

Roadmap to Solving Single Ventricle Heart Disease

Additional Ventures

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Single ventricle (SV) heart disease care is at a pivotal moment. Enormous progress has been observed over the past half century – rerouting pathways for circulation, radically improving survival. However, much more is needed.

It is time to envision the next phase of SV care, one that is rooted in a fundamental understanding of both etiology and risk, built to overcome the complications and comorbidities that disrupt patient’s quality and duration of life, and focused on providing alternative solutions that deliver a functional rather than palliative solution. Achieving such a lofty goal will require collaboration not just at the scientific or clinical level, but rather, scientists, clinicians, engineers, patients, families, and funders must align themselves along with a living roadmap to solve this disease.

After recognizing the need for such a roadmap, a group of diverse investigators, clinicians, funders, and regulators met regularly over multiple months with the primary focus of developing targeted research programs to overcome the most pressing challenges in the SV field for three specific focus areas:

- Understanding the underlying etiology of SV heart disease,
- Managing and overcoming complications and comorbidities associated with SV heart disease and the Fontan circulation, and
- Developing functional cures for SV patients, including those living with the Fontan circulation.

After much discussion and debate, each team presented targeted research programs at a virtual workshop to a larger audience. Each program addressed key knowledge gaps in the group’s focus area through specific plans that included both the broad and directed research avenues needed to solve these gaps, that also defined the infrastructure, timescale, and capital required to implement the program. Finally, the findings were examined, synthesized, and restructured to incorporate the outputs of the workshop and preceding conversations and research. The result was the emergence of five key areas the field must address to understand and overcome single ventricle:

- I. Immature data and analytics infrastructure;
- II. Poor understanding of disease etiology, risk, and prevention;
- III. Limited focus on the underlying biology of outcomes;
- IV. Suboptimal ability to address clinical sequelae in patients, today; and
- V. Treatments are palliative, not curative.

From this analysis, the resulting roadmap was crafted, representing a harmonization of the individual teams’ efforts and outputs, and is intended to outline concrete recommendations to accelerate progress in a collaborative, team-driven approach over the next decade. The following recommendations are approved for release by the participants of the workshop, intended to be a launching point to serve as a living document that will be revisited and refined as scientific and clinical understanding evolves, and as progress is made.

TABLE OF CONTENTS

ROADMAP TO SOLVING SINGLE VENTRICLE HEART DISEASE 0

SINGLE VENTRICLE HEART DISEASE: AN OVERVIEW 3

ROADMAP DEVELOPMENT 5

OVERVIEW OF CRITICAL SCIENTIFIC AREAS 6

I. IMMATURE DATA AND ANALYTICS INFRASTRUCTURE 6

II. POOR UNDERSTANDING OF DISEASE ETIOLOGY, RISK, AND PREVENTION 6

III. LIMITED FOCUS ON THE UNDERLYING BIOLOGY OF OUTCOMES 6

IV. SUBOPTIMAL ABILITY TO ADDRESS CLINICAL SEQUELAE IN PATIENTS TODAY 7

V. TREATMENTS ARE PALLIATIVE, NOT CURATIVE 7

OVERVIEW OF FIELDWIDE RECOMMENDATIONS 8

I. LAY THE FOUNDATION: DEVELOP A COMMUNITY RESOURCE 9

II. UNDERSTAND THE ORIGINS OF SV DISEASE 10

III. DEFINE BIOLOGICAL MECHANISMS OF OUTCOMES 11

IV. EFFECTIVELY PREDICT, PREVENT, & ADDRESS CLINICAL SEQUELAE 12

V. FOCUS ON FUNCTIONAL CURES, NOT PALLIATIVE APPROACHES 13

APPENDIX - COLLABORATORS & PARTICIPANTS 14

Single Ventricle Heart Disease: An Overview

In human hearts, four distinct chambers form during development: two atria and two ventricles. However, in some individuals, one ventricle does not form properly and is either smaller, underdeveloped, or is missing a valve. Such conditions are referred to as single ventricle (SV) heart defects, which encompass a spectrum of diagnoses including, but not limited to:

- Hypoplastic Left Heart Syndrome
- Tricuspid Atresia
- Double Inlet Left Ventricle
- Double Outlet Right Ventricle
- Single Left Ventricle
- Pulmonary Atresia with Intact Ventricular Septum
- Unbalanced Atrioventricular Canal

Despite research efforts, little is known about the underlying etiology of SV heart disease, although mounting evidence suggests that the basis is multi-factorial and is comprised of genetic, epigenetic, and/or environmental contributions. Studies have demonstrated that SV is a genetically complex disease that is heterogeneous in both etiology and in presentation. Additionally, extra-genetic factors, such as environment and epigenetic patterning, are also emerging as important factors for disease risk, progression, and outcomes. However, beyond prenatal diagnosis from routine screening, nothing yet can be done to alter the course of disease *in utero* or inform outcomes.

