

## Screening for regenerative therapy responders in heart failure

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Risk of outcome variability challenges therapeutic innovation. Selection of the most suitable candidates is predicated on reliable response indicators. Especially for emergent regenerative biotherapies, determinants separating success from failure in achieving disease rescue remain largely unknown. Accordingly, (pre)clinical development programs have placed increased emphasis on the multi-dimensional decoding of repair capacity and disease resolution, attributes defining responsiveness. To attain regenerative goals for each individual, phenotype-based patient selection is poised for an upgrade guided by new insights into disease biology, translated into refined surveillance of response regulators and deep learning-amplified clinical decision support.

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**Keywords:** biomarkers • deep learning • heart failure • heterogeneity • imaging • prediction • regenerative medicine • stem cells • stratification

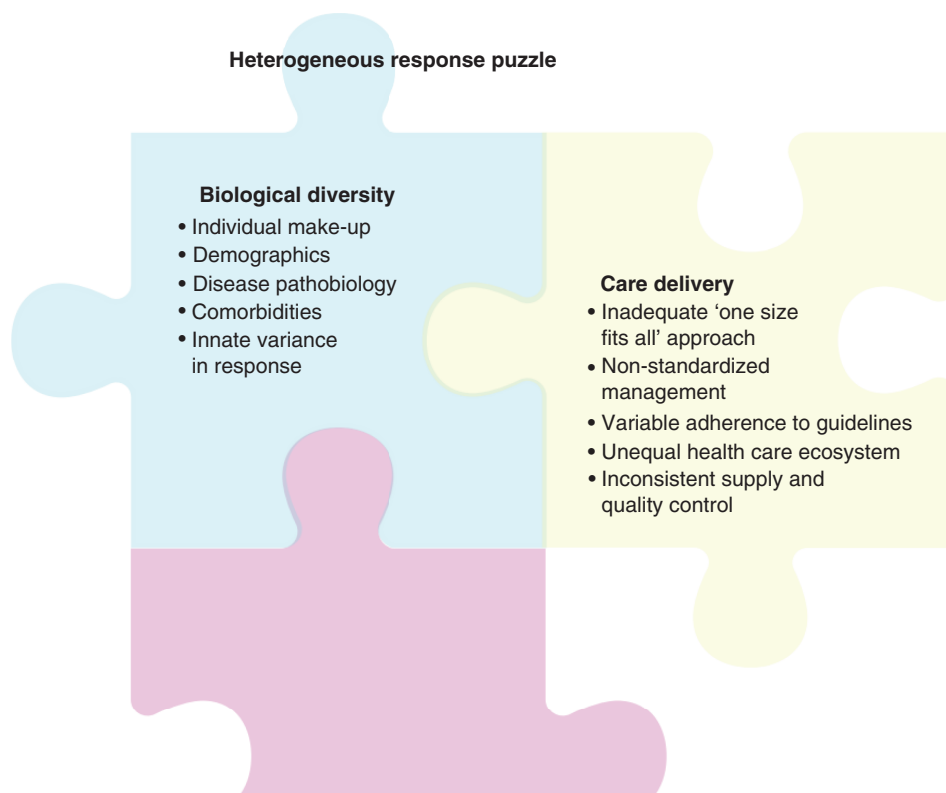
*“It is more important to know what sort of person has a disease than to know what sort of disease a person has.”*  
Hippocrates (Greek physician, c. 460–370 BC)

### Therapeutic response disparity

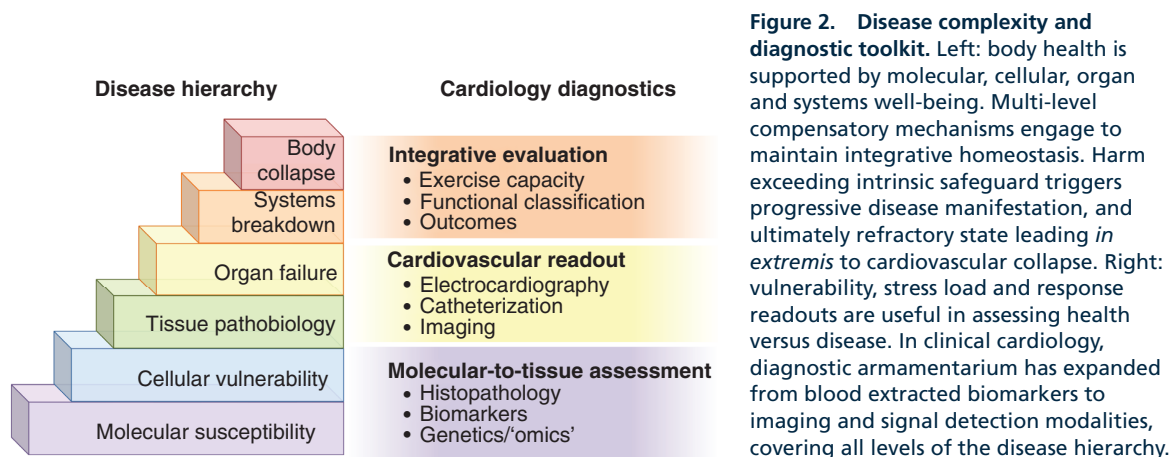
From refractory patients to super responders, individual response to treatment is commonly unpredictable across disease conditions and management strategies. Predicting therapeutic effectiveness remains limited in the setting of all major causes of morbidity and mortality [1–6]. The clinical reality of mixed benefits mandates a better understanding of individual variation with the goal of achieving tailored care [7].

