Review

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Personalized laboratory medicine: a patient-centered future approach

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Abstract: In contrast to population-based medical decision making, which emphasizes the use of evidence-based treatment strategies for groups of patients, personalized medicine is based on optimizing treatment at the level of the individual patient. The creation of molecular profiles of individual patients was made possible by the advent of "omics" technologies, based on high throughput instrumental techniques in combination with biostatistics tools and artificial intelligence. The goal of personalized laboratory medicine is to use advanced technologies in the process of preventive, curative or palliative patient management. Personalized medicine does not rely on changes in concentration of a single molecular marker to make a therapeutic decision, but rather on changes of a profile of markers characterizing an individual patient's status, taking into account not only the expected response to treatment of the disease but also the expected response of the patient. Such medical approach promises a more effective diagnostics with more effective and safer treatment, as well as faster recovery and restoration of health and improved cost effectiveness. The laboratory medicine profession is aware of its key role in personalized medicine, but to empower the laboratories, at least an enhancement in cooperation between disciplines within laboratory medicine will be necessary.

Keywords: advanced omics technologies; diagnostic marker; genome; metabolome; molecular profiling; proteome; transcriptome.

Introduction

Personalized laboratory medicine can be described as a "child" of the modern age. As a result of decades of development of high throughput omics technologies, it is now becoming an important part of diagnostics and therapy [1], and it is expected that it will contribute to more accurate diagnoses and safer and more effective treatment, consequently leading to better outcome, higher quality of life and improved cost effectiveness. We have to be aware, however, that before finding its rightful place in the

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medical laboratory science, more studies are needed, and everyone working in this profession can help accelerate its adoption if we try to understand the importance and benefits of these new approaches to healthcare [2].

Postgenome era and advanced omics technologies

After 2002, when the human genome sequence was published (known as the postgenome era), new analytical methods have begun to emerge that no longer focus on one analyte (biochemical marker) but aim to acquire complete profiles of all chemically or functionally similar molecules in a biological system. In clinical chemistry, we already had a similar approach, for example, with serum protein electrophoresis, but developers of new methods were far more ambitious. The aim was to develop tools that would enable us to acquire a profile of thousands or tens of thousands of molecules, like a urine protein profile that contains more than 2000 different proteins and peptides. Simultaneous development of new instrumental techniques and biostatistical tools enabled the rise of advanced omics technologies, which cover all areas of cell biology, e.g. genomics, transcriptomics, proteomics, lipidomics, metabolomics, epigenomics, microbiomics, etc. [3, 4]. One individual omics field studies one specific group of molecules. Genomics studies the entire genome rather than just individual genetic mutations, using microarrays and/or next generation sequencing (NGS). Similarly, transcriptome analysis includes the entire mRNA set, again using NGS or biochip technology. Proteome analysis of a cell or tissue means studying the entire protein content of a biological specimen, usually using mass spectroscopy, which is also used in metabolomics, assessing the metabolites profile in individual biological systems or tissues [5].

The latter in its smaller scale are already established in the diagnostic laboratories. Metabolites are used as biomarkers for diagnosis, progression and response to treatment, and they give insight into the biochemical mechanisms of disease. Metabolic screening of organic acids with gas chromatography-mass spectrometry (GC-MS), amino acid screening with ion-exchange chromatography, hormone screening and screening with tandem-mass spectroscopy for acylcarnitine analysis, especially in neonates, have already dramatically changed the diagnostics of inborn errors of metabolism and endocrine disorders [6–8]. Inborn errors of metabolism are a major health problem; they present with nonspecific clinical symptoms and their consequences range from minor disabilities to sudden death. Timely diagnosis and disease-specific treatment have major effect on outcome of patients, as many of the disorders clinical signs can be prevented with a proper treatment. To address this need for faster screening and diagnosis strategies, metabolic profiling is a promising candidate [9].

