DEPARTMENT OF RENAL MEDICINE
Centre for Genetics and Genomics

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RaDaR: an Integrated Strategy for Rare Disease

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RaDaR
UKKA
UK Kidney Association
Rare Renal
Kidney Research UK
Funding research to save lives
MRC Medical Research Council

NIHR | BioResource
St Peter's Trust
for Kidney, Bladder and Prostate Research

Understanding Rare Diseases is challenging

- Many different rare diseases, each affecti[illegible]00
  - Rare diseases in total affect an estimated[illegible] population and a large proportion of renal failure
  - Each clinician manages few pa[illegible]some diseases so may lack expertise
  - Most patients do not kno[illegible]n their disease although networks easier to form in social media
- Potential market fo[illegible] therapies is seen as small
  - Historically unattractive to commercial and academic research funders
- Hard to assemble large enough cohorts to perform studies that are powerful enough to answer important questions robustly
  - Especially true for non-monogenic rare diseases

Rare ≠ Monogenic

2 UK initiatives to address these challenges

- **NIHR BioResource for Rare Diseases**
- **RaDaR** – the Rare Renal Disease Registry
- Different approaches but some commonality:
  - Recruitment from multiple centres across a country
  - Aggregation of large datasets
  - Use of routinely collected hospital record data to enrich dataset

Rare Diseases WGS Study

13,037 DNA samples from patients at 57 UK hospitals

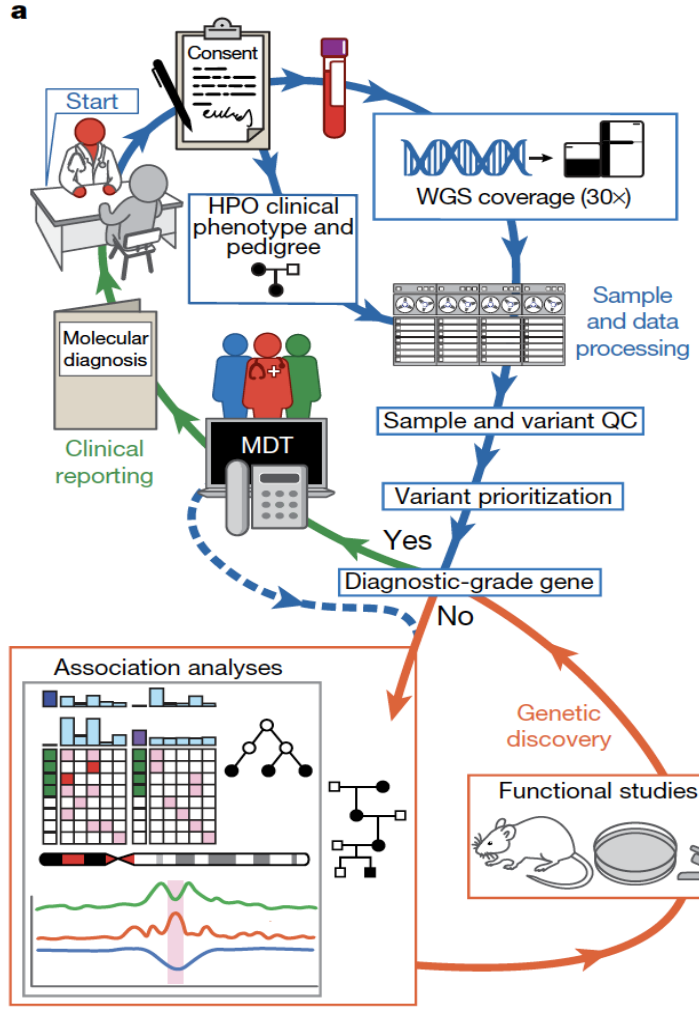
Recruitment 2012-2015

NIHR BioResource Rare Diseases

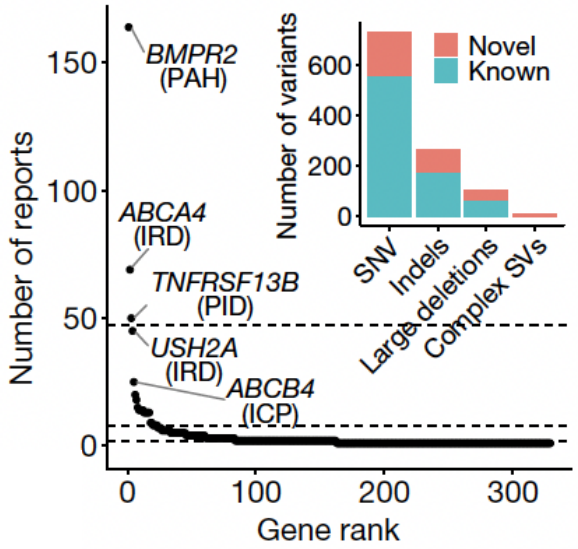
NIHR | BioResource

Genomics england

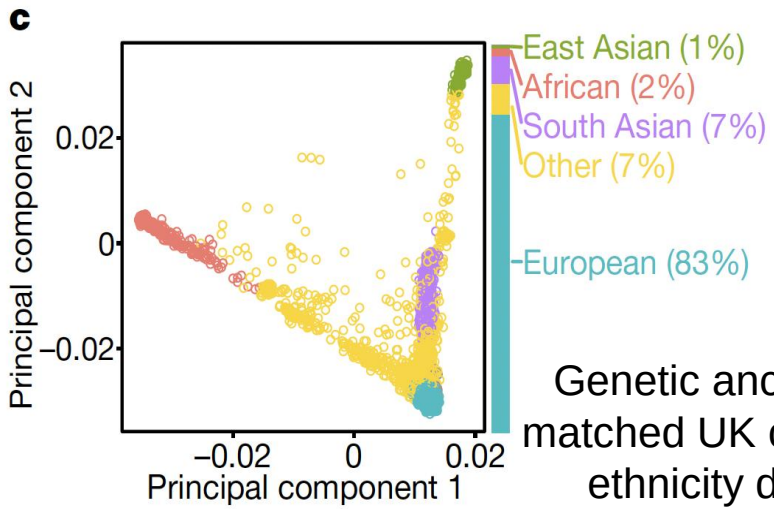
Bleeding, thrombotic and Platelet Disorders	BPD	Multiple Primary Malignant Tumours	MPMT
Cerebral Small Vessel Disease	CSVD	Neurological and Developmental Disorders	NDD
Ehler-Danlos Syndromes	EDS	Neuropathic Pain Disorders	NPD
Genomics england Rare Diseases Pilot-II	GEL	Pulmonary Arterial Hypertension	PAH
Hypertrophic Cardiomyopathy	HCM	Primary Immune Disorders	PID
Intrahepatic Cholestasis of Pregnancy	ICP	Primary Membranoproliferative Glomerulonephritis	PMG
Inherited Retinal Disorders	IRD	Stem cell and Myeloid Disorders	SMD
Leber Hereditary Optic Neuropathy	LHON	Steroid Resistant Nephrotic Syndrome	SRNS
biobank	UK Biobank – Extreme Red Cell Traits		UKBio



Diagnostic Grade Reports issued for 1100 variants in 329 genes



Turro et al Nature 2020



Genetic ancestry matched UK census ethnicity data

Variation in coverage at disease genes was much greater for WES platforms that would have missed 2.67-10.5% SNVs reported in this study

