Additional Ventures 2026 Research Roadmap

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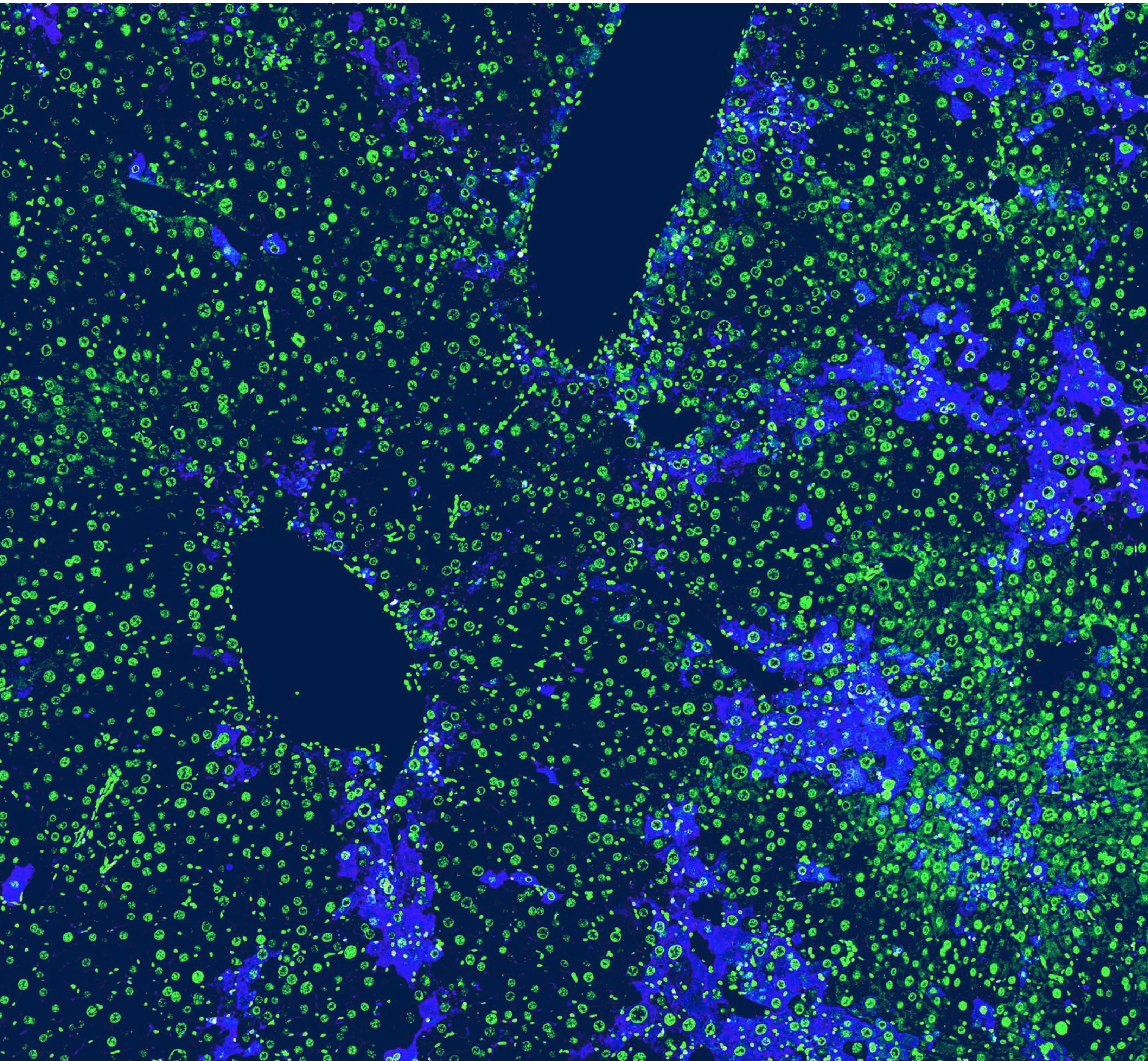


About Additional Ventures

We are a purpose-driven organization leveraging evidence-based research and deep subject matter expertise to make an outsized impact. Our relentless optimism powers bold, high-risk innovations to solve some of humanity's most complex challenges.

Our biomedical research work focuses on a rare form of congenital heart defects called single ventricle heart disease. While this field is in its infancy, with limited knowledge of cause, risk, outcomes, or treatments, we are confident that through coordinated strategic and interdisciplinary work, dynamic teaming, and flexible funding, we can illuminate a functional cure for patients and their families.

Future of Single Ventricle Research: A Roadmap to Progress

At Additional Ventures, we believe that the field of single ventricle heart disease is at an inflection point. After half a decade of focused investment, we now see a level of clarity in the biology, the engineering challenges, and the clinical realities associated with single ventricle — clarity that simply did not exist when our 2020 Research Roadmap was developed. Given this progress, we're confident that the field is positioned to move from incremental improvements toward a curative standard of care.

Our 2026 Research Roadmap reflects both the complexity of single ventricle heart disease and the urgency of acting at this moment. It is more than a list of priorities; it is a coordinated strategy to build the scientific, clinical, and engineering infrastructure that a curative future requires.

The 2026 Roadmap eliminates siloes and brings together engineering, biology, and clinical care as connected levers of change. Drawing on our institutional learnings, it maps clear relationships between root causes and outcomes and identifies where meaningful progress is most possible. Most importantly, it centers what has long been missing: a shared commitment to defining what should happen, when, and why across the entire single ventricle care journey.

A Shift in Mindset

Today, despite progress, the field continues to navigate uncertainty. Single ventricle heart disease is a condition that is deeply multifaceted in its anatomy and physiology, and also in the evolving nature of physiologic adaptations, comorbid complications, and clinical variability. Clinicians are tasked with treating a moving target where outcomes are shaped by anatomy and surgical strategy, and by the lifelong interplay between the heart, altered systemic circulation, and other organs.

Yet, we lack an integrated system for monitoring and modifying the health of patients with single ventricle physiology. The field lacks validated tools to track the integrity of the circulation, predictive models to flag risk, and established standards to personalize care. Without these tools, clinicians are forced to make high-stakes decisions about care and treatment without the foundational data needed to guide them. Patients can appear stable by conventional measures, only to experience rapid and irreversible decline. Our goal is to close this gap, not just through better tools, but by building the evidence base that makes those tools meaningful.

A Curative Standard of Care

In single ventricle heart disease, "curative" has been used to describe a spectrum from full restoration of biventricular physiology to interventions that permanently interrupt the cascade of complications that define the current palliative pathway. At Additional Ventures, we define a curative standard of care as one in which interventions fundamentally change the trajectory of the disease rather than manage its consequences.

Our pursuit of a curative future is centered on solutions that reshape the course of single ventricle physiology, reduce lifelong morbidity, and meaningfully extend healthy lifespan through more stable, predictable outcomes. The 2026 Roadmap sets out the strategic investments and evidence required for the field to move beyond reactive palliation and toward an approach that is proactive, restorative, and capable of delivering truly transformative results.

Build the Foundation

Over the last five years, Additional Ventures' investments have revealed a clear opportunity to develop functional cures that improve quality and length of life for patients living with single ventricle heart disease. Within the roadmap, this strategy is known as "Repair". It's a multi-dimensional effort to restore missing pump function and mitigate organ-level sequelae.

Within the Repair strategy, we aim to build the interoperable, data-driven infrastructure required to deliver curative solutions, scalable interventions, and patient-centered care models. That means creating the enabling conditions:

- Comprehensive, organ-level datasets
- Functional biomarkers and prediction models
- Preclinical platforms to validate new tools and therapies
- Engineering solutions that anticipate the needs of growing children

These conditions are actionable leverage points, grounded in engineering, biology, and outcomes science. Whether through regenerative tissue platforms, mechanical support systems, or novel therapies for liver, lymphatic, and brain health, the 2026 Roadmap's aim is to define, develop, and validate interventions that directly support patient stability and well-being, guided by a collective belief that better is possible.

Since 2020, we have witnessed a remarkable transformation: the embracing of outcomes-driven science and development of new models for collaboration; the early emergence of imaging platforms, computational tools, and regenerative therapies that once felt aspirational; and a shift in the culture of inquiry to be more integrated, more focused, and more committed to translating insight into action.

Together, we can work towards a future where we replace intuition with insight and turn decades of progress into lasting change. We invite researchers, funders, clinicians, and engineers to join us in shaping the next phase of this work — because when we build essential infrastructure with intention, we move from managing disease to designing pathways toward a future with better outcomes.

INTRODUCTION: Rebuilding Physiology from First Principles **06**

Approach To Prioritization **09**

DOMAIN I: Add Back a Pump **11**

Build a Biologic Pump 13

Build a Mechanical Ventricle 19

DOMAIN II: Address Sequelae **24**

Systemic Circulatory Regulation 27

Lymphatic and Immune Equilibrium 31

Liver Health 35

Kidney And Gut Perfusion 39

Cardiac Integrity And Rhythm Stability 43

Neurodevelopment 47

Fundamental Biology is Key to Unlocking Single Ventricle **51**

Redefining the Future for Single Ventricle Patients **56**

Introduction: Rebuilding Physiology from First Principles

Single ventricle heart disease is not merely a structural defect of the heart; it is a systems-level condition that rewrites the physiology of the entire body. The defining feature is the absence of a second functional pump, which forces all systemic and pulmonary blood flow through a single ventricle. A longstanding surgical strategy has been to manage this limitation by passively redirecting blood flow without a subpulmonary pump. This approach, culminating with Fontan completion, has prolonged survival; but it is a compromise, not a cure.

Fontan physiology induces chronic venous hypertension, reduced cardiac output, and impaired organ perfusion. These hemodynamic abnormalities create an environment of increased stress that progressively reshapes the biology of nearly every organ system. Liver fibrosis, lymphatic dysfunction, neurodevelopmental delays, renal impairment, and arrhythmias are not merely side effects. Rather, they are the long tail of a non-physiological state, imposed from the earliest stages of life and amplified by both surgical interventions and intrinsic abnormalities in the patient's biology.

As survival improves, the cost of that compromise becomes clearer. Most children with single ventricle heart disease now reach adulthood, but few reach it without complication. The absence of a subpulmonary pump initiates a cascade of compensations and maladaptations that drive long-term morbidity and early mortality. To change the future, we must go beyond optimizing palliation. Broadly speaking, three strategic pathways exist for improving outcomes in single ventricle disease: prevent, replace, or repair.

Prevention aims to alter the earliest origins of disease, ideally in utero.

Replacement envisions structural cures through transplantation or engineered organs.

Repair focuses on the present. It seeks to restore physiologic function by addressing what is missing and treating what is failing in those already living with the disease.

