# General Report & Recommendations in Predictive, Preventive and Personalised Medicine 2012: White Paper of the European Association for Predictive, Preventive and Personalised Medicine

Olga Golubnitschaja, Vincenzo Costigliola and EPMA

*The EPMA Journal* 2012, **3**:14

Golubnitschaja *et al. The EPMA Journal* 2012, 3:14
http://www.epmajournal.com/content/3/14

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The
EPMA
Journal

**REPORT**                                                                                   **Open Access**

# General Report & Recommendations in Predictive, Preventive and Personalised Medicine 2012: White Paper of the European Association for Predictive, Preventive and Personalised Medicine

Olga Golubnitschaja[1]*, Vincenzo Costigliola and EPMA

## Abstract

This report is the collective product of word-leading experts working in the branches of integrative medicine by predictive, preventive and personalised medicine (PPPM) under the coordination of the European Association for Predictive, Preventive and Personalised Medicine. The general report has been prepared as the consortium document proposed at the EPMA World Congress 2011 which took place in Bonn, Germany. This forum analysed the overall deficits and trends relevant for the top-science and daily practice in PPPM focused on the patient. Follow-up consultations resulted in a package of recommendations for consideration by research units, educators, healthcare industry, policy-makers, and funding bodies to cover the current knowledge deficit in the field and to introduce integrative approaches for advanced diagnostics, targeted prevention, treatments tailored to the person and cost-effective healthcare.

**Keywords** predictive, preventive and personalised medicine, integrative medicine, common/rare disease, diabetes/cancer/cardiovascular/neurodegenerative diseases, co-morbidities, well-being concept, research, education, healthcare, ethics, economy

*Correspondence: Olga.Golubnitschaja@ukb.uni-bonn.de
[1]Department of Radiology, Rheinische Friedrich-Wilhelms-University of Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn Germany

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# Changing Long-Held Beliefs is Never Easy: A Proposal for Multimodal Approaches in Female Healthcare - An Integrative View

Olga Golubnitschaja, Secretary-General of EPMA, and Vincenzo Costigliola, President of EPMA

**Worldwide cardiovascular disease (CVD) is the leading cause of mortality in women: cardiovascular health in females is not improving as fast as that of males**

Worldwide a third of all deaths of women and half of all deaths of women over 50 years old in developing countries are caused by CVD [1]. Several studies have been recently dedicated to the question of CVD-related death with particular focus on gender-dependent aspects. Although CVD is traditionally considered as the major health burden of male subpopulations surprising statistics have been collected for worsening the situation in females. New trends obviously demonstrate a shifting of the problem into healthcare of female populations: from 25 countries selected by World Health Organisation in the years 1990-2000, more than a half (15 countries, 60%) currently demonstrate either increase in CVD-related death in females or, even if the rates are decreased then less compared to men [2]:

1st group: increased CVD-related death in females

- Ukraine                    63%
- Kazakhstan                 58%
- Belarus                    48 %
- Russian Federation         33%
- Romania                    20%
- Japan                      13%
- Mexico                     2%

2nd group: CVD-related death is less decreased in females *versus* males

- Norway          17% less
- Germany         4% less
- Hungary         4% less
- Luxemburg       4% less
- USA             4% less
- Italy           2% less
- Portugal        2% less
- Armenia         1% less

*Conclusion:*

Taking into consideration that from altogether 25 selected countries only 10 countries demonstrate a decrease in

CVD-related death rates in women compared to men, the situation is rather worsening for female cardiovascular healthcare or – if improving then not as effectively as for males. These facts should be accepted as highly alarming for the acute reconsideration of current strategies in female cardiovascular healthcare.

**Although CVD is common, significant gender-related differences have been recognised only recently**

Evidence-based publications indicating significant gender-related differences in CVD diagnosis, manifestation and treatments as well as particular problems shifted to the female subpopulations appeared quite recently [3–5]. Delayed recognition of the mounting problems creates a consequent delay in covering multifaceted knowledge deficits accumulated in CVD-related female healthcare which societies around the world are currently facing. Consequently there is an urgent need to elaborate the targeted measures forcing the improvement. The logic steps might be proposed as follows:

1. identify single lacks and gaps that altogether have resulted in current unsatisfactory situation;
2. analyse rapidly worsening *versus* improving regional healthcare situations and identify the most specific particularities of both;
3. elaborate effective strategies for covering the recognised deficits at all levels of stakeholders that should be obligatory involved in the process of reorganisation including applicative science, social, economical and political levels;
4. consider to force the practical implementation of innovative approaches in predictive diagnostics and targeted prevention that are rapidly developing in pre-clinical trials;
5. create / readdress sufficient budgets for educational measures, training purposes and staffing the experts essentially involved in the field.

*Conclusion:*

For the concrete recommendations, several crucial aspects should be properly addressed by well funded

analytical studies. The most relevant aspects for their detailed analysis are summarised below.

## Women experience longer stays in hospital related to CVD and suffer greater complications and disability than men: negative social and economical impacts

Worldwide the leading cause of admission to hospital is CVD with consequent impacts for healthcare costs. Therefore, a precise analysis of demographic statistics is very important for the economy of CVD healthcare to cover potential deficits. Current reports [1, 6] indicate that women diagnosed with CVD suffer from

- higher levels of discomfort
- higher and longer pain attacks
- significantly more of the consequent activity restrictions
- longer disability
- longer hospital stays

In this context it is becomes clear, why women have been reported to consume more hospital resources than men [7]. Those statistics have been collected for CVD in general but, the particular significance is reported for diagnosed atrial fibrillation, heart failure and acute myocardial infarction [7–11]. Hence, the American National Hospital Discharge Survey reports stable rates of hospital admission for men *versus* permanently increasing ones for the age-matched women with diagnosed heart failure [10]: the female gender-specific increase comprises about 19% in North America since 1990. Further, high risk of stroke as the secondary complication is the gender particularity acknowledged in women diagnosed with atrial fibrillation, in contrast to non of the predisposition as observed in men [8].

### Conclusion:
Consequent negative impacts of the above listed risk factors should be considered as abusing the economy of healthcare and social systems, which the contributing female fellows in active age are involved in.

## "Atypical symptoms" or inadequate diagnostic approaches in females?

Just simply using a logic thinking, one can expect significant gender dependent differences in predisposition to, risk factors for and symptoms of cardiovascular disease, when anatomic, physiologic, biochemical and psychological characteristics of men and women are compared.

Deeper insights into cardiovascular-relevant gender particularities provide further strong argumentation for strictly different predisposition, manifestation and prognosis as well as targeted preventive measures and appropriate treatment modalities for both sexes. Briefly summarised female particularities are as follows:

- Sex hormones are decisive for the sort of CVD and period of life, as well as gender-specific disease manifestation;
- High prevalence of gender specific vascular dysregulation is also known as "vasospastic syndrome" (VS): in premenopausal women, the prevalence can be 30% and higher, whereby VS is more characteristic for intellectual professionals. Psychosocial gender particularities, such as emotional stress, starvation to reach an extremely slim stature, etc., are strong contributors to VS worsening inadequate vasoconstriction in females. Untreated VS may predispose to a spectrum of severe CVD-related complications manifested later in life [12]. Despite high prevalence and potentially tremendous impacts for women health/care, VS has not been systematically investigated through large-scale scientific projects;
- There is a gender specific menopausal stress of or even damage to cardiovascular system followed by post-menopausal predisposition to ageing-related CVD that is significantly higher in women compared to age-adjusted men: female hormone-related protective anti-ageing mechanisms are lost in menopause;
- Gender specific smaller vessel lumens is the strongly contributing risk factor for poorer outcomes under both ageing-related and -unrelated ischaemic conditions as well as under invasive treatments applied to cardiovascular system in women.

Consequently, the majority of studies, e.g. dedicated to acute coronary syndrome report "atypical symptoms" in women by diagnostic procedure standardised for male patients [13–18].

### Conclusion:
There is clear evidence for urgent necessity in gender-dependent diagnostic profiles. Those profiles can be created by systematic biomedical studies considering the role of all contributing factors.

## Current CVD diagnostics is elaborated for men but not for women

Despite the above listed argumentation, the symptomatology of CVD elaborates the manifestation models and patient questionnaires traditionally tailored to men as the main carriers of CVD. The absolute majority of large-scale studies dedicated to CVD symptoms include women as one tenth till maximum one quarter portion of the whole patient collective that makes any female-related particularity to non-significant variable [19]. Hence, potentially important prodromal or acute symptoms relevant for female-specific manifestation are not considered at all. Consequently, using currently practised templates, women are highly restricted in a choice defining their real CVD-related problems [13].

**Conclusion:**

This leads to inaccurate description of female-specific symptoms in general and individual ones in particular – the reason, why current preventive measures are untailored to women, CVD manifestation is rather unexpected and frequently remains undiagnosed at early stages in female patients.

### Women experience delayed care in the case of CVD emergency: Lack of knowledge or long-held beliefs to be changed?

The above given facts partially explain statistics registered worldwide [20–28] demonstrating that in the case of CVD emergency and compared to male CVD patients, women experience

- later hospitalisation after symptom onset of acute CVD
- longer period of time before the treatment initiation, if any provided
- less likely intensive care settings
- illegibility for usual therapies, due to co-morbid disorders more frequent in female CVD patients
- less likely or delayed application of reperfusion therapy.

The performed socio-demographic studies have concluded the risk factors for delayed CVD-related hospital admission as follows: female gender, older age, ethnic minorities, low income, low education level and living alone [29]. Thereby, the female gender risks carry either 1. psychological or 2. educational and/or 3. physiological character:

1. by the psychological barrier for troubling others
2. by lack of knowledge to recognise an acute emergency, e.g. in the case of heart attack
3. by physiologically higher pain threshold compared to men [30].

**Conclusion:**

These risk factors should be obligatory taken in consideration to improve individual outcomes.

### Women with acute myocardial infarction have higher rates of mortality than men of the same age: female-specific complications or untailored treatment approaches?

Theoretically, due to physiologically higher pain threshold compared to men, the rate of undiagnosed acute myocardial infarction and unrecognised silent infarcts is much higher in female patients [30, 31]. However, practically there are several factors contributing to higher rates of mortality of women with acute myocardial infarction. Among them are "atypical symptoms", inaccurate diagnostic approaches, untailored and delayed treatments, as summarised above. Data collected in several studies are consistent demonstrating early mortality (4-6 weeks) after acute myocardial infarction to be

approximately double as high in female as in male patients [32–41]. Moreover, women below 50 years of age are of particular high risk of death related to acute myocardial infarction [1]. Thereby, in-hospital mortality was significantly higher in women across all age groups [41]. This is clear evidence for untailored treatments currently applied to female patients with acute myocardial infarction, rather than older age frequently used as the main argument to excuse higher mortality in females.

**Conclusion:**

Well funded studies are essential to be carried out covering evident knowledge deficits in treatments tailored to gender-specific profiles of patients with acute myocardial infarction. There is an urgent need in creation of multi-drug cocktails considering greater burden of co-morbid diseases in women with acute myocardial infarction.

### Short-term mortality after coronary intervention is higher in women than in men: The next acute problem related to gender-untailored treatment approaches?

Vascular complications remain more prevalent in women undergoing coronary intervention, and female gender is an independent risk predictor of in-hospital mortality [42]. The balloon angioplasty era generally resulted in poor outcomes in women [1]. But also the improved stent-application approaches are related to the statistics unfortunate for female gender: higher procedural risk and decreased efficacy is still more typical for women. An operative mortality by artery bypass indicates 1.5-times higher risk for women compared to men [43]. Evidently gender-dependent physiological particularities play the central role: smaller vessels and lumens represent an additional technical problem for successful coronary intervention in women. Further, aggressive anticoagulation medications are more problematic for female patients suffering more from access-site haematomas and bleeding complications [44].

**Conclusion:**

Innovative technical and pharmaceutical approaches are urgently needed to better satisfy gender-dependent particularities under coronary intervention in women.

### Diabetes, CVD, cancer…What else?
### Although the coincidence is common in women, consistent data do not exist to recognise co-morbidities by patient profiling

Co-morbid diseases are frequent in women with CVD. Hence, CVD is the best acknowledged co-morbidity in diabetics. Moreover, it is well documented that female diabetics demonstrate poorer outcomes of CVD. Hence, the best recognised risk factor for high operation

mortality by and low efficacy of valvular replacement is the combination of female gender and diabetes [5]. Further, cardiovascular diseased women, in particular female diabetics, have poorer prognosis of oncologic diseases [45].

The most frequent oncologic co-morbidities in female diabetics are

- endomentrium carcinoma (4.8-times higher prevalence in type 1 diabetes and 2.2-times higher in diabetes generally)
- ovarian carcinoma (2.42-times higher risk in female diabetics *versus* general female subpopulation)
- liver cancer (2.0-times higher risk)
- lymphoma (1.9-times higher risk)
- uterus carcinoma (1.7-times higher risk)
- rectum cancer (1.7-times higher risk)
- stomach cancer (1.6-times higher risk)
- leukaemia (1.4-times higher risk)
- kidney cancer (1.4-times higher risk)
- pancreatic cancer (1.3-times higher risk)
- breast cancer (1.2-times higher risk)
- lung cancer (1.1-times higher risk)

as documented in the literature [46]. Nevertheless, there is a significant knowledge gap concerning "typical" *versus* "atypical" co-morbidity profiles in females.

Women develop CVD at higher age than men, and the consensus built in literature that the factor of age is the main reason for particularly frequent manifestation of accompanying disorders and severe complications observed in the cohort of cardiovascular diseased women compared to the male patient cohort. However, due to typical for 21st century demographic trends in favour of elderly populations, co-morbidities and more complex clinical situations now should be considered as less unique cases but rather as the persistent challenge in healthcare that required new strategies for improved treatment regiments.

Common risk factors moderating the outcomes in the most frequent female pathologies, namely DM type 2, CVD and breast cancer are progressing age, overweight, poor diet, physical inactivity and depression [47–49]. Moreover, modifiable risk factors persist from childhood and adolescence into adulthood and tend to cluster with synergistic negative effects for consequent manifestation of co-morbid pathologies [47, 50–58].

### Conclusion:

Co-morbidities and complex clinical situations in elderly populations should be considered as the persistent challenge that requires new strategies in healthcare. Integrative medical approaches are strongly desirable to analyse common risk factors as well as their individual and synergistic effects. Frequent *versus* rare co-morbidity profiles in cardiovascular diseased patient cohorts should be created for advanced treatment regiments.

### Breast cancer and CVD

In contrast to well acknowledged CVD / Diabetes link, CVD and breast cancer co-morbidity is poorly understood. This is an extremely unlucky situation, since compared to all other pathologies both co-morbidities demonstrate the highest frequency of incidence in females. The probability to identify a female postmenopausal patient above 55 years old diagnosed with sporadic invasive breast cancer but completely CVD-free is rather low. However, the coincidence of CVD and breast cancer in one individual, co-prevention, co-diagnosis and co-treatments are not considered at all.

What are current problems and knowledge gaps in prevention, diagnosis and treatments of breast cancer with co-morbidities?

- Worldwide 8-12 women from 100 are diseasing on breast cancer. Around 50% of DCIS (*ductal carcinoma in situ*) will progress to invasive and metastasis disease if untreated, with 20% of recurring ones despite "appropriate" treatments [49].
- Causative factors such as co-morbidities and epigenetic ones underlying recurrence of DCIS or progression to invasive disease are currently not known.
- Currently we need to treat 50 high-risk women to prevent one breast cancer: the role of negative prediction is underestimated [49].
- 95-98% are sporadic breast cancer cases *versus* 2-5% familial ones: the majority of sporadic breast cancer cases are peri- and post-menopausal women who are at significantly higher risk of CVD.
- Co-morbidities in breast cancer are considered rather from view point of psychological aspects and palliative care but not as the realistic model to navigate biomedical research, effective diagnostic approaches and treatment multimodalities.
- Consistent data do not exist to recognise breast cancer co-morbidities by patient profiling.
- Cost-effective healthcare promotion in breast cancer and its common or even persistent co-morbidities such as CVD and diabetes is not provided.
- Critical gaps between current research performance and clinically applicable results are dramatic.

### Conclusions and recommendations:

If any, there is a very limited research activity around the world dedicated to integrative preventive and/or diagnostic and/or treatment approaches of both co-morbidities. The above listed challenges and knowledge gaps request a systematic reconsideration of current strategies in research and healthcare of the co-morbidities: the experts should be better motivated for really innovative integrative approaches. The most effective approach is the targeted prevention by screening for individuals at high risk followed by tailored treatments of pre-stages.

Prevention by modifiable risk factors should be prioritised and forced.

### Do medication strategies aim at curing the patient or treating single organs?

Since 18th century, cardiac glycosides are used to treat congestive heart failure and attrial fibrillation [59]. The natural steroid toxin Digitalis-derived cardenolides – *Digitoxin* and *Digoxin* – are the most prevalent medicaments currently used in clinical practice. The medication forces the contractility in cardiac myocytes through inhibition of the Na+/K+-ATPase that indirectly increases Ca+ concentrations. During last decade, conflicting results have been published about potentially negative side-effects of the medication. However, recent studies have clearly documented a higher rate of invasive breast cancer among ever-users of *Digoxin* compared to never-users [60]. The side-effect is particularly evident for postmenopausal *Digitoxin* users [61]. Moreover, a positive association between *Digoxin* usage and incident male breast cancer has been demonstrated [62].

Another example: *Metformin* seems to be effective against a pancreatic dysfunction in pre-diabetes and early diabetes stages. However, the application of *Metformin*-controlled blockade of apoptosis in young and middle-aged patients with diagnosed pre-diabetic stages should become well investigated in terms of long-term side-effects such as potential cancer development (pancreas and other organs?) later in life. Current regulations request 3-year long follow-up studies that are apparently of insufficient duration for reliable statements.

### Conclusions and recommendations:

Currently the cases in medical practice are not unique anymore, when a patient is taking around 20 and more tablets prescribed for parallel treatments of single disorders, which are frequently considered as independent from each other. How much they are independent and how much overlapping within the treatment-frames? How much are single medications synergic with and contra-productive to each other? How much is multimodal medication depending on the profile of co-morbidities and on individual patient profile? All the questions should be obligatory addressed by long-term follow-up studies in accordance to reconsidered guidelines in order to avoid treatments of single organs and pathologies instead of desirable synergic multimodal approaches.