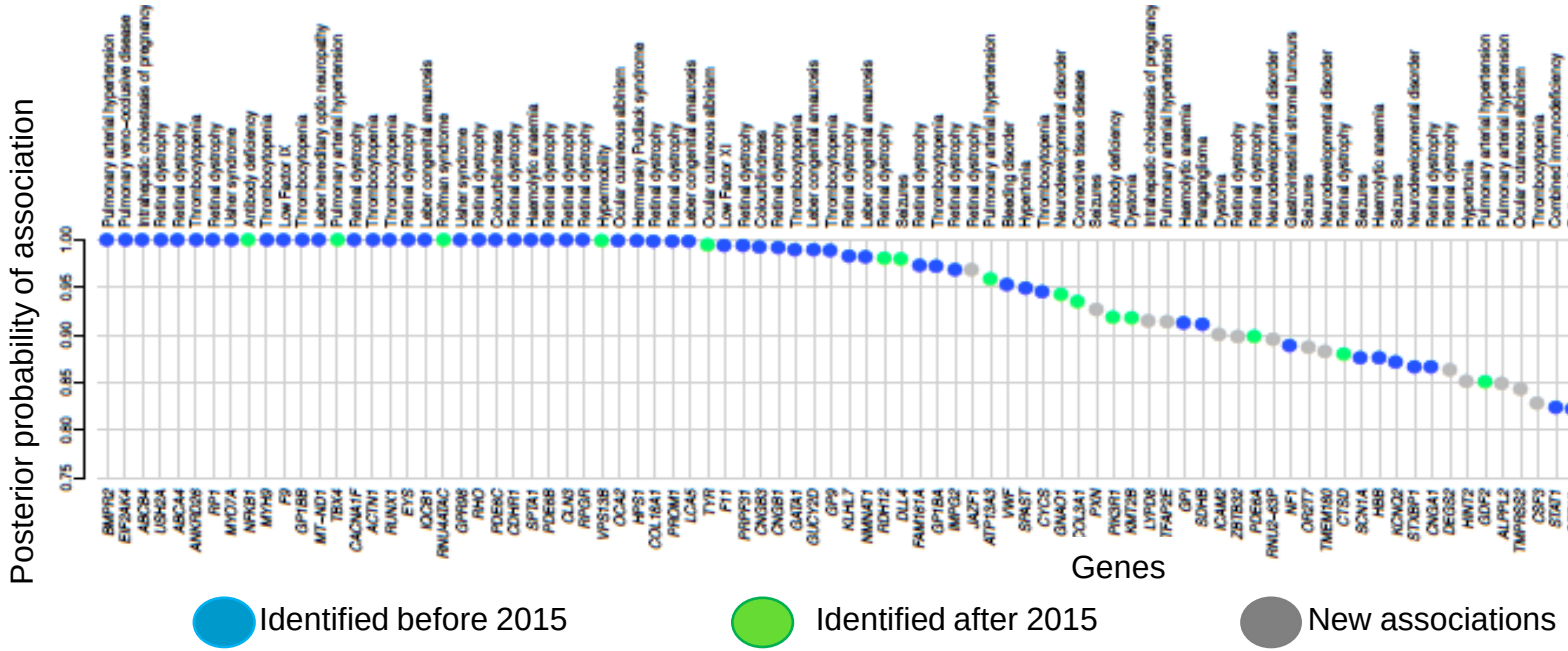
NIHR BioResource Rare Diseases

NIHR | BioResource WGS Study

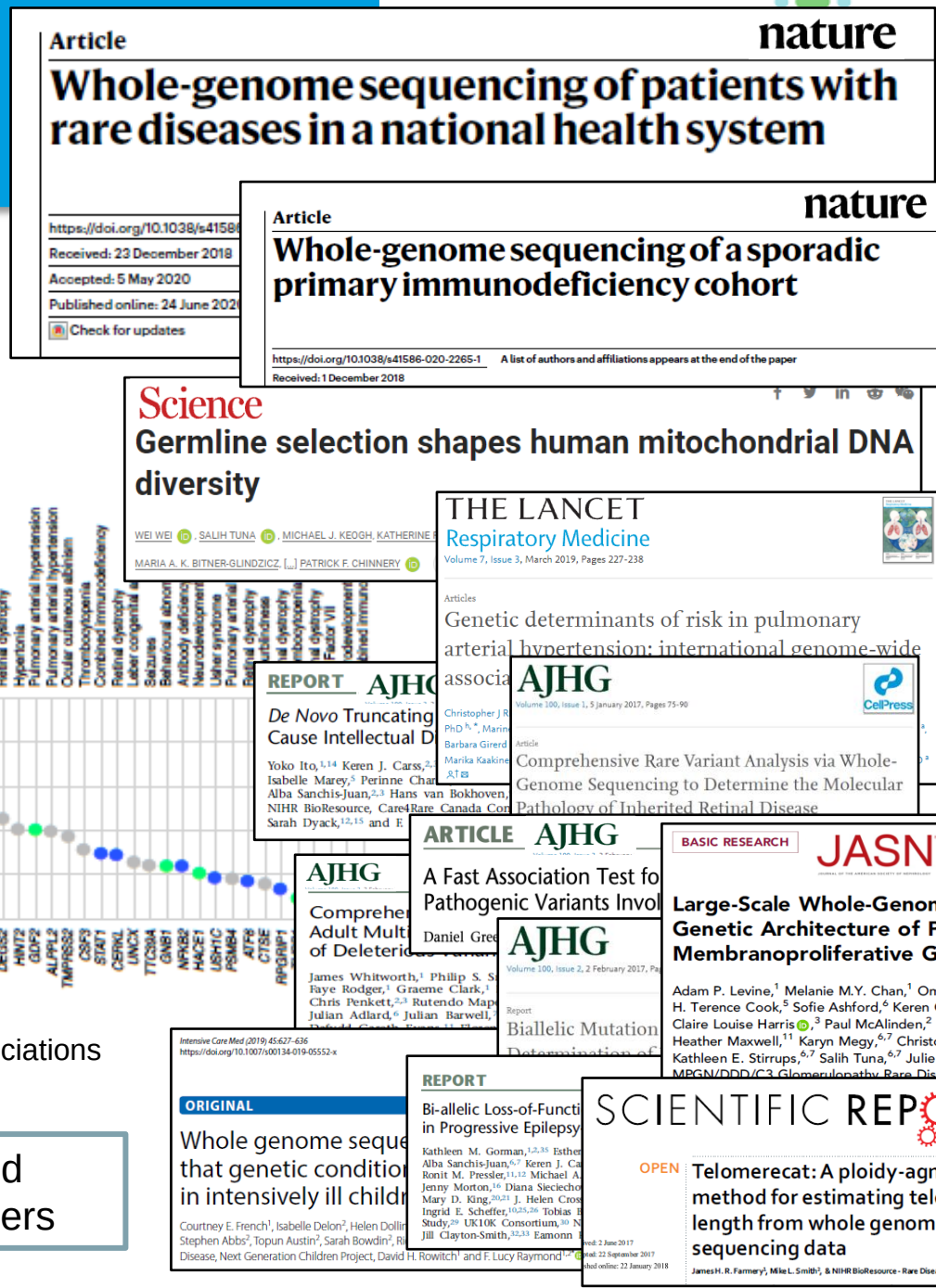
13,037 DNA samples from patients at 57 hospitals

Strong evidence for 99 genetic associations

Groups of rare disease patients based on HPO term driven clustering



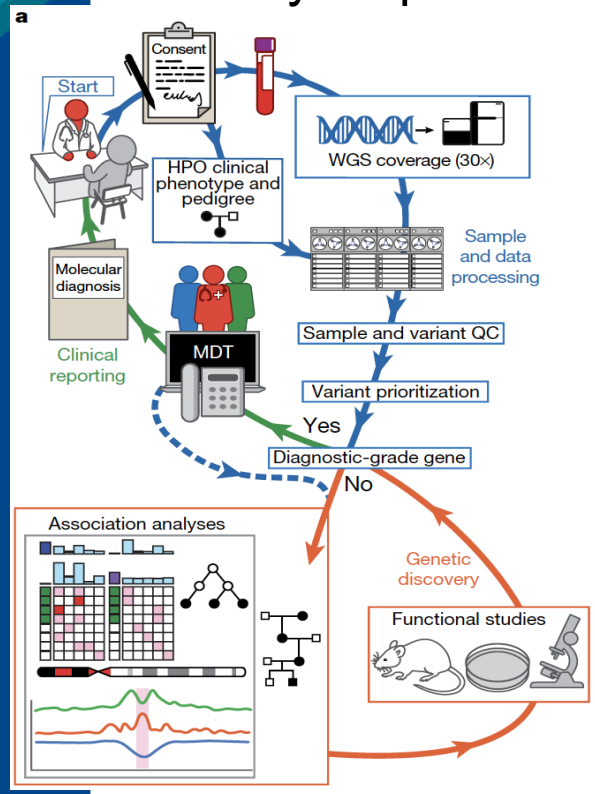
Of these 99 associations, 61 are consistent with firmly established evidence and a further 18 have been reported in the literature 2015-20, either by us or by others



The 100,000 Genomes Project and beyond

NIHR | BioResource

‘infinity loop’



88,597 participants with rare disease or cancer, and their families

120,239 whole genomes
> 30x coverage

\+

NHS patient records

\+

Deep phenotyping with HPO codes

Data from 100KG beginning to emerge:

- Numerous novel ultrarare disorders
- Genetic basis of Posterior Urethral Valves
- *IFT140* as a cause of mild ADPKD
- etc

Basis for UK-wide clinical Genomic Medicine Service

RaDaR: Rare Renal Disease Registry

RaDaR

UKKA
UK Kidney Association
Rare Renal

- Established by the RA in 2010 and hosted by UKRR with funding from MRC/KRUK/BKPA

MRC Medical Research Council

Kidney Research UK
Funding research to save lives

Kidney Care UK

- ~100 disorders in 30 Rare Disease Groups (RDGs)
  - Clinicians – Research and clinical collaborations
  - Patients – Clinical provision, education, drive research
  - Scientists

pkd charity
Polycystic Kidney Disease

alport uk
a brighter future for people living with alport syndrome

MPGN/DDD
Support Group

- Aims to connect clinicians/scientists and patients and to facilitate clinical and academic research

Components of RaDaR

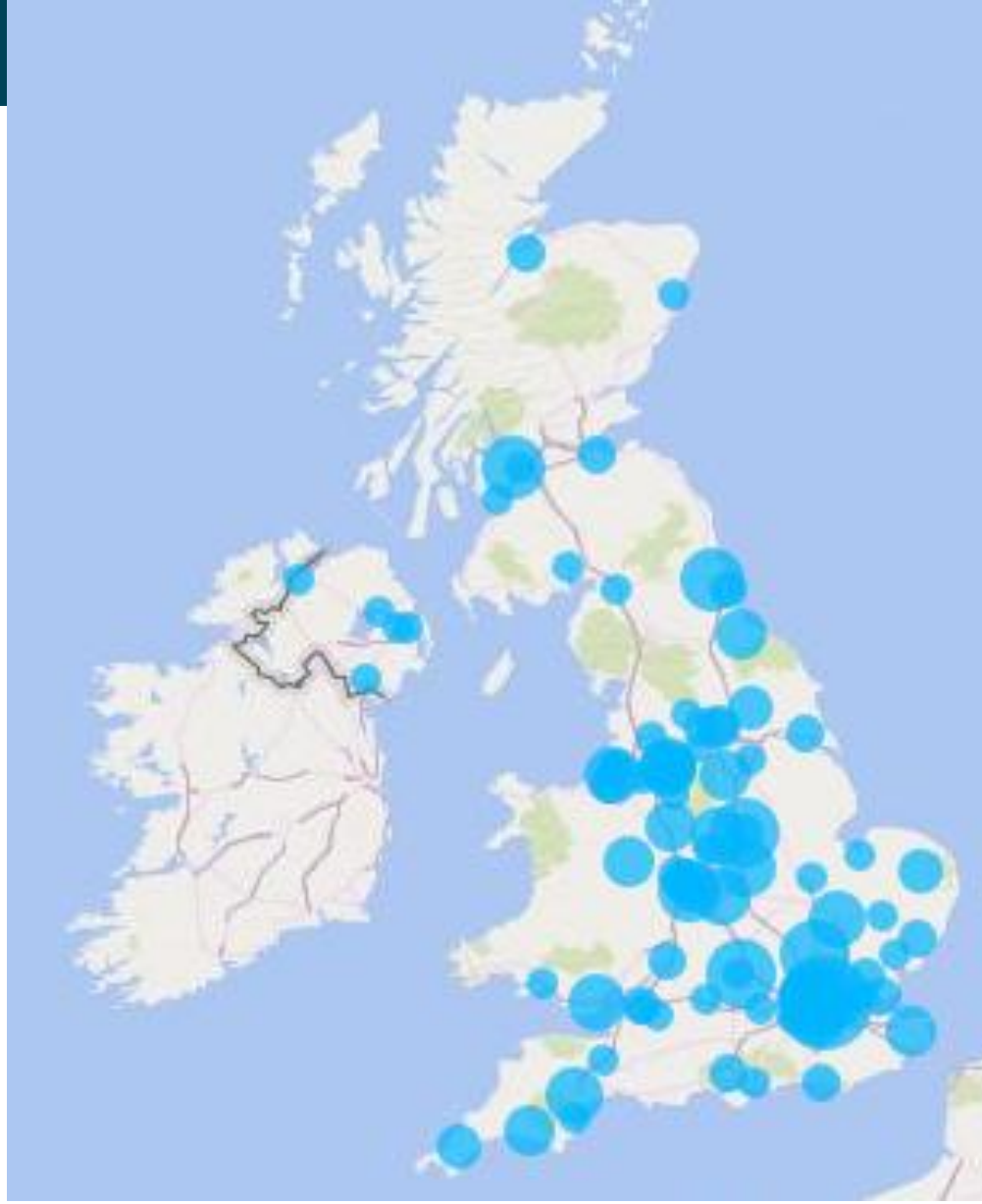
- Comprises a support/clinical management network
  - https://rarerenal.org
  - Clinical guidelines and information for clinicians
  - Patient education, communication and details of patient meetings
  - Registry summary
  - Social media presence (@RenalRadar)
- Patient research register with clinical data
  - All participants give **written informed consent** for analysis of their clinical records and linkage to their data held in any other research or clinical database
  - Also agree to be contacted about studies they might be eligible for in the future

