Precision Medicine: Implications For Value Chains and Business Models in Life Sciences

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"Precision medicine gives us the chance to marry what's unique about America – our spirit of innovation, our courage to take risks, our collaborative instincts – with what's unique about Americans – every individual's distinctive genetic makeup, lifestyles, and health needs. In doing so, we can keep ourselves, our families, and our nation healthier for generations to come."
(Barack Obama, Former President of the United States)

Abstract

Precision Medicine (PM) is expected as one of the biggest change in the upcoming years. It aims at preventing and treat disease based upon a person's unique genetic makeup, lifestyle habits, and environment. The topic attracted a huge attention from scholars in the biomedical field of research. By contrast, literature is very little if not absent in business studies. It is surprising: this revolution dramatically reshapes the structure of Life Science industries. It implies profound impact on business model of companies and institutions, it pushes a new paradigm of sustainable development for healthcare systems at the global level. However, little is known about whether, to what extent, and to what directions these dynamics are impacting on the whole life science value chains and markets, from research to care delivery. Findings from our case study investigation show that PM is a multi-faced phenomenon grounded on novel forms of innovation eco-systems and bundled-based models. We also reveal a dramatic shift in the value chain, moving upstream from recovery and surgery to prevention and monitoring.

KEY WORDS: Precision Medicine; Healthcare systems; Business Model Innovation; Innovation Eco-systems; Digital Transformation.

1. INTRODUCTION

In 2017 the U.S. Food and Drug Administration (FDA) approved what FDA itself called the 'first gene therapy' ever [1], developed by Novartis. It aims at treating an often-lethal type of blood and bone marrow cancer. It is a customized treatment based on a novel and complex production process: patient's 'T cells' are extracted and transported from the hospital to an innovative manufacturing centre, where cells are genetically altered taking into account patient and disease DNA. These modified cells are then infused back into the patient and expected to kill leukaemia. One-time treatment costs about half a million dollars, though this amount is not charged at all if the patient doesn't respond to the therapy in the short term. This appears as the beginning of a breakthrough revolution from both medical and business model views. However, this therapy raised doubts and scepticism, not just at the biomedical level. Experts started questioning if the organizational model of the company is able or not to manufacture and deliver personalized therapies quickly enough across the globe, and if this model is sustainable or not. US hospitals, after having started using this new drug, admitted they have no expertise or capacity to administer it. One year after commercialization has begun, the company is still delivering the treatment for free, being unable to charge for a therapy that works from a medical standpoint but that doesn't fully meet market, organizational, and institutional specifications. As a response for this, in January 2019 Novartis acquired the French company 'CELLforCURE' – one of the biggest manufacturer for gene therapies in Europe – to expand production capacity and internalize innovative competences. At the same time, it is planning to create manufacturing facilities closer to the clinics adopting this treatment to deal with time issues, paving the way for a future in pharma which moves from centralized factories to distributed production networks.

This is called 'Precision Medicine' (PM) (Collins & Varmus, 2015; Mirnezami et al., 2012; Song, 2017). It aims at preventing and treating disease based upon a person's unique genetic makeup, lifestyle habits and environment. It rejects the 'one-size-fits-all' framework of mainstream medicine, where patients presenting similar symptoms receive a similar treatment. By contrast, PM pursues the vision of a tailor-made healthcare service. Each individual is a unique organism, as well as the disease: as pathologists began to stratify diseases using molecular and cellular data, the number of diseases has exponentially grew, and it continues to do so, revealing the limits to refer at lung cancer or diabetes - for instance - as one single disease (whilst they are actually clusters of similar but different pathologies).

[1] The FDA defines gene therapy as a medicine that "introduces genetic material into a person's DNA to replace faulty or missing genetic material" to treat a disease or medical condition.

Beside the promise of a new era of medicine, the above mentioned experience of Novartis rose a key consideration: whilst vast majority of effort has been so far focused on the huge biomedical complexity of this challenge, strategic and organizational implications have been dramatically underestimated. Is this business sustainable? Here we address this assumption. It is a hot topic. As above said, FDA August 30, 2017 approved the first Cellular and Gene Therapy product after decades of failed attempts: about one year and half later, in January 2019 there are already 16 approved treatments in that category. There is much more than this, since PM embraces many other medical fields, besides genetics, and several technologies. The 43% of all drugs being developed and tested in this moment has something to do with PM, whilst this percentage grows to 93% in oncology (source: Statista, 2019). It's literally impressive. In 2015 USA lunched the 'Precision medicine initiative', a strategic plan pursuing the vision to become 'world leader' of that revolution. Now almost 40 countries have own version of this plan. The concept of PM is not new and theorized since many decades.2 However, it is boomed only recently due to advances in genomics, cost reduction of DNA tests, diffusion of digital technologies such as artificial intelligence. In academia, the debate began in 2009 with a couple of articles using the term "Precision Medicine", though the topic starts growing exponentially in 2012, with 22 articles in one year, then to 593 in 2015 and 2,137 papers published in 2017 (source: Web of Science). However, almost all of these contributions belong to the biomedical research area, there are a few in the economic field, whilst the debate is very little if not absent in the scientific community of business and management.

Given this premise, this work aims at providing a better understanding about magnitude, directions and factors of sustainability of PM from a managerial view. We support it is fruitful field of research. Theoretical contribution of our study is relevant: this is the first extensive contribution explicitly focused on business issues. We identify key dimensions and discuss theoretical foundations for an in depth understanding of these dynamics. Managerial implications are also strong: we push forward the idea that in absence of novel as well as adaptive business models for PM - which should be implemented simultaneously with the release of the new treatments – we will don't see any revolution at all.

The next section explores the concept of PM and its ontology, considering overlaps and differences compared to similar constructs. Section 3 introduces a literature review focused on economics and business findings from prior research. Section 4 reports and discusses

[2] For example, a blood transfusion or a bone marrow transplantation do not come from a randomly selected donor: it's a kind of tailored-made matching process to reduce risks of complications.

empirical insights coming from a qualitative survey, covering the whole health value chain, from research to care providers and considering medical technology players. In doing so, we pay special attention to how digital transformation affects the above-mentioned dynamics. Finally, some conclusions are drawn in section 5.

