Global Perspectives in CKD: Opportunities and Challenges to improve outcomes around the world

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Professor of Medicine
University of British Columbia
My goals for this presentation

• Describe current state of CKDs as a public health problem

• Opportunities and Challenges

• Review ISN and related initiatives and programs

• Stimulate discussion
What we know

CKD is a Public Health problem

• CKD increasingly recognized in multiple countries
CKD as a cause of years of life lost (YLL) moved from #25 in 1990 to #21 in 2005 to #17 in 2015.

Global Burden of Disease

1.35% of Total DALYs (1.2-1.47%)
Annual growth 1.06%

http://vizhub.healthdata.org/gbd-compare/
International estimates of CKD are consistent ~ 10-16% of adults

James, Hemmelgarn and Tonelli, Lancet 2010

Newer estimates of prevalence: variability.....
Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis

Nathan R. Hill1*, Samuel T. Fatoba1, Jason L. Oke1, Jennifer A. Hirst1, Christopher A. O’Callaghan2, Daniel S. Lasserson1, F. D. Richard Hobbs1

• Methods: A systematic review and meta-analysis of observational studies estimating CKD prevalence in general populations; pooled data using a random effects model.

• Results: 100 studies of diverse quality; 6,908,440 patients.

• Global mean (95%CI) CKD prevalence of 5 stages
  • 13.4%(11.7–15.1%), and stages 3–5 was 10.6%(9.2–12.2%)
  • Weighting by study quality did not affect prevalence estimates.
  • Stage-1 (eGFR>90 +ACR>30): 3.5% (2.8–4.2%);  
  • Stage-2 (eGFR 60–89+ACR>30): 3.9% (2.7–5.3%);  
  • Stage-3 (eGFR 30–59): 7.6% (6.4–8.9%);  
  • Stage-4 = (eGFR 29–15): 0.4% (0.3–0.5%); and  
  • Stage-5 (eGFR<15): 0.1% (0.1–0.1%).

PLOS ONE, July 2016 | DOI:10.1371/journal.pone.0158765
Chronic kidney disease and cardiovascular risk in six regions of the world (ISN-KDDC): a cross-sectional study


• Design: Cross-sectional study in 12 countries from six world regions: Bangladesh, Bolivia, Bosnia and Herzegovina, China, Egypt, Georgia, India, Iran, Moldova, Mongolia, Nepal, and Nigeria.
  • Volunteers in screening programs & high risk clinics

• Results: CKD prevalence (N=75 058)
  • 14·3% (95% CI 14·0–14·5) in general populations
  • 36·1% (34·7–37·6) in high-risk populations.
  • Awareness very low:
    • CKD 6% in general populations; 10% in high-risk populations
  • Awareness also low for HTN 56% and DM 69%
Methods: Collected data from 19 general-population studies from 13 European countries.

- KDIGO stages; CKD-Epi eGFR; ACR 30-299, 300+; age- and sex-standardized (EU27).

Results: Adjusted CKD prevalence

- Stages 1-5: 3.3% (3.3%-3.3%) in Norway TO 17.3% (16.5%-18.1%) in northeast Germany.
- Stages 3–5: 1.0% (0.7%-1.3%) in central Italy TO 5.9% (5.2%-6.6%) in northeast Germany

Variation stratified by diabetes, hypertension, and obesity status followed the same pattern as the overall prevalence.

Conclusion: Identified substantial variation in CKD prevalence that appears to be due to factors other than the prevalence of diabetes, hypertension, and obesity.

Advantage: Individual data pooling
Some of the drivers of CKD:
Prevalence of Diabetes and HTN is increasing around the world
Increasing prevalence of diabetes worldwide
? Implications for CKD

WORLD 592 million people living with diabetes

WORLD 387 million

Africa 93%
Middle East and North Africa 85%
South East Asia 64%
South and Central America 55%
Western Pacific 46%
Europe 33%
North America and Caribbean 30%
The clinical problem
We have made little progress where RRT is available only to the most fortunate.