Clinically, the path for such patients has changed dramatically, as fifty years ago, a diagnosis of SV was considered universally fatal. After a series of surgical innovations were introduced into practice, the survival and health outcomes for SV patients were drastically improved. In current practice, a child born with SV typically undergoes two or three, staged surgical procedures typically, beginning with a Norwood procedure or shunt, followed by the Glenn procedure, and finally, ending with the Fontan procedure. While the specific surgical path is dependent on the diagnosis and physiology of the child, the overall goal is to create a new parallel flow pattern that compensates for the dysfunctional ventricle, allowing all venous blood returning from the body to go directly to the lungs for oxygenation. As such, clinical innovation has rerouted a pathway for survival in these patients.

Indeed, the survival rate post-Fontan surgery is rising, with excellent transplantation-free outcomes in current surgical era (5-year survival of 95%, 10-year survival of 91% and an estimated 30-year survival of 85%). Yet, these survival milestones are undermined by significant comorbidities and complications in individuals that have undergone the Fontan procedure (known as having a “Fontan circulation”), leading to premature morbidity and mortality, and a poor quality of life.

Damaged ventricles are layered on top of intrinsic abnormalities in other organs that have an increased likelihood of failure, at least partly attributed to the altered hemodynamics of the cardiovascular system as a consequence of the Fontan circulation. These issues often worsen over time, reducing both the quality and duration of life – a condition sometimes referred to as “Fontan circulatory syndrome”. Complications include, but are not limited to:

- Myocardial dysfunction
- Pulmonary vascular dysfunction
- Arrhythmias
- Bleeding and stroke
- AV valve regurgitation and dysfunction
- Protein-losing enteropathy
- Plastic bronchitis
- Lymphatic obstruction
- Liver disease
- Renal failure
- Neurodevelopmental defects
- Psycho-social challenges

While studies to understand the drivers of these complications are underway, they are limited in scope and scale, reducing the ability to draw relevant conclusions about the causes, treatments, and prevention strategies. To some degree, many of the current knowledge gaps are rooted in an incomplete understanding of the disease etiology and epidemiology, but the challenges are further compounded by a lack of clinical tools, including a suboptimal detection timeline, limited diagnostics, a lack of treatment options, and an insufficient interdisciplinary research lens. These solvable challenges preclude the robust and timely identification of risk factors, hinder the potential to stratify this complex population, and limit progress on the development of improvements for disease management, treatment, and therapeutic development.

Currently, heart transplantation is the closest option to a functional cure; however, this procedure faces tremendous challenges that compromise the overall quality and duration of life. A combination of extensive organ waiting list time, limited donor supply, immune complications, organ rejection, and mounting complications and comorbidities limit the feasibility of heart transplant as a curative approach. For example, the overall availability of donor hearts is limited, causing the process of donor-recipient matching to be

highly selective. This selectivity is further exacerbated by the fact that many Fontan patients are referred too late and are thus ineligible for a transplant. While clinicians are working on ways to avoid transplant for SV patients, the ability to better prognosticate and identify an SV patient with impending failure before it is too late is another important avenue to explore. Therefore, both alternative methodologies and improvements to the referral process are critically important.

In light of these critical issues, researchers are investigating a variety of novel approaches to functionally cure patients prior to palliation or after the Fontan procedure. To do so, researchers are exploring regenerative medicine solutions to heal or repair an injured heart, mechanical and biological devices to serve as a conduit for flow, and tissue engineering approaches to create *de novo* tissues, ventricles, and even entire organs. If researchers are successful, SV could become a curable disease where patients can expect a normal duration and quality of life. This will only be possible through advancements in multiple discrete fields and improved coordination of current and future research efforts.

