Mini Review

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Central role of laboratory medicine in public health and patient care

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Abstract: Clinical laboratories play a vital role in the healthcare system. Objective medical data provided by clinical laboratories supports approximately 60–70% of clinical decisions, however, evidence supporting this claim is poorly documented and laboratories still lack visibility, despite their indisputable impact on patient care and public health. The International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) Task Force on Outcome Studies in Laboratory Medicine (TF-OSLM) was recently developed to support directed research evaluating the role of laboratory medicine on clinical outcomes. Establishing and documenting this evidence is key to enhance visibility of the field in the eye of the public and other healthcare professionals together with optimizing patient outcomes and health care system operations. In this review, we discuss four areas that exemplify the contribution of laboratory medicine directly to patient care. This includes high-sensitivity cardiac troponin (hs-cTn) and N-terminal pro-B-type natriuretic peptide/B-type natriuretic peptides (NT-proBNP/BNP) for the diagnosis and prognosis of myocardial infarction and heart failure, respectively, and procalcitonin for the management of sepsis and antibiotic stewardship. Emerging markers of traumatic brain injury and the role of laboratory medicine in the fight against the COVID-19 pandemic are discussed along with an introduction to plans of IFCC TF-OSLM.

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Background

Laboratory medicine is the single largest medical activity in healthcare worldwide [1]. Clinical laboratories play a central role in patient care delivery by providing and ensuring the quality of medical laboratory testing to support clinical decision-making. Indeed, clinical laboratories supply healthcare professionals with the objective data necessary to provide high-quality, safe, effective, and appropriate care for disease prevention, diagnosis, treatment, and management [2]. It is estimated that the number of laboratory tests available to clinicians has doubled to at least 3,500 tests in the past 20 years. In addition, the global *in vitro* diagnostics (IVD) market was valued at $87 billion USD in 2021 and is projected to reach $135 billion USD in the next 10 years, growing at a rate of 4.6% annually [3]. It is indisputable that healthcare systems cannot operate without the information provided by clinical laboratories in hospital and community settings. While it is estimated that clinical laboratories provide approximately 90% of the objective data in medical records and influence 60–70% of clinical decisions [4], evidence supporting these claims is not well documented. A recent report by Rohr et al. completed an interview survey of 40 oncologists and 39 cardiologists and assessed in how many cases they ordered IVD testing and in how many cases IVD was used for initial diagnosis, treatment monitoring, or post-treatment follow-up. Overall, IVD testing was used in 88, 77, and 72% of patients for initial diagnosis, treatment monitoring, and follow-up, respectively, demonstrating the clear value of IVD in patient assessment [5]. However, this report and others are limited in scope and study design. The values of the clinical laboratories are usually evaluated based on the cost but not the contribution to the health system since delineating and quantifying the value of laboratory medicine to patient care is extremely challenging but essential to improve visibility. Despite its immense contribution to

healthcare, clinical laboratories often operate within a "black box." Outcome studies demonstrating the value of laboratory medicine outside of the clinical laboratories are thus urgently needed to advocate for better visibility of laboratory sciences. This in turn can lead to actionable changes and collaborations across healthcare sectors to optimize the contribution of laboratory medicine to patient care and improve health, economic, and operational outcomes globally.

How do we demonstrate value?

To clearly demonstrate the value of laboratory medicine across clinical settings, value measures must be adequately defined and standardized. Studies may focus on the economic value of implementing laboratory-driven patient care protocols to minimize downstream intervention and cost. In contrast, other studies may focus on direct patient impact, including earlier or more accurate diagnosis leading to changes of patient management as well as reduced morbidity and/or mortality. Outcome studies are also complicated by intermediate variables that may indirectly or directly affect measured outcomes. Measured outcomes may also be many steps beyond sample measurement and thus causation can be difficult to establish. The effectiveness of the intervention initiated by a particular test result may also vary across patient populations, requiring several sufficiently powered studies in disease subpopulations. The International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) Committee on the Impact of Laboratory Medicine on Clinical Management and Outcomes (TF-ICO) was established in 2012 to "evaluate the available evidence supporting the impact of laboratory medicine in healthcare, and to develop study design for new retrospective and prospective studies capable of generating evidence of the contribution made by laboratory medicine." In a review by TF-ICO, key examples of evidence supporting the value of laboratory medicine were presented, including screening (e.g., prenatal and cancer), risk stratification (e.g., cardiovascular disease), diagnosis (e.g., kidney disease, infection), and treatment selection (e.g., pharmacogenetics and antibiotics) [2]. However, the authors highlighted the limitations of current evidence, particularly the lack of direct and standardized implementation studies, and suggested potential solutions to address gaps, including developing standardized protocols for prospective patient-centered studies and benchmarking new and existing tests with commonly accepted effectiveness measures [2].

