

# The role of laboratory medicine in a value-based healthcare system: the example of heart failure patient management in the Italian context

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**Abstract. – OBJECTIVE:** As of today, healthcare systems worldwide face severe challenges that undermine their sustainability. The value-based healthcare (VBHC) approach has been proposed as a strategic and methodological framework to ensure the delivery of the best patient outcomes with economic efficiency. Through the illustrative example of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) for heart failure (HF) patient management in the context of the Italian National Healthcare system, this article explores the role that *in vitro* diagnostics (IVDs) can play in enabling value-based care models.

**SUBJECTS AND METHODS:** 14 healthcare professionals representing the relevant professional figures involved in HF patient management met to revise the current HF patient journey and design a new care pathway that, leveraging on BNP/NT-proBNP, reflects the VBHC principles.

**RESULTS:** The literature recognizes the dosage of BNP/NT-proBNP as the gold standard for diagnosing HF. However, as of today, these IVDs are not employed at their full potential regarding HF patient

management. A new patient journey is proposed so that patients are diagnosed early and properly monitored in the aftermath of hospitalization, improving outcomes at contained costs.

**CONCLUSIONS:** As testified by the example of HF patient management in Italy, laboratory medicine can represent a lever for adopting value-based care models. Still, large-scale adoption of VBHC will call for structural reforms that revise how healthcare delivery is organized, measured, and reimbursed.

*Key Words:*

Value-based healthcare, *In vitro* diagnostics, Heart failure, Natriuretic peptide, Patient journey, Italy.

## Introduction

In a time of ceaseless innovation in healthcare technology and countless therapeutic options

available to enhance the quality of life, healthcare systems worldwide still need to face severe challenges that undermine their sustainability<sup>1,2</sup>. Population growth and aging, with the consequent increase in the incidence of chronic diseases, is reported to translate into a high demand for healthcare services and hence into high pressure on resource utilization<sup>1</sup>. The risk of misalignment between healthcare needs and resource availability raises questions on whether incremental interventions still represent a viable option. New solutions for healthcare management have then been proposed<sup>3</sup>. Among them, the value-based healthcare (VBHC) approach answers the need to rationalize healthcare expenditure by centering the discussion on citizens' healthcare needs<sup>4</sup>. Offering a strategic and methodological framework to guide healthcare decisions, VBHC helps all relevant stakeholders align their interests and activities in pursuing a shared goal – that is, value maximization. As formulated by Porter and Teisberg<sup>4</sup>, value is measured by the increase in the outcomes that matter most to patients relative to the cost sustained in the entire care cycle. In other words, VBHC aims to deliver healthcare in such a way that the best patient outcomes are achieved while preserving economic sustainability. Patient centricity and the removal of inefficiencies in care delivery constitute two of the main pillars of VBHC, together with the overcoming of organizational silos and an end-to-end approach to patient management. Indeed, organizational silos hinder multidisciplinary collaboration and the capacity to account for the whole care cost<sup>4</sup>. At the same time, an end-to-end approach to patient management is deemed necessary to achieve the best outcomes, given that it offers a holistic view of the impact of healthcare decisions on the patient's journey.

Laboratory medicine, particularly *in vitro* diagnostics (IVDs), may be critical in implementing VBHC. In fact, through prevention, screening programs and diagnosis, IVDs often mark the starting point of patient journeys and have cascade repercussions on the following care steps: even though accounting for only 2% of global healthcare expenditure, IVDs influence 70% of clinical decisions<sup>5</sup>. In addition, data derived from laboratory tests provide insightful information regarding patient outcomes, as testified by their frequent employment as surrogate endpoints in clinical studies<sup>6</sup>. Given its impact on multiple phases of the care pathway and its potential as a quality measure for the services offered,

laboratory medicine can be a strategic lever when designing value-based care pathways.

This article aims to understand IVDs' role in enabling the adoption of value-based care models. It does so by analyzing the illustrative case of natriuretic peptides for managing heart failure patients within the context of the Italian National Healthcare System.

