THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

Integrating Care in Health Systems

The role of technology in transforming care pathways and achieving the Triple Aim

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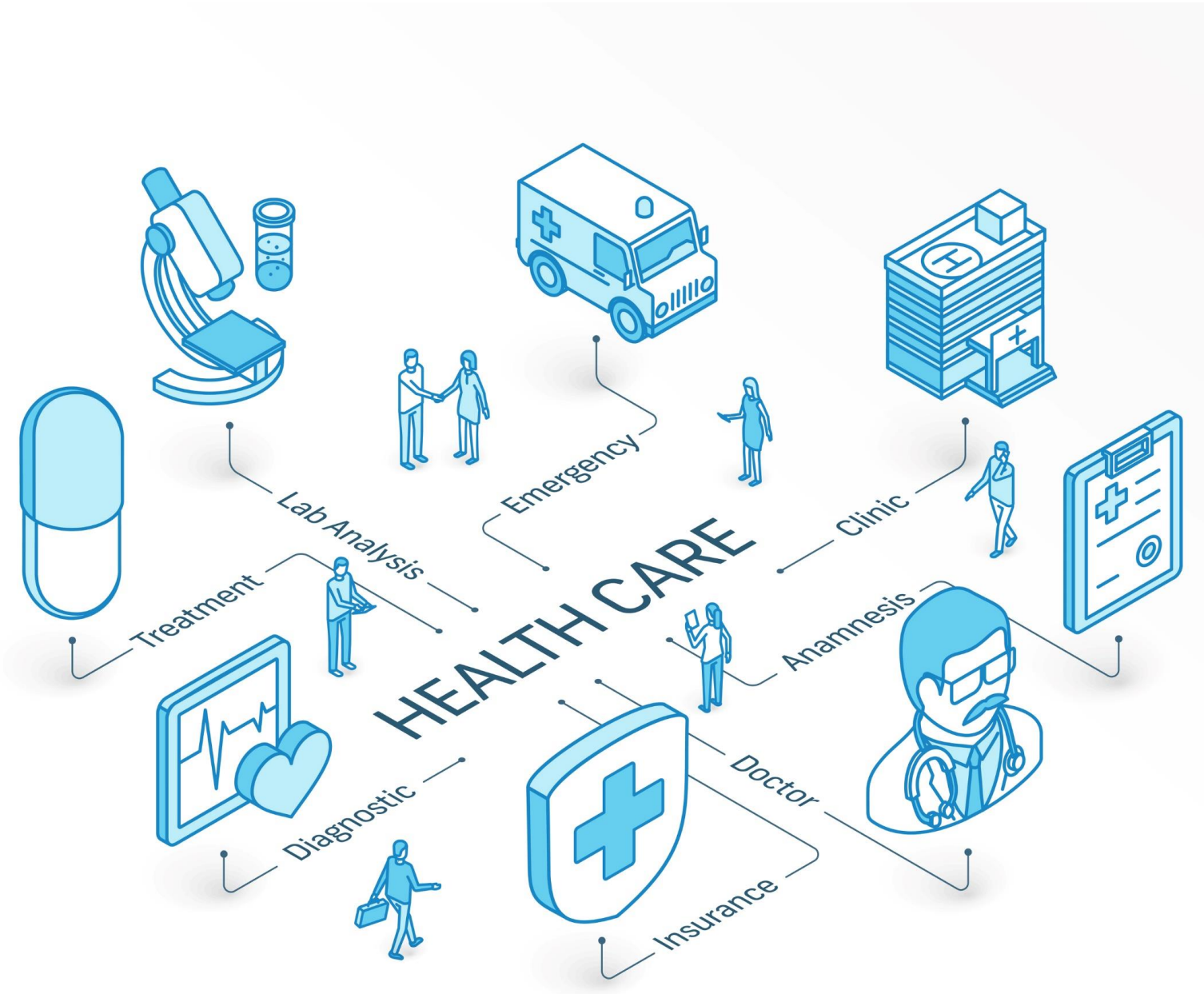

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Executive summary

Health systems face enormous challenges, many of which have been compounded by the coronavirus pandemic. To address the complexity that exists at all levels of these systems, it is increasingly important for multidisciplinary stakeholders to coordinate their efforts, be they in the public or private sectors. Increasingly, there is a trend towards closer collaboration between health system stewards, including policy makers, governments and global institutions, and health industry professionals. The potential for the latter to provide value-based solutions to the former is high if efforts are coordinated.

Integrated care is a central theme in contemporary health policy and industry collaboration is crucial for accelerating progress towards it. Integration should not be viewed as the destination, rather, it is an ongoing journey that health systems take to align services in a manner that is person- or patient-centric. A multitude of technologies exist to support integrated care efforts, with potential to lower per patient costs, improve patient experience, and raise population health. Reconfiguring and optimising care pathways is the central feature of integrated care. When thought of mechanistically, integrated care involves identifying current processes of care, including the labour and technology currently deployed, then redesigning these processes with superior technologies and organisational innovation. Technologies that foster connections between care settings, reduce delays in care, optimise the length of stay during episodes of care, and ensure the right care is given at the right place and at the right time, are needed to support these efforts. In turn, innovations that demonstrate short, medium, and long-term benefits to patients, payers, and providers are likely to be rewarded.

Waste is a central target for enhancing health system efficiency and, for this reason, the topic has received lots of attention in recent years. Research in this area is particularly necessary in the context of rising demand for health services, rising expenditure, and the need for cost containment. Wasteful practice has been categorised into six areas that include: failure of care delivery, failure of care coordination, overtreatment or low-value care, pricing failure, fraud and abuse, and administrative complexity[1]. In the United States (US), wasteful practices are estimated to account for 25 percent of total health expenditure (Shrank et al. 2019)[2]. This problem is not isolated to the US; in 2017, the Organisation for Economic Cooperation and Development (OECD) estimated that up to a fifth of all health care spending could be redirected from wasteful activities, providing fiscal space for health systems to meet increasing demand without reducing coverage and overall performance[3]. The route to eliminating this waste involves incremental changes, based on strong data, according to Chalkidou and Appleby (2017)[4]. Evidence-based health technologies that provide value by reducing waste or improving efficiencies are central to the evolution of health systems.

The coronavirus pandemic appears to have exacerbated the problems that health systems face. Health workers' health and wellbeing has been severely tested (Hall et al. 2021; Mehta et al. 2021)[5,6] and the long-term effects on capacity and resilience are yet to be evaluated. It is reasonable to expect significant challenges in repairing or maintaining the wellbeing, motivation, and capacity of health workers as the world moves beyond the immediate threat posed by the coronavirus. Health equity concerns have also been exacerbated, fuelling further debate about the role of wider social determinants of health in the production of healthier populations[7].

Evidence suggests that digital health technologies will have an even larger role in health reforms and integrated care solutions in the years to come, although the extent to which this occurs, and the types of technologies that are adopted will depend on the evidence that emerges on their effectiveness and value in different settings[8]. Alongside these technologies, medical devices and drugs that demonstrate real-world effects not only in outcome domains, such as reduced readmission rates and length of stay, but also in process measures, such as improved patient experience, will cater to contemporary policy requirements and payer definitions of value that are enshrined in health technology assessment methods.

This report outlines the central themes governing efforts towards integrating care in Europe, considering the effects of the coronavirus pandemic. The drivers for integrated care are introduced, discussing how demographic changes and disease trends have shaped health system reforms. Simultaneously, care practices

evolve with technology, rapidly changing the interactions between populations and their providers. The report touches on growing innovation in biopharmaceuticals and minimally invasive technology which are revolutionizing treatment standards for common diseases. In addition, the report further discusses the role of digitisation with regards to patient experience, artificial intelligence, and precision medicine which are modernizing models of care. Other technologies promote better patient experience and satisfaction, which are linked with improved health outcomes, fewer adverse events, and less inefficiency. For instance, health care information exchanges allow patients to be involved in and knowledgeable about their medical care, virtual reality is allowing patients to better understand planned procedures, and user feedback systems allow care processes to adapt and improve based on patient experience.

Increasing availability of health data explains the most profound changes in medical practice. As such, the success of technologies depends on demonstrable, data-driven improvements in the coordination of care. The health workforce is under increasing scrutiny in the context of integrated care because new skill mixes are needed to achieve alignment, whilst managing the after-effects of the pandemic on the workforce. Most signals indicate that primary care will lead clinical services; however, evolution in payment models suggests that several stakeholders will be engaged in the delivery of integrated care services and much of their involvement will be driven by the incentives created by bundled and blended payments. In this context, medical technologies are more likely to be adopted if they show evidence-based benefits to many health system stakeholders.

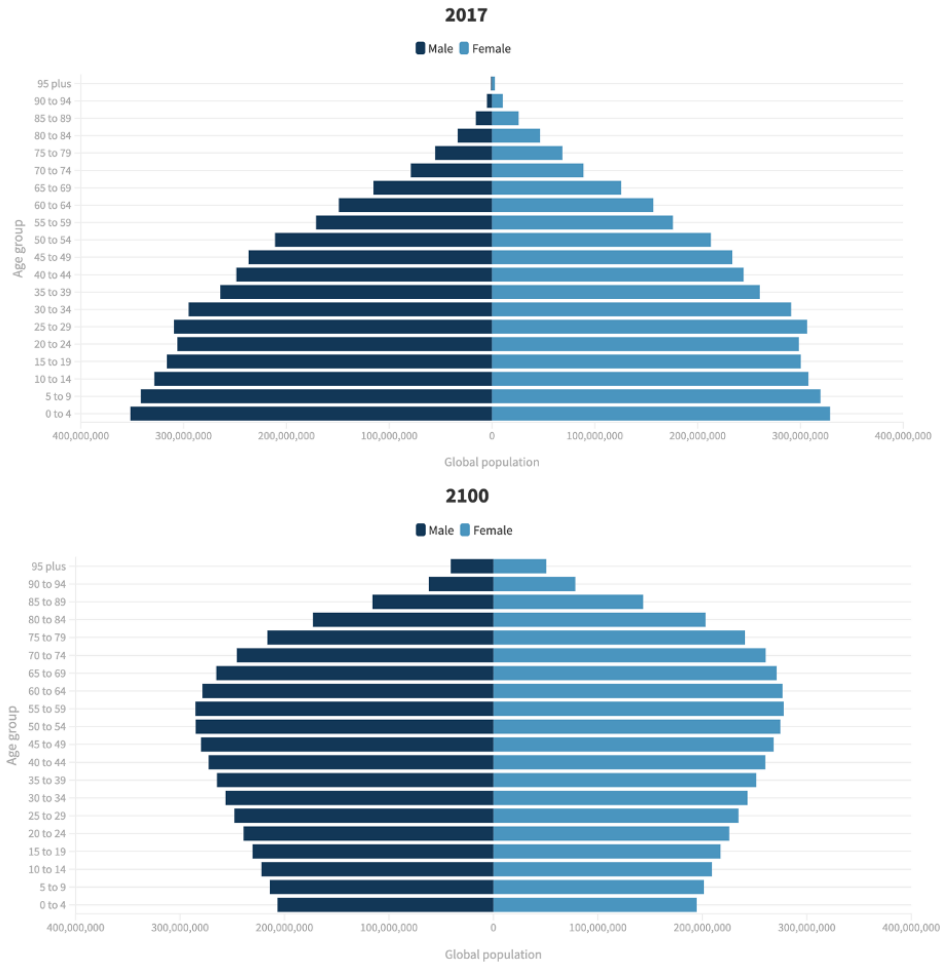
As the market evolves across these dimensions so too have the regulatory conditions. The report points to the role of data in the changing regulatory environment, with recommendations about the type of indicators that firms need to use to convince payers or providers that their products can support their push for integrated care, thereby reducing health system waste and inefficiency. Minimally invasive procedures are used as an example of technology and organisational innovation in health care that align with integrated care efforts and the end goal(s) these serve.