This roadmap is dedicated to repair. Focusing on repair does not detract from the importance of other pathways, but allows us to direct our focus toward the most immediate and scalable opportunity for meaningful change. It is where deep scientific questions intersect with tractable clinical challenges, and where strategic investment can benefit both the single ventricle population and others with complex cardiovascular disease.

The Repair strategy demands a multi-dimensional framework that progresses across interdependent axes: engineering, biology, clinical interventions, and systems design. It does not lend itself to a linear plan. Instead, we borrow the metaphor of a Rubik's cube to describe its structure, where forward movement depends on the simultaneous alignment of multiple elements, and solving one face opens new opportunities elsewhere.

Additional Ventures is committed to a bold and focused strategy that is grounded in systematically correcting what is missing or malfunctioning by adding back a pump and addressing sequelae, not as separate tasks, but as parallel tracks of a unified effort to restore whole-body physiology.

- **Domain I: Add Back a Pump.** The absence of a subpulmonary pump is the defining physiologic limitation in single ventricle disease. Restoring that function — through mechanical or biological means — represents the most direct path to normalizing circulation.

- **Domain II: Address Sequelae**. Single ventricle stress manifests across the lymphatic system, liver, kidney, gut, brain, and heart. Understanding and mitigating these effects is essential to improving lifespan and quality of life.

Threaded through both domains is a vital, unifying thread: patient biology. Outcomes can differ markedly even among individuals with similar anatomy and surgical history. Emerging insights into pathobiology — from immune activation to lymphatic function to cellular resilience — suggest that these underlying differences matter. Progress will depend on building systems-level models of disease, identifying upstream signals of decline, and defining mechanistic links among structure, flow, and function. This can be accomplished through investing in data systems, animal models, spatial biology, computational modeling, and dynamic biomarkers as embedded, central pillars of discovery, development, and deployment.

This roadmap is a strategy to move beyond incremental change and toward solutions that can rebalance the system itself, restoring a more stable and sustainable foundation for lifelong health. Behind every scientific priority is a patient living with the realities of this disease — navigating interventions, limitations, and uncertainty. Therefore, our goal is not to simply delay deterioration, but to alter what is possible. By investing in strategies that restore physiology and address its consequences, we move toward a future defined not by survival alone, but by the possibility of curative solutions.

The Additional Ventures Research Roadmap

Domain 1
Add Back a Pump

Build a Biologic Pump

Build a Mechanical Ventricle

Domain 2
Address Sequelae

Systemic Circulatory Regulation

Lymphatic and Immune Equilibrium

Liver Health

Kidney And Gut Perfusion

Cardiac Integrity And Rhythm Stability

Neurodevelopment

Fundamental Biology

Fundamental biology is key to unlocking single ventricle

Approach to Prioritization

A condition as complex and multi-systemic as single ventricle heart disease demands a portfolio mindset, one that reflects the biological interdependence of complications, compounding risks over time, and the non-linear path from intervention to outcome. It must also be grounded in clinical reality: where therapies are available but inadequate, palliation predominates over cure, and biological insight has yet to yield meaningful intervention.

Our goal is to invest where efforts can deliver the most durable impact on survival, quality of life, and systemic resilience. In some areas, that means accelerating translation where biological opportunity meets clinical need. In others, it means committing to discovery science to illuminate mechanisms, trajectories, and leverage points still poorly understood. Impact depends not only on technical feasibility but on alignment with the broader shift from palliation to cure.

We apply a five-part framework that integrates biological opportunity, translational potential, and clinical context:

1. **Burden:** How significantly does the complication affect outcomes and healthcare utilization? Do current treatments meaningfully reduce risk?
2. **Tractability:** Are there actionable scientific, clinical, or technological interventions that can be deployed within the near or mid-term?
3. **Downstream Impact:** Will solving this problem prevent or mitigate additional complications or systemic decline?
4. **Readiness:** Are tools, models, or regulatory precedents in place, or can enabling platforms be built?
5. **Momentum:** Is there growing collaborative energy, converging insight, or clinical urgency that makes this the right moment to act?

This framework highlights where catalytic investments can yield the greatest systemic benefit, whether through immediate translation or long-term discovery. It also identifies domains where foundational knowledge is the rate-limiting step. Discovery in these areas — clarifying mechanisms and interdependencies — can enable entirely new classes of intervention. Some priorities will be investment-ready; others will need sustained support for hypothesis generation, model development, or systems-level data infrastructure. Both are essential to changing the long-term trajectory of single ventricle disease.

Principles for Investment

Embrace synergy, not simplicity

No sequela exists in isolation. Investing across interrelated domains multiplies impact.

Balance risk and momentum

Some fields lack tractability but hold disproportionate promise; others show early progress but require coordination and refinement to scale.

Target systems, not symptoms

Focus on shared mechanisms and leverage points that reduce overall burden and build resilience.

While our programs are designed to move discoveries toward translation and ultimately into the clinic, we prioritize based not on linear progression alone, but on strategic potential across diverse domains of opportunity. Rather than choosing between organs, we are choosing between leverage points that shift the system. By grounding our prioritization in biological understanding, clinical urgency, and scientific opportunity, we aim to invest not only where change is possible now, but where discovery will enable transformation in the future, altering the trajectory of single ventricle disease across the lifespan.

Domain 1
Add Back a Pump

Build a Biologic Pump

Build a Mechanical Ventricle

Domain 1: Add Back a Pump

Fundamental Goal: Restore physiologic circulation by introducing a second functional ventricle

The surgical innovation of the Fontan procedure created a pathway to survival for children born with a single ventricle heart. But it did not solve the problem of circulation. In the absence of a subpulmonary pump, blood must flow passively to the lungs, generating chronically elevated venous pressure and reduced cardiac output. This circulatory imbalance is a hemodynamic compromise that underpins nearly every long-term complication of the Fontan circulation.

Adding back a pump addresses this problem at its source. Rather than managing the consequences of flow dysfunction, this domain seeks to correct the architecture of circulation itself. By introducing a second functional ventricle, either biologic or mechanical, we propose a future-oriented strategy: designing surgical interventions and pump technologies in tandem, optimized for early deployment and lifelong durability.

This domain includes two complementary strategies:

Biologic Pump: Develop tissue-engineered constructs to create a living ventricle capable of growth, adaptation, and integration into native physiology.

Mechanical Pump: Create a purpose-built subpulmonary assist device designed specifically for the needs of young children with single ventricle physiology.

These approaches recognize that survival is not the endpoint. The Fontan, while lifesaving, is not a cure and will never be a cure, so long as the circulation remains incomplete. These also do not prescribe a single solution. Instead, each strategy identifies an inflection point where technology, biology, and purpose converge, aiming for the introduction of a pump that could reset the trajectory of an entire patient population. Like all domains in this roadmap, it is rooted in scientific realism and driven by patient-centered ambition.

The strategies that follow outline the central challenge, the scientific and clinical leverage points, the most promising technologies, and the barriers that must be overcome, alongside our recommendations for building each pump. Together, they offer a vision not just of better management, but of restored circulation and a future that goes beyond the boundaries of palliation.

DOMAIN 1

Build a Biologic Pump

The Challenge

Recreating a functional, contractile ventricle from biologic components remains a major challenge in regenerative medicine. While engineered heart tissue has advanced significantly in recent years, no existing construct yet meets the mechanical, electrical, and durability demands of a pump suitable for pediatric circulation. Achieving this will require breakthroughs across several axes of tissue engineering, as well as a coordinated approach to development, testing, and integration.

Leverage Points

Proof-of-concept success in small animal models has demonstrated the feasibility of engineered cardiac tissue generation and vascularization.

Progress in pluripotent stem cell differentiation has enabled more consistent production of cardiomyocyte progenitors at scale.

Growing investment in biomanufacturing infrastructure provides a platform for scalable production and shared protocols.

Promising Technologies

The scientific foundation for building a biologic ventricle is stronger than ever. Over the last decade, cardiac tissue engineering has evolved from 2D culture systems to 3D constructs that exhibit contractile force, electrophysiologic coupling, and organized microarchitecture. Engineered heart tissues have demonstrated pressure generation and pulsatile flow in small animal models, and increasingly mimic features of native myocardium when matured.

Advances in 3D bioprinting and scaffold fabrication have improved control over geometry, cellular distribution, and material properties, supporting the construction of volumetric tissues with vascular channels and mechanical anisotropy. Computational modeling and synthetic vascular design pipelines now allow researchers to predict perfusion dynamics, optimize flow networks, and test construct integration virtually before physical testing. These tools reduce trial-and-error and enable more rapid design iteration.

Emerging platforms such as organoids, biohybrids, and organ-on-chip systems offer new environments for studying cell behavior, stress response, and tissue remodeling. These systems complement traditional in vivo testing by accelerating discovery and hypothesis validation. Additionally, machine learning-based reduced-order models now allow real-time simulation of electromechanics and fluid dynamics, linking engineered tissue design with the hemodynamic requirements of Fontan circulation.

Recent work in bioartificial heart scaffolds using decellularized matrices, as well as biohybrid systems that combine living muscle with engineered structure, are expanding the design space. Together, these advances suggest that constructing a biologic pump is not only conceptually feasible but increasingly technologically realistic.

Barriers to Progress

Engineered tissues often lack the contractile strength and electrophysiological synchrony required for pump-level performance.

Even hypoimmune cell sources carry unknowns around long-term host integration and immune response.

Transitioning from lab-scale to functional constructs suitable for surgical implantation demands sophisticated bioreactors, materials, and quality control.

There is a lack of validated large-animal models and platforms for long-term assessment of engineered cardiac function under realistic hemodynamic loads.

Developing a biologic substitute for the subpulmonary ventricle represents one of the boldest, yet most promising, frontiers in the effort to fix single ventricle physiology. To move this vision forward, we outline seven foundational recommendations for the field that should be undertaken in parallel, where possible.

RECOMMENDATIONS

Recommendation 1:
Determine the Optimal Cell Source Strategy

Cardiomyocytes are the central pillar of a functioning biopump. However, these cells are terminally differentiated and require a pluripotent cell source as the “precursor” material. Whether autologous, allogeneic, or universal donor-based, a practical, scalable, and safe source of cardiomyocytes and other necessary cell types for therapeutic use is essential. This requires:

- Mapping the implications of genetic etiology on autologous use
- Advancing hypoimmune technologies and/or immune cloaking for allogeneic sources
- Developing long-term immunological models to assess tolerance, sensitization, and chimerism in growing children
- Devising a tissue maturation and immunomodulation strategy that can avert the immunological response that can arise even in autologous tissue implantation

Clarity on this question is critical to guide investment in biomanufacturing pipelines and regulatory strategy.

