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Congenital diaphragmatic hernia: current repair strategies and future directions in treatment

Abstract

Congenital diaphragmatic hernia (CDH) is a serious and life-threatening birth defect caused by malformation of the diaphragm, allowing abdominal organs to herniate into the thoracic cavity and compress the lungs. While minor cases can be corrected surgically, large and complex defects require synthetic or biological patch repair. Synthetic materials like expanded polytetrafluoroethylene (ePTFE) offer high mechanical strength but suffer from poor tissue integration and increased infection risk. Biological scaffolds offer biocompatibility and potential for remodeling but often lack mechanical durability. This paper reviews the current landscape of CDH treatment, including patch materials in clinical use, market trends, and emerging innovations in biomaterials that seek to overcome existing limitations.

Keywords: congenital diaphragmatic hernia, patch repair, tissue engineering, biomaterials

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Abbreviations: CDH, congenital diaphragmatic hernia; ePTFE, expanded polytetrafluoroethylene; ECM, extracellular matrix; SIS, small intestinal submucosa; ATP, adenosine triphosphate; PHMP, posthepatic mesenchymal plate; FETO, fetoscopic endoluminal tracheal occlusion; ECMO, extracorporeal membrane oxygenation; NICU, neonatal intensive care unit; hAFMSCs, human amniotic fluid-derived multipotent stromal cells

Introduction

Hernia is a condition in which an internal organ protrudes through a muscular wall, such as the abdominal wall, the inguinal canal, or the diaphragm.[1] Congenital diaphragmatic hernia is a type of hernia characterized by the incomplete formation of the diaphragm, allowing the abdominal organs to herniate into the chest cavity and compress the lungs (Figure 1).[2] In the United States, about 1 in 2,500 babies are born with congenital diaphragmatic hernia.[2] Despite improvements to CDH treatment and prognosis, CDH is associated with significant morbidity and mortality, with at least 25% of affected infants dying during the neonatal period.[3] Although mild cases of CDH can be repaired using sutures, larger and more complex defects require a patch to cover the defect to restore structural integrity and the barrier between the abdominal and thoracic cavities, though some studies show that patch treatment is associated with poorer long-term outcomes including hernia recurrence, lung complications, and small bowel obstruction.[4,5]

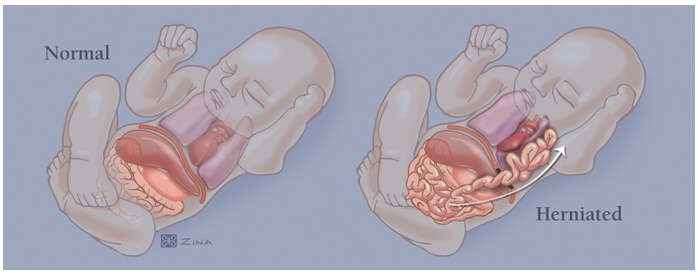

Figure 1 Diagram of congenital diaphragmatic hernia.[5]

The figure shows a diagram of two infants, one with a typical and healthy arrangement of organs and one in which the diaphragm is herniated, causing he small intestine to appear in the chest and compress the left lung. Image from UC Davis Health.[5]

These patches are most commonly made from expanded polytetrafluoroethylene (ePTFE), a synthetic material used for its mechanical strength and minimal tissue reactivity.[6,7] However, synthetic patches commonly used in CDH treatment cannot degrade or integrate with the host tissue to form functional muscle, leading to increased infection risks and long-term complications as the infant grows, particularly in the absence of tension-free repair techniques.[8–10] As a result, biological patches made of decellularized extracellular matrix (ECM) or porcine small intestinal submucosa (SIS) have been explored as alternatives.[11] However, there is a lack of long-term data for decellularized ECM patches, and SIS patches are associated with high recurrence rates due to an inability to withstand the mechanical forces of the diaphragm, particularly as a result of reduced scarring and fast resorption rates.[11] Muscle flap repair, in which donor tissue is excised from neighboring skeletal muscle and inverted to cover the defect, has also been explored, but donor site weakness and abdominal wall bulges are common.[12]

We report here an overview of current treatments in congenital diaphragmatic hernia, including the market size, existing products, preclinical research, and clinical trials. We consider the trade-offs between mechanical durability and tissue integration in biological and synthetic patch materials and discuss emerging biomaterial innovations that aim to address the shortcomings of existing repair strategies.

