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Contents

September Editorial
Gratitude and Fidelity

Gratitude and fidelity are children of the same mother. Those who know how to be grateful are usually faithful to their principles and to their friends; and whoever is faithful to his own has the gratitude of all the kind. **Erich Fromm** said in *The Art of Loving* that "only the person who has faith in himself is able to be faithful to others." Faith in what one does, the conviction that we are doing the right thing, is what strengthens fidelity between people and cultivates affection. **Cicero** said in *De Officiis* that "we should measure affection, not like youngsters by the ardor of its passion, but by its strength and constancy." All of this gives stability to human relationships, be they as a couple, family, friendship, professional career or necessity. Without doubt, love is above all; and, it is probable, that without love only relationships of convenience have some temporal consistency; but even if there is love, without fidelity and the capacity for gratitude, even love itself has an expiration date. In *Characteristics*, **William Hazlitt** argued that "to be capable of steady friendship or lasting love, are the two greatest proofs, not only of goodness of the heart, but of strength of mind."

Perhaps, in moments like the present, where almost all values are in crisis -from the most elementary morality to the most orthodox religiosity, passing through the principles of honesty, transparency, goodwill and solidarity- friendship, love, labor relations and social commitments are approached as temporary experiments of uncertain duration. It should not be a new circumstance, when on September 9, 1779, **Boswell** put in the mouth of **Samuel Johnson**: "It is as foolish to make experiments upon the constancy of a friend, as upon the chastity of a wife." Constancy is the element that engages fidelity, loyalty, and gratitude. **François de La Rochefoucauld** described, in his *Maxims* of 1665, two types of constancy in love; the one that comes from the constant discovery in our beloved of new grounds for love; and another that comes from making it a point of honor to be constant.

Constancy in love conceives fidelity and the fruit of both is the gratitude that feeds them. When this chain fails, the alarms go off and the error status paralyzes the relationship. Error is an atavistic behavior of the human species, which can be partially repaired by virtue.

The doctor-patient relationship is a bit of all this in harmonic fusion when it works correctly; and it is a mere marriage of temporary convenience when the service is simple mercenary or when the need is simple temporary interest. The patient cannot go to the doctor as if he were going shopping or as if he were seeking the mercy of Charities. The doctor is not a civil servant behind a counter or a mechanic in a car garage, no matter how much he is dedicated to repairing biological machines; some, with sheet metal problems; others, with electrical or body problems; and many, with serious engine problems. There are also biological machines that work very well, but with serious problems in driving style, which prevent them from circulating normally in a hyper-regulated world subjected to the whim of disrespectful norms with the different, with the disabled, with dissidents, with those who have learned that being free allows them not to have to say amen to everything.

The patient puts his life in the hands of the doctor, which represents an act of supreme trust; the patient tells the doctor what he tells no one else, assuming that the Hippocratic code is as sacred as the secret of confession; the patient submits to the orders, instructions and remedies that the doctor proposes, with the blindness of faith. Faced with this sublime dedication, vulgarized by custom and subjected to the vices of charity, the doctor has to compromise his life, his honour, his professionalism with the patient; affection, mutual trust, fidelity and gratitude will arise between them, for what one offers and the other accepts, for what one gives and the other receives, for what one explains and the other understands, and for what nature allows and reason prohibits.

"The most powerful cause of error is the war existing between the senses and reason," wrote **Pascal** in his *Pensées* of 1670. This struggle is frequent in medicine when opinion takes precedence over knowledge or when the battle focuses not on fighting disease with scientific efficiency but on winning dialectical wars to impose an absolutist and dogmatic hegemonic thought. However, following the thought of **Thomas Jefferson**, set forth in his first inaugural address on March 4, 1801, "error of opinion may be tolerated when reason is left free to combat it."

The violation, by the doctor or the patient, of the moral and professional principles that maintain this unique relationship, leads to mistrust, disinterest, non-compliance, conflict, error and litigation. When the end of the relationship becomes a divorce, with legal connotations, the toxic intervention of third parties, with unilateral interests, will be irremediably destructive, with an unsatisfactory outcome for the parties. When the error, not infrequently bilateral, is the cause of the failure of the relationship, then only high doses of humility and reflection can bring harmony and reason, minimizing the traumatic effect of the breakup. Unfortunately, the system already ensures that the doctor-patient relationship, except in Primary Care, is not lasting and sectarianly conflictive. In areas of specialization that require chronic care, the patient rarely has the same doctor as the interlocutor, prostituting the relationship of some and turning others polygamous. This circumstance affirms the depersonalization of the doctor-patient relationship, reduces trust and multiplies the possibilities of error.

Many errors in medicine arise from miscommunication, mistrust, ignorance, inconsistency, non-compliance, and improper diagnosis and/or treatment. Some mistakes are the responsibility of the doctor; others, of the patient and his environment. They both contribute to damaging the relationship. Both should understand, as **Pearl S. Buck** pointed out, that "every great mistake has a halfway moment, a split second when it can be recalled and perhaps remedied." Many errors arise from the innocent or interested search for non-existent absolute truths, especially in biology. **Samuel Butler**, in *Truth and Convenience*, already

announced that "there is no such source of error as the pursuit of absolute truth." Neither the patient can ask medical science for the impossible, nor can medicine promise what it is incapable of giving.

When we insist on promising solutions to unsolvable problems, when we play God with fabulous prognoses and magic remedies, when we novelize diseases that are poetry without rhyme, when we do not recognize the limits of knowledge, we are humiliating the truth. White lies can be compassionate; not so imprecision. The confidence of the patient cannot be mocked in the limbo of his ignorance. The patient expects the doctor to be the interpreter to fill the knowledge gap. **Charles Caleb Colton** said in *Lacon* that "ignorance is a blank sheet, on which we may write; but the error is a scribbled one, on which we must first erase." It is illegitimate to fill out scribble sheets based on error; and when it is done, to ignorance and error must be added dishonesty and lack of professionalism.

Today's healthcare market, with interpreters hidden behind glass windows, computer screens or telephone distance, is more vulnerable than ever to fatally damaging the doctor-patient relationship, depriving both of the moral and emotional privilege of gratitude and fidelity, which throughout history have made medicine the most honorable and committed service that one human being can offer to another for the well-being of both.

