BBA - Molecular Basis of Disease 1870 (2024) 167339

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Advancing personalized medicine: Integrating statistical algorithms with omics and nano-omics for enhanced diagnostic accuracy and treatment efficacy

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ARTICLE INFO

Keywords:
Genomics
Global health
Metabolomics
Nano-omics
Personalized medicine

ABSTRACT

Medical laboratory services enable precise measurement of thousands of biomolecules and have become an inseparable part of high-quality healthcare services, exerting a profound influence on global health outcomes. The integration of omics technologies into laboratory medicine has transformed healthcare, enabling personalized treatments and interventions based on individuals' distinct genetic and metabolic profiles. Interpreting laboratory data relies on reliable reference values. Presently, population-derived references are used for individuals, risking misinterpretation due to population heterogeneity, and leading to medical errors. Thus, personalized references are crucial for precise interpretation of individual laboratory results, and the interpretation of omics data should be based on individualized reference values. We reviewed recent advancements in personalized laboratory medicine, focusing on personalized omics, and discussed strategies for implementing personalized statistical approaches in omics technologies to improve global health and concluded that personalized statistical algorithms for interpretation of omics data have great potential to enhance global health. Finally, we demonstrated that the convergence of nanotechnology and omics sciences is transforming personalized laboratory medicine by providing unparalleled diagnostic precision and innovative therapeutic strategies.

1. Introduction

In the past century, the advancement of medical laboratory services has led to significant enhancements in clinical care. These services enable precise measurement of thousands of biomolecules, facilitating diagnosing diseases, monitoring individuals' health status, evaluating disease prognosis, assessing the effectiveness and side effects of treatments, and screening populations for specific diseases etc. and this situation confirms the expression "without diagnostics, medicine is blind" [1–3]. Medical laboratories have become an integral component of high-

Abbreviations: BV, biological variation; CV_I, within-subject biological variation; CV_G, between-subject biological variation; II, index of individuality; EFLM, European Federation of Clinical Chemistry and Laboratory Medicine; MS, mass spectrometry; RI, reference interval; DL, decision limits; AL, action limits; UL, upper limit; LL, lower limit; popRI, population-based reference interval; CLSI, clinical and laboratory standard institute; prRI, personalized reference interval; PI, prediction interval; HSP, homeostatic set point; CV_P, within-person biological variation; CV_A, analytical variation; pDL, personalized decision limit; popRC, population-based relative changes; popDL, population-based decision limit; DC, delta check; RCV, reference change value; prRCV, personalized reference change value; CV_T, total variation; NMR, nuclear magnetic resonance; ctDNA, circulating tumor DNA; CTC, circulating tumor cells; AD, Alzheimer's disease; MI, myocardial infarction; PET, positron emission tomography; HF, heart failure.

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https://doi.org/10.1016/j.bbadis.2024.167339
Received 4 April 2024; Received in revised form 25 June 2024; Accepted 3 July 2024
Available online 8 July 2024

quality healthcare services, exerting a profound influence on global health outcomes. In addition to their direct influence on healthcare systems, data derived from medical laboratories have been utilized for numerous purposes related to healthcare systems. These include contributions to epidemiological research, informing the selection of optimal strategies for public health interventions, facilitating judicious allocation of healthcare resources, and aiding in the formulation of evidence-based healthcare policies etc. and thus medical laboratories have been considered as a key factor in global health security [2,4,5].

In the last three decades, healthcare and medicine have effectively incorporated measurement technologies from diverse fields, especially physics. This fusion has not only expanded the scope of analytical methods available to medical practitioners but has also markedly improved the precision and effectiveness of diagnostic procedures. By harnessing the principles and instruments developed in physics, healthcare professionals can now offer more accurate diagnoses, tailor treatments more closely to individual needs, and monitor patient outcomes with unprecedented detail. This interdisciplinary approach has paved the way for innovations in medical imaging, laboratory analysis, and patient care, illustrating a profound shift in how medical science leverages technology to enhance patient outcomes and overall health. Notably, the adoption of one instrument, "mass spectrometry" (MS) has been pivotal, enabling the detection of thousands different molecules within a single run [6]. Historically, MS has been instrumental in the scientific revolution. A century ago, it played a crucial role in elucidating the structure of atoms, leading to groundbreaking advancements in physics and technology during the twentieth century. At the onset of the twenty-first century, this same instrument emerged as a pivotal tool in medicine and biology, facilitating groundbreaking developments in these fields. With omics technologies particularly using MS, thousands of molecules can be detected in a single sample taken from an individual. The utilization of multiple molecules from a single sample enhances the accuracy of disease diagnosis decisions. However, utilizing multiple molecules from a single sample for accurate diagnosis is challenging; it can cause misinterpretation of data. To avoid this, new personalized decision-making tools based on individuals' own data obtained from multiple analytes using personalized statistical algorithms are essential. Precision diagnosis and monitoring can be achieved by accurate interpretation of serial omics data.

Interpretation of laboratory data is a comparative procedure and requires reliable reference values for both healthy individuals and patients. Currently, references used for decision-making in medical practice frequently rely on data derived from population studies. But the medical decisions based on population references are typically made for individuals [7]. However, due to the heterogeneous nature of the population, the laboratory data of individuals can be misinterpreted, leading to medical errors in some cases.

The references derived from population data are mostly based on the statistical distribution of measurement results of samples collected from the population [8]. Consequently, it is assumed that if the measurement results of the samples taken from an individual fall within the predefined limits (such as the central 95 % of the population data), such results can be considered normal. In other words, in current medical practice the individual is considered as a member of the population rather than an individual with specific characteristics. Consequently, treatments are standardized based on population data rather than tailored to each person's specific needs.

Although individuals are members of the population, and even the population exhibits statistical homogeneity, this does not negate the presence of differences among individuals within a statistically homogenous population. As stated by ancient Greek philosopher, Hippocrates "*Every human is distinct, and this affects both the disease prediction and the treatment*" [9,10]. This can be observed clearly from biological variation (BV) studies of the analytes. Each analyte exhibits random BVs, comprised of two main components: within-subject BV (CV_I), which represents fluctuations around a set point within an individual, and between-subject BV (CV_G), which reflects variations observed among the set points of different individuals. The ratio of CV_I to CV_G is known as the index of individuality (II) which reflects the individuality of the analytes. It is accepted that if the II of an analyte is lower than 0.6 then this analyte has a marked individuality [11]. From the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) BV Database [12], it is well known that the II for the majority of analytes is lower than 0.6. The II serves as a good example, demonstrating that even within statistically homogenous groups, marked individuality for certain analytes may be present and therefore it is important to distinguish between statistical homogeneity and metabolic homogeneity, as these concepts are not synonymous. Consequently, it can be concluded that no two individuals on our planet are identical. Due to differences observed among individuals, it is essential to utilize personalized reference values when interpreting laboratory data for each person accurately.

In this manuscript, we aim to review (i) recent developments in personalized laboratory medicine, particularly interpretation of personalized laboratory data, (ii) personalized omics, specifically genomics, metabolomics and proteomics, and (iii) how to implement these novel statistical approaches and omics technologies to enhance global health.

2. Interpreting individuals' laboratory data: essential tools and strategies

Production and interpretation of laboratory data, also known as the total testing process, is a complex procedure and must be handled in a systematic way. The total testing process comprises five main steps detailed by Lundberg et al. [13–15] (Fig. 1). These steps encompass the pre-pre-analytical phase, involving laboratory test ordering by physicians, followed by the pre-analytical phase, which encompasses patient and sample preparation. Subsequently, the analytical phase involves the measurement of samples, while the post-analytical phase focuses on reporting laboratory data using appropriate units and reference intervals. Finally, the post-post-analytical phase involves the interpretation of laboratory data by physicians to facilitate clinical decision-making [13,14,16]. Accurate production and interpretation of laboratory data require that each phase in the total testing process cycle be

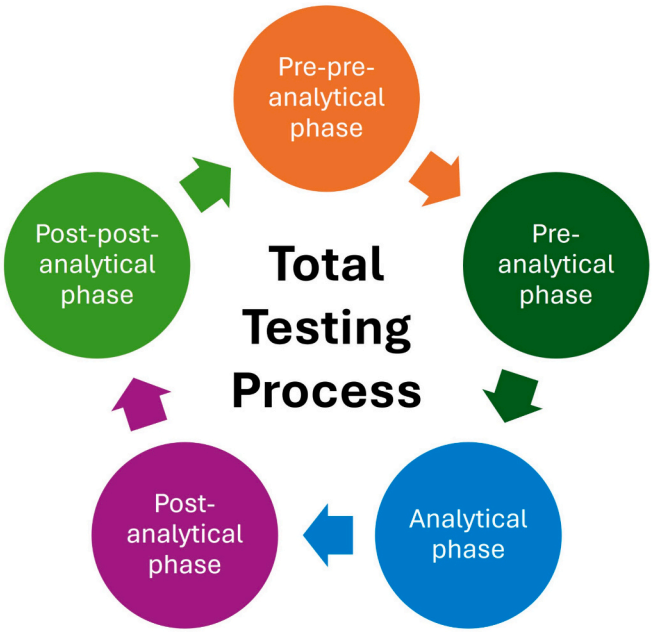

Fig. 1. The total testing process. It consists of five main steps and is influenced by the brain-to-brain loop concept proposed by Lundberg [15,21].

managed correctly. Otherwise, medical errors originated from laboratory data are inevitable. It has been shown that misinterpretation of laboratory data is the second largest error rate related to laboratory data [14,17–20]. Therefore, interpretation of laboratory data accurately is crucial for decreasing medical errors and increasing patient safety. Interpretation of laboratory data is a comparative procedure which requires reliable reference data such as reference intervals (RI), decision limits (DL) or action limits (AL).

