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Precision cardiovascular medicine: shifting the innovation paradigm

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Abstract

Despite the development of potent drugs for modifiable risk factors and advances in mechanistic biomedical research, cardiovascular diseases (CVDs) collectively remain the leading cause of death globally, indicating a need for new, more effective therapies. A foundational challenge is the multilevel heterogeneity that characterizes CVDs—from their complex pathobiological mechanisms at the molecular and cellular levels, to their clinical presentations and therapeutic responses at the individual and population levels. This variability arises from individuals' unique genomic and exposomic characteristics, underscoring the need for precision approaches. Other key challenges include the long navigation times, high costs, and low success rates for drug development, often compounded by the poor "druggability" of new targets. In this article, we explore how these challenges have inspired novel technologies that offer promise in improving health outcomes globally through an integrative precision medicine approach. Key to this transformation is the use of systems biology and network medicine, whereby the application of artificial intelligence to "big data", ranging from clinical information to unbiased multiomics (e.g., genomics, transcriptomics, proteomics, and metabolomics) can elucidate disease mechanisms, yield novel biomarkers for disease progression, and identify potential drug targets. In parallel, new

computational approaches are helping translate these discoveries into novel therapies and overcome druggability barriers. The transition to a precision-based research and innovation paradigm in cardiovascular medicine will require greater interdisciplinary collaboration, data science implementation at every stage, and new partnerships between academia and industry. Global policy leadership is also essential to implement suitable models of research funding and organization, data infrastructures and policies, medicines regulations, and patient access policies promoting equity.

KEYWORDS

cardiovascular disease, cardiology, precision medicine, systems biology, network medicine, heterogeneity, artificial intelligence

Key points

- Heterogeneity in the complex pathobiology and presentation of cardiovascular diseases (CVDs)—the leading cause of death globally—limits the effectiveness of conventional “one-size-fits-all” therapies.
- Integrative systems approaches, which involve unbiased omics analyses (especially proteomics and single-cell analyses), bioinformatics, and network science, now offer the potential for a precision medicine innovation paradigm to tackle CVDs.
- Artificial intelligence (AI) is driving new opportunities in patient profiling and computational precision drug design and development.
- Various RNA therapeutics in development offer promise for effective precision therapy and could help address conventional drug development obstacles, such as cost and time.
- Interdisciplinary and intersectoral collaboration throughout the research and innovation pathway, underpinned by global health policy leadership, is necessary to implement a precision cardiovascular medicine paradigm.

Introduction: challenges are opportunities

“The greater the obstacle, the more glory in overcoming it.”
Molière

Challenges are opportunities. Clinical problems and unanswered questions in cardiovascular medicine have driven enormous global efforts aiming to understand the underlying

causes of cardiovascular disease (CVD) (1–10). Such needs have also triggered a series of highly valuable technological innovations. Investigation into cardiovascular research in its current form began over a century ago (11–14). In the last several decades, our community has focused on educating the public about lifestyle modifications and dietary interventions to prevent or manage CVD (15). The successful development of effective medicines, such as statins and the newer proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, has significantly contributed to reducing the incidence of certain cardiovascular conditions (16–19). Additionally, advances in basic science have identified various molecules and pathways, including interleukin (IL)-1 β and IL-6, which highlight the role of inflammation beyond traditional modifiable cardiovascular risk factors (20).

Despite these efforts and remarkable advancements, a substantial risk persists for many patients (17, 21–23). While some therapies, such as glucagon-like peptide-1 receptor (GLP-1R) agonists, can reduce the burden of chronic diseases (24, 25), there is still a dire need to identify additional strategies to address the complex interplay across these diseases. While there is a benefit to optimal treatment of type 2 diabetes in terms of being able to reduce the excess mortality risk associated with CVD, this effect was only seen in patients with no previous diagnoses of CVD. This suggests a strong rationale for fine-tuning therapeutic strategies to combat complex diseases (26). From 2010 to 2019, the number of deaths caused by hypertension increased among adults aged 35–64 in 86.2% of counties in the United States (27). The burden of CVD is projected to grow over the next few decades. The number of elderly patients with calcific aortic valve stenosis, a major complication of chronic kidney disease, is projected to more than double by 2050 in the United States and Europe (28). Overall, CVD continues to be the leading cause of death globally (17), resulting in 19 million deaths worldwide in 2020. This toll increased by 18.7% in the past decade and will likely rise to 26 million by 2030 (28–30).

Difficult problems require innovative solutions. One of the foundational challenges that complicates CVD treatment is the heterogeneity of the complex pathobiological mechanisms and

clinical presentations of CVDs. High-throughput, multimodality, multiomics data have ushered in a new era of big data in CVD research, with each type of data introducing a new layer of complexity to the existing challenge of identifying novel mechanisms and biomarkers (31). Addressing these numerous challenges is necessary for advancing precision CVD medicine.

In this article, we explore how key challenges in cardiovascular medicine have inspired novel technologies that offer promise in improving health outcomes globally. We illustrate how systems biology, network medicine, and artificial intelligence (AI), supported by technological innovations in omics, are providing meaningful biological insights into the complexity of disease heterogeneity—fostering new discoveries and targets for precision medicine interventions. We then discuss computational drug discovery and new classes of medicines that may overcome the limitation of conventional small-molecule drugs. Finally, we outline the interdisciplinary and intersectoral actions, underpinned by global policy leadership, necessary to implement a precision-based paradigm for innovation in cardiovascular medicine globally.

Current challenges in CVD research

Biology of heterogeneity in CVD

CVD heterogeneity is evident in the diversity observed in clinical presentations, underlying causes, and responses to treatments. This variability arises from individuals' unique characteristics at the genomic (e.g., single-nucleotide polymorphisms) and exposomic (e.g., air pollution or pesticides) levels (32–37) (Figure 1A), underscoring the need to discover new mechanisms and drug targets to advance precision cardiovascular medicine (38). Multiomics approaches have provided more detailed explanations of how such genomic or exposomic signatures contribute to the development of complex diseases (32–36, 39). Recent evidence suggests that human pathobiology is also heterogeneous at multiple levels, from cellular responses to disease mechanisms and clinical features (Figure 1A). Such heterogeneity presents major challenges that have hindered our ability to gain a comprehensive understanding of disease mechanisms and develop more effective therapies for complex human diseases, which have proven to be even more intricately mechanistic than traditionally thought (35, 38, 40–44). Between 1954 and 1977, epidemiological findings of the renowned Framingham Heart Study established risk factors for coronary heart disease and stroke, with a particular emphasis on dyslipidemia and hypertension (45–47). Notably, elevated low-density lipoprotein cholesterol (LDL-C) became a viable target for lowering the incidence of CVD events primarily via statin therapy. Despite the efficacy of statins in reducing LDL-C levels and the incidence of major CVD events, a significant residual risk remains (48).

Clinical, epidemiological, and genetic evidence also points to the presence of phenotypic heterogeneity within CVDs, encompassing conditions such as myocardial infarction, angina pectoris, hypertrophic cardiomyopathy, and heart failure (49–54). For example, genomic mutations in cytochrome P450 2C (CYP2C9),

solute carrier anion transporter family 1B1 (SLCO1B1), and adenosine triphosphate (ATP)-binding cassette super-family G member 2 (ABCG2) impact the response to drugs such as statins (55, 56). Additionally, interacting pathologies can lead to CVD, including patients with a predisposition to venous or arterial thrombosis—there is even evidence of familial clustering in some cases, leading to inherited hypercoagulable states. Genetic, environmental, and other phenotypic modifiers can also contribute to this group of conditions, making the diagnosis and management of these disorders particularly challenging (57). Many pathways that contribute to human diseases influence disease severity by interacting within a large and complex biological network of genes, proteins, and signaling pathways.

In parallel with clinical evidence, findings from single-cell RNA sequencing datasets have suggested that each cell type associated with CVD, such as macrophages, represents a heterogeneous population (58–66). The balance between subsets of immune cells (e.g., pro- vs. anti-inflammatory macrophage subpopulations) in a local microenvironment, such as the atherosclerotic plaque, may determine the risk of disease progression or the onset of clinical complications (e.g., myocardial infarction) (67, 68). As various new technologies capable of unbiased screening for target discovery continue to emerge (e.g., plasma proteomics of clinical samples and single-cell RNA sequencing of cells within cardiovascular tissues or blood), subsequently generated datasets become larger and more complex (69, 70). To identify promising new targets from large datasets analyzing complex factors, we must involve analytic platforms capable of processing the vast amounts of data generated (71).

Complex pathobiological mechanisms for CVD

CVDs are complex entities shaped by multiple factors. It has become increasingly clear that simply focusing on a single molecule or pathway does not allow a comprehensive understanding of the complex interactions and interdependencies among molecules and pathways acting within a larger biological system. Despite their phenotypic diversity, CVDs exhibit common underlying pathophysiologies. This is seen in conditions such as atherosclerosis, which is shared among vascular diseases such as coronary and peripheral artery diseases (CAD and PAD, respectively). The progression of atherosclerosis, however, involves different components of the immune system. CVDs—including heart failure, arrhythmias, hypertension, cardiomyopathies, and thrombosis/embolism—may exhibit varying degrees of complex pathobiological mechanisms that involve factors such as immune response, lipid metabolism, neurohormonal activation, structural variations, sympathetic nervous system modulation, and endothelial dysfunction (72).

Along with lifestyle factors and environmental factors, genetic heterogeneity also plays an important role in complex disease phenotype. Modern technologies such as whole-genome, whole-exome, and targeted sequencing provide sequence information of DNA bases, giving insights into genetic variation. Both allelic and locus heterogeneity can contribute to the development of CVD (43).