### Demographic and female gender-related challenges: Recommendations for synergic multimodal approaches

#### Challenges

- CVD is strongly attributable to modifiable risk factors such as life-style, predominantly sedentary behaviour, and nutrition. Unfavourable demographic and epidemiologic trends in childhood and adolescence may lead to high CVD-predisposition (overweight, obesity, diabetes type 2) in societies followed by unprecedented burden on healthcare systems.
- Gender-related social and economical challenge: related to CVD, women experience longer stays in hospital, suffer greater complications and disability consuming more material and financial resources than men with same diagnosis.
- Although CVD is the leading cause of mortality in women worldwide, cardiovascular health in females is not improving as fast as that of males.
- Significant gender-related differences in presentation and treatment success of CVD have been recognised only recently; the consequent knowledge gap should be urgently covered in diagnostic, operation and medication technologies.
- Current CVD diagnostics is untailored for female gender.
- Women experience delayed care in the case of CVD emergency.
- Women have higher in-hospital and short-term rates of mortality than men with acute myocardial infarction, and after coronary intervention.
- Atrial fibrillation related mortality and stroke risk are higher in women than in men.
- Heart failure associated mortality declines in men much more significantly that in women.
- Co-morbid diseases are frequent in women with CVD: Female diabetics demonstrate poorer outcomes of CVD as well as cardiovascular diseased women have poorer prognosis of oncologic diseases.
- Clustering of risk factors: overweight and obesity causes the leading severe diseases in women, namely diabetes type 2, CVD and breast cancer.

#### Desirable approaches

- Creation of gender-specific profiles for CVD-diagnostics and treatments by well-funded large-scale studies with parity of both sexes including "omics"-based blood analysis, molecular imaging and elaboration of gender-specific questionnaires for accurate description of prodromal and acute symptoms of CVD.
- Consideration of CVD-specific sex-determinants such as mutated maternal mitochondrial DNA that emerges complications and fatal outcomes of CVD.
- Performance of large-scale population studies to identify most frequent profiles of co-morbid pathologies for effective treatments suitable for corresponding combination of co-morbidities such as depression/diabetes/CVD/breast cancer in female patients.
- Creation of strictly individual treatment priorities and regiments request personalised medical approaches

of high plasticity and new generation of multi-cocktail drug compositions.

• New drug delivery systems that allow for targeted treatments.

• Reasonable convergence between diagnostic and pharmaceutical industry in development of predictive/ prognostic approaches based on new multifunctional targets for diagnostic and treatment purposes.

• Besides general prevention in populations, there is an urgent need for targeted prevention in childhood, adolescence and adulthood as the most cost-effective approach that requests complete reconsideration of current diagnostic and treatment programmes offered in healthcare systems: major CVD risk factors overweight, obesity and diabetes type 2 are the most frequent nutritional disorders in industrialised countries.

• Creation of new programmes in healthcare systems for effective promotion of and financial motivation for healthy life-style.

## Recommendations for innovative strategies to promote PPPM-related approaches in combating co-morbidities [64]

Long-held beliefs are firmly embedded in formal guidelines but also in public service performance and culture. However, important is that guideline committees follow the scientific evidence supporting the process of moving away from a target-based treatment towards approaches tailored to the individual patient-profile [63].

Following approaches should be considered by healthcare-responsible organisations, research units and funding bodies to cover current knowledge deficits in the field and to introduce integrative approaches for effective prediction, prevention and tailored treatments:

1. creation of predictive molecular profiles of the disease, co-morbidities and pre-stages;
2. understanding of disease initiation: molecular, subcellular, cellular, intercellular, and single-organ levels as well as the organism as the whole;
3. disease progression should be considered as an interplay between promoters, contributors and inhibitors resulting in individual outcomes (similar to a geometric system of vectors by summarising directions and contributing power);
4. tailored treatment algorithms: specific targets, targeted pathways, multi-drug cocktails, frequent *versus* rare complications and co-morbidities, multimodal approaches;
5. effective primary and secondary prevention of co-morbidities but not this of single diseases separately from each other;
7. new strategies in overall psychological supervision of individuals at high risk and patients at different disease stages;

8. new European and inter/national guidelines for population screening that would make good use of gathered knowledge to advance cost-effective healthcare and improve individual outcomes;
9. promotion of integrative (bio)medicine to force practice-oriented research and cost-effective healthcare;
10. creation of a critical mass of experts stuffing for integrative (bio)medical disciplines;
11. education at two levels, namely in professional groups and in general population;
12. elaboration of new guidelines regulating the process of the paradigm change from a treatment of targets to a treatment tailored to the person with all her(his) individual particularities taken into consideration.

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# Summary Report - Special Session "Healthcare in Overview Across the Globe"

The "Healthcare in Overview across the globe" session started the 2nd day of the Congress in the impressive Bundeshaus - former Parliament of Federal Republic of Germany. The session included overview presentations from the respective EPMA national representatives regarding the healthcare systems in Germany (Prof Dr F Paul), United Kingdom (Dr K Grosios), Japan (Prof Dr H Iso), Slovak Republic (Dr M Kapalla), Macedonia (Prof Dr K Richter), and Turkey (Dr M Dündar).

The members of the discussion panel included: Dr A Benini (Missionary of the Organisation of United Nations), Dr P Kulpa (General Director of Chief Sanitary Inspectorate, responsible for public health in Poland), Dr T Georgieva (Health Commission of the Bulgarian Parliament), Dr M Marzan (Medical Director of "Ana ASLAN" International Foundation, Bucharest, Romania) and Prof Dr S Suchkov (on behalf of the Government of Russia).

The audience included professionals involved in healthcare across Europe from public, private or third sector and at any level, whether clinicians, healthcare allied professionals, healthcare managers, academics, researchers, politicians, patients and public. This was one of the few times where many of the Congress participants were able to hear and appreciate the principles and organisation under which healthcare is founded and operates in different European countries and how each healthcare system perceives and delivers PPPM. It is unlikely that such a session has been held before anywhere in Europe or worldwide.

### Key recommendations:
- No European body, other than EPMA, is promoting the joint philosophy and integrative approach encompassing all three Predictive, Preventive and Personalised elements of medicine, in order to support a paradigm shift from late-stage intervention healthcare to Predictive Preventive and Personalised Medicine (PPPM) –driven healthcare;
- Individually, the three PPPM elements are increasingly becoming a recognised concept and are gradually integrated into healthcare systems across Europe in various forms. Some, such as various primary and secondary prevention programmes and health promotion campaigns, have existed for many years and others, such as efforts to develop predictive tools and deliver personalised care, are now being established;
- PPPM has the potential to help us deal with many of the concerns facing healthcare systems in relation to disease and economic burden; whether in high, middle or low income countries;
- Careful consideration of many related issues (scientific, regulatory, ethical, etc) and, primarily, education (involvement from clinicians, governments, regulatory bodies, patients and public) are paramount;
- Development of quality standards and approaches is critical;
- In the same way that multidisciplinary and multi-sectoral involvement is essential to developing PPPM interventions, multinational cooperation would, additionally, provide maximum benefit.

### Specific points, which could be considered as EPMA working group activities:
- PPPM in developing (middle-to-low income) countries;
- PPPM Health Economics Statistics for PPPM research, IP issues for PPPM research (particularly early stage/academic research EPMA database on biomarkers);
- Database of EU-funded or other EU and Worldwide-large PPPM-related projects and initiatives;
- The role of rare diseases in PPPM;
- PPPM in Health (i.e. apparently healthy individuals).

# Summary Report - Special Session
# "PPPM in Diabetes Mellitus"

The First International EPMA World Congress was held on September 15th- 18th, 2011 in Bonn, Germany. Participants from 43 countries were present to discuss ideas and strategies for advancing the concept of Predictive, Preventive and Personalised Medicine (PPPM). Given the growing epidemic of Diabetes mellitus, PPPM in Diabetes mellitus was a focal point of discussion during the General Session which was followed by a session dedicated to emerging concepts and developments in the field.

The General Session emphasised the importance of Education in relation to PPPM in Diabetes Mellitus given the prevalence of worldwide diabetes which affects over 300 million individuals or 6-7% of the world population. The predicted upward trajectory in the incidence and prevalence of this disease likely reflects the inadequacies of existing diabetes education and prevention programmes, worldwide. Clearly, the growing burden of type 2 diabetes mellitus relates to the epidemic of overweight and obesity and thereby dietary habits and life style choices. Indeed, type 2 diabetes is now afflicting even children while in the not-too-distant-past, it was considered to be manifested in individuals in their 4th decade of life. Given the fact that dietary habits and life style choices cannot be "regulated" by any governmental agency, it then follows that "behavioural modifications" and promotion of adopting healthier dietary habits and life style choices must be initiated very early in life (e.g., kindergarten). Thus, the General Session emphasised the concept that the global burden of diabetes mellitus necessitates multifaceted initiatives on a global scale and identification and promotion of effective means of translating emerging scientific information into effective public health policy.

The session dedicated to PPPM in Diabetes Mellitus was composed of a series of oral presentations by experts in their respective fields.

## Highlights of Oral Presentations:

It is firmly established that endothelial cell dysfunction/injury is a major culprit for the development of both the macrovascular (e.g., atherosclerosis) and microvascular (e.g., retinopathy and nephropathy) complications of diabetes mellitus; indeed, endothelial dysfunction is even a feature of the prelude stage of type 2 diabetes mellitus (i.e., impaired glucose tolerance). Accordingly, an overview has been presented of the impact of diabetes mellitus on endothelial function followed by a more detailed discussion of circulating markers (e.g., endothelial microparticles) emanating from damaged endothelial cells as potential markers for predicting endothelial dysfunction early in the disease process and long before the manifestation of target organ complications of diabetes mellitus. Emerging data has been shown regarding the impact of progression of type 2 diabetes mellitus on circulating levels of endothelial progenitor cells (EPCs); these cells are mobilised in from the bone marrow in response to injury and are believed to participate in repair and regeneration of the damaged endothelium. The reduced number of EPCs could likely serve as an early diagnostic indicator of endothelial cell injury. It is known that progressive obliteration of retinal microvessels is a characteristic feature of diabetic retinopathy and the consequent ischaemia and sight-threatening macular oedema and ultimately leading to preretinal neovascularisation. As alluded to earlier, EPCs participate in repair and regeneration of damaged endothelium. Nonetheless, since diabetes mellitus reduces the number of EPCs and impairs their function, the idea of introduction of non-diabetic EPCs into diabetic patients is advanced as an effective means of promoting wound healing and could guide their future use for treatment of extensive retinal or macular ischaemia in diabetic patients. The idea of ex vivo expansion and functional optimisation of EPCs (i.e., to correct diabetes-related deficits) for effective cell therapy of vasodegenerative disease of the retina was discussed along with potential adverse consequences of cell-based therapy (e.g., pathological neovascularisation).

The clinical management of diabetic retinopathy has been stressed as a particular challenge in diabetes care, due to frequent visual loss by diabetic maculopathy and proliferative diabetic retinopathy (PDR) and sufficient limitations of currently applied technologies regarding effective treatment of secondary complications.

With a view to the secondary complications, inflammatory indicators as potential predictive indicators of diabetic nephropathy have been overviewed. The emerging role of inflammation in manifestation of this complication of diabetes mellitus has been demonstrated. The more established inflammatory markers include monocyte chemoattractant protein-1, CD68 and cyclooxygenase-2. An imbalance between increased pro-inflammatory but reduced anti-inflammatory cytokines has been proposed as the next class of prognostic biomarkers. Collectively, the presented data offer the promise of a novel markers generation for early identification of diabetic nephropathy by assessment of their temporal relations in the renal tissue, plasma and/or urine.

Particular interest is dedicated to the determination of factors contributing to increased predisposition to cancer in diabetic patients such as a) stress-related factors (e.g., metabolic disturbances, hormonal dysregulation) which can lead to exacerbated oxidative/ nitrosative stress, b) mitochondrial dysfunction leading to disturbances of bioenergetics, impaired repair capacity leading to chromosomal and mitochondrial DNA damage and c) increased risk for infectious diseases and consequent induction of proto-oncogenic activity as well as activity of particular pathogenic bacteria. The stress proteome profiling using peripheral leukocytes and plasma proteins has been proposed as the approach offering the potential for clinical application given availability of advanced predictive diagnostics of secondary complications in diabetes types 2.

A potential application of polymorphic gene markers for monitoring disease progression in metabolic syndrome is currently under consideration such as several polymorphisms of apo-genes including APOA1, G-57A, APOA1 C83T, APOC3 Sst1, etc.

Dental aspects are considered to be of particular importance in the development of diabetes and its secondary complications. Hence, there is a number of characteristics of inflammation common to both diabetes mellitus and periodontitis. Periodontitis is a disease characterised by chronic inflammation of the periodontium (i.e., tissues supporting the dentition) which causes progressive loss of soft tissue attachment and bone support for the teeth, eventually causing loss of teeth. A healthy periodontium is of significance and importance for the general health, nutrition and articulation, among others. Importantly, periodontitis is increasingly recognised as one of the most frequent complications of diabetes mellitus. Indeed, epidemiological data indicate a three to four fold increased risk for progressive periodontal destruction in diabetic patients compared to those without diabetes mellitus. Given the chronic inflammatory basis of periodontitis, inflammatory cytokines/chemokines play a crucial role in the pathogenesis of both diabetes mellitus and periodontitis as its secondary complication. From the technological point of view, the potential use of gingival crevicular fluid (CGF; fluid from the inflamed gingival tissues surrounding the teeth) is proposed for assessment of inflammatory mediators. Consequently, some cytokines expressed in the GCF (e.g., IL-1β, IL-6, etc.) may be non-invasively detected as elevated to predict periodontitis in diabetic patients.

Advanced technologies have been presented in the field of drug delivery systems (DDS) and their potential application in personalised medicine: the pivotal role of polymers in DDS; these included natural polymers (e.g., proteins, collagens, etc.), artificial polymers (e.g., cellulose derivatives) and synthetic polymers (e.g., biodegradable (e.g., polyesters) and non-biodegradable (e.g., acrylic polymers)). The appearance of novel, more effective and custom-made DDS for personalised medical solutions including those related to diabetes mellitus is expected as technologically available soon.

## The specialised section has elaborated following recommendations:

The formidable challenge to public health posed by the global burden of diabetes mellitus is well-recognised. Less clear is effective measures that would halt this growing epidemic. The participants in the "PPPM in Diabetes Mellitus" session generally agreed that a number of measures focused on prevention and early identification methods deserve due consideration as described below:

1. The fact that the prevalence and incidence of type 2 diabetes mellitus continues to show an upward trajectory suggests that current measures are either not sufficiently effective and/or implemented/ followed. The reasons for failure of nations (developed or otherwise) across the globe to halt the burden of type 2 diabetes must be carefully explored and effective solutions identified.

2. The pivotal role of obesity in fuelling the increasing prevalence and incidence of diabetes is well-acknowledged. Thus, public health policy should seriously address the pervasive problem of advertising of high calorie, but low nutritional value, food items to children. In addition, the agricultural industry should be provided with incentives (e.g., tax and subsidies) to produce and market affordable nutrient-rich foods that are less calorie-dense than processed foods. These measures should be coupled with effective educational programmes (e.g., via the use of mass media) to inform the general public about the importance of healthy dietary habits as well as appropriate governmental policy (e.g., in relation to sales tax, food stamp, etc.) that would promote consumption of food items of high nutritional value. Since type 2 diabetes mellitus is now afflicting even children, effective and suitable educational measures/ programs must be implemented _very early_ in life and continued throughout life. Thus, life style choices, such as dietary habits and physical activity, must remain a major focus of prevention strategies.

3. A wealth of knowledge does indicate that macro- and microvascular abnormalities contribute importantly to the pathogenesis of diabetic complications and associated morbidity and mortality. Importantly, despite major strides in our ability to address major risk factors (e.g., dysregulation of glucose and lipid metabolism as well as blood pressure), the incidence of diabetic complications (e.g., nephropathy,

retinopathy) remains high. As a result, the costs associated with taking care of these individuals coupled with loss of work productivity will continue to present major challenges for all nations and this problem is particularly grave for less affluent societies. Such considerations further emphasise the need for identification of effective preventive strategies.

4. A central component of preventive strategies is identification of individuals at risk for development of diabetes mellitus. The use of demographic and life style factors has been helpful but the observational nature of these parameters limits their usefulness.

Further, aside from considerations related to associated costs, assessment of indices of glycaemic control (e.g., glucose tolerance testing) are not necessarily efficient in identifying individuals at high risk for development of the disease. Importantly, however, the era of genomics, proteomics and metabolomics offers the promise of eventually identifying novel, efficient and cost-effective biomarkers for identifying individuals at risk of developing the disease and/or its complications; as described earlier, these aspects were the central focus of presentations in the session dedicated to "PPPM in Diabetes Mellitus".

# Summary Report - Special Session "PPPM in Cardiovascular Diseases"

It is imperative that patients, physicians, and researchers look into the potential benefits that predictive, preventive, and personalised medicine may offer patients with cardiovascular diseases. Any added benefit to this patient group will have immediate consequences for hundreds of millions of patients and relatives due to the high proportion of people suffering from the diseases [1, 2]. More than 17 million die each year from these diseases, including 7.6 million deaths from coronary heart disease and 5.7 million from cerebral stroke [1]. There is also a substantial room for prevention of cardiovascular diseases through predictive, preventive, and personalised approaches.

The session "PPPM in Cardiovascular Diseases" has addressed the following questions pertaining to patients with cardiovascular diseases:

- Based on the Hippocratic request of 'first do no harm', how can we understand the inferential powers of the traditional evidence-based medicine hierarchy and avoid any unintended consequences of the 'genomics revolution'?
- What is the role of patient education of PPPM in cardiovascular diseases and how can we inspire hope without creating unintended hype and risks of commercialisation of products that offer more harms than benefits?
- What is the role of professional education of PPPM in cardiovascular diseases and how can we inspire hope without creating unintended hype and risks of commercialisation of products that offer more harms than benefits?
- What is a realistic timeline for the incorporation of PPPM into clinical practice? When can industry and academia realistically deliver new PPPM interventions compared to the expectations of patients (that is today)?
- What are the implications of PPPM for prevention of cardiovascular diseases?
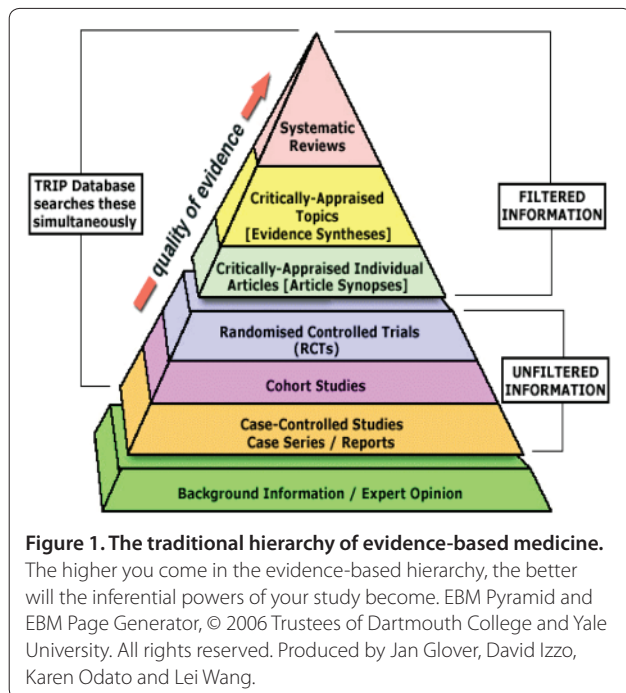
### How can we understand the inferential powers of the traditional evidence-based medicine hierarchy and avoid any unintended consequences of the 'genomics revolution'?

