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OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Phrama scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.
PPPM
as a new model of and thus a unique tool in
global restructuration of national and
international healthcare services

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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-nosological (or pre-illness) conditions, the latter being left in the shade.

Those speculations along with latest advances in science and technology combined with worldwide practice and personal experience have led us to conclude that the key link in the modern healthcare strategy, namely, a link of predictive, preventive and personalized medicine (or PPPM) is missing.

The link, I would stress, that might exert reliable control over morbidity, mortality and disabling rates and significantly reduce the cost of treatment for those who had fallen ill.
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! *(next Fig)*
Impacts to be assumed for the practical implementation of predictive biomarkers into PPPM

- 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
PPPMM as 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 (*next two Figs*)
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 *genes* and 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 *(next two Figs)*
Genomic biomarkers and their impact into pathway-targeted cancer therapies

(a) Routine sequencing of cancer genomes will identify many new genes that are involved in cancer;
(b) Detailed mechanistic studies will be required to determine how these genes contribute to tumorigenesis and how they influence therapeutic efficacy.
Autoimmunity-related genomic biomarkers
(interaction of T1D associated genes - gene networks)
As an allied portion of *genomics* and thus an area of study to examine the impact of *genetic variations* on the response to medications is *pharmacogenomics*.

The latter is aimed at tailoring drug therapy at a dosage that is most appropriate for an individual patient, with the potential benefits of increasing the clinical efficacy and safety. *Pharmacogenomics* will thus guide therapeutic decisions and monitor the response to therapy on one hand and speed the development of novel therapeutics, on the other one.
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 and their epitopes to be valuable for *predictive* diagnosing and thus may eventually have a great impact on PPPM.
Proteomics, in turn, is the study of the **proteins** and **protein pathways** involved in a disease for identifying **subclinical** defects and imbalances suitable for **preventive** intervention using the appropriate proteins as **biomarkers**.

Among the latter are **cancer-** and **autoimmunity-related biomarkers**.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Cancer type</th>
<th>Specificity</th>
<th>Example of non-cancer pathology</th>
<th>Primary clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-fetoprotein</td>
<td>Hepatocellular, non-seminoma-tous testicular</td>
<td>Moderate</td>
<td>Prostatitis</td>
<td>Staging</td>
</tr>
<tr>
<td>Human chorionic gonadotrophin-β</td>
<td>Testicular, ovarian</td>
<td>Low</td>
<td>Pregnancy</td>
<td>Staging</td>
</tr>
<tr>
<td>CA15-3</td>
<td>Breast</td>
<td>Poor</td>
<td>Cirrhosis, benign diseases of ovaries and breast</td>
<td>Disease monitoring</td>
</tr>
<tr>
<td>CA19-9</td>
<td>Gastro, pancreatic, stomach</td>
<td>Poor</td>
<td>Gastritis</td>
<td>Disease monitoring</td>
</tr>
<tr>
<td>CA125</td>
<td>Ovarian, cervical, uterine, fallopian tube</td>
<td>Moderate</td>
<td>Pancreatitis, kidney or liver disease</td>
<td>Disease monitoring</td>
</tr>
<tr>
<td>CA27-29</td>
<td>Breast</td>
<td>Low</td>
<td>Non-malignant disorders</td>
<td>Disease monitoring</td>
</tr>
<tr>
<td>CEA</td>
<td>Colorectal, pancreas, lung,</td>
<td>Low</td>
<td>Non-malignant disorders, such as</td>
<td>Selection of therapy</td>
</tr>
<tr>
<td></td>
<td>breast, medullary thyroid cancer</td>
<td></td>
<td></td>
<td>for benign prostatic hyperplasia</td>
</tr>
<tr>
<td>Epidermal growth factor receptor</td>
<td>Colon, non-small cell lung cancer</td>
<td>Low</td>
<td>Non-malignant disorders, such as</td>
<td>Selection of therapy</td>
</tr>
<tr>
<td></td>
<td>Her2/Neu</td>
<td>Moderate</td>
<td>Benign breast disease</td>
<td>for benign prostatic hyperplasia</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate</td>
<td>High</td>
<td>Benign prostatic hyperplasia</td>
<td>Screening; disease monitoring</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>Thyroid</td>
<td>Poor</td>
<td>Grave’s disease thyroiditis</td>
<td>Disease monitoring</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Autoimmune disorder</th>
<th>Autoantigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis (MS)</td>
<td>Myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG) and others</td>
</tr>
<tr>
<td>Autoimmune myocarditis</td>
<td>Cardiac myosine</td>
</tr>
<tr>
<td>IDDM1</td>
<td>Insulin, GAD-65</td>
</tr>
<tr>
<td>Graves disease (diffuse toxic goiter)</td>
<td>TSH receptor (TSHR)</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis (autoimmune thyroiditis)</td>
<td>Thyroid peroxidase (TPO), thyroglobulin (TG)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>dsDNA</td>
</tr>
<tr>
<td>Rheumatoid arthritis (RA)</td>
<td>Citrullinated cyclic peptide, IgM</td>
</tr>
</tbody>
</table>
Meanwhile, a combination of genomic and proteomic biomarkers are becoming of great significance to predict risks of the chronization and thus of disabling since chronic diseases are preceded by a long subclinical (symptom-free) phase or a period of latency (next Fig).
A stepwise progression of autoaggression