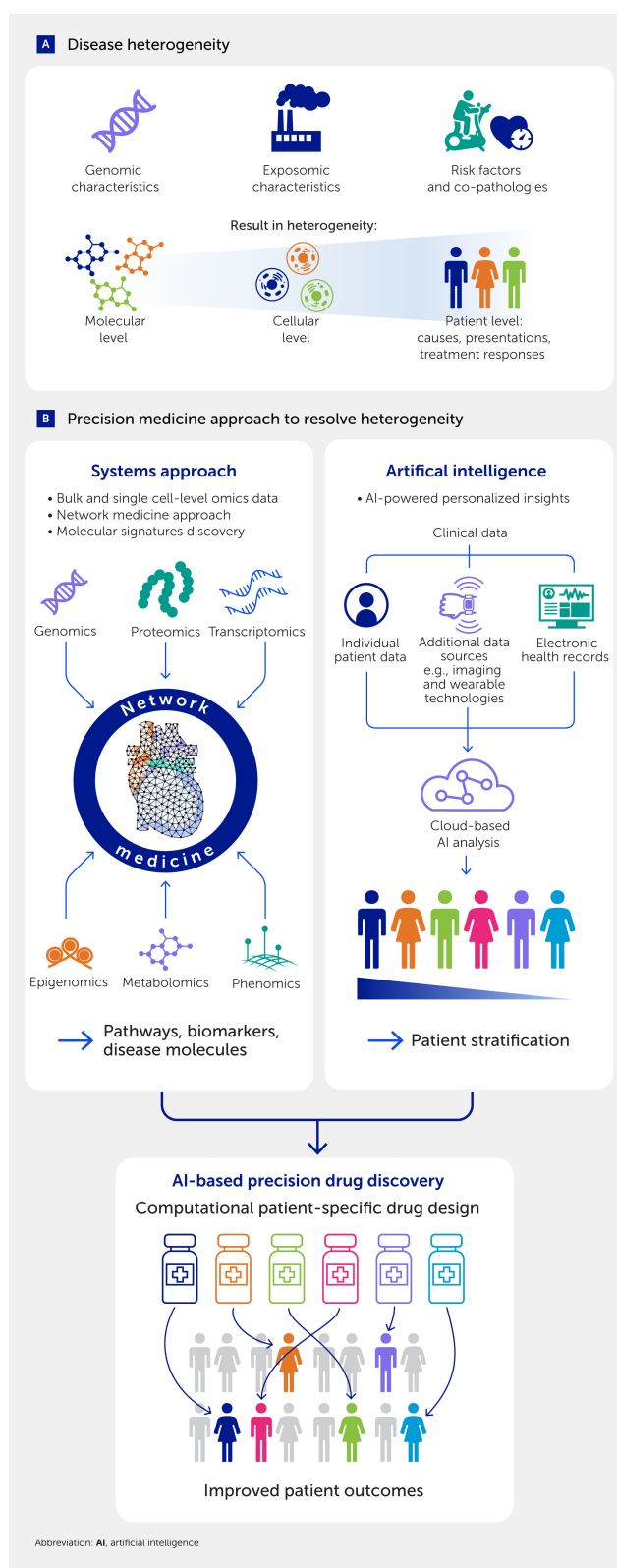


FIGURE 1

Precision cardiovascular medicine as a solution to heterogeneity in cardiovascular diseases (CVDs). **(A)** The heterogeneity in CVDs arises due to many different factors and manifests at multiple levels. **(B)** A multipronged systems approach leads to precision medicine. On one front, the integration of multiomics data using network medicine techniques unveils molecular pathways and disease biomarkers. Simultaneously, an artificial intelligence (AI)-powered approach utilizes clinical data to offer translational endpoints, such as patient stratification and the development of precision drugs and therapies. Together, these approaches hold the potential to significantly enhance patient outcomes.

Large biobanks and databases of multi-ancestry genetic studies now play a crucial role in advancing our understanding of CVDs and thus aid the precision medicine approach (73, 74). While the traditional linear biology approach has been valuable for dissecting individual mechanisms and driving critical discoveries, it does not allow a comprehensive understanding of complex disease pathobiology (75). Preclinical research is powered by many studies built on cell lines and inbred mouse strains (76, 77). The availability of these tools has enabled many mechanistic advances but has failed to capture the heterogeneity observed in the patient population. The use of large animal models and outbred mice could be an important consideration for a systems biology approach. Furthermore, the use of human primary cells to capture the heterogeneity of cells (68) could bring new insights into factors governing inflammation and disease progression. Multi-organ-on-a-chip technologies could be used to mimic the complex cross-organ interactions that regulate cardiovascular diseases (78, 79). These approaches could be bolstered by the utilization of patient-derived induced pluripotent stem cells (iPSCs) reprogrammed into diseased cell types (e.g., endothelial cells, cardiomyocytes, and macrophages) which in turn could be used to perform clinical-trials-on-a-chip for screening patient specific drugs (80, 81). Developing new treatments informed by a holistic view of a complex biological system requires a transition toward a more integrated approach, involving unbiased omics data at multiple levels (e.g., epigenetic, transcriptomic, and proteomic) from the same samples. The identification and understanding of the underlying processes that govern the clinical outcomes are fundamental to the success of precision medicine.

Long navigation time, high costs, and low success rates for drug development

Other major challenges in cardiovascular medicine include the timelines and costs for target discovery and drug development. Estimated development times for new drugs, from target discovery to launch, range from 5 to 20 years—averaging at 9.1 years for innovative medicines (e.g., first-in-class drugs) (82, 83). However, development times for RNA-targeted therapeutics are generally shorter (82, 84, 85). During the COVID-19 pandemic, open science approaches that mobilized the sharing of data and ideas between academic institutions, the pharmaceutical industry, and governmental institutions, helped accelerate the development and implementation of RNA therapeutics (86, 87).

Low success rates of new drugs in clinical development present another major hurdle. Approximately 90% of drugs fail between their entry into phase I trials and regulatory approval (88, 89). If preclinical drug candidates are included, success rates fall below 10%. The most common cause of failure is the lack of anticipated effects, with the exception of genetic disorders, followed by toxicity/side effects, poor pharmacokinetic parameters, and poor overall clinical development strategies (88–91). For example, hidden drug cardiotoxicity can lead to the discontinuation of clinical trials as well as the withdrawal of drugs post-approval (92). The conventional drug discovery approach that targets a single causal

factor also shows limited effectiveness in finding new drugs for complex human diseases, as they involve multiple and overlapping molecular pathways and pathologies. This is, in part, due to this approach relying on a simplified hypothesis for a drug target. Such simplistic hypotheses are often tested using monoclonal cell lines and inbred mice, models that do not fully recapitulate the heterogeneity of complex chronic diseases in humans. Phenotype-driven drug discovery, as opposed to target-based strategies, can address diseases for which mechanisms remain incompletely understood and has been widely used in the pharmaceutical industry (93). Network analysis-powered prediction of the potential impact of each candidate target in human disease may also limit the failure of new drugs at the clinical development stage to a certain extent, owing, in part, to its ability to predict off-target adverse effects (94–96). The benefits of such a comprehensive systems approach to drug discovery ultimately lower the overall costs of development and yield a more efficacious and safe therapeutic agent. These approaches can predict the toxicity profiles of drugs, which in turn avoids the selection of compounds that may fail in later drug development stages due to harmful effects (97, 98).

Following the development of numerous drugs targeting previously identified causal proteins, the need to assess the potential ability of a novel target to be modulated positively or negatively by treatments, colloquially known as “druggability,” remains a key challenge in the development of new drugs (99, 100). Fortunately, technological advances have provided solutions to this challenge. The accumulation of biological and chemical data and the rapid evolution of high-performance computing have enabled the development of various computational strategies, including AI, and helped to design new, effective compounds or predict the potential effects of existing drugs via phenotypic screening. The use of such new technologies and novel computational approaches in drug discovery has opened possibilities for making traditionally undruggable targets druggable (101–103). New platforms, particularly those focused on RNA-targeted therapeutics, also offer precise methods for modulating previously undruggable targets while also reducing development timelines and costs (84, 104–106).

Precision cardiovascular medicine: through systems biology

The essence of the solution to these challenges is the concept of precision medicine (Figure 1). The National Institutes of Health and the Food and Drug Administration of the United States define precision medicine as an innovative approach that considers individual differences among patients. The goal is to use the right treatments in the right patients at the right time. Each individual possesses unique genomic characteristics, experiences distinct exposures (i.e., environmental factors), and exhibits various combinations of traditional risk factors (e.g., dyslipidemia, hypertension, diabetes, lifestyle, diet, and sex). Moreover, the same stimuli and therapies may elicit heterogeneous responses in

different individuals. Considering the specific characteristics of each patient to tailor medical care and interventions with the goal of optimizing treatment effectiveness and minimizing adverse effects is key to precision medicine (107). This necessitates an approach that enables comprehensive molecular profiling, fosters integration to comprehend complex interactions among diverse components, and facilitates the development of predictive models for diseases and biological processes. Systems biology serves as a valuable framework for fulfilling these objectives: it is an interdisciplinary field where the central tenet is that the behavior of a biological system as a whole arises from the complex interplay between its constituent parts (leading to emergent system properties), which cannot be fully understood by studying them individually (108, 109). Below we discuss different aspects of systems biology and potential solutions to challenges in CVD research.

A systems approach to unraveling the biology of heterogeneity

As discussed, CVD arises from diverse factors affecting complex molecular networks. Such complex mechanisms imply that a traditional reductionist approach to exploring a single cause of disease in the average population, testing a linear hypothesis focused on a single target, and developing a “one-size-fit-all” medicine is overly simplistic (75) and may account for reduced efficacy in a substantial group of patients for which the approved drug has been developed (110). This major challenge has driven our efforts to develop a more holistic, integrative systems approach involving unbiased omics analyses, bioinformatics, and network science to establish precision medicine (Figure 1B) (38, 40, 111, 112). The generation of large amounts of biomedical data, or “big data”, ranging from clinical information in electronic health records (EHRs) to the molecular measurement of analytes using different omics platforms (e.g., genomics, transcriptomics, proteomics, and metabolomics) has also prompted the need for analytical frameworks that can holistically interrogate disease pathobiology. Studying CVDs using multiple omics modalities also requires a systems approach because of the involvement of not only complex tissues, including the heart, vasculature, and valves, but also various common underlying mechanisms—termed endophenotypes—including inflammation, immunity, thrombosis, fibrosis, and calcification.

A systems approach enables the construction of integrated models through the concurrent analysis of entities from different omics layers (e.g., genes, proteins, and metabolites) involved in each disease (Figure 1B). Combining different interacting units (e.g., genes and metabolites) into networks enables the identification of key molecular components and the nature of their interrelationships (e.g., regulatory or co-expression) (112). Similarly, AI and machine learning can pinpoint the key combinations of genomic features that are predictive of disease progression (Figure 1B). A systems approach thus enables simultaneous identification of biomarkers for disease progression and potential drug targets. This includes assessing off-target effects and mechanisms of action, enhancing the translational

value of these investigations. Over the past two decades, systems-based research has been effectively applied to cellular systems to reveal a wide variety of emergent biological functions. This approach has complemented and addressed the limitations of the reductionist paradigm prevalent in biomedicine, especially following the influx of high-throughput data during the post-genomic era (109, 113–116). The incorporation of clinical data and disease etiology using AI and an advanced systems approach also allows for better patient stratification into groups based on drug responsiveness, a central tenet of the precision medicine approach (Figure 1B).