The traditional evidence-based hierarchy refers to the fact that different experimental designs have different inferential powers. In other words, what are we able to infer based on the results of a specific experimental design? The evidence hierarchy for establishing firm evidence for any intervention looks like the pyramid in

Figure 1. The higher you come in the layers of the pyramid, the higher is the quality of research you can get, and the better are your inferential powers based on the research. Accordingly, the more easy and valid will it become to translate the research findings into practice. It is very much like playing cards. If you have research findings from a properly conducted systematic review of several randomised clinical trials, then this trumps the results of a single randomised clinical trial. If you have research findings from a properly conducted randomised clinical trial then this trumps the results of a cohort study. It was The Cochrane Collaboration which coined the word 'systematic review' back in 1993, and there is now a handbook for systematic reviews on interventions [3, 4] and one on diagnostic tests [5, 6].

Judgments on the quality of evidence and recommendations of an intervention in healthcare are complex. Therefore, the evidence hierarchy is the best framework for evaluating the effects of interventions. Sometimes, however, you need to downgrade or upgrade the inferential powers of a piece of research. If a systematic review of several small trials with high risk of random errors ('play of chance') and high risk systematic errors ('bias') is not well conducted, then the inferential powers of the systematic review needs to be downgraded. If a cohort study is well-conducted and shows an extraordinary large intervention effect (say, penicillin for pneumonia, insulin for diabetic coma, drainage of an abscess), then the evidence has to be upgraded. There is no need for a randomised trial when it comes to interventions with a parachute-like intervention effect. However, such interventions are extremely rare in clinical practice. Furthermore, the research process is conducted as a forward running process (i.e., one has to construct the proper research design before one knows the beneficial and harmful effects of an intervention). The research process should not be seen in retrospect where one assesses the intervention effects based on insufficient study designs.

A systematic and explicit approach for making judgments can help in preventing wrong recommendations and may improve medical communication. During the 2000s the GRADE Working Group was developed [7,8]. GRADE stands for Grading of Recommendations Assessment, Development and Evaluation. Recommendations to administer or not administer an intervention, should be based on the trade-offs between benefits on one hand, and risks, burden, and potentially, costs on the other. If benefits outweigh risks and burden, experts will

**Figure 1. The traditional hierarchy of evidence-based medicine.**
The higher you come in the evidence-based hierarchy, the better
will the inferential powers of your study become. EBM Pyramid and
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Karen Odato and Lei Wang.

recommend that clinicians offer a treatment to patients
with the disease in question. After going through the
process of grading evidence, the overall quality will be
categorised as high, moderate, low, or very low. The
uncertainty associated with the trade-off among benefits,
risks, and burdens will determine the strength of
recommendations. GRADE has only two levels of recom-
mendations; strong or weak, which is based on the avail-
able evidence:

- If clinicians are very certain that benefits do or do not
  outweigh risks and burdens, they will make a strong
  recommendation.
- If clinicians believe that benefits, risks, and burdens
  are finely balanced, or if appreciable uncertainty
  exists about the magnitude of benefits and risks, they
  should offer a weak recommendation. In addition,
  clinicians are becoming increasingly aware of the
  importance of patient values and preferences in
  clinical decision making. When, across the range of
  patient values, fully informed patients are liable to
  make different choices, guideline panels should offer
  weak recommendations.

When developing new interventions, investigators and
industry are wise in conducting their research in different
phases in which scientific evaluation of the benefits and
harms is adjusted to the level of knowledge obtained. The
different research designs used in the different phases
will depend on the intervention one wants to examine
(Table 1).

When it comes to preventive and therapeutic inter-
ventions, randomised clinical trials are at the top of the

evidence hierarchy. The main weakness of most
randomised trials is that they usually only tell us what the
outcome of groups of participants randomised to one
intervention or the other is, giving us a summary of an
effect on groups of participants, but do not give us infor-
mation on how the individual responds. Personalised
therapies offer what we all request: an in depth, person-
alised assessment of our heath status and a personally
tailored approach to improve or remove any medical
problems. If personalised medicine offers 'parachute-like'
intervention effects, then randomised trials may not be
needed (but as we do not know the parachute like effects
before we have the trial results, the randomised clinical
trial is still the correct starting point). Moreover, most
personalised therapies are likely to offer limited benefit to
a restricted group of patients. Such effects are hard to
detect. Therefore, personalised medicine must - like
other interventions - undergo randomised clinical trials
before they can be implemented. We need to demonstrate
that the 'personalised approach' is offering more benefits
than harms compared with the 'group-based approach'.
Therefore, when personalised therapeutic interventions
show promise in phase II randomised clinical trials then
they should undergo proper assessments in large phase
III randomised trials compared with the more simple
group-based approach. Only in this way we can assure
that the personalised approach is offering the benefits it
promises.

The *omics development will be able to chop up even
large disease areas like cardiovascular diseases in a
number of smaller disease entities. Hereby, such smaller
disease entities will, with further refinement, end up as
rare diseases, i.e., less than 1 out of 2000 people will have
the specific disease. To conduct large phase III random-
ised clinical trials in such rare diseases is complex and
costly. Therefore, the European Union has established the
European Clinical Research Infrastructures Network [9,
10]. ECRIN is a pan-European infrastructure consisting
of national clinical research infrastructures designed to
support multinational clinical research. By making
Europe a single area for clinical trials and taking
advantage of its population size to access patients, latent
scientific potential is unlocked. ECRIN consists of 21
countries covering more than 90% of the EU population.
More countries are expected to join within the following
years. ECRIN has been supported by EU FP 6 and FP 7
during 2004 to 2011 (with a total of about EURO 6.8
million). With the support of France, Spain, Italy, and
Germany, ECRIN is expected to obtain European
Research Infrastructure Consortium (ERIC) status in
2012.

ECRIN is working for harmonisation of regulatory
issues and transparency in clinical research as well as for
easier conduct of trials in prevalent and rare diseases.

**Table 1. Phases in prognostic, diagnostic, preventive and/or therapeutic research**

| Phases | Prognostic factor | Diagnostic intervention | Preventive or therapeutic intervention |
|---|---|---|---|
| Phase I | Healthy participants | Healthy participants | Healthy participants |
| | - longitudinal observational studies of the natural history or clinical course of healthy individuals; definition of the outcome(s) of interest; generation of hypotheses on the association between certain characteristics and the outcome(s) of interest. | - cross sectional observational studies (small cohort studies) to determine the normal range of the test in question. | - observational studies<br>- randomised clinical trials<br>designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of an intervention. |
| Phase II | Patients with disease in question | Patients with disease in question | Patients with disease in question |
| | - longitudinal observational studies on clinical course of patients with specific disease; definition of the outcome(s) of interest; generation of hypotheses on the association between certain clinical or patient characteristics and the outcome(s) of interest. Testing and measuring associations; verifying independency of associations; generating prognostic indexes; checking validity. | - cross sectional observational studies (larger case-control or cohort) testing patients and healthy controls to determine the specificity and sensitivity of the test in question compared with a 'gold standard'. | - randomised clinical trials<br><br>Phase II trials are performed on larger groups (200 to 300) and are designed to continue safety assessments and to assess how well the drug works. |
| | - randomised clinical trials on the impact of applying the prognostic score in clinical practice. This phase may also include cluster randomised trials or before-after studies. | - randomised clinical trials on the impact of applying the diagnostic test in clinical practice. This phase may also include cluster randomised trials or before-after studies. | |
| Phase III | Patients with disease in question | Patients with disease in question | Patients with disease in question |
| | - randomised clinical trials on the impact of applying the prognostic score in clinical practice. | - randomised clinical trials on the impact of applying the diagnostic test in clinical practice in comparison with current 'gold standard' diagnostic test. | - randomised clinical trials<br>often multicentre trials on large patient groups (300–10,000 or more depending upon the disease studied) aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. |
| Phase IV | Patients with disease in question | Patients with disease in question | Patients with disease in question |
| | - observational studies<br>- randomised clinical trials | - observational studies<br>- randomised clinical trials | - observational studies<br>- randomised clinical trials |
| | These study the impact of applying the prognostic score in clinical practice. This includes large observational studies (clinical databases), randomised clinical trials, or cluster randomised trials. | These study the impact of applying the diagnostic test in clinical practice. This includes large observational studies (clinical databases), randomised clinical trials, or cluster randomised trials. | These study the impact of applying the new intervention in clinical practice. This includes large observational studies (clinical databases), randomised clinical trials, or cluster randomised trials. |

ECRIN started the servicing of multinational trials in 2010, and more than six trials are presently being conducted with the support of the ECRIN infrastructure. ECRIN plans to expand the network and strengthen the national partners; create a common European culture among professionals and patients communities; support cross-border connection of investigation networks; develop data management and monitoring tools for multinational trials; and make funding available for multinational clinical trials. The expansion includes other world regions, forming the basis for global trials. Such organisation will improve Europe's attractiveness for investigator- and industry-initiated trials, boost Europe's scientific competitiveness, and result in better healthcare.

Within cardiovascular diseases, stem cell therapy for regenerative medicine is one of the interventions that need further assessments [11]. To establish personalised autologous or allogeneic stem cell treatment algorithms, one has to consider whether one stem cell line is better than another to initiate development of new blood vessels or cardiomyocytes; whether there are differences in the individual persons inherent ability to respond to the intervention; whether clinical phenotype/co-morbidity has an influence on the efficacy of the stem cells; etc. Such questions demand a concerted and collaborative action.

There is a worldwide decrease in initiation of clinical trials with new treatment regimens within the pharmaceutical industry due to the increased costs to develop and test new interventions, and the more and more demanding regulatory requirements. This can very soon be a great problem for many diseases without

effective treatment regimen. Moreover, some new treatments with the patient's own stem cells are without any interest for the biotech industry, since these cannot be commercialised. Therefore, there is a need for a review of whether regulatory demands have become too bureaucratic to develop new general and personalised treatments. In addition, the national and European Union foundations have to support financially and logistically national and international academic investigator-initiated clinical trials within areas, which are without any commercial interest, but potentially can have a great impact for the individual patient and groups of patients.

### What is the role of patient education of PPPM in cardiovascular diseases and how can we inspire hope without creating unintended hype and risks of commercialisation of products that offer more harms than benefits?

Patients are an invaluable partner in the planning and conduct of medical research. Therefore, initiatives like The James Lind Alliance (http://www.lindalliance.org/) and The COMET (Core Outcome Measures in Effectiveness Trials) Initiative (http://www.comet-initiative.org/) having the aim to involve patients in clinical research design and definition of relevant outcome measures should be strongly encouraged [12–14]. It is through discussion with patients and their representatives that researchers can learn about which interventions patients would like and which outcome measures would matter to them.

There should be ongoing information to the public about the status of personalised medicine, e.g., stem cell therapy in cardiovascular diseases and whether some preventive initiatives can improve the outcome of the therapy.

Patient organisations should follow the development within the areas and establish ongoing information to the patients about the status of, e.g., stem cell therapy in cardiovascular diseases and whether some preventive initiatives can improve the outcome of the therapy.

Furthermore, it is through liaison with patients and their organisations and representatives that researchers may impact political systems, so that more investment can be obtained for conducting clinical research. It is only through the conduct of randomised clinical trials and systematic reviews of such trials that we can learn how to optimise preventive, diagnostic, and therapeutic interventions.

However, discussion with patients and their representatives need to be taken on equal terms. This necessitates education in the complex pathophysiology of cardiovascular diseases as well as the complexities of evidence-based medicine. People need to know why randomised trials are conducted and why patient series and cohort studies cannot provide reliable and valid

information about the effects of interventions. They also need to know that there is no 'quick fix'. Research takes time, it needs to be properly conducted [15, 16], and this necessitates investment of time, money, and patience. In addition, this contact forum can also be of importance to the patients understanding the validity of the many treatment regimens for different diseases, which are presented by clinicians in different media.

ECRIN has since 2005 celebrated the International Clinical Trials Day each year around the 20th of May [17]. This day is celebrated to commemorate the day of 20th of May 1747 when James Lind started his famous trial [18], and to make the public aware of clinical trials. Such events can raise interest and should be followed by a dedicated educational activity on evidence-based medicine, which should be directed by both schools and adult-learning institutions.

The way forward is to create hope by demonstrating to patients and to citizens that opportunities for identifying new preventive, diagnostic, prognostic, and therapeutic interventions are vast. The fact that we now understand the evidence-based hierarchy much better enables us to only implement interventions that offer more benefit than harm [19]. By teaching the public how interventions are assessed in randomised clinical trials and systematic reviews of such trials, we may prevent unnecessary hype is created and harmful interventions to enter clinical practice.

### What is the role of professional education of PPPM in cardiovascular diseases and how can we inspire hope without creating unintended hype and risks of commercialisation of products that offer more harms than benefits?

#### The medical profession

Medical professionals need much better education on evidence-based medicine and need to think of randomised clinical trials as indelible part of their work, and not as an extraordinary rare activity that deserves extra monetary incentives.

There is a need to educate much more physicians and nurses in conducting clinical research. Moreover, there is a need to educate more clinicians in conductance of systematic reviews of previous research [3, 5]. Only in this way are we able to close the gaps in our knowledge.

Furthermore, there seems to be a need for much more pregraduate as well as postgraduate education in evidence-based medicine. It is first when those responsible for the clinical decisions master the evidence, it becomes correctly implemented.

#### The drug and device industries

The drug and device industries need to implement current knowledge about evidence-based medicine into

their clinical development plans and become much more transparent about their results.

Furthermore, the industries need to

- support much larger clinical trials on preventive, diagnostic and therapeutic interventions;
- be willing to conduct comparative randomised trials in which their products are compared with other interventions;
- support technical solutions for the implementing of, e.g., stem cell therapy in a broad public content and not only for a few highly specialised hospitals;
- support investigations which can outline the influence of patient's genomic and clinical phenotype on the efficacy of preventive, diagnostic, and therapeutic interventions.

### The governmental institutions

Governments and supranational organisations need to implement research programmes that focus on clinical research for common as well as rare diseases that affect the populations. In the EU, Horizon 2020 has been created to establish new growth and jobs in Europe [20]. Running from 2014 to 2020 with an €80 billion budget, the new EU programme focuses on a number of research questions in academia and industry. Horizon 2020 will invest in research infrastructures like ECRIN.

What is needed is complementary supranational and national research programmes that focus on clinical research for common as well as rare diseases that affect the populations with support for

- conductance of high quality systematic reviews of interventions;
- large-scale, multicenter clinical trials on preventive, diagnostic, and therapeutic interventions;
- research to evaluate the genomic and clinical phenotypic influence on stem cell function;
- research to evaluate the genomic and clinical phenotypic influence on benefits and harms of clinical interventions.

The way forward is to create hope by demonstrating to medical professionals, industry, and governmental institutions that opportunities for identifying new preventive, diagnostic, prognostic, and therapeutic interventions are vast. The fact that we now understand the evidence-based hierarchy enables us only to implement interventions that offer more benefit than harm. By teaching the public about how interventions are assessed in randomised clinical trials and systematic reviews of such trials, we may prevent unnessesary hype and harmful interventions to enter clinical practice.

### What is a realistic timeline for the incorporation of PPPM into clinical practice?
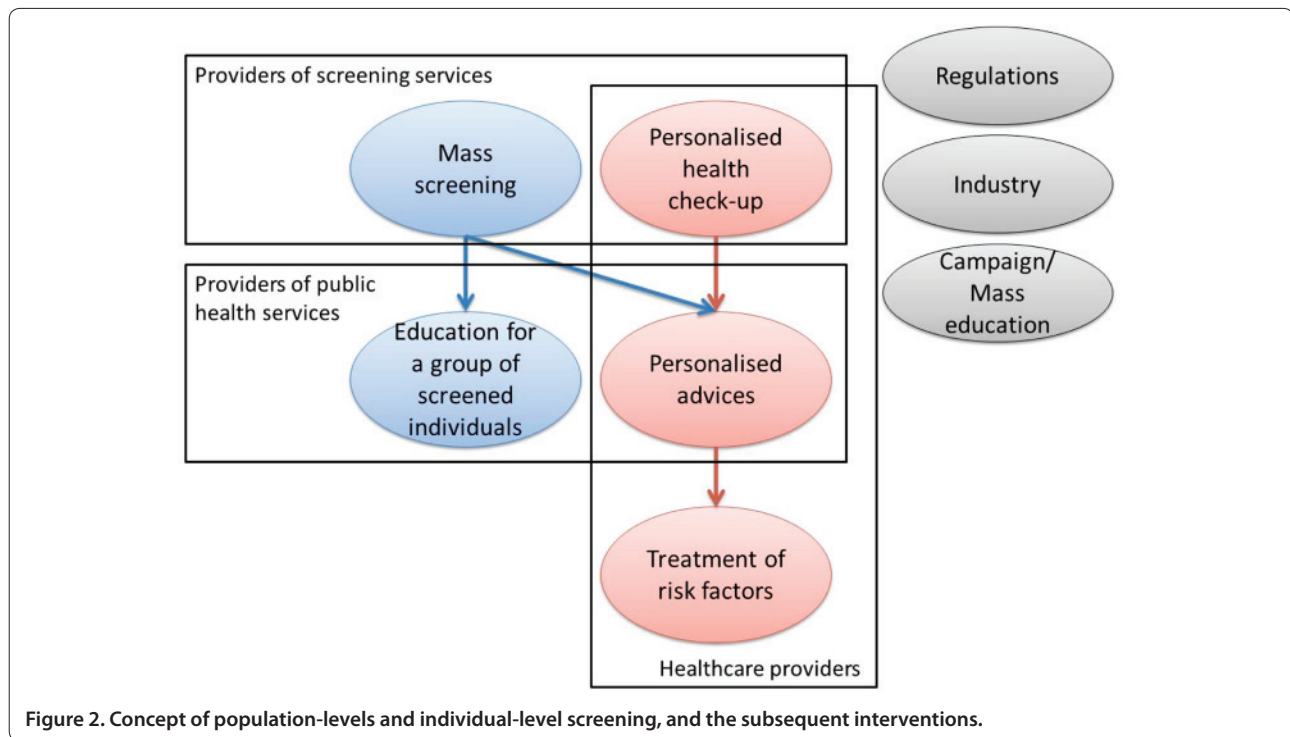
Patients and relatives alike want interventions that work now. Global medical research delivers constantly new reports on randomised clinical trials - about 25000 publications a year from all medical fields [21]. They need to become integrated with what we already know. Based on updated meta-analyses with trial sequential analyses [22–24] in systematic reviews - taking both the risks of systematic errors [15, 16] and risks of random errors [22–24] into account - we need to design new randomised trials in fields where the evidence is still not conclusive. In fields where the evidence is conclusive, the interventions have either to be implanted in clinical practice or research programmes redirected in case the intervention does not work or is causing more harm than benefit. Such activities takes time, but due to the constant flow of new research findings patients and relatives may rest assured that new preventive, diagnostic, prognostic, and therapeutic interventions are on their way.