Healthy physiology

Current challenges in CDH repair stem from the difficulty of replicating the complex structure and function of healthy skeletal muscle in the diaphragm.[11] Skeletal muscle is hierarchically organized, and this complexity enables the muscle to perform repetitive, coordinated contractions while maintaining strength and flexibility across a range of mechanical demands.[13] As a result, skeletal muscle plays a critical role in voluntary movement, posture maintenance, and respiratory function.[13]

The functional contractile unit of skeletal muscle is the sarcomere, which contains myosin and actin filaments that can contract using molecular energy provided by adenosine triphosphate (ATP).[13] These sarcomeres are linked end-to-end to create a long fiber, known as a myofibril, which are surrounded by mitochondria that create ATP.[13] Many of these myofibrils are wrapped in the sarcolemma, a type of

plasma membrane, within one myocyte, also known as a muscle fiber (Figure 2).[13] Each skeletal muscle is typically composed of hundreds to thousands of muscle fibers that are enclosed by connective tissue, depending on the size of the muscle in the body.[14]

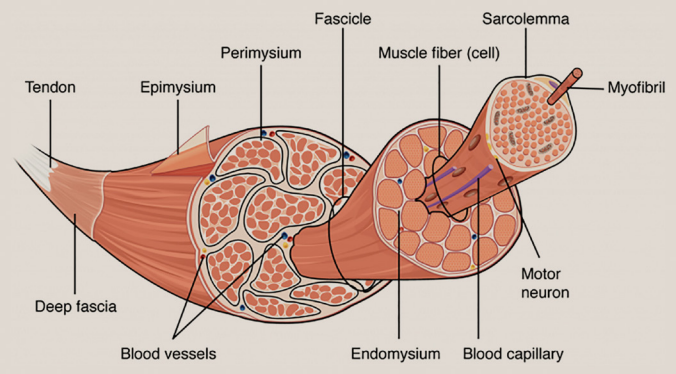

Figure 2 Structure of skeletal muscle.[13]

The figure shows the hierarchical structure of muscle, from myofibril to muscle fiber to fascicle within the muscle, as well as key membranes and the connection to the tendon.

The diaphragm is a large skeletal muscle located at the base of the lungs and is the primary muscle used for breathing. [15] When the diaphragm contracts, it pulls downward and flattens, creating a negative pressure gradient that pulls air into the lungs, as seen in Figure 3.[15] When the diaphragm relaxes, it returns to a curved structure, compressing the lungs upwards and creates a positive pressure gradient to expel the air.[15]

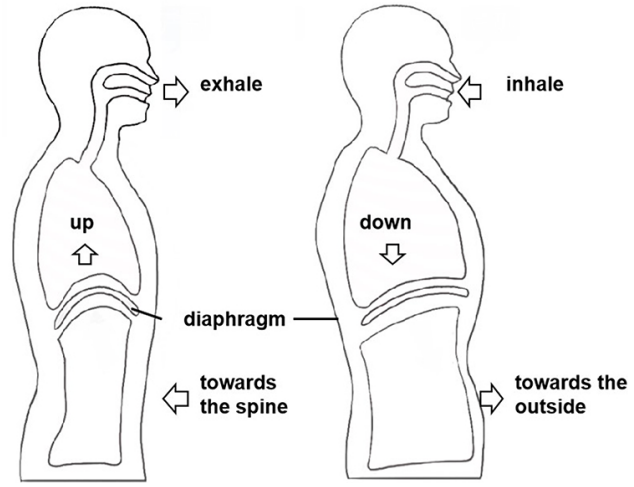

Figure 3 Diaphragm changes during normal breathing.[16]

The figure shows a schematic of how the diaphragm changes during breathing, from cured upwards during exhalation to flattened during inhalation.

