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Taking steps to improve care and planning for patients in British Columbia with 22q11.2 deletion syndrome

No data, no problem, no action! Better institutional and provincial data sharing is needed to ensure evidence-based recommendations for the condition known as 22q11DS or DiGeorge syndrome can be developed, implemented, and updated.

ABSTRACT

Background: Patients diagnosed with 22q11.2 deletion syndrome, also known as 22q11DS or DiGeorge syndrome, have a diverse array of congenital anomalies and chronic health conditions. Because no study has reported on the coordination of multidisciplinary health services in British Columbia required by individuals with 22q11DS, we set out to determine which health care services these patients access and what barriers in health informatics affect institutional and provincial data sharing.

Methods: A retrospective review of patient care at BC Children's Hospital (BCCH) was conducted using the provincial discharge abstract database and databases from hospital specialty services involved in the care of patients with 22q11DS. Data were collected for patients seen at the hospital from April 2001 to March 2018. This 17-year review considered patient age at diagnosis, distribution of patient ages within the study cohort, number and type of specialty services accessed, and length of follow-up.

Results: A total of 293 patients with 22q11DS were identified from the hospital discharge abstract databases (DAD) and seven BCCH specialty clinic databases. Data could not be retrieved from some clinic databases due to coding and reporting discrepancies, which prevented the amalgamation of data from all hospital specialty services. Data from the DAD and seven BC Children's Hospital specialty services were then amalgamated, and duplicates were removed to identify 293 unique patients with 22q11DS. On average, patients accessed five services, with 13 new patients being seen each year and followed for an average of 7 years. Most of the pediatric care was provided by the Cleft Palate/Craniofacial Program, Cardiology, Endocrinology, and Otolaryngology. Using BC Women's Hospital Medical Genetics 22q11DS data (n = 400), we were able to corroborate the size of our study cohort and to estimate the prevalence of 22q11DS in BC for the study period.

Conclusions: Barriers to data retrieval and sharing at institutional and provincial levels were found to limit care coordination for patients with 22q11DS, who require ongoing, complex, multidisciplinary management. Incongruent and incomplete data systems in BC are hindering our ability to provide this coordinated care and plan transition, leaving us without the evidence needed by provincial health care providers, local experts, policymakers, and national and international 22q11DS research centres.

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Background

In 1965 Dr Angelo DiGeorge first described the syndromic presentation of infants with thymic aplasia, hypoparathyroidism, and cardiac outflow tract anomalies.[1,2] DiGeorge syndrome was later grouped with other phenotypically similar syndromes seen in clinical practice (e.g.,

velocardiofacial syndrome, conotruncal anomaly face syndrome, Opitz G/BBB syndrome, and Cayler cardiofacial syndrome).[1,2] With the advent of cytogenetic testing in the 1980s and fluorescent in situ hybridization (FISH) studies in the 1990s, a common underlying microdeletion was identified in all these syndromes: 22q11.2 deletion.

The condition now known as 22q11.2 deletion syndrome (22q11DS) is the most common microdeletion syndrome with a prevalence of roughly 1 in 3000 to 1 in 6000 live births.[3] Affected individuals have a 50% chance of having an affected child; however, more than 90% of these deletions are de novo, with both parents being unaffected.[3,4] Patients diagnosed with the syndrome have a diverse array of congenital anomalies and chronic health conditions.[3] Specifically, 22q11DS is the second most common cause of patients presenting with both congenital heart disease (CHD) and global developmental delay (GDD).[3] Clinical features are variable depending on age, with the most common presentations including two or more of the following: distinctive facial features **[Figure 1]**; conotruncal cardiac anomalies; palatal anomalies or functional defects with hypernasal speech and/or nasal regurgitation; immunodeficiency; hypocalcemia; cervical anomalies and/or scoliosis; GDD, learning, and behavioral challenges; and psychiatric illness.[3] Many patients have neurodevelopmental disorders, including attention deficit hyperactivity disorder, learning disorders,[4] and autism spectrum disorder (ASD).[5] Although the majority of individuals with this syndrome will not develop neuropsychiatric complications, a portion of young adults are at increased risk of concurrent neuropsychiatric disorders such as anxiety, depression, and schizophrenia.[3,4,6] Anticipatory guidance and early developmental interventions to support learning, behavior, and mental health are essential.