Introduction

The global health market is rapidly changing and becoming increasingly complex. As medical science, public health and health systems evolve, the diseases that dominated human life such as neonatal disorders, diarrheal illness, tuberculosis, malaria, measles, and malnutrition are being replaced by a growing prevalence of non-communicable, chronic diseases including ischemic heart disease, stroke, chronic obstructive pulmonary disease, dementia, and diabetes[9]. High-income countries experienced this evolution decades ago, but this shift is now occurring in low- and middle-income countries, many of which are projected to become the most populous centres on the globe by the year 2100[10].

Consequently, global life expectancy has increased from 67 to 74 years between 2000 to 2019[11]. With an aging demographic there is an associated increase in multi-morbidity whereby people have numerous chronic illnesses that each have their own multifaceted treatment pathways[12]. Furthermore, multi-morbidity is expanding to younger age demographics as new conditions are identified, public health risk factors change, and disease screening programs improve. In addition to these pre-existing changes, globalisation is posing other unique challenges, such as the coronavirus pandemic and antimicrobial resistance, which add new layers of complexity.

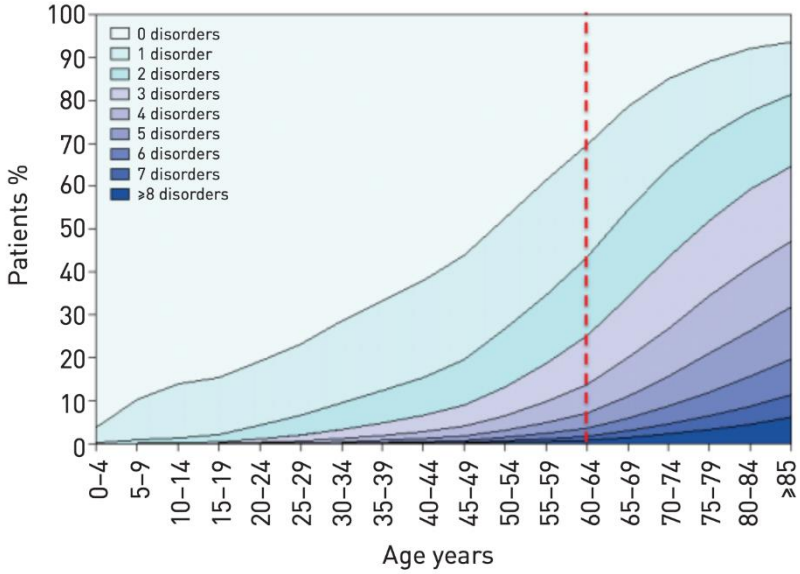
Figure 1: Expected demographic change by 2100, a challenge for health systems.



The graphics in Figure 1 show the expectation for ageing populations and the gradual inversion of the population pyramid. Ageing populations are likely to place increasing demands on health systems, commensurate with the need to manage more conditions, for longer[13].

In high-income countries, many age-related, non-communicable diseases remain the primary cause for national mortality, as they did 20 years ago, but their prevalence continues to increase due to increasing comorbidity[12]. Now, elderly patients may have ischemic heart disease, prior strokes, diabetes, and chronic kidney disease. In addition, chronic illnesses such as musculoskeletal disorders, drug use disorders, headaches, osteoarthritis, and falls contribute an increasing proportion of morbidity (figure 2).

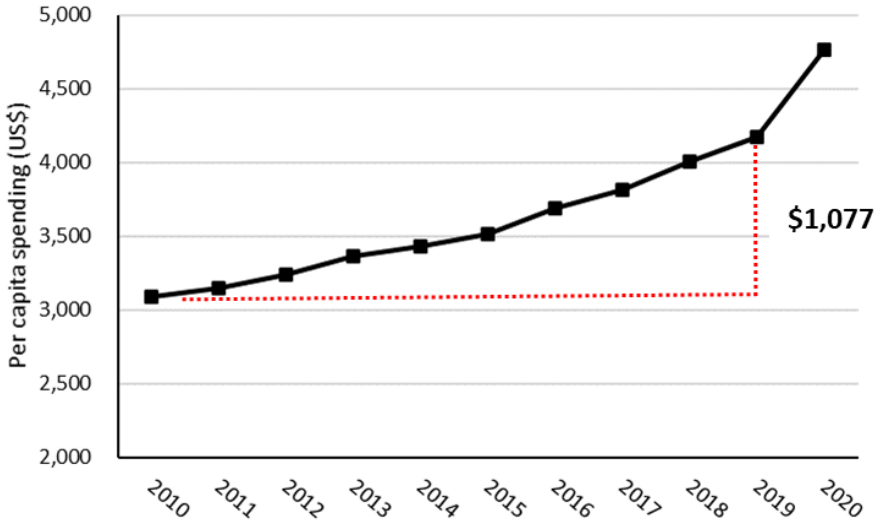
Figure 2: The proportion of patients living with multiple disorders, by age group.



The proportion of patients living with multiple disorders, by age group. Ageing is associated with an increase in the number of disorder that patients are likely to live with. This means that ageing populations are increasing demands on health systems as more intensive care is provided for multi-morbid patients, adding complexity to current treatment paradigms. Technology solutions that help to coordinate the multidisciplinary needs of patients and, separately and in addition, help to exercise preventive or curative interventions, are needed[12].

This scenario has created substantial demand-side pressure on health services, leading to increasing expenditure in high-income settings. Several factors explain expenditure growth, including demographic changes, financing mechanisms, household income, health care prices, and administration costs. However, technology is consistently found to be the single largest driver of expenditure growth in health systems[14], which – among other factors – is why value-based health technologies are increasingly important around the World. After years of austerity since 2008, the COVID-19 pandemic has spurred growth in health expenditure in OECD countries (figure 3).

Figure 3: Mean per capita spending growth in European OECD countries, expressed in US dollars, adjusted to current prices using data expressed in purchasing power parities.



Per capita expenditure growth from 2010 to 2019 (shown by the red line) was US$1,077. Missing data for 2020: Belgium, Czech Republic, Denmark, Finland, France, Greece, Hungary, Latvia, Luxembourg, Slovak Republic, Spain, Switzerland, and Turkey. Source: OECD Health Statistics (2021).

Technology is a central piece to the evolution of our global health system, and it is changing how we understand and treat illnesses as well as organize and deliver health care. With the explosion of medical knowledge along with technological innovation and capacity it has been challenging to learn how best to integrate and adapt all this high-tech potential within the existing health care system. Each adaptation requires increasing specialization and human understanding thus requiring more individuals and unique steps in the delivery of health care. So, while technology is a critical solution to advancing our global health system, it is also the source of our medical system's growing complexities and can make it difficult to pinpoint where there is room for value creation.

Therefore, it is helpful to understand how the latest technology and innovative ideas are currently being applied at the various levels of the health system to identify where there is space for value creation and efficiency. This report will explore how the latest technologies, with a focus on cardiovascular care, are creating value and efficiencies at three key tiers of the health system: (1) health system policy and organization (the macro level), (2) health care delivery and practice (at the meso level), and (3) medical knowledge and product development (usually deployed at the micro or clinical level). Understanding the current direction of technological advancement may then provide a starting point for identifying innovative project ideas that solve health system gaps.

Rationale

This report aims to synthesise the latest evidence on integrated care, drawing on the various dimensions of policy making and research informing this transition in the delivery of care. The focus of the report is Europe, specifically, France, the UK, Germany, Spain, and Italy; however, North American resources are also referenced.

The report is designed to give a succinct summary of a vast literature that is relevant to this topic by characterising disease trends, socioeconomic trends, developments in the practice of care, changing workforce skills, and the evolving regulatory environment. These issues are principally viewed through the prism of cardiovascular disease, for which efforts to integrate care are most pressing given the burden this represents and that care management in this space tends to transcend several health provider settings and technology types.

1. Future directions for health policy and system organization

1.1 Global level trends

International public-private partnerships are a cornerstone for tackling emerging global health problems such as the coronavirus pandemic. These health problems do not abide by national borders, affecting all people, and therefore require a unified international approach. The intricacy and breadth of these problems necessitate bringing together expertise from different levels including governmental agencies, non-governmental organizations, large pharmaceutical and medical device firms, small-and-medium sized enterprises, and academic centres.

The coronavirus pandemic appears to have exacerbated the problems that health systems face, increasing the need for international cooperation. In particular, the pandemic has shone light on the health status of minority ethnic groups in society and the comorbidities that have at least partly driven higher mortality rates from coronavirus infection[15]. Elsewhere, technology that is not limited to mRNA vaccines has undoubtedly produced solutions to the pandemic. For instance, the expansion of telehealth services and digital solutions was largely celebrated early on[16,17]. Evidence from oncology services suggests that access to care was improved with telecare, reducing the median time between patient referral and an initial visit to an oncology team by 1.5 days[18]. This example shows how technology can shape global health systems, improving their efficiency and therefore changing the status quo of health care when the need exists.

