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Editorial

The Future of Adult Congenital Heart Disease Research: Precision Health Services Delivery for the Next Decade

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Contributions to the field of congenital heart disease (CHD) by Canadians are well known. Much has been written about Maude E. Abbott of Québec: Prevented from practicing medicine in Montréal, she took on the task of running McGill University's pathology museum, producing the first atlas of CHD.[1] The description of an absent sinus (inflow tract) of the morphologically right ventricle with a single morphologically double-inlet LV, infundibular outlet chamber with normally related great arteries, the Holmes heart, so named for the first Dean of McGill's Faculty of Medicine, was published by Maude Abbott in 1901 at the recommendation of William Osler.[2,3] The Holmes heart was subsequently imaged with the use of magnetic resonance imaging and used for the cover of the 6th edition of Perloff's Clinical Recognition of Congenital Heart Disease in 2012.[4] Abbott's meticulous recording of both anatomy and first-time documentation of longevity and death makes her possibly the first CHD epidemiologist of the 20th century. Modern techniques in surgical repair, resulting in first-time survival of children born with complete transposition of the great arteries were led in Canada by William T. Mustard at the Hospital for Sick Children in Toronto. Mustard used a pericardial patch to simplify the lifesaving procedure originally described in 1959 by Åke Senning in Stockholm,[5] publishing his results in 1964.[6] To this day, that hospital remains a leading Canadian and international pediatric institution. Emerging from one of the largest pioneering adult-CHD (ACHD) programs in North America, Gary Webb of Toronto, led first-time efforts to establish a regional, provincial, and national care plan for ACHD patients and training of emerging ACHD specialists. Webb launched the first network dedicated to ACHD professionals, the Canadian Adult Congenital Heart (CACH) Network,[7] securing a position as a recognized affiliate of the Canadian Cardiovascular Society in 2010. In an initiative that brought together international leaders in CHD, the first consensus conference on the care of ACHD patients was held in Canada in 1996, with proceedings published in 1998.[8]

Robust scientific inquiry is new to ACHD compared with other cardiovascular diseases. "Adult congenital heart disease" was coined as a new subspecialty by J.K. Perloff in 1991.[9] The following 10-15 years were dominated by single-centre studies reporting postoperative longevity for up to 200 or 300 patients with increasingly well characterized anatomic substrates—from Toronto, the Mayo Clinic, the University of California in Los Angeles, and the Royal Brompton in England. As a field, we began our journey first by marvelling that in patients with repaired atrial septal defect, tetralogy of Fallot, atrioventricular septal defects, and baffle procedures for complete transposition of the great arteries, long-term survival was possible, as reported in single-centre studies with strong surgical teams.[10-14] We soon realized that the road ahead would be marked by emerging complications; as aptly put by Jane Sommerville in a lecture published in the *Canadian Journal of Cardiology* in 1990: "Out of the blue and into the pink. Is it so rosy for the cardiologist?"[15]

Fuelled by the need to organize care for our patients, the 32nd Bethesda Conference, held in 2000,[10] set forth a research mandate that was 3-fold: to document the changing profile of CHD in adult life, to determine the special health care needs of adults with congenital heart disease, and to organize delivery systems of adults with CHD. Inspiring collaboration characteristic of the global ACHD community, the International Society for Adult Congenital Cardiac Disease[16] brought together leading centres and professionals from across the world.[17] Meeting the data challenge, several groups in Canada and Europe began to assemble registries to address specific challenges that lay before us. The Canadian-led Cardiac Disease in Pregnancy (CAPREG) registry, ongoing since 2001,[18] was unique in providing early tools for risk stratification for a growing number of women with complex ACHD wanting to become pregnant.[19] The forward-thinking **Con**genital **Corvitia** (CONCOR) national registry for adults with congenital heart disease in The Netherlands began DNA banking in 2000.[20] The Québec CHD database was used to provide first-time empirical population-based measurements demonstrating a rising prevalence of CHD in adults.[21] Starting in 1985, the steep rise in the prevalence of adults with CHD, resulting in an equalization of the numbers

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of adults and children with CHD, was expected to reflect national and international trends.[21] By 2010, the numbers of adults with all forms of CHD exceeded the numbers of children, with adults making up fully two-thirds of the population.[22] Extrapolated to the rest of Canada, this corresponds to 257,138 patients living with CHD in 2010, 166,428 of whom were adults. Using comprehensive population data sources, the term "geriatric adult congenital heart disease" was coined,[23] ushering in a growing body of data demonstrating the life-long complications of CHD.[24] In collaboration with the Centers for Disease Control and Prevention (CDC) in the US, these data were used to estimate the magnitude of the problem in the US, indicating that 1.4 million adults had CHD out of a total CHD population of 2.4 million.[25]

In summary, there is a strong tradition of Canadian contributions to the improvement of CHD outcomes, from early records of surveillance and pathology to interventional innovation and state-of-the-art pediatric care, to the organization of health services, patient care, epidemiology, and population health. Influencing the field of CHD in Canada and elsewhere, leading ideas for the advancement of knowledge in ACHD continue to emerge with strong international contributions and collaborations.

