



H3Africa Kidney Disease Research Network (U 1U54HG006939-01)

Dr. Dwomoa Adu and Professor Akinlolu Ojo

On behalf of the Network

The University of Ghana Medical School

The University of Michigan



Africa

Sub-Saharan Africa

- 50 African countries – pop \approx 800 million
- Average life expectancy at birth - 48 years (*cf* U.S. 1902)
- GDP per capita – USD \$1,500
- Living on <\$1.00/day – 50%
- Health expenditure per capita - \$2 to \$26
- Cost of predialysis CKD treatment - \$25/year
- Estimated prevalence of predialysis CKD – 50 million
- Cost of ESRD care - \$20,000/year (ppp)
- Estimated annual incidence of ESRD – 500,000
- Prevalent dialysis/kidney transplant population - 79,000

Characteristics of Countries with Participating Clinical Centers

Country	Population (million)	Prevalence of CKD	Life expectancy at Birth (years)	Per Capita GDP	Health expenditure per capita (% GDP)
Ethiopia	90.8	12.0%	56.9	\$1,000	\$7 (3.6%)
Ghana	24.8	12.4%	60.9	\$2,500	\$9 (10.6%)
Kenya	41.1	13.3%	59.4	\$1,600	\$11 (12.2%)
Nigeria	155.3	10.4%	47.6	\$2,500	\$20 (5.8%)
Total	312				

WHAT IS CHRONIC KIDNEY DISEASE

- **The persistent and usually progressive reduction of kidney function as measured by the glomerular filtration rate**
- Retention of urea and creatinine
- Proteinuria and/or haematuria
- Hypertension
- Late stage anaemia and bone disease

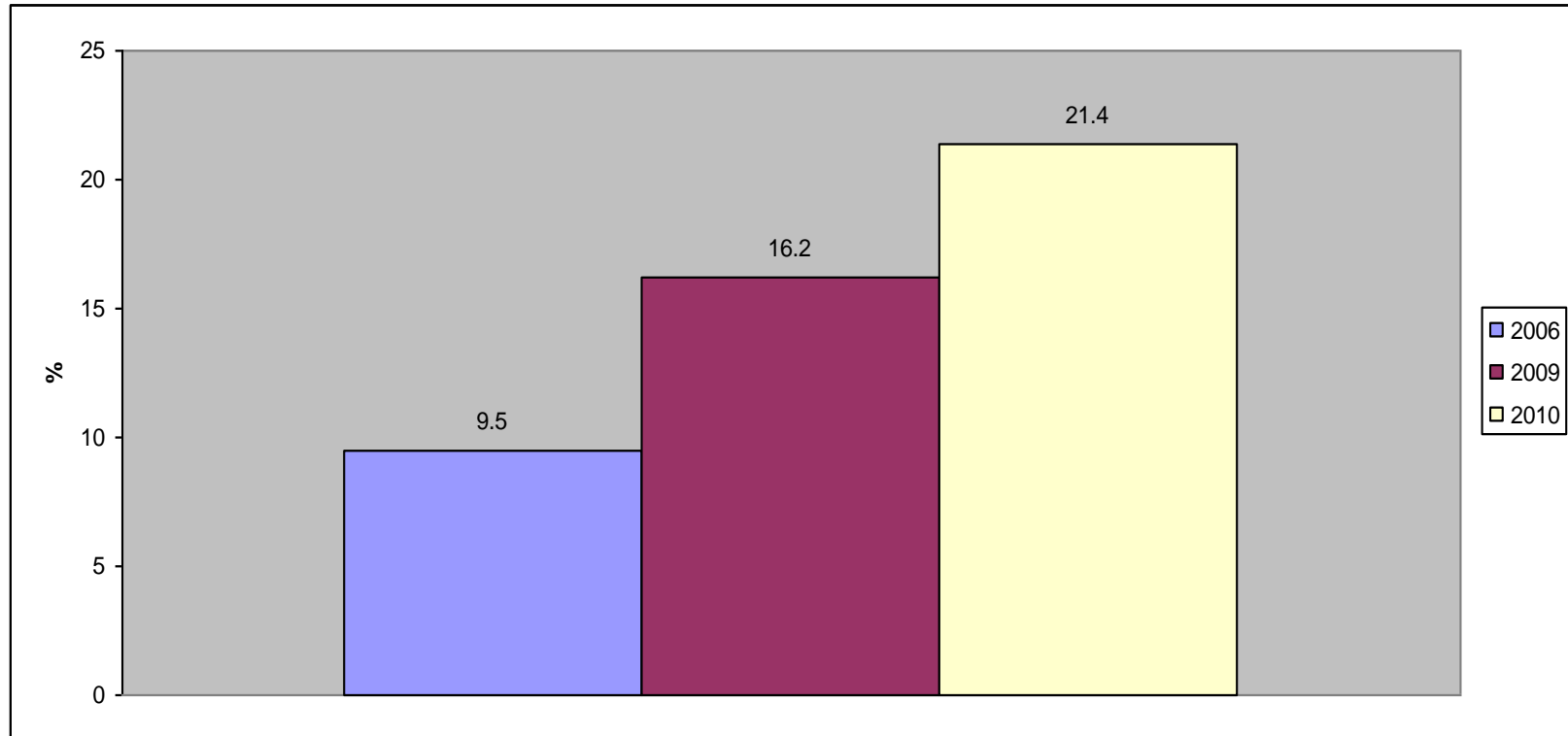
K/DOQI Stages of CKD

Stage	Description	GFR mL/min/1.73m ²
1	Kidney damage with normal or ↑GFR	≥90
2	Kidney damage with mild ↓GFR	60-89
3	Moderate ↓GFR	30-59
4	Severe ↓GFR	15-29
5	Kidney failure	<15 or dialysis