A valuable example of how public-private partnerships are being utilized is in the field of antibiotic research and development (R&D). Antimicrobial drugs have been a critical component to reducing morbidity and mortality from communicable infectious diseases, which once dominated the global burden of disease. However, growing antimicrobial resistance is mitigating the effectiveness of available antimicrobial drugs. If antimicrobial resistance continues to grow, current modelling suggests that by 2050 more people will die from drug resistant infections than from cancer[19]. Despite the need for new antimicrobials, the R&D pipeline for them is sparse due to longstanding economic disincentives, scientific challenges, and regulatory barriers. To overcome these barriers which were prohibitive to individual firms, several large public-private partnerships have been established that share human and scientific resources, investment cost, as well as financial risk. Examples of public-private partnerships include the international Combatting Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the EU's New Drugs for Bad Bugs (ND4BB) program, and the US's Biomedical Advanced Research and Development Authority (BARDA). CARB-X has invested US$361M in 92 different projects since it was established in 2016, ND4BB has a €700M fund split across seven core projects, and BARDA has an annual fund of approximately US$180M[19]. These programs have made major strides in adding novel antibiotics to the development pipeline.

This example reiterates that innovative, value-added solutions may require public-private partnerships for implementation. At an individual firm level, development of antibiotics is not economically feasible, but given that antibiotics fill a major health care gap there is room for compromise and collaboration in reaching a solution that is financially worthwhile for the private firm and sensible from a governmental and health system perspective. As health system solutions become more niche and complex, there may be a need for more public-private partnerships to make innovative projects financially viable.

Similar efforts are taking place in the drive towards integrated care, whereby diverse stakeholders are increasingly finding incentives and other reasons to collaborate. Integrated care is a central part of health reforms around the World and the global trend is towards increasing efforts to achieve integration. The topic has received considerable attention from academics aiming to isolate the effects of integrated care and to identify optimal models, encompassing social and technical systems, which serve the needs of relevant populations. The definition of integrated care has been flexible in recent years, but it tends to encapsulate the notion of coordinated care that is seamless, continuous, and fosters patient satisfaction[20]. The WHO defines integrated care as:

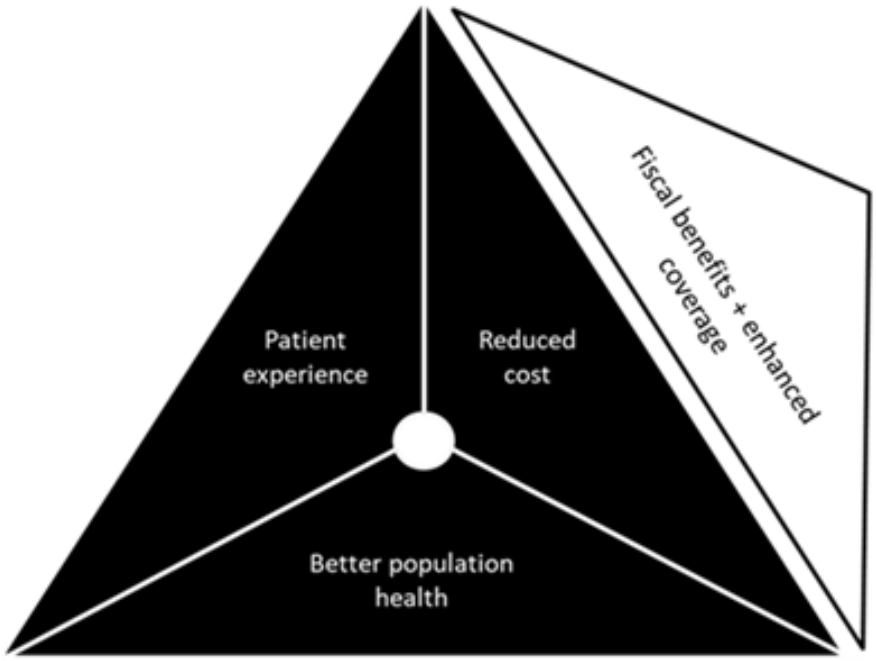
"An *approach to strengthen people-centred health systems through the promotion of the comprehensive delivery of quality services across the life-course, designed according to the multidimensional needs of the population and the individual and delivered by a coordinated multidisciplinary team of providers working across settings and levels of care. Care should be effectively managed to ensure optimal outcomes and the appropriate use of resources based on the best available evidence, with feedback loops to continuously improve performance and to tackle upstream causes of ill health and to promote well-being through intersectoral and multisectoral actions.*" [21]

Integrated care should be viewed as an umbrella policy that aims to deliver people or patient-centric care that is highly coordinated and multidisciplinary. As such, integrated care can be achieved by reorganising existing systems at the macro, meso, and micro levels using policies or regulations, new processes of care delivery using the same or similar inputs, and by deploying novel products / technologies.

The pursuit and achievement of integrated care is a core strategy for the achievement of the Triple Aim, which encompasses improving population health, enhancing patients' experiences of care, and reducing costs per capita [22]. The need for integrated care is growing for the reasons mentioned above, however realisations about the overuse and misuse of resources in health care are also driving these efforts.

These trends necessitate the production of more cohesive and better coordinated care delivery across all levels of health *and* social care. Moving forward, the exact configuration of integrated care systems is likely to evolve across several dimensions (e.g., financing, care pathways, technology, data sharing). Technologies that can reduce waste and/or improve efficiencies in the management of increasingly complex patient groups and enhance coordination will contribute directly to the Triple Aim.

Figure 4: The Triple Aim in health systems: a central role for technology



Integration is an overarching approach to achieving better health outcomes and better patient experience at a lower cost (the Triple Aim). Health equity is another essential objective for health systems, particularly in the post-pandemic environment. Integrated care is therefore the sum of three main intervention categories in health systems and, despite recent evidence, the expectation is that integration will lead to achievement of the Triple Aim. Technologies and products should demonstrate their contribution towards the Triple Aim using short-term, medium, and long-term outcomes; where relevant, products should demonstrate the ability to improve the coordination of care directly or indirectly. For example, more cost-effective curative products that simplify care pathways and reduce the burden of coordinating care between settings provides benefit to integrating care systems and the Triple Aim. This is likely to give a competitive advantage beyond a product's therapeutic and economic credentials. Transcatheter Aortic Value Implantation (TAVI) is one such procedure that can simplify care pathways by bypassing ICU admission, reducing hospital length of stay, reducing the need for rehabilitation, and improving outcomes, experience, and efficiency.

To this (evolving) end, there are guiding principles that health systems follow. Quality is a central concept that guides policy decisions and is rooted in Donabedian's "Seven Pillars"[23]. Kruk *et al*. stated that high-quality care "involves thorough assessment, detection of asymptomatic and co-existing conditions, accurate diagnosis, appropriate and timely treatment, referral when needed for hospital care and surgery, and the ability to follow the patient and adjust the treatment course as needed." To achieve this, health systems must invest in short, medium, and long-term strategies that facilitate the production of high-quality care, thereby facilitating the production of health, fair financing, efficiency, and responsiveness to changing needs[24].

The integration of various components of the system relies on more than guiding principles, however. For instance, quality data are needed to inform stakeholders of gaps in health needs and closely aligned to this, patient experience. Therein, gaps in service needs and resources can be addressed. This relates to identifying the medical equipment required (capital) and workforce volume and skill-mix (labour) that must be purchased using value-based methods. National research programs are funding this research, such as the Department of Health and Social Care[25] and NIHR[26] in the UK. As such, stakeholders working towards integrated care must be aware of the evolving regulatory environment in which decisions are made, including methods for conducting Health Technology Assessment (HTA) and economic evaluation of alternative medical devices, drugs, and providers.

In summary, there are various lenses through which attempts to strengthen health systems are made. This creates complexity for stakeholders trying to pinpoint their short, medium, and long-term objectives. Currently, there are two major frameworks that describe the objectives of health systems, those given by the WHO's "building blocks"[27] and those more typically referenced for developed health systems as captured by the Triple Aim[22]. Integrated care and quality improvement are two major Global approaches to achieving these aims. Integrated care through system and organisational restructuring or redesign is itself a complex endeavour needing evidence-based solutions. Fortunately, the evidence base is expanding, providing insight into what to do and what not to do to achieve integration. For example, in the last five years, an average of 181 peer-reviewed articles on integrated care were published per year (PubMed, title search), whilst for the five years preceding this period i.e., 2010 to 2014, this number was 81 per year. This shows that interest in integrated care is growing and the body of evidence available to inform private and public stakeholders is substantial.

1.2 National or system level trends

1.2.1 Structural reforms

NHS England and other UK health systems have implemented several structural reforms aimed at achieving integration[28]. Structural reform involves the introduction of local partnerships and collaborations that are, in effect, seeds for systemic change. Therefore, Strategic Transformation Partnerships (STPs) were organised at the local level with government and NHS funding that was made available on a competitive basis; this involved awarding funds to "vanguard" sites who developed innovative STP proposals for consideration by NHS England. These developments provided a signal to private firms that integration was being funded

centrally and that an opportunity to collaboration with the public sector had emerged. Similar signals should be identified in other European jurisdictions so that products that could potentially contribute to local or regional integration goals are introduced to providers and payers in a timely manner and with compelling value propositions.

The effects of these reforms in England remain difficult to isolate, although some positive results seem to converge, such as those by Morciano *et al*. (2021) and Keeble *et al*. (2019)[25]. Keeble *et al*. reported an attenuation in the rate of emergency admissions growth for the STP pioneers of integrated care in England (a 1.93% rate of admission versus 4.84% for non-STPs). Both articles provided a similar analysis using the same dataset, albeit for different time periods; Keeble *et al*. used 2010 to 2013 as their baseline period with a follow up to 2016. Morciano *et al*. followed cohorts up to 2018 and reported a significant *net* reduction in emergency admissions of 3.1% point at the third year of integrated care implementation versus non-integrating regions.

On the other hand, a very recent article by Stokes *et al*. (2021), provided negative findings about the effects of integrating care in England, using indicators for patient experience, cost, and health improvement (those that mirror the Triple Aim). When comparing risk-adjusted outcomes for two vanguard STP sites with the rest of England for three years, the cost per capita of secondary care increased, and population health status and patient experience measures did not differ to non-integrating regions[29]. The findings could suggest, once more, that the effects of integrated care may take years to mature into positive findings, assuming these are likely. These findings are highly generalised, representing averaged data rather than specific outcomes from the various components that are integrating care, such as specific technologies. The extent to which products or processes have reduced costs, enhanced patient experience and improved outcomes in this area of policy is unclear, which suggests that there is an opportunity for impact at this level to be articulated as evidence matures.