Territories are sized in proportion to the absolute number of people who die of CKD each year.

Log (all) $R^2=0.5963$

White et al, WHO Bull 2008; Nugent et al, NCP 2011
Many people do not receive RRT

Global RRT 2010: Unmet Needs

Estimates 27-53% of patients needing RRT receive RRT

Variability in care globally

- Access to prevention and treatment
- Access to dialysis
- Access to transplantation
- Access to trained nephrologists (and teams of health care providers)
Variable Prevalence of Dialysis & differential uptake of modalities

Among the big five European countries, Germany has the highest prevalence of ESRD and Italy has the lowest

* ESRD as dialysis and may be driven by availability and economic concerns
Access to Care within and between countries

- Geography
- Race
Opportunities to advocate for Ethical approaches to renal replacement therapies

2016: Affordable dialysis prize awarded to Vincent Garvey. Joint prize from: The George Institute for Global Health, the International Society of Nephrology and the Asian Pacific Society of Nephrology and supported by the Farrell Family Foundation. Runs off solar power, can purify water from any source, has low running costs and can be sold for less than a thousand dollars.

Define travel for transplant and safe practices
ISN : New vision statement

’A future where all people have equitable access to sustainable kidney health’
The ISN: A philanthropic organization with mission to

• Bridging the Gaps of available care though advocacy and collaborations with our global partners

• Building Capacity in healthcare professionals via granting programs, education and research

• Connecting our Community to develop a stronger understanding of the management of kidney disease
The CKD Story and CKD as a Global Health Problem

• Achievements to date
  • Definitions and classification system
  • Increasing awareness of CKD as public global health problem
  • Growing number of consortia and collaborations for basic and clinical science
  • New therapies for some specific conditions/aetiologies of CKD
  • Genetic and molecular mechanisms being more carefully studied and understood

• Gaps in knowledge
  • Mechanisms of disease(s); responders and non responders
  • Epidemiology and burden in different locations
  • Genetic and environmental interactions

• Shortcomings described by the community
  • Limited possibilities to influence the course of the disease
  • Failure of trials (study design, populations, size, duration…)
  • Insufficient number of mechanistic targets identified
  • Culture of clinical trials and inquiry lacking
Opportunity and Challenges

• Epidemiology of disease(s)
  • Understand variability in incidence, prevalence and progression
• Measurement of kidney function
  • Precision vs accuracy vs reproducibility
  • For purposes: clinical, research, advocacy
  • Meaningful change
• Interventions
  • Systems, therapies
• Research
  • Evidence base
  • Evidence based care
  • Mechanisms and Targets
  • Participation in clinical trials/observational cohorts
    • LMIC and HIC
Clinicians, researchers, translational scientists, industry and others identify and address gaps.....

Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy

Adeera Levin†, Marcello Tondo‡, Joseph Bonventre, Josef Coresh, Jo-Ann Donner, Agnes B Fogo, Caroline S Fox, Ron T Gansevoort, Hiddo J L Heerspink, Meg Jardine, Bertram Kasiski, Anna Kottgen, Matthias Kretzler, Andrew S Levey, Valerie A Luyckx, Ravindra Mehta, Orson Moe, Gregorio Obrador, Neesh Pannu, Chirag R Parikh, Vlad Pekovic, Carol Pollock, Peter Stenvinkel, Katherine RTuttle, David CWheeler, Kai-Uwe Eckardt† on behalf of the ISN Global Kidney Health Summit participants*
Key messages

- A global collaborative effort of all stakeholders is required for a multifaceted action plan to combat the growing burden of CKD and its complications.
- More work is needed to understand the causes and pathophysiology of CKD at the individual patient level, and at the population level in regions where CKD is endemic.
- Existing data and biomaterial sources must be better used by promoting collaborative efforts and reducing administrative hurdles.
- The clinical and research workforce needs to grow substantially in order to address the global burden of CKD, especially in low and middle income countries.
- A concerted effort is required to increase the number, size, and quality of clinical trials investigating how to reduce the burden of CKD and its complications.