FIGURE 1. Pediatric male patient diagnosed with 22q11DS.

Reprinted with permission from Basset AS, McDonald-McGinn DM, Devriendt K, et al.[4]

We recommend the addition of a genetic diagnosis (if known) to the discharge summary and abstract.

While the phenotype, prevalence, and care requirements of patients with the syndrome are described in the literature, little information exists on coordinating health services and the care these patients require throughout life. The ability to study and characterize this population in British Columbia is limited by the diversity of specialty services accessed at tertiary health centres. These difficulties directly interfere with the implementation of best practice guidelines for the care of patients and their families.

BC Children's Hospital (BCCH) specializes in health care for the most complex children in the province, including those affected by 22q11DS, and thus can provide clinicians with insight into the provincial 22q11DS population.

We proposed a study of BCCH patients with two objectives: to investigate current health care utilization and coordination for 22q11DS patients in BC; to investigate current barriers in data sharing and health informatics for this population. We expected that individuals with 22q11DS would make frequent visits to specialty services and require specialized multidisciplinary care for a number of years. We also expected to find significant challenges in institutional and provincial data sharing.

We hoped that by determining which health care services 22q11DS patients access and what barriers affect data sharing we might catalyze new collaborations involving pediatric subspecialties, community primary care providers, researchers, and policymakers and provide a foundation for improved care and planning for transition to adult health care.

Methods

We obtained ethics approval for this study from the University of British Columbia Children's and Women's Clinical Research Ethics Board (H18-00814).

Patients diagnosed with 22q11DS and treated at BCCH from April 2001 to March 2018 were considered eligible for inclusion in a retrospective review. The hospital discharge abstract database (DAD) was searched for patients treated at BCCH diagnosed with *ICD-10* code D82.1 (DiGeorge syndrome). A separate search of the outpatient clinic database sought additional patients associated with *ICD-10* code D82.1 or text describing a diagnosis of "DiGeorge syndrome" or "22Q deletion/transition."

To account for patients not found in the DAD because alternative identifiers were used, we contacted 12 clinics, programs, and services directly involved in the care of these patients: Cardiology, the Cleft-Palate/Craniofacial Program, Complex Care, Cytogenetics, Endocrinology, Immunology, Medical Genetics, Nephrology, Neurology, Orthopaedics, Otolaryngology, and Rheumatology.

We also queried Population Data BC (PopDataBC), the provincial resource for interdisciplinary health research, using *ICD-9* code 758.32 (velocardiofacial syndrome), *ICD-9* code 279.11 (DiGeorge syndrome), and *ICD-10* code D82.1 (DiGeorge syndrome).

Due to retrieval limitations, we could not obtain data from Immunology, Neurology, and Rheumatology at BCCH. We also could not make full use of data from the Cytogenetics service, from the Medical Genetics service based at BC Women's Hospital, or from PopDataBC.

A cohort of patients with 22q11DS was eventually identified by combining both the

DAD and databases for seven BCCH specialty services **[Figure 2]**.

After identifying eligible patients, we performed an analysis of those from the DAD to take advantage of the breadth of data available, including clinic visit details and follow-up time. The Cytogenetics service at BCCH was able to provide additional data outlining specific methods used in the diagnosis of 80 anonymized patients diagnosed with 22q11DS. Due to health authority restrictions and the later inception date for the service (2007), cytogenetic data were not available for the entire study cohort.

To achieve our primary study objective, we quantified the number of patients found in institutional and provincial databases and took note of their demographic characteristics, including age and place of residence, and diagnostic details. Next we classified the admission rates of new and returning patients with 22q11DS over the 17-year study period. Finally, we analyzed the distribution of patients across all health care services at BCCH.

To achieve our secondary objective, we considered limitations in data retrieval and amalgamation to identify current obstacles in data sharing and health informatics.

