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Opinion paper

Key questions about the future of laboratory medicine in the next decade of the 21st century: A report from the IFCC-Emerging Technologies Division

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ABSTRACT

This review advances the discussion about the future of laboratory medicine in the 2020s. In five major topic areas: 1. the "big picture" of healthcare; 2. pre-analytical factors; 3. Analytical factors; 4. post-analytical factors; and 5. relationships, which explores a next decade perspective on laboratory medicine and the likely impact of the predicted changes by means of a number of carefully focused questions that draw upon predictions made since 2013. The "big picture" of healthcare explores the effects of changing patient populations, the brain-to-brain loop, direct access testing, robots and total laboratory automation, and green technologies and sustainability. The pre-analytical section considers the role of different sample types, drones, and biobanks. The analytical section examines advances in point-of-care testing, mass spectrometry, genomics, gene and immunotherapy, 3D-printing, and total laboratory quality. The post-analytical section discusses the value of laboratory medicine, the emerging role of artificial intelligence, the management and interpretation of omics data, and common reference intervals and decision limits. Finally, the relationships section explores the role of laboratory medicine scientific societies, the educational needs of laboratory professionals, communication, the relationship between laboratory professionals and clinicians, laboratory medicine financing, and the anticipated economic opportunities and outcomes in the 2020's.

Abbreviations: AI, Artificial intelligence; DBS, Dried blood spot; DTC, Direct-to-consumer tests; DTCGT, Direct to consumer genetic testing; FAIMS, Field asymmetric ion mobility spectrometry; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; IVD, *in vitro* diagnostic; LDT, Laboratory developed tests; NBS, Newborn bloodspot screening; NCD, Non-commutable disease; NGS, Next generation sequencing; P4 medicine, Predictive, preventative, personalized and participatory medicine; POCT, Point-of-care testing; OOP, Out of pocket; TLA, Total laboratory automation; VOCs, Volatile organic compounds

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1. Introduction

In 2015, a preeminent critical review was published on the future of laboratory medicine as part of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) "Shaping the Future Initiative" [1]. A chronological history of predictions for the future of laboratory medicine from as early as 1887 was collated to demonstrate the merits, restrictions and potential inherent bias of the predictive process. The review examined laboratory organization and staffing, automation and robotics, computing and information technology, analytical techniques and technologies, point-of-care testing, telemedicine, micro-technology, nanotechnology, proteomics, evidence-based medicine, and microscopy and histology. Since this extensive historical review, others have also examined "the future of laboratory medicine" [2–6]. Consistent themes emerging from these reviews were the areas of nanotechnology, biosensors, microchips, genomics, and proteomics [1]. Reviews have also predicted that laboratory medicine will be more patient-centred in the future. Patients are increasingly proactive and informed as they access information via the internet.

The internet has led to proactive and better informed patients. This is supported by current opinion that emphasizes a future based on effective practice [2]. Patient factors that have already started to disrupt laboratory medicine include chronic disease prevention, increased population longevity and patient demand for direct-to-consumer testing. The consumer is now clearly in the centre of the health care strategy of P4 medicine (predictive, preventative, personalized and participatory medicine). Consumers are now more likely to seek testing from a variety of vendors as part of a deregulated, connected, global landscape. This new landscape brings with it associated challenges potentially interpreting test results that could be like comparing "apples and oranges". As such, the need to support quality and harmonization across the total testing process of both current and emerging tests is an industry imperative.

We are continuing to witness an explosion of new technologies and methods. We also continue to see significant advances in technology, and in response, the role of the laboratory and the laboratory professional continues to evolve. As an example, the rapid growth of "omics" testing has generated massive amounts of data, and medical scientists now require enhanced statistical and interpretative skill training to cope with this data explosion. New working models between academics, hospitals and *in vitro* diagnostic (IVD) companies (translational medicine, companies on campus) need to be established to support the quality and harmonization of medical tests [7].

Discussions of the future bring forth both pessimistic and optimistic opinions on the role of the central laboratory. History demonstrates that crystal ball gazing is thwart with danger and even learned opinions about the future can be drastically wrong. It is however essential to look to the future in order to proactively support the quality and application of new technologies in laboratory medicine. Early detection and recognition of an emerging technology is difficult, however emerging technologies and their transformative potential are the key to change in laboratory medicine (Box 1).

The simplified view of the evolution of a technology starts with an idea that evolves to a proof of concept experiment followed by an R&D program to evaluate the scope, benefits and potential of the technology which may, in turn, lead to commercialization and widespread adoption. If the idea is novel, then a patent application may be part of the process and a published patent application may be the first public information available on the technology. Also, the technology may start life in an area unrelated to laboratory medicine, so its potential may not be immediately apparent.

Table 1 updates our previous survey of predictions relevant to laboratory medicine [1]. As well as specific predictions about laboratory medicine, we also include predicted trends in healthcare, strategic technology trends and disruptive technologies because they may directly or indirectly impact the organization, staffing, funding, and scope of laboratory medicine. Five major topic areas, the "big picture", pre-analytical, analytical, post-analytical, and relationships explore the next decade perspective on laboratory medicine and the likely impact of the predicted changes by means of some carefully focused questions that draw upon some of the predictions.

2. Healthcare - the "big picture"

The United Nations predicts that by 2025, the world's population will have grown by 1 billion since 2011 to reach 8.1 billion (https://www.unfpa.org/annual-report) partly due to increased numbers of women reaching reproductive age, despite the overall drop in the fertility rate. With this rapid expansion comes an increased burden on existing healthcare resources and a requirement to provide better access to healthcare for all. It is expected that nearly two thirds of the population will live in an urban area by 2030 due to accelerated migration and increased urbanisation. However, access to healthcare will remain limited. Hence, laboratory services will have to be designed to support the population and be delivered at a low cost while maintaining quality. Our predictions related to the "big picture" of healthcare are detailed in the answers to the following questions.

2.1. What will our patient populations look like in the next decade of the 21st Century?

2.1.1. Snapshot of global population

The world's population numbered nearly 7.6 billion as of mid-2017 (Table 2), indicating that the world has added approximately one billion inhabitants over the last twelve years. Sixty per cent of the world's population live in Asia (4.5 billion), 17% in Africa (1.3 billion), 10% in Europe (742 million), 9% in Latin America and the Caribbean (646 million), and the remaining 6% in Northern America (361 million) and Oceania (41 million). China (1.4 billion) and India (1.3 billion) remain the two most populous countries of the world, comprising 19 and 18% of the global total, respectively [9].

The world's population continues to grow, albeit more slowly than in the recent past. Today, it is growing by 1.10% per year, yielding an additional 83 million people annually. The world's population is projected to increase by slightly more than one billion people over the next 13 years, reaching 8.6 billion in 2030, and to increase further to 9.8 billion in 2050 and 11.2 billion by 2100. There is inherent uncertainty in population projections, which depend on assumptions about plausible future trends in specific demographic variables such as fertility and mortality.

Of the additional 2.2 billion people who may be added between 2017 and 2050, 1.3 billion will be added in Africa (Fig. 1). Asia is

Box 1
Definition of an emerging technology.

> An emerging technology can be defined as; "a radically novel and relatively fast growing technology characterised by a certain degree of coherence persisting over time and with the potential to exert a considerable impact on the socio-economic domain(s) which is observed in terms of the composition of actors, institutions and patterns of interactions among those, along with the associated knowledge production processes. Its most prominent impact, however, lies in the future and so in the emergence phase is still somewhat uncertain and ambiguous."; (Rotolo et al. 2015 [8]).

Table 1
Predictions about the future of laboratory medicine, healthcare.

Year of prediction (date in future)	Predictions	Reference
Medical diagnostic and Healthcare Technologies		
2013 (future)	Transplants without the waiting list; Preventing inherited diseases; Gene therapy comes of age; Remote monitoring in clinical trials; Written in blood (noninvasive whole-genome sequencing); *Star Trek* diagnostics; AIDS vaccine; Health data commons; Six-figure drugs; Costlier generics.	Philippidis 2013 [204]
2014 (2020)	Health consumers - Informed and demanding patients are now partners in their own healthcare; Healthcare delivery systems - The era of digitised medicine – new business models drive new ideas; Wearables and mHealth applications - Measuring quality of life not just clinical indicators; Big data - Health data is pervasive – requiring new tools and provider models; Regulatory compliance and patient safety - Regulations reflect the convergence of technology and science; Research and development - The networked laboratory with partnerships and big data amidst new scrutiny; The pharmaceutical commercial model - Local is important but with a shift from volume to value; The pharmaceutical enterprise configuration - Single, global organization responsible for insight enablement; New business models in emerging markets - Still emerging, but full of creativity for the world; Impact of behaviors on corporate reputation - A new dawn of trust.	Taylor et al. 2014 [205]
2015 (future)	Need to enhance the value of laboratory medicine via - new roles for laboratory professionals focused on optimizing patient outcomes; standardized protocols for prospective patient-centered studies of biomarker clinical effectiveness; benchmarking of tests with commonly accepted measures of effectiveness; agreed definition and validation of effectiveness measures.	Hallworth et al. 2015 [2]
2016 (future)	Miniaturization and microfluidics (mini-MS, nanopore-based analysers).	Blaustieg 2016 [3]
2016	Metabolomics.	Dias & Koal 2016 [4]
2016 (21st century)	Big data, Machine learning.	Obermeyer & Emanuel 2016 [206]
2017 (future)	Global, untargeted metabolomics.	Sandlers 2017 [6]
2017 (future)	Geopolitics – cooperation between laboratories and healthcare regions; Automation in microbiology; Mass spectrometry; High throughput NGS; Companion tests; Challenges of quality of rapid tests; Evolutionary destabilization of laboratory medicine.	Beaudaux 2017 [5]
2017 (2018–21)	Real-world evidence; Digital mobile engagement; Internet of things for asset tracking; Patient reported data; Robotics at hospitals; Blockchain for operations management and patient ID; Cognitive and artificial intelligence; Tech-aided back office operations; Medical device vulnerability; Digital/virtual healthcare services.	Bazzoli 2017 [207]
2017 (future)	Augmented reality; Google Brain; Recreational cyborgs; Medical 3D printing; Gamifying behavior change; New diseases; Real-time diagnostics; Holographic data input; Crowdsourcing through social media; Multi-functional radiology; In silico clinical trials; Reformed medical education; Optogenetics; Robot assistants; Wearables and beyond; Real-time data; Medical tricorders; Artificial intelligence; Genomics; Patient empowerment.	Mesko B Pt 1 & 2 [208]
2017 (2027)	Internet Of Things; Sensors; 3D Printing; Virtual reality; Robotics; AI; Machine learning; Enterprise resource planning; Supply chain management; Big Data; Cloud; Real-time analytics; Autonomous vehicles, Blockchain.	Priestley 2017 [209]
2017 (2045)	Radical life extension; The Robots are coming; Coastal changes; New energy sources; 3D Print your organs and meat; World will get very small; The job skills/info gap; Water as a major asset; Super computers replacing your doctor?; The nanobots are coming; Self-driving trucks and cars; Driverless trucks; Internet of things.	Goldman 2017 [210]
2018	Companion diagnostics; Bringing genomics into cancer care; Continuous monitoring; Hand-held devices for the developing world; Printed paper diagnostics; Biomarkers speed up clinical trials; Mobile phone apps; Personal genomics in medicine; Epigenetics; “Wellness” diagnostics.	Elvidge 2018 [211]
Strategic technology trends		
2013 (2018)	Trends for 2014 - Mobile device diversity and management; Mobile apps and applications; The internet of everything; Hybrid cloud and IT as service broker; Cloud/client architecture; The era of personal Cloud; Software defined anything; Web-scale IT; Smart machines; 3D printing.	Gartner 2013 [212]
2014 (2025)	Trends for 2015 - Computing everywhere; The Internet of Things; 3D printing; Advanced, pervasive and invisible analytics; Context-rich systems; Smart machines; Cloud/client computing; Software-defined applications and infrastructure; Web-scale IT; Risk-based security and self-protection.	Gartner 2014 [213]
2015 (2020)	Trends for 2016 - The device mesh; Ambient user experience; 3D-Printing materials; Information of everything; Advanced machine learning; Autonomous agents and things; Adaptive security architecture; Advanced system architecture; Mesh app and service architecture; Internet of things platforms.	Gartner 2015 [214]
2016 (2020)	Trends for 2017 – Artificial intelligence and machine learning; Intelligent apps; Intelligent things; Virtual and augmented reality; Digital twins; Blockchain; Conversational systems.	Gartner 2016 [215]
2017 (2025)	Trends for 2018 - AI Foundation; Intelligent apps and analytics; Intelligent things; Digital twins; Cloud to the edge; Conversational platforms; Immersive experience; Blockchain.	Panetta 2017 [216]
2018	Trends for 2019 – Autonomous things, Augmented analytics, AI-driven development, Digital twins, Empowered edge, Immersive experience, Blockchain, Smart spaces, Digital ethics and privacy, Quantum computing.	Gartner 2018 [217]
Disruptive Technologies		
2018 (2018)	Smart nappies; Distributed ledgers; Robotic care companions; Smart controls and appliances.	Cupani 2018 [218]
2018 (2038)	Computerized shoes and clothing; Human organ printing; Drone freight delivery; Artificial human blood substitute; Diagnostic toilets; Predictive gene-based healthcare; Medical tricorders.	Cupani 2018 [218]
2018 (> 2038)	Genomic vaccines; Smart glasses and contact lenses; Implantable phones; conversational machine interfaces.	Cupani 2018 [218]

