Towards a new paradigm for the measurement of human survival

Human life expectancy is continually lengthening and looks set to do so even more in coming decades. Experts are therefore vetting the validity of traditional human survival measurement models and phasing in new biomarkers to determine it more precisely. The insurance industry is watching this paradigm shift with great interest.

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In October 2012, Sir Tim Hunt, and other 49 Nobel Prize winners wrote a letter to the *Financial Times* stating that: «We are just at the start of a new revolutionary understanding of how our own bodies work with incalculable consequences for our future health and longevity.»

This quotation is the best reflection of the purpose of this paper. The changes that we will be seeing in the years and decades to come as regards a healthy life and the extension of human longevity will be –if they are not already– of such significance that it is becoming urgent to rethink whether the traditional models for measuring human survival should be reformulated.

Man, already known as the *transparent man*, his data on health, including his own individual genetic map, his personal habits (some of them voluntarily uploaded onto the social networks), make it possible to evaluate with complex statistical techniques, the risk of suffering diseases within a specific period of time and, in short, to calculate life expectancy with a degree of precision that had been unthinkable up to now.

The comment made by Manuel Patarroyo, winner of the Príncipe de Asturias prize and developer of a synthetic vaccine against malaria, illustrates the future that lies ahead very well. He believes that by 2050 doctors will have the genome sequence of each patient on their computers and will thus be able to predict the diseases that we will suffer with a certain degree of probability and, in this way, apply personalized preventive treatment.

Privacy and non-discrimination rights must be respected before these models are introduced. Their reliability and predictive relevance are currently being scientifically corroborated and will actually become the guidelines for the protocols of both new preventive medicine and clinical medicine and, in turn, will extend to pharmacological treatments based on the patient's individual genetic profile. A conflict will emerge between the ethical approach, which must protect human dignity, and actuarial accuracy. At the end of this paper we will

