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PPPM as an Avenue to Predict and to Prevent Chronic Disorders

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Over the course of its history, medicine has given special attention to the already diseased individual, focusing on a type of disorder (*nosology*) rather than on one’s health or the so-called *pre-illness* conditions, the latter being left in the shade.

The link that might exert reliable control over morbidity, mortality and disabling rates and significantly optimize the cost of treatment for those who had fallen ill! The name of the link is Predictive, Preventive and Personalized Medicine (Fig).
PPPM associated with Subclinical and Predictive Diagnostics

Evolution of prediction: from the Oracle of Delphi to fortunetellers to cutting edge contemporary medicine where evidence based prediction has become reality.
To achieve the practical implementation of PPPM concept, it is necessary to create a fundamentally new strategy based upon the pre-early (subclinical) recognition of biomarkers of hidden imbalances and defects long before the illness clinically manifests itself.

This strategy would give a real opportunity to secure preventive measures whose personalization could have a significantly positive influence on demographics! (Fig)
Impacts to be assumed for the practical implementation of *PPPM* into the practice

- to predict the likelihood of developing disease
- to estimate the length of the asymptomatic period
- to provide predictive information about disease course, severity, and complications
- to serve as a warning to avoid potential disease-triggering factors
- identify high-risk individuals who might be suitable candidates for preventive intervention trials
Human cardiovascular disease is a consequence of a complex interplay of genetic, epigenetic and environmental factors.

Conventional cardiology attempts to prevent disease by modifying established risk factors and to treat manifest disease, often after complications have occurred and irreversible tissue changes have taken place.

Current therapies (eg, those for heart failure) are administered uniformly across a heterogeneous spectrum of disease etiology, severity and genetic background.

Now we have the opportunity to expand our medical armamentarium to include molecular phenotypes (signatures) that distinguish subtle subclassifications of disease and allow us to better tailor both prevention strategies and therapeutics.
PPPM as thus the big change to forecast, to predict and to prevent is rooted in a big and new science to be rooted from the achievements of genomics, proteomics, metabolomics and bioinformatics which are being implemented into the daily practice to secure visualizing of lesion foci that was previously unknown to clinicians (Fig. x2)
Genomics  Transcriptomics  Proteomics  Metabolomics

DNA  RNA  Protein  Metabolites
In reality, **Genomics** as a set of molecular tools to probe genome and to thus identify and to select *genomic biomarkers* has allowed for identifying newer *genetic variations* that affect health to form *subclinical* and *predictive* risks to be screened and unveiled, and then the *subclinical* pathology to be diagnosed, monitored and terminated to *prevent* illness.
Population resources – trios or case-control samples

Whole-genome genotyping

Genome-wide association

Fine mapping

Gene mining

Gene sequencing & polymorphism identification

Identification of causative SNPs

Pathway analysis & target identification
Over the last decade genome-wide association studies (GWASs) have identified many loci associated with late-onset cardiovascular diseases including coronary artery disease, and correlates of myocardial function.

Genetic loci with multiple trait associations have also provided novel biological insights.

For example, of the 46 genetic loci associated with coronary artery disease, only 16 are also associated with conventional risk factors for cardiovascular disease whereas the remaining two thirds reflect novel pathways.
Well, genes can say a lot about an individual’s **predisposition** to a disease, but cannot reveal what is happening in cells at the protein level.

The latter would attribute to **proteomics** to identify individual proteins to be valuable for **predictive** diagnosing and thus may eventually have a great impact on **PPPM**
Meanwhile, a combination of *genomic* and *proteomic biomarkers* are becoming of great significance to *predict risks* of the *chronification* and thus of *disabling* since chronic cardiovascular diseases are preceded by a *long subclinical (symptom-free)* phase or a period of *latency*.
In reality, *proteomics per se* is the continuation of *functional genomics* and, at the same time, a prologue to *metabolomics*.
The latter **(metabolomics)** illustrates the functional state of the cell at the level of **metabolism** on a real time basis, requiring the use of the term **'metabolome',** demonstrating a set of **metabolic pathways** in the cell at a given time point.
Tissue-derived information we would accumulate might be combined with the:

- individual's medical records;
- family history;
- data from imaging;
- instrumental and laboratory tests to develop *personalized* and *preventive* treatments.