Since the introduction of tandem mass spectrometry, this method has become widely applied in newborn screening, as more than 30 different disorders can be screened in a single run [10]. The aim of newborn screening is early identification of treatable conditions associated with significant morbidity or mortality. To reduce false-positive rate, second-tier tests that use original dried blood spot (DBS) card can be introduced, especially in the cases of certain diseases, such as combined remethylation disorders, methylmalonic acidemia and propionic acidemia where propionylcarnitine is used as diagnostic marker for all three disorders. Propionylcarnitine has also high false-positive rate in premature newborns. However, simultaneous determination of the biomarkers 3-hydroxypropionic acid, methylmalonic acid and methylcitric acid in DBSs, used for screening test, allows to differentiate between those patients, markedly reducing time to diagnosis and initiation of treatment as recall is not needed [11].

When metabolomics is combined with genomic screening, they represent a powerful tool enabling early diagnosis followed by timely intervention resulting in an important impact on the outcome of the affected patients. For instance, patients with phenylketonuria identified through tandem mass spectroscopy screening can importantly benefit from identification of causative phenylalanine hydroxylase (*PAH*) gene mutation. If the patient has tetrahydrobiopterin (BH4)-responsive mutation, the lifelong Phe-restricted diet can be at least partly substituted with BH4 treatment as shown in Slovenian phenylalanine hydroxylase deficiency population [12]. The identification of causative mutations regardless the disease has lately been revolutionized by NGS enabling simultaneous detection of causative variant in numerous genes, whole exome or whole genome in one experiment [13]. This approach has particularly been successful in patients with unspecific clinical presentation where single causative gene cannot be reliable pinpointed. Such an example of a successful molecular diagnosis acquired with whole exome sequencing is a patient with an unspecific but complex clinical presentation of primary immunodeficiency, multifocal gastric carcinoma and malignant melanoma treated at the University Children's Hospital in Ljubljana. In search for the molecular diagnosis, he was unsuccessfully genetically tested for numerous single genes from his

childhood year onwards. Only family-trio whole exome sequencing with unbiased phenotype ontology approach in his early adulthood has led to identification of the causative variant in the *LRBA* gene encoding lipopolysaccharide-responsive, beige-like anchor protein [14]. Of course, only speculation can be made regarding the impact of the possible treatment such as bone-marrow transplantation on the disease outcome if the molecular diagnosis could be made in his childhood.

Molecular profiling, for example, of tumor tissue, can show us all its characteristics and enables a more targeted and more efficient approach to treatment [15]. The omic approach also shows promise in the discovery of new diagnostic markers or biochemical pathways responsible for development and progression of disease, as it enables discovery of molecules that are expressed differently in pathological specimens. Again, this approach is familiar to clinical chemists, but the key difference of the new approach is in the number of discovered biomarkers. When using proteomics to study the protein profile with several thousands of proteins, it is very likely that we will discover a few dozen proteins that could be characterized as biomarkers. Later on, of course, these will have to be clinically evaluated and their diagnostic sensitivity and specificity determined, as well as any positive and negative predictive value they exhibit [16]. Only clinical studies will be able to confirm the true diagnostic value of newly discovered molecules and enable the incorporation of these markers into diagnostic algorithms (Figure 1).

The main advantage of omics technologies is the ability to "find what we are not looking for". Classical analyses only measure molecules (parameters) for which the reagents are available and for which we decided in advance that we want to measure them. We are well aware that when albumin concentration in urine is normal, the values of other proteins can be altered, but this cannot be confirmed if we are not looking for them. With proteomic analysis of urine, we get the complete profile with over 2000 proteins simultaneously, including the proteins that would otherwise probably not be measured and that can contribute to faster and more accurate diagnosis, or can help monitor the disease progression and identify new therapeutic targets [17, 18]. In science, this approach is referred to as "a non-hypothesis-driven" approach.

Advanced omics technologies and personalized laboratory medicine

What is special about personalized laboratory medicine is that it does not rely on changes in the concentration of one particular molecule (diagnostic marker), but rather on changes in the profile of many molecules, which enable us to get more exact and "personal" description of the patient status. One could say that advanced technologies, analyzing the complete set of genes, proteins, mRNA and metabolites in the selected sample, give us an individual's genomic, proteomic, metabolomic or molecular print.

