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Development, validation, and implementation of biomarker testing in cardiovascular medicine state-of-the-art: proceedings of the European Society of Cardiology—Cardiovascular Round Table

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Abstract

Many biomarkers that could be used to assess ejection fraction, heart failure, or myocardial infarction fail to translate into clinical practice because they lack essential performance characteristics or fail to meet regulatory standards for approval. Despite their potential, new technologies have added to the complexities of successful translation into clinical practice. Biomarker discovery and implementation require a standardized approach that includes: identification of a clinical need; identification of a valid surrogate biomarker; stepwise assay refinement, demonstration of superiority over current standard-of-care; development and understanding of a clinical pathway; and demonstration of real-world performance. Successful biomarkers should improve efficacy or safety of treatment, while being practical at a realistic cost. Everyone involved in cardiovascular healthcare, including researchers, clinicians, and industry partners, are important stakeholders in facilitating the development and implementation of biomarkers. This article provides suggestions for a development pathway for new biomarkers, discusses regulatory issues and challenges, and suggestions for accelerating the pathway to improve patient outcomes. Real-life examples of successful biomarkers—high-sensitivity cardiac troponin, T2* cardiovascular magnetic resonance imaging, and echocardiography—are used to illustrate the value of a standardized development pathway in the translation of concepts into routine clinical practice.

Keywords

Biomarker • Heart failure • Myocardial infarction • Pathway • Troponin • Ejection fraction • Magnetic resonance

1. Introduction

Through adoption of lifestyle modifications and evidence-based therapies, there has been considerable progress in reducing cardiovascular diseases (CVD) morbidity and mortality. However, cures for most CVD remain elusive and individual patient treatment responses are difficult to predict and may differ from those seen in randomized trials. Awareness that current approaches to diagnosis and management of CVD may be overly simplistic is driving interest in the potential of personalized medicine to improve clinical outcomes. Central to this process is a more precise approach to diagnosis that permits recognition of high-risk individuals at an early stage of disease, and better prediction of therapeutic responses.

Evolving technologies in the fields of multi-omics (e.g. genomics, proteomics, metabolomics), clinical imaging, and data science further complicate the effort to discover new cardiovascular biomarkers that improve the understanding of disease, translate into novel therapeutic targets, and lead to new instruments for predicting and monitoring treatment responses. The aim of this round table meeting, and this document, is to provide an overview of the development, validation, and implementation of new biomarkers in clinical practice.

Additional participants in the ESC CRT are listed in the appendix.

2. What is a biomarker?

Biomarkers are variously defined. The European Medicine Agency (EMA) defines a biomarker as 'A biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals'.¹ The World Health Organization (WHO) suggests that a biomarker is 'almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological'.²

There is some controversy on whether biomarkers should include only molecules circulating in the blood (sometimes referred to as 'wet biomarkers') or encompass clinical characteristics and non-invasive measures such as medical imaging, electrocardiography, and blood pressure measurement. In oncology, molecules measured in tissue biopsies are commonly used, but this is rare in CVD. In CVD, the more comprehensive definition of biomarkers that includes circulating molecules and imaging parameters, as well as all relevant measurable clinical characteristics is more usual.

Using this broad definition, reports of cardiovascular biomarkers in the medical literature can be counted in the thousands, but the number of biomarkers used routinely in clinical practice is remarkably small.^{3,4} The explanations may include an incomplete or superficial understanding of disease pathophysiology, or variability in test availability and utilization. A poor appreciation of the development pathway leading to clinically actionable biomarkers is often a major barrier to successful implementation.

3. Development pathway for new biomarkers

Biomarker discovery and implementation often involves use of big data, data mining, systems biology, and reverse translational research, but a detailed description of these areas is beyond the scope of this article.

In sharp contrast with oncology, the validation of biomarkers as surrogates for therapeutic efficacy and safety remains unsatisfactory in cardiovascular medicine. The reality is that very few putative biomarkers make it into routine practice. The reasons for this are varied, but almost certainly

include incomplete understanding of the complex pathophysiology of CVD and a reductionist approach to the diagnosis of common phenotypes such as heart failure and hypertension. Indeed, the use of biomarkers often reveals gaps in knowledge when applied to real-life scenarios.

The group agreed that most cardiac biomarkers fail to translate into clinical practice because of a poor appreciation of the essential performance characteristics of biomarkers and the rigour required in their identification, testing, and validation. This is particularly true of many 'omic' markers where discovery is often acclaimed before consideration of the clinical potential or relevance.

The group identified a list of attributes shared by successful biomarkers and suggested an ideal development pathway that, if considered from the outset, might improve the chance of successful translation (Figure 1). Of particular importance is the requirement that successful biomarkers, or indeed any diagnostic technique, must meet clearly defined clinical needs and their use must be demonstrated to improve the efficacy or the safety of patient management. In addition, biomarkers should show superiority over current standards of care (SOC)—something that is rarely demonstrated—and be practical and scalable using validated reproducible technologies at a realistic cost. Ideally, biomarkers should be based on the assay of easily accessible tissues (blood or urine) or on non-invasive physiological measurements (ultrasound, magnetic resonance).

