Impacts and outcomes of kidney research in Canada

A 2018 Report by

THE KIDNEY FOUNDATION OF CANADA

The foundation of kidney care.

Decoding kidney disease at the molecular level

FRONT COVER: DR. NINA JONES

Dr. Nina Jones is an Ontario-based scientist, and a research partner with The Kidney Foundation of Canada. She is a professor at the University of Guelph's Department of Molecular and Cellular Biology, and a Canada Research Chair. The cell biologist has worked for more than a decade to improve the lives of people with kidney disease – both in her lab at the University of Guelph, and as a Kidney Foundation volunteer.

"I believe in giving back to the community that has supported our work," she says, noting that funds raised by the Foundation provide vital support to scientists. "A large portion of our biomedical research grants comes from fundraising. Without that support, we would not be able to continue our research."

Her research is primarily focused on cell signalling; how individual cells and proteins interact and communicate with each other inside the body. Her lab studies a specific cell type called the podocyte, and its tentacle-like extensions. Podocytes are a crucial component of the filtration barrier of the kidneys. The lab also studies Nck proteins, which appear to play a significant role in maintaining the unique shape of podocytes. They are so important, Dr. Jones notes, that when these molecules are absent from young mice, they are born with kidney disease.

The discoveries made by Dr. Jones and other scientists lay the groundwork for generating innovative therapies. The ultimate goal is to develop targeted medicines to prevent and better treat kidney conditions.

"Our approach is to study signalling proteins in detail, and how their interactions control podocyte development and maintenance of the filtration barrier. Once we know more about how these molecules function, they can be targets for future therapies," she explains, adding: "We can't do targeted medicines until we know what the targets do."

Dr. Jones first connected with The Kidney Foundation of Canada in 2006, after joining the faculty at the University of Guelph. She is not a nephrologist by training, but her work caught the attention of the Foundation. She was awarded a three-year grant to support research in her new lab. The following year, Dr. Jones was chosen to take part in the KRESCENT program. The national training initiative attracts participants from a range of disciplines in nephrology.

"As a result of KRESCENT, we now have a highly networked group of leading scientists across the country, sharing expertise in kidney health and disease. Beyond the research collaborations that KRESCENT has cultivated, I feel that my work has been strengthened by the guidance and support of senior program mentors, and these scientists remain an important resource. The opportunities provided by the KRESCENT program have been invaluable for our research," she says.

Today, Dr. Jones participates in Kidney Foundation and KRESCENT review panels, helping to select the best grant ideas and to launch the next generation of kidney researchers. She has worked with and mentored dozens of young scientists. While the Jones Lab is focused on the smallest units of the body, she wants graduates to keep the big picture in mind.

Through outreach activities like the annual Kidney Walk in Guelph, her students learn first-hand the human impact of kidney disease. They walk with kidney donors, patients and transplant recipients and hear their stories. They also raise money for kidney research and programs for Canadians living with renal damage.

"When I started this research, one of the things that surprised me was the number of people affected by kidney disease," she reflects, noting it impacts about one in 10 Canadians. "There is not enough known about this disease. It is therefore important to raise awareness in both the public and scientific communities."

Research by the numbers

The Kidney Foundation of Canada supports research into all aspects of kidney health, disease, and treatment, and has provided Canadian researchers with more than $120 million in grants and awards since the start of the Foundation in 1964. Over this time period, research has transformed the options and care for people living with kidney disease. However, while advancements have been made, much more needs to be done and we continue to search for a cure and envision a time when people with kidney disease can thrive and live longer and fuller lives.