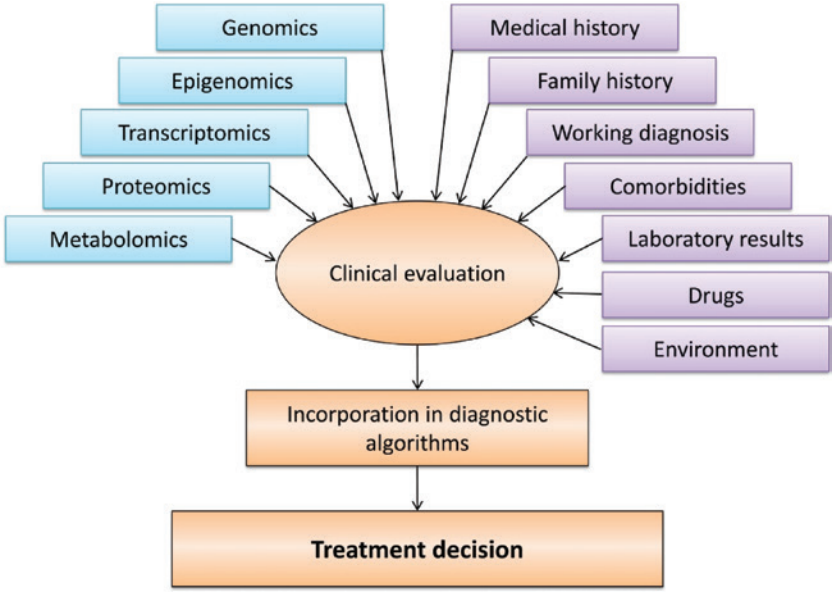

Figure 1: Advanced omics technologies in new diagnostic discoveries.

Similar to a fingerprint, the genomic print of an individual is unique and is already used in forensic medicine for identification. If not individual omics analyses, the combination of them certainly personalizes the acquired dataset, which is the basis for "molecular" identification of an individual [19]. Although there is no universally accepted definition of personalized medicine, the European Commission has in 2013 defined personalized medicine as "a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention" [20]. The European Federation of Clinical Chemistry and Laboratory Medicine/European Society of Pharmacogenomics and Personalised Therapy (EFLM/ESPT) working group on Personalized Laboratory Medicine, with the aim to adapt this definition within the scopes of the working group activities, has proposed to modify the definition as "personalized laboratory medicine refers to model using molecular profiling for accurate diagnostics and for supporting decision for therapeutic strategy for the single person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention". In recent years, the term "precision medicine" has emerged, the name stemming from the fact that the use of molecular profiling improves the precision with which the patients are diagnosed and treated [21]. According to the Precision Medicine Initiative, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person". It allows a more accurate prediction in that diagnostic, therapeutic or prevention strategies will work for particular groups of patients [22]. The terms personalized medicine and precise medicine are often used interchangeably; however, some point out the distinction that the term personalized medicine implies that unique treatments can be designed for each individual, whereas the term precision medicine allows for classification of individuals into subgroups and tailoring of diagnostics and treatment to these subgroups rather than individually [23].

Regardless, the definition used the goal of high-performance advanced omics technologies is to design molecular profiles such as a protein profile of pathological urine or the metabolic profile of selected body fluids. After comparing the patient's sample profile with the profiles of the control (healthy) samples, we can quickly recognize the deviations in the patient's pattern. Based on profiles or prints of different molecules, we can recognize the molecular/biochemical specificities of the individual and use them in personalized diagnostics and targeted therapy. Undoubtedly, this approach potentially offers faster and more effective diagnostics, better and safer treatment and hence faster recovery and restoration of health. We can conclude that personalized medicine in its true sense represents a new approach to diagnostics and therapy, based on the results of advanced technologies.

The cardiomyopathies are a nice example of the use of omics in the management of complex diseases. Cardiomyopathies are characterized by clinical heterogeneity and phenotypic overlapping, making it difficult to define clear diagnostic criteria and a precise guideline for the best therapeutic strategy. From the genetic point of view, cardiopathies present a complex picture due to variable expressivity and incomplete penetrance. Until now, several genes have been associated to each inherited form of cardiac disorders, even if the overall mutation detection rate is variable, ranging from 60% to 80% in long QT syndrome to as low as 20%–40% in dilated cardiomyopathy [24].