2. THEORETICAL FOUNDATIONS AND LITERATURE REVIEW

2.1. Defining 'Precision Medicine': a broad construct

PM is often defined as a new approach for disease prevention, diagnosis and treatment grounded on individual specific profile, meaning variability in genes, lifestyle, and environment (Mirnezami et al., 2012; Park et al., 2017; 'US Precision Medicine Initiative', 2015; 'European Alliance for Personalised Medicine', 2018; Ramaswami et al., 2018). The goal is to provide healthcare services tailored to an individual's disease or symptoms, in contrast with mainstream medical practices based on population sampling and disease categorization. Though these principles are quite shared, the concept of PM also shows uncertain boundaries, it is debated and subject of discussion. It covers a broad spectrum of diversified solutions and medical decisions: from personalized drugs, to procedures to predict which treatment strategies will work better for a particular disease in the body of a specific person. This approach pushes forward a renewed construct of 'accuracy' also in the healthcare system as a whole. As a such, the terms 'Precision Healthcare', or 'Personal Health systems', have been introduced referring to the provision of ongoing high-quality monitoring and customized health services to people (Schartinger et al., 2015). To that aim, care of patients goes beyond boundaries of hospitals and enter in daily life (e.g. think at those wearables which monitor biometrics like heart beat). Novelty and broad spectrum of this breakthrough approach led to introduce first the notion of '3P', and then '4P medicine' (Hood & Friend, 2011; Pathinarupothi et al., 2018): Precise (a), Personalized (b), Predictive / Preemptive (c), Participatory (d).

'Precision' (a) and 'Personalized' (b) medicine are used synonymously by a number of scholars (e.g. Ramaswami et al., 2018; Zaric, 2016), whilst others establish a clear-cut distinction between the two terms. Accordingly to this second view, "Personalization' is the creation of drugs, or medical devices, or healthcare services that are unique to a patient. By contrast, "Precision" means the capacity to classify individuals and diseases into several fine-

grained sub-populations, that significantly differ in the response to treatments, increasing quality of the cure, reducing side effects and generating cost savings (Parimbelli et al., 2018). Beside precision and personalization, this stream of research combines biology, environmental studies and digital technologies to enhance healthiness and *Prevent* disease (c), rather that treat them when too late. So, the paradigm moves from cure-based to care-based services (Park et al., 2017). Diagnostics and therapeutics becomes - more than even - highly interdepend and closer each other (Kukk et al., 2015). This approach extends the scope beyond medicine/healthcare, and literally draws a new business landscape at the cross-road among different sectors, including wellness industries, nutrition, digital wearables & IoT, green and circular economy, and more. Progress in artificial intelligence is regarded as the main driver towards 'highly accurate predictions', spanning a wide range of future anticipations: patient's future health, emergencies, research and trials outcomes, costs and resource needs within hospitals, etc.

A fourth trait of this revolution aims at establishing a *Participatory* (d) open medicine (Shaikh et al., 2014). Large and integrated datasets are of course fundamental for highly precise predictions. Data sharing is therefore a fundamental pillar to put this paradigm into practice, engaging researchers, care providers, public healthcare systems, but also patients/people.

This challenge goes even beyond the well-known difficulties in convincing healthcare players talk each other and share knowledge and data. There are further complications: PM expands the scope from highly-controlled scenario of hospitals to daily life of people, as required by the above discussed prevention-based approach. If at the first glance a wide collaboration from patients is expected – it's to save their lives – earlier studies about PM revealed scepticism: outside hospitals people feel to be healthy, free, less available to be constantly monitored, suspicious against novelty, concerned about their privacy (Kichko et al., 2016; Schartinger et al., 2015). People still struggle in understanding the breakthrough value of a 'social contract' where open sharing of clinical data boosts the healthcare system as a whole. Some scholars argue that without specific legal provisions for data privacy in this field, and some form of legal obligation for health data sharing – including people, not just organizations – the PM revolution will never happen (Kichko et al., 2016).

2.2. Literature overview: initializing a research agenda for PM management

The concept of PM as above defined attracted a huge attention from scholars. However, contributions belong almost entirely to biomedical fields of research. Some exploratory

studies regarding economics of PM are noticed, though there are few, limited in their scope, mainly published in medical journals only, and still in their infancy (Phillips, 2017). A scientific debate is very little if not absent in business and management studies. It is surprising: the above-mentioned considerations about what PM means paves the way for a dramatic reshaping structure and boundaries of Life Science industries and markets, implying profound impact on business model for both companies and healthcare bodies, calling for more and more adaptive as well as open systems. This impact could be theoretically huge - one of the biggest ever - though nobody knows its real magnitude, or if this revolution is sustainable or not. PM implies a significant change of the healthcare landscape since it affects the relationship between how medical care is delivered and dynamically organised (Song, 2017). Little is known about whether, to what extent, and to what directions these changes are impacting on the whole healthcare value chain, from research to care delivery. The discovery of PM biomedical principles is accelerating and commercialization began. However, literature reports preliminary evidences showing that adoption into hospitals has significantly lagged, and not because of failure of treatments: key motives are recognized to be as not technical (Ginsburg & Phillips, 2018). Our literature review contributes to the debate by grouping together three key clusters of issues: the adoption of digital technologies as key enabler for adaptive PM systems, the need for new patterns of supply chains, the cost debate and its implications for the reimbursement system. Next subsections deepen these arguments.

2.2.1. Precision medicine and Digital Transformation

The challenge of digital transformation in healthcare systems, and for Life Sciences value chains in general, has been recognized as a crucial precondition for PM success and diffusion (Gastaldi et al., 2018). This revolution first depends on availability of ubiquitous data sources such as wearable sensors, smartphones, cloud computing, and IoT (Internet of Things). Second, artificial intelligence systems (Pathinarupothi et al., 2018) is strategic for mining this data and 'augment' the decision-making processes, to make them more precise. In particular, it serves the purpose to predict adverse events thus reducing waste of resources and mortality rates, as well as offering information to hospitals prior to admission for a better management of staffing and resources in general (Bates et al., 2014). Furthermore, several other emerging technologies have been cited as key enablers for PM, such as 3D printing (Huang et al., 2013) or crowdsourcing science (Shaikh et al., 2014). In particular, a better understanding of those strategic and organizational processes for the governance of data generation, gathering, and integration behind these dynamics emerges as a promising field of research (Jones et al.,

2015). Complex information technology platforms are needed, to store and analyse billions of heterogeneous data from millions of devices and patients (Hood & Friend, 2011). An example of such complexity is the following: a single human genome mapped through next-generation sequencing (NGS) means about 3 gigabytes. However, only about 0.1% of the genome is different amongst individuals, but counting for about 3 million variants (Andreu-Perez et al., 2015). It means huge computational power and optimized algorithms that target and identify only the few relevant data / insights. New sources of data are also becoming more and more popular in biomedical sciences, such as data from smartphones and social networks. This scenario rises serious ethical and privacy issues. Existing studies show that healthcare organizations struggle in dealing with such technologies and challenges (Gastaldi et al., 2018), calling for studies aimed at understanding those facilitators that can unlock this huge potential.