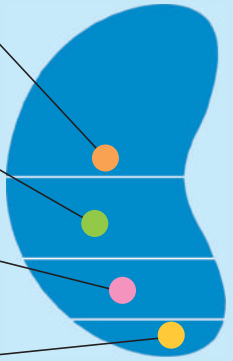
Total invested in Research in 2018:
$4,069,244

BIOMEDICAL RESEARCH GRANTS
$1,889,536
46%

KRESCENT PROGRAM
$997,000
25%

PARTNERSHIPS
$862,000
21%

ALLIED HEALTH AWARDS
$320,708
8%



TOTAL
$4,069,244

In 2018, The Kidney Foundation provided funding to:

40 Biomedical Research Grants

19 KRESCENT Awards

7 Allied Health Awards

2 Alport Syndrome Awards

68 Principal Applicants

95 Co-Applicants

98 Collaborators

30 Research Institutes

8 Provinces

2 Partnerships in large networks

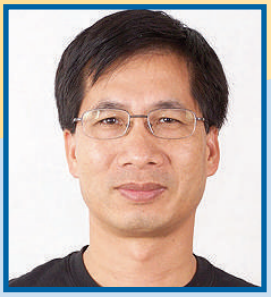
TOP 10 RESEARCH THEMES FUNDED IN 2018:

- Transplantation
- Kidney Biology
- Renal Failure
- Dialysis
- Chronic Kidney Disease
- Glomerulonephritis
- Cancer
- Genetics
- Diabetes
- Hypertension

2018: New Funded Researchers by Program

BIOMEDICAL RESEARCH GRANTS

Dr. Clara Bohm
Co-Applicants: Todd Duhamel; Navdeep Tangri; Jennifer M. MacRae; James M. Zacharias; Claudio Rigatto
University of Manitoba, MB
2018-2020: $99,973
Project Title: Effect of an Exercise Rehabilitation Program on Symptom Burden in Hemodialysis; a Randomized Controlled Study
Category: Dialysis



Dr. Xing-Zhen Chen
University of Alberta, AB
2018-2020: $100,000
Project Title: Regulation of PKD2 function and associated disease via the S4-S5 linker to C-terminus interaction
Category: Kidney Biology

Dr. Nicoletta Eliopoulos
McGill University, QC
2018-2020: $100,000
Project Title: Treatment of Renal Cell Carcinoma Using Gene-Modified Mesenchymal Stem Cells
Category: Cancer

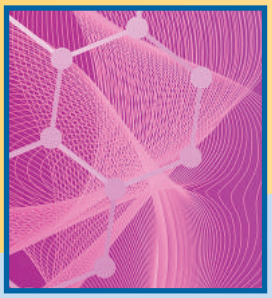
Dr. Paul Goodyer
McGill University Health Centre Research Institute, QC
2018-2020: $100,000
Project Title: Priming the Renal Progenitor Cell
Category: Kidney Development

Dr. Maxime Bouchard
Co-Applicant: Oraly Sanchez-Ferras
McGill University, QC
2018-2020: $100,000
Project Title: Collective cell migration in urinary tract morphogenesis and disease
Category: Kidney Development

Dr. Andrey Cybulsky
McGill University Health Centre Research Institute, QC
2018-2020: $100,000
Project Title: Protein Kinase SLK in the Kidney
Category: Glomerulonephritis

Dr. Amit Garg
Co-Applicants: David Mazer; Nadine Shehata; Shay McGuinness
Lawson Health Research Institute, ON
2018-2020: $49,500
Project Title: Risk of acute kidney injury in patients randomized to a restrictive versus liberal approach to red-blood-cell transfusion in cardiac surgery: A sub-study protocol of the TRICS-III non-inferiority trial
Category: Renal Failure

Dr. Indra Gupta
Co-Applicants: Aimee K. Ryan; Sero Andonian
McGill University Health Centre Research Institute, QC
2018-2020: $100,000
Project Title: Claudin Function in Kidney Development and in Disease
Category: Urology



Dr. Ziv Harel
Co-Applicant: Joel G. Ray
St. Michael's Hospital, ON
2018-2020: $61,344
Project Title: Assessing Kidney Disease and Its Outcomes in Pregnancy
Category: Screening & Prevention of Renal Disease

Dr. Christopher Kennedy
Ottawa Hospital Research Institute, ON
2018-2020: $100,000
Project Title: Nox5-containing urinary microparticles in renal injury associated with diabetes and hypertension
Category: Hypertension