Recommendation 2:
Solve Cell Scaling and Maturation in Tandem

Generating a functioning subpulmonary pump will require the production of billions of cardiomyocytes that not only survive but behave like mature myocardium. This means developing protocols that simultaneously address:

- High-purity, high-volume, reproducible GMP-compliant cell production that is affordable
- Robust strategies for electrophysiological and structural maturation, including electromechanical stimulation, metabolic programming, and co-culture environments, at the cell and tissue scale, or exploration of gene editing as a means of rapid maturation

Without high-quality cells at scale, even the best scaffolds or structural designs will fail. Bioreactor platforms that produce clinically relevant volumes and physiologic performance are critical, which may include the need to mature at a tissue-level scale, rather than during cell manufacturing. However, realizing a full-scale, functional construct will also depend on advancements in fabrication technologies and organ-scale conditioning platforms.

Recommendation 3:
Use Computational Modeling to Guide Design

Computational modeling can transform how biologic pumps are conceived and tested, but only if these tools are built on high-quality data and validated against real-world performance. The field must invest not only in using models but in making them reliable and clinically meaningful:

- Pairing models with experimental data from in vitro, organ-on-chip, and large-animal studies to ensure realistic predictions.
- Linking cellular and tissue-level behavior with organ-scale hemodynamics to capture deformation, growth, and remodeling over time.
- Incorporating excitation-contraction coupling and arrhythmia risk into predictive models.
- Predicting pump impact on venous pressures, cardiac output, and flow, and informing device placement and growth scaling.
- Developing standardized datasets and validation protocols to ensure reproducibility and regulatory confidence.

By building models that are not only sophisticated but also empirically grounded, the field can shift computational tools from theoretical assets into reliable engines for design, risk reduction, and translation.

Recommendation 4:
Prioritize Functional Vascularization and Host Integration

Failure to perfuse is one of the leading causes of graft failure in engineered tissues. Future biologic pumps must be:

- Densely vascularized with arterial, capillary, and venous networks that integrate quickly with host tissue
- Supported by strategies for angiogenic signaling and perfusability
- Designed for surgical integration that enables not just attachment but functional flow control

This will require a deep collaboration between vascular biologists, cardiac surgeons, and biomaterials engineers.

Recommendation 5:
Invest in Advanced Fabrication Technologies to Enable Construct Realization

Even with optimal cells, materials, and design specifications, the field cannot deliver a biologic pump without fabrication platforms capable of building it at scale and fidelity. Engineering a volumetric cardiac construct with functional geometry, cellular organization, and vascular networks will require innovations in manufacturing that are both precise and reproducible, including:

- Multi-material 3D bioprinting that supports layer-by-layer construction of myocardium, vasculature, and interface structures.
- Methods for assembly for speed and structural fidelity in thick tissues.
- Potential integration of biosensors and real-time quality control during fabrication to ensure construct viability and function.
- Standardization of workflows to ensure reproducibility across institutions and regulatory readiness.

Building the biologic pump is both a biological and manufacturing challenge. Meeting it will require collaboration across tissue engineering, materials science, and biofabrication disciplines.

Recommendation 6:
Develop Organ-Scale Bioreactors for Pre-Implant Conditioning

Once engineered, cardiac constructs may require maturation and conditioning in vitro to achieve functional readiness for implantation. This requires bioreactors capable of simulating the complex environment of the beating heart, providing mechanical load, electrical pacing, nutrient delivery, and flow. Priority areas include:

- Pulsatile perfusion systems to mimic cardiac preload and afterload.
- Electrical stimulation protocols to promote alignment, coupling, and contractile strength.
- Long-term culture capability with controlled oxygenation, pressure, and nutrient delivery.
- Monitoring of construct performance (e.g. pressure generation, conduction velocity, metabolism).

Conditioning is not optional; it is essential for preparing tissues to survive and function post-implant. These platforms will also serve as a final checkpoint for performance, safety, and consistency before entering preclinical testing.

Recommendation 7:
Leverage Existing Large-Animal Models and Build Human-Linked Testing Pathways

With a validated large animal (ovine) Fontan model established, the priority shifts from creating new models to fully exploiting and refining the one we have. This model provides a rare and invaluable platform for testing biologic pumps under realistic hemodynamic conditions and for generating the high-quality data needed for translation.

- Expand physiologic, imaging, and histologic mapping of the existing ovine model to create robust ground truth datasets for pump performance, vascularization, immune response, and long-term remodeling.
- Use the ovine model to iteratively test implantation techniques, integration strategies, and growth accommodation over time, capturing functional outcomes, durability, and failure modes.
- Align testing protocols and endpoints with regulatory expectations to de-risk early clinical trials.
- Explore frameworks for modeling patient-specific anatomy and physiology based on human imaging data and evaluate ethical pathways for first-in-human compassionate use when appropriate. These models will be essential for de-risking early clinical trials and guiding regulatory approval.

By maximizing the capabilities of an established large-animal model and linking its data to patient-specific human contexts, the field can accelerate translation, reduce uncertainty, and ensure that early clinical efforts are grounded in the strongest possible evidence.

DOMAIN 1

Build a Mechanical Ventricle

The Challenge

Single ventricle circulation lacks a subpulmonary pump, resulting in chronically elevated venous pressure and reduced cardiac output. While mechanical circulatory support (MCS) has transformed heart failure care, existing devices are neither designed for subpulmonary physiology nor optimized for pediatric patients. Most are high-pressure, left-sided pumps built for adult-scale anatomy and disease. For the single ventricle population, what is needed is not a conventional ventricle assist device (VAD), but a dedicated, low-pressure, small-profile mechanical ventricle that can support pulmonary flow, accommodate somatic growth, and operate for years without replacing one problem with another.

At present, there are no commercial devices that meet this specification. While some technologies have been explored for short-term bridge-to-transplant support, none are purpose-built for long-term subpulmonary assistance in young children. As a result, Fontan failure proceeds without viable options for durable physiologic support leaving clinicians with few tools, and patients with limited futures.

Leverage Points

Decades of VAD and MCS development in the adult heart failure space have yielded robust hardware platforms, surgical expertise, and regulatory pathways that can inform pediatric adaptations.

Miniaturization of pump components, including magnetically levitated impellers, compact motors, and wearable battery systems, opens the possibility of pediatric-scale solutions.

Digital design and simulation environments allow for virtual prototyping and evaluation in realistic anatomic and hemodynamic models — reducing development time and risk.

Growing understanding of Fontan pathophysiology provides clearer performance targets for what a subpulmonary assist device must achieve to deliver benefit.

Promising Science and Technology

Rapid progress across several engineering domains makes the development of a dedicated subpulmonary pump more feasible than ever. Advanced fluid dynamics modeling allows teams to simulate pressure gradients, flow uniformity, and energy efficiency across multiple pump geometries before a device is built. Wearable and wireless energy transfer systems, already in use for some pediatric cardiac implants, reduce infection risk and improve patient mobility. Meanwhile, customizable control algorithms, informed by real-time hemodynamic monitoring, are enabling closed-loop systems that can adapt output to changing physiologic demand throughout childhood.

Growth-accommodating design principles are gaining traction, including modular housings or expandable inflow/outflow configurations that could reduce the need for repeat surgeries. Recent work on soft robotics and flexible actuation materials may offer low-profile alternatives to traditional rotary pumps, with better size-to-flow ratios and fewer shear-related complications. Critically, computational modeling tools, which now increasingly coupled with clinical imaging data, can simulate the interaction of a mechanical pump with native Fontan anatomy, supporting precision tailoring for individual patients and stages of disease.

Barriers to Progress

Absence of commercially available subpulmonary assist devices leaves a gap between engineering ambition and clinical deployment.

Limited consensus on timing, indication, and surgical strategies for implanting mechanical pumps in Fontan patients hinders clinical translation.

Size and growth challenges remain critical, as most devices are either too large at implantation or too static for long-term use in children.

High regulatory burden and low market incentive make pediatric MCS development difficult without public or philanthropic investment.

Unknown long-term interactions with Fontan anatomy, including effects on native remodeling, arrhythmia, and organ function, pose risks that must be studied prospectively.

RECOMMENDATIONS

Recommendation 1:
Design a True Mechanical Ventricle, Not an MCS Retrofit, and the Accompanying Surgical Approach

The needs of the single ventricle population are distinct from adult heart failure patients. The goal is not acute support, but durable restoration of forward pulsatile flow. Devices must be:

- Compact and physiologically compatible with pediatric anatomy
- Capable of operating under low preload and unique pressures
- Programmable for long-term use, not short bursts of support

This requires a clean-sheet design approach that prioritizes lifespan, integration, and developmental compatibility for the accompanying surgical approaches.

Recommendation 2:
Engineer for Growth and Changing Demand

Perhaps the most challenging aspect of pediatric deployment is designing a device that can support a growing child. To address this:

- Devices must be miniaturized for infant use, yet be scalable to support somatic growth
- Support algorithms should adjust flow and resistance dynamically with patient activity
- Future designs may need modular architecture, with components that can be exchanged, expanded, or upgraded over time

Solving for growth compatibility is what distinguishes pediatric innovation from miniaturized adult devices.

Recommendation 3:
Solve Power and Durability Without Trade-offs

Power systems for pediatric devices must be efficient, reliable, and unobtrusive, particularly over decades of use. Priorities include:

- Minimally invasive charging systems or durable external driveline solutions with low infection risk
- Battery technologies that minimize replacement frequency
- Redundant components or self-monitoring systems to enable fail-safe operation

This will require tight integration between mechanical engineers, materials scientists, and clinicians to match the realities of childhood activity and family life.

Recommendation 4:
Integrate Closed-Loop Sensing and Physiologic Responsiveness

Single ventricle physiology is patient-specific, and growth of patients is nonlinear. Devices must be smart, not just strong. Key capabilities should include:

- Real-time sensing of venous pressure, flow, preload, and oxygenation
- Algorithms to adjust RPM, flow rate, or pulse frequency in response to systemic needs
- Interfaces for external tuning and monitoring as the patient develops
- This will enable precision physiology rather than one-size-fits-all support.

ADDITIONAL VENTURES

Domain 2
Address Sequelae

Systemic Circulatory Regulation

Lymphatic and Immune Equilibrium

Liver Health

Kidney And Gut Perfusion

Cardiac Integrity And Rhythm Stability

Neurodevelopment

Domain 2: Address Sequelae

Fundamental Goal: Prevent or reverse complications driven by Fontan physiology

Single ventricle circulation is not a stable solution; it is a chronic physiologic stressor that drives progressive, multi-organ consequences. While the surgical stages of palliation have extended survival, they have not secured well-being. As a result, the long-term trajectory of single ventricle patients is defined less by the success of earlier surgeries and more by the chronic complications that emerge downstream — among them, liver fibrosis, lymphatic failure, neurodevelopmental delays, renal dysfunction, and arrhythmias. These sequelae are the outcomes that ultimately determine quality and length of life. Organ injury in Fontan physiology reflects developmental windows of susceptibility, yet little is known about how early-life circulatory transitions shape long-term liver, lymphatic, gut, kidney, and brain resilience. Identifying reversible versus irreversible developmental windows is essential for intervention timing.