Although skeletal muscles like the diaphragm serve crucial physiological functions for movement, they also serve as barriers for internal organs.[1] When these barriers are not maintained, hernia occurs, in which an internal organ protrudes through the muscular wall.[16]

CDH etiology

While other types of hernia—such as ventral, inguinal, and umbilical hernias—occur due to muscle weakness and increased strain in instances such as heavy lifting, chronic coughing, or pregnancy, congenital diaphragmatic hernia (CDH) is fundamentally distinct.[17] CDH is a developmental defect that arises during embryogenesis, reflecting a failure in the normal formation of the diaphragm rather than mechanical failure of the tissue.[3]

It was previously thought that CDH was the result of improper fusion of diaphragm muscle components; more recent evidence suggests that the defect arises from disrupted formation of the posthepatic mesenchymal plate (PHMP), allowing the liver to herniate prematurely into the thoracic cavity, thereby physically impeding the growth and expansion of the developing lungs (Figure 1).[18]

The etiology of CDH has been linked to genetic, environmental, and metabolic causes.[3] A leading theory is the Retinoid Hypothesis, which posits that impaired retinoic acid signaling—a pathway dependent on vitamin A metabolism—plays a central role in diaphragmatic malformations.[18–21] Retinoic acid is known to regulate gene expression during early development, and disruptions in this pathway have been shown to recapitulate CDH-like phenotypes in animal models.[3] However, the exact mechanisms by which altered retinoid signaling lead to PHMP disruption and diaphragmatic defects remain under investigation.[18–21]

Genetic causes of CDH have also been studied, and both chromosomal abnormalities and single-gene mutations have been associated with an increased risk of CDH. [22,23] Mutations in GATA4 and LRP2, as well as syndrome disorders such as Pallister-Killian syndrome, 8p23.1 deletion syndrome, and Fryns syndrome, have been implicated as potential causes of CDH. [22,23] Furthermore, exposure to teratogenic agents like mycophenolate mofetil, allopurinol, and lithium during pregnancy has also been reported to be associated with CDH.[24]

Overall, CDH is a complex congenital disorder with diverse and multifactorial origins. Understanding the molecular and genetic mechanisms behind CDH, as well as diaphragm formation as a whole, is a crucial area of future research for developing better CDH treatments and improving clinical outcomes.

CDH patch market size and growth

The global incidence of congenital diaphragmatic hernia appears to be increasing, with recent population-based studies estimating a prevalence as high as 2.6 per 10,000 live births worldwide but up to 7.2 per 10,000 live births in some regions, depending on registry type and diagnostic methodology.[25] While this apparent rise is partially attributable to improvements in prenatal imaging and diagnostic accuracy,[26] other contributing factors include shifts in maternal demographics. Notably, an increasing average maternal age at childbirth—an independent risk factor for congenital anomalies—has been linked to higher rates of CDH and other developmental disorders.[27,28] As a result, the prevalence of CDH is rising in middle-income countries such as China and Brazil, largely due to improved prenatal diagnostic capabilities,[26,29] but also higher-income countries like the United States, where the increase can be linked to rising maternal age and higher rates of substance use, which can increase likelihood of CDH.[27,30,31]

These shifts in CDH occurrence translate into market changes for CDH treatments, in particular diaphragmatic patches; although there is not publicly available data on the exact market size and growth for CDH patches specifically, CDH patch treatments contribute to larger markets including the cardiovascular and soft tissue patch market and the hernia repair devices market.[6,32]

The global cardiovascular and soft tissue patch market was valued at $3.8 billion in 2021, with the U.S. market alone valued at $1.2

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billion dollars (Figure 4).[6] The market is expected to increase steadily with a compound annual growth rate of 8.4% from 2022 to 2030 and is primarily driven by the increased prevalence of both congenital heart disease and all types of hernias, including CDH.[6] Soft tissue patches specifically, which are dominated by hernial patches, accounted for the largest revenue share of 42.0% of the total cardiovascular and soft tissue patch market in 2021.[6]