### What are the implications of PPPM for prevention of cardiovascular disease?

#### Targeting the appropriate population

Primordial prevention is an early effort to prevent cardiovascular diseases, mainly through formation and modification of 'desirable' lifestyles and behaviours. Primary prevention is to control cardiovascular risk factors through modification of lifestyles and the use of interventions [25]. Preventive measures can be classified into population-level (public health) and individual-level interventions (Figure 2). For individual interventions, it is critical to select an individual or a group of individuals to administer the particular intervention. This process is based on appropriate *prediction* of future cardiovascular risk. Then, *personalised preventive* measures should be given according to the *predicted* risk. In order to evaluate the appropriateness of the intervention for better public health, it is important to evaluate population-level impact using population-attributable fraction (PAF) as well as its effectiveness for the specific targeted individuals [26]. It is sometimes necessary to compare PAF of the condition that the new intervention could eliminate with that of the other conditions which existing measures have been targeting. This is because the existing measures may be replaced at least in part by the implementation of a new measure due to the limited resources that can be allocated to public-health sector. Therefore, the harmonisation of new and existing measures is necessary with collaborative effort of academic, governmental and industrial specialists and stakeholders, as well as considering cost-effectiveness of new measurements. There is at least one example in which such harmonisation has not been sufficient. New public-health screening system was initiated in 2008 in Japan targeting the metabolic syndrome. Individuals were screened whether or not they have abdominal obesity, based on pathophysiological understanding of that condition. The implementation of

**Figure 2. Concept of population-levels and individual-level screening, and the subsequent interventions.**

this new screening and subsequent interventions to individuals with metabolic syndrome led to the discontinuation of other services, especially for hypertension. Interventions for those with hypertension without abdominal obesity were de-emphasised and sometimes ignored. Two consequent problems have been recognised. First, the benefits and harms of the screening program and the subsequent interventions have not been evaluated rigorously by randomised trials. Second, it has been shown that the PAF of metabolic syndrome is much smaller than the PAF of non-overweight people with cardiovascular risk factors [27, 28]. The Japanese government is amending the existing strategies to focus more on the problems of non-overweight people being high risk individuals for cardiovascular diseases.

**Personalised prevention**

Apart from issues related to an intervention itself, emphases are placed here on *prediction*: the identification of appropriate individuals (screening methods) and the allocation of appropriate interventions for particular individuals (risk stratification). From a view of public health, mass screening is one of the most practical and successful methods for identifying people with high, intermediate, and low cardiovascular risks at one time. Refinement of the risk stratification algorithms can be achieved by introducing additional categories for intermediate risk using new biomarkers (e.g., high sensitivity CRP), new risk factor categories (e.g., high-normal

blood pressure or impaired fasting glucose), and the evaluation of their cost-effectiveness.

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# Summary Report - Special Session "PPPM in Cancer"

## Definitions

- *Biomarker* is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Thus, a biomarker is a physical measurement; it is a protein, RNA expression (gene arrays), DNA (SNPs), metabolite, circulating cell, etc.
- *Clinical endpoint* is a characteristic or variable that measures how a patient feels, functions, or survives.
- *Surrogate endpoint* is a biomarker intended as a substitute for a clinical endpoint
- *Theranostic* is the combination of therapeutics plus diagnostics
- *Companion biomarker* is an *in vitro* diagnostic medical device required for the new approval of a therapeutic treatment that serves to improve the risk/benefit profile of the treatment of a previously diagnosed condition through the stratification of patients. The use of biological information is functional to develop better drugs quicker; prescribe for each patient the best treatment and optimise the costs; and use the expensive treatments for the patients who will benefit from it.
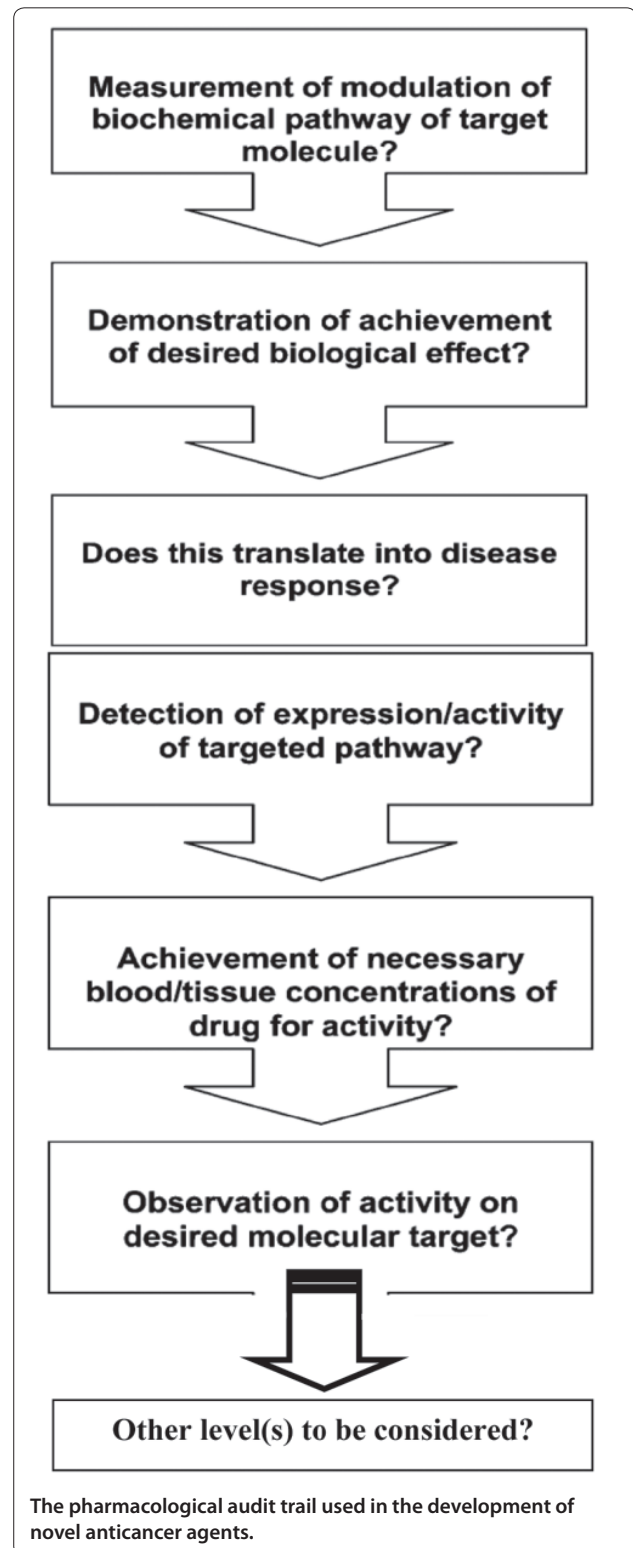
## The promises of biomarkers

In 2010, more that 50,000 papers that dealt with biomarkers have been published. Biomarkers are a child of the genomics technologies because they reduce risk in drug development (pharma companies), and improve patient outcomes (healthcare providers).

The use of a biomarker is strategically important for earlier diagnosis, patient stratification, assessment of drug toxicity and efficacy, disease risk, staging, and prognosis.

## Types of biomarkers

- *Translation biomarker*: applicable in preclinical and clinical settings.
- *Disease biomarker*: relates to a clinical outcome or measure of disease.
- *Efficacy biomarker*: reflects the beneficial effect of a given treatment.
- *Staging biomarker*: distinguishes among different stages of a chronic disorder.
- *Surrogate biomarker*: a valid substitute for a clinical outcomes measure.
- *Toxicity biomarker*: reports a toxicological effect of a drug in *in vitro* and *in vivo* systems.
- *Mechanism biomarker*: reports a downstream effect of a drug.



Measurement of modulation of biochemical pathway of target molecule?

Demonstration of achievement of desired biological effect?

Does this translate into disease response?

Detection of expression/activity of targeted pathway?

Achievement of necessary blood/tissue concentrations of drug for activity?

Observation of activity on desired molecular target?

Other level(s) to be considered?

**The pharmacological audit trail used in the development of novel anticancer agents.**

### Examples of prognostic biomarkers used in oncology

| Name | Definition | Examples |
| --- | --- | --- |
| Biological progression markers | Measurements of cellular proteins associated with tumour appearance or progression | CEA, FP, CA-125, hCG, PSA |
| | Measures of tumour burden | |
| Risk markers | Risk markers describe risks of cancer occurrence or cancer progression | Somatic mutation, amplification and overexpression of oncogenes and tumour suppressor genes (e.g., PTEN, BCR-ABL, HER-2/neu, RAS, AKT) |
| | | Aneuploidy |
| | | Genetic predisposition (e.g., APC, BRCA1/2, MLH1, MSH2, Li-Fraumeni syndrome, ataxia telangiectasia) |
| | | Genetic polymorphisms (e.g., CYP1A1, GSTM1, GSTP1, SRD5A2) |
| | | DNA methylation |
| | | Environmental and lifestyle (e.g., HPV or HBV infection, tobacco use) |
| | | Multifactorial risk model (e.g., Gail model for breast cancer risk) |

### Example of predictive biomarkers used in oncology drug development

| Name | Definition | Examples |
| --- | --- | --- |
| Drug effect/ pharmacodynamic | Biological effects produced by a drug that may or not be directly related to neoplastic process | Effect on molecular target (e.g., EGFR inhibition, RAS farnesylation inhibition) |
| | | Induction of enzyme activity relevant to drug toxicity (e.g., CYP1A1, CYP1A2) |
| | | Functional (and molecular) imaging of drug interaction at target tissue |
| Cellular, histopathological, and imaging | Biological effects occurring during neoplastic progression (causally related to cancer) | Quantitative pathology or cytology of cancers, precancers, high-risk tissue |
| | | Anatomical imaging (e.g., MRI, CT) |
| | | Functional imaging (e.g., FDG-PET) |
| | | Genomic and proteomic expression profiles |
| | | Proliferation biomarkers (e.g., PCNA, Ki-67) |
| | | Apoptosis biomarkers (e.g., BCL-2 expression, TUNEL) |
| | | Differentiation biomarkers (e.g., cytokeratins) |



**Development stages of biomarker validation in the clinical development of a novel drug.**
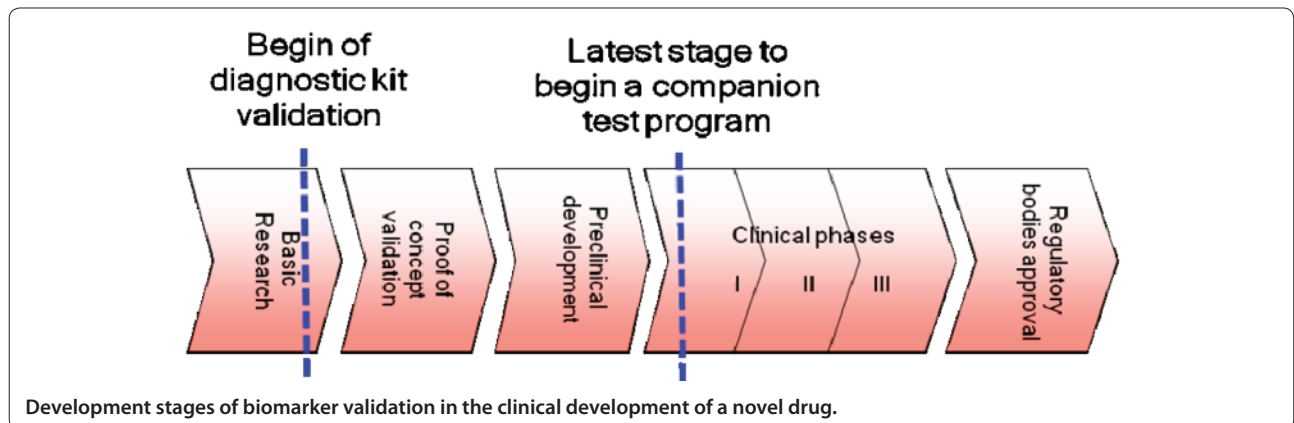
- *Target biomarker*: reports interaction of the drug with its target.

## What do we miss?
- Difficulty to access cohorts and appropriate banking; need for easier access to repository cohorts (retro- and prospective) and biobanks.
- No validation, follow-up, comparison, or standardisation reference of biomarker tests.
- No biomarker inventory validated in Europe.
- Need to develop Europe-specific guidelines for biomarker qualification and clinical validation.

## What do we need?
- Dissemination, communication, and implementation of biomarkers.
- Improve linkage of biomarkers to clinical information (and patient information).
- Coordination between disciplines & technologies: acceleration of partnerships between academic, medical research, clinicians, pharma, diagnostic, and biotech companies).

## Why does this happen?
- Relevance, specificity, validation of biomarkers (access to repository banks) is still an issue of discussion and standardisation.
- Some biomarkers are only developed for drug discovery phase.
- Hurdles with regulatory, price and reimbursement of the drugs/diagnostics duo or the companion diagnostics.
- Hurdles linked to commercialisation model.
- Drug and biomarker development are not the same businesses.
- Lack of specific guidelines to facilitate the incorporation of personalised medicine into the health-service infrastructure; therefore, there is a very heterogeneous approach to the use of such biomarkers.

From these premises it appears that, despite the process towards personalised medicine, aimed at better predicting, preventing and treating diseases based on a patient's individual characteristics, is gaining pace in Europe, a long-term structured approach to foster innovation in this area and to facilitate the rapid uptake of personalised medicine into clinical practice are lacking. The EPMA plays an important role to advance this area further and promote collaborative interactions among health agencies.

During 2010, the Health Directorate of the EC's Directorate General for Research and Innovation organised a series of workshops on stratification biomarkers and personalised medicine. The aim of these workshops was to take stock of the current situation in personalised medicine, and to identify further needs and opportunities from a research point of view.

With these premises, the EPMA should provide a platform for professionals to:
a) discuss the values of incorporating biomarkers into pharmaceuticals and diagnostics development, and of their potential applications in disease management such as early prediction, detection, and prevention of medical conditions;
b) facilitate tailored therapeutics that could be safer and more effective for individuals.

In the Session on Predictive, Preventive and Personalised Medicine in Cancer, the distinguished experts with acknowledged expertise address the problem of currently missing clear strategy of personalised treatment in oncology. Particular attention is paid to the following questions:
a) Which biomarkers are useful?
b) Are they ready for clinical use?
c) How does biomarker investment add real value in the drug/diagnostics development pathway?
d) What are the key challenges with the identification and validation of biomarkers?
e) Is there a difference in the process for safety biomarkers compared to efficacy biomarkers?
f) What should be done to address the challenges in the short-, medium-, and long-term?
g) How much do inter-individual differences account in drug metabolism and response?
h) What other factors could help medicine personalisation?
i) How far could biomarkers play a role to avoid adverse drug reactions?

## Conclusions
- High density biomarker data will change our view on health and disease and will impact on research, drug development and healthcare application.
- Complexity of innovative PPPM related biomarkers is to be expected.
- "Complex" multiplexing technologies will be the tools (Molecular Imaging / Profiling, Genomics, Transcriptomics, Proteomics, Metabolomics, etc.).
- A standardised validation of biomarkers is crucial for PPPM application in routine medical practice (tools and profiles).
- Classical anamnesis together multiplexed assays will become the new gold standard.
- Appropriate statistical planning is crucial for the outcome of PPPM related studies.

## Recommendations
It is important to remember that the EPMA brings together stakeholders involved in all areas of personalised

medicine: it is a unique opportunity to identify key challenges where actions are needed at the EU level to progress research, and to promote a development and implementation of PPPM in healthcare in a global scale.

- Cancer is a multi-factorial, whole-body disease that causes multiple organ and metabolic alterations. Usually not only one single intracellular signal pathway; not one single index/parameter. A paradigm shift from traditional single-factor strategy to multiple-parameter systematic strategy will be important for the prediction/prevention, early-stage diagnosis/ therapy, and assessment of preventive and therapeutic.

- Practitioners working in PPPM need new methodologies for the handling of the vast amounts of clinical information 5-year survival rates, while useful, are inadequate as a sole predictor of individual patient response. Significant advances being made in Bioinformatics and IT solutions for predictive, preventive and personalised medicine nowadays allow for integrative approach in making clinical decisions.

- An integrative approach should be effectively promoted in application of diagnostic and therapy monitoring technologies rather than prioritising individual ones, e.g. molecular profiling against medical imaging or genomics taking precedence over proteomics among "fishing expeditions for biomarkers".

- In order to properly evaluate potentially promising biomarkers, these biomarkers need to be subjected to rigorous prospective, randomised clinical trials. The unique role and value of both retrospective and prospective studies is indicated.

- In PPPM field, the most important role of biomarkers is in the realm of prediction and prognosis. The proper use of predictive and prognostic biomarkers would be critically important in prediction of the disease and efficacy of potentially cyto-toxic and disease-inducing forms of aggressive treatment. In many cases, it would be in the patient's best interest to avoid potentially harmful forms of treatment, if these could be reliably predicted (prior to treatment) to be ineffective and futile. First do no harm!

- There is a consensus in the necessity of panels rather than individual biomarkers to be clinically applied to more successful cancer diagnostics and treatment, specially due to the nature of human cancers which frequently undergo genetic alterations and mutations. It is important that researchers find ways to successfully decipher large quantities of information and find meaningful combinations of clinically useful biomarker panels.

- For several pathologies and patient cohorts, the role and significance of biomarkers is not strictly "black or white", but rather various "shades of gray". In other words, the expression, meaning and impact of biomarkers may be inconsistent; subgroups of patients may express different biomarkers within the cohort. Accordingly, strict rules and methodologies of validation may have to be revised in order to be reasonably flexible to recognise and scientifically categorise these "shades of grey" in according to the individual patient profiles.

- In terms of early detection, targeted prevention and treatments, of particular importance are novel but critically important forms of "multiple biomarkers" related to inflammatory process, to be recognised and factored.

- In terms of the biomarker nature, most protein "biomarkers" have not been fully analysed at the individual amino acid level. From a technical point of view it makes a good sense to use mass spectrometry-based protein analysis to obtain the exact protein sequence for a patient profiling. Hence, many protein assays are based on antibodies that recognise general areas of proteins (i.e., N- and C-termini, and small groups of amino acids); however, many cancer-causing mutations are very subtle. The use of current "generalised" antibodies might overlook patient-to-patient variations in protein structure. An example that illustrates the point, there is the current interest to develop antibodies that are capable of differentiating normal from mutated versions of proteins (e.g., KRAS and BRAF). Currently used "Western blot" and ELISA analysis do not have this capability.

- Further innovation in diagnostics considers identification of protein expression changes in cells in a range of different dynamic states in a form of "protein atlases". These protein atlases may enable future work to identify small changes in cell phenotypes to indicate possibly pre-clinical changes in an organ or tissue.