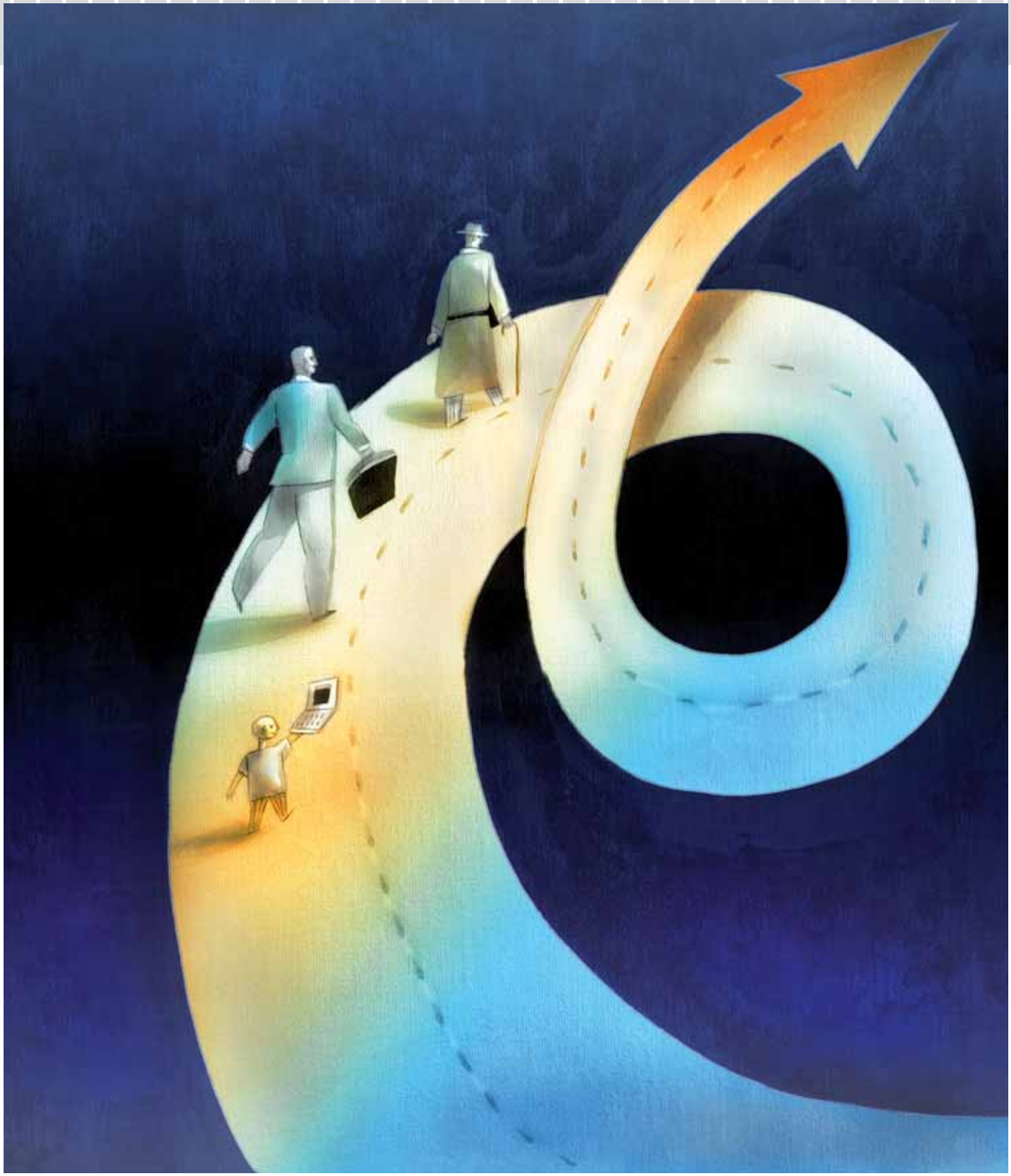


ILLUSTRATION STOCK

attempt to propose guidelines for understanding on the basis of a new concept of *actuarial justice or fairness*.

We must not forget also that this new life insurance scenario will result in a significant reduction of the level of uncertainty in the risk of mortality for the human being.

THE TRADITIONAL BASIS FOR MEASURING HUMAN SURVIVAL

The principles underlying the measurement of human survival for the construction of actuarial models should be questioned. This process of redefinition and practical application of the

technical basis will be gradual over time and, in fact, some of the hypotheses are already being corrected by the industry. Others are in the course of practical materialization through actuarial academic research in respect of the evaluation processes for life insurance companies' reserves. Lastly, other principles are being reformulated through biomedical research and from this area of knowledge they will be transferred to clinical and predictive medicine, as well as to actuarial techniques.

If we want to avoid the risk of actuarial petrifaction, we must place traditional biometrics principles under scrutiny. We will try to provide the solutions that the international life insurance markets are adopting and, if they have not done so yet, to reflect upon what can be the consequences of the new paradigm. We will also prospectively address what will be the human survival metric applied to life insurance in a scenario where biological age will be considered the cornerstone of this new proposed paradigm.

During the past century, actuary science has shown its value but with some weakness managing long term risk of survival. George Bernard Shaw once said «all great truths begin as a blasphemy», and these words of the Irish writer apply precisely to the new proposals that have been formulated early in this century as the basis for supporting human survival models.

Let us revisit traditional actuarial biometry principles.

■ **Stationary in time.** Under this principle the mortality rate of an individual of a given age is unrelated to calendar time. This principle has been superseded in the preparation of dynamic survival tables with the incorporation of age and/or generational improvement factors –in fact in the construction of survival models from the late 1990's– which can be said to have become a widespread practice in the insurance industry. Thus, survival improvements over time are taken into account in the pricing of annuity insurance policies.

In the case of mortality risk insurance this principle has also been superseded. Although mortality tables do not take into account improvements in time, the insurance industry has developed so-called forward pricing products that incorporate into the time axis the mortality improvements of the population base on which the premium calculation is made.

■ **Independence.** The technical bases do not incorporate into the price the risk of contagion between individuals in the same insured group, i.e. they are considered to be independent risks. It is true that the Solvency II Directive incorporates this sub-risk of pandemic catastrophe and that certain life insurance companies take into account pandemic risk in their reinsurance programs. But pricing models do not include the risk of contagion and, therefore, the costs associated to this sub-risk must be paid from the insurer´s own resources.

Traditionally, actuaries that define the price of insurance have disregarded the risk of infectious disease contagion in their technical calculations. The difficulty in measuring the consequences of a pandemic outbreak may be behind the reason for acting in this way.

But we should be warned of the fact that the pandemic risk is the real threat to the results of long term life insurance risks. Let us look at some recent cases of global infectious diseases.

