

## LABORATORY MEDICINE IS FACED WITH THE EVOLUTION OF MEDICAL PRACTICE

### LABORATORIJSKA MEDICINA SUOČENA SA RAZVOJEM MEDICINSKE PRAKSE

Paul Collinson

*Departments of Clinical Blood Sciences and Cardiology, St George's University Hospitals NHS Foundation Trust and St George's University of London Cranmer Terrace, London, England*

#### Summary

Laboratory medicine and clinical medicine are co-dependent components of medicine. Laboratory medicine functions most effectively when focused through a clinical lens. Medical practice as a whole undergoes change. New drugs, treatments and changes in management strategies are introduced. New techniques, new technologies and new tests are developed. These changes may be either clinically or laboratory initiated, and so their introduction requires dialogue and interaction between clinical and laboratory medicine specialists. Treatment monitoring is integral to laboratory medicine, varying from direct drug measurement to monitoring cholesterol levels in response to treatment. The current trend to »personalised medicine« is an extension of this process with the development of companion diagnostics. Technological innovation forms part of modern laboratory practice. Introduction of new technology both facilitates standard laboratory approaches and permits introduction of new tests and testing strategies previously confined to the research laboratory only. The revolution in cardiac biomarker testing has been largely a laboratory led change. Flexibility in service provision in response to changing clinical practice or evolving technology provides a significant laboratory management challenge in the light of increasing expectations, shifts in population demographics and constraint in resource availability. Laboratory medicine practitioners are adept at meeting these challenges. One thing remains constant, that there will be a constant need laboratory medicine to meet the challenges of novel clinical challenges from infectious diseases to medical conditions developing from lifestyle and longevity.

**Keywords:** evidence based medicine, drug monitoring, analytical methods, infection, cardiac biomarkers, point of care testing

#### Kratak sadržaj

Laboratorijska medicina i klinička medicina su međusobno zavisne grane medicine. Laboratorijska medicina najefikasnije funkcioniše ako deluje sa kliničkog stanovišta. Danas u celini medicinska praksa se stalno menja. Uvode se novi lekovi, postupci, kao što se menja i upravljačka strategija. Razvijaju se nove tehnike, nove tehnologije i novi testovi. Ove promene su klinički ili laboratorijski inicirane, zbog čega njihovo uvođenje zahteva stalnu saradnju između kliničkih i laboratorijskih specijalista. Praćenje tretmana pacijenata je integralni deo laboratorijske medicine, kao npr. preko direktnog merenja leka do praćenja nivoa holesterola kao odgovora na tretman lekom. Sadašnji trend tzv. »personalizovane medicine« je odgovor na ovaj proces uz razvoj odgovarajuće dijagnostike. Tehnološka unapređenja utiču na razvoj moderne laboratorijske prakse. Uvođenje novih tehnologija potpomažu standardni laboratorijski pristupi kao i uvođenje novih testova i strategije ispitivanja koja je predhodno potvrđena u istraživačkim laboratorijama. Tako je npr. revolucija u razvoju srčanih biomarkera dovela do veklih promena u laboratorijskoj praksi. Fleksibilnost u laboratorijskom sistemu unapređuje kliničku praksu i tehnologije koje dovode do značajnih promena u sistemu upravljanja laboratorijom, a zavisno od očekivanja, demografskih promena i razvoja resursa. Zato stručnjaci u oblasti laboratorijske medicine moraju da budu spremni da prihvate ove promene. Jedna činjenica ostaje konstantna, a to je da će uvek biti stalna potreba za laboratorijskom medicinom koja je spremna da prihvati kliničke izazove od infektivnih oboljenja do medicinskih stanja zavisno od načina i dužine života.