- It is imperative that the PPPM community creates a committee based on the EPMA group to develop a rigorous strategy leading to a more productive means of identifying biomarkers that would be clinically relevant.

- Since an integrative medical approach by PPPM is a new field, consequently new guidelines need to be developed.

- Due to a substantial lack of guidelines and specific recommendations on the use of biomarkers in cancer medicine, the creation of a committee by the EPMA-consortia to draft strategic recommendations on the use of PPPM related biomarkers in cancer treatment has been proposed.

## Appendix

**The elaborated list of statements and questions proposed by the EPMA experts to promote the field and evaluate the implementation of PPPM strategies over the next years**

### Question 1a-f: Biomarkers

(1a)   Why are there so many published biomarkers, yet very few in clinical practice? What is wrong in the validation process?

(1b)   What are the key challenges with the identification and validation of biomarkers?

(1c)   Which biomarkers are useful?

(1d)   How much do biomarkers account inter-individual differences in drug metabolism and response?

(1e)   Should molecular profiling (genomics) take precedence over proteomic analysis in initial "fishing expeditions" for biomarkers?

(1f)   Is pre-surgical genomic analysis of potential value in determining individual patient drug response?

### Question 2a-d: First Do No Harm – Avoiding the unintended consequences of genomics

(2a)   Myth from reality: Will we really soon reach an era of "customised care" for cancer? Is cancer care just a question of clarifying which gene or pathway is deranged and in which patient?

(2b)   Liaisons with industry can be dangerous but also extremely beneficial to PPPM. The proposed strategy: Exaggerating certain actions vs. lack-of-action.

(2c)   Patient organisations (POs): Reciprocal discussion and education is recommended; more inputs from POs is needed, to share scientific knowledge with patients and to promote the philosophy of participative medicine.

(2d)   Create a consensus with POs dealing with patient fears and expectations.

### Question 3a-e: Cancer relevant (?) mutations

(3a)   How important is the mutations analysis of individual genes (real risk of cancer for mutation carriers according to the last data)?

(3b)   What are the national standards for the mutation testing in Europe and USA (if they do exist)?

(3c)   What about reimbursement of such testing; other economic considerations?

(3d)   Follow-up of mutation carriers: is there any fixed/finalised protocol? Is the task to make regular observations depend only on the desire of the mutation-carrier?

(3e)   Creation of a comparative analysis and critical review regarding the situation in different countries for the mutation testing / carriers treatment

### Question 4a-d: Multi-parameter systematic strategy for PPPM in cancer

(4a)   Cancer is a multi-factorial, whole-body disease that causes multiple organ and metabolic alterations. The matter is usually neither about only one single intracellular signal pathway, nor one single index/parameter.

(4b)   A paradigm shift from traditional single-factor strategy to multiple-parameter systematic strategy will be important for the prediction/prevention, early-stage diagnosis/therapy, and assessment of targeted preventive strategies and therapeutics.

(4c)   How do we extract relevant information: molecular biology developments are bringing a real "*renaissance*" of basic biomedical sciences and yet the risk is to become overwhelmed by an ocean of data or not be capable of appropriately interpret?

(4d)   What is required for the development of *omics technologies, bioinformatics, systems biology, and computation biology in order to provide the fundamental conditions to realize the multi-parameter systematic strategy for each aspect?

# Summary Report - Special Session
# "PPPM in Neurodegenerative Diseases"

## Introduction

The application of predictive, preventive and personalised treatment could not be more relevant to neurodegenerative disorders (NDD) given the occurrence of predictably hereditary cases, having a long preclinical period (pre-symptomatic phase) and being still incurable.

On the other hand, the ageing population leads to an increasing occurrence of acquired NDD. Regrettably, at time of diagnosis is too late to begin with a neuroprotective treatment since neuro-axonal degeneration is irreversible, as ongoing neurodegenerative cascades are already initiated and can at best be modulated beneficially.

In all neurodegenerative diseases there is a great unmet medical need, calling for early diagnosis, prognostic evaluation, personalisation of therapeutic regimes and a better prediction of treatment outcomes. Fortunately, advancing technology and methodology can help to make

- The correct diagnosis significantly earlier in the disease process.
- The PPPM approach could represent the "golden answer" to the challenges in NDD management.
- EPMA should assist by trying to effectively disseminate to all identified relevant players every piece of evidence that becomes available in the support of the new paradigm.
- For example the latest report of ADI (Alzheimer Disease Association) - the World Alzheimer report for 2011 which covers specifically the topic of "The benefits of early diagnosis and intervention", includes good evidence that the prevention NDD can bring savings to the healthcare systems.
- Education should be addressed in two main directions: towards the post-graduate level and also towards the young medical students.

Main topics to cover are:

1. To promote earlier diagnosis, to apply effective early interventions for people in the early stages of dementia and at premotor phases of Parkinson's disease and comparable disorders. This is cost-effective for the governments: invest to save.
2. There should be evidence-based practices in early intervention around the world
3. Care services should ensure that evidence-based clinical tests and interventions are made available to people in the early stage of NDD
4. The need of reliable markers indicative of a pathological process before symptoms manifestation and those that could be indicative of disease modification by drug therapy.

## Animal models and translational approaches

Better animal models of neurodegenerative diseases might be useful to identify the appropriate molecular targets responsible for disease at different stages of the process (to block those processes) and/or the relevant endogenous repair mechanisms (to stimulate protection/repair).

Future research on animal models of NDD should shift their focus from well-established models of end-stage symptoms towards the development and evaluation of new models that mimic disease triggering and progression more accurately. A major requisite will be an increased interaction between basic scientists and clinician scientists with respect to PPPM in neurodegenerative diseases. Diverse opportunities should be offered to basic science trainees to experience the realities of the clinical routine and, for young clinician scientists, to gain exposure to the bench or clinical research. Scholarship or fellowship programmes that support basic science students to participate in clinical research and clinician scientist trainees to work in basic science labs will go a long way to breaking down the barriers.

Although understand genetic risk factors for NDD is essential, we need to move beyond simply identifying risk genes and start to tease out how lifestyle, environment, etc. affect expression of those risk genes. So a major area of focus should be on epigenetics and compound risk ("multiple hit hypotheses") in relation to NDD. Another key area for development is simple, early stage diagnostics. We need well-validated but simple and cheap ways of detecting disease at its earliest stages. An example is the link between changes in olfaction and later onset dementia and/or PD. If that link can be validated then implementing simple "sniff test" protocols into routine clinical practice could form the basis of a large prospective trial. EPMA and its contacts could coordinate and fund such an effort. Of course if the trial is successful we need to have solutions to offer to patients. So EPMA support for on-going searches for targets and therapeutants effective in early stage disease is equally important.

## Population imaging – a strategy to identify new imaging biomarkers in NDD

MRI neuroimaging offers an elegant approach to find new biomarkers in NDD. Good anatomical resolution, i.e. white and grey matter distribution, the ability to detect vascular changes such as in the microvasculature and to depict aspects of brain function or inter-connectivity of distinct brain regions while being non-invasive are great advantages of this method.

The European Population Imaging Infrastructure (EPI2) intends to provide a dedicated environment for coordination of data acquisition at different locations or different time points in controlled population cohorts to be directly compared and communally analysed, thereby exponentially increasing the impact of population imaging studies and contributing to the aims of PPPM in NDD. EPMA, with its broad scope and global coverage may facilitate the deployment of necessary tools and the collaboration of centres interested and involved in population imaging.

Currently, no specific biomarkers are available that can identify persons at risk for neurodegenerative disorders. Imaging parameters are promising, and brain imaging may become of major importance to identify people that could benefit from preventive intervention.

This development is further supported by current advances in data acquisition and analysis, as well as by the establishment of larger databases and the fusion of imaging with individual clinical data.

An example that supports the use of this approach is the finding of small vessel disease and microbleeds being risk factors for dementia. The relevance of this finding is now under investigation also in interventional trials.

## Biomarkers in NDD – requirements and development

There is a need of reliable markers that are indicative of a pathological process before symptoms manifestation and those that could be indicative of disease modification by drug therapy.

Many of the biomarkers in the clinics show group differences (e.g. between normals and diseased), but none so far has been able to reliably diagnose Alzheimer's or Parkinson's diseases in their preclinical stages in an individual subject. It is possible that this depends on inaccurate diagnosis, since at present the diagnosis depends on clinical or pathological phenotypes, which suffer however from heterogeneity. This, added to the phenotypic convergence, indicate the limit of present-day understanding of these diseases.

## Biomarkers (BMs) may help:

1. to identify individuals "at risk" to direct prevention efforts, greatest impact;
2. to identify people at early disease stage, prior to the development of the full clinical phenotype to allow intervention with disease modifying therapies which may potentially improve clinical outcome;
3. in differential diagnosis and in monitoring disease progression;
4. to identify pathway-specific phenotype (endophenotype): phenotype associated within populations with particular diseases mechanisms. Will allow

enrichment of clinical trials by classifying subgroups and to anticipate who will benefit;
5. determine the clinical efficacy of new neuroprotective therapies.

The main drawback of currently available BMs such as neuroimaging and cerebrospinal fluid (CSF)-based BMs is that they are only available in large medical centres of heavily urbanised areas and are very expensive. Also, most clinics are not capable of conducting lumbar punctures to obtain CSF sampling, which is, per se, invasive. Thus it will be impossible to apply personalised treatment to the vast majority of the diseased population or to catch most individuals at an early stage to begin with neuroprotection therapy, which in the long-term will be cheapest treatment.

The major efforts in neurodegenerative diseases nowadays involve BMs for both preclinical and clinical stages: preclinical BMs that help predict clinical therapeutic potential, and clinical biomarkers indicative of a target/ biology process and dose selection.

## To meet these challenges the following recommendations are suggested:

1. to perform genetic predictive studies in combination with clinical assessment or/and additional BMs, in populations at risk to begin preventive therapy;
2. to identify the preclinical (asymptomatic) stage, since at this time window the directed prevention efforts will have the greatest impact. Emerging innovative technologies and the understanding of the disease process itself will contribute to better prediction and/ or early diagnosis;
3. BMs should be accessible, cost and time effective. This will help to decrease time and cost of clinical trials. Strong recommendation to development of less invasive and cheaper BMs including serum/plasma protein-based BMs and blood transcriptomics-based BMs;
4. to associate genetic data with neuroimaging, neurological and biochemical patterns to allow the survey of genetic factors related to the rate of progression of neurodegenerative disease;
5. neurochemical BMs measured in the periphery (proteomics/transcriptomics in blood, CSF and other tissues), may be useful adjuncts to imaging and clinical assessment tools to provide valuable information about pathogenic mechanisms during clinical testing of neuroprotective/disease modifying drugs, which is especially relevant to personalised treatment;
6. biomarker tests must be standardised to ensure they can be measured correctly and consistently in all clinical settings;
7. to underpin public–private collaboration comprising scientists from academia and from pharmaceutical

and diagnostics companies, to develop the best methods to evaluate the progression from normal ageing to preclinical diseases stages and from mild to severe stages. It means that companies would need to share information with one another, as well as with academia.

## Optical coherence tomography – an example for novel BMs in NDD

Optical coherence tomography (OCT) is a non-invasive and fast method to demonstrate retinal abnormalities or alterations, such as neuro-axonal degeneration, in neurodegenerative diseases. OCT can be used to measure the retinal nerve fiber layer thickness, the total macular volume and evolves as a method to quantify changes within distinct ganglional cell layers of the retina. Retinal nerve fiber layer thinning is a feature in multiple sclerosis patients, that also occurs independently from episodes of optic neuritis and can therefore be used to assess the neurodegenerative portion of diseases in neuroinflammatory diseases, such as MS. OCT can therefore contribute to a multimodal description of ongoing neurodegeneration, and complements imaging methods such as conventional MRI or MR spectroscopy. Studies in a variety of neurological diseases, also in their earlier phases, are ongoing and will help to evaluate the diagnostic and prognostic use of OCT parameters in these diseases.

## PPPM aspects in Alzheimer's disease: "From the World Alzheimer Report 2011: The benefits of early diagnosis and intervention"

Skills and technology are advancing and we are currently at a stage where diagnosis can be made increasingly early in the disease process. This progress should be translated to organisational as well as to clinical practice and scientific research, considering the following points:

- Every country should have a national dementia strategy. National dementia strategies should promote early diagnosis and intervention through awareness raising, training of the health and social care workforce, and health system strengthening.
- All primary care services should have basic competency in early detection of dementia, making

and imparting a provisional dementia diagnosis, and initial management of dementia.

- Where feasible, networks of specialist diagnostic centres should be established to confirm early stage dementia diagnoses and formulate care management plans. Practice based registers should be maintained in order to audit diagnostic activity, and to promote shared care with specialist services.
- In resource-poor settings with limited or no access to specialist dementia services, earlier dementia diagnosis can still be achieved, for example through scaling up the WHO mental health Gap Action Programme (mhGAP) evidence-based intervention guide across primary care services.
- In complex health systems, explicit recommendations should be made regarding the roles of primary care, memory clinics and community care services in dementia diagnosis, early stage and continuing care.
- The availability of effective drug and non-drug interventions for people with dementia and their carers should be publicised to health and social care professionals through initial training and ongoing professional development, and to the public through population health promotion, and health and social care facilities.
- Purchasers and providers of dementia care services should ensure that evidence-based interventions are made available to people in the early stage of dementia, and audit this process.
- More research should be commissioned and funded, including investigation of:
  - The efficacy of drug and non-drug interventions specifically designed to meet the needs of people in the early stages of dementia.
  - The real-world costs and benefits of scaling up earlier diagnosis and early-stage dementia care services, specific to the settings in which the economic evidence is to be applied.
  - The effect of earlier diagnosis on outcomes (overall health, cognitive functioning, quality of life, etc.) for people with dementia and their carers.
  - The progress towards closing the 'treatment gap'.

# Summary Report - Special Session "Targeted Prevention in Nutrition, Behaviour and Physical Activity"

## Overview

Targeted prevention is the premise for an effective personalised medicine strategy, i.e. of the medical model proposing the customisation of healthcare. In this approach all decisions and practices are tailored to the individual patient by use of multi-faceted information, ranging from patient's family history, social circumstances, environment and behaviours and including genetics and molecular biomarkers. Predictive and preventive medicine is in many regards an extension of traditional public health and clinical medicine tools, with efforts for integrating the cutting edge of genetic research. The prediction of future disease can allow health care professionals and the patient themselves to be proactive in warranting lifestyle modifications (behaviour, nutrition and physical activity), enhancing physician's intervention and counselling. In this perspective predictive medicine changes the paradigm of medicine from being reactive to being proactive and has the potential to significantly decrease the incidence and prevalence of both common and rare diseases.

Relationship between diet and physical activity patterns, and the major nutrition-related chronic diseases are well established by epidemiological and intervention studies. Both are evidence-based approaches, mostly still on-going and starting in recent decades. On these basis recommendations are made to help prevent death and disability from these diseases, and are validated and refined by clinical practice and population intervention measures. Population nutrient intake and physical activity goals should contribute to the development of regional strategies and national guidelines to reduce the burden of nutrition related diseases: obesity, diabetes, cardiovascular diseases, including stroke, neurodegenerative disease, several forms of cancer, osteoporosis and dental disease. The place of nutrigenomics, i.e. the study of the effects of foods and food constituents on gene expression and, more, of the influence of genetic variation on nutrition stems from the possibility of correlating gene expression or single-nucleotide polymorphisms with nutrient's absorption, metabolism, elimination or biological effects. The ultimate goal is to develop rational means to optimise nutrition, with respect to the subject's genotype. Actually, genomics is of help in specific widespread conditions, such as methylenetetrahydrofolate reductase (MTHFR) polymorphisms, and the
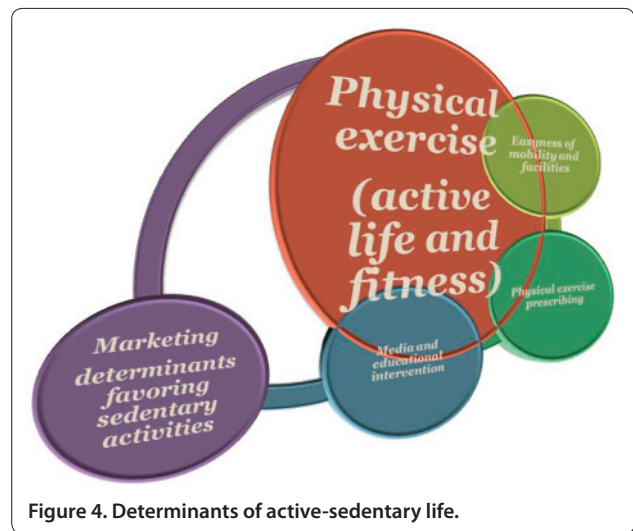
derived procedures are useful for preventing stroke, infertility, malformations and several adult's disease.

The research of biomarkers of the early phase of diet-related diseases has the aim of warranting nutritional intervention to restore health. Since nutrigenomics investigates the effect of different genetic predispositions in the development of diseases, once a marker has been found and measured in individuals, the extent to which a person is susceptible to the development of a disease will be quantified. As a consequence, personalised dietary recommendation can be given for individuals. The aims of nutrigenomics also includes being able to demonstrate the effect of bioactive food compounds on health and the effect of healthy foods on health. This should lead to the development of functional foods, a still controversial concept, that could keep people healthy according to their individual needs.

Despite nutrigenomics has been associated with the idea of personalised nutrition based on genotype, the present evidence and expert guidelines are still based on more traditional epidemiological and clinical studies. Actually mostly epidemiology allows to define the effects of a nutritional regime, assessing causality/relationship between specific nutrients and specific nutrient regimes (diets) on human health.

Expert recommendation, counselling and dietary prescription for nutrition are tailored mostly according to age, gender, climate, work and associated or foreseeable disease. The lines take into consideration alimentary education by media and in the schools, the paediatrician-family doctors networks, specific intervention in the workplace and in the schools and other types of interventions, driven by national governments or local administrations. The main drawback: the success rate of intervention against traditional habits and hostile marketing actions, promoting "unhealthy" dietary and lifestyle habits is still very limited or inconsistent. In this context power of outcome analysis is of paramount relevance and relies on the consistency of the guidelines adherence assessment and on the robustness of outcome indexes chosen. When pertinent "markers" are unreliable, the maintenance of any intervention is unfounded and guidelines easily disregarded (Figure 3)

In this perspective the contribution of EU is crucial, because there is the potential of sharing objectives – regarding healthy nutrition – through integrated intervention and research programmes involving several

**Figure 3. Effectiveness of expert and health professionals' action.**



**Figure 4. Determinants of active-sedentary life.**

EU Commissions: research and innovation, agriculture, health and consumers, education and culture and others.

