H^2UMANISM: Holistic Healthcare Supply Chain Management for Precision Medicine

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Abstract In this book chapter, we present in a holistic manner, recent approaches for improving supply chain management, which especially target and/or enable precision medicine applications. Precision medicine regards the provision of more than individualized and specially targeted medical services. Characteristic examples are the use of biomarkers for disease prevention, individualized medication therapies, specialized physical and biochemical examinations. However, in order to provide such services nowadays in a timely and cost-efficient manner, more intelligent supply chain services are needed, exhibiting speed, lower cost and flexibility. In this chapter, we present a novel framework (which we term H^2UMANISM) for developing advanced and optimized supply chain management approaches and tools for such precision medicine services and then summarize relevant already existing solutions. Then we review the emerging challenges that will need to be addressed for achieving the envisaged framework and conclude with some suggestions for future work.

1 Introduction

Precision medicine is an emerging approach for disease treatment and prevention that takes into account the variability in genes, environment, and lifestyle exhibited by each individual [1]. Even though the exact term is relatively new, the original concept is older and has been with the healthcare practitioners quite some years, e.g., blood transfusions is a form of precision medicine since transfusions take place only

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between specific blood type combinations. However, the role of precision medicine in today's daily healthcare practice is still practically limited and unsystematic. Quite many of the healthcare stakeholders, e.g., pharmaceuticals, insurance companies, etc., have expressed clear desire for a broader expansion of precision medicine to many sectors of healthcare in the coming years, leading to fruitful and fascinating results in many different ways.

Precision medicine involves a multitude of features, which regard the healthcare services themselves, the patients, and a number of additional aspects required to develop such a broad model for the practice of healthcare. The most important feature is naturally the part that relates to the healthcare itself. Driven by scientific advances, the healthcare services that allow for precision medicine are those where it has been made possible to customize the provided service via a novel discovery in pharmacology, biology or biochemistry. A characteristic example is the use of genetic information to create personalized drug treatments (i.e., pharmacogenomics [2] or biopharmaceuticals [3]) for the design of targeted vaccines and treatments, e.g., one such treatment is expected for cancer.

Patients cannot actually affect the evolution of methods employed. However, the acceptance of the anticipated services and products will be determined purely on the desire of societies, and the patients especially, to accept paradigm shifts with respect to the traditionally established practices. For example, societies are used to the "one-pill-to-fit-them-all" approach for the design of drug, namely that a drug needs to fit all the population unilaterally (with extreme exceptions of course) in order to acquire approval. However, precision medicine may lead to personalized drugs, namely drugs that would be valid for a (small) group of people and not for the general population, leading to provisional and targeted licences. Such paradigm shift might not be easily adopted, especially by the elderly.

In addition to the aforementioned fundamental factors, other key aspects of precision medicine include the involved legal framework (regarding both personal data and liability issues), the infrastructure required for implementing it, and the logistics services needed for supporting the overall operations. The logistics parts turns out to be the keystone factor to ensure efficiency and reliability for a precision medicine framework. Mainly, this is attributed to inherent precision medicine supply/value chain challenges that influence the handling of the majority of resources, e.g., transfer of blood samples/donations in a timely manner to their respective processing facilities, determination of equipment location to serve optimally broader populations, etc.

In this chapter, we focus specifically on the intersection of supply chain management with precision medicine. We investigate the existing state-of-the-art of such research and development on logistics, targeting specifically applications suitable for precision medicine. Our goal is to realize the suitability of existing approaches, suggest a holistic joint framework, and identify the steps that need to be taken in the near and longer-term future by the associated research and development communities in order to enable the full vision of precision medicine.

The rest of this book chapter is organized as follows. In section 2 we introduce a joint supply chain management-precision medicine framework for realizing precision

medicine via intelligent logistics. In section 3, we present existing works, dedicated to providing solutions for various aspects addressed in section 2. In section 4, we present the emerging challenges, not already addressed in the presented literature, and we provide suggestions for future work directions that could have noteworthy contribution towards the envisaged framework. Finally, section 5 summarizes the presented content and concludes the chapter.

2 Framework for Healthcare Supply Chain Management for Precision Medicine

There is a lot of overlap between the terms "precision medicine" and "personalized medicine". According to the National Research Council [1], "personalized medicine" is an older term with a meaning similar to "precision medicine". However, there was concern that the word "personalized" could be misinterpreted to imply that treatments and prevention are being developed uniquely for each individual. In precision medicine, the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors. However, some people still use the two terms interchangeably.

In order to realize such a vision that includes genetic, environmental and lifestyle factors, and in order to do this efficiently and in a commercially viable manner for humans that can be globally distributed, this requires a robust framework for precision medicine and associated logistics. This can be made more concrete via the following example. Traditionally, approved medications regards the general population and therefore, revenue may be expected by the distribution of the medication nationally or globally. However, under the precision medicine paradigm, quite many of the newly anticipated medications will be far more targeted towards specific groups of the populations, so that revenue cannot be expected at the broad population magnitude of the traditional paradigm. Specially conceived logistics will need to be applied to reach out for the more particular groups, which will be rather distributed, potentially globally, in order to ensure the necessary margins of profit for the pharmaceutical companies, therefore stimulating the necessary incentive for such a model to exist.

In this book chapter, we are involved with the proposition of such a framework for regarding logistics for precision medicine. We suggest that this framework touches five fundamental pillars for providing the required services and efficiency, which in turn they can realize the envisioned precision medicine services. Such pillars are the transportation, tracking/monitoring, expendables, scheduling and optimal placement, as depicted in Fig. 1. In the following, we describe separately each of these pillars within the envisioned framework and then provide an overall overview how these functions can provide an efficient and effective basis for developing precision medicine services.

