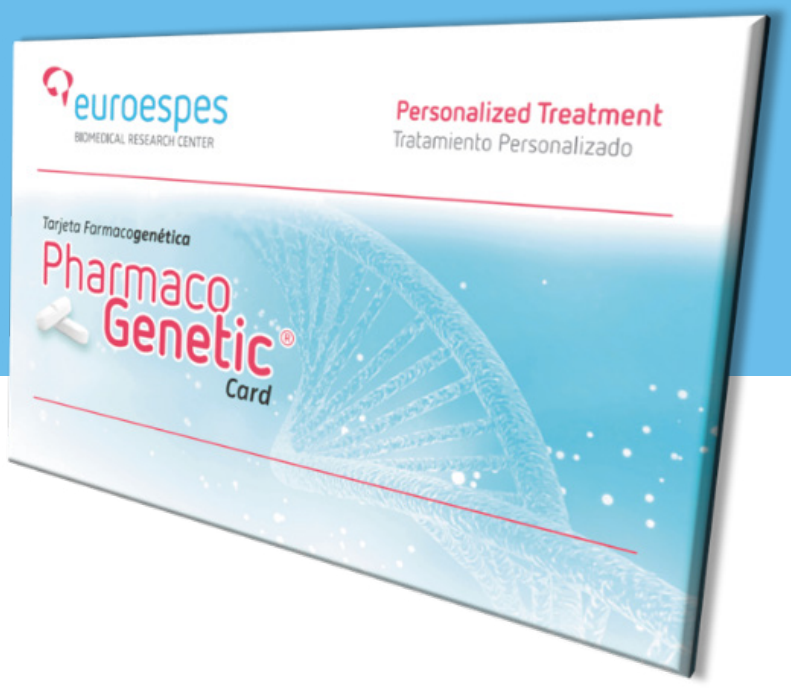
Promotional Section

Alzheimer's Prevention Plan (APP) Home and Face-to-face

The APP identifies populations at risk of Alzheimer's disease (AD) and discriminates against other memory disorders and other forms of dementia. As the initial component of the APP is the identification of the genetic risk, in order to avoid unnecessary costs and discomfort due to the displacement of people, we have established a dual APP: (i) Home APP to perform genetic tests on a saliva sample that the interested person sends to the EuroEspes Medical Center with no need to travel; and (ii) face-to-face APP for those who wish to complete a complete diagnostic protocol, including genetic tests, at our Medical Center. Those people whose home APP detects an obvious risk can later join the face-to-face APP to complete the diagnostic set and enter the personalized prevention program through pharmacogenetic intervention.

Parkinson's Prevention Plan (PPP) Home and Face-to-face

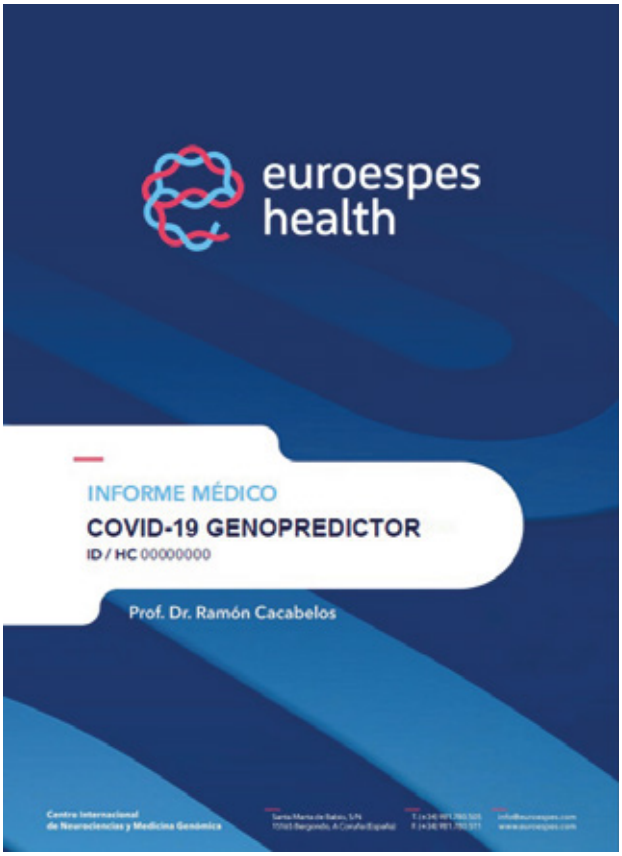
The PPP identifies the population at risk of suffering from Parkinson's disease, differentiating familial Parkinson's disease and other forms of parkinsonism (vascular, toxic or traumatic). The PPP also includes (i) a home PPP for all those asymptomatic people with a family history of Parkinson's or who detect incipient symptoms of tremor, rigidity or bradykinesia; and (ii) a PPP in person at the EuroEspes Medical Center where they would carry out the complete diagnostic protocol, including genomic screening. Patients following the home regimen who show genetic or environmental risk for Parkinson's would take the in-person PPP to complete the diagnostic set, and start the personalized prophylactic plan according to their pharmacogenetic profile.