CKD PREVALENCE WORLDWIDE

Country	Study	CKD Prevalence	95% CI
USA	Coresh et al. 2007	13.1%	12.0%-14.1%
Australia	White et al. 2010	13.4%	11.1-16.1
UK	Stevens et al. 2007	8.5% (ckd 3-5)	
Nigeria	Afolabi et al. 2009	10.4% (ckd 3-5)	
DRC	Sumaili et al. 2008	12.4%	11-15.1

KIDNEY DISEASE AS A PROPORTION OF MEDICAL ADMISSIONS AT KORLE BU HOSPITAL



10% OF DEATHS ON MEDICAL WARDS DUE TO CKD

CKD OVERVIEW AFRICAN AMERICANS

- Familial aggregation of CKD higher in African Americans than in White Americans
- African-Americans have a 3.7 times higher age adjusted risk of ESRF as compared with European Americans
- Studies using mapping by admixture-linked disequilibrium technique show polymorphisms in MYH9 and APOL1 genes are associated with ESRF

ESKD PHENOTYPES ASSOCIATED WITH APOL1 GENETIC VARIATION (G1 and G2) IN AFRICAN AMERICANS

- Hypertensive nephropathy
- Non-monogenic Focal Segmental Glomerulosclerosis
- HIV associated nephropathy
- Sickle cell nephropathy
- Earlier onset of ESKD