When the doctor-patient binomial is intersected by political, administrative, corporate, industrial and economic interests, asymptotic deviations occur that never benefit either the doctor or the patient, but the elements that force the intersection. As the doctor is the principal beneficiary of scientific progress to better serve his patients, he should be alert to the diabolical forces that persist in keeping him within the status of a subjugated proletarian. Usually, the knowledge arrives late to the foot soldier, when the information is withheld in captaincies and generalates. On the contrary, the error is always diverted to the bases so as not to damage the cupola. It was **Cicero** who said in his *Philippians* that "any man can make mistakes, but only an idiot persists in his error." **John Locke** refined the thing in *An Essay Concerning Human Understanding* by saying that "all men are liable to error; and most of them are, by passion or interest, under temptation to it." Assuming error as human, says **Ilya Ehrenburg** that "people seldom learn from the mistakes of others, not because they deny the value of the past, but because they are faced with new problems." Faced with the challenges posed by the future in the doctor-patient relationship, in terms of new diagnostic technologies and new therapeutic approaches, doctors and patients need to reset the principles of their relationship, just like medical services and health care, in general, have to renew *hardware* and *software* (and perhaps also "health programmers").

It may be for the patient to understand, as **William Blake** would say, that "the errors of a wise man make your rule, rather than the perfections of a fool"; and to the doctor, assume with humility, as **Bertolt Brecht** would advise, that "intelligence is not to make mistakes, but quickly to see how to make them good." After all, we should not forget what **Clarence Day** previously announced in *This Simian World* in 1920: "This is a hard and precarious world, where every mistake and infirmity must be paid for in full."

Ramón Cacabelos
Professor of Genomic Medicine

30 Years Serving Health and Community

This year marks three decades since the founding of EuroEspes, with the opening of the **Institute for Diseases of the Central Nervous System**, in A Corunna. In 1991, the Institute represented the first monographic center in Spain, especially dedicated to Alzheimer's disease, when dementia was still a minor medical and social health problem in the health model of the country.

From the Institute we published the first studies on dementia and brain aging, we established the first diagnostic protocols with criteria that were later implemented inside and outside of Spain, we contributed to the development of the first anti-Alzheimer's disease treatments, and we supported the development of the first associations of relatives of Alzheimer's patients in different communities and provinces.

As World Alzheimer's Day is observed annually on September 21, we would like to, in this Bulletin, take advantage of the anniversary to express our gratitude to all the families who, through their efforts and sacrifice, have succeeded in transforming those conditions of maximum precariousness and ignorance into a better understanding of what this disease is and what the presence of an Alzheimer's patient in the family means.

The family is the first to perceive memory failure and cognitive dullness; the family is the one that often takes the initiative to seek medical help; the family is fundamental in the therapeutic follow-up; and the family is the one who must bear the burden of years of progressive destruction, from marginality, isolation and silent suffering. Today, fortunately, social awareness and the weight of family contributions and experiences are helping to conceive of the socio-sanitary and socioeconomic problem of dementia differently, although there is still a long way to go.

From the point of view of practical medicine, from 1991 to 2021 there have been important advances in the diagnostic and therapeutic approach to dementia. However, if we compare the investment policy in Alzheimer's research with other diseases, the results are poor. The most significant improvements in the establishment of diagnostic criteria were established between 1995 and 2000; and the first three generations of anti-dementia drugs were developed in the last two decades of the last century, with no drug for Alzheimer's having been put on the market from 2003 to this year. Anticholinesterase agents (Tacrine, Donepezil, Rivastigmine, Galantamine) and Memantine are products of low efficacy because, instead of protecting

neurons, they make them work harder to improve memory. It took many years to understand and accept that dementia was a process of premature death of neurons that begins 2-3 decades before the disease manifests its symptoms.

The approval of Aducanumab by the FDA (*US Food and Drug Administration*) two months ago points to a paradigm shift in the treatment and early diagnosis of Alzheimer's disease, since Aducanumab is an antibody to clean beta-amyloid deposits and block the evolution of the disease in early periods or in presymptomatic phases.

For this, they also have to change the diagnostic protocols. Genomics is needed to predict risk and implement prophylactic treatments. It took decades for the scientific community to accept the genomic component of Alzheimer's disease and to discover the more than 600 defective genes that predispose to a neurodegenerative process; and there is still resistance to admitting this inescapable reality.

The **EuroEspes Biomedical Research Cente**r, created in 1995, made great economic and scientific efforts to identify the genes associated with Alzheimer's disease, to understand their pathogenic effect and to develop the first genetic kit for the diagnosis of Alzheimer's. We were the first in Spain, and one of the first in the world, to promote the idea of a dementia prevention plan to identify the population at risk and implement personalized prevention programs. That initiative led us to research, discover, promote, and implement personalized treatment programs for affected people and their descendants. We launched the first Alzheimer's pharmacogenomics proposals in 2000 and since then we have not stopped implementing and improving therapeutic strategies to protect the brain of patients and improve their quality of life and that of their families.

More than 10 years ago, we released the first version of the **EuroEspes PharmacoGenetics Card** for the personalization of pharmacological treatment. The Card evolved and today it is an **Intelligent Pharmacogenetic Card** with coverage for over 3000 drugs in common use in the world, without excluding any pathology, be it cerebral or systemic.

Just as sickness has no holidays, science does not stop, no breaks are allowed. Scientific knowledge is the source from which medicine draws in order to evolve and put all the technological progress that can help fight disease and preserve health at the service of people's well-being.

This vocation for progress led us to create the **International Center for Neurosciences and Genomic Medicine**, from which we serve the medical, scientific and technological needs of the community, nationally and internationally. Knowledge of the **Human Genome** has allowed us to establish early identification programs for diseases of the nervous system (Alzheimer's disease, Parkinson's disease, Psychosis, Depression, Stroke), systemic diseases (cardiovascular accidents, arteriosclerosis, hypertension, diabetes) and cancer. The new DNA technologies, the complete analysis of the genome, and the identification of genomic clusters associated with a specific disease allow us to anticipate the problem and intervene prophylactically, and in a personalized way.

Pharmacogenetics is the routine way for determining whether a drug is suitable or not, if it does good or causes harm, if it is responsible for any side effect due to direct toxicity or interaction with another drug. We are all susceptible to receiving some treatment throughout our lives and we should all know our pharmacogenetic profile to know the drugs we can consume and the ones we should avoid.

The knowledge of Epigenetics helps us understand how genes are expressed and how they go awry, causing disease. Epigenetic **Biomarkers serve** as diagnostic support and inform us if the treatments deliver the result we want.

The evolution of Medical Sciences does not stop; but medicine is a subsidiary of scientific knowledge and technological progress. Our mission has been, is, and will continue to be to put that knowledge at the service of people's well-being, anticipating the disease, intercepting it once it appears, and having maximum guarantees that the treatments we prescribe are the correct ones based on the pharmacogenetic profile of each person.

Jaime Cantizano (OndaCero) and Dr. Ramón Cacabelos in the Royal Chapel of the Hostal de los Reyes Católicos in Santiago de Compostela, on the occasion of World Alzheimer's Disease Day.