A central consideration for the English vanguard proposals was the implementation of electronic medical records, such that NHS Trusts were expected to go “paperless”. The effectiveness of these efforts has been extensively investigated and documented by health service researchers. For instance, Cresswell *et al*. 2017[30] investigated NHS providers’ experiences with integrated digital systems as part of this effort and found a different set of risks associated with the use of multimodal versus standalone ePrescribing systems. Standalone systems are described as software platforms that are designed for a single purpose but can communicate with existing electronic records. In this context, these systems were found to offer more opportunities for providers to innovate as they offer greater flexibility, which was seen as advantageous by informatics experts who were participants in this research, citing lower risks to patient safety. This topical research shows the competing issues that providers must navigate when integrating digital systems, which is a prerequisite for effective integrated care. It also points to the design requirements that health technology firms must anticipate when proposing products that can support integrated care efforts. The need for flexibility and adaptability in the development of integrated care systems was also evidenced by Looman *et al*. (2021)[31], who identified drivers of successful implementation of integrated care in European countries. The authors found that successful systems tend to adopt an incremental growth model rather than disruptive innovation(s) and they find a balance between flexibility and formal structures of integration. This lends further insight into how technologies cannot be overly disruptive to current models of care in the short-term, largely because disruption can worsen immediate demand-side pressures. Therefore, close collaboration and sympathetic deployment of value-based technologies is likely to lead to longer-term term success for both private and public stakeholders.

Having followed years of trials and tribulations with the deployment of digital infrastructure, the NHS in England is now able to pivot to exploit the new capital and to harmonise patient pathways across health and social care. Investment in the NHS during the coronavirus pandemic is likely to have consolidated this infrastructure, although the destination of the unprecedented spending on the NHS in 2020 / 21 is yet to be fully accounted for in the wider context of health reform. A similar scenario can be expected for other European health systems[32].

The emergence of health systems from the coronavirus pandemic has changed the conditions in which health services are being provided. Digital products and data sharing expanded during the pandemic, demonstrating higher levels of care coordination than before the crisis; this is integration. More importantly, backlogs or waiting lists for services have increased significantly. For instance, Mohammed et al. found that over 45,000 cardiac procedures were not performed in England due to the COVID-19 pandemic. Furthermore, many common cardiac procedures, such as coronary catheterization, percutaneous ablation, septal defect repairs, and care device implantations, performed during the COVID-era experience higher 30-day mortality rates compared to the preceding pre-pandemic years[33]. The reduced number of procedures and higher mortality may be due to a combination of procedural backlogs due to reduced service capacity, but also patients delaying or forgoing their presentation to hospital out of pandemic-related fear. Blecker et al. discovered that there was a significant decrease in the number of non-COVID hospitalizations during peak of the COVID pandemic in early 2020 for common medical ailments such as myocardial infarction, heart failure, septicaemia, stroke, COPD, and abdominal infections[34]. Backlogs and health care avoidance exemplify a reduction in health care access that perpetuates health inequities and further inefficiency.

We can characterise these inefficiencies in a Welfarist sense, which views untreated diseases or ailments as a welfare loss to society, which we can estimate in terms of an accrual of Disability-Adjusted Life Years (DALYs) or a loss of Quality-Adjusted Life Years (QALYs). The sooner backlogs can be reduced to pre-pandemic levels (and beyond), the more Welfare can be attained. *Time* is of the essence because the longer that the population lives with a condition, the larger the proportion of population life years are spent in disability. In another dimension, the better an intervention can improve the *state* of disease (or health) as compared to alternative interventions determines the aggregate gains in Welfare. As an example, minimally invasive technologies have demonstrated benefits in terms of reduced time spent with a condition and improvements in health status. Now, more than ever, whilst exploiting improvements in care coordination, these types of technologies are needed to reduce backlogs in care caused by pandemic-related care avoidance, waiting time growth, and delays caused by patients' coronavirus status[35].

1.2.2 Payment reforms

Bundled payments are considered an essential approach for incentivising providers to align services. Whereas initial lump-sums are necessary to develop infrastructure that can facilitate service alignment, in the long-term, these systems must also be available to monitor care costs to multiple stakeholders; this is a prerequisite for setting prices and reimbursement that incentivises service alignment and improvements in the quality of patient care. In a recent literature review by Feldhaus and Mathauer (2018)[36], which identified 37 eligible articles, 74% of these were from the US and reported that bundled payment led to improved efficiency and cost savings, demonstrated by reductions of between 9.4 and 13.4 percent in emergency department visits, admissions, and CT scans. In a more recent analysis performed by the Commonwealth Fund[37], in high-income settings there are currently 23 bundled payment initiatives, 15 of which are based in the US. Most initiatives in the US are condition-specific, including either maternity care, orthopaedics, oncology, cardiovascular care, respiratory care, and some mental health disorders such as attention deficit/hyperactivity disorder. Elsewhere, Taiwan, Denmark, the Netherlands, New Zealand, Portugal, Sweden, and England have bundled payment schemes that are mostly condition-specific, except in England, where a long-term care bundled payment for health and social care was introduced in 2012 for multiple conditions [37].

More specifically, in the Netherlands, a payment reform was introduced into primary care to improve patient-centredness by incentivising provider behaviour. General practitioners are paid a global amount based on the population (mix and size) they serve and other contractual parameters, but there is a second component to their payment which is shaped by quality indicators. This is called the "shared savings program" in which GP networks can agree to take responsibility for all patient expenditures (across the full continuum of care – including services by out-of-network providers). If the GP outperforms their benchmark group in these indicators (and their spending) they shall receive a share of the savings achieved, contingent on the performance of care activities which are measured using a scoring system. Quality indicators informing this score are defined by chronic conditions, including COPD, diabetes, patient satisfaction, guideline-indicated

prescription drug use and measurement is based on the percentage of patients who use care. Patient satisfaction scores are measured on a 10-point scale with patients responding to statements asking them to rate, for example, "the ease with which you could make an appointment"[38]. Initial evidence suggests that this scheme has reduced per patient expenditure, with no impact on patient satisfaction and unclear effects on the achievement of care activities, such as prescription drug use[38].

The ideas behind this payment scheme are not new. The payment and contract design, including the quality indicators used to incentivise care and payment via savings is novel. The unforeseen consequences of this payment method are yet to be seen, but experience elsewhere suggests that these need to be monitored[39]; for instance, the impact of the scheme on vulnerable patient groups whose care is not directly incentivised should be evaluated. This is a consequence of ongoing development of bundled payment schemes in the Netherlands despite early evidence suggesting cost growth to insurers of between 13 and 52 percent in diabetes care, chronic obstructive pulmonary disease, and vascular risk management between 2008 and 2015. Notably, cost increases from the use of bundled payments were found to be higher for those with multi-morbidity [40]. In another dimension of the Triple Aim, recent evidence from Sweden finds that bundled payments also had no statistically significant effect on a range of patient reported outcome measures one and six years after hip replacement surgery (an effective study period of 2008 to 2018); however, for some of the measures there were positive, albeit insignificant effects on patient reported outcome measures. [41] These types of reform are instrumental to driving health systems towards integrated care, but the precise mix of incentives required to achieve pre-determined objectives depends strongly on context. Multi-morbid patients seem to be a particular challenge in the design of bundled payment schemes, albeit not the only one[42]. This area of national payment policy is likely to continue to evolve towards more sophisticated and effective models of payment. Products that can help contain costs in the conditions and settings for which bundled payments are designed to improve care and likely to be increasingly interesting to providers.

The potential of mixed payment models as a means of achieving integrated care is echoed in the recent article by Looman *et al*. (2021)[31]. Of the drivers of successful implementation of integrated care, under the financing domain, long-term funding with a mix of innovative payment methods was found to be a driver of successful role out of bundled payments. Payment methods are therefore an essential means of defragmenting health and social care provision and long-term funding commitments by payers to these models of payment are a signal of both intent and likely success. Taken alongside the evidence on the effects of integrated care, long-term funding that is not compromised by annual budget cycles appears to be essential to create incremental transformation from uncoordinated, fragmented systems into integrated care systems. Once implemented, the effects on long-term outcomes may then be realised, but this evidence is yet to emerge strongly.

1.2.3 Health Technology Assessment

According to the newest definition by O'Rourke et al.,

> "*HTA is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system*[43]*"*

Clinical and economic evaluations are major inputs to an HTA, but these methods do not capture wider normative aspects of value that are formalised using HTA. For instance, HTA might not include implementation evidence that can reduce disruption in the deployment of a new product, although promising examples have recently emerged as relates to economic evaluation. Dopp et al. provided three case studies in which the financial barriers to implementing evidence-based practices were overcome using implementation research; one of these involved scaling [the Centers for Medicare & Medicaid Services'] Oncology Care Model– a payment reform in oncology care – using multi-stakeholder input to increase uptake of the model, which is an evidence-based approach to reducing cost and improving quality[44].

Across Europe, regulatory efforts in recent years can be characterised as activities intended to harmonise data and methods, to increase the routine use of HTA in the purchasing of products and services. A core component

of HTA is economic evaluation, which involves modelling the expected costs and benefits or utilities associated with alternative strategies for achieving the same health outcome. However, the methods are much more expansive and include evidence synthesis, quality appraisal, comparative effectiveness research, and budget impact analysis, all of which are weaved together to assess a decision to adopt and / or reimburse technology. The organisation of care pathways, including the organisation of staff or labour, and policies for integrating patient experience into value-based decision making are major challenges for European institutions. To navigate the various challenges associated with introducing new products into care pathways, the current configuration of these pathways needs to be visualised. A detailed understanding of the patient journey and their experience of care is developed using process mapping, which is essential for the effective implementation of promising products. Process mapping coincides with the suite of methods encapsulated by HTA and there is increasing evidence that this is essential in quality improvement and, by extension, integrated care[45].

From a regulatory perspective, there is increasing interest in HTA. The harmonization of methodological and legal frameworks in Europe signals new opportunities for innovative medicines and devices to be evaluated and considered for reimbursement across markets. T*he "Regulation on Health Technology Assessment" is a recent output of the European Pharmaceutical Strategy, which intends to improve patient access to innovative technologies by consolidating HTA efforts under common European funding and using harmonised methods. This should lead to less duplication of analytical effort and faster access to beneficial care.* To achieve this, EUnetHTA's Joint Action 3 consultation is a concrete example of regulatory developments coinciding with methodological ones to produce new standards and clarity around the use of HTA in Europe[46].

In HTA, value is assessed across various dimensions that would not be considered traditional to an economic evaluation, but increasingly fold into the methods that encompass HTA. For instance, process evaluations have a growing role in identifying the current pathways of care through which multi-morbid patients transition through. A promising intervention in this realm is virtual reality and simulation of care scenarios that can be used to immerse patients in their procedures before they take place [47]. This extends to giving patients experiential insight about treatment options before they choose, which could be a core strategy for improving patient experience and satisfaction. Similarly, recent evidence suggests that patients who are engaged in their care through interactive learning using health information technology have better satisfaction with their care[48]. The benefits from patient participation extend beyond better patient feedback; importantly, better clinical outcomes, such as few adverse events, are associated with patient participation [49,50]. Multicriteria decision analysis also has an increasing role in providing evidence to inform decisions using multiple stakeholder views, including those of citizens and patients[51]. As such, increasingly, scientific methods are being deployed to inform decision making, with greater influence from patients in those decisions.

