Development of a cardiac inherited disease service and clinical registry: A 15-year perspective

Inherited heart conditions are a major cause of sudden unexpected death in young people. This paper describes how New Zealand's (NZ) cardiology and genetics communities responded to the challenge of detecting individuals at risk. The Cardiac Inherited Diseases Group (CIDG), initially comprising four people, developed a national multidisciplinary network, genetic testing, and the world's first national and fully funded molecular genetic autopsy service (using genetic testing to ascertain cause of death). This was underpinned by a national, ethically approved consent based registry for inherited heart conditions and sudden death—the Cardiac Inherited Diseases Registry New Zealand (CIDRNZ). Here we present the timeline for the registry's development and key features that may be useful for others developing their own cardiac inherited disease service.

Study design

This study is a descriptive timeline of the growth of the registry and the associated service. Demographic, clinical and genetic data are stored on a secure database, from which the data for these analyses were extracted on 10 October 2017.

Results

Overview of timeline

CIDG was established in Auckland, NZ, in 2000 (Supplementary Figure 1). The group established a clinical and genetic registry to track probands and facilitate family screening, CIDRNZ, with regional ethical approval in 2002 and national approval in 2009. The registry is web-based and was purpose-built by a local software company, with the clinical risk and governance managed by the Auckland District Health Board where the registry head office is based.

Over the subsequent 15 years the registry evolved to a multidisciplinary national service with three coordinators (based in Auckland, Hamilton, and Wellington), 2746 registrants, covering at least seven forms of cardiac inherited disease with a strong focus on investigating sudden unexplained death in the young (SUDY) (Figure 1).

Molecular autopsy and investigation of SUDY

The registry story really began in 2001 following the sudden death of a 12 year-old warming up for a hockey game, with the certified cause of death being epilepsy. The family was referred to the senior author by a pediatrician, as the clinical history was suspicious for LQTS. No DNA had been saved at autopsy, so using the child's neonatal screening card we found a previously identified mutation, p.R243C in the *KCNQ1* gene. This suggested LQTS type 1 as the likely cause of death.[1] The mother was also a carrier and had ECGs consistent with LQTS type 1 under exercise provocation, but we were able to reassure the family that the child's sibling did not carry the mutation. The emotive impact of this discovery and its evident value to the family proved a powerful motivator to those involved.

Simultaneously, there was emerging evidence that DNA should be saved at autopsy after sudden death,[2] and cardiac genetic investigation of families was being pioneered in the United Kingdom and the Netherlands.[3,4]

CIDG received national funding for molecular autopsy in 2008 and members worked with colleagues in Australia to develop of a best practice document for the investigation of SUDY.[5] Subsequently, combining NZ and Australia data over 3 years led to a population-based report in 2016 showing the annual incidence of sudden cardiac death was 1.3 cases per 100,000 persons 1–35 years of age.[6]

Now in NZ, investigation of SUDY is fully integrated within CIDRNZ and every family is given a standard brochure following a sudden death. This describes the registry and the process of investigation, led by the forensic pathologist and guided by the CIDRNZ team.

Registry demographics and genetic screening

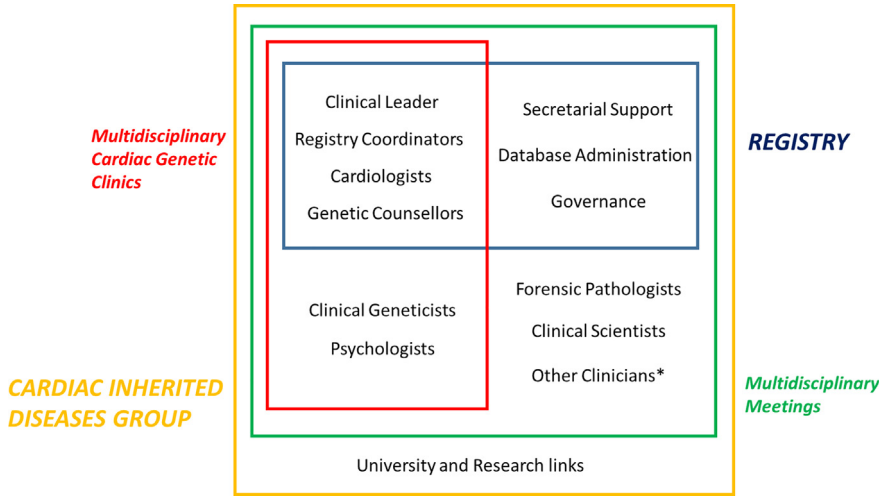
In October 2017, CIDRNZ included 941 probands with suspected cardiac inherited disease and their families (Table I). Twenty-two percent of probands were registered due to a sudden death or resuscitated sudden death. Hypertrophic cardiomyopathy and LQTS were the most common conditions comprising 32% and 30% of probands respectively. The probands were predominantly male (56%) with a mean age of 42 years, and predominantly European (54%) followed by NZ Māori (15%) and people of Pacific Island descent (6%).