Stage of subclinical autoaggression

Stage of full-term autoaggression

Subclinical (cryptic) latency

A stepwise (subclinical-clinical) course to be developed

Clinical illness

Genetic influence

Normal Immunity

Benign Autoimmunity

Pathogenic Autoimmunity

Environmental factors
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 (next two Figs)
Bioinformatics would service PPPM

The diagram shows the integrated “knowledge environment” that enables clinicians to query critical information from across disparate data sources to find relationships between an individual patient’s EMR information of persons-at-risk family records.
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.
Biobanks would provide the proper information about patient's proteomic, genetic and metabolic profiles to be used to tailor medical care due to the individual's needs and personalized scenarios.

An understanding of the factors underlying the burden of a disorder and later on of the clinical illness would provide policymakers, healthcare providers and medical educators with an opportunity to guide preventive initiatives at both individual and community levels (next Fig).
Impact on Sustainability in Three Main Dimensions of Biobanking

PPPM

Operational Efficiency

Social Acceptability

Financial Accomplishment

Biobanking as applicable to PPPM

Impact on Sustainability in Three Main Dimensions of Biobanking
Well, two key objectives of **PPPM** are:

(i) screening for *subclinical imbalances and defects* with *a pre-selection* of suitable *targets* for the next step of PPPM protocol, i.e., *drug-based prevention*;

(ii) repair of the *imbalance* and *defects* mentioned to restore the function and to thus *prevent* the clinical illness

**PPPM** is thus a model of healthcare services being tailored to the individual and dictates a construction of **PPPM-based algorithms** to *diagnose, to predict, and to prevent* in time!
• **Predictive branch** of PPPM is mainly designed to meet the interests of healthy individuals, its purpose being to determine whether susceptibility to a particular disease is increased or not.

• • **Preventive branch** is aimed at taking measures to avoid development of clinical manifestations rather than cure or treat it on manifestation.

• • • **Personalized medicine** proposes the customization of healthcare, being tailored to the *individual patient* and/or to the *person-at-risk* by the mutual integration of:

  family history, medical records and other information including genomic, proteomic and metabolomic *biomarkers-based* profiles to be integrated *via bioinformatics*
PPPM thus uses *diagnostic* and *predictive* tests of newer generations based on *biomarkers*, to individually determine the health conditions a person is predisposed to and to reveal biomarkers of the probable or the already existing pathological processes, and thus to select the *targets*.

*PPPM-oriented survey* should be based on *biomarkers* and *algorithms* to differ essentially from those employed in traditional clinical strategies, namely,

(i) algorithms for *predictive* and *subclinical* diagnostics on one hand, and

(ii) algorithms for *preventive* therapy, on the other one
Individuals, selected in the first stage, undergo the second stage, which uses a panel of phenotypic biomarkers, while monitoring every:

- potential patients,
- persons-at-risks predisposed to the disease, and/or
- persons at subclinical stages of the disease.