Heart failure (HF) was chosen as the therapeutic area for exploration because of the high disease and economic burden and in light of the complexity intrinsic to HF patient management. Heart failure affects about 64 million patients worldwide<sup>7</sup>. In Italy, about 200,000 patients are hospitalized for HF annually<sup>8,9</sup>. Italian annual healthcare costs are estimated at 11,000€ per patient, 85% due to hospitalization<sup>10,11</sup>. HF occurrence is also expected to increase dramatically over the next years due to population aging and the growing prevalence of comorbidities<sup>12-14</sup>. Comorbidities negatively impact clinical outcomes and pose challenges to patient management since they call for the collaboration of professionals with different specialties that often work in separate care settings. Although care has remarkably improved and new pharmacologic agents have been introduced over the past decades, the prognosis of HF is generally poor, with high mortality, with 50% of HF patients dying in the 5 years following diagnosis. Studies<sup>15-19</sup> report that almost 25% of hospitalized HF patients are readmitted within 30 days, which rises to 50% in a 6-month period. There is a need for novel strategies that, leveraging laboratory medicine, promote early diagnosis and efficient monitoring on top of the management of symptoms in outpatient settings<sup>20</sup>. Among the available biomarkers, the decision was to focus on B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), given that their dosage has been recognized for many years by national and international guidelines as the gold standard for HF diagnosis<sup>21</sup>. For example, the European Society of Cardiology reports the BNP/NT-proBNP level assessment as Class I Recommendation for all patients with suspected heart failure<sup>22</sup>. The Heart Failure Society of America and the Japanese Heart Failure Society recommend the dosage of BNP/NT-proBNP to assess HF severity and prognosis, monitor the efficacy of HF treatment, and screen patients susceptible to HF<sup>23</sup>. A question remains open, however, on what impact the virtuous dosage of BNP/NT-proBNP may have on the evolution of the HF patient journey into

a care model where outcomes are maximized while overall costs are contained.

Similar to the case of heart failure, chosen for discussion, the Italian National Healthcare System, a public system with universal coverage, only constitutes an illustrative example of how to implement VBHC care pathways.

## Subjects and Methods

### *The Multidisciplinary Approach*

Fourteen healthcare professionals, including general practitioners (GPs), internists, cardiologists, scientific and laboratory directors with high expertise, were invited to join a multidisciplinary team. The group members were selected in such a way as to ensure geographical representation, and that all professional figures involved in heart failure patient management were present.

To have a basis for discussion, the group first conducted a literature search to retrieve publications that discuss the role of BNP/NT-proBNP in heart failure patient management. A search was carried out on PubMed/MEDLINE with the keywords “heart failure”, “diagnostics”, “laboratory medicine”, “biomarker”, “natriuretic peptide”, “NT-proBNP”, “BNP”, “healthcare”, “value-based healthcare”. Articles in English reporting clinical studies, expert opinions, surveys, and guidelines were retrieved and assessed for relevance. The team members were grouped into working panels to discuss the literature in light of their professional experience and share the local requirements of the contexts where they operate. Hence, they revised the current HF patient journey in search of urgent unmet needs and worked on a proposal for the care pathway evolution. The authors then met in a plenary session where, drawing from the HF example, they could understand what role laboratory medicine can play in implementing value-based healthcare.

### *The Case for Discussion: Heart Failure and BNP/NT-proBNP*

Heart failure is a complex clinical syndrome characterized by symptoms and signs due to structural or functional impairment of ventricular filling or blood ejection<sup>22-24</sup>. Typical symptoms include breathlessness, limb edema, and fatigability, often associated with signs, such as high jugular venous pressure and pulmonary rales, while natriuretic peptide levels are typically elevated<sup>19,22</sup>. Myocardial dysfunction is often the

underlying defect; however, impairment of valves, pericardium, endocardium, or conduction system may also result in HF, reason why an etiological diagnosis is needed to inform the treatment strategy<sup>22</sup>. Heart failure is often associated with comorbidities such as diabetes, obesity, coronary artery disease, atrial fibrillation, hypertension, peripheral artery disease, cerebrovascular disease, anemia, and chronic kidney disease<sup>12-14</sup>. HF requires long-term follow-up and treatment in its chronic form and emergency care in its acute form. Correct and early diagnoses are highly beneficial for patients, as they allow for timely initiation of therapy in the case of chronic HF and prompt interventions in acute episodes.