Clinical development programs focus initially on feasibility, safety and signs of efficacy, with stratification of responders and nonresponders typically considered during *post hoc* surveillance. Accordingly, contributors delineating best responders remain partially understood (Figure 1). Emphasis is placed on deciphering the impact of the individual's genetic make-up, primary disease severity, comorbidities, vulnerability to adverse effects, adherence to treatment regimen and/or social confounding factors [8–10]. This recognized complexity highlights the necessity for multi-parametric assessment to guide clinical decision making in candidate characterization, therapeutic delivery and outcome analysis.

The experience of regenerative science-driven practice advancement exemplifies the need to enhance responder screening in the context of deploying new therapies [11]. Propelled by the promise of curative technologies, uptake of regenerative medicine in cardiology is however constrained by heterogeneity in patient outcome [12]. The clinical readiness of the regenerative toolkit is indeed lagging, requiring informed means to ensure targeted benefit [13,14].



**Figure 1. Heterogeneous response puzzle.** Unpredictable refractoriness to therapeutic interventions is a major challenge in healthcare. Mixed results have not fully characterized multi-factorial causes. Biological diversity among individuals and nonuniform care delivery refute a 'one size fits for all' paradigm. Personalized approaches are required to overcome heterogeneous outcomes in practice.



**Figure 2. Disease complexity and diagnostic toolkit.** Left: body health is supported by molecular, cellular, organ and systems well-being. Multi-level compensatory mechanisms engage to maintain integrative homeostasis. Harm exceeding intrinsic safeguard triggers progressive disease manifestation, and ultimately refractory state leading *in extremis* to cardiovascular collapse. Right: vulnerability, stress load and response readouts are useful in assessing health versus disease. In clinical cardiology, diagnostic armamentarium has expanded from blood extracted biomarkers to imaging and signal detection modalities, covering all levels of the disease hierarchy.

The present Special Report offers a perspective toward achieving theragnostics strategies, namely diagnostic-guided treatment improvements [15], in the setting of regenerative therapy for heart failure.

### Multi-level pathophysiology

Heart failure reflects a compromise in force generation [16,17]. A normal heart cycle orchestrates billions of cardiomyocytes, turning  $\sim\mu\text{m}$  of contraction/cell into a  $\sim 5$  l/min organ output to fulfill body needs. Susceptible to diverse pathologies, aberrancy in this force-generating system evolves from latent molecular defects to advanced symptomatic disability (Figure 2). Congenital cardiomyopathy, due to a monogenic defect, exemplifies progression from a primal sarcomeric deficit into overt organ failure [18]. Distinctively, myocardial infarction, caused by

coronary blood flow blockade, results in metabolic, electrical, mechanical and/or structural damage ultimately leading to ischemic cardiomyopathy [19]. Isolated cardiac dyssynchrony, with disparity in wall motion and conduction, precipitates suboptimal pumping function [20]. Regardless of the initial insult, an assault on the cardiac force-generating hierarchy provokes a common downward end-stage spiral (Figure 2 left). While treatments in later stages of disease are often limited to symptom mitigation and palliation, pinpointing the disease substrate at an earlier, presymptomatic phase of pathogenesis would offer proactive management options [21,22]. Adequate detection of silent risk and prognostication of outcome are thus required for actionable therapeutic targeting.

