The potential and limits of personalized medicine

Position paper issued by the Swiss Academy of Medical Sciences[1]

0. Summary

Personalized medicine (PM, sometimes also known as individualized medicine) opens up new perspectives for understanding the origins and course of diseases, but also new approaches for the development of treatments. Recent years have seen dramatic advances in the field of PM; at the same time, however, various problems have become more pressing, and this position paper seeks to identify the key issues and outline possible ways of addressing them.

At present, PM is mainly applied in the following areas:

- prediction
- diagnostics
- therapeutics (including outcome evaluation)
- drug development

In the area of *prediction* (estimation of disease risk), both the potential and the limits of PM are apparent. In the case of monogenic (single-gene) disorders, PM can deliver sound predictions. But the vast majority of disorders arise from complex interactions of multiple genes and environmental factors. For oligogenic disorders (involving up to 10 genes), a prediction may still be made in some cases, but for polygenic disorders this is not usually possible, and genetic tests are therefore of limited value. Overall, a detailed family history is frequently more meaningful than predictions based on comprehensive genetic testing.

In *diagnostics*, PM already plays an important role. In oncology, in particular, different types of cancer are increasingly been diagnosed on the basis of their "genetic fingerprint". But also in other fields, such as cardiology, PM represents a valuable new diagnostic tool for many physicians.

In *therapeutics*, too, significant advances have been made possible by PM. It is now increasingly common for therapeutic agents to be approved which are only effective in groups of patients with specific molecular characteristics. This trend can be observed especially in oncology. As a result, not only is the efficacy of treatment improved for the patients concerned, but adverse effects are also reduced.

In *drug development*, no pharmaceutical company can now afford to ignore PM-related data. It is taken into account at every stage of the development process, including the planning of clinical trials.

However, because of the rapid pace of progress, various problem areas have emerged where action needs to be taken. The areas identified in this position paper are deficiencies in knowledge, proliferation of experts, dubious offerings, transparency, informed consent, data

[1] This position paper was prepared by Professor Andreas Papassotiropoulos of the Division of Molecular Neuroscience at Basel University. The draft was discussed in detail at a meeting of the SAMS Executive Board on 3/4 September 2012, and the revised version was subsequently adopted by circular resolution.

protection, demonstration of efficacy for new treatments, and patents and freedom of research.

To address these issues, the position paper outlines a number of possible measures:

1. Remedying deficiencies in knowledge

Though PM is still in its infancy, scientific knowledge is growing at a dizzying pace. It is therefore important that physicians should have adequate knowledge in the fields of epidemiology, medical genetics and medical statistics in order to make sense of the findings of PM. In addition, patients who seek information online expect their physicians to have an appropriate level of knowledge.

2. Strengthening medical genetics

Genetics is a key component of PM. Physicians are increasingly expected to be able to engage in genetic analysis and counselling. Appropriate coverage and strengthening of medical genetics in basic medical education would therefore appear to be indispensable.

3. Developing specialties

Because every disorder has its own distinct genetics and complexity, there is a need to promote appropriate specialist training and continuing education programmes, so that physicians have the opportunity to acquire PM-related knowledge in their own specialty. Patients, for their part, are entitled to know which physicians have the knowledge that is required to answer PM-related questions.

4. Giving greater weight to family history

Awareness of the importance of the family history should be promoted in medical education and training. In addition, there is a need for clinical guidelines on its interpretation and use, and efforts to impart the necessary knowledge and skills to medical students should be intensified.

5. Preventing unwelcome developments and creating transparency

Freely accessible PM-related services must be subjected to scientific review, so that potential users know what they should expect. This also includes measures to ensure transparency regarding potential conflicts of interest of any kind. Developments which cannot be regulated call for the adoption of clear positions on the part of the medical community.

PM offers tremendous opportunities to improve prediction, treatment and follow-up care for the benefit of patients. With sound scientific knowledge and evidence-based action, as well as appropriate setting of priorities, it should be possible to make the most of these opportunities while at the same time preventing unwelcome developments. To meet patient needs, it is crucial that the data collection and processing techniques associated with PM do not replace, but are integrated into, the personal relationship between physician and patient.

1. Background

Progress in medicine has always been closely linked to advances in technology. Whether through the development of new histological staining methods, the use of electromagnetic waves, or the production of novel metal alloys – to mention just a few examples – technology has repeatedly opened up new perspectives for medicine.