Natriuretic peptides, among which B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), are circulating biomarkers that help assess the presence and severity of hemodynamic cardiac stress and heart failure. They are cardioprotective hormones released by cardiomyocytes in response to any damage, including pressure or volume overload and in response to activation of the neuro-endocrine-immune system<sup>25</sup>. Circulating BNP and NT-proBNP levels are usually very low, with a high negative predictive value to exclude the presence of HF; on the other hand, their concentration increases significantly in HF patients as a mechanism to restore normal hemodynamics. BNP/NT-proBNP promotes arterial vasodilation, diuresis, and natriuresis, exerts anti-hypertrophic and anti-fibrotic effects, and counteracts the activation of the renin-angiotensin-aldosterone, sympathetic nervous and endothelin systems<sup>26</sup>. BNP/NT-proBNP may assist clinicians in identifying patients at high risk or with organ damage, in screening and early diagnosis, and in predicting the prognosis<sup>23,27</sup>. Conversely, the role of BNP/NT-proBNP as guides to treatment remains unclear. BNP and NT-proBNP have different diagnostic cutoffs, and their concentrations should be interpreted in light of many factors, such as age, kidney function, arrhythmia, and obesity<sup>26</sup>. As anticipated, the European guidelines for HF diagnosis and treatment recommend the dosage of BNP or NT-proBNP in all cases of suspected HF, for the assessment of chronic HF, for the definition of advanced HF, and as a step in the diagnostic workup of acute HF<sup>22</sup>. BNP/NT-proBNP represents a tool for cardiovascular risk prediction in patients undergoing major non-cardiac surgery<sup>28</sup>. From a diagnostic point of view, BNP and NT-proBNP are very similar

biomarkers, and either can be used in different patient-care settings. However, BNP, but not NT-proBNP, is a substrate for neprilysin. A new class of medication for HF, namely angiotensin receptor neprilysin inhibitors (ARNIs), exert their effect through neprilysin inhibition, and this mechanism leads to a paradoxical slight increase in BNP levels despite improvement in cardiac function<sup>23</sup>. The STRONG-HF study<sup>29</sup>, a multinational, randomized clinical trial, demonstrated that an intensive treatment strategy of rapid up-titration of guideline-directed medication and close follow-up based on NT-proBNP concentration monitoring after an acute HF admission reduces symptoms, improves the quality of life, and reduces the risk of 180-day all-cause death or readmission due to HF, compared with usual care. In the present clinical practice in Italy, biomarker levels are commonly used to diagnose HF and monitor chronic patients in agreement with European guidelines<sup>22</sup>. Overall, BNP/NT-proBNP measurement is considered pivotal for the diagnostic process of HF<sup>24,27</sup>.

## Results

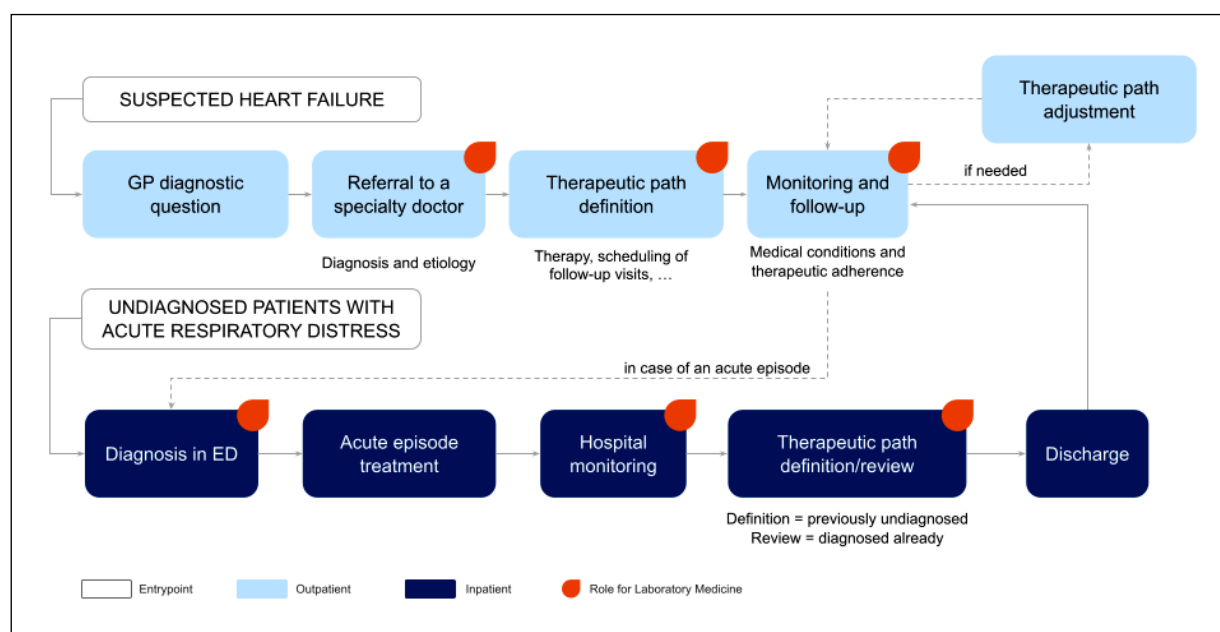
The authors, divided into working panels, discussed the role of IVDs in managing HF patients, came up with a shared opinion on unmet