Recently, the advent of next-generation sequencing opened new frontiers in genetic diagnostics of cardiopathies, exploiting the high-throughput parallel sequencing and the simultaneous analysis of several samples with a significant reduction of time and cost for the genetic analysis of the complete panel of associated genes. The use of NGS in molecular diagnostics also enhances the success rate of identified causative variants in cardiac disorders, improving it from Sanger Sequencing era.

In the context of personalized laboratory medicine, the key idea is that genetic data can be used as a powerful clinical tool with potential applications in precision diagnostics and therapeutics. For example, in long QT syndrome, an arrhythmogenic disorder, the identification of the causative gene allows precision targeted therapy in patients affected by potassium or sodium channel dysfunction [25].

Moreover, in some clinical cases, determining the causative mutation can have a prognostic value. For example, in hypertrophic cardiomyopathies, patients with variants in sarcomere proteins (SP) have higher cardiovascular and sudden death-related mortality during follow-up [26]. Also in Brugada syndrome, a rare form of genetic disorder with high susceptibility to ventricular tachycardia, the presence of mutation on the principle gene (SCN5A) is associated with an increased risk of major arrhythmic events in carriers compared with non-carriers [27].

These examples highlight how genetic alterations may be considered as risk markers for sudden cardiac death, suggesting that the mutation analysis may have a role in prognostic models and in deeper characterization of clinical phenotype. Hence, the use of high-throughput

sequencing platforms and the application of genomics in clinical practice are aimed at assisting physicians in selecting the best management strategies for each patient, taking into account the impact on outcome, as well as the risk-benefit ratio of particular diagnostic or therapeutic approach [28].

On the other hand, not only new technologies support personalized medicine. The right combination of old technologies, for example, in the field of hematology, can contribute to personalization of medicine. The development of multilaser cytometers, monoclonal antibodies directed toward an increased number of antigens, new fluorochromes and the development of software for data analysis [29] shifted the role of multiparameter flow cytometry (MFC) from being crucial for the diagnosis and classification of hematopoietic neoplasms [30] toward the precision hematology. MFC is now used in hematology not only to delineate or define subtypes of acute leukemia but also to monitor a therapy response by measurable residual disease (MRD) testing [31] and can be further used to refine risk assessments and treatment decisions [32]. It has the capability of identifying and enumerating subpopulations within complex cellular mixtures. As previously stressed, not the single parameter change but deviations from the relevant normal pattern, such as alterations in the level of expression, the timing of expression, the appearance of antigens not normally expressed, and changes in the range of expression at a particular maturational stage, are diagnostically relevant [30, 33]. Differences in antigen expression can take a variety of forms and can be considered a biomarker that can complement genetic markers observed in a particular patient. Due to the genetic diversity, subtle disturbances in hematopoiesis that are not recognized by morphology and different residual tumor cell burden, the power of MFC as a proteomic tool is most evident in the diagnostic work-up of myelodysplastic syndromes (MDS) and MRD monitoring in acute myeloid leukemia (AML-MRD). MFC application in MDS and AML-MRD requires, however, specific analytical expertise and experience with analysis and data interpretation being to some degree subjective [33, 34].

Today we are at the beginning of this new era, and a collaborative work between clinicians and laboratorians will be important to further investigate the role of genetic testing and to increase its utility in the management of cardiac disorders.

However, the management of such a large amount of data, produced by genomic, proteomic, transcriptomic, etc., analyses is not simple, and that fact highlights an additional challenge associated with advanced omics technologies. High-performance bioinformatics tools for the selection, screening, sorting and connecting of thousands of data points need to be developed prior to final interpretation, and the final value of advanced technologies for medicine will thus largely depend on artificial intelligence that is experiencing intense development as well [35, 36].