The ideal characteristics of a biomarker depend in part on the intended use. In the context of personalized medicine, distinction may be drawn between prognostic, predictive, and pharmacodynamic markers. Prognostic biomarkers assess the likely course of a disease with or without therapy and predictive biomarkers identify individuals who are more likely to respond to a given specific or targeted therapy. Pharmacodynamic biomarkers measure the effect of a drug on the disease state itself. Table 1 illustrates some of the ideal characteristics of biomarkers designed for use in screening, diagnosis, or prognostic assessment.⁵

4. Regulatory process and challenges

In Europe, licensing of new biomarkers is in the form of a CE-Mark, which is granted by groups called Notified Bodies. Licensing is mandatory for all products (including devices and biomarkers) available in the European Economic Area. The CE-Mark indicates that the product conforms to the requirements of the *In Vitro* Diagnostic Devices (IVD) Directive (98/79/EC). This is being replaced by the IVD Regulation (2017/746) which makes clinical performance data and scientific validity reports mandatory (including benefit/risk analysis and periodic safety and clinical performance reports), in addition to analytical performance data.⁶ For imaging biomarkers that use analysis software, the software 'device' should be built within a specific regulatory framework to meet the appropriate standards (i.e. under ISO13485 and other standards). The EMA provides support for qualification of innovations used in research and development of pharmaceuticals.⁷ The Committee for Medicinal Products for Human Use (CHMP) provides an opinion on the acceptability of a novel methodology or imaging method for a specific use (non-clinical or clinical studies). The CHMP may also provide advice for further development towards qualification.

The requirements for accepting a biomarker in the regulatory field of drug development depend on the intended use and context, for example: proof of concept, dose finding, characterization of safety,

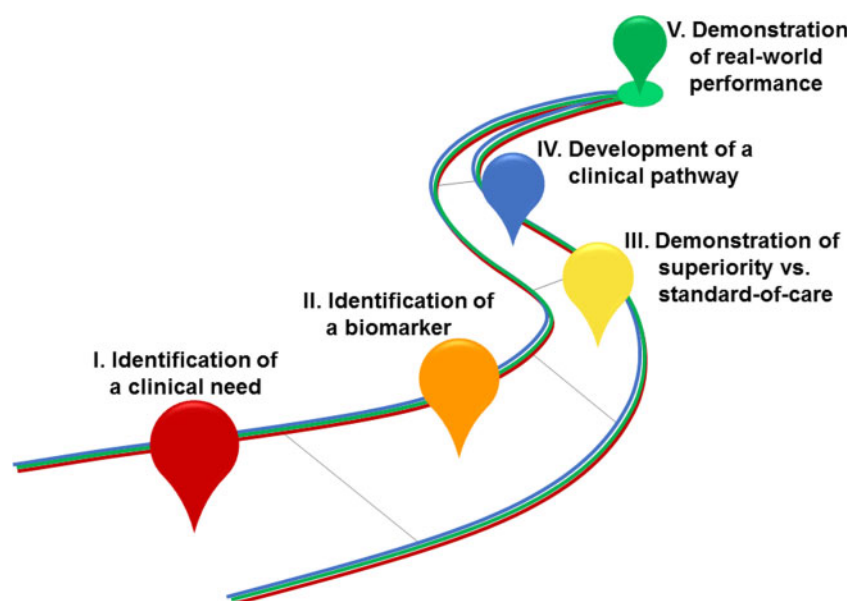


Figure 1 Pathway from discovery to implementation of a new biomarker.

Table 1 Ideal characteristics of biomarkers designed for use in screening, diagnosis, or prognostic assessment

Intended use of biomarker	Ideal characteristics
Screening	High specificity Known reference values Incremental value above existing markers Implications for therapeutic or lifestyle interventions Low cost
Prognosis	High specificity Low intra-individual variability Adds to known prognostic indicators/models Responds to therapy and predicts treatment success
Diagnosis	High sensitivity Therapeutic implications Low cost

Adapted from Ref.⁵

or a phase III clinical trial. Considerations in the development of a biomarker for clinical use from a regulatory perspective are shown in Table 2.

Companion diagnostics play an important role in regulatory approval. A companion diagnostic is a device or bioassay that is essential for the use of a medicinal product. If the labelling of a medication recommends that it should be used in conjunction with a predictive biomarker, the commercial assay will require a CE-mark. The challenge is to demonstrate that the companion diagnostic used to select patients is accurate and validated, and that patients are neither deprived of efficacious therapy nor exposed to harm.

5. Examples of successful cardiovascular biomarkers

In spite of >50 000 PubMed entries on cardiac biomarkers over the past 20 years and large investments from the private and public sector, the number of novel cardiovascular biomarkers approved as blood tests or imaging markers that have been adopted into clinical practice is extremely small. Moreover, the evidence supporting some of the biomarkers that are used in routine practice is relatively weak. The reasons for this unsatisfactory state of affairs are many and include the considerable investment necessary to meet regulatory requirements,⁸ the often poor intellectual property and reimbursement opportunities, and the inability to file patents on new markers. However, many putative markers also fail to meet the fundamental standards advocated in this document. To illustrate what can be achieved if a systematic approach is followed, we consider three examples—high-sensitivity cardiac troponin (hs-cTn), T2* cardiovascular magnetic resonance (CMR) imaging, and echocardiography—and show how their development into clinically useful biomarkers can be viewed in the context of the suggested development pathway (Figure 1). These are summarized in Figure 2.