(*continued on next page*)

Table 1 (*continued*)

Year of prediction (date in future)	Predictions	Reference
2018 (Improbable but not impossible)	Human head transplants; e-Tagging of humans; Robotic care companion; Smart nappies.	Cupani 2018 [218]

Table 2
Population of the world and regions, 2017, 2030, 2050 and 2100 (medium-variant scenario).

Population (millions)/Region	2017	2030	2050	2100
World	7550	8551	9772	11184
Africa	1256	1704	2528	4468
Asia	4504	4947	5257	4780
Europe	742	739	716	653
Latin America and the Caribbean	646	718	780	712
North America	361	395	435	499
Oceania	41	48	57	72

Source: United Nations, Department of Economic and Social Affairs, Population Division (2017). *World Population Prospects: The 2017 Revision.* New York: United Nations.

expected to be the second largest contributor to this future growth, adding just over 750 million people between 2017 and 2050. Africa and Asia will be followed by Latin America and the Caribbean, Northern America and Oceania, where growth is projected to be much more modest. In the medium-variant projection, Europe is the only region with a smaller population in 2050 than in 2017. Beyond 2050, Africa will be the main contributor to global population growth.

2.1.2. The World's population is expected to continue to growth until the end of the 21st century

Africa will play a central role in shaping the size and distribution of the world's population over the next few decades. Africa's share of global population, which is projected to grow from roughly 17% in 2017 to around 26% in 2050, could reach 40% by 2100. At the same time, the share residing in Asia, currently estimated as 60%, is expected to fall to around 54% in 2050 and 43% in 2100.

Life expectancy in Africa in 2010–2015 stood at 60.2 years, compared to 71.8 in Asia, 74.6 in Latin America and the Caribbean, 77.2 in Europe, 77.9 in Oceania and 79.2 in Northern America. Globally, life expectancy at birth is projected to rise from 71 years in 2010–2015 to 77 years in 2045–2050 (Fig. 2). Africa is projected to gain nearly 11 years of life expectancy by mid-century, reaching 71 years in 2045–2050. Such increases are contingent on further reductions in HIV/AIDS, and successfully combating other infectious and non-communicable diseases. Asia, Europe, and Latin America and the Caribbean are projected to gain around 6 or 7 years of life expectancy by 2045–2050, while Northern America and Oceania are projected to gain around 4 or 5 years.

The 2030 Agenda for Sustainable Development recognizes [10] that international migration can be a positive force for economic and social development, offering a mechanism to rebalance labour markets between areas of origin and destination and thereby increase the global productivity of labour. Migration across international borders can also help to promote investment and higher standards of living in countries of origin through remittances sent by migrants to families and communities back home, and to accelerate the global diffusion of new ideas and technologies.

2.1.3. Population ageing can no longer be ignored

As fertility declines and life expectancy rises, the proportion of the population above a certain age rises as well. This phenomenon, known as population ageing, is occurring throughout the world. According to data from World Population Propects (2017 revison), the number of older persons — those aged 60 years or over — is expected to more than double by 2050 and to more than triple by 2100, rising from 962 million globally in 2017, to 2.1 billion in 2050 and 3.1 billion in 2100. Parallel to ageing stands the growth in the frequency of civilizational diseases, e.g. diabetes. This reflects tremendous and welcome advances in health and overall quality of life in societies across the world. But the

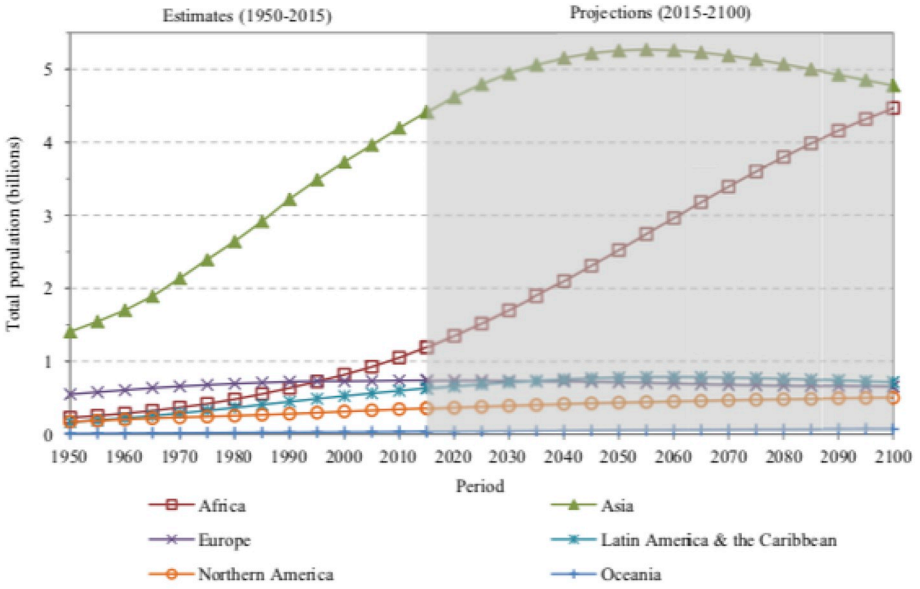

Fig. 1. Population by region: estimates, 1950–2015, and medium-variant projection, 2015–2100.

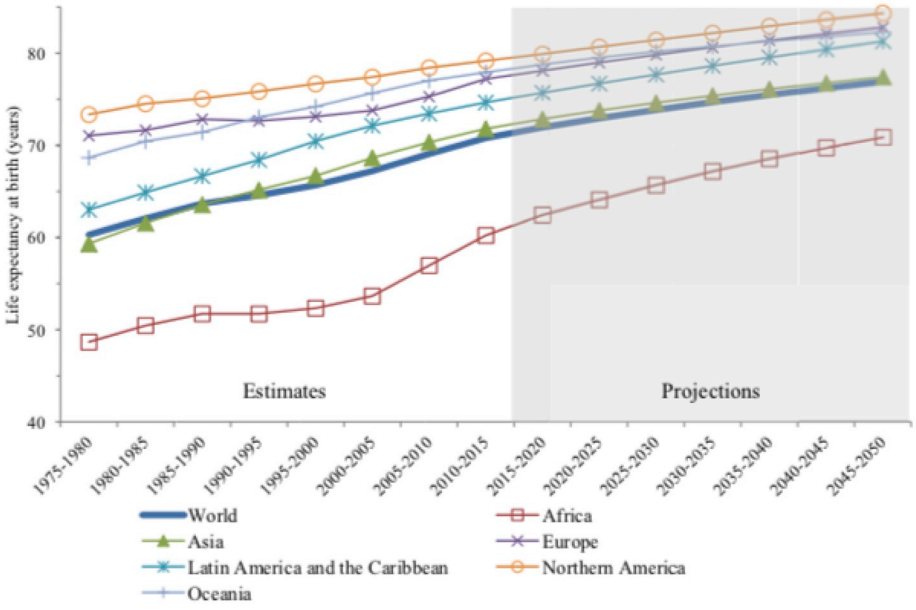

Fig. 2. Life expectancy at birth (years) by region: estimates 1975–2015 and projections 2015–2050.

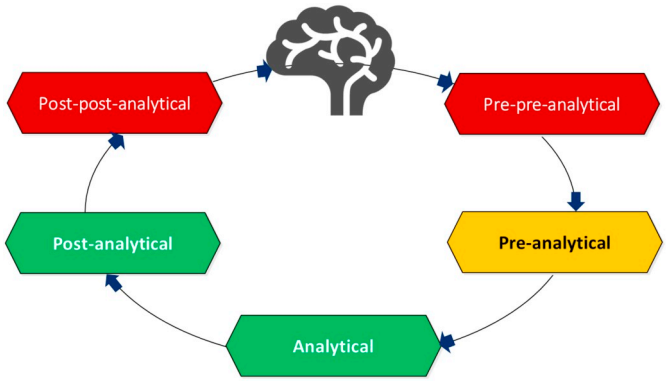

Fig. 3. The current brain to brain loop (also known as the Lunberg cycle) encompasses the total testing process, incorporated laboratories in the central process of analytical and post analytical decisions (green) with some influence on the pre-analytical phase (yellow) and little influence on both the pre-pre-analytical and post-post-analytical components (red). With the advent of DCT and home-based collection the location of testing (analytical) and interpretation of results (post-analytical) is likely to increasingly fall outside the realm of laboratory professionals [193]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

social and economic implications of this phenomenon are profound, extending far beyond the individual older person and the immediate family, touching broader society and the global community in unprecedented ways.

Currently, Europe has the greatest percentage of population aged 60 or over (25%). Rapid ageing will occur in other parts of the world as well, so that by 2050 all regions of the world except Africa will have nearly a quarter or more of their populations at ages 60 and above. The number of older persons in the world is projected to be 1.4 billion in 2030 and 2.1 billion in 2050, and could rise to 3.1 billion in 2100. Over the next few decades, a further increase in the population of older persons is almost inevitable, given the size of the cohorts born in recent decades. Population ageing is projected to have a profound effect on the support ratio, defined as the number of workers per retiree.

Globally, the number of persons aged 80 or over is projected to increase from 137 million in 2017 to 425 million in 2050, and further to 909 million in 2100. In 2017, 27% of all persons aged 80 or over reside in Europe, but that share is expected to decline to 17% in 2050 and to 10% in 2100 as the populations of other regions continue to increase in size and to grow older themselves.

A study of the World Economic Forum [11] estimated that the global economic impact of the five leading chronic diseases — cancer, diabetes, mental illness, heart disease, and respiratory disease — could reach $47 trillion over the next 20 years. The estimated cumulative output loss caused by the conditions, which together already kill > 36 million people a year and are predicted to kill tens of millions more in the future, representing around 4% of the annual global GDP over the coming two decades.

Non-commicable disease (NCD) are often linked to living on fatty, sugary foods and little exercise, but now disproportionately affect those in poorer nations. > 80% of NCD deaths are among people in low and middle income countries. The WEF study, which was conducted with the Harvard School of Public Health [11], found the cumulative costs of heart diseases, chronic respiratory diseases, cancer and diabetes in these poorer countries are expected to top $7 trillion in 2011–2025, an average of nearly $500 billion a year. Mental health, which is typically omitted from lists of leading NCDs, will account for $16 trillion, a third of the overall $47 trillion anticipated costs.