2.2.2. The new for cross-fertilization and 'updated' supply chains

The few studies we noticed often converge in citing the need for new form of collaborations and configurations of both R&D systems and adaptive supply chains, which connect multiple domains and stakeholders, from researchers to investors, from healthcare professions to patients, from regulators to payers, from diversified disciplined and sectors (Coccia, 2014; Gastaldi et al., 2018; Horgan, 2018; Zaric, 2016). Novel forms of healthcare eco-systems are emerging. It is a form of cross-industry innovation which is largely unclear in its directions. Nevertheless, a better understanding of these mechanisms is crucial to interpret how the new PM-centric supply chains are emerging and evolving (Jones et al., 2015; Phillips et al., 2017). In doing so, it is important to account for the entrance of new unexpected players with different corporate cultures and expectations, like Facebook or Twitter, which own huge amount of data about people lifestyle habits and environment (and, more and more, even about people's health).

2.2.3. Cost Reduction or cost Explosion?

PM is claimed as emblematic example of disruptive innovation, which breaks the Porter's rules and pursues simultaneously higher quality of healthcare services and significant cost savings (Schilsky, 2010; Moors, 2018). Molecular genetics, screening, big data, early diagnosis and targeted therapies are expected to offer benefits not just for sick people under treatment, but a more optimized healthcare system for all, more informed responses to population-level health threats, and more efficient use of resources (Horgan, 2018). Precision

in medicine support sustainable development of global healthcare systems, for instance by reducing days of hospitalization, not necessary tests, optimization of workforce planning and in general resources, and so on. However, though we noticed a pretty large consensus on the promise for a better care, the issue of cost-saving is controversial, whilst levels of sustainability are uncertain (Schartinger et al., 2015). Some scholars argue that reduction of resource usage take place only in specific circumstances, e.g. scenarios where PM permit to avoid treatment that might useless if not harmful (Zaric, 2016). Other studies support that PM means higher costs, due to sophisticated technologies and huge investments at the research level, uncontrolled proliferation of tests (due to the emphasis on prevention), lack of evidence on validity (Trosman et al., 2017). Furthermore, insurance companies have developed over time their routines on financing health services "once the damage is done", and addressing situations under the control of care providers. It generates path dependence and organizational barriers against PM diffusion which largely belong to uncertainly of costs (Schartinger et al., 2015). Within a system aimed at prevent instead of treat, the problem of cost estimation and reimbursement management should be reconsidered from scratch. Treatment and diagnosis offered by care providers are specific moment in time, whilst prevention occurs in the long period. In other words, reimbursement as in mainstream medicine is a one-time stand-alone activity, whilst in the PM scenario should be an iterative process that may appear to insurance companies and payers as very expensive and difficult to manage (Gould, 2018). In short, without a better understanding of cost models for PM, coupled with significant rethinking of the reimbursement system, it is unlike that the PM revolution take place at large scale. However, factors of success and directions of these changes remain uncertain.

3. CASE STUDY ANALYSIS

3.1. Methodology

Our empirical analysis relies on a qualitative explorative survey based on in depth multiple-case study investigation (Eisenhardt, 1989; Flyvbjerg, 2006; Gerring, 2007; Yin, 1994). The procedure we used consists of three main steps. First, we ran an extensive analysis on publicity available information on the well-known Lexis-nexis database looking for the most inspiring cases of PM all over the world from an economic and managerial perspective. In doing so, the subject of analysis was 'projects' showing features belonging to the PM paradigm as above defined. This screening process led to a short list of 30 high potential cases with regards to our aims. In step two we filtered four case studies satisfying three criteria: a)

consistency with our theoretical framework; b) diversified portfolio of cases in terms solutions and scope, to cover almost the whole healthcare value chain, from research to care delivery; c) availability of companies to take part our study.

In the third phase of our empirical analysis we deepened strategic and organizational implications of four innovation claimed as cases of PM, meaning: a) the first case ever of treatment based on RNA interference, developed by the biopharmaceutical company Alnaylam; b) how Merck used biomarkers as innovative driver for preventive medicine in oncology; c) an innovative wearable device invented by Medtronic for patient-centred diabetes care delivery; d) how algorithm and big analytics applied by 3M to deliver tailored healthcare services via dynamically adaptable organizations within hospitals. Information collected via direct interviews has been integrated with further data from different sources like: scientific literature, professional journals, 'grey' literature (industry reports, policy papers and books), official web sites of the company. We collected 9 interviewers with top managers and project managers employed by the mentioned companies. The interview protocol was designed around the following topics. First, we asked the definition of PM accordingly to the company. Second, we focused on the identified project covering the following arguments:

- Overall description;
- Adoption of digital technologies and solutions;
- Impact on healthcare delivery and reimbursement system;
- Results and impact on costs;
- Critical factors and future challenges.

The interviews have been anonymised to mask the identities of the experts, and fully transcribed to ensure reliability of the methodological procedure and findings. We design this methodology to satisfy validity parameters often cited by similar surveys in management studies. First, a multisource strategy contributes to construct validity. Second, the choice for a multiple case studies methodology supports literal replications, to increase external validity. Then, our interview protocol supports reliability as third key criteria. Basic information about the four cases are reported in table 1. The next subsections discuss these four cases, whilst section 4 introduces an overall discussion focused on key findings, and evidences that cut across that four projects.