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Neovital incorporates Ebiotec products to its commercial portfolio

The general directors of Neovital Health, Roman Albardias, and EuroEspes Biotecnología (Ebiotec), Jaime Pombo, have signed an agreement by which Neovital will incorporate Ebiotec products into its commercial portfolio for all of Spain. The Ebiotec products, LipoEsar, DefenVid, MineraXin-Plus, Animón Complex and MakaliSex will use the new brand of Neovital with the name of LipoEsar-Neo, DefenVid-Neo, MineraXin-Plus-Neo, Animón Complex-Neo and Makalisex-Neo, respectively. Instead, Atremorine, the epinutraceutical agent, approved by the European Patent Office for the prevention and treatment of Parkinson's disease, will be marketed by Neovital under the brand Miconeo-BNR, as a compound derived from *Leonotis leonurus* has been incorporated into the original product.

New commercial portfolio of Neovital with Ebiotec nutraceutical products

The use of tobacco during pregnancy affects the placental development and brain size of the fetus

Tobacco has a prevalence of 22.18% worldwide and is considered the major risk factor for lung cancer. Tobacco contains approximately 5,000 chemicals, including nicotine, and 97 other dangerous components. Smoking is the leading cause of death, potentially foreseeable (7 million deaths from direct tobacco use and 1.2 million deaths from passive exposure). Exposure to tobacco during pregnancy damages maternal health and affects fetal growth, leading to a decrease in body size at birth and a reduction in head circumference and, consequently, brain development. In addition to maternal smoking, it is estimated that maternal exposure to second-hand smoke causes 11.1% of cases with embryo-fetal brain involvement.

Maternal smoking and passive exposure to tobacco smoke are associated with cognitive and behavioral deficiencies in the offspring. There is increasing evidence of attention deficits, impaired learning and memory, decreased IQ, cognitive dysfunction and behavior problems in childhood, although not all studies agree on establishing a negative relationship between maternal exposure to tobacco and the deleterious effects that tobacco can cause in offspring.

The size of the head circumference at birth is an important physical measure, easily accessible and associated with intellectual development. Exposure to tobacco during pregnancy can affect cognitive ability and increase the risk of attention deficit hyperactivity disorder, although the results of studies conducted so far are inconclusive.

Maternal smoking is recognized as an unfavorable factor that causes oxidative stress in placental tissue, and impairs placental development because of reduced blood flow, leading to decreased placental weight and histological changes, as well as increased risk of Placenta previa, placental abruption, and spontaneous abortion. These findings suggest that maternal tobacco exposure during pregnancy causes a decrease in brain size at birth due to placental impairment.

Tadashi Shiohama and colleagues from the Department of Pediatrics at Chiba University School of Medicine in Japan conducted a large prospective study of 84,856 couples and their children and confirmed the negative impact of maternal smoking during pregnancy

on size of the cranial circumference in the offspring. Smoking mothers have children with a reduced head circumference. This study also found that quitting smoking can reduce neurological decline in offspring even after pregnancy.

Reference

Shiohama, T., Hisada, A., Yamamoto, M. et al. Decreased head circumference at birth associated with maternal tobacco smoke exposure during pregnancy on the Japanese prospective birth cohort study. Sci Rep 11, 18949 (2021). https://doi.org/10.1038/s41598-021-98311-2.

Initiatives to sequence the genome of newborns

The United States and the United Kingdom are working on an initiative to sequence the genome of all newborns. Approximately 5-7% of people are born with rare diseases that, if treated early, may not be life-threatening. The only way to identify these diseases is through genomic sequencing. The lower cost of genome sequencing makes this initiative economically feasible in developed countries.

Genomics England, a British government state company, hopes to start a pilot research project involving up to 200,000 babies. Although it would initially look for genes for rare childhood diseases, it would also store genome data to predict drug sensitivity and risks for adult diseases, such as cancer. Some American researchers are also excited to start a national program for whole genome sequencing of newborns. The UK program already performs whole genomes analysis in clinical care. In the United States, sequencing the genome of each newborn is probably still a long way off. Even with low-cost technologies, newborn genome detection nationwide requires drastic changes in diagnostic and healthcare infrastructure and hundreds of millions of dollars in investment. Some companies already market newborn tests that sequence many genes or the entire genome, at a cost of several hundred to a couple of thousand dollars.

An ethics group funded by the US National Institutes of Health (NIH) cautioned in a 2018 report that the evidence to date "does not support the sequencing of the entire genome of all babies at birth." The report noted that the health consequences of many mutations are unknown, and many genetic diseases remain untreatable. Rather than genome-wide sequencing, sequencing advocacy groups and clinical geneticists advocate speeding up the existing, slow, national system for early disease detection in newborns.

The idea of reading a newborn's genome dates back at least to the first draft of the human genome, published in 2001. In a television interview broadcast that year, Francis Collins, then director of the National Human Genome Research Institute, predicted that it would be "feasible" within 20 years to produce a "kind of genetic card" from a baby's DNA sequence. In 2010, NIH held a workshop to plan four pilot projects to explore newborn genome sequencing.

A project, led by Stephen Kingsmore, now at Rady Children's Hospital in San Diego, California, has proven to be very helpful in sequencing seriously ill newborns to find out if they have a genetic disease. For example, in October 2020, a couple brought their seriously

ill 5-week-old boy to the Rady's emergency room; a CT scan showed brain abnormalities. Kingsmore's team found a mutation in the baby's genome for a severe vitamin B metabolic disorder, and days later, after proper treatment was implanted, the child was cured. His sister had died years before, probably from the same mutation, without conventional medicine able to identify the defect. In June, Kingsmore reported at an NIH-sponsored meeting on gene therapy of 23 studies in the past decade by him and other groups. Genome sequencing led to a genetic diagnosis in 36% of 1,839 seriously ill children, mostly infants. In 533 patients, 29% of the total, the findings led to changes in medical care, saving the lives of many babies.

Other NIH pilot studies tested genome sequencing as a screening tool for all babies, healthy and sick, comparing it to standard newborn screening. That program began in the United States in the 1960s to identify phenylketonuria (PKU), a metabolic disorder that leads to intellectual disability unless babies are on a special diet. Currently, PKU and about 30 to 70 other treatable disorders are being studied using biochemical tests. Whole genome sequencing could search for those monogenic diseases and hundreds of diseases that now have no reliable biochemical test, such as neonatal diabetes, hemophilia or cystinosis. But the technique is not infallible. NIH-funded research and related studies found that whole genome sequencing, or DNA encoding proteins (Exome), misses 12% or more of cases detected in newborns. This is because sequencing does not detect some genetic changes, as analysts can ignore others, even those associated with a disease in the newborn, if that change has not been shown to be harmful. But the studies also suggested that the two methods could be powerful if combined because sequencing could confirm an ambiguous biochemical test result.