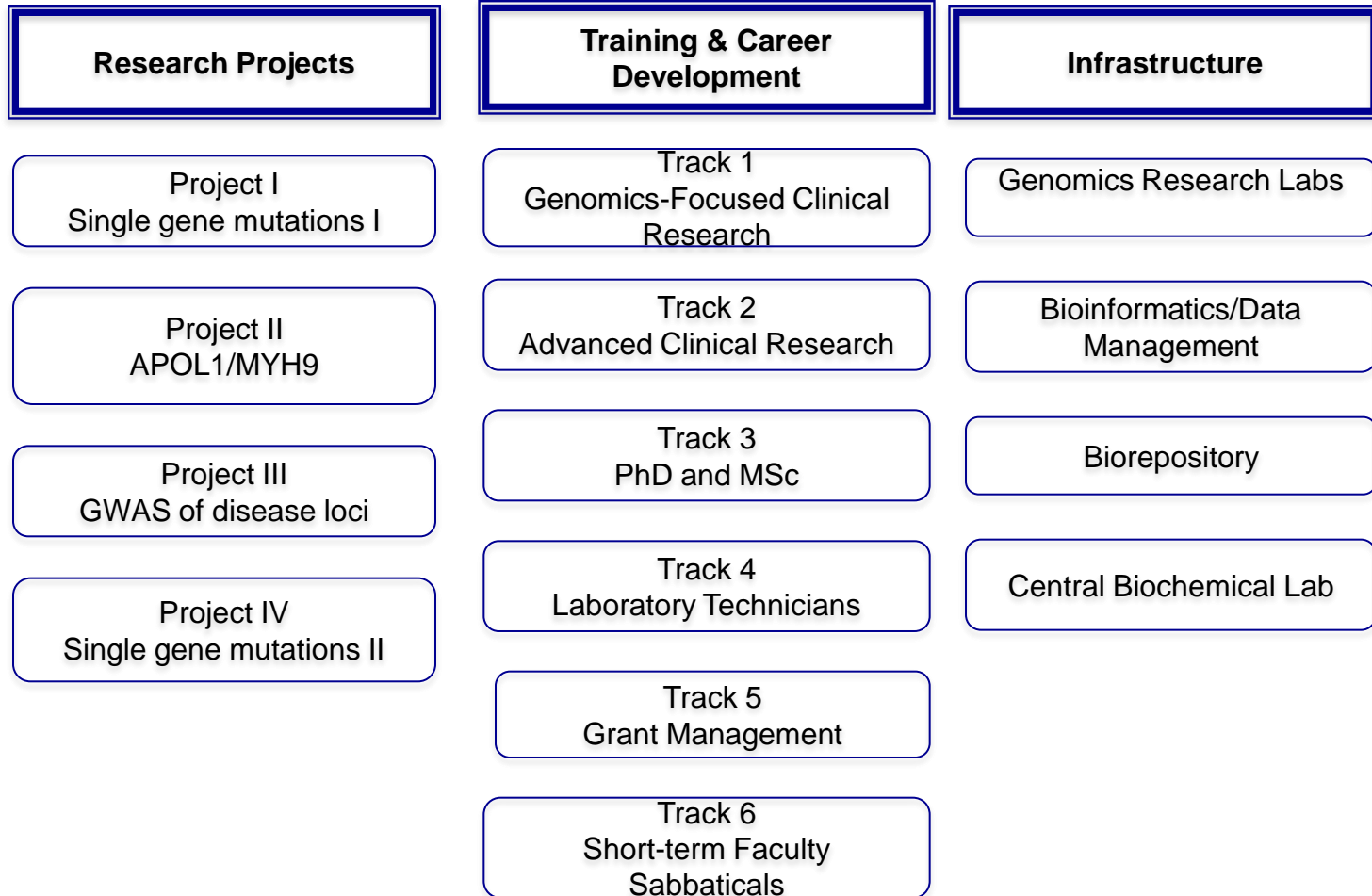
WHAT IS KNOWN IN AFRICA

- CKD is common in Africa and occurs at an earlier age than in the USA or Europe
- In Yoruba from Nigeria, the allele frequency of G1 and G2 is 46% and 7%, respectively
- In Ghana the allele frequency of G1 is 41% and in Ethiopia is 0%

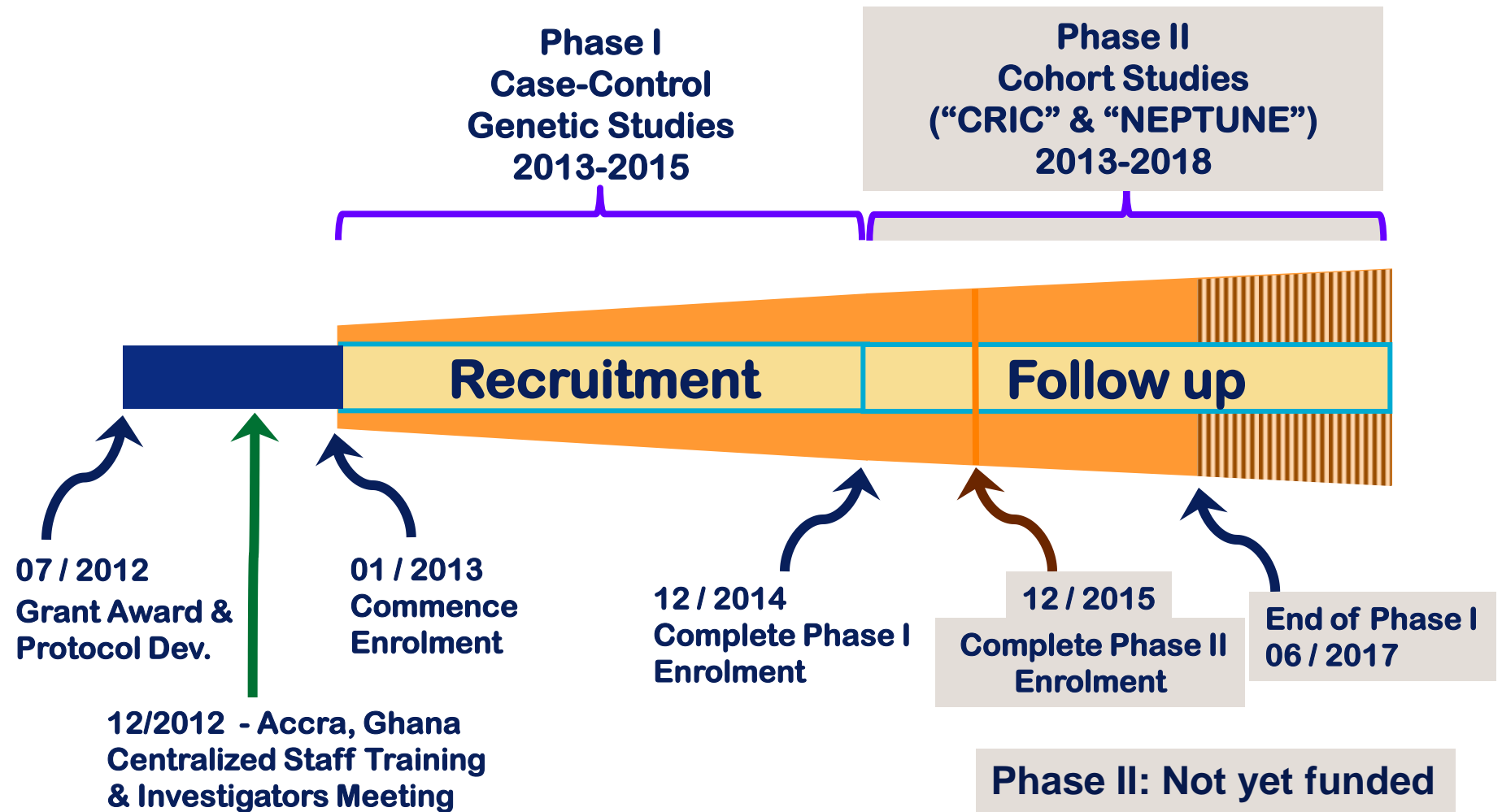
H3Africa Kidney Disease Research Network (U54): Objectives