1.2.4 Trends in workforce skill-mix

As health care demand and costs balloon while physician supply shrinks, there is a growing trend for classically physician-only responsibilities to be delegated to non-physician advanced practice professions such as nurse practitioners (NP), physician assistants (PA), and nurse anaesthetists. There is a growing supply of these health professionals and they cost health care systems a fraction of the cost of physicians. Additionally, the need for solutions to wider labour shortages, such as the supply of registered nurses, suggests that labour-saving technologies can play a vital role in addressing concerns about patients accessing care.

A 2015 study found that the rate of growth of advanced practice clinicians such as NPs and PAs was 73.8% from 2007 to 2013, compared to 34.3% growth of physicians[52]. It is estimated that allowing NPs and PAs to prescribe controlled substances reduces outpatient care costs in the range of 11.8 to 16.0%[52]. This decrease in cost does not seem to be associated with increased requirements for care. This change is also occurring in operating rooms, with a growing number of hospitals employing certified nurse anaesthetists and anaesthesia assistants to provide and monitor intraoperative anaesthesia while a single anaesthesiologist oversees several operating rooms[53,54]. The workforce mix in Europe is difficult to estimate, but OECD data indicates that the number of professionally active nurses has remained constant since 2010, at around 9.8 nurses per 1000

population. According to figures from the European Labour Authority, despite an initial fall in the number of health care worker vacancies since the second quarter of 2019, by the second quarter of 2021 vacancies had increased by 36%. In this same period, of all occupations, nursing ranked as that with the most severe shortage of labour, suggesting that pre-pandemic labour conditions were worsened by the event[55]. Expanding on this point, according to a recent study, nurse responsibilities expanded since 2010 with eight countries authorising nurse prescribing, including Finland, the Netherlands, Cyprus, Estonia, Poland, Spain, France, and Switzerland (Vaud only).[56] This suggests that demands on health care workers have grown and the coronavirus pandemic may have exacerbated the effect of these on worker recruitment and retention.

The WHO's State of the World's Nursing 2020 report found that nurses make up approximately 59% of the health profession workforce. The WHO estimates that there is a global shortage of 5.9 million nurses, most of which is concentrated in LMICs[57]. The strains on the nursing profession are further being exacerbated by the COVID-19 pandemic. A 2021 survey led by the American Association of Critical Care Nurses of over 6,000 US registered nurses found that 92% of respondents believe that their hospitals have been depleted of nurses due to the pandemic and that their career will be shorter than they intended. A further 66% of nurses believe their work experiences during the pandemic have caused them to consider leaving the profession[58]. These insights may signal further workforce shortages in future.

1.3 Provider level

Care provision at the meso / provider level is strongly influenced by efforts to integrate care between care settings, including primary, community, secondary, and tertiary care. Key aspects in the development of provider level care models are summarised below, indicating trends towards care pathway optimisation within hospital settings, increasingly into the community, and the use of innovative devices that support both hospital and community management of complex multi-morbid patients.

1.3.1 Disease management programs

Disease management programs (DMP) were and continue to be used as a means of aligning the care needs of home care patients with chronic disease; the strategy has been focused on care pathways rather than the whole system. First deployed nearly 20 years ago in Germany, the development of these programs has been usurped by "integrated care" as a more prominent strategy with newer, expansive terminology. Nonetheless, the industry sector remains increasingly actively involved in the development of disease management programs and care pathways that include the use of their products. In the UK, integrated care systems were introduced as a focal point of policy in the 2015 "Long Term Plan" by NHS England. Integrated care systems remain at the centre of efforts to reform the NHS here with the intention of bringing NHS providers and commissioners of health and social care into closer collaboration. In 2016, a scheme known as Sustainability and Transformation Partnerships was launched as a means of growing local partnerships across England. These partnerships are now formally referred to as Integrated Care Systems, although the extent to which their objectives have been met is unclear. A significant recent development for ICSs in the UK is an increase in social insurance contributions to fund social care. This development intends to strengthen the foundation for managing chronic diseases across the traditional structures of the NHS and now, social care providers.

In a recent study by Simcoe, Catillon and Gertler (2019)[59], in one US health maintenance organisation, a diabetes disease management program was found to improve health outcomes and costs. The study controls for confounders (such as voluntary disease management program enrolment) by using a difference-in-difference design and found that earlier HbA1c monitoring is associated with better health outcomes and cost reductions. Moreover, the effect of enrolment on health outcomes and costs was observed within one or two quarters. This is evidence of the positive effect of disease management programs in a US context; however, the authors highlight the mixed evidence on the effectiveness of these programs. Recent evidence supports the effectiveness of DMPs, using different outcomes; in their working paper, Ugolini *et al*. (2020)[60] report that general practitioner involvement in diabetes care planning improves patient compliance to prescribed actions in Italy and, in France, adherence to follow up medical care in diabetes patients is associated with a reduction

in patients' long-term hospital admissions (Bussiere *et al*. 2020)[61]. This suggests that there remains an important role for DMP, but the deployment of these programs will have to account for multiple disease pathways that are likely to interact in increasingly integrated systems.

1.3.2 Medicines management

As multi-morbid patients become more prevalent in the population so too does the intensity of therapy that they receive. Drugs are a mainstay of therapies for most diseases and expenditure on medications represents approximately 16 percent of total health expenditure in OECD countries. Since 2015, per capita expenditure on pharmaceuticals in France, Germany, Spain, the UK, and Italy has grown, which is a trend reversal on the period following the financial crisis of 2008/9. Amidst this return to pharmaceutical spending, polypharmacy remains a concern. This refers to multi-morbid patients who take at least five medications daily, according to a recent systematic review that explored the definitions applied in recent research[62]. As such, as a larger proportion of the population becomes multi-morbid, prescription drug volume and expenditure are expected to rise. This poses a challenge to health systems seeking to contain drug expenditure and those costs incurred from adverse drug reactions[63]. In one of these dimensions, generic substitution policies remain a favourable option to contain rising drug costs.

Quality care, which encompasses patient safety, also encompasses the management of medicines. Various strategies have been employed by health systems to address the concomitant risks that polypharmacy poses. These risks include suboptimal compliance or adherence to dosing, drug-drug interactions that may be harmful or reduce therapeutic effects, and financial hardship to citizens. A recent systematic review of North American and European guidelines for managing complex polypharmacy patients, which included a formal quality appraisal of guidelines in the UK, Germany, the US, Mexico, and the Netherlands, derived novel recommendations for managing these high-risk patients (Muth *et al*. 2019)[64]. The article demonstrates the breadth of decision making that should be considered, which now includes guidance across both clinical and self-management dimensions of care. As such, contemporary guidelines for managing multi-morbid patients put greater emphasis on providers' role in supporting patients' self-management by, among other approaches, participating in shared decision making; this intends to develop an appropriate level of patient and carer involvement in treatment decisions. The authors recognise that geriatrics, mental health, and primary care sectors are generally better organised to manage multi-morbid and polypharmacy patients; this leaves many other sectors of the health system, including many diseases, which are currently poorly organised to implement the best care practices contained in the guideline review.

The biopharmaceutical market has responded to these challenges by offering health systems alternatives that circumvent many of the challenges posed by polypharmacy. A prominent, topical example is that of inclisiran, which is a small-interfering RNA lipoprotein cholesterol lowering drug that is administered twice a year to reduce cholesterol by approximately 50% in high-cholesterol, at-risk patients[65]. This innovation mitigates the need for daily statins and therefore reduces associated compliance / adherence issues. The adoption of this alternative relies on a vaccine-based approach to the reduction of cholesterol, which could result in downstream benefits such as alleviating demand for primary care or fewer hospital admissions for acute cardiovascular diseases such as stroke and heart attacks.

1.3.3 Medical device management

Medical devices provide an increasingly significant role as preventive and curative interventions. In cardiovascular care, the heart failure (HF) epidemic points to the need for technology solutions that can help manage the care of this growing patient group.[66] Of all conditions, heart failure is of particular significance because most patients present with multi-morbidities and this worsens with age[67]; Chamberlain *et al*. found that 86 percent of all HF patients presented with a least two comorbidities and hypertension, hyperlipidaemia, and arrhythmias were the most prevalent chronic conditions[68].

Multidisciplinary efforts are needed to manage these complex patients, therefore solutions that foster integrated care between primary, community, and secondary care settings are necessary. Currently, efforts to

relieve pressures rely on medicines and secondary care interventions. Left-Ventricular Assist Devices play a prominent role in the management of HF patients, particularly those in an advanced stage of disease and who are transplant ineligible. Although since discontinued, evidence on the cost-utility of the HeartWare™HVAD™ by Medtronic in England suggests that these devices are cost-effective versus standard of care (optimal medical management) at a willingness-to-pay threshold of £50,000 per QALY[69]. The threshold is higher for LVADs for advanced HF patients because they fall into the end-of-life care designation.

Although Schueler *et al*.[69] found that the Medtronic device is cost-effective, an earlier systematic review reported that most LVADs are not cost-effective in the base case analysis[70]. Probabilistic sensitivity analyses tend to show that these devices can be cost effective, but this only highlights the uncertainty associated with value assessments in this space. As such, the reimbursement of these devices and related technologies by payers requires careful development of financial and economic data by firms. Economic evaluations show how demand-side pressure is reduced not simply in secondary or tertiary care settings, but also in the primary care settings where multi-morbidities associated with HF are most frequently managed.

1.4 Patient level

1.4.1 Patient experience

Patient experience and patient satisfaction are related concepts that are of increasing importance in discussions about integrated care; it is a core part of the Triple Aim and must be considered by providers and firms. Technically, satisfaction is a product of initial patient expectations; therefore, patient expectations must be studied before an assessment of their satisfaction can be ascertained. Recent evidence suggests that by involving patients in the development, implementation, and evaluative methods for care pathways, improvements across various dimensions of quality are observed, including better psychology and physical outcomes, quality of life, satisfaction, continuity in care, and the feeling of empowerment[71].