5.1 High-sensitivity cardiac troponin

5.1.1 Clinical need (step I)

The clinical needs for an hs-cTn were three-fold: (i) electrocardiogram (ECG) did not detect 50% of the acute myocardial infarctions (AMIs); (ii) existing markers (CK-MB; myosin) were not specific to the heart; and (iii) alterations in existing markers (CK-MB; myosin) were not rapid enough to detect early changes.

5.1.2 Identification of a biomarker (step II)

Cardiac troponins were identified in the 1980s but it was not until the 1990s that cTnT and I assays were introduced into clinical practice.^{9–12} By 2009, the tests were technically advanced enough to

Table 2 Regulatory issues to consider when developing a biomarker for clinical use	
Requirements	Examples
Demonstrate the technical, preclinical, and clinical validation of the biomarker	Sensitivity, specificity, ROC curve analyses
Demonstrate clinical utility	Impact of using a biomarker on benefit: risk ratio of a medication
Demonstrate stability of biomarker	Time/patient characteristics, impact of a medication on the biomarker
ROC, receiver operating characteristic.	

	Cardiac Troponins	T2* CMR	Left Ventricular Ejection Fraction
Clinical Need	• Under-detection of AMI • Non-specific blood markers • Delayed diagnosis	• Delayed diagnosis of transfusion related cardiac iron overload in thalassaemia major • High mortality	• Standardised and reproducible measure of LV function
Biomarker Identification	• Troponin I & T	• CMR measurement of rate of decay of magnetisation in the presence of inhomogeneities caused by iron deposition (T2*)	• Left ventricular ejection fraction
Superiority Over SOC	• Improved sensitivity & specificity for AMI compared to CK, myosin, ECG • Predictor of mortality • Rapid diagnosis (hs-cTnT)	• Myocardial Fe correlated with myocardial T2*, but not with serum ferritin or liver Fe • Improved T2* with chelation therapy	• LVEF related to mortality, • Changes in LVEF after therapy related to improved survival and symptoms
Development of Clinical Pathway	• Validated assay • Clinical practice guidelines	• Models to define the risk of iron overload • Clinical practice guidelines	• Clinical practice guidelines
Real World Performance	• High “rule out” performance	• Reduction in mortality rates	• Large registries confirm prognostic value of LVEF in patients with LV systolic dysfunction

Figure 2 Summary of examples of clinically useful biomarkers that have been systematically developed in the context of the suggested pathway shown in Figure 1. AMI, acute myocardial infarction; CK, creatinine kinase; CMR, cardiovascular magnetic resonance; ECG, electrocardiogram; Fe, iron; hs-cTnT, high-sensitivity cardiac troponin; LVEF, left-ventricular ejection fraction; SOC, standard of care.

measure the marker in healthy individuals ('high sensitive'). Clinical studies demonstrated that measurement of cTn improved sensitivity and specificity for the diagnosis of myocardial infarction^{9,10} and that cTn is a predictor of mortality.^{13–16} However, the original cTn assay had some limitations, most notably low sensitivity in the first hours of AMI, which resulted in delayed diagnosis and treatment.¹⁷ It was recognized that the ability to accurately detect lower cTn concentrations would substantially shorten the time to diagnosis.^{18–20} Consequently, new high-sensitivity assays were developed from 2009 onwards.

5.1.3 Superiority over SOC (step III)

In large cohort studies, hs-cTn has demonstrated superior sensitivity and specificity over conventional cTn assays for the early diagnosis of AMI, especially when compared to markers such as myosin, CK-MB, and also ECG.^{19,20} Such important observations led to a new definition of the disease, where troponins played a central part (e.g. non-ST segment elevation MI). The implementation into clinical practice led to a higher proportion of patients benefiting from care, and to a reduction of the

European Society of Cardiology (ESC)-recommended observation time for AMI from 6 to 3 h in 2011, and from 3 to 1 h in 2015, which has led to cost savings and reduced length of stay in emergency rooms.²¹ Hs-cTn has also demonstrated benefits in terms of prognosis and response to therapy. In treatment trials, for example those with P2Y12 inhibitors, a reduced risk of CVD events was shown in patients with non-ST segment elevation MI and elevated hs-cTnT levels but not in those with negative hs-cTnT.²²

5.1.4 Development of a clinical pathway (step IV)

A validated, clinical assay has been developed for hs-cTn. The ESC algorithm incorporating baseline values and absolute changes in hs-cTnT within the first hour that safely and accurately ruled-in AMI within 1 h in 77% of unselected patients with acute chest pain.²³ This was prospectively validated in the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE),²⁴ and the High Sensitivity Cardiac Troponin T assay for Rapid Rule-out of Acute Myocardial Infarction (TRAPID-AMI) studies, with the later focusing on the particularly demanding early presenters.²⁵

Widespread implementation in routine clinical practice has been facilitated by integration of cTn into the ESC guidelines since 2002,²⁶ and hs-cTn since 2011.²⁷

5.1.5 Real-world performance (step V)

Real-world cohort data have demonstrated the utility of hs-cTn in clinical practice. In a retrospective analysis of the SWEDEHEART registry, the switch from to hs-cTnT from cTnT was shown to be more effective for risk prediction, and to guide appropriate treatment.²⁸ In addition, the use of the ESC 0/1 h algorithm has been assessed in prospective studies.^{24,29–31} In one study, the algorithm assigned 62% of patients to the rule-out and 13% to the rule-in groups. The safety of rule-out was very high with a 30 day major adverse cardiac event incidence of 0.2%.²⁹

5.1.6 Summary

Although hs-cTn is an example of a successfully implemented biomarker, biomarker for myocardial infarction, one of the early barriers to implementation was a perception that the previous gold standard of CK-MB was adequate. In addition, political and regulatory barriers contributed to slow implementation because of lack of initial reimbursement for the newer marker.