1. Comprehensive phenotyping of the first ever kidney disease cohort of 8,000 cases and controls in four African countries
2. Genome science training and career development program for African scientists in tandem with the Michigan Predoctoral Training Program in Genetics (Dr. John Moran) and the U-M Genome Science Training Program (Dr. Michael Boehnke)
3. System biology training and U.S. platform extension to Africa (Dr. Matthias Kretzler)
4. Two genomic research laboratories in West Africa using sustainable, low capital-intensity laboratory technology platform (Dr. David Burke)
5. Mechanism for high throughput whole genomic sequencing (Dr. Rob Lyons and Dr. Michael Boehnke)
6. Conduct four genetic and translational research projects of CKD and childhood onset nephrotic syndrome

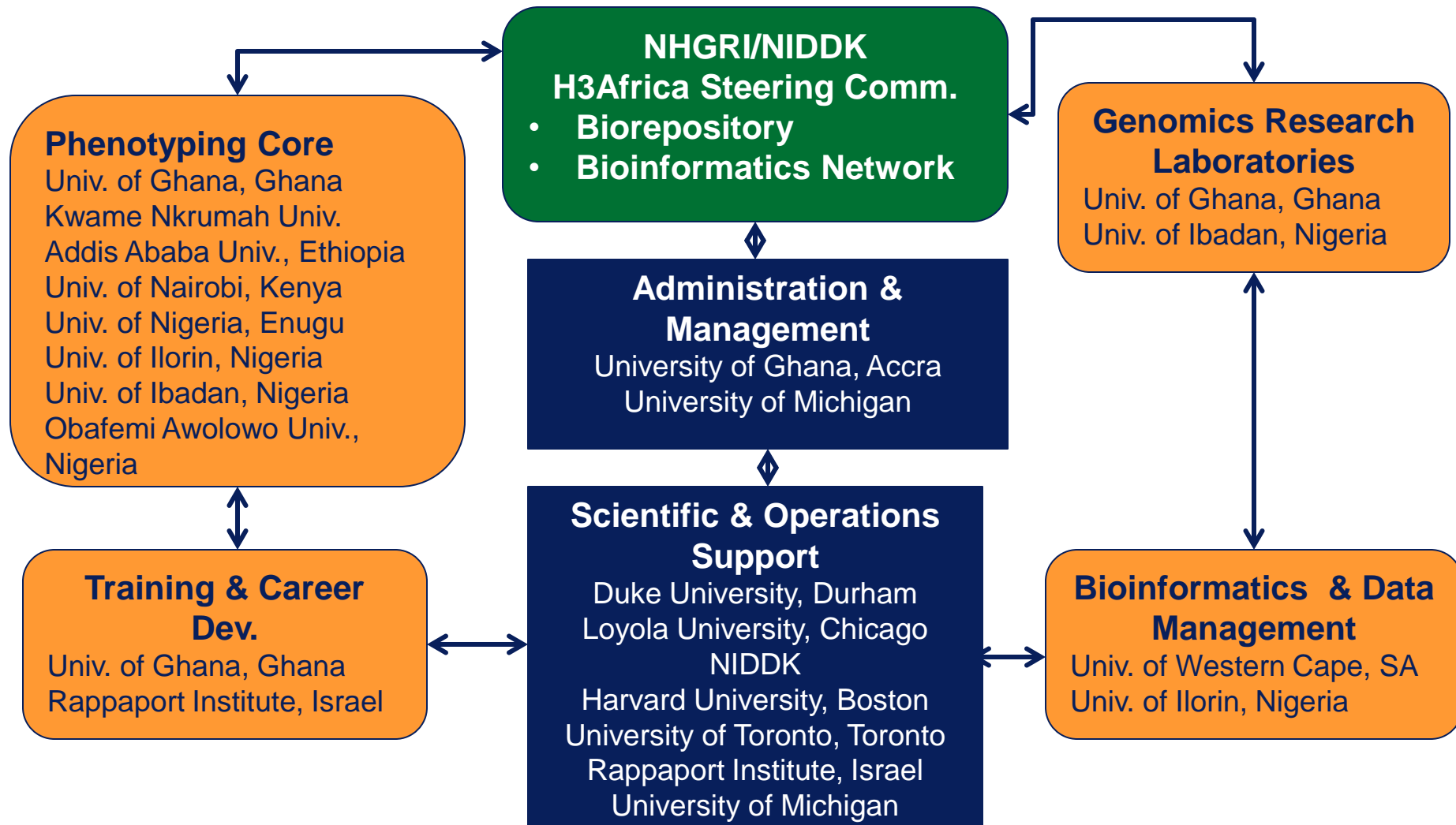
Functional Composition of the Research Network



H3Africa: Timeline for Research Studies



Operational Framework of the H3Africa Kidney Disease Research Network



Continuous Quality Control and Improvement

- Annual training of study personnel
- Quality Control Committee (comprised of investigators and study coordinators)
- Periodic assessment of 50 random samples of DNA materials and urine pellets for proteomics
 - Quarterly in Year 1
 - Twice yearly in Year 2 to 5
- Quarterly quality control reports to all clinical centers on
 - Phenotyping data
 - Biological specimen

