Opinion Paper

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From research cohorts to the patient – a role for “omics” in diagnostics and laboratory medicine?

https://doi.org/10.1515/cclm-2022-1147
Received November 10, 2022; accepted December 16, 2022; published online January 4, 2023

Abstract: Human pathologies are complex and might benefit from a more holistic diagnostic approach than currently practiced. Omics is a concept in biological research that aims to comprehensively characterize and quantify large numbers of biological molecules in complex samples, e.g., proteins (proteomics), low molecular weight molecules (metabolomics), glycans (glycomics) or amphiphilic molecules (lipidomics). Over the past decades, respective unbiased discovery approaches have been intensively applied to investigate functional physiological and pathophysiological relationships in various research study cohorts. In the context of clinical diagnostics, omics approaches seem to have potential in two main areas: (i) biomarker discovery i.e. identification of individual marker analytes for subsequent translation into diagnostics (as classical target analyses with conventional laboratory techniques), and (ii) the readout of complex, higher-dimensional signatures of diagnostic samples, in particular by means of spectrometric techniques in combination with biomathematical approaches of pattern recognition and artificial intelligence for diagnostic classification. Resulting diagnostic methods could potentially represent a disruptive paradigm shift away from current one-dimensional (i.e., single analyte marker based) laboratory diagnostics. The underlying hypothesis of omics approaches for diagnostics is that complex, multigenic pathologies can be more accurately diagnosed via the readout of “omics-type signatures” than with the current one-dimensional single marker diagnostic procedures. While this is indeed promising, one must realize that the clinical translation of high-dimensional analytical procedures into routine diagnostics brings completely new challenges with respect to long-term reproducibility and analytical standardization, data management, and quality assurance. In this article, the conceivable opportunities and challenges of omics-based laboratory diagnostics are discussed.

Keywords: clinical mass spectrometry; multi-omics; pattern recognition; quality assurance; translational precision medicine.

What are we talking about?

The concept “omics” has no binding definition. This word affix goes back to the Latin word “omnis”, everything. Detecting a large number of analytes with biochemical commonalities, to capture patterns beyond the quantification of single substances, could be considered as a basic characteristic of omics methods. Or even attempting a complete and comprehensive description of a biochemical subdomain in a biological sample. However, at present, complete analytical coverage is hardly achievable even in sub-areas such as lipids. Omics-areas as subject of scientific work include genomics, proteomics, metabolomics, lipidomics, transcriptomics, glycomics, and breathomics.

Various analytical platforms are used in medical diagnostics that output results for multiple analytes in one analytical run, e.g., in newborn screening, plasma amino acid profiling, or serum electrophoresis. But also in these cases, only single values are reported, or simple ratios (e.g., phenylalanine to tyrosine) [1]. Newborn screening for inborn errors of metabolism is sometimes referred to as metabolomics, because in one single analytical run, a larger number of analytes from different substance classes are detected. However, this is far from a comprehensive “omic” mapping of a biochemical sub-area and, ultimately, single values are output, as a multi-analyte method.

In some cases, “sub-omics” concepts are used, e.g., the multi-parametric quantification of bile acids in blood as a component of lipidomics. Lipidomics, in turn, is often considered as a subset of metabolomics, i.e., the description of the totality of small molecules with good solubility in organic solvents within the totality of all small molecules.

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It should be noted that “omics” is generally used in a rather vague manner. For example, the quantification of several proteins (e.g., the determination of several therapeutic antibodies) using a mass spectrometric method is sometimes already referred to as proteomics, which is certainly not appropriate; this is mass spectrometric multi-target analysis.

Oomics methods can be targeted, i.e., defined target analytes are determined more or less specifically; or they can be untargeted, mapping individual analytes without necessarily identifying them.

From a clinical diagnostic point of view, delineation of different “sub-omics” is not necessarily goal-oriented; that is, it can be assumed that information from different biochemical areas can provide added diagnostic value across substance boundaries – what can be referred to as “multi-omics” [2]. While the integration of genomics, metabolomics, proteomics, transcriptomics, etc. is attractive, it is hardly technically feasible with a single analytical platform. This is primarily due to diverse physiochemical properties and wide concentration ranges.