5.2 T2* cardiovascular magnetic resonance

5.2.1 Clinical need (step I)

Thalassaemia major is a genetic disorder in which ineffective erythropoiesis results in severe anaemia.³² Patients require lifelong transfusions, which can lead to iron overload and cardiomyopathy, with heart failure being the leading cause of death.^{32,33} The cardiomyopathy is reversible with early treatment, but diagnosis is often delayed due to unpredictable iron deposition and late-onset symptoms.^{33,34}

5.2.2 Identification of a biomarker (step II)

T2* CMR measures T2* relaxation, which is the rate of decay of magnetization in the presence of in-homogeneities of the magnetic field, including those caused by iron deposition.³⁵ Septal T2* has been proved to be representative of the mean total cardiac iron concentration.³⁶ T2* CMR for tissue iron quantification was made available in 1990.³⁷

5.2.3 Superiority over SOC (step III)

Myocardial iron deposition was shown to reproducibly, correlate with myocardial T2*, but not with serum ferritin or liver iron, which can only detect advanced disease.^{33,38} T2* was highly predictive of cardiac complications.^{33,38} Randomized controlled trials of iron chelation in thalassaemia patients have shown that improvement in myocardial T2* correlates with improvement in left-ventricular ejection fraction (LVEF).^{39,40}

5.2.4 Development of a clinical pathway (step IV)

Studies have shown that very low cardiac T2* <10 ms was highly predictive of cardiac events.^{38,41} A three-tier risk model has been developed to define the risk of iron overload.³² Cardiac T2* measurements for diagnosis and to guide treatment have now been incorporated into clinical practice guidelines for β -thalassaemia major.³²

5.2.5 Real-world performance (step V)

Registry data from UK showed a remarkable 71% reduction in the mortality rate due to iron overload after 1999.⁴² This was most likely related to the introduction of T2* CMR and appropriate early use of iron chelation therapy.

5.2.6 Summary

T2* CMR was developed and validated in the early 2000s.³³ Unlike hs-cTn, there was rapid uptake into clinical practice. This may have been driven by the poor performance of traditional methods for the diagnosis of cardiac iron overload, technical developments in CMR, and the continuing high morbidity and mortality despite chelation therapy.⁴³ In addition, hs-troponin is a marker for the most frequent of all cardiac diseases, whereas T2* CMR is a marker for a quite rare cardiac disease.

5.3 Left-ventricular ejection fraction

5.3.1 Clinical need (step I)

Left-ventricular (LV) systolic performance is impaired in many CVD and has been repeatedly shown to be a marker of adverse prognosis. Consequently, in heart failure with reduced ejection fraction (HFrEF), many therapies, including pharmacological, interventional, and device-based, aim to improve LV function. Accordingly, there is a need for standardized, precise, and reproducible methods to measure this parameter.

5.3.2 Identification of a biomarker (step II)

LVEF defined as: '(LV end-diastolic volume-LV end-systolic volume) divided by LV end-diastolic volume', can be assessed using different imaging modalities including invasive left ventriculography, two-dimensional echocardiography (intravenous contrast and three-dimensional echocardiography improve accuracy), ECG-gated imaging radionuclide ventriculography with single-photon emission-computed tomography or positron emission tomography, CMR imaging, and computed tomography. The various methods have different performances; two-dimensional echocardiography being the least reproducible but least costly and most often used in daily clinical practice.

5.3.3 Superiority over SOC (step III)

In most major HFrEF outcome trials, LVEF is strongly related to mortality, and morbidity (e.g. heart failure). In addition, changes in LVEF after medical or device therapy have been related to improved survival and symptoms. Changes over time, or before vs. after treatment are related to long-term outcomes.

5.3.4 Development of a clinical pathway (step IV)

In almost all heart failure guidelines from the ESC, LVEF is included as the main marker of LV function (and changes in LV function) and considered a strong prognostic marker in HFrEF. In most ESC guidelines assessment of LVEF has a class I recommendation ('must do'), with level of evidence A (supported by one or more randomized clinical trials or meta-analyses) (e.g. in the STEMI,⁴⁴ non-STEMI,²⁷ heart failure,⁴⁵ and valvular heart disease guidelines⁴⁶).

5.3.5 Real-world performance (step V)

Large real-world outcome registries on CVD have confirmed the strong prognostic value of LVEF in patients with LV systolic dysfunction. Similarly, registries on different cardiovascular therapies have shown the strong prognostic value of change in LVEF.

5.3.6 Summary

LVEF is the standard measure of LV function with varying degrees of accuracy and reproducibility, depending on the imaging technique. All non-invasive imaging techniques can measure LVEF. Particularly, in HFrEF, this imaging biomarker provides strong prognostic information.