But, in this sense, how is the whole databank provided by omics-technologies could be comprehended?
It is **bioinformatics** to suit the goal by applying mathematical modeling techniques to thus secure constructing and maintaining unified **biobanks** and **databanks** necessary for **personal health monitoring** based on principles of **genotyping** and **phenotyping**.

As a result, the **patient** becomes a **data carrier**, whilst learning about possible risks of a disease, and the **physician** can reasonably select a kind of **preventive** and **personalized** protocol rooting from the **predictive** assays made (Fig).
By integrating bioinformatics and clinical informatics, both offers unique infrastructure, tools, techniques and applications to bridge those areas.

This facilitates the sharing of data and information across diverse disciplines and professional sectors.
Individuals, selected in the first (genotypic) stage, undergo the second stage, which uses a panel of phenotypic biomarkers, whilst monitoring every:

- potential patients,
- persons-at-risks predisposed to the disease,

and/or

- persons at subclinical stages of the disease.
PPPM will require the integration of clinical information, stable and dynamic genomics, and molecular phenotyping.

Bioinformatics will be crucial in translating these data into useful applications, leading to improved diagnosis, prediction, prognostication and treatment.

So, our viewpoint would support the contributions of genomic and proteomic approaches in developing a preventive and personalized approach to cardiovascular medicine.
In the era of personalized medicine there is increased interest in the incorporation of individual biomarkers in risk score algorithms in order to improve cardiovascular risk stratification followed by the prompt initiation of preventive measures whilst evaluated the predictive and prognostic value of currently used biomarkers like

- cardiac troponins,
- non-HDL-cholesterol,
- apolipoproteins,
- natriuretic peptides (NPs)

as well as promising future biomarkers like

- copeptin,
- choline and
- lipoprotein-associated phospholipase A2 (LP-PLA2).

For instance, **galectin-3** is an active biomarker of mortality!
MARKERS OF CARDIAC MYOCYTE STRAIN
- BNP
- NT-proBNP
- MR-proANP

MARKERS OF CARDIAC MYOCYTE REMODELING
- ST2
- Chop
- Galectin-3

MARKERS OF CARDIAC MYOCYTE INJURY
- High Sensitivity Troponins

MARKERS OF CONCOMITANT INJURY/INFECTION SEEN IN HEART FAILURE
- NGAL

ACUTE KIDNEY INJURY
- Procalcitonin

PNEUMONIA
- Norepinephrine
- RAAS
- Endothelin-1
- Copeptin
- Matrix metalloproteinase
Meanwhile, *ST2* is released by stressed cardiac myocytes and also predicts mortality in myocardial infarction.
MARKERS OF CARDIAC MYOCYTE STRAIN
- BNP
- NT-proBNP
- MR-proANP

MARKERS OF CARDIAC MYOCYTE REMODELING
- ST-2
- GDF-15

MARKERS OF CARDIAC MYOCYTE INJURY
- High Sensitivity Troponins

MARKERS OF CONCOMITANT INJURY/INFECTION SEEN IN HEART FAILURE

ACUTE KIDNEY INJURY
- NGAL

PNEUMONIA
- Procalcitonin

MARKERS OF INFLAMMATORY PROCESSES
- IL-6
- Fas (Apo 1)
- TNF-α
- CRP
- Pentraxin-3
- Myeloperoxidase

MARKERS OF NEUROHORMONAL ACTIVATION
- Norepinephrine
- RAAS
- Endothelin-1
- Copeptin
- Matrix metalloproteinase

Increased Ventricular Wall Stretch
Copeptin is a stable arginine vasopressin precursor associated with increased risk of heart failure to be used to exclude acute myocardial infarction.
Copeptin

MARKERS OF CARDIAC MYOCYTE STRAIN
- BNP
- NT-proBNP
- MR-proANP

MARKERS OF CARDIAC MYOCYTE REMODELING
- ST2
- Galectin-3
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Increased Ventricular Wall Stretch
Most of the latter are directly associated with development of atherosclerotic cardiovascular disease.

So, we would need absolute proofs to confirm clinical applications of the biomarkers mentioned, evaluating not only their diagnostic and prognostic value but also their **integrability** into routine practice.

