Tailoring of medical treatment: hemostasis and thrombosis towards precision medicine

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By integrating genetic, biomarker, phenotypic, and psychosocial characteristics that distinguish one patient from others with similar clinical presentations, the aim of precision medicine is to target treatments to individual needs. Presently, simplified individual pharmacokinetic analyses spare hemophilia patients from unnecessary exposure to replacement treatments and ultimately reduce costs. Likewise, successful clopidogrel use in vascular medicine is based on the integration of genomics, lifestyle and environmental data. Beyond the development of medical devices that are unique to a patient, or treatments tailored to specific molecular and non-molecular targets, through the use of big biobanks and electronic medical records that integrate biological information with clinical data, it is likely that algorithms will be developed to classify individuals into subpopulations differing by their susceptibility to bleeding and/or thrombosis, by the severity of their diseases, and/or by their response to specific treatments. An inherent risk of such strategies is differential access to treatments for individual patients, families, and communities, since costs for therapies depend on the size of the target population. Fostering standardization of care in the era of precision medicine implies a public health perspective and a supportive institutional environment to harmonize the interests shared by healthcare providers, patients and communities, to acknowledge the individual roles and responsibilities in decision-making, and to balance the generation of long-term knowledge and short-term health gains. Integrating efficacy, safety, and cost-effectiveness is a challenge for precision medicine and the opportunity for it to generate early measurable health benefits and to live up to its promise.

A clinical case

A 19-year old patient was referred to our Hemophilia and Thrombosis Center because of an ischemic stroke (confirmed by magnetic resonance imaging) that occurred after 3 months of oral contraceptive use. The girl was the daughter of a patient already attending the Center for type I von Willebrand disease, but her personal and family history had been uneventful. The reason for the referral was to decide whether she should be given long-term treatment with a low dose of aspirin. The laboratory work-up revealed that, in addition to type I von Willebrand disease, she was homozygous for the prothrombin G20210A mutation, and the same thrombophilic mutation was found in other members of the family. Heterozygous factor V Leiden or the G20210A prothrombin mutation may compensate for low factor VIII or IX levels in hemophilia, resulting in more efficient thrombin generation and ensuing attenuation of clinical symptoms[1] and the risk of thrombotic complications.[2] This information was interpreted to account for the poor bleeding tendency of the patient. She was informed that: (i) despite recommendations concerning drugs to avoid in patients with von Willebrand disease, chronic daily treatment with low-dose aspirin (100 mg/day) was conceivably helpful in her case, and (ii) prophylaxis with low-molecular weight heparin/warfarin would be possible in specific, at-risk situations. Over the last 10 years in which she took low-dose aspirin daily, she had no inappropriate bleeding events, no stroke recurrence, and had two successful pregnancies.

When guidelines cannot be relied on

To give advice on an appropriate treatment, there must be a high level of evidence available, based on multiple randomized controlled clinical trials, which the guidelines can draw on to justify their recommendations. Thus, the strength of guidelines is when they are applied to areas in which large trials have provided convincing evidence of the benefit of certain interventions.[3] However, in spite of the fact that each patient is treated with the treatment that everyone else with that condition receives, certain medical interventions are more effective or cause fewer side effects in some patients than in others.[4] This is usually accounted for by inherent limitations of guidelines. The problem-solving approach of clinical trials employs methods (inclusion/exclusion criteria, randomization, etc.) theoretically free from bias, and is finalized at answering a single question at a time. In real-world practice, however, there is a context rather than a single question: patients simultaneously raise multiple clinical problems; there are no inclusion or exclusion criteria, and it is uncommon that the individual patient in front of us fits into the inclusion criteria for the trials used to formulate the guidelines while not having any of the exclusion criteria.[5] Thus, in everyday practice, the evidence from guidelines applies to a middle segment of a patient population, but not to the two extremes [patients not entirely meeting the eligibility and/or exclusion criteria of the trial(s) on which the guidelines are based]. If the prevalence of a disorder is low, large prospective studies, and, in turn, evidence-based recommendations for clinical management, remain improbable. In such settings, registries are the only manner to collect enough data on optimal therapeutic approaches, and to attempt risk– and cost–benefit evaluations for different treatment options. However registries have a variety of limitations, the first and foremost being the lack of randomization. All in all, there are areas in medical practice in which there is uncertainty concerning the real state of a patient,[6] and for which definitive conclusions cannot be drawn. In addition to uncertainty concerning the real state of a patient,[6] a lack of compliance of healthcare professionals with guidelines may also be related to doctors' preferences with respect to the outcome of the decision.[7] "Less algorithmic" individualized guidelines are now available to help doctors define the best strategy for a given patient.[8] Since an algorithm is a problem-solving system in which there is a single answer to a given question, the advent of individualized guidelines acknowledges (but does little to attenuate) the uncertainty associated with any medical decision. Being made in a context of uncertainty and risk, since statistics cannot take into account the individual context of each medical decision, medical decisions cannot be free from