Network medicine for multiomics data integration

Networks form the cornerstone of the systems approach in biomedicine (109, 117) and have been used to analyze rich omics data generated in the past few decades. Being multifactorial, complex chronic diseases, CVDs have benefited greatly from the application of systems and network medicine (38, 118, 119). Currently, a myriad of network-based approaches are readily applicable to a vast array of high-throughput molecular, interaction, and ontological data that are publicly available. These approaches are instrumental in inferring key molecules, subnetworks, and pathways related to CVD, providing invaluable information that may help to better identify novel drug targets for preclinical and clinical testing (120). Network methods have been built and implemented for gene regulation (121–125), protein–protein interactions (126–131), and metabolic interplay (132) to shed new light on the drivers of CVDs. Genetic risk loci identified by genome-wide association studies (GWAS) on features such as the PR interval (133), QRS duration (134), and atrial fibrillation (135, 136) have been studied using gene networks. The structural properties of omics-derived networks help in identifying CVD phenotypes that correlate with network features such as functional modules in CVD (137, 138), congenital heart disease (139), cardiac development, hypertrophy, and heart failure (140). Network medicine has helped identify candidate disease genes for CAD (121, 141) or CVD in general (142). Analyzing proteomic data with the assistance of network-based approaches has revealed the global impact of macrophage activation in vascular disease (94) and helped identify the mechanisms behind indoxyl sulfate-triggered pro-inflammatory macrophage activation (95). Similarly, pathway network analysis allows us to study macrophage activation through PCSK9 (143) and in vein graft disease (144), vascular calcification (145), and rheumatic heart valve disease (146). Simultaneous analysis of global transcriptomics and proteomics of calcific aortic valve disease has revealed important associations with various inflammatory diseases (129). Moreover, horizontal integration of the same omics datatypes measured under different conditions or sources reveals correlated features in various layers. For example, integration of proteomics from valvular interstitial cells—either in two-dimensional (2D) cultures on flat surface or three-dimensional (3D) models on hydrogels—with their extracellular vesicles showed correlated proteins relevant to calcification (147). The unbiased proteomics and systems biology of abdominal aortic aneurysms of

mouse models and patients revealed potential novel mechanisms (148). Integrative omics analyses have also been used to study blood pressure regulation and hypertension (149, 150). Parallel to the advances on the omics front, the use of systems pharmacology in CVD has gained prominence (151–155).

The systems approach to drug discovery

Systems biology—involving unbiased omics screening, bioinformatics, and network analysis—has facilitated the discovery of both diagnostic and prognostic biomarkers for CVD. A key strength of this approach is its ability to discover promising targets with improved accuracy in predicting drug efficacy in patients (Figure 2) (38, 94, 95, 144, 156–158). This approach has also enabled us to identify potential targets with a higher likelihood of clinical significance through the integration of different omics datasets and holistic analysis of the disease. Using a systems biology approach, we can find connections between drug target genes and a potentially beneficial clinical outcome (94, 112, 159, 160) (Figure 3). Analyzing which proteins have showcased a shared tendency to change within the human interactome predicted potential regulators of macrophage activation (161). Protein network databases also help to identify proteins closely associated with a node or disease target by “proximity” that can be targeted by new or repurposed drugs to interfere with the disease network. Investigating pathways, key driver genes (162), and network modules associated with a potential drug target can provide key information to researchers by allowing them to choose appropriate cell culture methods, animal models, or even patient stratification in clinical trials.

Future perspectives in the systems approach to cardiovascular medicine

One of the important promises of systems medicine is its focus on the patient rather than the disease. Specific genes and individual disease-causing mutations can contribute to an individual’s apparent monogenic CVD phenotype, such as cardiomyopathies. However, in some cases, “additive” modifier genes may also play a role, paving the way for precision genetic medicine (163). For example, a previous study aimed to identify genetic drivers of dilated cardiomyopathy, a diagnosis of exclusion among cardiomyopathies (164). After examining 51 curated genes, they identified 19 that showed high evidence but could only explain a minority of cases, suggesting the need for further studies to unearth the mechanism of disease development. We predict, however, the realization of precision medicine goals at scale in the next decade. The implementation of network-based approaches has accelerated research on integrative single-cell omics (165) and spatially resolved omics (166), which will further unlock the heterogeneity in complex diseases (Figure 1) (38, 111, 167). In the context of CVD, identifying the degree of heterogeneity of cell populations in complex tissues such as atherosclerotic plaques, calcified aortic valves, or cardiac muscle can lead to important insights into pathobiological

mechanisms. For example, single-cell RNA sequencing has helped identify the diversity of the cardiac cellulome (168). Studies that combine network medicine and machine learning methods can be used to fine-tune our understanding and help identify a more accurate representation of the regulatory underpinnings of cellular heterogeneity (68, 103, 129–131, 147, 169). Moreover, the transfer of fundamental concepts across fields, such as a newly proposed statistical mechanics framework for single-cell biology (170), can further accelerate advances in systems medicine. As discussed, the integration of multiscale omics data may also facilitate the development of precision therapies. Finally, recent advances in harmonizing network biology methodologies with the power of machine learning (171–173) will soon come to full fruition, as high-resolution molecular data are increasingly converging with corresponding clinical and EHR data from individuals.

Innovative technologies for driving precision cardiovascular medicine

Proteomics headlines the multiomics universe of CVD research

Omics technologies, which offer an unbiased survey of multiple genes and proteins, have significantly increased the likelihood of identifying potential therapeutic targets. This process can be effectively complemented with targeted proteomics and the more recently defined proteoforms resulting from post-translational modifications. Such an approach can facilitate successful target discovery and clinical translation (Figure 4), as discussed later in this section.

The high demand for continued discovery of additional therapeutic targets has driven the development of global, unbiased platforms such as epigenomics, transcriptomics, proteomics, and metabolomics. In particular, mass spectrometry-enabled protein research has long been recognized as a promising means to identify novel biomarkers and therapeutic targets for CVD (174–176). Today, mass spectrometry is a mainstay not only for proteome profiling (177) but also metabolome profiling (178, 179). When combined with other omics approaches, such as epigenomics (179) or transcriptomics (180), it provides solid foundations for systems biology and multiomics data integration strategies (Figures 1–4) (38, 167, 181).

Proteins are one of the major determinants of the cellular phenotype, driving initiatives such as the Human Proteome Project to facilitate translational research to improve overall human health (182). Unbiased proteomic approaches are consistently used to identify molecular drivers of CVDs, such as coronary heart disease (183), abdominal aortic aneurysms (148), and calcific aortic valve disease (129). In the last example, transcriptomics and proteomics were used to distinguish fibrotic and calcific regions from non-diseased regions of aortic valve leaflets but reported only a weak correlation between the quantified transcripts and proteins (129). These findings emphasize that protein abundances may not necessarily occur in proportion to their transcript abundances (184,

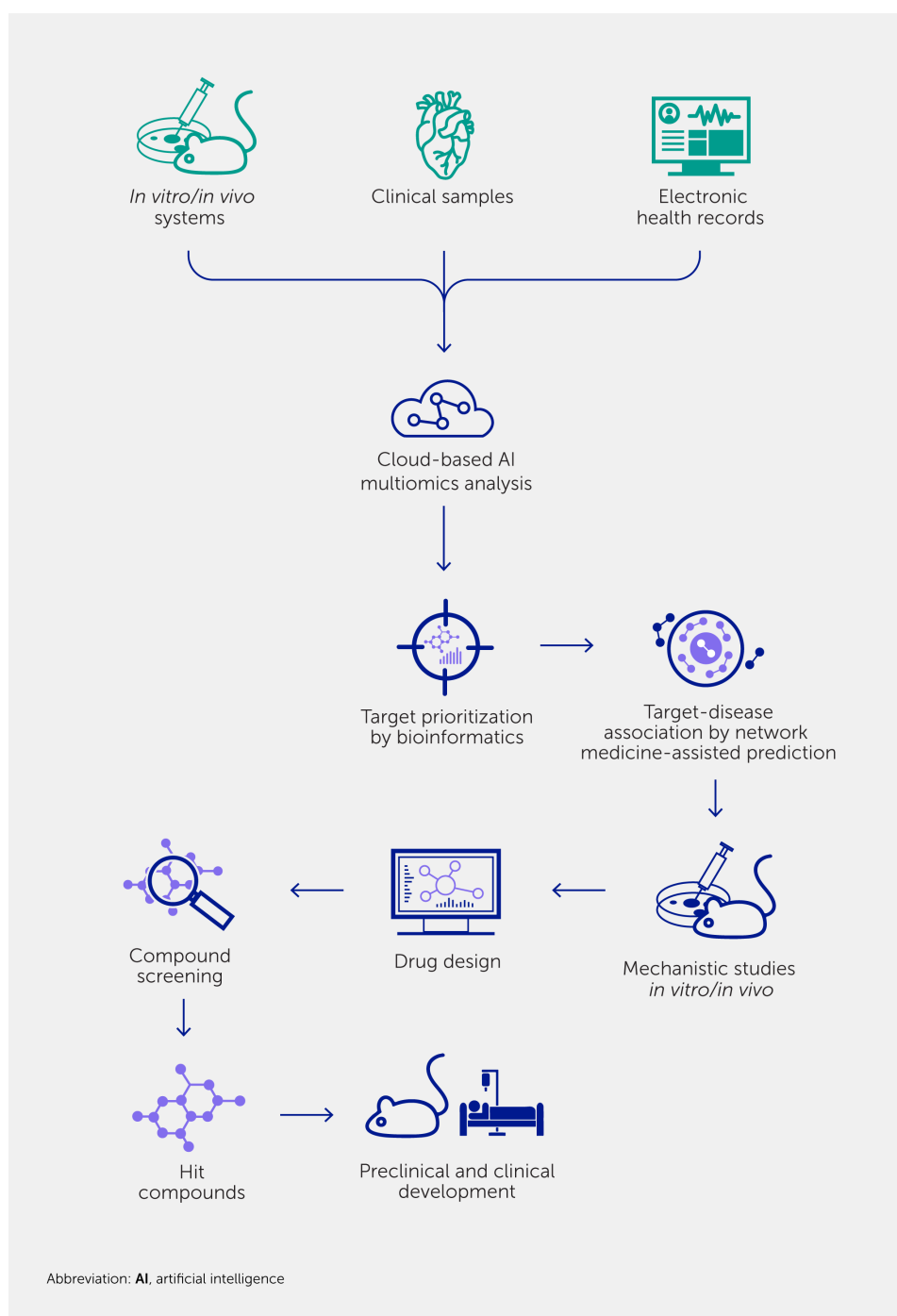


FIGURE 2

A multilayer systems approach to target discovery and drug development. The hypothesis-driven, reductionist approach may have contributed to low success rates of new therapies based on conventional, basic science-driven clinical development. A systems approach involving unbiased omics, followed by bioinformatics for target prioritization and network medicine-assisted prediction of clinical impact, may facilitate the process and increase the success rate of identifying new targets. Comprehensive *in vitro* and *in vivo* experiments substantiate new concepts. Such models enable earlier implementation of drug design than conventional models.