For over a decade now, another revolution has been under way in the biomedical field, based on two parallel developments. Firstly, increasingly rapid, high-resolution and comprehensive methods of molecular analysis have become available, which are also ever-more affordable (e.g. genome-wide polymorphism analysis, genome-wide DNA and RNA sequencing, epigenomics, proteomics, metabolomics). Secondly, the development of integrated analytical methods in bioinformatics has made "big data" more amenable to interpretation.

As a result, new perspectives are opening up for our understanding of physiological and pathophysiological processes, the origins and course of diseases, and therapeutic effects. In addition, this new information and knowledge is becoming universally accessible online – rapidly and sometimes in an unfiltered manner. The combination of complex technological developments, their application in medical science and the global availability of information will alter our way of thinking about health and disease, thus transforming medicine itself. This will inevitably lead to radical changes and raise numerous questions of a scientific, ethical and health-policy nature. In Switzerland, therefore, as elsewhere, the time has now come to actively address these developments and the associated questions. Here, medical science has a responsibility to promote an evidence-based and ethically sound opinion-forming process.

2. Definition

As the above-mentioned advances in "omics" technologies have made it possible to obtain and (to a certain extent) interpret large amounts of medical information – including whole-genome sequences – from individuals, the term "personalized medicine" has become widely used. Also in use are the terms "individualized", "customized", "stratified" or "precision" medicine. It should be borne in mind that the medical approach known as personalized medicine is not concerned with specific personal characteristics, but with individual biological structures and processes.

For the purposes of this position paper, PM can be defined as a medical procedure in which *an individual's molecular data is obtained and analysed using information technology tools with a view to individualized prognostic assessment, counselling and/or treatment for the individual concerned*.

Depending on the type of data collected, the definition can be narrowed (e.g. through restriction to genomic data, the approach known as "genomic medicine") or broadened (to include other data – e.g. anamnestic or disease-related data, known as "data-based medicine").

However, the procedure described above only deserves the name "medicine" if the process begins prior to data collection and extends beyond the establishment of a prognosis or a recommendation. If PM is to meet the individual needs of the patient or user, raw data is not sufficient: what is required is a personal relationship to a professional or physician. Thus, submitting a biological sample (possibly accompanied by a completed questionnaire) and subsequently receiving a printed recommendation does not (in itself) amount to PM.

The explosion in the use of the above-mentioned terms suggests that this approach may represent a novel concept in medicine. Although the methods employed by PM are indeed novel, the underlying idea is as old as medicine itself. The aim of PM is to *optimize healthcare for every individual at every stage of a disease, from prevention to treatment* [1], by analysing individual biological traits, environmental factors and contextual influences throughout the individual's lifespan. In fact, this goal has characterized medical thinking since the time of Hippocrates. Focusing on the unique individual is a mark of any appropriate medical endeavour. According to databases of contemporary medical literature, the use of the term "personalized medicine" has increased exponentially since the beginning of this century. But the topic is also discussed in a few articles dating back to the 1970s and 1990s. In these publications, fears are even expressed about the survival of PM – i.e. the emphasis on individuals and patient-centred care – in view of the increasingly technological and "algorithmic" nature of medicine [2, 3]. These concerns reflect the insight that human beings are more than the sum of the data, which can be collected about them. Essentially, they can only be fully comprehended in face-to-face encounters. It is therefore vital that the data collection and processing techniques associated with PM do not replace, but are integrated into, the personal relationship between physician and patient.

3. Applications of personalized medicine

As explained above, the concept of PM is neither new nor unusual, but is fundamental to medical thinking. Nonetheless, medicine has reached a point where technological and analytical advances are vastly expanding the repertoire of preventive, diagnostic and therapeutic options, and in some cases transforming diagnostic and therapeutic processes. It will therefore be useful first to describe the areas in which modern PM is applied. As the most rapid and wide-ranging advances – and the most relevant for medical practice – are currently being made in genomics, particularly frequent reference will be made to this field. Although similar progress is also already evident in the fields of gene expression profiling, epigenomics, proteomics and metabolomics, this will probably not fundamentally alter the scope and application of PM.

At present, the applications of PM come under four headings: (1) prediction, (2) diagnostics, (3) therapeutics (including outcome evaluation) and (4) drug development.

3.1. Prediction

"Prediction" refers to presymptomatic risk assessment and diagnostics (including prenatal screening) with the aim of early prognosis, diagnosis and possibly treatment or preventive measures [4]. In a few cases, genome-based prediction already forms part of our healthcare system, e.g. for Huntington's chorea. Given the implications not only for the individual, but for the entire family receiving a genome-based prediction of a dominant trait, the intensive counselling efforts required by law are certainly appropriate and necessary. While this position paper does not aim to explore the ethical dimensions of genome-based prediction, it is important – indeed, indispensable, given the overabundance of so-called predictive tests – to specify when exactly genome-based prediction is *scientifically* justifiable and feasible.