Figure 1. Implementing clinical care: precision medicine. The purpose of a comprehensive system of precision medicine is to establish the information base and infrastructure to provide more precise individual information, to make (new) clinical treatment more efficient. This system is aimed at integrating huge amounts of data with the goal of improving health, and implies targeting treatments to the needs of individual patients on the basis of genetic, phenotypic and psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations.[11]

biases.[5] Especially (but not exclusively) in areas of uncertainty, the safety and quality of care we provide often relies on additional information that may be relevant for the patient in front of us and that the individual physician has gathered. For example, in a program for patients undergoing percutaneous coronary interventions, which was implemented in nine large US centers, informing physicians of a patient's bleeding risk led to a reduction in the occurrence of bleeding (from 1.7% to 1%, -44%).[9] Regardless of whether the reduction was truly brought about by the precision of the prediction, or by raising the general awareness of the risk, implementation of personalized bleeding risks helped doctors to identify subjects truly at risk of bleeding and to use techniques to avoid hemorrhage appropriately.

The promise of precision medicine

How precision medicine will enter clinical care and affect the vision of medicine is now being delineated, and the manner in which it will allow for more efficient clinical research and facilitate scientific discoveries is being clarified.[10] Precision medicine (Figure 1) implies targeting treatments to the needs of individual patients on the basis of genetic, phenotypic and psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations.[11] Inherent to this definition is the concept of integrating (in electronic health records) individual-level information (e.g. genomics, biomarkers, physiological, lifestyle and other environmental factors) with the ultimate aim of providing better clinical care for each patient.[12] In addition to a dramatic improvement and price reduction in genome sequencing,[13] the prospect of applying precision medicine broadly is supported by large-scale biological databases, powerful methods for characterizing patients (e.g. proteomics, metabolomics, genomics, diverse cellular assays), mobile healthcare technology, and computational tools for analyzing large sets of data.[14] Although imaging techniques[15] and individual differences in terms of the unique circumstances of the person (personality, resources, culture, individual behavior) and of his/her environment (family, friends, communities, religion) are keys to improve healthcare,[16] genomics is the leading driver of an early identification strategy, once individual profiles (e.g. polymorphisms) are available.[17] Following the original observation of a common association between ankylosing spondylitis (or insulin-dependent diabetes) and the alleles of genes of the HLA system,[18] the concept of employing genetics to make major contributions to clinical practice has been progressively extended to the entire human genome. In particular, since cancer is a disease of the genome, oncology has been the obvious target of such a strategy.[19] For example, targeting HER2 overexpression with the monoclonal antibody, trastuzumab, improved outcome in metastatic breast cancer;[20] the tyrosine kinase inhibitor, imatinib, transformed the care of patients with chronic myeloid leukemia to a manageable chronic disease,[21] and the identification of somatic mutations in the *BRAF* gene in the majority of malignant melanomas[22] enabled the development of vemurafenib which specifically targets the underlying molecular lesion.[23] Large–scale cancer whole genome sequencing projects are now expected to provide a complete catalogue of genomic alterations in primary cancers, to elucidate the mutational patterns and influences across the natural history of cancers, and to provide targeted therapies and newer approaches to cancer prevention.[24,25]