185). Moreover, tissues comprise various cell types such that “bulk RNA and proteome” data provide average signals, thereby eliminating the opportunity to glean potential “disease-driver subpopulations.” While single-cell transcriptomic technologies have been successfully implemented to reveal the extent of cellular

subpopulations and heterogeneity in tissues (144), single-cell proteomics (186, 187) is still too recent a technology, requiring extensive expertise to yield a similar widespread implementation.

Targeted proteomics is already valued in a clinical setting, namely, to monitor steady-state kinetics of candidate LDL-C

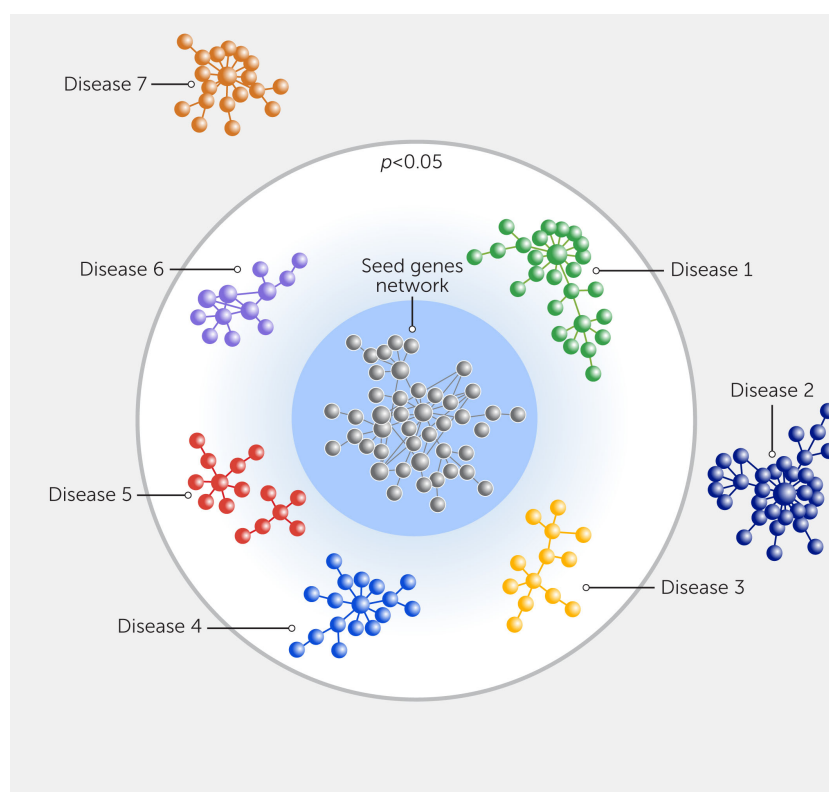


FIGURE 3

Network prediction of the clinical impact of seed genes on various diseases. The network proximity of the seed genes from analyses (gray), which could be obtained from differentially expressed genes or proteins and various disease gene modules obtained using databases. The p value indicates the significance of proximity to the given disease module and other disorders, as compared with random expectation.

lowering targets such as apolipoprotein B (APOB), cholesteryl-ester transfer protein (CETP), and PCSK9 in cardiovascular outcome trials (188–190). Innovations in targeted mass spectrometry technologies enabled tracer kinetics studies in humans that captured the complex metabolic profiles of several high-density lipoprotein (HDL)-associated proteins, supporting the notion that HDL is a heterogeneous lipoprotein class consistent with its multiple functions (191, 192). These findings underscore that effective CVD drugs may require targeting a subpopulation with distinct functions rather than the entirety of a given molecule or cell class.

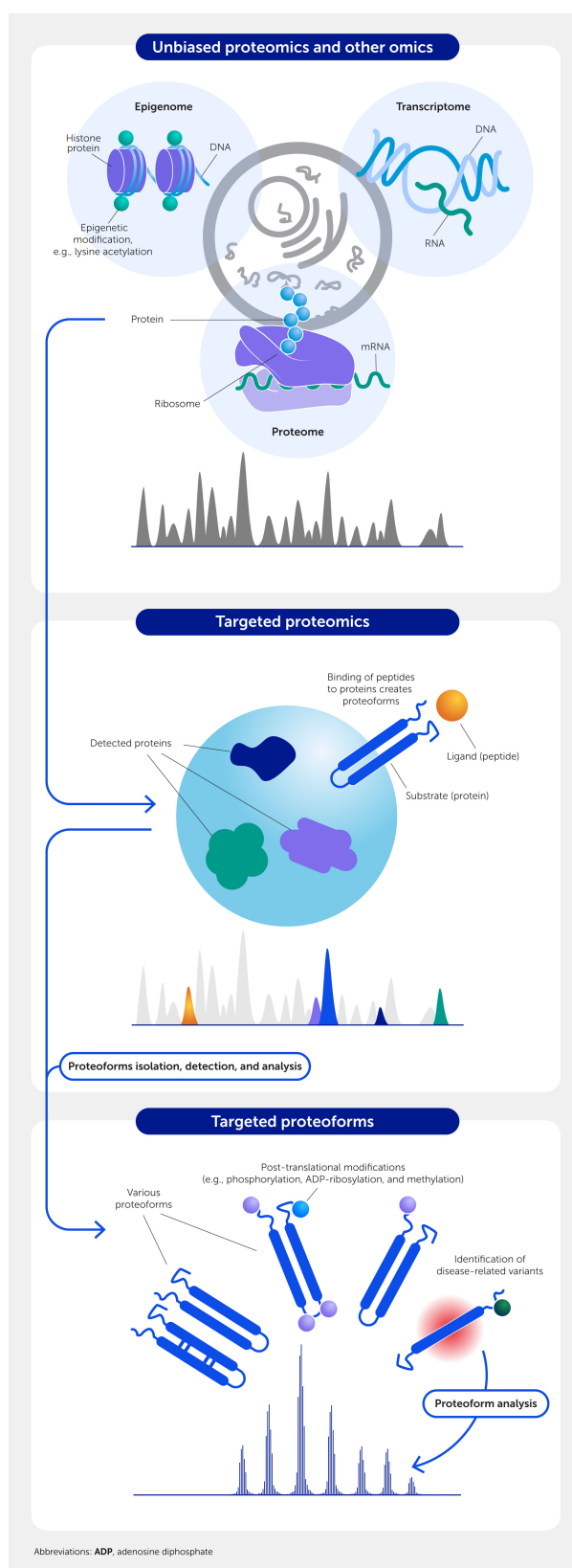
Proteins themselves comprise various isoforms—known as proteoforms—that may result from genetic variants, messenger RNA (mRNA) splice variants, and post-translational modifications, of which only one form may be causal to the disease of interest. Therefore, the proteomics community has initiated the Human Proteoform Project, an ambitious endeavor to generate a reference set of proteoforms for the human genome (193). Although mass spectrometry is a central technology supporting this initiative, it is, in essence, a multiomics endeavor (Figure 4) (193).

As first predicted over 20 years ago, mass spectrometry-enabled proteomics is providing CVD researchers multiple avenues through which to identify therapeutic targets. In all likelihood, the next CVD breakthrough targets may be identified using omics. Before its arrival on the market, however, the methodology will require

extensive validation studies that, in part, may very well entail one or more additional proteomic technologies.

Single-cell technologies to tackle the complex biology of cellular heterogeneity

As discussed, disease heterogeneity is a major challenge in cardiovascular medicine. For example, statins reduce the risk of acute complications such as myocardial infarction in many, but not all, patients. This can be attributed to factors such as the potency and pharmacodynamics of different statins, as well as patient heterogeneity. This may also result from different patterns of heterogeneity of atherosclerosis-associated cells (e.g., macrophages) among patients. Evidence has linked sustained pro-inflammatory activation of macrophages with vascular disorders (67, 194–196). An earlier paradigm of macrophage heterogeneity proposed a pro-inflammatory M1 phenotype and an anti-inflammatory/pro-resolving M2 phenotype (197, 198). More recent evidence (our own included) however, suggests that macrophage heterogeneity is more complex than the M1/M2 dichotomy, and involves more subpopulations (67, 199–202). While the overall balance of macrophage subpopulations may regulate disease mechanisms or severity, traditional assays only examine average levels of gene or protein

**FIGURE 4**

Drug-target discovery depends on multiple omics strategies. Unbiased screening of the epigenome, transcriptome, and/or proteome identifies candidate targets that can be validated using targeted mass spectrometry/proteomics. Ultimately, a specific proteoform (post-translationally modified form) of the protein may be the best target in some cases.

expression in the entire population of cells (e.g., Western blot analysis and bulk RNA-sequencing) and cannot assess how individual cells behave. This challenge has driven the development of various platforms for single-cell analysis and their integration (Figure 5).

This challenge has been the catalyst for rapid and expansive development of single-cell technologies that enable deeper sequencing in more cells, platforms for simultaneous surveying of various omics layers in cells, and computational and bioinformatics infrastructure for innovative data analyses (Figure 5A). Technologies such as droplet-based, well-based, and sequential barcoding platforms can be chosen based on the underlying application. Single-cell analysis has extended beyond profiling RNA expression levels at the single-cell level with the ability to map surface expression of receptors (203) and chromatin accessibility (204). While these omics datasets can either be individually mined, they can also be paired with mRNA expression (205) by these cells to provide truly integrated multiomics characterization (206). Furthermore, recent advances in single-cell proteomics (207, 208) powered through mass spectrometry allow unbiased characterization of the proteome at the single-cell level. Spatial transcriptomics and spatial proteomics have also become widely available platforms that provide critical information relating to the spatial disposition of cellular heterogeneity. Leveraging these technologies allows for the construction of multilevel spatial multiomics maps through

disease progression within the heart to identify signaling pathways specific to different cell types (59, 130, 209, 210). Assays that characterize different types of omics at single-cell resolution allow for the simultaneous measurement of epigenetics, transcriptomics, and proteomics. These include single-cell assays for transposase-accessible chromatin (ATAC)-sequencing for chromatin accessibility, single-cell profiling of histone modifications (211), spatial transcriptomic profiling (e.g., Slide-seq) (212), and surface receptor profiling (e.g., cellular indexing of transcriptomes and epitopes sequencing; CITE-seq) (213). Recent developments have expanded even into the realm of single-cell metabolomics, which provides opportunities to evaluate substrates and metabolites within the same cell (214–217). Such approaches will significantly advance integrative single-cell omics research.

The wide range of available, free software packages that can be used to analyze these datasets has also removed barriers to entry for many researchers, enabling them to embrace these approaches to address their specific research needs. This transition has coincided with the decreasing cost of cloud computing and the secure computing capabilities provided by research institutions and private companies that allow rapid, cost-effective processing of these large datasets (Figure 5A).