Results

Coding and reporting discrepancies prevented the collection and amalgamation of data from all relevant provincial and institutional clinics, programs, and services. These discrepancies primarily involved the Medical Genetics database, which could only be used to estimate the prevalence of 22q11DS diagnoses in BC for the study period (n = 400). The database could not be amalgamated with the hospital discharge database because of incongruent ICD-10 coding, search criteria, and patients not diagnosed with 22q11DS or who did not meet study criteria (e.g., referrals for family and fetal losses). Amalgamation of Cytogenetics, Immunology, and Neurology data with the DAD was also not possible because of limitations in the clinical records and/or distribution processes used by these services. PopDataBC search results were inconclusive due to *ICD-9* coding deficiencies.

By increasing awareness of 22q11DS and supporting data sharing, we can improve care, implement transition planning, and translate knowledge into practice.

These limitations were addressed by analyzing subsets of data and amalgamating patient data from the discharge abstract database (n =

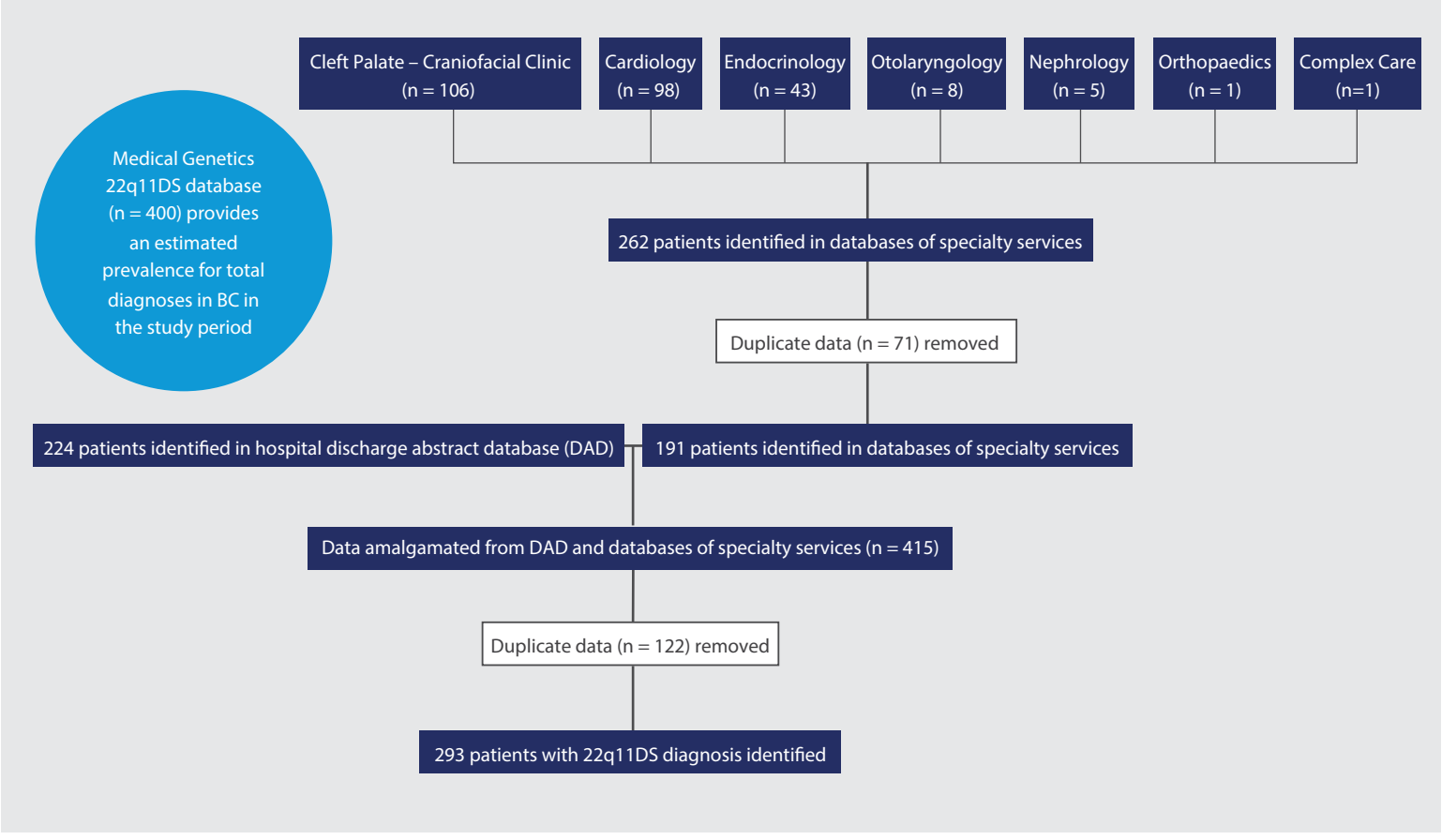

FIGURE 2. Data retrieval process used to address database discrepancies and duplication and identify patients with 22q11DS treated at BC Children's Hospital (BCCH) from April 2001 to March 2018. Discrepancies within Medical Genetics database prevented data amalgamation within our study; however, their data (n = 400) provided an estimated prevalence for total diagnoses in BC in the study period, including referrals for proband, family, and fetal losses.

224) and other BCCH sources (n = 191) and removing any duplicates (n = 122) to identify a total of 293 unique patients.

Demographic characteristics

Of the 293 patients studied, 57% were female (n = 166) and 43% were male (n = 127). The median age at genetics diagnosis was 3 years (IQR = prenatal to age 21 years).

Age distribution was calculated based on patient date of birth. Looking at the records for all patients in the study cohort, 33% were within the transition age range (12 to 19 years) as defined by the British Columbia ONTRAC adult transition program.[7] Additionally, 23% of patients were older than 19 years and 44% were younger than 12 years.

Upon further analysis of age distribution, patients not captured in the DAD and seen by specialty services (n = 69) had a median year of birth of 1996 (IQR 1992 to 2006), whereas patients within the DAD (n = 224) had a median year of birth of 2004 (IQR 1999 to 2009).