**Ključne reči:** medicina zasnovana na dokazima, praćenje lekova, analitičke metode, infekcija, srčani biomarkeri, ispitivanje pored pacijenta (POCT)

Address for correspondence:

Paul Collinson  
St George's University Hospitals NHS Foundation Trust  
and St George's University of London  
Cranmer Terrace, London SW17 0QT

## Introduction

Laboratory medicine and clinical medicine are not separate entities. Both form part of the practice of medicine as a whole. Clinical history and examination produced a diagnostic hypothesis, usually expressed as a differential diagnosis list. Subsequent investigations including laboratory testing act to refine the diagnostic hypothesis towards a management plan. It has been stated that laboratory testing directly affects 70% of the clinical decisions in the patient pathway. Clinical patient assessment raises the prior probability of disease so that when appropriate laboratory testing is used, diagnostic sensitivity and specificity are improved. Indiscriminate testing result in reduction of the diagnostic efficiency of laboratory testing and is a waste of valuable resource. Laboratory medical practitioners therefore need to understand not just the analytical components of testing but how and where testing will be applied and what it will be used for. However, an understanding of test utilisation includes not just the clinical condition being investigated but also the process of patient flow. Laboratory medical practitioners should be laboratory based but outward facing. Clinicians need to understand the strengths and weaknesses of testing and also how this fits into the decision-making process. They often have little appreciation of those factors in analysis which laboratory medicine takes the granted, such as analytical performance (detection limit and imprecision) and do not consider where turnaround time may directly improve patient pathways. Dialogue between laboratory medicine practitioners and clinicians and education of each by the other is essential. Such a dialogue will allow clinicians an understanding of the strengths and weaknesses of testing and the laboratory community of where there is clinically unmet need (1, 2).

Medical practice undergoes a continuous process of change. There are a number of different drivers of change. There may be development of new drugs, new treatments or changes in management strategies. Introduction of new techniques, new technologies and new tests occurs on a regular basis. Changing practice or external pressures may require review of service configuration. Finally there is always the challenge of meeting future needs. Laboratory medicine has developed in parallel with medical practice. In some cases, medical practice will lead laboratory medicine development but equally laboratory medicine can be the standard setter and the innovation leader, developing to support or extend clinical medical practice.

## Laboratory medicine, new drugs new treatments and changes in management strategies

Treatment monitoring may be direct, indirect or target focussed. When drug treatments are devel-

oped and introduced there is typically a need for direct laboratory medicine support. Drug monitoring is developed for the majority of agents, initially by the pharmaceutical company that introduces the new drug. Such drug measurement is to enable them to characterise the pharmacokinetics of their agent and facilitate clinical trials. There may or may not then be transition from the research to the clinical laboratory depending on whether the drug requires therapeutic drug monitoring (TDM). TDM for drugs is based on the value proposition that standardised measurement and interpretation has a direct impact on patient care. Although the major application is in drugs with a relatively narrow therapeutic range and clear toxic side-effects there is also a role in compliance monitoring. The role of the laboratory in TDM is central as knowledge of the underlying pharmacokinetics of the drug defines the ideal sampling strategies and optimal analytical techniques. Changes in laboratory methodology can significantly improve both the analytical accuracy and availability of TDM. This is illustrated by the transition from radioimmunoassay to non-isotopic fully automated real-time immunoassay. Laboratory medicine also has a significant role to play by application of evidence-based medicine to show where TDM is inappropriate. The laboratory also has a challenge in addressing the recreational drugs area. Novel agents are constantly being developed by ingenious chemists and the challenge is to be able to detect these agents in comatose individuals or where there is evidence of unexplained neurological syndromes subsequent to ingestion (3).