The Changing Research Landscape: What Are the New Building Blocks for Our Field?

The evolution of scientific inquiry is being affected by the advent of big data. Deductive reasoning began to prevail in Western civilization in the 17th century, giving rise to the scientific method.[26] Where deductive reasoning is hypothesis driven, constructing primary data sources to answer the query, inductive reasoning learns directly from what may be primary or secondary data, and abductive reasoning proceeds to the most probable explanation when a set of observations are incomplete.[27] The advent of machine learning (ML) is changing our ability to learn from clinical observations and research data. Unlike traditional prediction models, where variables are chosen based on *a priori* knowledge and are limited in number, ML creates input-output maps, learning from examples or raw data patterns, making it possible for us to use more diverse forms of unstructured data.[28] With ML, data can be hypothesis generating rather than the other way around, where a data set is constructed to test a hypothesis as in classic scientific query based on deductive reasoning. ML-generated algorithms learn directly from the data to arrive at predictive analytics.[29]

Big data analytics in medicine have been successfully applied to genomic data, imaging data, and physiologic data, or what is also called medical signal analytics. Besides developing new analytical methods, the challenge is in collecting, fusing, sharing, and compressing data to optimize the ability to extract answers to meaningful clinical questions.[30] Techniques to infer regulatory networks from big biologic data have been applied to the understanding of cardiac morphogenesis and development.[30] The use of medical signal analytics for patients in intensive care units has the potential to lead to earlier detection and prevention of acute medical deterioration for cardiac patients.[30]

Digital health refers to the use of electronic communication and surveillance systems to exchange health information between different points and participants in the organizations that make up contemporary health care delivery systems. It is not a modality of care but a tool to help bridge gaps in communication, and it can increasingly be used for health services interventions.[31] There is no longer a question that health information technology and patient-centred care have converged to change the relationship between those who deliver care and those who experience it.[32] Complex health systems interventions are defined as those with multiple interacting components requiring complex and flexible organizational implementation strategies with a wide range of outcomes.[33] Transition of care provides one such example, as patients migrate from pediatric to adult health care systems. Digital health has the potential to improve the delivery of evidence-based care in cardiovascular disease.[34] Digital tools have been applied to both chronic disease management and the acute identification of changes in heart rhythm. From a research point of view, digital tools can improve patient recruitment, facilitate consent, and analyze nontraditional study end points.[34] In the US and Canada, the roadmap to innovation for health care transformation and the application of digital tools to improve quality of care have been applied to the improvement of cardiovascular disease outcomes.[35-37]

In summary, the convergence of big data, ML, and digital health technology creates a unique research ecosystem for our field at a time when we are at a tipping point in terms of population growth and health services needs. There is a unique opportunity to harness specific elements of the rapidly evolving research landscape to meet the growing health care needs of ACHD patients.

Health Services Delivery: What Are the Needs?

For those with CHD, expenditures in adulthood account for $>$ 60% of total health care costs.[38] In Canada as elsewhere, cost containment for populations with chronic lifelong morbidity challenges our ability to sustain delivery of high-quality care.[33] In ACHD populations, increasing comorbidities require repeated interventions, particularly valvular interventions,[39] resulting in significant increases in health services utilization during childhood,[40] during transitions in care,[41] in adulthood,[42] and into the geriatric years,[23] with national trends of increasing costs well shown with the use of Canadian Institute for Health Information data for CHD populations.[43] Similarly, international data sources have shown increasing health services utilization for a growing population of ACHD patients with heart failure. [44]