RaDaR

UKKA
UK Kidney Association
Rare Renal

30,000 participants from 105 hospitals

Rare Disease Cohort	Cohort Size	Lab result Link
Alport Syndrome	901	711
APRT Deficiency	<10	<10
Atypical Haemolytic Uraemic Syndrome	282	221
Autosomal Dominant Polycystic Kidney Disease	7637	5840
Autosomal Dominant Tubulointerstitial Kidney Disease (FUAN)	209	157
Autosomal Recessive Polycystic Kidney Disease/Nephronophthisis	228	170
BK Nephropathy	51	42
Calciphylaxis	57	39
CKD due to Genetic Factors in people of African ancestry	64	33
Cystinosis	150	127
Cystinuria	466	307
Dent Disease and Lowe Syndrome	61	31
Fabry Disease	46	34
Fibromuscular Dysplasia	40	25
HNF1b Mutations	84	52
Hyperoxaluria	121	94
Idiopathic Nephrotic Syndrome	4106	3012
IgA Nephropathy	4134	3502
Inherited Renal Cancer Syndromes	99	<10
Membranoproliferative Glomerulonephritis / Dense Deposit Disease	1122	794
Membranous Nephropathy	2381	1614
Mitochondrial Renal Disease	<10	<10
Monoclonal Gammopathy of Renal Significance	173	121
Pregnancy	672	523
Pure Red Cell Aplasia	<10	<10
Retroperitoneal Fibrosis	141	91
STEC-associated HUS	169	88
Tuberous Sclerosis	240	129
Tubulopathy	352	193
Vasculitis	4621	2890



https://ukkidney.org/rare-renal/metadata

RaDaR data and the Renal Registry

- All data held and processed at the UK Renal Registry
  - Established 1995 to collect data from all UK RRT patients with Section 251 (NHS Act 2006) approval for patient data without consent
  - Aim is to assure quality and consistency of dialysis/transplantation
- RaDaR data is all from research-consenting patients so less stringent controls on use/access/linkage within this robust information governance framework
- UKRR database and informatics infrastructure
  - Automated datafeeds from all renal units in the country
  - Very good capture of initiation of RRT and death

Assembly of a large registry

- Broad, publicly available eligibility criteria for each RDG
- Small payment to each site for each subject recruited to study
  - National Institute of Health Research (NIHR) fund to support recruitment to ethically approved research at NHS sites
  - Sites incentivised to recruit but not resourced to input data
- Manual entry of (**very few**) mandatory fields at recruitment
  - Development of site-based mechanisms to enrich dataset by automated data transfer
  - Used existing UK Renal Registry Infrastructure to do this (esp lab results/medications)
  - **Avoid lengthy wish-list of clinical data entered manually by recruiting sites**

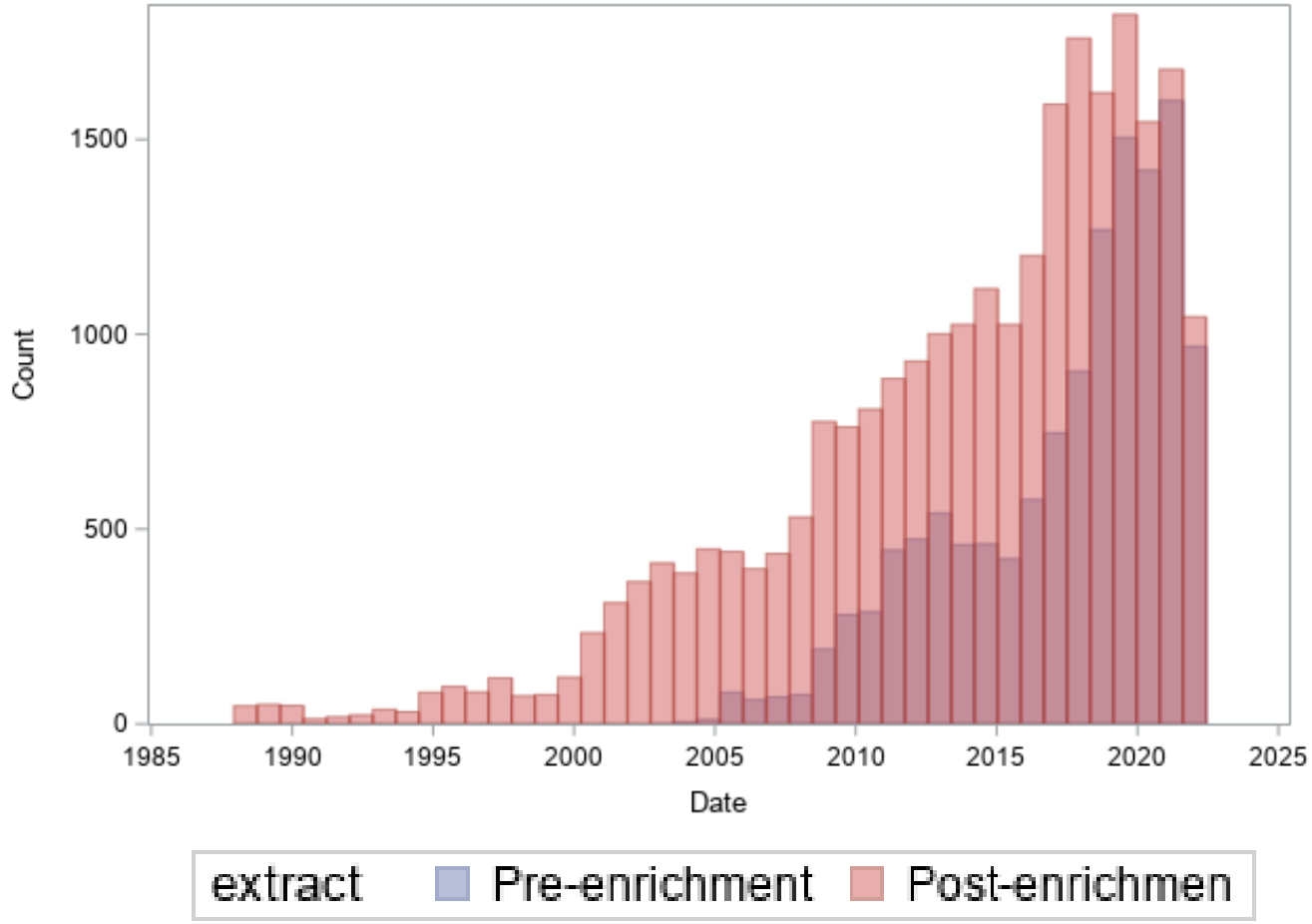
Automatic data feed

- RaDaR receives daily data feed from renal units
  - All or last 10 historic and all future values for each field
  - >60% of participants linked (increasing)
- Biochemistry and other laboratory results
- Clinic letters, imaging and other reports (variable)
- **This feed also goes to Patient View/Patients Know Best to allow participants to access their own data**

Data enrichment

With help of informatics staff at sites (especially those recruiting large numbers of patients) laboratory dataset was substantially enriched

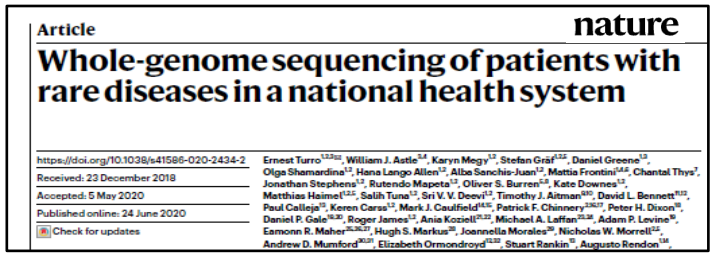
Creatinine values at one site



RaDaR data allows capture of large-scale clinical and renal outcome data

- Age at onset/presentation
- Presenting clinical features
- Medication use
- Rate of progression
- Outcomes including Death and initiation of Renal Replacement Therapy
- Secondary care use (with Hospital Episode Statistics data link)

Types of studies

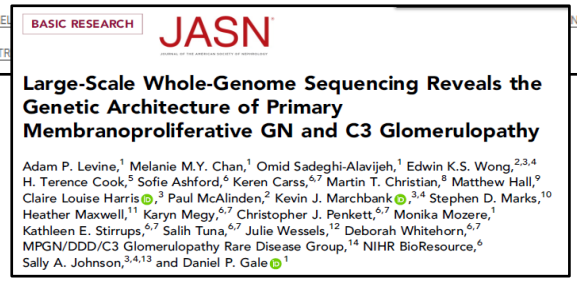

Article

nature

Whole-genome sequencing of patients with rare diseases in a national health system


Science

Germline selection shapes human mitochondrial DNA diversity


BASIC RESEARCH JASN

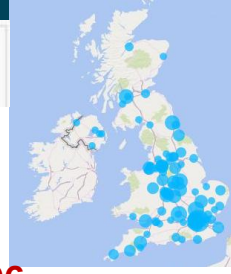
Large-Scale Whole-Genome Sequencing Reveals the Genetic Architecture of Primary Membranoproliferative GN and C3 Glomerulopathy