These numbers suggest NCDs, called the world biggest killers by WHO “have the potential to not only bankrupt health systems but to also put a brake on the global economy. In 2010, the global direct and indirect cost of heart diseases, which currently kill > 17 million people a year, was around $863 billion and is estimated to rise 22% to $1044 billion by 2030. The need for immediate action is critical to the future of the global economy.

We are at a critical turning point for effective and cost efficient laboratory medicine paractices that are capable of adjusting to future population demand in healthcare globally. Clearly, the increase in the population and increased percentage of aged population leads to increased rates of morbidity, placing increased pressure on heath care systems worldwide. To tackle the predicted wave of NCDs, stakeholders in the sector need to codify and disseminate best practices, develop the global enablers for value-based healthcare, and create new platforms for deeper collaboration. Digital health, the cultural transformation aided by disruptive technologies is the only way forward. Smart algorithms and health chatbots could assist medical professionals in designing treatment plans and finding the best-suited methods for every patient. Together with robotic companions, they can take over

repetitive, monotonous tasks, so physicians, lab specialists and nurses can concentrate on their actual jobs instead of, e.g., fighting the treadwheel of bureaucracy.

2.2. What will the total testing process looks like?

The brain-to-brain loop describes the process from the medical practitioner's decision to order a test through collection, analysis, interpretation and action (Fig. 3). This process also known as the total testing process is likely not to be a discrete loop in the future due to the impact of integration of laboratory tests into care pathways, empowerment of patients, and digitalization of care.

Integration of laboratory tests to care pathways will contribute to the continuum of care. They will target the improvement of several outcomes (clinic and economic) and will involve more healthcare stakeholders and multidisciplinary teams in the care process. The aim of a care pathway is to enhance the quality of care by improving patient outcomes, promoting patient safety, increasing patient satisfaction, and optimizing the use of resources. A more efficient management of chronic diseases, centered on patients, is driving the switch to care pathways and the reorganization of healthcare services, and it is also stimulating more junctions between primary, secondary and tertiary care sectors [12]. New clinical governance frameworks and financing models are therefore emerging with objectives focused on quality assurance, risk management, technology assessment, patient satisfaction, and patient empowerment [12]. Therefore, the role of some primary care players (e.g., pharmacists) will expand even in areas such as test ordering, counseling or testing. Reported public confidence in,the knowledge and skills of pharmacists justifies expanding the scope of pharmaceutical practice [13]. The efficiency of expanding the role of the clinical pharmacist has been reported for chronic pain and opioid management [14]. In this setting, the collaboration with providers around primary care based chronic pain management is a promising strategy for improving pain management in an interdisciplinary primary care team, facilitating appropriate and safe prescribing [14]. Community pharmacist-led interventions have been shown to contribute to improved adherence and better disease control (e.g., hypertension, cholesterol management, chronic obstructive pulmonary disease and asthma control) [15,16]. The added value of the community pharmacist could also be evident in point-of-care based screening [13]. However, the need for communication and training of the new players involved in the care pathways will be clearly more pronounced as well as the evolution of regulation of this changing field [14].

Empowerment of patients is a second trend relevant to the brain-to-brain loop. In our ageing population, the burden of chronic diseases is increaseing globally and as the technologies of information and communication change, opportunities arise to empowerpatients in their own care. Several studies demonstratethat self-management processes relying on mobile health interventions are effective in improving self-management behavior or patient-reported outcome measures associated with chronic diseases [17]. Smartphone mobile applications have demonstrated benefits to provide additional support and help to improve glycemic control and clinical outcomes in diabetic patients [18]. The efficiency of patients empowerment, collaborations between healthcare workforces, and monitoring of diseases will depend on co-design and co-participation to ensure usability and acceptance [19]. Empowerment, access to self-monitoring, the building of home care service and the global consumerization trend will allow patients and the general population to be in control of ordering tests. These factors, as well as direct-to-consumer testing (see next question), will impact test ordering and potentially its regulation.

Digitalization of healthcare with new generations of electronic medical record systems that digitally connect information from one practice, provider, or facility to another using the same data-sharing platform, and from cloud computing is another factor impacting the brain-to-brain loop [20,21]. Telehealth and telemedicine will allow more efficient remote monitoring and triage even in “smart-cities” or in rural settings [22]. Solutions are currently heterogeneous and their efficiency will depend on their ability to become more interoperable [21]. The integration of artificial intelligence could also influence the process of ordering or activation of reflex or repeat testing. Intelligent ordering systems coupled to data analysis and machine learning could also mean more efficient tools for appropriate test prescription. Digital and dynamic pathways involving multidisciplinary teams and more efficient integration of primary and secondary care sectors will also facilitate the delivery of value-based health-care systems [23]. It will be necessary to build an enabling IT platform that facilitates an integrated dataset across primary and secondary care to measure outcomes and costs across patient pathways. The evolution of the loop and the integration of services, associated with better control of test ordering, will have a significant economic impact (Fig. 4).

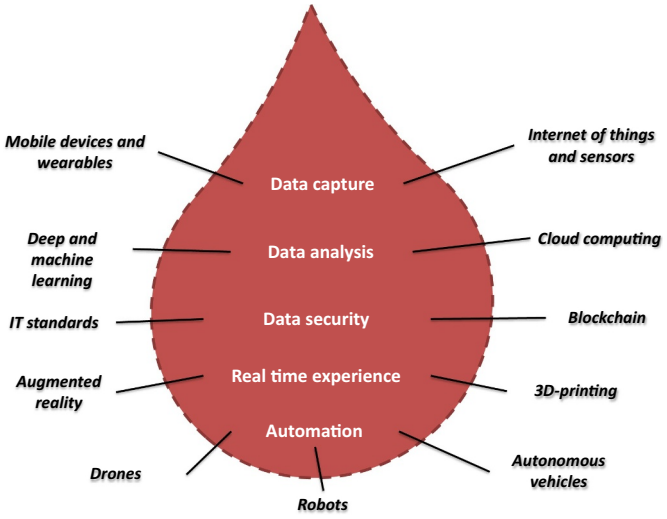

Fig. 4. Prerequisites for a SMART laboratory. The consolidation of laboratories, the evolution to integrated care network as well as an environment of consumerization are disrupting laboratory services and operations. The switch to SMART (Speed Metrics Automation Remote Technologies) digital laboratories based health ecosystems depends on several prerequisites for successes. Intelligent processes, integration of big data and real-time data management, automation, blockchain, Internet of things and enhancement of user experiences are key element of the smart digital laboratory. Safety, security and cost-effectiveness are pillars for the credibility and transferability of such smart digital laboratory environment. This transforming ecosystem will also trigger novel human - machine interfaces and we will be the gatekeepers for this new ecosystem.

2.3. What is the future of direct access testing: will patients still need a doctor's prescription?

Direct-to-consumer tests (DTC) refer to tests sold directly to consumers via the internet, television, pharmacies, parapharmacies, supermarkets or other marketing channels without involving a doctor's prescription or the involvement of health care professionals [24,25].

The rise in DTC testing can be attributed to technological advances and information and advertising campaigns (BRCA testing is a good example) [26]. The internet currently enables unprecedented ease of access for DTC genetic testing, with saliva collection kits mailed directly to consumer's homes from anywhere in the world [27]. The public awareness of the availability of DTC, particularly in relation to genetic testing, has increased in recent years [28,29]. DTC is also stimulated by trends like value-based care and patient empowerment where continuous monitoring and self-monitoring are encouraged [30]. The increased use of DTC is also clearly related to the switch from patients to consumers [31]. Moreover, “consumerization” raises the question of

demand-driven testing and therefore of the diversity of the test menu, the quality of the services as well as the cost and pricing of DTC. The diversity of the "menu" of available DTC tests and testing companies is increasing and able therefore to respond to the increasing demand of such new health consumers. In addition to rapid test for pregnancy, HIV or HCV, DTC now includes more and more genomic testing including pharmacogenetic tests [32].

The advent of DTC has triggered many questions and concerns. The question of pricing is of course important for the consumers and patients but could also have a potential impact on laboratory tests prices as the two systems, "traditional laboratory medicine" and DTC, coexist. Another important question related to DTC is the influence on test ordering rates. Findings suggest that DTC requests are typically accommodated, promote higher prescribing volume, and have competing effects on treatment quality [33]. The consequences of DTC results on individuals and families as well as the rights of consumers are other importantconsiderations. DTC might have the potential to prompt behavioral changes in response to adverse test results [25]. Some internet-based genetic tests have the capacity to cause significant confusion or harm to consumers who are unaware of the risks or potential variability in quality [27]. Potential benefits of DTC include personal control over genetic information and health management decisions, whereas potential risks include misinterpretation of results, psychosocial distress, and lack of informed consent [34].

DTC tests represent a major paradigm shift in healthcare. They are expected to evolve in response to commercial competition and current concerns over quality and legality. The DTC model is expected to change and to offer more education for patients and healthcare professionals [35]. For example, oncology nurses can provide education, support, and advocacy to enable patients to truly understand the positives and negatives associated with tests [34]. Broad use of these tests coupled with planning and discussion with health providers regarding genetic risks and potential protective behavior changes have been proposed as preventive tools to reduce health disparities and improve equity in health outcomes [36]. As public access to DTC genetic testing increases, the 'Patient-Doctor-Counselor Model of Delivery of Genetic Services' may be more appropriate for the provision of this service than the current model of direct access by patients [37]. On the basis of their knowledge and experience, clinical geneticists could play a role by providing information to both healthcare providers and to the public for a better use and understanding of the tests and their impact [38].

Scientific evidence of the benefits of DTC tests remains unclear as does evidence of the control of the performances and quality of the tests [25]. Also, some organizations such as ACOG have stated "direct-to-consumer genetic testing should be discouraged because of the potential harm of a misinterpreted or inaccurate result" [39]. In order to protect patients and consumers and ensure the quality standards applied in laboratory medicine, more data and evaluations of DTC test performance are needed to safeguard and promote patient safety. Studies have demonstrated the importance of confirming DTC raw data in a clinical laboratory that is well versed in both complex variant detection and classification [40]. Some other factors are also affecting the use of DTC, for example, DTC genetic testing has historically demonstrated differences by education, income, and race; these disparities could jeopardize potential benefits by limiting access and use [36]. Proliferation of such products in the absence of regulation has the potential to damage public trust in accredited and established clinical genetic testing during a critical period of evidence generation for genomics [27].

Concerns over misleading DTC test results combined with the need to control data as well as risk of data being sold [41,42] have re-triggered the need for regulation, for the evolution of the legal framework for DTC tests and also for identifying ethical responsibilities of DTC providers. Depending on the country or region, changes in the legal framework have been initiated but the regulatory landscape remains fragmented or contrasted. In Europe, for example, there are countries (e.g., France and Germany) which essentially ban DTC genetic testing, while in others (e.g., Luxembourg and Poland) DTC genetic testing may only be restricted by general laws, usually regarding health care services and patients' rights [43,44]. Changing the legal framework needs also to integrate the consumer rights and equity. In one hand, the need to consider the libertarian right to DTC genetic testing [45,46] and on another hand, the policies regulating DCT genetic tests should prioritize equitable distribution of benefits [36].

2.4. Future role of robots and total laboratory automation?

A number of predictions for the future of the clinical laboratory (Table 1) identify a major role for static and mobile robots in line with predictions for other areas of industry and commerce [47].