Regarding place of residence in British Columbia, most patients resided in the Fraser Health Authority (45%) or the Vancouver Coastal Health Authority (18%), and no obvious differences were found when comparing specialty services patients and DAD patients.

Diagnostic information

Diagnostic information was analyzed using data for 80 patients provided by the Cytogenetics service at BCCH. The Cytogenetics database was established in 2007 and captures a portion of genetic diagnoses in the province. All of the data provided were anonymized, thus preventing amalgamation with other data. We used this subgroup of patients primarily as a proxy to gain an initial understanding of the genetic diagnosis of 22q11DS in BC. We found increasing genetic diagnoses of this condition at BCCH with the advent of the Cytogenetics database. Specifically, cytogenetic testing confirmed 3 diagnoses in 2007 compared with 12 in 2017. From the 80 patients with available genetic data, 46% were diagnosed at or before 1 year of age, 10% were diagnosed in adolescence, and 13% were diagnosed in adulthood **[Table 1]**. Of the prenatal cytogenetic diagnoses, 86% were made with peripheral blood samples and 14% with prenatal diagnostic studies (i.e., amniotic fluid, tissue of conception, or fetal blood).

Since the introduction of cytogenetic testing in the early 2000s, there has been a shift to chromosomal microarray analysis (CMA). With the implementation of CMA in 2009 and the Treatable Intellectual Disability Endeavor (TIDE) protocol in 2011, the scope of CMA requisitions in BC has expanded and we have seen more 22q11DS diagnoses made with this technology. Nearly all genetic diagnoses from 2013 onward have been with CMA.

Admission rates and follow-up

On average, 13 new patients were admitted or seen as outpatients at BCCH each year of the study and followed for 7 years. The PopDataBC platform was not able to yield a cumulative denominator for total provincial 22q11DS diagnoses per year because *ICD-9* coding was used primarily for billing purposes rather than to identify underlying diagnoses. Nevertheless, our proxy of 13 new patients annually reflects the reported birth prevalence of the syndrome (1:3000 to 1:6000)[3] and average annual births in BC since 2001 (n = 43 400).[8]

TABLE 1. Age at genetic diagnosis of 22q11DS by fluorescent in situ hybridization (FISH) or chromosomal microarray analysis (CMA) for 80 patients in Cytogenetics database of BC Children's Hospital, 2007 to 2018.