Capitalizing on the momentum in the SV field and adjacent genomics, engineering, and regenerative medicine fields through strategic investment in discovery science, infrastructure, and research tools is essential for continued progress. Fundamental questions about the contributing molecular and cellular mechanisms, initiating factors and events, genetic risk, conduits for improved flow, *de novo* organ development, lymphatic and end-organ intervention, and much more remain.

This scientific and clinical roadmap aims to define an approach to address the most pressing challenges in the SV field – challenges that are only overcome by supporting meaningful, multidisciplinary

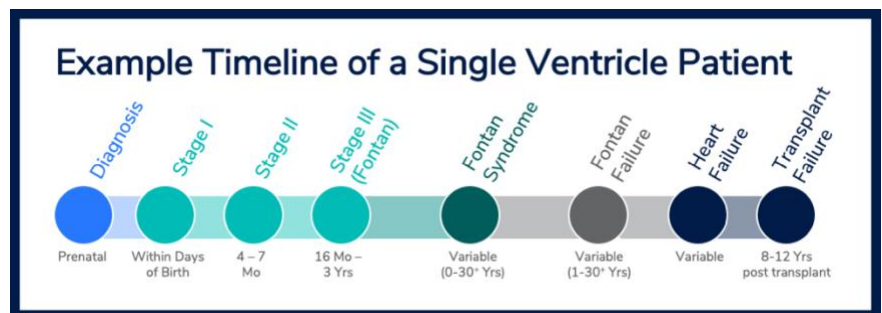


Figure 1. While not all SV patients follow the above trajectory, many follow a similar timeline. To begin, patients experience three staged palliative surgeries that occur within the first several years of life to create a new systemic circulatory flow. However, patients often experience “Fontan Syndrome,” which can compound and result in Fontan Failure and ultimately, Heart Failure. If transplanted successfully, a subset will experience transplant failure over the next decade (although outcomes are variable). The individual order of the nodes of this timeline are not fixed, as for example, some patients may never reach a Fontan procedure and go immediately to transplant and others may never reach Fontan failure.

collaboration and driving intense focus to selected research themes and hasten discovery. Thus, we hope that this roadmap serves as a unifying force with the research, clinical, and funding communities to accelerate progress and yield high-impact results.

Roadmap Development

To understand the most pressing challenges and barriers to progress within the single ventricle heart defect community, we interviewed over 100 key opinion leaders, conducted a review of the published literature, and attended relevant conferences. The leaders, literature, and attended conferences represent a broad diversity of disciplines (including scientific, engineering, clinical, and regulatory) and provided a holistic lens to understand both the scope of the problem and potential avenues of investment. In synthesizing our findings, we organized our exploration around three key areas (more information on each can be found in [Appendix 1-3](#)): 1) understanding the underlying etiology of SV heart disease, 2) managing and overcoming complications and comorbidities associated with SV heart disease and the Fontan circulation, and 3) developing functional cures for SV patients, including those living with the Fontan circulation.

We then formed small working groups, one for each focus area, which were comprised of 12-13 investigators across disciplines, and tasked each with designing a holistic targeted research program to address key knowledge and clinical care gaps in their focus area. The programs yielded a broad overview of the projects necessary to close the identified gaps, including the experiments and experimental tools, the rationale behind the projects, and the timescale, and budget required to complete each component. Groups also demonstrated how their program was differentiated from existing efforts and the unique value that would be added to the field.

In the subsequent weeks, the team at Additional Ventures worked to further examine and refine the major focus areas and to consolidate the three individual targeted research programs into a cohesive, central plan. Interestingly, a fourth and fifth focus area emerged as fundamental to the goal of understanding and overcoming SV (Figure 2). Below are the resulting five focus areas:

- I. Immature data and analytics infrastructure
- II. Poor understanding of disease etiology, risk, and prevention
- III. Limited focus on the underlying biology of outcomes
- IV. Suboptimal ability to address clinical sequelae in patients, today
- V. Treatments are palliative, not curative



Figure 2. Brief depiction of the workflow to generate the scientific and clinical roadmap for SV.