Already, mobile robots are being used to deliver clinical specimens [TUGâ robot, Aethon), and dual-arm robots are employed in analytical procedures [48]. A recent development has been the use of a cobot (collaborative robot) in a shared workspace. Cobots are an emerging type of robot that are safe next to people, easy to train and deploy, and affordable. They are designed to automate repetitive tasks (e.g., picking and placing) involving relatively light payloads (e.g., 5 kg). Two Universal Robot UR5 cobots have been deployed in a Danish hospital to automate sorting of blood specimens [49]. The first cobot picks up samples, places them in a bar code scanner, identifies cap color (via a camera), and places tubes in racks according to cap color. A second cobot picks up the racks and places the racks in a feeder for centrifugation and subsequent analysis. The footprint of these cobots met the space constraints in the laboratory, did not need safety cages, processed 7–8 tubes/min, and allowed the laboratory to absorb a 20% increase in specimens with no additional staff.

A future impetus to implementation of robots in laboratory medicine may be from the growing uses of robots in other hospital areas. For example, robots are being used for surgery (da Vinciâ Surgical System, Intuitive Surgical), delivery of medications and linens [TUGâ robot], disinfection (Disinfectant Robot, Xenex), pharmacy dispensing, rehabilitation (exoskeleton, ekso Bionics), patient interactions (telepresence robot, iRobot). Also, sobots (social robots) are used as companions and healthcare assistants [50] and for hospital reception and greeting (e.g., humanoid Pepper robot, SoftBank Robotics) [51].

Another application of robotics is total laboratory automation (TLA) in the form of analyzers directly attached to specimen transport tracks. This is now commonplace and seems unlikely to be displaced by the 2020s. The choice of systems and available features continues to expand. For example, recent TLA systems offer bidirectional, variable-speed magnetic sample transport, multi-camera vision systems, and RFID tracking [52,53]. Also, the scope of TLA has been expanded to include microbiology (e.g., BD Kiestra, Becton Dickinson). Track-analyzer interfaces were an important issue in the early days of TLA. The rise of the robots, may make the TLA-static and mobile robot interface an important consideration by the 2020s.

2.5. How will laboratories be engaged in green technologies, and sustainability?

Sustainability is an emerging goal. Climate change and environmentalism continue to be national and international issues [54]. The general population is more and more aware of sustainability and more likely to use sustainability arguments to guide their choices and to adopt new practices [55]. Around the world, governments, businesses and individuals are making real efforts to ensure that their activities are more environmentally friendly. This involves 'greening' the sector with particular attention to energy, processes, waste, water use, infrastructure adaptation and buildings. Healthcare facilities and laboratories are significantly and undeniably impacting the carbon footprint with, for example, the annual production of two million tons of waste by U.S. hospitals [54].

Investment in sustainable alternatives might result in positive economic impact. Generalizing results to hospitals nationwide from selected hospitals that have implemented programs to reduce energy use and waste and achieve operating room supply efficiencies indicate that savings through these interventions could exceed $5.4 billion over five years and $15 billion over 10 years [56].

The clinical laboratory community has the opportunity by the 2020s to drive and set new standards and actions for sustainability. The role and knowledge of laboratory professionals combined with their position in the health care system make them key players in creating environmentally sustainable health care practices. Such a sustainable thinking will ensure that resources are used efficiently and responsibly and will provide an opportunity to create new value to the mission of health care, rather than settling for less [57]. Actions will require significant physical, financial and human resources. Providing safe and affordable care to patients and their families must remain paramount in the decisions that are made, but good environmental stewardship can be achieved [57].

Emerging technologies will play an important role in this quest. Artificial intelligence (AI) and data science applied to laboratory medicine will help to optimize the workflows, use of reagents and resources and also contribute to greener practices. AI could clearly contribute to maximize energy efficiency as well as measuring and controlling carbon and water footprint. “Smart” test ordering will be also encouraged [58]. Indeed, sustainable approaches include also the ability to reduce unnecessary tests [59]. Results from a paediatric cardiology study that focused on rationalization of blood test requests showed significant cost savings on biochemistry tests but also around 17.8 t of carbon dioxide across a 32-month follow-up period [59]. Manufacturers of *in vitro* diagnostic (IVD) reagents are also concerned and have made efforts to reduce their carbon and environmental footprint and reagent packaging. Therefore, discussions and partnerships with IVD should ensure better sustainability of the supply chain, reagents production and design of instruments.

3. Pre-analytical phase

The pre-analytical component of testing is a substantial part of the total testing process. Pre-analytical errors are currently recognised as the greatest contributor to errors in the total testing process [60,61]. This is mitigated in part with point of care testing (POCT), but has the potential to present new challenges as we move into different matrices and modes of collection and storage (e.g., dried blood spots, home-based collections and biobanks). Whilst laboratory medicine has continued to grapple with complete control of pre-analytical components, it is likely to see new challenges emerging in the future. In particular, the use of different matrices, saliva, DBS, breath and transcutaneous non-invasive approaches are likely to give patients greater control of sampling and testing. Our predictions related to the “pre-analytical” component of testing are detailed in the following questions.

3.1. How will drones be employed in healthcare?

Drones have begun to have an impact in healthcare. A drone is an pilotless aircraft guided by remote control or onboard computers. There are three main types: fixed-wing drones (including hybrids that can take off and land vertically); single rotor drones; and multirotor drones (e.g., 3, 4, 6 or 8 rotors). Drones have been implemented extensively by the military (e.g., surveillance), and are being tested for delivery services (e.g., Amazon, Domino's Pizza, Flytrex). In addition, applications in warehouse management have been proposed [62–65].

The potential prime applications of drones in laboratory medicine are for collection and delivery of blood specimens. Preliminary studies have demonstrated the feasibility of drone delivery of blood products [66]. One example is the Zipline fixed wing drones (round trip range of 160 km, payload 1.75 kg) that are being used for delivery of blood and vaccines in Africa [67]. Drones are also being used for specimen delivery [68,69]. Comparison of the stability of analytes (19 chemistry and hematology tests) in samples held stationary versus being flown (258 km long, 3 h duration flight) in an active cooling box on a hybrid vertical take-off and landing drone showed no bias except for glucose and potassium. Flown samples (2.5 °C cooler than the stationary samples) had an 8% and 6.2% bias for glucose and potassium respectively, but this was consistent with the magnitude and duration of the temperature difference between the flown and stationary samples [68]. Also, studies with blood and sputum culture specimens flown for ~30 min (20–25 km flight) in a fixed-wing drone showed no differences between flown and stationary specimens for the microbes studied [69].

In the US, the future of legally operated commercial drones largely depends on the Department of Transportation's efforts to establish a structure to integrate drones into the national airspace [70,71]. In Lugano, Switzerland, a partnership between Matternet and Switzerland's national postal service (Swiss Post), is developing a medical transport network based on quadcopter drones (20 km range, average speed 36 km/h, 2 kg payload) [71–73]. In 2017, the Swiss Federal Office for Civil Aviation (FOCA) granted a certification allowing these delivery drones to fly autonomously over cities at any time of day or night, paving the way for this service [72].

Recently in Naples (Italy) the transport of samples through drones with visual navigation has been implemented with success between two neighboring hospitals thanks to the project Philotea (*Public Health Integrated Logistic Operation Transport Emergency*) with the participation of the Italian Society of Clinical Biochemistry and Laboratory Medicine, CARPITECH srl, *DJI Eliteconsulting, Wip lab srl e Drone Group Srls*.

Based on current commercial and military applications, drones appear well suited for healthcare applications of not only delivery services, but also inventory management and general surveillance and monitoring (of processes and patients). Two factors that could drive drone implementation by the 2020s are favorable economics (20–50% saving over on-demand ground transportation), speed of delivery [73], and integration of drones into the airspace.

3.2. What will be the role of laboratories in managing biobanks?

Biobanking is a resource-intensive activity that is undertaken with the hope that the effort will pay discovery dividends in the future. Traditionally, biobanks keep samples of interest under a suitable archival condition in a dedicated storage system until such time when a research question requires their testing [74]. Often, the limited clinical information that is available at the time of collection is manually attached to archived samples. Furthermore, they may not contain the relevant clinical information for the research question, thereby necessitating further laboratory testing or repeat clinical review. These limitations place a constraint on the number of samples that can be banked, subject to available resources. They may also introduce systematic bias when the sample is retested due to degradation, thereby raising the risk of erroneous research conclusions. For example, up to 35% of observed variance in plasma protein concentration can be explained by storage time in a biobank [75].

Yet, aclinical laboratories routinely discard a high number of left-over clinical samples, which are a rich and untapped resource. A novel type of biobank (a ‘live’ biobank) removes the need for sample storage and manual input of clinical information. In this model, the (next generation) electronic medical record will identify suitable candidate patients that meet the criteria of a research study [76,77]. After obtaining relevant consent, these candidate patients will automatically be assigned a research reference number. Through integration with the laboratory information and automation systems, an aliquot of the candidate patient sample will be made when the patient visits the institution. The aliquot of sample will be labelled with the research reference number, thus de-identified. The de-identified aliquot sample will be immediately tested for the desired biomarker, which minimises sample degradation. The relevant clinical information, and perhaps

even social factors and costs [78,79], can be retrieved retrospectively and prospectively via the reference research number (linker) and integrated with the biomarker results. This live biobank model is self-replenishing, automates patient recruitment, optimises samples already collected, minimises unnecessary sample storage costs (just-in-time banking), reduces manual annotation [80], ensures the integrity of the sample (results), and automates the information gathering. It is expected to accelerate translational research and cohort studies in a highly efficient manner.

At the same time, traditional biobank will continue to evolve and expand with key activities targeted at improving operational processes (consent, collect, process, annotate, bank, distribute) to increase the number and variety of biospecimens available for research to span the entire disease spectrum. This may be achieved by involvement of commercial entities or adopting a network approach, which may also help control costs operations synergy. The funding of biobank will remain a challenge and may require public-private partnership for long-term sustainability while complying with regulations to maintain tissue and data quality and prevent illegal and unethical practices. Given the high cost associated with biobanks, there is an acute focus on ensuring the best quality for the banked biospecimens. This will be mediated by adoption of best practices, guidelines and accreditation through organizations such as the College of American Pathologists and International Society for Biological and Environmental Repositories [81].

3.3. What type of samples will be tested?

The frequency of testing using alternative sampling types (e.g. saliva and dried blood spots) provides the option for microsampling and gives consumers greater control as to when, where and by whom their sample is collected. This is potentially a paradigm shift for traditional central laboratories where macro (venous blood) samples represents the majority of the work. Indeed, the current large-scale automation has been tailored to support high throughput of these macro samples. Advancements in instrument technology, mass media attention (e.g. from startup ventures such as Theranos), and drive by consumers for convenient sampling has increased the momentum for less invasive and convenient sample collection.

Alternative matrices, such as dried blood spots (DBS) and saliva, are now used more frequently. A recent review of the literature on DBS testing using mass spectrometry (MS) techniques outside of newborn screening found over 100 different analytes had been quantitated from this micro-sampling technique, predominantly for small molecular weight molecules related to drug monitoring [82]. There are many applicable examples, including the patient monitoring of amino acid disorders such as phenylketonuria and maple syrup urine disease with DBS MS testing. In addition to blood, urine, saliva and sweat can be collected onto filter paper and dried, allowing remote collection, which potentially further expands the options for patients. This means patients, especially those with long distances to travel, do not need to attend a pathology service for a blood collection and the sample can be transported by mail.

4. Analytical

The analytical component of the total testing process has already seen significant disruption as a result of the progress in POCT, MS, and genomics. Each of these areas has seen an exponential increase in publications in recent years; this increase is predicted to continue (Fig. 5) as these technologies disrupt current laboratory practice. It is also likely that there will be further evolution of within-lab technologies and translation of analytical technologies that sit outside of the traditional laboratory. This section addresses our predictions related to the "analytical" component of laboratory medicine.