Personalized laboratory medicine and pharmacogenomics

One of the first areas in which personalized medicine was used in clinical practice is pharmacogenomics, an area that studies genetic changes shaping both individual's processing of drugs and response to treatment. It turned out that the "one fits all" theory does not hold up in all therapies. After the administration of the same dose of the same active ingredient to different individuals, the response can be very different. The response may be excessive and associated with adverse drug reactions (ADRs) or too weak, with little or absent pharmacological effects. Both can be followed by additional clinical complications, which worsen the patient's condition and increase the cost of treatment. Studies have shown that in Europe, 3.6% of all hospital admissions are due to ADRs and that ADR occurrence rate during hospitalization is 10.1% [37]. Differences in response to the active substance stem from patient-related factors (genetic factors, body weight, smoking, liver function, kidney function, physical activity or feeding status) and from the properties of the drug (physicochemical properties of the active substance and interactions with other substances can lead to adverse effects) [38].

It is estimated that genes are responsible for 30%–95% of variability in response to the drugs, mostly genes encoding "absorption, distribution, metabolism and excretion" (ADME) associated proteins. Variants (at the DNA level) or changes in the expression at the RNA or protein level can alter the activity of, e.g. metabolic enzymes, transport proteins or receptors with which the drug interacts after administration. In this way, mutations may alter the pharmacokinetic (e.g. metabolic rate) and/or the pharmacodynamic properties of the active substance [39]. The pharmacogenomics information is increasingly present in the drug labels approved by medicine agencies around the world (European Medicines Agency [EMA], Food and Drug Administration [FDA], Pharmaceuticals and Medical Devices Agency, Japan [PMDA] and Health Canada [Santé Canada] [HCSC]) and is thus accessible by doctors and patients [40, 41].

Contrary to factors such as kidney or hepatic function, the characteristics of DNA do not change over time. With the help of pharmacogenetic testing before the introduction of a new therapy, we can predict the response of an individual to the applied drug and their likelihood of an ADR. By incorporating the genetic information into the treatment, we enter the field of individualized therapy, which is part of personalized or "Patient-oriented" medicine [42].

The focus on patients is formulated in the holistic approach of "predictive, preventive, personalized and participatory medicine (P4 medicine)". The paradigm shift from "reactive" to P4 medicine requires a revised role of laboratory medicine in health care systems. This is especially true for cancer medicine [43], demanding genome- and phenome-wide approaches with focus on patients and their involvement in treatment decisions. This more complex laboratory medicine becomes multifactorial and requires accurate interpretation of health-related data of the individual patients where an effective information and communication technology (ICT) support is also needed [44]. Implementation of complex laboratory tests is the matter of reasonability measured by added value to data interpretation and cost-effectiveness. In addition to this, personalized laboratory medicine needs to take advantage of data interpretation in order to support P4 medicine in turn [45].

Molecular testing in the routine practice

In relation to the routine genetic testing required for the pretreatment patients' selection, clinicians and oncologists need to receive clear and specific information from the pharmacogenomic tests. This will help them to guide patient's therapy, and thus defined results should be obtained in a reasonable time (in terms of turnaround time [TAT]) and at a reasonable cost to allow a rapid personalized therapeutic strategy. In this context, in vitro diagnostics (IVD) methodological approaches with competitive cost and with a high level of standardization are recommended, even if this does not allow immediate discovery of unexpected information. Actually, CE IVD commercially available tests are designed to find only specifically requested information, both in the pharmacogenetic ADME test as in targeted therapy (e.g. lung, colon and melanoma cancer panels). In the case of multitarget methods as Sequenom Mass ARRAY, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS platform or some targeted approaches by NGS, designed to overcome the high number of cumbersome reactions, requested to obtain essential information from germline and/or somatic genetic profiles.

Pharmacogenetic testing in oncology

In pharmacogenetics area, one of the most important tests that should be considered mandatory before starting treatment with five fluorouracil-based drugs is represented by specific dihydropyrimidine dehydrogenase (DPYD) single nucleotide variants (SNPs) detection, which allows the identification of the most important SNPs clinically relevant to the catabolism of the five fluorouracil-based drugs, as evidenced by the Clinical Pharmacogenetics Implementation Consortium (CPIC®) (https://cpicpgx.org/) [46]. The pretreatment identification of patients at risk to develop acute and grave toxicity has important healthcare implications both for patients, primarily, and for the hospital economy.