Table 1. Case Studies Overview

	Company & Project	Sector / domain	Key actors	Relevance of Digital Technologies
A)	Managerial impact of genomics based treatments: the Alnylam experience	Drug Development and its commercialization;	Biotech company; regulation body; hospitals;	Low levels
B)	Oncology and personalized therapeutic approaches: the Merck experience	Drug Development and use of biomarkers;	Pharma and life science company; hospitals; clinical laboratories;	Medium (big data analytics)
C)	Medtronic and diabetes management: toward a patient-centred diabetes care delivery	Medical devices and hospital experience;	Medical technology and solution company; hospitals;	High (big data analytics, devices/Iot)
D)	3M and Predictions of Potentially Preventable Events as driver for tailored healthcare services	Medical technologies and hospital experience;	Medical technology and life sciences company; hospitals; insurance companies;	Very high (big data, artificial intelligence, cloud computing)

3.2. Managerial impact of genomics based treatments: the Alnylam experience

Alnylam is the worldwide leading biopharmaceutical company for therapeutics based on Ribonucleic Acid Interference (RNAi), which is a form of precision therapy based on biological pathway which selectively silences and regulates the expression of specific genes. Alnylam incorporated in 2003, it is headquartered in Cambridge (US) and now has 749 employees (2018). The mission of the company is to address the needs of patients who have limited or inadequate treatment options through breakthrough innovation. In the last years it experienced a significant jump in its turnover – from 47 to 89 millions dollars – thanks to some big achievements. The latter includes the FDA approval and the beginning of commercialization for a therapy called Patisiran aimed at treat the 'Hereditary Transthyretin Amyloidosis' (hATTR), a relatively rare disease based on genetic mutations. It affects about 10,000 people, though due to under-diagnosis the right number is likely significantly greater.

This therapy is an emblematic case of PM as innovative treatment. First, it is very accurate in its action since it target and silence just the specific messenger RNA blocking the production of proteins that causes the disease. Second, it is grounded on a 'pre-emptive' approach: Patisiran can not reverse damage caused by the disease, but it is strong in prevent and delay progression. Moreover, this technology supports accurate diagnosis even when the disease is

at its infant stage: on average, 4 years in advances compared to diagnoses based on mainstream methods. The promise of this protocol is to pursue both better health and simultaneously cost savings for the healthcare system. A pilot study in Abruzzo region (Italy) estimated an additional cost of 9,300 euros per patient, whilst costs incurred by hospital and patient family that falls from approximately 29,800 to approximately 12,500. Both trials and commercialization phases implied a huge effort to reshaped organizational activities around specific features of this innovative product. For instance, they rethought the patient experience: the treatment need specific technologies and medical capabilities for the drug administration. However, instead of do this within the hospitals, Alnylam is implementing the following process: a) the production of Patisiran takes place within the hospitals offering this treatments; b) the patient goes at the hospital, buy the drug, and bring it at home; c) Alnylam is settling up agreements with suppliers and partners to permit drug administration within patient's four walls, in a comfortable situation and with less costs for the hospital. Another specificity of this project is that Alnylam recognized that the new paradigm pushed forward by Patisiran implied heavy training for all healthcare workers engaged in trials and, after, during commercial phase. The budget for this activity has been defined as "disproportionately high" compared to other similar comparable cases. In contrast with other PM cases we studied, Digital technologies played a minor role in this project. Alnylam is starting developing machine-learning system combined with advanced phenotype technologies such as imaging and wearables to uncover genetic and metabolic drivers of disease, and to advance its prevention-based solutions. However, this activity regards other projects. Sales in this early stage are more than satisfactory: about 11 millions in the first year (in US). After a great commercial beginning, also supported by a very positive media coverage, the project is now facing problems with the treatment price, which is perceived as very high. It may appear as surprising given the relevant above mentioned cost savings. Accordingly to what emerged during our interviews, the company struggle let the market perceive the overall value of this innovation since cost savings are gained by stakeholders which are not the payer. In other words, "*If distribution of benefits and costs are de facto fragment over too many players… it very difficult to convince that overall cost-benefits balance is positive and get legitimacy.*" Moreover, this innovation represents a big jump for a definitely more accurate diagnoses, and it is designed to stop the disease - not to cure - thus preventing future disabilities/costs. The issue is that these benefits are largely associated with indirect cost savings, whilst extant healthcare system is focused on direct costs: its imprinting is "pay for cure", not "pay to prevent". Despite different regulation systems, Alnylam in its experience felt to perceive this

as a kind of healthcare culture which cut across all countries in which the company is present, with minor differences. During our interview, a Managing Director at Alnylam concluded: "*Medicine is facing a scientific renaissance which pushes the whole healthcare value chain to reassess and place much more emphasis on diagnostic processes. However, it means rethink valuation criteria for both operational and clinical efficiency. It is indeed much more a business model revolution, than a matter of medical research. The issue we ourselves – as whole medical community – struggle in understanding directions of this big change*".

3.3. Oncology and personalized therapeutic approaches: the Merck experience

Merck is an international company active in Healthcare, Life Science and Performance Materials, with approximately 52,000 employees in 66 countries. Between the several challenges that Merck is facing, it is developing effective therapeutic approaches to fight cancer. In particular, here we focused our attention on therapies based on the use of Erbitux®, a monoclonal antibody that combats the growth of tumor cells in many colorectal cancers.

There are some cases where Erbitux® cannot have its intended effect. From here, we can describe a typical case of predictive medicine. Merck has developed, in addition to the conventional examinations of tumor tissue, the use of biomarkers (Kraus, 2018) from the RAS gene family to predict a patient's potential response to the treatment and for the choice of the most appropriate first-line therapy of metastatic colorectal cancer (Harthy et al., 2018).

