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# Skeletal system in adult congenital heart disease

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## 1. Introduction

About one-third of children and adults with congenital heart disease have non-cardiac congenital abnormalities. Musculoskeletal abnormalities are the most common anomalies and occur for a wide variety of genetic and acquired reasons. The implications of these musculoskeletal abnormalities can vary greatly but many are associated with an increase in morbidity and even mortality. Recognising these associated lesions and directing patients towards expert multi-disciplinary case is essential.

## 2. Musculoskeletal system and exercise capacity

Patients with congenital heart disease have significantly reduced exercise capacity which is more pronounced in those with complex lesions. Whilst there are many recognised factors determining this, such as ventricular dysfunction, restrictive lung disease or increased pulmonary vascular resistance, recent studies have suggested that abnormal skeletal muscle function is also an important contributing factor.

Greutmann M et al. showed, in a heterogenous cohort of young patients with congenital heart disease, that respiratory and skeletal muscle weakness is common in these patients and has a significant impact on peak oxygen consumption [1]. In addition, Smith MP et al. showed in a population of 583 patients with congenital heart disease that lung function correlates with handgrip strength, suggesting that strength training might help to improve lung function [2].

Adults with congenital heart disease have reduced skeletal mass, impaired skeletal muscle endurance, impaired isometric muscle strength and slower oxygenation kinetics than the general population [3], factors that contribute to reduced aerobic capacity. One specific population where the peripheral muscle function is increasingly recognised as key is in patients with univentricular physiology, palliated with Fontan circulation. Reduced skeletal muscle mass is an important contributor of reduced exercise capacity in this population [4]. Reduced exercise capacity in Fontan patients is associated with an increased risk of major cardiovascular events and redcuded quality of life. In addition, peak oxygen consumption is an independent predictor of unexpected hospitalizations and mortality in this population [5]. Improvement in exercise capacity over time is associated with better clinical outcomes, lean mass, hepatic and renal function, as well as lower central venous pressure and brain natriuretic peptide [6]. Furthermore, declining of exercise capacity is associated with increased risk of death in these patients.

## 3. Scoliosis in congenital heart disease

Scoliosis occurs in 2–4% of the general population and, when severe, it can adversely affect lung function and exercise capacity. While most cases of scoliosis are idiopathic, scoliosis can also be congenital, neuromuscular or syndrome related. Marfan syndrome is a prime example of the latter, in which a genetic defect results in both skeletal and cardiovascular abnormalities (Fig. 1). The overall prevalence of scoliosis in adult patients with congenital heart disease ranges between 2% and 40% [7], much higher than the general population. Similarities can be noted between the features of scoliosis in the congenital heart disease population and idiopathic scoliosis. Both affect predominantly females, although the female-to-male ratio is slightly lower in patients

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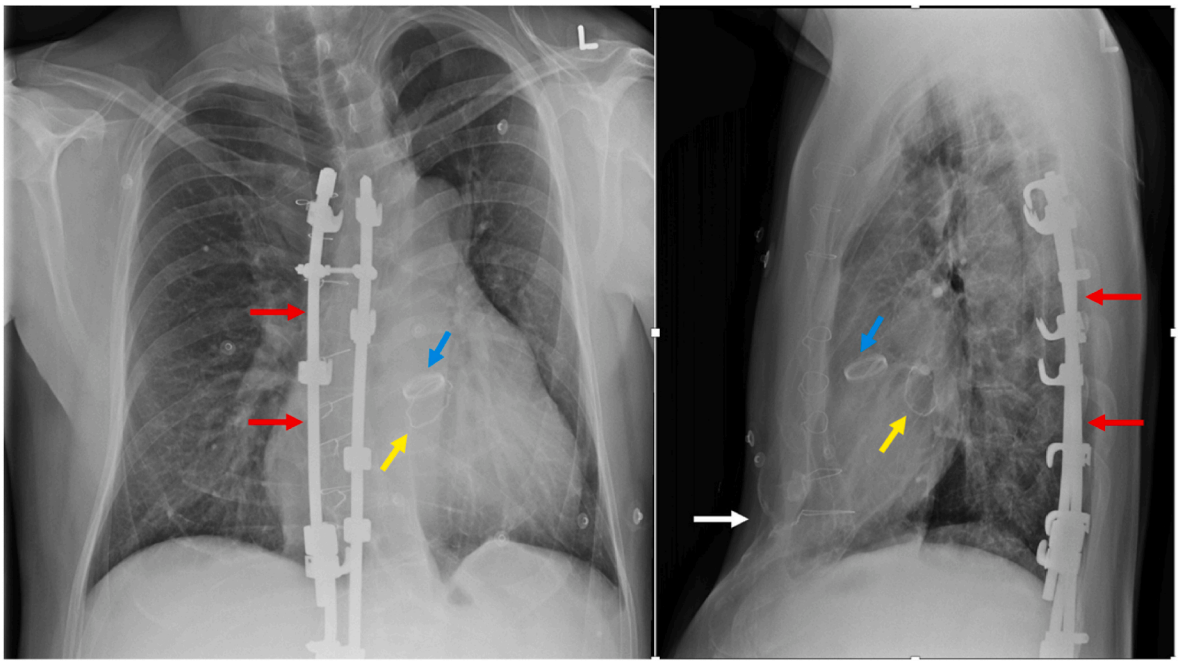