The rapid utilization of single-cell RNA-sequencing technologies (218) has enabled the construction of a wide range of single-cell atlases (219). Multi-tissue cell atlases of various model organisms

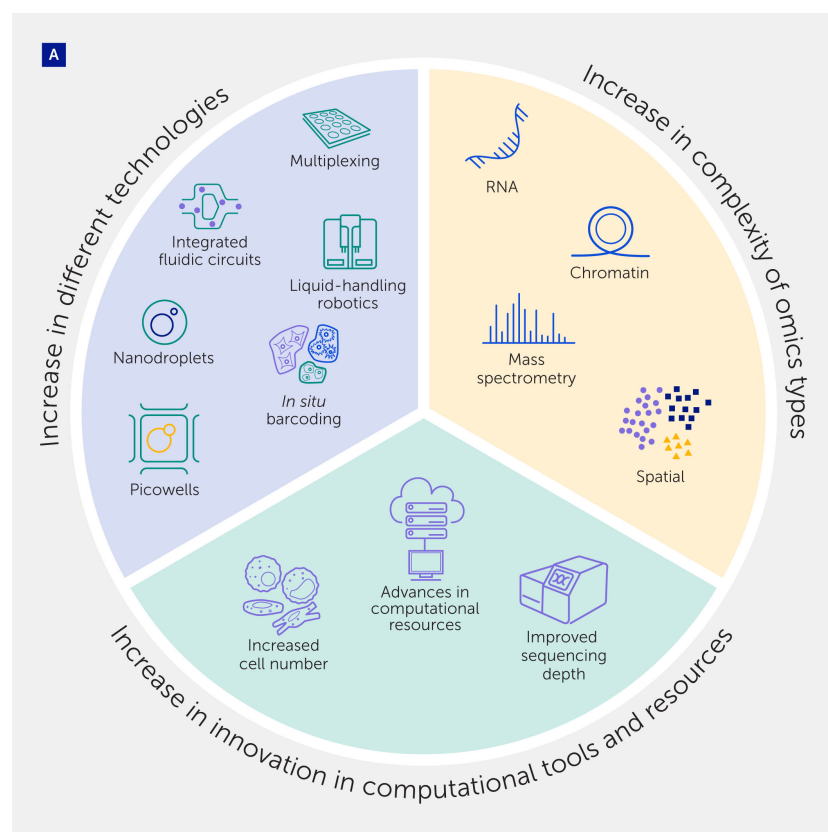


FIGURE 5 (Continued)

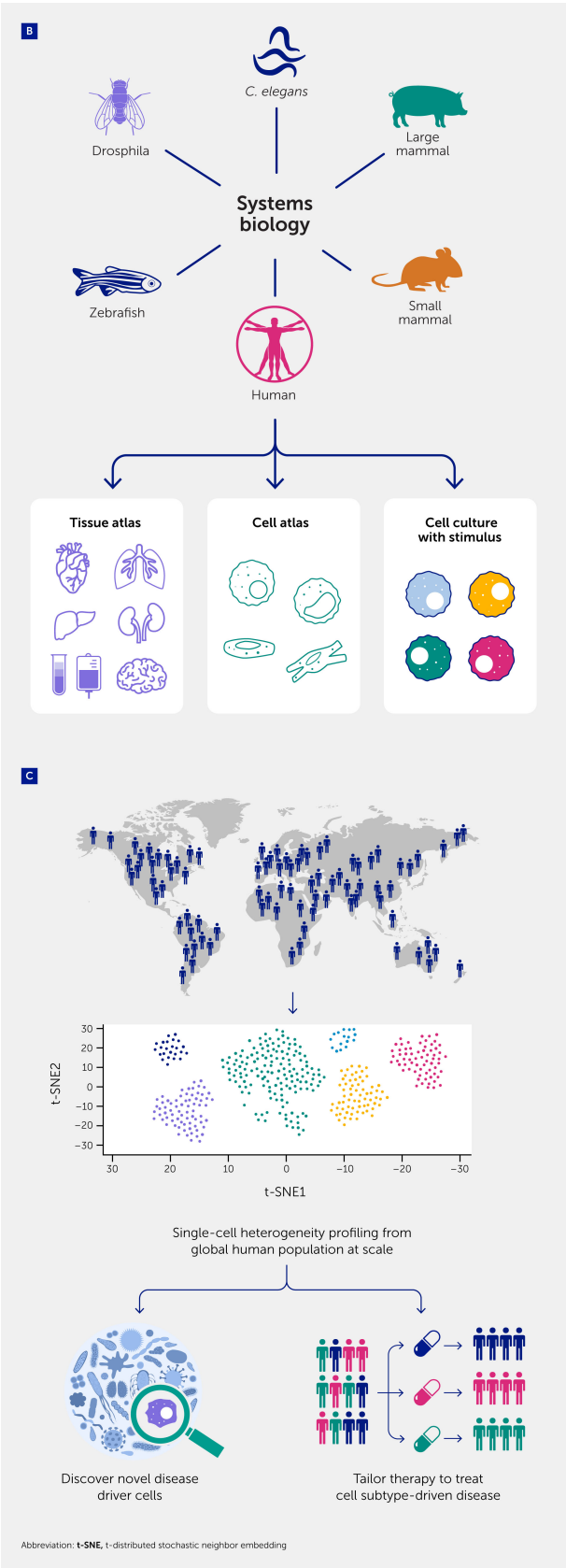


FIGURE 5 Integration of single-cell analyses for precision medicine. **(A)** An array of technological advances have occurred in platforms used for single-cell analysis, together with advances that have increased the complexity of omics types analyzed, and innovations in computational tools and resources. **(B)** Systems biology studies in animals and humans are now translating these advances into multi-tissue, single-cell atlases to provide *in vivo* landscapes of cellular heterogeneity. **(C)** Further extension of single-cell technologies to profile populations at scale could shape the future of biomedical research, establishing innovative diagnostics/ biomarkers and tailored therapies for diseases driven by specific cell subtypes.

have provided an important understanding of the *in vivo* landscape of cellular heterogeneity (220–222). Human-centric atlases have mapped specific organs that have been instrumental in identifying the various cell types and subtypes that make up an organ (219, 223, 224) (Figure 5B). Specific cell atlases discern how the same cell identified in multiple tissues has different underlying transcriptional signaling (58, 62–64, 225–227). Furthermore, recent studies have deployed single-cell RNA-sequencing technology to identify novel cell subtypes that could be disease drivers within specific disease settings (130, 228). These studies help shed light on specific cellular signaling aspects that regulate cellular heterogeneity.

While unbiased single-cell omics datasets have become increasingly cost-effective, generating, annotating, and sharing them remain expensive and resource-intensive. Reproducibility and data access are important aspects of large omics datasets that have made major strides recently. Easy and accessible computational pipelines are now widely available (229, 230). Journal requirements that make detailed single-cell datasets publicly available also help extend their utility once generated, which will also facilitate comparisons of datasets to enhance reproducibility.

Importantly, using publicly available unbiased single-cell omics data, researchers can fine-tune their approaches and generate follow-up experiments using targeted approaches to either validate these findings in a larger dataset or perform hypothesis-testing experiments. In this regard, the development of methods to perform targeted single-cell mRNA sequencing significantly reduces the costs of sequencing and facilitates the sequencing of a large number of cells (231). Similarly, the utilization of high-parameter flow cytometry (232) as well as sequential staining of tissue sections are becoming increasingly attractive (232, 233). Large-scale panels of validated probes and antibodies allow for the rapid adoption of these platforms across a wide range of tissues.

The characterization of cellular heterogeneity through these approaches helps to identify key cell types within *in vivo* settings. However, future studies can also use both unbiased and targeted approaches within monoculture systems to evaluate cellular heterogeneity in response to classical stimuli (234–236). Past efforts have typically utilized bulk omics studies to identify heterogeneity in responses (94) but are not limited in their capacity to highlight how different cells within a monoculture system can respond differently to the same stimulus (Figure 5B). Single-cell RNA sequencing and single-cell ATAC sequencing (237, 238) will allow the identification of novel subpopulations within a single cell type.

While single-cell technologies have developed rapidly, a few key questions remain (239). It is of critical importance to leverage cellular heterogeneity information to identify new mechanisms that translate into the clinic. We also need to consider the contribution of a small subset of disease driver cells to disease progression. Another point of consideration is the temporal dynamics of measured proteins and genes and their relative contribution to chronic disease. Most importantly, we also need to ask how understanding macrophage heterogeneity can provide molecular bases for the development of new diagnostics and therapies (240, 241). Recent studies offer examples of how cell heterogeneity data can be translated into drug development (169). How can we associate the information of subsets of cells associated with CVD with high-risk patients? Further extension of

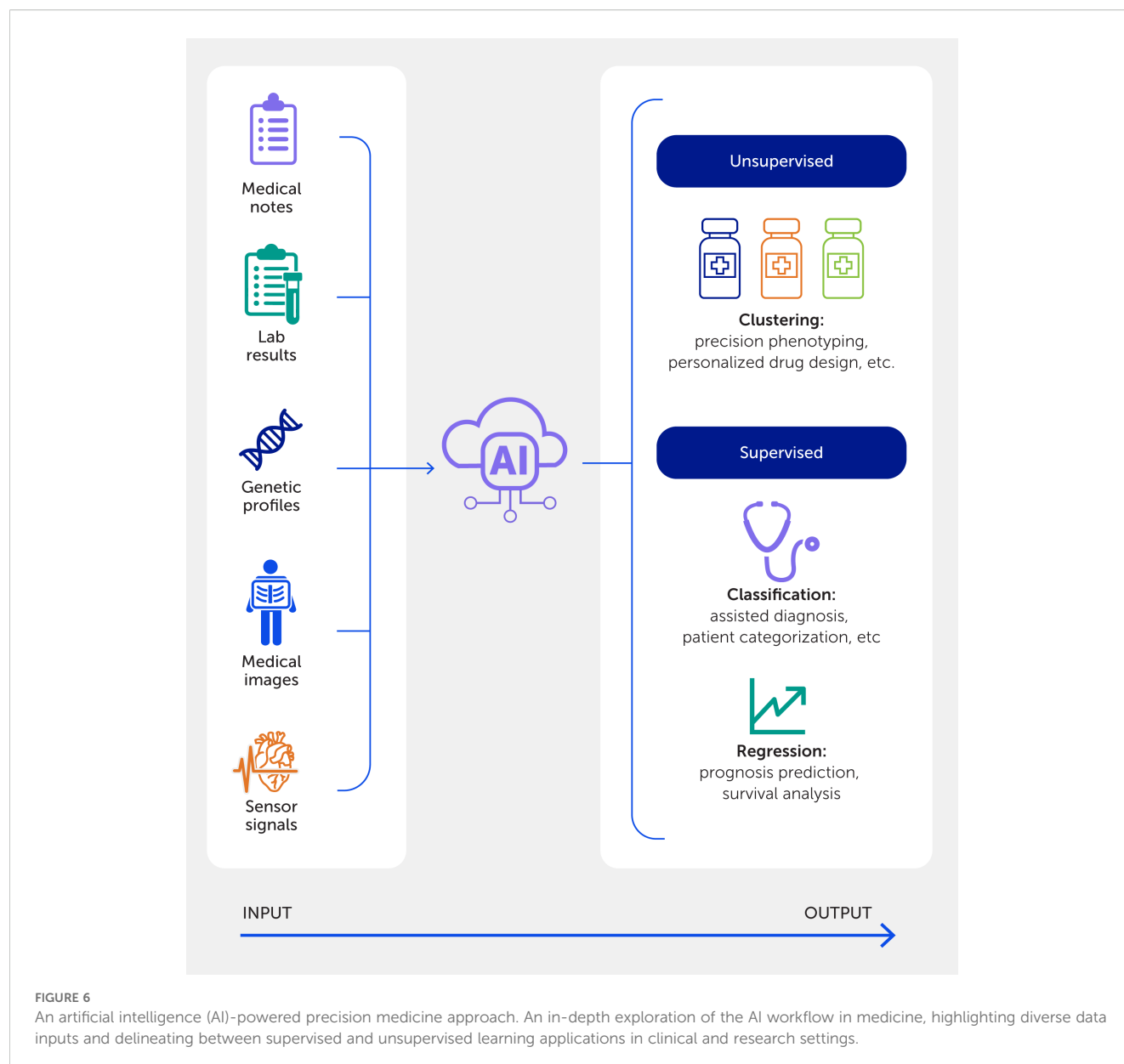
single-cell technologies, such as high-content live cell tracking for longitudinal monitoring and histologic localization of high-dimensional single-cell data in disease tissues, may help to facilitate clinical translation (31, 242–245). The combined use of single-cell data and computational drug screening methods (68, 169), discussed below, may also lead to potential new therapies. These methods may help us develop new approaches in precision cardiovascular medicine (246), establish innovative diagnostics/biomarkers (247), and enable intelligent enrollment criteria trial design, focused data interpretation, and improved patient safety in clinical trials (248, 249) (Figure 5C).