As a general point, it should be noted that prediction of any kind (including genome-based prediction) involves probabilistic statements. However, the appropriate communication of probabilities is a complex matter [5, 6].

The validity of a prediction is based on the *effect size* of the predictor. Accordingly, in *monogenic disorders*, where the effect size of a genetic variation is high by definition, PM can make a significant contribution. In *oligogenic disorders* (e.g. certain types of cancer), which are influenced by a small number of genetic variations (rarely more than 10), accurate

prediction is much more difficult. This is partly because environmental factors play a major role in oligogenic disorders, but also because the disease-associated variants may interact, complicating any calculations and thus making it more difficult or impossible to generate accurate predictions. Nonetheless, using genetic epidemiological studies in conjunction with genome-wide analysis, it is possible to model and often "predict" effect sizes and gene-gene interaction effects, although the validity of the predictions is naturally much lower than for monogenic disorders (see e.g. [7]).

This problem is accentuated in *polygenic disorders* (e.g. coronary heart disease, hypertension, dementia, psychiatric conditions). In most cases, the multiplicity of risk-associated genetic and non-genetic (environmental) factors, and the highly complex interaction patterns, mean that reliable prediction is impossible at the individual level. It should not be forgotten that even a significant genetic risk factor identified on the basis of statistical group analysis (e.g. the apolipoprotein E4 allele in Alzheimer's disease) may be of little value when it comes to individual prediction [8, 9]. It should also be borne in mind that every disorder has its own genetics and complexity. The genetics of hypertension differs from that of pancreatic cancer, which in turn differs from that of bipolar affective disorder, even though all these conditions can be subsumed under the heading of polygenic disorders.

In recent years, high-resolution genome-wide association studies (GWAS) – analysing millions of genetic polymorphisms in very large case-control populations (sometimes over 100,000 subjects) – have identified numerous replicated genetic risk factors and susceptibility genes for a variety of polygenic disorders. These studies represent a major advance in our understanding of the pathophysiology of the disorders concerned and have already led to new therapeutic developments [10].

However, when it comes to calculating individual disease risk on the basis of the identified variants – a prospect exploited for promotional purposes by certain companies – the results are sobering: despite massive investments in extensive genetic studies, the identified variants by no means fulfil the criteria which are applicable for predictive tests. Given the complexity of polygenic disorders, this is scarcely surprising. But it is interesting to note that, as has been repeatedly observed, any – however significant – "predictive" effect of genetic risk variants is statistically abolished if *family history* is taken into account in the model (see e.g. [11]).

In other words, *if one wishes to estimate the individual risk of a polygenic disorder, a detailed family history is by far superior to genetic testing for risk-associated variants.* A thorough family history will always document the totality of genetic and non-genetic (but shared) risk factors within the family, as well as the complex patterns of interaction among these factors, and is thus much more meaningful than any – however comprehensive, but ultimately isolated – genetic analysis. For practitioners, the thorough family history represents a highly effective tool for carrying out a sound risk assessment, very much in the spirit of PM. Unfortunately, history-taking (both family and personal) is often neglected in day-to-day practice and is not optimally integrated into healthcare [12].

3.2. Diagnostics

Today, PM already makes a significant contribution to the diagnostic and prognostic assessment of disorders, with a huge potential for further development. The pioneering discipline is oncology, which employs modern PM-based methods to arrive at a molecular diagnosis and molecular characterization of malignancies. Oncology's advantage lies in the fact that genomic, epigenomic, and proteomic studies can be carried out directly on tumour tissue, permitting detailed subtyping of the disease in question. In a variety of cancers (breast, colon, lymphoma, leukaemia, etc.), PM has produced major and clinically relevant

advances in knowledge. Several complete genomes have already been sequenced – for malignancies such as acute myeloid leukaemia and non-small-cell and small-cell lung cancer [13-15]. Large international consortia are working on the complete characterization of tumour tissue – from DNA to protein – e.g. for glioblastoma and for breast cancer.