Genuine epigenetic differences in identical twins

Identical twins are living proof of how genetics shapes our looks and traits. Recent studies show that twins carry a molecular signature on their DNA that no one else has; this imprint attaches to your cells early in development and remains with them into adulthood. This signature does not influence the health of a twin, but could offer insight into how identical twinning occurs. The signature could also test whether a person had a "faded twin," an identical twin who died in utero, reports Jocelyn Kaiser in *Science* (Sept. 28). Up to 12% of pregnancies start out as multiples (including fraternal twins), according to some estimates, but only 2% of twin pairs survive.

Identical twins occur when an egg divides after being fertilized, resulting in two embryos with the same DNA. Scientists know how fraternal twins occur, which results when two eggs are fertilized - both genetics and age can tip women who ovulate toward producing two or more eggs at a time. But experts do not really understand what factors lead to identical twins, which make up about four out of every 1,000 births.

An international team, led by van Dongen and twin genetics researcher Dorret Boomsma, searched for clues in the epigenome. There are patterns of chemical labels, called methyl groups, which clump together in genes, turning them on or off. Using blood and cell samples, the researchers scanned the epigenomes of over 3,000 identical twins, as well as a comparable number of fraternal twins and the parents of some twins. They identified 400,000 different places in each person's genome. About 800 locations had differences in methylation that set identical twins apart from everyone else.

Some of the methylated or unmethylated labels made sense, such as the labels on genes involved in cell adhesion that could influence how easily a fertilized egg divides into two embryos. But changes in other locations, such as the ends of chromosomes, had no obvious explanation. These regions have been associated with aging; however, the life expectancy of identical twins is similar to that of other people.

Understanding epigenetic changes and whether they are a cause or an effect of an egg dividing will require laboratory studies using embryonic structures made from human and animal stem cells or embryos. The work could shed light on some rare disorders that involve epigenetic changes. A growth disorder, known as Beckwith-Wiedemann syndrome, for example, is more common in identical twins than in single births.

Brain endophenotypes of Obsessive-Compulsive Disorder (OCD)

OCD is a relatively common mental illness (2-3% of the population) characterized by intrusive and unwanted obsessive thoughts and compulsive behaviors. Genetic studies confirm that first-degree relatives have a 4-5 times greater risk than the general population for developing OCD. A recent meta-analysis of genomic studies (GWAS) reports an estimated common heritability, based on a single polymorphism (SNP), of 28% for OCD. This genomic incidence is among the highest found for neuropsychiatric disorders. There is a significant genetic correlation between OCD and subsyndromic obsessive-compulsive symptoms.

To understand the relationship between the genotype and the phenotype of different diseases, the information provided by endophenotype studies is often used. Endophenotypes are characterized by their heritability and deviant expression both in patients with OCD and in unaffected relatives.

Executive control dysfunctions (cognitive flexibility, working memory) represent a possible endophenotype of OCD. Executive control deficits are detected in patients with OCD and in close relatives. Functional neuroimaging studies during executive control tasks have shown functional alterations related to OCD mainly in the orbitofronto-striatal and fronto-parietal circuits. In working memory, these dysfunctions have been related to poor updating and short-term maintenance of information in OCD.

Genetic defects can cause working memory-related alterations in the frontal and parietal regions. Morphometric studies with functional neuroimaging techniques have identified several central regions associated with candidate genes related to the serotonergic, dopaminergic, and glutamatergic systems. Genetic variants that involve the serotonergic and glutamatergic systems affect the volume of gray matter in the orbitofrontal cortex. Glutamatergic genetic variations also affect the anterior cingulate cortex and the thalamus; and dopaminergic genes influence the activity of the putamen.

Stephan Heinzel from the Department of Psychology at Humboldt University Berlin, together with colleagues from Hamburg and Bonn, conducted an elegant endophenotypic study in OCD patients and first-degree relatives with functional magnetic resonance imaging. The Germanic researchers observed that behavioral outcomes showed a deficit in

working memory performance in both OCD patients and first-degree relatives. A complete brain analysis showed decreased neuronal activity in the bilateral lower parietal lobe and dorsolateral prefrontal cortex in both patients and relatives. Most importantly, OCD polygenic risk scores predicted neuronal activity in the orbitofrontal cortex. The results indicate that the genetic risk of OCD may partly explain the alterations in brain response during working memory performance. These findings can help in the diagnosis of OCD and in monitoring the therapeutic efficacy with conventional drugs or with new drugs in development.

Reference

Heinzel, S., Kaufmann, C., Grützmann, R. et al. Polygenic risk for obsessive-compulsive disorder (OCD) predicts brain response during working memory task in OCD, unaffected relatives, and healthy controls. Sci Rep 11, 18914 (2021). https://doi.org/10.1038/s41598-021-98333-w.

Covid-19 News

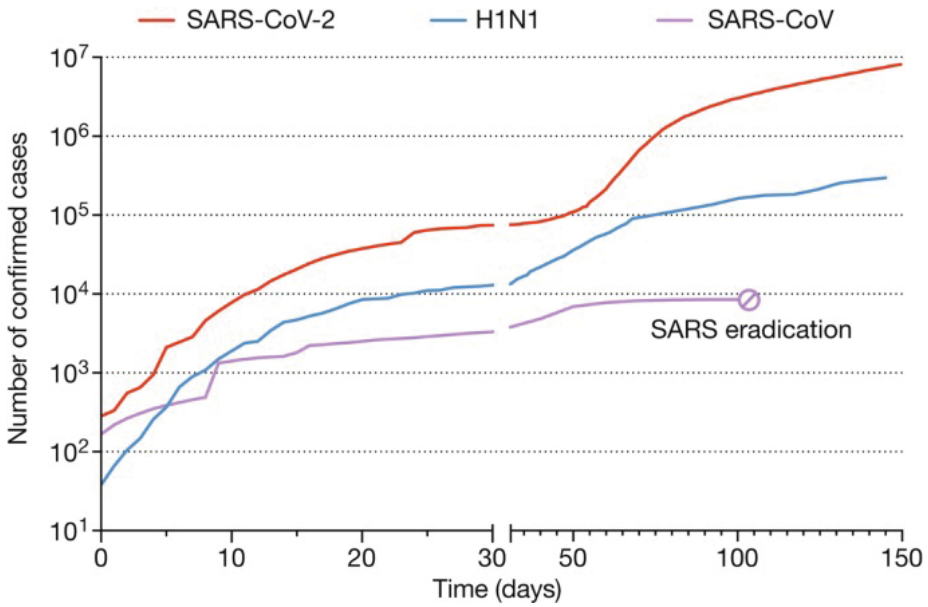
Where are we headed to?