4.1. What will be the role and look of high-throughput in medium-sized and central laboratories?

With increasing population numbers and lower budgets, future health care systems will face similar challenges as today, i.e., doing more with less. For the high-throughput laboratories, this means that indicators, such as throughput, footprint, and cost per test, will remain a driver for technological development.

Higher grade of automation and integration of more and more

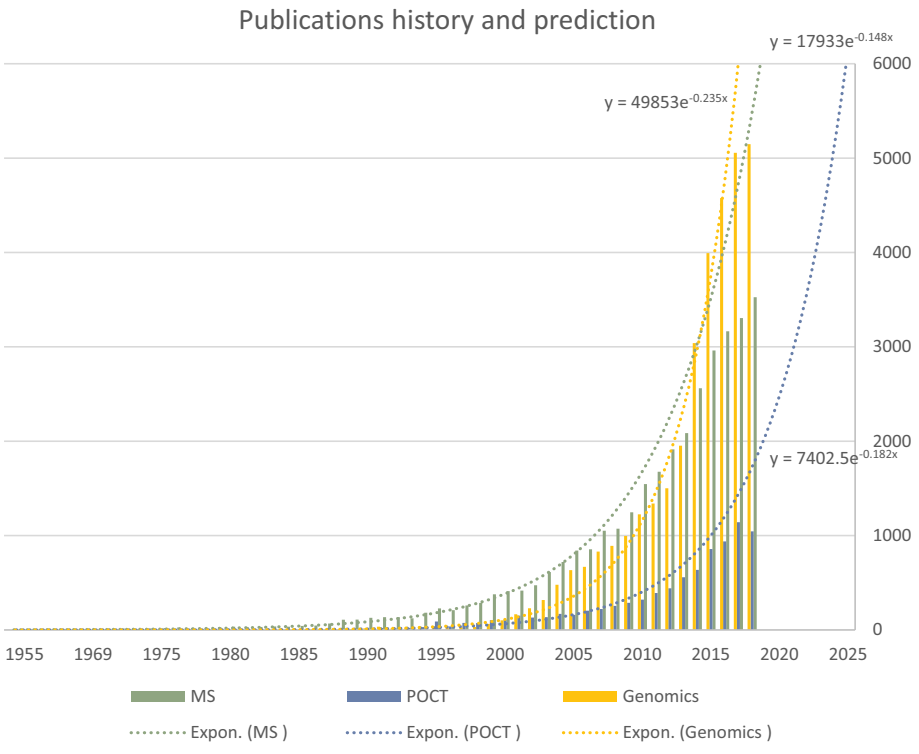

Fig. 5. Publication history and prediction to 2025, with the abscissa axis giving the publication year and the ordinate axis providing the total number of publications wtth the search term for that year.. The data is based on a PubMed search (conducted on 19/5/2019) encompassing the dates 1/1/1900 to 31/12/2018 for the search teams "clinical mass spectrometry", "point of care testing" and "clinical genomics". This is indicative data using common names and is not an exhaustive search. The predictions are based on exponential trend lines to 2025.

disciplines will lead to higher efficiency and increased throughput.

Cost-pressure will most probably lead to more consolidation and a trend to larger laboratories. Even though patient-centric sampling and point-of-care testing will almost certainly change the workflow, the majority of tests will still be done in centralised high-throughput laboratories, because high analytical performance and cost efficiency cannot be matched by current POCT. The evolving new models in which the central laboratory is bypassed will inevitably lead to further contraction and change of the boundaries between disciplines. The vision of a comprehensive Blood Sciences central laboratory will be reality with serology, endocrinology, hematology and other disciplines consolidate in one lab. The central laboratory will offer an increased number of DCT testing services, and drivers for change include chronic disease, number and cost of testing and consumerism.

4.2. How will POCT evolve?

The future balance between testing in laboratories and self-testing or testing at the point of care is difficult to forecast accurately. Several themes emerge from the predictions relating to POCT in Table 1. These include a prominent role for mobile health (mHealth) and associated real time medical data, the emergence of wearable analytical devices, and new types of point of care analyzers (e.g., medical tricorders, diagnostic toilets, printed paper diagnostics) [83]. The advent of smartphones in 2007 changed many aspects of our everyday lives. This technologically convergent device serves as a telephone, still/video camera, MP3 player, a source of news and weather, and provides electronic storage and real-time access to the wealth of information available via the internet. In addition, the capabilities of a smartphone can be expanded via an ever-growing number of easily downloaded applications (apps).

The potential of a smartphone for healthcare applications was quickly realized and it has been used in a number of different ways [84]. Medical apps for fitness and health have been very popular and are expected to grow almost exponentially between now and 2025 [85]. A device that plugged-into a smartphone to create a medical test device was the next phase of development and current capabilities range from glucose testing to ultrasound scanning. A further development has been medical test devices that connect wirelessly to a smartphone (e.g., Bluetooth connected pregnancy test; Clearblue Connected Ovulation test) [86,87].

Another use of a smartphone in POCT exploits the built-in camera for urinalysis [88]. An app guides the user (aided by a chatbot nurse, named Emily) through the Dip.io home-based urinalysis testing process. The camera scans a conventional dipstick placed on a color chart (color board). It then uses color recognition, computer vision, and AI to ensure accurate testing under differing conditions and with different smartphones. Results, after classification in the cloud, are automatically sent to the patient's electronic medical record. The menu of tests based on this imaging technique is expected to expand to include urinary albumin:creatinine ratios.

The expanding scope of smart devices for mHealth is exemplified by the growing number of smart wearables, i.e., clothing or accessories that have sensors integrated or woven into their structure and that can provide health information unobtrusively during daily living [89–91]. Wearables includes devices worn on the wrist (e.g., Apple Watch® for monitoring heart rate and rhythm; Embrace smartband to detect epileptic seizures) [92–94], a mouthgard (e.g., measure linear and rotational acceleration, impact location and direction, and counts every impact for concussion assessment) [95]; clothing (e.g., CardioInsight Noninvasive 3D Mapping System) [96]; and different types of wireless patches (e.g., Smartcardia - vital signs temperature, pulse, blood pressure, blood oxygen levels, cardiac rhythm and cardiac electrical activity) [97] that in some cases are flexible and stretchable (e.g., e-skin with pressure and thermal sensors) [91].

One predication in Table 1 is for noninvasive whole genome sequencing, but such a Tricorder-like device seems unlikely based on the current state of sequencing technology. However, the quest to build a real Tricorder has taken a step forward as a result of the recent Qualcom Tricorder XPRIZE. The winning entry, DxtER™, was not a single handheld device, but instead a family of sensors in combination with an AI program that combined data and produced a diagnosis [98]. Another direction for point of care analyzers is to add a diagnostic capability to a toilet. This is not a new idea, but it continues to resonate with researchers and recent developments focus on urine testing via dipsticks and a smart-toilet prototype that can collect urine for testing several times a day [99]. In addition, printed paper diagnostic devices (uPADs) are another emerging area of technology [100], as they are inexpensive and easy to manufacture and have been adapted to a wide range of analyses with developing countries in mind.

Two other emerging technologies that may be relevant to the future of noninvasive POCT are breath analysis (volatolomics) and voice analysis. Breath contains a mixture of substances, in particular volatile organic compounds (VOCs) and the pattern of these compounds has been linked to disease [101]. The non-invasive nature of breath sampling is attractive for POCT and several analytical systems have been developed (e.g., nanosensors, gas chromatography, field asymmetric ion mobility spectrometry (FAIMS)) [102–104]. Voice analysis as a diagnostic modality is relatively new. Algorithms have been developed for voice analysis and have had some success in detecting the presence of coronary artery disease [105].

Providing medical testing via a health and wellness kiosk is another aspect of point of care. Existing health kiosks (e.g., > 3600 in the U.S.) provide a limited range of testing (e.g., blood pressure, retinal screening) [106], but in the future testing in this type of location might be expanded to include laboratory tests. Indeed, in Canada, touchscreen kiosks have been placed in pharmacies that then enable customers to order chemistry tests. A finger stick sample is taken by the pharmacist, and then the sample analyzed in the pharmacy for up to 21 analytes (e.g., the baseline panel checks cholesterol, triglycerides, blood sugar, and basic liver function) [107]. It seems likely that the amount and modes of access to POCT will have increased by the 2020s. Perhaps mHealth is best positioned because of the ubiquity of smartphones, their connectivity, which underpins a future vision of widespread telehealth with data sent in real-time to a patient's medical record for assessment, and interpretation by a medical professional.

4.3. How will mass spectrometry technology be applied?

Mass spectrometric analysis has expanded in the last 15 years from traditional gas chromatography separation coupled to-mass spectrometry (MS) [108] through the breakthrough of coupling of liquid with MS [109]. The now well established expanded newborn dried bloodspot screening program is an early clinical application example [110]. Today, routine applications range from elemental analysis through to the identification of microorganisms. It the improved sensitivity and specificity of MS that is the driver for their translation and implementation into the diagnostic setting [111–113].

More laboratories are adopting this technology, exemplified by the increase in MS methods in endocrine external quality assurance programs. As an example, serum testosterone analysis was the first MS steroid analyte added to diagnostic testing in Australia (introduced in 2010) based on participation in the external quality assurance programs (the RCPAQAP) [113]. A similar scenario is seen in the external quality assurance program from the UK (UKNEQAS) for serum 17-hydroxyprogesterone where over half the laboratories employ MS technology for analysis [114]. MS applications with peptide hormones (e.g. plasma renin with some automation of the extraction phase) has also been achieved [115].

As the MS instrumentation and processes continue to evolve, there is increased speculation of their future applications. A survey of 63 clinical laboratory representatives conducted by the American Association of Clinical Chemistry in conjunction with the Mass Spectrometry Separation Sciences devision was designed to determine the future of

clinical mass spectrometry testing looking forward to 2020. This survey asked "of the environments where mass spectrometry tools ARE NOT currently in use, in which ones would you like to see the technology take hold by 2020?" The top response (~50%), was "anatomical laboratory applications". This was followed by further expansion into microbiology, chemistry, real-time surgery and other clinical laboratory applications. Toxicology and TDM, although traditional applications of MS, were also prominent, which may be due to the changes to sample type and location of testing. Protein, immunoglobulin and peptide analysis were also identified in the survey responses [111].

There is an increase in publication and special issues related to mass spectrometry. From 2008 to 2018, the number of clinical MS publications tripled and predictions from this data suggest that clinical mass spectrometry publications will again increase by five-fold by 2025. (Fig. 5). This is due to the expansion of clinical MS applications into peptide analysis, other omics (e.g. proteomics), ion knife and ion pen, histopathology and microbiology [116–123]. Currently, a significant proportion of MS testing is based in laboratories using laboratory developed tests (LDT), with some commercial kits. More recently, prototypes of fully automated MS laboratory solutions and the emerging use of MS in non-traditional sites, such as near patient testing in physician offices [124], or as part of real time surgery.

In this recent survey [111] the question "in 2020, which of the following laboratory processes would you anticipate will be automated on your mass spec testing line" [111]. The majority of respondents expected sample acquisition, sample preparation, data analysis software and interface all to be automated by 2020. Certainly companies such as ThermoFisher have already launched a prototype" blackbox" fully automated LC-MS/MS system that improve automation, data analysis and is operator friendly. As we move towards the 2020s, we predict the drivers of automation and sample throughput will see improvements in connectivity and turnaround time with full integration of MS with chemistry platforms and direct import of results into the LIS [125].

Our predicted changes to mass spectrometry testing in the next decade span the total testing process and include:

1) Increase in the number of clinical laboratories providing MS-based testing applications;
2) Increase in the type of testing, expanding across all disciplines of laboratory medicine;
3) Miniturisation of mass spectrometry instruments;
4) Automation, including placing on routine laboratory track systems;
5) Sensitivity and the use of smaller sample volumes to allow for DCT testing and monitoring patients;
6) Moving away from immunoassay for most endocrine (peptide and non-peptide hormones) and drug testing;
7) Increased focus on mixed mode mass spectrometry applications, particularly quadrupole-time of flight instruments for biochemistry applications.
8) Location of instruments outside of traditional laboratory settings for near patient testing;
9) Improvements in connectivity; and
10) Improved big data management bring omics applications into the diagnostic laboratory.