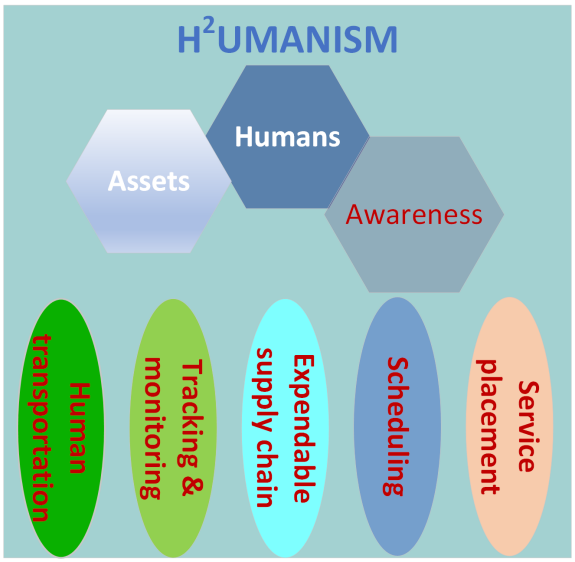

Fig. 1 H^{2}UMANISM framework, its five pillars and its target-objectives, namely humans, assets, and information awareness.

2.1 Transportation

The transportation part of supply chain management for healthcare and precision medicine in particular regards mainly aspects with quite different requirements and features:

- Human transfer,
- biological samples transfer,
- equipment transfer.

Transfers of humans will be one of the critical transfers within the functional framework of precision medicine. As explained above, precision medicine will regard treatments and medications specially targeted/designed for smaller groups of people. In both cases, it is expected that humans will be required to be transferred to special locations to receive their treatments and/or medications (i.e., for medications that cannot be provided in the ordinary ways through pharmacy stores and need special administration by medical personnel, such as chemotherapy).

Precision medicine related human transfers will not constitute yet another form of human transfer that can be accommodated with the existing public transportation means, or at least straightforwardly. A multitude of reasons impose considering such transfers in a different manner:

- Regularity of transfers.
- Distribution of humans/patients.
- Criticality of transfers.

- Handling of transfers.
- Efficiency.

We analyze them in detail in the following.

Regularity of transfers. Not all the cases of precision medicine will require the transfer of humans to hospitals or medical units. There will be particular cases where the patients will need to be transferred to the medical facilities in order to facilitate their treatments. This means that an expected small subset of the population will be in need for transfer from their houses to medical institutions. Furthermore, the regularity of such transfers is expected to exhibit significant variance, since the treatments are typically administered for specific intervals and few types of patients get into longer term therapies.

On the other hand, a quite larger subset of the population is expected to transfer for testing purposes. This will be necessary in order to identify their suitability for specialized treatment. This may involved plain testing, e.g., simple blood tests that can be administered in ordinary laboratories, or more specialized testing, which will necessarily take place in specialized facilities. The latter essentially bear the characteristics of the transfers described above, while the first do not bear any special features that would require special attention. They can be essentially facilitated like ordinary test, e.g., ordinary bloodworks, thus, there is no realistic need to optimize such transfers from a logistics perspective (as they would involve nothing really more complicated that performing additional analysis to the tests already administered, therefore, no additional transfers will be needed). The more targeted testing, which in addition requires special administration, will necessarily generate human mobility, and it can be treated similarly to the specialized treatment mentioned above. Again, distribution of humans and availability of the testing locations will be an issue, since such facilities do not necessarily coincide with the treatment locations, therefore different destinations will need to be considered. However, mathematically, the nature of problem will be the same and the same tools can be used for determining the corresponding transfers. In fact, the problem can be treated as a single one, where there are two types of flows to be optimized, namely one regarding the treatments and one the testing, which can potentially lead to more efficient solutions, especially when the same persons are involved in both treatments and testing.

Distribution of humans/patients. It was already mentioned that since precision medicine will target special groups of people for specific treatments, eventually, such inference of smaller subgroups of the general populations where testing and/or treatment will be applicable, will necessarily dictate transfers of individuals. This means that when considering a specific treatment/testing, a percentage of the population (possibly a small one) will be relevant to the targeted treatment/testing. Such percentage of the population is expected to be distributed across a country or even globally, depending on the exact implementation of the precision medicine service. For example, a treatment that will be decided to be administered in a couple of locations across a country will require the population to be transferred at these locations. In these cases, the logistics challenges refer to the optimal selection of locations to minimize population movements and/ or optimizing the movements of populations given the constraints of fixed numbers and locations of treatment facilities.

As such, issues related to determining the locations, given various criteria, e.g., serving the highest possible percentage of the population at the lowest cost, ensuring reduced cost and timely transfer for the rest of the population, etc., will be key for the eventual determination of the corresponding facility locations. In any case, the human transfer problem will need to be addressed efficiently and dynamically, as the conditions and assumptions made will change as the services and population grows. For instance, an aging population means that more humans will be required to be transferred in the long term, therefore increasing the operational scale in the future. The logistics tools will need to have taken scalability issues under consideration and determine meaningful dimensions for the various parameters of each system/component.

The geographic distribution of the population at the time, and also the anticipated geographic distribution in the short and longer-term future will need to be taken into account. In addition, issues such as the age distribution per area and and various preconditions potentially leading to diseases for the population per area need to be considered in order to design successful logistics services with respect to the human transfer aspect. For example, if the population of a sparsely populated area is expected to develop epidemic diseases, e.g., heart or thyroid issues, such population will need with higher probability precision medicine services, compared to a more densely populated area where the population exhibits significantly lower epidemic probabilities.