needs and designed a new HF patient journey reflecting the VBHC principles.

### *The HF Patient Journey: the State of the Art*

To understand how healthcare delivery for HF patients can reflect a virtuous value-based care model, the very first need was to track how HF patients are currently managed within the Italian Healthcare System (Figure 1). As of today, HF patients can enter the care pathway through two distinct access points, namely primary care (in the case of suspected or chronic HF) or Emergency Departments (for acute HF).

In the primary care setting, the general practitioner clinically evaluates symptomatic and at-risk patients and raises a diagnostic question for suspected HF. Hence, patients are referred to a specialty doctor to run the relevant diagnostic tests, including BNP/NT-proBNP assessment. As recommended by current guidelines, treatment is initiated based on laboratory results<sup>22,24,30</sup>. Diagnosed patients are then monitored in primary care facilities; the therapeutic plan may be adjusted based on the changes in BNP/NT-proBNP levels, which are routinely reassessed. On the other hand, patients experiencing acute episodes access care through Emergency Departments. Once stabilized, patients are first monitored within the hospital, where a therapeutic plan is defined. Following discharge, monitoring continues in primary care settings.



**Figure 1.** Heart failure patient journey: state of the art in the Italian National Health System.

### ***The HF Patient Journey: Areas for Improvement***

The current patient journey was critically discussed to identify potential improvement areas. It was first recognized that, when it comes to the referral of patients, there are no institutional direct communication channels for GPs to contact specialty doctors, making personal networks the only viable alternative. Severe events often result from a delay in the HF diagnosis. Since no risk stratification campaign exists in Italy and HF symptoms are non-specific, GPs can fail to detect patients at risk or in early stages of the disease. Indeed, studies<sup>31</sup> report that almost 80% of HF diagnoses are made only after patients enter the hospital to treat an acute episode. Similarly, patients diagnosed with HF by their GP may not be appropriately monitored and may need hospitalization in the aftermath of a deterioration in their health conditions. Considering both diagnosed and *de novo* patients, acute heart failure represents a significant burden for Emergency Departments<sup>30</sup>. The system lacks an intermediate care setting to refer patients who register a moderate (as opposed to severe) deterioration in their health conditions.

In the current care model, laboratory medicine plays a role in the diagnosis, therapeutic path definition, and monitoring and follow-up phases. Nonetheless, BNP/NT-proBNP tests are not reimbursed through public financing in all Italian Regions. Regional differences also represent an issue regarding the list of healthcare professionals who can order the test and the settings where they can do so. In some Regions, for example, BNP/NT-proBNP cannot be requested by doctors operating in Emergency Departments. On top of the regulatory limitations, potential prescribers often lack a clear picture of the entire spectrum of diagnostic tests available and a deep understanding of their peculiar characteristics (such as sample stability and critical value). If laboratory professionals are not consulted, the risk is to order tests inappropriately, both in terms of when they are requested and which of them is.