Direct treatment monitoring is well-established as a part of laboratory medicine. Hormonal treatment is entirely dependent on laboratory medicine. Monitoring thyroxine dosage by measurement of thyroxine and thyroid-stimulating hormone is standard clinical practice. Goal directed therapy is a more recent innovation. The development of effective cholesterol lowering therapy in the form of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (HMG CoA reductase inhibitors, statins) and subsequent clinical trials (4, 5) lead to acceptance of the pivotal role of cholesterol lowering in treatment of atheromatous coronary vascular disease (6). This paradigm shift in management has resulted in the routine measurement of cholesterol reduction in response to statin therapy to achieve targets recommended by clinical guidelines (7). Determination of antibiotic resistance patterns rapidly became a crucial part of infection management. As novel antibiotics are introduced, resistance testing is required to monitor emergence of resistance patterns. A crucial component of antibiotic stewardship is the ability to avoid treatment of nonbacterial infections with antibiotics, to discontinue ineffective treatments and to limit treatment duration. Laboratory real time measurement of markers to help in the assessment of whether sepsis is present and whether antibiotic therapy is

being effective and can be discontinued has been developed in response to this challenge (8, 9). Specific diagnostic tests have been developed to tailor individual treatments to individual patients, the concept of »personalised medicine«. Tailored treatment is most advanced in the area of cancer chemotherapy. The recognition of specific subtypes of tumours due to particular oncogene mutations has resulted in specific targeted therapies. The role of the laboratory is to identify susceptible tumour types to target the use of these novel (and often extremely expensive) therapies. Examples include her-2 neu for herceptin therapy in breast cancer and Kras for Cetuximab for colorectal cancer (10).

Changes in clinical practice and management pathways may also require changes in the laboratory. An example is the recognition of the increasing incidence of fatty liver either as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) (11). These present to the hepatologist initially as a sustained elevation of alanine transaminase (ALT). Standard management is to proceed to liver biopsy if the diagnosis is unclear. However, liver biopsy is an invasive procedure with morbidity and mortality. Alternative strategies have been proposed to avoid the need for liver biopsy by reintroduction of measurement of aspartate transaminase (AST) and use of the ALT/AST ratio as part of a management algorithm (12).

### **Laboratory medicine, new techniques, new technologies and new tests**

Introduction of new techniques and new technology has always been part of the core role of laboratory medicine. The transition from manual techniques to early automation such as the autoanalyser and now to fully integrated robotic computerised systems has proceeded rapidly and produced an exponential growth in the efficiency and productivity of laboratories. This has coincided with an exponentially increasing demand for testing by the clinical community. Increased demand is due to the interaction of a number of different factors including increasing complexity of the available medical treatments, a shift to more sophisticated community-based care which utilises diagnostics and an increasing number of older patients with multiple comorbidities. It is interesting to speculate whether the ready availability of testing has also contributed to its increasing utilisation.

Technological change has resulted in a number of largely managerial challenges for the laboratory. Increased automation has partially offset the shortage of skilled laboratory staff but also led to a need to reconfigure laboratories to exploit economies of scale. The introduction of laboratory networks with centralisation to produce a hub and spoke model has been a response to this pressure. Such a model brings

its own complications with a need to have staff distributed according to demand and workflow plus the need to maintain 24/7 provision of acute care across the entire network. It also imposes logistics challenges with any need for sample movement and tracking. The key to underpinning such a service is a good and reliable, fully integrated, robust information technology (IT) infrastructure. The lack of such an infrastructure is a common problem as has recently been highlighted.

Novel technologies capable of direct clinical impact are also now present in the central laboratory. Advanced automation of molecular diagnostics with next-generation sequencing means that tests which were previously labour intensive and expensive, such as screening for familial hypercholesterolemia (FH) are more available. The laboratory can embrace this technology focusing it at the clinical problem of diagnosis in patients with hypercholesterolemia by providing sequencing of the four principal FH genes, but combining this with scoring for polygenic hypercholesterolemia (13). The routine use of tandem mass spectrometry allows efficient measurement of immunosuppressant drugs as well as steroid hormone measurement but »traditional« laboratory questions such as standardisation remain (14).