Criticality of transfers. The degree to which a human transfer associated with a precision medicine testing or treatment is critical varies considerably, depending on the disease type, the human under consideration, and the form of the precision medicine service offered. Judging by the existing use cases of treatment and testing over the general population, where the associated variance of level of critically varies considerably, it is not possible to project the corresponding level of criticality for a paradigm shift as the one of precision medicine.

It is possible that since precision medicine will potentially regard eventually all types of diseases, that, a similar behavior as the one experienced today, will be also observed for precision medicine critical cases. On the other hand, since precision medicine will be mainly concerned with profiling of patients, a smaller percentage of the population will need a critical transfer for testing or treatment.

In any case, the logistics around such critical or non-critical human transfers will need to be flexible. In fact, they will need to be telescopic, in the following sense. Initially, appropriate studies can be performed to determine the existing rates of critical versus non-critical transfers (in many countries these are well-known percentages). Based on them and a comparative study between the amount of traditional medicine that will turn to precision medicine, a proper connection can be drawn to infer the amount of critical human transfers expected for precision medicine at the time and further predict the evolution of the figure in the short and longer-term future. A flexible logistics framework, will be capable of expanding its human transferring capacity dynamically when critical conditions arise, e.g., in virulent epidemic scenarios, or seasonally when specific conditions will be expected, i.e., flu cases surge.

Handling of transfers. The overall handling of human transfers in a holistically considered logistics-precision medicine framework can differ considerably and it is typically a matter of public policy in each country. There are four main types of approaches depending on two employed criteria, as shown in the following Table 1:

	dedication	criterion
health system	public - dedicated	public - non-dedicated
criterion	private - dedicated	private - non-dedicated

Table 1 Types of approaches for handling human transfers.

According to this table, there are four different approaches, namely public-dedicated, public-non-dedicated, private-dedicated and private-non-dedicated. The first criterion is whether the handling of determined human transfers will be holistically handled through a public health system, or left to private management.

The decision between public-private essentially regards those countries where the health system is basically centered around a public pillar, since for those relying totally on a private model, handling of human transfers will be similar. However, even the publicly founded health systems have the option of utilizing a private logistics framework for human transfers, in order to ensure the viability of the defined precision medicine system, as well as additional quality of service criteria.

A private versus a public system supporting human transfers will regard financial issues, i.e., how is the cost covered (e.g., by private insurance, public fees, etc.), the availability of the service and the type of offered transfer services. A public system is expected to cover even the more distributed populations, while a private one would probably offer higher quality of service, perhaps at higher cost.

Efficiency. The efficiency of the human transfers will be one of the main objectives, or even the most critical objective for the precision medicine framework, in order to ensure the viability of the framework and allow for the necessary revenues that would generate further incentive. Efficiency can be defined in many different ways, but in the sense of logistics for precision medicine, the following features may be used to characterize the efficiency of the logistics services, especially for human transfers:

- cost,
- availability,
- flexibility, and
- carrying-capacity.

The cost of the transfers, either individually or totally for the scope of the framework (national or international) will be a major factor for ensuring the viability of such a framework. Minimizing the cumulative and/or the individual transfer cost will be of primary importance for all the involved stakeholders. The availability of the services will determine whether the precision medicine services themselves can be provided in a meaningful manner, probably to people that they in most need. Again, this can be a determinant longer-term factor for ensuring the viability of the framework, since in

case that the desired availability level cannot be provided, it will become quite tough to modify the then established negative opinion. In addition, the supporting logistics will need to provide different grades of service availability, e.g., a guaranteed one for critical cases, or a plain but cheaper for cases in non-immediate need. Flexibility will be needed in order to accommodate dynamically the emerging cases while optimizing cost and availability, essentially making the underlying scheduling problem tougher (more on this will be described in subsection 2.4). The carrying-capacity of the overall framework, including all involved stakeholders, will be indicative of the efficiency of such a framework and will further guide future evolution and goals.

2.2 Expendables

Similarly to traditional medicine practices, precision medicine will also require various types of expendables, varying in size, use, criticality and usage frequency. Such articles can be reusable or disposable, but in any case regular supplies are needed by the practitioners, especially for testing purposes. In the case of precision medicine, it is expected that more specialized expendables will be needed, at least partially, and their provision will have to be performed specific, relatively few and distributed locations.

Expendables are already handled by each traditional healthcare system, at national or more localized manner, depending on whether a public or private system is adopted. Fundamentally, similar tools could be used in the logistics associated specifically with expendables for precision medicine. However, a key fundamental difference will be that as far the specific expendable equipment for precision medicine is concerned, will be that the potential market is necessarily smaller, distributed and more targeted. This means that the suppliers will be potentially more restricted and fairly more distributed than in the existing state. Similarly, consumers are expected to be more distributed geographically and restricted in number, as the special expendables will regard special treatments/testing administered by a more restricted number of physicians at specific locations nationally, or globally.

2.3 Tracking and Monitoring

A significant part of precision medicine will regard the monitoring and tracking in various capacities in precision medicine. The following list is an indicative starting point for identifying the facets that will demand tracking and monitoring at various capacities:

- biological samples,
- portable equipment,
- medical records,
- medications,

- patients.

All the above will require different forms of tracking and/or monitoring. For instance, biological samples and medications will need to be tracked and traced for purposes of safety and proper administration. The corresponding logistics services will need to to employ traditional methods for tracking of the samples and medications from their origins to their eventual destinations, while also tracking environmental conditions to secure the integrity of the samples and/or medications. Solutions for such cases can be readily obtained through Internet-of-Things (IoT) and RFID technologies. We provide more details on that in section 3.3. Portable equipment tracking can be also considered within the same approach, where RFID and IoT technologies can be used as the main enablers for keeping track real-time information of the geographic location and possibly state of the equipment. Additional features could also include the potential real-time use of the equipment, which can be associated with additional aspects of precision-medicine, such as quality of the employed precision, thus further improving the precision of the results, etc.