Anticipated problems & solutions

- Insufficient enrollment
 - Recruit other clinical centers in West Africa
- Quality control (Data and Biospecimen)
 - Site visits to clinical sites
 - Retraining
 - On-site specimen storage
- Communication Break down and systemic disruptions (coup d'etat, strikes, Force Majeure)
 - Back up for data and biospecimen
 - Additional clinical centers



H3Africa Kidney Disease Research Network (U 1U54HG006939-01)

Explanation of Collaborations & Projects

Collaborations

Center	
University of Ghana	PI – Dr. Adu Dr. Osafo –Substantial clinical research experience in Ghana, 3 studies with >1,000 CKD participants
Kwame Nkrumah University of Science and Technology	Dr. Plange-Rhule - well established investigator and genetic epidemiology program, MEPI program
University of Ibadan	Well established nephrology investigator (Tunde Salako), genomic science lab led by Dr. Amodu –Harvard postdoc, MEPI in place
Obafemi Awolowo University	Established nephrology investigators, access to sickle cell disease population
University of Abuja	Nephrology investigators, visibility and access to Federal Government officials
University of Nigeria	Leading nephrology investigators and access to CKD patients

Collaborations

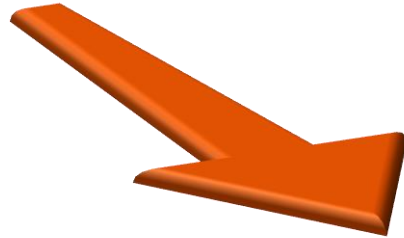
Center	
University of Western Cape	Nicki Tiffin – Leading bioinformatics expertise, well established bioinformatics infrastructure and training program
University of Ilorin	Bioinformatics expertise (Bewaji), well established nephrology research program (Olanrewaju), access to pediatric population
Loyola University	Dr. Cooper - >30 years experience of clinical and genetic epidemiology research in Africa; Dr. Tayo: Well established investigator in statistical genetics, significant research experience in Nigeria and Ghana
Duke University	Dr. Gbadegesin: Well established molecular geneticist & pediatric nephrology research expertise
University of Michigan	Expertise in statistical genetics, human genetics, excellent training programs, expertise in clinical/ translational research in kidney disease, grant management & administrative support; Dr. David Burke - Innovative low cost and rugged genotyping platform MICHOR (Michigan CTSA) – RedCap, data management and storage, biorepository expertise

Collaborations

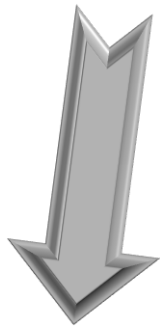
Center	
University of Toronto Hospital for Sick Children	Rulan Parekh – Established pediatric/adult nephrology investigators, original group to discover the association between MYH9 and non-diabetic CKD in African Americans
Harvard University (Beth Israel Deaconess)	Martin Pollak – Renowned nephrologist/genetic research expertise, original discovery of the APOL1- FSGS association
NIDDK	Dr. Jeff Kopp – Renowned investigator, world wide collaboration, responsible for the original work on APOL1 and kidney disease
NHGRI	Dr. Debo Adeyemo - Well established investigator with expertise in statistical genetics of chronic diseases
Ruth and Bruce Rappaport Research Institute, Tel Aviv	Dr. Karl Skorecki and Dr. Walter Wasser: Expertise in molecular genetics, world class genetic research facility. Responsible for new findings on APOL1 in Ethiopian Jews.

Research Projects in the H3Africa Kidney Disease Research Network

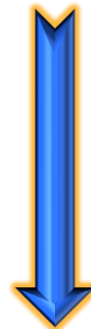
H3Africa Initiative



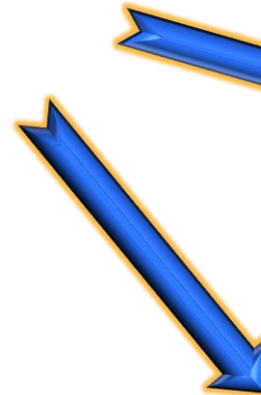
H3Africa Kidney Disease Research Network



Longitudinal Cohort Study
(N=3150)



Renal Candidate Genes
(MYH9, APOL1, etc)
Studies
(N=8000)



GWAS



Monogenic Disease
Childhood Onset NS
(N=50 families)

H3Africa Kidney Disease Research Network (U54): Research Projects

1. Mutation analysis of known nephrotic syndrome/FSGS genes (*i.e.*, *NPHS1*, *NPHS2*, *WT1*, *PLCE1*, *ACTN4*, *TRPC6*, and *INF2*) in patients with familial NS/FSGS. (Gbadegesin & Hildebrandt)
 2. Whole exome DNA sequencing in kidney disease families in whom mutations in key NS/FSGS have been excluded (Gbadegesin & Hildebrandt)
 3. Genetic typing and analysis of known variants in the *APOL1* and *MYH9* genes patients with sickle cell nephropathy, hypertensive nephrosclerosis, diabetic nephropathy, FSGS, HIV-associated nephropathy (Jeff Kopp, Martin Pollak & Rulan Parekh)
 4. GWAS (Bamidele Tayo and Adebowale Adeyemo)
 5. Kidney Disease Cohort Study (Adu, Ojo)
- } Pending R01 funding