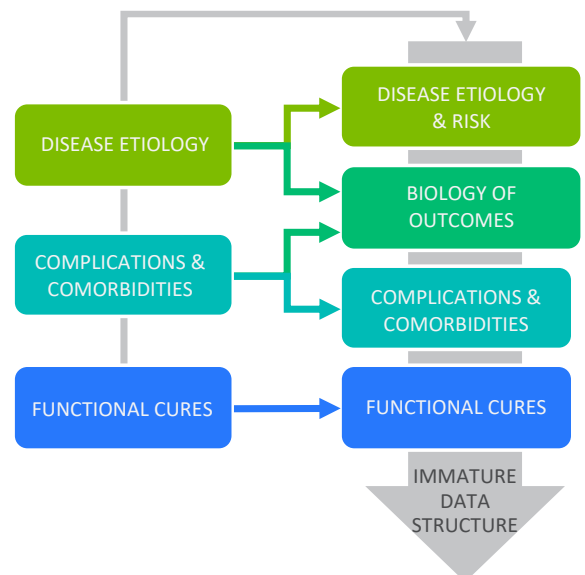


Figure 3. Through the workshop and subsequent analyses, the initial three focus areas were expanded to five. Four centered on specific biological or clinical knowledge gaps, while the fifth emerged as a deep, central infrastructure need that lays the foundation for the critical path to move forward.

In the following pages, we communicate the **five significant knowledge and infrastructure gaps** that are hindering progress within the SV field and provide a strategic roadmap that defines the broad and directed research avenues needed to solve these gaps. The comprehensive, multidisciplinary programmatic solutions are intended to align funder investments and highlight the infrastructure, timescale, and resources required to implement the program. We hope that such a roadmap will galvanize coordination of SV research and clinical care support globally.

Overview of Critical Scientific Areas

Using a multidisciplinary lens and a systems-based approach, the key challenges were identified that hinder progress in improving and optimizing outcomes for patients with SV heart defects. As previously discussed, five areas emerged from this analysis, in which investment is required to move the needle:

I. IMMATURE DATA AND ANALYTICS INFRASTRUCTURE

Paramount for much of the research described in subsequent sections is the prerequisite for creation of a sustainable data infrastructure and analytics center focused on SV patients. While organic, data-driven programs have emerged over time, this has led to a number of disparate databases, biobanks, and registries that are often not interoperable, complete, easy to access, or self-sustaining. In order to address the needs of the community and maximize the impact that data can have to move the field forward, the following issues must be addressed:

- Limited data sharing among different datasets has led to piecemeal information and requires clinicians to input data multiple times.
- Shared, strong infrastructure is lacking, limiting interoperability, accessibility, and findability.
- Resources, both human capital and funding, to support the full execution of databases and registries are limited.
- Data tools and analytics have not kept pace with the needs of the field.

Researchers and clinicians alike have advocated for a central rallying point for the field, aligning the scientific direction, clinical education, and resources. To do so, a common infrastructure for data sharing, clinical testing, and research is needed.

II. POOR UNDERSTANDING OF DISEASE ETIOLOGY, RISK, AND PREVENTION

The genetic basis of SV heart disease is mostly unknown, with the molecular mechanisms underlying SV heart defects equally unexplored. Furthermore, there are no data on non-genetic factors impacting the etiology of SV heart defects, including the role of epigenetic, hemodynamic, and environmental (e.g. placental, maternal exercise) factors. Such a gap limits the development of predictive measures of disease, risk stratification tools, preventative non-therapeutic strategies, and therapeutic interventions to correct developmental abnormalities.

III. LIMITED FOCUS ON THE UNDERLYING BIOLOGY OF OUTCOMES

Due to major surgical advances, vast improvements in survival past the age of five have been observed. One caveat is that the majority of treated patients experience a number of complications and comorbidities that can severely impact quality and duration of life. The field is still early in understanding what drives the onset of each complication and comorbidity. Thus, a deeper

exploration of the biological and environmental mechanisms of the correlates to outcomes are required to mitigate risk while also providing a personalized approach to each patient's journey.

IV. SUBOPTIMAL ABILITY TO ADDRESS CLINICAL SEQUELAE IN PATIENTS TODAY

It is well appreciated that SV patients experience a number of complications and comorbidities across a broad range of end-organ systems. Currently, no predictive measures (such as biomarkers) exist to map the trajectory of heart and other organ system function, nor are there preventative treatments to modify or mitigate outcomes. Furthermore, treatment options are limited, and novel interventions are underexplored. While efforts to understand and address the clinical sequelae are underway, they are limited in scope and scale, reducing the ability to draw relevant conclusions about potential treatment effectiveness and intervention.