Despite current gaps in standardized evidence, there are key examples of laboratory tests in the past 10 years that have revolutionized patient care and served as major breakthroughs in their respective clinical settings (Figures 1 and 2). These clinical case examples clearly demonstrate the unquestionable impact of laboratory medicine and serve as

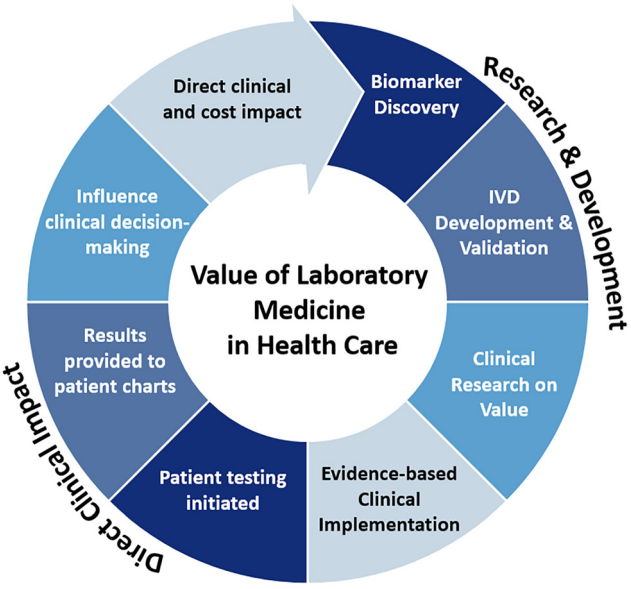

Figure 1: Overview of the value of laboratory medicine to patient care and public health from research and development to clinical implementation and impact.

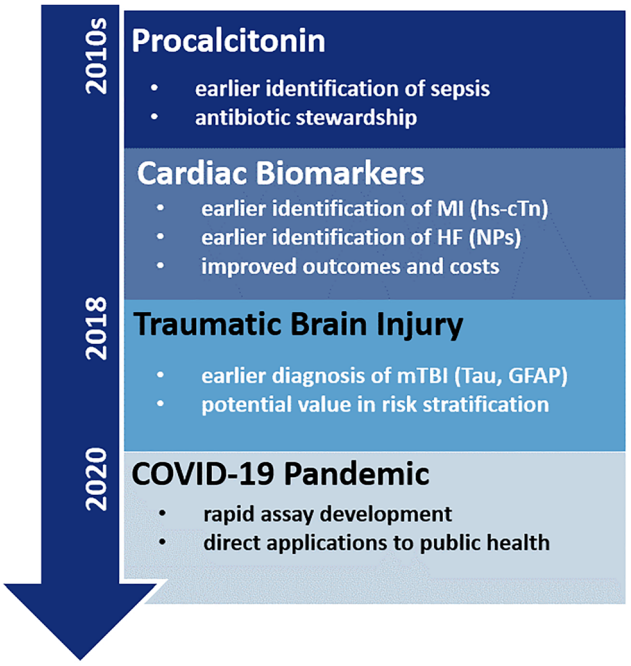

Figure 2: Summary of clinical case examples presented in this review that exemplify the value of laboratory medicine.

templates to establish good quality evidence in other instances.