But other specialties as well as oncology are using PM to expand the diagnostic and prognostic armamentarium. In cardiology, for example, metabolomic and proteomic approaches are being used to study whether it is possible to discriminate between different stages of acute myocardial infarction and unstable angina [16, 17]. In addition, various blood-based gene expression tests are being validated for assessment of the severity of coronary artery disease [18, 19]. In summary, it may be concluded that PM certainly plays a clinically important role in improving diagnosis (including prognosis) for a wide variety of conditions.

3.3. Therapeutics (including outcome evaluation)

In the area of therapeutics, PM is well advanced. Once again, oncology is the pioneering discipline, particularly in its focus on pharmacogenetic parameters. Of course, developments in this area of treatment – and in outcome evaluation – go hand in hand with developments in diagnostics, i.e. improved subtyping based on molecular characteristics of tumours. Increasingly, for the treatment of various types of cancer, substances are being approved which are only effective in certain molecular subgroups [4]. Here, too, large-scale programmes are under way (e.g. in France, the US, Norway and the UK) with the goal of developing individually effective treatments on the basis of complete molecular characterization of tumour biopsies. The relevance of these developments lies not only in improved efficacy, but also in the avoidance of unnecessary and potentially harmful treatments and in the evaluation of therapeutic outcomes. Benefits should arise not only for oncology, but in principle for all areas of clinical medicine – e.g. the spectrum of cardiovascular, metabolic, neuropsychiatric or dermatological disorders. If appropriately used, PM will help to significantly improve therapeutic options across the whole of medicine.

3.4. Drug development

The use of PM-related methods is also of major importance in the development of new drugs. Genomics, epigenomics and proteomics play a key role at every stage of the development process (target identification, target validation, lead development, preclinical phases, clinical phases, market) [1]. In addition, it is becoming evident that even *before the introduction of a new drug* selective efficacy should be evaluated using PM-based methods. While the clinical trials required for this purpose (in particular, Phase III studies) may become even more elaborate as a result, PM-based stratification of subjects will lead to increased effect sizes, so that the number of participants to be recruited for a study can be reduced. It is obvious that PM will have significant and clinically beneficial effects on drug development. Essentially every pharmaceutical company now takes PM into consideration in the development of new drugs for all areas of clinical medicine.

4. Problem areas

In connection with PM, as for any other technological advances, numerous questions arise which need to be discussed as early as possible in order to prevent unwelcome developments. Below, eight problem areas are listed which require particular attention.

4.1. Deficiencies in knowledge

The relevance and the findings of PM cannot be appreciated or correctly interpreted without statistical and epidemiological knowledge. Central to PM are probabilistic statements *which always need to be understood in a given context*. An 80% probability of responding to a

particular drug and an 80% probability of developing an incurable disease have quite different meanings for the individuals concerned. The statistical significance calculated for a susceptibility gene says nothing in itself about its predictive value. A risk allele with an odds ratio of, say, 3 may still be of no relevance for the prediction of the trait in question. Surprisingly enough, the debate about PM reveals striking deficiencies in various parties' grasp of basic statistical and epidemiological principles. These deficiencies in knowledge need to be remedied as rapidly and systematically as possible. In addition, concrete measures should be taken to counter the lack of attention paid to (family) history-taking, as discussed above.

4.2. Proliferation of experts

PM encompasses a broad range of knowledge, including aspects of medicine, biology, biotechnology, information sciences and ethics. As a result, academic discussion of PM is conducted along multidisciplinary lines, as is indeed desirable. However, the purpose of PM should not be overlooked: PM aims to *optimize healthcare for every individual at every stage of a disease, from prevention to treatment*. As the voices of experts can exert an influence within this extremely important field, it is time to recognize the harm which may be caused by self-proclaimed experts and the need for PM experts to meet certain minimum requirements.

4.3. Dubious offerings

"You carry a gene variant which leads to higher intelligence, if you were breast-fed." The availability of "predictive" tests of this kind is apt to discredit PM in its entirety. Such genetic tests are offered on a direct-to-consumer (DTC) basis by well-known companies, operating internationally, as well as genetic tests designed to predict a good or bad memory, schizophrenia or suicidal tendencies. The real problem revealed by these unscientific offerings is that, in the PM sector, a market has become established which cannot be controlled or regulated. In Switzerland, DTC tests of this kind – not ordered by a physician – are essentially prohibited. Here, however, prohibitions are of little use, as they are so easy to circumvent in a globalized world. This means that it is all the more important to subject these offerings to a scientific review, and to make the findings universally accessible, so that potential users of these services know what they should expect. A number of national and international professional bodies have already adopted clear positions, issuing warnings about these services. For example, recommendations concerning Internet-based genetic testing have been published by the Expert Commission for Human Genetic Testing (GUMEK) (www.bag.admin.ch/gumek).

