RESEARCH PROTOCOL

Queensland Renal Biopsy Registry

Short title: QLD Renal Biopsy Registry

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1.0 Study Title: Queensland Renal Biopsy Registry

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3.0 Governance

The Statewide Clinical Renal Network (SCReN) has facilitated formation of a steering committee (Governing body)

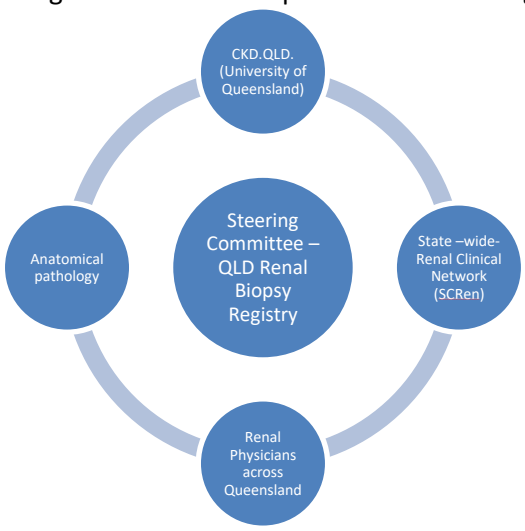
Purpose

To establish a registry of patients with biopsy-proven renal disorders, through the collaboration of CKD.QLD (University of Queensland), the SCReN and Renal Physicians from other Hospital and Health Services across Queensland.

RELATIONSHIPS

Governance / Reporting Structure:

- The Qld.Renal Biopsy Registry Steering Committee will report to SCReN through the Chair of the committee.



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4.0 Introduction

The diseases of the kidney can be broadly classified into acute kidney injury (AKI) and chronic kidney disease (CKD). AKI is abrupt decline in kidney function and CKD is progressive loss in kidney function over a period of months to years. AKI occurs in about 17% of patients admitted to the hospital in Australia and New Zealand. Patients who develop AKI have higher rates of morbidity and mortality, and quarter of them may progress to CKD. The impact of AKI on the heath care budget is substantial when compared to the hospital costs to patients without AKI. AKI is mainly due to sepsis, hypovolemia, following major surgery, exposure to nephrotoxins, and is often associated with other organ failure. A renal biopsy is required in AKI of unknown aetiology to obtain information for diagnosis, management and prognosis. In a Spanish study renal biopsy confirmed AKI in children, adults and elderly was 5.7, 12.5% and 32.9% respectively.

CKD pose a significant burden to health care system and in 2012 direct and indirect costs in managing CKD was $4.1 billion (http://kidney.org.au/). Approximately 1in 10 Australians have indicators of CKD and 10% of patients visiting a general practitioner have CKD (http://kidney.org.au/). CKD can progress to end stage renal disease requiring renal replacement therapy (RRT). At the end of 2014 overall prevalence of people receiving RRT in Australia was 947 pmp. Three most common causes of kidney disease requiring long-term RRT were diabetes, glomerulonephritis and hypertension (http://www.anzdata.org.au/). Nephrologists have to perform a kidney biopsy to diagnose and prognosticate glomerulonephritis and tubulo-interstitial disorders. In 2014 20% of the patients who started long-term RRT were due to these disorders of the kidney. There is paucity of information on management strategies and therapeutic outcomes of these patients as there is lack of consensus in definitions, recommended treatment modalities, and clinical / research collaboration. The Renal Biopsy Registry will facilitate specific target-guided therapy, “evidenced” rather than empirical therapy. The Registry will help identify potentially mixed pathology, identify population–based or regional patterns, and trends in certain sorts of kidney disease e.g. environmental problems, CKDu, environmental, occupational, and toxic nephropathies etc, and will characterize apparently newish syndromes e.g. proton pump inhibitor -associated nephropathies. In many developed countries renal biopsy registries have been initiated to address these issues but no similar registry exists in Australia. We therefore aim to establish a renal biopsy registry in Queensland and later expand the registry across Australia.