Our approach is centered on addressing these systemic complications as tractable domains of intervention rather than inevitable side effects. By focusing on outcomes, we are focusing on what truly matters to patients and families: not just years lived, but lives lived well. Fixing sequelae is the essential work of building a future beyond palliation.

The following approaches advance a portfolio-based strategy to prevent, reverse, or mitigate the complications driven by single ventricle and Fontan physiology, addressing a complex, evolving system of interrelated risks and dependencies. Each outcome domain represents a critical axis of vulnerability and of opportunity:

Systemic Circulatory Regulation targets the circulation, examining the complex interplay of increased central venous pressure with multiple organ systems, including the role of vascular remodeling, and the use of models to improve surgical outcomes, define functional parameters, and identify intervention points.

Lymphatic and Immune Equilibrium tackles the breakdown of lymphatic and immune balance that accelerates Fontan failure, advancing imaging, modeling, and molecular insight to predict, prevent, and restore function across the lymphatic-immune axis.

Liver Health recognizes hepatic fibrosis and Fontan-associated liver disease (FALD) as a silent but universal threat, and calls for predictive biomarkers, antifibrotic therapies, and new surveillance infrastructure.

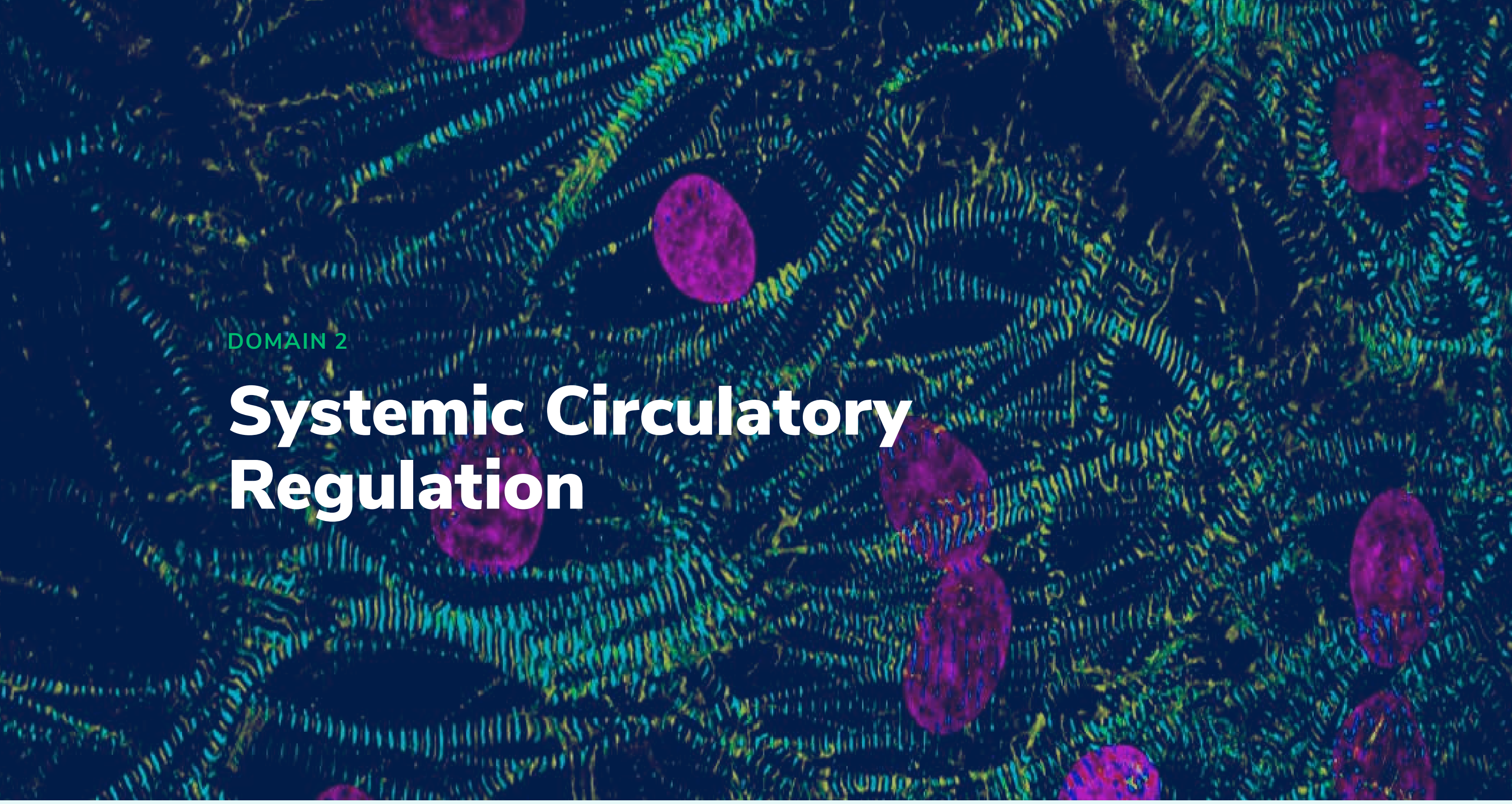
Kidney and Gut Perfusion reframes fluid and nutrient dysregulation as signals of systemic failure, driving investments in perfusion tracking, protective pharmacology, and organ-on-chip discovery platforms.

Cardiac Integrity and Rhythm Stability focuses on protecting both structure and rhythm by anticipating failure before it occurs through integrated modeling, early detection, and novel interventions that sustain mechanical and electrical function essential to survival, all in context of the patient's biology and anatomy.

Neurodevelopment elevates brain health as a core metric of success, integrating developmental surveillance and research into the brain-heart axis.

What links these domains is a shared strategy to treat outcomes as leverage points, not endpoints. These complications offer measurable, patient-centered targets through which we can assess impact, align stakeholders, and design interventions that matter.

Each section that follows outlines the challenge, key scientific and clinical leverage points, promising technologies, and the barriers we must overcome. Together, they form a roadmap, one that acknowledges the complexity of single ventricle disease and the Fontan system while illuminating paths to progress.



DOMAIN 2

Systemic Circulatory Regulation

The Challenge

At the core of Fontan physiology lies a circulatory paradox: survival has been achieved by removing the subpulmonary pump, but at the cost of chronically elevated central venous pressure and reduced cardiac output. This unbalanced circulation strains every organ system — distorting vascular tone, altering endothelial signaling, and driving maladaptive remodeling across veins, capillaries, and lymphatics.

Over time, these pressures propagate systemically: hepatic sinusoids scar, mesenteric veins distend, renal filtration falls, and cerebral autoregulation adapts to congestion. Yet despite this recognition, the mechanisms of systemic vascular adaptation and failure remain underexplored, and tools to measure or modify them are limited. The result is a circulation that functions adequately at rest but fails under stress

Leverage Points

Opportunities for circulatory regulation lie at the intersection of mechanics, biology, and modeling. Computational and imaging-based flow models can now simulate the Fontan vascular network from revealing how pressure and shear forces trigger endothelial activation, inflammation, and fibrosis. Coupled with physiologic data, these models can define functional parameters of stability such as optimal venous pressure, pulsatility, and resistance thresholds. Integrating patient-specific anatomy and physiology enables prediction of outcomes from surgical or device interventions before they occur.

Beyond modeling, vascular biology offers direct therapeutic targets: chronic venous congestion induces endothelial-to-mesenchymal transition, smooth muscle hypertrophy, and impaired nitric oxide signaling — changes that may be reversible. Linking circulatory metrics to multi-organ outcomes could shift care from managing sequelae to controlling the environment that produces them.

Promising Science and Technologies

New tools are making systemic circulation visible and measurable. 4D flow MRI, contrast-enhanced ultrasound, and near-infrared spectroscopy now map pressure and flow in real time, while computational fluid-structure models integrate these data with vessel compliance and venous return to test surgical and device-based scenarios.

At the molecular level, endothelial-on-chip systems recreate Fontan-like pressures to study permeability and remodeling, and AI-driven modeling links macrocirculatory forces to cellular responses. Together with tissue-engineered vascular grafts and biomimetic materials, these innovations offer new routes to restore balance and reestablish physiologic gradients.

Barriers to Progress

The field lacks consensus on optimal venous pressures and resistance ranges, and hemodynamic data remain fragmented and largely descriptive. The interplay between vascular biology and hemodynamic load — how endothelial and smooth muscle changes evolve under chronic congestion — remains poorly defined.

Preclinical models replicating the low-pulsatility, high-pressure Fontan environment are scarce, limiting mechanistic discovery and validation. Clinically, most interventions remain empiric and focused on temporary decompression rather than sustained regulation of tone, flow, or remodeling.

RECOMMENDATIONS

Recommendation 1:
Map and Model the Systemic Circulation Across Scales

To define what drives stability or failure, the field must first characterize the systemic circulation from macrovessel architecture to microvascular exchange. We recommend:

- Further developing multi-scale computational models that integrate hemodynamic, anatomic, and vascular biological data
- Linking imaging, exercise testing, and simulation data to clinical outcomes to establish functional thresholds for venous pressure, resistance, and adaptability
- Creating digital twins of the Fontan circulation to predict responses to surgical or device-based interventions

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Recommendation 2:
Define Mechanobiologic and Hemodynamic Modifiers of Disease Expression

- Determine how venous hypertension, low pulsatility, oscillatory shear, and hypoxia/reoxygenation shape endothelial, epithelial, and stromal programs across development and chronic phases.
- Identify windows of susceptibility and dose-response relationships linking hemodynamic loads to molecular states and organ-level function.
- Quantify genetic effects within pathophysiologic context (e.g., altered shear, elevated venous pressure) and assess the impact of targeted interventions on developmental and disease trajectories.