- Registry study
  - Epidemiology of disease in a defined area
- Genetic association studies
  - Collaboration with NIHR | BioResource
- Retrospective and prospective longitudinal Cohort studies: Natural History, outcomes and clinical practice
- Randomized Controlled Therapeutic Trials

RaDaR Natural History Analysis

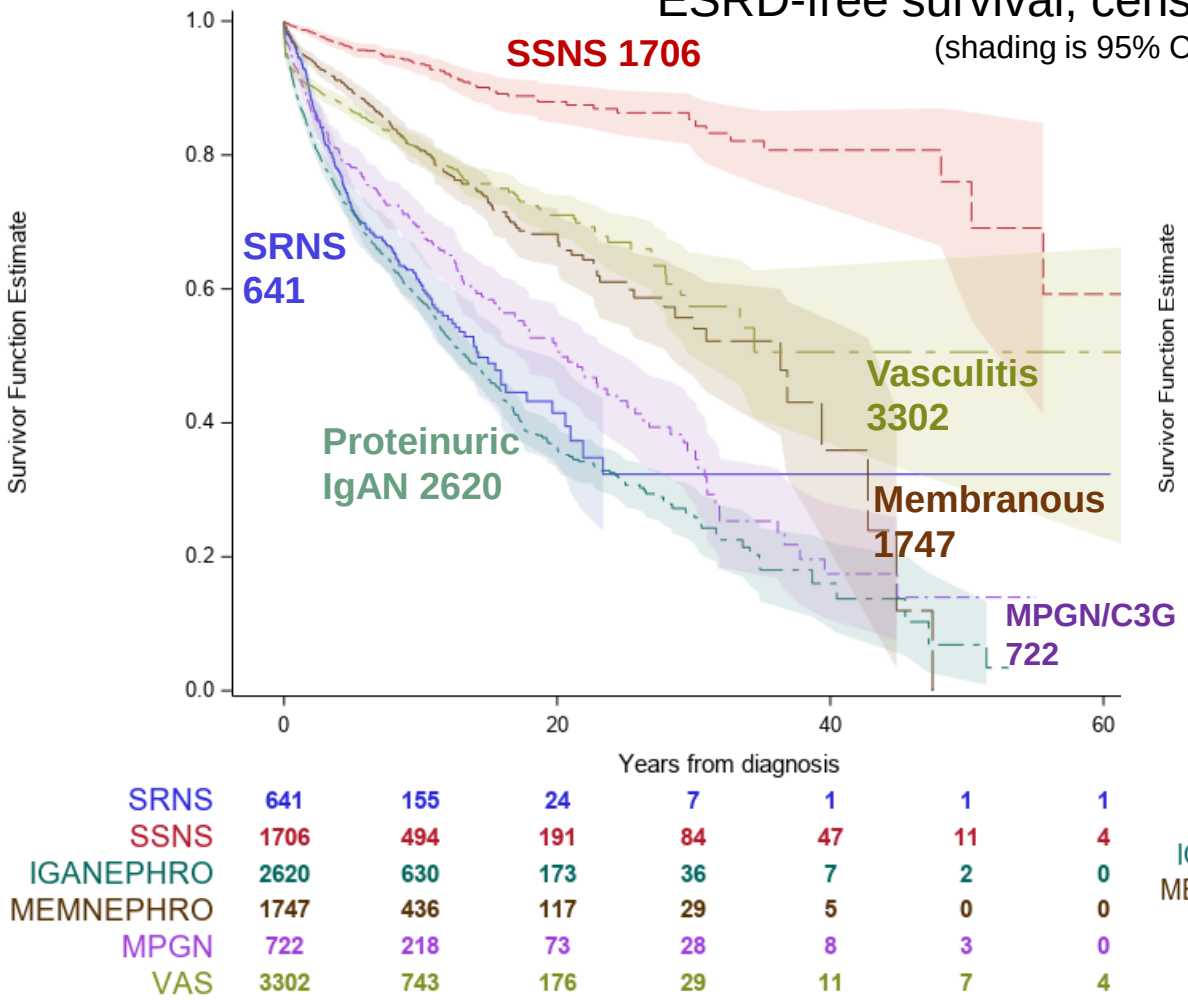
- Ascertainment and data collection similar across all disorders so comparisons between them are possible
  - Prevalence/distribution
  - Treatments – effect and uptake
  - Outcomes and predictive factors
- Engagement with academic and commercial collaborators
  - In general individual patient-level data is not shared unless compelling scientific case for doing so
  - For commercial partners our statistician answers their questions using our data

Renal outcomes – glomerular diseases

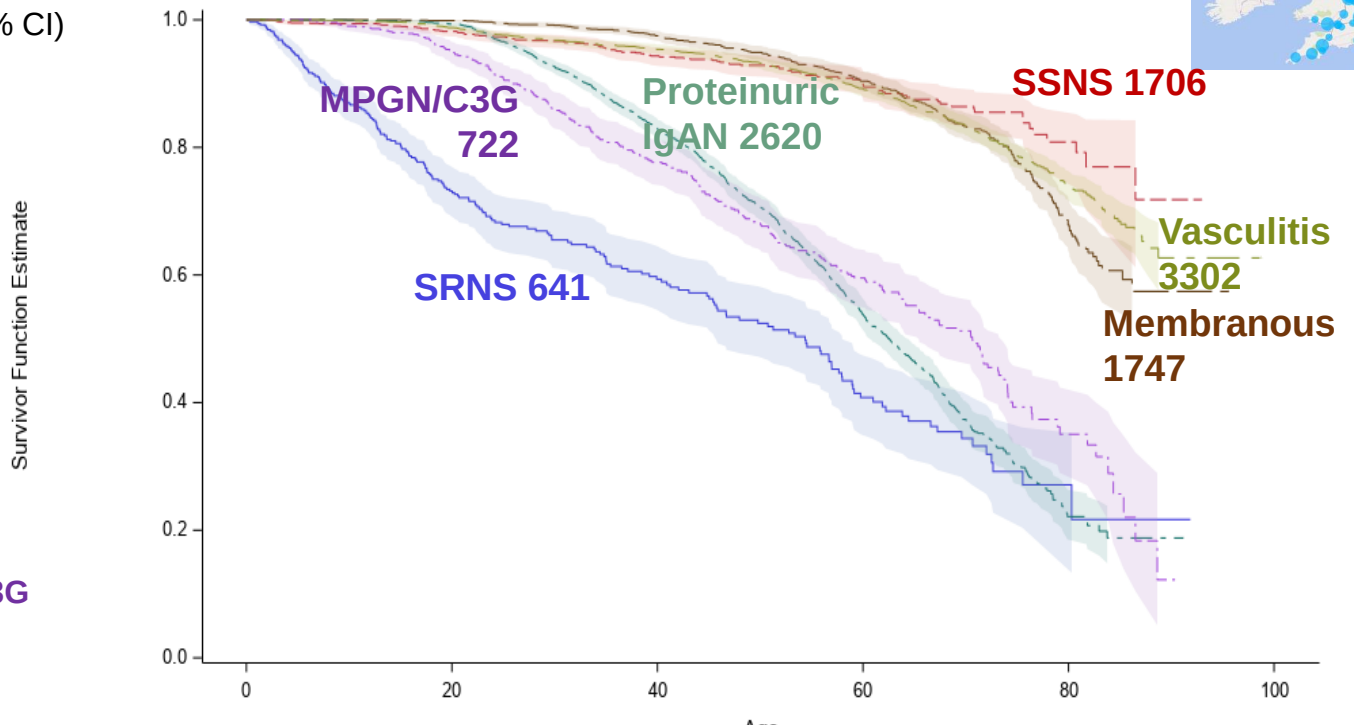


ESRD-free survival, censored at death

(shading is 95% CI)



SRNS	641	155	24	7	1	1	1
SSNS	1706	494	191	84	47	11	4
IGANEPHRO	2620	630	173	36	7	2	0
MEMNEPHRO	1747	436	117	29	5	0	0
MPGN	722	218	73	28	8	3	0
VAS	3302	743	176	29	11	7	4



SRNS	641	481	276	184	140	105	61	32	7
SSNS	1706	1437	1093	915	735	574	378	201	52
IGANEPHRO	2620	2613	2546	2228	1718	1155	611	246	38
MEMNEPHRO	1747	1747	1735	1689	1585	1407	1067	612	163
MPGN	722	703	582	439	365	292	198	111	27
VAS	3302	3210	3064	2921	2755	2523	2069	1371	427

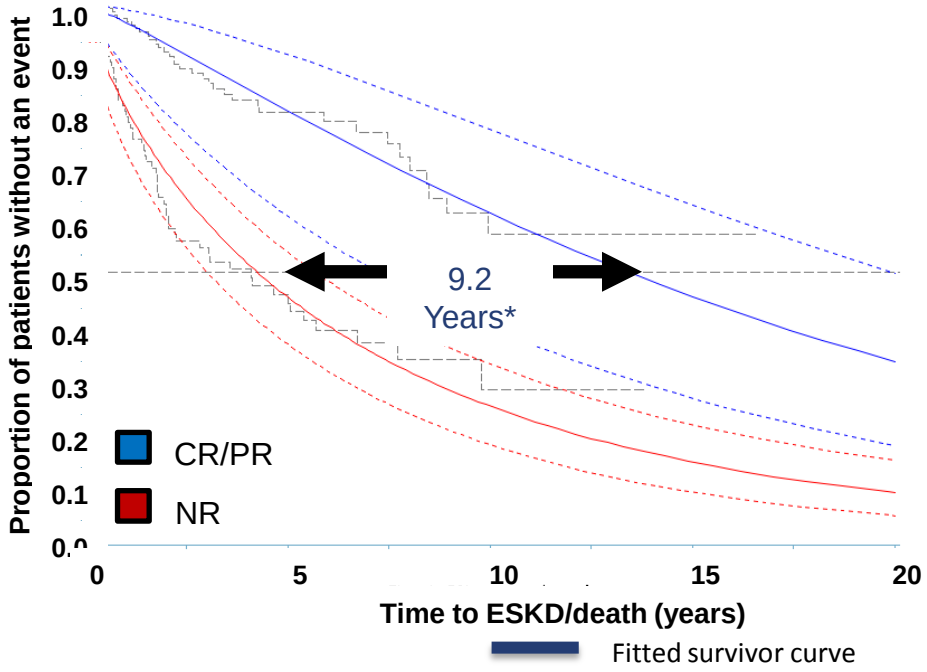
NB Ascertainment and survivor biases operate - recruitment 2010 onwards