IT IS BELIEVED THAT BY 2050 DOCTORS WILL HAVE THE GENOME SEQUENCE OF EACH PATIENT ON THEIR COMPUTERS AND WILL THUS BE ABLE TO PREDICT THE DISEASES THAT WE WILL SUFFER WITH A CERTAIN DEGREE OF PROBABILITY AND, IN THIS WAY, APPLY PERSONALIZED PREVENTIVE TREATMENT

In 2004, the World Health Organization warned that there had been 9 million cases of tuberculosis that resulted in 2 million deaths and concluded that, although the incidence of such disease occurs mostly in countries with low incomes (80% of the cases), it was increasing in developed countries. One of the causes for this increase is demographic growth and movement (immigrants, refugees and displacements) associated with poverty and exclusion. According to the World Health Organization 2011 data, an estimated 500,000 people suffered from tuberculosis in Europe that led to 44,000 deaths. It is already the second largest mortal infectious disease after AIDS and costs the EU 6,000 million Euros per year.

Other diseases that can give rise to pandemic outbreaks are influenza, the variant of Creutzfeldt-Jacob or mad cow disease, Influenza A virus, hemorrhagic fever or bird flu. Influenza virus subtype H7N9 has killed almost 100 people in China, Influenza virus subtype H9N2 has infected very few people to date.

Finally, we must refer to dengue fever that affects approximately 50 to 100 million people per year; it could affect 40% of the worldwide population. This tropical and subtropical disease has already reached Europe and, in fact, the first cases were recorded in France and Croatia in 2010.

■ **Homogeneity**. Under this principle, risks of an equal nature result in the same insurance price. However, it is complex to define the homogeneity risk for life insurance where the principle of equity determines the premium. And we are not referring to the consequences arising from the non-discrimination directives that are promoting a larger mutualization of risks that are not necessarily homogenous.

Thanks to new predictive pricing models, the industry has embraced a new range of *preferred or super-preferred* products, where the individual risk profile allows for hyper-segmentation rating, even resulting in the absolute personalization of life expectancy without any possible homogenization. This would be the case of the *Life Settlement* products also known as death bonds.

The incorporation of predictive biomarkers capable of measuring the individual risk profile will challenge, and may even supersede, this homogeneity principle.

Other principles in the general theory of survival measurement are:

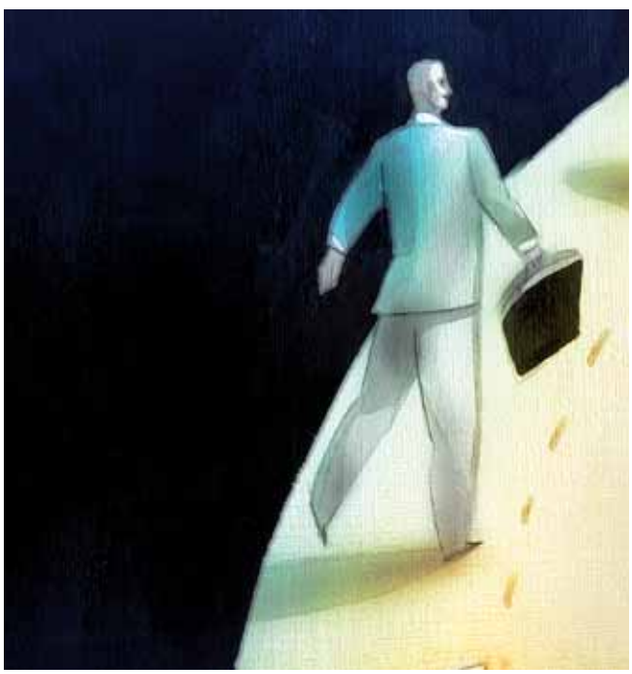
● *The risk of mortality increases exponentially with age*. Gompertz developed this principle more than 200 years ago; observations in the dynamics of longevity in advanced populations in terms of life expectancy at birth have evidenced that the rectangularization of the life expectancy curve up to old age and in very old age (ages from 95-100) makes this mortality principle not applicable. This rectangularization phenomenon is also seen, with less intensity however, with regard to health. Therefore, it is expected that in the future mortality and morbidity rates will increasingly become independent from age.

Actuarial science has just begun, from the beginning of this century, to take into account this new phenomenon when preparing survival tables or internal longevity models.

The phenomenon of understanding mortality that Vaïno Kanisto defined as that whereby a proportion of deaths occur in increasing lower age intervals and around the modal age, leads us to understand the three dimensions of human survival, as evidenced by observations on population evolution. These dimensions are horizontalization, verticalization and extension. The 2005 M-Project, which involved the work of the prestigious demographic and mathematic experts Cheung and Robine, has attempted to evaluate these dimensions and reveals a new way of understanding the survival risk.