**Fig. 1.** PA and lateral chest X-rays of a patient with Marfan syndrome. The chest X-Ray shows, scoliosis treated with Harrington rods (red arrows), pectus excavatum (white arrow), a mechanical aortic valve (blue arrows) and a mitral annuloplasty (yellow arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

with CHD (1.2–1.4:1) [7,8] than what is reported for idiopathic scoliosis (1.6:1) [9]. Moreover, although a preponderance of right thoracic curves is present in both idiopathic and congenital heart disease associated scoliosis, this is less marked in patients with congenital heart disease [7,8,10].

The role of genetic factors in the development of idiopathic scoliosis is widely accepted. The high prevalence of scoliosis in patients with Marfan and Di George syndrome is an indicator of a common genetic pathway affecting both the cardiovascular and musculoskeletal systems. However, to date, there is no evidence of genetic factors relating scoliosis to congenital heart disease outside established genetic syndromes.

The association between previous surgeries and scoliosis is of particular interest in the congenital heart disease population, both with regards to the development of scoliosis as well as its effect on perioperative risk. Patients with congenital heart disease are likely to undergo one or more thoracotomy and/or sternotomy during their lifetime [8,11,12]. Whilst thoracotomy in infancy is a recognised risk factor for scoliosis [11,12] the association between median sternotomy and scoliosis is less clear. Total or partial resection of ribs, as is performed during thoracoplasty, has been described to lead to scoliosis [13]. Scarring and fusion of ribs have also been postulated as possible causes of scoliosis in children who have been treated with a posterolateral or parascapular thoracotomy for tracheoesophageal fistulae, esophageal atresia [14,15] or patent ductus arteriosus. Even in the absence of rib fusion, chronic fibrotic pleural thickening and the inevitable disruption to the thoracic skeletal equilibrium can contribute to the development of scoliosis. The potential to develop scoliosis should become part of the decision process when contemplating the type of surgical approach.

There is conflicting and limiting data on the relationship between scoliosis and cyanotic heart disease. Although the aetiology of this association remains unclear, impaired oxygenation and deficient blood supply to the vertebral bodies or supporting tissues may be implicated in the development of scoliosis. Pathology studies have documented cortical thinning and medullar cavity expansion in patients with cyanotic heart disease [16]. The reduction in cortical bone is likely a function of marrow expansion and failure of subperiosteal bone growth, as manifested by reduced total bone width. Bone marrow hyperplasia results in expansion of the medullar space, coarsening of the trabecular pattern and thinning of cortical bone. Predisposing these patients to skeletal abnormalities.

Scoliosis itself is an independent risk factor of significant lung dysfunction in patients with congenital heart disease [17], and increases the perioperative risk in these patients. When lacking data or expertise to judge disease severity, the presence of scoliosis can be considered as a marker of disease severity and outcome in this population, although it does not appear to provide independent prognostic information.