### Therapy puzzle

Heart failure management incorporates lifestyle modifications, pharmacotherapy, interventional and surgical procedures, device implantation and heart transplant. Reperfusion therapy for myocardial infarction has reduced acute mortality; yet survivors suffer from a high incidence of heart failure [23,24]. Bi-ventricular pacing for cardiac resynchronization therapy (CRT), despite evidence for benefit in heart failure, does not eliminate nonresponders, accounting for a third of all recipients [25]. CRT indications are based on the New York Heart Association functional classification, left ventricular (LV) ejection fraction and QRS duration with bundle branch block [26], criteria nonspecific for the dyssynchronous myocardium (Figure 2 right). Scar size has been identified as a culprit impeding effective CRT pacing [27]. Thus, for advanced heart failure with extensive tissue damage, reparative approaches may be valuable [28]. Among regenerative strategies aimed at cardiac repair, the use of adult stem cells is the most advanced in clinical translation [29,30].

### Responsiveness outlook

Grading therapeutic responsiveness according to clinical outcome stratifies super-responders, hypo-responders (with partial success) and nonresponders (refractory/failing therapy). Selectively targeting super-responders offers a practical approach to maximize current modalities [31]. Rescue of nonresponders and refinement for hypo-responders require an overhaul of treatment/delivery options and/or deeper understanding of efficacy determinants. To optimize and standardize effectiveness, specific and selective biomarkers are needed, fortified by deep learning algorithms using real-world experience [32]. Next-generation biomarkers would contribute to: early diagnosis through subclinical detection of molecular defects, enabling proactive intervention; preemptive control of risk factors in identified vulnerable individuals or at risk cohorts; and informed discovery of druggable pathways underpinning disease pathogenesis with development of corresponding therapeutic solutions.

### Pretherapy stratification

Selection of optimal candidate biotherapeutics and/or recipients prior to therapy is ongoing. Limited uniformity in stem cell procurement necessitates standardized sourcing, manufacturing and quality assessment before patient delivery [33]. Uncertainty in clinical grade product repair proficiency has propelled development of potency assays [34], and cardio-reparative guidance protocols [35]. In fact, recent clinical trials incorporate prespecified cell potency criteria as exemplified by the CardiAMP Heart Failure trial using bone marrow mononuclear cell therapy for ischemic heart failure [36]. In parallel, release criteria for successful regenerative capacity enhancement of mesenchymal stem cells have been integrated into the C-CURE [37] and CHART-1 [38,39] heart failure clinical trials to ensure procurement of cardio-reparative cardiopoietic cells [40,41]. The DREAM-HF clinical trial employs mesenchymal precursor cells in subgroups of patients with advanced heart failure to address the biological plausibility of regenerative immunotherapy [42]. Beyond optimization of the biotherapeutics, the potential value of candidate recipient selection has been considered using distinct strategies. In this regard, genetics impact regenerative efficacy. In contrast to noncarriers, carriers with confirmed pathogenic or likely pathogenic cardiomyopathic variants exhibit non/hypo-response following autologous or allogeneic bone marrow-derived mesenchymal stem cell treatment [43]. Notwithstanding, genetic variants have been proven conclusive in a relatively modest portion of refractory patient cohorts warranting exploration of nonpolymorphic determinants of therapy evasion [44]. Alternatively, plasma profiling of circulating biomarkers in the setting of bone marrow mononuclear cell therapy for acute myocardial infarction offers a tool to probe for likelihood of response [45]. Furthermore, phenotype-based stratification prior to intervention could facilitate screening of putative super-responders. Conventionally, selection of candidates for cardiac stem cell therapy relies on a cut-off value, such as LV ejection fraction <40%. Recent clinical study sub-analyses, however, document signs of cardiopoietic stem cell efficacy associated with a tight phenotypic profile, namely a range of LV dilatation, a marker of organ remodeling [46,47]. Candidate titration was validated in a

		Current practice	Emerging paradigms
Treatment	Disease stage	Advanced	Early
	Management	Reactive	Proactive
	Compliance	Suboptimal	Optimal
	Options	Limited	Customized

**Figure 3. Disease management evolution: from reactive to proactive.** Current practice targeting advanced disease is suboptimal offering limited options. Emerging paradigms are poised to ensure optimized and customized treatment solutions.

model of staged infarction size. While intramyocardial stem cell delivery was beneficial, outcomes diverged based on pretherapy LV end-diastolic volume (LVEDV). Super responders, defined as achieving functional and structural restitution, presented with an LVEDV equivalent to 200–370 ml in human heart [48]. In end-stage disease (pretherapy LVEDV equivalent to >370 ml in human heart), cell therapy hindered further deterioration into terminal heart failure syndrome, compared with the untreated cohort, but did not improve function or structure compared with pretherapy [31]. LV enlargement dependent response implicates a ‘Goldilocks principle’ for success with cardiac regenerative interventions [48]. Disease severity should be considered for: exclusion of nonresponders; and adjustment of therapeutic goals matched to the individual patient. In advancing toward adoptable regenerative care, narrowing the pool of patient responders would thus benefit from companion diagnostic criteria delineating pathogenesis.