Clinical case examples

Cardiac biomarkers in myocardial infarction (MI) and heart failure (HF)

Cardiovascular disease remains the leading cause of death globally, accounting for approximately 32% of global mortality [6]. The development and clinical implementation of key cardiac biomarkers has led to paradigm shifts in healthcare, enabling more rapid diagnosis and prognostication of common cardiac diseases, including MI and HF, and minimizing downstream resource utilization and strain. In particular, timely diagnosis of acute MI is critical to ensure appropriate initiation of effective evidence-based management and revascularization. Detection of MI was initially limited to symptomatic assessment, echocardiogram, and non-specific biomarkers, including creatinine kinase-MB, myoglobin, and lactate dehydrogenase [7]. Cardiac troponin (cTn) was initially proposed as a potential biomarker of MI in the 1990s due to its fundamental regulatory role in cardiac tissue, myocyte-specific expression, and increased concentration following myocardial injury in circulation [8]. The pathophysiological mechanism behind elevated cTn in MI is unknown but may be related to apoptosis, increased cell wall permeability, and/or myocardiocyte necrosis [8]. The clinical utility of cTn was initially limited due to poor assay performance at low concentrations. IVD development of high-sensitivity cTn (hs-cTn) assays in 2010 has facilitated earlier rule-out of MI, reduced emergency department length of stay, reduced admission rates, and earlier MI treatment [8]. By quantifying cTn at low concentrations with acceptable precision, detecting even small levels of myocardial damage and serial differences in cTn concentrations is now possible. There is overwhelming evidence to support the direct role of hs-cTn measurement in patient outcomes, including reduced length of stay, admissions, and lower rates of adverse events, as reviewed elsewhere [9, 10]. Indeed the Fourth Universal Definition of Myocardial Infarction now defines MI as "the detection of an increase and/or decrease of a cardiac biomarker, preferably high-sensitivity cardiac troponin, with at least one value above the 99th percentile" [8]. Additional guidelines also recommend hs-cTn measurement, including the 2020 European Society of Cardiology guidelines on the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation [11] in addition to the 2021 American Heart Association (AHA) co-sponsored guideline for the evaluation and diagnosis of acute chest pain [12]. This highlights the impact one laboratory test can have on patient care management in hospital and emergent community settings.

In addition to hs-cTn measurement in the detection of acute MI, natriuretic peptides have revolutionized the identification of HF in acute and ambulatory settings. HF is estimated to affect at least 26 million individuals globally and is increasing alarmingly in prevalence [13]. It is currently one of the costliest medical diagnoses to manage given long hospitalizations and frequent readmissions. Health expenditures related to HF are estimated to increase dramatically with the aging population, placing a heavy burden on patients, families, and healthcare resources. Thus, strategies to prevent delayed diagnosis and resultant higher mortality are essential. B-type natriuretic peptide (BNP) was first discovered in 1988 [13]. Since its discovery, significant resources have been dedicated to immunoassay development for the precise measurement of BNP and its precursor, N-terminal pro-B-type natriuretic peptide (NT-proBNP), for reliable HF diagnosis and prognosis. The pathophysiological mechanisms behind elevated NT-proBNP and BNP in HF settings are not fully elucidated. In theory, upon myocardial wall stress, pre-proBNP is released mainly from the cardiac ventricles and processed into the prohormone, proBNP [14]. ProBNP is further processed into two forms: biologically active BNP and biologically inactive NT-proBNP which are increased with HF-induced wall stress [14]. Findings from large clinical studies support the value of implementing BNP or NT-proBNP into clinical care management of HF [14–18]. For example, the Canadian Prospective Randomized Multicenter study, IMPROVE-CHF, found that assessing NT-proBNP in patients with dyspnea resulted in decreased duration of the initial ED visit, improved diagnosis, and provided health cost savings [15]. Incorporating NT-proBNP into the diagnostic workup of HF has also been shown to be a cost-effective method to improve patient care [16]. BNP measurement has also demonstrated similar value. For example, one study analyzed the efficacy of a BNP based screening program in patients with patients at-risk for heart failure. It was found that implementing BNP-based screening along with collaborative care reduced the rates of diagnosed HF, emergency cardiovascular hospitalizations, and symptomatic left ventricular dysfunction [17]. Further, NT-proBNP and BNP are both included as key features in clinical practice guidelines on HF diagnosis and management, including those from the ESC, cementing their key role in HF management [18].