AI supporting translational discoveries for complex CVD

Medical scientists have faced challenges in analyzing the massive biological and clinical datasets necessary to address the complexity and heterogeneity of human diseases. Exponential technological advances and their integration into basic science and clinical activities, such as omics and EHRs, have accelerated this trend. Over the last several decades, the field of AI has led to a major technological revolution that has already significantly impacted practically every aspect of the human experience, including medical research and practice (250, 251). However, the use of AI-powered technologies in medical sciences is not necessarily new. In the 1980s and 1990s, decision support systems, such as Health Evaluation through Logical Processing (HELP) or DXplain, assisted physicians through the diagnostic process (252, 253). However, with the increase in computational power and the availability of large volumes of data, AI has unveiled its extensive capabilities in the last decade.

The application of AI in cardiovascular sciences has focused on two main tasks: prediction and clustering (Figure 6) (254–256). Prediction tools are used to estimate future prognosis and survivability of CVDs, including heart failure (257–259) and cardiomyopathies (260–263). AI prediction has also been implemented successfully to assist diagnosis (264–266), especially by using medical imaging data (e.g., echocardiogram, computed tomography, or magnetic resonance imaging) (267–274). Although not as common as contemporary AI-based prediction technologies, unsupervised learning has been used to cluster patient populations into different phenotypes (275–278), aiding the design of more precise therapeutic paths. Further, a new AI tool called AlphaMissense, which builds on the protein structure prediction tool AlphaFold2 (279), can be used to evaluate specific genetic variations (e.g., rare missense variations)—addressing the previous “bottleneck” in the bioinformatic analysis and assignment of causality to link a particular candidate genetic variant to the phenotype.

Considering differences among individuals, recent target discovery efforts have used large clinical data sources such as gene expression datasets associated with specific diseases and EHRs in addition to, or in place of, preclinical samples from cultured cells or animal models to address the biology of disease heterogeneity at the population level (71). The 21st Century Cures Act, initiated by the United States Government in 2016, promoted the use of clinical



data sources such as the EHR (“real-world data”) in drug development and regulatory decision-making (280). Generative AI programs can autonomously create new content by learning patterns from existing data. AI’s role in changing the regulatory paradigms will involve improvements at all stages, from creating regulatory documents and designing the protocols to patient and site matching. The ability of AI to navigate huge datasets and construct detailed patient profiles based on demographics, medical history, and genetics to create “digital twins” can be used to simulate outcomes using virtual trials. These are the new AI frontiers: promises of refined therapeutics, improved patient care, and enhanced regulatory processes.

In the near future, integrating health records, clinical medical knowledge, and data provided by “smart” devices, such as phones and watches with AI technologies, will lead to unprecedented changes in our understanding of cardiovascular medicine (281).

Technology companies such as IBM (282–284), Microsoft (285), Google (286), and Apple (287) have recognized its potential and have announced significant investments accordingly. The use of AI in continuous real-time monitoring, precision drug design, precision phenotyping, and the precise prediction of the development of CVDs represents a major breakthrough driven by new technology in the history of medicine.

Data science-powered drug development

The cost and time required for drug discovery have increased annually, presenting the pharmaceutical industry with major challenges in developing and marketing new drugs (82–85, 288). Another challenge is the low success rate of new targets progressing to clinical stages and achieving favorable outcomes in clinical trials

(88, 89, 91). As discussed earlier, generating compounds for undruggable targets is a major obstacle in the development of innovative drugs (99, 100). On the other hand, valuable medical, biological, and chemical data have accumulated, and the performance of computers in handling “big data” has evolved. To save cost and time, computational approaches have increasingly contributed to various aspects of drug discovery. In particular, the computational exploration and design of effective therapeutic compounds are major emerging fields. Such innovative technologies may also help to make traditionally undruggable targets druggable (101).

One such technique uses the quantitative structure–property relationship (QSPR) and quantitative structure–activity relationship (QSAR)—a prevalent statistical approach that correlates molecular structure with properties or biological activity using quantifiable descriptors. These descriptors are often generated through density functional theory (DFT) (289), a widely applied quantum theory to calculate the electronic structures of atoms and molecules. Selecting the most relevant descriptors among them poses a significant challenge, as they encapsulate molecular characteristics responsible for the observed biological activity or chemical properties (290). Recent advancements have introduced novel QSAR methodologies that enrich the analysis of bioactivity. Nevertheless, QSAR models require rigorous testing and validation to assess their predictive accuracy and practical applicability (291).

One resource for drug identification is the Connectivity Map (CMap) (292). This database includes changes in many gene expression profiles (“signatures”) that occur when various compounds are exposed to various cell types. The CMap has been expanded to include over 1 million signatures using over 20,000 small molecules through the introduction of the L1000 assay, a low-cost, high-throughput, and highly reproducible gene expression profiling method (293, 294). The L1000-based CMap quickly identifies small molecules that modify gene expression signatures by either reversing or mimicking the changes caused by certain diseases. Therefore, such approaches have been widely used for rapid drug repurposing (102, 103, 295–297). This phenotypic screening as a counterstrategy to traditional target-based drug discovery has been successful in the development of “first-in-class” drugs (298, 299).

In target-based drug discovery, which generally favors the development of “best-in-class” drugs, the identification of compounds that interact with target proteins is a key task (300, 301). Drug–target interactions (DTIs) have been experimentally surveyed using high-throughput screening. However, the number of compounds that can be tested this way is limited compared with the theoretical number of drug-like compounds—estimated to range from 10^{23} to 10^{60} (302). It is therefore desirable to narrow-down candidate compounds using computational approaches. Computational DTI prediction can be divided into ligand-based, docking-based, and chemogenomic approaches.

Ligand-based approaches exploit the principle that compounds structurally similar to a known binder of a target protein are likely to interact with that protein in a similar manner. While such methods are rational and easy to follow, nothing can be predicted when there is no compound known to bind the target protein.

Docking-based approaches calculate the binding affinities between compounds and target proteins by simulating their 3D structures. Although this approach can evaluate interactions with any compounds, it requires knowledge of the *in vivo* structure of the target protein. The prediction thus becomes more difficult for compounds that interact with membrane or receptor proteins owing to their complex, flexible structures.

Chemogenomic approaches utilize the compound’s physicochemical features, such as molecular fingerprints, and the protein’s genomic features, such as amino acid sequences. Machine learning models learn the pattern of these features required for the interactions by using known DTI datasets, and then the model predicts whether an unknown compound indeed interacts with the target protein. This approach has attracted attention recently because it overcomes the inherent disadvantages of the ligand-based and docking-based approaches (303). Various frameworks employing classical machine learning methods, such as support vector machine or random forest approaches, and advanced techniques, such as deep learning (DL), have been proposed as relevant computational models and have already improved DTI prediction accuracy significantly (304–306).

Scientists have also attempted to computationally design novel compounds with desired molecular profiles (e.g., bioactivity, drug metabolism, pharmacokinetics, or synthetic accessibility). In this field, denoted *de novo* molecular design, various generative models based on DL architecture, such as the recurrent neural network, variational autoencoder, and generative adversarial network models, have emerged (307–309). Benefiting from the remarkable development of AI, these AI-powered generative models create feasible, plausible, yet entirely new compounds that have never been synthesized in the real world. These generated compounds can be used seamlessly as a new compound library for DTI prediction. Moreover, by providing the L1000-based CMap signatures to the aforementioned generative models, the design of novel compounds that induce desired gene expression signatures has been used in an attempt to expand the applicable range of L1000-based CMap (310, 311).

Notably, computational approaches are beginning to be used to predict the tertiary structure of proteins. A recently developed AI-based algorithm, AlphaFold2, predicts 3D protein structures from the amino acid sequences with high accuracy (312). AlphaFold2 may accelerate DTI prediction, especially via docking-based and chemogenomic approaches, because it can provide accurate protein structures whenever an experimental protein is unavailable and extract more structural features than the amino acid sequences can when used alone (313). Through such improvements, computational approaches will likely have an increasingly important role in compound exploration for drug discovery.

New therapeutic platforms: from proteins to RNAs

Most CVDs are currently treated with small-molecule drugs that are orally administered to bind to proteins contributing to disease mechanisms. As we discussed, however, some new targets

are undruggable with conventional strategies. Therapeutic options other than small molecules include monoclonal antibodies against proteins, e.g., evolocumab and alirocumab targeting PCSK9 for familial hypercholesterolemia (314). While these types of drugs are effective and can overcome some druggability issues, targets are limited to cell membrane proteins or circulating proteins, and their production costs are high. Innovative technologies that enable targeting of undruggable targets include targeted protein degradation, such as proteolysis-targeting chimera (PROTAC) molecules that can degrade a target protein by controlling the ubiquitin–proteasome system. Compared with small molecules that block protein function but leave protein levels unchanged, small interfering RNA (siRNA) and PROTAC-based approaches can help modulate protein levels directly. While PROTAC technology has mainly been used for cancer targets, recent advances have extended its application to non-cancer diseases, particularly immune, inflammatory, and neurological disorders (315).