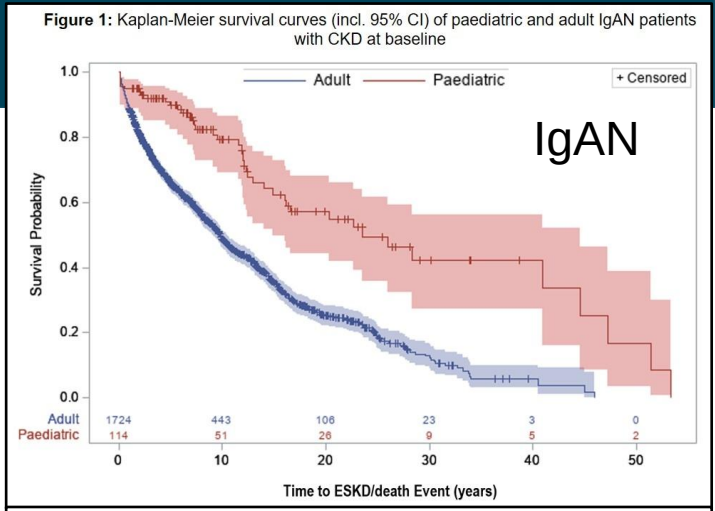
RAS blockade/IS but not SGLT2i in common use over this timeframe

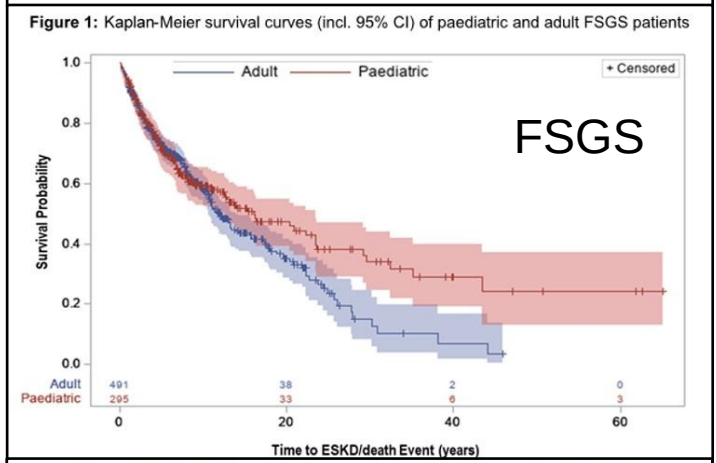
Unpublished RaDaR data

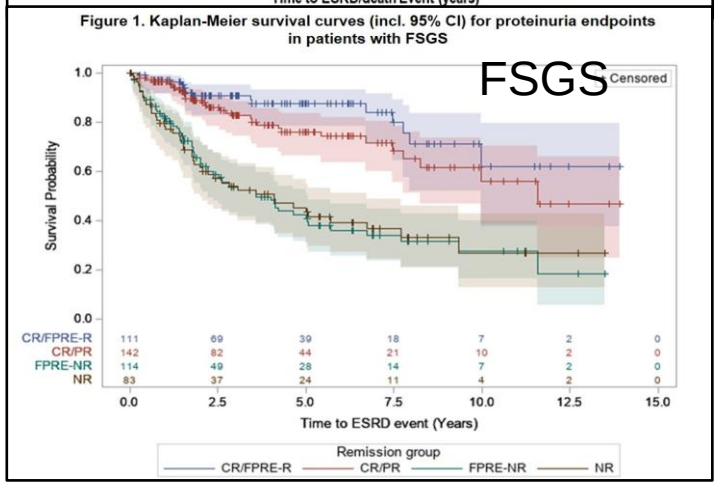
Commercial collaboration

- Looked at renal survival in children and adults with IgAN and NS with biopsy-proven FSGS
- Also looked at association of proteinuria response and renal survival in FSGS
  - Presented at ASN in 2021: PO1529, PO1530, PO1577

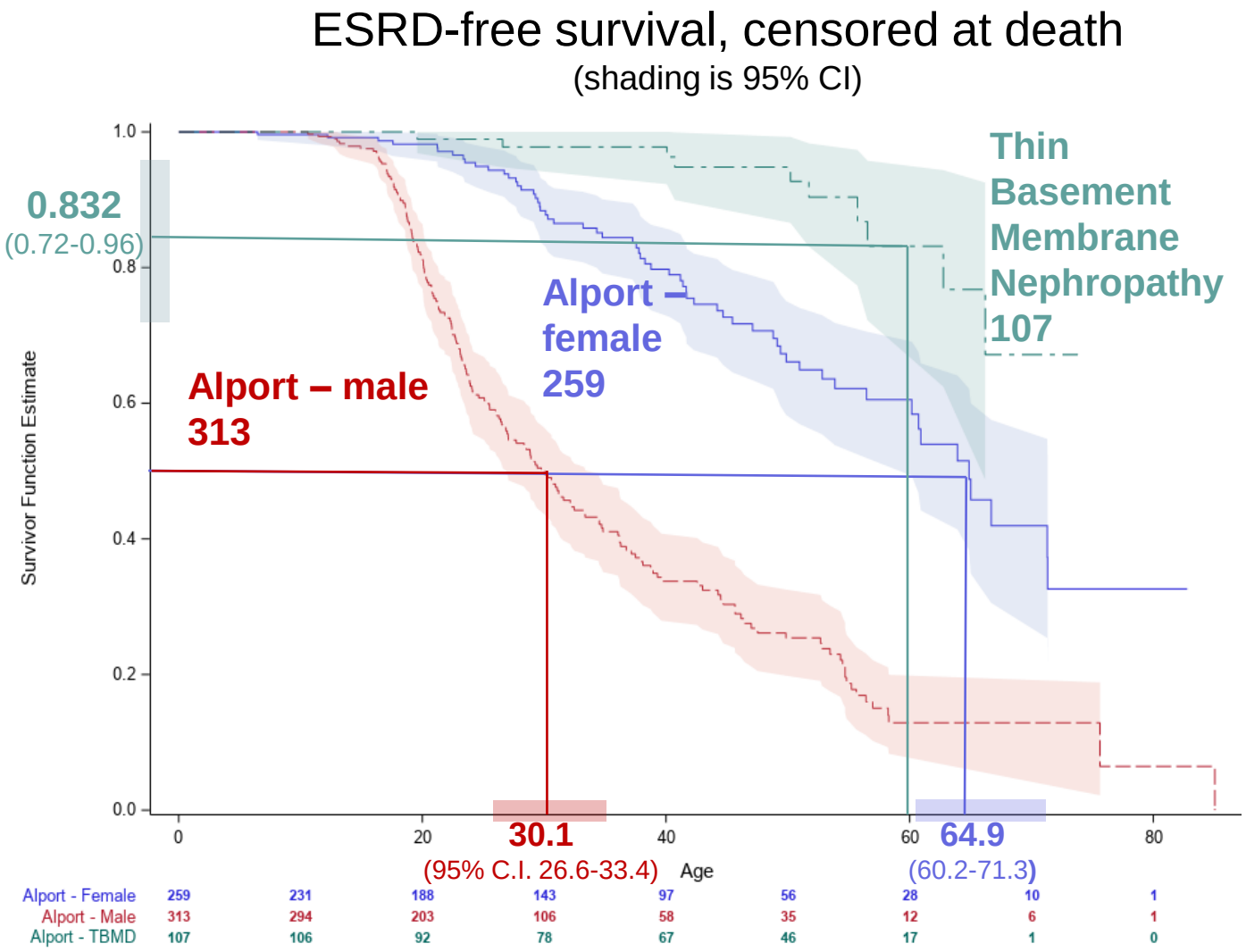








Alport Syndrome



- Median age at RRT in Alport Syndrome: 30.1(male) and 64.9 (female)
- For TBMN 83.2% have not required RRT before age 60

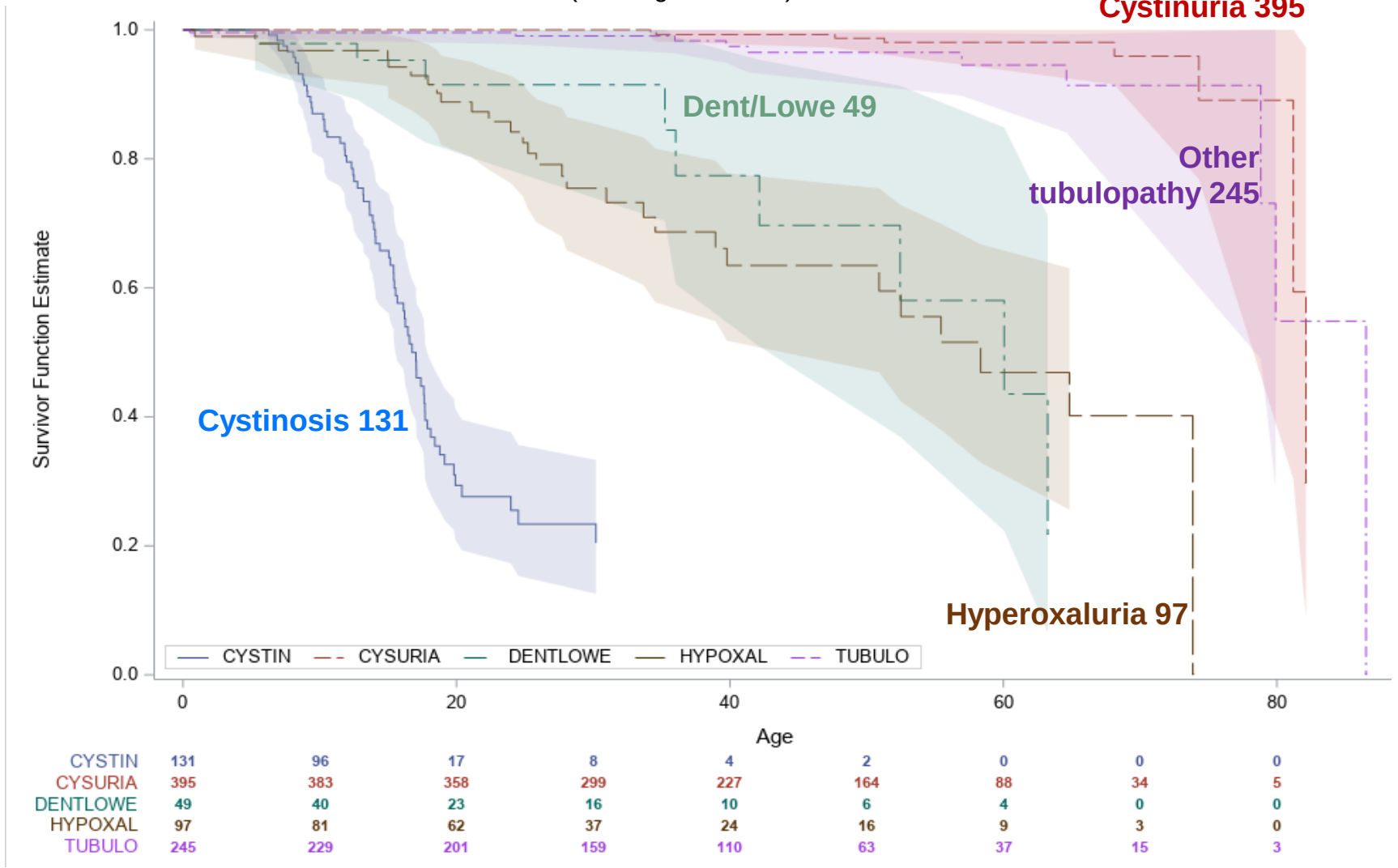
Ascertainment and survivor biases both possible