CKD = chronic kidney disease.

Performance Measurement Framework

- Accountability
- Transparency
Global Kidney Health Atlas:

In This Issue of JAMA

Assessment of global kidney health care status

Aminu K Bello1, PhD; Adeera Levin2, FRCPC; Marcello Tonelli3, FRCPC; Ikechi G Okpechi4, PhD; John Feehally5, FRCP; David Harris6, FRACP; Kailash Jindal7, FRCPC; Babatunde Salako2, FRCP; Ahmed Rateb1, MD; Mohamed A Osman1, MD; Bilal Qarni1, BSc; Syed Saad1, BSc; Meaghan Lunney5, MSc; Natasha Wiebe1, MSc; Feng Ye1, MSc; David W Johnson8, 9, 10, PhD
Global Kidney Health Atlas:
Kidney Care assessed on 6 dimensions of UHC
With the ISN Regional Boards

- Surveyed 125 countries (96% response) ~93% world population
- Robust methodology: 3 languages (English, French, Spanish)
- Baseline data for all regions, countries, and globally
Country capacity, readiness and response for optimal kidney care

• Universal Health Coverage (UHC) Domains
  • Health workforce
  • Health service delivery
  • Essential medicines and technologies
  • Health financing
  • Leadership and governance
  • Health Information systems

• Nephrology community response
  • Strategies and policy frameworks
  • Capacity for research and development
GKHA: Variability in the Availability of renal registries for CKD, Dialysis, Tx and AKI around the world:
Global distribution of nephrologists, rate per million population (PMP)

<table>
<thead>
<tr>
<th>Country</th>
<th>Nephrologist (pmp)</th>
<th>Trainee (pmp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>8.83</td>
<td>1.87</td>
</tr>
<tr>
<td>LIC</td>
<td>0.32</td>
<td>0.18</td>
</tr>
<tr>
<td>LMIC</td>
<td>2.53</td>
<td>0.77</td>
</tr>
<tr>
<td>UMIC</td>
<td>7.18</td>
<td>1.21</td>
</tr>
<tr>
<td>HIC</td>
<td>28.52</td>
<td>6.03</td>
</tr>
</tbody>
</table>

Countries with the lowest number of Nephrologists:
- Democratic Republic of Congo
- Yemen
- Burundi
- Tanzania
- Togo
- Uganda
- Ethiopia
- Malawi
- Mozambique

Countries with the highest number of Nephrologists:
- Switzerland
- Lithuania
- Taiwan
- Japan
- Japan
- Uruguay
- Greece
- Slovenia
- Spain
- Argentina
- Germany
- Japan

Health workforce
## Nephrologist Density by ISN Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>24.2</td>
</tr>
<tr>
<td>Western Europe</td>
<td>21.04</td>
</tr>
<tr>
<td>Eastern &amp; Central Europe</td>
<td>16.33</td>
</tr>
<tr>
<td>NIS &amp; Russia</td>
<td>15.68</td>
</tr>
<tr>
<td>Latin America &amp; the Caribbean</td>
<td>15.23</td>
</tr>
<tr>
<td>North &amp; East Asia</td>
<td>12.37</td>
</tr>
<tr>
<td>Middle East</td>
<td>6.17</td>
</tr>
<tr>
<td>Oceania &amp; South Asia</td>
<td>3.98</td>
</tr>
<tr>
<td>Africa</td>
<td>3.64</td>
</tr>
<tr>
<td>South Asia</td>
<td>1.17</td>
</tr>
</tbody>
</table>

Health workforce
Nephrology care provider shortages by ISN region
Healthcare services for identification and management of CKD: Primary Care

Health service delivery
Healthcare services for identification and management of CKD: Secondary Care

Data visualization showing various health services including blood pressure, pathology service, height & weight, radiology service, serum glucose, UACR/UPCR, HbA1c, serum cholesterol, creatinine without eGFR, creatinine & eGFR, urinalysis (quantitative), and urinalysis (qualitative). The services are color-coded for different income levels: low income, lower-middle income, upper-middle income, and high income.
Availability of RRT (caveat Available is not the same as accessible)