The impact of life-long exposure to circulatory abnormalities and myocardial dysfunction in adult populations with CHD is coming to light. This effect is amplified in adults with increasing survivorship resulting in longer time windows to express signs and symptoms of multisystemic complications (Fig. 1). Observations in comprehensive longitudinal cohorts have enabled measurement and prediction of adverse outcomes in more than 80,000 patients observed for nearly 3 decades, showing ongoing disease burden, including atrial arrhythmias,[45] pulmonary hypertension,[46] stroke,[47] neurocognitive anomalies,[48] coronary disease,[49] cancer,[50] and liver complications in Fontan patients.[51] Findings on the importance of comorbidities have been demonstrated in Europe

with the Dutch CONCOR registry database, where mortality, including endocarditis, arrhythmias, heart failure, and pulmonary hypertension have all been shown to contribute significantly to mortality in a broad range of patients of varying ages.[52] In the UK, the significant burden of CHD-associated comorbidity and acquired risk factors has been demonstrated in primary and secondary care settings.[53]

Moreover, sex differences in health services utilization have also been shown with the use of the Dutch CONCOR database and the Québec CHD database, with a protective effect conferred to female patients.[54] These findings underscore the importance of gender-driven variations in health behaviour that have a significant impact on outcomes.[54,55]

Using a population-based approach to the organization and planning of ACHD care in Canada, we determined that 1 regional ACHD center for a population of 2-3 million adults would be required to improve access to specialized ACHD care and meet guideline recommendations for referral in the United States and Canada.[56,57] Despite universal health insurance, access to care for ACHD and CHD patients stands to be improved. In 2010, fewer than 30% of ACHD adults in Canada were being systematically followed in ACHD centres.[58] We determined that wait times for nonurgent procedural consultations were 4-5 months, exceeding Canadian recommended targets in two-thirds of all CACH Network sites for consultations and in 85% of surgical sites for ACHD operations.[58] Moreover, specific periods along the life course with CHD remain problematic. In particular, where patients appear stable and transfer is mandated by age 18, gaps in care are observed with > 50% of patients falling out of care from 12 to 18 years of age[42] and only 47% having at least 1 follow-up in an ACHD centre before age 22, with substantially worst transfer rates in the US.[59,60] Moreover, we have shown that only 20%-25% of ACHD patients receive follow-up care in ACHD centres in accordance with guideline recommendations.[57,61]

Beyond considerations of ACHD expert centres' care needs, for the majority of an ACHD patient's life, the burden of health care management is largely carried by the patient and their family. Through the life course, a patient will spend more time outside the hospital with subclinical disease, while family members are continuously engaged in surveillance for prevention of complications, ensuring timely delivery of services, and adherence to care. This support is particularly important during the vulnerable periods between episodes of illness. Increasingly, health services interventions in the form of digital support, which is especially appealing to youth, that promote empowerment and self-management are being sought to facilitate health management.[62,63] Moreover, needs vary with age and the changing physiology of disease, with risk profiles evolving as comorbidities magnify the effect of disease. Nowhere is it more evident than in the CHD patient, for whom family members must necessarily be at the centre of care dynamics across the life span, underscoring the need for measures of patient-centred care.[64] Thus, numerous opportunities exist for gaps in health services delivery across a care-continuum that extends across the life-span.

In summary, the delivery of health services and care for the CHD patient across the life span poses a number of challenges. Increasingly, complex health systems interventions will require flexible organizational implementation strategies across the life span that are able to measure a wide range of outcomes relevant to the patient, family, clinicians, health administrators, and policy makers. Thus, there is a need to provide health services that are proactive instead of reactive to episodes of illness. Applied to precision medicine, this means delivering care that is personalised, preventive of episodes of illness, predictive of adverse events, and participatory in that it engages patients and families.[65]

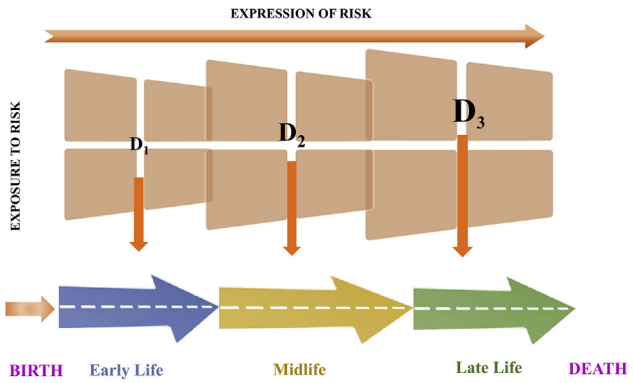

Figure 1. Time windows that magnify the expression of risk over the life span. The long-term impact of life-long exposure to risk is amplified in adults with increasing survival, resulting in longer time windows enabling the expression of risk for multisystemic complications. D, disease, where 1, 2, and 3 are complications of congenital lesions that result in multisystem complications.