By illustration and irrespective of the underlying mechanism, the proven predictive ability to accompany the diagnostic and predictive tests has been documented for:

(i) HLA-related biomarkers in combination with autoAbs and other biomarkers (e.g., cytokines, autoreactive CTLs, etc) to monitor chronic autoimmune inflammation (T1D, MS, SLE);

(ii) genomic biomarkers in combination with cancer-associated antigens and other biomarkers (e.g., components of the signaling pathways defined) to monitor cancerogenesis.
A strategy of *preventive treatment* should contain, at least, two critical steps.

For chronic autoimmune and/or infectious diseases:

(i) *quenching of autoagression* or *blocking the infectious process*; and,

(ii) *restoration of the tissue* affected.

For cancerogenesis:

(i) *killing the malignancy* and *prevention of metastatic formation*; and,

(ii) *restoration of the primary tissue* affected.
T1D is a chronic autoimmune inflammation comprising stages of *subclinical pathology* and *clinical manifestations* and resulting in a destruction of pancreatic *beta*-cells capable of producing insulin.
A stepwise development of T1D

Factors to provoke T1D

Population of \( \beta \)-cells to function

Genetic predisposition

Population of \( \beta \)-cells to function

Factors to provoke T1D

Clinical manifestations

100% death of \( \beta \)-cells

Clinical manifestations link to \( \beta \)-cell death to illustrate ceasing in insulin secretion.

A subclinical stage is characterized by depletion of \( \beta \)-cells and fall in insulin secretion levels to have a biased burst.

Stage 1

Stage 2

Stage 3

Stage 4

Stage 5

Stage 6

Benign autoimmunity (autoimmune insulitis)

Pathogenic autoimmunity (latent or asymptomatic insulin deficiency)

Glucose intolerance

T1D clinical manifestations

1. A subclinical stage is characterized by depletion of \( \beta \)-cells and fall in insulin secretion levels to have a biased burst.
2. Clinical manifestations link to \( \beta \)-cell death to illustrate ceasing in insulin secretion.
For this model, about half of the total risk is *genetically predisposed*, and about half of the risk is in the HLA and *other regions* to be useful for *gene-based predictive testing*!
Hypothetical stages of diabetes development:

1. **Subclinical stages** are determined by identification of proteomic biomarkers, i.e., anti-islet autoAbs as early as 5-10 years before the clinical onset of disease (Fig. 54).

2. **How diabetes develops**:
   - The attack on beta cells begins when immune cells called T-lymphocytes and B-lymphocytes invade the islets of Langerhans, where the beta cells reside. The T-cells probably cause most of the damage (top detail), but as those cells do their mischief, the B-lymphocytes spit out antibodies against proteins made by beta cells, usually starting with insulin.

3. As the attack on the islets continues, damaging them severely, other types of autoantibodies may appear, such as ones targeted to the proteins GAD and IA-2 (bottom detail). The order and time at which these additional autoantibodies arise can vary.

**Autoantibodies and diabetes risk**:
- Whether autoantibodies to insulin, GAD and IA-2 contribute to the beta cell killing is not known, but studies have shown that the molecules can signal greatly enhanced risk for diabetes. Risk increases with the number of diabetes-related autoantibody types in the blood.
Tumor initiation is provided by oncogenic mutations and inactivation of tumor-suppressor genes and depends on the stepwise acquisition of specific functions by cancer stem cells (CSC) and circulating tumor cells (CTCs) to be identified by genomic tailoring approach on one hand and proteomic-immunonomic approaches, on the other hand (Fig. 56).