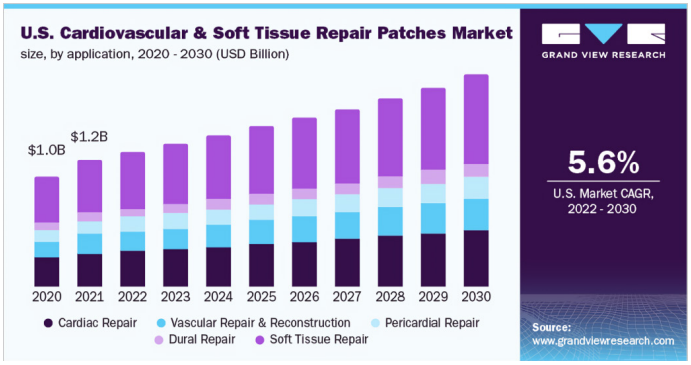

Figure 4 Expected growth of U.S. Cardiovascular and soft tissue repair patches market from 2020 to 2030.[6]

The figure shows the expected growth of the of U.S. cardiovascular and soft tissue repair patches market from 2020 to 2030, of which soft tissue repair, including hernia patches, make up the highest percentage. The image shows a total market worth of $1.2 billion in 2021, with a CAGR of 5.6%.

Of patch materials currently on the market, ePTFE accounts for 61.4% of patch products available, with tissue engineering and biomaterial scaffolds making up less than a third of the market (Figure 5).[6] However, tissue engineering and biological patches are expected to be the fastest growing material percentage of cardiovascular and soft tissue patches over the next decade.[6]

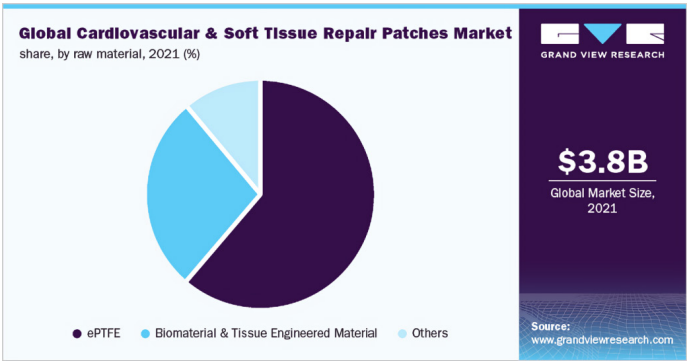

Figure 5 Raw material of products in the global cardiovascular and soft tissue repair patches market.[6]

The figure shows a pie chart of the materials used in the global cardiovascular and soft tissue repair market, with ePTFE making up the largest percentage (more than half), followed by biomaterial & tissue engineered materials.

Looking more broadly, hernia treatments in general are increasing on the global scale, but the U.S. still dominates the treatment market, with the North American market encompassing 50.5% of the market revenue share (Figure 6).[32] However, middle-income countries like China, India, and parts of Asia are the fastest growing geographies for all types of hernia repair, which is dominated by mesh patch treatments, in line with previously discussed advancements in imaging and diagnostic modalities that have also been applied to prenatal screening.[32]

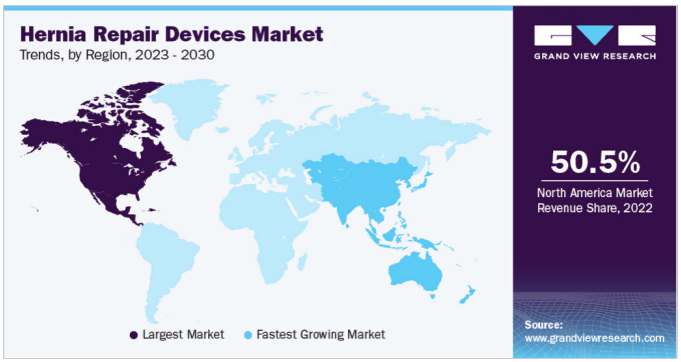

Figure 6 Geographic analysis of the global Hernia Repair Devices market.[32]

The figure shows a map of the world, with North America encompassing 50.5% of the global hernia repair devices market as the largest market and Asia having the fastest growing market.