Six hundred forty-five probands (68%) have undergone genetic screening (including sudden death victims), with a confirmed pathogenic genetic variant in 216 (23%) and a gene variant of uncertain significance (VUS) identified in a further 37 (6%) (Supplementary Table I, Supplementary Figure 2).

In addition, 1805 family members have been registered, 629 (35%) of whom are clinically affected by cardiac inherited disease or carry a pathogenic mutation. From the 216 probands with pathogenic mutations identified, 771 family members have undergone cascade genetic screening: 408 (53%) were carriers of the pathogenic mutation identified in the family proband. Detailed family history and pedigree information obtained from the proband enables family members to be identified and contacted for screening.

Clinical data in the registry includes reported ECGs, exercise/Holter tests and other investigations, reason for referral (worst symptom/event, referral pathway), records of encounters with the clinical service, family pedigrees, genetic testing results, and autopsy and pathology results (for sudden death referrals). These data are entered mainly by the registry coordinators and are available to the multidisciplinary team across NZ.

Figure 1



* i.e. Neurologists, metabolic specialists brought in as necessary

Interplay between different members of the multidisciplinary Cardiac Inherited Diseases Group New Zealand.

Discussion

The CIDRNZ is respected for its work in developing the molecular autopsy as part of the investigation of SUDY. While that work has been central to our research output, the primary motivation has always been the detection of presymptomatic individuals at risk in the community so that they can be offered protective therapies through the associated clinical service, such as medications and implantable cardioverter defibrillators. This has been effective, with roughly half of all expected LQTS cases having been identified in Auckland City (a prevalence of 2.2 per 10,000 people), where the registry began.[7]

Key features for success of the registry

For those who may wish to establish a similar registry and clinical service, there are several key elements that have been central to CIDRNZ's establishment and success (Table II).

Multidisciplinary approach

No single discipline can provide this service; a collaborative team approach is essential.[8] At the center is cardiology with clinical genetics/genetic counselors being the major partners, and input from forensic pathology and psychology. Nurses and allied professionals can be trained in inherited heart disease and can raise the profile of these conditions, improve family history taking and increase the referrals to the registry.[9]

Fortnightly multidisciplinary meetings (including nationwide videoconferencing with up to five regional centers) are the cornerstone of our service, and help foster collaboration and education. Key decisions include

Table I. Clinical characteristics of probands in the Cardiac Inherited Diseases Registry New Zealand

Probands, n	941
Age (mean, ± SD)	42 years ±22
Male, n (%)	524 (56)
Deceased	193 (20)
Ethnicity	
European	505 (54)
Maori	139 (15)
Pacific Islander	61 (6)
Asian	28 (3)
Indian	26 (3)
Other	10 (1)
Not stated/Unknown	172 (18)
Cardiac inherited disease, n (%)	
Arrhythmogenic right ventricular cardiomyopathy	35 (4)
Brugada syndrome	49 (5)
CPVT	15 (2)
Dilated cardiomyopathy	46 (4)
Hypertrophic cardiomyopathy	305 (32)
Long QT syndrome	280 (30)
PCCD	5 (1)
Resuscitated SCD*	48 (5)
Sudden death	158 (17)
Referral source, n (%)	
Adult cardiology	572 (61)
Pediatric cardiology	76 (8)
Clinical genetics	11 (1)
Pediatrics	45 (5)
Pathology	128 (14)
Self/Family	17 (2)
General practitioner	4 (0.5)
Other/Unknown	88 (9)

CPVT, catecholaminergic polymorphic ventricular tachycardia; PCCD, progressive conductive cardiac defect; SCD, sudden cardiac death.
* Excludes those where there is a clinically apparent cause.