## 4. Upper limb malformations and congenital heart disease

Upper limb defects are the commonest skeletal abnormalities associated with congenital heart disease. These include aplasia, hypoplasia or dysplasia of the nails, fingers, thumbs, metacarpals, radii or humeri and deformity of the shoulder gridle [18]. The cardiac lesions most frequently associated with these defects are atrial septal defect (ASD), ventricular septal defect (VSD), atrio-ventricular septal defect (AVSD), conotruncal defects and coarctation of the aorta (CoAo). The reasons for this are not completely understood but we do know that during the fourth to seven weeks of embryogenesis, cardiac and limb bud differentiation temporally coincide [18]. Although some of these malformations are inherited as autosomal dominant traits, the majority are spontaneous mutations.

### 4.1. *Holt-Oram syndrome*

Holt-Oram syndrome is the most common form of heart-hand syndrome, with prevalence estimated at 1 case per 100,000 total births. The syndrome was first described by Mary Holt and Samuel Oram in 1960 who reported a 4-generation family with atrial septal defects and thumb abnormalities [19]. It is caused by mutations that inactivate the transcription factor *TBX5*, which plays a significant role in the development of both the upper limbs and the heart [20]. Holt-Oram syndrome is inherited in an autosomal dominant pattern with complete penetrance, although in up to 40% of cases it can be sporadic. Sporadic disease might represent a de novo germline mutation in *TBX5*.

Upper limb manifestations are always present with malformations or fusions of the carpal bones being the most prevalent findings. Patients frequently also have malformations of the thumbs (triphalangeal, hypoplastic or absent), fingers and less commonly the radius. The limb lesions are normally bilateral and symmetrical but when unilateral the left side is predominantly affected [18]. Universal involvement of the thumb and the absence of significant lower limb or visceral abnormalities are key in the diagnosis.

Approximately 75% of patients with Holt-Oram syndrome will have an associated congenital heart disease with ASD and VSD being the most common defects. ASDs are normally secundum, while the VSDs can be either perimembranous or muscular. Cardiac anomalies may also include conduction defects, such as progressive atrioventricular block and atrial fibrillation. The conduction abnormalities are frequently present even in the absence of septal defects.

There is not necessary clustering of lesions within an affected family and no correlation between the severity of cardiac abnormalities. All members of the family will manifest some degree of skeletal abnormality but the presence of congenital heart disease is not universal [18].

### 4.2. VACTERL association

VACTERL association is a condition involving the presence of multiple congenital abnormalities. VACTERL stands for vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities. The diagnosis is made when at least three of these abnormalities are present in the same patient. Affected individuals may have additional abnormalities that are not amongst these characteristic features.

VACTERL association occurs in 1 in 10,000 to 40,000 newborns [21]. In a small subset of patients, there is evidence of inherited factors but overall, the genetic causes described in humans account only for a small percentage of reported cases [21].

In VACTERL, the most common congenital heart defect is VSD, present in up to 80% of patients. Although vertebral abnormalities are the most common musculoskeletal association, radial abnormalities, polydactyly, syndactyly, and thumb abnormalities are also present.

### 4.3. Trisomy 13 – patau syndrome

Trisomy 13 or Patau syndrome is one of the most common trisomies and occurs in 1 per 5000 total births [22]. Upper limb abnormalities are common and include polydactyly, narrow distal phalanges, hyperconvex nails, finger flexion, trigger thumbs and simian creases [18]. Patients also have midline facial defects such as, cyclopia, cleft lip and cleft palate. Facial features include a sloping forehead, small malformed ears, anophthalmia or microphthalmia, micrognathia, and preauricular tags [23]. Central nervous system abnormalities are also common.

Congenital heart defects occur in 80% of patients with VSD, perimembranous or malalignment, and patent ductus arteriosus being the most common [18]. Other congenital heart diseases such as tetralogy of Fallot, atrio-ventricular septal defect or double outlet left ventricle are less commonly associated.

Median survival of patients with Patau syndrome is 7–10 days and 90% do not survive to one year. Aggressive management with surgical and medical intervention may extend median survival to 733 days [24]. Patients surviving past infancy have a severe psychomotor disorder, failure to thrive, intellectual disability, and seizures.