Smart Pharmacogenetic Card PGx-60/4000

The most advanced bioinformatics product in the world with its personalized pharmacogenetic profile:

- to know the medicines you can take and which you should not take
- so that your doctor knows which drugs to prescribe and which drugs harm you
- to avoid toxicity and side effects when you have to take medication for any health problem
- to avoid life-threatening drug interactions if you have to take several medications simultaneously for long periods of time
- to avoid unnecessary expenses on products that are not useful to you
- to preserve your health with the appropriate medication for your genomic profile
- for the health of their children, who share 50% of their genome
- for life, because your genome does not change



COVID-19 GenoPredictor

The COVID-19 GenoPredictor is the only genetic test in the world that allows predicting vulnerability to SARS-CoV-2 infection with potential lung damage, immunological status and immune response capacity to coronavirus infection, and pharmacogenetic profile that allows us to personalize the pharmacological treatment appropriate to the genome of each person in case of need for treatment.

Carrying out this genomic test is recommended for people at high risk (heart disease, lung disease, hypertension, diabetes, stroke, cancer, immunosuppressed), people exposed by the nature of their work (high public attendance centers, frequent trips), people with a family history of risk, people infected by coronavirus and health personnel.

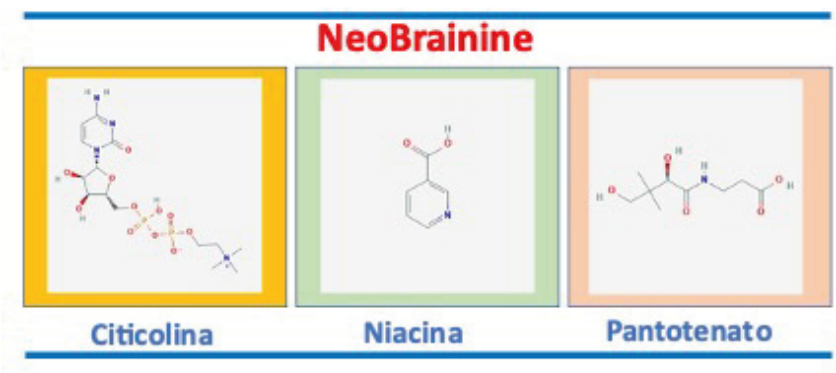
NeoBrainine

NeoBrainine is a new neuroprotective product for the prevention and treatment of various types of dementia and cerebrovascular risks (migraine, cerebral ischemia, thromboembolic events, stroke). NeoBrainine is a hybrid bioproduct, created by the team of scientists led by Dr. Ramón Cacabelos, that integrates citicoline, pantothenic acid and niacin molecules. Citicoline is a choline donor, acetylcholine precursor -an essential neurotransmitter for memory-; it is an essential component of the phospholipids of neuronal membranes and is an intermediate metabolite in nucleotide synthesis.