Table II. Key features of a cardiac genetic registry and service

Clinical leadership	Knowledgeable leader/s with a passion for the subject, a relevant sub-specialty skill and dedicated time for the project is essential.
Coordinator	Paramedical/nursing/genetic counselor. This person is the face of the service, coordinating family screening tests, interdepartmental liaison, consenting processes, data entry.
Governance	Medicolegal governance can take many forms. For CIDG this is within a district health board - also every clinician signs a confidentiality agreement so that data within the registry does not get into clinical notes without the individual's permission.
Ethical and cultural approval, and process for informed consent	This is country-specific. In NZ CIDG has national ethical approval by the same body that approves research projects, since there is no other. N is a bicultural society, and Māori representation has been essential for all major steps including design of consent forms and information sheets.
Multidisciplinary cardiac genetic clinics	The coordinator: prepares the clinic list, draws the family tree, arranges cardiac tests. The cardiologist: interprets cardiac tests, clarifies aspects of the clinical and family history of note with the family, arranges genetic testing, delivers results. Genetic services (geneticist, genetic counselor): Arranges genetic testing, counsels family, delivers results.
In-hospital presence	A coordinator within the hospital can recruit patients as they present, and educate cardiology, intensive care and emergency department personnel. Well-taken family histories combined with a simple in-hospital referral system results in the detection of large numbers of pre-symptomatic family members, and can save money on unnecessary diagnostic tests in a new case by finding they are part of a known family.
Multidisciplinary meetings	Organized at regular intervals and with good use of remote video/teleconferencing with regional coordinators. Discussions revolve around referrals, approving genetic tests, genetic testing results, and interpreting cardiac test results.
Database	Ideally, a secure web-based family-orientated database, with facility to record clinical and genetic testing results, link to demographic data from public health records, and provide a platform for audit, quality control and research. CIDG has a bespoke system but there are suitable commercial alternatives.
Regional collaborations	The ideal registry knows no borders, just as families travel the country and the world. Respectful collaboration with neighboring clinics is a must, and most easily achieved at the outset.
University and research links	This area has benefitted hugely from translational research. What is research one day is best practice the next. Registry data should be there to learn from for future generations.

deciding which patients will undergo genetic testing, interpreting test results and deciding on treatment plans (Supplementary Figure 2). The decision to undertake genetic screening on a proband is based on the strength of the clinical evidence of cardiac inherited disease (including family history) and the likely yield of genetic testing for the specific disease under suspicion.

Leadership and coordination

When establishing a new discipline in medicine, strong leadership is essential. In our service, this is a pediatric cardiologist (JRS); in other centers, this is a clinical geneticist or adult cardiologist.[10] There must also be a coordinator; in our service, this is a cardiac physiologist (JC), other registries have genetic counselors or senior nurses. Funding our service is challenging, with no dedicated national funding provided until 2008, and perseverance has been crucial.

High profile and simple referral process

We promote a simple message to all clinicians - if you are considering inherited heart disease, refer to CIDRNZ. The key patients to refer are (1) anyone with a proven or suspected inherited heart condition, (2) anyone with an idiopathic cardiomyopathy, (3) anyone with unexplained cardiac arrest (ages 0–40), and 4) any unexplained sudden natural death (ages 1–40). We offer contact details as well as online referral via the website (www.cidg.org.nz), and anyone suspected of having inherited heart disease can be registered. Our registry has a wider scope than national registries focused specifically on SUDY[11,12] by including living probands (people with symptoms or incidental findings, and survivors of cardiac arrest), and has the benefit of including DNA storage as part of the registry process compared with registries which only collect clinical data.[13]

Registry infrastructure and research collaborations

Central to our process is ethical approval and informed consent. Every participant gives their permission for their information and DNA to be used in de-identified research into their condition (given by next of kin for deceased persons). As a result, over 50 publications have arisen from CIDRNZ, including collaboration with other registries internationally.[6,14]

Ongoing challenges and future directions

Cardiac genetics is in its infancy. Registries inform the interpretation of new genetic variants and provide a portal for us to contact patients with new discoveries and treatments. As new genes are discovered and genetic variants are reclassified, we can revisit DNA samples and

genetic datasets to further advise our patients and their doctors as to their level of risk. We perform re-evaluation of genetic variants as additional pedigree members are identified, permitting ongoing assessment of the phenotype/genotype co-segregation for each variant.

A hurdle in NZ is discrimination against a patient on the basis of pre-symptomatic cardiac or genetic testing. Laws to protect patients from such discrimination, as present in the United States, are needed elsewhere.

In NZ, healthcare is funded mostly on a regional basis, increasing the difficulty of providing an equitable nationwide service.[15] Health service managers need to ensure adequate resources are in place to manage these many families across the globe.

Conclusion

Anyone involved with families who have suffered a young sudden death will be moved by their tragic event. The desperate need of the family to know why, comes with the question of whether it will reoccur in anyone else. A registry such as CIDRNZ can potentially reduce such deaths, whilst presenting opportunities to find hitherto unknown causes.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.11.013.