V. TREATMENTS ARE PALLIATIVE, NOT CURATIVE

The current standard of care of SV is palliative, not curative, as the passive flow caused by the Fontan procedure is thought to lead to long-term hemodynamic issues and palliation can fail over time. Additionally, other unknown issues may contribute to the high number of post-Fontan related deaths and heart failure cases leading to transplant. Unfortunately, the standard of care to treat a failing Fontan is often off-label, as clinicians primarily utilize adult-approved devices or a heart transplant; however, both techniques have challenges. As such, the field is shifting from a rescue focus to one of rebuilding the current paradigm, but this shift requires a concerted, multi-disciplinary effort guided by basic scientists, engineers, and clinicians, and supported by funders.

The challenges described above may seem insurmountable, with the science of today appearing deeply complex. Indeed, it is critical to recognize that no single scientist or lab can answer the multifaceted questions that exist; meaningful science and clinical care can no longer be siloed or performed in a vacuum. The overarching complexity is well demonstrated by the SV paradigm, a disease that requires not only a diverse set of expertise across the basic, translational, and engineering sciences, but also a breadth of knowledge across medical fields.

In the remaining sections, we highlight a series of recommendations that we believe can move the needle for SV understanding and care, which cross the boundaries of discipline and field, necessitating great minds across the scientific and funding communities to come together to tackle a common set of goals and coalesce as true partners to fund, manage, and support efforts moving forward.

Overview of Fieldwide Recommendations

From the working groups’ comprehensive targeted research programs and the subsequent analyses post-meeting, we developed the following scientific, clinical, and infrastructure recommendations for the entire SV field to promote aligned, collaborative investment.

Our overarching recommendations are divided amongst the five key critical scientific areas into four specific areas of strategic investment (Figure 3), which are represented in each individual square. While lofty and difficult goals to achieve, we believe that collaborative, concerted investment in these areas will move us towards a future state that is rooted in a deep understanding of the etiology of disease, risk, and outcomes, results in the ability to address all complications and comorbidities, and realizes the introduction of true functional cures, not palliative options.

CURRENT STATE	AREAS OF STRATEGIC INVESTMENT				FUTURE STATE
Immature Data & Analytics Infrastructure	Large-Scale Sequencing	Longitudinal Clinical & Imaging Data	Comprehensive Biobank	Harmonized Data & Analytics Platform	Foundational Clinical & Research Community Resource
Poor Understanding of SV Disease Etiology	Deep Phenotype-Genotype	Model Organisms	Non-Genetic & Modifiable Risk Factors	Normal Cardiac Development	Understand the Origins of SV Disease & Risk
Limited Focus on the Underlying Biology of Outcomes	Outcome Origins	Substrate-Outcome Relationship	Predictive Models	Early Detection	Defined Biological Mechanisms of Outcomes
Suboptimal Ability to Address Clinical Sequelae in Patients, Today	End-Organ Trajectory Mapping & Biomarkers	Personalized Medicine Approaches	Alternative Interventions	Learning Networks	Effectively Predict, Prevent, and Address Clinical Sequelae
Current Treatments are Palliative, not Curative	Enabling Technologies	Standardization & Scale	Cross-Disciplinary Teams	Bionic, Regenerative, & Transplant Approaches	Introduction of Curative Solutions

Figure 3. Through our work with the community, five key areas emerged as important to moving the needle for SV disease research and clinical care. To transition from the current state to the future state, collaborative, concerted investments must be made. Each investment is listed in the middle four boxes. While not every funder will be interested in every investment, we hope that the aligned efforts across the funding and research community will move us towards the future state of SV, where we understand the disease, outcomes, and sequelae deeply, and can provide true functional cures.

In the subsequent sections, we further define and explore each of the twenty areas of strategic investment – providing a description of each and in future callouts, we provide potential specific projects and programs, and with the scope and scale required to bring about marked progress. Where possible, we also highlight avenues of investment that are currently “ready-to-go,” and those that may require the development of foundational tools or enabling technologies. Finally, we outline some of the specific mechanisms of funding such endeavors, highlighting specific modalities. In providing these recommendations and the funding mechanisms, we aim to create a resource to the community that simplifies the path forward towards overcoming SV disease.