This phenomenon is going to imply a dramatic shift in the healthcare value chain, decreasing the hospital stays, the risk of recurrences, complications, and avoiding the prescription of costly and ineffective drugs and preventing potentially harmful side-effects. In addition, this evolution is changing the organization and management of clinical laboratories. As stated by the Medical affairs Director, *"in Italy when we launched this new therapies, much of the Italian hospitals are not able to carry out these tests and analysis, lacking of adequate technologies and technical skills*". Consequently, Merck in partnership with Kelyon developed an online platform that offers the possibility to carry out the analysis of the KRAS gene at the chosen Reference Center and to have the online test result in a short time and in full compliance with current regulations regarding privacy. According to a participatory medicine approach, RAS-Aktive may include streams for the management of molecular biology tests where the subjects can be oncologists and molecular biologists, or oncologists, supervisors, pathologists and molecular biologists, but may also provide to manage requests for kits from microbiologists with a stream authorization to the internal customer. This platform facilitated the exchange of biologic material, clinicopathological data and diagnostic

reports within the network. To date, this plaform has allowed to carry out more than 20.000 tests. But this dramatic shift requires also the development of a platform for data gathering, integration and analysis, where different actors can interact to develop an ecosystem for innovation, called Translational Innovation Platform (TIP). In fact, Merck was the first pharma company to collaborate with multiple diagnostic providers to support RAS biomarker testing. Through this platform, Merck developed several collaborations developing an ecosystem for innovation. Just to cite some of these we can remember the followings:

- the collaboration with Sysmex Inostics for development and commercialization on blood-based RAS biomarker mutation status test for metastatic colorectal cancer (mCRC);
- the Collaboration with Biocartis and to develop a new liquid biopsy technology for RAS biomarker testing;
- the collaboration with AmoyDx to develop liquid biopsy RAS biomarker based upon real-time PCR technology.

The last point concerns the necessity to shift from traditional reimbursement models towards patient outcomes or risk-sharing models for drug and diagnostic coverage. As stated by the Market access Manger "*in Italy, Merck waited for ten years the fully reimbursement of these new therapies"* and, as described above, this kind of medicine needs strong investments by pharma and diagnostic firms. Consequently, "*reimbursement models could be provide the incentives to invest in a long-term view, also by considering the benefits for a diagnostic test to pair with a specific treatment".* Finally, the Merck Italy CEO launches a new challenge, he said "*Digital biomarkers is becoming an important concept*". In fact, the company is investing on the development of a range of diagnostic tools and patient compliance monitors from non-invasive wearable biomarker sensors.

3.4. Medtronic and diabetes management: toward a patient-centred diabetes care delivery

Medtronic is a global leader in medical technology, services, and solutions specialized in several devices and in particular in cardiac, vascular, diabetes, minimally invasive and restorative therapies, with approximately 86,000 employees in more than 150 countries. In this paper, we focused out attention on diabetes. More than 422 million adults worldwide live with diabetes (NCD, 2016), with a global cost that is estimated to be 825 billion US dollars per year, and it mostly depends on the costs of diabetes complications (WHO, 2016), such as retinopathy, nephropathy, neuropathy and cardiovascular disease. An opportunity to fight

diabetes is certainly provided by PM and research and artificial intelligence, also thanks to the use of wearables, sensors and smartphone technologies. In this context, the Medtronic Minimed 670G is a game changer, a typical case of personalized medicine. Approved by FDA in 2016, it is a wearable continuous glucose monitor (CGM) and insulin sensor-augmented pump connected to a data management systems, that allows an automatically adjustment of bas insulin delivery every five minutes in sensor glucose data. This solution leads to improved clinical outcome, glycemic control and hypoglycemia rates by tailoring and personalizing the diabetes mellitus care (Bergenstal et al., 2016; Garg et al., 2017; Nicolucci et al., 2018; Stone et al., 2018). In contrast with mainstream approach, from two to eight blood glucose measurements a day, the real-time nature of this solution with 288 glucose levels measurement each day allows patients to intervene when glucose values change rapidly and prevent glucose excursions and exposure to hyper- and/or hypoglycaemia.

Here the clinical outcomes are not in question, but which is the impact of this solution on healthcare delivery chain? In the words of the Goverment Affairs & Regulatory Director "*This solution allow diabetes care to go directly at home, minimizing clinic visits and improving the number of contacts with the care team*". This solution allows to provide care also to patients who live far from the diabetes centre that are at risk to limit their care, by providing similar quality of care to face-to face-visits and by facilitating the everyday decision-making process of patients living with diabetes. He said "*This change impacts on current processes and organization of care, the nature and role of health care organizations, their information systems, organizational structures and facilities*". For medical staff, it would enable more flexible follow-ups whereas, for hospitals, the result would be more efficient use of resources. As it is estimated that 50–70% of routine follow-up clinical consultations could be replaced by remote monitoring, use of digital health records and virtual house calls, that could allow to save up to 25% of the cost of their care. "*Diabeter led to save 8,6% in direct annual costs of type 1 diabetes patients, mainly driven by a much lower patient hospitalization rate than that of other Dutch pediatric diabetes clinics"*. Medtronic acquired Diabeter Dutch clinic network in April 2015. Diabeter is specializes in providing comprehensive and individualized care for children and young adults with type 1 diabetes. Between visits, the Diabeter team supports the patients by e-mail, Skype, and phone to continuously adjust and maximize their treatment. Patients then receive an e-mail called "Ther@pie mail" with information on trends, target settings, treatment plans, and next contacts with Diabeter. Patients are offered an emergency hotline that gives them immediate access to a medical doctor at Diabeter 24 hours a day, 7 days a week. Secondly, personal

CGM has a very deep impact on research (Fagherazzi and Ravaud, 2018; Sherman, 2016). In the words of our interviewed: "*the real-world data is a unique source for clinical evidence by allowing retrospective analysis of complete profiles, facilitating an individualized approach to diabetes management*". Big data analytics present a great potential for improving diabetes care. For example, historical patterns can be analysed to predict activity and lead to pro-active insulin adjustment to prevent hypoglycaemia and diabetes-related complications, as well a powerful potential for identifying new digital markers and patterns of risk. From here the partnership between IBM Watson Health and Medtronic to fully unleash the potential of the personalized medicine based on these new devices. "*We are moving from a world in which patients are characterized by only a few recent measurements of fasting glucose levels and glycated haemoglobin to a world where we have available various key parameters at thousands of time points simultaneously*". This is disrupting the way diabetes is prevented and managed in traditional clinical settings. Hybrid research materials, based on a variety of data sources such as devices, e-health records and e-questionnaires, will ultimately help research scientists identify innovative risk markers of diabetes and diabetes-related complications, analyse new biological pathways, evaluate multiple morbidity more easily and nest clinical trials. Moreover, with more and more data available, AI methods will also help to devise more accurate risk prediction models for diabetes and diabetes-related complications that will, in turn, help to personalize treatment, care, surveillance and management strategies, thereby boosting our advance towards PM in diabetes. This is the meaning of the "third P" that stands for prevent medicine*,* where medicine meets different fields such as wellness, nutrition, digital wearables & IoT. Thirdly, the development of this form of PM implies a move to bundled payments for the entire diabetes care cycle. Traditional payment systems that support volume over value, as well as fragmented and disconnected care-delivery methods, are limiting patients' access to optimal care, particularly those with chronic medical conditions. As stated by the Value, Access & Policy Manager "*Transforming care delivery also means transforming payment models*". Payments should be bundled for the entire care cycle and preferably be connected to outcomes, that must be measured for the entire care cycle for each patient, and related to risk-sharing contracts that enable providers to save money due to fewer complications and hospitalizations. For example, this system is working very well in Diabeter Dutch clinic. Finally, these technologies impact on users in a complex and ambivalent way. Scholars report generally positive user experience alongside a number of important challenges, ranging from variable levels of trust to concerns about physical bulk, technical glitches and difficulties incorporating closed-loop systems into everyday life (Farrington,