### 4.4. Trisomy 18 – edwards syndrome

Trisomy 18 or Edwards syndrome is the second most common trisomy after trisomy 21. At the time of first trimester screening the incidence of trisomy 18 is 1 in 400 but since the majority of those diagnosed prenatally will not survive to birth, the prevalence is 1 per 5000 live births. Although the prevalence is higher in females than males (3:2), the fetal loss is higher in males and females have better survival than males [25].

The characteristic upper limb defect is a 'clenched fist' in which the index finger overlaps the third finger, and the fifth finger overlaps the fourth [18]. Camptodactyly, syndactyly of the second and third digits, thumb aplasia, hypoplastic nails, ulnar or radial deviation, radial hypoplasia or aplasia and simian creases also occur. Other skeletal abnormalities include arthrogryposis, rocker-bottom feet with prominent calcanei, talipes equinovarus, dorsiflexed great toes, short neck, short sternum, narrow pelvis, and limited hip abduction.

More than 90% of the infants with trisomy 18 will have cardiac malformations with VSD and polyvalvular disease being the most common [26] Other less common cardiac malformations include atrial septal defects, patent ductus arteriosus, overriding aorta, coarctation of aorta, hypoplastic left heart syndrome, tetralogy of Fallot, and transposition of great arteries [25].

The median survival for Edwards syndrome ranges from 3 days to 14.5 days. Almost 40% of foetuses die during labour, and one-third of the surviving foetuses are delivered preterm. The survival percentage is 60%–75% at the first week, 20%–40% at one month, and 10% at one year. Only 5–10% of Edwards syndrome patients survive beyond the first year of life [25,27].

### 4.5. Ellis-van creveld syndrome

Ellis-van Creveld syndrome is a very rare, autosomal recessive skeletal dysplasia, with inter- and intra-familial variability. Mutations in the *EVC1* and *EVC2* genes are associated with this syndrome.

The characteristic anomalies of the upper limb in Ellis-van Creveld syndrome are short limbs, postaxial polydactyly, dysplastic nails, and distal limb disproportionate dwarfism. There is often fusion of capitate and hamate bones and radiographic evidence of abnormal tubular bones [18]. Patients also have short ribs and dysplastic teeth.

Congenital heart defects occur in about 50–60% of cases including single atrium, defects of the mitral and tricuspid valves, patent ductus arteriosus, VSD, ASD and hypoplastic left heart syndrome. The type of congenital heart disease is the main determinant of longevity.

## 5. Other specific syndromes

### 5.1. Marfan syndrome

Marfan syndrome is an autosomal dominant disease caused by mutations in the fibrillin-1 gene (*FBN1*) on chromosome 15 [28]. The mutation in this protein leads to abnormalities in multiple organs and systems including ocular, cardiovascular, musculoskeletal, lung, skin, and central nervous system. It occurs in 1 in 3000 to 5000 individuals and the life expectancy depends on the aortic complications.

Patients with Marfan syndrome display multiple skeletal abnormalities involving hands and feet, chest wall, spine, extremities and craniofacial. The most frequent anomalies found in these patients are wrist and thumb sign (60.2%), pectus carinatum deformity (39.7%), pectus excavatum or chest asymmetry (30.1%), flatfoot (33.5%) and reduced upper segment to lower segment ratio or increased arm span-to-height ration (36.9%), (Fig. 2) [29].

The limbs of patients with Marfan syndrome are characterized for being long (dolichostenomelia) and they have arachnodactyly (long and thin fingers). Patients normally have a positive thumb sign, also known as the Steinberg sign, where the entire distal phalanx of the thumb protrudes beyond the ulnar border of a closed fist (with or without the assistance of the examiner). They also exhibit a positive wrist sign, also known as the Walker-Murdoch sign, where the tip of the thumb covers the entire fingernail of the fifth finger when wrapped around the contralateral wrist.