Capacity of RRT services across countries in ISN regions

- **Western Europe**: 100%
- **South Asia**: 80%
- **North & East Asia**: 80%
- **North America**: 100%
- **NIS & Russia**: 80%
- **Eastern & Central Europe**: 90%
- **Latin America & the Caribbean**: 90%
- **Middle East**: 90%
- **Oceania & South East Asia**: 90%
- **Africa**: 60%

**Countries (%)**

- **Acute HD**: 100%
- **Acute PD**: 61%
- **Chronic HD**: 100%
- **Chronic PD**: 80%
- **Transplant**: 79%
- **Acute HD**: 100%
- **Acute PD**: 61%

**Essential medicines and technologies**
Availability of ACE Inhibitors

Essential medicines and technologies
CKD medications coverage

Essential medicines and technologies
### Kidney healthcare system coverage

#### AKI
- Western Europe
- South Asia
- Oceania & South East Asia
- North & East Asia
- North America
- NIS & Russia
- Middle East
- Latin America & the Caribbean
- Eastern & Central Europe
- Africa

#### Non-dialysis CKD
- Western Europe
- South Asia
- Oceania & South East Asia
- North & East Asia
- North America
- NIS & Russia
- Middle East
- Latin America & the Caribbean
- Eastern & Central Europe
- Africa

#### Dialysis
- Western Europe
- South Asia
- Oceania & South East Asia
- North & East Asia
- North America
- NIS & Russia
- Middle East
- Latin America & the Caribbean
- Eastern & Central Europe
- Africa

#### Kidney Transplantation
- Western Europe
- South Asia
- Oceania & South East Asia
- North & East Asia
- North America
- NIS & Russia
- Middle East
- Latin America & the Caribbean
- Eastern & Central Europe
- Africa

<table>
<thead>
<tr>
<th>Description</th>
<th>Publicly funded &amp; free</th>
<th>Publicly funded with some fees</th>
<th>Solely private through health insurance providers</th>
<th>Solely private &amp; out-of-pocket</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney healthcare financing</td>
<td>Filled</td>
<td>Filled</td>
<td>Filled</td>
<td>Filled</td>
</tr>
</tbody>
</table>

**Healthcare financing**
Availability of clinical practice guidelines for kidney care

AKI and CKD guidelines, overall

CKD guidelines, by region

AKI guidelines, by region

Nephrology community response
Advocacy for kidney care

- AKI 19%
- CKD 42%

Nephrology community response
Capacity for Research

Health services delivery

- Phase 4
- Phase 3
- Phase 2
- Phase 1

Legend:
- Green: Western Europe
- Orange: Latin America
- Blue: Overall

Scale: 0% to 120%
# Kidney Care Scorecard

<table>
<thead>
<tr>
<th>Countries</th>
<th>Universal coverage for RRT</th>
<th>Availability of PD and Tx</th>
<th>Funding for CKD</th>
<th>Adequacy of workforce component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chronic hemodialysis</td>
<td>Kidney transplantation</td>
<td>Acute hemodialysis</td>
<td>Acute peritoneal dialysis</td>
</tr>
<tr>
<td>Albania</td>
<td></td>
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<td></td>
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<tr>
<td>Algeria</td>
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<tr>
<td>Andorra</td>
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<td></td>
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<tr>
<td>Anguilla</td>
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<td></td>
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<tr>
<td>Argentina</td>
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<td></td>
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</tr>
<tr>
<td>Armenia</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bahrain</td>
<td></td>
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</tr>
</tbody>
</table>

**Legend**:
- **Pub Free**: Publicly funded
- **Pub $**: Partially funded
- **Mix PP**: Mixed funding
- **Priv OOP**: Patient pays
- **Priv HI**: Private insurance
- **Multi Sys**: Multiple systems
## World Bank Country Group CKD Gaps Summary