Because defined genotypes may directly influence drug response in terms of efficacy and ADRs, a joint report between laboratorians and pharmacologist should be formulated to clearly and robustly relate genetic results with phenotype. The pharmacologist interprets laboratorian's comments by editing the final prediction and drug dosage considerations (see Table 1).

At the clinical level, the identification of new variants is not routinely requested because pharmacogenetic studies require deeper clinical validation of genetic information with larger case series and functional *in vitro* evaluation of variants before the inclusion into clinical practice [47]. Nevertheless, the possibility to constantly implement new putative multimarker findings into the analysis must not be excluded.

Regarding the already known clinically effective pharmacogenetic modifications, preemptive genetic testing should be emphasized. The role of preemptive pharmacogenetic testing is especially important in the case of thiopurine treatment as their relative narrow therapeutic index may cause serious or life-threatening side effects (e.g. myelotoxicity). Thiopurine S-methyltransferase (*TPMT*) gene variants alter the metabolism of thiopurine immunosuppressants, the azathioprine, 6-mercaptopurine and thioguanine. A total of 28 variant alleles of *TPMT* gene decrease the catalytic activity of the enzyme [48]; however, only the *2, *3A, *3B, *3C or *4 have clinical channel, included to FDA drug label (https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm) and CPIC guideline [49, 50], and recommended to be tested in advance. Accordingly, this can be done in 27 accredited laboratories across Europe (http://www.orpha.net).

Table 1: Summary of geneticist's and pharmacologist's comments and conclusions that should be included in a final pharmacogenetic DPYD test to adequately orient therapeutic decision making by clinicians (modified from https://www.pharmgkb.org/guideline/PA166122686).

Pharmacogenetic test for *DPYD* gene	**Genotype**	**SNPs detected**			
	Wild type (*1)[a]	rs3918290 (*2)[a] IVS14+1G>A	rs67376798 c.2846A>T	rs55886062 (*13)[a] c.1679T>G	Homozygous
Results					
Geneticist	Homozygous wild-type *1/*1	Heterozygous *1/*2	Heterozygous *1/rs67376798A	Heterozygous *1/*13	Homozygous variant *2/*2 *13/*13 rs67376798A/rs67376798A
Comments	This genotype is associated to a normal DPD activity and "normal" risk for fluoropyrimidine toxicity	This genotype is associated to a reduction of DPD activity	This genotype is associated to a reduction of DPD activity	This genotype is associated to a reduction of DPD activity	This genotype is associated to total DPD deficiency
Conclusions					
Pharmacologist	Use label recommended dosage and administration	Use at least 50% reduction of the drug dosage	Use at least 50% reduction of the drug dosage	Use at least 50% reduction of the drug dosage	Increased risk from severe to fatal toxicity: selection of an alternative treatment is mandatory

[a]Reference haplotype using star (*) system nomenclature.

One of the crucial roles of personalized laboratory medicine is to draw clinicians attention to the available testing opportunities in order to be able to avoid fatal outcomes of thiopurine treatment, which may occur in 0.03%–0.56% of Caucasians [50]. TPMT genotype-phenotype correlations and the corresponding therapeutic recommendations for thiopurine treatment are summarized in Table 2 (adapted from CPIC).

Somatic variants evaluation for targeted therapy

Slightly different could be the case of somatic detection of tumor DNA variants to look for targeted anticancer therapy. In this situation, it is reasonable to perform in first line the detection of known variants, but it must be kept in mind that this may not be sufficient. In fact, the identification of novel unknown variants may give rise to an unexpected therapeutic challenge for patients carrying wild-type sequences identified during the primary mutations screening.

The *BRAF* gene mutational status detection in melanoma, for example, firstly requires performing the detection in codon 600 (mutated in 90% of the mutated samples), available in a large number of commercially available test (i.e. real time, pyrosequencing and mass spectrometry-based approach), but for wild-type samples, the analysis of the entire exons 11 and 15 with sequencing-based technologies (i.e. Sanger sequencing or NGS panel tests) can reveal variants, both novel or rarely described and potentially treatable [51]. Performing an approach with a higher coverage – and TAT – in first line would be unnecessary and expensive. On the other hand, in somatic mutation testing, the use of single methodological approach, even if CE IVD, could be extremely reductive, and the parallel use of larger-scale sequencing-based technology is strongly encouraged.