I. LAY THE FOUNDATION: DEVELOP A COMMUNITY RESOURCE

CURRENT STATE	AREAS OF STRATEGIC INVESTMENT				FUTURE STATE
Immature Data & Analytics Infrastructure	Large-Scale Sequencing	Longitudinal Clinical & Imaging Data	Comprehensive Biobank	Harmonized Data & Analytics Platform	Foundational Clinical & Research Community Resource

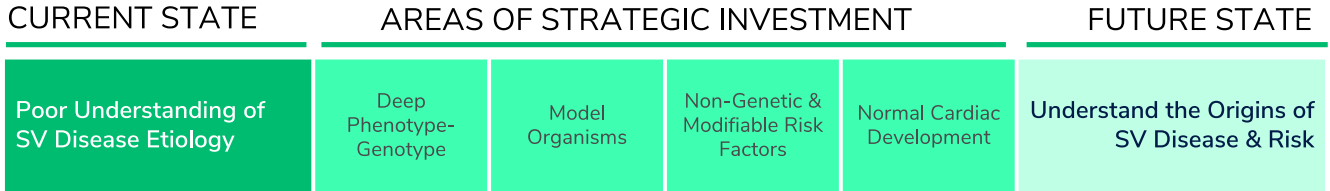
The understanding of the underlying causes of SV disease is in its infancy, and their relationship to clinical outcomes and treatment guidance predominantly unexplored. Thus, to fully uncover the factors needed to understand and effectively treat single ventricle disease, we recommend the *development of a large and comprehensive set of correlated genetics data, clinical records, and biospecimens that will be made available to the entire scientific and medical community.*

The following resources should be prioritized to accomplish such a goal:

- **Recommendation I:** Create a fully annotated whole genome sequencing (including epigenetics) library of 5,000+ SV patients to act as both an open data resource and platform for variant discovery and analytics for a diverse set of users, while enabling federated analyses in compliance with all national regulations.
- **Recommendation II:** Develop an SV longitudinal patient registry that includes comprehensive, curated clinical data that incorporates a detailed history, deep phenotyping, imaging, and long-term follow up, which can be linked to the genetic and epigenetic data. The resulting registry should incorporate data visualization tools for real-time and basic research analytics.
- **Recommendation III:** Build a diverse SV biorepository with both a variety of human tissue samples and cell lines at a range of developmental and clinical time points that is standardized in protocols and optimized for access to researchers and clinicians.
- **Recommendation IV:** Create an open-access data platform that unites the above efforts through a shared software infrastructure that allows diverse users to utilize a broad array of data repositories to allow for the generation of genotype-phenotype portals to readily access information about the relationship between genes and clinical phenotype. Such a resource should also provide data storage and data analytics tools, while enabling federated analyses in compliance with national regulations, IRB approvals, and data-use permissions.

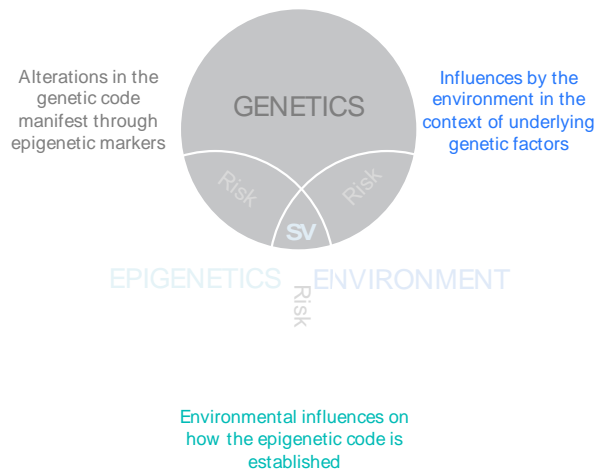
Success will require collaboration amongst funders, clinicians, scientists, patients and their communities, and existing registries. Such collaboration is the cornerstone of any effort to determine how best to design, align, and support the development of said resources in parallel. Likewise, the resulting platforms should be interoperable and allied.

II. UNDERSTAND THE ORIGINS OF SV DISEASE



The genetic basis of SV heart disease is mostly unknown, save for 2-3 rare mutations, and the molecular mechanisms underlying SV heart defects is similarly opaque. Furthermore, there are no data on non-genetic factors impacting the development of SV heart defects, such as the role of epigenetic, hemodynamic, and environmental (e.g. placental, maternal exercise) factors. Excitingly, advancements in technology have dramatically enhanced our capacity to understand the contribution of variants, regulatory elements, and alterations in chromatin structure to the expression of genes.