Unpublished RaDaR data

Tubular diseases

ESRD-free survival, censored at death

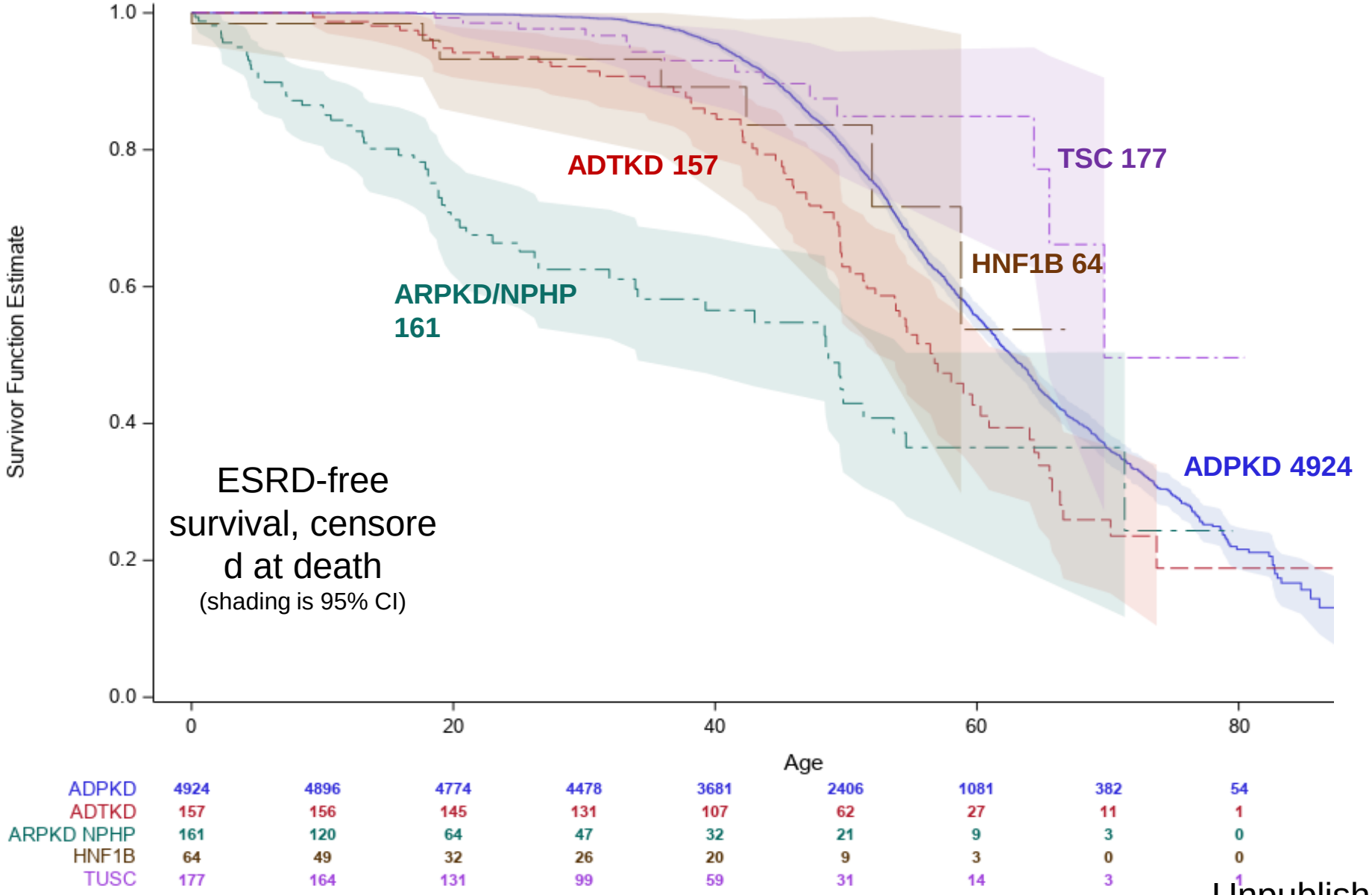
(shading is 95% CI)



CYSTIN	131	96	17	8	4	2	0	0	0
CYSURIA	395	383	358	299	227	164	88	34	5
DENTLOWE	49	40	23	16	10	6	4	0	0
HYPOXAL	97	81	62	37	24	16	9	3	0
TUBULO	245	229	201	159	110	63	37	15	3