In conclusion, a molecular biology laboratory should be able to adequately select the most appropriate technology and/or methodological approach to be sure to cover all the clinical requests and to minimize the risk of giving uncompleted information for patient's healthcare.

The impact of personalized laboratory medicine on healthcare budgets

In addition to the beneficial effects of personalized approach on efficacy of diagnostics and treatment, it is also important

Table 2: TPMT genotypes, phenotypes and the therapeutic recommendations for thiopurine treatment, adapted from CPIC.

Genotype	Examples of diplotypes	Likely phenotype[a]	Recommended dosing			Classification of recommendation
			Azathioprine	6-Mercaptopurine	Thioguanine	
Two or more functional (*1) alleles	*1/*1	High activity (~86%–97% of patients)	Start with normal starting dose (e.g. 2–3 mg/kg/day) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment	Start with normal starting dose (e.g. 75 mg/m^2/day or 1.5 mg/kg/day) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment	Start with normal starting dose. Adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on thioguanine. Allow 2 weeks to reach steady state after each dose adjustment	Strong
One functional allele (*1) and one nonfunctional allele (*2, *3A, *3B, *3C or *4)	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4	Intermediate activity (~3%–14% of patients)	If disease treatment normally starts at the "full dose", consider starting at 30%–70% of target dose (e.g. 1–1.5 mg/kg/day) and titrate based on tolerance. Allow 2–4 weeks to reach steady state after each dose adjustment	Start with reduced doses (start at 30%–70% of full dose: e.g. at 50 mg/m^2/day or 0.75 mg/kg/day) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In those who require a dosage reduction based on myelosuppression, the median dose may be ~40% lower (44 mg/m^2) than that tolerated in wild-type patients (75 mg/m^2). In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing mercaptopurine over other agents	Start with reduced doses (reduce by 30%–50%) and adjust doses of thioguanine based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing thioguanine over other agents	Strong (medium for thioguanine)
Two nonfunctional alleles (*2, *3A, *3B, *3C or *4)	*3A/*3A, *2/*3A, *3C/*3A, *3C/*4, *3C/*2, *3A/*4	Low or deficient activity (~1 in 178 to one in 3736 patients)	Consider alternative agents. If using azathioprine start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. Azathioprine is the likely cause of myelosuppression	For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily, e.g. 10 mg/m^2/day given just 3 days/week) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing mercaptopurine over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy	Start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of thioguanine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing thioguanine over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy	Strong

[a]See Supplementary Data online for estimates of phenotype frequencies among different ethnic/geographic groups (CPIC guideline PMID: 23422873).

to consider its impact on healthcare costs. Targeted therapy is expensive, and the molecular testing itself carries certain cost, and because the number of such tests is expected to rise significantly, the financial burden on healthcare budgets is bound to become a challenge. However, personalized laboratory medicine also enables us to identify individuals who will likely benefit from targeted therapy and thus increases the cost-effectiveness of the treatment itself. In fact, health care insurances often reimburse the cost of targeted therapy only for patients with proven predictive biomarkers for the selected treatment [52, 53].

The role of laboratory medicine in the future of personalized medicine

Personalized laboratory medicine represents a new approach to patient management, which is based on the molecular recognition of the individual's condition, but we can benefit fully from the mass data acquired with advanced omics technologies only with the development of high-performance intelligent systems for data analysis. Given the high data output of these technologies, the possibility of misuse of the acquired data has increased. The mass data available from omics analyses precisely characterizes an individual, and it is therefore imperative to ensure the safety of this data and to consistently follow the ethical principles in laboratory medicine. The results of a survey conducted by the joint working group for personalized laboratory medicine at the EFLM and ESPT showed that the laboratory medicine professionals are aware of their role in the personalized medicine as a new healthcare model. However, certain measures will need to be introduced and, in particular, the organization of the profession will have to be changed. It will be necessary to introduce advanced technologies and to allow laboratory medicine experts to acquire competences in interpretation and counseling and, in particular, to enhance cooperation between disciplines within the laboratory medicine [54, 55].

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