Precision Delivery of Health Services: How Do We Move Forward in the Next Decade?

As medicine moves into the digital information age, a research pipeline is being formed from cell biology to health services delivery, the currency of which is data, which are rapidly increasing in volume, complexity, and variety. At the distal end of this pipeline there is an opportunity to develop strategies to provide the precision delivery of health services that will improve outcomes for new and recurrent cardiovascular and systemic disease events. This will become increasingly relevant as comorbidity, complex care needs, and costs rise with increasing longevity of ACHD patients. Precision delivery is defined as the predominant use of an individual's personal electronic health data to predict risk and personalise health services to augment their value.[66] As we build this body of knowledge, it will enable our field to move from risk to benefit measurement[67] and from outcomes to trajectories. As a growing number of diseases are expressed over the lifespan, trajectories are becoming an important construct that moves beyond the notion of episodic illness and toward the long-term mapping of the life course with conditions such as CHD. Applied ML methodologies can be used to map such trajectories and precisely design the delivery of health care with the use of data sources including longitudinal follow-up.

Figure 2A illustrates what we have observed, analyzed, and learned over the past 10 years: Risk in CHD changes over the life course, clusters of risk factors often occur in predictable patterns, and, as age advances both biologically and chronologically, our patients migrated from periods of health to episodes of disease that drive complex cardiovascular conditions. Figure 2B illustrates how health services can be

deployed precisely, informed by genetic determinants of biology, deep phenotyping that can be harnessed from advanced imaging and an understanding of an individual's environmental determinants of health behaviour captured through digital tools and increasing recognition of the microbiome as having a clear footprint in the expression of disease.[68,69] Capitalizing on data science, ML and other artificial intelligence methodologies will increasingly enable us to analyze disparate but complementary data sets to develop dynamic risk and benefit profiles, changing the care we deliver as the patient evolves over the course of his or her own trajectory. The term "costonome" is here coined to denote the objective of delivering cost-effective health services across the life span.

In summary, our ability to deliver health services that are personalised, proactive, and dynamic in a manner that is consistent with the judicious allocation of costly health services for patients with life-long complex care needs will be optimized by our ability to harness big data, ML, and digital health, but the challenges specific to CHD research will need to be addressed if we are to keep pace with rapid progress in ongoing cardiovascular research.

Congenital Heart Disease Research: What Are the Challenges?

The genotype-phenotype mismatch

From a biologic standpoint, causative variance of CHD is high and disease frequency is low, challenging our understanding of the genotype-to-phenotype association. There are more than 40 genes implicated in nonsyndromic CHD, which accounts for the majority of CHD cases.[70] A number of developmental syndromes, such as trisomy 21, Turner syndrome, and 22q11 deletion, are associated with prominent CHD phenotypes that are seen in up to 50% of carriers and may include atrioventricular septal defects, coarctation of the aorta, and other conotruncal anomalies. Nonetheless, as a result of the low frequency of chromosomal anomalies in the general population, these patients account for a minority of CHD patients.[71] Familial mutations accounting for CHD may be autosomal dominant, recessive, or X-linked, are genetically heterogeneous, and are expressed with variable clinical manifestations.[72,73] Again, however, they are seen in a minority of CHD patients. From an anatomic point of view, the large variation in phenotype with a small number of contributing genes makes disease classification difficult.[74] This underscores the challenge of enrolling homogeneous patient subgroups to optimize the internal validity of clinical trials. In adult drug trials for non-CHD patients, eg, in heart failure, ACHD patients are systematically excluded to avoid bias. Even within ACHD populations, therapeutic trials are scant for medical therapies as basic as diuretics and afterload reduction.[75]

Because CHD patients benefit from increased reproductive fitness, efforts are ongoing to better elucidate the genetic variants associated with cardiac malformations. Subchromosomal structural mutations referred to as copy number variants can now be characterized at high resolution to identify insertion or deletions that are emerging as important contributors to a wide range of both syndromic and nonsyndromic CHD. Networks such as the Congenital Heart Disease Genetic Network Study funded by the National Institute of Health Heart, Lung, and Blood Institute (NHLBI) and the Dutch CONCOR registry, together with emerging biotechnology, will contribute to large-scale efforts to elucidate the pathogenesis in large numbers of patients.[20,71,76]