Three different steps are described during cancerogenesis:

- **Initiation** is a rapid and irreversible DNA lesion which occurs after exposure to a carcinogen (physical carcinogen, chemical carcinogen, viral carcinogen).
- **Promotion** is due to prolonged, repetitive or continuous exposure to substances which maintain and stabilize the initiated lesion.
- **Progression** is the acquisition of non-controlled multiplication properties, independence acquisition, loss of differentiation, local invasion and metastasis.
**PPPM** is a new healthcare model that notifies people of the health conditions they’re disposed to and it reveals the *biomarkers* and thus the *agents* to improve and to thus secure the health and individual biosafety.

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.
**First of all,** it is the impact of human responsibility for the own health and for the health of their children, and active involvement into the **preventive** measures for strengthening of the public health and country’s biosafety.

**Secondly,** a creation of legal basis to satisfy all society needs for the **protection** of individual health – regulations of the state insurance in the PPPM.

And, **thirdly,** for sure, it’s necessary to radically change the system of **medical training,** and designing novel approaches to build the **academic schools** of new generations.
Due to our viewpoint, all healthcare professionals of the future should be educated to deliver *patient-centric care* as members of *interdisciplinary teams*, emphasizing *evidence-based practice*, *quality improvement approaches* and *bioinformatics*.

That concerns the need for novel training programs since the society is in bad need of large-scale dissemination of *novel systemic thinking* and *minding*.

And upon construction of *the new educational platforms* in the rational proportions, there would be not a *primitive physician* created but a *medical artist* to be able to enrich flow-through medical standards with creative elements to gift for a *patient a genuine hope to survive* but, in turn, *for a person-at-risk – a trust for being no diseased*.

So, the existing medical education would strongly need to be restructured to involve along with traditional graduate and post-graduate training, *pre-graduate* preliminaries to disclose for schoolchildren the mysteries of the evidence-based medicine and *PPPM* as the entity
Based on current trends and own experience, we have tried a non-canonical approach towards reshuffling the traditional educational tandem “School-University” to create a team of talented and gifted teenagers to be engaged into PPPM-related areas.

The Team has been given a roof under the aegis of European Association of Predictive, Preventive and Personalized Medicine (EPMA), Brussels, EU, and started up to move ahead now.

The First Anglo-Russian Students’ Workshop on PPPM and Translational Medicine
Lancaster University
4th September 2012

Location: TR1/TR2 Gordon Manley building
Chairs:

Professors Frank Martin, PhD (UK)
Director, Environmental and Biophotonics Center, and Chairman, Dept for Biochemistry, Lancaster University, UK

Professor Sergey Suchkov, MD, PhD (Russia)
Dept of Pathology, School of Pharmacy, I.M. Sechenov First Moscow State Medical University, and Dept of Clinical Immunology, Moscow State Medical & Dentistry University, First Vice-President and Dean, School of PPPM, University of World Politics and Law, Moscow, Russia
EPMA-World Congress 2011
September 15th-19th, Bonn, Germany

International Research Team of Youngers
EPMA World Congress 2013
Europarlament, Brussels, EU, Sep 2013
Section For Young Professionals (Session)
Our global challenge is that the new guidelines should create the robust *juristic* and *economic* platforms for advanced medical services utilizing the cost-effective models of risk assessments followed by tailored *preventive* treatments focused on the precursor stages of chronic diseases.
Some comments:

Individuals to be under *regular monitoring* that helps to detect pathological shifts at *subclinical* stages have a higher life expectancy and are able-bodied up to 8–15 years more than those under traditional treatment.

This means that the society would save more than *US$20,000–40,000 per person annually.*

At the community level, the annual savings from each individual may vary from *several thousands* to *several tens of thousands* U.S. dollars.

In the area of oncology, for instance, the latter means that as little as a 10 percent reduction in cancer would translate into *a savings of 4.4 trillion US dollars* to society.

As you might feel, besides the *scientific* and *clinical* challenges, there are *economic* hurdles.
The opportunity arises for unusual and, even extraordinary, strategic partnerships between:

➤ governments, academic and business sectors.

The healthcare industry, public policy sector, and consumer industries will be required to develop new and creative business models and products.

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 guarantied.
Let Us Meet Again

We welcome you all to our future conferences of OMICS Group International

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