The omics related to mass spectrometry can be simply divided into two broad categories, untargeted and targeted studies. The current untargeted studies usually look at two populations and compare the mass spectrometry profiles using sophisticated computer programs. These are usually considered discovery tools and used in the research environment. Targeted omics, on the other hand, is looking at the "discovered" analytes that are of clinical interest and for translation in to the clinical diagnostic workflow. In fact, targeted metabolomics profiling by MS has been performed historically for a variety of small molecular weight analytes including steroids [108] and for newborn dried blood spot screening [110]. MS applications related to clinical biochemistry, both untargeted and targeted, now span the traditional small molecular weight compounds (metabolomics), with steroids sometimes specifically described as steroidomics, to lipid (lipidomics) and peptides and proteins (proteomics). Whilst, the presumption is that all analytes in their respective category will be identified, the reality is that the sample preparation and analytical range and setting of the mass spectrometer influence the output.

The untargeted discovery studies provide big data, require statistical management and are likely to remain in the research space. On the other hand, in the coming decade we predict increased targeted, and to a lesser extent untargeted, omics applications will be employed in diagnostic laboratory setting. Indeed, lessons learnt for newborn bloodspot (NBS) screening of acylcarnitines and amino acids, show that not all differences will be clinically relevant. In addition, the broad introduction of precision NBS will improve the positive predictive and redefine the analytical pathways. Hence, we will need to prioritize the translation of these targeted applications.

4.4. How will genomics be applied?

"Omics" refers to the totality of a field of study. Many types of omics have been described, including: glycomics, lipidomics, metabolomics, genomics, proteomics, transcriptomics, and volatolomics. Omics information has the potential to lead to improvement in many facets of human life and society, including the understanding, diagnosis, treatment and prevention of disease; advances in agriculture, environmental science and remediation; and our understanding of evolution and ecological systems. Today, there is an increasing need for researchers and clinicians to understand the scope and results of omics research and incorporate this information into diagnostics, therapeutics and studies of disease etiology.

One of the best-known examples of omics is genomics. Genomics is defined as: "a branch of biotechnology concerned with applying the techniques of genetics and molecular biology to the genetic mapping and DNA sequencing of sets of genes or the complete gene set of selected organisms, with organizing the results in databases, and with applications of the data (as in medicine or biology)". Indeed, the field of genetics is not only one of the most rapidly advancing areas of the life sciences, but also one that has a major impact on all of our lives because of its central role in medicine and biotechnology. Furthermore, advances in genomics, and more broadly in biomedical research, have been greatly facilitated by significant and sustained throughput increases, cost decreases, and improvements in ease of use of genomics technology.

The ability to assay genomes comprehensively has been made possible by the enormous reduction of costs and development of many informative assays in the past few decades. Technology advances, particularly new sequencing systems, have enabled many research projects that are producing stunning insights into biology and disease. Extending beyond sequence per se, assays have been developed to determine nucleotide modifications, chromatin state, nuclear organization, and dynamics of those features achieving the low costs and high quality needed to use comprehensive genomic information in many research applications or in individual health care. Much is expected in the way of diagnostic insights from many large scale sequencing projects currently underway or planned (e.g. 100,000 Genomes Project, Cancer Genomics Atlas, Cancer Genomics Project, BGI Million Human Genomes, Million Veteran Program, MacKenzie's Mission, GenV) [126–128][1].

4.5. How will 3D-printing impact the laboratory?

3D-printing (stereolithography) can be traced back to the 1980s. It is a rapid prototyping process by which an object is fabricated layer-by-

[1] Mackenzie's Mission (reference 128) is the first project under the Federal Government's $500 million Genomics Health Futures Mission - part of the Australian Government's Medical Research Future Fund.

layer from digital information using photopolymers and UV light. Subsequently, the scope of printable materials has expanded beyond polymers to include cells and the printing of tissues and organs [129,130]. Already, on site 3D-printing is being used to digitally supply spare parts at railway maintenance sites [131], and possible applications for 3D-printing in the clinical laboratory include in-laboratory printing of spare and replacement parts for laboratory equipment, or even analyzers (3D printing of microfluidic analytical devices has been well-described for over a decade) [132]. By the 2020s, as 3D-printed organ technology matures, the laboratory may also have a role in pre-transplant testing of printed organs and providing support to patients transplanted with printed organs.

4.6. How will laboratories manage total laboratory quality?

The management of total laboratory quality will leverage heavily on informatics. In the pre-analytical phase, expert systems will guide clinicians in appropriate test selection, based on the clinical information provided during consultation [133–135]. The test recommendations will be based on pre-test probability and clinical evidence. This will reduce the biggest source of pre-analytical error —inappropriate testing— and will allow the laboratory to monitor test utility based on clinical rationale and outcomes. Other innovations such as a sample collection decision support system [136], automated robotic phlebotomy [137], algorithms that detect sample collection errors [138,139], and expanded application of novel sampling technologies such as fully traceable automated blood tube dispenser with positive patient identification [140] are expected to improve the quality of specimens and minimise harm.

Recently, several faulty reagents were recalled after patients were adversely affected by erroneous results [141,142]. These episodes underscored the inadequacy of traditional internal quality control (IQC) alone in monitoring the analytical process, as well as the IQC system of the reagent manufacturers. To address this issue at source, external quality assurance (EQA), laboratories and laboratory professional bodies can work closely with manufacturers to improve their quality control process, by advising on quality requirements, and provide access to clinically relevant biological materials to ensure the reagents are assessed adequately prior to release [143]. EQA and networked laboratories with a unique access to a large number of reagent users can also centrally coordinate reagent evaluation to increase the power of error detection, which is difficult to achieve individually. Within individual laboratories, patient-based quality control techniques, such as moving average, will supplement or even supplant IQC as they can detect error better, use existing laboratory data, are suited for tests for which IQC materials are suboptimal or unavailable [141,142,144–146]. In the future, User familiarity with these patient-based quality control techniques and informatics limitations are barriers that need to be overcome.

Meanwhile, clinically useful reference values will be increasingly derived using the indirect approach [147]. At the same time, the laboratory will move beyond simple result reporting to providing post-test probabilities, risk analysis and interpretative comments [148,149], performed by automated expert systems or from specialist input. Moreover, the human-machine interface of laboratory result display will be redesigned to improve ease of information gathering and track unattended clinically significant results. Similarly, patient-facing reports will be reformatted and integrated into a healthcare plan that can help patients understand their condition and management better. Finally, automated closed-loop critical result reporting systems [150], and automated audit (e.g., using the next-generation electronic medical records) will help laboratories monitor the appropriateness clinical follow-up actions for high-risk results.

5. Post-analytical

Appropriate interpretation of test results is fundamental to clinical decision making and this is influenced by well-developed reference intervals and decision limits. This section addresses our predictions related to the “post-analytical” phase testing and includes the increasing role of AI.

5.1. How will the value of laboratory medicine to improve patient outcomes be demonstrated?

Value in healthcare is largely a 21st century concept and has only recently been discussed in laboratory medicine although it is rapidly gaining momentum [151]. This move is being driven by the continuous and significant increases in healthcare costs and increasing concerns that healthcare delivery cannot be financially sustained to meet patient expectations of service or safety. Current healthcare systems are fragmented with healthcare disciplines, even within a single healthcare institution, most often managed and operated independently as separate silos [152]. Current reimbursement for healthcare disciplines largely operates on a fee-for-service, or in the case of laboratory medicine, cost-per-test business model [153].

In laboratory medicine, a cost-per-test business model encourages management to focus on the quality of analytical performance, the volume of activity and the cost of delivering analytical services. In the past, we have seen an era during which quality of laboratory testing has been under pressure with large-scale automation and consolidation of laboratories being emphasized to achieve economies of scale in order to reduce costs. Opportunities for future stepwise reductions in clinical laboratory costs are likely to have diminished [153]. Of course it must be realized that no matter how cheaply a medical test can be performed, if the result does not influence patient care then its cost has been a waste for the whole healthcare system.

In order to contain costs and maintain or improve healthcare standards, physicians, laboratory medicine specialists and healthcare institution administrators need to align in a team-based approach that allows clinicians to understand current costs, institute administrators to understand patient demands and for the team to provide a direction to focus on healthcare outcomes. It is in this context many healthcare disciplines are discussing the aspects of value [154]. Key to any changes to management practice is the ability to measure the effect of such change. The calculation of value for all contributors to healthcare would not only demonstrate the benefits of medical testing in general but also would provide a rational basis by which healthcare is resourced, organized and delivered.

Laboratory medicine delivers medical test results to clinicians and other stakeholders and facilitates decision making for the best health outcome for the individual patient, while minimising risk and at reasonable cost [153]. Consequently, the real value of the clinical laboratory is found in other units, with the benefits appreciated by other stakeholders. Thus the value of laboratory medicine lies outside the laboratory. This will only be fully appreciated through analyses of the impact of medical testing based on the adoption of a value proposition for laboratory medicine. This implies that the appropriate utilisation of medical testing can deliver clinical, operational and/or economic benefits spread across the whole clinical care pathway, addressing the interests of all stakeholders.

The value proposition of any product or service is the link between the provider and the needs of the customer [151]. It describes the utility of the product or service in terms of benefit to the customer. Value in healthcare can be considered in terms of patient outcome. In this context, the process of the healthcare system is the patient's clinical care pathway. Health is achieved when the patient successfully completes the clinical care pathway. Medical testing provides information to enable clinicians and other stakeholders to make better decisions about the care of individual patients. The value of laboratory medicine could be expressed as how the medical test result changes the speed of the patient along the care pathway.

A number of critical steps are required for developing a value proposition for any individual medical test. For initial simplicity we can

limit these to [153]:

1) Who are the stakeholders? The stakeholders include the patient at the centre being supported by carers and the clinical team including laboratory medicine; the provider such as the hospital or clinic; the healthcare purchaser whether it be government or insurers; and healthcare policymakers. The analyses of costs and benefits need to include the impact for each of these stakeholders.
2) What is the unmet clinical need? Identifying the unmet need of the medical test under investigation requires precise and clear definition of the clinical presentation. A successful value proposition calculation cannot be achieved using unclear mixed clinical presentations. For example the value proposition for the timely delivery of troponin results in order to deliver the decision for the safe rule out of acute coronary syndrome or myocardial Infarction was assessed in patients presenting to emergency departments with signs and symptoms of myocardial infarction and without ST elevation on an ECG examination (NSTEMI) to provide an accelerated diagnostic pathway [155].
3) What is the clinical pathway? When mapping the clinical pathway for which the medical test is intended, the target patient group and clinical setting must be clearly defined similar to defining the unmet need. A description of how the medical test result is used with regard to whether the test is for diagnosis, monitoring of disease progression, for prognosis, or if a new test, its position and role in guiding the clinical pathway is required. It may be an additional test, a replacement test or used to triage patients. The clinical management decision influenced by the medical test result needs to be described such as whether it is used to guide a therapeutic or some other intervention.
4) What are the benefits? The benefits of the medical test result to healthcare delivery and the patient need to be well demonstrated through the collection of robust data, including clinical trials of the medical test under evaluation. Laboratory medicine specialists are likely to have to take a lead in organizing multidisciplinary teams to undertake this research. The potential benefits derived from introducing the test including measurement of the true positive and true negative rates within the target patient group as well as clinical, operational and economic outcomes including reduction in time for patients to complete the clinical care pathway. Potential harms arising from the use of the medical test must also be identified including false negatives, false positives, adverse health outcomes, economic outcomes and any data on increasing time for the clinical pathway.