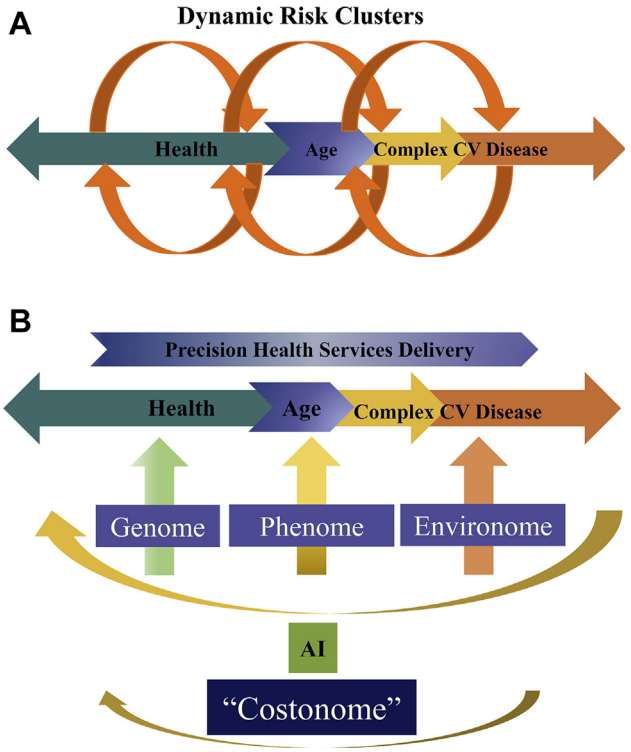

Figure 2. Precision health services delivery in congenital heart disease across the life span. (**A**) The dynamic nature of clusters of risk factors as patients age and periods of health migrate to episodes of disease that drive complex cardiovascular conditions. **(B)** How health services might be personalised with machine learning—informed prediction models that capture genetic determinants of biology, ie, deep phenotyping harnessed from advanced imaging and an understanding of an individual's environmental determinants of health behaviour captured through digital tools. The term "costonome" is coined here to denote the objective of delivering cost-effective health services across the life span. AI, artificial intelligence; CV, cardiovascular.

In summary, despite the challenge, the biologic imperative is critical if we are to build our capacity as a field in the 21st century. The advent of advanced biotechnology, diminishing costs of population-scale genome-sequencing capabilities, and the emergence of networks should be coupled with population health research to advance our progress.

The data-to-evidence gap

In ACHD, knowledge gaps remain in the area of clinical trials, either with prospective randomization with control groups or even in comparative effectiveness trials. Truly prospective randomised trials (RCTs) are scant in ACHD.[77,78] For comparative purposes, from 2007 to 2017, a Medline and Pubmed search with uniformly applied concept filters in adults $\geq$ 18 years revealed $>$ 2,000 RCTs for coronary artery

Table 1. Data-to-evidence gap in ACHD clinical practice guidelines

Guideline	Recommendations (n)	Classes of recommendations (n)			Level of evidence (n)		
ESC 2010							
Lesion group		I	II	III	A	B	C
Shunts	24	10	8	6	0	2	22
LVOT	26	11	15	0	0	1	25
ROVT	9	11	15	0	0	0	9
TGA	22	12	9	1	0	0	22
UVH	4	0	4	0	0	0	4
Proportions	n = 85	45%	47%	8%	0%	6%	93%

ACC/AHA 2018								
Lesion group		I	II	III	A	B-R	B-NR	C
Shunts	25	10	11	4	0	0	7	18
LVOT	15	9	6	0	0	0	8	7
ROVT	32	13	19	0	0	0	21	11
TGA	15	6	9	0	0	0	4	11
UVH	12	5	7	0	0	1	0	11
Proportions	n = 99	43%	52%	4%	0%	1%	40%	59%

Class I, strong strength of recommendation; class II, moderate or weak strength of recommendation; and class III, no benefit. Level of evidence: A, high quality of evidence with randomized clinical trials (RCTs); B-R, moderate quality from 1 or more RCTs or meta-analyses with moderate-quality RCTs; B-NR, moderate quality from well designed nonrandomized studies, observational studies, or registry studies; C, limited data or consensus based on clinical experience.

Almost half of the guideline-proposed strong recommendations are based largely on limited data. In 2010, > 90% (45% and 47%) of recommendations were class I or II and 93% were supported by level of evidence C. By 2018, there were still > 90% of recommendations in class I or II with an increase in moderate-quality evidence, although almost 60% were still supported by poor evidence.