Am Heart J 2019;126–130.
0002-8703

https://doi.org/10.1016/j.ahj.2018.11.013

Nikki J. Earle, PhD
Department of Medicine, The University of Auckland, Auckland, New Zealand
Greenlane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand

Jackie Crawford, NZCS
Greenlane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand

Ian Hayes, MBChB, FRACP
Genetic Health Service New Zealand, Northern Hub, Auckland, New Zealand

Mark I. Rees, PhD
Neurology Research Group, Institute of Life Science, Swansea University Medical School, Swansea University, United Kingdom

John French, MBChB, PhD, FRACP
Cardiology Department, Liverpool Hospital, Sydney, New South Wales, Australia

Martin K. Stiles, MBChB, PhD, FRACP
Department of Cardiology, Waikato Hospital, Hamilton, New Zealand

Kathryn E. Waddell-Smith, MBChB, PhD, FRACP
Greenlane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand

Tom Donoghue, MNurs, RN
Department of Cardiology, Wellington Hospital, Wellington, New Zealand

Rachael Monkley, PGDipNurs, RN
Department of Cardiology, Waikato Hospital, Hamilton, New Zealand

Katherine Neas, MBChB, FRACP
Genetic Health Service New Zealand, Central Hub, Wellington Hospital, New Zealand

Andrew Aitken, MBChB, FRACP
Department of Cardiology, Wellington Hospital, Wellington, New Zealand

Rexson Tse, MBBS, FRCPA
Department of Forensic Pathology, LabPLUS, Auckland City Hospital, Auckland, New Zealand

Donald R. Love, DSc, FRCPath
Pathology Genetics, Sidra Medicine, Doha, Qatar

Jonathan R. Skinner, MBChB, MD, FRACP
Greenlane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand
Reprint requests: Jonathan R. Skinner, Greenlane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, 1142, New Zealand
E-mail: JSkinner@adhb.govt.nz

On behalf of the Cardiac Inherited Diseases Group

References

1. Skinner J, Chong B, Fawkner M, et al. Use of the newborn screening card to define cause of death in a twelve year old diagnosed with epilepsy. J Paediatr Child Health 2004;40:651-3.
2. Tester DJ, Ackerman MJ. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. J Am Coll Cardiol 2007;49:240-6.
3. Behr E, Wood DA, Wright M, et al. Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. Lancet 2003;362:1457-9.
4. Tan HL, Hofman N, van Langen IM, et al. *Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives.* 2005:207-13.
5. Vohra J, Skinner J, Semsarian C. Cardiac genetic investigation of young sudden unexplained death and resuscitated out of hospital cardiac arrest. Heart Lung Circ 2011;20:746-50.

6. Bagnall RD, Weintraub RG, Ingles J, et al. A prospective study of sudden cardiac death among children and young adults. N Engl J Med 2016;374:2441-52.
7. Earle N, Crawford J, Smith W, et al. Community detection of long QT syndrome with a clinical registry: An alternative to ECG screening programs? Heart Rhythm 2013;10:233-8.
8. Ingles J, Yeates L, Semsarian C. The emerging role of the cardiac genetic counselor. Heart Rhythm 2011;8:1958-62.
9. Waddell-Smith K, Donoghue T, Graham M, et al. The inpatient cardiology visit: Missing the opportunity to detect inherited heart conditions. Heart Lung Circ 2014;23(Suppl 2):e18-9.
10. Zentner D, Thompson TN, James PA, et al. The Cardiac Genetics Clinic: a model for multidisciplinary genomic medicine. Med J Aust 2015;203:261.e1-6.
11. Burns KM, Bienemann L, Camperlengo L, et al. The sudden death in the young case registry: Collaborating to understand and reduce mortality. Pediatrics 2017;139, e20162757.
12. Toukola T, Hookana E, Junttila J, et al. Sudden cardiac death during physical exercise: Characteristics of victims and autopsy findings. Ann Med 2015;47:263-8.
13. Ingles J, McGaughran J, Vohra J, et al. Establishment of an Australian National Genetic Heart Disease Registry. Heart Lung Circ 2008;17:463-7.
14. Lahrouchi N, Raju H, Lodder EM, et al. Utility of post-mortem genetic testing in cases of sudden arrhythmic death syndrome. J Am Coll Cardiol 2017;69:2134-45.
15. Earle N, Crawford J, Gibson K, et al. Detection of sudden death syndromes in New Zealand. N Z Med J 2016;129:67-74.