Procalcitonin (PCT) in antibiotic stewardship and sepsis

Bacterial-derived sepsis presents a major healthcare issue, with an estimated 18 million new cases per year worldwide and a mortality rate of 30–50% [19]. Timely differentiation of bacterial from viral infection is therefore essential for care management in community and critical care settings. White blood cell (WBC) count and C-reactive protein (CRP) are conventional laboratory tests used in the diagnosis of infection. However, both CRP and WBC counts are non-specific to sepsis and can be elevated in inflammatory diseases or infection of other origin [19]. Blood culture is often considered the gold standard for identifying bacteremia, providing information on the specific strain and antimicrobial sensitivity. However, turnaround time is not ideal and does not support the early identification needed to initiate appropriate treatment. Unfortunately, the lack of a fast, sensitive, and specific biomarker for bacterial infection and sepsis has led clinicians to prescribe antibiotics without confirming the causative infectious agent, unnecessarily increasing antibiotic use and risk of antibiotic resistance. PCT is a biomarker of increasing interest in the diagnosis and management of sepsis [19–22]. PCT is the precursor to the hormone calcitonin [19]. Produced by the calcitonin 1 gene (*CALC-1*) and subsequently processed into mature calcitonin via proteolytic cleavage, PCT expression is typically limited to the neuroendocrine and thyroid C-cells. Upon bacterial infection, PCT production is activated in parenchymal tissue through a variety of cytokines (interleukin-6, tumour necrosis factor-α, and interleukin-1β). PCT accumulates during bacterial infection as these other tissues are not capable of cleaving PCT to calcitonin (its mature form) [19]. In turn, upon viral infection, interferon-γ factor is secreted, attenuating PCT production. Measurement of PCT in patients suspected of bacterial infection therefore has unique value given its specificity. In addition, its rapid rise following infection presents advantages over the delayed kinetics of CRP [19].

Recent clinical studies highlight the value of measuring PCT to distinguish between bacterial and viral infection as well as decrease unnecessary antibiotic use [19–22]. For example, a multicenter randomized trial of 266 patients diagnosed with sepsis analyzed the impact of a PCT-guided approach to antibiotic discontinuation compared to a standard-of-care approach [20]. This PCT-informed course of antibiotic treatment was shown to reduce the length of antibiotic treatment, mortality rates, and cost of hospitalization relative to that of standard care. Furthermore, this study by Kyriazopoulou et al. also found that PCT-guided antibacterial stewardship led to a reduced rate of infection-associated adverse events such as *Clostridioides difficile* and multidrug-resistant organisms, demonstrating the significant real-life and long-term benefits of implementing a PCT-guided algorithm for septic patient care [20]. A recent patient-level meta-analysis of 26 randomized controlled trials further supports the value of PCT-guided antibacterial stewardship [22]. This report by Schuetz et al. found that when PCT was used to guide antibiotic treatment decisions for patients with acute respiratory infections, a decrease in antibiotic exposure and side effects was observed. This clinical benefit was maintained across different clinical presentations and a variety of clinical settings such as the intensive care unit, emergency department, and primary care [22]. In addition to adult settings, PCT measurement in the identification of neonatal sepsis has demonstrated encouraging findings although patient outcomes were not analyzed and further studies are needed [23].

Taken together, integrating PCT-related strategies into clinical practice affords healthcare practitioners the ability to make tangible steps towards personalized medicine by tailoring antibiotic treatment strategies to the patient on an individual level. Notably, numerous clinical practice guidelines on bacterial infection diagnosis and management include PCT measurement [24, 25]. This serves as a surrogate marker of value and underlines the direct impact of PCT integration on patient care.