ACC, American College of Cardiology; ACHD, adult congenital heart disease; AHA, American Heart Association; ESC, European Society of Cardiology; LVOT, left ventricular outflow tract: subvalvar, valvar, and supravalvar aortic stenosis and coarctation; RVOT, right ventricular outflow tract: pulmonary stenosis and tetralogy of Fallot; TGA, transposition of the great arteries: dextrotransposition of the great arteries, and congenitally corrected transposition of the great arteries; Shunts: atrial septal defect, ventricular septal defect, atrioventricular septal defect, patent ductus arteriosus; UVH, univentricular heart: all types.

disease and > 2,500 RCTs for heart failure, but there were only 165 RCTs for ACHD. After manual exclusion of trials related to Eisenmenger syndrome, pulmonary hypertension, bicuspid aortic valve, and Marfan syndrome, only 17 remaining RCTs were identified. Further exclusion of studies reporting "rationale and design" of an RCT left only 15 ACHD RCTs published over that 10-year period. This is critical to our ability to generate clinical practice guidelines (CPG) in which recommendations are supported by strong evidence.

Whereas the class of recommendation reflects the expected size of the treatment effect, the level of evidence (LOE) reflects the certainty of the expected treatment effect.[79] The Grades of Recommendation, Assessment, Development, and Evaluation define the strength of a recommendation as the extent to which we can be confident that adherence to the recommendation will do more good than harm and the quality of evidence as a measure of the extent to which we can be confident that an estimate of effect is correct.[80] Table 1 presents the evolution of the evidence gap in supporting our CPG recommendations for ACHD. The 2010 European Society of Cardiology CPG for ACHD generated a total of 85 recommendations for the range of anatomic lesion groups. Of these, just under one-half were class 1 recommendations. It should be noted that > 90% were supported by consensus opinion only. By 2018 for the 99 recommendations of the American College of Cardiology/American Heart Association CPG for ACHD, the same proportion are class 1, although the level of evidence has strengthened with a higher proportion of LOE B—supported recommendations, most of which are based on nonrandomized clinical trials. Taken together, these observations indicate we are making strong recommendations in > 90% of cases with an expected large size of treatment effect based on the poorest level of certainty of treatment effect in 99% of cases.

In summary, clinical practice in ACHD continues to be largely supported by poor evidence or consensus opinion. Small numbers, costs, and the difficulty in carrying out internally valid studies in our heterogeneous patient populations continue to be challenges. Thus, despite enormous progress, at this time as a field we lag significantly behind our colleagues in performing cardiovascular trials that would allow us to generate evidence comparable to that existing in non-CHD populations.

From data sources to data science: how do we get there?

Moving from data sources to data science constitutes our greatest challenge. This is so for health care data in general but perhaps more so in CHD because of the challenges in CHD research outlined above. Although evidence needs data, data do not need evidence. Data science is rapidly growing as a field where a number of methodologies are being developed to extract the science out of data in both its structured and its unstructured forms.

The quest for uniform central data repositories that would overcome the challenge of small numbers has been a source of ongoing discussion since the early 1990s. Although networks typically involve primary data collection, registries or databases may collect primary medical or surgical data or may apply secondary analyses to existing data sources.[81,82] Other data collection platforms assemble referral centres to voluntarily share data to address specific research queries. Tools that merge patient management tasks, clinical data, and reporting functions have been launched and developed in Canada and elsewhere.[83]

Pediatric cardiologists have made headway into innovative data collection collaboratives. Developmental disease networks have been well established to create a biorepository of genetic data aimed at investigating the phenotype-genotype correlation in subjects with CHD.[76] The Extracorporeal Membrane Oxygenation Registry (ECMO) maintained by the Extracorporeal Life Support Organization manages data on newborns from 230 centres.[84] The NHLBI-funded Pediatric Heart Network was designed as a multicentre cross-sectional data acquisition platform meant to facilitate clinical trials in children with the Fontan procedure.[85] Dedicated to improving quality of care, organizations such as the Pediatric Improvement Collaborative for Hypoplastic Left Heart Syndrome have led the way as a learning network in pediatric cardiology, collecting real-time data and applying quality improvement initiatives designed to improve outcomes.[86] The Pediatric and Congenital Heart Surgery Database has had an exponential increase in enrolment and is now beginning to track surgical outcomes in adults.[87-89]