Features such as medical records, which in many cases have been digitized, can be tracked efficiently using modern technologies such as blockchain. We provide additional details for this direction in subsection 3.2. Records in the traditional printed form can be tackled with RFID technologies, e.g., RFID stickers with serial numbers, thus incorporated smoothly in the rest of workflow for tracking a patients records, even legacy ones. Using these enablers, modern logistics can deal with document tracking in a holistic manner.

Finally, patients can be tracked with the newly arrived wearable device technologies and IoT/5G establishing the required connections for real-time monitoring of their state. In fact, the patients' state can be associated potentially with geographic information, and therefore linked with other logistics services, e.g., transfer in case of emergency, etc.

In general, as we will explain in more detail in section 3.1, several of the existing technologies in various sectors can readily be used, or extended straightforwardly to provide the necessary tools and solutions for yielding flexible, efficient and intelligent logistics services, as described above.

2.4 Scheduling

Scheduling in the supply chain management for precision medicine refers to problems in which decisions on job scheduling and transportation are integrated into a single framework [6]. The work in [6] presented a scheduling approach for two processing centers located in different cities. Each processing center has its own customers. When the demand in one processing center exceeds its processing capacity, it is possible to use part of the capacity of the other processing center subject to a job transshipment delay. The problem is modeled as a parallel-machine scheduling problem with transshipment between the machines, including different objective functions and constraints. This approach can be used to model the corresponding

service of two precision medicine centers, where both operate complementary, e.g., in two different major cities. The goal would be to sustain the overall cumulative capacity, even at the cost of higher transportation of humans, not necessarily to the closest center.

Significant work has been done in the field of scheduling for supply chain management, namely the scheduling required for the transportation of shipments from their sources to their last-mile destinations, where in our case the shipments regard humans, assets (equipment, samples, medication) or results. Reference [7] contains various such approaches, classified in different categories such as cooperative and non-cooperative scheduling, etc. As mentioned in [7], the field of supply chain scheduling is relatively new, approximately 20 years old, even though scheduling is a far older domain.

Scheduling in logistics have also considered another critical field of supply chain management, namely production planning for medication and or expendables for precision medicine. This joint consideration is meaningful in the case of large corporations producing various and diverse productions, e.g., vehicles, samples, etc. Production planning is a process to develop tactical plans based on setting the overall level of manufacturing output (production plan) and other activities to best satisfy the current planned levels of sales (sales plan or forecasts), while meeting general business objectives of profitability, productivity, competitive customer lead times, and so on, as expressed in the overall business plan. Application examples include the pharmaceutical and petroleum industries [8, 9], chemical processing [10], and computers [11], while in precision medicine, similar and tougher problems are expected due to the scale of operation and distributed geography of the involved stakeholders.

2.5 Optimal Service Placement

It has been explained already that the provision of precision medicine services is expected to be restricted to specific, geographically distributed locations, compared to the traditional medical service provision, where availability of services is broader. This is due to the specialized nature of the anticipated precision medicine services. Therefore, one of the key enablers for the overall framework of precision medicine will be to determine, possibly optimally, where such customized and/or specialized services will be placed at a national or global level, in order to ensure cost minimization, response time optimization, and commercial viability of the corresponding services.

From a logistics perspective, such problems of optimal service placement can be resolved by employing various techniques. One suitable approach is that of Voronoi diagrams [12]. A Voronoi diagram is a partition of a plane into regions close to each of a given set of objects. In the simplest case, these objects are just finitely many points in the plane (called sites). For each seed there is a corresponding region, called a Voronoi cell, consisting of all points of the plane closer to that seed than to any other [12]. In this case, the sites correspond to service points and the rest of

the points of the plane to population. Another approach would be to consider the population as points and given the number of service locations desired K apply a K-means algorithm [13] to determine clusters of points, corresponding to members of the population assigned to a cluster. The service locations in this case would be placed in the centroid of each cluster and the distance metric applied would be the geodesic one.

Another modern approach is to perform clustering with machine learning. Clustering determines the intrinsic grouping among the unlabeled data present, which in this case correspond to the population served. Then for each cluster the location of the service point is determined in various ways, e.g., in K-means, the center of each cluster is determined by the algorithm itself. Clustering depends on the user, what is the criteria they may use which satisfy their need, etc. One could be interested in finding representatives for homogeneous groups (data reduction), in finding "natural clusters" and describe their unknown properties ("natural" data types), in finding useful and suitable groupings ("useful" data classes) or in finding unusual data objects (outlier detection). There is a broad classification to the following four categories. *Density-based methods* consider the clusters as the dense region having some similarities and differences from the lower dense region of the space. These methods have good accuracy and the ability to merge two clusters. Examples include DBSCAN (Density-Based Spatial Clustering of Applications with Noise), OPTICS (Ordering Points to Identify Clustering Structure), etc. *Hierarchical based methods*, where the clusters determined form a tree-type structure based on the hierarchy. New clusters are formed using the previously formed one. It is divided into two sub-categories: Agglomerative (bottom-up approach) Divisive (top-down approach). Examples include CURE (Clustering Using Representatives), BIRCH (Balanced Iterative Reducing Clustering and using Hierarchies), etc. *Partitioning methods*. These methods partition the objects into k clusters and each partition forms one cluster. This approach is used to optimize an objective criterion similarity function such as when the distance is a major parameter example K-means, CLARANS (Clustering Large Applications based upon Randomized Search), etc. *Grid-based Methods*. In this approach, the data space is formulated into a finite number of cells that form a grid-like structure. All the clustering operations done on these grids are fast and independent of the number of data objects. Examples include STING (Statistical Information Grid), wave cluster, CLIQUE (CLustering In Quest), etc.