Dr. Joan Krepinsky
Co-Applicant: Neel Mehta
McMaster University, ON
2018-2020: $100,000
Project Title: Role of miR-299a in regulating renal fibrosis
Category: Hypertension

Dr. Serge Lemay
McGill University Health Centre Research Institute, QC
2018-2020: $100,000
Project Title: Role of Dok-4-mediated interactions in growth factor signaling and acute kidney injury
Category: Kidney Biology, Renal Failure

Dr. Amber Molnar
Co-Applicants: Swapnil Hiremath; Ayub Akbari; Scott Kenneth Brimble; Pierre Antoine Brown
McMaster University, ON
2018-2020: $100,000
Project Title: Risk factors for sub-optimal dialysis initiation
Category: Renal Failure

Dr. Rulan Parekh
Co-Applicants: Guido Filler; Janusz Feber; Michael J. Paterson; Damien Noone; Armando Lorenzo
The Hospital for Sick Children, Research Institute, ON
2018-2020: $99,994
Project Title: Patient centered outcomes in childhood onset nephrotic syndrome
Category: Glomerulonephritis

Dr. Paul Ronksley
Co-Applicant(s): Marcello Antonio Tonelli; Eddy Lang; Chandra Thomas; Matthew T. James; Brenda Hemmelgarn
University of Calgary, AB
2018-2020: $100,000
Project Title: Predicting emergency department use among patients receiving hemodialysis care
Category: Dialysis

Dr. Alp Sener
Co-Applicant: Ayub Akbari
Lawson Health Research Institute, ON
2018-2020: $100,000
Project Title: Evaluating the protective role of a novel mitochondria-targeted hydrogen sulphide donor molecule against ischemia reperfusion injury in an ex vivo model of human donation after cardiac death renal transplantation
Category: Transplantation

Dr. Tomoko Takano
McGill University Health Centre Research Institute, QC
2018-2020: $100,000
Project Title: Role of the Rac 1 activator, beta-PIX, in the pathogenesis of proteinuria
Category: Glomerulonephritis

Dr. Sandra Turcotte
Université de Moncton, NB
2018-2020: $100,000
Project Title: Studying the interaction between miR-2355 and the Sushi-domain-containing protein 4 to investigate a role for the complement system in VHL-inactivated renal cell carcinoma
Category: Cancer

Dr. George Yousef
Co-Applicants: Michelle Downes; Antonio Finelli; Kenneth R Evans
St. Michael's Hospital, ON
2018-2020: $100,000
Project Title: Understanding the attributes of papillary renal cell carcinama subtypes: molecular analysis, biomarker discovery and implications to therapy
Category: Cancer

ALLIED HEALTH RESEARCH GRANTS

Dr. Tania Janaudis-Ferreira

Co-Applicants: Kaberi Dasgupta; Ruth Sapir-Pichhadze; Nancy Mayo; Sara Ahmed; Nicolas Fernandez
McGill University Health Centre Research Institute, QC
2018-2020: $100,000
Project Title: Getting on with your life with a transplanted kidney: GENTONTRAK. Development of a self-management workbook to improve quality of life in kidney transplant recipients
Category: Quality of Life

Dr. Diana Mager

Co-Applicant: Peter A Senior
University of Alberta, AB
2018-2020: $99,889
Project Title: Vitamin D and frailty: longitudinal assessment of risk factors in adults with diabetes and chronic kidney disease
Category: Diabetes

ALLIED HEALTH SCHOLARSHIP

Ms. Lisa Lillebuen

University of Alberta, AB
2018-2020: $5,000
Project Title: Allied Health Scholarship – Nursing
Category: Nursing

KRESCENT ALLIED HEALTH DOCTORAL FELLOWSHIP

Ms. Vanessa Silva e Silva

Supervisor: Joan E. Tranmer
Queen's University, ON
2018-2020: $46,250
Project Title: Determining the influence of processes, structure and inter-professional relational networks within organ donation programs in Ontario
Category: Organ Donation