4.1 Plain language statement

Each kidney is made of about one million tiny structures called nephrons. Kidneys fail when diseases injure these nephrons Kidney injury may occur in short term called acute kidney injury (AKI) or kidney function may worsen over months to years known as chronic kidney disease (CKD). People suffering from AKI recover their kidney function with treatment but in some, AKI may lead to CKD. About 14% of Australian adults have CKD with higher rates with age and in indigenous Australians. [http://kidney.org.au/cms_uploads/docs/kha-economic-impact-of-eskd-in-australia-projections-2020.pdf]. Some of these patient’s progress to end stage kidney disease (ESKD). Glomerular and tubular disorders can result in AKI and CKD and as a group is the second leading cause of ESKD in Australia and New Zealand among those who opt for dialysis and transplantation. There is a great variation in outcomes of these disorders. There is some information on the epidemiology, but the variation is still poorly understood.

When the cause of kidney disease is unclear, develop treatment plan and or assess prognosis renal physicians perform a kidney biopsy. The biopsy is sometimes used to define the extent of damage and evaluate how well the treatment is working. And the things usually examined on biopsy are nephrons, the functional unit of the kidney. It is composed of tiny filters known as *glomeruli*, the fluid from these filters

are modified in conduits called *tubules* and in association with *interstitium,* the tissue surrounding and supporting these structures. “Glomerular disorders, Glomerulonephritis and Glomerulopathies” [GN] and tubulointerstitial nephritis refer to a range of kidney conditions which cause inflammation of these structures in the kidney. This occurs due to a problem with the body’s immune system.

The purpose of this study is to establish a state-wide renal biopsy registry to collect detailed clinical information of patients suffering from these disorders. Analysis of the database will provide opportunities for better understanding of the longitudinal course and outcomes of these patients. The data will be used to formulate guidelines for management. There is a long-term plan, pending additional ethical approval, to establishing a nationwide renal biopsy registry.

4.2 Background

Kidney injury can be either acute or chronic. The incidence of AKI in hospitalised patients using a KDIGO – guidelines was 16.9% in Australia and New Zealand [1]. Subsequent renal decline was greater after AKI (vs no AKI) (14.8% vs 10.8%); even if post-discharge kidney function returns to normal; overall, 25 percent of AKI patients progress to chronic kidney disease [2]. The first national report on AKI in Australia has shown that AKI is a growing problem and AKI affects living in socioeconomically disadvantaged areas had higher AKI hospitalisation and death rates in the population more than others. http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129552567. National renal biopsy registries provide useful information in biopsy confirmed acute kidney injury. Spanish data on renal registry study collected over a decade showed 16.1% of the biopsies were diagnosed with acute kidney injury [3]. Studies from this registry showed that the prevalence of biopsy-confirmed acute renal failure according to aetiology was vasculitis, 23.3%; acute tubulointerstitial nephritis, 11.3%; and crescentic glomerulonephritis types 1 and 2, 10.1%. This study also highlighted that the prevalence of the different causes differed significantly according to age group [3].

Approximately 1.7 million Australian adults have chronic kidney disease, and some may progress to end stage kidney disease [www.kidney.org.au]. The most common causes of CKD in Australia are diabetes mellitus, glomerular and tubulointerstitial disorders of the kidney and hypertension. Glomerulonephritides (GN) and tubulointerstitial disorders have an incidence of 0.7 -2.8 per 100,000/year [4] and are the second leading cause in patients with ESKD requiring renal replacement therapy in Australia and New Zealand [ANZDATA] [5]. Annual estimated cost of a hospital haemodialysis patient is about A$ 80,000. These disorders therefore pose a significant burden to the health care system as the risk of progression to end stage kidney disease (ESKD) is high. Renal biopsy registries have been started in many countries to understand their epidemiology, enhance nephrologists’ collaboration to improve patient care, and evaluate new clinical care [1,6]. There is a dearth of high quality clinical trials due to reasons such as lack of consensus in definitions, low prevalence of disease, difficulty in recruitment, high costs of trials and lack of collaboration. The creation of renal biopsy registry could facilitate to conduct high quality trials [7]. There is no established renal biopsy registry in Australia. Data on epidemiology of biopsy proven GN was first published from Victoria in 2001[8] and fifteen years later from Queensland [9]. There have been no significant changes over time with age, gender or incidence of biopsy proven GN in Australia [9]. A recent study on biopsy proven GN from New Zealand has shown age, hypertension and heavy proteinuria at diagnosis are strong predictors of progression to ESKD and death [10].