In keeping with the genetically-based improved care of patients with cancer, the concept that treatments should be tailored to the individual patient - taking into account relevant personal data – is spreading into all areas of medical practice. Recombinant clotting factor concentrates have revolutionized the care of hemophilia in the western world. However, their relatively short half-lives necessitate frequent intravenous administration of concentrates (at least 2-3 times a week) associated with peaks and troughs of circulating factor levels and occasional breakthrough bleeding when levels drop below 1%. In addition to being invasive, prophylaxis is demanding and not curative, and the cost is logarithms higher in the 25%-35% of patients with severe hemophilia A who develop neutraliz-

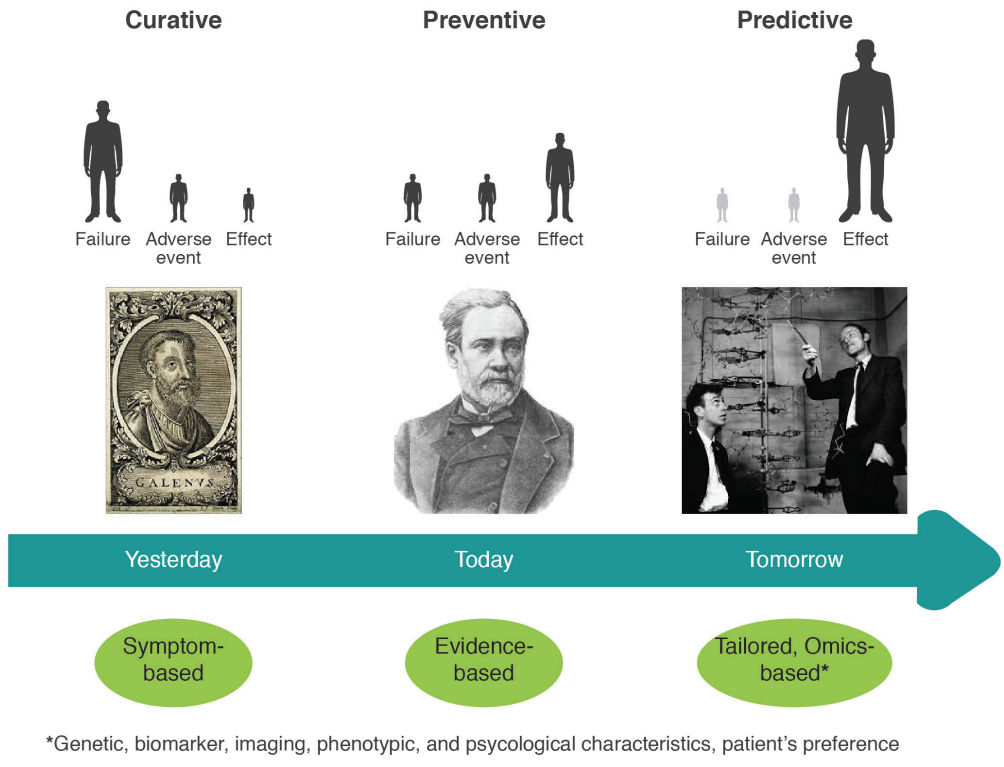

Figure 2. The promise of precision medicine. "Medicine was, in its history, first of all curative, then preventive and finally predictive".[18] This change in medical attitudes was due to the advances that have entered medical practice: new imaging techniques and powerful strategies in biological investigation have dramatically improved our ability to monitor early stages of disease development. In addition, increasingly effective treatments (organ transplantation; smart drugs; targeted strategies, vaccinations) have progressively reduced the rates of failures and side effects and in turn improved the cure of (chronic) diseases.

ing inhibitors.[26] Simplified pharmacokinetic studies have shown significant differences in the individual half-life of clotting factors.[27] This information has major implications for the management of prophylaxis in hemophilia. Appropriate treatments will spare patients from unnecessary exposure to replacement treatments and ultimately reduce costs. This may be especially important for novel clotting formulations with extended half-lives.[28]