6. Accelerating the pathway to improve patient outcomes

Everyone involved in CVD healthcare is a potentially important contributor to the development and implementation of biomarkers, with the goal of improving patient care (Table 3). For example, researchers and clinicians who identify and investigate the utility of new biomarkers, and the industry partners who develop and market the biomarker assays to a wider audience, all play an important role. The ESC and similar organizations can facilitate assessment of clinical needs, knowledge sharing, and data collection. They can also drive change through clinical practice guidelines, standardization, and interaction between researchers, industry, regulatory bodies, and community clinicians.

One of the main barriers to biomarker implementation is the behaviour of clinicians themselves. The concept of clinical or therapeutic ‘inertia’ defined as a failure to initiate or intensify therapy in spite of clear guidance is an increasingly recognized determinant of patient outcomes.^{47,48} The causes of clinical inertia are complex, including patient characteristics such as older age, poor life expectancy and multiple comorbidities, and healthcare provider attributes such as lack of knowledge, workload, and individual attitudes or beliefs about risk tolerance and uncertainty. The same factors influence uptake of biomarkers and emphasize the importance of key specialists in securing regulatory approvals, guideline placement, and uptake into clinical practice. Clinicians also need supporting infrastructures to assist them with knowledge transfer and application in front-line medicine. Information networks and other mechanisms that facilitate communication of knowledge about biomarkers, advances in biomarker research, or evidence of their clinical utility are still in their infancy, but are recognized as a major priority in personalized medicine.⁴⁹

To be used in clinical practice, a biomarker must first obtain licensing and regulatory approval. In line with this is the need to obtain reimbursement of the test. The availability and cost of assays can be barriers; development and validation of a new biomarker is often hindered by the lack of a validated SOC.

7. Future opportunities

Prevention of CVD depends on the ability to recognize high-risk individuals at an early stage of disease long before the development of adverse events. Evolving technologies in the fields of genomics, proteomics, metabolomics, and clinical imaging are playing a significant role in the discovery of cardiovascular biomarkers and in the understanding of disease pathophysiology.

The rapid development of the field of artificial intelligence (AI) has created new opportunities but also new challenges in the development and validation of novel biomarkers. Machine learning (ML) is currently used in the form of supervised or unsupervised learning in order to predict a given value or class.⁵⁰ Deep learning is commonly used for pattern recognition and classification, mimicking human cognition by using convolutional neural networks; these networks are characterized by the ability to learn based on prior experience, simulating human-like decision making.⁵⁰ ML can be used either to facilitate the measurement of a known biomarker in a faster and more accurate way (e.g. in measuring LVEF⁵¹) or to discover novel biomarkers. For example, the Fat Attenuation Index is an AI-powered method that quantifies coronary inflammation by analysing non-visible patterns within pericoronary fat in standard coronary CT angiography, and has striking prognostic value in external validation clinical cohorts.^{52,53} Similarly, pattern recognition using ML has the power to detect subclinical atrial fibrillation and predict stroke, from ECGs of patients on sinus rhythm.⁵⁴

The development of such biomarkers, however, needs to be strictly regulated to ensure their accuracy, reproducibility, and generalizability. The size and heterogeneity of the training dataset are crucial, to be representative of the population where the biomarker will be applied. To avoid data over-fitting, true external validation into completely independent cohorts is essential. As many of these AI algorithms follow a ‘black box’ approach, independent validation is often not possible. But the biggest challenge comes when these biomarkers include a real-time, self-learning algorithm. Currently, the regulators (and particularly the FDA) do not feel comfortable with real-time self-learning biomarkers, and they require ‘off line’ improvement and re-approval of an updated algorithm version. However, this is expected to change in the near future. There is a wave of AI technologies heading towards clinical adoption, and a new framework is needed for their assessment, approval, and prospective monitoring.

Most cardiology practice is based on simplified functional diagnoses (e.g. HFrEF and heart failure with preserved ejection fraction), but the emergence of personalized medicine as a goal of modern medical

Table 3 Priorities for improving the pace of development and implementation of cardiovascular biomarkers

1. Identify, and prioritize unmet clinical needs that can be solved with novel biomarkers
2. Identify robust biomarker candidates using a systematic approach (Figure 1)
3. Promote exchange of information among researcher groups, regulatory bodies, industry, and community clinicians, by relevant bodies including the ESC to critically explore the clinical value of these biomarkers
4. Develop and support central knowledge exchange platforms (e.g. central registry/biobank data collection) to drive standards in biomarker research
5. Focus clinical practice guidelines on unmet needs and potential solutions
6. Encourage interaction between key stakeholders, research funders, and regulators
7. Develop and regularly update a database of industry resources, such as contact information, and funding/grant availability
8. Provide education and training to scientists and clinicians to improve the understanding of biomarkers and facilitate rapid implementation of new biomarkers into clinical practice

practice offers new possibilities for therapeutic innovation. Biomarker discovery and implementation depend on collaborative efforts and must be founded on actionable, quantifiable clinical information that can be easily, rapidly, and correctly used to identify novel therapeutic targets, modifiable risk factors, and monitoring markers—all under pressure of providing value for money. It is crucial that more effort be made to ensure that putative biomarkers are subjected to prospective clinical trials to determine their impact on clinical outcomes. This approach will only work if it is patient centred, data driven, and value based.

Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Appendix. Additional participants

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References

1. European Medicines Agency. Glossary: Biomarker. <https://www.ema.europa.eu/en/glossary/biomarker> (17 December 2019, date last accessed).
2. World Health Organization International Programme on Chemical Safety. Biomarkers and Risk Assessment: Concepts and Principles. Environmental Health Criteria; 155. <http://www.inchem.org/documents/ehc/ehc/ehc155.htm> (17 December 2019, date last accessed).
3. Celutkiene J, Plymen CM, Flachskampf FA, de Boer RA, Grapsa J, Manka R, Anderson L, Garbi M, Barberis V, Filardi PP, Gargiulo P, Zamorano JL, Lainscak M, Seferovic P, Ruschitzka F, Rosano GMC, Nihoyannopoulos P. Innovative imaging methods in heart failure: a shifting paradigm in cardiac assessment. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:1615–1633.
4. Wang J, Tan GJ, Han LN, Bai YY, He M, Liu HB. Novel biomarkers for cardiovascular risk prediction. *J Geriatr Cardiol* 2017;**14**:135–150.
5. Dhinra R, Vasan RS. Biomarkers in cardiovascular disease: statistical assessment and section on key novel heart failure biomarkers. *Trends Cardiovasc Med* 2017;**27**: 123–133.
6. European Union. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on In Vitro Diagnostic Medical Devices and Repealing Directive 98/79/EC and Commission Decision 2010/227/EU. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R0746> (17 December 2019, date last accessed).
7. European Medicines Agency. Qualification of Novel Methodologies for Medicine Development. <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development> (17 December 2019, date last accessed).
8. Van Norman GA. Drugs, devices, and the FDA: part 1: an overview of approval processes for drugs. *JACC Basic Transl Sci* 2016;**1**:170–179.
9. Katus HA, Remppis A, Looser S, Hallermeier K, Scheffold T, Kubler W. Enzyme linked immuno assay of cardiac troponin T for the detection of acute myocardial infarction in patients. *J Mol Cell Cardiol* 1989;**21**:1349–1353.
10. Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, Goldmann B, Katus HA. The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;**327**:146–150.
11. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;**335**:1342–1349.
12. Hamm CW, Goldmann BU, Heeschen C, Kreyman G, Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med* 1997;**337**:1648–1653.