Age category	Number of diagnoses in category
Prenatal	10
0–1 year	27
2–5 years	10
6–10 years	5
11–19 years	7
20–30 years	11
31+ years	10
All diagnoses	80

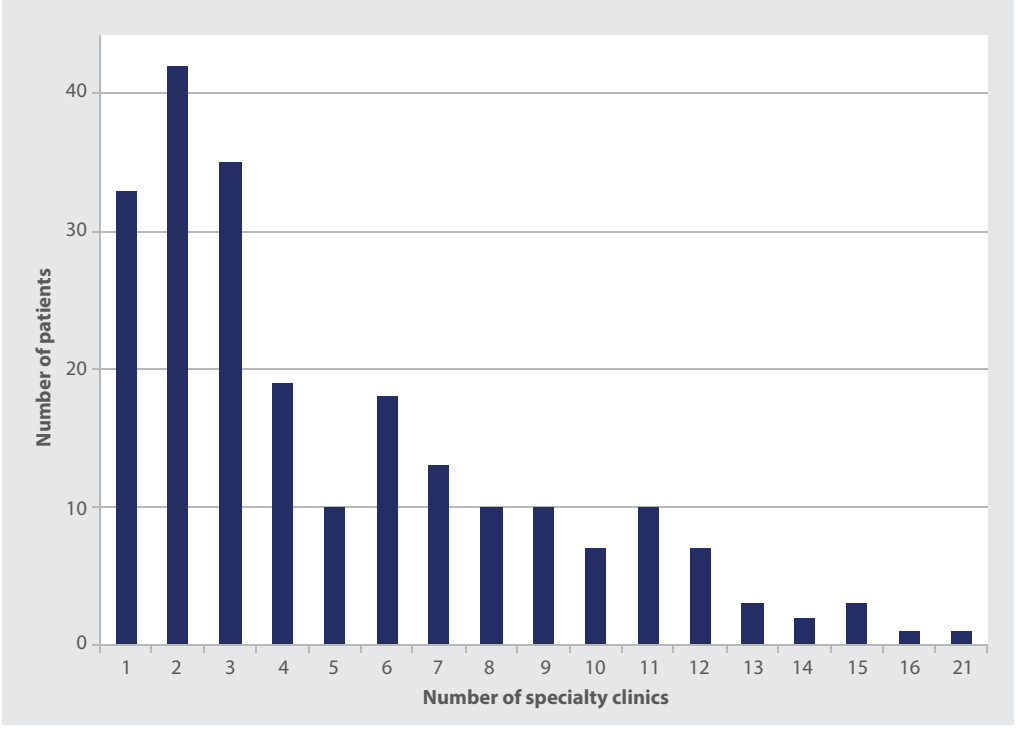

FIGURE 3. Number of specialty services accessed by 224 patients with 22q11DS identified in the provincial discharge abstract database, 2001 to 2018.