Although antiplatelet treatment significantly reduced stroke and coronary events in secondary prevention trials, 10%-20% of patients have recurrent events during long-term follow-up.[29,30] Residual platelet reactivity (i.e. an incomplete response to the antiplatelet treatment) in subjects on treatment with clopidogrel or aspirin predicts recurrent events.[31,32] Similar to haplotypes of cyclooxygenase-1 that modulate platelet response to aspirin,[33] polymorphisms in the *CYP2C19* gene (most often *CYP2C19*2*) associated with a 20%-25% production of inactive metabolite, diminish the response to clopidogrel.[34] Compared to wild-type subjects, carriers of polymorphic alleles of the *ABCB1* gene, which modulates clopidogrel absorption, had a higher rate of cardiovascular events at 1-year follow-up.[35] Among subjects under treatment with clopidogrel, carriers of these polymorphisms had a 50% higher risk of cardiovascular death, acute myocardial infarction, and stroke.[35] In addition to genetically determined cases, an incomplete response to clopidogrel may be the result of poor compliance by the patient, clinical conditions leading to an abnormally high platelet turnover (e.g. high pretreatment platelet reactivity, high glucose levels, inflammation, hypercoagulable states, low fibrinolytic potential), or the simultaneous administration of interfering drugs.[36] Appropriate information should be collected prior to the day of a potential vascular intervention so that, at the time of prescribing, relevant data are available to the practitioner. Thus, the integration of genomics, lifestyle and environmental data is key to successful clopidogrel treatment. Prospective randomized trials did not demonstrate a clinical benefit of using platelet function testing to adjust antiplatelet treatment.[37-39] However, low event rates in current antiplatelet practice would require very large numbers of enrolled patients to provide reliable conclusions. Whether, however, electronic health records should be pre-populated with other data, in addition to genetic and pharmacogenomics data, providing clinicians with new critical information about the risk of an "incomplete response" to clopidogrel is so far unknown.[40,41]

Toward precision medicine: challenges and opportunities

It is conceivable that precision medicine-based interventions will improve clinical outcomes for individual patients and minimize the risk of failure or adverse health outcomes in those less likely to have a response to a particular treatment. (Figure 2) It is also obvious that our ability to handle vast amounts of new knowledge and treatment options within the framework of everyday practice is critical to define the impact of an initiative that is

expected to transform morbidity and mortality patterns. Hurdles to overcome and directions to be followed in the early phases of precision medicine in order for it to gather strength and to live up to its promise have been identified (Table 1). In particular, it is imperative that the investment in precision medicine is oriented to a public health perspective to help ensure accessibility and generalizability, to assess methods of implementation, and to provide an appropriate balance between generation of long-term knowledge and short-term health gains.[42] Nevertheless, how precision medicine, by identifying the needs and improving the outcomes of an individual patient, might be a means of providing the best available health care at a population level is matter of debate.[11,43] Points for debate, stemming from real-life practice in hemostasis and thrombosis, are summarized in the following paragraphs.

• Costs should be affordable. Considerable planning of daily activities that would be taken for granted by most people living without hemophilia is still required, particularly in children and adolescents. However, compared to the on-demand strategy, the prophylactic use of clotting products to maintain circulating clotting factor levels ≥1% of normal has resulted in a dramatic reduction in bleeding frequency and associated complications e.g. hemophilic arthropathy. By paying a cost for factor concentrates (≈€ 150,000/adult/year) that is higher than that of on-demand treatments, the life expectancy of European and America patients with severe hemophilia on prophylactic treatment has normalized to that of age-matched healthy males in their community.[44] In terms of calculation of human capital, the healthier a population, the more productive it is.[45] The quality of life of patients with severe

Table 1. Providing the appropriate health care infrastructure to deliver precision medicine in routine clinical settings: health plans and issues for debate.