● *Human life is finite*; in fact the maximum age for survival tables is around 120-130 years. Whilst it is true that man is finite, the fact that maximum survival reaches 120 years of age is a different matter. Let us reflect on this point; first of all by analyzing the records of maximum human longevity, we can feel comfortable with this age limit established in the standard longevity tables.

However, several questions arise. Firstly, going back to the results of the observations on the dynamics of longevity, demographic experts and actuaries are finding it difficult to find a pattern for statistically modeling limits for life, or what is technically called the survival extension risk. As a larger number of people become older, this sub-risk may be measured more precisely and the higher end of the survival table can be estimated.



A second question that arises refers to the conclusions of the so-called *fragility theory*, based on the biological observation of different animal species and human populations with high longevity records. This led Professor Leonid Gavrilov, of the Aging Center of the University of Chicago, to coin the term *actuarial kinetics* which attempts to explain the evolution of mortality of extreme old age which, being constant, i.e. there is no biological wear, would mean that there is no theoretical top limit where the mortality rate would be equal to one. We must bear this theory in mind for future modeling, particularly if a disruptive jump occurs in human longevity as a result of cellular and genetic therapies.

The French doctor and biophysicist, Roland Moreau, author of the book *Immortality for Tomorrow* concludes that «by the year 2027 almost all those born that year will reach the age of 100 and, if that is the case, some will reach 130 and, therefore exceed the biological limit of 120 years achievable by human beings» and «if the biogenetic engineering therapies are effective and alter the causes of ageing, the maxim limit for life could probably be exceeded».

● *Mortality rates must be positive and in the long term the hypothesis must be biologically reasonable*. These two principles are part of the ten rules proposed by Plat in 2009 in his definition of the features that a survival model must have. These premises mean that the longevity process is not reversible in time as we grow old. Only from the knowledge provided by the aging biological mechanisms can we assess if the survival rates should be at least positive. Very recently, biomedicine has shown that it is possible to recover

certain level of personal aging. In fact, taking the actual biological age of an individual as a reference, when an individual changes his lifestyle habits towards more healthy parameters, that individual's biological clock can be turned back. This has been evidenced by longevity's main biomarker: the telomeric length of chromosomes.

Just to mention one piece of evidence, a paper published in September 2013 in the prestigious scientific journal *The Lancet* concluded that in a healthy life style group the telomeres average length increased by 10% and, the more people changed their life style, the more dramatic their improvement in telomere length. By contrast, in the group that did not change life style, telomere length reduced by 3%.

In addition to life style changes, in the near future cell regeneration therapies will enable rejuvenation and/or repair of body tissue or organs, as was confirmed by laboratory tests conducted on animals and thus delay the biological clock. Harvard's Genetics Professor and molecular Engineer, George Church, refers to the potentialities of cell therapies and believes we will be young until death since, if we are already able to reverse a cell in laboratories, we will soon be able to do it within the body.

THE NEW PARAMETERS FOR HUMAN SURVIVAL MEASUREMENT: BIOPARAMETERS

Survival of an individual will be measurable before a disease occurs. This is the real news and the challenge for actuarial and biomedical science since it is a fact that pre-symptom prediction does not exist in traditional clinical medicine. In order to understand better the measurement process for morbidity or mortality throughout the different stages that an individual may undergo from when there are no symptoms until death, bioactuarial models will have different calculation parameters and algorithms.

The study of the human survival process will be represented through the Bio-Faro Pyramid which I have developed jointly with the professor and genetics researcher Antonio López Farré and the validity of which was confirmed with Ana Villanueva, a doctor specialized in the field of medicine for insurance.

For each stage of human health the bio-faro pyramid allows a group of genetic or molecular biomarkers so that individual risk may be stratified. The base of the pyramid refers to the personal family history which for certain diseases of monogenic origin has a certain predictive capacity for the development of a disease on the basis of family descent.

As we climb the pyramid, the predictive capacity increases and is therefore more precise for the purposes of survival metrics. Actuarial science combined with insurance medicine have proved to be effective in the metrics whenever the disease has become apparent, the investigation focuses on asymptomatic disease prediction. Predictive biomarkers must be considered jointly in the algorithm calculation with the individual life style parameters. Genetics and epigenetics play a central role in the calculation of risk stratification.