KRESCENT NEW INVESTIGATOR AWARD

Dr. Casimiro Gerarduzzi

Hôpital Maisonneuve-Rosemont, QC
2018-2021: $195,000
Project Title: The role of matricellular proteins in kidney repair and development
Category: Kidney Biology

Dr. Samuel Silver

Queen's University, ON
2018-2021: $210,000
Project Title: Primary care physician involvement and quality of care for patients on dialysis
Category: Chronic Kidney Disease

KRESCENT INFRASTRUCTURE SUPPORT

Dr. Casimiro Gerarduzzi

Hôpital Maisonneuve-Rosemont, QC
2018-2019: $25,000
Project Title: The role of matricellular proteins in kidney repair and development
Category: Kidney Biology

Dr. Samuel Silver

Queen's University, ON
2018-2019: $25,000
Project Title: Primary care physician involvement and quality of care for patients on dialysis
Category: Chronic Kidney Disease

KRESCENT POST-DOCTORAL FELLOWSHIP

Dr. David Collister

Supervisor: Michael W. Walsh
McMaster University, ON
2018-2020: $130,000
Project Title: Dialysis symptom Control-Restless Legs Syndrome (DISCO-RLS) trial
Category: Dialysis

Dr. Paraish Misra

Supervisors: Darren Yuen; Christina Nostra
University of Toronto, ON
2018-2021: $195,000
Project Title: Characterizing the potential of stem cell-derived insulin-producing cells as a treatment for diabetic nephropathy
Category: Diabetes

Christopher Kennedy

Preventing kidney damage from anti-inflammatory drugs

People with kidney disease are at an increased risk for further damage to their kidneys if they take anti-inflammatory drugs such as ibuprofen or acetylsalicylic acid (Aspirin). We sought to understand the reason for this phenomenon in hopes of identifying ways in which people taking anti-inflammatory drugs could avoid unwanted side effects in the kidney.

Our findings revealed that a specific receptor for prostaglandin E2 (a hormone produced in the kidney that controls blood flow) contributes damage to the kidney when people take anti-inflammatory drugs. Our hope is that this receptor, called the EP4 receptor, can be targeted. Indeed, we hope that we will find drugs that activate the EP4 receptor, which would then maintain adequate blood flow in the kidney when people with kidney disease need to take anti-inflammatory drugs. This work was published in the journal *Antioxidants and Redox Signaling*.

WHAT THIS MEANS FOR PATIENTS:

We believe that these findings will lead to the creation of drugs which will eliminate the risk of further kidney damage in people with kidney disease who need to be taking anti-inflammatory drugs.

Ahmed Al-Jaishi

Standardizing vascular access

When making a choice about the type of vascular access (a method of introducing or removing substances from the blood), careful consideration must be taken to help facilitate informed consent and create an appropriate implementation plan.

The first step in this project was summarizing existing literature to estimate how often patients with arteriovenous fistulas (a type of vascular access) experience specific complications for every 1000 days a patient has the fistula in place. One of the main outcomes of this review was the discovery of the urgent need to standardize reporting of methods and definitions of vascular access complications in future clinical studies. This is so we can compare results across studies and make more informed decisions on outcomes that are well defined.

To complement the work from the abovementioned review, we worked closely with a multi-disciplinary team of nephrologists, vascular access surgeons, radiologists, and FDA regulators to publish a list of standardized definitions for clinical trials involving arteriovenous fistulas. We proposed standardized definitions of arteriovenous access end points to guide the design of future clinical trials seeking approval from the Food and Drug Administration. The use of the standardized definitions allows the efficient design of clinical trials ensuring the outcomes are relevant for patients, clinicians, and regulatory bodies.

WHAT THIS MEANS FOR PATIENTS:

These findings provide more information about the best method of vascular access. Given that vascular access is a vital component of hemodialysis, finding a method with the greatest success rate would greatly improve outcomes for kidney patients. In addition, these findings can ensure better reporting of information surrounding vascular access complications, which is vital to future improvements of this model.