Issues	Outline(s)	Suggested readings
General	By means of preemptive pharmacogenomic data and clinical decision support integrated into an electronic medical record, prescribers can deliver genome-guided therapy at the point of care.	(14),(17), (40), (68) *
Coping costs with changes	The investment in precision medicine should not worsen existing health disparities and should generate early measurable health benefits.	(69)
Avoiding ethnicity/ race-driven discrimination	Using genomic, clinical, personal and environmental data collected from very large numbers of individuals from various populations, and connecting their health records, "non-responders" to a treatment might be identified as largely belonging to definite minority, racial, ethnic groups or underserved populations. Appropriate protections needed against discrimination in the access to treatments.	(70),(71) **
The "unpatients' issue"	Detection of susceptibility genes in the absence of the simultaneous development of a preventive or therapeutic *ad hoc* strategy will increase physician visits, laboratory tests, and patient anxiety. The poor information about the pathogenicity of most genetic variants is a barrier to the translation of experimental findings to clinical care. A systematic approach to determining genetic causality is mandatory.	(71),(72) ***
The impact of "Personomics"	Similar to "omics", the unique attributes of people have a major impact on an individual's susceptibility to disease: how that disease will reveal itself phenotypically, and how the individual with the disease will respond to treatment.	(16),(42)
Re-classifying diseases	(i) Identify the true penetrance of certain inherited conditions as ascertained via a population-based approach; (ii) Develop new diagnostic tests to allow for newer prognostic implications; (iii) Handle and interpret massive amounts of genomic/non-genomic data, far beyond the expertise of medical professionals not trained to deal with complex data sets.	(74) ****
Precision prevention	Family history was the most important genetic risk factor in the Framingham Heart Study, and also accounts for gene-environment interactions. Health data collection in families is an inexpensive tool for identifying individuals/families that require earlier and more intensive screening for major diseases. The availability of molecular profiling tests, e.g. individual germline DNA sequencing, calls for educating clinicians to the knowledge bases needed to assist them in taking actions based on genetic test results.	(63),(75),(76) *****
Monitoring the implementation	Creating *ad hoc* regulatory agencies; Safeguard against the marketing and distribution of fraudulent products.	(77)
Identifying new areas of research	Handling the information gathered: descriptive statistical associations will not necessarily advance the information of how molecules interact mechanistically to produce diseases or lead to rational therapies. N-of-1 trials: the inclusion of N-of-1 trial data into randomized controlled trial meta-analyses improves the precision of yielded treatment effects. Improving the possibility that N-of-1 trial data allow for individual information to be shared with individuals who do not share a specific genome. Targeted therapies: (i) identifying patients who will best respond to already proven interventions; (ii) searching for reliable biomarkers to target the patients likely to present the best benefit-risk balance for a given active compound. (iii) dose adjustment, methods to optimize the benefit-risk ratio of the drugs chosen; biomarkers of efficacy; toxicity, and treatment withdrawal. Revised clinical guidelines: when clinical trials will assess the efficacy, safety, and cost-effectiveness of targeted therapies, new guidelines are mandatory.	(10),(11),(42), (78),(79),(80)

*Enabling clinicians and patients to acquire and process molecular testing, to interpret results, and identify specific pathways affected. **Example: low levels of 25-hydroxyvitamin D as an independent risk factor for coronary artery disease or fatal stroke in white people, but not blacks. ***Asymptomatic subjects carrying a mutation: emotional and ethical issues. ****Taxonomy of disease based on molecular and clinical parameters. *****Targeting preventive strategies to the specific subsets of a population that will derive maximal benefit.

hemophilia on prophylactic treatment has significantly improved, and these patients are increasingly involved in working activities. However, the cost for prophylaxis is not affordable for the large majority of countries. Thus, most hemophilia patients worldwide receive no treatment or only sporadic on-demand therapy. Such patients are condemned to shortened lives of pain and disability.