Nevertheless, there is a paucity of data on management strategies and therapeutic outcomes of these disorders. There is an increasing incidence of crescentic GN over the last decade and 75% is due to Anti neutrophil antibodies associated GN [ANCA GN] [9]. There is gross variation in biopsy proven ANCA GN across two metropolitan Queensland hospitals though they provide services to a population of about a million each. (Unpublished observations –LF/DR): Silica dust from mining industry is considered as a risk

factor [11,12]. There is also a suggestion that there is a relation between the effect of severe cyclones and storms on the incidence and clinical phenotype of ANCA associated vasculitis [13]. The exact reasons either for increasing trend or for disparity in different locations are not known. Aboriginal adults have an increased incidence of CKD and kidney failure [14]. It may be explained by low birth weight and infection causing GN in their childhood but not entirely understood [15]. Lupus Nephritis, another form of GN has been shown to be predominantly seen in Australians of Asian descent [16]. Dysregulation of the alternative pathway of complement involving the kidney can result in atypical haemolytic uremic syndrome (aHUS) and C3 glomerulopathy. Alternative pathway may also be involved in other forms of glomerulonephritis such as anti-neutrophil cytoplasmic antibody mediated GN and immunoglobulin A (IgA) nephropathy [17]. Even though there is some information that genetics, geography, environment, race and socio-economic conditions play a role there is not enough data on the longitudinal course, management strategies and therapeutic outcomes of these patients, and there is little clinical and or research collaboration. Australian Institute of Health Welfare reports that there is not enough information on managing glomerulonephritides (http://kidney.org.au/cms_uploads/docs/kha-economic-impact-of-eskd-in-australia-projections-2020.pdf). There are no long –term studies from Australia on the outcome of biopsy proven acute kidney disorders or tubulointerstitial nephritides

A comprehensive database including patient demographics, co-morbidities, laboratory investigations, histological diagnosis, treatment and outcome of biopsy proven renal disorders is therefore required.

Renal transplant histology is variably obtained at surgery after clamp release. Allograft biopsy is more frequently performed when acute or chronic rejection, recurrence of native disease, denovo GN, tubulointerstitial nephritis, calcineurin toxicity, microangiopathy and unexplained renal dysfunction are considered. Some centres perform protocol biopsies as well. Data accrual across the state reflects varying immunosuppression and its effects that contribute toward allograft health and provide valuable information in optimising therapy.

Queensland has a population of about 4.8 million, a mix of socioeconomic status that includes indigenous Australians and peoples that are culturally and linguistically diverse. Queenslanders live in metropolitan cities, smaller towns and rural and remote areas. Queensland is approximately 1/5th of the country by size and has approximately 1/5th of the dialysis population. As a state, Queensland is representative of both the national Australian population in general, and the renal population.

Existing Renal Biopsy/GN Registries:

Several renal biopsy exist to address the natural history of medical renal disease, describe their clinical features, evaluate treatment, understand risk factors for complications, support studies and health services research in these disorders.

- ***Danish Renal Biopsy Register (1985)***
  Renal biopsy registry was established in the kingdom of Denmark in 1985 with the aim of accumulating comprehensive clinical and pathologic information related to all renal biopsies done in Denmark**.**

- ***The Toronto Glomerulonephritis Registry [1986]***
  [https://www.symptoma.com/en/research/profile/toronto-glomerulonephritis-registry-group]
  A regional program for studying the natural history of the different types of glomerulonephritis and the effects of drug therapy on them was established in Toronto. Data for all patients with histologic evidence of glomerulonephritis seen at the participating hospitals are collected on standard forms

and stored in a computer. Randomized controlled trials of different types of therapy for glomerulonephritis are conducted under the coordination of the central registry.

- ***The Czech registry of renal biopsies (1993):***
  Renal Biopsy registry was established in Czech Republic '. Aims of this registry are to study the epidemiology of renal disorders based on histologic diagnosis and to identify the most frequent clinical syndromes [15]

- ***Spanish registry of Glomerulonephritis [1994]*** [http://www.nephropathology-esp.org] studies the epidemiology of renal diseases in Spain was established to know the prevalence and incidence of biopsied renal diseases and study the relationship between clinical data and histologic patterns.