Study Cohorts

Sample Sizes of the Participants and Controls			
Diagnosis-specific eligibility	Age	Cases	Controls
Steroid resistant nephrotic syndrome¹	<18	200	200
Focal Segmental Glomerulosclerosis	18-70	200	200
HIV nephropathy	18-70	500	500 ²
Sickle cell nephropathy	18-70	500	500 ³
Hypertensive non-diabetics with CKD	18-70	800	800
CKD due to diabetic nephropathy	18-70	800	800 ⁴
CKD – Unknown etiology	18-70	1,000	1,000
Total		4,000	4,000
<p>¹Includes 50 families with index cases and affected family members</p> <p>²Patients with HIV and no nephropathy</p> <p>³Patients with sickle cell disease and no nephropathy</p> <p>⁴Patient with diabetes mellitus and no nephropathy</p>			

Phenotyping data to be collected

Type of Procedure/Contact	Baseline Study Visit
Eligibility Assessment/Confirmation	X
Informed Consent	X
Medical Record Consent	X
Contact Information	X
Labs: Serum Creatinine, Serum Glucose, Hemoglobin,	X
Demographic Information	X
Medical History [CV, Renal and Health Behaviors]	X
Genetic Blood Sample	X
Labs: CBC, Metabolic Panel, Lipids, etc.	X
Urinary Assay: Creatinine, Protein, Albumin, Urea Nitrogen	X
Urine sample collection	X
Blood Pressure	X
Ankle Brachial Index & Anthropometric Measures	X
HCV, HBsAg, HIV, Hgb electrophoresis and HbA1c	X
Physical Activity and Physical Functioning Assessment	X
Concomitant Medications	X
MDRD Symptom Index	X
KDQOL - Quality of Life Questionnaire	X
Diet History Questionnaire	X
Recent Medical History – Event Data	X

REDCap: Data & Computing Environment Security

- Web-based clinical research data management system
- Developed at the Vanderbilt University & used by nearly all CTSA
- Interactive tools for:
 - Participant registration
 - Data entry and verification
 - Repository of all study forms
 - Individual participant calendars
 - Cumulative site calendars for expected study activities
 - Calculator of creatinine-based e-GFR
 - access to the National Drug Data File (NDDF) in the Medication Reference
 - Link to the Network website
 - Generate individual participant and investigator-specific reports
 - Seamless data downloads to common statistical packages (SPSS, SAS, Stata, R)

REDCap: Data & Computing Environment Security

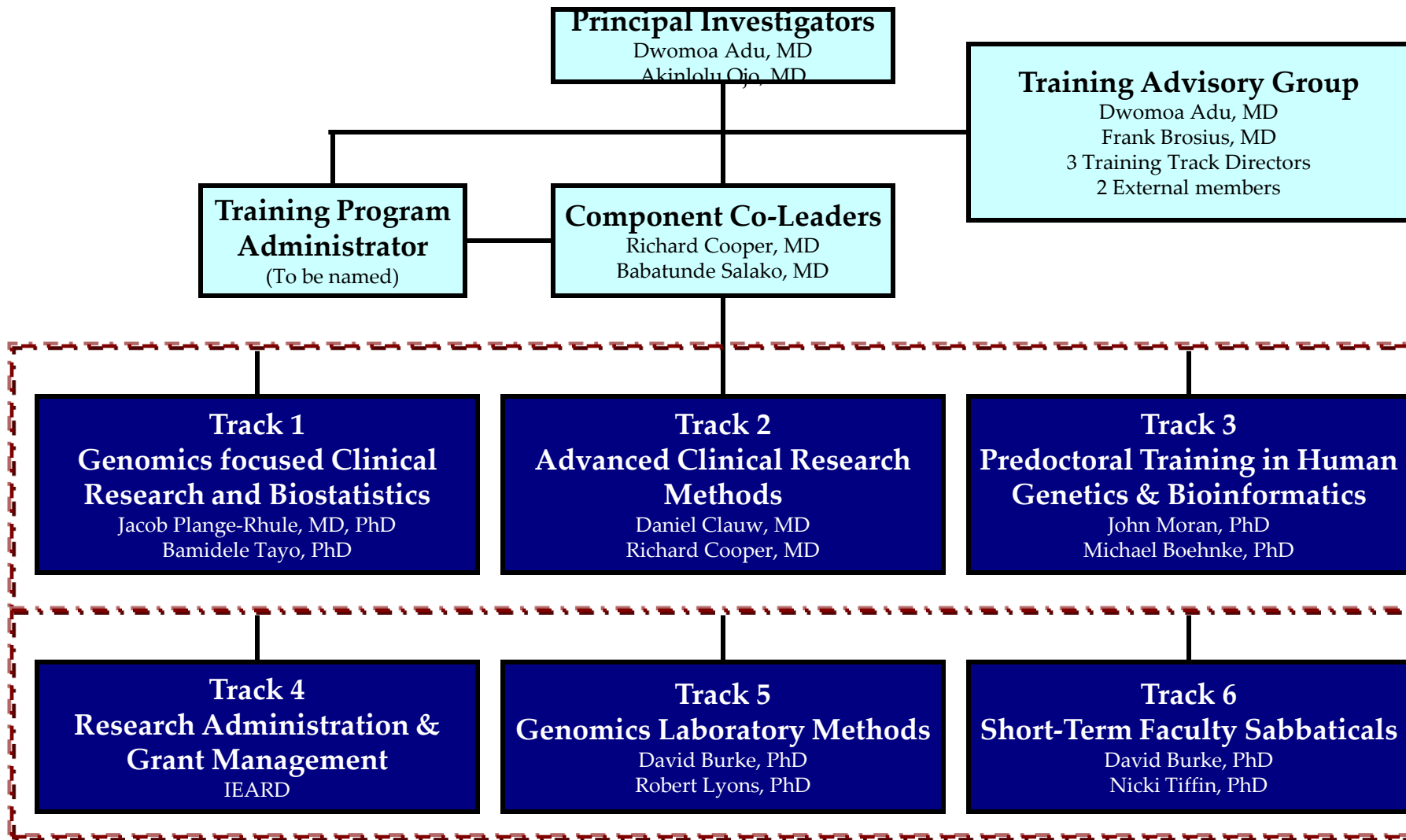
- Duplicate servers at University of Ghana & SANBI, Cape Town, SA
 - Professionally managed and equipped tier-2 data center with tightly controlled access.
 - Remote data access employs SSL encryption and 2-tier Level 1 and Level 2 password challenges via LDAP authentication
 - Compliance with HIPAA security and privacy requirements
 - Compliance with the HITECH Act
 - Audit trails on user access to and modification of data
 - Clinical centers BMCE required to meet best practices established in the Federal Information Security Management Act (FISMA)