2.6 Envisaged Framework

From the previous discussion, it becomes apparent that a holistic logistics framework for supporting precision medicine is viable but needs to factor in a significant amount of aspects that will serve the operation of the required healthcare objectives. The main aspects presented regard the transportation of humans, the transportation of expendables and biological samples, and the traceability of medical test results/ equipment/ samples/ humans. Logistics have been called for providing solutions for

these three aspects in various capacities already, even for existing healthcare systems with diverse characteristics. For instance, handling of donated blood by the National Health System in the U.K., was totally restructured to accommodate for quality and time related factors. However, until now, such efforts are scattered and they do not address holistically the needs of even an healthcare system.

For this reason, in this chapter we advocate the need for a more intelligent, flexible and efficient holistic logistics framework for precision medicine, which jointly considers the needs/requirements of humans, testing, equipment, treatment and result tracing. In this framework, which we term Holistic Healthcare sUpply chain MAnagement for precISion Medicine (H^2UMANISM), the three main axes are humans, medicine (testing/treatment/results) and services. The required functionalities are transportation, tracing and administration (of medical services). The assumed environment is considered at the national or global level. Therefore, H^2UMANISM potentially touches a whole nation or the world itself. This means that the involved operations research related problems, such as scheduling, will be rather tough. Furthermore, they will need to be dynamically modified to ensure proper adaptability and cost efficiency.

A considerable amount of research and development will be required to integrate all the functionality described above in a joint optimized framework. In any case, the convergence substrate will need to be that interconnected information systems. From the previous discussion, it became apparent that some solutions exist already and they are sufficiently suitable and robust. Capitalizing on them and utilizing the information systems implementing them will set a solid basis for developing the more holistic vision.

A possible roadmap for developing the framework in total would now begin from the existing services and the involved population. Considering the precision medicine services offered nowadays, the type of such services and how they can be distributed at a national or global level, given the specific parts of the population involved, a service placement optimization would take place. The next step would involve optimizing the jointly the transportation of humans and biological samples in a cost and time effective manner. Thirdly, ensuring proper traceability and availability of the services, results and records would produce a first complete instance of the H^2UMANISM framework.

As the number of precision medicine services and features increase and become available through the advances of medicine and biotechnology, their integration to the operational framework will either be straightforward or require a component-based reconsideration, where the order of component reconsideration will again follow the aforementioned sequence. Naturally, it might turn out that as the number of services increases, it may not be possible to simply extend the by the time established optimization techniques and technological tools. In these cases, it will be required to re-establish them.

3 Existing Logistics Approaches enabling Precision Medicine

Along the previous lines, in this section we present several approaches from the literature, which partially address aspects of the envisaged framework. We provide details that will be useful for comprehending the maturity level of the associated technologies, and can serve as basis for further research and development.

3.1 Logistics Challenges

To accomplish precision medicine requirements, all involved stakeholders need to achieve just-in-time production and complete traceability of resources and transported items/ products throughout the supply chain [5]. Indeed, health supply chains should address numerous complexities and risks within different points of the supply chain in order to support precision medicine unique requirements. First, precision medicine supply chains should orchestrate the logistics process in a way that optimized the scheduling and planning of required materials (e.g. pharmaceutical products, blood cells or other biological elements, and so on). Second, precision medicine supply chains are by nature expensive because of the inherent handling and sensitivity requirements of the transmitted materials, such as temperature storage conditions that must be controlled throughout the distribution process. Finally, the logistics processes of supply chains should inform the manufacturing and storage capacities of the involved stakeholders in order to optimize the production and deliveries of the required materials.

Precision medicine re-engineers the continuous mass production approach used for traditional pharmaceutical products towards a patient-driven and on-demand production and delivery model. Since therapies are produced independently in different facilities, coordination is of paramount importance to synchronize the flows of personalized therapies and associated medical assets both upstream (from the hospital - patient back to the manufacturer) and downstream in the supply chain [32].

Scholars have recently started to conceptualize the organization and unique requirements of precision medicine supply chains [5, 30, 34] and identify pertinent ways that information technologies may streamline manufacturing and logistics processes [31]. Supply chain and logistics coordination represents an emerging investigation topic with only but a few studies addressing alternative optimization ways for precision medicine supply chains [e.g., [33, 35]]. A critical element of supply chain coordination refers to optimization of current distribution channels in the biopharmaceutical distribution processes. This is critical to address the inherent time and cost constraints related to the provision of personalised biopharmaceutical treatments for progressive and degenerative diseases, such as last stage cancers, Parkinson, or Alzeheimer, that are based on genes or human cells, commonly referred to as Advanced Therapy Medicinal Products [42, 43]. Individual examination dimensions include redesign of the distribution and transportation network through algorithmic approaches [36, 37, 44], as well as optimization models pertaining the

capacity and strategic locations of plants, logistics providers, and other supply chain stakeholders [38, 39]. This precision-medicine redesign of healthcare supply chains has been reported to also influence the design of clinical trials [40, 41]. From a technological stance, precision medicine supply chains are expected to be majorly re-engineered in the future through the deployment of two emerging technologies: blockchain and Internet-of-Things. Both technologies are further discussed in the forthcoming subsections.