Recommendation 3:
Define Mechanisms of Vascular Remodeling and Adaptive Capacity

Chronic congestion and altered flow provoke structural and molecular adaptations that shape circulatory reserve. The field must:

- Characterize how endothelial, smooth muscle, and skeletal muscle cells respond to sustained pressure and low shear stress
- Use vascular- and muscle-on-chip platforms to study signaling pathways that govern tone, permeability, and remodeling under Fontan-like conditions
- Identify markers of adaptive versus maladaptive remodeling and link them to exercise tolerance and vascular reactivity
- Integrate biological and mechanical data into predictive models of circulatory adaptability

Recommendation 4:
Use Modeling to Optimize Surgical and Interventional Design

Predictive modeling can inform how to reshape the circulation for better systemic performance. We recommend:

- Applying computational simulations to test and refine surgical geometries, shunt configurations, and conduit designs that improve venous flow and exercise reserve
- Developing standardized frameworks for hemodynamic modeling in preoperative planning and postoperative surveillance
- Linking model predictions to measured exercise and hemodynamic outcomes to validate and refine simulations
- Integrating virtual surgery and stress modeling platforms into device development and clinical training

Recommendation 5:
Identify and Test Circulatory Modifiers and Functional Therapies

Beyond structural repair, pharmacologic, rehabilitative, and device-based strategies may enhance systemic adaptability. Priorities include:

- Testing vasoactive and endothelial-targeted agents that improve compliance or enhance flow redistribution during exertion
- Evaluating mechanical assist technologies or circulatory support systems that restore physiologic pulsatility
- Defining biomarkers and physiologic thresholds to track progress and personalize intervention timing

Summary

Systemic circulatory regulation is foundational to sustaining Fontan physiology. The intertwined effects of venous congestion, low pulsatility, and altered vascular biology shape outcomes across every organ system, yet remain among the least mechanistically defined components of Fontan failure. Advancing this field requires an integrated framework that links hemodynamics, vascular biology, and predictive modeling, enabling early detection of destabilizing trends and the design of interventions that restore physiologic gradients rather than merely decompressing symptoms. By transforming how the circulation is measured, modeled, and modulated, the field can shift from managing downstream sequelae to engineering a more resilient systemic environment that supports long-term function and quality of life.

DOMAIN 2

Lymphatic and Immune Equilibrium

The Challenge

Fontan physiology imposes chronically elevated central venous pressure, which in turn disrupts normal lymphatic flow and architecture. Over time, these pressures lead to dilation, leakage, and rerouting of lymphatic channels. The result is a spectrum of complications, most notably protein-losing enteropathy (PLE), plastic bronchitis (PB), and systemic inflammation, that are not only life-altering but often resistant to conventional therapies. These disorders reflect not only lymphatic dysfunction but also its interplay with venous congestion, low cardiac output, and immune dysregulation. The lymphatic system thus becomes both a victim and amplifier of Fontan failure. Intervening in this domain holds promise not only for symptom control but also for broader restoration of physiologic homeostasis across circulatory, metabolic, and immune systems.

Leverage Points

Shifting from reactive management to proactive intervention will require both earlier recognition and more diverse treatment strategies. Detecting lymphatic flow derangements before symptoms become entrenched could transform outcomes, particularly if detection is coupled with anatomy-specific interventions that relieve pressure or redirect flow. Advances in imaging and modeling now allow visualization and quantification of lymphatic flow, vessel permeability, and endothelial integrity with unprecedented precision. Critically, because lymphatic dysfunction is fundamentally coupled to venous congestion, future approaches must account for communication between the venous and lymphatic systems. Defining the pathways governing permeability, valve integrity, and endothelial remodeling is essential for identifying actionable therapeutic targets. When integrated with molecular and cellular data, these tools can reveal the mechanisms that drive leakage, inflammation, and remodeling. In parallel, scalable pharmacologic and image-guided interventions that target tone, pressure, and immune-endothelial cross talk will offer a continuum of care that spans prevention, stabilization, and restoration.

Promising Science and Technologies

Momentum is building across multiple fronts. In the procedural realm, image-guided techniques such as thoracic duct decompression and selective lymphatic embolization have already altered the clinical course for some patients, though primarily in tertiary centers with concentrated expertise. On the biologic and mechanistic side, molecular therapies targeting lymphangiogenic pathways raise the possibility of reshaping dysfunctional lymphatic networks rather than just managing symptoms. In parallel, bioengineering is pushing the boundaries of what can be modeled or replaced, lymphatic endothelial-on-chip platforms are offering new windows into mechanisms, and tissue-specific grafts hint at regenerative solutions that once seemed out of reach.

Barriers to Progress

Even with these advances, fundamental questions remain unanswered. Mapping lymphatic anatomy and flow dynamics in the setting of Fontan physiology is still incomplete, and the clinical course varies so widely from patient to patient that risk prediction is elusive. Without reliable animal models or biomarkers, researchers struggle to link early imaging findings to long-term outcomes such as PLE or PB. Layered onto these gaps is the possibility that some patients carry intrinsic developmental vulnerabilities: genes implicated in single ventricle heart formation also influence lymphatic vessel development, suggesting that genetic predisposition may compound the hemodynamic stresses unique to Fontan circulation. Finally, access to specialized lymphatic interventions remains uneven, and pharmacologic tools to modulate lymphatic and immune balance are only beginning to emerge.

RECOMMENDATIONS

Recommendation 1:
Build an Integrated Mechanistic Understanding of Lymphatic Dysfunction

Fundamental discovery is still needed to connect structural findings with the underlying biology of lymphatic failure in Fontan physiology. The field must prioritize:

- Developing animal and computational models that replicate venous pressures and lymphatic remodeling patterns across all stages of palliation
- Constructing single-cell and spatial atlases of lymphatic endothelium in affected tissues (intestine, lungs, thoracic duct) and prospective trials to identify early molecular signals that predict dysfunction.
- Establish standardized imaging protocols to monitor lymphatic function and integrate with histopathology and transcriptomic data to define key pathogenic pathways.

Recommendation 2:
Develop Interventional and Pharmacologic Strategies for Lymphatic Restoration

Minimally invasive, anatomy-specific interventions and pharmacologic modulation should evolve as complementary rather than competing strategies. Priorities include:

- Refining catheter-based techniques to safely target pathologic lymphatic channels in pediatric and complex anatomies
- Integrating pharmacologic agents that stabilize lymphatic tone, reduce permeability, or promote adaptive remodeling
- Repurposing drugs used in rare lymphatic disorders and testing anti-inflammatory or endothelial-stabilizing compounds in Fontan disease

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Recommendation 3:
Investigate Immune-Lymphatic Interactions and Therapeutic Targets

Immune activation and lymphatic dysfunction are tightly coupled in Fontan physiology, perpetuating systemic inflammation and protein loss. The field should prioritize:

- Mapping immune cell trafficking, cytokine signaling, and barrier interactions in gut, lung, and lymphatic tissues
- Characterizing immune phenotypes and inflammatory mediators that correlate with lymphatic leak or remodeling
- Testing targeted anti-inflammatory therapies, cytokine inhibitors, and microbiome-based interventions to restore balance
- Exploring how lymphatic interventions influence immune homeostasis and vice versa, identifying points of synergy for therapy

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Recommendation 4:
Develop Biomarkers and Predictive Tools for Early Detection

Reliable indicators of early dysfunction are essential for preemptive care. We recommend:

Defining panels of circulating, stool, or imaging-derived biomarkers to track lymphatic integrity and immune activation

Validating these markers in longitudinal studies to differentiate preclinical from established disease

Applying AI-assisted analysis to integrate imaging and biomarker data into predictive models for risk stratification and therapy initiation

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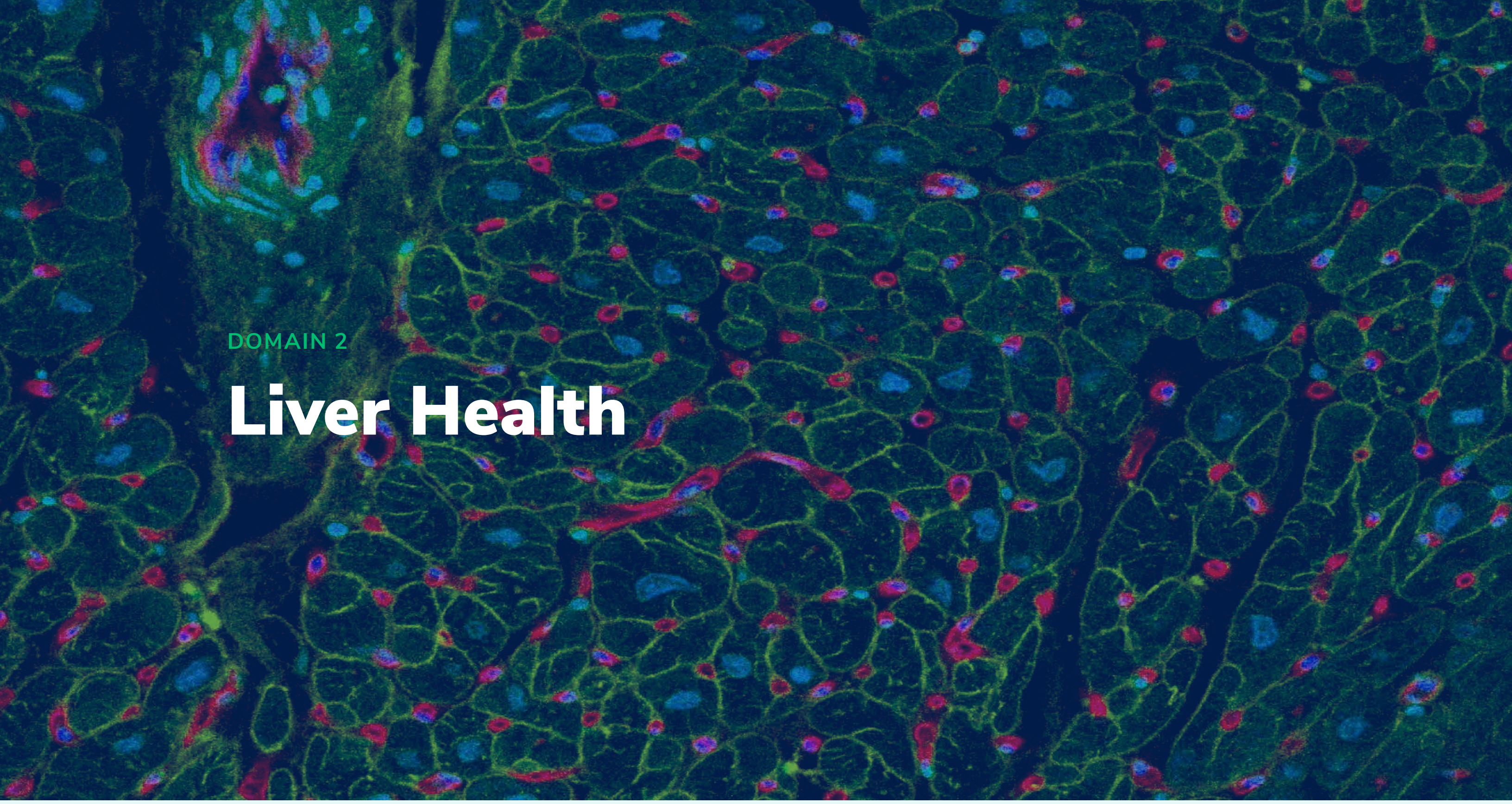
Summary:

Restoring lymphatic and immune equilibrium represents one of the most transformative opportunities in Fontan medicine. By uniting imaging, modeling, mechanistic biology, and immunologic insight with scalable interventional and pharmacologic tools, we can move from managing crises to maintaining balance. In doing so, we not only treat PLE and PB but restore the physiologic stability upon which the entire Fontan system depends.