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Training & Career Development Plans

Administrative Structure of the Training & Career Development Component



Training & Career Development Component: Objectives

1. Develop expertise in clinical research and biostatistics (Track 1) and advanced clinical research methods (Track 2)
2. Develop a new cadre of experts in bioinformatics, human genetics and biostatistics (Track 3)
3. Train new cadre of grant administrators to enhance the extramural research grant management and administration capacity of African institutions (Track 4)
4. Increase the technical competence and promote the retention of African laboratory technicians through short-term training and on-the-ground collaborative support (Track 5)
5. Institute leadership training and foster research independence through the use of short-term faculty sabbatical exchange programs between the University of Michigan Genetics and Bioinformatics and African scientists (Track 6)

Training & Career Development Component: The Training Tracks

Plan for the trainees to return to their home institution in Africa

- Overseas training will be limited to individuals who have significant commitment in their own country
- Instead of the F1 student visa, all training components in the U.S. will be done under the J-1 Exchange Visitor Program

Tracking & Evaluation of the Training and Career Development Component

- Tracking database: Database captured information on trainees will be used to track retention of trainees at their original African institutions
- Qualitative Assessment: Structured surveys, focus groups & interviews will be used to obtain feedback
- Metrics of Trainee Success: Learning and perceived competence; career choices & satisfaction; career productivity & progression



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Data Sharing, Human Research Participant & Ethics, Biorepository

Informed consent

- Adult participants
 - Comprehensive written informed consent
 - Must opt in for genetic research
- Pediatric participants
 - Written informed consent by at least one parent
 - Plus, Either*
 - Assent by child age 10-14 years
 - Or*
 - Written informed consent by child age >14 years
 - Must opt in for genetic research

Material Transfer Agreements

- Between each participating clinical center and the UGMS
- Between UGMS and University of Western Cape
- Between UGMS and the University of Michigan
- Letter from Ministry of Health of participating countries:
 - Support for H3Africa projects
 - Commitment to biomedical research
 - Consent to international transfer of DNA materials, other biological specimen and research data

Human Research Participant Protection

- Risk Level – Minor increase over minimal
- Potential risks
 - Injury and infection from phlebotomy
 - Loss of privacy and confidentiality
 - Psychological harm and discrimination from inadvertent release of PHI (insurability, employment)
- Benefits – Indirect benefits only
 - Information on treatment of hypertension, diabetes or kidney disease
 - Contributing to improved understanding of the genetics of kidney disease

Release of genetics and other research data

- The following results will be made available to the participants and treating physicians **THROUGH** the Clinical Center Principal Investigator:
 - HIV
 - HCV
 - Hepatitis B
 - Hemoglobin electrophoresis,
 - Serum creatinine
 - Urine albumin:creatinine ratio
- Critical laboratory results will be communicated to the Clinical Principal Investigator (within 7 business days of the assay)
- Genetic data will not be released or reported to the participants
- Only aggregate data will be published or presented in scientific fora

Measures to minimize risks to human research participants

- Thorough explanation and dialogue during the informed consent process to ensure:
 - Full disclosure of the nature of the research and the participation being asked of the participant
 - Adequate comprehension on the part of the potential participant
 - That participant's decision to enroll is a voluntary choice
- Unfettered access to Human Research Participant Advocate if available
- Contact information of Clinical Center PI
- Security of research data, de-identification and publication of aggregate data
- Study procedures performed by trained personnel