Andras Kapus

Understanding the mechanism of chronic kidney scarring

A common mechanism underlying chronic kidney disease (CKD) is chronic kidney scarring (fibrosis). During this process scar tissue accumulates in the kidney, which destroys the normal organ architecture and function. The molecular and cellular events responsible for the scarring process are not completely understood. The role of tubular cells (the main cell type that regulates the removal of waste products and spares nutrients and water) in kidney disease has been a subject of debate. Based on previous work by us and others, we have hypothesized that during chronic injury, tubular cells undergo a major functional and structural change and start producing mediators which cause the production of excessive fibrous material by neighboring connective tissue cells. Moreover, we hypothesized that two intracellular proteins (MRTF and TAZ) are central to this reprogramming. Upon injury, these factors enter the cell's nucleus and induce fibrosis-causing gene expression. If this is the case, these molecules can be targeted with specific drugs, which therefore might prevent or lessen kidney scarring.

We used a variety of cell and molecular biology approaches and animal models of fibrosis to test these hypotheses. Our results show that epithelial cells undergo major fibrotic reprogramming and both MRTF and TAZ play key roles in this process, and their inhibition decreases kidney scarring.

WHAT THIS MEANS FOR PATIENTS:

With this information, the kidney research community is now further equipped to create drugs which target the above-mentioned proteins and hopefully prevent the development of chronic kidney disease by reducing fibrosis (scarring).

Dr. Soham Rej

Statins in the treatment of lithium-induced nephrogenic diabetes insipidus

Lithium is a commonly used treatment in several medical conditions, including bipolar disorder and major depressive disorder. It is also being studied in dementia, stroke, and even cancer. Currently, lithium is used by approximately 350,000 Canadians and more patients could potentially benefit from using it. However, doctors are avoiding lithium because lithium use can increase the risk of chronic kidney disease by three times through Nephrogenic Diabetes Insipidus (NDI), a type of diabetes caused by kidney defects. A recent preliminary study found that statins (commonly used cardiovascular medications) are associated with a lower risk of NDI in lithium users.

In this study we will test a statin called atorvastatin (Lipitor) in treating NDI in people using lithium. As of August 2018, we have recruited 55 out of a goal of 60 patients for this study and are on target to complete this study in a timely fashion by July 2019.

WHAT THIS MEANS FOR PATIENTS:

If successful, this pilot study will generate the information needed to plan future large clinical trials that can confirm whether statins can treat NDI and potentially prevent chronic kidney disease in lithium users. Patients suffering from disorders such as bipolar disorder, dementia, major depressive disorder, and others won't have to worry about their lithium medication causing them irreversible kidney damage.

Dr. Sacha De Serres

The role of dendritic cells in antibody-mediated rejection in kidney transplantation

In the last 20 years, considerable progress has been achieved in kidney transplantation. However, the life expectancy of transplanted kidneys has not increased as much as expected. In Canada, the percentage of kidneys from deceased donors that are still functional five years after transplant is only slightly above 80%. In other words, young patients transplanted today may need two, three or even more transplants during their lifetime. In an ideal world, once a patient receives a kidney, he or she will have this graft functioning for his or her entire life. While we are not sure why kidneys (or other transplanted organs) do not last very long, it is most often due to late rejection, which is caused by anti-HLA antibodies (proteins important for defense against invaders such as bacteria, viruses and infection). Although many agents have been tested to treat this type of rejection, so far none of them has been very successful.

The purpose of this research project is to better understand the mechanism of anti-HLA antibody production. The hope is to find an immunological target(s) that will stop rejection from happening.

WHAT THIS MEANS FOR PATIENTS:

We hope to be able to find ways to prevent organ rejection and thus patients will only need to get one transplant during their lifetime and will have a better, healthier quality of life.