• Costs for therapies depend on the size of the target population: the smaller the population, the more expensive the drug. At least initially, gene therapy in hemophilia is likely to command a high price to recoup research and development costs. Such economic considerations may have major implications for differential access to treatment for hemophilia families, communities and society. One of the claims is expected to be that successful gene therapy offers the advantage of continuous endogenous expression of clotting factor. While improving quality of life, this would eliminate breakthrough bleeding and micro-hemorrhages and comorbidities, thereby reducing the cost of care for the healthcare system, and the need for frequent medical interventions. Point-of-care ultrasound detection of affected joints – reliably correlating with magnetic resonance imaging detection of cartilage damage, effusion, and synovial hypertrophy - carried out inside Hemophilia Centers at each patient's visit, could have major implications for the management of hemophilia patients.[46,47] Repeated evaluations of patients' joints will provide hints as to whether this strategy is worth the cost required.

• The results of testing should be actionable, thus informing prognosis and/or supporting rational prescribing.[48] In patients with severe hemophilia B, a single intravenous administration of an adeno-associated virus vector (AAV8) encoding an optimized *F9* gene resulted in long-term (>4 years), dose-dependent increases in circulating factor IX to levels between 1% to 6% of the normal value without persistent or late toxicity.[49] By providing stable, long-term therapeutic levels of coagulation factor IX, gene therapy has the potential to change the treatment paradigm for hemophilia.[50] With the availability of *ad hoc* genomic data, actionable tests should help to identify: (i) which patients will have loss or reduction of transgene expression and/or persistence of high titers of anti-AAV8 IgG - with subsequent successful gene transfer with vector of the same serotype (in the event that transgene expression falls below therapeutic levels); (ii) spread of vector particles to non-hepatic tissues, including the gonads; (iii) insertional mutagenesis (deep sequencing studies have shown that integration of the AAV genome can occur in the liver).[51]

• Stroke, the fourth leading cause of mortality and the leading cause of neurological disability in western countries, involves an intricate interplay of environmental and genetic factors. Genes not only influence susceptibility to stroke but also affect the response to pharmacological agents and in turn the outcome of the disease. A significant number of patients experience drug-induced adverse reactions; a poor clinical outcome, and recurrent stroke events. Several single nucleotide polymorphisms in genes encoding for metabolizers, transporters and target receptors influence the pharmacokinetics and pharmacodynamics of drugs used in the treatment of stroke.[52] Clinical trials have related candidate gene variants with abnormal drug response in stroke treatment.[53] However, these results need to be replicated in genome-wide association studies. A broad research program prospectively testing targeted therapeutic strategies based on pharmacogenetics, and ultimately encouraging approaches to build the evidence base needed to guide clinical practice, is likely to be cost-saving in this setting.[54]

• Defining effective strategies to improve communication and outcomes is mandatory in precision medicine-based approaches. Because of the limited time spent on direct care of patients, these days physicians and medical students know very little about their patients as people.[16] Trainees spend less time interviewing and examining their patients, and duty-hour regulations progressively erode the time residents devote to history taking and physical examination skills.[55] On the other hand, residents spend a good amount of time at the computer,[56] getting to know an electronic facsimile of a patient – the "iPatient"[57] – well