H3Africa Kidney Disease Research Network - Data Sharing Plan

- Network investigators will have time-limited proprietary access to research data ensure ample “academic capital” for the investigators
- Research data will be shared worldwide through:
 - Provision of data files to the NHGRI (or other federal) data repositories
 - Provision of access to research data to scientists who engage in collaborative research relationships with the Network

H3Africa Kidney Disease Research Network - Data Sharing Plan continued

- Website with portals for the public, potential collaborators and investigators
- Solicit collaborative projects through scientific meetings and media

Examples of Data Sharing and Collaboration

- Plan to hold a symposium on the H3Africa Kidney Disease Research Network at the African Renal Association/African Pediatric Nephrology Meeting, Accra, Feb 20-23, 2013
- Ancillary study proposal by Sarah Tishkoff and Duncan Johnstone, Department of Genetics and Biology, University of Pennsylvania
- Chronic Renal Insufficiency Cohort (CRIC) Study
- Nephrotic Syndrome Study Network (NEPTUNE)
- Weizmann Institute of Science, Rehovot, Israel – Whole Exome and NextGen Sequencing

Human Research Participant Advocate (Pending availability of funding)

- Perform random and “for cause” protocol audits to assist
- Promote collaborative efforts aimed at improving overall data integrity and participant safety
- Ensure adequate human subject protection staff training.
- Authority to suspend any research project
- Report directly to the Dean
- Work closely with the IRB/Ethic Boards
- Assist with Data Safety Monitoring Plans (DSMPs)
- Review adverse event reports to identify issues or patterns that might require changes to the research project
- Consult IRB/Ethics Committee to address areas of mutual safety or ethical concerns

H3Africa Kidney Disease Research Network

Country	Institution	Key Personnel	Title	Role
Ethiopia	Addis Ababa University	Y. Menghistu	Consultant Nephrologist/Assistant Professor	Center PI
Ghana	University of Ghana	Dwomoa Adu	Consultant Nephrologist	PI
		Charlotte Osafo	Lecturer in Nephrology	
		Alexander Nyarko	Professor	
		Michael Mate-Kole	Consultant Nephrologist/Professor	
		Ivy Ekem	Snr. Lecturer/Consultant Hematologist	
		Vincent Boima	Physician Specialist/Nephrologist	
		Kwame Afram	Consultant Nephrologist/Professor	
	Kwame Nkrumah University of Science & Technology	Jacob Plange-Rhule	Associate Professor	Center PI
		Benjamin Eghan	Senior Research Fellow	
		Yaw Adu-Boakye	Specialist Physician/Int Med.	
		Elliot Tannor	Medical Practitioner	
Kenya	University of Nairobi	S.O. Mc'Ligeyo	Consultant Nephrologist/Associate Professor	Center PI
		James Ochanda	Associate Professor in Biochemistry & Director, Center for Biotechnology & Bioinformatics	
		Joel W. Ocheng	Research Fellow & Lecturer	
		Isabella Oyier	Investigator	

H3Africa Kidney Disease Research Network

Country	Institution	Key Personnel	Title	Role
Nigeria	University of Ibadan	Tunde Salako	Professor/Consultant Physician	Center PI
		Olukemi Amodu	Snr. Research Fellow	
		Adebowale Ademola	Lecturer/Consultant Physician	
	University of Ilorin	Akinkemi Fedipe	HOD, Family Medicine	
		Chijioke Adindu	Snr. Lecturer/Consultant Physician	
		Timothy Olarenwaju	Consultant Physician	
Obafemi Awolowo University	University of Abuja	C. O. Bewaji	Professor, Bioinformatics	
		Fatiu Arogundade	Assoc. Prof/Consultant Physician	
	Samuel Ajayi	Consultant Physician/Nephrologist		
	Manmak Manven	Consultant Physician/Nephrologist		
University of Nigeria, Enugu	University of Nigeria, Enugu	Ifeoma Ulasi	Snr. Lecturer/Consultant Physician	
		Chuba Ijoma	Snr. Lecturer/Consultant Physician	
South Africa	University of Western Cape (SANBI)	Nicki Tiffin	Snr. Lecturer, Bioinformatics	
		Junaid Gamiedien	Snr. Lecturer, Bioinformatics	

H3Africa Kidney Disease Research Network

Country	Institution	Key Personnel	Title	Role
Israel	Technion – Israel Institute of Technology, Rappaport Research Institute	Karl Skorecki Walter Wasser	Professor & Director Professor	
U.S.	Loyola University	Richard Cooper Bamidele Tayo	Professor/HOD Assistant Professor	Center PI Stat. genetics
	Duke University	Rasheed Gbadegesin		Molecular genetics
	University of Michigan	Akinlolu Ojo Matthias Kretzler Michael Boehnke John Moran David Burke Daniel Clauw Frank Brosius	Professor Professor Professor Professor Professor Professor Professor	PI Stat. genetics Genetics Genetics TAG TAG
	NHGRI	Adebowale Adeyemo	Deputy Director, CRGGH	
	NIDDK	Jeffrey Kopp		
	Harvard University	Martin Pollak	Professor	
Canada	University of Toronto	Rulan Parekh	Professor	



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DISCUSSION