<table>
<thead>
<tr>
<th>CKD Care</th>
<th>LIC (%)</th>
<th>LMIC (%)</th>
<th>UMIC (%)</th>
<th>HIC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to serum creatinine and eGFR in primary care</td>
<td>-</td>
<td>18</td>
<td>40</td>
<td>68</td>
</tr>
<tr>
<td>Access to quantitative urinalysis in primary care</td>
<td>-</td>
<td>32</td>
<td>43</td>
<td>71</td>
</tr>
<tr>
<td>Governmental recognition of CKD as a health priority</td>
<td>59</td>
<td>50</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Government funds all aspects of CKD care</td>
<td>13</td>
<td>21</td>
<td>40</td>
<td>53</td>
</tr>
<tr>
<td>Availability of CKD management and referral guidelines</td>
<td>46</td>
<td>73</td>
<td>83</td>
<td>97</td>
</tr>
<tr>
<td>Existence of current CKD detection programs</td>
<td>6</td>
<td>24</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>Availability of dialysis registries</td>
<td>24</td>
<td>48</td>
<td>72</td>
<td>89</td>
</tr>
<tr>
<td>Availability of academic centers for renal clinical trial management</td>
<td>12</td>
<td>34</td>
<td>62</td>
<td>63</td>
</tr>
</tbody>
</table>
Conclusions: GKHA project

• Demonstrates
  • Inter- and intra-regional variability in current capacity for kidney care worldwide
  • Important gaps in services, facilities and workforce in many countries

• Provides key opportunities for
  • Engaging key governmental and non-governmental stakeholders to support countries in improving the quality of kidney care
  • Accountability of countries in a scorecard process
  • Developing policy implications for including CKD and AKI in the global health agenda
CKD – Global perspective

• Common, harmful, treatable
• Linked to other NCDs (DM, HTN, CVD)
• Variability in approaches, resources, policies
  • Between and within countries and regions

• Role of health care systems
  • in prevention and control of CKD prevention
  • in integrating with national and international NCD management strategies

• Need for better understanding and unified advocacy approach to CKD
Recognize the diversity of the human condition

- Culture
- Resources
- Access to care
- Access to education
- Perspectives
  - Patients
  - Providers
  - Funders
Opportunities for Integrated Approaches to Kidney Health

- Better data
  - Registries
  - Economic impact

- Collaborative work within and outside the health care profession

- Better research
  - Descriptive
  - Mechanistic
  - Interventional
Explore and commit to better understanding

• Descriptive studies:
  • Large cohort studies with bio-banking
  • Long term follow up to understand variability and risk

• Well designed physiological studies
  • Understand mechanisms of disease and interactions
  • Human physiology and complex interactions

• Large clinical trials
  • With representative populations
  • Simple and multiple interventions
Unbalanced representation of world populations in clinical trials

VIEWPOINT
Access to medications and conducting clinical trials in LMICs
Ikechi G. Okpechi, Charles R. Swanepoel and Francois Venter

October 2014:
2851 Clinical Trials registered
Europe > SA, A, India and China together

Medication access caught in regulatory issues

Adherence and monitoring

NatRevNeph Feb 2015
......Challenge TO conduct Clinical Trials worldwide
The paradox...

Resources for the treatment of kidney diseases
$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$ $$

Evidence base to inform clinical care
Clinical Trials:

• Essential to inform care and therapeutic strategies

• Build on observational data and clinical experience

• Main requirements:
  • Number of patients
  • Adherence to protocol
  • Ascertainment of study outcomes
  • Appropriate statistical analysis
Essential components of answering key questions in clinical trials

• Size
• Diversity / Generalizability
• Duration

• Defining and measuring meaningful outcomes
  • To patients
  • To payers
  • To regulatory agents
Challenges in the conduct of clinical trials

- Design
- Personnel to conduct the trials
- Patient Enrolment and maintenance
  - Select suitable population at risk of the event
- Measuring outcomes
  - Data collection
  - Data analysis
Challenges in the conduct of clinical trials in all locations worldwide