Several facial features can be found in patients with Marfan syndrome with retrognathia and down-slanting palpebral fissures being the

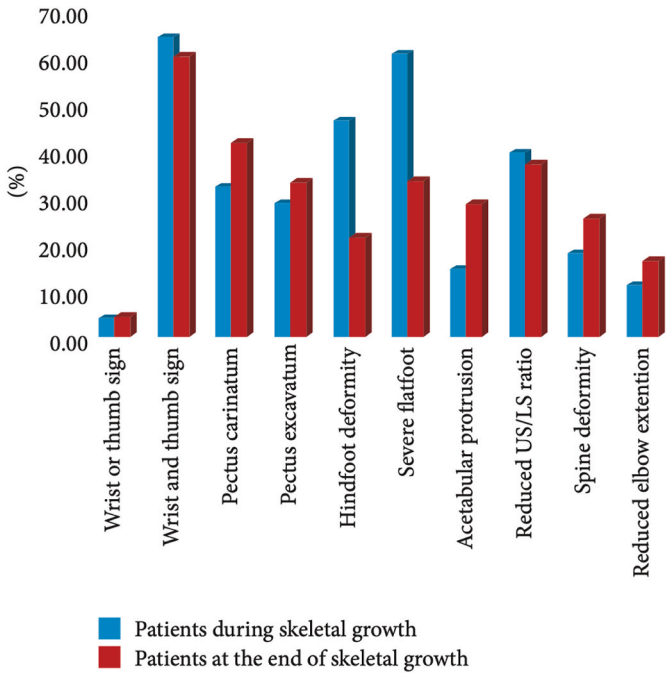


**Fig. 2.** The histogram shows the prevalence of skeletal deformities in 146 patients affected by Marfan syndrome before and after the end of skeletal growth. Reproduced with permission from [43].

most common. Other defects include dolichocephaly, enophthalmos and malar hypoplasia. Chest wall deformity is present in up to 70% of patients with Marfan syndrome. Pectus carinatum is more common than pectus excavatum and both can lead to exercise-related symptoms. Scoliosis is a frequent manifestation of Marfan syndrome and affects more than 50% of this population (Fig. 1). Moreover, hyperkyphosis is common compared to patients with idiopathic scoliosis where hypokyphosis is more prevalent. Dural ectasia results from enlargement of the spinal canal secondary to vertebral bone enlargement, most commonly in the lumbosacral region, and has been observed in 56%–65% of patients with Marfan syndrome [30].

Congenital anomalies of the cardiovascular system, such as septal defects, valvular abnormalities as well as acquired dilation of the aorta, are common in patients with Marfan syndrome. Aortic root disease, leading to aortic regurgitation, aneurysmal dilatation, and dissection, is the primary cause of morbidity and mortality in up to 60%–80% of patients. Mitral valve prolapse is present in 40%–55% of patients with Marfan syndrome, is more common in women and increases with age.

### 5.2. 22q11.2 deletion syndrome

The 22q11.2 Deletion Syndrome (22q11.2 DS) is the most common microdeletion syndrome in humans with a prevalence of 1 per 5950 births. Although some cases are of autosomal dominant inheritance, 90% percent are de novo [31]. 22p11.2 DS, Di-George and velocardiofacial syndrome are often used synonymously. However, it is important to acknowledge that approximately 10% of patients with Di-George and velocardiofacial syndrome do not have a 22q11.2 deletion, and not all patients with 22q11.2 deletion demonstrate classical features of Di-George and velocardiofacial syndrome [32].

Dysmorphic facies, congenital heart disease, palatal malformations, learning difficulties and immunodeficiency are the most common clinical features in patients with 22q11.2 DS. Additional findings include hypernasal speech, hypocalcemia, hearing loss, renal anomalies, growth hormone deficiency, autoimmune disorders, central nervous system anomalies, skeletal abnormalities, ophthalmologic abnormalities, enamel hypoplasia, laryngo-tracheo-esophageal abnormalities and hypothyroidism [32]. Learning disabilities are common and psychiatric disorders become manifest in adolescence and adulthood, including anxiety, depression and schizophrenia.

The most common musculoskeletal manifestations in patients with 22q11.1 DS are cervical spine anomalies, scoliosis, and clubfoot. The cervical abnormalities include anomalies of the first and second vertebra which occasionally can cause neck instability and neurological symptoms. Scoliosis is also common in these patients and is present in approximately 45% of the adults with 22q11.2 DS [33]. Upper and lower limb deformities can also be present and include polydactyly, syndactyly, camptodactyly, arachnodactyly and rotation deformities.

Conotruncal malformations are the most frequent congenital heart disease in these patients, including tetralogy of Fallot, truncus arteriosus, type B interrupted aortic arch as well as other arch abnormalities. ASDs, pulmonary valve stenosis, double-outlet right ventricle, transposition of the great arteries, vascular rings, and heterotaxy syndrome are less common but have also been reported.