2018). It is imperative that clinicians consider the user experience with these technologies to identify intervention targets for sustainable use (Messer et al, 2018), concerning clinical but also psychological aspects. Otherwise, the "fourth P" that stands for participatory medicine, can encounter several hurdles difficult to handle.

3.4. '3M' and Predictions of Potentially Preventable Events as driver for tailored healthcare services

'3M' is a multinational conglomerate corporation operating in different sectors, ranked n.97 in the 2018 Fortune 500. It invests about 5.8% of sales in R&D and produces about 3,000 patents per years. Healthcare is a key segment for this company: it accounts for 18.4% of total sales and grew by 4% annually. In recent years PM has become a key business area for the healthcare unit. However, this organization explores that trend from a different perspective compared to what we reported in previous sections. Instead of leveraging on genomics and related medical disciplines, 3M apply the precision dogma by using data and algorithms for optimization of healthcare resources and adaptive management systems. PM accordingly to 3M is therefore "*the identification of the correct resource for the correct person, with correct timing, towards better care services at lower cost*", as said during our interviews by a managing director at 3M Health Information Systems. Given these pillars, 3M developed patented methodologies and software to date support about 6,000 hospitals around the world to integrate, filter and classify data by granular clusters for tailored care-management services. These systems generate predictions and advise in real time managers over decision making processes with regards to accurate resource allocation, revenue management, improvement of patient care and experience, and – above all – agile planning. In particular, the focus of this case study regards those 3M solution for the predictions of potentially preventable events such as - inter alia - admissions, complications, readmissions. It helps to avoid unnecessary care and reduce costs via resource optimization and adaptive systems. Typically planning activity within hospitals considers all patients affected by the same disease as a relatively homogeneous class to estimate costs and resource absorption. Some further variables such as age or gender could be accounted for adjustments. By contrast, the precision-based approach advanced by 3M moves from the proven circumstance that variance within a diagnostic related group is often greater than variance across different groups. For instance, an asthma patient may cost 60 or 3,000 dollars: standard values based makes no sense. Therefore the 3M's algorithm stratifies patients by several variables and lead to fine-grained stratification which flexible to objectives and dynamic over time. Sometimes it

updated on a daily base. Beside diagnosis, it covers: severity of illness, medical history, checks, discharge status, age, gender, length of stay, etc. This is not 'customization': predictions are not individual, but it's definitely a more accurate classification leading to thousands of sub-groups, instead of few dozens. This methodology rooted on the PM paradigm is leading to promising results. For instance, within the St. Joseph's Hospital Health Center in Syracuse (US) the rate of patients who experienced unexpected complications declined by 48% (from 58.5% to 30.4% per 1,000 discharges). Several other hospitals using this technology have achieving similar results and increased their agility. This case also shows a strong emphasis on prevention, moving from the assumption that the 'one-size-fit-all' approach must be overcome even at this level, as suggested by the following example. Patients are offered message reminders via smartphone about appointments: it's a pretty diffuse practice. For lower risk patients this is sufficient, whilst patients at risk deserve more than a text message. 3M implement its methodology and software within the Denver Health Medical Center in Colorado (US) to account for that. Patients are thus stratified by several sub-groups using a multitude of variables and receive different forms of attention on that basis. It is also a case of 'participative medicine': 3M has been able to create data pipelines sourcing from 1,700 hospitals in US. This adaptive system reads and aggregates all this data from independent sources to offer better prediction based on a sort of 'collective brain'. It is affecting the way by which supply chain and CRM are managed. For instance, if children with asthma are hospitalized more frequently than expected, or at higher cost than expected, the hospital may ask health insurance company to renegotiate contracts. In doing so, the hospital CFO have granular data to support and dynamically adjust his/her position. Furthermore, the hospital could start a discussion with local families to identify reasons of that asthma unexpected diffusion in children, and manage together the issue. This is real case happened in Iowa, US. If something like that already occurs at national level, artificial intelligence makes it possible at the local level, in the short term, without expensive surveys. Among factors of success, the first key issue is the need for new metrics. The way by which hospitals measures its dynamics is inconsistent with the above discussed approach: if the organization uses the wrong metrics, maybe it can perceives a satisfied patient – maybe - but unlikely it can have a reliable picture about cost savings. Without that, gain legitimacy in the whole organization is hard, and therefore implementation may fail. The development of right metrics and dashboard for PM based forms of healthcare optimization is still at the early stage and it has been cited as 'the' key challenge for the future during the discussion with 3M. Second, we reported the need for sponsorship at the top management level as crucial to

overcome scepticism of healthcare workforce and to push implementation of new practices and learning of new IT skills. In short, it's largely a question of new capabilities, which cuts across several professional families. A third critical factor emerged in the above mentioned situations regards ethical issues. The fact a machine affects decisions about who is the patient which deserves the most attention is matter of discussion and it is slowing diffusion and implementation of this class of technologies.

4. DISCUSSION

The four cases show both convergent and divergent findings, both expected and unexpected evidences. Among confirmations, the need for a shift towards a culture based on prevention and integration of data and systems here emerges as central to the debate. These aspects are here widely discussed for the first time with lens of business and innovation theories. The cases also outline further evidences suggesting there are lots of ethical issues, such as: the need to access this advance to all and to rich people only; the fact a machine affects decisions about who is the patient which deserves the most attention; the issue of data privacy. However, here we focus the discussion on the novel contribution from our empirical investigation, which we organized around three key issues as follows. The first issue describes how different strategies live together under the same notion. The second and third issue describe two fundamental traits common to all type of strategies and business models in PM.