In addition to technological development within the laboratory there has been innovation with the development of methods of performing analyses at the point of care, point of care testing (POCT). Uptake and utilisation of these novel technologies has been different in Europe and the United States due to different regulatory environments. The use of point of care, blood gas testing is standard in Europe, with many traditional central laboratory tests required for urgent care incorporated within blood gas analysers. The role of laboratory is collaboration with the clinician the supervision and quality assurance, which can be facilitated by appropriate IT infrastructure.

Laboratory medicine may take the lead in introducing new tests. Cardiac biomarker measurement has had a crucial role in defining diagnosis, management strategies and latterly treatment options in patients with ischaemic heart disease. The measurement of aspartate transaminase was the first independent biomarker that allowed a definitive diagnosis of myocardial infarction (15, 16). The progressive evolution of cardiac biomarker measurement ultimately resulted in the introduction of troponin testing. Measurement of cardiac troponin provides diagnostic information but also serves as the key test to direct the patient along therapeutic pathways. The laboratory had a key role in introducing this test to clinicians. The first major initiative which contributed to the redefinition of myocardial infarction was a consensus conference of clinical biochemists (17).

To this day the laboratory provides the focus for development of the application of troponin testing.

Here, the particular expertise of the laboratory is required. Although clinical guidelines are entirely consistent in the recommendations for diagnostic strategies using troponin in particular the adoption of the 99<sup>th</sup> percentile (18), it has been found that these recommendations have not been universally adopted (19). It is important that laboratory medicine helps with the implementation of such guidelines.

One of the challenges of medical progress is a tendency to retain previous testing strategies and not remove obsolete tests from the clinical repertoire. A good example is the introduction of the measurement of cardiac troponin. It is only comparatively recently that tests which have been superseded for the detection of myocardial injury, such as aspartate transaminase and lactate dehydrogenase or tests which are methodologically inadequate, such as creatine kinase isoenzyme MB measured by a immunoinhibition, have been removed from cardiac panels (19–21). They have often been retained despite specific guideline recommendations (22).

### Service configuration

Laboratory medicine must be responsive to new treatment strategies which utilise testing in novel ways. Provision of testing may present interesting logistic challenges requiring either reorganisation of services or the implementation of novel technologies. The use of selective catheterisation to localise parathyroid tumours is an example where the ability to measure parathormone effectively in real time is required to support surgical exploration of the neck. Similarly, the progressive increase in the amount of cross sectional imaging (computed tomography and magnetic resonance imaging) utilising contrast, has required pre-imaging assessment of renal function. Many patients arrive for their imaging without having been pre-investigated. This problem can be dealt with by the use of point of care creatinine measurement in the imaging department.

Introduction of rapid diagnostic strategies in

patients with chest pain initially utilised serial measurements of creatine kinase (CK) and its MB isoenzyme (CK-MB) (23, 24). These could be provided by dedicated stat instruments either in the laboratory or in close proximity to the patient (POCT). The most recent recommendations for cardiac troponin have suggested measurement on admission and at 3 hours (25). Current laboratory methodology can provide this degree of analytical sensitivity and imprecision but this does not match the turnaround time is required by the clinician. Although POCT is the obvious answer, as yet it cannot match the analytical performance goals (26). An understanding of the analytical performance of troponin testing will also inform clinical colleagues as to what is the optimal decision-making algorithm. Although rapid diagnosis with testing on admission and one hour and calculation of a delta has been endorsed within the most recent set of guidelines (25), questions have been raised as to whether routine analytical performance of even laboratory troponin assays allows the proposed very small delta changes in troponin to be precisely and accurately measured (27).

### Meeting future needs

Finally, there is the appearance of new diseases and a need for a laboratory response. The recent Ebola and Zika virus outbreaks highlighted a crucial need for diagnostics but a lack of laboratory tests suitable both analytically and logistically suitable for the clinical situation where the outbreaks occurred. Although infectious diseases are the most spectacular examples it must be remembered that as yet we do not have good laboratory tests for the diagnosis of acute cerebrovascular disease (brain attack) or for what is now the largest single cause of death, dementia. There is much yet to be done.

### Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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