Emerging biomarkers of traumatic brain injury (TBI)

TBI is a major source of disability worldwide with an estimated global annual incidence of 27–69 million [26]. Structural brain injury visualized by CT (e.g., contusions, subdural or subarachnoid haemorrhages) and/or MRI (e.g., diffuse axonal or vascular injury) are well established as predictors of TBI outcome [27]. However, clinicians often rely on self-reported symptoms to diagnose concussion or mild TBI (mTBI). In order to longitudinally manage acute and chronic effects of mTBI, more convenient and economic diagnostic measures are needed to diagnose mTBI, distinguish between mild and moderate head injuries, and gauge recovery post-injury. Blood biomarkers for mTBI present unique advantages as they would be minimally invasive and cost-effective with the potential to accurately identify patients who require referrals for neuroradiological assessment or follow-up examination. Until recently, no reliable circulating markers for mTBI existed.

In 2018, the US Food and Drug Administration (FDA) approved the use of two blood biomarkers, specifically glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) to assist clinicians in deciding whether to order a head CT following suspicion of

mTBI [28]. GFAP is a structural protein found in astrocytes, while UCH-L1 is an enzyme found in high abundance in neurons. Both have been shown to correlate with structural brain injury and TBI clinical severity [28]. Recent studies have reported day-of-injury GFAP and UCH-L1 plasma concentrations have good to excellent prognostic value for predicting death and unfavourable outcome when using point-of-care assays [28]. In addition to GFAP and UCH-L1, there is increasing interest in the measurement of circulating tau for mTBI prognostication. Tau is a microtubule-associated binding protein that helps stabilize microtubules within the axon under normal physiological conditions [27]. Post-translational modifications, including phosphorylation, are necessary for the biological functioning of tau. However, abnormal phosphorylation following TBI contributes to cleavage from the microtubules and subsequent aggregation [28]. Furthermore, following TBI, tau undergoes proteolytic cleavage and leaks into the circulation and cerebrospinal fluid (CSF). Recent evidence in small patient studies has supported the clinical utility of tau in the diagnosis and prognosis of patients with TBI [29–31]. Specifically, tau measurement demonstrated value as a prognostic biomarker for informing safe return to play decisions for athletes who experienced sport-related concussions [29, 30]. One study noted that tau concentrations 1 h after concussion incidence was predictive of the number of days it took for concussion symptoms to resolve and have the athlete safely return to play [30]. Other non-sports-related evidence also supports the use of tau as a biomarker for TBI [31]. Aside from adult settings, preliminary evidence suggests that serum tau concentrations may assist in the differentiation of child and adolescent patients with degrees of mTBI [32].

While the field of TBI blood biomarkers is in its infancy, emerging evidence supports value in a setting where laboratory medicine was thought to have limited impact. With that, studies analyzing the clinical outcomes are urgently needed to support patient and healthcare value. Indeed, TBI blood biomarkers are already being incorporated into clinical use for adults with TBI, including S100B to the Scandinavian Guidelines and the US FDA's approval of GFAP and UCH-L1 for reducing unnecessary and expensive CT head scans [33, 34].

Molecular and serological tests in COVID-19

The central role of laboratory medicine in public health and patient care is perhaps best illustrated by coronavirus disease 2019 (COVID-19). Following the first global wave of the SARS-CoV-2 pandemic in early 2020, laboratory professionals mobilized quickly to isolate the genetic information of SARS-CoV-2 and develop molecular tests to diagnose current infection and support public health protocols. Initially, nucleic acid amplification tests (NAATs), including RT-PCR, were developed and approved by regulatory bodies to detect SARS-CoV-2 infection, even at low viral loads. Additional efforts were dedicated to developing rapid tests, including antigen tests (e.g., lateral flow assays) and point-of-care loop-mediated isothermal amplification (LAMP) assays to support community testing as well as rapid isolation and return to work strategies. As of September 2022, it is estimated that 682 RNA-based assays and 985 antigen-based assays have been developed globally to detect SARS-CoV-2 [35]. Laboratory medicine continues to contribute vitally as we transition into an 'endemic' by developing bivalent assays for the detection of multiple flu/coronaviruses as well as ensuring assays remain accurate as new variants emerge. In addition to molecular and antigen test development, laboratory professionals have been instrumental in guiding appropriate test implementation, utilization, and quality standards. The IFCC Task Force on COVID-19 developed and published guidelines on molecular and rapid antigen SARS-CoV-2 testing, providing recommendations on clinical indications and target population, assay selection, verification of assay performance, as well as test interpretation and limitations [36, 37]. These resources have been invaluable to laboratories and public health programs around the world.