DOMAIN 2

Liver Health

The Challenge

While there is broad scientific consensus that chronic hepatic injury is nearly universal in Fontan patients, what is often described as Fontan-associated liver disease (FALD) is neither uniformly defined nor consistently measured. The liver, directly downstream of the venous pressures inherent to Fontan circulation, is subjected to long-standing passive congestion. Over time, this state drives progressive distortion, fibrosis, and regenerative nodularity, ultimately increasing the risk for cirrhosis and hepatocellular carcinoma (HCC). While fibrosis is consistent, the exact spectrum of pathology remains unsettled.

Importantly, these processes are often silent, limiting opportunities for timely intervention. Liver involvement in Fontan physiology is not only a localized complication but also a systemic signa, reflecting the burden of congestion and foreshadowing broader circulatory decline. Addressing it will require clearer definitions, robust surveillance infrastructure, and targeted therapeutic strategies.

Leverage Points

Though the natural history of FALD is incompletely defined, there are clear opportunities to intervene earlier and more systematically. Surveillance approaches such as elastography, contrast-enhanced MRI, and serum biomarkers could help detect fibrosis when progression might still be slowed or reversed, particularly if applied consistently across centers as a standard part of surveillance. Early hemodynamic interventions may reduce venous pressure and improve hepatic inflow and outflow, mitigating injury at its source. Meanwhile, predictive models that identify which patients are at greatest risk for progression could allow clinicians to tailor monitoring protocols and prioritize early treatment.

Promising Science and Technologies

Innovation is beginning to shift the landscape. Drugs developed to treat other fibrotic liver diseases could be repurposed to slow or reverse fibrosis in Fontan patients. Efforts to remodel hepatic vasculature, whether through device-based or pharmacologic strategies, include exploration of ways to relieve sinusoidal congestion and restore perfusion. Imaging technologies are also advancing, MR elastography and contrast-enhanced ultrasound now provide increasingly precise assessments of stiffness, nodularity, and blood flow, moving the field closer to noninvasive, longitudinal monitoring.

Barriers to Progress

Disease trajectories vary widely, even among patients with similar hemodynamics, leaving clinicians with little ability to predict outcomes or stratify risk. The regenerative capacity of the congested Fontan liver is poorly understood, raising questions about which patients can recover and which may experience irreversible decline. Compounding the problem, there are still no validated noninvasive tools that reliably track progression or therapeutic response in this unique population. Together, these gaps slow both clinical decision-making and therapeutic development.

RECOMMENDATIONS

Recommendation 1:
Clarify the Definition and Natural History of FALD

Progress in both research and care is hindered by the absence of a unified framework for what constitutes FALD across stages. To build a foundation for consistent surveillance, trial design, and mechanistic investigation, we must:

- Conduct studies that distinguish the histologic and physiologic features of congestion, fibrosis, cirrhosis, and malignancy in Fontan physiology
- Compare and validate imaging and biopsy-based scoring systems to identify reliable markers of disease stage and trajectory
- Map age- and stage-specific patterns of hepatic progression to inform future surveillance models and risk stratification frameworks

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Recommendation 2:
Model FALD Progression In Vitro and In Vivo

Effective therapeutic development is constrained by the lack of representative preclinical models. We recommend:

- Creation of hemodynamic animal models that reproduce Fontan-level hepatic venous pressure over time
- Use of patient-derived liver organoids, especially those subjected to mechanical stress or venous stasis, to study fibrosis mechanisms and drug responses
- Longitudinal multi-omics profiling of explanted or biopsied tissue to map molecular trajectories of disease from early congestion to malignancy

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Recommendation 3:
Develop Non-Invasive Biomarkers for Early Detection

Liver biopsy is impractical for routine monitoring, particularly in pediatrics. The field must broaden its toolkit for detecting early, subclinical signs of hepatic stress and fibrosis. We prioritize:

- Identification and validation of circulating and cellular biomarkers, including fibrosis markers, indicators of endothelial permeability, and signals of regenerative activity, specific to FALD
- Evaluation of imaging-based biomarkers, such as elastography, contrast-enhanced MRI, or Doppler ultrasound parameters, that may correlate with histologic severity or functional decline

- Creation and validation of composite risk algorithms that integrate molecular, imaging, and clinical data to stratify patients and predict disease progression

Recommendation 4:
Explore Hepatic Protective Therapies

No therapies are approved for Fontan-related liver injury. The field should pursue a dual strategy: developing new interventions (both pharmacologic and device-based) to directly address hepatic vulnerability and evaluating the potential to repurpose or adapt existing solutions from other liver and vascular diseases. Priorities include:

Designing and testing pharmacologic agents to reduce fibrosis, improve microcirculation, or enhance hepatocellular resilience

Exploring repurposing opportunities for drugs developed for other hepatic diseases

Investigating device-based approaches that could alleviate sinusoidal congestion, optimize hepatic perfusion, or reduce portal hypertension

Establishing early-phase translational studies to assess safety, feasibility, and signals of efficacy across pediatric populations

Recommendation 5:
Define the Role of Hepatic Status in Long-Term Decision Making

Liver disease is under-integrated in risk models for Fontan candidacy, reintervention, and transplant planning. We propose:

- Generating evidence on how hepatic status (via biomarkers, imaging, or functional metrics) predicts surgical and long-term outcomes
- Characterizing how hepatic dysfunction evolves in relationship to cardiovascular parameters over time, and how this relationship influences clinical outcomes and decision-making
- Identifying and piloting liver endpoints in clinical trials or observational studies on whole-system health

Summary:

Liver sequelae exemplify the chronic, system-wide toll of Fontan circulation, but also present a modifiable domain for action. By advancing earlier detection, targeted protective strategies, and a deeper understanding of disease biology, we can extend the therapeutic window and prevent irreversible hepatic damage. As with the heart, the liver is central to the long-term health, resilience, and transplant eligibility of single ventricle patients.

DOMAIN 2

Kidney and Gut Perfusion

The Challenge

Impaired end-organ perfusion is widely recognized as a feature of Fontan physiology, driven by chronically low cardiac output and sustained central venous hypertension. Whether this consistently translates into clinically meaningful kidney and gut disease remains unsettled. Reports of renal injury exist, but the prevalence, mechanisms, and long-term trajectory are not well defined. Similarly, intestinal congestion may impair nutrient absorption and contribute to systemic inflammation, although the specific mechanisms remain incompletely understood.

When present, these effects are unlikely to be abrupt or symptomatic in the early stages. Instead, they unfold over time, eroding reserve capacity and compounding risk for other complications. Still, the full scope and significance of kidney and gut involvement remain poorly characterized, reflecting both a lack of standardized surveillance tools and limited foundational data on prevalence, progression, and phenotype.

Leverage Points

If kidney and gut dysfunction prove to be meaningful contributors to Fontan decline, several points of intervention could be leveraged. Enhancing systemic flow, through pharmacologic optimization or mechanical support, can help improve organ perfusion. Protecting the microvasculature, particularly by safeguarding endothelial health and supporting lymphatic drainage, may prevent ongoing injury at a tissue level. Developing sensitive biomarkers for renal and enteric function may also enable earlier detection of subclinical decline, long before overt clinical deterioration sets in.

Promising Science and Technologies

Emerging technologies create opportunities to test these possibilities more rigorously. Renoprotective drugs currently under study in adult heart failure could be explored in congenital contexts, offering pharmacologic tools to test and preserve kidney function. Imaging methods such as contrast-enhanced ultrasound and MRI now allow real-time visualization of mesenteric and renal perfusion, providing insights once confined to invasive testing. In parallel, organ-on-chip platforms are emerging as scalable, physiologically relevant models, enabling researchers to recreate perfusable gut and kidney tissues under Fontan-like stress and to test potential interventions in vitro.

Barriers to Progress

Progress is slowed primarily by the absence of foundational data. Pediatric-specific evidence of Fontan-associated kidney and gut pathology remains sparse, leaving open the question of whether these are consistent sequelae or isolated findings. The interplay between systemic perfusion, venous congestion, organ-specific vulnerabilities, and non-hemodynamic contributors is complex and poorly modeled. Without standardized classification systems or registries, the true scope of renal and gut complications is difficult to quantify, and discovery lags as a result. Moreover, there is little longitudinal evidence linking early subclinical changes to hard outcomes, making it challenging to prioritize investment or define trial endpoints. Together, these barriers keep kidney and gut health at the periphery of Fontan care when, in fact, they are central to whole-system resilience.

RECOMMENDATIONS

Recommendation 1:
Generate Gut and Kidney Organoid and Organ-on-Chip Systems for Discovery

To accelerate early-stage testing and better replicate Fontan physiology in vitro, we recommend:

- Developing kidney and gut organoids from patient-derived or stem cell sources to model the effects of altered pressure and flow
- Utilizing microfluidic systems to study flow-responsive changes in gene expression, barrier function, and nutrient handling
- Building integrated multi-tissue platforms to study the interdependence of gut, kidney, and lymphatic networks under Fontan-like stress conditions

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Recommendation 2:
Characterize the Natural History and Phenotypes of Kidney and Gut Dysfunction

Before precise interventions can be deployed, the field must first understand the scope and variability of kidney and gut complications in Fontan patients. We recommend:

- Clarifying the prevalence, timing, and clinical presentation of dysfunction across age groups and subtypes
- Developing standardized criteria to define and grade severity of dysfunction, enabling cross-study comparability
- Investigating early physiologic, imaging, or biomarker-based signals that may predict future decline or identify distinct disease phenotypes

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Recommendation 3:
Improve Tools for Perfusion Assessment

Detection of early-stage perfusion compromise is essential, but existing tools are imprecise or impractical for regular use. We propose:

- Advancing imaging approaches (e.g., Doppler, ultrasound, MRI) to noninvasively assess renal and mesenteric flow dynamics
- Developing composite perfusion indices that integrate flow, pressure, and systemic markers to better quantify systemic compromise
- Exploring longitudinal tracking methods to capture fluctuations in perfusion status over time

Recommendation 4:
Understand the Systemic Impact of Underperfusion

Perfusion deficits affect not only isolated organs but systemic function. We recommend:

- Studying how reduced renal and gut perfusion impacts growth, neurodevelopment, and nutrient or drug handling, especially in pediatric patients
- Constructing physiologically informed pharmacokinetic and pharmacodynamic (PK/PD) models that reflect altered absorption and clearance in Fontan physiology
- Identifying perfusion-related endpoints and functional markers that could be incorporated into interventional trials

Summary:

The kidneys and gut are dynamic sensors and effectors of systemic health. Preserving their function requires earlier recognition, targeted therapeutics, and integrated models that reflect the interdependence of circulation, perfusion, and organ resilience. With the right tools, this "silent casualty" of the Fontan circuit can become a tractable and high-impact domain for intervention.