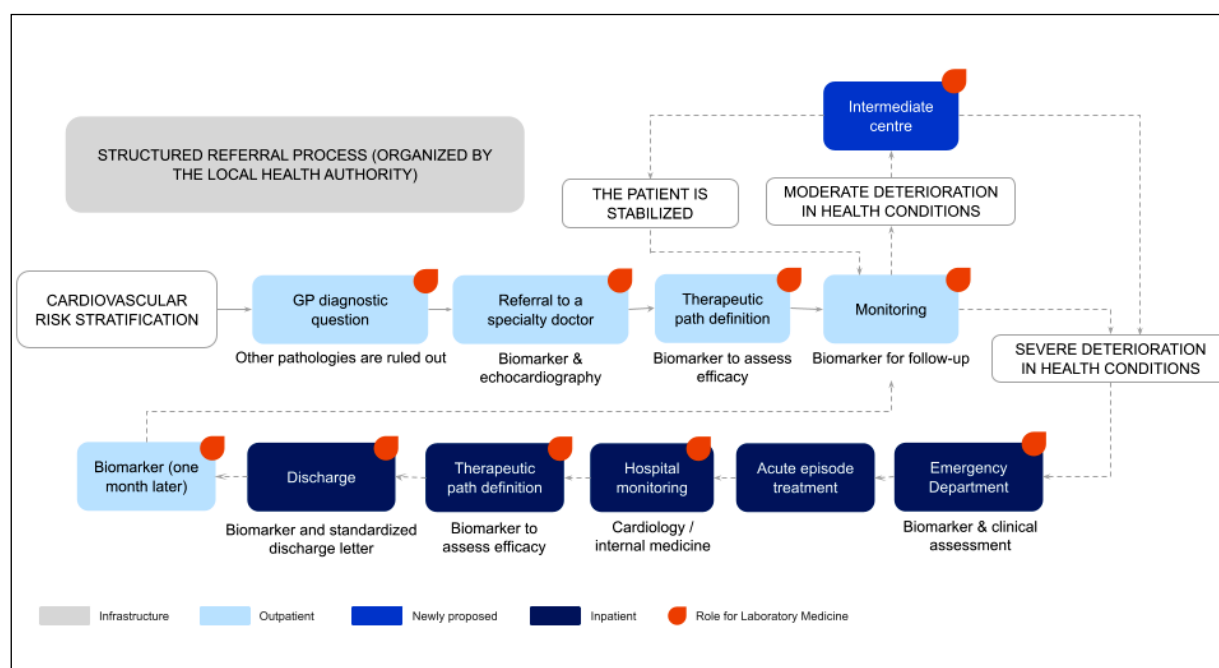
As anticipated, HF patient management calls for the coordination of several healthcare professionals who usually work in different departments and/or care settings. Poor communication channels, organizational silos, and improper IT infrastructures hinder communication and cooperation, translating into worse patient outcomes. Indeed, multi-professional collaboration is not incentivized by the current Italian Healthcare System design. The allocation of resources

through budget silo disregards the cost sustained throughout the entire care cycle, hence losing opportunities for budget-efficient redistribution. Investing in early diagnosis could result in lower expenditure for pharmaceuticals, but this benefit cannot be appreciated in a system where the focus is on cost containment within single organizational silos. At the same time, the payment mechanism of diagnosis-related groups (DRGs) awards hospitals that treat the most severe patients, independent of the quality of the service offered.

### ***A Newly Designed HF Patient Journey***

In light of the identified areas for improvement, the team designed a new HF patient journey that aims to maximize the value for patients and the healthcare system (Figure 2).

In the proposed plan, general practitioners, who are properly educated and informed about HF risk profiles and symptoms, identify patients at risk or in the early stages of the disease. Based on a first clinical evaluation, GPs rule out other conditions, such as anemia or infections. The authors suggest that efforts are made to allow GPs themselves to request the exams needed to answer their diagnostic questions, among which are BNP/NT-proBNP tests. Alternatively, they refer patients to specialty doctors through a dedicated, official communication channel orchestrated by the Local Health Authority. Once the diagnosis of HF is confirmed, a therapeutic path is defined. Patients are monitored in the primary care setting with face-to-face visits or remotely, when possible, through telehealth. Patients who register a moderate deterioration in their health conditions, that is, emergency interventions are not necessary according to the GP, are referred to intermediate structures for laboratory tests and treatment reconsideration. These facilities represent a bridge between the primary care and hospital settings and are deemed useful by the authors to reduce the relevant work burden of acute HF in Emergency Departments. In the case of a severe deterioration in their health conditions, patients access the hospital, where they are stabilized. Once patients are ready for discharge, BNP/NT-proBNP levels are reassessed to offer a baseline for follow-up. To facilitate the transition to primary care and overcome communication silos, information on the clinical picture, the biomarker(s) used in the hospital and hence to be used for monitoring, and the prescribed therapy, are delivered to the GP through a standardized discharge letter that offers a brief but exhaustive patient report. Finally,