Treatments and existing products

The management of congenital diaphragmatic hernia (CDH) requires a multifaceted approach, combining both life-saving interventions and long-term reconstructive strategies to address the severity and complexity of the defect.[33] Treatments for CDH will vary widely depending on the defect size, the infant's cardiopulmonary stability at birth, and the presence of any comorbidities.[33] These interventions can be broadly categorized as adjunct therapies that help to stabilize the infant at birth or reparative, often overlapping across the course of treatment.[33]

Adjunct therapies

Treatments for CDH can begin before and shortly after birth in order to increase survival rates and long-term outcomes.[33] Fetoscopic endoluminal tracheal occlusion (FETO) is a newly developed *in utero* intervention designed to promote fetal lung growth in cases of severe pulmonary hypoplasia, or underdeveloped lungs.[34] This technique involves the insertion of a balloon into the fetal trachea to promote fluid retention within the lungs, thereby increasing their volume and promoting healthy lung development.[35] FETO has been found to significantly improve survival rates for neonates with moderate to severe CDH deformities.[34–37] Shortly after birth, pharmacological agents, including inhaled nitric oxide and sildenafil, may be administered to reduce pulmonary hypertension and improve oxygenation.[34,38] Extracorporeal membrane oxygenation (ECMO) provides cardiopulmonary bypass to stabilize infants that cannot be oxygenated by conventional ventilation and inhaled pharmaceuticals.[39] This treatment is crucial for stabilizing neonates with severe CDH in the hopes of preparing them for reparative surgery.[39]

Patch repair

Although temporary treatments, like ECMO, FETO, and inhaled pharmaceuticals can improve outcomes by helping to stabilize infants in the neonatal intensive care unit (NICU) preceding surgery or promote lung development, the only treatment for CDH is surgical repair.[40] As mentioned previously, defects that cannot be repaired with sutures require a patch, which can broadly be classified as synthetic, non-resorbable bioscaffolds, or resorbable scaffolds (Figure 7).[40]

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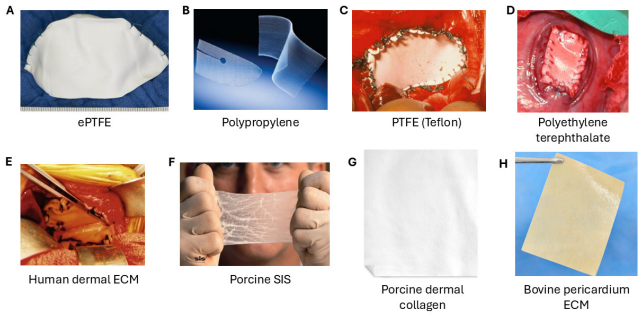

Figure 7 Types of Patches Used for the Repair of Congenital Diaphragmatic Hernia.[40,49–55]

The figure shows images of patches used for CDH repair, including A) ePTFE Gore-Tex® patch by W.L. Gore and Associates,[40] B) PerfixTM Marlex (polypropylene) Mesh flat sheet mesh for inguinal hernia repair by Bard,[49] C) Teflon synthetic hernia patch (non-expanded PTFE),[50] D) Dacron (polyethylene terephthalate) patch by DuPont for cardiac repair, similar to the material used for CDH,[51] E) AlloDerm® (human cadaveric dermal ECM) by LifeCell Corporation,[52] F) Surgisis® (porcine SIS) patch by Cook Medical,[53] G) Permacol® (porcine dermal ECM) by Medtronic,[54] H) Peri-GuardTM (bovine pericardium ECM) hernia repair patch by Baxter.[55]