All these considerations are pertinent to stakeholders developing integrated care because patient perspectives are increasingly recognised as key to improving the legitimacy, experience and overall quality of care patients receive. Evidence on patient and public involvement in product evaluations is scarce, with only one study identified in a recent systematic review reporting that 45 percent of all novel, feasible, and implementable ideas in the primary care setting were sourced by public participants[72]. Despite this scarcity, patient and public involvement is a user-centred trend in developed health systems that is likely to grow with integrated care. As such, knowing the user (the patient) is key and survey methods are central to understanding user preferences. In a recent evidence synthesis using survey results and stakeholder perspectives, users are seeking reducing length of hospital stays, shorter recovery times, less invasive procedures, fewer complications, and longevity in their care products and in the results from their procedures[73]. An applied example of this is a 2015 study of patient-defined goals for treatment of severe aortic stenosis which found that patients' preferred outcomes tended to focus on independence, longevity, minimizing symptoms, and facilitating ongoing participation in a specific activity or hobby. Understanding what patients' health and life goals are can then be used to select the most appropriate treatment option for severe aortic stenosis which can range from medical management to minimally invasive transcatheter aortic valve implantation to surgical treatment with surgical aortic valve repair.

1.4.2 Long-term care

Due to an aging population, increased prevalence of dementia, and more complex comorbidities, a growing portion of health care spending is being directed towards long term care. This includes medical and nursing care, personal care, and assistance services for people dependent on others for activities of daily living. Most long term care services are provided through residential facilities such as nursing homes, while the remainder is offered through hospitals, home care programs, social providers, and patient families. According to an OECD report, on average 1.5% of GDP was spent on long term care services in 2018[74]. Long term care funding has

grown significantly over the last 15 years and is now outpacing growth in overall health care spending in many OECD countries.

Evidence is emerging that the cost of long term care may be controlled by better integration, as was recently shown in the English study by Morciano *et al*. (2021) which was a difference-in-difference analysis of hospital admissions before and after regional integration[28]. The study found a significant absolute reduction in emergency admissions for adult and elderly care patients (although not for younger ones) of 3.3% and 3.7% respectively, at the third year after implementation (but not before) compared to non-integrating sites. This shows the potential of integrated care to reduce hospital resource use associated with long-term elderly care, which is a particular concern in the post-coronavirus context.

1.4.3 Mental health

It is estimated that one billion people suffer from some form of mental health disorder. In 2010 the economic cost of mental health was estimated to be approximately $2.5 trillion per year due lost productivity and poor health[75]. The cost is expected to balloon to $6 trillion by 2030. While there is a growing recognition of the prevalence as well as health and economic impact of mental health disorders, countries typically spend only a fraction of their health budget on these illnesses. The coronavirus pandemic has exacerbated the need for access to mental health treatment[76] and, yet, estimates indicate that for every US$1 spent on mental health care, US$4 are returned to health systems[75]. This suggests that products that support patients' mental health needs, alongside their physical and social needs, are an attractive investment for payers.

2. Advancing medical knowledge and product development

There are so many new health technologies that are constantly emerging from several sectors, and with a multitude of applications to health care. The technology landscape is often characterised as rapidly changing, which occurs in parallel to the evolution of disease, reforms to structures tasked with ameliorating the effects of disease in populations, and wider changes in societal expectations. In short, advancing medical knowledge breeds new technologies that fit (better or worse) to a perpetually complex system. Lags between the emergence of technologies, their routine adoption, and the evaluation of them mean that at any point in time, we must contend with imperfect information. However, some health technologies align to wider themes and objectives, creating some signals as to their utility to health systems today and into the future. This utility is invariably linked to health systems goals, including sustainability considering well-documented demographic and health trends.

2.1.1 Care Information Exchanges

Technology is key to achieving integrated care, but it should not be considered the sole solution. Systems thinkers in health and social care tend to refer to sociotechnical systems as being a central construct of health systems[77]. This means that both technology users and patients' experiences should be integrated into technology design. Telemedicine is one area of user-centred technology design for which recent evidence is positive [78,79]. Underpinning the success of these technologies are electronic health records, which are increasingly incorporating sociotechnical aspects into their design. The initial linking of electronic health records between providers has been central to health system integration, as previously mentioned. Now, care information exchanges are being introduced as a means of providing direct access for patients to their medical information, ensuring it is accurate and up to date for every health care transaction. A recent study by Everson and Butler (2020)[80] suggests that care information exchanges work best in a hospital context if multiple technological tools (including secure messaging, provider portals, and use of a health information exchange portal) are used to access and integrate patient information.

Whereas care information exchanges have lagged behind progress made in other aspects of health information technology, their role in integrating health systems is becoming increasingly important. These

exchanges have the potential to gather essential data from patients about their experience and satisfaction with providers. They can reduce information failures in the delivery of care to reduce patient harm and foster patient safety, whilst collecting long-term outcomes data, such as quality of life after receiving treatment(s). In a recent systematic review, care information exchanges were effective at improving diabetes care, as measured by a mean HbA1c reduction (across articles) of 0.405 percent[81]. This is an important development in the literature because HbA1c levels are a major mortality predictor and few studies have associated information exchanges to clinical outcomes in this way.

2.2 Genomics and biopharmaceuticals

The future of pharmaceutical development is trending towards more precise disruption of specific pathological processes by using genomics to tag and/or target therapies. Key examples of this precise biotechnology are mRNA vaccines, bacteriophages, monoclonal antibodies, and chimeric antigen receptor T-cell (CAR-T) therapy.

In the field of antibiotic R&D, the scientific challenges with developing truly novel antibacterial drugs forced developers to look at other agents to treat antibiotic-resistant infections. These include novel products such as immunotherapeutics, bacteriophages, lysins, prebiotics and probiotics, and peptides. Of these, bacteriophage therapy is likely the most heavily researched and involves harnessing the power of phage viruses, which only invade and infect bacterial cells. Like mRNA vaccines, bacteriophages capitalize on our understanding of the genetic sequencing of target pathogens so that they can be sought out and destroyed while preserving human cells. Key barriers to progressing this technology include scientific challenges with product formulation for clinical use and mitigating the risk of propagating bacterial resistance[82].

Monoclonal antibodies (mAbs) are a type of biologic therapy where antibodies are manufactured to bind to a specific cellular target that can produce various molecular functions such as apoptosis, block signalling pathways, or induce signalling pathways. Monoclonal antibodies are now commonly used in treatment of a wide variety of cancers and autoimmune conditions. This past year the FDA approved the 100th mAb product, which reflects the exponential growth of this novel technology[83]. In the field of cardiology, Abciximab is mAb that functions to" disrupt atherosclerotic plaque, thrombus formation, and platelet aggregation by binding glycoprotein IIb/IIIa, vitronectin, and Mac-1 receptor."[84] However, Abciximab is not readily available and has been discontinued in the US. Evolocumab and alirocumab are anti-PCSK9 mAbs that are designed to treat hyperlipidaemia and particularly used as second-line treatment for familial hypercholesterolemia.

Research into mAbs laid the ground for development of CAR-T therapy which isolates an individual's T-cells, genetically modifies them to express a receptor that targets a unique tumour antigen, and then infuses the product into a patient with that tumour. The CAR-T cells then target and destroy the tumour cells through a variety of molecular mechanisms. The first CAR-T therapy was approved by the FDA in 2017 and now there are five approved therapies, which are primarily used in the treatment of lymphoma and other hematologic malignancies. There is emerging research examining the role for CAR-T in treatment of refractory lupus as well as post-transplant immune conditions[85].

2.3 Minimally invasive procedures and robotics

Minimally invasive procedures are a growing field within medicine whereby operations are completed using innovative equipment and surgical techniques that minimize disruption to the body's tissues. The result is smaller incisions, less damage to tissue, and reduced blood loss leading to faster recovery and often fewer complications than traditional open surgical methods.

The field of cardiology has been an early adopter of this technology with the use of percutaneous coronary intervention for stenting, ablation procedures, valve replacement and repairs, and endovascular repairs. These procedures are quickly becoming the gold standard for treatment of a wide variety of cardiac disease and are resulting in shorter hospital admissions, faster recovery periods, as well as fewer complications, which all

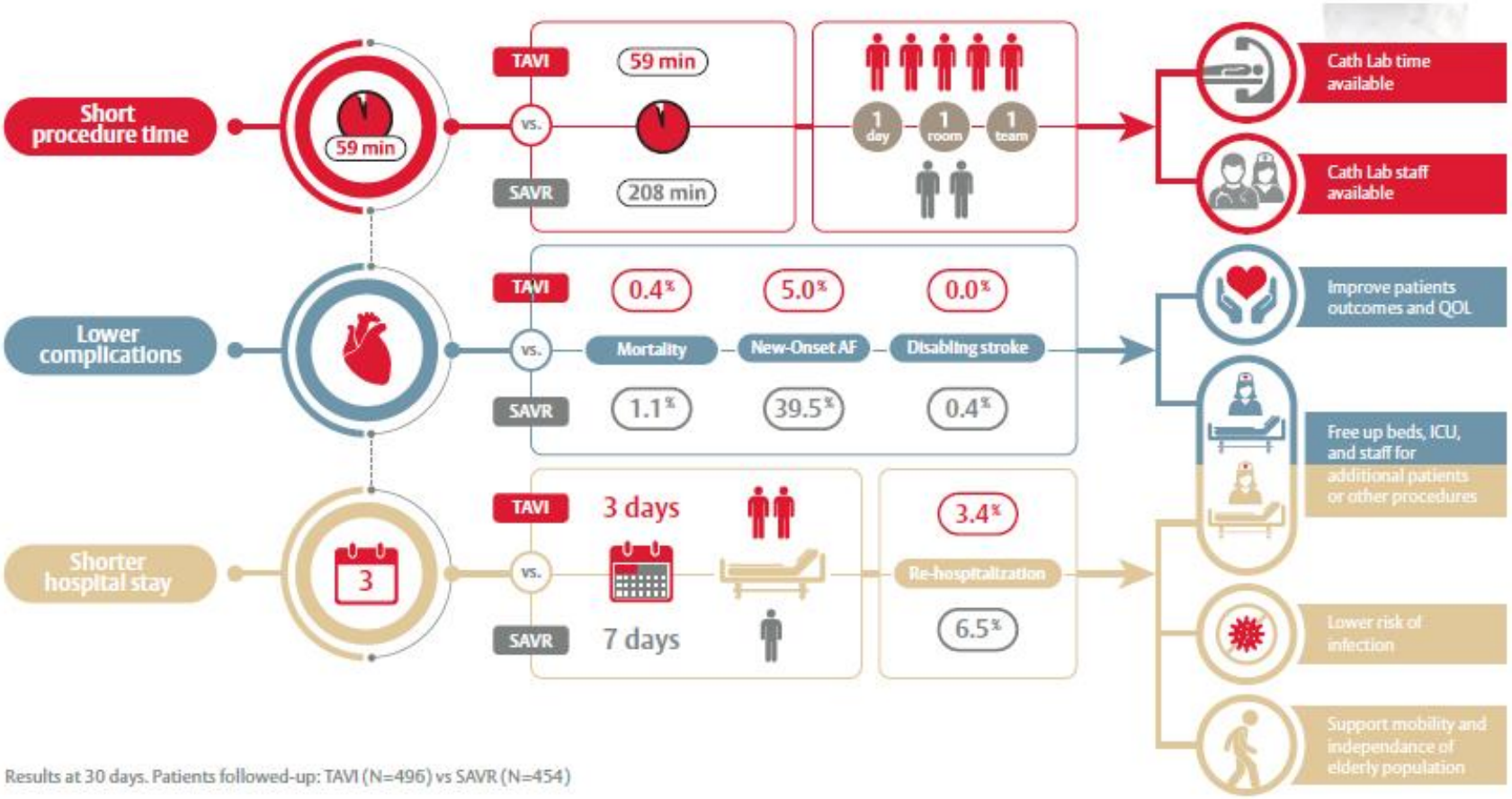
address user preferences for care and outcomes[73]. This field continues to progress as technologies are refined to allow for more challenging approaches such as transcatheter tricuspid valve interventions (e.g., minimally invasive annuloplasty and transcatheter valve replacements) and transcatheter pulmonic valve replacements[86].