Unpublished RaDaR data

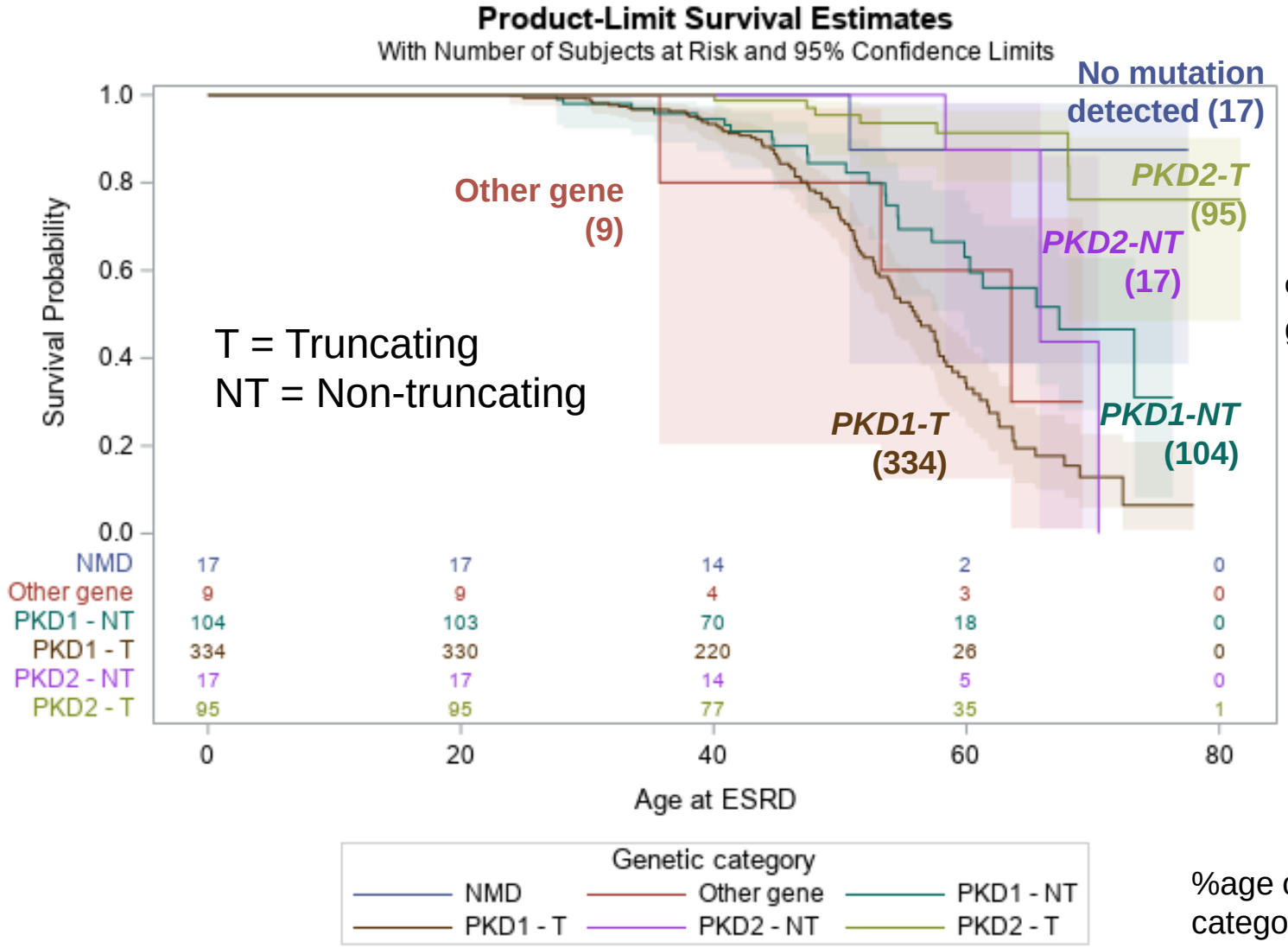
Cystic renal diseases

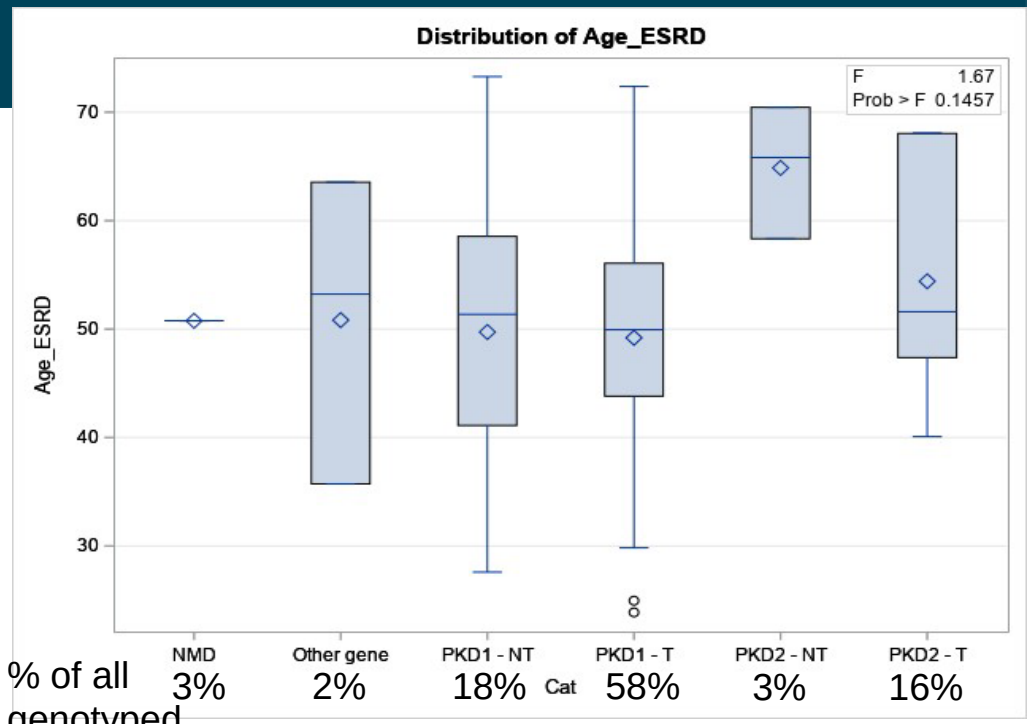


ADPKD	4924	4896	4774	4478	3681	2406	1081	382	54
ADTKD	157	156	145	131	107	62	27	11	1
ARPKD NPHP	161	120	64	47	32	21	9	3	0
HNF1B	64	49	32	26	20	9	3	0	0
TUSC	177	164	131	99	59	31	14	3	1

Unpublished RaDaR data

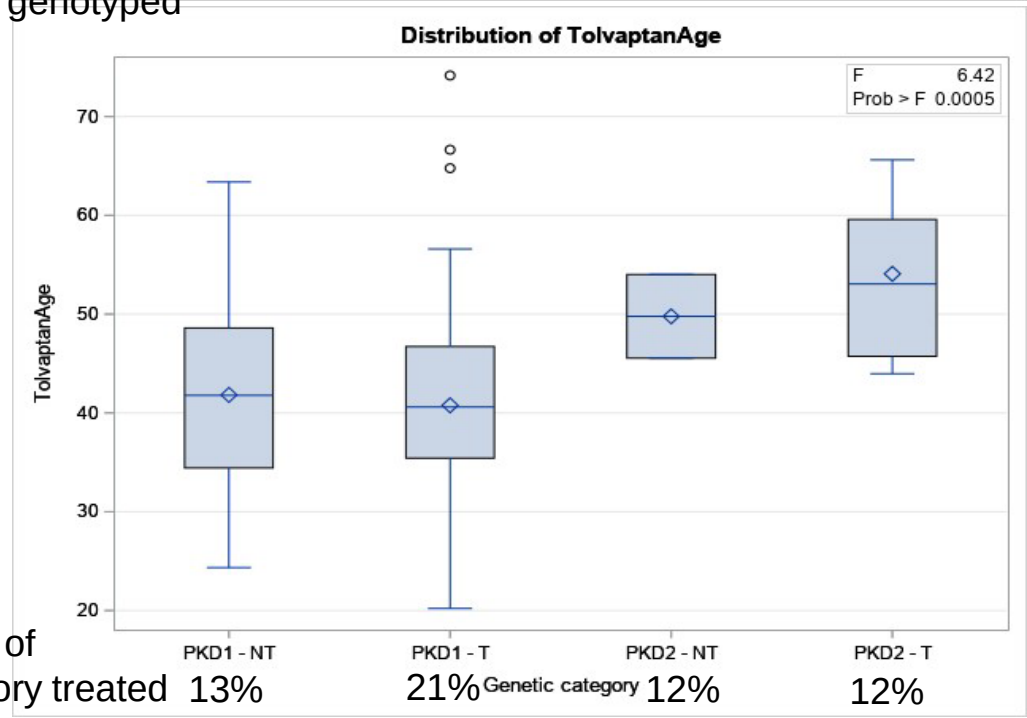
ADPKD analyses: genotype, ESRD and treatment – work in progress





% of all genotyped

NMD 3% | Other gene 2% | PKD1 - NT 18% | PKD1 - T 58% | PKD2 - NT 3% | PKD2 - T 16%



%age of category treated

PKD1 - NT 13% | PKD1 - T 21% | PKD2 - NT 12% | PKD2 - T 12%

Rate of eGFR loss (ml/min/year) from first reading below 75 ml/min

Adult at time of diagnosis

Disease	N	Median
Autosomal Dominant Polycystic Kidney Disease	1622	-3.62
IgA Nephropathy	931	-2.86
Vasculitis	929	-0.15
Membranous Nephropathy	725	-1.83
Steroid Sensitive Nephrotic Syndrome	384	-0.40
Steroid Resistant Nephrotic Syndrome	91	-2.99
MPGN/C3G	167	-2.50
Cystinuria	119	0.36
Alport Syndrome	107	-2.38
Pregnancy	98	-1.72
ADTKD	42	-2.81
Retroperitoneal Fibrosis	42	0.33
Monoclonal Gammopathy of Renal Significance	39	-5.81
ARPKD/Nephronophthisis	20	-2.08
Atypical Haemolytic Uraemic Syndrome	19	1.59
Tubulopathy	19	-0.71
HNF1b Mutations	14	-0.90
Tuberous Sclerosis	13	-1.49