- ***Italian nephrologists [1996]*** collect the data relating to renal biopsies in a national registry, Italian Registry of Renal Biopsies [http://www.irrb.net] to conduct epidemiologic studies in health care to answer the several open questions in both prevention and treatment of renal diseases.

- ***Japanese Society of Nephrology [2007]*** started the first nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry [J-RBR], to record the pathological, clinical, and laboratory data of renal biopsies [18]**.**

- ***The British Columbia GN Network and Registry [2013]*** [6] is a unique model in that it combines robust data capture, data linkages, and health care delivery and evaluation into one integrated system. This registry includes all patients in provincial renal database who had a renal biopsy, irrespective of diagnoses. They collect extensive data to study the risk of progression to ESKD and healthcare resource utilization. This registry comprises of both these elements capturing data prospectively utilising the existing health infrastructure.

5.0 Study Aim and Objectives

To establish a registry of patients with biopsy-proven renal disorders enabled by a collaboration of the State Wide Clinical Renal Network [SCReN], Renal Physicians from Hospital and Health Services across Pathology Queensland and CKD.QLD [The University of Queensland].

The principal aim of the Registry is to improve patient care and outcomes. The Registry will do this by profiling renal biopsy proven disorders in Queensland which will facilitate early recognition, benchmark management to best practice, and provide a platform to validate new care strategies.

Specific objectives include:

- Development of a prospective collection of clinical, laboratory, pathology, treatment and outcome data of patients with biopsy proven medical renal disease
- Consolidation of data into a collated data set [Registry]
- Evaluation of patient data to identify and facilitate improved clinical care and management
- Support clinical research
- Identification and development of health policies targeting patients with biopsy proven renal disorders
- Develop links and collaborations with other registries nationally and internationally

5.1 Hypothesis:

A Renal Biopsy Registry will facilitate research and provide a single access point of data for treating clinicians, patients and their families, supporting improved patient care, management and research, with an understanding for health economics and supporting improved health service delivery in the future.

No comprehensive information on role of geography, environment, race and socioeconomic conditions causing these disorders. There is not enough data on incidence, prevalence, longitudinal course, management strategies and therapeutic outcomes of these patients, and, there is little clinical and or research/ collaboration. To address this problem developed countries have established registries. The plan is to establish a Queensland renal biopsy registry. The long-term objective is to expand to a national renal biopsy registry once the Qld registry is established both in feasibility, governance and first outcomes. This is an observational study.

6.0 Study Method

6.1 Study Design

Definition of biopsy proven renal disorders for purpose of the registry:
Data of the patients who underwent l histopathological examination of their renal tissue will be collected in this registry. Malignancy related renal biopsies will be excluded from this registry

Glomerulonephritides / Glomerulopathy:
Proliferative glomerulonephritis is characterised by increased glomerular cellularity with the proliferation of indigenous cells and/or leucocyte infiltration; the main categories of proliferative glomerulonephritis are immune-complex proliferative GN, pauci-immune GN, anti-Glomerular basement membrane (GBM) GN, proliferative monoclonal immunoglobulin GN, and C3 GN. Other non-proliferative glomerulopathies include the presence of immune complex deposition without cellular proliferation (in membranous nephropathy), podocytopathies (minimal change disease and focal segmental glomerulosclerosis-FSGS), the deposition of amyloid or monoclonal immunoglobulin deposits, and glomerular changes secondary to diabetes mellitus, in the absence of any of the conditions described above.

Tubulointerstitial disorders
Tubulointerstitial kidney diseases are those in which the tubules and interstitium, rather than the glomeruli, are the primary sites of injury. These conditions include acute tubular injury from ischaemia or toxins, as well as tubulointerstitial nephritis due to viral infections, drug reactions and hereditary conditions. Some systemic diseases may also cause tubulointerstitial kidney disease, such as the cast nephropathy associated with multiple myeloma, and interstitial nephritis associated with autoimmune conditions such as systemic lupus erythematosus

Phase 1A: Retrospective Data
Retrospective analysis of data collected for the study on epidemiology of Biopsy proven Glomerulonephritis in Queensland - LR 10/48
This retrospective analysis reviewed the data from all adult native renal biopsies performed in the state of Queensland from 2002 to 2011--comparing results with centres from across the world. Pathology reports of 3697 adult native kidney biopsies were reviewed, of which 2,048 had GN diagnoses. Age, gender, clinical indication and histopathology findings were compared. Further

analysis of this data will provide information on treatments administered and outcome of the patients with glomerular disorders.