In human metabolism the concentration/activity of analytes is under the control of hormonal mechanisms or other numerous physiological factors. Thus, the concentration/activity of the analytes fluctuate within an interval. This variability influences the interpretation of laboratory data, leading to the preference for using intervals rather than strict cut-off values, especially for healthy individuals. It should be noted that the measurement result of an analyte outside the RI can be considered as an abnormal value but not a diagnostic indicator for a certain disease. Usually, for laboratory data there is a grey zone between abnormal and diagnostic value. Hence, for the diagnosis of the diseases, using intervals and even reference intervals are not usually appropriate, and a DL is necessary for the diagnosis of the diseases.

The accurate diagnosis of diseases constitutes the initial crucial step toward effective treatment. However, in certain instances, treatment may be initiated based on analyte concentration/activity exceeding or falling below the decision limit by a defined degree, referred to as an AL. Taken together, if the elevated analyte level indicates pathology, we can assert that RI (UL) $\leq$ DL $\leq$ AL. Conversely, if lower analyte levels indicate pathology, then RI (LL) $\geq$ DL $\geq$ AL (Fig. 2).

Currently laboratory data are interpreted using RIs based on population data. Briefly, population-based RIs (popRIs) are estimated using measurement results of the analyte obtained from single samples taken from at least 120 reference individuals following Clinical and Laboratory Standard Institute guideline (CLSI EP28-A3C) [8]. The measurement results are ranked from the lowest to the highest, and the central 95 % of the measurement results are accepted as the RI. In other words, the lower and upper limits of RIs are estimated from the lowest 2.5 % and highest 97.5 % of the data from reference individuals.

An important dilemma arises when the popRI of an analyte is derived from population data but is applied to make decisions for individual patients [7]. Utilizing a population-derived interval as a "reference" for individual decision-making is inappropriate and can lead to misinterpretation of laboratory data. Therefore, accurately interpretation of laboratory data should be based on individuals own data, i.e. RI for an individual's analytes should be estimated using his/her own data, rather than data obtained from the population (Fig. 3). This situation highlights the need for the development of novel statistical algorithms designed to estimate personalized reference intervals (prRI) based on individuals' own data. Recently, we applied a statistical tool typically used for estimating "prediction intervals" (PI) to derive prRIs [22–24].

2.1. Personalized reference intervals

PrRIs are estimated by analyzing measurement results from repeated samplings taken from individuals when they are in apparent good health. As briefly mentioned above, it is accepted that the concentration/activity of an analyte fluctuates around a homeostatic set point (HSP) and the upper and lower limits of the fluctuation determine the UL and LL of prRIs (Fig. 3). The UL and LL of the prRI can be estimated using the mathematics of PI [22]. It's worth noting that in statistics, estimating the PI for a dataset is a complex process, with various approaches employed based on the type of available data and the interval for the future parameters of interest. The prRI of an analyte can be expressed using to following general formula:

$$\mathrm{prRI} = f(S_t) \pm f(R) \pm e \quad (1)$$

where $f(S_t)$ is the time dependent set point of the RI, f(R) is the random biological variation and e is the measurement error. $f(S_t)$ is under the influence of lifelong physiological variations including ultradian, circadian and infradian rhythms [25]. Not all these rhythms or variations equally impact the concentration/activity of the analytes. The type of dominant physiological rhythm varies depending on the analytes involved [26]. For instance, ultradian rhythms, characterized by within-day variations, predominantly govern episodic hormonal secretion [27]. Conversely, circadian rhythms exhibit dominance in regulating daily serum melatonin [28] and cortisol levels [29] and infradian rhythms, spanning monthly or seasonal cycles, is dominant over gonadotropic hormones [30], vitamin D and calcium levels [31,32]. Therefore, caution should be paid when determining the set point for each analyte in establishing its prRI. There are two primary methods for determining the HSP for an analyte: constant HSP and varying HSP [25]. Using constant HSP is the pragmatic way and provide a very easy calculation

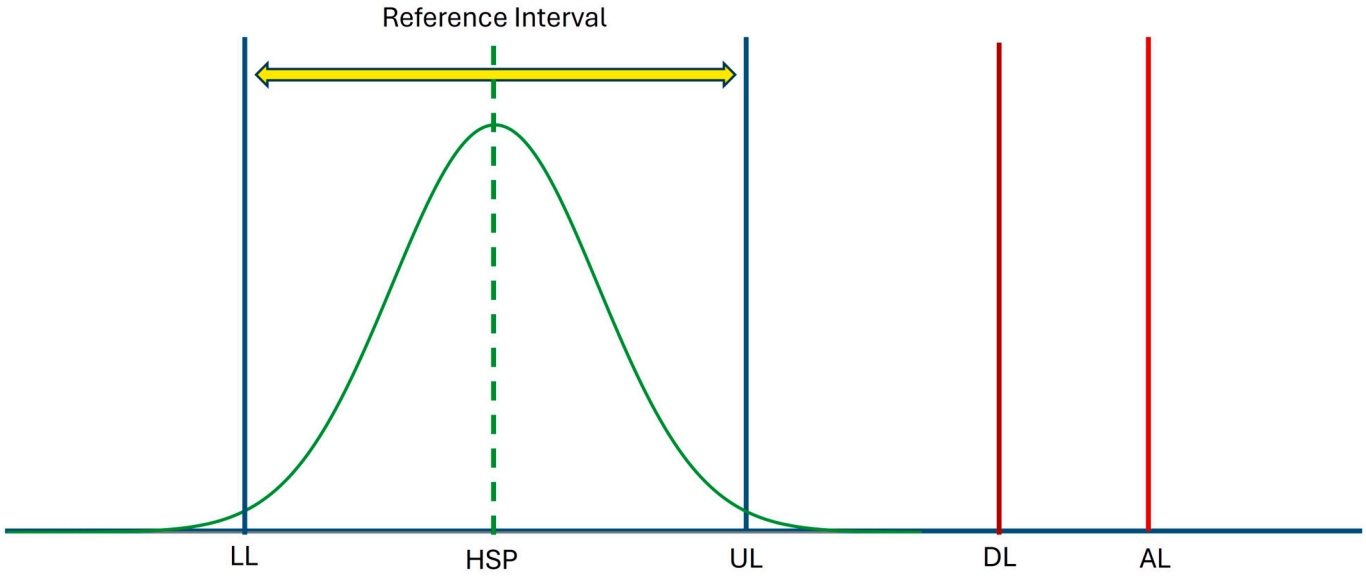

Fig. 2. Reference interval (RI), decision limit (DL) and action limit (AL).
In the Figure, the elevated analyte level indicates pathology, therefore RI (UL) $\leq$ DL $\leq$ AL. Conversely, if lower analyte levels indicate pathology, then RI (LL) $\geq$ DL $\geq$ AL.

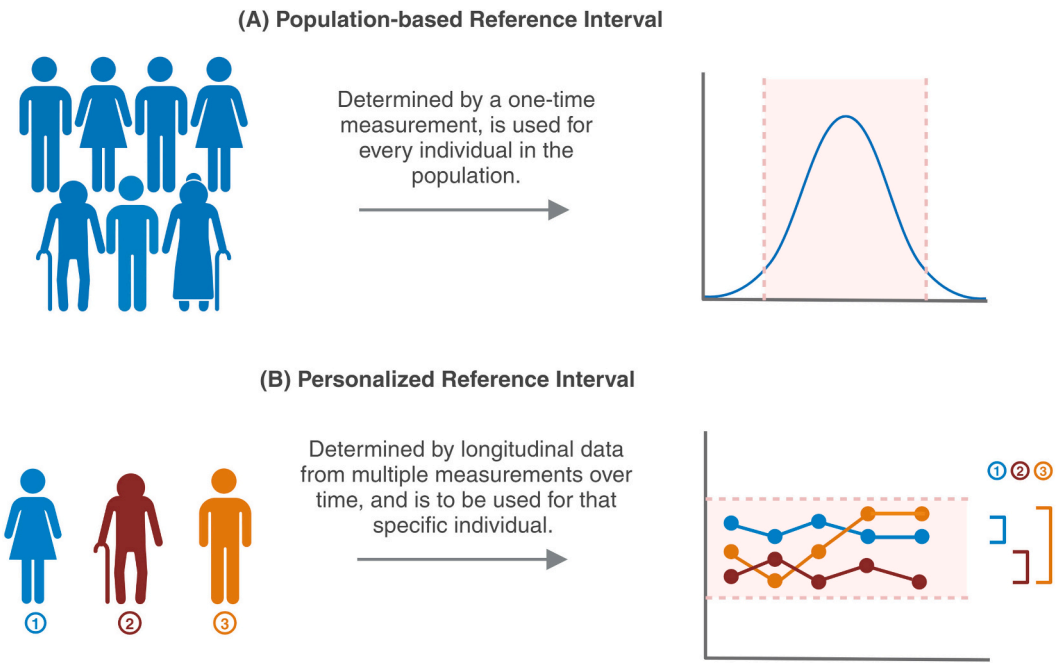

Fig. 3. Population (A) and personalized (B) reference intervals. Population based reference intervals does not represent individuals reference intervals. Created with BioRender.com.

method for prRIs [22]. It's important to note that the HSP is subject to physiological variations. To mitigate this, samples should be collected at consistent times of day for ultradian variations and at consistent times of months or seasons for infradian variations. In other words, if samples are collected randomly throughout days or months, the HSP of the analytes will vary significantly, affecting the accuracy of calculated prRIs. Typically, samples for popRIs are collected in the morning time (usually from 08:00 am to 12:00 am), reducing the impact of ultradian variations on HSP. However, this doesn't mitigate the influence of infradian variations on HSP.