Dr. Elena Torban

Fuzzy gene and its role in kidney diseases

In the Western world, between two to six out of every 1,000 newborns are born with small, abnormally-shaped kidneys and/or defects of the lower urinary tract – the group of diseases known as Congenital Anomalies of Kidney and Urinary Tract (CAKUT). In the most severe cases, kidneys are not formed at all. In order to understand the basis for the CAKUT defects, it is important to study the molecular programs involved in development of the kidney and the lower urinary tract.

Our group focuses on a novel gene known as "Fuzzy", which is crucial for normal kidney development. We discovered that in mice with a lack of Fuzzy functions, the kidneys are smaller and the kidney tissue is disorganized. In the project funded by The Kidney Foundation of Canada, we will use mutant mice and cells to examine how Fuzzy contributes to kidney development and how its disruption leads to kidney defects. As a result, this will give us a better understanding of pathogenesis of CAKUT and of potential treatments.

WHAT THIS MEANS FOR PATIENTS:

With this information, we will be better equipped to detect specific genes and mechanisms that underlie various CAKUT forms and to devise personalized treatments to help patients with specific mutations in specific genes.

MEDAL OF RESEARCH EXCELLENCE RECIPIENT 2018

Dr. Peter Nickerson

Dr. Peter Nickerson is recognized as a leader in transplantation medicine both in Canada and around the world. His innovative research and contributions to health policy are helping to improve access to, and the quality of organ transplantation in Canada. As part of a team of renowned transplant researchers at the University of Manitoba, Dr. Nickerson is working to unravel the complex factors that influence the success or rejection of a transplanted donor organ. His research focuses on mechanisms of acute and chronic kidney transplant rejection, immunogenetics, non-invasive diagnostics monitoring immune activation, and health policy and system design.

Dr. Nickerson spearheaded the team that designed and implemented a national transplant program that oversees interprovincial organ sharing. Rolled out by Canadian Blood Services under a mandate from the Federal, Provincial and Territorial Ministers of Health, this system includes state-of-the-art national kidney-paired donation and highly-sensitized patient matching programs in Canada allowing difficult-to-transplant patients to find a compatible donor. Over 1000 Canadian patients who would likely have otherwise have remained on dialysis have received a kidney transplant because of this system.

The Kidney Foundation has also benefitted from Dr. Nickerson's expertise, as he has served as a member of the Biomedical Scientific Committee both as a member and as Scientific Officer. He has also acted as the Chair of the Research Committee for the Manitoba Branch of The Kidney Foundation of Canada. And most recently, he has been appointed the Co-Chair of The Kidney Foundation Research Council – this Council oversees all the Foundations' research programs. Thank you, Dr. Nickerson, for all of your contributions!

Thank you to the kidney community!

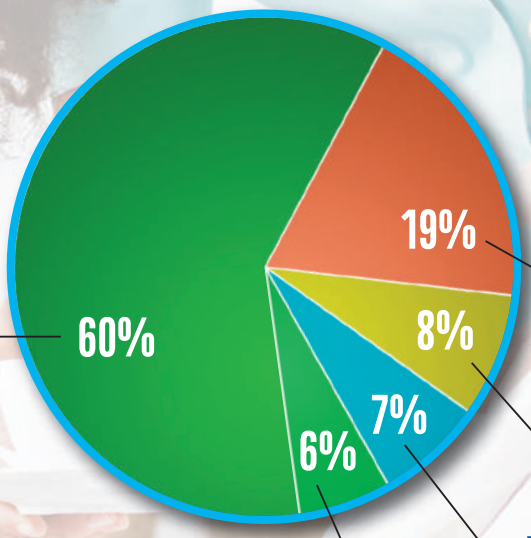
The Kidney Foundation would like to extend a huge thank you to the 70 kidney researchers and 15 kidney patients who generously volunteered their time and expertise to help the Foundation meet its research goals. Researchers and patient partners collectively volunteered over **2,200 hours** of their time to act as peer reviewers, to provide direction to The Foundation's research activities through their role on the Research Council, and to help The Kidney Foundation develop a strategic research framework through the continuing work of the *HORIZONS 2022* initiative.