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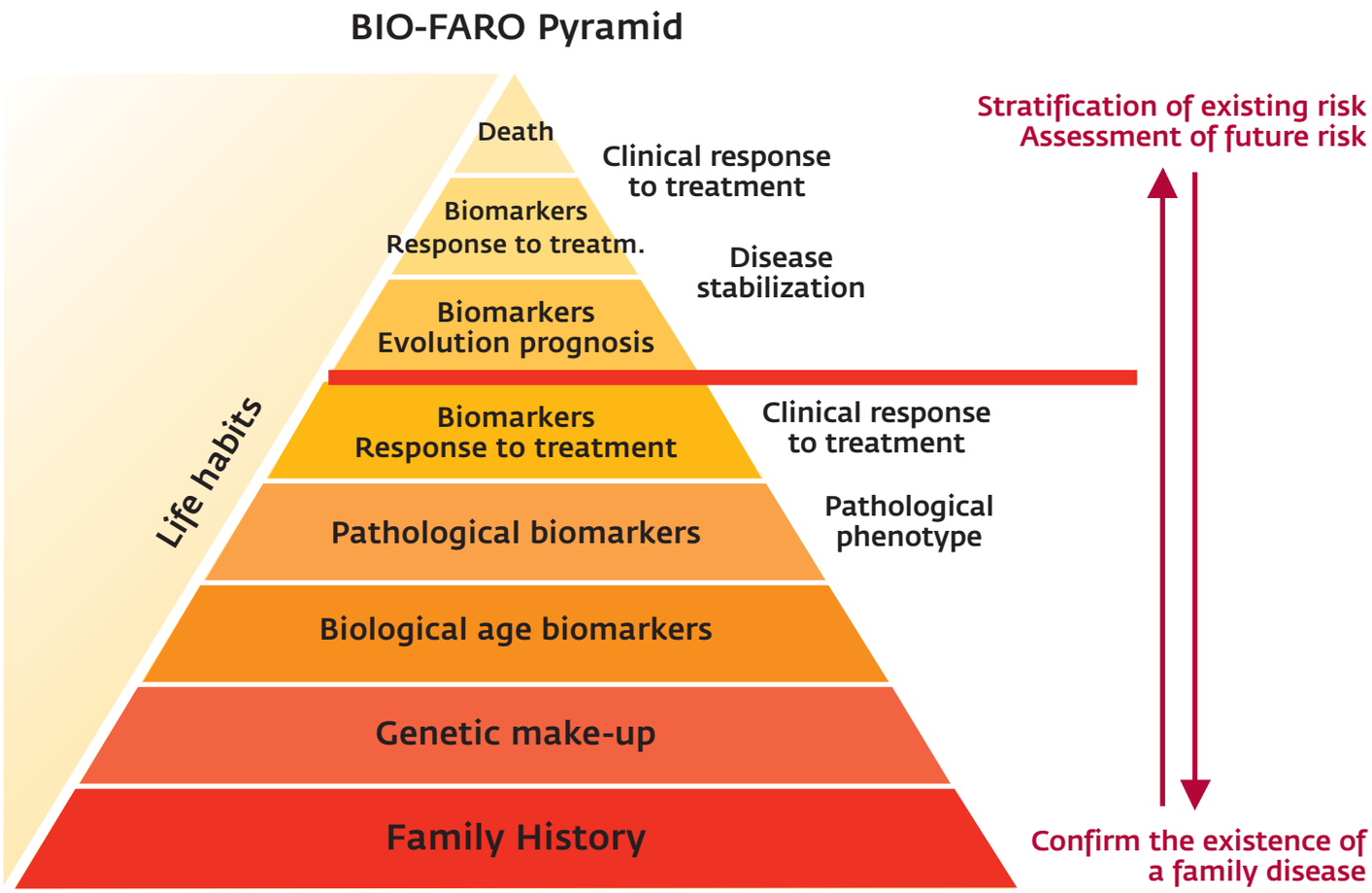

Figura 1. Biomarker stratification pyramid

Source: Lopez Farré, Rodríguez-Pardo, Villanueva Alonso.

BIOLOGICAL AGE

Biological age is increasingly being used in biomedical research; the step towards clinical or predictive medicine in clinical protocols is conditioned by the preparing of a calculation algorithm that is acceptable for the medical scientific community.

The new actuarial predictive underwriting models, known by the letters PUW in English, attempt to measure an individual's probability of dying with multi-variant techniques, taking into account not only the chronological age but also the life style. These models enable the correction of the mortality rates calculated solely by age with a set of variables that explain the mortality.

The predictive underwriting models are nothing more than a statistical approach to an individual's biological age. We will go on to see how the models proposed from biomedicine can converge with those proposed with PUW techniques.