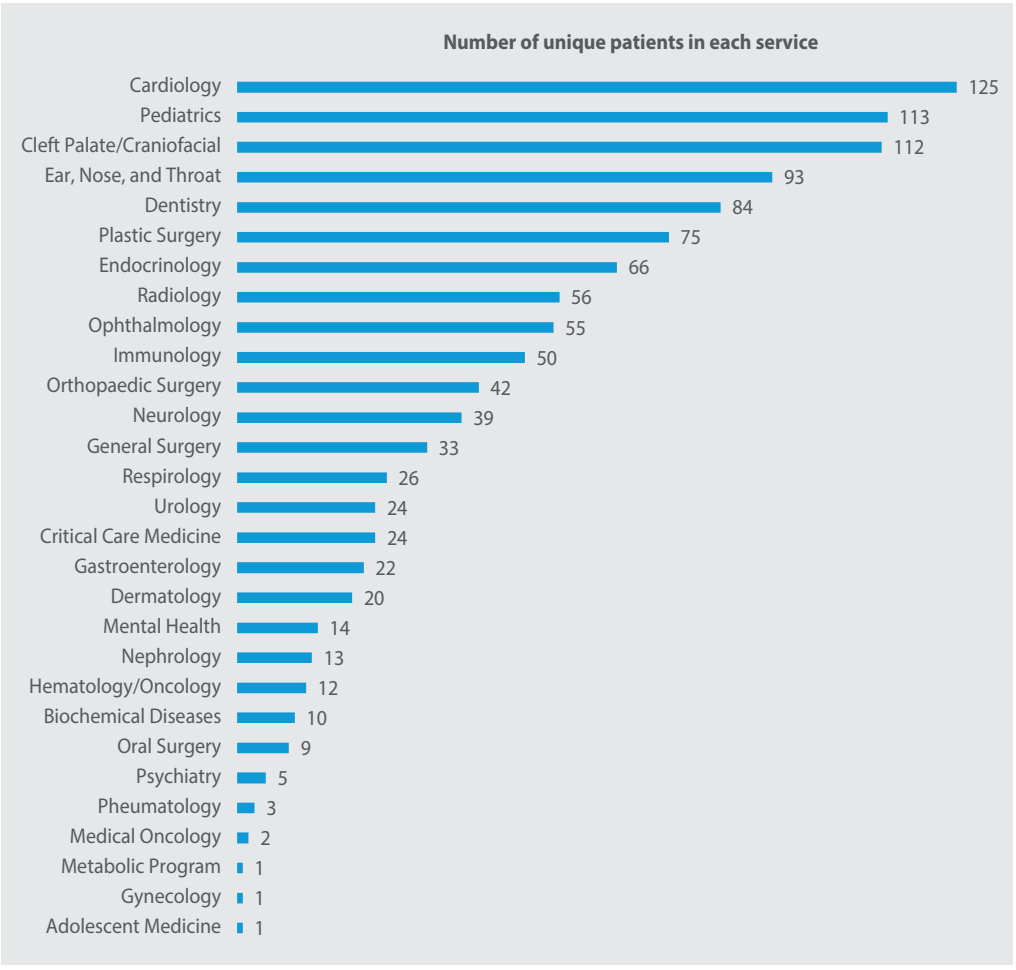

FIGURE 4. Distribution by specialty service of unique patients seen with 22q11DS identified in the provincial discharge abstract database, 2001 to 2018.

TABLE 2. Selected specialty services accessed by 224 patients with 22q11DS identified in the provincial discharge abstract database, 2001 to 2018.

Specialty service	Median age in years at visit (IQR*)	Number of unique patients	Total visits
Cardiology	1 (0–7)	125	1234
Pediatrics	2 (0–5)	113	937
Endocrinology	7 (4–12)	66	582
Otolaryngology	5 (3–8)	93	536
Dentistry	7 (4–10)	84	509
Cleft Palate/Craniofacial	6 (4–7)	112	357
Orthopaedic Surgery	9 (5–13)	42	326
Ophthalmology	3 (1–7)	55	310
Plastic Surgery	5 (3–8)	75	189
Radiology	3 (1–9)	56	84
Immunology	1 (0–4)	50	70

* IQR = interquartile range

Specialty services used

Each 22q11DS patient identified in the DAD (n = 224) was seen by an average of five clinics, programs, or services **[Figure 3]**. More than 50% of these patients visited more than three specialty services at BCCH.

The specialty services accessed by patients were analyzed to determine which had the largest cohort of unique patients **[Figure 4]**. The majority of patients in the DAD received care from Cardiology (Cardiac Surgery and Cardiology) (n = 125), Pediatrics (General Pediatrics, Developmental Pediatrics, and Social Pediatrics) (n = 113), the CP/CFP (Specialty Pediatrics, Plastic Surgery, ENT, Orthodontist/Dentistry, Audiology, Speech Language Pathology, Nursing, and Social Work) (n = 112), and Otolaryngology (Ear, Nose, and Throat Clinic, and Surgery) (n = 93). Each of the specialty services provides access to a number of different subspecialists and allied health professionals, which means many patients saw more than five specialists during their care. The most common service combination was Cardiology, CP/CFP, and Developmental Pediatrics, with 73% of patients seen by one or more of these specialty services and 36% seen by two or more. When looking at unique-patient visit volume, Endocrinology had 10% of the total visits for all 22q11DS patients at BCCH during the study, even though the service cared for only 6% of these patients **[Table 2]**. Finally, while the majority of patients seen by Cardiology and Pediatrics were age 2 or younger, as these patients aged their care shifted to other specialties, namely Otolaryngology, CP/CFP, and Dentistry.