**Biomarkers in clinical research**

It is important to distinguish the requirements for biomarker analyses in (bio-) medical research from the requirements in medical laboratory diagnostics. Typical relevant application for a “research use test” are in the field of drug development. Especially the question whether a drug candidate in a test system (cells, animal model) exerts any biological effect at all or not – as a screening tool for potential effects of newly synthetized compounds. Here, the change of readout peak patterns in a model system may be sufficient without specific identification of individual analytes. Analytics in the context of pharmaceutical development are regulated by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and are completely independent of in vitro diagnostics (IVD).

In the context of clinical (biomarker) research, mass spectrometry (MS)-based multi-metabolite kits are now offered for decentralized use (for example by Biocrates); and service providers conduct metabolomics testing in corporate laboratories (Metabolon, Biocrates, Lipotype and others).

In terms of definitions, there is also a lack of clarity regarding the word “clinical”. Clinical research is sometimes understood merely as the opposite of in vitro investigations or animal studies, i.e., as soon as humans or human samples are the object of investigation (e.g., also in cohort studies). However, “kline” is borrowed from the Greek, meaning bed. Thus, in a narrow sense, clinical studies are those that deal with seriously ill patients.

**Translation into diagnostics**

The basic oomics concept offers two different lines of translation into medical diagnostics: first, biomarker discovery starting from (multi-)omics procedures with the highest possible coverage aiming to identify single markers, often via retrospective or prospective cohort studies. Single markers identified in this way can then eventually be quantified in routine diagnostics using conventional platforms. For example, the goal of MS-based proteomics studies may be to identify single diagnostically valuable proteins that are subsequently translated into a diagnostic test in form of immunosays, applicable to routine diagnostic high-throughput analyzers. A second concept of translation into diagnostics can in principle be to actually use analytical methods with a high analyte coverage in routine diagnostics, and to apply pattern recognition methods based on this [3]. In principle, this does not necessarily require the identification of individual analytes, e.g., eluting in one chromatographic peak. The risk of failure is high in both scenarios [4].

**Why can omics be interesting for medical doctors?**

Omics methods have so far been the domain of biomedical research and have not yet found their way into standard diagnostics in laboratory medicine. However, there is much to suggest that a translation of omics procedures and a holistic analytical approach has the potential to significantly enrich laboratory diagnostics and ultimately improve clinical outcomes – which is the goal of medicine [5].

The holistic omics concept can be viewed as a link between genetics and the environment. It represents the grand vision of a systems biology understanding of health and disease. A possible “whole picture” can be expected to be more informative than the sum of individual pictures from subsystems. Accordingly, in a diagnostic dimension, a high discriminatory power between physiological and pathological conditions can be hoped for.

**Unmet needs**

Diagnostic gaps and unmet needs exist in today’s laboratory diagnostics especially in (i) tumor diseases with regard to early detection and prediction of individual biological behavior (especially prostate and breast carcinoma), and (ii) in the non-invasive diagnostics of atherosclerotic vascular
diseases [6, 7]. These two disease areas contribute most to fatal outcomes and thus might benefit the greatest from improved diagnostics.

**Multidimensionality and “probabilistic” results**

Many physicians have the expectation that complex, polygenic diseases will require complex, multiparametric laboratory testing, rather than the classic single-marker approach, to improve accuracy of diagnosis. Here, a growing number of physicians have high hopes and anticipations for artificial intelligence [8] and machine learning [9], although few have a clear understanding what actually happens in these procedures.

**Actionable results**

The nuts and bolts of any laboratory parameter is the intended purpose (what is to be achieved) or intended use (how is the product to be used). Results of tests are usually only of medical value if they are actionable, i.e., if they can usefully inform concrete medical decisions. It is not a question of obtaining information as a value in itself, which can later possibly be used for scientific evaluation. This is the essential difference between clinical laboratory diagnostics and biomedical clinical research, where results should primarily be “interesting” but do not have to be directly “useful” and actionable.

**Where do we currently stand?**

The concept of genomics is the oldest omics field and has also received by far the most public attention. In fact, complete sequencing of base pairs has been accomplished for years [10]. Nevertheless, the unraveling of epigenetics is only just beginning, and so even “genomics” must still be viewed as a concept and a vision.