DOMAIN 2

Cardiac Integrity and Rhythm Stability

The Challenge

In the Fontan circulation, the heart functions at the nexus of mechanical and electrical vulnerability. The single ventricle bears systemic workload without the support of a subpulmonary pump, leading to chronic preload deprivation, high afterload, and progressive valvular stress. These mechanical forces remodel the myocardium and atria, creating conditions ripe for arrhythmogenesis. Meanwhile, arrhythmias, particularly intra-atrial reentry tachycardia, disrupt filling and output, accelerating ventricular and valvular decline. Each area of dysfunction amplifies the other, driving a cycle of interdependent failure.

Although both rhythm instability and structural dysfunction often appear late in the disease course, subtle perturbations in conduction, strain, and valve mechanics emerge years earlier. Identifying these preclinical warning signs could transform care from reactive to anticipatory. Achieving this requires tools that integrate mechanical and electrical modeling, enable early detection, and guide interventions designed for growth, conduction preservation, and long-term resilience.

Leverage Points

Protecting cardiac integrity demands a systems-level perspective. The mechanical and electrical domains must be studied and managed together, since scarring, dilation, fibrosis, and pressure imbalance underpin both valve failure and arrhythmia, and the underlying biological substrate may act as an exacerbating force. Computational modeling now offers an opportunity to integrate these processes, linking chamber geometry, valve motion, and conduction pathways in predictive frameworks that can forecast risk before symptoms arise.

Surgical and device design represent another leverage point. Techniques that minimize atrial manipulation, optimize conduit geometry, and reduce suture-line scarring could prevent both mechanical inefficiency and rhythm substrate formation. Parallel innovations in imaging and monitoring, ranging from advanced echocardiographic strain mapping to wearable rhythm sensors, make it possible to continuously track subtle deviations from baseline. Finally, by embedding modeling into surgical planning and postoperative surveillance, clinicians could iteratively test a variety of scenarios to personalize care and preempt deterioration.

Promising Science and Technologies

Rapid progress in technology is redefining what is possible for Fontan patients. Integrated electromechanical models now simulate how hemodynamic load, chamber deformation, and conduction interact to influence function and arrhythmia risk. 4D flow MRI and echocardiography can detect minute abnormalities in flow or strain that precede overt dysfunction, while high-resolution electroanatomic mapping allows precise localization of arrhythmogenic substrates even in surgically altered anatomy.

At the discovery level, tissue-engineered and growth-accommodating valves are being designed specifically for pediatric single-ventricle physiology. Cardiac organoids and iPSC-derived myocytes offer new avenues to study the cellular basis of electrical and mechanical adaptation under Fontan-like stresses. Finally, AI-driven data integration that draws on imaging, biomarker, and telemetry data promises to create real-time predictive models of decline that could trigger timely intervention.

Barriers to Progress

Despite this momentum, several critical obstacles impede progress. First, conventional clinical markers such as ejection fraction or BNP correlate poorly with true physiologic reserve, obscuring early warning signs. Second, the complex congenital anatomy of Fontan hearts limits the accuracy of risk prediction and complicates catheter-based or surgical rhythm interventions. Third, repair and replacement options for the atrioventricular valve remain constrained, particularly in small or asymmetric annuli, and growth-compatible solutions are still in development. Fourth, data linking mechanical and electrical deterioration are fragmented across imaging, electrophysiology, and clinical monitoring domains, limiting system-wide insight. Finally, intervention thresholds, specifically when to ablate, repair, or replace, remain poorly defined, leaving clinicians to act only after irreversible decline has begun.

RECOMMENDATIONS

Recommendation 1:
Model and Map the Mechanical-Electrical Interface

A unified understanding of how mechanical and electrical forces interact is essential for predicting deterioration and guiding targeted intervention:

Develop multi-scale computational models linking atrial geometry, ventricular strain, valve dynamics, and conduction pathways to identify high-risk regions for arrhythmia or heart failure.

Apply modeling frameworks to optimize surgical and device designs, including valves, patches, and ventricular assist devices, that minimize scar formation and preserve conduction integrity.

Study how surgical techniques (e.g., suture placement, patch geometry, conduit design) influence long-term atrial and ventricular conduction, and arrythmia risk.

Recommendation 2:
Advance Valve Repair and Replacement Strategies Specific to Fontan Anatomy

Sustaining long-term cardiac integrity requires valve solutions explicitly engineered for the unique geometry, loading conditions, and growth demands of Fontan anatomy:

Engineer growth-accommodating and tissue-engineered valves tailored to single ventricle hemodynamics.

Develop design principles and use computational modeling for atrial and valve repairs that integrate electrophysiologic and flow-preserving priorities.

Use computational modeling and preclinical simulation to determine repair versus replacement thresholds and optimize designs for asymmetric annuli.

Recommendation 3:
Expand Understanding of Arrhythmia Mechanisms and Risk Prediction

Effective prevention of arrhythmia-driven decline depends on a clearer delineation of the mechanisms, substrates, and risk factors that govern rhythm instability in this population:

Investigate genetic and developmental predispositions to conduction abnormalities in Fontan patients.

Examine how Fontan-specific hemodynamics, low preload, high venous pressure, and atrial dilation, drive electrophysiologic remodeling.

Integrate electroanatomic mapping, imaging, and histopathology to classify arrhythmia subtypes and mechanisms.

Recommendation 4:
Identify Early Markers and Predictors of Ventricular Decline

Preserving ventricular function demands earlier identification of subtle markers of decline, before conventional metrics detect dysfunction:

Investigate genetic and developmental predispositions to ventricular abnormalities in Fontan patients.

Combine mechanical and electrical markers and interventional timing into unified predictive models and develop monitoring tools to enable proactive detection and timely treatments.

Explore fibrosis biomarkers, atrial size, and autonomic tone as early warning signs of failure.

Recommendation 5:
Define and De-Risk Early Intervention Strategies for Arrythmia

Improving outcomes will require shifting rhythm management upstream, defining when early interventions mitigate long-term remodeling and reduce the need for high-risk rescue therapies:

Determine thresholds for early rhythm or valve intervention that prevent pathologic remodeling

Support clinical trials that measure outcomes of early ablation, pacing, or valve repair in anatomically or genetically high-risk patients.

Establish guidance frameworks for safe, staged electrophysiologic and mechanical interventions in pediatric populations.

Summary

Cardiac integrity in the Fontan circulation is a dynamic equilibrium between structure and rhythm. The same forces that distort the ventricle and valves also destabilize conduction; conversely, arrhythmia accelerates mechanical decline. By integrating mechanical and electrical modeling, advancing growth-compatible valve and pacing technologies, and intervening before failure becomes entrenched, the field can redefine what it means to preserve the Fontan heart, as a foundation for systemic resilience and long-term survival.

DOMAIN 2

Neurodevelopment

The Challenge

The brain is uniquely vulnerable in children with single ventricle heart disease. From fetal development through adolescence, this population faces an elevated risk for neurocognitive delay, executive dysfunction, motor and speech delays, behavioral disorders, and reduced overall quality of life. These outcomes are shaped by a convergence of stressors: chronic hypoxia, circulatory instability, early and repeated surgeries, exposure to cardiopulmonary bypass, systemic inflammation, and social-emotional adversity.

Unlike some sequelae that manifest later in life, neurodevelopmental impacts often emerge early, sometimes before the second stage of palliation, and can profoundly shape life trajectory. Yet neurodevelopmental care remains fragmented, under-resourced, and inconsistently integrated into congenital heart care models.

Mental health concerns — including anxiety, depression, and post-traumatic stress — are prevalent yet under-addressed, particularly during adolescence. Moreover, dysregulation of the autonomic nervous system may link brain function with systemic complications, suggesting a broader role for the brain-heart axis in Fontan physiology.

Leverage Points

Opportunities exist to move from passive observation to active brain protection, though most remain underutilized. Critical windows of development — in utero, infancy, and early childhood — represent periods of heightened vulnerability and potential intervention. Surgical and perioperative practices could be optimized to better preserve cerebral perfusion and limit hypoxic or inflammatory injury. Given the role of systemic and neuroinflammation in shaping brain outcomes, defining immune phenotypes, cytokine networks, and inflammatory endotypes is critical for risk prediction and therapy design. Beyond the operating room, embedding neurodevelopmental screening into routine cardiac follow-up and ensuring access to early enrichment or intervention services could alter trajectories that otherwise lead to long-term deficits.

Promising Science and Technologies

Emerging advances across pediatric neurology, developmental science, and cardiac surgery point to new possibilities. Brain-focused perfusion strategies guided by near-infrared spectroscopy and advanced flow monitoring help clinicians safeguard cerebral blood flow during bypass and circulatory arrest. Several neuroprotective agents are under active investigation for neonatal brain injury, with potential relevance to this population. At the systems level, longitudinal registries linking developmental outcomes with physiologic and surgical variables are beginning to uncover causal pathways and resilience factors, laying the groundwork for more targeted interventions.

Barriers to Progress

Despite these promising directions, progress is slowed by structural and knowledge gaps. Neurodevelopmental services are often siloed from cardiac care teams and introduced too late to make a meaningful difference. Follow-up is inconsistent, and the absence of standardized testing or shared benchmarks obscures the natural history of neurodevelopment in this population. Without coordinated approaches to measurement and risk stratification, it remains difficult to compare outcomes across centers or to design interventions that can be implemented widely.

RECOMMENDATIONS

Recommendation 1:
Illuminate Developmental Trajectories and Early Risk Markers

Protecting brain health requires early detection of deviations, but current tools are inconsistently applied and poorly integrated. We recommend::

- Identifying key developmental domains (motor, language, cognition, behavior) that are most sensitive to early physiologic stress
- Exploring how timing of surgery and oxygenation shape neurodevelopmental trajectories
- Investigating advanced neuroimaging, physiologic, and behavioral markers that may serve as early predictors of long-term cognitive or behavioral outcomes

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Recommendation 2:
Understand and Mitigate Perioperative Brain Injury

The earliest stages of life carry the greatest risk for neurologic injury, particularly around surgery. To protect the developing brain, we recommend:

- Studying the neurophysiologic impact of different perfusion and bypass strategies in neonatal and infant surgery
- Investigating potential neuroprotective strategies, including pharmacologic therapies or modified surgical techniques, that may reduce reperfusion injury or inflammation
- Studying variation in neurologic outcomes across surgical strategies to identify modifiable contributors to early brain injury

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Recommendation 3:
Study Intrinsic and Systemic Contributors to Brain Injury and Health

Neurologic outcomes are not just the result of surgery; they reflect the patient’s whole physiologic landscape. We must:

- Investigate how hypoxia, inflammation, lymphatic congestion, and perfusion deficits interact to shape brain structure and function
- Identify intrinsic (e.g., genetic, anatomic) factors that shape cognitive and behavioral resilience
- Develop integrated models that link Fontan physiology with neurocognitive outcomes over time

Recommendation 4:
Explore the Role of the Brain-Heart Axis and Autonomic Regulation

Emerging evidence suggests that the autonomic nervous system may modulate both cardiovascular and neurologic outcomes. To better understand this bidirectional relationship, we recommend:

- Mapping autonomic tone and variability (e.g., HRV, baroreflex sensitivity) as potential biomarkers of multisystem stress or dysfunction
- Studying how patterns of dysautonomia correlate with fatigue, arrhythmia, and cognitive outcomes
- Investigating feasibility and rationale for autonomic-targeted interventions (e.g., neuromodulation, vagal stimulation) as a means of improving multisystem resilience and physiologic adaptability

Summary:

Neurodevelopmental outcomes are a central determinant of long-term success in single ventricle care. Protecting brain health requires shifting from episodic, reactive support to an integrated, proactive framework that begins early and continues throughout childhood. Progress depends on systematic measurement, consistent risk stratification, and coordinated implementation of interventions across surgical, medical, and developmental domains. By aligning care models, research priorities, and clinical practices around brain protection, the field can meaningfully alter cognitive and behavioral trajectories and enable children with single ventricle physiology to achieve durable, functional well-being.