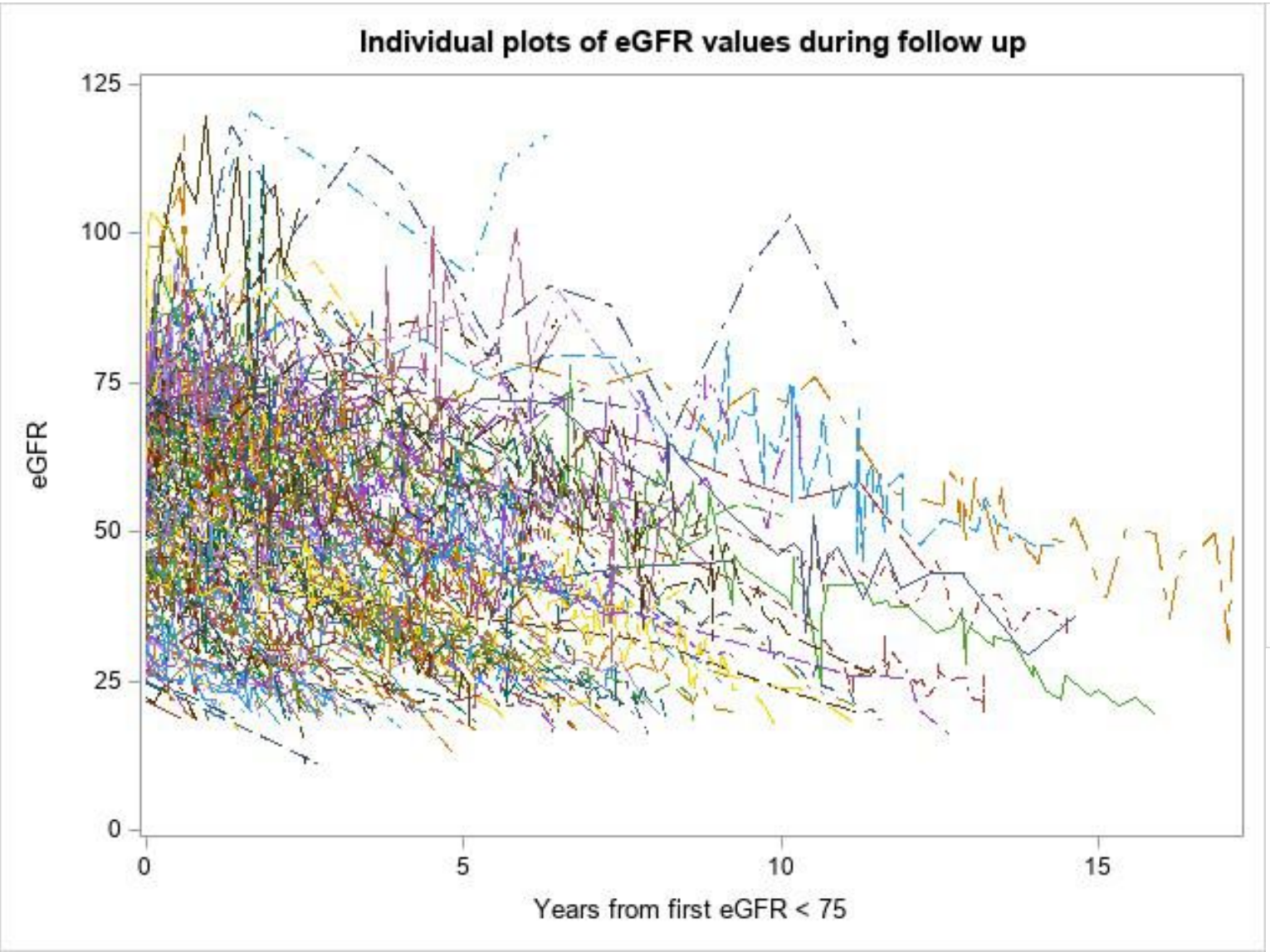
Child at time of diagnosis

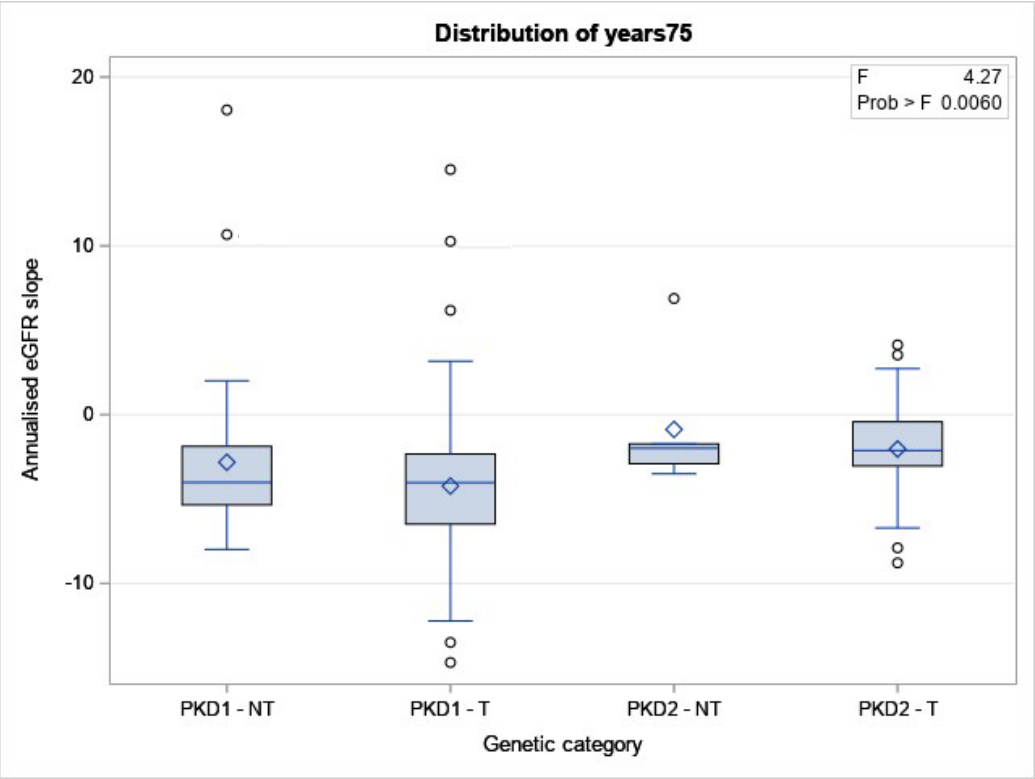
Disease	N	Median
Steroid Resistant Nephrotic Syndrome	144	-11.6
Steroid Sensitive Nephrotic Syndrome	86	2.52
MPGN/C3G	59	-0.67
ADPKD	57	-3.17
Cystinosis	38	-4.82
ARPKD/Nephronophthisis	18	-1.51
Vasculitis	16	-2.01
IgA Nephropathy	14	-7.44
Alport Syndrome	12	-8.95
Tuberous Sclerosis	12	-1.98

NB In SHARP CKD study rate of eGFR loss was <2ml/min/year (Haynes et al JASN 2014)

Unpublished RaDaR data

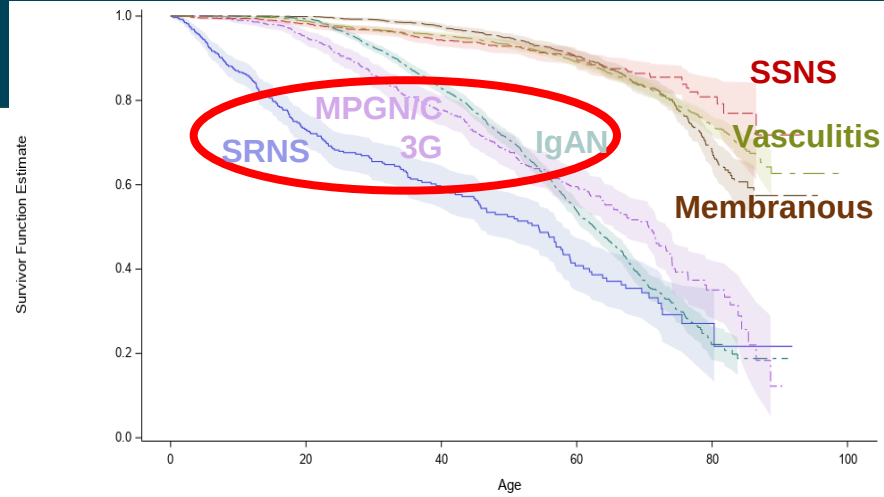
ADPKD: eGFR loss between 75 and 20 ml/min





Unpublished RaDaR data

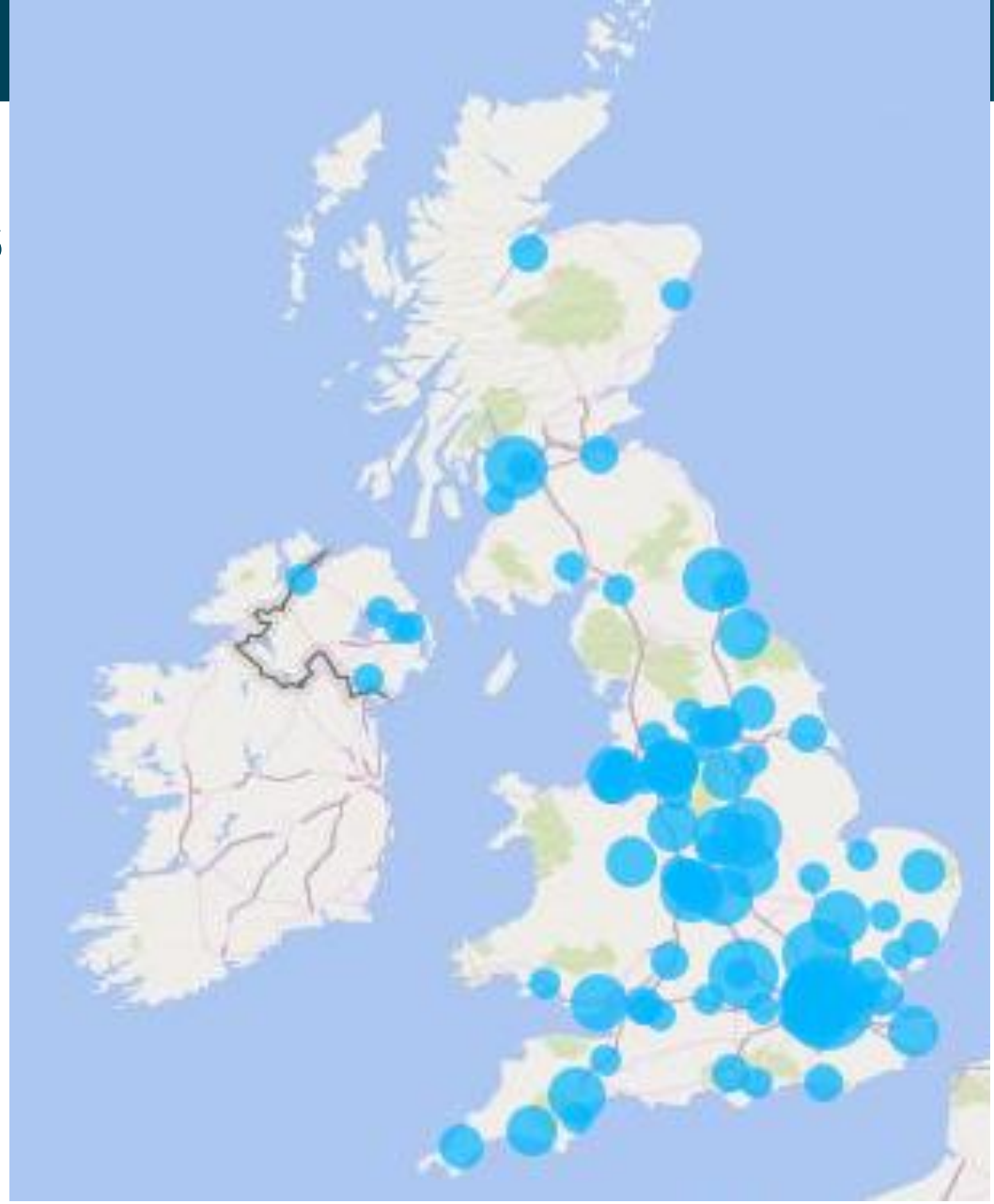
RaDaR can help design clinical trials



- Reveals diseases with particularly great unmet medical need
- Allows large-scale studies of natural history/outcomes
  - Where eGFR decline is rapid this might be a feasible trial endpoint
  - This information particularly important to regulators considering new therapies
- Identify number and proportion of RaDaR participants with particular genetic/phenotypic features, allowing feasibility of clinical trial to be assessed by biotech/pharma companies
  - Also allows estimation of eventual market size
  - Can reveal gaps in knowledge of natural history

RaDaR can help deliver clinical trials

- RaDaR holds geographical distributions
  - Integration with clinical data allows identification of sites with patients likely to be eligible for clinical trials
- RaDaR consent includes participants' permission to be contacted to inform them of trials that are relevant to them
  - Patients informed how to contact sites recruiting to studies they are potentially eligible for
  - This is an important motivator for many people to sign up to RaDaR
- Active collaborations to improve recruitment to interventional studies are in place and proving successful in enabling recruitment



RaDaR Summary

- Powerful source of real-world data about patients with rare renal diseases
- Linking RaDaR data with clinical/research genomic data can reveal robust associations in rare diseases
- Catalyst for clinical trials and therapeutic development
- Much more to do:
  - Genomic, multi-omic/biomarker and interventional studies
  - Linking with Hospital Episode Statistics and other data sources to enrich data on non-renal co-morbidities
  - Socio-economic deprivation associations
  - Ancestry, ethnicity and pharmacogenomic associations
  - International collaborations will be needed for insights into rarer disorders

Take home messages

- Studying rare diseases in an era when powerful molecular techniques (eg WGS) are widely available requires large, adequately controlled cohorts to gain important new insights
- Early and full engagement with patient groups has provided powerful momentum
- Assembling cohorts and collecting rich enough phenotypic dataset has required distributed recruitment and participation across disease areas and on a National scale
  - One day the scale required will be Continental, then Global
- Big data collection/processing and analysis presents its own challenges

Acknowledgements

https://rarerenal.org

@RenalRadar

RaDaR participants and their families

Rare Disease Group members and patient representatives

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Adam Levine

Willem Ouwehand

Chris Penkett

Kathy Stirrups

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