Apart from the unscientific nature of certain offerings, developments in the area of DTC genetic testing highlight another problem – *the lack of genetic counselling* (cf. also Section 4.5). Some DTC services are certainly valid, such as the detection of mutations in genetic disorders with a dominant or recessive pattern of inheritance (e.g. Huntington's chorea). But users receive the results in a direct, unfiltered form, without the necessary additional information or appropriate counselling. This practice cannot legitimately be defended by invoking people's – naturally indisputable – right of freedom to obtain information. In fact, what is involved is an ethically unacceptable omission, since the "information" in question concerns complex medical matters which require careful interpretation.

4.4. Transparency

PM is of substantial interest not just scientifically, but also economically. The potential economic benefits of this new direction in medicine are significant. Precisely for this reason, and because the health of every individual is at stake, the greatest possible transparency is essential. Everyone – experts, influential contributors to debates, PM service providers, initiators of public discussion platforms or online forums – must justify their personal interest

and disclose any commercial ties. Although this is a natural requirement for a sensitive area of this kind, the question of implementation needs to be tackled very seriously.

4.5. Informed consent

In cases where large amounts of data possibly relevant to health are to be collected in a single step and in the absence of a clearly defined medical question, the requirement that the subject should receive full, comprehensible information about the benefits and risks of the procedure must be seen in a new light. Of course, whenever genetic testing is performed, a duty already exists to inform subjects about the possibility of unexpected results, the significance of which may be unclear; to date, however, such findings have been of incidental importance given the actual purpose of the test. The new testing options deliver such an abundance of potentially relevant information that to provide comprehensive information is problematic even from a purely quantitative viewpoint. Counselling is further complicated by the fact that the significance of a great deal of the information remains unclear and may change in the near future. The specification of requirements for valid informed consent in relation to PM is a matter calling for careful ethical and legal assessment.

This question raises particular difficulties if tests are to be performed in persons lacking capacity, especially children and newborns, and also in cases of prenatal or paternity tests.

4.6. Data protection

By definition, the information and data collected in connection with PM is highly personal and sensitive and therefore deserves special protection. The personnel involved – not just medical professionals – are not yet fully aware of this responsibility. Internet users should be explicitly informed about the risks associated with the use of such sensitive data (their own and that of third parties!).

4.7. Demonstration of efficacy of new treatments

When testing the efficacy of new drugs, PM allows subjects to be stratified into different subgroups. If a substance appears to be ineffective in the whole population but to show good efficacy in a subgroup, the problem arises of deciding to what extent the evidence of efficacy for this (possibly small) subgroup can be considered adequate. The option of claiming orphan disease status for such subgroups would need to be dependent on a careful demonstration of clinical efficacy and an appropriate adverse effect profile.

4.8. Patents and therapeutic/research freedom

It is conceivable that the manufacturer of a substance could patent a package consisting of the collection of specific diagnostic data, a linking algorithm and an individualized treatment specified on this basis. This could, firstly, restrict the therapeutic freedom of the attending physician (e.g. to incorporate the treatment of other factors not covered by the algorithm); at the same time, and above all, such a patent could impede research seeking to improve individualized treatment for this condition.

5. Possible measures

The following measures are designed to address the problem areas described above and are not intended to be definitive. PM is still in its infancy and it may be assumed that, as time goes by, additional points will emerge in other areas, requiring further evaluation. Nonetheless, a need for action already exists today.

5.1. Remedying deficiencies in knowledge

Knowledge in the fields of epidemiology, medical genetics and medical statistics should be improved among the medical profession. Many questions associated with PM involve

statistical and epidemiological matters. In addition, we must be aware that in the online era most patients consult the Internet and expect their physician to provide explanations, interpretations and answers. Here, a lack of knowledge will engender unnecessary unease and anxiety.

5.2. Strengthening medical genetics

The analysis and interpretation of genome sequences is an important component of PM. Accordingly, all physicians who treat patients are increasingly expected to be able to provide genetic counselling. Appropriate coverage and strengthening of medical genetics in basic medical education would therefore appear to be indispensable.