Data collection mechanisms for ACHD patients have made great strides. The CONCOR database in The Netherlands is notable for a unique clinical data collection strategy, including DNA, at more than 20 sites since 2004.[20] In Belgium, a growing number of large cohorts are contributing important data to the changing survival of ACHD cohorts.[90] Smaller European cohorts are rapidly emerging, such as the **S**wiss **A**dult **C**ongenital **He**art Disease **R**egistry (SACHER), with the intention of collecting well characterized clinical data.[91] The Alliance for Adult Research in Congenital Cardiology (AARCC) has led multicentre international collaborative research, assembling more than 30 ACHD centers to produce important data in response to timely clinical questions.[92] The **R**egistry **o**f **P**regnancy **a**nd **C**ardiac Disease (ROPAC), now in its third iteration, has amassed 10 years of data. In Canada, the CAPREG registry continues to make important contributions.[19] Innovative tools, such as **Ca**rdiac **P**atient **S**ystem (CAPS), which originated in Toronto and is used in numerous Canadian and some European centres, merge clinical management functions with data collection, enabling queries for specific questions.[93] The **Congen**ital **E**valuation, **R**eporting **a**nd **T**racking **E**ndeavor (CONGENERATE) platform codeveloped in Québec and piloted in the US, continues to be used in Québec. It enables structured clinical data collection in real time as reports are generated for communication purposes, thereby avoiding the need for duplication of data entry.[94]

There is growing interest in data sources across the life span of CHD patients. The Québec Congenital Heart Disease Database, assembled from outpatient, inpatient, and death registry claims data, collected information on every CHD patient in the province from 1982 to 2000 and at 5-year intervals since then. Data sources are merged and designated algorithms are applied to harvest uniform validated longitudinal data on every patient born with a CHD diagnosis since 1982. The resulting cohort of ~ 100,000 patients tracked for up to 35 years with unique identifiers has been used to generate meaningful population-level data in Canada and elsewhere.[22,25] Since the publication of the first paper from the Québec CHD database, there has been a steady increase in secondary analyses of similar data sources in Canada,[95] the US, and Europe.[82] International efforts are ongoing to identify innovative data sources. In the absence of unique identifiers made possible with universal health insurance, US data sources such as the National Inpatient Sample use episodes of care rather than patients as units of measurement.[96] Internationally, data sources in Belgium, Denmark, Sweden, and Spain have been increasingly used to analyze ACHD data directly.[82]

Widely varying CHD nomenclature systems, which impair the ability to compare like with like, have been addressed in a variety of important ways with the International Nomenclature Project and the development of International Pediatric and Congenital Cardiac Codes informed by surgical anatomy and more recently with the mapping of the International Classification of Disease (ICD) to its 10th version, enabling highly specific CHD diagnoses to improve the quality of research in Canada.[97] These efforts have also been used to inform electronic health record data standards for CHD to attempt more uniform coding and data collection procedures.[98]

Although "big data" carries the promise of significant benefit to scientific discovery, numerous issues related to the governance of privacy are emerging. Three lines of inquiry will help to shape the future of the personal data ecosystem. From a legal-policy standpoint, data sharing is currently largely driven by "informed choice" models. It can be argued that directives addressing these models will be unmanageable as the scope of public data explodes. More forward-thinking frameworks are looking to capitalize on legal reforms interpreted in the context of patient empowerment and the unavoidable business models that ensue.[99] International instruments for global privacy governance of health data have begun to formulate policy. Leading the way, a number of disease-based biobanks are now being governed by well articulated instruments created by international organizations. Examples include the UNESCO *Universal Declaration on the Human Genome and Human Rights*, as far back as 1997, and the Global Alliance for Genomics and Health *Framework for Responsible Sharing of Genomic and Health-Related Data*, as recently as in 2014.[100] In Canada, a number of initiatives are coalescing around the Canadian Institute of Health Research initiatives Health Research Data and Strategy for Patient-Oriented Research, embedding principles of Canada's Digital Charter.[101,102] The third line of investigation moving us forward are the increasing number of toolkits specifically designed for privacy-preserving data mining methods.[103] A number of software solutions are becoming available to address data distribution constraints impairing collaborative and cooperative computing.[104] From a practical standpoint, the Québec CHD database has worked in close collaboration with governmental commissions on access to information to

create third-party data backbone structures that create scrambling algorithms to anonymise data sources. Working with other investigators, we have combined results of the Québec CHD database with those of the CONCOR registry, enabling us to query specific questions.[54] Thus, as we learn from the practical solutions that we are creating in response to necessity, the numerous challenges ahead are being met with a growing number of solutions originating from the triangulated perspective of legal policy, instruments of international collaboration, and software engineering.