4.1. Precision Medicine as a class of innovations converging to the same value proposition

We argue PM is actually a broad class of different healthcare innovations. What they have in common is the research of the right healthcare bundle of solutions for the right patient, at the right time, and nothing else, which also means remove the unnecessary. On the other hand, our investigation shows there are several strategies to pursue that goal. In other words, PM is not genomics, neither prevention or digital heath: it is everything makes the healthcare system capable to provide people *only what they really need* to stay healthy. Our work outlines both theoretical and empirical evidences suggesting that these different strategies can be grouped around four dominant models, as summarized in table 2.

Table 2. Different strategies in Precision Medicine

Product-based	**(I)** **PRECISION TREATMENT** Example: Alnaylan	**(II)** **PRECISION PATIENT CARE** Example: Medtronic
Platform-based	**(III)** **PRECISION THERAPEUTIC APPROACH** Example: Merck	**(IV)** **PRECISION HEALTH SYSTEMS** Example: 3M
	Focus on Technology-based innovation (Pharmaceutical and Biological Sciences)	**Focus on Business Model Innovation**

Even if all the four models have the same basic characteristics, we can distinguish some situations where they are more relevant. The first quadrant, called "precision treatment", corresponds to a strategy based on a strong product, by leveraging the outcomes of scientific research especially focussed on technological advances, i.e. in pharmaceutical and biological fields. The strategy here is based on a precision treatment of a very specific disease.

The second quadrant - "precision patient care" - describes a strategy based on a strong product and/or medical devices, by leveraging on novel adaptive business models. In comparison to the first quadrant, here the attention shifts to the relevance of solutions such as wearables, sensors and smartphone technologies, that allow to provide home care, continuous monitoring and measuring of health data, also by following the patient 24-hours a day, 365 days a year. "Precision patient care" means shift the focus from the single treatment to the whole interaction between patient and healthcare professionals, structures and services, also by including patients in discussions of plans and goals, providing them education and being supportive to their families.

The third quadrant, called "precision therapeutic approach", correspond to a strategy grounded in pharmaceutical and biological sciences and focussed on the development of a platform instead of a single product. Here digital technologies are not so relevant as in the previous quadrant. The critical factor is the capability to develop and manage a platform of collaboration, where oncologists interact with pathologists and biologists, analysis centers interact with health care organizations, where pharma companies interact with molecular

diagnostic providers. Just through this platform, companies are able to provide a strong and real support for a "personalized therapeutic approach".

Finally, the fourth quadrant identifies the strategy called "precision health systems". This strategy is grounded again on business model innovation. Here to become "precision", medicine needs participative and agile platforms which read and aggregate several type of data and applications sourced from physicians, patients and their families, health care organizations, health insurance companies, independent actors. This can allow a dramatic shift in the health care organization management systems as well in health insurance reimbursement programs. A shift from diagnosis-related group based care to adaptive value-based care. This evolution can lead to a dramatic impact on the whole system of care, both on provider and payer sides, towards a real "precision health system".

4.2. Precision Medicine as Innovation – wannabe 'Open' - Ecosystems

The need for rethinking value chains and supply chains has been noticed in all the cases we investigated. In particular, the cases Merck and Medtronic are emblematic in showing how the relationship between diagnosis and treatment is likely at the dawn of a new era, as well as boundaries among activities carried on by research bodies, on one side, and by hospitals, on the other, are less clear (e.g. some pharma companies working on PM are thinking to become also care providers). The case of Anaylam and Medtronic highlight how the healthcare value chain and supply chain are under the tension of breakthrough forms of care delivery, assigning new roles to hospitals and suppliers. The breath-taking advances in science of Merck and Alnaylan emerged as ineffective without strong reorganization of activities and new skills at every level of the value chain. The case 3M supports PM as revolution largely at the business model level, through novel architectures and adaptive management systems, even without any kind of advance in medicine. As a such, PM initiatives hardly fits with mainstream healthcare value chains. The usual flow grounded on preventing/ diagnosing / preparing / intervening / recovering /monitoring and managing is questioned. The focus becomes much more upstream on preventing phase than on intervening and recovering phases. The monitoring phase shifts from a single phase to a continuum of activities. The diagnosing phase is conducted through wearables and continuous measurement systems at home, leading to a dramatic decrease in office and hospital visits as well as in the organization of clinical laboratories and diagnostic activities and skills.

Value creation architectures we investigated emerged as more consistent with theoretical foundations of innovation eco-systems, meaning project-based and adaptive networks where

the success of novel projects and focal organization – the orchestrator - depends on the efforts of other innovators in the environment (Adner & Kapoor, 2010). PM as innovation ecosystem emerged in our study as evolving bundles of interlinked business models (Shaw & Allen, 2018). These dynamic systems are also characterized by input-output relationships that – in contrast with the supply chain view – are un-linear, multi-agents and multi-directional. They are forms of rapid learning healthcare system, aimed at enabling an open and adaptive solution to health prevention and control, and grounded on heterogeneous knowledge-based services (Garcia-Quevedo et al., 2011; Shaikh et al., 2014). PM is also a 'stakeholders' architecture', where the interplay between governance, eco-system and growth regard public entities, local communities, and citizens as key actors (Anbarasan and Sushil, 2018(Mendez-Picazo et al., 2012). However, this is a very peculiar kind of innovation eco-system. It co-exists with tensions that inhibit its potential and evolution, as tensions that are only weakly present in other eco-systems like those in software or tourism (to cite examples of well-known forms of innovation eco-systems). The first tension is the relationship between innovators and regulatory bodies. There are several other industries affected by regulation and standards, but healthcare is unique from that standpoint. It suffers the pressure of institutional forces like any others, thus altering the self-adjustment mechanisms by which agents of eco-systems and, above all, focal company govern expectations and efforts of innovators and new ventures (Moodysson & Zukauskaite, 2014; Ribeiro-Soriano & Galindo-Martin, 2012). A second tension regards the fact that innovation eco-systems are 'open' by nature. Our empirical findings confirm that PM 'must be' *Participative*. It requires new platforms for data gathering, integration and analysis, somewhat consistent with prescriptions of the so called sharing economy (Matzler et al., 2015) and platform economy (Kenney & Zysman, 2016). However, institutional, organizational and ethical barriers are impeding the emergence of open systems in Precision Medicine. Though our cases offer some guidance to achieve that goal, it still remain one of key challenges towards the diffusion of PM. In short, the innovation called PM is pushing healthcare value chains to become innovation eco-systems, in a body that reject them. They want to be a fish in a bowl without water: it's indeed disruptive, but you live only for a while.