RNA-targeted interventions, a new class of innovative therapeutics, may overcome some of the aforementioned challenges (84, 104–106). Their advantages include (i) each gene of interest is potentially targetable by RNA therapeutics, whereas protein-targeted small molecules or antibodies can target only 0.05% of the human genome (316); (ii) manufacturing costs are lower than those of protein-targeted therapeutics; and (iii) development times are substantially shorter than those for conventional medicines. RNA interventions include antisense oligonucleotide (ASO), siRNA, clustered regularly interspaced short palindromic repeats (CRISPR)-based genome editing, aptamer, and mRNA vaccines (317–321).

The first ASO drug was fomivirsen, approved by the United States FDA in the late 1990s for the treatment of cytomegalovirus (CMV) retinitis (322, 323). Mipomersen, an ASO targeting apolipoprotein-B-100 mRNA, was the first RNA-targeted therapy approved by the FDA for a CVD—familial hypercholesterolemia (324). Inclisiran, an siRNA targeting PCSK9, has proved safe and effective for lowering LDL (by approximately 50%) and cardiovascular outcome trials are ongoing (325). Another developmental ASO, pelacarsen, is directed against lipoprotein(a) [Lp(a)], which is linked clinically with CVD, including aortic stenosis. Specifically, pelacarsen targets the production of apolipoprotein(a) [Apo(a)], a key component of Lp(a) disulfide-linked to apolipoprotein B100. Pelacarsen proved safe and lowered Lp(a) levels by up to 80% in phase 2 trials (326). Clinical trials of siRNAs that reduce both normal and mutated transthyretin (TTR), causing TTR amyloidosis, reported attenuated progression not only of the associated peripheral neuropathy but also cardiomyopathy (327, 328). In addition to these developments, the COVID-19 mRNA vaccines showed that delivering native or chemically modified (e.g., pseudo-uridine) mRNA by encapsulation in lipid nanoparticles is another potential option to treat various diseases, including CVD. Yet, all such methods are directed toward interacting with proteins.

We know from increased usage of next-generation sequencers that most of our coding genome is transcribed as RNA (329). Only a

small percentage codes for proteins, leaving a majority of transcribed RNAs as non-protein-coding RNAs (ncRNAs). In addition to the well-known ncRNAs, ribosomal RNAs (rRNAs), and transfer RNAs (tRNAs), other regulatory ncRNAs have been identified and characterized in recent years, including microRNAs (miRNAs), circular RNAs, and long ncRNAs (lncRNAs) (330). Not surprisingly, the dysregulation of ncRNAs is linked to various CVD etiologies, and hence, these ncRNAs are being investigated as potential CVD diagnostic biomarkers or therapeutic targets (331).

Preclinical and clinical trials of miRNA-based therapeutics for CVDs are ongoing (332) while most projects on lncRNA-targeted therapeutics are still in the preclinical stage. lncRNAs are associated with many human diseases and many efforts are underway to develop technologies to target them therapeutically (333, 334). lncRNAs involve diverse modes of action, providing different opportunities to modify their functions (e.g., via siRNAs, ASOs, CRISPR/Cas9, small molecules). Some mitochondrial lncRNAs have reached clinical trials as cancer therapies (334). Accumulating preclinical evidence has implicated lncRNAs in the pathogenesis of various CVDs, including atherosclerosis, myocardial infarction, heart failure, and arrhythmias, providing molecular bases for their clinical applications as therapeutic targets or biomarkers (331, 335, 336). While lncRNA-targeted therapeutics have high potential, their clinical development is lagging. This may be due to our incomplete understanding of their mechanism of action, necessitating more mechanistic studies of each lncRNA. In addition, innovative computational methods should help elucidate their interactions with miRNAs, coding RNAs, and proteins. The combined use of such targeted systems approaches will help translate advances in lncRNA biology into clinical CVD medicines.

These novel modalities can also be partnered with a wide array of drug delivery strategies to maximize their effectiveness (337) and reduce off-target effects (338). These have been key partnerships for emerging modalities, such as RNA-targeted therapeutics (339). While these drug delivery methods remain unproven in the clinic, they have accelerated preclinical research by serving as powerful tools for *in vivo* intervention (95, 144).

Transforming cardiovascular medicine: innovative approaches and collaborative initiatives

Interdisciplinary and multistakeholder drug discovery drives innovation

Facilitating drug discovery and development for innovative precision medicine requires new paradigms. New technological developments can help solve specific technical limitations and promote scientific discoveries. These discoveries can be accelerated by models that integrate multiple innovative technologies to holistically address the biology of heterogeneity, identify promising drug targets, predict their clinical impacts, and design, generate, and test new drugs. Dynamic and close collaboration between biologists

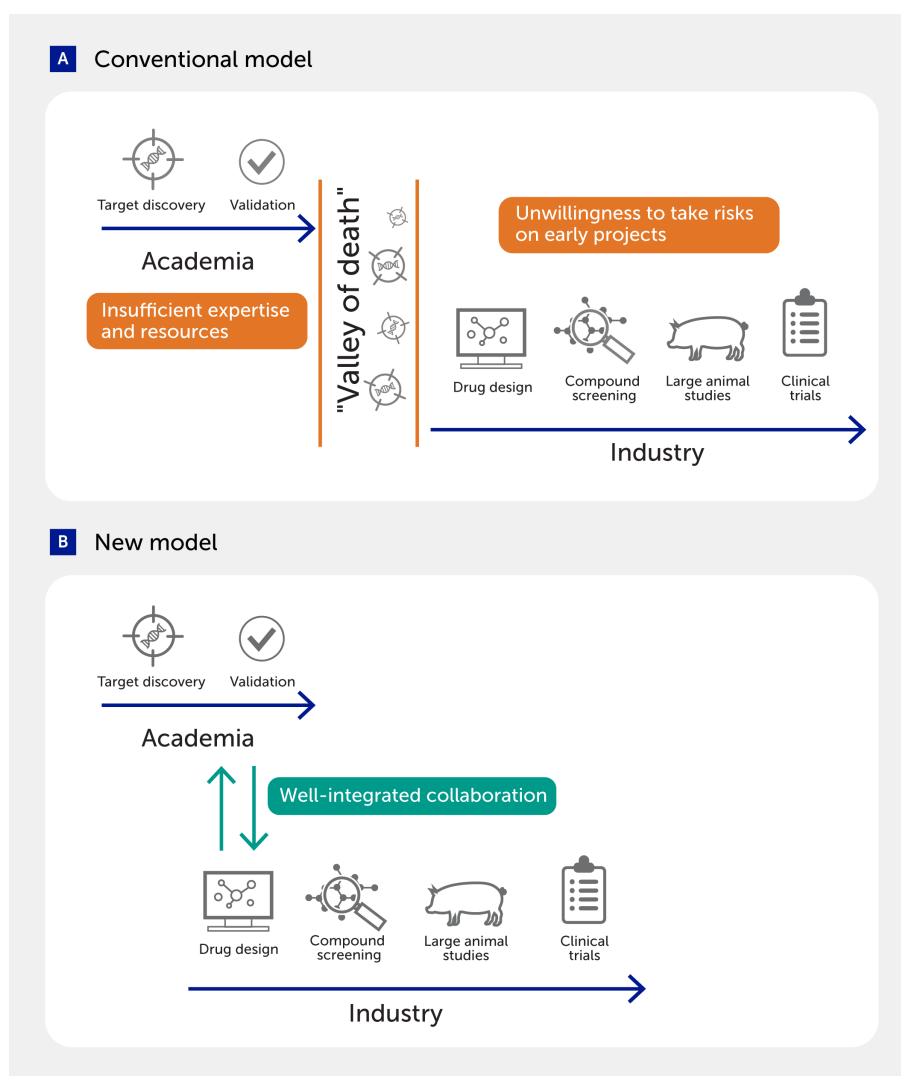


FIGURE 7

Academia-industry collaboration to fill the gap in drug discovery. (A) Several challenges often impair the transition of targets discovered in academia to drug development in industry. (B) New models that integrate actions in the two sectors may facilitate the translation of discoveries into the clinic.

and data scientists is essential to establish fully integrated drug discovery research, as discussed above. Such seamless approaches also require innovative cross-sector collaboration.

One of the major obstacles is the large gap between target discovery research in academia and drug development in industry (Figure 7). Many ideas or targets identified in academic research do not bridge this gap for various reasons, including the lack of expertise and funding in academia and industry's unwillingness to invest in early, high-risk projects. To solve these major challenges, several models of academia-industry collaboration have been established to merge the strengths of both sectors (89, 340–344). Establishing novel concepts by exploring uncharted territories and pursuing high-risk projects is a typical strength of academic investigators, while industrial scientists have specific expertise in drug design and development and are more strongly supported by infrastructure and financial resources (341, 342). Indeed, one study

indicated that academia-industry collaboration showed higher clinical development success rates than those commonly seen in either academia or industry with no collaboration (89). Other types of collaborative arrangements include precompetitive research between pharmaceutical companies for sharing resources and expertise, and public-private partnerships (345–348).

Collaborative data science: key to precision medicine

As discussed, the major challenges in CVD have prompted precision medicine approaches that in turn necessitate new technologies; these disruptive innovations not only solve challenges, but also generate new concepts. The key, essential component in this synergistic relationship is data science (349).

Among new technologies across various disciplines, the evolution of data science has been particularly rapid. It is now critical for us to recognize the importance of implementing this discipline and involving data scientists in every stage of cardiovascular medicine innovation, from basic science, discovery, and translational research to the clinical development of new therapeutics and ultimately their use in clinical practice. We must also recognize the diversity of data science as characterized by various subspecialties (e.g., biostatistics, bioinformatics, biophysics, network science, computational biology, and machine learning-based approaches), which enables the construction of a multidisciplinary data science team to cover a wide range of needs. More resources need to be allocated to support the development of data scientists at the institutional and government levels to bolster future biomedical innovation in both academia and industry. Finally, infrastructures that support interoperability between the multiple data sources involved are also vital to enhance the synergistic relationships between data science and cardiovascular medicine (350).

Lessons learned from COVID-19: are we ready for the next pandemic?

During the COVID-19 pandemic, over 770 million people were infected with the SARS-CoV-2 virus globally, leading to 7 million deaths (351). The scientific community came together to respond to the rapidly evolving demands that arose as a result. Public, political, and scientific awareness enabled resources to be redirected toward combating this global threat. This also triggered research interests in investigating the extensive, long-term consequences of viral infection on a large scale (352).