### Restoring disease substrate

Clinical decision making is assisted by identifying in real-time the origin and extent of disease, and responsiveness to therapy. Among cardiology modalities (Figure 2), analytical extension of echocardiography and magnetic resonance by tissue deformation imaging (speckle tracking) has enabled detection of early myocardial dysfunction and prediction of cardiac events [49]. Applied in regenerative medicine protocols, speckle tracking has proven useful in guiding stem cell delivery targeted to an early stage of mechanical dyssynchrony [50]. This diagnostic methodology enables proactive intervention for reparative prophylaxis and tissue repair (Figure 3). Regional motion abnormality is thus considered a theragnostic target reflecting organ symptomatology and underlying pathobiology [51]. Indeed, cell therapy has the potential to correct the molecular disease substrate, transitioning infarcted hearts from a cardiomyopathic trajectory back to predisease state [52].

### Knowledge overflow

The growth of medical knowledge has shortened its doubling time, from 50 years in 1950 to a mere 3.5 years in 2010 and down to 0.2 years in 2020 [53]. New knowledge influx exceeds the decision making capacity of a singular healthcare provider. Steadily, for example, numerous biomarkers, at each level of the disease hierarchy (Figure 2), have been introduced to facilitate disease management. In particular, cardiac biomarkers are a major focus of interest, exemplified by a number of families ranging from natriuretic peptides; neuro-hormones reflecting the renin-angiotensin and sympathetic nervous system; extracellular matrix proteins and metalloproteases associates with organ remodeling; inflammation and oxidative stress biomarkers; myocardial enzymes and proteins leaked from damaged tissues; and cardiovascular disease risk factors [54]. Beyond blood extracted markers, diverse bio-sampling approaches, as well as imaging modalities and bio-signal detection platforms, have extended the intricacy in interpreting information from biomarker-based datasets (Figure 2 right). Data processing relying on human manpower is limited in the context of stem cell therapy, where the complex identities of the biotherapeutics and recipients exaggerate the multifaceted nature inherent to biomarker readouts. Public repositories, such as Gene Expression Omnibus (<https://www.ncbi.nlm.nih.gov/geo/>) and ProteomeXchange Consortium (<http://www.proteomexchange.org/>), list an increasing number of decoded altered transcripts (~700 out of >20,000) and proteins (450 out of 4000) in failing hearts [52,55]. Concomitantly, in specialty clinics, an expert can extract, in a single echocardiography session, over 100 parameters with 2D, M-mode, Doppler and speckle-tracking analysis. Thus, a pressing challenge is to

		Traditional process	AI-empowered workflow
Clinical decision making	Reasoning	Subjective	Objective
	Workload	Intensive	Automated
	Dataset		
	Scale	Limited	Large
	Iteration	Limited	Ongoing
	Integration	Limited	Multimodal

**Figure 4. Artificial intelligence supported clinical practice.** With increasing overflow of new knowledge, clinical decision making benefits from AI-empowered algorithms. AI: Artificial intelligence.

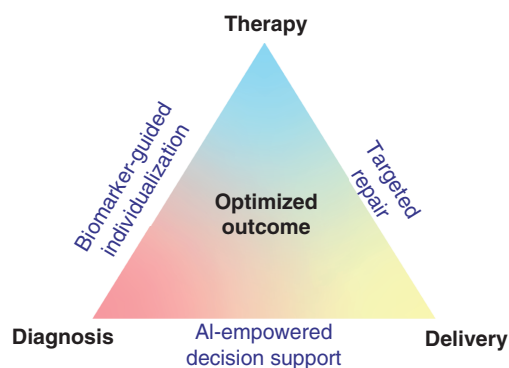
translate the ever-growing, versatile knowledge base into a user-friendly algorithm amenable for daily practice (Figure 4).