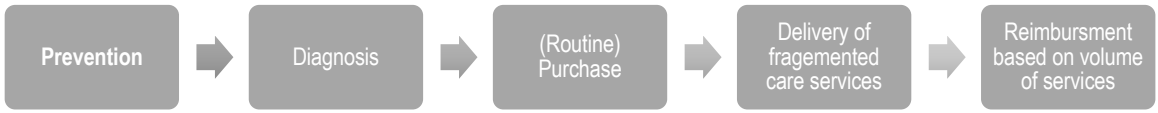
4.3. From "Cure" to "Care": towards the Bundled-based model free from time-constraints

Our investigation further emphases what is already know: PM is largely a question of prevention. It's in the DNA of this revolution: the best way to optimize resources is of course to act before the damage is done. There is nothing new in saying the prevention is better than

cure. However, the digital transformation introduced exponential technologies like big data analytics or artificial intelligence that represent a big jump in terms of predictions. Cases like Medtronic or 3M add that this vision calls for a cultural shift from interventions constrained by time to constant monitoring and action. On the other hand, there is a path dependence effect of healthcare systems which are grounded on routines designed for a cure-based medicine. This is particularly clear in reimbursement systems, which is not designed to account for never-ending monitoring, or indirect costs (those that matter the most when it comes to events not yet happened), or adaptive systems as those reported in our case study survey. The impact on procurement systems is also profound. The extant model is literally flipped as in figure 1.

Figure 1. Procurement and Reimbursement: mainstream view vs Precision medicine

(A) PROCUREMENT AND REIMBURSEMENT AS IN THE MAINSTREAM HEALTHCARE SYSTEMS



(B) PROCUREMENT AND REIMBURSEMENT AS IN PRECISION MEDICINE FRAMEWORK

The four projects we discussed are innovation eco-systems composed by bundles of highly interdependent data and services, that can't be decoupled. As a such, they also need bundle-payments and specific metrics to be appreciated in their benefits over the well know triple aim. Extant metrics do not capture how much a delivered healthcare service is indeed what a specific individual really need (as key factor to appreciate the value of cases Medtronic or Merck). Measurements in healthcare largely fail in capture specific cost-savings of PM, so the latter appears as very expensive (as happens in the cases Alnylam and Medtronic). Mainstream metrics may help to capture effects on overall health population at large scale, but fails in understanding the dynamics between actions of care providers and the systems of

patients around them (as key goal achieved in the 3M case). PM initiatives as a bundled-based model which requires the redesign of valuation and refund procedures, as well as of revenue models, for both companies and healthcare (institutional) systems. Furthermore, the popular practice of grouping types of hospitalizations and healthcare services into homogenous classes becomes a non-sense, whilst the new era of dynamic and flexible pricing is beginning, similarly to what already happens buying a flight ticket or a product on Amazon. The fact that cost of a blood test is different from individuals to individuals, if booked at 2pm or 5pm over the same day, becomes the new normal. These changes require adaptive platforms for data gathering, integration and analysis, more and more consistent with prescriptions of the so called sharing economy (Matzler et al., 2015)(Matzler et al., 2015)(Matzler et al., 2015)(Matzler et al., 2015)(Matzler et al., 2015)(Matzler et al., 2015) and platform economy.

5. CONCLUSION

This contribution investigates the emergence of the so called 'Precision Medicine' from a business standpoint. Theoretical and empirical evidences offer both confirmations and new perspectives. In doing so, we push forward the idea that the debate starts from healthcare but it directly regards different fields and industries. The Precision Medicine revolution is facing immense challenges to become a golden standard, which are largely strategic, organizational, and cultural, more than scientific. However, if it will indeed deploy its huge potential, boundaries of healthcare are going to be dramatically redesigned, leading to platforms made by adaptive eco-systems which engage dynamically diverse sectors, including both closed domains like nutrition or digital wearables, but also unexpected ones such as media, entertainment, green industries, and so on. It is much more than forms of cross-fertilization, it is the promise for new blue ocean markets. We argue that a greater 'awareness' – of both scholars and practitioners - is now needed to make further steps forward. We revealed strong evidence that people are struggling in understanding what PM really is, including professionals in the field (especially people with medical background only). For instance, there is who implicitly assume it is something almost equal to genomics, whilst PM is a portfolio of several platforms spanning from biomedical science to pure digital solutions. Someone think that this revolution is far away in time, other talks about as if it is already routine within leading organizations. In that direction, we clarify that PM is indeed a disruptive value proposition delivered through four main patterns of strategies and solutions. The recognition of these differences is a key precondition to advance the theoretical understanding of the phenomenon as well for – in terms of managerial implications - better

design of strategies, business models, metrics. Our findings also have relevant implications for policy makers. We offer insights to facilitate - from a regulatory body standpoint - the transformation of the healthcare value chain through innovative multidisciplinary initiatives aimed at pursuing simultaneously better and more accurate health outcomes, decreasing of costs, improving and differentiated access to care. This study also illustrates how reimbursement and other regulatory policy are not only a political decision but are being shaped and strongly influenced by end-user profiles, expectations on what PM should be, readiness toward innovation (Moors et al., 2018). Our findings are in line with recent studies suggesting digital services in healthcare encourage patients to participate in the treatment process, thus fostering patients' experience satisfaction (Lee, 2018). Furthermore, R&D, associated regulatory process and incentive are largely unchanged and burdensome to develop innovative medicines: they need to catch up with the science.

Limitations of this work should be taken into considerations to set future research agenda. Identification and analysis of case studies showing a higher diversification of players – in terms of capabilities and sectors - is needed. Second, the assumption accordingly to which PM initiatives are indeed platforms sharing features with the construct of innovation eco-systems must be deepened. Finally, our discussion suggests several assumptions that should be validated through quantitative studies.

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