5.3. Developing specialties

PM entails further specialization, or subspecialization, and it differs markedly from one medical discipline to another. As mentioned above, every disorder has its own distinct genetics and complexity. Today, it is already the case that general genetic knowledge is no longer sufficient to comprehend the genetic complexity of each individual polygenic disorder, or to keep pace with the growth of scientific knowledge. At the same time, every GP, cardiologist, surgeon, psychiatrist, dermatologist, etc., will soon be confronted with questions from patients concerning PM in their particular field. Appropriate specialist training and continuing education programmes should therefore be promoted, so that physicians have the opportunity to acquire the specific PM-related knowledge they need for their own clinical purposes, without having to undergo specialist training in the entire field of medical genetics. Patients, for their part, are entitled to know which physicians have the knowledge that is required to answer PM-related questions. Ultimately, (keeping abreast of) PM-related knowledge will become an integral part of every medical specialty.

5.4. Giving greater weight to family history

Awareness of the importance of the family history should be promoted in medical education and training. In addition, there is a need for clinical guidelines on its interpretation and use, and efforts to impart the necessary knowledge and skills to medical students should be intensified.

5.5. Preventing unwelcome developments and creating transparency

As discussed in more detail above, certain developments which cannot be regulated nonetheless call for the – visible – adoption of clear positions on the part of the medical community. Freely accessible PM-related services must be subjected to a scientific and universally available review, so that potential users know what they should expect. Here, the medical sciences have a particular responsibility. This also includes measures to ensure transparency regarding potential conflicts of interest of any kind.

6. Outlook

PM is continuously changing the way we think about medicine. It offers tremendous opportunities to improve prediction, treatment and follow-up care for the benefit of patients. Only with sound scientific knowledge and evidence-based action – as well as appropriate priority-setting in basic education, specialist training and continuing education – will it be possible to make the most of these opportunities while also averting unwelcome developments.

Although the primary focus of PM is on medicine at the individual level, its importance for the entire discipline and for public health should not be overlooked. Not only can the collection of large amounts of data give rise to interesting lines of research, but there is also a need for

careful monitoring of how a multitude of individualized recommendations affects the health behaviour of the population as a whole. The effects of increased demand for counselling and the ethical questions raised by PM also need to be analysed in depth.

Literature

1 Chan IS, Ginsburg GS. Personalized medicine: progress and promise. Annu Rev Genomics Hum Genet. 2011;12:217–44.

2 Gibson WM. Can personalized medicine survive? Can Fam Physician. 1971;17:29–88.

3 Arnold RM, Forrow L. Rewarding medicine: good doctors and good behavior. Ann Intern Med. 1990;113:794–8.

4 Meyer UA. Personalized medicine: a personal view. Clin Pharmacol Ther. 2012;91:373–5.

5 Hoffrage U, et al. Medicine. Communicating statistical information. Science. 2000;290:2261–2.

6 Kurzenhauser S, Hertwig R. How to foster citizens' statistical reasoning: implications for genetic counseling. Community Genet. 2006;9:197–203.

7 Grassmann F, et al. Modelling the genetic risk in age-related macular degeneration. PLoS One. 2012;7:e37979.

8 Relkin NR, et al. The National Institute on Aging/Alzheimer's Association recommendations on the application of apolipoprotein E genotyping to Alzheimer's disease. Ann N Y Acad Sci. 1996;802:149–76.

9 Seshadri S, et al. Genomewide analysis of genetic loci associated with Alzheimer disease. JAMA. 2010;303:1832–40.

10 Hirschhorn JN, Gajdos ZK. Genome-wide association studies: results from the first few years and potential implications for clinical medicine. Annu Rev Med. 2011;62:11–24.

11 Ripatti S, et al. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. Lancet. 2010;376: 1393–400.

12 Guttmacher AE, et al. The family history – more important than ever. N Engl J Med. 2004;351:2333–6.

13 Lee W, et al. The mutation spectrum revealed by paired genome sequences from a lung cancer patient. Nature. 2010;465:473–7.

14 Ley TJ, et al. DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. Nature. 2008;456:66–72.

15 Pleasance ED, et al. A small-cell lung cancer genome with complex signatures of tobacco exposure. Nature. 2010;463:184–90.

16 Mateos-Caceres PJ, et al. Proteomic analysis of plasma from patients during an acute coronary syndrome. J Am Coll Cardiol. 2004;44:1578–83.

17 Sabatine MS, et al. Metabolomic identification of novel biomarkers of myocardial ischemia. Circulation. 2005;112:3868–75.

18 Rosenberg S, et al. Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. Ann Intern Med. 2010;153:425–34.

19 Wingrove JA, et al. Correlation of peripheral-blood gene expression with the extent of coronary artery stenosis. Circ Cardiovasc Genet. 2008;1:31–8.