### Artificial intelligence decision support

Handling large datasets is critical for the enhanced management of lifelong diseases, as it is for responding to urgent needs of acute outbreaks. Incorporation of artificial intelligence (AI) is a transformative approach ushering the future of medicine [56]. Applicable to cardiac practice, disease diagnosis has been refined by AI in the setting of electrocardiography and cardiac imaging. The classic electrocardiogram, invented by Einthoven 125 years ago, has evolved into a microcomputer-based system with automatic analysis in the last 40 years, and recently through AI-powered applications has further adopted a predictive capacity to screen individuals with asymptomatic LV dysfunction or high-risk atrial fibrillation during normal sinus rhythm [57,58]. Indeed, AI-assisted preselection of patients at risk would enable proactive treatment planning [59], including potential use of regenerative solutions. A 3D print enhanced by AI processing is also poised to contribute to preinterventional planning in complex cases, and in training of new regenerative procedures. At present, AI diagnostics iteratively assimilate information from multiple modalities within the same level, or between neighboring levels, of the disease hierarchy (Figure 2). Deep learning, which learns from unlabeled data and without human supervision [60], is expected to achieve comprehensive diagnosis through cross-sectional integration across the disease pyramid (Figure 4). AI has been deployed to accelerate research cycles that have required 10–15 years of investment, up to US\$2.8 billion in expenses per drug through advanced clinical testing, with a 10% success rate to reach US FDA approval [61]. As conventional empirical approaches are considered an Achilles heel in clinical development, applications of AI to design clinical trials would assist in improved selection of patients, recruitment and monitoring of large cohorts. In fact, deep learning has been introduced to ensure quality control of clinical grade regenerative products [62]. It is anticipated that emerging cardiac regenerative therapy will increasingly rely on AI-based guidance for optimal use of cutting-edge technologies, and to maximize the precision of applied reparative options (Figure 5). In this regard, a call for an AI-augmented multinational biorepository of pertinent datasets is timely to enable image-based pilots, followed by phenomenological predictions in larger cohorts [63–65].

### Summary

Regenerative medicine principles extend the reach of traditional therapeutic goals by offering the opportunity to achieve targeted cures [66–68]. However, recognized outcome heterogeneity has hampered adoption of the regenerative toolkit [69,70]. Biological diversity among recipients, unpredictable biotherapeutic efficacy and inconsistent care delivery, all underscore refractoriness to therapy. Supported by randomized controlled studies, and enriched by a mechanistic-driven reasoning, the diagnosis–therapy–delivery paradigm has advanced from empirical to evidence-based to pathobiology-informed decision making (Figure 5). Indeed, ongoing efforts to standardize effectiveness



**Figure 5. Iterative optimization of individual outcome.** The diagnosis–therapy–delivery triad is increasingly transformed by reliance on biomarker-guided personalized care, targeted cures and AI-empowered clinical decision making. AI: Artificial intelligence.

have encompassed a (patho)phenotype-based optimization in patient selection, a (bio)marker-enforced proactive intervention aiming on the disease substrate and more recently an AI-powered approach to support quality control of regenerative products, clinical trial design and practice delivery (Figure 5).

### Future perspective

Regenerative medicine ushers an era of curative aspiration. To overcome heterogeneity in the therapeutic response and maximize the reach of regenerative therapy, achievable upcoming milestones include: in discovery science, advancement of knowledge that decodes disease pathobiology and biological diversity; in clinical development, automation and scale up manufacturing of standardized patient-ready regenerative products; and in care delivery, roll-out of individual-centered practice guidelines optimizing indications, procedures and outcome readouts. Ongoing digital transformation amplifies population-validated datasets in an increasingly maturing regenerative medicine ecosystem.

#### Executive summary

##### Clinical unmet needs

- Variance in individual therapy response is commonly encountered in practice.
- New therapies are challenging due to limited clinical experience and absence of long-term pharmacovigilance.
- Heterogeneous outcomes associated with regenerative therapies compromise standardized adoption.
- Advanced heart failure relies on palliative strategies with phenotype-based readouts nonspecific to underlying disease.
- Proactive regenerative interventions may refine heart failure management.
- Individualized theragnostic algorithms would empower regenerative care.

##### Decision support for patient selection

- Genetic make-up determines regenerative response. Carriers of cardiomyopathic variants appear to benefit less from stem cell therapy, encouraging preinterventional screening to identify best responders.
- Structural parameters of heart remodeling, namely left ventricular size, appear to predict stem cell effectiveness. Disease severity stratification may help streamline patient selection.

##### Transforming future practice

- Evolving biomarkers-guided individualized diagnosis, targeted repair and artificial intelligence-empowered decision making have the potential to transform clinical practice and optimize outcomes.

#### Author contributions

S Yamada contributed toward conception and design, data acquisition, analysis and interpretation, drafting the work, final approval of the manuscript and agreement to be accountable for all aspects of the work; R Jeon, A Garmany and A Behfar contributed toward data acquisition, final approval of the manuscript and agreement to be accountable for aspects of the work; A Terzic contributed toward conception and design, data acquisition, analysis and interpretation, drafting the work, final approval of the manuscript, financial and administrative support and agreement to be accountable for all aspects of the work.

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No writing assistance was utilized in the production of this manuscript.

### Ethical conduct of research

This Special Report refers to human and animal experimental investigations conducted under respective regulatory and ethical approvals.

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