There are expectations that the global effort in vaccination against COVID-19 will help control the pandemic caused by coronavirus-2. However, uncertainties remain about the type of long-term association the virus will establish with the human population and, in particular, whether COVID-19 will become an endemic disease. Although the trajectory is difficult to predict, the conditions, concepts and variables that influence this transition can be anticipated. The persistence of SARS-CoV-2 as an endemic virus, perhaps with seasonal epidemic peaks, can be fueled by groups of susceptible people, by the decrease in the immune response after infection or vaccination (which occurs in 100% cases), due to mutational changes in the virus through antigenic drift that will decrease protection, and because of re-entry of the virus into zoonotic reservoirs that will end up reinfecting humans.

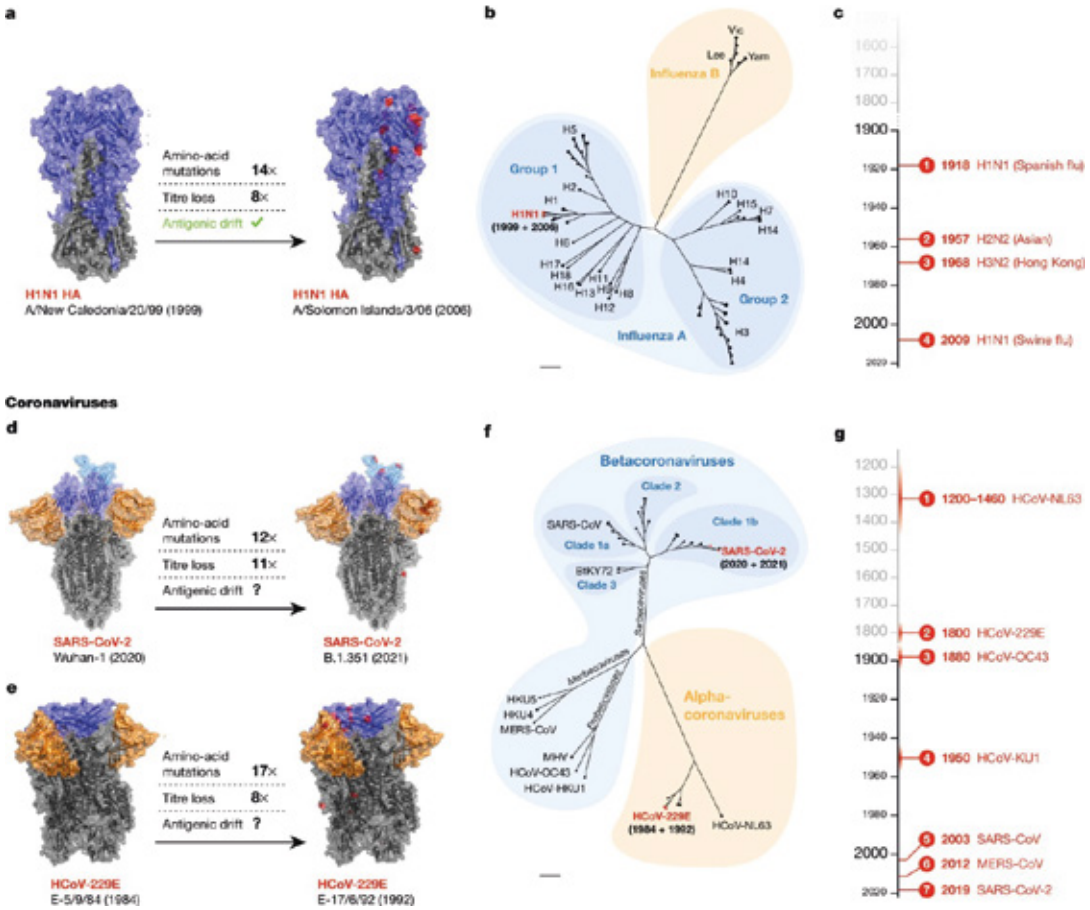
In an excellent article, Spanish researcher Amalio Telenti, currently at Vir Biotechnology, San Francisco, and at the Scripps Research Center, in La Jolla, California, offers a critical and in-depth analysis of what we should expect in the future about evolution of the coronavirus, taking as a reference the evolutionary pattern followed by other pandemics.

From an epidemiological point of view, the questions that science has to answer are: (i) What are the effects of geographic and socioeconomic variations in vaccine and disease coverage on the ability to turn the pandemic into an endemic disease or epidemic?; (ii) What is the contribution of immunosuppressed populations to the rapid evolution of SARS-CoV-2?; from a virological perspective; (iii) What are the mechanisms by which viruses adapt to different hosts, thus crossing species barriers?; (iv) Is the evolution of the viral sequence effectively reduced by vaccination?; from an immunological perspective; (v) What are the correlates of vaccine protection and natural immunity?; (vi) Will the evaluation of protection require the consistent application of reproducible immunological tests in populations to follow the incidence and severity of the disease?; (vii) What is the impact of antigenic drift?; (viii) What are the criteria for the renewal or promotion of vaccines?; and (ix) What is the role of mucosal immunity in limiting viral dissection and preventing serious disease?

All these unknowns require an epidemiological surveillance system with reliable diagnostic tools and deep sequencing accessible at an international level to establish a continuous and sustained global surveillance of the disease and its variants. Current vaccines will cease to be effective and it will be necessary to evolve towards the development of vaccines against Pan-sarbecovirus, with vaccines and monoclonal antibodies that will address both the SARS-CoV-2 variants and the future introduction of pandemic coronaviruses in the human population. A major therapeutic revolution will also be necessary. Until now, the management of patients has been poor and many deaths may not have been caused by the coronavirus but by the poor therapeutic approach of infected patients. Effective treatment of COVID-19 and its future mutagenic variants requires the development of next-generation therapeutic strategies in the form of cheap oral antiviral agents. In parallel, it is necessary to develop prophylactic protocols with long-acting monoclonal antibodies for people in whom vaccination is not effective (> 40% of the population shows a poor immunogenic response). Ultimately, the utopian desire of science, which clashes with the interest of politicians and industry, is to address inequalities in pandemic healthcare and worldwide access to the most effective vaccines and therapies.



Evolution of the SARS, H1N1, and SARS-CoV-2 pandemics.
Source: Telenti et al. Nature 596: 495-504 (2021).



Evolution and mutagenesis of Influenza and Coronavirus viruses
Source: Telenti et al. Nature 596: 495-504 (2021).