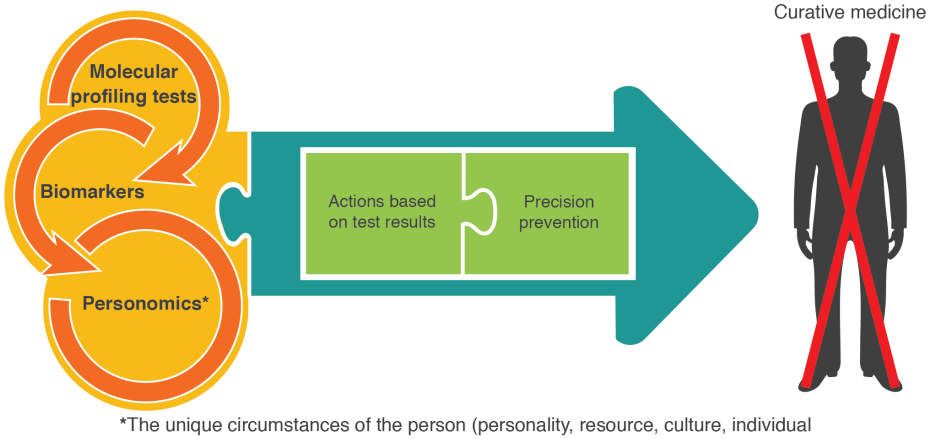

Figure 3. Perspectives in precision medicine. Tests of increased susceptibility to prevent the development of diseases are steadily increasing in different areas of clinical medicine. In a precision prevention-based health system, curative medicine is expected to be needed only in a very limited number of cases "*only in desperation*".[18]

before they have met the actual person in a hospital bed or outpatient clinic. Genomics of diseased tissues document mutations that confer sensitivity to drugs not approved for that specific indication.[58] Under such newer scenarios, empathy and humanity are required to let doctors enter into a process aimed at clarifying the context of the treatment. Negotiating an effective and newer equitable partnership with practitioners was the obvious direction to be followed after hepatitis and human immunodeficiency virus transmitted by blood products called for a newer doctor-patient relationships in the bleeding disorder community.[59,60]

• Forging an effective and newer patient-physician alliance[61] in the era of precision medicine should be aimed at precision medicine-oriented information. Major directions to be pursued are how to handle patients' expectations, educate them regarding new medical concepts, and deliver results to individuals. In this respect, if information available on the Internet is increasingly generating more aggressive patients, a surreptitious and coercive interpretation of guidelines will further and definitely mark the advent of the age of medical defensiveness, and healthcare systems will continue to contribute poorly to the well-being and life expectancy of the least-advantaged people and the potential for a renewed patient-physician alliance will fade to become merely virtual. If, instead, through shared reasoning, strong public health-healthcare partnerships ensure that all people have access to the intended benefits of technology and track efficacy, safety, and effectiveness outcomes in the real world; if dying is accepted as part of the natural history of each one of us; if patients consider their doctor as a travel companion whose life and commitment have been a constant, prolonged challenge to the power of death, disease, solitude, and pain, then there is room for hope.

Attempting to remedy a not optimal genome: perspectives.

Faced with the spread of information from guidelines, the concept that, when appropriately formulated, every clinical question can be solved by an approach that employs the theory of probability has gathered strength and relevance.[5] Thus, medical students and patients now envisage medical practice as relatively simplified problem-solving. However, although the "one-size fits all" approach is broadly used in prevention and management across the vast majority of clinical settings, the need for the right drug at the right dose in the right patient is being increasingly recognized in real-life practice,[19] given that there are areas in which guidelines cannot be relied on for how to deal with a specific issue.[62] In these areas, which are often very important for the clinician, it remains imperative to identify in advance which patients are less likely to benefit from a given intervention. Although it is still too often a theoretical concept - because of the lack of convenient diagnostic methods or treatments, and of drugs corresponding to each subtype of pathology - precision medicine argues for improved risk predictions, behavioral changes; lower costs, and gains in public health, and the community should be aware and engaged in its progress. The promise of precision medicine involves every aspect of medical care, and calls for active collaboration between researchers, doctors, patients and other stakeholders. It demands newer levels of medical education and up-to-date diagnostics, informatics and algorithms to assist healthcare providers with information management and decision making. Integrating efficacy, safety, and cost-effectiveness is a challenge for precision medicine and the opportunity for it to generate early measurable health benefits and to live up to its promise. Indeed, the investment in precision medicine-based treatment decisions[19] should be harmonized with information emerging from evidence-based medicine to help the standardization of care. Within the framework of open discussions and a supportive institutional environment - to acknowledge and fulfil the individual roles and responsibilities in decision-making - interests shared by individual patients, families, and communities, the diagnostics and pharmaceutical industries, and healthcare providers (governments, industry, payers, and other stakeholders) should be aligned.[63] Major advances in medical practice lend credence to the possibility that we are heading towards hospitals that ban relatives and visitors (mobile telephones and webcams will keep patients in touch with their relatives and friends), where hospital files are e-files, where remote consultations will be the rule, and where nursing will be based on the least possible contact – a virtually total "asepsis". While some might suppose that doctors will no longer have to stumble to find the right words for the unavoidable, it is highly likely that in the near future medical decisions will have to be taken by integrating patients' "omics" with characteristics and preferences and other individual-level data. The number of genes that presently confer susceptibility to (or protection from) diseases is steadily increasing. The availability of molecular profiling tests calls for new school curricula to educate clinicians of the 21st century to the knowledge needed to assist them in taking actions based on genetic test results. Precision prevention (Figure 3) implies that doctors will become advisers for individuals who are not ill. With appropriate protections (see the "unpatients' issue" in the Table 1), each individual will have full knowledge of his/her health capital and will be able to manage it as his/her banking account. Longevity will, it is to be hoped, continue to increase each year, not only in industrialized countries. Whether, in addition to definitely changing the ethical dimensions of the relation among patients, their doctors and other healthcare providers, precision prevention-based health systems will also lower costs of future medical practice is so far unknown.