3.2 Exploiting Blockchain for re-engineering healthcare supply chain processes towards precision medicine

Blockchain is a peer-to-peer (P2P) decentralized digital ledger that records the transactions of registered nodes in a network through the application of consensus algorithms. In practice, a Blockchain consists of a series of interlinked records, called ”blocks”, which may store a plethora of transaction data types that may vary depending on the scope of the information system supported by the technology (e.g. electronic health records, log events of medical assets transits, logs of quality checks, logs of medical treatments, and so on). Blocks are linked using cryptographic algorithms and also store a timestamp of each transaction. The employment of cryptography and hashing methods ensure such principles as data confidentiality, integrity, and availability. Blockchain applications may also include programmable logic automations in the form of 'smart contracts'; small parts of computer code that automate a workflow of events triggering the next action when certain conditions are met [23].

Although Blockchain as an underlying infrastructure technology has been primarily investigated within the financial sector, scholars have started to examine its potential for other industries, such as healthcare, as a means to streamline supply chain operations or monitor important health-related transactions. For example, scholars have discussed how Blockchain may be used to facilitate interoperability and secure exchange of Electronic Health and Medical Records [14, 15, 16]. Moreover, Patel [19] proposes a framework for cross-domain sharing of medical images through Blockchain to establish a distributed ledger of radiological studies. Also, Sadri et. al. [29] examine the use of Blockchain as a backbone platform for tracing blood in donation supply chains. A comprehensive review on the potential applications and challenges of blockchain for precision medicine is provided by Hashim et al. [4].

In the context of healthcare supply chain management, Blockchain may address the inherent challenges that refer to the complexity of health/ medical supply chains, which may result to shortcomings in the form of inaccurate information, lack of transparency and limited data semantics per supply chain transaction. This is primarily evident in pharmaceutical supply chains, which require increased levels of control and traceability of drugs and other related products [17]. In effect, the application of Blockchain technology in the pharmaceutical industry may increase visibility

across the pharmaceutical supply chain through the development of an immutable (chronological) ledger of all transactions between potentially untrusted and physically distributed stakeholders. Such records may register the time and location of a transaction and the identity of stakeholders that are involved.

Liu et al [22] present a digital platform that combines Blockchain and Internet of Things to provide a decentralized traceability solution in the drug supply chain. The authors also discuss a practical roadmap for the drug industry that governs the design, development, application, and evaluation of such platforms. A similar design approach is followed by Uddin who presents the overarching architecture of a drug traceability system combating drug counterfeiting in the pharmaceutical industry [21]. Singh et al. [25] complement extant supply chain traceability efforts by examining how sensor technologies may input information related to drug temperature during the transit of pharmaceutical products across the supply chain. Along this rationale, several research studies discuss various implementations of Blockchain networks with Internet-of-Things technologies as a means to increase efficiency and effectiveness of pharmaceutical supply chain operations [26, 27, 28]. Agrawal et al. [24] discuss how Blockchain may be employed to support drug recalls. The authors distinguish between downstream and upstream drug supply chain transformations. Downstream efforts emphasize on the improved scheduling and delivery of pharmaceutical products from the manufacturer to the end-user; upstream efforts focus on cost and time-related improvements concerning drug recalls.

Blockchain technology may also be integrated with other anti-counterfeiting solutions, such as Radio-Frequency Identification (RFID) and Near-Field Communication) NFC, to provide a more interoperable and decentralized holistic infrastructure platform [18]. The following sub-section discusses the prospect of Internet-of-Things (IoT) technologies as a complementary group of technologies to increase healthcare supply visibility and support supply chain logistics. Although Blockchain represents a promising technology to address the traceability challenges of pharmaceutical supply chains, there are still several technological, regulation, and organizational challenges (e.g. stakeholders agreement, interoperability and scalability issues, security issues, and lack of standardized regulations to name but the important ones) before the technology may be fully adopted by the industry [20].

3.3 Internet-of-Things as a core enabler for intelligent healthcare supply chain management towards precision medicine

Combining the various definitions of Internet-of-Things (IoT) in the literature, we can conclude that it is a global dynamic network of interconnected "things" that are uniquely identifiable, interconnected and can communicate information about their identity, properties and location in real-time. In other words, IoT introduces a new paradigm shift where Internet and the Web is extended in the physical realm and a plethora of digital and physical entities are linked and hold sensing/actuating, processing, storing, and networking capabilities [45]. IoT has become a reality

we are already experiencing in social and business contexts due to the advance of communicating and sensing technologies (e.g., RFID, NFC, sensors/actuators, ubiquitous sensing and cloud computing, wireless sensor networks) in the last two decades.

The fact that "things" (e.g., people, animals, products, assets, computing devices, machines etc.) can communicate anywhere, anytime, with anything and anyone information about their properties (e.g. identity, status, location, origin, ownership) and their surrounding environment has enabled many novel applications. There is a vast range and diversity of IoT-enabled applications in various social and business contexts. Telecommunications, healthcare, recycling, product lifecycle management, supply chain management and environment monitoring are just a few of the IoT application areas.

Essentially, IoT enables the collection and exchange of information about "things" that may move. Thus, it enables tracking and tracing of "things" while they move between locations. This capability is the core functionality of higher-level applications that need timely information on the location of objects moving in the respective application context. To name but a few of such applications, one can consider detection of patients and medical equipment in hospital settings or products in the backroom of retail stores.

Supply chain management necessitates accurate tracking and tracing of products, assets and resources and is an early adopter of IoT technologies for monitoring the products moving between various stages of the supply chain (from the production plant to the distribution/logistis center and, then to the retail store). Actually, the retail industry has run the adoption of IoT technologies in supply chain management utilizing Radio-Frequency Identification (RFID) technology for inventory management purposes.