13. Ottani F, Galvani M, Nicolini FA, Ferrini D, Pozzati A, Di Pasquale G, Jaffe AS. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. *Am Heart J* 2000;**140**:917–927.
14. Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. *Lancet* 1999;**354**:1757–1762.
15. Hamm CW, Heeschen C, Goldmann B, Vahanian A, Adgey J, Miguel CM, Rutsch W, Berger J, Kootstra J, Simoons ML. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med* 1999;**340**:1623–1629.
16. Newby LK, Ohman EM, Christenson RH, Moliterno DJ, Harrington RA, White HD, Armstrong PW, Van De Werf F, Pfisterer M, Hasselblad V, Califf RM, Topol EJ. Benefit of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes and troponin T-positive status: the PARAGON-B troponin T substudy. *Circulation* 2001;**103**:2891–2896.
17. de Winter RJ, Koster RW, Sturk A, Sanders GT. Value of myoglobin, troponin T, and CK-MBmass in ruling out an acute myocardial infarction in the emergency room. *Circulation* 1995;**92**:3401–3407.
18. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010;**56**:254–261.
19. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Bredthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;**361**:858–867.
20. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Fröhlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, Lackner KJ, Münzel TF, Blankenberg S. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;**361**:868–877.
21. Ambavane A, Lindahl B, Giannitsis E, Roiz J, Mendivil J, Frankenstein L, Body R, Christ M, Bingisser R, Alquezar A, Mueller C; for the TRAPID-AMI Investigators. Economic evaluation of the one-hour rule-out and rule-in algorithm for acute myocardial infarction using the high-sensitivity cardiac troponin T assay in the emergency department. *PLoS One* 2017;**12**:e0187662.
22. Wallentin L, Lindholm D, Siegbahn A, Wernroth L, Becker RC, Cannon CP, Cornel JH, Himmelmann A, Giannitsis E, Harrington RA, Held C, Husted S, Katus HA, Mahaffey KW, Steg PG, Storey RF, James SK; Plato Study Group. Biomarkers in relation to the effects of ticagrelor in comparison with clopidogrel in non-ST-elevation acute coronary syndrome patients managed with or without in-hospital revascularization: a substudy from the Prospective Randomized Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2014;**129**:293–303.
23. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, Moehring B, Ziller R, Hoeller R, Rubini Gimenez M, Haaf P, Potocki M, Wildi K, Balmelli C, Freese M, Stelzig C, Freidank H, Osswald S, Mueller C. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. *Arch Intern Med* 2012;**172**:1211–1218.
24. Reichlin T, Twerenbold R, Wildi K, Gimenez MR, Bergsma N, Haaf P, Druey S, Puelacher C, Moehring B, Freese M, Stelzig C, Krivoshei L, Hillinger P, Jager C, Herrmann T, Kreutzinger P, Radosavac M, Weidmann ZM, Pershyna K, Honegger U, Wagoner M, Vuillomenet T, Campodarve I, Bingisser R, Miro O, Rentsch K, Bassetti S, Osswald S, Mueller C. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. *CMAJ* 2015;**187**:E243–E252.
25. Mueller C, Giannitsis E, Christ M, Ordóñez-Llanos J, deFilippi C, McCord J, Body R, Panteghini M, Jernberg T, Plebani M, Verschuren F, French J, Christenson R, Weiser S, Bendig G, Dilba P, Lindahl B, Twerenbold R, Katus HA, Popp S, Santalo-Bel M, Nowak RM, Horner D, Dolci A, Zaninotto M, Manara A, Menassanch-Volker S, Jarausch J, Zaugg C; TRAPID-AMI Investigators. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med* 2016;**68**:76–87.e4.
26. Bertrand ME, Simoons ML, Fox KA, Wallentin LC, Hamm CW, McFadden E, De Feyter PJ, Specchia G, Ruzyllo W; Task Force on the Management of Acute Coronary Syndromes of the European Society of C. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2002;**23**:1809–1840.
27. Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, Bax JJ, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Windecker S, Achenbach S, Badimon L, Bertrand M, Botker HE, Collet J-P, Crea F, Danchin N, Falk E, Goudevos J, Gulba D, Hambrecht R, Herrmann J, Kastrati A, Kjeldsen K, Kristensen SD, Lancellotti P, Mehili J, Merkely B, Montalescot G, Neumann F-J, Neyes L, Perk J, Roffi M, Romeo F, Ruda M, Swahn E, Valgimigli M, Vrints CJ, Widimsky P; Authors/Task Force Members. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the ESC. *Eur Heart J* 2011;**32**:2999–3054.
28. Eggers KM, Lindahl B, Melki D, Jernberg T. Consequences of implementing a cardiac troponin assay with improved sensitivity at Swedish coronary care units: an analysis from the SWEDEHEART registry. *Eur Heart J* 2016;**37**:2417–2424.
29. Twerenbold R, Costabel JP, Nestelberger T, Campos R, Wussler D, Arbucci R, Cortes M, Boeddinghaus J, Baumgartner B, Nickel CH, Bingisser R, Badertscher P, Puelacher C, Du Fay de Lavallaz J, Wildi K, Rubini Gimenez M, Walter J, Meier M, Hafner B, Lopez Ayala P, Lohrmann J, Troester V, Koechlin L, Zimmermann T, Gualandro DM, Reichlin T, Lambardi F, Resi S, Alves de Lima A, Trivi M, Mueller C. Outcome of applying the ESC 0/1-hour algorithm in patients with suspected myocardial infarction. *J Am Coll Cardiol* 2019;**74**:483–494.
30. Bandstein N, Ljung R, Johansson M, Holzmann MJ. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. *J Am Coll Cardiol* 2014;**63**:2569–2578.
31. Stoyanov KM, Hund H, Biener M, Gandowitz J, Riedle C, Löhr J, Mueller-Hennessen M, Vafaie M, Katus HA, Giannitsis E. RAPID-CPU: a prospective study on implementation of the ESC 0/1-hour algorithm and safety of discharge after rule-out of myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:39–51.
32. Pennell DJ, Udelson JE, Arai AE, Bozkurt B, Cohen AR, Galanella R, Hoffman TM, Kiernan MS, Lerakis S, Piga A, Porter JB, Walker JM, Wood J; American Heart Association Committee on Heart Failure and Transplantation, Council on Clinical Cardiology, Council on Cardiovascular Radiology and Imaging. Cardiovascular function and treatment in beta-thalassemia major: a consensus statement from the American Heart Association. *Circulation* 2013;**128**:281–308.
33. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, Firmin DN, Wonke B, Porter J, Walker JM, Pennell DJ. Cardiovascular T2-star (T2) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J* 2001;**22**:2171–2179.
34. Anderson LJ, Westwood MA, Holden S, Davis B, Prescott E, Wonke B, Porter JB, Walker JM, Pennell DJ. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2 cardiovascular magnetic resonance. *Br J Haematol* 2004;**127**:348–355.
35. Westwood M, Anderson LJ, Firmin DN, Gatehouse PD, Charrier CC, Wonke B, Pennell DJ. A single breath-hold multiecho T2 cardiovascular magnetic resonance technique for diagnosis of myocardial iron overload. *J Magn Reson Imaging* 2003;**18**:33–39.
36. Carpenter JP, He T, Kirk P, Roughton M, Anderson LJ, de Noronha SV, Sheppard MN, Porter JB, Walker JM, Wood JC, Galanella R, Forni G, Catani G, Matta G, Fucharoen S, Fleming A, House MJ, Black G, Firmin DN, St Pierre TG, Pennell DJ. On T2 magnetic resonance and cardiac iron. *Circulation* 2011;**123**:1519–1528.
37. He T. Cardiovascular magnetic resonance T2 for tissue iron assessment in the heart. *Quant Imaging Med Surg* 2014;**4**:407–412.
38. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, Wu D, Taylor J, Westwood MA, Anderson LJ, Pennell DJ. Cardiac T2 magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation* 2009;**120**:1961–1968.
39. Tanner MA, Galanella R, Dessi C, Smith GC, Westwood MA, Agus A, Roughton M, Assomull R, Nair SV, Walker JM, Pennell DJ. A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. *Circulation* 2007;**115**:1876–1884.
40. Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A, Gotsis ED, Tanner MA, Smith GC, Westwood MA, Wonke B, Galanella R. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. *Blood* 2006;**107**:3738–3744.
41. Patton N, Brown G, Leung M, Bavisli K, Taylor J, Lloyd J, Lee SH, Tay L, Worthley S. Observational study of iron overload as assessed by magnetic resonance imaging in an adult population of transfusion-dependent patients with beta thalassemia: significant association between low cardiac T2 < 10 ms and cardiac events. *Intern Med J* 2010;**40**:419–426.
42. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassemia major in the UK and relation to T2 cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2008;**10**:42.
43. Modell B, Khan M, Darlison M. Survival in beta-thalassemia major in the UK: data from the UK Thalassemia Register. *Lancet* 2000;**355**:2051–2052.
44. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehili J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the ESC. *Eur Heart J* 2016;**37**:267–315.
45. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the ESC. Developed with the special

- contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**: 2129–2200.
46. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, Roffi M, Alfieri O, Agewall S, Ahlsson A, Barbato E, Bueno H, Collet J-P, Coman IM, Czerny M, Delgado V, Fitzsimons D, Folliguet T, Gaemperli O, Habib G, Harringer W, Haude M, Hindricks G, Katus HA, Knuuti J, Kolh P, Leclercq C, McDonagh TA, Piepoli MF, Pierard LA, Ponikowski P, Rosano GMC, Ruschitzka F, Shlyakhto E, Simpson IA, Sousa-Uva M, Stepinska J, Tarantini G, Tchétché D, Aboyans V, Windecker S, Aboyans V, Agewall S, Barbato E, Bueno H, Coca A, Collet J-P, Coman IM, Dean V, Delgado V, Fitzsimons D, Gaemperli O, Hindricks G, Iung B, Jüni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, McDonagh T, Piepoli MF, Ponikowski P, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Zamorano JL, Kzhdryan HK, Mascherbauer J, Samadov F, Shumavets V, Camp GV, Lončar D, Lovric D, Georgiou GM, Linhartova K, Ihlemann N, Abdelhamid M, Pern T, Turpeinen A, Sribinowska-Kostovska E, Cohen A, Bakhutashvili Z, Ince H, Vavuranakis M, Temesvári A, Gudnason T, Mylotte D, Kuperstein R, Indolfi C, Pya Y, Bajraktari G, Kerimkulova A, Rudzitis A, Mizariene V, Lebrun F, Demarco DC, Oukerraj L, Bouma BJ, Steigen TK, Komar M, De Moura Branco LM, Popescu BA, Uspenskiy V, Foscoli M, Jovicic L, Simkova I, Bunc M, de Prada JAV, Stagmo M, Kaufmann BA, Mahdhaoui A, Bozkurt E, Nesukay E, Brecker SJD; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.
 47. Milman T, Joundi RA, Alotaibi NM, Saposnik G. Clinical inertia in the pharmacological management of hypertension: a systematic review and meta-analysis. *Medicine (Baltimore)* 2018;**97**:e11121.
 48. Keeling P, Clark J, Finucane S. Challenges in the clinical implementation of precision medicine companion diagnostics. *Expert Rev Mol Diagn* 2020;**20**:593–599.
 49. Organisation for Economic Co-operation and Development (OECD). Policy Issues for the Development and Use of Biomarkers in Health. <https://www.oecd.org/health/biotech/49023036.pdf> (1 September 2020, date last accessed).
 50. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* 2019;**25**:44–56.
 51. Bhuvana AN, Bai W, Lau C, Davies RH, Ye Y, Bulluck H, McAlindon E, Culotta V, Swoboda PP, Captur G, Treibel TA, Augusto JB, Knott KD, Seraphim A, Cole GD, Petersen SE, Edwards NC, Greenwood JP, Bucciarelli-Ducci C, Hughes AD, Rueckert D, Moon JC, Manisty CH. A multicenter, scan-rescan, human and machine learning CMR Study to test generalizability and precision in imaging biomarker analysis. *Circ Cardiovasc Imaging* 2019;**12**:e009214.
 52. Oikonomou EK, Williams MC, Kotanidis CP, Desai MY, Marwan M, Antonopoulos AS, Thomas KE, Thomas S, Akoumianakis I, Fan LM, Kesavan S, Herdman L, Alashi A, Centeno EH, Lyasheva M, Griffin BP, Flamm SD, Shirodaria C, Sabharwal N, Kelion A, Dweck MR, Van Beek EJ, Deanfield J, Hopewell JC, Neubauer S, Channon KM, Achenbach S, Newby DE, Antoniades C. A novel machine learning-derived radiotranscriptomic signature of perivascular fat improves cardiac risk prediction using coronary CT angiography. *Eur Heart J* 2019;**40**:3529–3543.
 53. Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Hutt Centeno E, Thomas S, Herdman L, Kotanidis CP, Thomas KE, Griffin BP, Flamm SD, Antonopoulos AS, Shirodaria C, Sabharwal N, Deanfield J, Neubauer S, Hopewell JC, Channon KM, Achenbach S, Antoniades C. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. *Lancet* 2018;**392**:929–939.
 54. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ, Carter RE, Yao X, Rabinstein AA, Erickson BJ, Kapa S, Friedman PA. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet* 2019;**394**:861–867.