In addition to the search for drugs and medical devices that are unique to a patient or to a limited group of patients (e.g. the use of mobile technology to serve as an effective reminder to monitor medication adherence such as the international normalized ratio), the future in hemostasis and thrombosis is expected to help physicians to classify patients into sub-populations that differ by their susceptibility to bleeding and/or thrombosis, by the biology/prognosis of those diseases they may develop, and/or by their response to a treatment. According to one meta-analysis, genotype-guided treatment schemes have so far been less informative than clinical dosing for warfarin and its analogues.[64] However, a prolonged period of observation would be needed to address this issue properly.

Follow-ups ranged from 4 weeks to 6 months (median, 12 weeks) for both the genotype-guided and clinical-dosing algorithm studies evaluated in that meta-analysis.[64] These are the early days of precision medicine. It has long been known that much of cancer biology is based on the central tenet that it is a genetic disease.[65] However, the concept that our treatments should be more precisely tailored to specific molecular targets contributed little to cancer treatment until the 21st century. Major achievements sometimes take more time than anticipated by the original hype.[66] To obtain sufficient funding, researchers need to create hype, and this may lead to unrealistic expectations on the part of patients and clinicians.[67]

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Research in the heart of hematology: chronic myeloid leukemia 2017

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One of the great success stories of modern hematology is reaching its next and possibly final phase: the achievement of treatment-free remissions in stable deep molecular responders with chronic myeloid leukemia (CML) which may well be equivalent to cure. Although only the minority of patients achieve treatment-free remissions, the absolute numbers of patients currently in discontinuation studies (Table 1) and in durable treatment-free remissions (40- 60%) are impressive and argue for a change in the treatment strategy for CML. The progress since last year cannot be overlooked.[1] The goal is to define patients in whom treatment can be stopped safely and to establish a strategy for treatment discontinuation.[2]

This is not the first amazing success in some 50 years of basic and clinical research underlying the success story of CML: the detection of oncogenes and of kinase activity in many of them was fortuitous, since it was a byproduct of the search for human leukemia viruses. In realization that most animal leukemias could be induced by viruses, this was a high priority research field in the late 1960s and early 1970s. Large national programs funded with billions of dollars, such as the Special Virus Cancer Program and the National Cancer Act for the "conquest of cancer", had been started in the USA. With modern molecular biology methods, so-called footsteps of viruses were looked for. The detection of reverse transcriptase in human leukemic cells[3] and of virus-related RNA and DNA in human cells and in the human genome[4,5] were at the time interpreted as breakthroughs on the path to detection of human leukemia viruses. Whereas ultimately no such viruses were found associated with common human leukemias, oncogenes proved central in human carcinogenesis. An example is the role in CML of the *ABL* oncogene which, in 1980, was detected in the acutely transforming defective Abelson leukemia virus in which parts of the virus genome had been replaced by cellular sequences.[6] It was shown that most retroviral oncogenes were present as so called protooncogenes in the human genome pointing early to ubiquity and important functions of these genes in