### 5.3. Down syndrome

Down syndrome is the most common trisomy, present in 16 per 10,000 live births. Although the clinical aspects of the syndrome were described by JL Down in 1866, the link between trisomy 21 and Down syndrome phenotype was not described until 1959. The Down phenotype involves manifestations that affect multiple bodily systems, including, musculoskeletal, cardiovascular, and neurological systems. Atlantoaxial instability, small stature, short fingers and hypotonia are the most common musculoskeletal abnormalities and atrioventricular septal defect is the most common congenital heart disease in this population. Other common features are reduced neuronal density, cerebellar hypoplasia and intellectual disability. These patients are also more likely to develop certain health conditions, including hypothyroidism, autoimmune diseases, obstructive sleep apnoea, epilepsy, hearing, and vision problems, haematological disorders (including leukaemia), recurrent infections, anxiety disorders and early onset Alzheimer disease [34].

The presence of Down syndrome is associated with a 40–50 times greater likelihood of CHD than in the general population. While approximately half of live-born infants with DS are diagnosed with congenital heart disease, compared with ~1% in the general population, the precise incidence of congenital heart disease in Down syndrome is still unclear. Even in population-based studies that minimize referral bias, the reported incidence varies widely from 23% to 79%. In studies based on diagnostic ultrasound congenital heart disease is seen in 29–56% of karyotype-proven Down syndrome cases [35].

### 5.4. Congenital heart defects and skeletal malformations syndrome

Congenital heart defects and skeletal malformations syndrome (CHDSKM) is an autosomal dominant syndrome characterized by atrial and ventricular septal defects with aortic root dilation. Skeletal defects include pectus excavatum, scoliosis, and finger contractures. Failure to thrive is also observed during infancy and early childhood.

CHDSKM is caused by germline mutations in the *ABL1* gene. In younger children, dysmorphic features include broad forehead, small nose, deep-set eyes, and small chin, whereas in older patients, the face appears elongated, with a narrow maxilla, long and narrow nose, and pointed chin. Other skeletal abnormalities include pectus excavatum, scoliosis, finger contractures, and hindfoot deformity [36].

### 5.5. Hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy is characterized by abnormal proliferation of skin and periosteal tissues involving the extremities. It is characterized by three clinical features: digital clubbing, periostosis of tubular bones, and synovial effusions.

Hypertrophic osteoarthropathy can be a primary entity or can be secondary to extra-skeletal conditions. Patients with cyanotic congenital heart disease are at risk of developing hypertrophic osteoarthropathy. Although there are several theories about the pathophysiology of this condition, the main driver is the presence of high levels of growth factors in the peripheral circulation. In patients with congenital heart disease, the presence of a shunt compromises the maturation of platelets; megakaryocytes bypass the lung circulation and lodge in the capillaries of the digits releasing growth factors that promote vascularity and fibroblast activity leading to soft-tissue and bone formation [37]. Clubbing may be the only clinical manifestation of the disease and bone remodelling in patients with long-standing clubbing can cause acro-osteolysis, osseous resorption at the terminal phalanges of the fingers and toes, which can be easily seen in a plain radiograph. Periostosis is the imaging hallmark of hypertrophic osteoarthropathy and manifests along the shafts of tubular bones with tibia, fibula, radius, and ulna being the most affected [37]. The prognosis of secondary hypertrophy osteoarthropathy is related to the underlying heart disease.

## 6. Conclusion

Congenital cardiac lesions are often part of a wider genetically determined syndrome with important non-cardiac manifestations. This includes abnormalities of the musculoskeletal system. In addition, treatment for congenital heart disease and some of its long-term complications may also adversely impact musculoskeletal structure and function. These complex associations provide insight into the nuances of fetal development, genetics of cardiovascular disease and into the physiology of bone and muscle metabolism. As such this is yet another area of congenital heart disease worthy of further exploration and research.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Rafael Alonso-Gonzalez reports was provided by Toronto General Hospital. Rafael Alonso-Gonzalez reports a relationship with Toronto General Hospital that includes: non-financial support.

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