Data sharing

A number of barriers hindered acquiring data for this patient population. First, the current *ICD-10* coding platform is sensitive but not always specific for the presence of a genetic 22q11.2 deletion. This contributes to variability across databases in the coding of this syndrome, especially in cases where patients present phenotypically without a genotypic deletion. In BC the only way to ensure a genetic diagnosis is to cross-match the patient with local cytogenetic databases. These databases are at three locations across the province, with the BCCH Cytogenetics service accounting for only a portion of provincial diagnoses. As well

as having different inception dates, none of the cytogenetic testing services were established for data sharing or research.

Second, disparities in data sets across specialty services and administrative networks prohibit amalgamation with Cytogenetics or Medical Genetics data and leave some patient information in isolated databases. BC Children's Hospital and BC Women's Hospital both provide services for children with 22q11DS and their families. Family-centred care is facilitated by the placement of Medical Genetics at BC Women's Hospital, but can pose a logistic barrier for the study of pediatric patients with a variety of genetic conditions. The current extensive Medical Genetics database is sensitive for 22q11DS, but can lack specificity. While referral data for probands, family members, and fetal loss are captured, not all these data describe patients with an underlying deletion, and our study did not have the resources to overcome this challenge.

Third and finally, the PopDataBC platform does not provide a reliable denominator for our provincial 22q11DS population, which can be attributed primarily to physicians coding for the presenting condition (e.g., cleft palate), rather than the underlying genetic syndrome. Furthermore, although the majority of patients are seen at BCCH for complex CHD and palatal defects, a discreet subset of patients is served at regional centres (e.g., Victoria, Kelowna, Prince George, and Surrey) and their data are not captured.

Conclusions

This study highlights the complexity of health care for patients with 22q11.2 deletion syndrome and identifies the data sharing and transition planning challenges we need to address (see Key practice points). On average, pediatric-aged 22q11DS patients are seen by specialists and subspecialists at five tertiary care programs and are followed for 7 years.

Since 2009, chromosomal microarray analysis has been the diagnostic tool of choice for suspected 22q11DS and the gold standard for investigating intellectual disability (ID), ASD, and multiple congenital anomalies.[9] The increased use of CMA has allowed physicians to circumvent difficulties associated with the phenotypic heterogeneity in clinical presentation and permitted early detection and management of a complex medical condition.

Through improved data sharing systems for 22q11DS and other rare disorders, we will have the opportunities to enhance the patient and family experience, increase system efficiency, and improve health outcomes.[10]

Study challenges

We found that diagnostic coding varied across databases and administrative networks and that patients with 22q11DS were frequently entered into the discharge abstract database under their presenting diagnoses (e.g., cleft palate, CHD, ASD, ID) and were therefore missed in our search. We also found that some specialty services patients were originally referred by smaller outreach subspecialty consultation clinics or were entered into local health authority or private databases with different patient diagnostic coding and, therefore, not captured by the provincial DAD. This small but distinct cohort of patients with minimal hospitalizations and/or outpatient consultations at BCCH was missed when we used hospital discharge summaries to identify patients. The 8-year median age difference between patients captured only in specialty service databases compared to the DAD patients reflects the delayed or attenuated interaction with our tertiary pediatric care centre over the study period.

In a North American context, our results demonstrate an annual increase in the cumulative 22q11DS patient cohort over 17 years, a trend consistent with findings from a study at Seattle Children's Hospital.[11] This trend is predominantly attributed to improved diagnostic technology (i.e., CMA), greater awareness of the syndrome, and an increase in referrals to tertiary care centres.[11] Additionally, improved pediatric surgical survival rates and the success of modern pediatrics have produced a growing population of young adults with multimorbidity complex care needs.