**Figure 2.** The newly proposed HF patient journey.

one control visit in the hospital is scheduled one month after discharge. The use of the same biomarker (BNP vs. NT-proBNP), ideally performed by the same laboratory/instrumentation, will allow clear comparability of results and easier primary care follow-up of patients.

### ***A Value-Based Care Model: Clinical and Organizational Gains***

The proposed model offers an illustrative example of value-based care delivery: putting the patient's needs at the very core, the actors of the system collaborate adopting a multidisciplinary, end-to-end approach to patient management. At the same time, the case of HF illustrates how the virtuous use of laboratory medicine positively impacts the entire patient journey: IVD testing at different times in the HF care pathway allows patients to stay longer in the early stages of the disease. As GPs are properly informed of the HF risk profiles and symptoms, they can better identify patients in need of diagnostic investigations and educate patients about preventative measures against disease progression. Similarly, appropriate biomarker assessment during monitoring and follow-up – in the case of patients at early HF stages or in post-acute management – results in patients being taken care of as soon as their health conditions worsen, preventing severe exacerbations. This all surely re-

lies upon the coordination between healthcare professionals; the institution of a structured referral program will be crucial to ensure the continuity of care in the delicate transition of patients to the different care settings, facilitating, for example, pharmacological reconciliation. On top of this, thanks to the insights provided by laboratory results, care pathways can be tailored to the peculiar needs of patients, with journeys being differentiated based on the disease severity. The proposed intermediate structures, for example, could represent the reference point for patients with moderate symptoms. The revised patient flows, together with a lower number of acute cases, would benefit healthcare settings: as mentioned, Emergency Departments bear today one of the highest burdens of HF care<sup>30</sup>; the redistribution of the workload would simultaneously guarantee high-quality care and the efficient use of resources.

### ***Value Creation and Measurement***

From a VBHC perspective, the revision of patient journeys should answer the ultimate goal to generate value, that is, improving outcomes at steady costs or lower costs while preserving outcomes. Hence, to understand whether the newly designed care pathway reflects the VBHC principles, outcomes and costs resulting from its implementation should be measured.

If, on the one hand, accounting for the expenses incurred in the care cycle is possible thanks to administrative work, measuring outcomes is, on the other hand, relatively more complex. No single outcome can capture the results of care<sup>32</sup>. Rather, a comprehensive list of indicators should be established and agreed upon in advance. Aware of this necessity, the Authors analyzed the Standard Outcome Set for Heart Failure proposed by the International Consortium for Health Outcomes Measurement (ICHOM)<sup>33</sup>. The Standard Set offers a spectrum of outcome measures encompassing several highly relevant domains for HF patients: survival and disease control, the burden of care, and functional and psychosocial health. Strictly clinical and administrative data, such as mortality and the number of hospital readmissions, are complemented by patient-reported outcome measures (PROMs) when it comes, for example, to symptoms or quality of life. If conceiving value is what matters most to patients, their perception of the service delivered should necessarily enter the criteria to assess performance, and PROMs perfectly answer this need.

On top of the indicators suggested by ICHOM, biomarker data could represent an insightful source for outcome measurement, especially in the disease control domain. When used for monitoring purposes, BNP/NT-proBNP tests are a non-invasive solution to track HF evolution over time. Also, laboratory data offer an objective assessment of the health status and can, therefore, partially compensate for the subjectivity intrinsic to PROMs.

## Discussion

### *From Theory to Practice: Evidence Generation*

The example of HF testifies how, by leveraging laboratory medicine, it is possible to re-design care pathways in a way that maximizes value for the patient while generating positive spillovers for the entire healthcare ecosystem. In the example discussed, the appropriate measurement of biomarker levels allows for timely interventions that lower the risk of acute episodes; the prevention of acute HF and, consequently, the lower number of hospitalizations benefit healthcare organizations in terms of lighter workload and economic burden. Simultaneously, the designed pathway would facilitate healthcare professionals in navigating the system and make them feel more confident in making decisions.