Retrospective analysis of Data
Data of all the patients who underwent renal biopsy from 2002-2018 will be collected. This includes the data collected for the study on "Biopsy proven Glomerulonephritis in Queensland - LR 10/48".

Phase 1B: CKD.QLD patient data linkage - prevalent patient data.
At time of writing, 9,005patients have consented to the CKD.QLD Registry via informed consent. Approximately 13% (1,000) of these patients have had a renal biopsy as part of their routine clinical care and diagnosis of their renal disease process. These patients will facilitate a platform of prevalent patient data, with outcomes, for the establishment of the Renal Biopsy Registry.
Note: CKD.QLD has an established collaborative framework with state data custodians including the Health Service Information Agency (HISA) and Pathology Queensland, in addition to all HSS Renal Services as founding Registry members (providing a logistic framework for chart audits if needed).

Phase 2: Collection of data prospectively.
Data of all incident consenting patients with biopsy proven renal disorders referred to the above public hospitals will be collected. Of note: an average of 300 renal biopsies are performed annually in the public [government funded] sector, each of which is stored in a single Queensland Health laboratory system. The data of incident patients with diagnosed biopsy-proven renal diseases from Queensland public health and selected private renal services will be collected.

6.2 Study Settings

6.2.1 Sample size

The study is an observational study on different subset of renal biopsy proven disorders and therefore no power calculations can be made. We estimate there are about 200 patients with biopsy proven glomerulo-tubulointerstitial disorders are seen annually in public hospitals.

6.2.2 Data to be collected

No blood or tissue samples will be collected or stored

- Patient demographic data including gender, age, weight at birth, ethnicity, postcode, current and past occupations.
- Co-morbidities, date of diagnosis, clinical features, pathology including serial renal function tests, immunological tests, imaging results, and renal biopsy.
- Renal management: Medications, plasmapheresis and dialysis if performed, time from referral to date of renal biopsy, time from referral to initiation of treatment.
- Referral patterns: renal function at referral to renal service and referral history.
- Patient outcomes: disease progression, commencement of renal replacement therapy,
- Death

6.2.3 Data analysis

Descriptive statistics and frequency distributions will be done for continuous and categorical variables respectively. The association between renal function and risk factors [e.g. age, sex, time

taken for referral, renal function on presentation, will be calculated and analysed by bi-variate [unadjusted] and multivariate analysis [adjusted].

All analyses will be undertaken using Stata 13.1 [Stata Corp. Stata Statistical Software: Release 13.1 College Station, Texas].

Regional mapping of biopsy proven renal cases across Queensland will be done using ARCGIS [Aeronautical Reconnaissance Geographic Information System ARCIS] to identify possible regional clustering which could give hints on aetiology, including possible exposures.

6.3 Study Participants

Inclusion criteria

All children or adults with renal biopsy proven medical renal disease.

Patients (potential participants) will be included in the registry only after the results of the renal biopsy have been discussed as part of their routine care. At this time the patient (potential participant) will be counselled on treatment options and once the plan is agreed the treatment will be implemented. Full clinical work up including renal biopsy will occur prior to the participant being included in the registry.

Exclusion criteria

Not willing to participate in the registry
Inability to obtain informed consent from the parent or guardian
Inability to understand English in the absence of an interpreter

Phase 1a participants [Retrospective]

"Waiver of Consent", for patients in Phase 1

Including data of those patients who were included in the study on Epidemiology biopsy proven GN (LR 10/48) and data of the patients who underwent renal biopsy till 2018 carries negligible risk and meets all qualifications for waiver of consent as per the National Statement [See Section 2.3, from pages 19-22, specifically 2.3.10 [a to I],: https://www.nhmrc.gov.au/guidelines-publications/e72]. The patients would have consented if they had been asked as the study is not interventional. It is impractical to collect consent from these patients and some of these patients might have died; there is sufficient protection of their privacy and there is an adequate plan to protect the confidentiality of data.