The second approach involves utilizing varying HSPs to calculate prRIs for analytes. While scientifically robust, this method is complex, requiring intricate mathematical equations and a deep understanding of the variation patterns for each analyte [25]. Despite the availability of robust mathematical algorithms like the Cosiner model [33] for calculating HSPs in time-dependent functions, there's a scarcity of information regarding the physiological rhythms and particularly the ultradian and infradian rhythms of many analytes commonly used in daily clinical practice for diagnosing and monitoring diseases. This shows the necessity for intensive studies to determine the patterns of physiological rhythms for the common analytes measured in clinical laboratories.

Taken together it is a pragmatic way to use constant HSP for most of measurands to estimate the prRIs. For certain analytes like melatonin, cortisol, vitamin D, calcium, etc., whose ultradian or infradian variations are well-understood, it's feasible to calculate different reference intervals for morning and evening, or for winter and summer seasons to mitigate the influence of variation on the HSP of the analytes [25].

As shown in Eq. 1, the general equation of prRI is very simple and has only two main components: Set point and the variation around the set point. Despite its simplicity, estimating prRI can be challenging, especially when preferring a nonstationary model. However, pragmatically, using the homeostatic model (stationary) is advisable. Because extensive study is essential before implementing the nonstationary model in daily practice.

PrRI based on homeostatic model have been extensively analyzed by our group [22–24,34,35] and briefly can be modified from Eq. 1 as follow:

$$\mathrm{prRI} = \mathrm{HSP} \pm \mathrm{TV_{set}} \tag{2}$$

$$\mathrm{HSP} = \frac{x_1 + x_2 + x_3 + \ldots + x_n}{n} \tag{3}$$

$$\mathrm{TV_{set}} = k \times \sqrt{SD_{I/P}^2 + SD_A^2} \tag{4}$$

where HSP is the arithmetic mean of the individual's repeated measurement results, n_i represents the result of the nth repeated measurement, where n denotes the number of repeated measurements, k is a coverage factor, and its value depends on the statistical model used to estimate the prRI of the analytes. $SD_{P/I}$ is the within-subject/person BV and SD_A is analytical variation.

In the TVset equation (Eq. 4) the critical parameter is the BV component, and it can be either within-subject (SD_I) or within-person BV (SD_P). Reliable BV data is essential to estimate reliable prRI. To achieve this, the EFLM BV Working Group and Task Group continually update the BV of several laboratory parameters [36–39], harmonize meta-analyses of published data related to BV [40–44], and launched ongoing BV databases [12].

Although SD_I and SD_P denote the same parameter, i.e. the fluctuation around the set point, in practice they are different. SD_I is derived from the repeated measurement results of a group of individuals, whereas SD_P is directly obtained from the repeated sampling measurements taken at different times from a single individual. Therefore, it can be concluded that while SD_I represents the population variation around a set point, SD_P represents the fluctuation of the analytes around individual's own set point. It is recommended that SD_P should be utilized to estimate the TVset. However, the limited number of repeated samplings for an individual is the limiting factor for deriving reliable SD_P.

An alternative approach proposed by Pusparum et al. utilizes non-parametric methods to estimate the prRI of omics data [45–47]. These methods make use of the concept of quantile function in longitudinal data, requiring only short time series data of one individual as well as her/his peers. A penalization procedure is proposed, allowing them not to require strong distributional assumptions. Using these methods, both the within and between subject variations as well as the lower and the upper limits or prRI are estimated using all available data.

It should be noted that RIs, either popRI or prRI are not usually adequate to make accurate diagnosis of diseases. Because the measurement result outside of the RI does not always indicate the presence of diseases. As mentioned above, indeed, it can be speculated that the measurement results falling the outside of the RI indicate the abnormality but for the diagnosis of the diseases we need a new limit which is known as DL.

2.2. Personalized decision limits

Ensuring reliable DLs is as crucial as ensuring reliable RIs and similar to prRIs, the DLs also should be personalized [25]. Otherwise, using prRI with population based DLs can cause misinterpretation of laboratory data and consequently misdiagnosis of diseases. The estimating of DL is based on the data of diseased individuals [48] and therefore deriving personalized DL (prDL) is not an easy task. Either PopRI or PrRI of a group of tests can be estimated using the measurement results of samples taken from healthy individuals. When determining the RI, there are no restrictions on the number of different analytes to be measured, given that the collected samples are suitable. Conversely, the situation for DLs is entirely distinct [48]. For each analyte, samples should be obtained from individuals with specific diseases related to the analyte, wherein the analyte holds clinical significance with respect to the diseases. Thus, for one analyte, there exists a single RI but multiple DLs. Establishing DLs for a population is relatively straightforward because various individuals with different diseases are present. However, determining prDLs directly is challenging and often impractical or even impossible due to the complexity of estimating DLs for different clinical situations related to an analyte. This difficulty arises because each individual would require the presence of different diseases for each analyte, which is not feasible for hundreds of analytes. Despite these difficulties, it does not mean that prDLs cannot be estimated. Although direct estimation is not feasible, indirect estimation can be accomplished through simulation studies.

The indirect prDL can be estimated using the following two steps procedure: In the first step, calculate the population-based relative changes ($popRC_{DL}$) for DL from the limit of the popRIs to the population-based DL (popDL) as shown below:

$$popRC_{DL} = \left|\frac{L_{popRI} - popDL}{L_{popRI}}\right| \tag{5}$$

where L_{popRI} is the limit of the popRI. If the higher level of the analyte is clinically significant, then L is the UL of the RI. Conversely, if the lower level of the analyte is clinically significant, then L is the LL of the analyte.

In the second step, the prDL of an analyte can be indirectly estimated by multiplying the limits of the prRI of the analyte with the $popRC_{DL}$, as outlined in the following equation.

$$prDL = L_{prRI} \pm L_{prRI} \times popRC_{DL} = L_{prRI}\,(1 \pm popRC_{DL}) \tag{6}$$

It should be noted that Eqs. 5 and 6 are adapted from popDLs, and therefore, clinical studies that cover long-term monitoring of individuals are essential for the validation of these equations.

Despite various challenges associated with estimating reliable prDLs, it can be speculated that for an individual, prDLs might be more effective than popDLs. This is because it is illogical to assume that a single DL which is derived from the population data is suitable for diagnosing diseases in different individuals. There is ample evidence that variations and set points of the analytes are not uniform but vary depending on the individuals.

2.3. Personalized action limits

Using the RIs and DLs, physicians can distinguish the data of healthy individuals and diagnose diseases as described above. However, if a patient's laboratory measurement result for an analyte is higher than the DL, this may not necessitate the initiation of treatment. Therefore, physicians may need new a limit to initiate treatment, known as action limit (AL). Estimating ALs is based on population data, and an algorithm similar to that used for DLs can be employed to estimate personalized ALs (prALs), as described below.

Similar to prDL, an indirect approach can be used to estimate the prAL using the following two steps procedure:

In the first step, calculate the population-based relative changes for AL ($popRC_{AL}$) from the limit of the popDL to the population-based AL (popAL) as shown below:

$$popRC_{AL} = \left|\frac{popDL - popAL}{popDL}\right| \tag{7}$$

In the second step, the prAL of an analyte can be indirectly estimated by multiplying the prDL of the analyte with the $popRC_{AL}$, as outlined in the following equation.

$$prAL = prDL \pm prDL \times popRC_{AL} = prDL \times (1 \pm popRC_{AL}) \tag{8}$$

It should be noted that, similar to popDLs, popALs are derived from population data. Therefore, clinical studies, including personalized pharmacogenomics, might be essential for the validation of prALs, which can be challenging.

2.4. Personalized reference change value

Laboratory data plays a crucial role in monitoring the health statuses of both healthy individuals and patients. To effectively utilize laboratory data for this purpose, it is necessary to employ statistical algorithms to analyze the longitudinal data analysis. These algorithms must account for all types of physiological variations associated with the analyte, as well as variations stemming from the measurement procedure.