All members of the community require access to cost-effective clinical laboratory practice that improves patient outcomes. Innovation in laboratory technologies has developed analytical instruments shared across the sub-disciplines of laboratory medicine, including increased availability of automation. The optimal use of these platforms requires an adjustment of staff skills to accommodate both the technical and clinical provision of clinical laboratory practice. These are major tasks for laboratory management and our professional societies. Utilisation of optimal laboratory management systems such as six-sigma procedures [156] and ISO15189 standards need to be extended. Utilisation of health economic outcomes research is needed to guide the introduction of new tests including companion diagnostics with the introduction of new pharmaceuticals for the practice of laboratory medicine to be based on a firm foundation of evidence. Increasing the productivity of clinical laboratories requires collaboration between the *in vitro* diagnostic industry, clinical laboratory specialists, clinicians and patient advocate groups. This is the direction for laboratory medicine to cope with the increased pressures and to play a leading role in developing an economically sustainable healthcare system.

5.2. How will artificial intelligence be applied?

AI is the simulation of intelligent behaviour by machines (e.g., robot, computer) and it encompasses deep learning, machine learning, expert systems and neural networks. Many views of the future listed in Table 1 identify AI and related developments (e.g., intelligent apps, intelligent things, machine learning, virtual and augmented reality, conversational systems) as important emerging technologies likely to have a major impact in healthcare and more generally, in our daily lives.

In recent years there has been rapid growth in AI and current applications include for example: speech recognition (conversational systems) (e.g., Apple Siri, Amazon Alexa); face recognition (e.g., Facebook); robotic vacuum cleaners; driverless cars; automated online assistants (chatbots); mobile check deposits; and voice-to-text.

In contrast, AI is not yet as pervasive in healthcare, but already a number of significant uses are available or under development. In 2018, the healthcare consulting firm Accenture estimates that the AI healthcare market will grow from $600 million in 2014 to $6 billion by 2021 [157].

There are several FDA cleared AI-based clinical decision support systems. These include: liver and lung AI oncology software to measure and track lesions and nodules in MRI and CT scans [158]; a system for automated, editable ventricle segmentations based on conventional cardiac MRI images [159]; a system designed to analyze computed tomography (CT) images for stroke indications [160]; a system that creates a 3D model of the coronary arteries and analyzes the impact of blockage from fractional flow reserved computed tomography data [161]; and a system for classification of skin cancer. Recently, the FDA approved an device (IDx-DR) that uses an AI algorithm to detect retinopathy in diabetics by analyzing digital images of the eye uploaded to a cloud server on which the IDx-DR software is installed [162].

Other developments include an AI-powered chatbot service that is replacing a telephone help-line for triage of urgent but non-life-threatening conditions [163], a facial recognition system for diagnosing rare genetic diseases from facial dysmorphic features [164], a screening app for autism [165], and a surveillance system for at-risk hospital patients [166].

Perhaps the best-known example of AI in healthcare is IBM Watson, which has found broad utility in managing hospital care more effectively, accelerating drug discovery, identifying appropriate cancer treatments, and matching patients with clinical trials. One application relevant to the reporting of clinical laboratory results is Watson for Genomics. This AI-based system rapidly analyzes and categorizes genetic alterations related to cancer progression revealed by genetic analysis of tumor tissue and then provides potential therapeutic options. Watson AI has also been exhibited for potential use as a productivity tool for generating patient medical problem lists in medical records [167], as well as monitoring patient diaries for tracking disease severity in patients with depression.

In the clinical laboratory, other AI-based technologies that may have a future role include diagnostic image analysis, digital twins, conversational systems, intelligent things, and augmented reality [168].

A core diagnostic modality in the clinical laboratory is the interpretation of images from body fluids or tissue. In the routine evaluation of peripheral blood and urine, automated instrumentation has been introduced. However, the examination of tissue samples (surgical pathology) has not advanced into an automated process. The emergence of combining digital whole slide imaging and artificial intelligence may lead to AI-centered diagnoses of tissue samples. Early applications include the detection of lymph node metastases [154] in which AI has demonstrated superior diagnostic performance compared to the use of panel of multiple pathologists. Not only was the AI algorithm faster, but had a sensitivity of 97% compared to the human pathologist with a sensitivity of 73.2% [169].

A digital twin is a virtual version of a system where it is possible to test the impact of change prior to implementation of the change in the real world. This AI-based technology is finding application in hospital planning and management [170], and in the future, a digital twin of a clinical laboratory may be an important management tool. A digital twin of a human heart has been achieved [171]; as yet, a digital twin for the entire human body has not been realized, but is an important future

direction. This type of patient-derived digital twin would be updated with real time sensor and other data to maintain the currency of the twin in order to assess current health and predict adverse changes in health, or to help personalize medical treatment.

The future role of conversational systems in the clinical laboratory is difficult to predict. Current medical uses include Alexa-based advice apps (e.g., the Boston Children's Hospital KidsMD skill provides health information for common illnesses and medication dosing [172], and the Mayo Clinic First Aid provides answers to everyday health issues or self-care instructions). Certainly, the hands-free aspect for issuing instructions and requesting information can be advantageous, and as the technology becomes more established, some significant roles in clinical laboratory may emerge by the 2020s.

The Internet of Things (IoT) refers to the wide range of devices (things) that can be connected to the Internet. In the clinical laboratory, one prospect is the connection of all laboratory components to a system from which they can be monitored and controlled. For example, a clinical analyzer can be a member of the IoT, and its connectivity permits remote monitoring for a proactive response to instrument issues. Another example, is an IoT temperature sensor inside a specimen transport container to obtain real-time data about sample conditions (e.g., temperature) during transit and delivery [173].

Another important AI-based technology is augmented reality, a technology that integrates digital information with a user's environment in real time. In healthcare, one application is in phlebotomy to make finding veins easier [174]. In other industries, augmented reality has been used to guide service and maintenance by displaying and overlaying instructions on equipment, an application now being explored by Sysmex to improve automated analyzer uptime [175].

Based on the current pace of development in AI, it seems highly likely that the clinical laboratory of the 2020s will make more use of AI-based technologies such as decision support systems to aid human image-based diagnosis.

5.3. Will there be a change to communication?

The strategies and opportunities of communication, interactions and data exchanges over the world and in healthcare in particular are exploding [176]. With the ubiquity of the internet, the digitalization of care is transforming the patient's relationship to health care professionals as well as the patient's journey through the health care system [177]. A failure to communicate and digitalize might result in a feeling of underperformances or of a bad user experience [177].

Different layers of communication or interaction could be considered for strong evolution as we move towards the 2020s:

5.3.1. Patient-centered communication

The distribution of relevant and validated information to the patient represents an important need for the medical community that aims to improve understanding of test results and improve outcomes. Different examples exist in the field of dedication adherence. Medication adherence remains an expensive and damaging problem for both patients and caregivers and it is reported that patients adhere to only 50% of drugs prescribed for chronic diseases in developed nations [178]. The digitalization of healthcare is clearly paving the way for innovative smartphone solutions and reminders to tackle this challenge. Digital solutions will also allow direct communication with healthcare workforces. For example, in radiology, direct communication between laboratory specialists and patients still needs to be improved [179]. Evolution is expected and could impact the efficiency of laboratory services and add value to the role of the specialist in laboratory medicine. Communication with patients will also improve the user experience.

5.3.2. Patient to patient communication and the building of communities

We are facing consumers and patients that have incorporated social media into their lives and education. Communities of consumers and patients are now built on social media. The content and messages in the “social media ecosystem” that are related to healthcare and laboratory testing need to be clear, accurate, validated and reliable. However, this “social media ecosystem” could offer novel opportunities. Closed groups could provided relevant and updated information on a condition or disease and therefore contribute to prevention and empowerment [29].

Changing health behaviors is critical and the application of social media has been explored in the context of cancer prevention [180]. Results highlighted that leveraging social media appeared as a promising strategy to impact modifiable behavioral risk factors for cancer [30]. Another important element is the ability of closed groups and communities on social media to be perceived as informational and emotional support for people living with chronic diseases. However, to maximize the impact of social media for empowerment, education and prevention the information much be improved and quality controlled.

5.3.3. The improvement of literacy

To activate patients to move from knowledge to change requires health literacy, because it increases health competence and health behavior [181,182]. There are several triggers for this: first, inadequate health literacy is associated with worse health outcomes, higher health care use and expenditure. Second, the population is ageing and the number of chronically ill people is rising. Improving health literacy in this group can offer greater opportunities to take an active part in society, be independent and improve quality of life. Third, most research on health literacy has been conducted outside Europe, hence relatively little is known about the development of health literacy interventions and its effects on outcome measures in European countries [182]. New digital health tools could contribute to better literacy and contribute to cost-effective personalized tools for health promotion and management of chronic diseases, and the current literature provides several examples such as gestational diabetes mellitus [183], cardiovascular diseases [184] and in patients with type 2 diabetes patients [185].

5.3.4. The exchange of health data and cloud computing

Cloud computing is an innovative paradigm that provides users with on-demand access to a shared pool of configurable computing resources such as servers, storage, and applications [186]. Cloud computing provide computational platform leverages metadata that could facilitate a better integration of healthcare data and a better use of healthcare resources and research [187]. Cloud computing appears also as a novel opportunity for genomic data analysis, large-scale reanalysis of publicly available archived data and collaboration [188]. Cloud computing could also trigger new public-private partnership services with the objective of a more efficient and sustainable use of resources [189].

5.3.5. The rise of distributed learning

With the rise of AI and machine learning, the infrastructures and applications of distributed learning are expanding [190]. One of the major hurdles in enabling personalized medicine is obtaining sufficient patient data to feed into predictive models [191]. Distributed learning can allow the combination of data from different hospitals, laboratory and sites and facilitate the “learning” of predictive models while avoiding many of the data sharing barriers [191]. Distributed learning by integrating knowledge databases also offers new perspectives for the training of health professionals [192].

5.4. What will be the educational needs of laboratory professionals?

More than ever, diagnostics play a crucial role in supporting doctors to make clinical decisions. With the rapid emergence of new and varied diagnostic tools, it is essential for healthcare professionals to keep themselves abreast with the latest developments through continuing education. The scientific activity of ongoing professional development is really important and necessary to raise the laboratory standards to

international standards and meet the challenges of the globalized future.

The pace of change and disruptive nature of emerging technologies bring with it training challenges. As an example, the current scientific workforce has had minimal exposure and training in MS and next generation sequencing (NGS), which has led to laboratories sometimes compromising by employing technical experts who have little prior exposure to quality systems. As a result, they can struggle to uphold standards such as ISO15189, which would be second nature to the clinical diagnostic scientist. Predicting requirements for training is challenging and is highlighted by the question posed by Jannetto and colleagues: “Will more technologists be trained or will the MS become simpler as proposed?” [125].

6. Relationships

In the last decades the profession has evolved in an unbelievable manner, providing a wide spectrum of new information mainly in the prognostic and predictive field. We advanced our understanding of the mechanisms of pathologies and opened new opportunities for laboratory medicine. In particular, a menu of molecular tests is now offered by the laboratory and continuous communication between laboratorians and clinicians is needed for correct test usage and interpretation of clinical significance.

6.1. What will be the relationship between laboratory professionals and clinicians?

It is easy to predict that the activity will be managed by a multidisciplinary team. In the near future, “taking care of the patient” will rely on the alliance between the patient, the clinician and the diagnostic professional, first and foremost the laboratory medicine professional. The interaction between clinicians and laboratory medicine professionals to date is fundamentally based on two issues: the appropriateness of test selection and ordering and the interpretation of the laboratory data. Next the interaction between laboratory professionals and clinicians will be throughout the whole diagnostic process.