Phase 1b participants [CKD.QLD Registry participants]

CKD.QLD Registry participants

Phase 1B: CKD.QLD - prevalent patient data. [Sub-study via patient data linkage]

Of these, approximately 13% have biopsy proven renal disease. In collaboration with the State wide clinical renal network our renal biopsy registry will be expanded to include the data of all patients with biopsy proven renal disease registered with CKD.QLD.

The informed consent for enrolment for the CKD.QLD registry includes permission to access all relevant clinical material on the patients, including medical history and pathology reports collected prior to enrolment in the registry.

Phase 2 participants [Incident]

Consent will be obtained from all the participants (Phase 2) who are diagnosed with biopsy proven renal disorders.

All consecutive patients diagnosed with biopsy proven renal disorders will be recruited to this study. Nephrologists will be the initial contact with the patients. At this contact these patients will be provided with the information and consent sheet. Consent is required to participate in this study. Parent/guardian consent is required if the patient is a child. Children 14-16 years, in the presence of the parent/guardian can provide implied consent.

6.3.1 Sample Size

The study is an observational study on different subset of biopsy proven renal disorders and therefore no power calculations can be made. We estimate that 300 biopsy proven renal disorder patients are seen annually in public hospitals.

6.4 Study Timeframe

Ongoing project

6.5 Ethical Issues

6.5.1. Ethics Approval

There is no risk of adverse event arising as this is an observational study

6.5.2. Confidentiality

6.5.3 Records Retention and Data security

Data will be stored in secure locked locations on Queensland Health government property at -each participating hospital. The primary central data repository will be located within the secured electronic filing system of the Metro North Kidney Health Service.

Physical Security: All computers which will store electronic health information data are contained in locked rooms with limited, staff ID-based, restricted access.

Technological Security: All study related documentation and participant data/data bases will be stored on a secure limited-shared file. Access to shared files within Queensland Health is restricted and password protected. The computers of all persons who can access health information data will be protected with automatic screen locking after 5 minutes of inactivity. In accordance with the high -quality security provisions of Queensland Health, computers and the electronic information that is stored upon them will be protected by the use of firewalls, secure encrypted pathways or other methods as recommended by the Information Technology department. All security protection measures are regularly updated.

Paper records: no paper records of any personal health information data will be created, at any time.

6.6 Reporting of Results

At a minimum of annual intervals during the study, results will be converted into a report of de-identified data for user groups, participating renal units, and collaborators, which will include, but is not limited to, Queensland Health, The University of Queensland, the Australasian and New Zealand Society of Nephrology, the Renal Society of Australasia, and Kidney Health Australia. In addition, outcomes will be published in academic journals and on the QRBR website: www.QRBR.org, for professional and patient information and dissemination.

Reports of the units will be publicly displayed if there is a minimal collection of the data of at least 80% of the patients. Analyses of this data will require permission from the steering committee of the renal biopsy registry.

7.0 Research Outcomes and Significance

Development of a Registry of biopsy proven renal disorders by consolidation and analysis of already accrued patients with renal biopsies, their treatment and their outcomes, which will lead to the better understanding of local (and eventually) regional, kidney disease patterns.

Review of preventative strategies, guidelines and (Qld) health service delivery recommendations

Quantifying the number of recruited participants for the registry

Generating annual reports on patient outcome and dissemination of report

Academic output including publications of guidelines/ research publications

8.0 Study Finances

8.1 Funding Source

Sustainability of this registry lies in the tangible benefits for kidney patient, family, clinicians and Queensland Health planners. With its concept established and with in-principle support of Queensland Nephrologists broadly, Pathology Queensland, and CKD.QLD, the renal biopsy registry has commenced with generous in-kind support of both clinicians and academics. The intent is to populate the Registry with existing resources, present outcomes and publish and utilise this evolving framework of collaboration to apply for both government and private granting opportunities

8.2 Conflict of Interest

No conflict of interest to declare from researchers.

9.0 Signature of Coordinating Principal Investigator

Title: Queensland Renal Biopsy Registry

I have read this protocol and agree to conduct this study in accordance with all stipulation of the protocol, the Declaration of Helsinki and GCP/ICH Guidelines.

Associate. Professor Dwarakanathan Ranganathan

Signature Signature Date

10.0 References

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