Although a **single biomarker** is a tangible entity that can be easily understood, aggregate measures comprised of multiple genes are also informative as the **combinatorial biomarkers**.
The simultaneous addition of combinatorial biomarkers of cardiovascular substantially improves the risk stratification for death from cardiovascular causes beyond that of a model that is based only on established risk factors.

And clinical potential may be evaluated by asking three fundamental questions:
(1) Can the clinician measure the biomarker as applicable to cardiac diseases?
(2) Does it add new information?
(3) Does it help the cardiologist to manage patients?

The incorporation of the multiplexed but consolidated biomarkers mentioned into clinical practice for the prediction of death from cardiovascular causes could be accomplished quickly, since the measurement of these biomarkers is already well established for diagnostic use.
The greatest limitation in personalizing cardiovascular medicine today is our inability to accurately predict risk for patients.

For instance, myocardial infarction results as a consequence of atherosclerotic plaque rupture, with plaque stability largely depending on the lesion forming extracellular matrix components.

Meanwhile, **MMP-1 serum** levels was found to be an independent biopredictor for coronary atherosclerotic lesions, while not allowing a stratification of plaque morphology.
Molecular Imaging as applicable to Cardiology
Cellular targets for molecular imaging agents

- Receptors/Proteins/Transporters
- Glucose metabolism
- Enzyme activity
- Phagocytosis

DNA → RNA → mRNA → Protein synthesis

Reporter gene expression

Viral vector

18F-FDG, 18F-FDG-6P, HK

Substrates, Inhibitors, Amino acid (AA)

Receptor probe, enzyme substrate

GLUT
In vivo MRI of human thrombi using a fibrin-targeting peptide conjugated to gadolinium–tetraazacyclododecane tetraacetic acid

(a) MRI before contrast enhancement
(b) EP-2104R injection causes signal enhancement and visualization of left ventricular thrombus (arrow)
(c) In a different patient, the post-EP-2104R image shows signal enhancement corresponding to aortic thrombus (arrow)
(d) Corresponding contrast-enhanced CT shows atherosclerotic plaque with calcification (arrowhead).

Integrating High-Throughput Measurements with the Phenotype: from Science to Medicine
(Omenn & Athey, NCIBI, 2010)
Multifactorial risk factor modification and control can have a profound and favorable impact on decreasing the incidence of initial and recurrent cardiovascular events.

Meanwhile, because the adult heart has negligible regenerative capacity, healing of the infarcted myocardium is dependent on sequential activation of inflammatory and fibrogenic signals.

So, a strategy of preventive treatment should contain, at least, two critical steps for postmyocardial infarction:

(i) quenching of inflammation and degeneration; and,

(ii) restoration of the tissue affected.
Look, acute cardiomyocyte necrosis in the infarcted heart generates Damage-Associated Molecular Patterns (DAMPs) (Fig. x2)
Initiation of the inflammatory response following myocardial infarction

Necrotic cardiomyocytes (CM) and damaged extracellular matrix release danger signals (DAMPs) triggering the complement cascade and activating TLR/IL-1 signaling. Leukocytes, in turn, are recruited in the infarcted heart through activation of a multi-step adhesion cascade.
Resolution of the post-infarction inflammatory response involves activation of multiple inhibitory signals and recruitment, or transdifferentiation, of leukocyte subsets with suppressive properties.
The geometric, functional and molecular alterations associated with post-infarction remodeling are driven by the inflammatory cascade and are involved in the development of heart failure.

So, we would have to treat but better to prevent!

The implementation of cardiovascular prevention strategies continues to reduce the incidence of myocardial infarction.

What should we do and which kinds of the preventive protocols could be exploited?
Prevention can be divided into 3 types:
- **primordial** (prevention of risk factors);
- **primary** (treatment of risk factors);
- **secondary** (prevention of recurrent cardiovascular events)
Therapeutic potential of HDL in cardioprotection and tissue repair

HDL may improve cardiac function in several ways:

- may protect the heart against ischaemia/reperfusion injury resulting in a reduction of infarct size and thus in myocardial salvage.
- can improve cardiac function in the absence of ischaemic heart disease.
- may improve cardiac function by reducing infarct expansion and by attenuating ventricular remodeling post-myocardial infarction

These different mechanisms are substantiated by *in vitro, ex vivo, and in vivo* intervention studies that applied the treatment mentioned.
Matrix metalloproteinase (MMPs)

MMPs are long understood to be involved in remodeling of the extracellular matrix. MMP-2 proteolyzes components of the sarcomere, and its intracellular activity contributes to ischemia-reperfusion injury of the heart.
RNA interference therapy may achieve \textit{in vivo} biomedical imaging and targeted therapy.
Targeting B cells in atherosclerosis

Atherosclerotic plaque formation is strongly influenced by different arms of the immune system, including B lymphocytes.