RFID is a key-enabler of IoT and has proven to be a perfect fit for tracking products, assets and resources in supply chain. RFID-enabled solutions that in essence monitor products and assets in the supply chain and support enhanced decision making have been at the forefront of IoT applications. RFID offers unique product and asset identification and real-time, continuous, accurate information on the location and status of them, requiring neither direct human contact nor line of sight. Both the academia and business community have acknowledged that such IoT technologies in the supply chain offer supply chain visibility at any point in time and, thus, streamline the supply chain processes and enable more effective decisions that are now based on more accurate, timely information about all stages in the supply chain [46]. Most available IoT applications in supply chain concern warehouses/ distribution centers with products RFID-tagged at pallet- or case-level and report several benefits with inventory accuracy (reaching 99%) to be the most significant one.

Although IoT technologies have been embraced by the commercial industry and there are several applications towards improved supply chain visibility and supply chain operations, the healthcare supply chain still lags far behind them. Recent studies of the level of digitization in healthcare supply chain conclude that the healthcare industry is far behind the other industries in terms of performance, costs, and best practices in the supply chain. There are higher logistics costs that give healthcare one

of the most expensive supply chains (studies periodically conclude that they are eight to 20 times higher than for other industries) and there is delay in the deployment of digitization technologies through the entire health sector [47].

Recent studies conclude that only technologies and practices considered classic in other industries, such as enterprise resource planning (ERP) systems, electronic data interchange (EDI), vendor managed Inventory (VMI), have been utilized for supply chain integration. There are only few empirical studies of adoption of more advanced technologies such as RFID and IoT in hospitals. RFID applications can support several areas in healthcare supply chain e.g., medical asset management, patient safety and management and toxic waste management but there are only few studies and more attention is deserved.

Hospitals usually install 2Bin systems for controlling inventory. The bins are referred to as primary and secondary, store the same item and have equal capacity. Bins are positioned back-to-back in racks with the secondary bin placed behind the primary bin. When the stock in the primary bin is exhausted, the bin is removed and the secondary bin becomes available. When we replenish the empty primary bin, the secondary one becomes the new primary bin. RFID-enabled 2Bin solutions have been proposed for real-time inventory management in order to control inventories and keep products in continuous stock. Each bin is RFID-tagged and when a bin becomes empty, hospital staff remove the tag and place it on an RFID-enabled replenishment board that has an RFID reader capable of reading all tags on the board. The RFID-monitored replenishment board produces replenishment alerts and, thus, increases inventory visibility [48]. Such smart bins when integrated with the hospital systems can improve the replenishment processes and prevent excess storage of high value products. The combination of such inventory data with clinical data could predict the emergence of certain outbursts of diseases and, hence, trigger proactive ordering of enough stock.

In the same spirit, Bendavid et al.[49] present a RFID-enabled traceability system for hospital operating rooms, which provides traceability of consignment and high value products and, simultaneously, promotes the redesign of replenishment processes. They report improved costing, service levels and reduction of inventory shrinkage and time saved that can be transferred to patient care activities.

Further, Shirehjini et al. [50] propose a real-time location system (RTLS) for position and orientation determination of equipment in hospitals. The system exploits passive (RFID) technology mounted on flooring plates and several peripherals for sensor data interpretation. It provides more accurate positioning and orientation information of the monitor equipment outperforming existing systems.

Apart from RFID-enabled tracking of medical assets, RFID has also been tested in hospitals for tracking and controlling the complete blood transfusion process from taking blood samples to the final blood transfusion. Errors and mistakes were prevented concerning the donation of blood and the administration to patients and process time has been reduced. Respectively, a common usage of RFID is that of drug counterfeiting. The unique identity (EPC-Electronic Product Code) in the RFID tag is compared with data in a central repository to ensure authenticity of drug

products[51]. Counterfeiting of drugs and pharmaceutical products brings significant financial losses, as well as is a major risk for patient safety.

Putting the patient on the spotlight, RFID is regarded as an effective means to improve patient management and tracking, prevent medication errors, and wrong patient surgery to name but a few benefits. Martínez Pérez et al. [52] present and validate a RFID-enabled solution for patient tracking and drugs developed for the emergency departments of hospitals. It locates patients, assesses patient care times and waiting times, identifies unitary doses of medication and ensures the correct matching between the patient and the prescribed medication.

Another RFID-enabled solution for monitoring and care improving of patients admitted in a medical center facility is designed and tested [51]. It supports medical staff in the identification and medical data retrieval of patients reassuring them of providing the right treatment to the right patient. Each member of the medical staff carries an RFID personal card and uses a PC or a mobile device (PDA) with an RFID reader to identify each patient through reading the RFID wristband. Thus, staff has instant access to patient medical information. Alerts and warning messages are sent to assigned nurses and doctors devices in order to prevent delays in pending tasks of the patients.

Overall, there are various pilots exploring RFID-enabled services in the healthcare supply chain but there is no specific evidence that such initiatives have rolled-out and reached their full potential [53]. The benefits for clinical performance and medical inventory management stemming from advance technologies such as RFID are recognized [54] but applications are still in its infancy. It is believed that the integration of the internal or external healthcare supply chain is an obstacle. The variety of flows and products in the health care supply chain also makes digitization harder. For example, medical supplies (such as needles, syringes, medical gloves etc.) processes differ from the ones of pharmaceutical products that are more automated. In addition, shortages in hospitals may put patients at risk; thus, it is harder to decide on automated inventory management based only on costs.