In summary, we have made strides in terms of data sources in ACHD. Harnessing the power of claims data where access to health insurance is universal and unique identifiers are used from birth to death, longitudinal data sources have been assembled in Canada, inspiring other jurisdictions to follow suit. We have used tools for the management of health services to collect clinical data. We have participated in networks where clinical data is being collected. After decades of planning uniform data repositories, advances in data science will allow us to move away from individual data sources toward the merging of large databases, making it possible to overcome the limitations of variations in data architecture. Despite the challenges of evolving technology and policy directives enabling data sharing, these advances have the potential to address the challenges in CHD research as we move forward. From biology to outcomes, quality of care, clinical trials, and population studies, data platforms are emerging in a large number of innovative ways.

The Future: Where Do We Need to Go?

Adult congenital heart disease research agendas

From 2010 to 2015, a number of influential organizations came together independently to map out research agendas for ACHD from a wide range of perspectives. Growing out of the International Society for Adults with Congenital Cardiac Disease, a nurse practitioner–led initiative convened a 2-round Delphi process identifying patient-centred research priorities: knowledge and education, quality of life, transfer and transition of care, illness experience, and psychosocial issues and health behaviour.[105] These findings resonate loudly as we move away from episodes of disease to periods of wellness, in a framework that incorporates not just the life span but also the health span with the worldwide expansion of CHD populations. In 2012, the CDC convened experts to identify gaps in CHD research relevant to a public health mandate. CHD life span prevalence rates, risk factors, long-term outcomes, and health services delivery were identified as priority areas.[106] Using survey methodology, the AARCC deployed a 45-question inquiry on clinical research priorities in ACHD.[93] Findings identified criteria for pulmonary valve replacement in tetralogy of Fallot, measurement of right ventricular function, and the role of medical therapies in Fontan patients as being high-priority areas for ACHD clinicians.[93] The NHLBI and the American Congenital Heart Association convened a group of multidisciplinary experts to identify high-impact research questions.[107] Heart failure and vascular disease in patients with tetralogy of Fallot and coarctation of the aorta were identified as important research areas. Multisystem complications, including long-term outcomes in patients with univentricular hearts, cognitive and psychosocial dysfunction, and pregnancy, were specified as high-impact areas of inquiry. Population-based data acquisition and translational research were highlighted as areas in need of progress.[107]

In summary, the themes common to each of these mandates from a range of stakeholders underscore the need for population-based patient-centred long-term outcomes in a field that is becoming increasingly multidisciplinary as patients age and the complexity of their care needs becomes manifest. Looking toward the next decade, a number of emerging research constructs will facilitate the discovery of knowledge and the creation of tools that will improve outcomes.

Table 2. Emerging research constructs and research methodologies that support them

Current	Future
Research concept	
CHD outcomes in pediatric and adult patients	CHD trajectories across the life course
Age (chronologic)	Aging (biologic)
Episodes of illness	Periods of wellness
Life span	Health span
Quality of care to standardise clinical practice	Quality of care to personalise clinical practice
Risk prediction	Benefit prediction[67]
Research methods and tools	
Epidemiology of disease	Life-course health development[108]
Knowledge translation	Implementation science[109]
Hypothesis-driven prediction models	Machine learning–generated prediction algorithms[110]
Randomised clinical trials for single drug benefit	Comparative effectiveness for composite medical therapies[111]
Digital health tool implementation	Digital health tool testing[34]
Claims data	Secondary big health data[112]

CHD, congenital heart disease.

Emerging research constructs

Without a doubt, the future lies in collaborative efforts between pediatric and adult clinician scientists in cardiovascular research to merge information obtained from complementary data sources. The resulting intellectual adjacencies will facilitate the emergence of new research constructs in health services research as we head into the next decade. The concept of age limited to calendar-year observations needs to incorporate determinants of aging measured biologically. This will allow us to change the focus from “pediatric” and “adult” CHD outcomes to life span determinants, not just of disease but also of health, as patients who live longer also want to live better. A paradigm shift needs to occur, from life span to health span, from outcomes to trajectories, from episodes of illness to periods of wellness, and from CHD populations to people with lived experience. Because we have spent decades looking for ways to decrease practice variation to ensure that quality of care reflects evidence-based practice, the data in our field have been slow to build and adherence to guidelines stands to be improved.[61] This need for personalised application of clinical practice directives is important in ACHD where age, comorbidity, and patient preference need to be

accounted for. Capitalizing on newer methodologies in health services research will be an important driver in achieving the shifting paradigms that will shape research in the next decade. Table 2 summarizes emerging constructs and supporting methodologies for ACHD health services research.

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