- Recommendation I:** Identify the genetic factors underlying SV in the context of deep phenotyping to develop a high-resolution map of SV-specific variants, including coding genes, regulatory elements, and chromatin structure, and evaluate the functional consequences of each variant.
- Recommendation II:** Develop animal and cellular models of SV disease to perform a systematic analysis that yields a comprehensive, time-resolved developmental map of the molecular, cellular, and physiological alterations across the heart and other organs.
- Recommendation III:** Explore non-genetic factors, in the context of deep phenotyping, that contribute to the presentation and penetrance of SV heart defects, including modifiable risk factors, biomechanical forces, and environmental influences, through a combination of epidemiological and genetics approaches and assess the impact of intervention in the development of disease from a genetic, epigenetic, and anatomical perspective.
- Recommendation IV:** Support ongoing efforts to define normal cardiac development at a time-resolved genetic, epigenetic, molecular, cellular, and physiological level to understand differences in SV patients that may provide insights into underlying disease mechanism and future therapies.



As expected, the line between sections of recommendations can overlap, as the requirements for fundamental knowledge are often aligned. Most of the above recommendations require building the foundational resource that is discussed in topic area I, specifically a large-scale patient registry with longitudinal clinical information to provide deep phenotyping that can then be linked with genomics and other ‘omics scale efforts. Such a resource, inclusive of both advanced data infrastructure and the clinical expertise needed to capture the relevant pathophysiology, is a prerequisite to identifying variants and ultimately to studying variant-to-function. However, elements of recommendation III can be implemented using existing epidemiological data sets, while Recommendation IV simply requires support and expansion of current efforts.

III. DEFINE BIOLOGICAL MECHANISMS OF OUTCOMES



While survival has dramatically increased, the majority of treated SV patients experience significant complications and comorbidities which can severely impact quality and duration of life, yet the field does not yet understand what drives the onset. Thus, a deeper exploration of the biological and environmental mechanisms that correlate to outcomes is necessary to mitigate risk while also providing a personalized approach to each patient’s journey.

- **Recommendation I-A:** Isolate the genetic, gene regulatory, and epigenetic factors that drive the onset or impact the trajectory of common complications and organ-specific dysfunction in SV disease through a series of exploratory *-omics* and variant-to-function assays, as well as in the patient population. Additionally, examine the factors that appear to lead to resiliency.
- **Recommendation I-B:** Develop appropriate model systems of the variants underlying clinical sequelae to create a comprehensive, time-resolved developmental map of the molecular, cellular, and physiological alterations across end-organs and the relationship to heart development and/or function.
- **Recommendation II:** Investigate how non-genetic factors, including alterations in flow, hypoxia, nutrition, and other post-natal exposures, interact with the underlying substrate to impact the development of complications and comorbidities that affect the heart and other end organs in the SV population.
- **Recommendation III:** Develop a predictive computational and clinical model that integrates factors that predict the onset of complications and comorbidities, and as well as those that promote resilience to map future trajectory and outcomes.
- **Recommendation IV:** Generate functional assays or diagnostics to systematically dissect SV disease-related clinical sequelae to act as early surrogate biomarkers of future heart and end-organ function to risk stratify patients and move towards proactive versus reactive medicine.

The recommendations provided here should create the foundational framework to progress towards predictive, personalized medicine approaches. While the first two aims will require large-scale and concerted efforts that could take a full decade to accomplish, the resulting information will be critical to the development and implementation of predictive models defining risk, outcomes, and therapeutic guidance, while also providing actionable mechanisms to amplify factors promoting resilience in the SV population.

IV. EFFECTIVELY PREDICT, PREVENT, & ADDRESS CLINICAL SEQUELAE

CURRENT STATE	AREAS OF STRATEGIC INVESTMENT				FUTURE STATE
Suboptimal Ability to Address Clinical Sequelae in Patients, Today	End-Organ Trajectory Mapping & Biomarkers	Personalized Medicine Approaches	Alternative Interventions	Learning Networks	Effectively Predict, Prevent, and Address Clinical Sequelae

Efforts to predict, prevent, and treat SV-related clinical sequelae are limited in scope and scale, reducing the ability to draw relevant conclusions about treatment and/or intervention timing, effectiveness, and outcomes. Additionally, no measures exist to map the trajectory of heart and other organ system function, nor are there preventative treatments to modify or mitigate outcomes. Furthermore, treatment options are limited, and novel interventions are underexplored.