Generally, the vast amount of data generated by the IoT technologies, which can uniquely identify and track assets in the healthcare supply chain and inform in real-time the stakeholders about their properties (e.g. location), have the potential to lead precision medicine activities. The offered accurate information (e.g. RFID-enabled medical records) can support the design of medical services customized to the special needs of each patient towards personalized precision medicine. Simultaneously, streamlined supply chain processes and efficient inventory management of medical supplies and pharmaceutical products will ensure the availability of all the necessary equipment, staff and resources for providing the right service to the right patient which is the vision and ultimate aim of precision medicine.

4 Emerging Challenges and the Road Ahead

A comparative analysis of the previously H^{2}UMANISM framework for supply chain management in precision medicine and the existing relevant approaches, uncovers several emerging challenges for the logistics services and systems involved in general. Such challenges need to be addressed in the near future, in order to enable the desired substrate for prompt, accurate and flexible precision medicine services. The following non-exhaustive list identifies the most characteristic ones and then we briefly analyze them.

- Time-constrained delivery.
- Priority services.
- Low-cost last mile delivery.
- Special handling.
- Security and protection of medical data.
- Efficient traceability of samples, treatments, equipment and results.

The time factor is perhaps the most important one in logistics in general, not just in precision medicine. Failure to meet the expected delivery times is often the cause of great frustration, and in many cases the reason for financial penalties. As in traditional supply chain applications, in precision medicine, time-constrained delivery will be desired rather frequently, in multiple capacities. The transportation of biological samples will be typically required to have expedited service, since the samples could spoil or even corrupt the samples. Transportation of equipment at the needed places will be also key for well-timed diagnoses, while expedited delivery of medications will be essential for the correct administration of treatment protocols. All these will need to be achieved in a highly distributed geographic region, possibly at a national or global level. The major challenge within this environment will be to schedule properly the deliveries, possibly combine multiple ones appropriately, and yield mathematically proven bounds on the determined schedules, while also respecting the determined routes. Candidate solutions have been identified in the recent literature, e.g., using the backpressure algorithm for jointly determining routes and schedules [55]. Thus, the major challenge will be to provided guaranteed bounds, while ensuring the efficiency with respect to other critical metrics, such as cost, quality, etc.

As in all logistics services, precision medicine will require different types of priorities as well. At least the three basic, gold-silver-bronze, will need to be offered, while it should be possible to add more. Again, the work in [55] has identified the solution of the backpressure algorithm as a candidate one, mapping the different priorities to the defined flows by the algorithm. The major challenge here in this domain will be to ensure that offering the different priorities will also ensure fairness, or at least that the expedited services (with guaranteed time delivery bounds) of some of the priorities (flows) will not lead to starvation of the rest, namely will not freeze the delivery of services for the rest priorities. A similar case holds for the handling of the transported items, e.g., whether they require special biological treatment/conditions, they are fragile, etc. Analogously to the case of priorities, the

handling type can be considered an additional form for service type, or even create a structured type of required service characterizing the priority and handling type, thus applying similarly all the aforementioned solutions.

Achieving the above at the lowest possible cost is a unilateral requirement, not just for logistics, but pretty much every business attempt. Several approaches can be used for this purpose and one suitable approach is that of using utility functions modeling the respective cost(s) and aiming at minimizing the corresponding cumulative utility value. The challenge in this case, is that the problem can be quite large and the utility function can depend on various inter-dependent parameters yielding non-convex optimization problems. Furthermore, since the underlying geographic distributions will be quite distributed, it will be tough to exploit locality of information for decomposing the original utility-based problem to simpler and easier to solve sub-problems in the local neighborhoods formed. Developing techniques to achieve this will be of high importance and possibly constitute a major technical challenge.

Security and protection of samples, the items and the results will be in any case of penultimate performance. Properly respecting the GDPR regulations, possibly across continents and countries with different regulations will be one of the major challenges. The Blockhchain technology is promising and could potentially address such emerging challenges. However, it will need to make advances, especially regarding the associated cost for the solutions it offers.

Finally, the traceability functionality will pose a multitude of challenges, from the very obvious regarding the communication, management, storage and analysis of the anticipated massive amounts of relevant data, to the less obvious that will have to do with GDPR issues. RFID and IoT solutions over 5G and the forthcoming 6G of mobile communications will possibly provide viable solutions for such cases, but the expected scaling issues related to the distributed geographic environment that precision medicine will be operating and the order of individuals that it targets eventually in a personalized manner. Ensuring such scalability will be a rather critical point for the viability of the whole framework.

The digital transformation of the healthcare sector is already making significant progress, at least for the developed countries, and is in progress in the majority of the developing ones. On the other hand the logistics sector exhibits higher maturity in the use of analytical tools, information systems and automated tracking processes. Bringing together the two fields will not be a straightforward union of the achieved state-of-the-art in supply chain management in the two fields, which would solely require the development of appropriate interfaces. It will not even be a more complex tackling of the intersecting technology via re-design of common functions and the development of containers for integrating functionality of one field into the functionality required for the other. It will take a clean slate approach, which will utilize techniques and technologies from the two fields that have proven their robustness in terms of efficiency and scalability, and evolve them further with new quantitative and technological features, thus enabling more targeted and adaptive solutions.

5 Conclusions

Precision medicine will be one of the most important factors for ensuring high quality of life for the elderly in the forthcoming years in a aging population, but also for properly mitigating rare diseases for the rest of the population. This chapter suggested that one of the pillars for providing advanced, flexible and efficient precision medicine service is the development of intelligent and targeted logistics, capable of supporting the envisaged precision medicine services in terms of speed, low cost and flexibility. Initially, we described a unified framework for logistics-precision medicine services, and then we reviewed relevant existing works, with the goal of identifying the degree at which such framework is realized. Leveraging on this analysis, we presented the emerging challenges that need be addressed and some directions that could aid in solving such challenges and achieving the discussed framework.

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