In monitoring procedure, the difference between measurement results of serial samples taken from the individual is important [49]. This can be evaluated by the equation of delta check (DC) as given below.

$$DC = x_i - x_j \tag{9}$$

where x_i and x_j are the ith and jth measurement results. It should be noted that both ith and jth are not strictly fixed and each of them contains a degree of variation originating from BV and analytical variations. The total variation of two measurement results is known as reference change value (RCV) and formulated as given below [50,51]:

$$RCV = z \times \sqrt{2} \times \sqrt{SD_I^2 + SD_A^2} \tag{10}$$

where z is 1.96, which represents the coverage factor for a 95 % probability in the standard normal distribution.

Eq. 10 represents the classical RCV equation, which calculates the total analytical and BV of two single measurement results. Therefore, if the difference between the measurement results of two samples taken at different times, i.e. DC is less than the calculated RCV, this difference is considered insignificant, as it falls within the natural biological and analytical variations. Conversely, if the DC exceeds the calculated RCV, it should be deemed significant, as it cannot be attributed solely to the inherent biological and analytical variability of the analytes. Note that, Eq. 10 proposes a monitoring approach grounded in objective criteria rather than the personal experiences of clinicians. However, this approach comes with its own set of limitations.

There are 2 main limitations for conventional RCV equation as detailed below. The first limitation is that the BV component of conventional RCV equation is derived from healthy individuals. Therefore, it is not rational to use Eq. 10 for monitoring individuals with diseases related to the analytes being monitored. Despite the limited data available, based on the published data in the literature, we can speculate that the BV of the analyte in diseased subjects are higher than that of the

analytes in healthy individuals [52]. It can be concluded that using conventional RCV equation in patient monitoring can give false alarm at least in some cases regarding significant changes in serial measurements.

The second important limitation of the conventional RCV equation is that it is based on population rather than personalized data. The SD_I in the equation is derived from the serial measurement of a group of individuals. Although SD_I implies the within-subject BV, indeed it is not individual specific, and it is estimated from the pooled SDs of a group of individuals SDs.

Taken together it can be concluded that just as the popRI fails to accurately represent individuals for disease diagnosis, the conventional RCV equation falls short in representing individuals during the monitoring of diseases. To overcome this problem, the conventional RCV equation should be personalized, i.e. its BV component should be derived from individuals' own rather than population data [53]. The personalized RCV (prRCV) equation can be written as given below:

$$\mathrm{prRCV} = t_\alpha \times \sqrt{2} \times \sqrt{SD_P^2 + SD_A^2} \tag{11}$$

where t_α is the T table value for $n - 1$ degrees of freedom, SD_P is the within-person BV, SD_A is the analytical variation. In a routine practice SD_A is calculated separately and combined with other parameters such as SD_P or SD_I to calculate the total variation, i.e. SD_T.

$$SD_T^2 = SD_P^2 + SD_A^2 \tag{12}$$

Using Eq. 12, the Eq. 11 can be simplified further as follow:

$$\mathrm{prRCV} = t_\alpha \times \sqrt{2} \times \sqrt{SD_T^2} \tag{13}$$

Eq. 13 provides a very simple way to calculate prRCV. It is not rational to separate SD_A from SD_T to obtain SD_P and then combine SD_A with SD_P to obtain SD_T again. Instead of this nonsense cycle, SD_T can be directly calculated using individuals repeated measurements. The RCV based on Eq. 13 is personalized and reflects individualized own changes during monitoring of the health statues and diseases for the individuals.

The prRCV calculated based on Eq. 13 involves a T distribution, whereas a non-parametric approach that does not rely on distributional assumptions for estimating prRCV has recently been introduced [54,55]. The method requires only a relatively short time series from multiple subjects. Both the variation within and between subjects are included in the model, and all model parameters can be directly estimated from the data. A penalization procedure is employed where the penalty parameters are calibrated and optimized such that they result in prRCV with good accuracy.

While current medical practice relies on analyzing individual analytes for diagnosing and monitoring diseases and other medical conditions, there's a paradigm shift underway. Omics data are gradually becoming increasingly important in medical practice particularly in personalized medicine. It's worth noting that the statistical principles employed to estimate RI, DL, and AL can also be applied to estimate these parameters for Omics data. However, because of the population's heterogeneity and the high-dimensional nature of omics data, estimating these parameters for the population poses a challenge. Despite the challenges encountered in establishing reference values for omics data within populations, it is relatively easier to estimate reference values for individuals when compared to the population. This is because there are limited repeated measurements for each individual.

It should be noted that for the current practice, personalized algorithms such as prRI, prDL, prRCV, and prAL should be used as complementary references in interpreting an individual's laboratory data alongside with their population counterparts, rather than separately. In other words, a two-line procedure can be used for accurate diagnosis and monitoring of diseases: the first line can be population-based references, and the second line can be personalized references.

2.5. Integrating of personalized references

Instead of using some references from population-based data and others from individualized data, integrating personalized references can enhance the accuracy of diagnosis, monitoring, and initiation of treatment. In this model, the individual is the center of algorithms, and all parameters are based on the individual's own data. A sequential algorithm should be used as detailed below.

In the first step, at least 5 repeated measurement results for an analyte should be collected, and prRI and prRCV should be estimated using these repeated measurements. In the second step, prDL can be estimated from prRI, and if necessary, prAL can be estimated from the estimated prDL of the individual for the given analyte. Additionally, during stable periods of the disease, repeated measurement results can be collected to estimate prRCV for monitoring diseases related to the analytes.

Integrating individualized references also provides the opportunity to evaluate the correct biomarker in the appropriate equation. For example, diagnostic biomarkers should be used in the prDL equation, while prognostic biomolecules should be used in the prRCV equation.

2.6. Individualized algorithms based on small sample size

In human metabolism, biomolecules are influenced by physiological variations. Detailed information on these variations affecting the concentration/activity of biomolecules can be found in [25]. Due to inherent variations in biomolecules, their concentration/activity patterns over time exhibit curves rather than linear trends. Accurate biological models require extensive data obtained from samples collected at various times of the day, across different months, and throughout seasons. This variability introduces challenges in correctly estimating the concentration/activity patterns of biomolecules. Furthermore, collecting extensive data is not realistic for individual laboratory measurands. Therefore, linear algorithms based on small sample sizes can be preferred for interpreting individualized laboratory data. In such cases, biological samples are usually taken at the same time of day to minimize the effects of other rhythmic variations.

A simple linear model can accurately predict trends, especially when there is insufficient data to create a more complex non-linear model. In other words, a linear model, being simpler, is often preferred when there is insufficient data to justify the complexity of a non-linear model. However, this is not a universal rule because if the correct relationship between variables is highly non-linear, a linear model may not detect important patterns, leading to poor predictive performance. Therefore, after creating a linear model, it is essential to analyze the differences between observed and predicted values to determine if the linear model is appropriate.

3. Omics and personalized laboratory medicine

Omics data, derived from the advancing field of omics technologies, are distinguished by their vastness, complexity, and high dimensionality [56–59]. These data include detailed information on biological molecules—genes, transcripts, proteins, and metabolites—present within an organism or a specific biological sample [60]. Omics data exhibit significant inter-individual and temporal variability, highlighting the unique biological makeup of each person and the dynamic nature of biological processes over time [61].

The integration of omics technologies into laboratory medicine has marked a pivotal shift toward the personalization of healthcare, where treatments and interventions are tailored to the individual's unique genetic and metabolic profile [62,63]. While it is true that omics technologies such as metabolomics and proteomics are not yet widely used in routine clinical practice, there are significant ongoing experimental efforts. For example, research is actively exploring how these profiles can be leveraged to tailor treatments and interventions, with promising preliminary results indicating the potential for future clinical

integration [64]. Omics disciplines offer unparalleled insights into the molecular underpinnings of individual health and disease. These technologies enable the precise characterization of biological samples at the molecular level, facilitating personalized diagnostic, prognostic, and therapeutic strategies (Fig. 4). By analyzing the comprehensive datasets generated by omics studies, healthcare professionals can tailor interventions to individual patient's unique genetic and metabolic profiles, significantly improving treatment outcomes.

The applications of omics can already be seen in various diseases, particularly in cancer and neurodegenerative diseases. Together with their characteristics, we explain the current applications and future potentials of omics data in personalized laboratory medicine.

3.1. Genomics

Genomics, focuses on the analysis of the complete set of deoxyribonucleic acid (DNA), where the variability among individuals is vast. Millions of genetic variants differentiate any pair of individuals. This genetic diversity forms the foundation of personalized medicine but poses significant hurdles in interpreting genetic information. Progress in bioinformatics has played a vital role in analyzing and understanding this data, identifying clinically relevant variants out of the vast array of genetic diversity [65].