- Design
- Personnel to conduct the trials
  - Training of personnel
- Patient Enrolment and maintenance
  - Select suitable population at risk of the event
- Measuring outcomes
  - Simple Data collection of relevant outcomes
  - Data analysis

Simplicity and practical considerations
- Large populations at risk
- Simple interventions/ sets of interventions
- Adherence to protocol
- Local culture and regulatory environment
New paradigms in clinical trials: increasing access for all and to all: Enrolment and Consent

- Changing face of informed consent
  - Electronic and digital informed consent (video)

- Changing research methods
  - Internet based trials recruitment more extensive (all with internet access)
  - App based trials
    - Conducted through smart phone

- Changing information technologies and practices
  - Increase access to participants
  - Reduced need for expensive infrastructure each location
The opportunity and challenge of conducting clinical trials worldwide

Opportunity
- Large populations
- Adherence / compliance culture +
- Access to care as secondary gain
  - Motivation?
- Unmet need

Challenges in LMIC
- Poor infrastructure health system
- Poor infrastructure research system
- Ethical practices
  - Availability of intervention after trial
  - Consent and literacy
  - Vulnerable populations
- Trained personnel
- Simplicity of data collection
- Simplicity of identification of eligible participants
Ethical Challenges in conducting Clinical trials (in LMIC)

• Access to care during and after the trial
• Access to drugs after the trial

• Ethics review boards: sophistication and availability
• Oversight issues: monitoring
Opportunities in the conduct of clinical trials with CKD focus or interest

- Patient numbers exist globally to ensure size of study appropriate
- Patient willingness and awareness increasing through social media…
- Growing # of networks
  - iNET CKD: ISN Network of Observational cohort studies with patient level data and samples
  - ISN ACT: Advancing Clinical Trials: awareness, education and opportunities
  - Oxford Clinical Trials: Infrastructure and experience
  - George Clinical: Infrastructure and experience
  - Australian Kidney Clinical Trial Network
  - PCORI, SONG, Can SOLVE CKD: Patient oriented research initiatives with Kidney focus….
STRENGTHENING KIDNEY RESEARCH CAPACITY

ISN iNET-CKD
NETWORK OF COHORTS

BUILDING UP RESEARCH SKILLS IN EAST AFRICA
In a country with a critical shortage of care workers, ISN Educational Ambassadors Vanessa Bijelj and Maria McKnight are working with doctors in Rwanda's hospitals teaching the theory and hands-on skills to build a renal pathology program so clinical care and research efforts can develop sustainably. These are vital steps towards establishing center and more precise diagnoses for patients with chronic kidney disease, providing adequate care for post-transplant recipients and targeting national prevention efforts.

ISN ACT
CLINICAL TRIALS

Connect with the global kidney trial community
To provide more high-quality clinical trials and studies in addressing ISN ACT’s objectives, clinician-trialists need to be involved and encouraged to join the capacity of the global clinical research community.

ISN H4KH INITIATIVE

81 CLINICAL RESEARCH GRANTS SINCE 2005
Changing paradigms in clinical trials

• Large pragmatic trials
• Use of Administrative data for randomization
• Simplicity of follow up and intervention(s)
• Simplicity of outcome data collection
  • Harmonization of meaningful outcomes
Integrated approach to improve Kidney Health
Tipping the balance

Towards more evidence base

Challenges          Opportunities
Worldwide Activities in Kidney Diseases

- Basic Science and Translational Consortia
- Patient Oriented Research Consortia (SONG;IHCOM)
- Collaborative Clinical Trials Networks

New Knowledge
New Paradigms
New Policies
Dissemination
Responding to a challenging global health environment

RESOURCES & POLITICAL WILL
Informed by experts and communities who understand the needs

Medical advances and innovation
Improved guidelines, standards of care
Research and data collection

Achieving better global kidney health
There are Opportunities and Challenges to inform (and improve) care worldwide.