Reference

Telenti, A., Arvin, A., Corey, L. et al. After the pandemic: perspectives on the future trajectory of COVID-19. Nature 596, 495–504 (2021). https://doi.org/10.1038/s41586-021-03792-w

COVID-19 in vaccinated people

COVID-19 cases are being identified in vaccinated people. This is an expected finding, assuming that around 20% of vaccinated patients do not respond to the vaccine and, therefore, do not produce anti-SARS-CoV-2 antibodies, which are ultimately responsible for protection against coronavirus infection.

Although we lack international data, where individual immunity, health conditions and the genomics of each person influence the immunogenic response to each vaccine, in our experience the vaccines that generate the most antibodies are those of Moderna and Pfizer, with antibody titers in over 50% of cases above 500 U/mL one month after the second dose of the vaccine. With the rest of the vaccines, over 70% of the cases present titers lower than 500 U/mL. The antibody titer in infected patients fluctuates between 20,000 and 80,000 U/mL; and in patients with COVID-19, subsequently vaccinated, the antibody titer can exceed 100,000 U/mL.

Post-vaccination COVID-19 is occurring in 5-10% of cases, possibly associated with people with a poor response to vaccines or with a deficient immune system, unable to generate enough antibodies. *The Centers for Disease Control and Prevention* (CDC) in the United States has reported that until September 20, 2021, about 181 million people have been fully vaccinated. In 50 States, 14,643 patients with severe COVID-19, who required hospitalization, have been detected after completing the anti-COVID-19 vaccination program. 69% of these patients were older than 65 years. In total, 4,493 people died of COVID-19 after vaccination, of which 44% were women and 86% were over 65 years old.

These data confirm the suspicion that between 5% and 10% of vaccinated people are not protected against COVID-19 and are at risk of becoming infected. Consequently, the health authority should assume that vaccination is not enough to protect the population, and that analysis of antibodies in vaccinated people is required to really know who is immunized and who is not.

Immune thrombocytopenic thrombosis induced by anti-SARS-CoV-2 vaccines with adenoviral vectors

Vaccine-induced immune thrombotic thrombocytopaenia (VITT) is a rare adverse effect of adenoviral vector vaccines against COVID-19. VITT resembles heparin-induced thrombocytopenia (HIT) in that it is associated with platelet-activating antibodies against platelet factor 4 (PF4); however, patients with VITT develop thrombocytopenia and thrombosis without exposure to heparin.

The clinical picture of VITT is moderate or severe thrombocytopenia along with arterial and/or venous thrombi, which often occur in unusual locations. These findings resemble the immunopharmacological reaction HIT, which presents clinically as thrombocytopenia and thrombosis in patients who have been previously exposed to heparin. VITT is more like the rare spontaneous HIT, which occurs in the absence of heparin.

HIT is caused by IgG antibodies that bind to neoepitopes on PF4 (also known as CXCL4), a 70 amino acid cationic protein found within platelets. Neoepitopes are exposed after heparin, an anionic polysaccharide, binds to a specific site on PF4, generating a cluster of tetramers. Specific IgG antibodies bind to PF4-heparin to form immune complexes, which activate platelets through FcγRIIa receptors, leading to intense platelet activation and the release of procoagulant-rich microparticles. Other cells, including monocytes, are also activated by these immune complexes, amplifying the hypercoagulable state in HIT1 patients.

VITT has been postulated to have a pathophysiology similar to HIT, and several studies have shown that high levels of anti-PF4 antibodies are present in samples from patients with VITT. However, VITT is a unique syndrome because it occurs without exposure to heparin, and the pattern of platelet reactivity *in vitro* does not exhibit the typical heparin dependence seen with HIT.

Angela Huynh, from the Department of Medicine, Michael G. DeGroote College, at McMaster University in Hamilton, Ontario, Canada, investigated with her colleagues, the mechanisms responsible for thrombocytopenic thrombosis that occurs in some people vaccinated with anti-SARS vaccines. Using alanine scanning mutagenesis, Canadian researchers found that the binding of anti-PF4 antibodies from patients with VITT was restricted to eight surface amino acids in PF4, which were within the heparin binding site, and that the binding was inhibited by heparin. In contrast, antibodies from HIT patients bound to amino acids that corresponded to two different sites on PF4. Biolayer interferometry experiments also revealed that anti-PF4 VITT antibodies had a stronger binding response to PF4 and PF4-heparin complexes than anti-PF4 HIT antibodies, albeit with similar dissociation rates. These findings indicate that VITT antibodies can mimic the effect of heparin by binding to a similar site on PF4; this allows the PF4 tetramers to clump together and form immune complexes, which causes platelet-dependent activation of the FcγIIa receptor (FcγRIIa; also known as CD32a). To date, this is the most plausible explanation for understanding VITT antibody-induced platelet activation that could contribute to thrombosis.