Analogous evidences, regarding relationship with disease onset and progression are available for physical exercise and behavioural profiles (lifestyle, habits): nonetheless, in these fields guidelines and recommendation are still more vague, and more detail and personalisation are, obviously, needed. National interventions are and were performed, with campaigns against alcohol, smoking and – primarily – sedentary life, achieving variable accomplishment of the goals. Efforts were concentrated on children and youngsters but it is evident that also an active old age is beneficial for the quality of life: actual physical exercise prescription instead of or along more expensive therapeutic approaches is an affordable medical practice; it has a positive cost-benefit analysis when the outcome are population and individual quality of life and appropriate resource use. Regrettably, national/regional interventions are extremely fragmented and erratic: the need of coherent EU policy is central and implies shared directives through health, education, mobility and research commissions.

Behaviour and physical fitness are in some way genetically-conditioned, but information and relationship, and as a consequence, markers, are scarcely defined and not yet established. The present epidemic of obesity and related disease is the consequence of nutritional, behavioural and sedentary life habits promoted by social organisations at the family, school, work, leisure and even sport level, by an hostile marketing, promoting unhealthy diets, by misleading or unreliable information and by "traditional", local or acquired, habits. The limits of infrastructures aimed at the mobility of citizens are mostly important. Knowledge and skills of health professionals in physical exercise prescribing is still insufficient (Figure 4).

For the near future it is awaited that neuroimaging methods such as magnetic resonance imaging (MRI) and positron emission tomography (PET) will provide further basic evidence regarding the still largely unknown interactions between physical exercise/dietary interventions and brain function, both in health and disease conditions affecting the central nervous system. Understanding these basic mechanisms is considered as a fundamental prerequisite for more concerted exercise and/or dietary prescriptions, particularly in at-risk subjects or prodromal phases of neurodegenerative disease conditions. It remains to be shown, however, whether neuroimaging will also provide reliable in vivo "biomarkers" for determining effects of exercise on an individual, personalised basis; i.e. whether neuroimaging parameters can be reliably used in an individualised work flow for determining effectiveness of preventive and/or therapeutic exercise and/or dietary interventions.

All determinants of health – genetic, food, behaviour, physical exercise, environment - are closely inter-related and the need of overlap when experts provide outlook and recommendation is evident.

The unfavourable contribution of pollution and environment is manifest in allergic and autoimmune disease, cancer, skin disorders, stress-related and cardiovascular diseases: many of these substances and environment pollutants are key quality markers of home/work environment and food.

The last decades have shown a remarkable good correlation between the high levels of air pollution (smoking, smoke exposure, $NO_2$, $SO_2$, $O_3$, diesel exhaust particles) and the high allergy and asthma incidence. Smoking and Diesel Exhaust Particles (DEP) were shown to seriously increase the titers of the allergy-related IgE antibodies, predisposing to skin allergy and allergic asthma. Environmental tobacco smoke (ETS) has an

adjuvant role in children: pre- and postnatal exposure to tobacco smoke leads, by the age of 3 years, to an increased risk of developing sensitisations to food allergens; avoidance of exposure to tobacco smoke only during pregnancy (but not after giving birth) does not significantly alter the odds ratio of sensitisation. In ragweed allergic persons simultaneous exposure to DEP and the main ragweed allergen, leads to a 16-fold increase in the antigen-specific IgE titer. This example underlines two arms of prevention: reduction in the anthropogenic pollution, as well as a good control over the spreading of foreign plant species. Both organic and inorganic mercury was shown in humans to trigger urticaria, dermatitis, and correlate with raised IgE titers against grass pollen. Dental restoration using amalgam is considered to be the largest source of mercury exposure for most people in developed countries. The amounts of mercury in blood and milk of lactating women correlates with the number of amalgam fillings. At least in the Baltic area, on a second line, the most important fish consumption biomarker was methylmercury among the women. As mercury tends to accumulate in the foetus/newborn, both during pregnancy as well as during nursing, small children are even more exposed. The genotype is known to have an influence on the adjuvant effect of DEP on allergies. European and Asian studies show that elevated lead levels positively correlate with the total IgE level in children, thus predisposing to an allergic background. Studies of the last decade document a strong accumulation of transitional metals in tumour tissues, underlining the role of these toxic elements in cancer aetiology. Further associations between toxic metals and neurodegenerative disorders like Parkinson, Alzheimer, and autoimmune diseases like lupus erythematodes, scleroderma, Hashimoto thyroiditis, ALS etc. are well documented in the medical literature. Various chemicals can not only induce allergies, but also can trigger "pseudoallergic reactions", which activate different allergy pathways without involvement of the immune system. Pesticides, like Dieldrin, DTT, DDE, Heptachlor and different PCBs can lead to release of inflammation mediators like histamine and leukotrienes in skin, neurodegenerative and environmental patients. Different genetic polymorphisms are involved in the human susceptibility to such chemicals.

The above-mentioned toxic agents become a new and important set of biomarkers of evident relevance in the biomonitoring of allergic, neurodegenerative, autoimmune and cancer patients. Clinical conditions reflect the interaction between the environmental factors and the genetic constellation of the affected person. Simultaneous analysis of these interactions gives an important tool in the personalised diagnostic, prevention and therapy: such research topics should become a priority.

A word of caution. Human nature is more complex than our genetic make-up, even conditioned and modified by "nurture" and environment, and includes psychological and spiritual aspects as well as physical ones. To be individualised, diagnosis and treatment need to take into consideration the human beings in their multi-faceted expression. The challenge for medicine therefore extends beyond biomedicine. The whole health system needs to set in motion a process whose central aim is the care of the individual patient by a person-centred medicine approach.

Traditional medicine is the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses. Traditional medical systems that have been adopted by other populations (outside their indigenous culture) are often termed alternative, complementary or non-conventional medicine. National laws and rules, international organisations, independent and commercial subjects are actively involved in the integration of several form of traditional medicine into the national healthcare systems: the need and the challenge is to promote the proper use of traditional medicine by developing and providing international standards, technical guidelines and methodologies. Assessment tools must be tailored to confirm with the effective predictive, preventive and/or personalised medical outcomes of different non-conventional medical cultures, as single or global interventions, compared to the current best practice approaches. Intervention based on cultural and anthropological understanding of differences, inequalities, shared needs and credence can be more effective, affordable and compliant. Moreover, if acknowledged as part of primary healthcare, they will increase access to care and preserve knowledge and resources. It is mandatory to ensure patient safety by upgrading adequately the skills and knowledge of traditional medicine providers and by validating and certifying professionals, beyond the plain fact that these health practices share and claim holistic, person-centred and inclusive approaches (Figure 5).

Awareness of the advantages of sustainability based on and environmental bioethics, is becoming a translational mechanism equally important of other fields of translational science and medicine. Prerequisites of health include the promotion of healthy practices respectful of cultural and environmental differences of populations, age groups, and individual biographical context. These practices should allow people to take better control of their life, generating and maintaining their own health.

Overcoming illness can also become the foundation for better future health if includes empowerment of resilience. This is a dynamic process whereby individuals

**Figure 5. Environment, Health and Bioethics.**



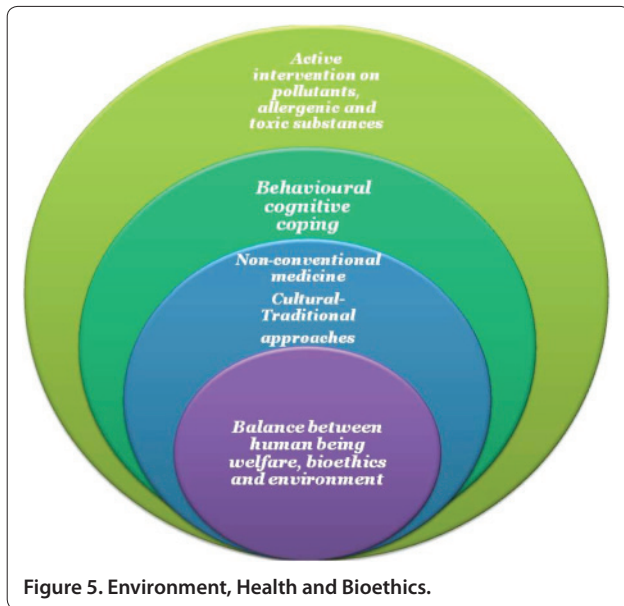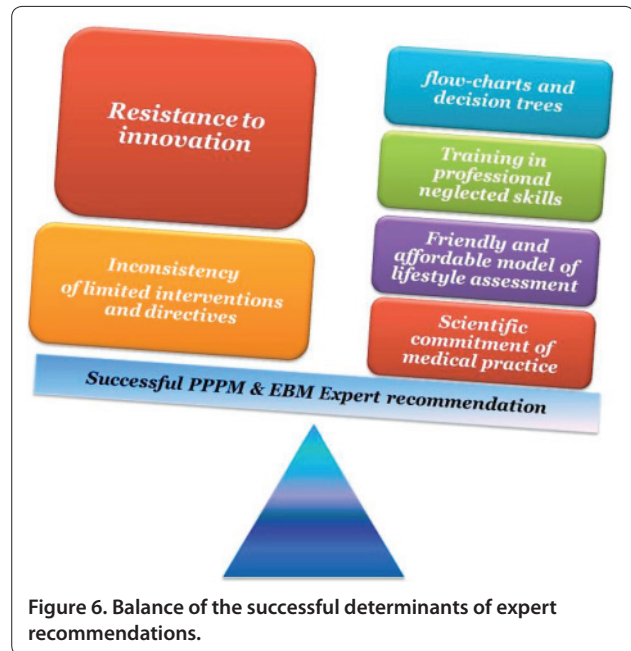**Figure 6. Balance of the successful determinants of expert recommendations.**

exhibit positive behavioural adaptation when they encounter significant adversity, trauma, tragedy, threats, or even significant sources of stress. The enhancement of resilience increases opportunity and capacity of individuals to manage their psychological, social, cultural, and physical resources that may sustain their well-being and capacity, individually and collectively. This allows for planning and negotiation for these resources to be provided and experienced in culturally meaningful ways.

Relationships that provide care and support, create love and trust, and offer encouragement, both within and outside the family, capacity to make realistic plans, having a positive awareness of self, improving communications skills, and the capacity to manage strong feelings and impulses modify the negative effects of adverse life situations. Personalisation of choice of diagnostic tests and treatments leads to less waste, reduced costs and greater satisfaction. In order to evaluate the success of such broadened medical interventions parameters need to be developed and adopted for assessing quality of life of patients and caregivers in terms of sustainable change, satisfaction, prevention of burnout as well as cost-effectiveness and technological excellence.

Knowledge and skills focused to behavioural cognitive interventions aimed at coping, adherence and self-efficacy of patients and health professionals are already available in few countries and institutions. They must be implemented by supranational directives obliging to validate assessment of methodologies and outcome. Presently used dietary- and physical exercise-assessment methods often present difficulties for researchers and respondents, and misreporting errors are common. Methods using information and communication technologies (ICT) may improve quality and accuracy: the already available friendly and most experienced applications (including those for smart-phones) should be encouraged and validated in their outcomes.

## Recommendations

1. Official nutritional-physical activity guidelines at national and international level are very similar and almost coincident. Nonetheless, adherence is limited everywhere and effective individual/epidemiological assessment difficult and scarcely comparable. Therefore, friendly and affordable model of lifestyle, physical exercise and nutritional assessment must be developed, with tools shared and suitable to be used at different level of professional expertise, for increasing skills and expertise aimed at enhancing actively pro-resilience healing approaches .

2. The commitment of health professionals in pro-active intervention for the enhancement of healthy nutrition and behaviour, and for promoting physical exercise in a sustainable way is insufficient. This is also due to the bias that lifestyle intervention are specialised jobs of dieticians, psychologists and physical trainer. Dissemination of knowledge of the strong innovative advancement in the interpretation of mechanisms and effects of food profiles and physical activity, stemming from molecular biology and functional imaging must be warranted. This will give motivation and scientific credit to medical doctors when pre-scribing, as actual medicines, diets, physical exercise regimens and behavioural changes.

3. Clinical nutrition and the epidemiological basis of the present knowledge on risk factors are presently two of the most neglected disciplines in the medical school curricula, worldwide, and in the continuous medical education (CME) actions. The recognition of available and effective clinical, epidemiological and teaching expertise, at least in Europe, and the support of the tools adequate for training and boosting appropriate skills are the premise for any intervention.

4. The use of multimedia in lifelong professional curricula, including e-learning expertise and tools focus to telemedicine monitoring and prescribing of diets and physical activity, must be appropriately selected, assessed and promoted, providing different and tailored professional tools (encompassing also flow-charts and decision trees) for medical doctors.

5. The European Commission should envisage supporting multi-center translational research activities conjoining epidemiological, clinical, and multimodal neuroimaging assessment of diets, physical exercise regimens, and behavioural interventions.

This type of translational research is expected to help unravel the promising, but largely unknown mechanisms by which healthy nutrition, behaviour and physical activity impact positively on the central nervous system and, ultimately, mediate sustained preventive and even therapeutic effects in healthy ageing and pathological conditions of the central nervous system.

Tailored medical practice is the product of tailored medical research, education and training.

# The Conception of Anti-Ageing Section in EPMA

## Introduction

Current scientific and technological progress and stability of social and economical spheres leads to increasing life expectancy in Europe. The number of residents aged over 60 years is expected to be doubled by 2020. The retirement age is shifted but majority of aged people keep on working, study, go to fitness-centres and travel. In our days many people prefer preventive healthcare measures against pharmacological and hospital-based medicine. Scientific researchers and medical doctors are facing the problem – to develop the comprehensive approach improving life quality, maintaining social activity, mental and physical health of the mature population, as well as preserving mental, physical and social health of young people. Therefore, concepts of anti-ageing medicine become a modern trend for researchers and healthcare industry.

Currently there are three main directions acknowledged in the anti-ageing medicine, namely

1. The direction of fundamental interdisciplinary research (study the mechanisms of social and stress-induced diseases, mental and physical diseases of older people).
2. Functional Medicine of regulation - prevention, early detection and correction of social and stress-induced diseases and syndromes - chronic fatigue, metabolic syndrome, CVD, hypertension, diabetes, infarct, osteoporosis, neurodegenerative diseases. They are associated with age, but environmental factors and lifestyle serve as provoking and triggering factors for diseases of "non-optimal adaptation".
3. In important role plays aesthetic medicine (plastic surgery, SPA, fitness, wellness).

The majority of diseases are classified now as multi-factorial, being associated with hereditary predisposition and life-style that require innovative approaches by integrative medicine. Consequently, anti-ageing medicine based on holistic approach, integrates knowledge in various areas of clinical disciplines, and also pays much attention to a new field of science - predictive medicine. Individualised patient profiling helps to identify persons at-risk and predicts pathologies before a clinical onset.

## Innovative approaches for studying ageing process, and developing anti-ageing technologies to extend life span and increase life quality

Breakthrough in any field of research is interconnected with development of innovative technologies and methodological approaches. The study of ageing, stress-resistance/adaptation needs to undergo a number of technological improvements based on the use of advanced bio-informatics and instrumental tools as well as new model systems.

Because ageing is a systemic condition, priority must be given to systemic approach to population's wide research of age-related changes occurring at the level of complete metabolome, proteome and epi/genome. It is necessary to develop uniform interdisciplinary understandable terms and definitions for describing verified actual data, research protocols and results. It is a great challenge for professionals, since generally accepted definitions of healthy longevity and age-related pathologies do not exist now.

## Methods to evaluate biological age and effectiveness of personalised therapies

Adequate health related markers and markers of disease predispositions need to be found. For this purpose we need to study status of healthy and aged persons in order to understand their mental and internal conditions (homeostasis), peculiarities of constitution and phenotype. Health quality markers are described in Chinese medicine in specific symbols potentially might be adopted and translated into the common neuro / physiological "language".

## Section of personalised predictive diagnostics

Methods of diagnosis of optimal postural stereotype (optimal body statics), optimal cerebral metabolism, criteria of optimal lymph circulation and intersticial transport are valuable for practical application. Further, the method of early preclinical diagnosis of stress-induced conditions (postural stress, "endoecological crisis") – non-specific grain for clinic behaviour of multifactorial diseases are well elaborated. However, the global standardisation as the essential element for the procedure tailored to the patient is currently missing. Many laboratories offer services for identification of partial personal profiles by sequencing selected genes (ONCO-gen, OSTEO-gen, CARDIO-gen, NEURO-gen, LIPID-gen, WEIGHT-gen, etc.). However, this information is far from being complete for clinical decisions: a number of post-genomic parameters should be essentially included into really predictive profiling. As the next step, molecular biological parameters should become correlated with clinical status to identify individual risks (e.g. predisposition to breast cancer) and to estimate potential impacts of postural and lymphodynamic disturbances in clinical onset of the disease. Hence, it is known that endo-ecological (interstitial) crisis and immune deficiency increase the risk of development of inflammatory, degenerative, oncologic diseases and other.

A correct interpretation of phenotypic, constitutional and molecular biomarkers to predict individual predispositions should be the issue of a series of large-scale studies.

## Personalised prevention and treatment

There is a huge number of fitness-, wellness-, SPA-centres and beauty salons for people who would like to extend their healthy period of life and, therefore, ready invest good money into preventive healthcare. Unfortunately for a number of those centres, the general level of preventive healthcare services is far from being optimal. Hence, according to the statistics collected for female clients, after some procedures a great portion of women feel discomfort with mammary glands (mastopathy) and suffer from negative side-effects. This is frequently a real problem of megalopolises. For examples, every year in Moscow, over 100.000 women consult doctors on different mammary gland problems appearing after regular treatments in SPA-centres and beauty salons in 15-20% of all cases. On one side women with predisposition to breast diseases, combination of muscle-tonic syndromes, signs of lymph congestion in upper aperture area need individualised preventive programmes such as professionally made detoxification, lymph drainage, etc. On the other side, preventive healthcare requires professionals well educated in multidisciplinary aspects such as contra-indications, predispositions, phenotypic features, individual molecular profiling, etc.

## Education

To promote the above listed aspects with the professionals and general population, the section aims at preparing the educational project at both professional and user levels. This is also the issue for national and international medical sessions and congresses related to the neuroscience, rehabilitation, health protection and anti-ageing medicine. *The EPMA Journal* (BioMedCentral, UK) is recommended to open a specialised section dedicated to the emerging field of PPPM in anti-ageing medicine.

## Innovative technologies and ethics

Innovative approaches such as evidence-based methods of express diagnosis for postural stress and "endo-ecological crisis" are recommended to be used in order to promote the participative element in PPPM and motivate patients to undergo individually created preventive programmes in health and disease. The adequate quality of the dialogue "doctor-patient" should correspond to the principles of medical ethics to apply innovative approaches of predictive diagnostics.

## The priority approach

The activities of anti-ageing section are planned in the context of post-genomic era and epigenetic bio/medical research to study environmental and internal factors, ethical aspects of PPPM, cultural particularities and impact of personal responsibility for health. The professional set-up is the following: integrative medicine, neurosciences, immunology, CVD, oncology, sport medicine, imaging and "omics"-technologies, economy of personalised medicine, medical ethics.

## Professional interactions

The anti-ageing section's working plan and achievements will be discussed and regulated in the course of meetings and symposiums coordinated by the EPMA-Board.