Pantothenic acid (D (+) - N- (2,4-dihydroxy-3,3-dimethylbutyryl) β-alanine) is an amide between pantoic acid with β-alanine; it is a water-soluble vitamin of the B complex, also known as vitamin B_5 or vitamin W, essential for life. Pantothenic acid is a fundamental cofactor in the synthesis of coenzyme A (CoA) and in the metabolism and synthesis of carbohydrates, proteins and fats.

Niacin or nicotinic acid ($C_6H_5NO_2$) is another water-soluble vitamin of the B complex (vitamin B_3, vitamin PP) involved in cell metabolism as part of the coenzyme NAD (nicotine-adenine-dinucleotide) and NAD-phosphate (NADP). Its derivatives (NADH, NAD+, NADPH, NADP+) are essential in energy metabolism and in DNA repair. Its main amide is nicotinamide or niacinamide ($C_6H_6N_2O$). Niacin is essential in the synthesis of steroid hormones and in the elimination of toxic xenobiotic agents.

The components of NeoBrainine (Citicoline, Niacin and Pantothenic Acid) exert essential neuroprotective functions for the normal functioning of the central nervous system.



Atremorine capsules

Atremorine has been approved by the European Patent Office for the prevention and treatment of Parkinson's disease.

In its usual presentation, Atremorine is dispensed as a powder to take with yogurt or other similar food, but not with water or liquids that can oxidize it or alter its properties. To avoid the use of powder and to facilitate the intake of Atremorine, EuroEspes Biotecnología (Ebiotec) launches Atremorine in capsules. The new presentation is now available nationally and internationally.

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DefenVid-90

EuroEspes Biotechnology (Ebiotec) launches a new presentation of DefenVid with 90 capsules. This new presentation covers a complete monthly treatment regimen. Ebiotec continues to maintain the presentation of 30 capsules.

DefenVid is an immunity enhancer epinutraceutical to combat immunodeficiency states or the fall in natural defenses associated with the use of antibiotics for bacterial infections or chemotherapeutic agents in cancer patients.

DefenVid is a powerful enhancer of cellular immunity at any age against viral infections.

The two presentations of 30 and 90 capsules are already available nationally and internationally.

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Complete Sequencing of the Human Genome

The team of geneticists from the Department of Genomics and Pharmacogenomics, led by Dr. Juan C. Carril and Dr. Óskar Martínez de Ilárduya Ruiz de Larramendi, Head of the Genomic Sequencing Unit, make available to users of medical services from the International Center for Neurosciences and Genomic Medicine, as well as from the national and international medical and scientific community, a service specialized in the complete sequencing of the human genome (> 20,000 genes) with NGS technology.