The task is not simple; the algorithm that determines biological age must be an effective combination of life style variables with bioparameter values which must take into account, at least, the following:

–The size of telomeres.
–The immunological profile.
–Metabolical profile.
–Genetic diseases biomarkers.
–Genetic tests.

We are now seeing the most recent advances proposed from biomedical research for measuring biological age. First of all, a definition was found for the features that a biological clock must comply with in order to perform its functions. According to Richard A. Miller, gerontologist at the University of Michigan, the biological clock must meet two conditions:

–Be capable of calculating life expectancy for a middle aged person more exactly than the chronological age.
–Must provide an exact value for biological age.

The University of California in Los Angeles, under the direction of Steve Horvath, Professor of Human Genetics in UCLA School of Medicine and Biostatistics in the UCLA Fielding School of Public Health, has perfected the traditional biological model based on saliva, telomeres and hormones. The new method has been able to show that the different organs of the body all age at a different speed. In fact the cells of healthy tissue surrounding a breast tumor are 12 years older than the body of the person and the healthy breast tissue is three years older that the rest of the body. The algorithm of the biological clock is based on 353 biomarkers that change with age and are present throughout the human body. The so-called Horvath's clock will be patented by UCLA University at the end of 2013, according to the media.

Another biological clock is the one developed by Kang Zhang, of the Genomic Medicine Institute in the University of California in San Diego. His molecular aging clock is inserted in the genome, is composed of chemical labels in DNA molecules that control whether genes are active in the cells. Epigenetic markers change with age, in the paper published in January 2013 in the *Molecular Cell* journal, scientists analyzed 485 thousand of such labels in the blood cells of 656 persons, and found 70,387 labels that predicted chronological age.

This biological clock has enabled us to see that men age an average of 4% faster than women, a fact that could explain the different life expectancy between the genders. Moreover, it has enabled it to be shown that tumor cells have aged, on average, 40% more than normal cells in the same patient.

These two biological clock models are only an example of what the human survival metrics will be in the next years. The change in paradigm is of such significance that the insurance industry must be attentive to the development of such biomarkers which, in the researchers' opinion, will also be used in clinical medicine before the end of this decade.

PAY AS YOU LIVE PRODUCTS

The next generation of life insurance products will be those where the price of the annual insurance premium will be fixed on the basis of healthy lifestyle behavior patterns. So if the insured can show at each annual renewal that he maintains a healthy lifestyle, the insurance will be renewed with favorable terms and conditions.

The healthy lifestyle may be evidenced either via questionnaire on living habits or by objective biomarkers that accurately determine the exact biological age of the insured.

This new vision for insurance risks has started to be sold, incipiently, in some insurance markets and, as an actuary friend of mine said, they could be called Pay as you Live.

Society will welcome this type of policy where price is linked to healthy personal behavior and pricing has already taken on board the new risk metering paradigm, i.e. biological age.

THE BIO-ETHICAL DEBATE AND THE NEW SURVIVAL MODELS

Bioactuarial models will enable the measuring of predisposition to disease or determining the life expectancy of an individual. These models will be able to be applied before birth at the embryonic stage and even at laboratory in vitro embryos by means of mass prenatal DNA sequence techniques. They will provoke an ethical debate which will have to be resolved before they can be used effectively by the insurance industry.

In any event, we have to put ethics before actuarial modeling factors but we must also strike a balance between the greater risk measurement precision provided by the new paradigm –where the individual's profile is the basis of measurement– rather than the traditional models where risk categories in most cases, are only made on the basis of chronological age.

We must make two considerations; the first one refers to the fact that the principle of fairness where each risk profile has a different actuarial value but need not necessarily clash with the principle of risk mutualization, whereby the solidarity mechanism of the insurance industry permits the incorporation to the insured group of those that are most vulnerable in terms of risk profile.

The second consideration refers to the breach of discrimination principles from the use of genetic profile data. Professor Carlos María Romeo Casabona, Director of the Inter-University Chair of Law and Human Genome at *Universidad de Deusto* (University of Deusto) and *Universidad del País Vasco* (University of the Basque Country) sheds light on the ethical-actuarial conflict when he says that any technique that involves the use of genetic markers to measure risk or predisposition to a genetic disease must be submitted to the following principles:

– Proportionality, that is to say that the advantages must exceed the disadvantages.
– Relevance, there must be clinical interest.
– Quality, it must be reliable.
– Predictivity, i.e. there must be sufficient predictive capacity for the risk that we wish to measure.

The contrast between the new survival models with ethical principals will allow us to reconcile ethics and insurance science and legislation will have to determine the framework for conduct.

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