Cancer is the second leading cause of death globally, following cardiovascular diseases, and poses a significant challenge to global health [66,67]. In cancer, genomic sequencing of tumors has revolutionized oncology, enabling the identification of specific mutations driving cancer progression. For example, detecting the BRCA1 and BRCA2 gene mutations has not only facilitated the early diagnosis of breast and ovarian cancers [68,69] but also guided targeted therapies, such as PARP inhibitors, improving patient outcomes [70,71]. In addition, whole-genome sequencing can diagnose rare genetic disorders by identifying causative mutations in a single test, a significant advancement over traditional sequential gene testing [72,73]. This advancement accelerates diagnosis and aids in selecting appropriate treatments, improving the quality of life for affected individuals. Looking forward, genomics holds the potential to further personalize treatments, predict disease susceptibility, and enable the development of new gene-editing technologies, revolutionizing preventive and therapeutic strategies in medicine [74].

3.2. Metabolomics

Metabolomics provides a snapshot of the metabolic processes occurring at a specific point in time by analyzing the complete set of small molecule metabolites. Genetic factors, lifestyle, diet, microbiome composition, and environmental exposures influence inter-individual variability in metabolomics [75]. This results in highly individualized metabolic profiles. MS and nuclear magnetic resonance (NMR) spectroscopy are the primary technologies used in metabolomics. These techniques require significant expertise and sophisticated equipment to accurately quantify the wide array of metabolites present in biological samples.

In neurodegenerative diseases like Alzheimer's, which are rising globally alongside the increasing aging population [76], metabolomics have uncovered alterations in specific metabolic pathways, including those involved in lipid metabolism and mitochondrial function [77]. These discoveries offer novel targets for therapeutic intervention and biomarkers for early detection and monitoring of disease progression. Metabolomics has also contributed to understanding host-pathogen interactions by profiling the metabolic changes induced by infections such as COVID-19 [78]. Identifying these metabolic signatures can help predict disease severity and guide treatment decisions. Metabolomics holds the potential to revolutionize personalized medicine by enabling precise and individualized treatment strategies based on a patient's unique metabolic profile [79]. Additionally, advancements in metabolomic technologies could lead to the development of more accurate and non-invasive diagnostic tools [80].

3.3. Proteomics

Proteomics, the large-scale study of proteins, their structures, and functions from a biological perspective, is essential for understanding the functional state of cells, tissues, and organisms. Unlike genomics, which provides information about the potential for disease, proteomics offers direct insights into biological processes and disease mechanisms. Techniques such as mass spectrometry (MS) and high-throughput, highly specific protein quantification using proximity extension assays are central to proteomics research. The complexity and dynamic nature of the proteome, which varies with time and environmental conditions, present both opportunities and challenges in clinical applications.

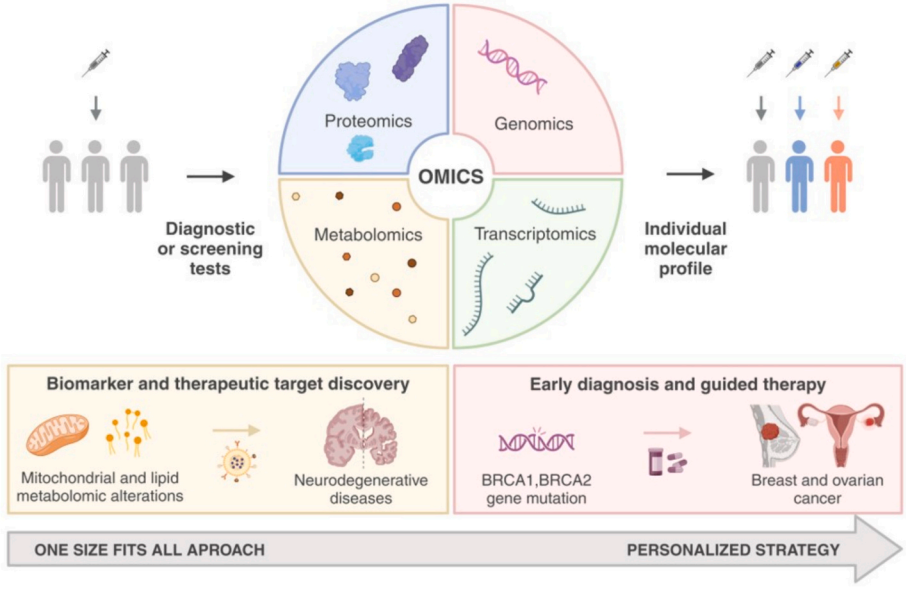

Fig. 4. Personalized omics data. Individuals' molecular profiles enable personalized diagnosis and monitoring.
Created with BioRender.com.

In clinical applications, proteomics technology has significantly advanced our understanding of cancer biology. For instance, the detection of prostate-specific antigen (PSA) is used for screening and monitoring prostate cancer; elevated PSA levels can indicate the presence of prostate cancer, prompting further diagnostic procedures and treatment planning [81]. Beyond cancer, proteomics also holds potentials for identifying biomarkers for a variety of diseases, enabling earlier and more accurate diagnoses [81,82]. It can also aid in the development of personalized medicine by identifying specific protein expressions related to individual patient responses to treatments [83]. The ability to analyze the dynamic and complex nature of the proteome in real-time also allows for better understanding of disease progression and response to treatment, ultimately improving patient outcomes.

The future of omics in clinical healthcare is promising, with applications extending beyond current examples. As omics technologies becoming more accessible and cost-effective, their integration into routine clinical practice is expected to increase. This shift from a one-size-fits-all approach to personalized medicine optimizes patient care based on individual molecular profiles, improving outcomes and healthcare efficiency. High-throughput sequencing and analytical platforms, along with bioinformatic tools and artificial intelligence, enable the generation and interpretation of omics data on an unprecedented scale. However, challenges remain in integrating diverse omics data and translating it into clinical practice [84,85].

4. Characteristics of omics data

Omics data are distinguished by their vastness, complexity, and high dimensionality [56–59]. This data encompasses detailed information on biological molecules—genes, transcripts, proteins, and metabolites—present within an organism or a specific biological sample [60]. A comprehensive list for omics data would be impossible due to the continuous evolution of omics technologies [56]. Significant inter-individual variability and temporal variability are present in omics data, reflecting the unique biological makeup of each individual and the dynamic nature of biological processes over time [61].

Both genomics and metabolomics rely on cutting-edge technologies that are rapidly evolving. The development of high-throughput sequencing and analytical platforms has enabled the generation of omics data on an unprecedented scale. Bioinformatic tools and artificial intelligence are increasingly used to manage and interpret this data, identifying patterns and correlations that were previously unattainable [84]. Despite these advancements, challenges remain, particularly in integrating omics data from different sources and translating this knowledge into clinical practice [85].

The application of omics technologies in personalized medicine is both promising and challenging. The inter-individual and temporal variability inherent in omics data requires sophisticated technologies and substantial financial investment for accurate analysis. While costs have decreased significantly, making these technologies more accessible, the field continues to evolve rapidly, demanding ongoing investment in technology and expertise to fully realize the potential of omics in personalized healthcare.

4.1. Omics data and diagnosis of diseases

The diagnostic potential of omics data lies in its ability to identify unique molecular signatures associated with specific diseases. Genomic data can reveal genetic predispositions and mutations that increase the risk of developing certain conditions, such as cancer, cardiovascular diseases, and genetic disorders. Metabolomics, on the other hand, can detect subtle changes in metabolite levels that reflect early disease states or responses to treatment. Proteomics further enhances this diagnostic capability by analyzing the protein expressions and modifications that occur in disease states, providing insight into the functional mechanisms underlying various conditions. By integrating these omics datasets, clinicians can achieve a more comprehensive and accurate diagnosis, often before clinical symptoms manifest [85]. This early detection is crucial for conditions where early intervention can drastically alter the disease course and improve patient outcomes.

The application of omics technologies-specifically genomics and metabolomics—plays a crucial role in every phase of the disease trajectory. In the early onset, for example, genomic analyses from liquid biopsies can detect circulating tumour DNA (ctDNA) in blood [86]. The method offers a non-invasive method to identify cancer at an early stage, often before symptoms appear. Studies have shown that ctDNA can be used for the early detection of lung cancer in high-risk individuals, allowing for earlier intervention and significantly improved survival rates [87–89]. Genomics analyses are also particularly valuable in diagnosing rare genetic disorders, where traditional diagnostic pathways can be lengthy and complex [72]. Whole-exome sequencing (WES) or whole-genome sequencing (WGS) can rapidly identify causative mutations, significantly reducing the diagnostic odyssey for patients and families.

Metabolomics has shown promise in identifying early metabolic changes associated with neurodegenerative diseases like Alzheimer's disease (AD) before clinical symptoms manifest [90,91]. Specific cerebrospinal fluid metabolites are considered the best candidates for AD diagnosis, namely the amyloid-β and the Tau protein. Proteomics technology has identified several candidate protein biomarkers for AD. These include apolipoprotein E, complement factor H, and various synaptic proteins, which can provide deeper insights into the disease's pathogenesis and offer potential targets for early therapeutic intervention [92]. Additionally, several candidate biomarkers from liquid chromatography-mass spectrometry (LC-MS) metabolomics data, such as uridine, cortisol, and cysteine, can indicate the onset of pathologic processes, potentially allowing for early therapeutic intervention aimed at slowing disease progression [93]. The integration of prRIs into the analysis of omics data, particularly to these potential biomarkers, represents a significant advancement in the personalized diagnosis of diseases [46,47]. PrRIs of these metabolites and proteins can significantly improve the early detection of various diseases, enabling preventative measures or early treatment to mitigate disease progression. For example, prRIs can be implemented in metabolomics for metabolites associated with the risk of diabetes and cardiovascular diseases, such as lipid profiles or markers of inflammation, offering a more precise baseline for interpreting the measured compounds [47].