# Determining the Priorities of the Predictive, Preventive & Personalised Medicine in Dentistry

This chapter results from the specialised EPMA section of DPPPD (Department of Predictive, Preventive and Personalised Medicine in Dentistry) Symposium held in Voronezh, Russia in February 2012. The meeting gathered 19 delegations from different European regions and countries and created a brainstorming event to the effective promotion of PPPM in Dentistry.

### Early and predictive diagnostics

In dentistry, this kind of diagnosis is not common, but there are some methods that fit to the concept: simple and advanced stomatoscopy, express cytobacterioscopy, electroodontodiagnosis, etc. In this context, a list of examinations for persons at-risk should be considered:

- conservative dentistry for children and adults (dental caries, periodontal diseases, diseases of the oral mucosa, etc.)
- oral surgery and maxillofacial surgery (tumour processes, arthropathy of maxillofacial area, abscesses, phlegmons, etc.)
- prosthetic dentistry (atrophy of soft and hard jaw tissues, partial and fully edentulism)
- dentistry in common systemic disorders (metabolic syndrome with secondary complications, etc.).

### Risk assessment and targeted prevention

For the risk assessment in dental disorders, an individual patient profiling is particularly recommended, since some predispositions may be detected at early stages before clinical onset of the pathology followed by the most effective measures of the targeted prevention. For example, prediction and prevention of periodontal diseases in patients with diabetes mellitus and disease pre-stages.

### Personalised patient treatments

There is a huge number of methods and approaches to treat diseases in dental practice, which needs new guidelines promoting treatments tailored to the person, i.e. more personalised dental approaches. For example, the diagnosis of caries (a dental disorder affecting 50-90% of populations worldwide) involves 52 identified but 18 most significant clinical parameters upon their ranking. Undoubtedly, personalised treatment should be carried out according to the diagnostic evaluation of individual indicators to improve the treatment outcomes.

### Interactive pathologies and co-morbidities in dental disorders

It is well known that almost all human pathological conditions might be present in the oral cavity. Early symptoms of organ pathologies (such as changes in the condition of the tongue at the first signs of diabetes, initial changes in the taste sensitivity in oncologic diseases) can be detected by means of duly organised preventive diagnostics in dentistry. On the other hand, intestinal dysbacteriosis detection may facilitate early detection of dysbacteriosis of the oral cavity, and consequent development of caries, gingival and oral mucosa disease progression. The research of the multifunctional biomarkers in dentistry should be forced through research activities to reply currently still open questions about physiological and pathologies interactions in diagnosis and effective treatments.

### Personalised nutrition for prevention of frequent dental pathologies

Nowadays the influence of colouring nutritional liquids such as Coke, Fanta, and others for the tooth enamel colour and periodontal condition is getting more and more determined. Imbalanced nutrition and non-optimal life-style obligatory belong to the most frequent risk factors in onset of dental disorders. Recommendations for personalised nutrition should be the essential part of the overall dental care.

### Economical impacts of predictive, preventive and personalised treatment in dentistry

Preliminary calculations of the economical impacts provide a view to tremendous cost reductions in overall healthcare by introducing the concept of PPPM in dentistry into routine medical practice. For the most common disorders such as inflammation related diseases, chronic infections, diabetes, etc. a minimum of 4-5-fold reduction of the overall healthcare expenses is predicted.

### Medical care in rare (dental) disorders

Rare dental disorders such as Papillon-Lefevre Syndrome represent a particular field, where the practical application of PPPM is strongly recommended and should be effectively promoted by the specialised EPMA section. Correct diagnosis and effective treatment of rare dental disorder provide us with the unique opportunity to create optimal strategic approaches for the personalisation of the medical care in dentistry.

### Psychological aspects and ethics in PPPM

Special attention needs to be paid to the ethically correct patient treatment approach that is well adapted to and supportive for individual patient cohorts, in particular for individuals with mental disabilities and retardation,

pregnancy, elderly patients, children and youth as well as patients with severe systemic pathologies such as Down's syndrome and others.

## DPPPD as the example of the regulated professional interactions within EPMA

The DPPPD networks the top scientists working with the PPPM related concepts and leading professionals in Dentistry.

### Structuring the EPMA DPPPD specialised section

The Voronezh Academy as the EPMA-Representative in "PPPM in Dentistry" is in duty to structure the section with the EPMA support. The process of the section structuring is triggered in 2012 with the DPPPD meeting in Voronezh, February 2012.

### Instruments to effectively promote the field of "PPPM in Dentistry"

- *Promotion of the PPPM related expertise through EPMA:* EPMA has a particular interest to develop long-term professional collaborations with organisations awarded with the status "institutional member" of EPMA. Due to this highly effective form of collaboration, institutional member may expect a particular promotion through the EPMA consortia.
- *Publicity:* EPMA-website, magazines, newsletters, newspapers and TV programmes around the world, interviews with representatives, etc.
- *Inter/national scientific meetings:* Regular EPMA World Congress, EPMA-related professional meetings, PPPM-related conference and meetings in specialised sections, etc.
- *Scientific articles:* Scientific articles dedicated to the whole spectrum of PPPM in Dentistry should regularly update professional information about current achievements, provide outlook for further developments and, therefore, create a robust platform for professional recommendations and new guidelines in the branch. *The EPMA Journal* (published by BioMedCentral in UK as the "open access" journal indexed in PubMed amongst others) publishes review-articles, position papers, Editorial articles, Letters to Editor in the category "PPPM in Dentistry" and others. Any category of PPPM-related scientific articles published in other international journals may be advised by the EPMA experts and receive the EPMA-label being peer-reviewed and approved by nominated Representative(s) of the EPMA-Dentistry Section.
- *Education:* In the years 2012-2015 creation of specialised didactic materials for PPPM-related educational programmes within the book-series "Advances in PPPM" (EPMA/Springer, Editor-in-Chief: Prof Dr O Golubnitschaja); based on corresponding didactic materials, creation of educational programmes. Arrangement of master-classes and practical training courses, development and implementation of facultative education programmes for professionals are all within the framework of DPPPD as the specialised EPMA Section.
- *Grant application:* Reasonable professional partnerships are regularly discussed at the EPMA telephone conferences and meetings in view of scientific projects and grant applications. The thematic set-up of the EPMA-labelled proposals are performed in accordance to the expertise acknowledged by the EPMA consortia (see the instruments listed above) in terms of compatibility of partners and innovation of the objectives. Proposals with the status "EPMA-labelled" receive a special priority by professional advices for appropriate funding programmes and instruments.

## Topics recommended for upcoming scientific projects

- Development of integrative medical approaches in dentistry by PPPM with multidisciplinary expertise of professional groups to be involved
- Innovative technological tools relevant for early and predictive diagnosis of dental disorders followed by elaborated measures for targeted prevention in groups at-risk
- Innovative treatment approaches tailored to the person
- Development of PPPM related approaches in diagnostics and multifunctional treatments of rare (dental) disorders
- New approaches for PPPM related participative medicine in dentistry: motivation of individuals at-risk and patient cohorts in view of medical ethics
- New economical models for the practical application of PPPM in dentistry and integration of dental PPPM approaches in healthcare sector
- Multidisciplinary educational programmes for professionals and general population – elaboration of more effective approaches.

# Summary Report - Special Session "Patient-Specific Modelling"

## Introduction

The individualisation of medicine and healthcare appears to be following a general societal trend. The terms "personalised medicine" and "personal health" are used to describe this process. It must be emphasised, however, that personalised medicine is not limited to pharmacogenomics as it is sometimes defined, but that the spectrum of methods and tools for personalised medicine is much broader, see Figure 7.

Applications range from individualised diagnostics, patient-specific pharmacological therapy, therapy with individual prostheses and implants to therapy approaches using autologous cells, and from patient model-based therapy in the operating room including electronic patient records [1] to the individual care of patients in their home environment [2] with the use of technical systems and services.

Although in some areas practical solutions have already been developed, most applications will not have fully evolved for many years to come, as their development and adoption in clinical practice will depend on close cooperation, in particular between medicine and informatics.

Medical and information technologies are essential to personalised medicine and personal health. The synergy of these two technologies to generate and process information about the patient provides the basis for most tools and systems employed in individualised medicine.

The information gathered in healthcare and related fields, however, becomes more complex than at any other time in the history of medicine. It is expected that even more data will be generated thanks to the "omics" fields, complemented by the data on the nutrition components, herbal components, medical drugs, sensor data and the data on the particular interrelations between all these components. Continually increasing complexity of medical information in healthcare together with the rising impact of personalised medicine clearly catalyses closer cooperation not only between medicine and informatics but also with mathematics, knowledge engineering, communication technology, statistics, science of complexity, linguistics, ethics and other related fields.

## Integrated (model-based) patient care

Often, semantics of research and clinical data is represented implicitly and is hidden in unstructured and disconnected descriptions of the data or just in the heads of human experts (researchers and caregivers). Meaningful 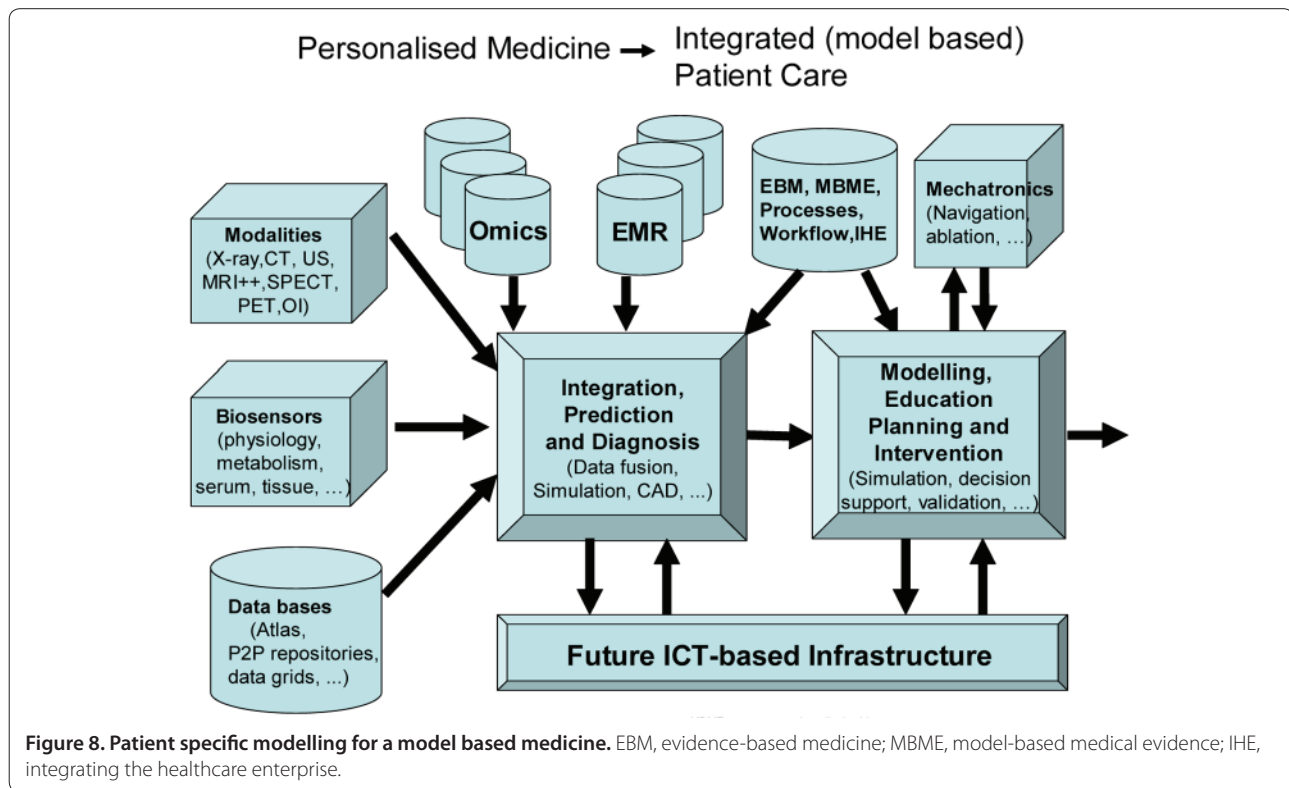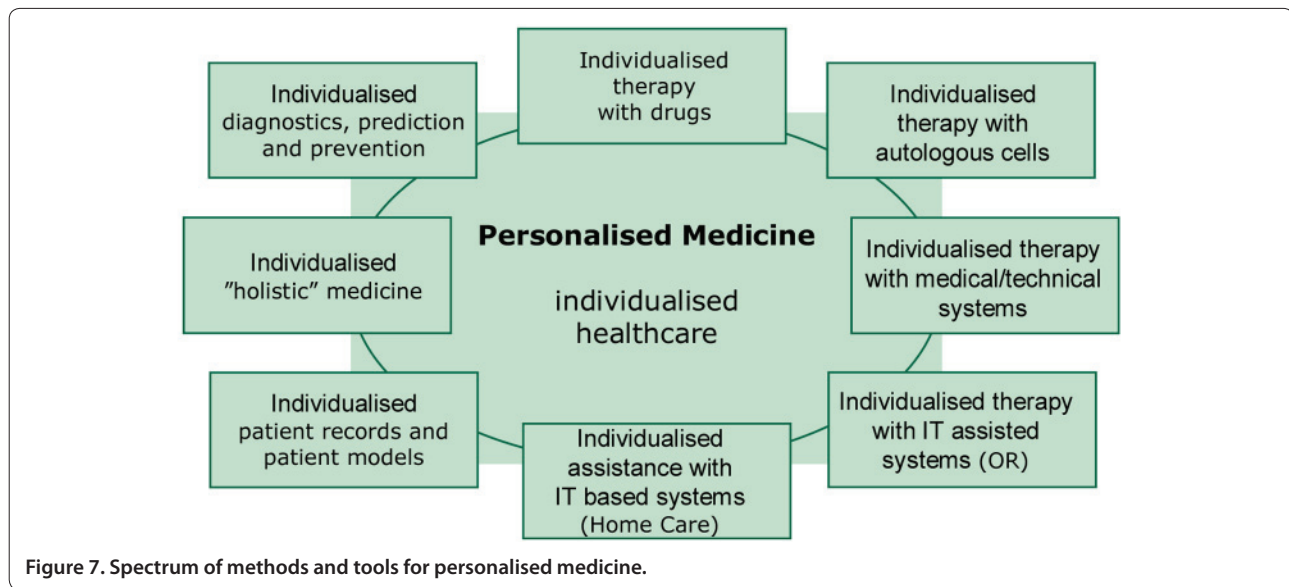semantics includes rich metadata, i.e. the predefined structure of data in medical records. In addition, it is extremely important to explicitly represent the patient-specific context of each discrete data item and how it relates to other data items, as well as how it fits within the entire health history of an individual.

A constantly growing stream of raw data is available today in both research and clinical environments, e.g. DNA sequences along with rare variants in research and sensor data along with personal alerts in healthcare. The representation of such raw data should adhere as much as possible to common and agreed-upon reference models (e.g. HL7/ISO RIM – Reference Information Model) and, depending on the clinical domain of discourse, to still to be defined Patient-Specific Models (PSM). This allows any observation to be represented in the same way in terms of its attributes such as ID, timing, code, value, method and status, as well as standard representation of clinical statements (e.g. observation of gall bladder acute inflammation indicated procedure of cholecystectomy or EGFR variations cause resistance to Gefitinib), where implicit semantics can become explicit and thus processable by decision support applications.

Wherever possible, patients are diagnosed and treated according to medical guidelines based on the general knowledge derived from observations of large populations of patients and controls, i.e. evidence-based medicine (EBM). There are still wide variations between individual patients, in terms of anatomy, physiology, metabolism, and genetics, that cannot be accounted for, or factored into medical procedure decisions, by EBM, or by standard methodologies of patient assessment that are currently available to physicians and the healthcare systems.

In real-life clinical settings a combination of all available medical information obtained from the medical record, scripts and elsewhere, has to be mentally integrated by the physician to create an abstract presentation or "model" of the patient, which must be as close as possible to reality to serve as a basis for decision making with respect to the medical procedure to be followed. This is commonly known as clinical judgment.

Transcending this traditional medical record centric activity, i.e. information component listing and summary report of the patient/human, we propose a strategy towards an ICT-based holistic presentation of the individual patient and corresponding medical process/procedure redesigns within a given domain of discourse, such as cardiovascular, neurological or oncologic disorders - see Figure 8.

**Figure 7. Spectrum of methods and tools for personalised medicine.**



**Figure 8. Patient specific modelling for a model based medicine.** EBM, evidence-based medicine; MBME, model-based medical evidence; IHE, integrating the healthcare enterprise.

With this holistic presentation of a specific patient, based on an importance rating driven collection of patient data as well as appropriate mathematical modelling methods, such as probabilistic relational models and process models as well as advanced ICT enabling tools, the practice of medicine will be substantially transformed towards model-based medical evidence (MBME) providing transparency of clinical situations, processes and decisions for patient and physician.

The patient-specific model is the central construct for a patient within such a personalised medicine environment, in order to provide a clinician with a real-time representation of critical information about the patient. The data of the patient-specific model reside within a probabilistic patient-specific database (PPD). The fields of the database consist of

a) absolute patient attributes, such as name, medical record number, etc.

b) descriptive patient attributes, such as biomarkers from the *omics and medical images; graphical physiological information, such as ECG or EEG; physiological values within expected value ranges; results of biochemical and biomedical modelling, in the form of results of equations; pathological findings, etc. and

c) probabilistic patient attributes, such as probability of tumour response to treatment, which are expressed in terms of probability and confidence level; conditional tables; etc.

Real-time functions on a patient-specific model will require the development or modification of a new form of database: a probabilistic database which will allow the utilisation of probabilistic data structures. This will incorporate a database design and a database management system which allows probabilistic database functions and storage capabilities.

## Recommendations

1. Research and development on functional interactive models for an individual patient's health, allowing for prediction of potential health problems under diverse model situations [3].

2. Research and development on the predictive and preventive potential of the new IT tools for *in vitro* and *in vivo* diagnostics and consequent evaluation and implementation of these tools in daily healthcare. This must progress in concert with *in silico* diagnostics - active computer processing of acquired analytical data, patient profile data, medical information and other related data in order to suggest reliable prediction and treatment of the patient [4].

3. Research and development on a "holistic approach" - a simultaneous systematic analysis providing a broad insight into various phenomena in order to reveal the underlying biomedical rules. Special emphasis should be given to the coupling of computer sciences, complexity theory, non linear dynamics and logic theory to enable the development of learning machines that extract the underlying rules and thus facilitate prediction that improves its accuracy while in usage [5].

4. Research and development on PSMs based on probabilistic graphical and related models enabling a mathematically structured integration of patient information from various independent sources in real time [6].

5. Development of probabilistic database management systems. While there are currently no commercial probabilistic database systems, several research prototypes exist and should be evaluated for their usability to manage PSMs [6].