In addition to the detection of SARS-CoV-2 infection through molecular and antigen assays, laboratory medicine has supported the pandemic by developing serological assays for the detection of antibodies against SARS-CoV-2. These assays have been key to evaluating vaccine efficacy and the use of monoclonal antibody therapies in immuno compromised patients. The IFCC Task Force on COVID-19 also published guidelines on the utility of serological antibody assays against SARS-CoV-2 in addition to the use of routine biochemical and hematological testing for patient monitoring and management in community and critical care settings [38, 39]. Taken together, laboratory medicine has played a leading role in managing patients with SARS-CoV-2 from initial identification to management of severe cases. Without the objective patient-level data supplied by laboratories throughout the pandemic, this global public health crisis would have been unmanageable and likely resulted in considerably higher morbidity and mortality.

IFCC strategic plans – call to action

A key mandate of IFCC is to develop and demonstrate the value of laboratory medicine in patient care and patient

outcomes in collaboration with clinical associations, corporate members, and IVD industry. To develop the evidence and increase visibility, a new IFCC Task Force on Outcome Studies in Laboratory Medicine (TF-OSLM) was established in 2021. This is in addition to the ongoing work of the IFCC Committee on Value Proposition for Laboratory Medicine (C-VPLM) that aims to advocate adoption of the value proposition in laboratory medicine/healthcare and develop a compendium of tools for laboratory medicine specialists to establish the value for individual medical tests within individual health care systems. One of the main strategic objectives of TF-OSLM is to promote directed research evaluating the role of laboratory medicine on clinical outcomes. A call for proposals was circulated to clinical laboratories and laboratory professionals, as well as corporate members, to initiate prospective and/or retrospective outcome studies in specific fields of clinical medicine, including critical care, nephrology, hematology, and cardiology. Standardized outcome studies are urgently needed to demonstrate the value of clinical laboratories and to develop the evidence that can then be used to advocate for enhanced visibility of clinical laboratory practice. Another key strategic objective of TF-OSLM is to build awareness and understanding regarding the critical role laboratory medicine plays in healthcare outcomes. Plans to accomplish this include enhanced public relations programs/campaigns and increased engagement of non-laboratory stakeholders and IVD industry. In addition to the creation of a database of publications accessible to IFCC members, case studies will also be published in lay form via social media and other public platforms for knowledge translation. This work has already begun with the inaugural initiation of the IFCC "Global MedLab Week" in April 2022 to celebrate the vital role of laboratory medicine and laboratory professionals in public health and patient care. This annual event is supported by IFCC members, including 96 full member countries/societies, 20 affiliate member societies, 6 regional federations, and 52 corporate members worldwide. Together, this work will be pivotal in enhancing visibility and demonstrating the value of laboratory medicine and laboratory professionals in patient care and public health.

Conclusions

Healthcare systems cannot operate without the information clinical laboratories provide. Without it, many important clinical decisions would be made using minimal objective evidence. The examples given in this review including cardiac biomarkers, antibacterial stewardship, TBI, and COVID-19 diagnostics truly exemplify the direct patient and system-level impact clinical laboratory testing has on patient care and public health. New prospective and retrospective studies aimed to directly demonstrate this indisputable value in other settings are urgently needed as laboratory professionals often remain invisible to the public eye. Increased visibility will ultimately lead to more appropriate resource allocation and the potential for laboratories to optimize their impact. The mandate of the IFCC TF-OSLM, including outcome studies with defined and standardized outcomes measurements as well as enhanced public relations programs/campaigns, will play an essential role in showcasing value to patients and other healthcare professionals.

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