With the ultimate goal of certifying this line of reasoning, projects in the field will be essential. As suggested by Porter<sup>32</sup>, these should focus on a single medical condition, and heart failure could be the first area of experimentation. Welcoming the designed HF model into the current practice would call for a series of organizational interventions, among which the creation of an institutional and direct communication channel for patient referral, education and training of staff on proper biomarker use, the opening of intermediate infrastructures and their integration in the referral program, the standardization of discharge letters, and the strategic use of telehealth (for example, for remote monitoring). On top of this, outcome and cost measurement efforts should be considered when shortlisting the activities to be implemented as part of the project. Indeed, as is familiar in management, measuring results shows the way towards excellence, as people can track progress over time and compare their performance within and outside their organization. In this regard, the previously presented outcome indicators could be adopted.

These kinds of measures require the joint work of healthcare organizations, governmental bodies, life science companies and IT solution providers, whose efforts should converge to create a favorable environment for the model adoption. In the case of HF in Italy, regional variability in reimbursement and prescription of BNP/NT-proBNP tests should be a topic of discussion between the different stakeholders, as should the possible tapping into the European National Recovery and Resilience Plan as a source of financing for some of the activities (intermediate centers and telehealth already fall under the Plan scope).

### *Priorities for a Large-Scale Implementation*

Pilots constitute a fundamental milestone to pave the way for VBHC, but cannot suffice alone for a large-scale adoption: structural reforms should be promoted at different governmental layers if wanting to reorganize the way healthcare services are delivered<sup>34</sup>. First and foremost, the unavailability of proper information technology platforms has proven over the past years to be one of the main obstacles to scale value-based care models<sup>35</sup>. Leveraging data sources already available (for example, electronic health records), efforts should be made to grant access and interoperability of information. At the same time, the nature of the activities in VBHC projects calls for a strict collaboration between public and private actors; to ensure that all interests are aligned towards value maximization,

life science and IT companies should be rewarded based on the degree to which their proposed solutions contribute to the goal achievement. Procurement processes should reflect this by proposing, for example, outcome-based payments. Indeed, contractual frameworks that favor the cooperation between public organizations and providers are already available: Pre-Commercial Procurement (PCP) for acquiring innovative solutions and Public-Private Partnerships (PPPs) for long-lasting contracts with risk-sharing clauses. However, the adoption of PCP or PPPs as contractual arrangements is still very limited in the healthcare arena<sup>36</sup>. Eventually, when it comes to the object of procurement, a best practice for implementing VBHC would have healthcare organizations contracting for a bundle of services to cover all the care needs of a given medical condition, as opposed to buying single pharmaceutical, diagnostic and/or digital products. In this way, the system could overcome the current resource allocation limits, enabling the bundled payment of care cycles.

## Conclusions

The VBHC approach represents an alternative for healthcare systems to escape the mere cost containment rhetoric, that often puts quality and equity principles in jeopardy, and adopt sustainable solutions that improve overall performance. The case of heart failure testifies how the optimization of diagnostic testing can positively impact the entire patient journey, with a consequent increase in outcomes: risk stratification, early diagnoses and efficient monitoring result in fewer severe cases. Considering the lighter pressure on human and economic resources, this benefits patients as well as healthcare organizations. However, implementing value-based models is far from a straight, one-step transformation of single care pathways. Rather, it requires an overarching strategy to revise how healthcare delivery is organized, measured, and reimbursed<sup>34</sup>. Only through parallel actions, that is, promoting projects with an experimental nature on the one hand and enacting structural reforms on the other, can the system shape the environment to welcome care models centered on citizens' actual needs.

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## Conflict of Interest

VC and DP are employees at Roche Diagnostics, Italy.

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## Informed Consent

Informed consent is not applicable.

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## Ethics Approval

Ethics approval is not applicable.

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## Authors' Contribution

VP, VC, DP: article conception. All authors: article drafting. All authors: manuscript revision and approval.

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## Availability of Data and Materials

The corresponding author is available to share experience and data upon reasonable request.

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