The optimal material for patch repair in CDH remains subject to debate, as no single material has demonstrated superiority across all clinical outcomes, including recurrence, integration, and long-term durability.[40] Synthetic materials are non-resorbable and do not integrate with the host tissue, but often provide excellent mechanical strength for withstanding the forces of the chest cavity, a weakness of other patch materials.[7] Apart from expanded polytetrafluoroethylene (ePTFE), such as Gore-Tex, commonly used materials for synthetic, non-resorbable patches include polypropylene meshes like Marlex, polyester-based materials such as Mersilene and Dacron, as well as various composite materials.[41–43] Although ePTFE patches have been associated with recurrence due to poor integration with host tissue,[44] recurrence rates can vary broadly depending on the patch type and study methodology.[9,45–47] Further, recent studies have suggested that recurrence in ePTFE patches is more related to the absence of tension-free repair rather than intrinsic properties of the patch.[7,48]

However, synthetic patches are correlated with higher rates of infection due to their microporous structure permitting the infiltration of bacteria while hindering the infiltration of immune cells,[10,48] but are still the most commonly used material to repair large defects, especially ePTFE Gore-Tex patches, which are the most common patch for CDH repair. Alternative materials like Dacron and Teflon are used clinically but have been associated with foreign body reactions and rejection, an issue that Marlex did not exhibit, but extensive fibrosis across all three materials limits their functionality. [40]

Biological scaffolds are advantageous for their biocompatibility and ability to allow for better cell infiltration and thus integration with host tissue.[40,46,56,57] Small intestinal submucosa (SIS) extracellular matrix patches such as Surgisis and Surgisis/Biodesign promote cellular infiltration and vascularization, addressing key limitations of synthetic patches.[56] However, while one study found Surgisis yielded similar recurrence rates to Gore-Tex ePTFE patches,[57] the most frequently used material for patch repair, other studies have found that the fast resorption rate and lack of scarring in Surgisis patches can result in mechanical weakness and higher recurrence rates.[58] Newly-developed 8-layered SIS patches demonstrate similar mechanical strength to synthetic patches and may address this issue, but comprehensive clinical data is not yet available. [40]

Acellular dermal extracellular matrix, both human cadaveric (AlloDerm) and porcine (Permacol), have also been explored as an alternative to synthetic patches.[46,60] AlloDerm is an acellular human cadaveric dermal extracellular matrix designed to promote cellular infiltration and integration with host tissue.[61] However, AlloDerm has also been associated with a lack of sufficient mechanical strength resulting in muscle laxity,[61,62] and long-term outcomes for dermal ECM patches are sparse.[40] Permacol is a resorbable acellular crosslinked collagen-based matrix from pigs,[54] and has been found to have better mechanical properties and reduced recurrence rates.[46] However, the increased strength due to the crosslinked collagen comes as a trade-off, with reduced cellular infiltration and tissue remodeling. [63] Other extracellular matrix bioscaffolds, including porcine bladder ECM (MatriStem) have been explored, but their clinical use is less common.[64]

Despite ongoing innovations in both synthetic and biologically derived materials, no consensus has emerged on the ideal patch for CDH repair.[40] The decision often depends on surgeon preference, defect size, and the balance between mechanical durability and host tissue integration. [40]

Preclinical development

Persistent challenges in CDH patch repair, including high long-term complication rates and poor tissue integration, have highlighted the urgent need for improved repair strategies for the treatment of large CDH defects.[40] In response, researchers have increasingly turned to more complex tissue engineering approaches that involve growth factor-functionalized bioscaffolds, bioactive materials, and stem cell implantation.[65–68] These studies aim to overcome the limitations of current patch materials by promoting true tissue regeneration, a benchmark that existing clinical bioscaffolds have yet to consistently achieve due to inadequate vascularization, insufficient mechanical strength, and limited long-term integration.[65–68]