The clinicians will participate in the creation of diagnostic algorithms made possible by the advent of machine learning and artificial intelligence. They will identify the crucial nodes for patient data progression in the various steps of neural networks, and together with laboratory professionals will decide new discriminating values to inform machine learning systems. If the clinicians need to learn more about the laboratory medicine world, the laboratory professionals have to better understand the clinical way of thinking. Moreover, the advent of omics will change dramatically the way to interpret the data, and indeed a shift from a single number interpretation to the interpretation of a pattern or an image will emerge. On the other hand, thanks to the advent of personalized medicine, absolute reference values will lose their relevance and personalized reference values will be developed to reflect the single patient's clinical history. These changes can be covered only by a close interaction between clinicians and laboratory professionals.

Robotization, automatic data validation and algorithmic reporting will force the presence of another brain to the Lunberg cycle: the “Artificial Intelligence Brain” [193]. Data ready to be used by patients with clinical advice and instructions could be available quickly and the laboratory professional probably will have a relevant role as patient consultants. This change could imply serious dangers if upstream of the trials there will not be a shared programming of the processes by clinicians and laboratory professionals working together. Certainly, the laboratory professionals will not be confined to the high automation laboratory, but will have an increasingly important role as a consultant for clinicians and also for patients, to explain the characteristics of clinical analyses, their potential and their points of weakness in view of an increasingly informed patient.

Clinicians and laboratory professionals will then have to work closely together to inform patients and consumers of the potential of predictive and preventive medicine to stem the fake news that is circulating freely on the web. Finally, in the IoT world and in the mobile Health world, the interaction between laboratory professionals and clinicians will be enriched with new methods of communication and comparison, and above all the narrow boundaries of the single hospital will no longer exist, but any data can be shared and discussed at a global level. The laboratory data will travel more and more and it will be important to ensure their privacy through the development of cyber security focused on health data.

6.2. How will laboratory medicine be financed?

The financing of laboratory medicine is a point of focus for governments, for many institutions and for the private sector in the global context of the explosion of healthcare costs. Financing laboratory medicine in the 2020s will be determined by the evolution of health care financing systems, demographic change and the need of sustainability for health and laboratory systems [194]. The sustainability of long-term care is clearly a prominent policy priority in many Western countries [195].

Three important factors should be considered for the evolution of the financing model:

First, the inclusion of diagnosis-related groups (DRG) in care financing [196]. The main design characteristics of a DRG-based payment system are an exhaustive patient case classification system (i.e., the system of diagnosis-related groupings) and the payment formula, which is based on the base rate multiplied by a relative cost weight specific for each DRG [45]. From different observations in Europe, Scandinavia, United States, Canada, and Australia, the advantages of the DRG payment system are reflected in the increased efficiency and transparency and reduced average length of stay [196]. However, the disadvantage of DRG is the creation of financial incentives towards earlier hospital discharges.

Second, the era of health technology assessment (HTA). HTA is a multi-professional and multidisciplinary evaluation approach designed to assess health technology in broadest sense of the term, from its instruments to the rearrangement of its organizational structures [197]. HTA helps to provide access to valuable innovation under fiscal constraint and re-thinking scientific dialogue and multi-stakeholder engagement, and re-thinking value, affordability, and access [198]. The definition and analysis of an appropriate technology transfer strategy and the correct balance among regulatory, financial and technical determinants are critical for the transformation of a promising technology into a viable technology, and for the decision of implementing liquid biopsy in the monitoring of therapy response in advanced disease, with examples in oncology and liquid biopsies [199].

In the evolution of HTA science, patients need to be involved throughout, and particularly at the early stages [198]. Areas for improvement included the need for a clearer definition of the end user(s), purpose, scope, and focus of HSS, the long-term full health system effects, including all relevant stakeholders as early as possible, and considering smart data systems and international collaboration to improve HSS's efficiency [200]. The principles of HTA are already applied in laboratory medicine and could stimulate increased productivity through technology and process innovations, and costs reduction [197].

Third, the shift to out of pocket payments will continue. A study showed that on average, Mediterranean countries spend less on total healthcare expenditure than the EU average, both as a proportion of GDP, as well as in per capita terms [201]. The 2008/2009 macro-economic and financial crises had a significant impact on the countries under review, and explain the persistent reductions in public health spending as part of the austerity measures put in force. On the flipside, Mediterranean countries have a higher presence of private health providers in total funding, thereby explaining the higher Out-of-Pocket health expenditures in these countries relative to the EU-average. In particular, the higher out-of-pocket expenditure may reflect the tendency for one-to-one relationships with private clinicians and the pursuit of person-centered care.

Other aspects to be taken into account include, benchmarking to monitor the relative performances, and the impact of new policies and incentives on clinical and economical outcomes [202]. The challenge of co-morbidity to improve healthcare and economic sustainability will also have to be addressed as patients with co-morbidity are responsible for more than half of all healthcare utilisation [203].

6.3. What will be the economic opportunities and outcomes?

6.3.1. IVD market overview

The global in vitro diagnostics (IVD) market was valued at $64,479 million in 2017, and is estimated to reach at $93,614 million by 2025, registering a compound annual growth rate (CAGR) of 4.8% from 2018 to 2025. North America is anticipated to be the highest revenue contributor throughout the forecast period (Fig. 6).

The IVD field has evolved with technological advancements in the diagnostic techniques and awareness about healthcare in the emerging market. IVD has a wide range of applications in the diagnosis of various diseases such as infectious diseases, diabetes, oncology/cancer, cardiology diseases, autoimmune diseases, nephrology, and HIV/AIDS. In addition, growth in the number of public and private diagnostic centers and point-of-care testing centers is expected to fuel the in vitro diagnostics market growth (Fig. 7). Market growth will be fueled by an increased awareness about healthcare, a rise in the incidence of chronic and infectious disease, and cost-effective diagnostic solutions. Similarly, increase in the use of automated instruments and point-of-care diagnostic solutions, is increasing government expenditure on healthcare in all the regions (North America, Europe, Asia-Pacific, and LAMEA). More accurate and faster test results are expected to boost the growth of the global IVD market. On the contrary, stringent regulations, policies, and unclear reimbursement rules are anticipated to restrain the market growth (Fig. 8).

Key findings of the IVD market are: 1) North America occupied a nearly one-third share of the global IVD market in 2017; 2) The instruments segment is anticipated to grow with the highest CAGR throughout the forecast period 2018–2025;. 3) The immunodiagnostics segment accounted for around one-third share of the global IVD market in 2017; and 4) Asia-Pacific is anticipated to grow at the highest rate during the analysis period, followed by LAMEA. Asia-Pacific provides lucrative opportunities for the key players operating in the in vitro diagnostics market due to focus of key players in the emerging economies and improvement in the healthcare infrastructure. However, current lack of awareness is estimated to hamper the market growth in Asia-Pacific.

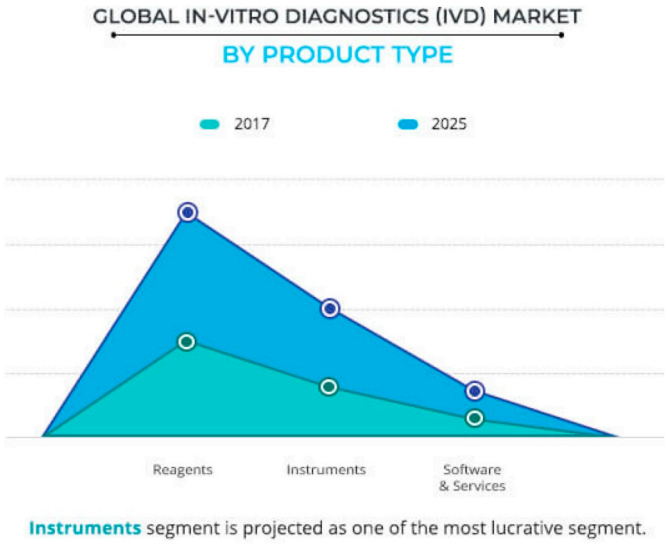

Fig. 6. Comparison of the IVD segment in 2017 and its prediction to 2025. The instrument segment is projected to be one of the most lucrative segments in 2025. Based on product type, instrument segment is expected to grow at a CAGR of 6.1% from 2018 to 2025. The growth of the instrument segment is attributed to the recent advancements in IVD instruments. Further, there is a growth in demand for fully automated instruments in the market, as they simplify the task and provide more accurate and reliable results. Based on product type, the reagents segment accounted the highest market share in 2017 due to the large number of reagents introduced in the market for the diagnosis of medical conditions using IVD process.

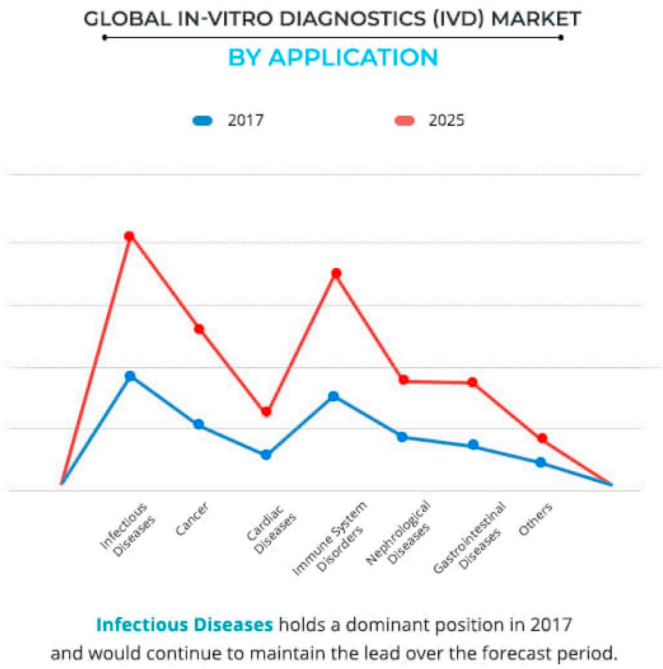

Fig. 7. According to application, the infectious diseases segment captured the highest IVD market share in 2017 due to increased prevalence of infectious diseases and rise in preventive healthcare awareness among the population. Based on techniques, the immunodiagnostics segment contributed the highest market share in 2017 due to the increase in usage of immunodiagnostics as these tests are the oldest and highly used techniques for the diagnosis infectious diseases, oncology detection, HIV/AIDS virus detection, and others. Based on application, the infectious diseases segment contributed the highest market share in 2017 due to increase in prevalence of infectious diseases and rise in awareness of preventive health measures.

7. Conclusions

Many factors and forces may contribute to laboratory medicine of the 2020s. At this juncture, based on our analysis of the “big picture” of healthcare, and selected aspects of laboratory medicine (pre-analytical factors, analytical factors, post-analytical factors, and relationships), several current and future developments emerge as being of likely importance to the future of laboratory medicine. These include health care funding, emerging technologies that expand the scope and utility of testing, new advances in point-of-care and mobile health, and implementation of artificial intelligence in its various forms (e.g., voice-activated assistants, image analysis, augmented reality, digital twins). Other factors that will, of course, contribute to the laboratory medicine of the 2020s, some of which may be unexpected (e.g., pandemics, a drug-resistant bacteria crisis). Whatever the future holds, laboratory medicine has a rich history of adopting new technologies and responding effectively to the changing needs of healthcare.

Fig. 8. The four sections of the Global in vitro diagnostics market. North America is expected to be the leading regional market for IVD through 2025 due to its well-penetrated healthcare system and higher healthcare awareness among the patients, including Obamas Affordable Care Act (ACA), change in technology, and rebounding American Economy. However, Asia-Pacific is expected to grow at the highest CAGR of 5.9% from 2018 to 2025 due to significant increase in the number of well-equipped hospitals with advanced healthcare systems to cater the needs of the large patient population.

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Dedication

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