Recent advancements in genomics have identified several genetic variants associated with an increased risk of AD, such as APP (Amyloid precursor protein), PSEN1 (Presenilin 1), and PSEN2 (Presenilin 2) [77]. In the future, integrating the genetic factors with potential metabolites and protein biomarkers to establish prRIs could enable a more nuanced assessment of AD risk. This personalized approach could inform early intervention strategies, such as lifestyle modifications or pharmacological treatments to delay onset or progression.

4.2. Omics data for disease monitoring and screening

Beyond diagnosis, omics technologies play a vital role in monitoring disease progression and response to treatment. Omics analyses can track changes in patients' genomic and molecular landscapes over time, offering insights into the disease trajectory and the efficacy of therapeutic interventions and the information on safety with reference to side effects to certain medications. For instance, genomics can be used for screening drug-resistant mutations in cancer, guiding adjustments in therapy to circumvent resistance mechanisms [94]. Metabolomics can assess the impact of treatment on metabolic pathways, identifying metabolic markers of response or toxicity [62]. Proteomics adds another layer by evaluating the expression and modification of proteins in response to treatment, which can reveal the molecular mechanisms of drug action and resistance [95]. This real-time monitoring enables a dynamic, personalized approach to treatment, where therapies can be adjusted

based on the patient's molecular response, leading to optimized outcomes, and minimized adverse effects. The role of prRCV is also apparent in enhancing these applications.

In cardiovascular diseases, which is the foremost global cause of mortality and a paramount global health concern [96], monitoring of genomic and metabolomic markers can guide lifestyle and treatment adjustments. Metabolomics has been used to identify biomarkers associated with the progression of atherosclerosis, such as choline, betaine, and microbiota-generated metabolite trimethylamine N-oxide (TMAO) [64,97,98]. Monitoring changes in these plasma metabolites, primarily derived from meat and phospholipids in the diet, can help assess the effectiveness of lifestyle interventions or statin therapy. Choline and betaine are compounds that play an essential role in metabolism, and they can fluctuate over time due to aging, seasonal changes, dietary intake, and other physiological factors such as physical activities and stress levels [98,99]. Studies also report the presence of intra-individual variability and high values of intra-class correlation in choline and betaine, suggesting more personalized ways in interpreting their measurements [100,101]. PrRIs and prRCV of these metabolites, taking into account these variabilities as well as individuals' baseline metabolic profiles, could significantly enhance the precision of such interpretation and monitoring, allowing for early identification of suboptimal responses to treatment and timely adjustments.

In cancer patients, employing personal genomics approaches is critical in monitoring cancer recurrence and treatment response. For instance, the analysis of ctDNA levels can provide an early indication of tumor recurrence or metastasis [86]. Furthermore, metabolomics can offer insights into the metabolic response to chemotherapy, predicting treatment success or failure. By studying metabolomic profiles over time, researchers can potentially predict treatment success or failure and personalize treatment strategies for individual patients.

Utilizing prRIs and prRCV in the context of omics data significantly enhances the personalization of disease monitoring. Traditional RIs are derived from population-based studies; they may not accurately reflect optimal values for every individual, particularly in the context of genetic diversity and unique individual biological makeup [45]. PrRIs considers an individual's baseline profile and inter-individual variability over time, providing a personalized benchmark against which changes in genetic or metabolic markers can be more accurately assessed. This approach improves the early detection of disease progression or treatment non-responsiveness, enabling more timely and effective interventions. Since prRIs provide a more personalized assessment of disease risks, targeted prevention strategies could also be enabled so that they are more likely to be effective for the individual. In the context of pharmacogenomics, prRIs can help identify the most effective and safest medications and dosages, reducing the risk of adverse drug reactions and improving treatment outcomes.

In conclusion, the application of omics technologies in disease monitoring, coupled with the use of prRIs and prRCV, represents a paradigm shift in personalized healthcare. These approaches can significantly improve patient outcomes across a wide range of conditions by enabling more precise tracking of disease progression and response to treatment. The adoption of prRIs in clinical practice requires comprehensive baseline data collection and sophisticated analytical tools, but the potential benefits for patient care and healthcare efficiency are substantial.

5. Nano-omics and personalized laboratory medicine

In the ever-evolving landscape of medical research, the fusion of nanotechnology and omics sciences has given rise to the revolutionary field of nano-omics, presenting a paradigm shift in personalized laboratory medicine [102–104]. Nano-omics integrates nanoscale materials with genomics, proteomics, metabolomics, and transcriptomics, unlocking unparalleled opportunities for tailoring medical approaches to individual patients that embodies the true spirit of personalized medicine, setting a new standard for precision in healthcare. Advancements in personalized laboratory medicine are propelled by nano-omics, offering not only high-resolution insights into cellular processes but also novel applications that redefine diagnostics and therapeutics [105] such as enhanced diagnostic accuracy, targeted drug delivery, personalized treatment plans, real-time monitoring of treatment efficacy, and improved prognostics and predictive analysis [106].

5.1. Potential applications of nanomics in personalized laboratory medicine

5.1.1. Enhanced diagnostic accuracy

Nano-omics introduces an unprecedented level of diagnostic precision through its ability to monitor molecular changes at the nanoscale in real time. This capability allows for the early detection of diseases by identifying subtle molecular deviations that precede visible symptoms and conventional diagnostic detectability [107]. For example, using gold nanoparticle-enhanced imaging, nano-omics can identify tumor-specific genetic mutations and protein expressions with extraordinary accuracy, facilitating early-stage interventions that significantly improve patient prognosis [108]. Nanoparticle-based liquid biopsy enhances cancer biomarker detection by binding to circulating tumor DNA (ctDNA) or exosomes in bodily fluids [109]. Magnetic nanoparticles with antibodies capture circulating tumor cells (CTCs) from blood samples, allowing genetic analyses to identify specific cancer mutations [110]. Nanoparticle-enhanced imaging improves resolution in PET and MRI. Gold nanoparticles in CT scans enhance contrast, distinguishing benign from malignant tumors with higher accuracy, aiding in detecting cancers like ovarian cancer [111]. Iron oxide nanoparticles in MRI identify early prostate lesions, enabling prompt intervention [112].

Quantum dots offer high-resolution molecular profiling [113]. Conjugated with antibodies, quantum dots specifically bind to cancer-associated proteins like HER2 in breast cancer, providing more accurate identification of HER2-positive cells than traditional immunohistochemistry [114].

Similarly, in cardiovascular diseases, nanoscale sensors embedded within stents detect early biomarkers of heart failure or artery blockages, enabling preventative measures before critical conditions arise [115]. Nano-omics enhances the early detection of MI through highly sensitive nanosensors that identify cardiac biomarkers [116]. Cardiac troponins (cTnI and cTnT) are crucial indicators of myocardial injury, and nanoparticle-based biosensors such as carbon nanotube field-effect transistors (CNT-FETs) or gold nanoparticle-enhanced immunoassays provide rapid and sensitive detection of these biomarkers at concentrations as low as a few picograms per milliliter [117]. Early identification of elevated troponin levels allows for prompt intervention, minimizing cardiac tissue damage. Moreover, nanoparticle-based imaging improves the specificity of imaging modalities like MRI and PET for MI diagnosis. Iron oxide nanoparticles enhance the resolution of cardiac MRI, highlighting areas of ischemic injury [118]. Additionally, radiolabeled nanoparticles used in PET imaging can identify inflammatory activity within atherosclerotic plaques, helping to predict plaque rupture and imminent MI [119].

In a neurodegenerative context, nano-omics technologies can be applied to analyze the intricate molecular pathways associated with diseases like Alzheimer's. Through the real-time monitoring of specific protein aggregates in neurons, researchers can gain insights into disease progression [120]. These insights not only aid in early diagnosis but also lay the foundation for the development of tailored therapeutic interventions targeting the root causes of neurodegenerative disorders. This groundbreaking application of nano-omics in neurodegenerative diseases will be possible by utilizing nanoscale sensors to detect subtle changes in the protein composition of cerebrospinal fluid. This real-time analysis provides crucial information about the progression of diseases like Alzheimer, allowing for early intervention strategies to delay or prevent cognitive decline.

To enhance diagnostic accuracy, the prRI and prDL should be integrated with data from nano-omics technologies where available and suitable. For each analyte, at least five repeated measurement results should be obtained from samples taken from individuals at appropriate time intervals. Eq. 2 should then be used to derive the prRI, and subsequently, Eq. 6 can be used to estimate the prDL for each analyte.