Fairly advanced is the field of pharmacogenomics. Here, one aims to identify genetic traits that lead to different pharmacokinetic or pharmacodynamic effects as the basis for personalized drug treatment (i.e., related to the detoxification of the cytostatic drug 5-fluorouracil, to give one common example). As this personalization can lead to substantial cost savings for therapeutic interventions, health technology assessment (see below) has been favorable hence resulting in insurance reimbursements for certain pharmacogenomics tests in some countries.

A second example of an already applied omics-based diagnostic is in the field of molecular pathology. In fact, transcriptome analyses and gene expression profiles from tissue samples are the first actual pattern recognition methods to have been successfully translated into personalized health care. Here, probabilities for the efficacy or failure of treatment procedures in individual cases (particularly for breast cancer) are read out from complex analysis platforms and are intended to impact individual clinical patient management. Typically, such analyses are performed centrally at the respective test manufacturers (e.g., Oncotype DX).

A successful proteomics application based on a pure pattern-recognition approach is MALDI-TOF-based identification of bacterial cultures in microbiology – which has become a standard technology during recent years.

**One-dimensional and multi-dimensional laboratory diagnostics**

Nowadays, clinical chemistry laboratory tests are generally “one-dimensional” in nature. This means that a single laboratory parameter (e.g., serum creatinine concentration) is interpreted in relation to its assigned biological reference range or medical decision limit, and individual decisions are made based on these. Examples include the initiation of differentiated nephrological diagnostics for a serum creatinine value above a decision limit, e.g., 110 μmol/L in a young man. Or the question of vitamin B12 deficiency, triggering the testing for methylmalonic acid in blood or urine, with clearly elevated values proving deficiency and resulting in initiation of a therapeutic intervention.

However, examination procedures which evaluate patterns of single values in the synopsis are hardly clinically established. In some areas, ratios or similar are calculated, e.g., the ratio of aldosterone to renin in the diagnosis of secondary hypertension, or the phenylalanine to tyrosine ratio in newborn screening for phenylketonuria. Scores are calculated from individual variables in a certain number of indications, e.g., the Model for End-stage Liver Disease (MELD) score for prognosis assessment in liver disease (composite tests).

As a rule, a diagnostic process is to be seen as a mosaic, in which the physician evaluates a multitude of anamnestic, physical and technical findings in the synopsis from their professionally based intuition. But a pattern evaluation of a multi-dimensional biochemical profile is currently not applied as an essential part of a diagnostic in clinical chemistry diagnostics. Clearly, the technological advances of multi-omics technologies have been an enabler in the
worldwide growing attempts in the field of translational precision medicine, toward personalized healthcare based on molecular pathology.

What are the main challenges and hurdles?

Adoption

A key question is to what extent physicians would accept findings that primarily indicate probabilities (e.g., for the presence of a disease or its prognosis), generated from a large number of individual measurement data from analytes which may not be unambiguously identified or absolutely quantified. This is difficult to predict. The use of transcriptome analyses in risk stratification in breast cancer speaks at least to a possible acceptance of this approach by some physicians.

Technological aspects

From the analytical perspective, the two main challenges of omics-protocols are (i) the enormous diversity of target compounds with respect to physicochemical properties, and (ii) the huge dynamic range of their concentrations.

Correct identification of analytes (primarily in untargeted analyses) poses another great challenge, especially since many metabolites exist as structural isomers or isobaric compounds. Strikingly, the concept of metrological traceability as a fundamental principle in laboratory medicine quality assurance [11, 12], and its application to omics-based diagnostics still is an almost uncharted territory [13].