Positive evidence continues to be produced, for instance, transcatheter aortic valve implantation (TAVI) is highly likely to be cost-effective relative to surgical aortic valve replacement (SAVR) in Singapore for intermediate to low risk aortic stenosis patients with a baseline ICER (of approximately S$34,000 per QALY) that is most sensitive to the cost of performing transfemoral TAVI operations[87]. Whilst TAVI may be a more expensive procedure to perform, the cost of complications in SAVR and longer length of stay lead to, on average, higher inpatient costs according to Ando *et al*. (2019)[88]. In France, these favourable findings have been emulated using the SAPIEN 3 device with severe aortic stenosis patients where TAVI is both cost saving (€12,742 per patient in the base case analysis) and leads to more QALYs over a 30-year time horizon. This finding is at least 80% likely across all willingness to pay thresholds[89]. A similar finding has been reported for Italy, where TAVI with the SAPIEN 3 device was found to be cost-effective with a cost per QALY gained of €2,989, which was robust across several scenarios. At a willingness to pay threshold of €30,000/QALY or above, TAVI with SAPIEN 3 was cost-effective compared with SAVR in 100% of probabilistic simulations[90].

This contemporary view of TAVI versus SAVR shows a significant evolution in the TAVI evidence. For instance, in Italy, the cost-effectiveness of TAVI in aortic stenosis was evaluated for inoperable, high-risk, and intermediate risk patients. At each level, the cost of TAVI procedures was offset by clinical effectiveness and safety over a 15 year time horizon, and the cost per QALY gained was within normally accepted willingness to pay thresholds in Europe[91]. Over a 10-year time horizon, a similar favourable result for TAVI versus SAVR was found for intermediate and severe risk patients in the Australian setting[92]. In a UK study, TAVI was cost-effective versus medical management for severe aortic stenosis patients and regardless of whether a 5- or 10-year time horizon was adopted, the cost per QALY fell below a willingness to pay threshold of £20,000[93]. This positive trend is echoed in other parts of Europe. For instance, TAVI is the treatment of choice for aortic stenosis in Germany according to data from 2015[94] and TAVR rates per million population are highest in Europe here[95]. Overall, there is considerable evidence signalling that TAVI is a cost-effective intervention versus standard(s) of care in Europe and more is likely to emerge as experience with the procedure matures.

Ando et al. state that TAVI procedural costs can be reduced by avoiding perioperative complications by obtaining vascular access under ultrasound guidance, using balloon-expandable valves for those at high risk for prosthesis-patient mismatch, and use of moderate sedation[88]. Care pathways can be improved by minimising intensive care unit stay, increasing early ambulation, avoiding urinary catheters, establishing clinical pathways post-TAVI, and planning for early discharge in selected patients. If achieved, the promising cost-effectiveness ratios for TAVI versus invasive valve replacement can enhanced and patient experience improved. From a cost-effectiveness point of view, the TAVI procedure's main cost is the device itself, whereas the majority of the SAVR's costs come from the ancillary aspects of undertaking open heart surgery and recovering from the procedure.

Figure 5: The role of minimally invasive procedures in supporting integrated care efforts, the example of TAVI versus SAVR[96].



In the graphic above, care pathway optimisation is achieved by shortening procedure time and length of patients' stay in hospital. Additionally, better inpatient outcomes (fewer complications), reduced workloads for staff (equipment and staff availability increased), and improvements in quality of life for patients combine to produce outcomes that support the Triple Aim. To fully embody integrated care, hospital care pathways must coordinate with other care settings to ensure patients unmet needs are served throughout the life course.

Arguments on the efficiency of TAVI versus SAVR can be supported by data on pathway / process optimisation as shown by health care worker time savings and improvements in patient experience.

One further advancement in the field of interventional cardiology and cardiovascular surgery is the incorporation of robotics, which allow the interventionalist to conduct the procedure apart from the patient. There are direct benefits to the operator who can reduce their own radiation exposure as well as prevent the orthopaedic injuries that often come with wearing heavy leaded protective gear throughout the day[97]. In addition, there is some limited evidence to suggest that robotic assisted percutaneous coronary intervention (PCI) may improve lesion coverage accuracy[98]. Robotic interventional cardiology also has the potential for the operator to be located at different hospital sites from the patient, so called telerobotic medicine. This technology could allow remote hospitals to gain access more easily to PCI-capability and reduce door-to-balloon time. Finally, there is emerging technology that offers a hands-free ultrasound guided system for central line placement, which is a necessary step in most minimally invasive cardiac procedures. The combination of remote central line placement and robotic-assisted PCI could make it feasible for an interventionalist to work entirely remotely and operate on patients across an entire geographic region. The study REMOTE-PCI has demonstrated the feasibility of this approach, although there are numerous barriers to its practical implementation such as managing intra-procedure complications, regulatory challenges, and technological limitations with real-time display and operator-device feedback [97,99].

The benefits to health systems from minimally invasive surgeries are more pronounced than ever, as hospital capacity must increase to address backlogs and waiting lists that have ballooned during the coronavirus pandemic. Reductions in length of stay and fewer complications have been documented across a range of conditions and procedures[100–102], indicating that minimally invasive strategies are among the most promising for improving productivity and efficiency. However, some evidence exists that demonstrates underutilisation of minimally invasive techniques in the US[103], which is a key barrier to achieving system-wide benefits in this setting. The extent to which this is the case in Europe has been explore by Ali et al., who reported severe underutilisation of TAVI in the UK setting versus several European neighbours (78 TAVI procedures per million population versus a European average of 141, and a highest rate of 292 in Germany). Poor patient access to TAVI has been linked to worse outcomes in severe aortic stenosis, raising the need for innovative pathway solutions and technologies that can raise throughput and address the burden of disease[95].

2.4 Artificial intelligence

Artificial intelligence (AI) is a ballooning area of technology that is only just starting to be applied to the field of health care. It holds the potential to revolutionize how modern medical care is conducted from R&D to bedside treatment. Natural language processing and machine learning are two key components of AI[104].

2.4.1 Natural language processing

Much of current health care data is stored as dictated human speech. For example, patient medical records are typed reports including their past medical history, allergies, and medications; radiographic images are interpreted as block texts by the radiologist; and treatment plans are dictated by physicians as documents. Accessing and utilizing this information is limited to the individual person that reads the text.

Natural language processing is the codifying of human language so that it can be stored, transferred, compiled, manipulated, and interpreted. As health data becomes increasingly digital, through electronic health records and health information exchanges, natural language processing offers the ability to access the wealth of information that is stored in existing health care files. Further, natural language processing allows this information to be accessed in real time to support decision making at the individual patient level as well as hospital and health system levels.

2.4.2 Predictive analytics & machine learning

Predictive analytics is the process of extracting data, interpreting this data, and then projecting an outcome. Predictive analytics is already being used in health care in limited contexts such as automated ECG interpretation. Machine learning goes one step further by feeding back the predicted outcome and the actual outcome into the process to learn on its own from experience. In conjunction with natural language processing, machine learning can facilitate the unburdening of many tasks from health care practitioners to computers. Neural networks and deep learning are further subsections within machine learning that attempt to mimic the human thought process using algorithms.

2.4.3 Applications of AI

There are numerous ways in which AI is being integrated into health care. These are some examples:

1) Virtual assistants: Companies such as Your.MD and Babylon Health offer patients an easily accessibly 24/7 virtual assistant that can book appointments, answer basic medical questions, and verify correct medication administration.

2) Radiographic interpretation: There is a growing number of AI programs that are applied to interpreting medical images, which have the potential to be more accurate, less expensive, faster, and more accessible than current human applications[105]. For instance, one study found that their AI program using Convolutional Neural Networks had similar sensitivity in detecting concerning lung nodules on CT scans of complex lung disease compared to that of an experienced radiologist[106]. Similarly, a recent 2021 study showed how a machine learning framework can be used to help identify distinct phenotypes of aortic stenosis with echocardiography in order to optimize the timing of aortic valve replacement[107].

3) Predicting health care outcomes: AI is being applied in risk stratification of patients and modelling patient morbidity and mortality, particularly in the field of cardiology. Tohyama *et al*. found that their machined learning-based model for predicting one year mortality of hospitalized patients with heart failure was highly accurate and more superior to conventional risk models[108]. Similarly, Sherazi *et al*. developed a machine learning prediction model for 1 year mortality of patients discharged from hospital following acute coronary syndrome which increased the accuracy of detecting major adverse cardiovascular events in these patients[109]. Another example is the use of Hypotension Prediction Index to guide hemodynamic treatment of patients undergoing moderate and high-risk surgery. [110]These technologies allow clinicians to intervene earlier and offer targeted treatment options based on individual patient risks.

4) Drug discovery & development: AI is also well suited to tackle the massive data analytic needs of pharmaceutical drug discovery which relies on sifting through thousands of molecules to identify potential candidates for further research and development. One example of its possible application in the R&D setting is machine vision image analysis which attempts to simulate and predict molecular interaction with the purpose of further narrowing the search to the molecules with the greatest likelihood of in vitro therapeutic success[111].

5) Operational efficiency: There is a role for AI in improving operational and administrative efficiencies within hospitals by identifying areas that could be streamlined or improved such as patient flow bottlenecks or patients at risk for readmissions. For example, Marafino *et al*. conducted a study that used predictive analytics targeted at identifying patients at risk for readmission within 30 days of hospital discharge[112]. This allowed for implementation of a comprehensive readmission prevention intervention that was associated with a reduction in 30-day readmission rates.