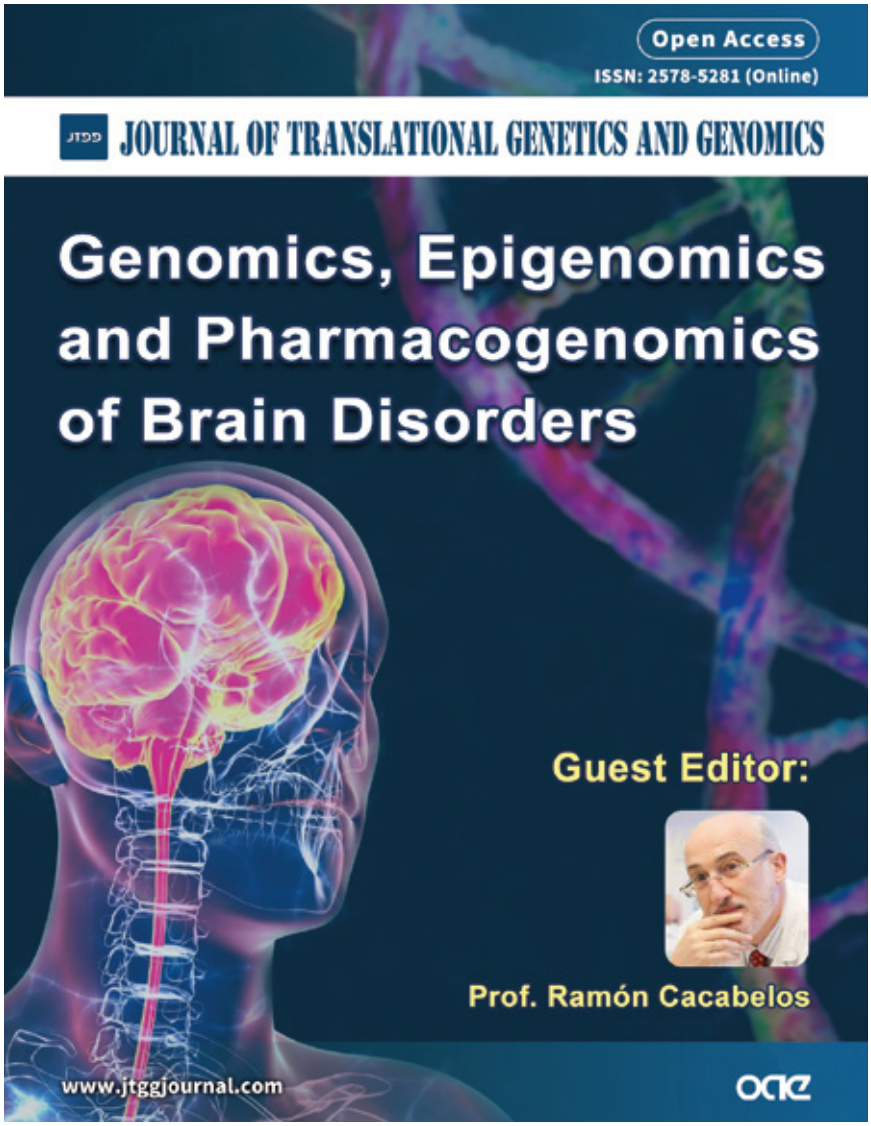
Reference

Huynh, A., Kelton, J.G., Arnold, D.M. et al. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. Nature 596, 565–569 (2021). https://doi.org/10.1038/s41586-021-03744-4.

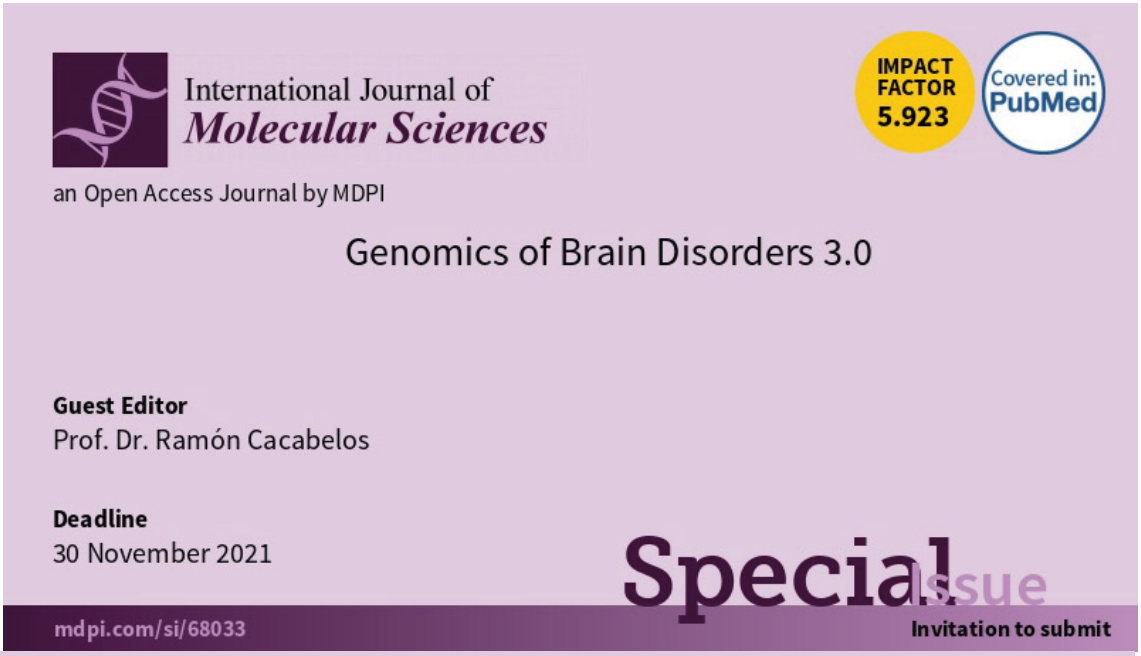
Editorial News

Special Issue of the *Journal of Translational Genetics and Genomics* (JTGG)

The publisher OAE Publishing Inc. (https://jtggjournal.com/), owner of the *Journal of Translational Genetics and Genomics*, prepares a special issue dedicated to the "Genomics, Epigenomics and Pharmacogenomics of Brain Diseases."