The United States FDA demonstrated flexibility and innovation during this time by modifying existing regulations to accelerate the approval process of life-changing medications for COVID-19 (353, 354). Similarly, the World Health Organization (WHO) played a central role in generating and distributing guidelines and tools to the global medical community (<https://covid19.who.int>). As a result, novel technologies, including mRNA vaccines and neutralizing antibodies (355, 356), were deployed with unprecedented rapidity to help reduce disease severity. Although these groundbreaking tools had already been in development (357, 358), the COVID-19 pandemic created the impetus to embrace these platforms to supplement conventional treatments. This new attention toward acute viral infection required the scientific, medical, and regulatory communities to restructure and shorten the drug development and implementation timeline (359). Governmental programs, such as the National Institutes of Health RECOVER program in the United States (360) (<https://recovercovid.org/>) to characterize post-acute sequelae of SARS-CoV-2 infection (PASC) syndrome or “long COVID” promoted the formation of multi-institutional and multidisciplinary nationwide collaborations by eliminating barriers to interactive science (361). Technologies developed through this global effort will be applied to counter other diseases, such as cardiovascular, pulmonary, and neurological disorders.

Knowledge gained in social, political, and clinical realms has shaped how our scientific community responds to worldwide challenges. The advent of new technologies has heightened the level of responsibility, as they allow the evaluation of interventions more quickly, more precisely, and at greater scales than was previously possible (362, 363). It will be essential to capitalize on the collaborations established during this crisis to address future pandemics successfully.

Revamping global healthcare policies to tackle the leading global cause of mortality

We have discussed that investing in innovative approaches and cutting-edge technologies will help develop treatments and interventions that improve CVD outcomes. However, we cannot afford to miss the forest for the trees. The “domino effect” of anthropogenic causes of mortality is the most pressing human health problem in modern times (364). Climate change leads to increased natural disasters, which, in turn, cause changes in food and water security. It also results in supply chain disruptions and population displacements. All of these consequences collectively strain the healthcare system. This strain exacerbates the impact of both lifestyle and environmental components on the development and progression of CVD. There is also a heightened risk of respiratory and vector-borne diseases due to these interconnected factors (365).

Concerted efforts applied to the population scale of the Millennium Development Goals and the Sustainable Development Goals (SDGs) are needed to increase public awareness of CVD and its risk factors (366, 367). Precision medicine approaches can be a huge asset to meet SDG 3.4, which aims to reduce premature mortality from non-communicable diseases through prevention and treatment. Prevention of these diseases should be emphasized by encouraging healthy lifestyles, tobacco cessation, and more nutritious dietary alternatives. Strengthening healthcare infrastructure, increasing equitable access to quality healthcare, reducing economic disparities (368), and promoting unanimous support to the WHO’s *Global Action Plan for the Prevention and Control of NCDs* (369, 370) are necessary to, in some measure, mitigate this so-called “disease of civilization” (371).

Political imperative to ensure global equity

The COVID-19 pandemic exposed the vulnerabilities of global healthcare systems: the lack of cooperation between governments and the private sector, unequal distribution of medical resources (including vaccines), and the neglect of needs in the global south. In the context of CVD, neglect of the disease burden in low-income and lower-middle-income countries (LICs/LMICs) and excluding such populations from research (including clinical trials) has led to major healthcare crises (372). Even though the disease burden is high in LICs and LMICs, these countries’ contributions to the global

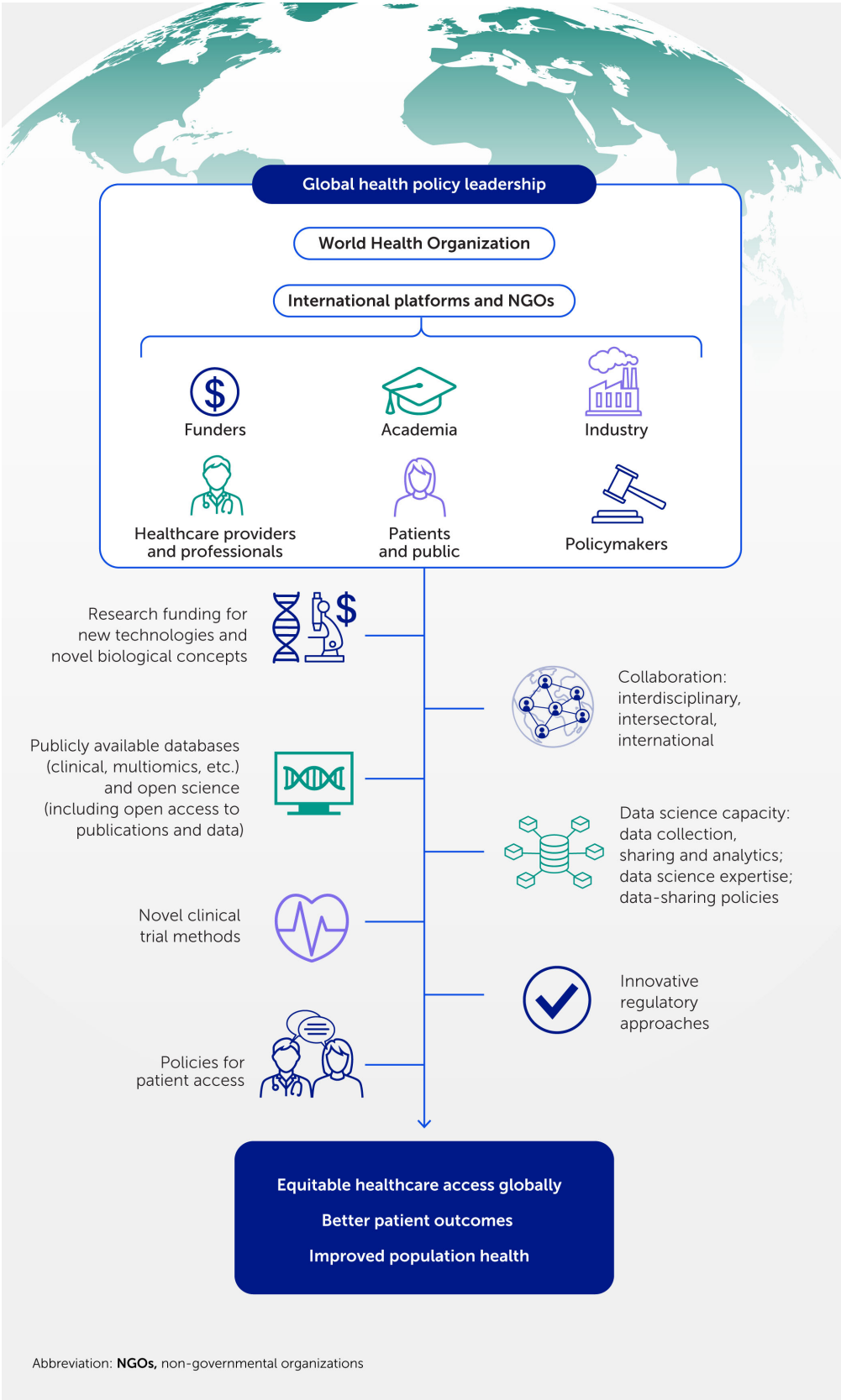


FIGURE 8
Global policy leadership fuels transformative cardiovascular innovations. Revolutionizing healthcare demands an unprecedented commitment from global policy leaders to foster interdisciplinary collaborations, funding, and support. This will drive innovation, enhance data science capacity, establish patient-centric public health policies, and concert efforts to reduce global inequality, addressing the silent pandemic of cardiovascular disease.

research output are minimal in part due to limited research capacity (373). Moreover, at present, global responses to the major global health threats from both noncommunicable and infectious diseases are hampered by geopolitical division, conflict, and power imbalances. (374) Achieving global health equity requires multisectoral, multifaceted, and multistakeholder engagements (375) through the emergence of global frameworks such as the WHO pandemic agreement adopted in May 2025 (376). While pandemics are temporary, continued cooperation and dedication of financial resources toward research and outreach are critical to mitigate future calamities. Effective global leadership is contingent upon the constructive global healthcare discourse among all member states, alongside proactive contributions from intergovernmental institutions. For this to happen, major policy stakeholders must recognize their lack of attention to the CVD burden and the insufficient healthcare infrastructure of the Global South, consequently amplifying their struggles. Concerted efforts addressing the issues plaguing individuals living in LICs/LMICs will be globally beneficial by reducing the burden of communicable and non-communicable diseases alike. Ultimately, addressing the disparities in global healthcare is not just a moral imperative but also a strategic necessity in safeguarding the well-being of all humans. By fostering collaboration, empathy, and a shared commitment to collective welfare, we can build a world where access to healthcare is a fundamental right for every individual, regardless of geographic location or socioeconomic status.

Therefore, transforming to a precision innovation paradigm in cardiovascular medicine will require more than the scientific and technological advances described above. Interdisciplinary, intersectoral and global collaborations throughout the research and innovation pathway (352, 377, 378), underpinned by global health policy leadership, are necessary to implement suitable models of research funding and organization, data infrastructures and policies, novel clinical trial methods, medicines regulation, and patient access policies (Figure 8).

Conclusions

We have discussed how major challenges and needs in clinical cardiovascular medicine have provided opportunities for the scientific and medical communities to implement innovations and develop the systems approach needed to facilitate the search for disease mechanisms and establish unconventional strategies in drug development. The rapid evolution of cutting-edge technologies has recently increased our understanding of the biology of heterogeneity at cellular and patient levels, which would enable the establishment of new paradigms of precision medicine for CVDs. Advanced computational methods help to make traditionally undruggable targets druggable. New platforms, such as RNA therapeutics, facilitate modulation of undruggable targets (379).

Disruptive innovation not only solves challenges, but also leads us to new paradigms. Establishing new concepts in turn requires the

development of new technologies. The key to successful cardiovascular innovation is a synergistic relationship between new technology and new paradigms, supported by a dynamic and intimate interplay between biomedical research and data science. In addition, cross-sector (e.g., academia–industry) or international partnerships can help to defend against global residual cardiovascular risks and address unmet medical needs. We saw this in action during the COVID-19 pandemic, where our community was forced to develop “borderless” solutions swiftly. This unprecedented challenge brought about a worldwide effort among scientists in academia and industry, leading to progress in comprehending virus transmission, effectively accelerating the development of novel technologies (e.g., mRNA vaccines), and reorganizing the medical community to improve responses to future crises. Such seamless collaboration across various disciplines, sectors, and nations will shift innovation paradigms to revolutionize borderless cardiovascular medicine and speed up the translation of discoveries into the clinic.

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Statements

Author contributions

MA: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing.

ARS: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

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Data availability statement

The original contributions presented in this work are included in the article. Further inquiries can be directed to the corresponding author.

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Conflict of interest

TA is employed by the Kowa Company Ltd., Nagoya, Japan, and was a visiting scientist at the Brigham and Women's Hospital. SU is currently an employee of Labcorp Laboratories, Saitama, Japan. These companies were not involved in the writing of this article or the decision to submit it for publication.

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