Fundamental Biology is Key to Unlocking Single Ventricle

Fundamental Biology is Key to Unlocking Single Ventricle

Critical to the recommendations across both roadmap domains is understanding the underlying biology of the patient. While some variation in outcomes can be explained through differences in surgical course, bypass time, and clinical experience, it is also well documented that outcomes can vary dramatically among individuals with similar anatomy and surgical history. Intrinsic differences in the etiology of single ventricle and the specific biological substrate may provide the key to unanswered questions of who is at risk for which complications and ultimately, how we can intervene.

Here, we outline what is known about single ventricle heart disease etiology and the links to other lesions and outcomes. Despite these noted advances, current genetic research on SV remains fragmented, constrained by underpowered studies, variable definitions, and siloed datasets. Most analyses focus on narrow phenotypes or single-gene associations, without the resolution to disentangle layered mechanisms. However, the field is at an inflection point: tools such as single-cell and spatial transcriptomics, biomechanical modeling, and multi-organ developmental atlases now offer the opportunity to move from association to causality and from gene lists to regulatory circuits and developmental programs. What remains is coordination, scale, and integration to build the integrated discovery engine that will power the next decade of SV breakthroughs and become a foundation for prediction, prevention, and cures.

WHAT WE KNOW

Current Understanding of Single Ventricle Etiology

Far from being a singular disease entity, SV represents a family of congenital heart defects that often present with additional cardiac and extracardiac findings. Isolated cases are the minority; most patients exhibit co-occurring lesions, variable severity, and diverse clinical trajectories. This complexity reflects a multifactorial origin involving a complex interplay of genetic, developmental, epigenetic, biomechanical, and environmental factors. While early investigations focused on single-gene causes, it is now clear that SV includes monogenic, oligogenic, and polygenic contributions, shaped by variable penetrance and modulated by non-genetic inputs throughout development.

Genetic studies have identified both syndromic and non-syndromic contributors to SV. Recurrently implicated non-syndromic genes, such as NOTCH1, MYH6, GATA4, NKX2-5, and NODAL, appear across cohorts and suggest shared developmental pathways. Syndromic associations with CHD7, GDF1, and KMT2D highlight the role of chromatin and transcriptional regulation. Still, these variants are rarely specific to a single defect, reinforcing the need for refined phenotyping and recognition of distinct genetic subtypes. Importantly, many of these same variants are associated with poorer neurodevelopmental outcomes, extracardiac anomalies, and reduced transplant-free survival—linking disease origins to prognosis.

Emerging work in epigenomics further supports early developmental disruption in SV. Abnormal DNA methylation signatures and accelerated epigenetic aging have been observed in both newborns and placental tissues from SV pregnancies, while animal models reveal that environmental insults, such as gestational hypoxia, can unmask or intensify congenital heart defects in genetically susceptible embryos. These studies underscore the interplay of genetic risk and environmental exposure and suggest that disease expression is not hardwired by DNA alone but shaped by context.

Technological Landscape and Discovery Gaps

Recent technological advances, such as single-cell sequencing, spatial transcriptomics, high-resolution imaging of cardiac development, multi-scale biomechanical modeling, and methods to map regulatory elements and alterations in chromatin structure make it possible to move beyond traditional candidate gene discovery to systems-level investigations of heart development and disease. In parallel, tools to interrogate how environmental and epigenetic inputs intersect with genetic background are enabling a more integrated and holistic view of disease etiology. These capabilities allow us to build a high-resolution map of single ventricle-specific variants, regulatory elements, and chromatin states, and to connect them to developmental processes and functional outcomes, including those shaped by Fontan physiology (e.g., elevated venous pressure and low pulsatility).

Despite these advances, single ventricle-related genetics research remains limited by scope, scale, and coordination. Most studies are fragmented, focused on isolated genes or narrow disease subtypes, underpowered to detect complex interactions, and based on small, heterogeneous cohorts without standardized deep phenotyping. Siloed registries and datasets with institutional barriers to integration have further stymied progress. As a result, we still lack a comprehensive, time-resolved developmental map of the molecular, cellular, and physiological alterations across the single ventricle heart and how these factors relate to clinical outcomes or inform treatment decisions.

Integrating comprehensive genomic data with standardized clinical phenotyping, environmental and epigenetic profiles, physiological measures, and long-term outcome tracking is essential to transform our understanding of single ventricle heart disease. By building a large, deeply phenotyped, multi-modal dataset anchored in single ventricle and expandable to other CHD populations, we can uncover shared mechanisms, identify genetic and environmental modifiers, and validate findings across diseases. This approach enables precise disease subtyping to drive individualized approaches to care, improves risk prediction, informs family counseling, and identifies molecular targets for preventive or curative therapies. Understanding origins is not only a scientific priority, but also a prerequisite for advancing risk prediction to intervene to modify or prevent complications and facilitate early diagnosis, precision therapies, and functional cures for this group of complex congenital heart defects.

Bridging Foundational Biology to Organ-level Insights

A mechanistic understanding of single ventricle pathophysiology (i.e., linking genetic and regulatory variation to cell-state transitions, tissue biomechanics under Fontan physiology, and organ-level function) provides the hypotheses, biomarkers, and stratifiers that each organ domain then operationalizes. In practice, this work delineates developmental and flow-mediated endotypes in the heart; determinants of lymphatic failure and protein-losing enteropathy in the lymphatic and gut systems; fibrosis trajectories in the liver; cilia- and mechanosensing pathway perturbations in the kidney; and neurovascular and hypoxia-response programs in the brain. These cross-organ mechanisms translate directly into surveillance panels, risk models, and targeted intervention strategies within each domain. And insights from mechanobiology and developmental timing also inform flow targets and design constraints for pump-based solutions outlined in Domain I.

Building a Large-Scale, Multi-Modal Discovery Engine Anchored in Single Ventricle, and Inclusive of CHD

To fully characterize the origins of single ventricle heart disease and its related sequelae, we recommend building a large-scale, multi-modal discovery engine anchored in single ventricle and inclusive of other CHDs. Creating a comprehensive, high-resolution dataset of this scope is essential for generating the mechanistic evidence needed to understand disease origins and to catalyze the development of targeted, transformative treatments. While single ventricle-specific data provide the deepest mechanistic insight, pathways, variants, and developmental disruptions implicated in SV are likely to overlap with other forms of CHD. As the SV dataset matures and the core infrastructure is fully established, integrating related CHD cohorts into a shared platform will uncover cross-disease modifiers, strengthen rare variant detection, and accelerate discovery across diagnoses.

This discovery engine must link genetic variation to biological mechanisms, developmental pathways, and clinical phenotypes through high-throughput variant-to-function studies in disease-relevant model systems; prioritization of variants and regulatory elements; standardized functional assays across organoid, animal, and stem cell models; and integrated multi-omic readouts to define how genetic variation shapes cell fate, tissue architecture, and developmental timing during key stages of heart morphogenesis. It should also drive cross-disease comparative studies by systematically comparing SV with other CHD populations to identify shared and distinct mechanisms, detecting modifier genes that influence disease severity across diagnoses, and integrating environmental and biomechanical data to reveal common risk modifiers and resilience factors.

This effort requires coordination, infrastructure, and long-term investment at a scale that extends beyond what individual academic labs or institutions can sustainably assemble. At Additional Ventures, we are actively advancing this discovery engine by designing the architecture, supporting foundational datasets, and assembling the partnerships needed to build a platform that serves the entire community. We are committed to ensuring that data generation, standards, and access are designed for maximal utility rather than limited by theoretical siloes.

Through this coordinated approach, the field can accelerate the foundational discoveries that will ultimately enable curative strategies for single ventricle heart disease.

Single ventricle heart disease has long been defined by complexity, uncertainty, and compromise. Yet the last five years have demonstrated that this complexity is not an immovable barrier, it is a system we can increasingly understand, measure, and reshape. With new tools in biology, engineering, data science, and clinical modeling, the field is entering a moment when curative strategies are no longer aspirational: they are visible, buildable, and within reach.

This 2026 Roadmap outlines a future in which we move beyond managing decline and work instead to restore what is missing, stabilize what is vulnerable, and prevent the cascade of complications that have too often dictated a patient's life trajectory. The Repair strategy of adding back a pump and addressing sequelae, is an integrated framework that aligns scientific opportunity with clinical need. It reflects a fundamental truth that progress will emerge from understanding the whole system — not any single symptom, organ, or technology.

Realizing this future requires more than scientific insight. It requires coordinated infrastructure, intentional design, and a commitment to building what does not yet exist. That is the role Additional Ventures has chosen to take on. We are investing in interoperable data systems, enabling platforms, large-scale mechanistic discovery, and translational pathways that individual laboratories or institutions cannot assemble alone. Our work is to create the conditions under which curative solutions become possible, and then inevitable.

But no single organization can achieve this transformation in isolation. The discovery engine we are building, the pump technologies we are advancing, and the sequelae-focused interventions we champion will only reach their full potential through deep partnership across academia, clinical centers, engineering disciplines, industry, and philanthropy. A future with curative options for single ventricle patients will be built by many hands, aligned around shared outcomes and a shared belief that better is possible.

We stand at a pivotal moment. The tools are emerging, the insights are converging, and the path ahead, while challenging, is clearer than ever. Together, we can replace intuition with insight, fragmentation with infrastructure, and palliation with true physiological restoration. The work before us is ambitious, but its purpose is profound: to change what is possible for every person born with a single ventricle heart.

We invite you to join us in shaping this future.

Redefining the Future for Single Ventricle Patients

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Additional Ventures is grateful to the many investigators and collaborators across the single ventricle research community who generously shared microscopy and scientific images to bring this roadmap to life.

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