Zhang et al. developed a 3D-bioprinted, spheroid-based tissue construct of human umbilical vein endothelial cells and human dermal fibroblasts for biological patch repair in a CDH rat model.[65] Their patch was able to successfully promote neovascularization, innervation, and muscle cell infiltration to regenerate muscle tissue in the defect site that was fully integrated with the surrounding endogenous tissue and boasted a survival rate of 100% across 710 days.[65] Maghin et al. similarly explored cell-based patch repair for CDH and developed a diaphragmatic tissue-specific bioreactor to create biological patch constructs from human skeletal muscle cells and human fibroblasts cultured on decellularized diaphragmatic tissue.[66] They determined that the biological patch promoted muscle cell maturation into functional myofibers and cellular remodeling in a CDH mouse model that allowed for patch integration and prevented hernia recurrence.[66] In another study, Liao et al. seeded decellularized diaphragm scaffolds with human amniotic fluid-derived multipotent stromal cells (hAFMSCs) for a CDH rat model, and determined that while decellularized diaphragmatic scaffolds alone promoted structural repair, scaffolds seeded with hAFMSCs showed greater muscle regeneration and improved diaphragmatic biomechanical functioning via electrical stimulation.[67] Additional studies have successfully combined cells or growth factors with scaffolds to create patches for other types of hernias, which hold promise for CDH applications as the technology matures.[69,70]

Clinical trials

Despite encouraging preclinical results, clinical trials for CDH tissue engineering and patch repair treatments remain extremely

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limited.[71] The relative rarity of CDH, as well as variability in defect size and severity, makes randomized trials particularly difficult to execute and requires large, multicenter collaborations in order to enroll a sufficient number of patients.[71] Even when multicenter trials are possible, variability in treatment protocols across centers and the difficulty of long-term follow-up also hinder data consistency and trial validity.[71] Recruitment for clinical trials is also limited by the acute clinical status of CDH neonates, which may increase parental hesitation and require swift decisions that precludes treatment standardization.[71] In 2005, a study comparing patient outcomes for CDH neonates treated with dermal ECM patches or SIS patches was terminated due to insufficient recruitment.[72]

While direct clinical testing in CDH is limited, several clinical trials in related hernia repair fields (e.g., inguinal and ventral hernias) and volumetric muscle loss have provided early insights into the feasibility, safety, and limitations of advanced muscle regeneration bioscaffolds.[73,74] For example, a recent clinical trial explored the use of biodegradable mesh scaffolds made of polydioxanone, a polymer commonly used in surgical sutures, for the prevention of herniation and re-herniation for abdominal surgery and fascial defects.[73] Separately, researchers at the University of Pittsburgh are evaluating the use of acellular bovine extracellular matrix (ECM) scaffolds to promote muscle regeneration and neovascularization in cases of skeletal volumetric muscle loss.[74] In parallel, there is growing clinical interest in cell- and factor-based therapies to enhance muscle regeneration.[73,74] One such approach involves the use of PLX-PAD, an allogeneic placental-derived mesenchymal stromal-like cell therapy, for promoting muscle restoration after hip fracture surgery.[74] Another currently enrolling trial is investigating the safety and effectiveness of IMM01-STEM, a biological treatment derived from pluripotent cell secretomes and possibly combined with stem cell therapy, in restoring muscle strength and function in obese older adults with muscle weakness.[74] Collectively, these emerging strategies reflect a broader movement toward integrating both scaffold materials and cellular and molecular cues to drive functional muscle regeneration, but significant challenges remain in translating these approaches to CDH treatment Appendix.[40,73,74]

Conclusion

CDH is a life-threatening congenital condition that is increasing in prevalence in the United States.[3,25] CDH treatment remains a significant clinical challenge due to its severity, surgical complexity, and long-term complication rates.[28] Current repair strategies rely heavily on synthetic patches like ePTFE, which provide structural strength but fail to integrate with host tissue and cannot grow with the infant.[40] Biological alternatives offer promise through improved biocompatibility, but the mechanical durability needed to withstand the physiological forces of the diaphragm is not always sufficient.[40] There is a growing interest in complex tissue-engineered scaffolds, but significant challenges in translating preclinical developments and advancing to clinical trials remain.[40,71] Continued preclinical innovation and clinical validation are critical for the development of next-generation CDH patches that can combine mechanical resilience with tissue integration to improve long-term outcomes for affected newborns.[40]

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Conflict of interest

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