6. Encourage developments that healthcare providers are not the legal patient record keepers and let new entities (independent health record banks - IHRB) be the sole health record keepers, sustaining a single EHR for an individual no matter where this individual has been treated. There should be multiple and competing IHRBs that will be regulated by new legislation that shifts the obligation of medical record keeping from healthcare providers to IHRBs [7].

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# Summary Report - Special Session "Biomarker Discovery, Validation, Standardisation and Practical Application in Medical Practice"

Most experts of the section are involved in the discovery and identification of biomarkers in preclinical and clinical research across academia, government agencies, and the pharmaceutical industry. Preliminary topics of interest belong mainly to practically incorporating biomarkers into pharmaceuticals and diagnostics development, their potential applications in diseases management such as early prediction, detection and prevention of medical conditions.

Statements belongs to a) define biomarkers, b) biomarker identification and characterisation, c) its current lack for practical application in medical practice, d) outlook/trends and e) request and recommendations.

## a) Statements to define biomarkers

There are many different ways to define biomarkers based on molecular properties, application, and methods. The National Institutes of Health (NIH) suggest an inclusive definition for biomarkers as "a characteristic that is objectively measured and evaluated as a indicator of normal biologic process, pathogenic process, or pharmacologic response to a therapeutic intervention". Therefore a biomarker can be DNA, mRNA, protein, metabolite, or lipid. These certain increased the complexity of biomarker research. Based on the application and suggested outcome/information, biomarker can therefore be classified in different clinical categories:

- Diagnostic Marker: identifies a disease
- Predicative Marker: identifies disease predisposition
- Prognostic Marker: predicts outcome
- Stratification Marker: predicts drug response (responder/non responder)
- Efficacy Marker: measures drug response
- Surrogate Endpoint: measures outcome
- Toxicity Marker: detects drug-induced toxicity
- etc.

## b) Statements to biomarker identification and characterisation

Novel innovative technologies have been developed and can be used for identifying, as well as characterisation and validation potential biomarkers. For example the so called *omics technologies (such as genomics, proteomics, and metabonomics etc.) have been developed and can be used for identifying potential biomarkers at several different molecular levels. Based on this novel technology the biomarker research has faced many significant challenges since the early 1990s. The fundamental issue that needs to be addressed therefore not to further improve the techniques it is how to improve the efficiency of drug discovery and development. The current research and development (R&D) cost for developing a new therapeutic drug is greater than $800 million. Additionally, it takes an average of 12 years to get a new drug to market with an attrition rate greater than 90%. Reviewing the overall pharmaceutical R&D process, it becomes clear that many of the drug failures are due our lack of knowledge in population diversity, which is responsible for difference in drug efficacy and toxicity. In fact, not a single approve drug is 100% safe and efficacious for all patients. For the panellist the key questions were: How can we discover biomarkers that can be used to distinguish patients who will respond and/or will have adverse effects? There is tremendous urgency to address this question. Biomarker also fit perfectly with the vision of personalised medicine, the new expectation of medical practice. This is why biomarker research has been a central focus in many clinical research labs across the scientific world.

## c) Statements to the current lack for practical application of biomarkers in medical practice

The use of biomarkers to investigate clinical relevant information allows proper classification of patients into therapeutic groups and knowledge of therapy outcome. Unique molecular alterations can predict therapy outcome in specific therapeutic groups. Integrating this information allows selection of personalised targeted treatment regimes, saving unnecessary drug toxicity and decreasing morbidity. The use of biomarkers as classifiers of patients (so-called stratification marker) would also allow information on therapy outcome. There are various examples of molecular markers that predict therapy outcome, but still await FDA approval to be included in the clinical setting. It is imperative to group biomarkers utilising well defined criteria to allow selection of approval process, prior to implementation to the clinical settings, based on benefit to patients, availability of infrastructure to allow implementation, availability of specific therapy and technology within the clinical setting to implement the test, and any other criteria deemed appropriate.

However, due to the lack of specific validation and standardisation strategies to characterise such biomarkers, there is a very heterogeneous approach for the use of such biomarkers in preclinical and clinical research. In the last decade, the field of proteomics, genomics and imaging analysis has expanded at a rapid rate. A range of exciting new technology has been developed and enthusiastically applied to an enormous variety of biological questions. However, the degree of stringency required in data analysis including correct prediction, normalisation and standardisation appears to have been underestimated. As a result, there are likely to be numerous questionable findings requiring further confirmation and/or validation. With this premise, the EPMA should provide a platform to outlines a number of key issues in research, including those associated with experimental design, protein identification and analytical completeness. Furthermore, the selection of predictive markers must be carefully assessed and should depend on different important parameters such as sensitivity and specificity, etc.. Unfortunately, biomarkers with ideal specificity and sensitivity are difficult to find. One potential solution is to use the combinatorial power of a large number of biomarkers, each of which alone may not offer satisfactory. Recent technological advances in protein chip technology and bioinformatics offer a great opportunity for simultaneous analysis of a large number of potential predictive markers. Although many significant results have been derived one limitation has been the lack of standards for presenting and exchanging such data. In the course of the panel discussion most recommendations belongs to set up proposal containing minimum information about a variety of bioanalytical experiment (sensitivity, specificity of the biomarker etc.) as well as patient information (age, gender, pathology etc.) that describes the minimum information required to ensure that the predictive value of biomarkers can be easily interpreted and that results derived from its analysis can be independently verified. The ultimate goal for upcoming biomarker studies is to establish a standard for recording and reporting analytical data, which will in turn facilitate the establishment of databases and public repositories and enable the development of data analysis tools. With respect to the EPMA objectives in the field, we should concentrate on defining the content and structure of the necessary information for the correct prediction of biomarkers rather than the technical format for capturing it.

### d) Outlooks and trends

Several trends have evolved over the last years which have facilitated knowledge transfer in predictive medicine from academia to industry, e.g.:

1.  A strong need to find new sources of innovation in the pharmaceutical industry in order to avoid "pipelines drying up" – softening the "not invented here"– argument.
2.  Personalised medicine will gain more importance.
3.  Pharmaceutical industry becomes more science-oriented. In fact, it even becomes more "academic" in structure e.g. establishing "Centres of Excellence".
4.  Academia becomes more "business-like" with an increasing need for third party funding and a redefinition of the "mission of the university".

Knowledge transfer can occur in many different ways, however the key vehicle is licensing of proprietary technologies.

Technology transfer offices (TTOs), which comprehensively were established in most countries not before the turn of the millennium, have demonstrably gained (more) maturity. In particular the life sciences have profited there from.

Licensing as well as patenting activities have taken off in most industries, including life sciences. Also, biomarkers from all relevant areas of *omics are *per se* patentable, thus fulfilling an important prerequisite for commercialisation.

Accordingly, the number of respective licensing agreements is swiftly increasing.

Typical agreements relate to biomarker discovery and co-development but also to specific biomarkers (-sets).

Most agreements are concluded between biotech and pharmaceutical companies. However, academic research institutions are a rich source of biomarkers which is reflected in the number of invention reports e.g. at PROvendis. Indeed, several licenses have been signed and there continues to be multitudinous negotiations between academia/TTOs and industry. Several biomarkers which have been identified in academia are now being marketed, including e.g. the multigene-panel of MammaPrint™.

Yet, the path of a biomarker from the academia to industry seems to be particularly winding.

To some degree this is misleading. Biomarkers are relevant for different steps in drug development and application. *Inter alia*, biomarkers are essential for studying mode of action of drug candidates. In this case, a detailed validation of a biomarker (by numerous independent scientific studies) will be more important to the industry than a monopoly position. Thus, although no license agreements will be signed, academia contributes enormously to drug development.

To some degree this is due to difficulties of establishing approved diagnostic biomarkers on the market as (often) significant efforts will be necessary convincing physicians and providers of other (allegedly competing) diagnostic tools that there will be a win-win-situation for all stakeholders.

To a large extend, however, reasons can be found within academia. These include the difficulty of

conducting/funding large scale studies with sufficient statistical power according to clinical development standards (however, initiatives such as the German National Biomarker database look promising). They also include more general issues of the present technology transfer landscape such as an ongoing need to educate scientists.

## Request and recommendations

### EPMA-mission in the field: request/recommendation for upcoming projects

- Creating novel innovative screening technologies (faster, more precise, cheaper)
- Using not only single biomarker per disease but their combinations and cell-based functional diagnostic systems
- Non- or minimally invasive diagnostic tools (saliva, urea, blood etc.)
- Knowledge exchange between biomedical researchers and biotechnology companies for advanced diagnostic tool production still need to be developed.

- Feasibility and validation studies: a number of key issues in research, development and clinical trial studies must be outlined,
- Transparent schemes for the establishing contact between researcher who discovered biomarkers and industry should be developed.
- The patenting system, at least in Germany, is not ideal; it is expensive and time consuming.

### *The EPMA Journal*: request/recommendation for upcoming publications

- Published results must associate with laboratory design, analytical validation strategies, analytical completeness and data managements.
- Further assistance for defining key parameters in assay evaluation and validation in research and clinical trial projects in prospective medicine must be outlined
- Prevalence, Sensitivity, Specificity, Accuracy, Likelihood ratio etc. should be defined
- Rare diseases and horizontal pathological processes like inflammation that underlie major pathologies should be considered in the special issues

# Summary Report - Special Session "Biobanking"

Ethically correct and technologically excellent bio-preservation and biobanking are central activities in field of PPPM. These activities are a major focus of the Europe, Middle East and Africa Society for Biopreservation and Biobanking (ESBB), which is a new society coming under the umbrella of EPMA. ESBB was formed in August 2010 with the broad mission of advancing the field of biobanking in support of research relating to healthcare, agriculture and the environment. ESBB has its focus on the EMEA region (Europe, the Middle East and Africa) and is also chapter of the International Society for Biological and Environmental Repositories (ISBER), a society with a global reach. ESBB works by exchanging, enhancing and disseminating relevant knowledge, by identifying and solving problems, and by encouraging high professional standards in the biobanking field. It is an open society for people interested in all aspects of biobanking, including biopreservation science, biobank management, quality assurance, informatics, automation, ethical, legal, regulatory and social issues. It holds annual conferences which bring together people interested in all these areas. In order to develop solutions to problems that may be identified at these conferences, the society encourages the formation of working groups that continue to function throughout the year.

In order for biobanks to provide the large sample sets that are required for many research studies, it is necessary for biobanks to form collaborative networks. There is an evident need for access rules and sample exchangeability to be created for multi-centre medical research networks in a global scale. For biobank networks to be effective, the different centres must collect samples according to the same standardised protocols so that samples are of similar quality, despite frequently observed unwillingness to share samples (the "My Syndrome") that is a major obstacle to be overcome in the field. Further, there is the need to find cooperative "Win-Win" solutions for sample supplier and researcher. Biobanks in the same network must also adopt common access rules that encourage multi-centre research collaboration. This experience will guide development of biobanking in centres collaborating in the new EurocanPlatform (European Platform for Translational Cancer Research).

Biobanks must safeguard the interests of patients who are asked to donate their samples and for this reason informed consent is required for research use of samples. The other aspect is the matter of tight collaboration with patient organisations and individual sample donors. If patients are fully informed and feel that their samples will be used by the institution treating them to advance medical care, they are probably more likely to give consent.

Biobanks also need to be well integrated with hospital practice, for reasons of quality, efficiency and economics. For example, the strong support of surgeons is required to ensure that samples are collected and processed with the minimum delay. If existing staff in the wards, operating theatres and pathology departments can take responsibility or at least facilitate the biobanking protocols this can result in increased efficiency and reduce the need to employ extra biobank staff.

To encourage the integration of biobanking into hospital practice and encourage patients to support biobanking initiatives, it seems likely that better education about the benefits of biobanking might be helpful. Again for reasons of economy and efficiency, this education about the benefits of biobanking might be best delivered in the context of education about PPPM in general to all sections of society: not only to current and potential patients, but also to healthcare professionals. To achieve this integration, educators in biobanking need to work closely with educators in other areas of PPPM. The union of ESBB and EPMA will help us to achieve this objective more effectively.

## Recommendations

To ensure the effective integration of high quality biobanking with predictive, preventive and personalised medicine, we make the following recommendations:

1. High quality biobanking is essential for the advancement of medical care, since it provides the samples needed for research purposes as well as for diagnostic and therapeutic purposes. This needs to be widely understood to ensure that this critical activity receives the full support it deserves.

2. Many different groups need to understand the value of high quality biobanking and it is particularly important that the medical profession is well informed on the subject so that they can educate other healthcare professionals and patients.

3. Biobanking must meet high ethical standards in order to win public trust and support. It must also meet high technical standards in order to provide samples that are fit for purpose. For these reasons, biobanking must be conducted in a professional manner, biobanks must have responsible, well trained staff and biobanks themselves must be certified and accredited.

4. Biobanks need to form cooperative networks in order to supply the large numbers of samples required for many research studies. Cooperative behaviour with sharing of samples is essential and needs to be encouraged, for example by suitable access policies.

5. Medical research needs to become an integral transparent part of routine medical care for the patients, in order to achieve that medical science is trusted to work with opt out and assumed consent for biobanking residual materials for observational research. In addition, biobanking for medical research needs the best results with regards to sample quality, annotation and consent rate. Surgeons, pathologists, and other medical and nursing professionals can play an important part in supporting high quality biobanking and should be partners in the process.

# Health Informatics and Bioinformatics if it is to be Practical in Predictive, Preventive and Personalised Medicine

***Informatics is central to preventive, predictive and personalised medicine,*** since it becomes essential to

- gather the complex data receiving from the emerging technologies, such as medical imaging, pharmaco-genetics, clinical *omics, pathology-specific molecular patterns, disease modelling, individual patient profiles, etc.
- undertake both the retrospective and prospective analysis of biodata, information and knowledge related to the epi/genome and its links to disease for translational medicine
- provide the help with information and knowledge to advance health related sciences and make healthcare services more reliable
- to analyse the complex technological inputs for making optimal clinical decisions
- learn from what has happened at the individual, process and health system levels to promote the integrative approach by PPPM
- create patient records and secure safety treatment of patient data bases
- promote standardisation in healthcare

***Currently there is a number of problems and challenges in creating the integrative bioinformatics for its application in daily clinical practice.***

After more than 20 years of standards development work there is no widely accepted and adopted standards for

- Grammar to communicate health care information – despite progress with standards like HL7v2.x and CDA
- Information structures – despite progress with models like HL7v3 RIM and OpenEHR
- Terminology – despite progress with SNOMED, LOINC, HUGO and many others
- Rules and knowledge – despite progress with GELLO and Arden Syntax.

Also, the bioinformatics itself faces serious concept related and technological problems. Hence, it is the bioinformatic analysis that has become the rate limiting step in genome sequencing. Further, huge data coming from epigenetics is massive and much more than generally recognised that represents a serious technological challenge for the storage and processing. The estimated size of human pangenome (individual genome multiplied with cell types/post-genome and world population) is $\sim 4 \times 10^{24}$ bytes (4YB). Therefore, making clinical sense of pangenomic information is very early in its development. Consequently, the current approach of diagnostic laboratories is concluded as unsustainable.

## Conclusions and recommendations

The central premise is that informatics is critical to the development of preventive, predictive and personalised medicine and even more important in its application but yet it is only receiving piecemeal attention.

Ten years after sequencing the human genome we do not have the knowledge, education or informatics tools to implement clinical genetics, genomics, proteomics, metabolomics or epigenetics into practical personalised medicine.

PPPM informatics needs to be a research and education theme in its own right. The healthcare related scientific community has too few informaticians and unfortunately many of those that we do have are without the breadth of understanding of the field to make the kind of advances that are needed. This is well illustrated by the existing gulf between health and bio-informaticians.

In terms of health policy, the attention should be focused on standardising registries. This is an area mostly funded by Governments and where the professions accept Government has a role. This approach should increase efficiency and improve outcomes of the registries, but of more consequence, it would be a strong driver for standardising communications in the broader health related scientific community and healthcare industry.

# Education in Predictive, Preventive and Personalised Medicine: EPMA Statement

**Innovative Initiatives in Education of Professionals**

The members of the Editorial BOARD of *The EPMA Journal* working weekly with the manuscripts and the peer-review procedure of the journal know very well, how difficult this task is. Different professional groups in personalised medicine have realised that they speak "different professional languages" less understandable for others. Consequently, great discoveries made/innovations triggered by one professional group, are frequently underestimated or even not valued at all by the others resulting in delays to the implementation of novel developments in personalised medicine across diverse areas. Therefore, in healthcare we need to develop a new culture among experts in order to promote the multidisciplinary field of personalised medicine. Our message is - the innovative PPPM-related educational programmes for professionals should be prioritised in the *Common Strategic Framework* (FP-8) as well as in other global and corresponding national programmes.

In order to promote innovative educational programmes, in collaboration with Springer and BioMedCentral, EPMA has developed worldwide pioneer initiatives creating the didactic materials for the field as follows:

**A.** *The EPMA Journal* that regularly updates both needs and achievements in the field of PPPM in application to major and rare pathologies.

**B.** The book-series "*Advances in Predictive, Preventive & Personalised Medicine*" (Book-series Editor-in-Chief: Olga Golubnitschaja, Figure 9); the book-series release is starting in 2012 with the following volumes:

- – "Healthcare Overview: New Perspectives", Volume Editor: Vincenzo Costigliola, Brussels, Belgium;
- – "New Strategies to Advance Pre/Diabetes Care: Integrative Approach by PPPM", Volume Editor: Mahmood Mozaffari, Augusta, USA;
- – "Neurodegenerative Diseases: Integrative PPPM Approach as the Medicine of the Future", Volume Editor: Silvia Mandel, Haifa, Israel;
- – "Drug delivery systems: Advanced technologies potentially applicable in personalised medicine", Volume Editor: Jorge Coelho, Coimbra, Portugal.

This important initiative should be obligatory supported and well used at the European level and worldwide.

**Educational Measures for Population: Promoting Participative Medicine**

Advanced personalisation in medicine is achievable solely in the case of participative medicine that meets the

**Figure 9. Book-series "Advances in Predictive, Preventive and Personalised Medicine" in preparation by EPMA/Springer to be released in the years 2012-2015 as the didactic material for specialised educational programmes – see [1].**

demands of patient advocacy groups focussed on individually created medical approaches. The reader will find a number of positive examples in each issue of *The EPMA Journal* and single volumes of the book-series "*Advances in PPPM*" concordant with this statement. It is evident that strong restrictions in the amount of education lead to dramatic deficits and costs that have repercussions in several branches of the society resulting in increased pressure within healthcare systems [2]. Our message is - new guidelines are essential to regulate the field in favour of educational measures for preventive programmes and advanced healthcare systems.

**References**

1. Advances in Predictive, Preventive and Personalised Medicine [http://www.springer.com/series/10051].
2. Golubnitschaja O, Costigliola V: **Common origin but individual outcomes: time for new guidelines in personalized healthcare**. *Personalized Med* 2010, **7**:561–568.