**B1 cells** are atheroprotective mainly via the production of natural IgM antibodies that bind oxidized low-density lipoprotein and apoptotic cells.

**B2 cells** are suggested to be proatherogenic. Thus, B cells represent a novel interesting target for therapeutic modulation of the atherosclerotic disease process.
Targeting Wnt signaling to improve wound healing after myocardial infarction
Meanwhile, regenerating the human heart is a challenge that has engaged clinicians around the globe for nearly a century.

Exciting progress has been made to establish cell transplantation techniques in recent years, and I would discuss briefly cell therapy approaches for heart regeneration.

The human heart harbors an adult \textit{stem cell} population consistent with true characteristics of \textit{stemness} such as self-renewal, clonogenicity, and multilineage differentiation potential. Recent evidence demonstrates the ability of resident human cardiac cells to differentiate into mechanically integrated cardiomyocytes as well as vascular smooth muscle and endothelial cells, thereby supporting cardiac regeneration.

Adoptive transfer of human cardiac stem cells results in modest repair due in part to lack of survival, proliferation, and commitment of the transplanted cells after myocardial infarction.

For instance, transplanted human CD34+ cells augment capillary formation, inhibit myocardial fibrosis and preserve left ventricular (LV) function in myocardial infarction. Moreover, exploitation of bone marrow–derived SCs effectively demonstrate improved cardiac function after transplantation of stem cells (Fig).
Moreover, modification of human cardiac progenitor cells (hCPCs) to enhance proliferation, survival, and commitment increases effectiveness of stem cells as a viable therapeutic modality. *Ex vivo* genetic modification is an effective strategy to enhance stem cell function.

Transplantation of bioengineered cardiac cells and tissue patches containing either progenitor cells or cardiomyocytes for cardiac repair is emerging as an exciting treatment option for patients with postinfarction left ventricular (LV) remodeling.

The beneficial effects may evolve directly from remuscularization or indirectly through mechanisms that mobilize and/or activate endogenous progenitor cells to promote neovascularization and remuscularization, inhibit apoptosis, and attenuate LV dilatation and disease progression.
Applications of engineered heart muscle (EHM) Schematic presentation of
(A) an EHM patch and
(B) an EHM pouch (red)
(C) Illustration of a multi-loop EHM with five loops fused together to form an asterisk-shaped stack with a solid center surrounded by 10 loops that are used for surgical fixation of the EHM graft
(D) The patch was fixed over the site of infarction in rats with six single-knot sutures
(E) The dimensions of an EHM pouch and an explanted rat heart are shown
(F) An EHM pouch was implanted over a healthy rat heart to simulate its use as a biological ventricular assist device
Meanwhile, cardiac regeneration, either by delivery of extra-cardiac stem cells or by enhancing endogenous mechanisms, will change the future of postinfarction restoration and further preventive treatment!
Genetic and pharmacological priming together with the discovery of new sources of cells have led to a "second generation" of cell products that holds an encouraging promise in cardiovascular regenerative and preventive medicine.

And due to the novel nature of cellular therapies, it is evident that the cardiac clinical community will play a critical role in their successful adoption.
Meanwhile, implementation of PPPM would require the adjusted technology for proper interpretation of *diagnostic* and *predictive* data before the current model “physician-patient” could be gradually displaced by a “medical advisor-healthy persons-at-risk” model.

This approach should be based on postulates which will change the incarnate culture and social mentality.
And, no doubt, next generations will speak about the XXI century as a time, when medicine became *preventive* and *personalized*, and its outcomes – *predictive* and *guaranteed* (including cardiology)
Thanks' for your kind attention!!!!!!!