Specific risks and challenges of diagnostics for chronic diseases

The majority of healthcare resources in developed countries (but increasingly globally) are used in the context of chronic, non-communicable diseases (diabetes, cardiovascular disease, dementia, tumor disease, etc.). Demonstrating the benefit of novel laboratory tests in this area is particularly challenging, as studies of very long duration (in the order of decades) and in large patient collectives (in the order of thousands of individuals) are required to clearly evaluate a possible additional benefit of a new laboratory test. For example, the benefit of cardiovascular risk prediction (with consequent attempts of disease primary prevention) based on an innovative test in the normal middle-aged population can only be meaningfully assessed after about 20–30 years. Here, the risks (and perhaps ethical challenges) of such studies also become apparent: if a patient is assumed to be at low risk of developing cardiovascular disease based on such a new test, primary prevention of statins may not be started (possibly even despite known classical risk factors such as a family history, for example). If that patient eventually suffers a myocardial infarction at age 60, this may be seen as harm caused by the unreliable and “false-negative” risk test.

In stark contrast to chronic diseases, acute clinically relevant questions such as “is there a bacterial or a viral infection?” can be evaluated in very short periods of time depending on the natural history of a disease.

Test mathematics

Screening tests in the low-prevalence range should be the subject of particularly critical scrutiny, as potentially large numbers of false-positive results are generated, with a very low level of positive predictive value.

What are the requirements for “diagnostic omics?”

Analytical procedures in which a result in clinically useable syntax is output from a large number of individual signals (e.g., “five-year risk of a cardiovascular event 65% higher than the average for the age group of the given gender”) require a high degree of robustness of the analytical platform used globally and over long time periods. This includes very good lot-to-lot consistency of the input materials used (i.e., reference materials, quality control materials, calibrators, labeled standards) and analytical harmonization if not standardization of the procedure [14]. Results must be equivalent from one and the same sample after proper collection, processing and storage, even years later. For clinically relevant readouts, data must realistically be generated multcenter on the respective platform used, also to adapt assessment algorithms from postmarket clinical studies (i.e., studies on application of already marketed tests for specific clinical decisions). This means that a solid standardization and documentation of a procedure must be realized globally, and over long periods of time. Development, implementation and adherence to a quality assurance program is crucial.
Secondly, controlled studies (potentially randomized clinical trials) to prove a clinical benefit of early diagnosis or risk prediction are required; that is, proof that clinical decisions made on the basis of the results of a novel procedure have had a significantly positive influence on the course of disease in a relevant number of patients in relation to well-defined outcome endpoints (e.g., increase in the five-year survival rate for an investigational procedure in the field of oncology). Thus, the clinical benefit of a diagnostic procedure is in general dependent on the available interventions which may be informed by the procedure, i.e., actionability. Consequently, early detection of a disease which is not treatable may be of limited value.

In addition to the necessity of high analytical robustness, a major analytical challenge for true omics methods in diagnostics is that typically large concentration ranges must be mapped (in metabolomics, e.g., mg/L range for substances such as creatinine to the low ng/L range for hormones).

A basic prerequisite for a reliable diagnostic application is also an exact characterization of the pre-analytical requirements, or rather their limits: under which conditions can samples be transported to laboratories and over which periods of time? Are special sample collection tubes required, possibly with stabilizer substances?

Likewise, a prerequisite for a useful diagnostic application is the sufficiently deep description of the biological variation of analyte concentrations, signatures, patterns and results, with correspondingly differentiated reference ranges. This includes the description of the inter-individual range of variation in relevant populations as well as the intra-individual range of variation over defined time periods. Additionally, the influence of a variety of factors on the analyte concentrations need to be investigated. These can include the influence of diet, status (fasting/postprandial), gender, age, time of day and others.

A clinical diagnostic investigation procedure must be mapped over decades, especially by continuous external quality assurance with interlaboratory tests [15, 16]. Both this periodic external quality assurance (EQA) and the laboratory’s own internal quality control based on commercially available quality control materials (which must be performed every working day) are completely new territory for omics procedures. Control samples must be specified in such a way that, for example, a test readout “low risk class”, “medium risk class” or “high risk class” can be verified in each analytical batch corresponding to the traditional target value with acceptance range in today's clinical chemistry single marker target quantification analyses. Overall, setting clinical performance specification is a fundamental challenge of omics-type applications in clinical diagnostics [6, 7, 17–19], in particular with respect to biomedical assessment [20, 21].

What questions remain open, and what are the prospects?