2.5 Precision medicine

Precision medicine is an integrative approach to disease management that uses patient genetics, lifestyle, and exposures as determinants of their health and illness phenotype to select and tailor treatment options[113].

Precision medicine capitalizes on the forefront of patient data analytics such as genomics, transcriptomics, epigenomics, proteinomics, and metabolomics to help uncover disease phenotypes and disease relationships that can then be targeted by novel pharmacotherapeutics and inform patient specific care plans.

Oncology is a field where precision medicine is rapidly growing with the advent of immunotherapies. Traditional cancer treatments, such as surgery, chemotherapy, and radiation are relatively blunt tools that uniformly destroy healthy and cancerous cells alike. However, immunotherapies, like monoclonal antibodies, check-point inhibitors, cytokines, and CAR-T therapies, use a patient's own immune system to target and ideally attack just the mutated cancer cells[114]. This type of medical precision has further advanced with the recognition that no single cancer is identical and there is variation between cancerous mutations across individuals. Thus, the concept of precision medicine is being applied to the selection of cancer treatment programs based on individual characteristics from their demographics, genome, environmental exposures, and other predispositions. Personalized medicine is a similar concept to precision and encompasses the idea that the entire treatment pathway is tailored to a specific individual.

Precision medicine is less developed in cardiology but there is growing recognition that these modern concepts can also be applied to the field[115]. One opportunity is in the treatment of hypertension, an illness that is estimated to affect more than a quarter of the global population. Yet, antihypertensive therapies are largely based on population-level studies that do not factor in sub-group phenotypes and certainly not individual genomics. We know that there is heterogeneity in clinical response to treatments, which means that a single antihypertensive regimen will not be optimal for all individuals. In a precision medicine era, antihypertensives would be selected based on correlating a patient's pathophysiological cause for their hypertension, determined with biochemical and molecular markers, with a therapeutic strategy proven to have improved outcomes in this patient subset[113]. For this process to even begin there is a need for increased characterization of individual patient phenotypes, genomics, and other patient-specific information in future cardiovascular research and product development so that therapies can eventually be individually tailored. Developments in the remote monitoring of blood pressure and heart rate are instrumental to these efforts and the least disruptive forms of monitoring may have a considerable advantage. For example, an AI platform known as DocMe® uses facial recognition technology to measure blood pressure and heart rate signs using readily available cameras, such as webcams and mobile phone cameras, without the need for physical contact[116]. The application of this technology is hard to fully anticipate, but the nature of the technology raises several questions about how remote monitoring – inside and outside care settings – may revolutionise data collection in cardiovascular care.

2.5.1 Preventative health care

With the increasing prevalence of chronic illness, there is a growing role for primary prevention and screening to identify disease risk factors and early stages of treatable diseases. Examples include vaccinations, smoking cessation tools, and screening for hypertension, high blood sugar, high cholesterol, cancers (colon, cervical, and breast), and sexually transmitted infections. A recent study showed that targeted preventative health care programs are associated with decreases in prevalence of ill health which can improve sustainable growth in national productivity. However, this must be balanced with over-detection of new chronic diseases with mild severity which can result in unnecessarily longer illness duration and higher rates of ill health[117].

Despite some evidence that runs contrary to popular wisdom that "prevention is better than cure", for example Stokes et al. 2021[29], interventions that can prevent exacerbations of pre-existing conditions or that can prolong years of life spent in health remain an attractive investment to payers in Europe. Uncertainty in the evidence of effectiveness and cost-effectiveness of novel products or processes that support care integration and preventative interventions must be carefully managed by payers and firms. Increasingly, long-term real-world data collection is attractive because the evidence produced reduces uncertainty. In the realms of preventative health care, where the effects of interventions can take longer to manifest in a population, long-term data may be a growing necessity to achieve and maintain reimbursement.

3. Summary and recommendations

Biotechnology and medical device firms have a key role to play in developing products and processes that support health systems in their efforts to achieve the Triple Aim: improved patient experience, reduced costs, and improve population health. Current global trends suggest that the vehicle for achieving the Triple Aim is integrated care[118], which amounts to the adoption of new policies, processes, and products at three levels of health systems: macro, meso, and micro. Connections between levels of the system must be fostered to then enable coordination of efforts between payers, providers, patients, and private firms. Innovations that demonstrate the ability to improve the coordination of (cost-effective) care that is more efficient, which manifests in improvements in health outcomes, patient experience, quality of life, costs in the short (within 90 days), medium (within two years), and long-term (within five years) are needed.

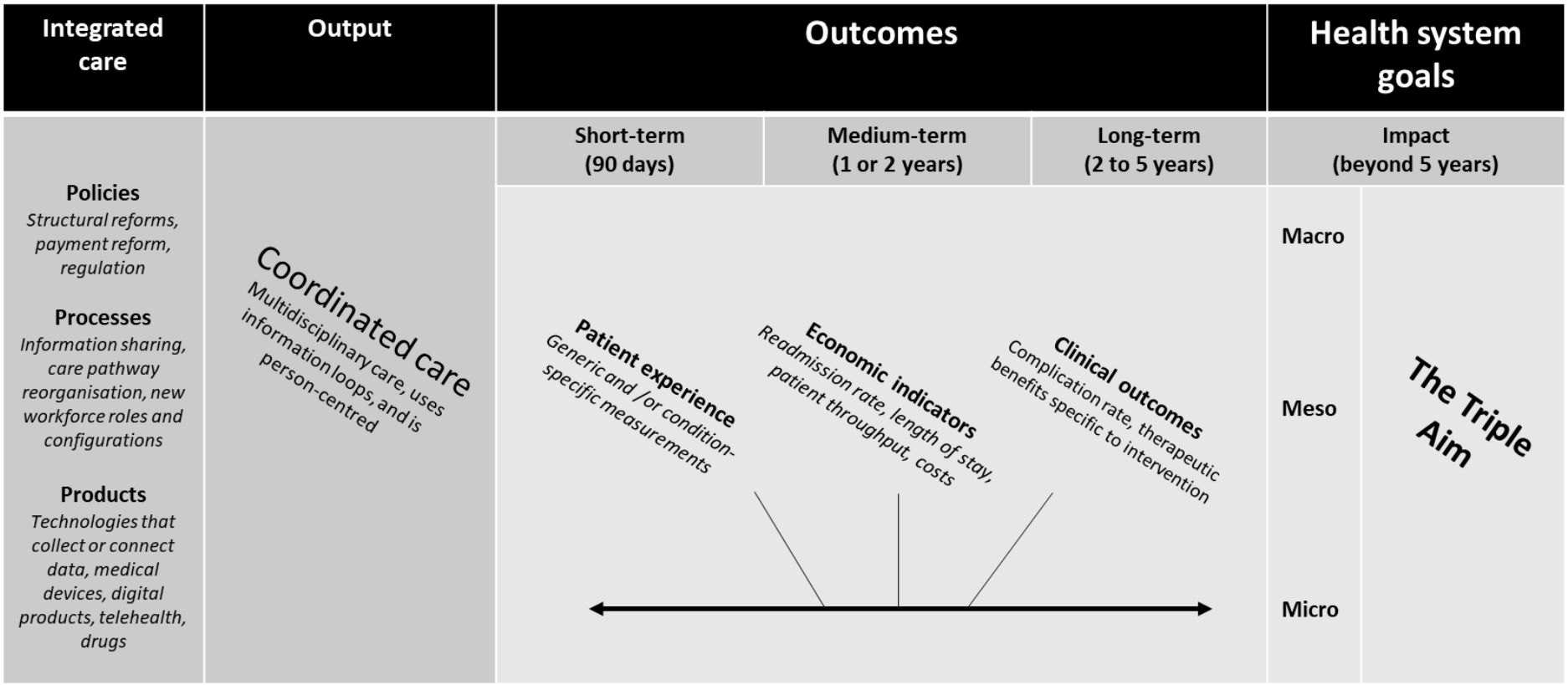
Recommendation one: as recent evidence raises more questions than answers about the effectiveness of integrated care systems, firms should develop evidence that shows how products (and accompanying changes in care processes) improve connections and coordination between carers and care settings, particularly those between primary care and secondary care. The principal factors for the success of any product are robust evidence showing an expectation of reduced resource use (and costs) and improvement in clinical and patient-reported outcomes. These measures should amount to a convincing argument for the cost-effectiveness of a new product as compared to current standards of care.

Recommendation two: in the product development plan, payers, patient groups, and providers should be engaged to ensure valid outcomes are measured over a meaningful time horizon (usually the long-term). Patient and public involvement is increasingly important to system and product design in health care and methods for gathering insight in this domain are needed. The literature does not point to a single set of operational indicators that should be used to measure the patient experience. This poses a particular challenge because there may not be consensus about data requirements. However, examples from the literature set a precedent that can be followed, and stakeholders and regulators should be approached early to establish agreement.

Recommendation three: cost-effectiveness analysis is likely to be used more often for both medical devices and non-pharmaceutical interventions, such as digital technologies, because value-based reimbursement is increasingly the payers' approach to purchasing. Frameworks for developing economic evaluations across European jurisdictions are mature and accessible. However, the way they are applied to non-pharmaceutical products, such as digital products, is young and maturing. This poses a challenge for firms who have non-pharmaceutical products, however those who innovate in this area are likely to be engaged by regulators and payers. Firms may wish to collaborate if there are potential product synergies for health system decision makers.

Recommendation four: given that the effects of integrating care can take a long time to manifest and causality may be difficult to demonstrate, the role of a technology in improving integration and coordination needs to be carefully articulated by firms. This amounts to the development of value propositions that convey logical cause and effect associated with products. There is a clear signal that integrated care is the central solution to health system challenges, despite inconsistent and immature evidence. This is reflected in global- and national-level trends towards integrated care. Private firms will maximise the likelihood of success by demonstrating how their solutions bridge gaps in care coordination, therefore facilitating the integration of systems. In conjunction with recommendation three, short, medium, and long-term outcomes should be considered for every product. Reductions in length of stay, readmission rates, and resource use remain important indicators of value. Data on improved patient experience and better health outcomes are increasingly important to the development of value propositions that link directly to the Triple Aim.

Figure 6: Schematic demonstrating the links between integrated care and health system goals.



Products / technologies can build connections between various levels and settings, amounting to (better) coordinated care; subsequent outcomes, including patient experience, expressed with economic indicators, and clinical effectiveness (encompassing broader health outcomes) should be demonstrated at relevant levels of the system (macro, meso, and micro). These indicators must show impact on the Triple Aim – enhanced experience, lower costs per capita, and improved population health. Although not mentioned explicitly, health equity is a core challenge to health systems, and it has been made more difficult following the coronavirus pandemic. Technologies that can equitably improve access to care are needed.

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