- **Recommendation I-A:** Map the trajectory of major complications and comorbidities of the brain, heart, and other end organs, and their impact on health, health-related quality of life, and well-being through unified, standardized protocols and long-term data collection on SV patients.
- **Recommendation I-B:** Generate functional assays or diagnostics that act as surrogate biomarkers for current heart and end-organ function, with the ultimate goal of adopting personalized medicine approaches to optimize outcomes and practice proactive medicine.
- **Recommendation II:** Optimize trajectories of end-organ structure and function by utilizing collective genotype, phenotype, and early diagnostics/biomarker data to modify pathogenesis, mitigate risk factors, and develop novel interventions to prevent health or quality of life decline.
- **Recommendation III-A:** Develop etiology-based therapeutics and novel alternative interventions, such as diet, exercise, and lifestyle factors, and explore repurposing approved medications to address complications and comorbidities and prevent decline in functional and end-organ status.
- **Recommendation III-B:** Develop interventions to optimize expression of favorable outcomes, such as those observed in resilient populations, to promote enhanced health, health-related quality of life, and well-being.
- **Recommendation IV:** Accelerate implementation and dissemination of best practices, tools, and targeted interventions for clinicians, patients, and families through learning health networks.

Many of the recommendations provided throughout this document are aimed at bettering the lives of future cohorts of SV patients, but the aims of this particular series more directly impact the thousands of patients who currently are living with SV disease and/or the Fontan circulation. While addressing each of the above recommendations will take time, application to the clinic is expected to be more near-term.

V. FOCUS ON FUNCTIONAL CURES, NOT PALLIATIVE APPROACHES

CURRENT STATE	AREAS OF STRATEGIC INVESTMENT				FUTURE STATE
Current Treatments are Palliative, not Curative	Enabling Technologies	Standardization & Scale	Cross-Disciplinary Teams	Bionic, Regenerative, & Transplant Approaches	Introduction of Curative Solutions

The current treatment of SV is palliative, not curative. While further improvements in the approach to Fontan palliation are possible, abnormal hemodynamics are an unavoidable consequence of this circulation and there is little reason to think that normalization of life expectancy and long-term quality of life can be achieved within the current Fontan paradigm. Further, in the absence of disease specific evidence-based therapies, clinicians primarily repurpose adult-approved devices or heart transplant to treat Fontan deterioration; at least partially successful, though both approaches have substantial limitations this is often. Recent advances in immunology, tissue engineering, and stem cell biology indicate the time is ripe for novel approaches to this decades-old problem.

- **Recommendation I:** Invest in the development of enabling technologies to generate and test novel functional interventions, such as large and small transgenic models, large animal models of Fontan circulation, computational models of cardiac development and blood flow, and non-invasive imaging and fetal delivery systems.
- **Recommendation II:** Invest in the standardization and scaling of stem cell production, including protocol harmonization, bioreactor development, biomaterial generation, and cost reduction strategies, for use in regenerative medicine, tissue engineering, and 3D printing approaches.
- **Recommendation III:** Create interdisciplinary physician, scientist, and modeling teams to create clinically informed, milestone-driven projects that enable the advancement of approaches to manufacture cardiac tissues, such as contractile patches, conduits, valves, ventricles, and hearts.
- **Recommendation IV-A:** Investigate novel “bionic” approaches to avoid or overcome the Fontan circulation challenges and restore adequate power to the circulatory system through 1) exploration into technologies to salvage or grow the hypoplastic ventricle or 2) the creation of an extracardiac conduit or implant to harness systemic circulatory power.
- **Recommendation IV-B:** Explore for whether the regenerative capacity of the fetal environment can be leveraged to enable repair and/or reversal of single ventricle anomalies *in utero*.
- **Recommendation IV-C:** Enhance and expand efforts to develop or label ventricular assist devices for use in single ventricle patients, and to develop artificial hearts for this population.
- **Recommendation IV-D:** Develop and refine strategies to improve heart transplantation, including improving identification of patients earlier in their course of failure, improving organ preservation of donor hearts, limiting sensitization of patients, and reducing the immune response to transplanted hearts, to increase donor quality and availability and to extend the lifetime and outcomes of a transplanted heart to become a lasting cure for single ventricle.

If researchers are successful in developing such cures, SV could become a curable disease where patients can expect a normal duration and quality of life. Concerted efforts to solve these issues in an efficient and effective manner are critical and require alignment and collaboration from scientists, clinicians, engineers and funders.

Appendix. Collaborators & Participants

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