The Kidney Foundation of Canada runs three research competitions: The Biomedical Research Grants competition, KRESCENT and the Allied Health competition.

In order to secure funding from the Foundation, researchers send in applications which provide detailed explanations of their research, their expertise, their collaborators, and the environment in which they intend to perform their research. To help The Kidney Foundation determine which projects have the best chance of success, we organize meetings of researchers who provide an in-depth review of each application. We then bring this committee of peers together to discuss, score and rank each application. The Kidney Foundation then provides funding to the top-ranked applications.

In 2018, for the first time, seven patient reviewers joined the scientific reviewers in judging the KRESCENT applications. The patient reviewers provided a score based on the clarity of the plain language summary, the relevance of the research to the patient community, and, if applicable, the appropriateness of the patient engagement plan. One of the outputs of this experience was the creation of the document: *"Best Practices in Writing a Plain Language Summary"* which is a fantastic new tool for researchers and can be found on the Foundation website.

Thank you to our scientific and patient experts for helping ensure The Kidney Foundation of Canada funds the best kidney research in Canada!



Biomedical Research Grants competition
1370 hours

KRESCENT competition & workshops
418 hours

Research Council & HORIZONS
198 hours

Patient Partners
147 hours

Allied Health competition
130 hours

TOTAL
2,247 HOURS

DIALYSIS TIMELINE

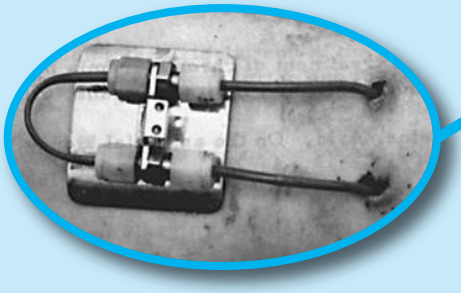
1943

First practical hemodialysis machine, called the "artificial kidney", made in the Netherlands by Willem Kolff

Photo: Museum Boerhaave Kolff's Artificial Kidney

1943

First use of peritoneal dialysis – occurred in San Francisco, USA. This type of dialysis uses the patient's peritoneum in the abdomen as a membrane across which fluids and dissolved substances are exchanged from the blood



1960

Scribner Shunt (invented by Belding Hibbard Scribner, Wayne Quinton & David Dillard) is made with Teflon. First reusable vascular access (method of introducing or removing substances from the bloodstream, used to remove the patient's blood so it can be filtered during dialysis) – this dialysis took place over 76 hours. CKD patients now have access to dialysis, but limited dialysis centres & available spots

Photo: CJASN

1962

Development of APD (automated peritoneal dialysis) by Fred Boen. Easy to use and practical for patients. They can now manage themselves on their own at home – at this point, dialysis takes place over 8-10 hours, every other day. Machines are big and unpractical & infections are common

Photo: asn-online.org

1962

Canada's first hemodialysis treatment for patients with chronic renal failure was performed at the University of Alberta Hospital

1962

Scribner opens the first official dialysis clinic for patients in Seattle. There were only 6 dialysis machines at the centre so demand far exceeded capacity. Decisions about who received treatment were carried out by an anonymous committee – the first bioethics committee

Photo: University of Washington

1966

Cost of medical treatments are covered in Canada according to the Medical Care Act – many patients have access to dialysis now

1973

By this time, 40% of dialysis patients worldwide were doing their treatments at home

1980s

Dialysis times shortened to 4 hour sessions, 3 times per week and has become much more accessible worldwide

1993

First home dialysis and first nocturnal hemodialysis in Canada – conceived by Dr. Robert Uldall. Nocturnal hemodialysis involves dialysis occurring while the patient is sleeping and is usually performed 6-7 nights per week

2018 AND ONWARDS

The Kidney Foundation of Canada, among other committed organizations, are funding research aiming to improve current dialysis methods and eliminate the burden of kidney disease!