A sober scientific review of omics methods can basically formulate the null hypothesis that such methods cannot have any diagnostic benefit because they are too complex to use in diagnostics, or that basic biochemical processes, for example, have been evolutionarily stabilized very well and are thus particularly robust against environmental influences whose imprint is actually to be read out. This null hypothesis would have to be refuted by studies.

Effort and return – medical and economic

Ommics procedures in patient-related medical laboratory diagnostics will require a great deal of effort for a market launch. Due to the complexity, which is disproportionately higher than for previous “one-dimensional” examination procedures, the effort for the development of such procedures up to a market launch will approach the dimensions required for the development of a novel pharmaceutical. On the other hand, the potential earnings prospects for diagnostics are generally much lower than for pharmaceuticals.

Studies with purely prognostic value are usually questionable. In the absence of an effective therapy option (for example the quantification of the risk of developing dementia or even a pre-symptomatic diagnosis) is problematic. The usefulness of laboratory tests is therefore fundamentally inseparable from the availability of treatment options in a specific situation, hence actionability.

Results of potential examinations without clear intended use, or without defined decision limits, could be understood “volatile” as an element in an intuitive overall picture of the physician of a patient. However, this contradicts the basic attitude of evidence-based medicine, which strives to place clinical decisions on a scientifically sound footing in a comprehensible manner [22, 23].

Once clinical validity and utility has been established, conceivable omics-based diagnostic services and products could take the form of, i.e., examination of samples in one or several medical laboratories based on in-house procedures (i.e., “laboratory-developed tests”, LDT); analytical kits implemented and applied on general laboratory equipment.

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in medical laboratories; or dedicated systems, i.e., special analytical systems with the dedicated purpose of the respective omics analysis [3].

**Health technology assessment (HTA)**

Compared to the formal requirements for placing an IVD on the market, the regulations for reimbursement by insurance companies represent a much higher hurdle overall. While the regulation of marketing essentially checks whether the intended use of an IVD is fulfilled and the product is safe, the HTA questions the actual medical added value of an IVD; specifically the additional benefit with regard to existing diagnostic procedures [24]. In Germany, this is the responsibility of the G-BA (Gemeinsamer Bundesausschuss) which carries out a scientifically very well-founded evaluation procedure. No resources from the statutory health insurance are granted for low-value tests. Such services can be offered individually by physicians, but then consequently only have a limited market potential, since the group of self-payers is rather small. National HTA agencies are established in many countries. In some countries, direct-to-customer (DTC) offerings are an essential business model, but ultimately only truly useful tests and high-value care will have lasting success. Fundamentally, DTC deals are problematic. Setting indications for complex laboratory diagnostic tests and, above all, interpreting them in an individual context is associated with major risks for the quality of life of the “customers” outside the scope of medical expertise and responsibilities. In particular, the use of risk metrics can deeply upset people, especially if the results are not interpreted and communicated by consulting physicians.

Overall, efforts of a utilization management are gaining importance worldwide. It is important to note that clinicians are generally not interested in additional data per se; ultimately, they are only interested in data that lead to measurably better treatment outcomes or cost saving. The subjective and emotional liking of data per se undoubtedly underlies much of the DTC business, but it is neither sustainable nor beneficial.

It remains to be said that clinical diagnostic laboratory tests must meet fundamentally different requirements compared to biomarkers in the field of biomedical research. The complexity of looking at individual patients is paradoxically much higher than when looking at more or less homogeneous cohorts in biomedical research, or even very homogeneous data e.g., from inbred animal models.

**Conclusions**

Omens has undoubtedly been “fashionable” in biomedical research for many years; a coveted topic for publications and grants from the publicly or industrially funded national and global research industry. This research industry is far from clinical reality [25]. With this opinion paper we tried to initiate a concise and sober analysis of the perspectives of true-omics analytical procedures in clinical diagnostics – beyond the language of research grant applications or advertising of the analytical industry with a typically inherent tendency of overselling. The journey from observations in cohort studies to clinical decision making in individual patients is enormous – and translating omics into the real clinical world of patient care is undoubtedly still a major challenge. From research cohorts to patients, several paths are conceivable – but the outcome today is still open.

**Research funding:** None declared.

**Author contributions:** All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Not applicable.

**Ethical approval:** Not applicable.

**Data availability:** Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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