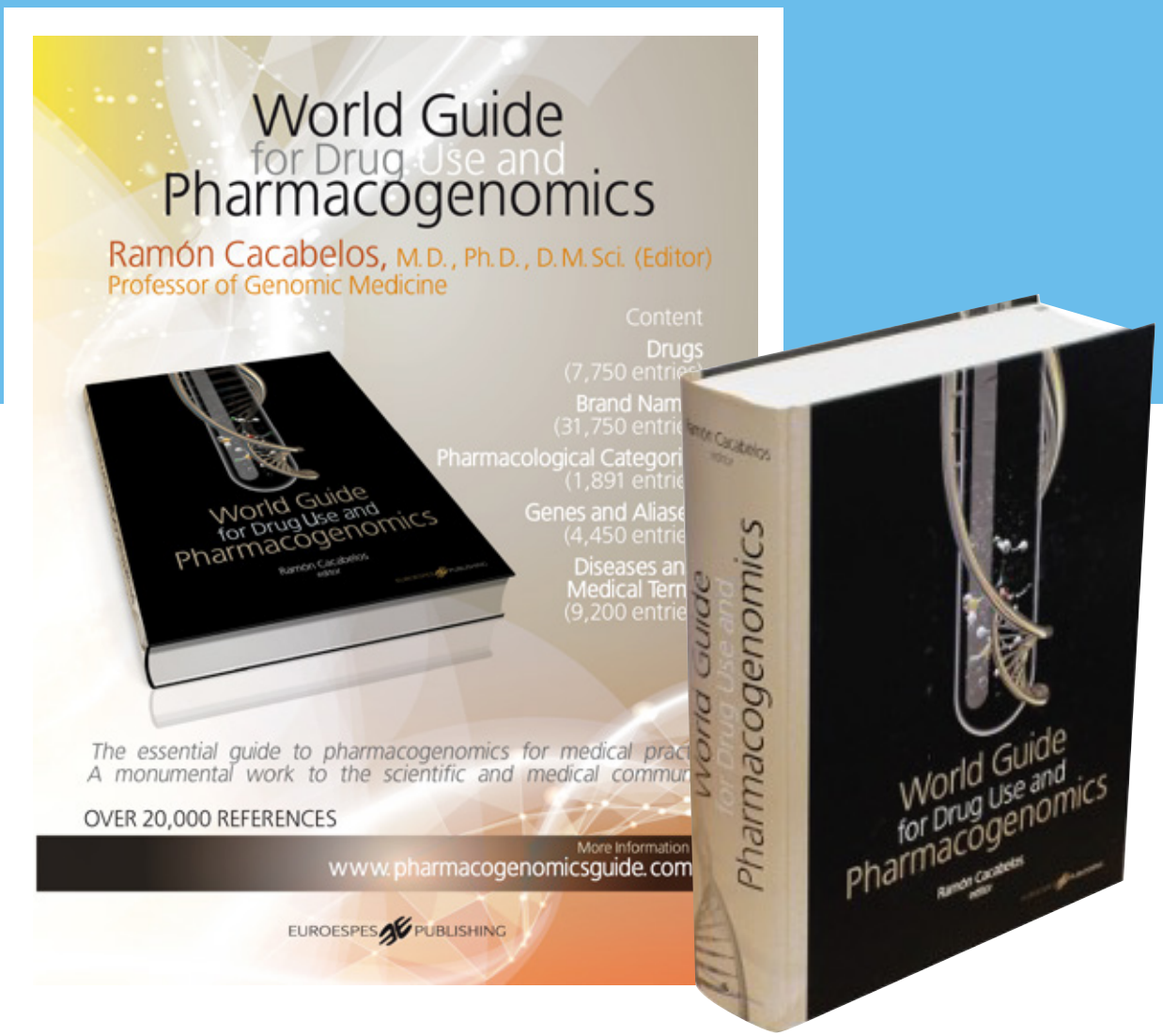
DermoGenetics Catalog

The Genomics and Pharmacogenomics Department of the EuroEspes Medical Center offers doctors and specialists in Dermatology the EuroEspes DermoGenetics Catalog. The Catalog includes the 1000 most relevant genes in skin diseases, from allergic reactions to skin cancer. This is the first Dermogenetics Catalog available in Europe.

Home Care: COVID-19 and Genetic Testing

Following our Community Care policy, facing the COVID-19 crisis, mobility restrictions in various national territories, and the difficulties of displacement of our national and foreign patients, the International Center for Neuroscience and Genomic Medicine has established a Home Care Service to our patients, to individuals and companies to carry out COVID-19 tests (PCR, Antigens, Antibodies) and genetic tests (see catalog at www.euroespes.com).

Phone No.: (+34) 981 780505.



World Guide for Drug Use and Pharmacogenomics

The First World Guide of Pharmacogenomics, edited by Dr. Ramón Cacabelos, incorporates for the first time the pharmacogenetic profile of commonly used drugs. In its more than 3000 pages the WGDUPGx catalogs (i) drugs approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Koseisho (Japan) and other international agencies, with their bioactive properties, side effects, metabolism and pharmacogenetic profile; (ii) genes of interest in human pathology and pharmacogenetics; and (iii) more than 9,000 illnesses and medical terms.

The World Guide for Drug Use and Pharmacogenomics is a fundamental reference in the library of universities, hospitals, medical departments and research centers.

Available from EuroEspes Publishing Co., Tel. (+34) 981 780 505.

EuroEspes Health Medical Bulletin

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