5.1.2. Targeted drug delivery

The targeted drug delivery systems developed through nano-omics are notably innovative, as they deliver therapeutic agents directly to the site of disease, thereby maximizing therapeutic efficacy and minimizing systemic side effects [107]. For instance, in cancer treatment, nanoparticle-engineered drug delivery systems like PEGylated liposomal doxorubicin (Doxil) recognize and bind to cancerous cells, releasing their medicinal payloads in a controlled manner [121]. This method not only spares healthy tissues from the harsh effects of chemotherapy but also allows for higher drug concentrations at the tumor site, enhancing the overall treatment effectiveness.

Beyond oncology, nanoparticle drug delivery systems offer targeted and sustained release of cardioprotective medications to prevent HF development post-MI. Liposomal formulations containing beta-blockers, ACE inhibitors, or aldosterone antagonists can specifically target ischemic myocardium, reducing myocardial remodeling and fibrosis.

Nanomaterials also play a critical role in regenerative therapies for MI and HF. Injectable hydrogels containing nanoparticles loaded with growth factors or exosomes can create a supportive matrix for cardiomyocyte regeneration. For instance, gold or silica nanoparticles functionalized with angiogenic growth factors stimulate neovascularization in the infarct region, improving myocardial repair and reducing HF progression. This approach is also expanding into treatments for inflammatory diseases, such as rheumatoid arthritis, where polymer-based nanoparticles deliver anti-inflammatory agents directly to inflamed joints, thereby reducing the disease's systemic impact [122].

5.1.3. Personalized treatment plans

The adaptability of nano-omics in treatment plans is rooted in its ability to integrate continuous biomolecular monitoring with personalized therapy adjustments [107]. By using data-driven insights gathered from individual molecular responses, physicians can tailor treatments to each patient's unique biological context. This is particularly crucial in managing diseases with high variability between individuals, such as diabetes, where glucose-responsive nanoparticles adjust the release of insulin in response to the patient's fluctuating glucose levels and metabolic needs. The ability to dynamically adjust treatment plans not only optimizes therapeutic outcomes but also enhances patient adherence and satisfaction by minimizing side effects and improving overall quality of life.

After integrating the prRI and prDL with data from nano-omics, the prAL estimated from the prDL may be a good indicator for initiating targeted therapy and personalized treatment.

5.1.4. Real-time monitoring of treatment efficacy

The real-time monitoring capabilities of nano-omics offer profound benefits in chronic and progressive diseases [123]. Nanosensors detect changes in blood biomarkers linked to tumor response [124]. For example, carbon nanotube-based sensors measure biomarkers like CA-125 in ovarian cancer, indicating tumor shrinkage or recurrence [125]. In vivo monitoring with nanoparticles, such as silica nanoparticles conjugated with doxorubicin, allows real-time drug release and distribution tracking via fluorescence imaging, providing insights into drug penetration and treatment efficacy [126].

In monitoring and treating heart failure post-MI, nano-omics allows comprehensive proteomic profiling, identifying molecular markers predicting HF onset. Circulating biomarkers like brain natriuretic peptide, galectin-3, and soluble ST2 are detected using nanoparticle-enhanced proteomic assays, enabling clinicians to stratify patients by HF risk and tailor early interventions [127].

For neurodegenerative conditions like Parkinson's and Alzheimer's, nano-omics technologies can track the progression of the disease at a molecular level, often before symptoms worsen. Quantum dots, for example, can track changes in specific protein aggregates, providing insights that guide adjustments in therapeutic strategies, potentially slowing disease progression and offering patients a better quality of life for a longer duration. The application of these technologies in remote monitoring also significantly reduces the burden on healthcare systems by allowing patients to remain at home while still receiving optimal care, thereby democratizing access to advanced medical monitoring. In diagnosing and monitoring neurodegenerative diseases, PET/MRI combines structural and functional imaging [128]. High-resolution MRI detects brain atrophy [129], while PET tracers like 18F-FDG and 18F-AV45 reveal reduced glucose metabolism and amyloid-beta plaque accumulation in Alzheimer's disease (AD) [130]. Nano-omics, such as nanoparticle-based liquid biopsies, identify biomarkers like tau and beta-amyloid with high sensitivity [131]. Magnetic nanoparticles coated with antibodies capture circulating tau and beta-amyloid, enhancing detection in the blood [132]. Imaging data then correlates these molecular changes with disease pathology.

Functional PET/MRI provides deeper insights into neurodegenerative diseases by analyzing connectivity changes [133]. Resting-state fMRI (rs-fMRI) evaluates brain network disruptions, like the default mode network in AD [134]. Combining this with nanoparticle-based proteomics overlays nanoscale protein expression data, identifying protein changes in specific brain regions.

Metabolic activity and neuroinflammation are key in neurodegenerative diseases. 18F-FDG PET imaging measures glucose metabolism, with decreased uptake indicating synaptic dysfunction in AD. TSPO-PET imaging with tracers like 11C-PK11195 assesses neuroinflammation [135]. Nanoparticle-based sensors reveal metabolic shifts, while nanoparticle-enhanced proteomics identifies inflammation markers, mapping these changes to brain regions identified via PET/MRI.

5.1.5. Improved prognostics and predictive analysis

Predictive analytics powered by nano-omics not only enhance diagnostic and therapeutic precision but also revolutionize prognostics. By comprehensively analyzing the molecular data, healthcare providers can forecast disease trajectories and likely patient responses to various treatments. This foresight enables preemptive medical interventions, significantly altering patient management strategies, especially in diseases known for their rapid progression or high mortality rates [106].

Chemoresistance poses a major challenge in cancer therapy. Nano-omics helps uncover mechanisms and evaluate resistance development. Nanoparticles isolate ctDNA for genomic profiling of resistant cells, identifying mutations associated with chemoresistance [136]. Lipid-coated magnetic nanoparticles capture KRAS-mutated ctDNA in colorectal cancer, predicting resistance to EGFR inhibitors [137]. Proteomic analysis with nanoparticles identifies drug resistance proteins. Modified polymeric nanoparticles isolate P-glycoprotein from cancer cell lysates [138]. Drug efflux studies with nano-delivery systems reveal efflux mechanisms. Gold nanoparticles with chemotherapeutics monitor intracellular drug levels, indicating active efflux pumps if expelled quickly [139].

Within personalized references, prRCV integrated with omics and nano-omics is a powerful tool to evaluate the effectiveness of treatment and the prognosis of diseases. Using prRCV, the differences between sequential measurements of analytes can be objectively evaluated, providing a great opportunity for real-time monitoring of diseases.

5.2. Challenges and future directions of nano-omics

The marriage of nano-omics and personalized laboratory medicine not only transforms diagnostics and therapeutics but also addresses the challenges of traditional approaches. Nevertheless, the potential of

nano-omics in personalized laboratory medicine is accompanied by challenges that warrant comprehensive exploration. The potential risks associated with long-term exposure to nanoparticles, the ethical considerations surrounding genetic privacy, and the need for robust regulatory frameworks are among the primary concerns that must be addressed. Furthermore, the high cost of nano-omic technologies and the need for specialized training for healthcare providers are significant barriers to its widespread adoption. As we navigate the complexities of this interdisciplinary field, the collaboration between nanotechnology and omics sciences holds the promise of reshaping global health [140]. The convergence of nano-omics and personalized laboratory medicine represents a transformative leap toward a future where healthcare is not only personalized but also dynamically responsive to the unique molecular signatures of each patient. This is why global health initiatives deploy nanoscale sensors in resource-limited settings for rapid and precise disease diagnostics as the future applications of nano-omics in personalized laboratory medicine. This approach has the potential to revolutionize healthcare delivery in underserved populations, ensuring timely and targeted interventions for various diseases.

6. Personalizing omics data to enhance global health

Transitioning to a personalized, predictive, preventive, and participatory approach in medicine, known as P4 Medicine, represents a paradigm shift toward tailoring medical decisions to individual patient characteristics rather than relying on population averages [141,142]. Integrating omics technologies into P4 Medicine holds vast potential to transform global healthcare by uncovering the molecular mechanisms underlying the onset and advancement of complex diseases such as cancer and neurodegenerative disorders, which significantly impact global health. By integrating diagnostic test data with a patient's medical history and findings from physical examinations, physicians can develop individualized treatment and prevention strategies, enhancing a more personalized and impactful approach to patient care. Chen et al. [143] created a longitudinal integrative Personal Omics Profile (iPOP), which combined genomic, proteomic, metabolomic, transcriptomic, and autoantibody profiles, showcased the dynamic changes in molecular and biological pathways during the transition to type 2 diabetes following two viral infections (HRV and RSV). The creation of iPOP brings forth a host of benefits including improved disease risk assessment, early diagnosis, precise monitoring, targeted therapies, enhanced understanding of disease biology, and more effective prevention strategies in healthcare [143,144]. Similarly, Rose et al. [145] systematically collected quarterly samples for up to 8 years from 109 participants in an iPOP-enhanced prospective longitudinal cohort study. This comprehensive profiling involved the analysis of genome, immunome, transcriptome, proteome, metabolome, microbiome, and wearable tracking data. The study identified several pathways relevant to type 2 diabetes, cardiovascular, and oncological pathophysiology and developed predictive models for insulin resistance using omics measurements. By demonstrating the distinctiveness of healthy profiles among individuals and demonstrating different models of intra- and inter-individual variability, it can pave the way for personalized interventions and precision health strategies [146].