Study limitations

The retrospective design of the study and the different inception dates of the databases we used impaired our ability to identify a cohort strictly adhering to the 17-year review period. As well, our study analyzed health care utilization as a proxy for care needs and did not include a formal qualitative component, thus limiting our holistic understanding of patients care needs.

Recommendations

Despite the extensive scientific understanding of 22q11DS, we do not have integrated case management and data sharing across subspecialties, which makes it difficult for primary care providers, community pediatricians, subspecialists, researchers, and health care planners to ensure evidence-based recommendations are being developed, implemented, and updated.

The results of our study highlight this problem and provide insight into the provincial population of 22q11DS patients. These results may also provide other Canadian jurisdictions with a population health perspective, given that the study took place at BC's only pediatric tertiary care centre. Furthermore, the results emphasize the multidisciplinary complex care needs of these patients and demonstrate the difficulties associated with data amalgamation at institutional and provincial levels.

To address these concerns, we recommend the following:

- Development of a Canadian (or international) 22q11DS patient data registry. A registry would enable prospective input of patient data with filtration criteria and subcategories to document and study the syndrome (e.g., deletion subtype, phenotypic presentation, surgical/medical procedures, transition visit recommendations) and ensure consistent documentation and coding of genetic diagnoses.
- Addition of a genetic diagnosis (if known) to the discharge summary and abstract. Inclusion of genetic diagnoses in the records for all patient encounters (inpatient admissions and outpatient visits) and the use of more specific ICD codes would support advances in tracking, understanding, and caring for patients locally, nationally, and internationally. Implementation of the *ICD-11* beta platform, including coding for deletions on chromosome 22 as distinct identifiers, can be expected to reduce current coding ambiguities.

- Introduction of a formal transition process for patients with 22q11DS moving from pediatric to adult care in BC. Consistent evaluation, knowledge translation, and quality improvement initiatives for health professionals would help patients as they move from pediatric to adult care, as already outlined in the 2011 pediatric care[4] and 2015 transition to adult care consensus guidelines.[6]
- Establishment of a provincial 22q11DS centre of excellence. A centre of excellence in BC would improve the care of adult 22q11DS patients, which has not yet advanced to international standards.[12] Such a centre could also address the complex care needs these patients and their families face from early childhood through to adolescence and adulthood by promoting better functional outcomes in health, mental health, independence, participation, and employment.

By increasing awareness of 22q11DS and supporting data sharing through collaboration between provincial health care providers, local experts, political figures and policymakers, and national/international 22q11DS Centres of Excellence, we can improve care, implement transition planning, and translate knowledge into practice. ■

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Competing interests

None declared.

Key practice points: Managing patients with 22q11DS

- The care of patients with 22q11.2 deletion syndrome, also known as 22q11DS or DiGeorge syndrome, can involve many health care providers, including allied health professionals, family physicians, community pediatricians, and other specialists and subspecialists.
- Patients with 22q11DS can present with significant clinical variability, leading to a wide range of ages at the time of diagnosis.
- Most 22q11DS patients will present at routine primary care visits with feeding problems, developmental delay, or early mental health concerns (e.g., speech, attention, or learning difficulties; anxiety, autism spectrum disorder).
- 22q11DS is actually a common "rare disorder," with an annual birth prevalence of 1:3000 to 1:6000.
- A significant proportion of family physicians will have patients with 22q11DS in their practices and will benefit from up-to-date best practice guidelines and data sharing.
- Chromosomal microarray analysis (CMA) is the current gold standard for an initial diagnosis of 22q11DS.
- A significant number of hospital specialty clinics, programs, and services provide care for 22q11DS patients, with most pediatric care delivered by cardiology, developmental pediatrics, cleft palate programs, endocrinology, and otolaryngology services.
- Education, information-sharing, and resource networks are fundamental for patients with 22q11DS, who often require several years of active multidisciplinary follow-up involving more than 10 health care providers, making planning the transition journey daunting for the majority of these patients and their families.
- We have the opportunity to model a best-practice "ON-TRAC"[7] transition care pathway for other rare disorders by developing an effective "triple aim (to improve health, care, and cost)"[10] transition program for 22q11DS, with improved data linking, family-centred approaches, and provincial collaboration.

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