Other special editions open to the International Scientific Community



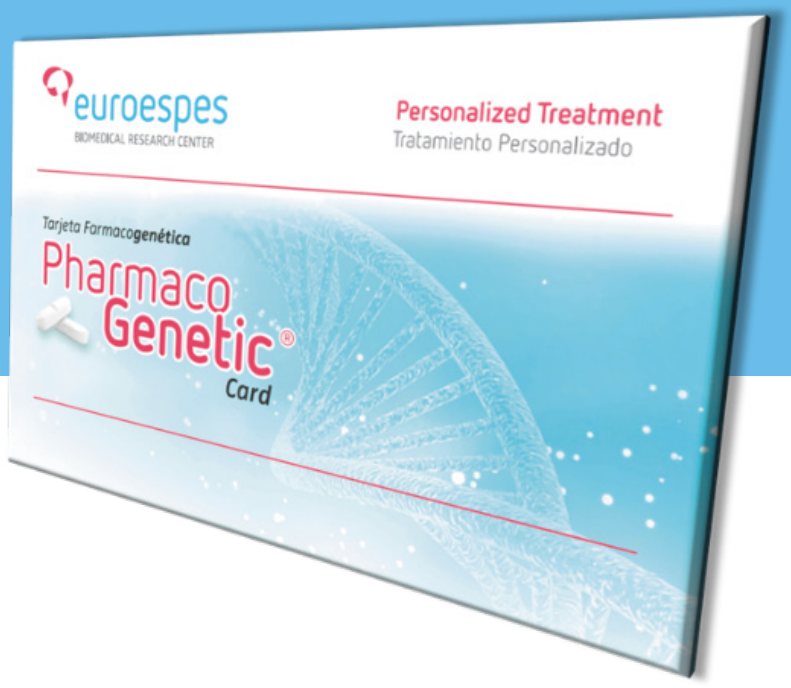
Promotional Section

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

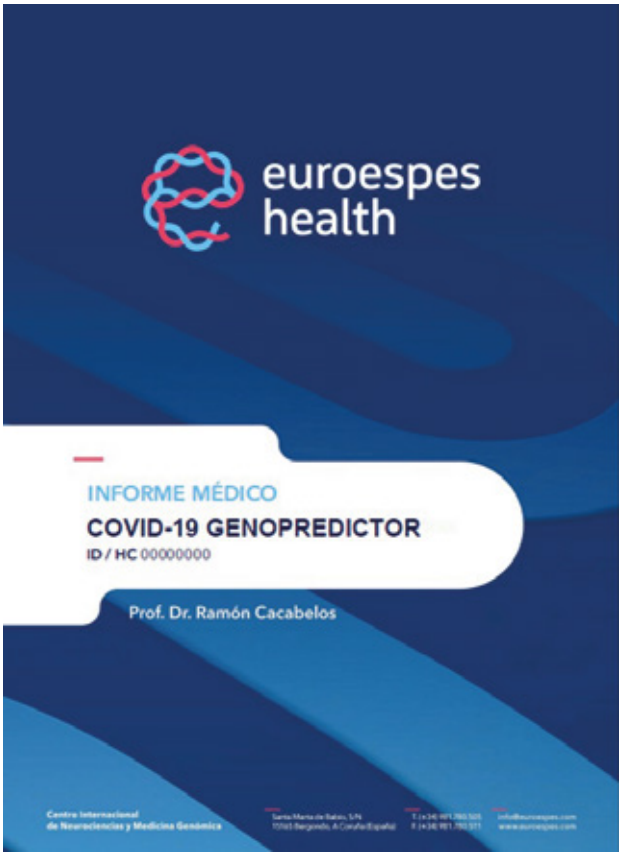
The PPP identifies the population at risk of suffering from Parkinson's disease, differentiating familial Parkinson's disease and other forms of parkinsonism (vascular, toxic or traumatic). The PPP also includes (i) a home PPP for all those asymptomatic people with a family history of Parkinson's or 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.

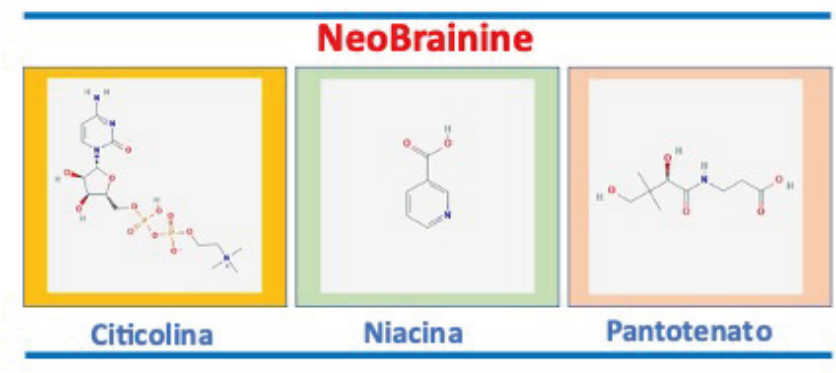
NeoBrainine

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 B5 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 B3, 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.

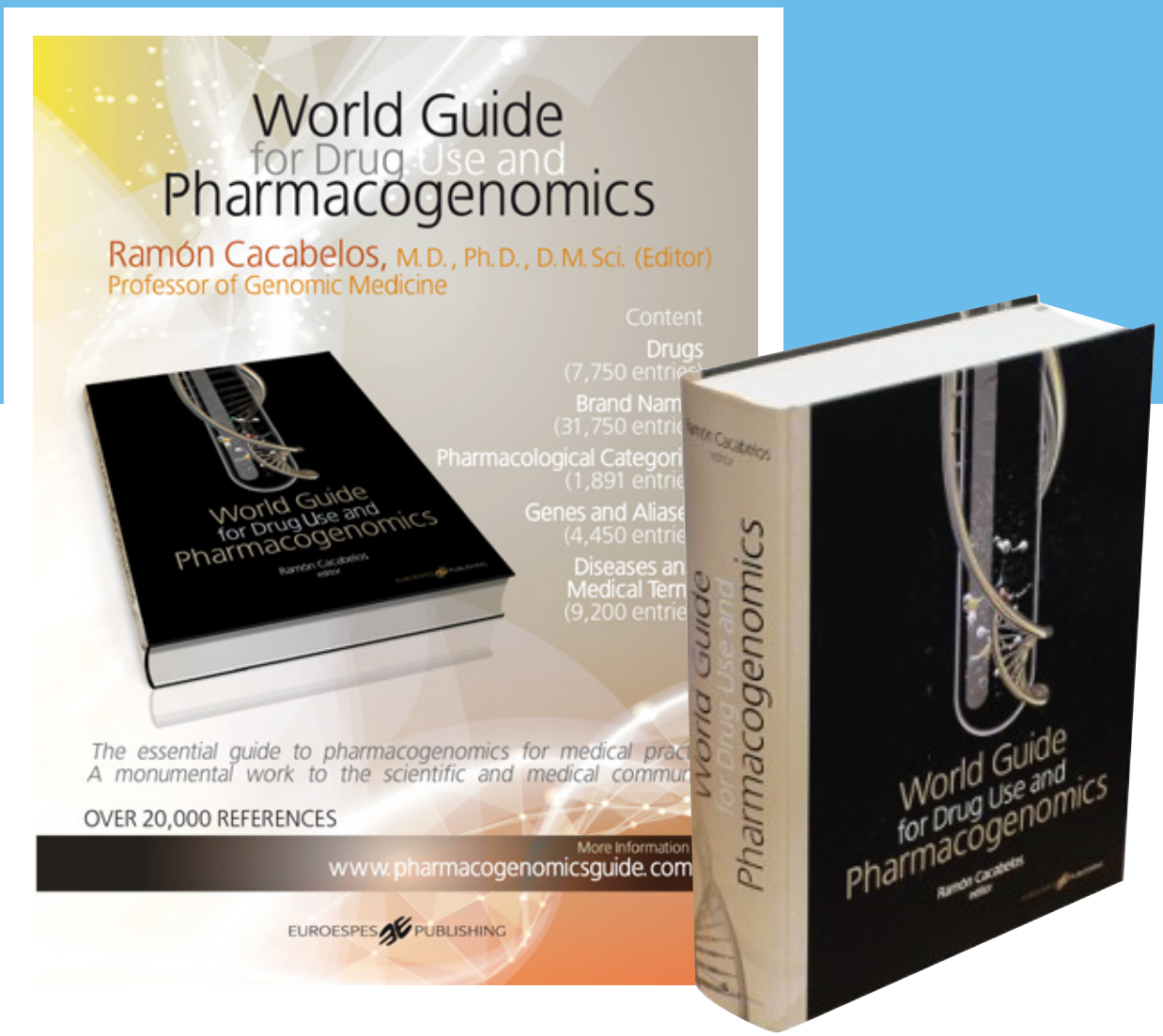
DermoGenetics Catalog

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.

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