The aging of the global population is imposing a serious burden on the global healthcare system, and therefore, it is necessary to minimize the negative effects of aging such as disease and loss of productivity. In a study investigating personalized approaches to understanding the heterogeneity of aging patterns and the aging process among individuals, longitudinal and comprehensive multiomics profiles (including transcripts, proteins, metabolites, cytokines, microbes, and clinical laboratory values) were examined over a period of 2–3 years. Molecular profiles were integrated into longitudinal healthy aging cohorts among 106 healthy individuals, identifying various individual aging models [147].

The Pioneer 100 Wellness Project (P100), launched by the Institute for Systems Biology, undertook a comprehensive approach by integrating clinical tests, metabolomics, proteomics, microbiomics, and daily activity tracking across three time points for 108 individuals over nine months [148]. This initiative aimed to pioneer a new research model, the 100 K Wellness Project, reminiscent of the Framingham Heart Study, leveraging personalized, dynamic data clouds to deepen insights into biomarkers, genomics, and exercise. By analyzing data from the P100 project, researchers uncovered relevant analytes linked to specific diseases like cardiometabolic conditions and inflammatory bowel disease. This personalized approach, driven by the insights gained from projects like the P100 initiative, holds immense promise in optimizing healthcare delivery, enhancing patient outcomes, and advancing our understanding of complex diseases and their management [149].

Big data plays a critical role in personalized laboratory medicine. However, when the number of features exceeds the sample size, complex models may overfit the data, leading to erroneous predictions. Therefore, advanced algorithms and models are needed for the high dimensionality of multi-omics data [150]. By leveraging machine learning tools and algorithms, predictive models that identify risks can be developed by integrating multi-omics data with clinical information (Fig. 5). This enables facilitating interventions by identifying patients' health statuses at an early stage.

7. Future perspectives and challenges

Looking ahead, the field of personalized statistical algorithms for omics data interpretation is poised for significant advancements. Ongoing research in bioinformatics and computational biology is expected to yield more sophisticated algorithms and tools for omics data analysis, enhancing the accuracy and efficiency of personalized medicine. Integrating personalized omics-based approaches into global health initiatives will be crucial for addressing health disparities and improving healthcare outcomes worldwide.

The completion of the Human Genome Project and milestones achieved in the Human Proteome Project, coupled with advancements in computational bioinformatics and "big data" processing, have played a significant role in advancing personalized medicine. These developments have enabled the precise implementation of diverse omics-based therapies and bioengineering techniques for disease diagnosis, prognosis, treatment, and risk classification [152]. Various omics databases offer researchers extensive biological data across diverse molecular levels including genomic, proteomic, metabolomic, and transcriptomic, facilitating integration and analysis [153]. These resources offer comprehensive insights into biological pathways, disease mechanisms, and more by extensively examining interactions between genes, proteins, and metabolites. Such information will contribute to the development of predictive models and more accurate diagnoses.

Regulatory bodies like the FDA are focusing on Precision Medicine to optimize patient benefits by integrating diagnostic data with individual medical histories values [154]. With the approval of 12 new personalized drugs in 2022, as documented by the Personalized Medicine Coalition, personalized drugs now account for at least one-fourth of new drug approvals in each of the past eight years. The rise in personalized drug approvals underscores the progress in diagnosis and treatment through personalized approaches [155].

The integration of personalized statistical algorithms into laboratory medicine by our group, as discussed earlier, carries significant potential for interpreting omics data, thus driving a revolution in precision medicine and enhancing global health. However, there are challenges stemming from the inherently intricate and high-dimensional nature of omics data, compounded by a lack of standardization in omics data analysis. This necessitates advanced computational methods and robust statistical models for effective integration. Standardization and reproducibility are essential for the reliability of omics data [156] across different studies and laboratories, yet they remain a significant challenge. The heterogeneous nature of omics data introduces new

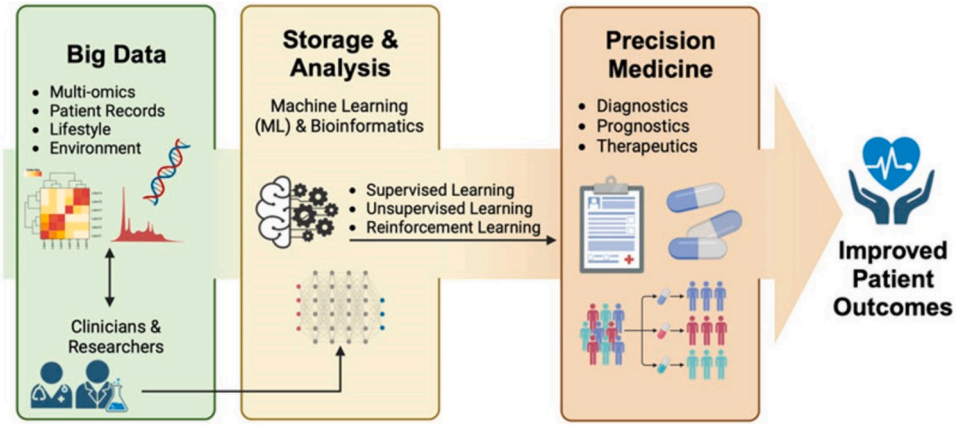

Fig. 5. By leveraging advanced computational algorithms and machine learning techniques, multiomics data can be analyzed to identify predictive biomarkers, therapeutic targets, and optimal treatment strategies tailored to each patient's needs.
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challenges, necessitating advanced computational tools and multidisciplinary teams to effectively integrate and interpret the data [157,158]. Datasets with numerous variables exhibit high dimensionality, leading to significant variance between samples, which can render clustering analysis less informative. This complexity adds further challenges to interpreting integrated data [159]. Moreover, the generation of multi-source heterogeneous raw data underscores the need for comprehensive bioinformatics and artificial intelligence platforms to support real-time processes, including mathematical modeling, integration, computational analysis, management, data fusion, and visualization. Therefore, leveraging data science and artificial intelligence efficiently holds the potential to enhance public health surveillance and monitoring by systematically collecting, managing, analyzing, and interpreting data within specified timelines [160–163]. Additionally, ensuring the privacy and security of sensitive personal information contained in omics data is paramount, necessitating the development of secure data storage and sharing platforms. The clinical translation of omics-based discoveries into practice requires validation in clinical trials and the establishment of regulatory frameworks. Furthermore, the prevailing high costs associated with omics technologies and data analysis can hinder their accessibility, especially in low-resource settings. This emphasizes the necessity for initiatives focused on cost reduction and enhancing global access to effectively tackle global health issues.

8. Conclusion

Medical laboratory services allow for precise measurement of numerous biomolecules, aiding in disease diagnosis, health monitoring, treatment evaluation, and population screening. They are integral to high-quality healthcare, significantly impacting global health outcomes. In the past three decades, the incorporation of omics technologies into laboratory medicine has revolutionized the landscape of personalized healthcare, by enabling precision medicine, early diagnosis, individualized treatment plans, improved drug development, integrated health data analysis, and tailored lifestyle interventions. Whole genome sequencing and other genomic technologies enable the identification of personalized genetic variants associated with diseases, allowing for more accurate diagnoses. They can detect specific cancer mutations, guiding the selection of the most effective chemotherapy for individuals. Tumor profiling allows for individualized treatment plans based on the tumor's genome, enabling the selection of the most effective therapies. Additionally, pharmacogenomics can evaluate a person's response to specific drugs, helping to prescribe the right drug at the right dose, thereby maximizing therapeutic efficacy and minimizing adverse effects. Nutrigenomic studies can help create personalized nutritional plans based on an individual's genomic characteristics, aiding in the prevention and management of chronic diseases and microbiomics can lead to personalized probiotics and dietary recommendations that support individuals' optimal health.

For an individual, multi-omics approaches — such as proteomics, transcriptomics, and genomics etc. — can be combined to obtain a more accurate and detailed picture of disease. This integration leads to more precise diagnoses and the development of effective, timely targeted therapies. This transformation is leading to more effective, efficient, and patient-centered healthcare solutions, ultimately improving patient outcomes and quality of life.

The utilization of personalized statistical algorithms to interpret individuals' omics data based on their own references is driving a revolution in personalized medicine, significantly enhancing global health. Making the benefits of personalized medicine accessible to everyone requires investment in international collaboration and infrastructure, technology, and human resources [164]. Therefore, global cooperation and coordination are crucial to ensure the widespread dissemination of the benefits of personalized medicine regardless of geographical location, making them accessible to all.

CRediT authorship contribution statement

Abdurrahman Coskun: Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Gökhan Ertaylan:** Writing – review & editing, Writing – original draft, Conceptualization. **Murih Pusparum:** Writing – review & editing, Writing – original draft, Conceptualization. **Rebekka Van Hoof:** Writing – review & editing, Writing – original draft, Software. **Zelal Zuhal Kaya:** Writing – review & editing, Writing – original draft, Software, Conceptualization. **Arezoo Khosravi:** Writing – original draft, Investigation. **Ali Zarrabi:** Writing – review & editing, Writing – original draft, Validation, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to correct English grammar and spelling. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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